ISOTHIOUREA-MEDIATED ACYLATIVE KINETIC RESOLUTION OF HETEROCYCLIC AND ACYCLIC TERTIARY ALCOHOLS

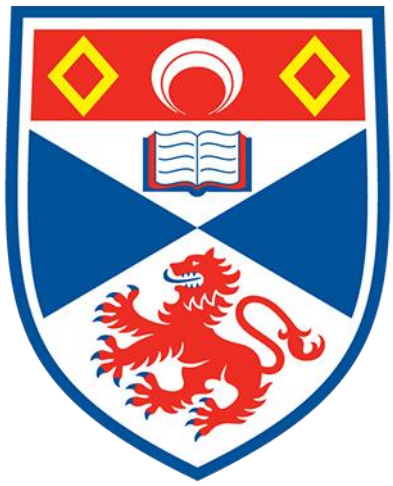
Samuel M Smith

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

2018

Isothiourea-mediated acylative kinetic resolution of heterocyclic and acyclic tertiary alcohols

School of Chemistry



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Samuel M. Smith

2018

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Acknowledgements

Firstly, I extend my thanks to my supervisor, Professor Andrew Smith, for the opportunity to work in his group and for his patience, understanding and passion for chemistry. Without his assistance, guidance and input, this thesis and work conducted herein would not have been possible.

I would like to extend my deepest thanks to Dr Mark Greenhalgh, who has collaborated with me on this project since joining the group, and for his chemistry knowledge and discussions, which really aided me in breaking through some brick walls I (quite often) hit.

Since conducting an undergraduate Masters project in the Smith group, I have met some great people, and made better friends. Special praise should go to Dr Louie Morrill, who I have known since coming to St Andrews, and has acted like a mentor to me throughout both of my Masters and PhD, and his input and guidance have been paramount to me getting to this stage. Outside of chemistry however, I consider him a great friend and the in-depth boxing chats and analyses have been riveting and I look forward to attending many more boxing events with him in the future.

In particular, I would like to thank certain past members of the group: Dr Dan Stark, for the beats in the lab, the gainz in the gym and putting up with me in the bay; Dr Alyn "DT" Davies, for that particular bloody night in the Lizard and resulting venture out to Cupar; Dr Ross Chisholm, for his organization of the ADS 6-a-side team, though football was only brought home after the reins were passed on to moi (as well as an EaStChem Cup and Golden boot; sorry Chiz!) and to all of the above, my insides will forever be scarred thanks to a particular Fisher & Donaldson challenge, something I would rather not do ever again (still, 8 and a half minutes though fellas!); Dr Tom "T-Dubz" West, for those…interesting? choice of patterned shirts and mismatched socks, and those all-important boxing chats; and to Dr James Taylor, for his insight into chemistry, those thrilling tea-fuelled football discussions on a Monday morning and constant ribs about Liverpool's shortcomings over the course of the season; and to Dr Claire Young for those rowdy ChemSoc quiz nights and all past members of the group I have missed out.

I would be remiss if I did not extend thanks to Nastja Matviitsuk and Jude Arokianathar as we started this journey together. Our trio became very close friends and I couldn't have started (and got through) this part of my life with 2 better people in tow. My final thanks must go to Calum McLaughlin for being an easy target to make fun of when the Scotland football or rugby teams (quite often) lose, and his continuation of the 6-a-side empire I built; Will Hartley for trying (and failing) to be a member of Oasis; Stefania Musolino for our wee trip around Europe to #5EUCapitals (ft. Jude) and to Jason Qu for a certain mobile game we both need to stop playing, and to all other current members of the group, I wish you the best in all of your future endeavors.

I would also like to extend my sincerest thanks and appreciation to Prof. Paul Ha-Yeon Cheong and Dr Daniel Walden for their amazing computational studies, which was of vital importance to this work; and to all of the technical staff that have been pivotal; Dr Tomas Lebl, Mrs Melanja Smith and Dr Siobhan Smith for the NMR services, University of St Andrews; ESPRC UK National Mass Spectrometry Facility at Swansea University; and Professor Alexandra Slawin and Dr David Cordes for the X-ray crystallographic service, University of St Andrews. This work was supported by the University of St Andrews (School of Chemistry).

Most importantly, I'd like to thank the people outside of the lab, outside of chemistry and outside of St Andrews that have been my rock over the last 9 years. My family. Particularly my parents, Ian and Marina. They are the best parents a guy could ask for. I know it started off quite rocky when first coming to St Andrews, but they stuck by me and after helping to get me through the first few weeks, I didn't look back, and I never imagined I would stay here for 9 years! The faith they have shown in me and my abilities, and their willingness to go out of their way to offer help when needed is something I will forever be grateful for. I hope that one day I can help to repay them for their constant and amazing support. Words cannot express how much they mean to me and how much they have got me through my time here. My brother Mark for those late night/early morning chats during wrestling pay-per-views, the Christmas Cup matches and those hard (and cold) times at the Vale, and my sister Michelle for letting me leach on her Sky Go account for a few years, but not for when she cancelled it without telling me, that was a dark time. And I wish her all the happiness with my brother-in-law, Wayne, one of the nicest fellas you could meet.

Abstract

This thesis describes the isothiourea-catalyzed acylative kinetic resolution (KR) of heterocyclic and acyclic tertiary alcohols. The protocols developed for the resolution of these challenging substrates provide access to biologically-relevant small molecules in highly enantioenriched form.

Chapter 2 describes the acylative KR of a range of 3-hydroxy-3-substituted oxindole substrates, bearing up to three potential recognition motifs at the stereogenic tertiary carbinol centre. Experimental and computational studies have identified a C=O•••isothiouronium interaction as the key stabilizing interaction for efficient enantiodiscrimination. This interaction was exploited in reactions using the isothiourea catalyst, (2*S*,3*R*)-HyperBTM, generally at low catalyst loadings (1 mol %) and isobutyric or acetic anhydride as acylating agent, enabling *s* values of up to > 200 (30 examples).

Chapter 3 focuses on extending the KR protocol to 3-hydroxypyrrolidinone substrates, which do not possess the benzannulation present in the core structure of the substrates resolved in Chapter 2. Re-optimization of the previous KR conditions found (2*S*,3*R*)-HyperBTM (2 mol %) as catalyst, acetic anhydride (0.7 equiv.) as acylating agent, in toluene at 0 °C as optimal, enabling *s* values of up to > 200 to be obtained (27 examples). Variation of the substitution patterns and electronic nature of the pyrrolidinone substrates were investigated, including extension of the protocol for the KR of α-hydroxy-β- and δ-lactam derivatives.

Chapter 4 investigates the complete removal of the cyclic structure of the substrate through the KR of a range of acyclic tertiary alcohols. No acylation was observed for acyclic α-hydroxy amides, and poor reactivity and selectivity was observed for α-hydroxy ketones and α-hydroxy phosphonates. However, acylation is readily achieved when using α-hydroxy esters, and this chapter focuses on the KR of these substrates. Optimization studies found (2*S*,3*R*)-HyperBTM (5 mol %) as catalyst, isobutyric anhydride (2.0 equiv.) as acylating agent in diethyl ether at rt as optimal, enabling *s* values of up to 140 (21 examples). The protocol is currently limited to the KR of α-hydroxy esters bearing an aromatic substituent and a methyl group at the carbinol stereocentre, with alkyl substituents larger than methyl leading to either low conversion or selectivity.

Publications

The work described in this thesis has formed the basis of the following peer reviews publications to date:

"A C=O•••Isothiouronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolution of Tertiary Heterocyclic Alcohols"

M. D. Greenhalgh, *S. M. Smith,* D. M. Walden, J. E. Taylor, Z. C. Brice, E. R. T. Robinson, C. Fallan, D. B.Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H-Y. Cheong, A. D. Smith

Angew. Chem. Int. Ed. **2018**, *57*, 3200-3206

"Evaluating polymer-supported isothiourea catalysis in industrially-preferable solvents for the acylative kinetic resolution of secondary and tertiary heterocyclic alcohols in batch and flow"

N. R. Guha, R. M. Neyyappadath, M. D. Greenhalgh, R. Chisholm, *S. M. Smith,* M. L. McEvoy, C. M. Young, C. Rodriguez-Escrich, M. A. Pericàs, G. Hähner, A. D. Smith

Green Chem. **2018***, 20,* 4537-4546

Abbreviations

aq	Aqueous
Ar	Aromatic
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Br	Bromo
BTM	Benzotetramisole
Bu	Butyl
c	Concentration
°C	Celsius
CF_3	Trifluoromethyl
CH_2Cl_2	Dichloromethane
CI	Chemical ionisation
cm^{-1}	Wave number
d	Doublet
DHIP	2,3-dihydroimidazo-[1,2-*a*]pyridine
DHPB	3,4-Dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
er	Enantiomeric ratio
equiv	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl Acetate
Et_2O	Diethyl Ether
g	Gram(s)
h	Hour(s)
HBTM	Homobenzotetramisole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz

i	*iso*
*i*PrOH	*Iso*-propanol
iPr_2NEt	*N*,*N*-Diisopropylethylamine
IR	Infrared
J	Coupling constant
KR	Kinetic resolution
LRMS	Low resolution mass spectrometry
M	Molar (mol dm^{-3})
m	Multiplet
m/z	Mass to charge ratio
$M+H^+$	Protonated molecular ion
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
mmol	Millimole(s)
mp	Melting point
NHC	N-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NSI	Nanospray ionisation
NO_2	Nitro
PG	Protecting group
Ph	Phenyl
Pr	Propyl
ppm	Parts per million
q	Quartet
quant.	Quantitative
R	Alkyl
rt	Ambient (room) temperature
s	Singlet
sept	Septet
t	*tert*
t	Triplet/time

T	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Tetramisole
TMS	Trimethylsilyl
Ts	4-methylbenzenesulfonyl (tosyl)
t_R	Retention time
δ_C	Carbon (^{13}C) NMR chemical shift
δ_F	Fluorine ($^{19}F\{^1H\}$) NMR chemical shift
δ_H	Proton (^1H) NMR chemical shift
δ_P	Phosphorus (^{31}P) NMR chemical shift
ν_{max}	Infrared absorption

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CHAPTER 1: INTRODUCTION

1.1 Organocatalysis

The ability to be able to mimic nature and synthesize compounds in enantiopure form in a completely efficient manner is an area of chemistry that is ever expanding. Ranging from natural product synthesis to fine chemicals and agrochemicals, the process of enantioselective synthesis is of vital importance for molecules that contain one or more stereogenic centres. One of the dominating factors for asymmetric synthesis is the need to develop and synthesize medicaments as a sole enantiomer, as the body treats enantiomers as separate entities.[1] Each enantiomer can have adversely different effects when introduced into the body, with one producing the desired therapeutic effect, with the other acting as a cytotoxin and cause severe side effects. Alongside enzymatic and organometallic catalysis, another area of asymmetric synthesis is termed organocatalysis and over the last century, this field of research has received a lot of attention and been utilized for the promotion of specific target transformations. Organocatalysis is described as the sub-stoichiometric use of an organic molecule in an organic transformation that has a marked effect in increasing the reaction rate.[2] This area has received increasing interest as an alternative to metal-catalyzed processes, due to many organocatalysts exhibiting a lack of sensitivity to moisture and air. More so, most organocatalysts are readily available or easily accessed in enantiopure form using cheap, simple starting materials, with both enantiomers easy to prepare by accessing both natural and unnatural chiral pools, with a wide range of structural modifications available.[3] A pioneering reaction in the field of organocatalysis was demonstrated by the Hajos-Parrish-Eder-Saur-Wiechert reaction using the amino acid, (*S*)-proline, as the organocatalyst.[4] Relatively few examples were demonstrated in this field between 1968 and 1997, however landmark contributions in 2000 by List[5] and MacMillan[6] showed the generality, synthetic utility and the power of organocatalysis, sparking an immense interest in this field. There are four main classes of organocatalyst, based on the mechanism of catalysis: Lewis base, Lewis acid, Brønsted base and Brønsted acid,[7] with the research in this thesis focused on the use of Lewis base organocatalysis.

1.1.1 Lewis base organocatalysis

Lewis bases are nucleophilic species,[8] which have been widely studied and researched as organocatalysts. These organocatalysts promote a given reaction through formation of reactive intermediates, leading to an increased reaction rate, *via* accessing either a lower energy LUMO of the electrophile, or a higher energy HOMO of the nucleophile in the reaction mechanism. The reaction is initiated by nucleophilic attack of the Lewis base (LB) to the substrate (S) to form an activated Lewis base-substrate (LB-S) complex, followed by a chemical transformation, leading to a Lewis base-

product (LB-P) complex. Upon release of the product (P), the Lewis base (LB) catalyst is regenerated and further turnover can take place (Figure 1).[9] This classification of organocatalysis is encompassed by a range of examples where the reaction mechanism passes through an activated intermediate, such as an enamine,[10] iminium ion[11] and ammonium enolate.[12]

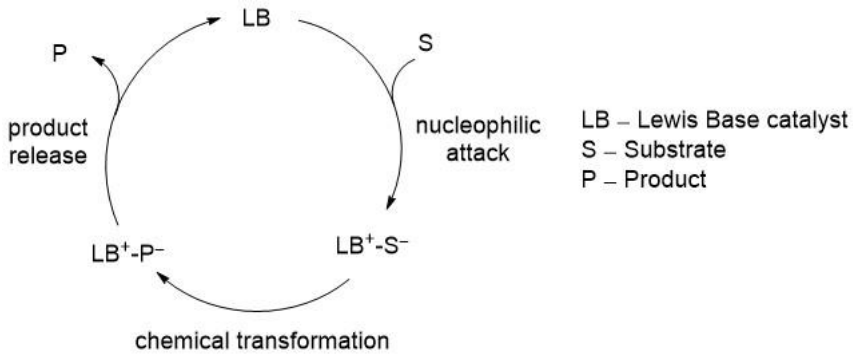
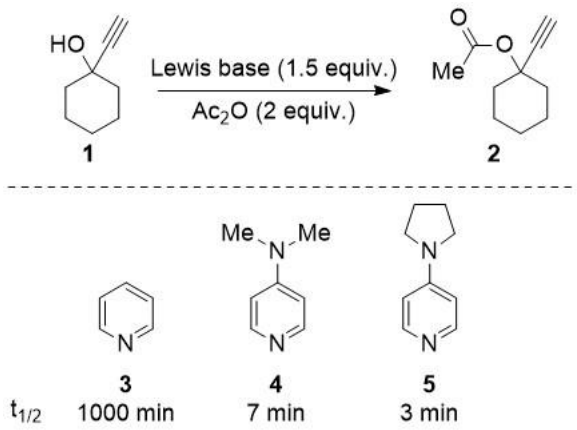


Figure 1 – General Lewis base organocatalytic cycle

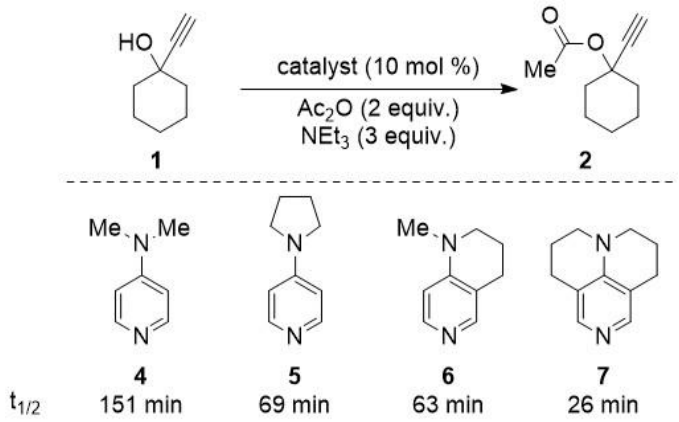
1.1.2 Acyl transfer with DMAP

In 1901, the acylation of an alcohol using acetic anhydride and pyridine was reported for the quantitative determination of terpenes,[13] with this work extended to carbohydrate chemistry in 1917.[14] In the late 1960's, 4-(dimethylamino)pyridine (DMAP) **4** was shown to be a powerful Lewis base catalyst for group transfer,[15] with a resulting 10,000-fold increase in the rate of acylation of alcohols compared to pyridine.[16] DMAP **4** has been established as the standard catalyst for a wide range of acyl transfer reactions, including esterification.[17] This activity is showcased by the efficiency of DMAP and 4-pyrrolidinopyridine (PPY) **5** for the esterification of a range of sterically hindered tertiary alcohols. It was shown that tertiary alcohols can be easily acylated using these pyridine derivatives as Lewis bases, with the rate determined as the time required for 50% conversion to the ester. A much faster rate of acylation was measured for DMAP **4** in comparison to pyridine, with PPY **5** shown to be twice as active as DMAP **4** in the acylation of 1-ethynylcyclohexan-1-ol **1** with acetic anhydride (Scheme 1).[18] The authors suggested that an increase in donor ability of the amino group at the 4-position of the pyridine would lead to an increase in the stabilization of the *N*-acyl pyridinium intermediate due to increased conjugation between the lone pair of the amino group and the carbonyl group. This stabilizing effect would lead to an increase in catalytic activity, either by increasing the concentration of this key *N*-acyl pyridinium intermediate, or through providing analogous stabilization of the subsequent acyl transfer TS, thus promoting nucleophilic attack by the alcohol to proceed at a faster rate.[19]



Scheme 1 – Acylation of alcohol **1** using DMAP **4** and PPY **5**

Further studies demonstrated enhanced catalytic activity of 4-(dialkylamino)pyridine for the acylation of alcohols, in which the 4-amino group is conformationally fixed in a ring fused to the pyridine.[20] The catalytic activity of DMAP **4**, PPY **5** and DMAP derivatives **6** and **7** were investigated in the acetylation of 1-ethynylcyclohexan-1-ol **1** with acetic anhydride in the presence of a stoichiometric auxiliary base. These results showed the rate of acylation using PPY **5** to be significantly faster than when using DMAP **4**, as seen by the half-lives in Scheme 2, with a further increase in rate observed with the inclusion of the 4-amino group into bicyclic structure seen in **6**. Incorporation of the 4-amino group into tricyclic structure **7** resulted in a further increase in acylation rate, with the half-life for acylation of **1** shown to be almost 6-times shorter than DMAP **4** (Scheme 2).



Scheme 2 – Rates of acetylation with various DMAP derived catalysts

1.1.3 Mechanistic and computational studies

It has been proposed that the acylation of alcohols using DMAP-derived catalysts proceed with nucleophilic attack of the catalyst into the anhydride, forming an *N*-acyl pyridinium species **8**. It is proposed that nucleophilic attack of the alcohol to **9** is facilitated through deprotonation of the alcohol by the carboxylate counter-ion in the acylation TS. A sacrificial base is required in the reaction medium

to neutralize the formation of acid, releasing the catalyst for further turnover (Figure 2). By taking advantage of the excellent acyl-transfer nature of DMAP, a chiral-derivative of DMAP could lead to enantioselective acyl transfer reactions and as such, could be used in enantioselective processes such as the acylative kinetic resolution of alcohols.

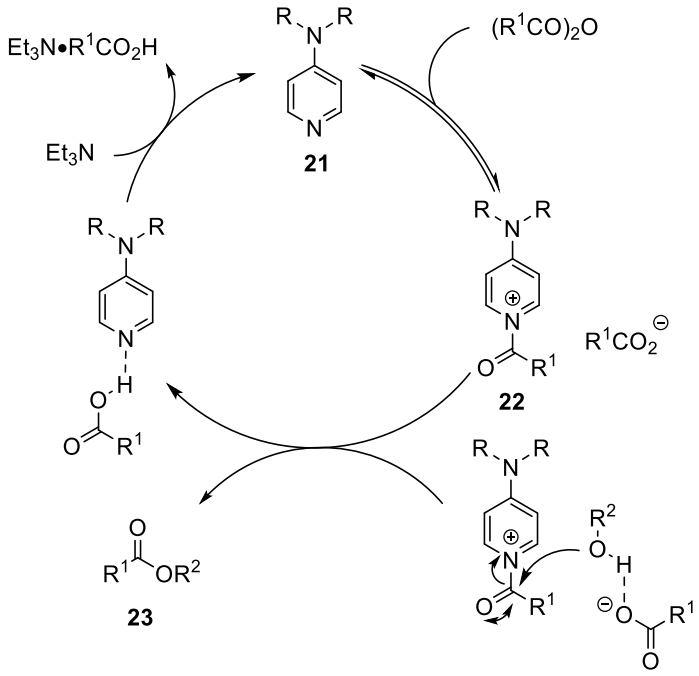
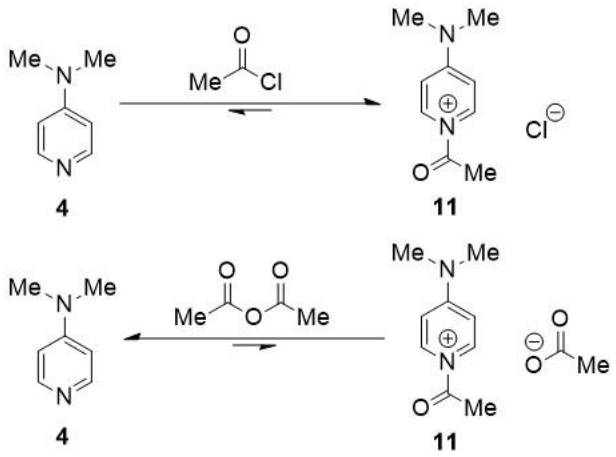


Figure 2 – Postulated 4-(dialkylamino)pyridine-catalyzed acylation reaction mechanism

The DMAP-catalyzed mechanism for the acylation of alcohols has been extensively studied, both experimentally and computationally. In the postulated reaction mechanism above, the pyridine species is acylated to give the *N*-acyl pyridinium species **11**, plus the counter-ion. NMR and IR studies have shown that the reaction of DMAP **4** and acetyl chloride provides full conversion to the *N*-acyl pyridinium species **11**. In contrast, only 5-10% acylpyridinium is formed in the presence of acetic anhydride.[21] Interestingly, it has been shown that the DMAP-catalyzed acylation of alcohols with acetyl chloride is significantly slower than the equivalent reaction with an anhydride. The acetate counter-ion is suggested to act as a base, deprotonating the alcohol, initiating attack into the acylpyridinium, with low reactivity observed for acylpyridinium salts bearing less basic counter-ions, such as chloride and tosylate (Scheme 3).[22]



Scheme 3 – Equilibrium for acetylation of DMAP with acid chloride and an anhydride

The DMAP-catalyzed reaction of *tert*-butanol with acetic anhydride was computationally investigated by Zipse in 2005. It was found that the reaction is initiated through formation of a ternary complex, comprised of the alcohol, anhydride and catalyst, giving the low energy intermediate **II**. The nucleophilic pathway proceeds with concerted acyl transfer onto DMAP **4**, by attack of the pyridyl nitrogen to the anhydride. Elimination of the acetate group in TS-**III** is facilitated by hydrogen-bonding between the anhydride and alcohol hydroxyl group, to give ion-pair complex **IV**, comprising of the acylpyridinium ion and the hydrogen-bonded *tert*-butanol-acetate ion complex. The hydrogen-bond between the alcohol and the acetate enhances the reactivity of the alcohol, promoting attack of the alcohol onto the acylpyridinium, with concerted cleavage of the C-N acylpyridinium bond and formation of the ester C-O bond shown in TS-**V**. Release of the ester product leads to complex **VI**, consisting of the catalyst-acid adduct, was shown to be highly energetically favourable, and exothermic, with cleavage of this complex to the individual components; ester, acid and catalyst, shown to be an endothermic process (Figure 3).[23] The computations showed a lack of a tetrahedral intermediate located for either the acylation of DMAP **4** by the anhydride, or acylation of alcohol by the acylpyridinium.

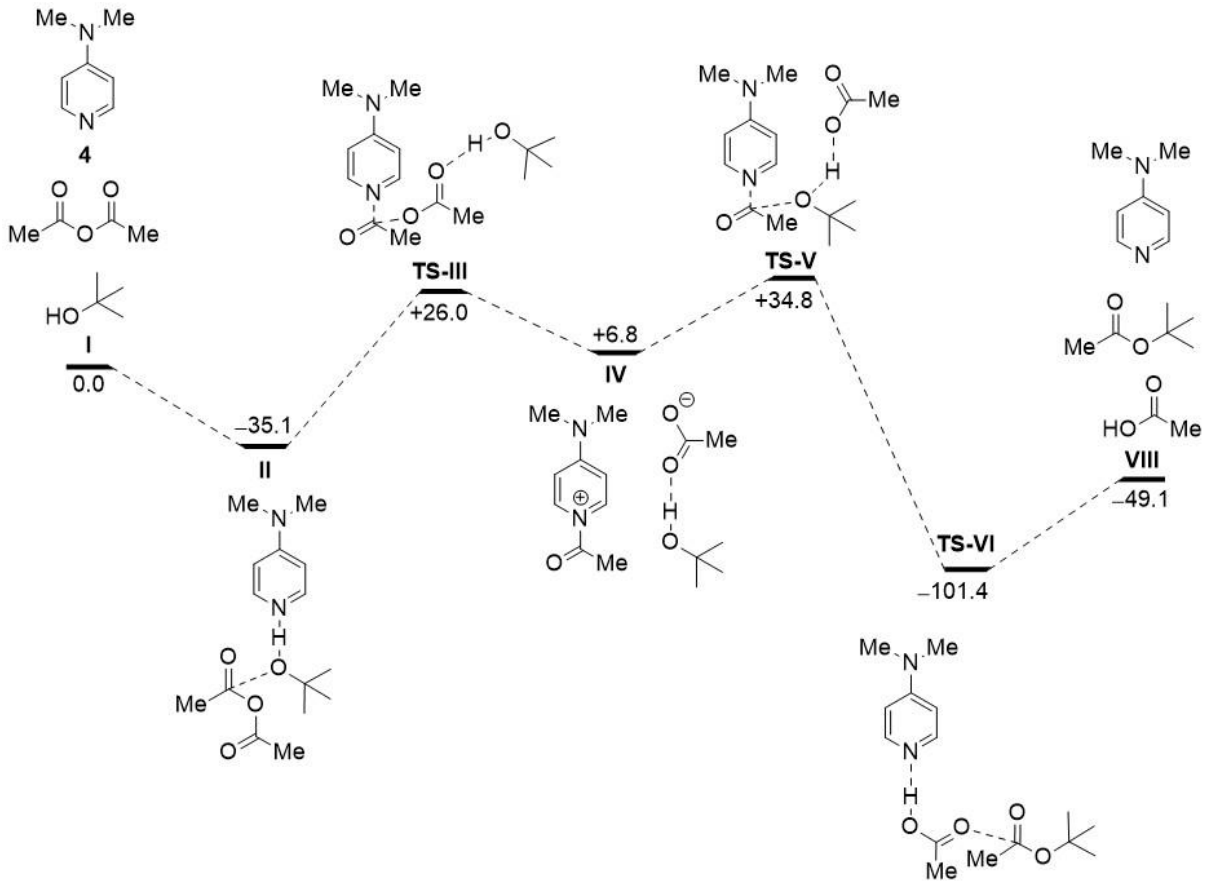


Figure 3 – Reaction mechanism energy profile (ΔH_{298}) in kJ mol^{-1} for DMAP-acylation

They found that the general base-catalyzed pathway for the acylation of tertiary alcohol proceeds with much higher energy than the nucleophilic pathway (DMAP-catalyzed). It is of note that for primary alcohols, it has been computed that the base-catalyzed mechanism is much lower in energy, and comparable to that of the nucleophile-catalyzed mechanism.[24]

1.2 Kinetic resolution (KR)

1.2.1 Introduction

A KR is a means of separating enantiomers from a racemic or scalemic mixture by exploiting the differing reaction rates with an enantiomerically pure reagent or catalyst. In a racemic mixture, the energy levels of the two enantiomers are degenerate. However, in the presence of a chiral resolving agent, the resulting diastereomeric transition states (TS) for the reaction have different Gibbs free energies. If there is a significant difference in these energy levels, one enantiomer will react at a much faster rate. A generic example is the resolution of a racemic alcohol, containing (*R*) and (*S*) enantiomers, with a chiral resolving agent (Figure 4). For example, if the diastereomeric TS formed for the reaction of the (*R*)-enantiomer is at a lower energy level than the corresponding pathway for the (*S*)-enantiomer, this barrier will be overcome more readily. Therefore, the (*R*)-alcohol will react

preferentially, resulting in the ester being enantioenriched in the (*R*)-enantiomer and the alcohol becoming enriched in the slow-reacting (*S*)-enantiomer.

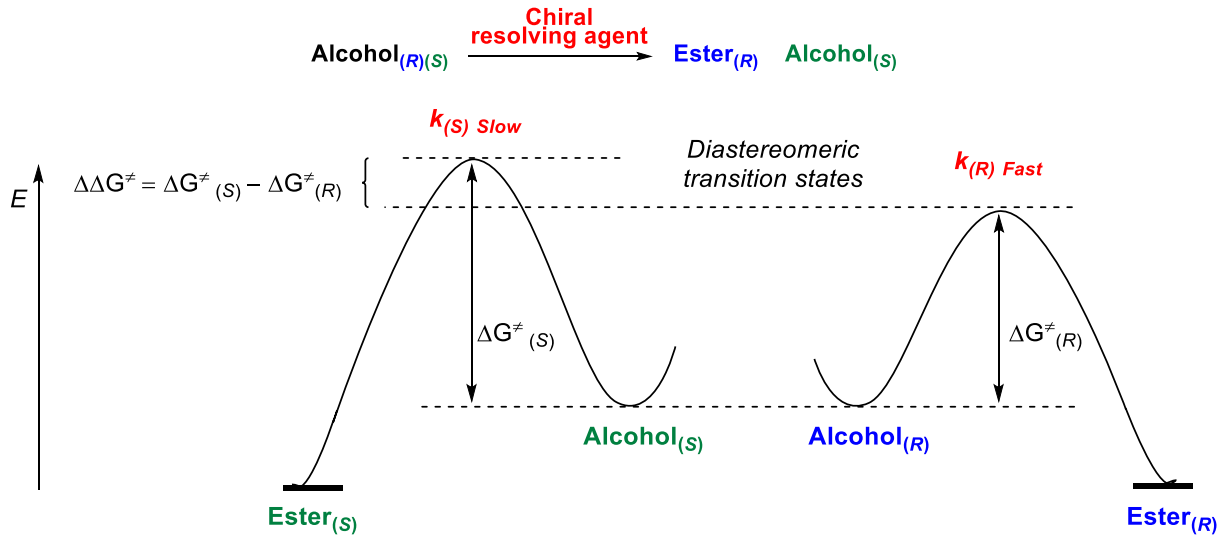


Figure 4 – Schematic free energy diagram for a kinetic resolution

1.2.2 Selectivity factor, *s*

The selectivity factor, *s*, of a given kinetic resolution is defined as the rate constant for the reaction of the fast reacting enantiomer over the slow reacting enantiomer. Also, the difference in Gibbs free energy between the two diastereomeric TSs, $\Delta\Delta G^{\neq}$, in the selectivity-determining step of the catalytic reaction, can be inserted into Equation 1, to calculate the selectivity factor.

$$s = k_{rel} = \frac{k_{(R)}}{k_{(S)}} = \frac{k_{fast}}{k_{slow}} = e^{\Delta\Delta G^{\neq}/RT}$$

Equation 1 – Determining *s* from ΔΔG of a reaction

Whilst determination of the selectivity factor can be challenging in a practical sense, a more convenient method is to use the reaction conversion, *c*, (measured by NMR/HPLC) and the enantiomeric excess, *ee*, of either the recovered substrate or the product of the reaction (Equation 2). This equation was originally outlined for enzymatic KRs by Sih,[25] and presented for more general use to describe any KR reaction, which is first order in substrate, by Kagan and Fiaud (Equation 2).[26] Throughout a kinetic resolution, the enantiomeric excess of the product, *p*, will start high and slowly decrease over time, whereas the *ee* of the starting material, *sm*, will increase. However, calculating a selectivity factor for this process using equation 2 has its limitations and requires numerous assumptions in order to be applied appropriately. For example, equation 2 only holds true for KRs that are first order in substrate; processes that are not covered by this assumption include those that are reversible; that involve the racemization of either the starting material or product under the reaction conditions; or form a product that has an influence on the reaction. A further assumption is that there

is no strong binding between one enantiomer of the starting material and the catalyst, such that one pathway would exhibit differing kinetics to the other.[27] The validity of using equation 2 can be most easily assessed by using Equation 2 to calculate *s* at various reaction conversions, with equation 2 proving applicable only when *s* is independent of conversion.

$$s = \frac{\ln[(1-c)(1-ee_{sm})]}{\ln[(1-c)(1+ee_{sm})]} = \frac{\ln[1-c(1+ee_{p})]}{\ln[1-c(1-ee_{p})]}$$

Equation 2 – Determining *s* experimentally

For KRs which are effectively described by equation 2, a graph of substrate *ee* vs. conversion, *c*, as a function of *s*, can be plotted to show how *ee* evolves with reaction conversion for KRs with different selectivity factors (Figure 5). For example, for a KR with *s* = 10, to recover a substrate in an *ee* of about 90%, a conversion of 62% is required, whilst to obtain an essentially enantiopure sample of recovered substrate, a conversion of 72% is needed. However, when *s* = 200, the recovered substrate can be obtained in enantiopure form at close to 50% conversion. Through inspection of Figure 5, it is apparent

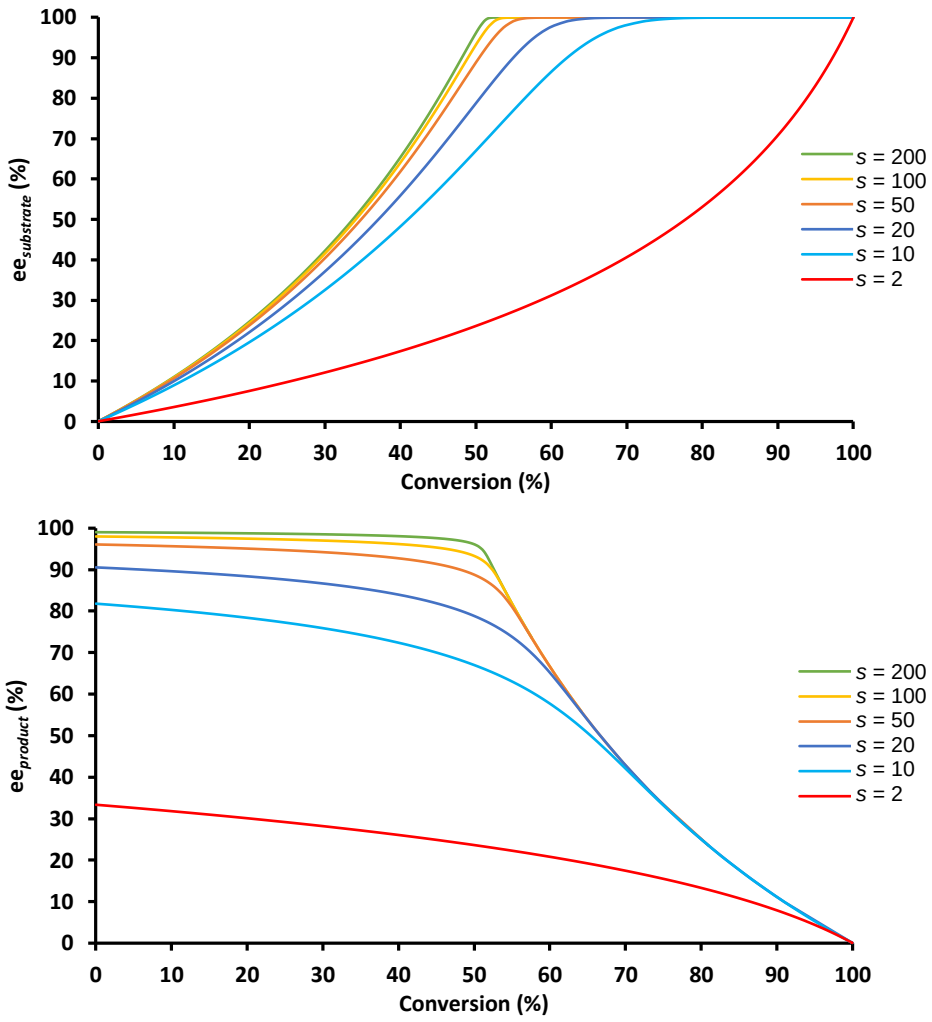


Figure 5 – Plots showing *ee* of starting material (top) and product (bottom) vs conversion as a function of *s*

that there is minimal difference between the plots at high values of *s*, and therefore, small changes in either *ee* or conversion can have a large impact on the magnitude of *s* (Figure 5).[28] The recognised threshold for kinetic resolutions to be considered synthetically useful was originally suggested as *s* > 10, [29] however due to a wide range of selective KRs, and the development of highly enantioselective reactions, a reassessment of this value to *s* > 20 could be considered more appropriate. At this level of selectivity, at least one enantiomer can be isolated in high enantiopurity, for example a conversion of 62% is required in order to obtain the recovered starting material in enantiopure form.

1.2.3 Considerations for selectivity factor

Another consideration when using *s* as a metric to describe the efficiency of a KR, is the 'accuracy' to which *s* can be realistically reported. Over the course of a KR, a reaction conversion can be calculated from the ee of the recovered substrate and isolated product (Equation 3), however potential inaccuracies from the measurements of the *ee* from the analytical equipment needs to be considered.[30]

$$\text{conv} = \frac{\text{ee}_{substrate}}{\text{ee}_{substrate} + \text{ee}_{product}}$$

Equation 3 – Determining conversion from ee of both recovered substrate and product

In most cases in the literature, results are not repeated and are reported from a single measurement. Recent studies in our group considered the error associated from the ability of an individual to measure *ee* values in an accurate and reproducible manner using analytical techniques, such as a chiral HPLC.[31] To investigate this, 20 individuals analyzed seven samples of a chiral compound of variable *ee*, ranging from 50-99% *ee*, with the error in *ee* shown to vary depending on the magnitude of the *ee* value. These absolute errors in *ee* were then added to experimentally-determined values of substrate and product *ee* for 100 KRs to assess how the error in *ee* translated to error in *s*. These findings allowed graphs to be plotted to correlate the error in *s* as a function of *s* and provide equations that relate the absolute error and % error in *s* as a function of *s* (Equations 4 and 5). These equations can then be used to provide a measure of expected analytical error in any value of *s*. Using these equations, some representative errors in *s* for values between 10 and 1000 are presented in Table 1.

Absolute error = $0.0003s^2 + 0.02s$ (Equation 4)

% error = $0.03s + 2$ (Equation 5)

s	Absolute error[a]	% error[b]
10	0.23	2.3
20	0.52	2.6
30	0.87	2.9
40	1.28	3.2
50	1.75	3.5
75	3.19	4.25
100	5	5
200	16	8
500	85	17
1000	320	32

[a] Calculated using Equation 3 and [b] Equation 4

Table 1 – Absolute and % errors in *s* for a range of values

In addition to the error in measuring *s* values, the practical significance of *s* should be considered to determine how appropriate it is to differentiate between values of *s*. Considering that the usual aim of a KR is to recover substrate in enantioenriched form, the significance between different values of *s* can be assessed by comparing the differences in theoretical yield of recovered substrate of a given enantiopurity for KRs with different *s* values. For example, for a KR with an *s* of 200, the recovered substrate can be obtained at 99% *ee* at a conversion of 51%. By comparison, for a KR with *s* = 1000, a conversion of 50% would be required to obtain the recovered substrate in the same level of enantiopurity. In practice, this 1% difference in conversion would be challenging to control, and the difference in yield of recovered material minimal, so it can be considered that a KR with an *s* of 200 is effectively equivalent to a KR with an *s* = 1000. Based on these findings a number of recommendations were made for the appropriate reporting of *s*. For KRs with $s < 50$, values should be reported to the nearest integer value; KRs with *s* = 50-200 should be reported to the nearest 10; and KRs with *s* greater than 200 should be simply reported as $s > 200$. Based on this work, all *s* values determined from work presented in this thesis have been reported using the guidelines outlined above.

1.2.4 Considerations for the development of practical KRs

When considering whether the development of a KR process provides a synthetic advantage over other methods for obtaining enantioenriched products, a number of factors must be taken into account.[28] KRs are most useful as a method for accessing synthetic targets in high levels of enantiopurity when the required target cannot be made with high enantioselectivity by other methods, or as a means to boost the enantiopurity of a target when moderate levels of enantioselectivity are initially achieved in an asymmetric reaction.

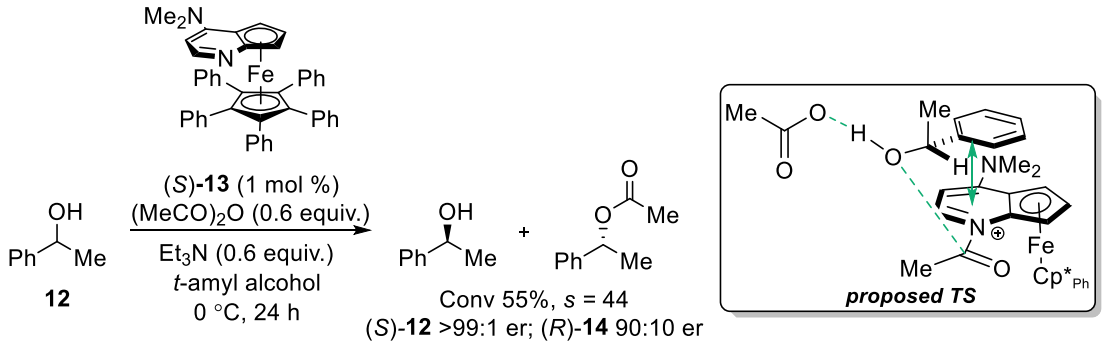
Taking into account cost considerations, KR is an extremely attractive technique, particularly if the procedure proves to be a cheaper or easier alternative than asymmetric synthesis, with racemates often less than half the price of their enantiopure equivalents. Conducting a KR in a catalytic manner, through the use of sub-stoichiometric amounts of a chiral resolving agent, is an inviting proposition. But for a KR to be considered practical, a number of criteria and conditions, must be satisfied:

- a cheap racemate, with no good route to the product *via* enantioselective, chiral pool, or classical resolution methods;
- inexpensive catalyst, which is highly selective at low loadings; the reaction to be safe and economical, with inexpensive reagents and minimal waste generation;
- the recovered starting material and product easily separable in a highly enantioenriched form and of high value.

The limitation of a simple KR however, lies in the maximum theoretical yield of 50%. If the slow reacting enantiomer of the substrate can be racemized under the reaction co-ordinate, then this yield can be improved upon, with a theoretical yield of product of 100%. Providing the cost of the additional materials does not outweigh the cost of the initial resolution, then this increases the practicality of the process, with this known as a dynamic kinetic resolution (DKR).

1.2.5 Chiral Lewis bases in kinetic resolution

As DMAP-derivatives have proved useful as Lewis base organocatalysts for the acylation of alcohols, a range of chiral Lewis bases has been developed, with most containing a DMAP- or related core structure, for use in the kinetic resolution (KR) of racemic alcohols. In 1997, a planar-chiral DMAP catalyst, developed by Fu, was used for the KR of secondary alcohols.[32] To date, most work on KR has been conducted using secondary alcohols as they are common in natural products, pharmaceuticals and intermediates in synthesis. Typically, to allow for effective enantiodiscrimination in the KR, most secondary alcohols bear an aryl and alkyl substituent. The KR of 1-phenylethanol **12**, using acetic anhydride and chiral-planar DMAP (*S*)-**13**, proceeded with 55% conversion, to give the recovered alcohol (*S*)-**12** in >99:1 er and ester (*R*)-**14** in 90:10 er, equating to a selectivity factor of 44 (Scheme 4).[33]



Scheme 4 – Examples of kinetic resolution by Fu using chiral-planar DMAP

Mechanistic and computational studies on this example have been conducted by Dinér. An energy difference of +3.0 kcal mol^{-1} for the reaction at room temperature was calculated in the lowest energy transition states for each enantiomer. This equates to a selectivity factor of 252, however experimentally, a selectivity factor of 27 was observed. Whilst the computations are in qualitative agreement with the experimental result, it is not quantitative and represents a huge overestimation. Computational studies identified the key interaction that stabilizes the TS for the acylation of the (*R*)-enantiomer as a π-π interaction between the aryl π-system of the alcohol and the π-system of the acylated DMAP catalyst.[34]

Along with Fu, Yamada,[35] Spivey,[36] and Fuji,[37] amongst others,[38] have developed their own DMAP-derived chiral Lewis base organocatalysts for use in KR. A chiral phosphine Lewis base has also been developed by Vedejs for use in this area (Figure 6).[39]

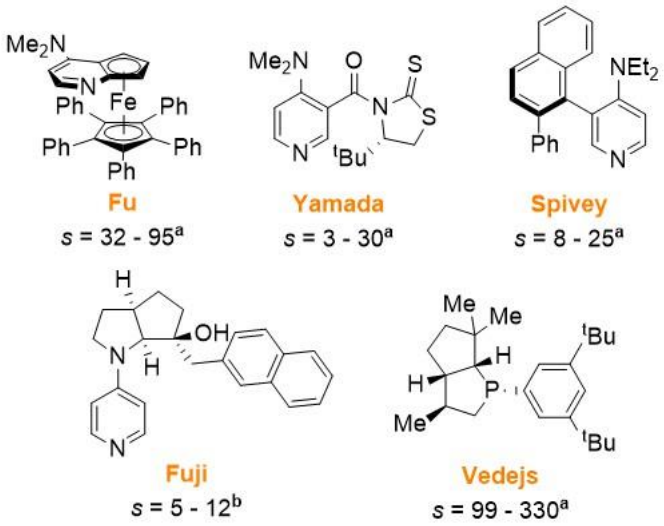
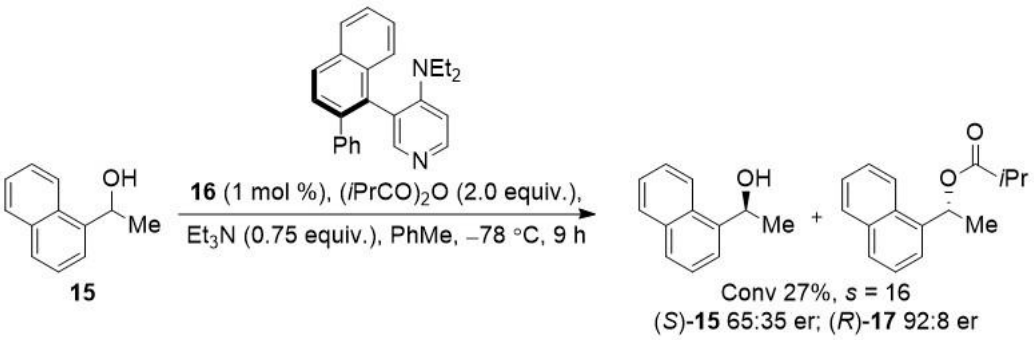


Figure 6 – A range of chiral Lewis bases utilized for kinetic resolutions of a) benzylic secondary alcohols and b) mono-protected *cis*-diols

Using the axially chiral DMAP analogue **16**, Spivey further investigated this area, with the KR of 1-(naphthalen-1-yl)ethanol **15** in the presence of isobutyric anhydride at –78 °C, giving a selectivity

factor of 16. This would correspond to a $\Delta\Delta G^{\neq}$ of +1.07 kcal mol^{-1} (Scheme 5). In 2012, Spivey and Zipse provided computational studies on the KR of **15**. They computed the $\Delta\Delta G^{\neq}$ between the diastereomeric transition states in the nucleophile-catalyzed reaction, to be +1.62 kcal mol^{-1} at –78 °C which again is an overestimation of the selectivity and corresponds to a selectivity factor of 65.[40] So whilst computations seem to overestimate the selectivity for a given KR, it does provide an insight into the interaction between substrate and catalyst that is present in the TS, as well as possible indications of how to further investigate chemical processes through catalyst design and application of different substrates classes.



Scheme 5 – KR of alcohol **15** using axially chiral DMAP analogue

The base-catalyzed mechanism was also computed, with the highest energy TS shown to be around 12.2-13.4 kcal mol^{-1} higher than the highest energy TS in the corresponding nucleophile-catalyzed mechanism. This suggests that the base-catalyzed mechanism is not a competitive pathway in this case.

1.3 Isothioureas in kinetic resolution of benzylic alcohols

In 2004, Birman developed amidine catalysts based on the 2,3-dihydroimidazo-[1,2-*a*]pyridine (DHIP) core, containing various electron-withdrawing groups. These were used as chiral acyl transfer catalysts for the KR of secondary alcohols (Figure 7).[41]

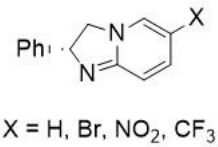
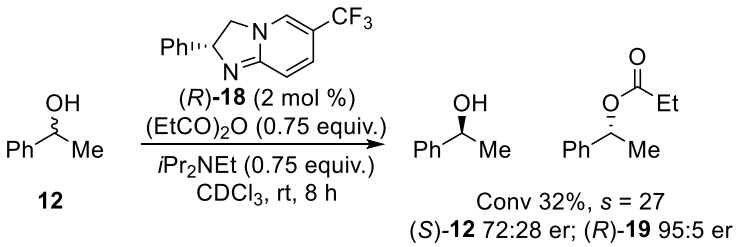


Figure 7 – 2,3-Dihydroimidazo-[1,2-*a*]pyridine core structure

Using CF_3-phenylimidazopyridine catalyst (CF_3-PIP) (*R*)-**18**, the KR of 1-phenylethanol **12** with propionic anhydride proceeded with 32% conversion to give the recovered alcohol (*S*)-**12** in 72:28 er and ester product (*R*)-**19** in 95:5 er, with *s* = 27 (Scheme 6).



Scheme 6 – Kinetic resolution of **12** using catalyst (*R*)-**18**

The reaction was proposed to proceed through a transition state, in which (*R*)-**12** preferentially reacts to give the product (*R*)-**19**. The phenyl group in the catalyst is pseudo-axial, blocking the approach of the alcohol on this face. It was hypothesized that the phenyl ring of the nucleophilic alcohol is locked in place, due to stabilizing π-cation interactions with the catalyst as the single key recognition motif, so the alkyl group can be in two positions (Figure 8). Only one configuration is favoured in the lowest energy TSs for acylation of each enantiomer of substrate, with the alkyl group pointing away from the *N*-acyl group, with the other disfavoured due to potential steric clashes. The origin of this enantioselectivity was computationally investigated by Birman and Houk, and more so, the key chiral recognition motif between alcohol and catalyst for the KR shown in Scheme 6.[42] Their findings lend theoretical support to the fact that the π-cation interaction, between substrate and catalyst, is key for chiral recognition in the TS, with the favoured TS shown to be +3.5 kcal mol^{-1} more favourable in energy. This difference in energy between the two diastereomeric TSs equates to a selectivity factor of 384, and is in qualitative agreement with the experimental selectivity factor of 27, though largely overestimated. These key recognition motifs between substrate and catalyst are also observed in a wide range of KR reactions of secondary alcohols.

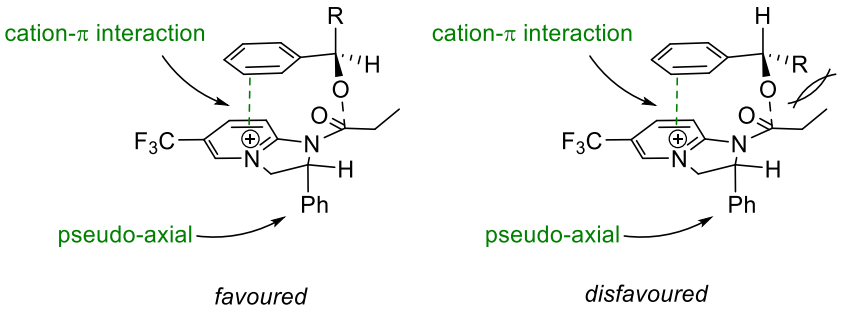


Figure 8 – Proposed transition state structures for the acylation of enantiomers of secondary alcohol

The core DHIP structure was further investigated leading to a number of catalysts that showed enhanced reactivity for KR of secondary alcohols in comparison to CF_3-PIP **18**. There was an increase in selectivity factors observed with the 2nd generation catalyst, Cl-PIQ (*R*)-**20**, which can be rationalized by an enhancement in π-π and π-cation stacking interactions between substrate and acylated catalyst.[43] The commercially available isothiourea tetramisole (*S*)-**21** was also investigated, along with

its benzannulated form, benzotetramisole (BTM), (*R*)-**22** (Figure 9).[44] In comparison to the amidine core-containing catalysts, the isothiourea catalyst BTM (*R*)-**22** gave a significant increase in selectivity in the KR of secondary alcohols.

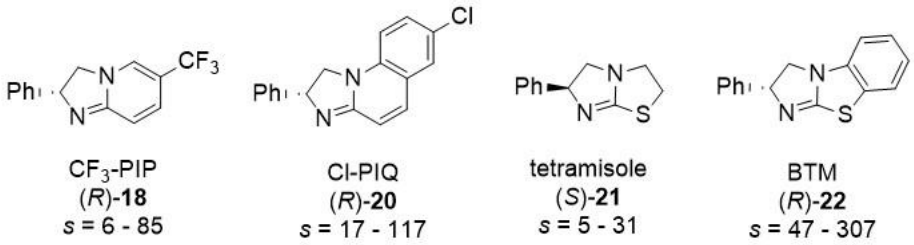


Figure 9 – Development of catalysts from DHIP to isothiourea structure. *s* values given for KR of secondary alcohols

At a similar time, Kobayashi developed an achiral isothiourea acyl transfer catalyst, 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (DHPB) **23**, containing a larger 6-membered ring than previous catalysts (Figure 10). Studies showed this catalyst to be more efficient for acyl transfer than the amidine or isothiourea catalysts previously reported, with the core DHPB structure identified for the development of a chiral acyl transfer catalysts.[45]

Building on this work, homobenzotetramisole (HBTM) (*S*)-**24**, containing the DHPB architecture, was developed by Birman. Though showing similar selectivities to (*S*)-**21** and (*R*)-**22** for the KR of benzylic secondary alcohols. The use of HBTM (*S*)-**24** allowed reduced reaction times and lower catalyst loadings. In the KR of aryl-cycloalkanols, (*S*)-**24** proved to be more selective than (*S*)-**21** and (*R*)-**22** with selectivity factors reaching up to 122.[46]

Birman showed the inclusion of a C(3)-methyl substituent, to give HBTM-2 (2*S*,3*R*)-**25**, led to higher selectivities in comparison to (*S*)-**24**.[47] Independent studies conducted by Smith found that introduction of a C(3)-isopropyl group, to give HyperBTM (2*S*,3*R*)-**26** was optimal.[48] HyperBTM (2*S*,3*R*)-**26** has since been applied as a catalyst in a range of organic transformations, such as Steglich rearrangements.[49]

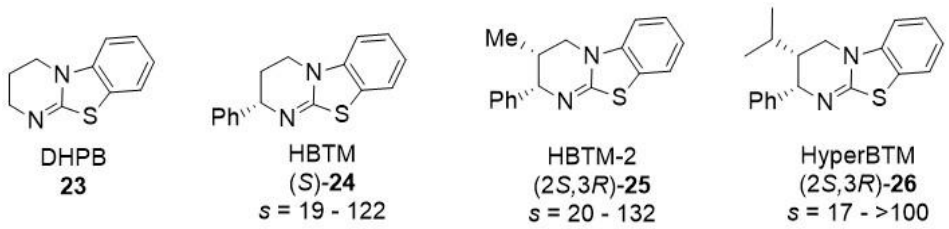
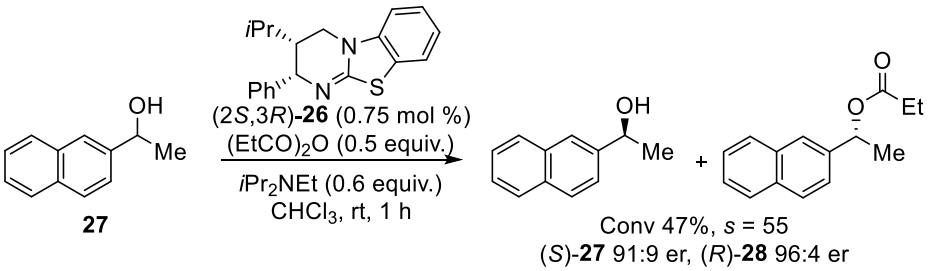


Figure 10 – Range of isothiourea catalysts to date

Whilst the acylative KR of secondary alcohols using chiral DMAP derivatives has extensively been studied mechanistically and computationally, there have been fewer analogous studies using chiral isothiourea catalysts, which are discussed in the following section.

1.3.1 KR of aryl-alkyl benzylic alcohols

In 2011, Smith demonstrated the use of isothiourea catalysts for the KR of secondary alcohols. Screening a range of catalysts showed the presence of an aryl group in the alcohol substrate is best for selectivity. In the presence of HyperBTM (2*S*,3*R*)-**26** and propionic anhydride, 1-(naphthalen-2-yl)ethan-1-ol **27** was resolved to give the unreacted alcohol (*S*)-**27** (91:9 er) and ester (*R*)-**28** (96:4 er), corresponding to a *s* of 55 (Scheme 7).[48] In these substrates, there is a single group that can act as recognition motif between substrate and acylated catalyst in the TS, enabling the high selectivities observed.



Scheme 7 – Kinetic resolution using isothiourea catalysts

A model was proposed for the transition state for the KR of secondary alcohol 1-(naphthalene-2-yl)ethan-1-ol **27** using propionic anhydride and HyperBTM (2*S*,3*R*)-**26**. There is a long range 1,5-*O•••S* interaction present in the acyl ammonium species (see section 1.3.6), with the C(2)-phenyl group sitting in a pseudo-axial position, blocking the *Re* face and forcing the alcohol to approach on the *Si* face. As the alcohol approaches, a π-π/cation-π interaction as key recognition motif between the catalyst and the aryl ring of the alcohol is postulated to stabilise the transition state. Deprotonation of the alcohol hydroxyl by the propionate counter-ion is thought to facilitate acylation of the alcohol to its corresponding ester. For the (*R*)-alcohol, the methyl group points away from the catalyst, however for the (*S*)-alcohol, this methyl group provides steric hindrance in the TS, disfavouring the acylation of this enantiomer and resulting in the selectivity observed (Figure 11).[48]

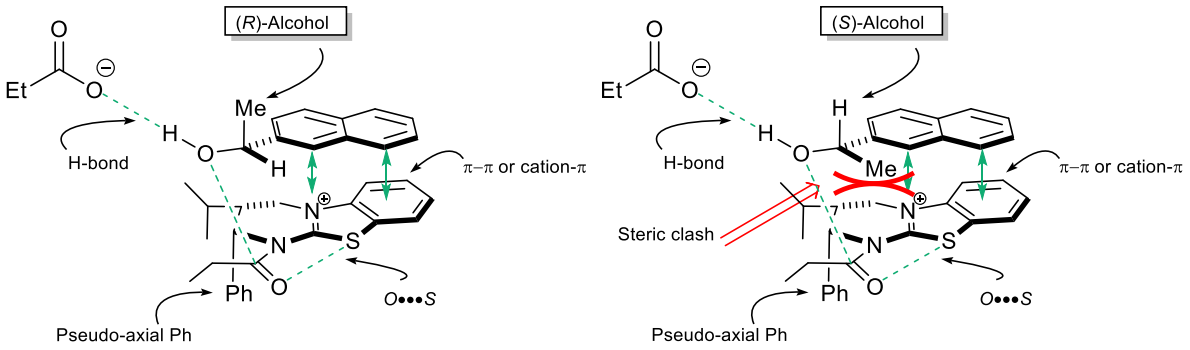
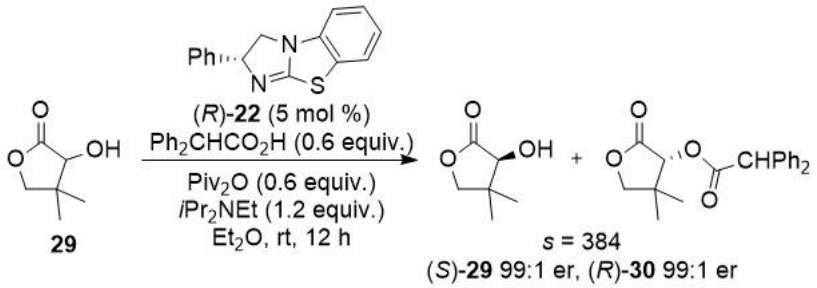


Figure 11 – Proposed transition states for the acylation of both enantiomers of secondary alcohol **27**

1.3.2 KR of lactones/phosphonates

In 2013, Shiina utilised isothiourea catalysts for the KR of 2-hydroxy-γ-butyrolactones. Using commercially available diphenylacetic acid and pivalic anhydride to form a mixed anhydride *in situ*,[50] the KR of pantolactone **29** was achieved using (*R*)-BTM **22**, giving both the recovered alcohol (*S*)-**29** (99:1 er) and corresponding ester (*R*)-**30** (99:1 er) in high enantiopurity, with excellent selectivity (*s* = 384) (Scheme 8).[51]



Scheme 8 – KR of pantolactone **29**

Computational studies suggested the key recognition motif in the TSs for acylation of both enantiomers of lactone **31** as a lactone-C=O•••isothiouronium interaction (Figure 12). The preferential acylation of the (*R*)-enantiomer observed experimentally was rationalized by the TS for acylation of the (*S*)-enantiomer being significantly higher in energy, due to the orientation of the lactone ring, with the ring lying more parallel to the catalyst structure, providing a significant steric clash from the C(2) and C(3)-substituents on the lactone ring, with the acyl phenyl rings. In comparison, the (*R*)-alcohol is oriented at a more perpendicular angle to the catalyst, with the C(2) and C(3)-substituents pointing away from the acyl phenyl rings. Experimentally, the selectivity factor for the KR of **31** was observed to be 40, representing a ΔΔG of +2.18 kcal mol^{-1}, however computations overestimate this energy difference at +5.13 kcal mol^{-1}. Though a significant difference to the experimental selectivity factor is calculated, computational analysis does provide a highly useful qualitative model for rationalization of selectivity, that the authors applied to understand the magnitude of selectivity observed in the KR of other substrates.

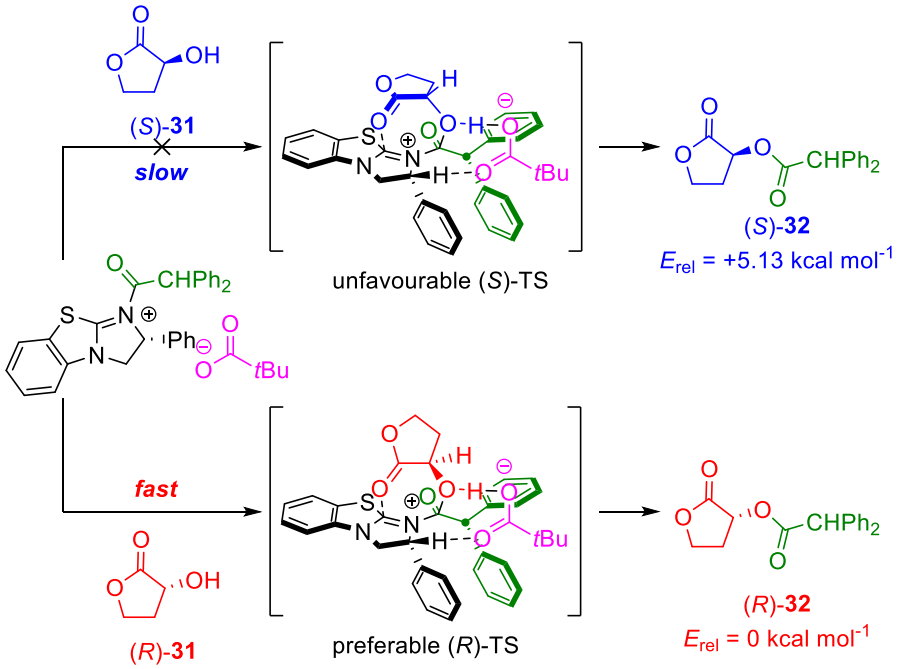
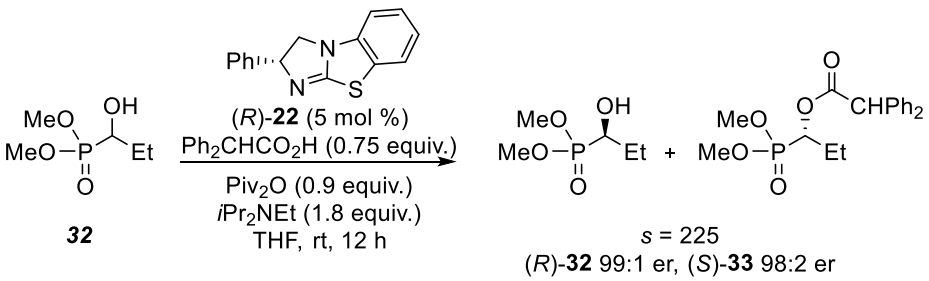


Figure 12 – TS for each enantiomer of γ-butyrolactone **31**

Using similar conditions, this work was extended to the KR of α-hydroxy phosphonates, with selectivity factors of up to >500 obtained. For example, the KR of phosphonate **32** using diphenylacetic acid and pivalic anhydride in the presence of (*R*)-BTM **22** as catalyst, gave the recovered alcohol (*R*)-**32** (>99:1 er) and corresponding ester (*S*)-**33** (98:2 er) in high enantiopurity, with a selectivity factor of 225 (Scheme 9).[52]



Scheme 9 – KR of α-hydroxy phosphonate **32**

Computational studies were again conducted to determine the TSs involved, with the key recognition motif between substrate and catalyst suggested to be the P=O•••isothiouronium interaction, analogous to that observed motif in the KR of butyrolactones. The calculated TSs show the TS for the slower reacting (*R*)-alcohol at a significantly higher energy, due to a steric clash between the alkyl group of the phosphonate and the acyl phenyl group, in comparison to the faster reacting (*S*)-alcohol, giving the observed selectivity (Figure 13). Computations were again conducted for this KR, with the energy difference calculated overestimating the selectivity factor that was observed experimentally.

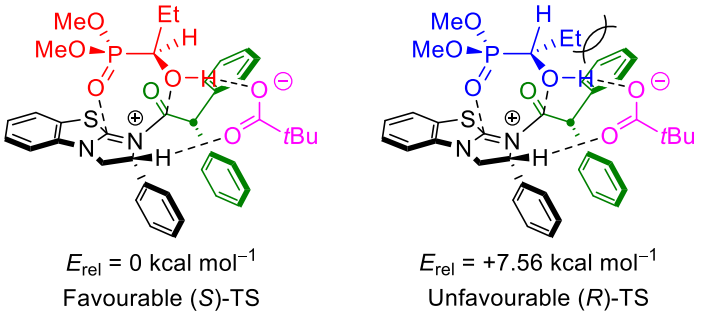


Figure 13 – Calculated TS structures for (*S*)-**32** and (*R*)-**32**

1.3.3 KR of secondary alcohols bearings two recogniton motifs

So far, all examples shown for the KR of secondary alcohols using acyl ammonium catalysis generally contain functionality, such as aryl, propargyl or carbonyl groups, that can act as the key recognition site between the substrate and the acylated catalyst, with the other an alkyl substituent (Figure 14). There are examples for the KR of benzylic secondary alcohols, containing a second potential recognition motif at the α-position. In these examples, the observed selectivity factors are low (*s* = 2-8), which is presumably due to competitive stabilizing interactions between the aryl-π group, and either the alkynyl-π, nitrile-π or carbonyl lone pair with the isothiouronium species, leading to minimal energy differences between the acylation TSs for each enantiomer of the alcohol.[53]

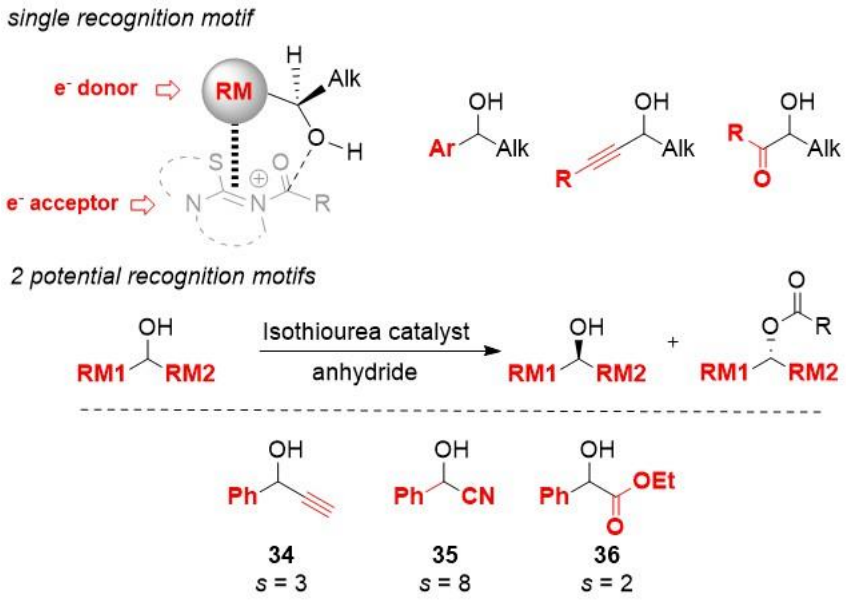
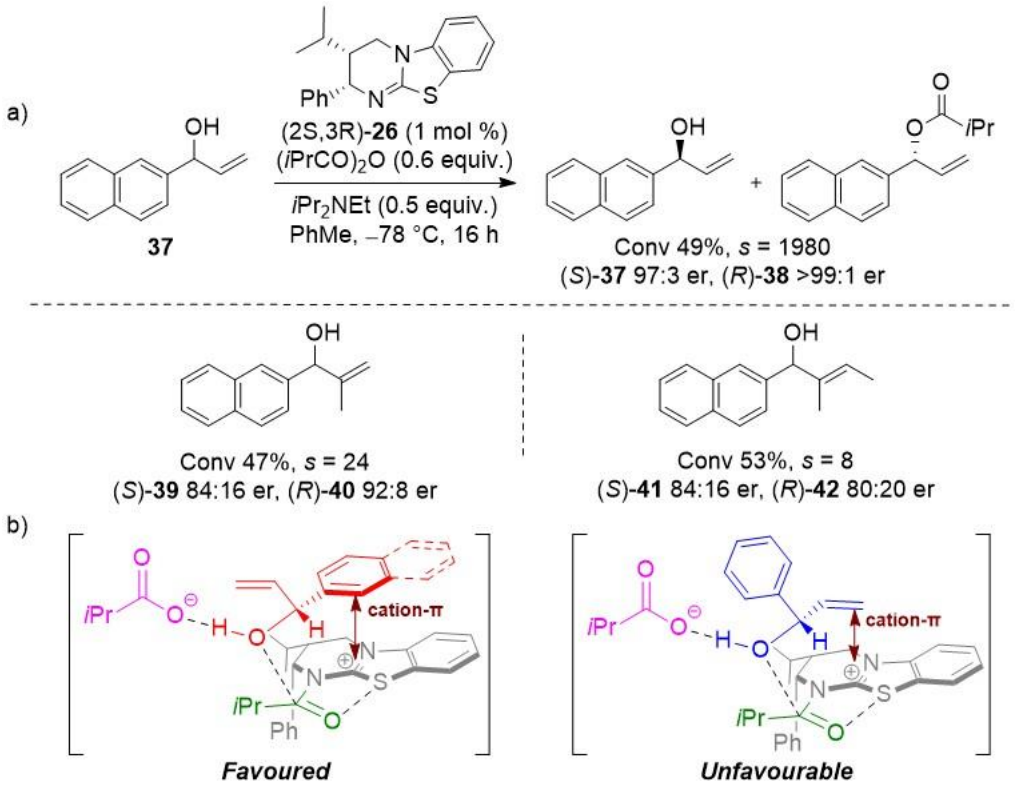


Figure 14 – Recognition motifs present in the KR of secondary alcohols

Building on previous work on the KR of benzylic, allylic and propargylic alcohols, in the non-enzymatic acylative KR of aryl-alkenyl alcohols, there are two potential recognition motifs to facilitate discrimination. In this work, there is potential for two π-cation interactions; the aryl π-cation or the alkenyl π-cation. The KR of alcohol **37** proceeded with unprecedented selectivity (*s* = 1980), with both

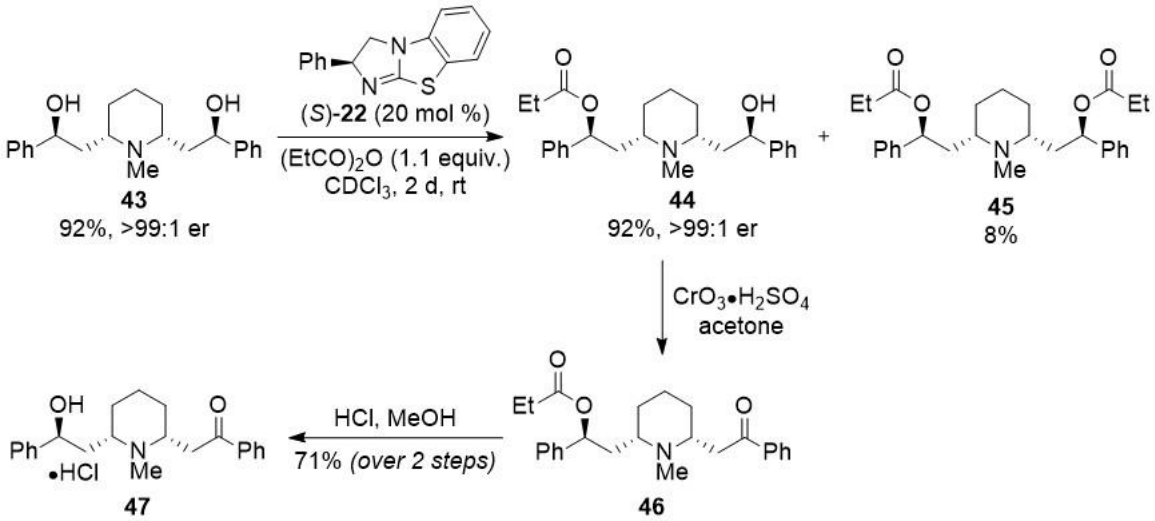
recovered alcohol (*S*)-**37** and ester (*R*)-**38** isolated in excellent enantiopurity (Scheme 10a), though this is not representative of the overall scope. Excellent selectivity was observed for these substrates, and it was found that the aryl π-system dominates over the alkene π-system as key recognition motif in the TS. However, the KR of alcohols with increasing alkene substitution gave much lower selectivity, which was rationalized by the increased substitution making the alkene π-system more electron rich, thus a more competitive recognition motif with the aryl substituent (Scheme 10b).[54]



Scheme 10 – a) KR of aryl-alkenyl alcohols. b) Stereochemical rationale

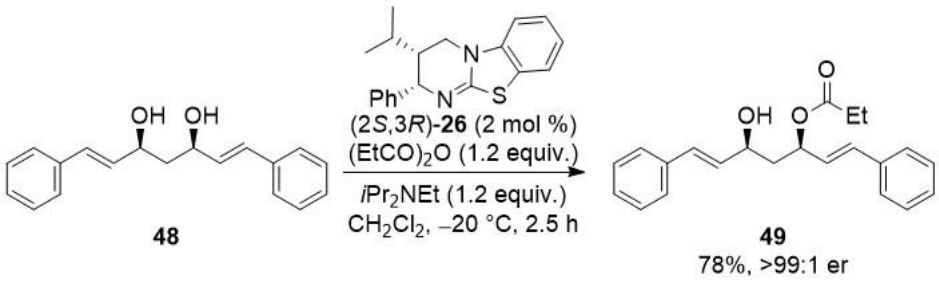
1.3.4 Other examples of isothiourea-mediated acyl transfers

In 2007, Birman utilized (*S*)-BTM **22** as an acyl transfer catalyst in the non-enzymatic desymmetrization of Lobelanidine **43** in the enantioselective synthesis of Lobeline **47**. Using just the catalyst (20 mol %) and isobutyric anhydride (1.1 equiv.) as acylating agent, the mono-acylated product **44** was obtained in excellent 92% yield and enantioselectivity (>99:1 er), with only 8% of diester product **45** obtained. The free alcohol was converted to the ketone **46** *via* a Jones oxidation, and the ester hydrolyzed to give (–)-Lobeline hydrochloride **47** in 71% yield. Using the opposite enantiomer of the catalyst, the unnatural enantiomer (+)-Lobeline was obtained in the same manner (Scheme 11).[55]



Scheme 11 – Enantioselective synthesis of (–)-Lobeline **47** *via* non-enzymatic desymmetrization

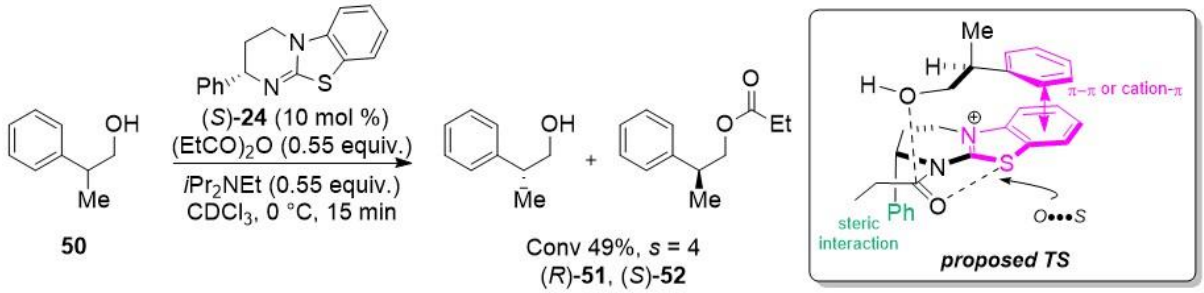
In work conducted by Bressy, isothiourea catalysts have also been shown in the desymmetrization/chiroablative kinetic resolution of acyclic *meso* 1,3-diols, with enantioselectivities of up to >99:1 er obtained. The reaction of diol **48** with propionic anhydride and HyperBTM (2*S*,3*R*)-**26** provided the desired monoester **49** in 78% yield and excellent enantioselectivity (>99:1 er) (Scheme 12).[56]



Scheme 12 – Isothiourea-catalyzed desymmetrization/chiroablative KR of *meso* 1,3-diols

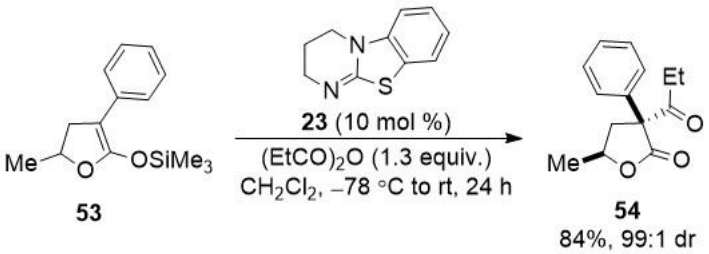
A recent study by Rychnovsky was conducted on the acylation of β-chiral primary alcohols using both enantiomers of HBTM **24**.[57] Enantioenriched alcohols were acylated in the presence of either enantiomer of the catalyst, and the faster was identified by measuring product conversion using ^{1}H NMR analysis. They developed a method that correlates the absolute configuration of the primary alcohol with the faster reacting enantiomer of the catalyst, with primary alcohols bearing a 'directing group' on the stereogenic centre, such as aryl π-system, proving successful for this method. They also described the first use of an isothiourea catalyst in the KR of primary alcohols. The KR of alcohol **50** was conducted with propionic anhydride and (*S*)-HBTM **24** (10 mol %) at 0 °C, however only modest selectivity was obtained (*s* = 4) (Scheme 13).[57] A TS model was proposed that shows the 'directing group' sitting over the catalyst, with the key recognition motif between substrate and catalyst as a π-

cation/π-π interaction. They identified other directing groups, such as heteroaromatic, nonaromatic π-systems (esters), and halogens (Br and Cl) that can also be used for their method.



Scheme 13 – KR of β-chiral primary alcohols

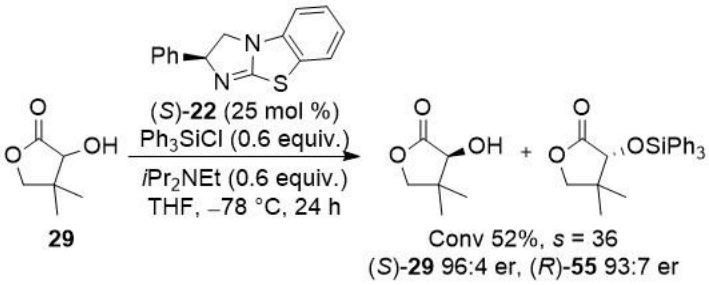
The use of isothiourea catalysts as acylating agents is not limited to KR, with these catalysts utilized in catalytic Steglich rearrangements.[58] In further work, Smith demonstrated the stereoselective *C*-acylation of silyl ketene acetals to give 3-acyl-3-aryl or 3-acyl-3-alkylfuranones with high diastereoselectivity. Upon treatment of silyl ketene acetal **53** with DHPB **23** and propionic anhydride, the tri-substituted furanone **54** was isolated in 84% yield with 99:1 dr (Scheme 14).[59] This work was further extended in an asymmetric manner, with enantioselectivities of up to 99:1 er obtained.[60]



Scheme 14 – *C*-acylation of silyl ketene acetals

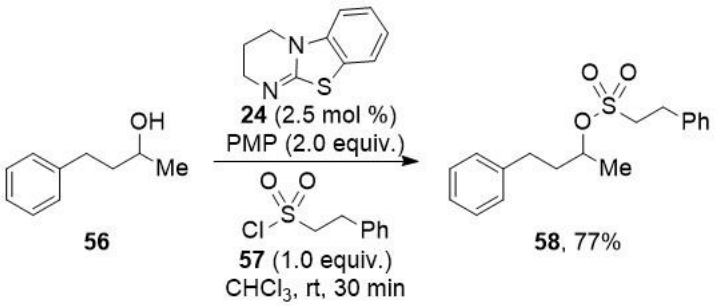
1.3.5 Non-acylative isothiourea-catalyzed reactions

Isothiourea catalysts have also been utilized for the non-acylative KR of secondary alcohols, with silylating and sulfonylating agents used as an alternative to acylating agents. In 2013, Wiskur developed a silylation based KR of α-hydroxy lactones and lactams, using (*S*)-BTM **22** as catalyst and triphenylsilyl chloride as the silyl source, enabling selectivity factors of up to >100.[61] (Scheme 15).



Scheme 15 – Silylation based KR of α-hydroxy lactone **29**

In 2015, Spivey showed the sulfonylation of primary and secondary alcohols using a range of Lewis base and Lewis base *N*-Oxide catalysts. In particular, isothiourea DHPB **23** was shown to be highly useful in the sulfonylation of alcohols, with the sulfonylation of secondary alcohol **56** proceeding in 77% yield, using sulfonyl chloride **57** and 1,2,2,6,6-pentamethylpiperidine (PMP) as non-nucleophilic base (Scheme 16).[62]



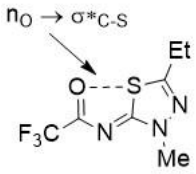
Scheme 16 – Sulfonylation of secondary alcohol **56** using DHPB **23**

1.3.6 *O•••S* Interactions

A key interaction that has been postulated in the acylative KR of alcohols using isothiourea catalyst is a long range 1,5-oxygen to sulfur interaction in the *N*-acylated catalyst. This is a prevalent interaction that has also been recognized in a number of small molecules and utilized in the conformational design of drug molecules. A review shows the low-lying σ* orbitals of the C–S bond that are available for interaction with electron donors, including oxygen and nitrogen atoms, providing a positive electrostatic effect, through a phenomenon referred to as σ-holes.[63] This n_X to $\sigma^*_{C\text{-}S}$ interaction has been exploited in medicinal chemistry, due to its presence in a wide range of biologically active molecules,[64] however studies have been restricted in literature to crystallographic, computational and various spectroscopic studies.[65]

This key structural feature between *O* and *S* can be seen in 1,4-, 1,5- or 1,6-relationships in X-ray crystallographic data reported by Nagao. This interaction is seen in (acylimino)thiadiazolo compound **59**, bearing this 1,5-relationship, with an *O* to *S* distance of 2.67 Å; significantly shorter than the sum of the van der Waals radii (3.32 Å) (Figure 15a).[66] This interaction is not limited to just sulfur, with other chalcogens also capable of participating in stabilising effects. Crystallographic data has been conducted that showcases this feature with selenium, in a 1,5-intramolecular non-bonded *O•••Se* interaction in a range of anthraquinone and 9-methoxyanthracene bearing 1,8-arylselenyl substituents **60** (Figure 15b).[67] Analogous interactions between *N* and *S* have also been explored, with a X-ray structure of 2-(2'-thienyl)pyridine **61** showing this two aromatic rings in a *syn* co-planar effect (Figure 15c),[68] with this interaction also observed with other chalcogens in computational studies.[69]

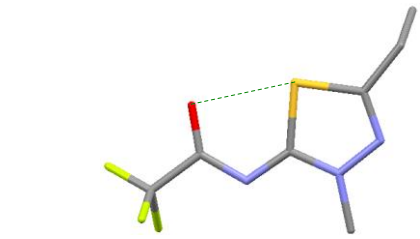
a)



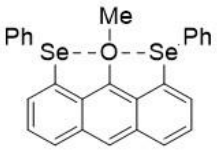
59

O•••S = 2.67 Å

Sum of van der Waals radii = 3.32 Å



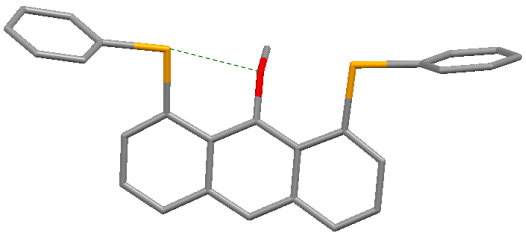
b)



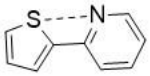
60

O•••S = 2.73 Å

Sum of van der Waals radii = 3.42 Å



c)



61

O•••S = 2.93 Å

Sum of van der Waals radii = 3.35 Å

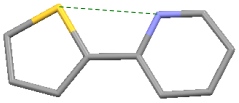


Figure 15 – Chemical and X-ray crystal structures showing intramolecular non-bonding 1,5-interactions (hydrogens omitted for clarity)

Birman and Houk used computational analysis to rationalize the selectivity observed in the isothiourea catalyzed dynamic kinetic resolution (DKR) of azlactones. It was postulated that a non-bonding *O•••S* interaction between the acyl carbonyl and the isothiouronium species is nearly coplanar, locking the conformation. Enantiocontrol is increased, as the catalyst directs the facial selectivity of the nucleophilic attack due to one face of the catalyst being blocked.[70] Romo and Tantillo conducted work on isothiourea-catalysed Diels-Alder/lactonization reactions, with a 1,5-*syn* coplanar arrangement shown by computational analysis. Computations suggest this *O•••S* interaction provides some stabilization in comparison to the alternative conformation, which has a disfavoured n_O to $\sigma^*_{C\text{-}H}/\sigma_{C\text{-}H}$ interaction. Analysis of the natural bond order of the *O-S* interaction suggests a stabilising contribution of –3.44 kcal mol^{-1} of intermediate **62** (Figure 16).[71]

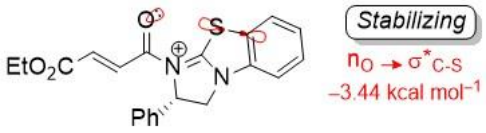


Figure 16 – Magnitude of the stabilising effect of *O•••S* interaction in species **62**

X-ray crystallographic data was obtained by the Smith group on an α,β-unsaturated acyl ammonium chloride derivative of HyperBTM **63**, generated from cinnamyl chloride and HyperBTM **26** (Figure 17).[72] Assuming the analogous α,β-unsaturated acyl ammonium carboxylate species is formed under

catalytic conditions, and adopts a similar conformation, it can be used to rationalize the observed enantioselectivities. Acylation of the heterocycle forces the phenyl group into a pseudo axial position, minimizing 1,2-strain and blocking one face of the acylated catalyst, enabling complete facial selectivity. The 1,5-*O•••S* interaction, between acyl *O* and isothiourea *S*, locks the conformation in place, preventing free rotation around the *N*-acyl bond. The *O•••S* distance was found to be 2.48 Å, significantly lower than the van der Waals radii of 3.32 Å, consistent with an attractive force between them. Subsequent computational studies conducted on the lactamization of phenacyl benzothiazole/benzoxazole species, with an α,β-unsaturated acyl ammonium intermediate, confirmed the significance of this *O•••S* interaction for locking the acyl isothiouronium intermediate with *O* and *S* syn-coplanar, thus contributing to the high enantioselectivities observed for this work.[73]

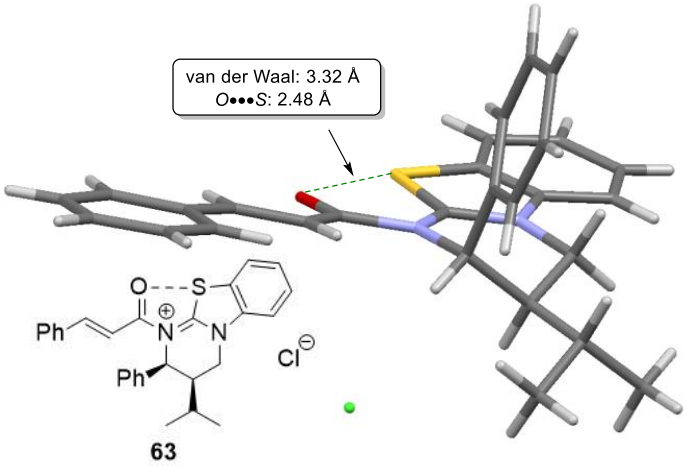
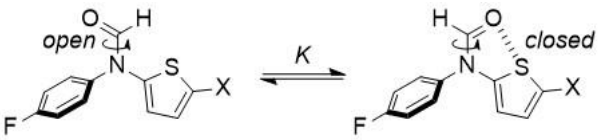


Figure 17 – X-ray crystal structure showing the half chair conformation, with *O* to *S* interaction

A recent experimental, solution-phase study on the origin of chalcogen-bonding interactions was conducted by Cockroft to further investigate *O•••S* interactions.[74] A range of neutral formamide and thioformamide species was designed in order to quantify the interactions between oxygen and sulfur in a 1,5 conformation. Evaluation of a range of polar and apolar solvents on the electrostatic and solvophobic influence on the chalcogen-bonding interaction found that the closed conformation (in which an attractive *O•••S* interaction is inferred) is preferred in nearly all cases, indicating this *O•••S* interaction is solvent independent. Further computational studies were conducted to investigate orbital delocalization contributions to this interaction. Changes in bond lengths were computed and natural bond order (NBO) analysis indicated that stabilizing contributions occur through non-bonding n_O to $\sigma^*_{C\text{-}S}$ orbital delocalization between a lone pair on the amide donor and the antibonding σ* orbital of the adjacent thiophene acceptor.



Scheme 17 – Equilibrium between open and closed conformations of formamides

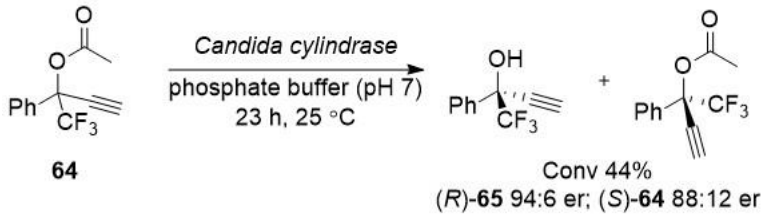
1.4 Resolution of tertiary alcohols

Compared to wide number of methods reported for the KR of secondary alcohols, the KR of tertiary alcohols has not been widely explored. The acylation of tertiary alcohols is more difficult than the acylation of secondary alcohols, due to increased steric hindrance at the carbinol centre.[18] Furthermore, for the KR of tertiary alcohols, the catalyst must efficiently distinguish between three substituents at the reaction centre (Figure 18).

Figure 18 – Difference in substituents in secondary and tertiary alcohols

1.4.1 Enzymatic kinetic resolution

In 1992, the enzymatic hydrolytic KR of tertiary acetylenic acetates was reported by O'Hagan.[75] Using *Candida cylindrase*, ester (±)-**43** was resolved with 44% conversion, with tertiary alcohol (*R*)-**44** obtained in 94:6 er and recovered ester (*S*)-**43** in 88:12 er, equating to $s > 20$ (Scheme 18). However, the enzyme used for this KR was dependent on the presence of the acetylene functionality being present in the starting substrate, with methyl, vinyl or nitrile groups as replacement to the alkyne shown to be inert to lipase hydrolysis, even after an extended reaction time.

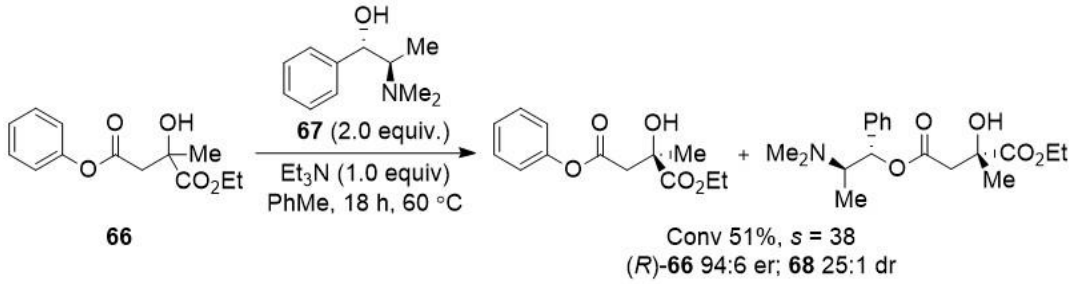


Scheme 18 – Enzymatic hydrolytic KR of ester **64**

1.4.2 Non-catalytic kinetic resolution

In 2009, Fagnou demonstrated the use of (1*S*,2*R*)-*N*-methylephedrine **67** as a stoichiometric chiral reagent in the KR of tertiary β-hydroxy esters (Scheme 19).[76] These resolutions proceeded through a transesterification reaction to give high selectivity factors ($s > 20$) even though the tertiary stereogenic centre is 3 atoms away from the reaction site. The KR of hydroxy ester (±)-**66** proceeded with $s = 38$,

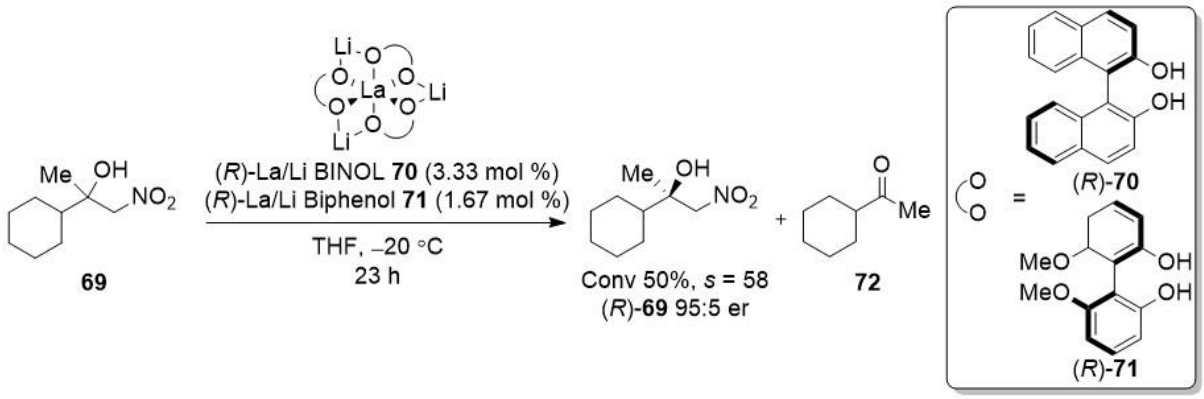
though this process requires the presence of aryloxy esters and the β-hydroxy group in the starting material for high selectivity, with an example of an α-hydroxy ester giving a selectivity factor of 1.3.



Scheme 19 – Kinetic resolution of β-hydroxy esters

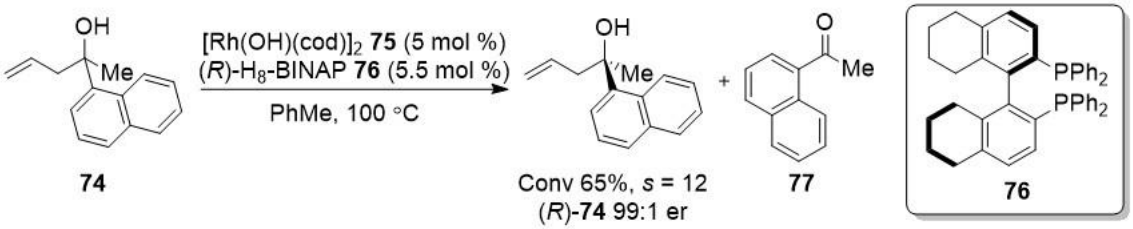
1.4.3 Metal-catalyzed kinetic resolution

The KR of tertiary alcohols using metal catalysts has also been developed. In 2006, Shibasaki used a bimetallic lanthanum and lithium catalyst, containing a 2:1 mixture of BINOL **70** and biphenol ligand **71** in a retro-nitroaldol reaction.[77] The KR of tertiary alcohol (±)-**69** proceeded with 50% conversion, with (*S*)-**69** undergoing a retro-nitroaldol to give ketone **72**, whilst (*R*)-**69** remained unreacted and obtained in high enantioselectivity (95:5 er), equating to *s* = 58 (Scheme 20). This method requires the presence of a nitromethyl group, though no mention of further substitution at the α-position to the nitro group was mentioned. The examples provided are limited to aliphatic groups at the carbinol centre, with only one example of aryl-alkyl substituents, and one example with variation of the methyl group, only an ethyl substituent.



Scheme 20 – Retro-nitroaldol KR using a bimetallic catalyst

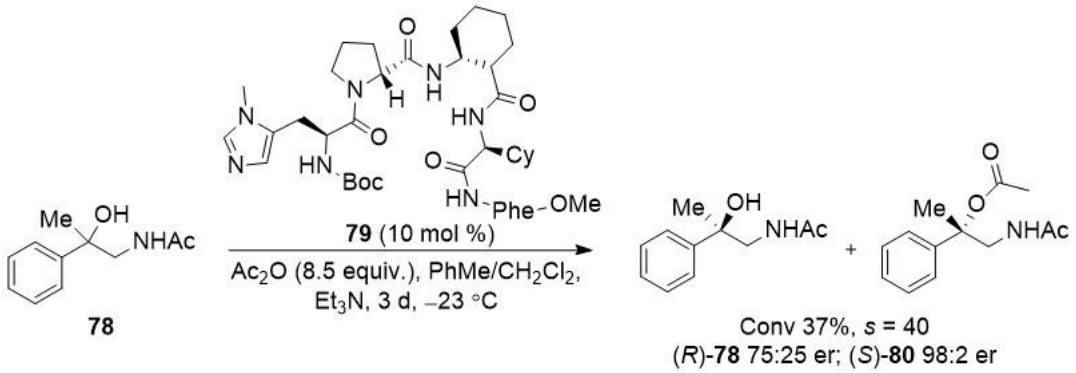
In 2008, Hayashi reported a methodology for the KR of tertiary alcohols using a rhodium catalyst **75** for the deallylation of homoallylic alcohols.[78] The KR of alcohol (±)-**74** proceeded with 65% conversion, with (*S*)-**74** undergoing a deallylation to give ketone **77** and recovered (*R*)-**74** isolated in excellent 99:1 er, to give an *s* = 12 (Scheme 21). This method is dependent on the presence of an allyl group in the starting substrate, however the scope was limited to only a small variation of the aryl and alkyl group, with no variation in the allyl substituent investigated.



Scheme 21 – Deallylation kinetic resolution of tertiary alcohols

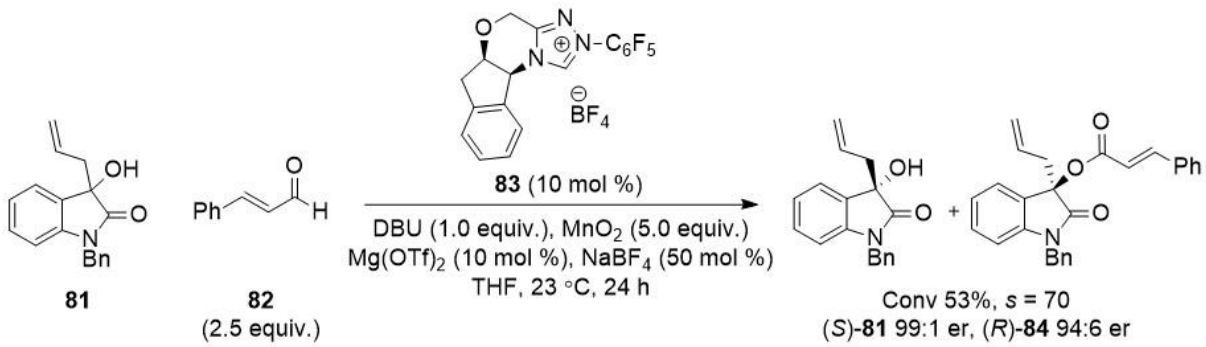
1.4.4 Acylative kinetic resolution of tertiary alcohols

The first example of an acylative organocatalytic KR of tertiary alcohols was reported by Miler in 2001, using a pentapeptide catalyst.[79] In the presence of pentapeptide catalyst **79** and acetic anhydride, the KR of alcohol **78** proceeded with 37% conversion, with the unreacted alcohol (*R*)-**78** obtained in 75:25 er and ester (*S*)-**80** in excellent 98:2 er, to give s = 40 (Scheme 22). A total of 60 tetra- and pentapeptides were synthesized, containing both natural and non-natural amino acids, and these were extensively evaluated in screening assays, before the implication that catalyst **79** would be a selective acylation catalyst in a KR was reached. This work was limited to only seven examples of tertiary alcohols in the KR protocol, all containing the acetyl amide unit, with little variation in the aryl substituent. Little variation is shown in the methyl group, with incorporation of an ester group as the only alternative, leading to acylation with no enantioselectivity (*s* = 1).



Scheme 22 – Acylative organocatalytic kinetic resolution

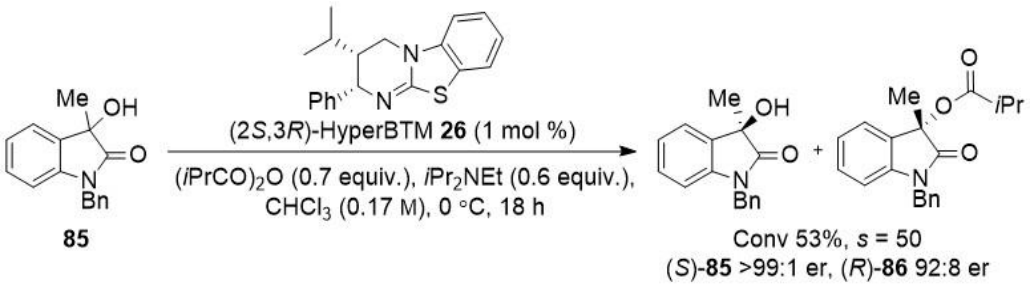
Most recently, Zhao set the benchmark for the KR of tertiary alcohols. In state of the art work, the KR of 3-hydroxyoxindoles were conducted using an N-heterocyclic carbene catalyst.[80] Using cinnamaldehyde **82** and NHC catalyst **83**, the KR of alcohol **81** proceeded with 53% conversion to give alcohol (*S*)-**81** in excellent 99:1 er and ester (*R*)-**84** in 94:6 er, equating to an *s* of 70 (Scheme 23). In this work, though excellent selectivities are observed, a large excess of cinnamaldehyde **82** (2.5 equiv.) and high catalyst loading (10 mol %) were required. The reaction mixture is made more complex with the inclusion of extra additives, such as $Mg(OTf)_2$ (10 mol %) and $NaBF_4$ (50 mol %), with their roles within the reaction mechanism not fully understood.



Scheme 23 – NHC-catalysed KR of 3-hydroxyoxindoles

1.5 Previous preliminary work on kinetic resolution

Initial preliminary work conducted within the Smith group has demonstrated that a combination of HyperBTM (2*S*,3*R*)-**26** and isobutyric anhydride can be used for the KR of 3-hydroxyoxindoles. Only a limited range of substrates had initially been investigated, with the KR of 3-hydroxy-3-methyloxindole **85**, proceeding with 53% conversion, giving s = 50 (Scheme 24). Inclusion of a phenyl group at the 3-position of the oxindole enabled selectivity factors of up to 130 to be obtained.



Scheme 24 – Preliminary result for the isothiourea-catalyzed KR of 3-hydroxyoxindoles

1.6 Aims and Objectives

It has already been established in the KR of secondary alcohols, that high selectivity factors can be attributed to inclusion of a recognition motif at the carbinol stereocentre that can efficiently allow preferential reactivity of one enantiomer over its antipode. In contrast, the KR of tertiary alcohols has not been widely explored. They are challenging substrates for KR, due to their sterically hindered nature making them difficult to acylate, and the challenging requirement for effective discrimination between three substituents at the carbinol centre by the catalyst. Incorporation of multiple recognition motifs, for example aryl and carbonyl, adds to this challenge, as acylation of both substrate enantiomers could be promoted by differing recognition sites during acylation, leading to poor overall selectivity (Figure 19).

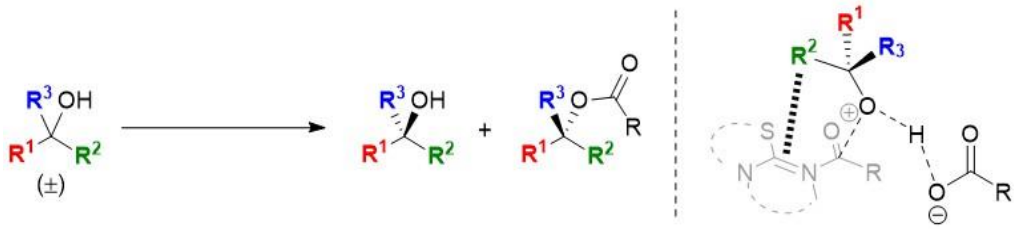
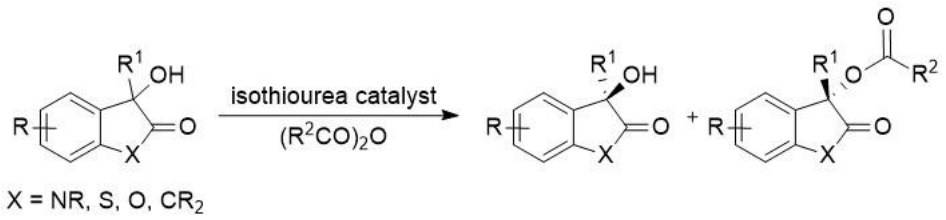


Figure 19 – Potential for various recognition motifs in KR of tertiary alcohols

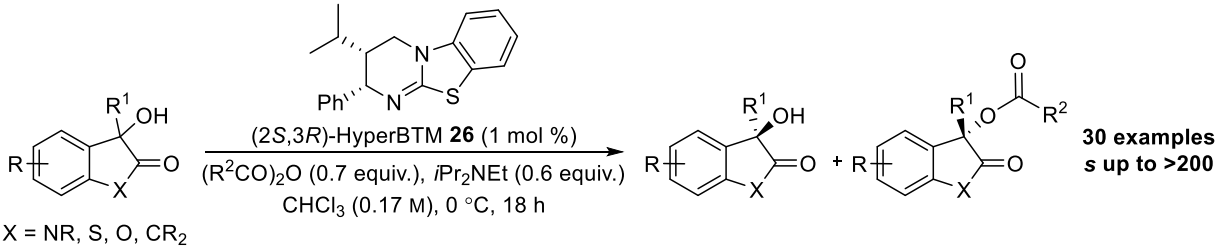
The aim of this work is to further investigate the isothiourea-catalyzed acylative KR of tertiary alcohols, that incorporate different recognition motifs at the carbinol stereocentre. The important structural features of the alcohol substrates will be investigated to allow rationalization of any enantiodiscrimination observed. Computational studies will be conducted to fully understand the mechanism of the KR process, and to determine the key interaction between the alcohol substrate and catalyst. Initially this work will focus on a range of 3-hydroxyoxindole substrates with varying substituents at positions, including alkyl, aryl, alkenyl and alkynyl groups. Following this, electronic perturbation of substituents on the 3-substituent will be investigated, as well as various *N*-substituents. Studies will then be conducted on the substitution pattern around the benzenoid oxindole in order to gauge the impact on selectivity, as well as evaluation of structural derivatives of the oxindole core (Scheme 25).



Scheme 25 – Kinetic resolution of 3-hydroxyoxindoles with isothiourea catalysts

CHAPTER 2: KINETIC RESOLUTION OF 3-HYDROXYOXINDOLES

This chapter describes the use of an isothiourea catalyst [(2*S*,3*R*)-HyperBTM] in the KR of 3-hydroxyoxindoles with an anhydride as the acylating agent, to afford the recovered alcohol and corresponding ester with good to excellent levels of selectivity (*s* up to >200). Structural derivatives of the core structure were also investigated to probe the full scope and limitations of the KR protocol (Scheme 26).



Scheme 26 – Kinetic resolution of tertiary alcohols

2.1 Previous preliminary work on kinetic resolution

The 3-hydroxyoxindole motif is a privileged motif, prominent in a range of bioactive natural products. Representative examples such as convolutamydine A, an antinocicptive; maremycin B, which has been found to be a secondary metabolite in a strain of Streptomyces;[81] and an alkynyl-substituted oxindole, which has shown improved anti-HIV properties compared to other HIV reverse transcriptase drugs showcase the importance of this structure (Figure 20).[82]

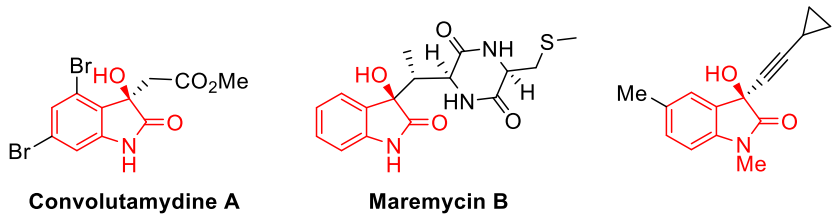
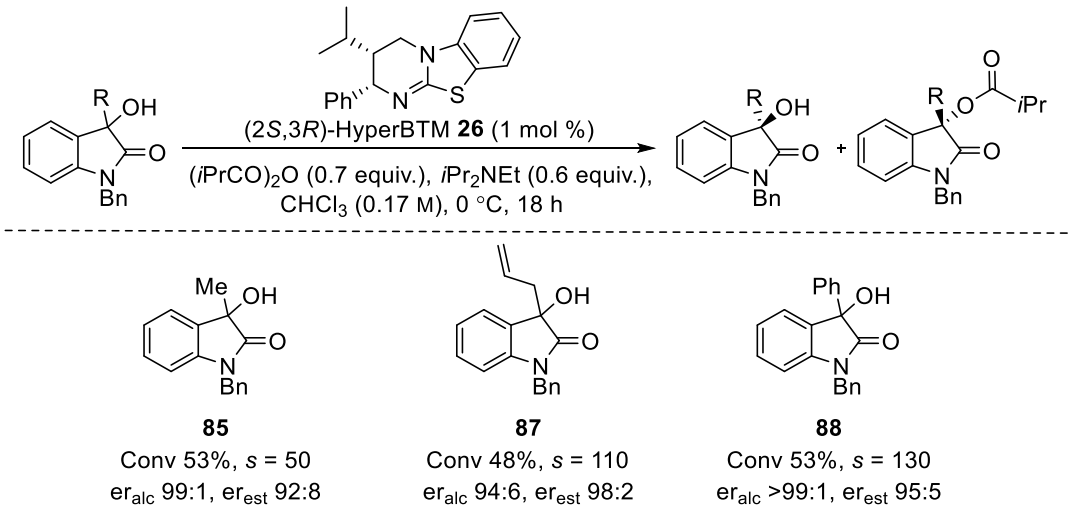


Figure 20 – Bioactive natural product containing the 3-hydroxyoxindole structure

Initial preliminary work had been conducted in the group on the isothiourea-catalyzed KR of a select number of 3-hydroxyoxindole substrates.[83] Optimization on the 3-allyl substituted alcohol **87** found the best conditions to be; (2*S*,3*R*)-HyperBTM **26** (1 mol %), isobutyric anhydride (0.7 equiv.) and *i*Pr$_2$NEt (0.6 equiv.) in CHCl$_3$ (0.17 M) at 0 °C, with the reaction time set at 18 h to give s = 110 obtained. Studies on a small set of 3-substituted oxindole derivatives **85, 87** and **88** found excellent selectivity factors (*s* up to 130) could be obtained under these conditions, with excellent discrimination observed with the 3-aryl substituted oxindole **88** bearing three sp^2 centres (Scheme 27).



Scheme 27 – Previous preliminary results

The absolute configuration of recovered allyl-substituted alcohol **87** after KR was determined by comparison of the specific rotation to that reported in the literature. Literature values show the (*S*)-enantiomer (95.5:4.5 er) with a specific rotation of $[\alpha]_D^{26}$ –8.9 (*c* 1.01, $CHCl_3$),[84] whilst the specific rotation for the isolated allyl-substituted alcohol **87** following KR (94:6 er) was $[\alpha]_D^{27}$ +8.5 (*c* 1.0, $CHCl_3$). From this, it can be deduced that the (*R*)-enantiomer is isolated from the resolution in this case. In addition, X-ray crystal structural analysis of **88** is also consistent with this assigned configuration (Figure 21). This assignment of configuration was therefore assumed for all subsequent alcohols recovered from the KR.

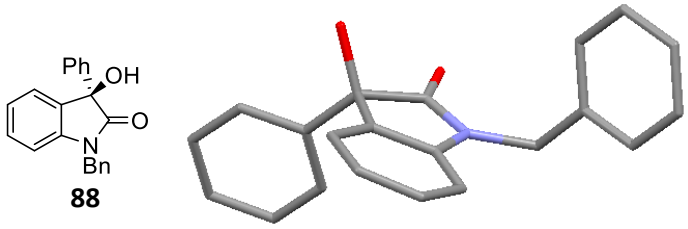


Figure 21 – X-ray crystal structure confirming the (*R*)-enantiomer of isolated **88**

2.2 Objectives

To build on these promising preliminary results, this chapter investigates the KR of a broad scope of 3-hydroxyoxindoles. To fully investigate the KR of alcohols with this core structure, and to probe the full scope and limitations of this method, the aims of this chapter are;

1. to synthesize a range of 3-substituted oxindoles bearing: alkyl, alkenyl and alkynyl groups; aryl and heteroaryl substituents, and various electron-withdrawing groups, such as esters, amides, ketones and nitriles, in order to observe whether the addition of multiple recognition motifs has an overall effect on the selectivity factor observed;

2. to vary the electronic nature of the *N*-substituent in order to observe how this affects selectivity;

3. to investigate substitution around the benzenoid core of the oxindole;

4. to vary the oxindole core structure, with replacement of the amide with thioamide, ester and thioester groups utilized, as well as removal of the ring carbonyl.

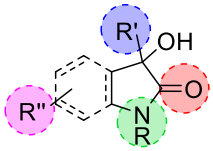
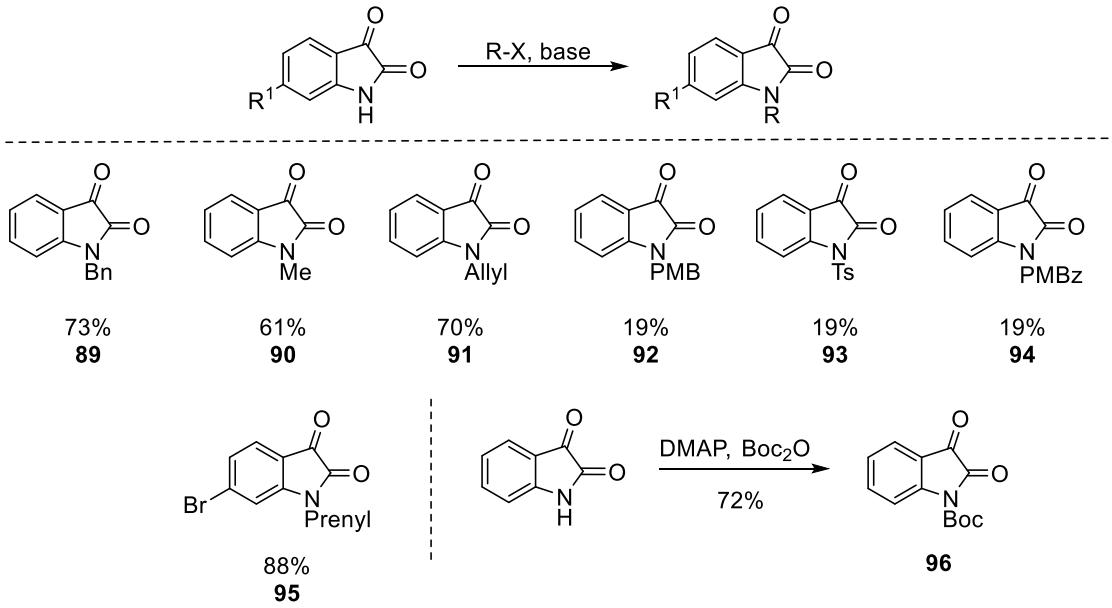


Figure 22 – Variations on and around oxindole core structure

Furthermore, computations will be conducted by Daniel Walden and Paul Ha-Yeon Cheong to determine the intermediates and transition state (TS) structures that are present throughout the reaction mechanism. Determination of the major recognition motif within the KR consistent with the observed levels of selectivity will also be computed.

2.3 Synthesis of *N*-substituted isatin derivatives

A range of *N*-substituted isatin compounds was synthesized in moderate to good yields, starting from either isatin or 5-bromo isatin, using a base and various alkyl halides (Scheme 28). Nucleophilic addition to these *N*-protected isatin derivatives **89-96**,[85] led to the formation of a range of functionalized 3-hydroxyoxindole derivatives.



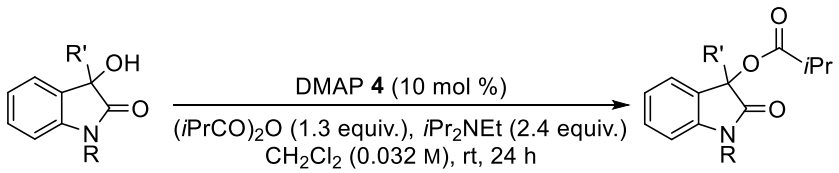
Scheme 28 – *N*-substitution of isatin

2.3 Aryl substitution

Building from the excellent selectivity observed with 3-phenyl substituted oxindole **88** (*s* = 130), various tertiary alcohols bearing a range aromatic and heteroaromatic groups, with varying electronic nature, were synthesized and tested under the KR protocol previously established.

2.3.1 Alcohol and ester synthesis

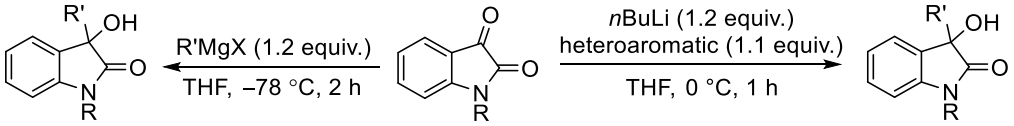
A range of 3-aryl substituted oxindole substrates was synthesized, *via* addition of aryl Grignard reagents or organolithium reagents to *N*-substituted isatin derivatives to give the desired alcohols in moderate to good yields. The Grignard reagents were either commercially available, or synthesized from the corresponding aryl bromide and magnesium, whilst the organolithium reagents were synthesized by deprotonation of heteroaromatic with *n*BuLi.[86] To calculate the selectivity factor of a KR, the enantiomeric ratio (er) of both recovered alcohol and ester need to be evaluated. Therefore, esterification of the alcohols was carried out using catalytic DMAP **4** and isobutyric anhydride as acylating agent (Scheme 29) and HPLC conditions were determined for the racemic samples of both synthesized alcohols and esters.



Scheme 29 – DMAP catalyzed esterification of tertiary alcohols

The corresponding ester were obtained in good to excellent yields, however treatment of 3-phenyl-3-hydroxyoxindole **109,** bearing the unprotected NH, to the esterification conditions, led to an inseparable complex mixture of a possible 3 compounds, presumably due to competitive *O*– and *N*–acylation under the esterification conditions and so was not further studied (Table 2).

Table 2 – Addition to *N*-protected isatin derivatives and esterification



Entry	R′	N-R	Alcohol		Ester	
			No.	Yield (%)	No.	Yield (%)
1	4-MeO-C_6H_4	Me	**97**	44	**98**	76
2	2-Naphthyl	Me	**99**	47	**100**	89
3	3,5-CF_3- C_6H_3[87]	Allyl	**101**	66	**102**	80
4	4-NMe_2-C_6H_4[87]	Allyl	**103**	77	**104**	45
5	2-Thienyl	Me	**105**	34	**106**	77
6	2-Furanyl	Me	**107**	24	**108**	81
7[a]	Phenyl	H	**109**	36	–	–

a) Deprotonation with NaH performed before Grignard addition

2.3.2 KR of aryl substituted oxindoles

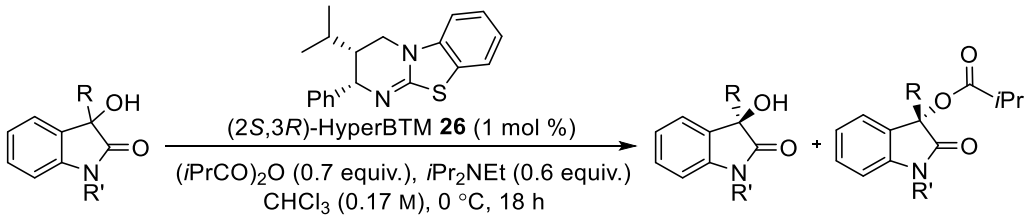
A small range of 3-aryl substituted alcohols was tested in the KR protocol. The KR reactions were carried out by addition of the (2*S*,3*R*)-HyperBTM **26** (synthesized by the Smith group, and also commercially available[88]) to a solution of alcohol in $CHCl_3$. The reaction was cooled to the required temperature and once reached, isobutyric anhydride and Hünig's base were added. The reaction vessel was sealed and the mixture stirred for 18 h. On completion, the mixture was diluted with EtOAc (20 mL) and washed with HCl (2 x 10 mL) and sat. aq. $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The alcohol and ester were purified by column chromatography and analyzed by chiral HPLC. The conversion and selectivity factor of the reaction was then calculated using the ee of the recovered alcohol and ester product, with the conversion also compared to that of the ^{1}H NMR to ensure consistency in the calculation.

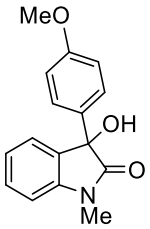
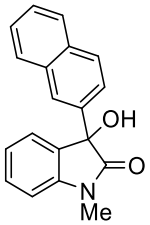
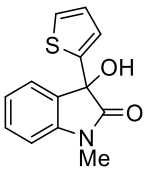
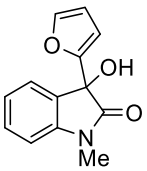
4-Methoxyphenyl substituted alcohol **97** required a slightly longer reaction time at 24 h, with lower conversion obtained after 18 h (31%), however excellent selectivity was observed (*s* = 100) (entry 1). The KR of 2-naphthyl substituted alcohol **99** proceeded with excellent reactivity and selectivity (*s* = 180) (entry 2). The electron-withdrawing 3,5-bis(trifluoromethyl)phenyl substituted alcohol **101** (entry 3) proceeded with good reactivity and selectivity (*s* = 60), though with reduced selectivity compared to **97**. Interestingly, there was a marked difference in selectivity between the 2-thienyl and 2-furanyl alcohols **105** and **107** (entry 4 vs 5). **107** was resolved with *s* = 90, compared to **105**, which gave *s* = 19.

Computational and experimental work conducted by Shiina showed thienyl rings are better recognition motifs than furanyl rings in the KR of 1-heteroarylalkanols,[89] however, our findings show lower selectivity with a 2-furanyl substituent. This would indicate that although a thienyl ring has been

shown to be a better recognition motif in the literature, in the case of this work, the electron-withdrawing nature of the heteroaryls are a more significant factor, with the furanyl ring being slightly more electron-withdrawing than the thienyl ring, thus giving an overall lower selectivity.[90] An interesting observation to note from the KR of these 3-aryl substituted oxindoles is that there is efficient and selective discrimination between three sp^2 centres during the KR in each example; the benzenoid sp^2 carbon, the 3-aryl sp^2 carbon and the carbonyl sp^2 carbon (Table 3).

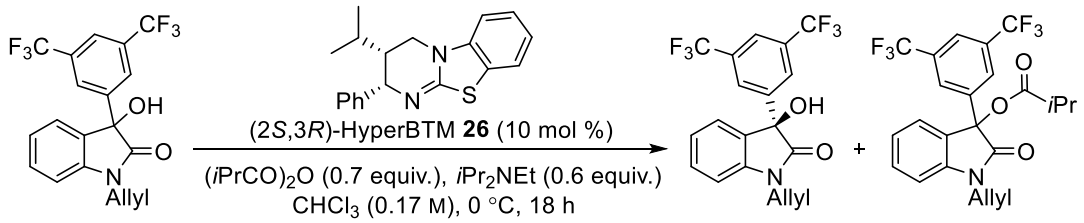
Table 3 – Kinetic resolution of aryl substituted alcohols



Entry		1[a]	2	4	5[b]
Alcohol					
		97	**99**	**105**	**107**
Conv (%)		46	51	56	49
Alc	er	90:10	99:1	>99:1	88:12
	Yield	48	45	52	36
Est	er	98:2	98:2	90:10	90:10
	Yield	41	32	33	42
s		100	180	90	19

a) 24 h. b) 0.6 equiv. $(i\text{PrCO})_2O$.

Two further examples on this project were conducted in the Smith group by Dr. Mark Greenhalgh.[87] The KR of 3,5-*bis*-CF_3-C_6H_3-substituted alcohol **101** proceeded with high excellent conversion and high selectivity (*s* = 60), with highly enantiopure samples of the recovered alcohol and ester product.

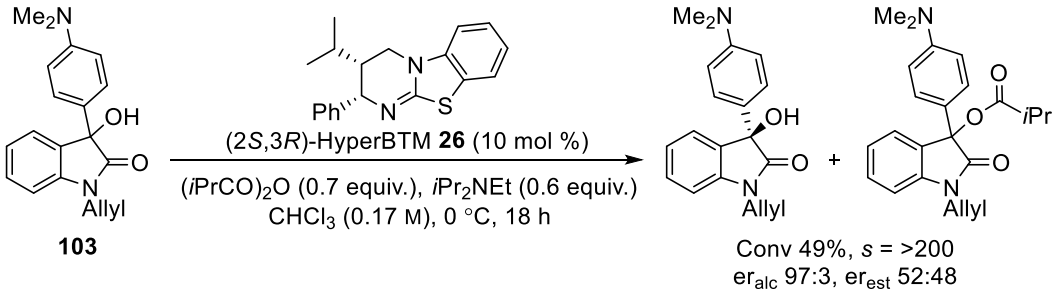


101

Conv 51%, *s* = 60
er_{alc} 96:4, er_{est} 95:5:5

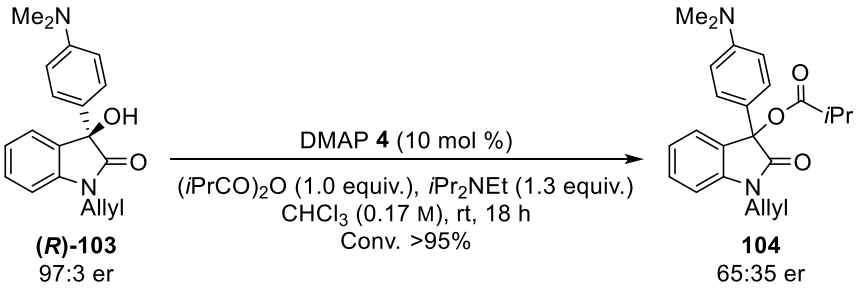
Scheme 30 – Unexpected result in the KR of alcohol **103**

The KR of 4-dimethylaminophenyl-substituted alcohol **103** gave highly enantiopure alcohol (97:3 er) at good conversion (*s* = >200), however a racemate was obtained for the ester (52:48 er). This anomaly can be attributed to racemization of the ester through reversible ionization due to the highly electron-donating 4-dimethylamino group (Scheme 31).[87]



Scheme 31 – Unexpected result in the KR of alcohol **103**

To test this theory, a control reaction was conducted using the highly enantioenriched sample of **(*R*)-103** (97:3 er) in the presence of isobutyric anhydride and DMAP **4**. This reaction proceeded with >95% conversion of the starting alcohol, with a significant reduction in er of the ester product (65:35 er) noted, compared to the starting er of the alcohol. This result demonstrates that racemization does occur upon acylation of the alcohol (Scheme 32).



Scheme 32 – Acylation of enantiopure alcohol **103**

This result is consistent with the previous observation that electron-withdrawing aryl substituents proceed with lower selectivity when compared to the KR of alcohols bearing electron-rich aryl groups at the 3-position, such as that observed for 4-dimethylaminophenyl subsitited **103**.

2.4 Alkenyl/alkynyl substitution

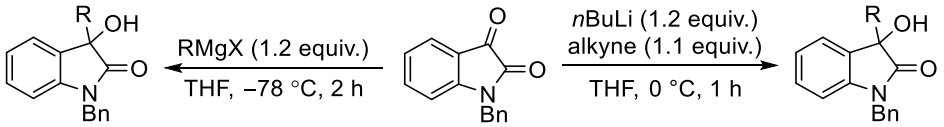
As excellent discrimination between three sp^2 centres was observed with the 3-aryl substituted oxindoles, substitution of the 3-aryl for alkenyl substituents was then investigated to see if this discrimination was again observed. It has already been shown by Birman that an sp centre is an effective recognition motif in the KR of propargylic alcohols.[91] Therefore, as a further extension, alkynyl substituents were incorporated at the 3-position of the oxindole to investigate the effect an

alkyne has on selectivity in this system, and to observe the comparison to substituents bearing sp^2 or sp^3 centres.

2.4.1 Alcohol and ester synthesis

A range of vinylic-substituted oxindoles was synthesized using the relevant Grignard reagent, with the alkyne-substituted oxindole synthesis conducted using *n*BuLi and the relevant alkyne. This small group of 3-alkenyl and 3-alkynyl substituted oxindole substrates were obtained in low to good yields. Esterification was carried out using the previously established conditions of DMAP **4** and isobutyric anhydride, to give the racemic esters in good to excellent yields (Table 4).

Table 4 – Grignard and organolithium addition to *N*-benzyl isatin **89** and esterification



89

Entry	R	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	Vinyl	**110**	45	**111**	68
2	-C(CH_3)=CH_2	**112**	18	**113**	63
3	-CH=C(CH_3)$_2$	**114**	18	**115**	87
4	Phenylethynyl	**116**	43	**117**	58
5	Cyclopropylethynyl	**118**	74	**119**	59

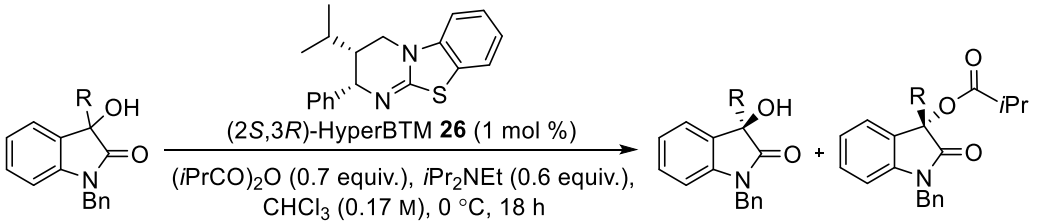
2.4.2 KR of alkenyl/alkynyl substituted oxindoles

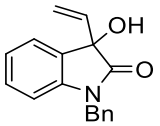
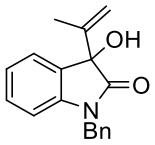
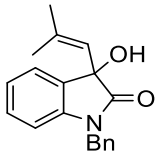
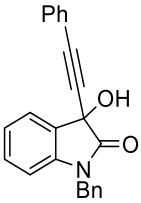
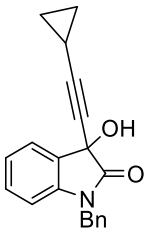
The KR of 3-vinyl-substituted alcohol **110** (entry 1, Table 5) gave a high selectivity factor for the resolution (*s* = 50). With a conversion of >60% observed when using 0.7 equivalents, and to obtain a reaction conversion close to 50%, fewer equivalents of anhydride were used. A further reason for this is that calculation of selectivity factor is not reliable at high conversion. The KR of the bulkier isopropenyl-substituted alcohol **112** gave *s* = 80, though a slightly longer reaction time of 24 h was required, due to lower conversion after 18 h (29%) (entry 2). The KR of alcohol **114**, bearing a tri-substituted alkenyl substituent at the 3-position required a higher catalyst loading (5 mol %) and a longer reaction time (72 h), giving s = 60 (entry 3). Again, excellent selectivity was observed with these KR, with effective discrimination between three sp^2 centres during the resolution in each example.

The KR of alkynyl substituted alcohols **116** and **118** (entries 4 and 5) proceeded with good conversion under the standard conditions, however the selectivity observed with these substrates were quite poor. In the work by Feng,[92] an enantioenriched sample of (*S*)-**116** was synthesized *via* a copper guanidine-catalyzed asymmetric alkynylation. Under the same HPLC conditions (DAICEL CHIRALPAK

IB; Hexane/*i*PrOH, 7:3; flow rate = 1.0 mL min^{-1}), the major enantiomer from the KR of alcohol **116** was confirmed to be (*R*)-**116**, consistent with the same sense of enantiodiscrimination as other examples. However, the lower *s* factors observed could be due to a less sterically hindered quaternary carbinol centre, leading to less discrimination between each enantiomer during acylation, or the alkyne acting as a competitive recognition motif, as has been previously shown in the KR of propargylic alcohols.

Table 5 – KR of alkenyl and alkynyl substituted alcohols



Entry		1[a]	2[b]	3[c]	4	5
Alcohol						
		110	**112**	**114**	**116**	**118**
Conv (%)		55	41	44	56	68
Alc	er	>99:1	83:17	87:13	68:32	91:9
	Yield	36	58	51	19	14
Est	er	91:9	98:2	97:3	64:36	69:31
	Yield	48	33	40	42	26
s		50	80	60	2	5

a) 0.6 equiv (*i*PrCO)$_2$O. b) 24 h. c) 5 mol %, 72 h.

2.5 Effect of varying *N*-substituent

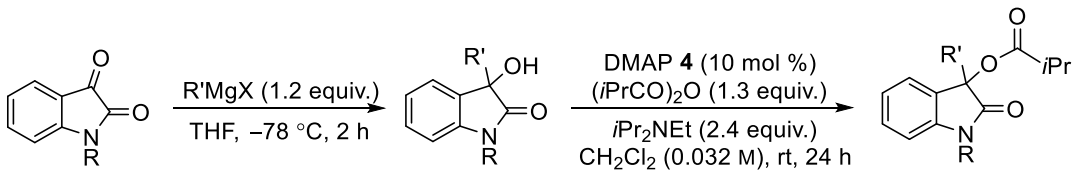
To investigate whether the *N*-substituent has any effect on the selectivity, a variety of substituents, from electron-donating to electron-withdrawing groups, were incorporated at the oxindole nitrogen. To gather a more comprehensive overview, substitution at the carbinol stereocentre on the oxindole with a methyl or phenyl group were utilised to allow direct comparison of the effect of the *N*-substituent.

2.5.1 Alcohol and ester synthesis

Methyl- and phenylmagnesium bromide (1.2 equiv.) were added to each of the following isatin derivatives; *N*-methyl **90**, *N*-allyl **91** and *N*-4-methoxybenzyl **92**, to give the desired tertiary alcohol in

moderate to excellent yields. Esterification was carried out using the previously established conditions of DMAP **4** and isobutyric anhydride, to give the racemic esters in good to excellent yields (Table 6).

Table 6 – Grignard addition to *N*-protected isatin derivatives and esterification

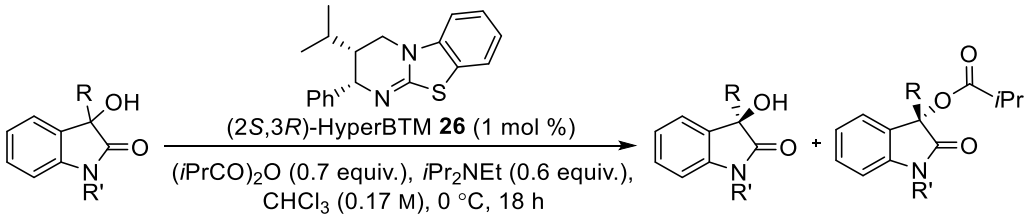


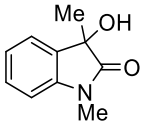
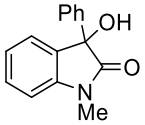
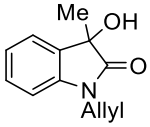
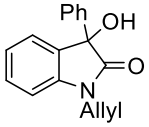
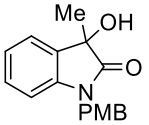
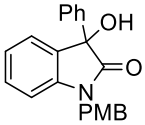
Entry	R′	NR	Alcohol		Ester	
			No.	Yield (%)	No.	Yield (%)
1	Me	Me	**120**	68	**121**	78
2	Ph	Me	**122**	82	**123**	78
3	Me	Allyl	**124**	74	**125**	66
4	Ph	Allyl	**126**	88	**127**	78
5	Me	PMB	**128**	37	**129**	75
6	Ph	PMB	**130**	40	**131**	70

2.5.2 3-Alkyl vs 3-aryl KR with varying *N*-substituents

For the *N*-methyl substituted oxindoles, good selectivity was observed for the KR of 3-methyl substituted alcohol **120** (entry 1, *s* = 39), while the KR of the 3-phenyl substituted alcohol **122**, proceeded with excellent selectivity (entry 2, *s* = 160), though a reaction time of 40 h was required for good conversion. The KR of *N*-allyl alcohols **124** and **126** both proceeded with excellent selectivity, with *s* = 140 and 120 respectively. Comparable selectivity was observed for the KR of 3-methyl substituted alcohol **128** and 3-phenyl substituted alcohol **130** bearing an *N*-4-methoxybenzyl substituent. The KR of alcohol **128** required a longer reaction time in order to obtain a conversion close to 50%, but the 3-phenyl substituted alcohol **130** gave a small increase in selectivity (entry 5 vs 6; *s* = 70 vs 90).

Table 7 – KR of 3-methyl- and 3-phenyl-substituted oxindoles with varying *N*-substituents



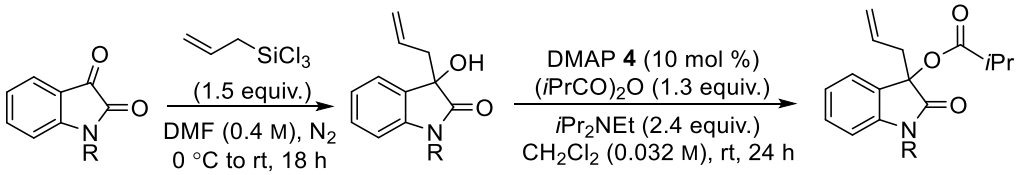
Entry		1	2[a]	3[b]	4	5[c]	6
Alcohol							
		120	**122**	**124**	**126**	**128**	**130**
Conv (%)		52	43	42	45	49	50
Alc	er	96:4	86:14	85:15	89:11	94:6	96:4
	Yield	36	57	49	49	43	36
Est	er	93:7	99:1	99:1	98:2	96:4	97:3
	Yield	48	41	42	40	49	37
s		39	160	140	120	70	90

a) 40 h. b) 0.6 equiv. $(i\text{PrCO})_2\text{O}$. c) 24 h

2.5.3 Electron-withdrawing *N*-substituents

Electron-withdrawing *N*-tosyl, *N*-4-methoxybenzoyl or *N*-Boc protecting groups have been shown in the literature to be labile in the presence of Grignard or organolithium reagents.[93] This was observed when isatin derivatives **93**, **94** and **96** were reacted with methyl- or phenylmagnesium bromide in THF at –78 °C, as well as with methyl- or phenyllithium in THF at 0 °C, with a complex mixture of products obtained and none of the desired products observed. As the alcohols bearing 3-methyl- or 3-phenyl-substitution could not be synthesized in the presence of an electron-withdrawing *N*-substituents, therefore, a direct comparison could not be made. However, incorporation of an allyl-substituent at the 3-position of the oxindole was possible with these *N*-substituents. The allylation of ketones using allyltrichlorosilane in DMF was reported by Kobayashi in 1994 for the synthesis of a range of homoallylic alcohols,[94] and Bisai demonstrated these conditions could be applied for the allylation of isatin derivatives, bearing a *N*-methyl substituent, as well as a free NH.[95] We found that this procedure was also compatible with isatin derivatives bearing electron-withdrawing *N*-substituents, as a much milder alternative to Grignard or organolithium reagents, proceeding without cleavage of the *N*-substituent, to give the desired alcohols **132**, **134** and **136** in good to excellent yields. Esterification was carried out using the previously established conditions of DMAP **4** and isobutyric anhydride, to give the racemic esters in good to excellent yields (Table 8).

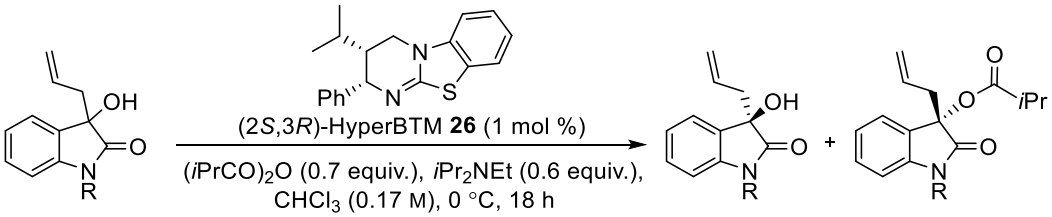
Table 8 – Allylation of isatin derivatives

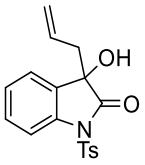
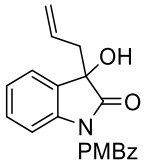
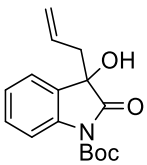
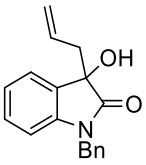


Entry	N-R	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	Ts	**132**	62	**133**	58
2	PMBz	**134**	80	**135**	59
3	Boc	**136**	72	**137**	81

The KR of the 3-allyl oxindoles, bearing electron-withdrawing *N*-substituents was then conducted (Table 9). The KR of the tertiary alcohols containing an *N*-tosyl **132** and *N*-4-methoxybenzoyl **134** proceeded with high conversion (>60%), however the observed selectivities were poor (entry 1; *s* = 7 and entry 2; *s* = 8). Pleasingly however, the KR of *N*-Boc alcohol **136** proceeded with good conversion (52%) and excellent selectivity (entry 3; *s* = 110), with the specific rotation of recovered alcohol consistent with that of the (*R*)-enantiomer reported in the literature.[96] This selectivity factor is the same as that observed in the preliminary work conducted by a Masters project studeny on allyl-substituted oxindole **87** (s = 110), bearing a *N*-benzyl substituent (Scheme 27).

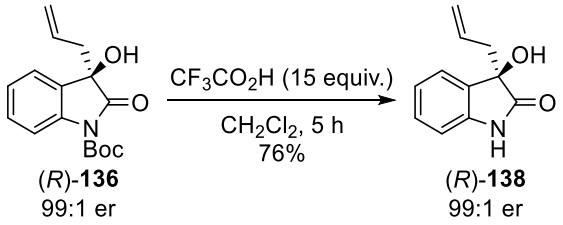
Table 9 – Kinetic resolution of alcohols bearing an electron withdrawing *N*-substituent



Entry		1	2	3	4[83]
Alcohol					
		132	**134**	**136**	**87**
Conv (%)		62	64	52	48
Alc	**er**	90:10	99:1	95:5	94:6
	Yield	33	41	31	-
Est	**er**	75:25	96:4	75:25	98:2
	Yield	50	45	57	-
s		7	8	110	110

The recovered (*R*)-alcohol from the KR of **136** was isolated in highly enantiopure form (99:1 er). The *N*-Boc group was subsequently deprotected using trifluoroacetic acid, with **138** obtained in high yield

without loss of enantiopurity, with the specific rotation matching that reported in the literature for the (*R*)-enantiomer[96] (Scheme 33).



(*R*)-**136** 99:1 er (*R*)-**138** 99:1 er

Scheme 33 – Deprotection of *N*-Boc group

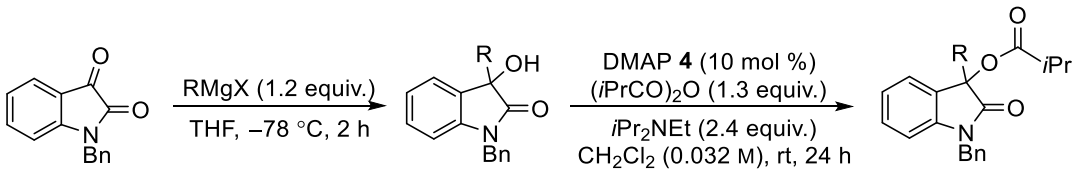
2.6 Other alkyl substituents

A range of 3-hydroxyoxindoles bearing 3-alkyl substituents, such as methyl, ethyl, isopropyl and allyl, was investigated in previous preliminary work. The oxindole core structure is present in a wide range of natural products, with varying substituents and functional groups at the 3-position. Therefore, to cover the full scope and limitations of the KR protocol, a range of 3-alkyl substituents was incorporated at the tertiary centre.

2.6.1 Alcohol and ester synthesis

Various methods were utilised to extend the scope of alkyl substituents at the 3-position of the oxindole. Addition of *tert*-butylmagnesium chloride and benzylmagnesium chloride to isatin **89** gave *tert*-butyl and benzyl substituted tertiary alcohols **139** and **141** in low yields (Table 10). Esterification was carried out under the previously established conditions of DMAP **4** and isobutyric anhydride, giving the desired esters in moderate to good yields. Esterification of sterically hindered **138** required a significantly longer reaction time of 72 h, and only provided the ester product in moderate yield (48%).

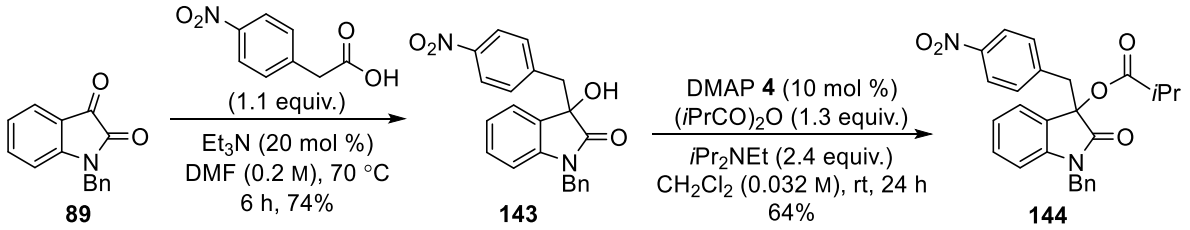
Table 10 – Grignard addition to *N*-protected isatin derivatives and esterification



Entry	R′	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	*t*Bu	**139**	18	**140**	48
2	Bn	**141**	25	**142**	74

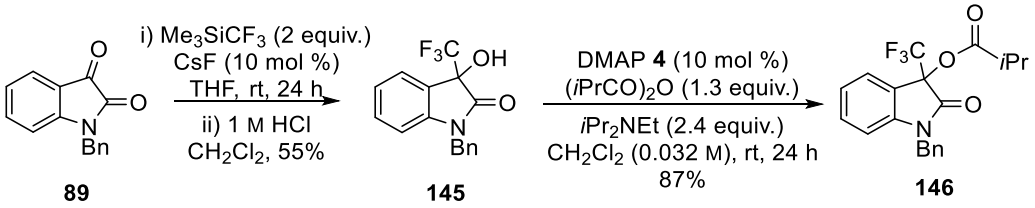
Following a method reported by Wang, 4-nitrophenylacetic acid and triethylamine (20 mol %) with *N*-benzyl isatin **89** gave the desired 4-nitrobenzyl substituted tertiary alcohol **143** in 74% yield. This reaction is proposed to occur following the decarboxylative [1,2]-addition, with a triethylamine

catalyst, however this process relies on electron-withdrawing substituents at the α-position of acetic acid derivatives, as shown in the literature.[97] The standard esterification conditions of isobutyric anhydride and DMAP **4** led to the isobutyrate ester **144** in good yield (Scheme 34).



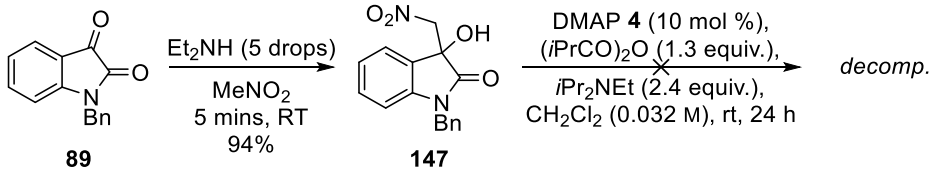
Scheme 34 – Decarboxylative [1,2]-addition of *p*-nitrophenylacetic acid to *N*-benzyl isatin **89**

N-Benzyl isatin **89** was treated with Ruppert-Prakash reagent (trimethyl(trifluoromethyl)silane), in the presence of cesium fluoride, to give the TMS ether of trifluoromethyl-substituted oxindole **145**, which was subsequently hydrolysed yielding the desired alcohol in 55% yield.[98] Esterification was carried out using the standard esterification conditions, giving the isobutyrate ester **146** in 87% yield (Scheme 35).



Scheme 35 – Trifluoromethylation of *N*-benzyl isatin **89**

A nitromethyl group was inserted into isatin **89** *via* a Henry reaction. Following the work by Ding *et al*,[99] **89** was dissolved in nitromethane and a few drops of diethylamine were added to the reaction mixture. After 5 mins, the reaction was complete and alcohol **147** was obtained in an excellent 94% yield. However, treatment of alcohol **147** under the esterification conditions led to immediate decomposition of the starting material into a complex mixture of products from which the ester could not be isolated (Scheme 36).



Scheme 36 – Nitromethane addition to *N*-benzyl isatin **89** and unsuccessful esterification

2.6.2 KR of alkyl variants

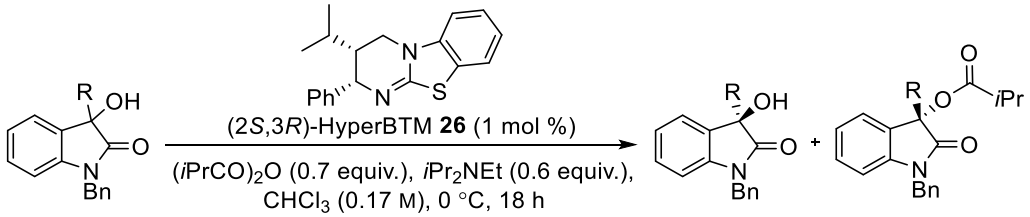
The KR of *tert*-butyl substituted alcohol **139** proceeded with very poor conversion (~1%), even after 48 h and a high catalyst loading (5 mol %). Enough ester was isolated to obtain an er by HPLC, with moderate selectivity observed. The lack of conversion can be attributed to the *tert*-butyl group

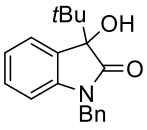
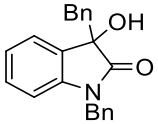
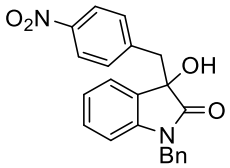
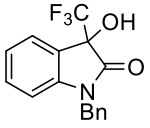
providing too much steric hindrance at the tertiary centre, with <5% conversion observed even at 90 °C (Table 11).

The KR of benzyl substituted alcohol **141** (entry 2) proceeded with good conversion, however the selectivity observed was quite low (*s* = 7). Such low selectivity is surprising when compared to the high selectivity obtained using allyl- and alkyl-substituted alcohols. The *p*-nitrobenzyl-substituted **143** (entry 3) proceeded with higher conversion and selectivity, compared to that of the parent benzyl (*s* = 21).

The KR of trifluoromethyl-substituted alcohol **145** proceeded with moderate selectivity (*s* = 10), with full consumption of anhydride, indicating an accelerated rate of reaction. In contrast, the KR of 3-methyl-substituted alcohol **85** was highly selective (*s* = 50) under the same conditions (Scheme 27), indicating the electron-withdrawing nature of the CF_3 has a negative effect on selectivity. To achieve a synthetically useful selectivity factor, alternative conditions were used; reaction temperature was reduced to –40 °C and fewer equivalents of anhydride (0.6 equiv.) used. These conditions still led to full consumption of anhydride however, though *s* = 32 was obtained.

Table 11 – Kinetic resolution of varied alkyl alcohols



Entry	1[a,b]	2[c]	3[c]	4[c,d]
Alcohol				
	139	**141**	**143**	**145**
Conv (%)	1	40	51	59
Alc er	50:50	71:29	91:9	>99:1
Alc Yield	59	49	45	27
Est er	91:9	83:17	90:10	85:15
Est Yield	1	35	45	45
s	10	7	21	32

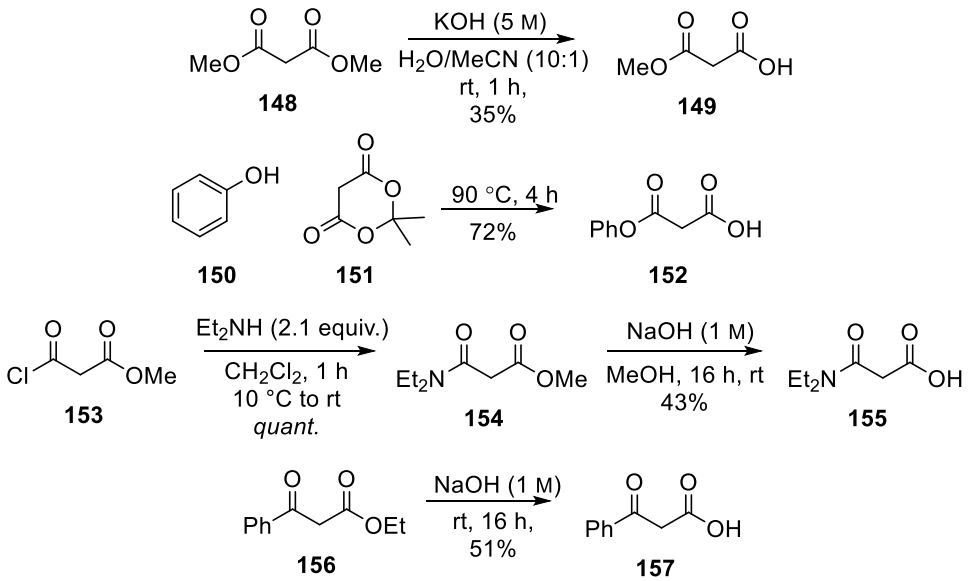
a) 48 h. b) 5 mol % (2*S*,3*R*)-HyperBTM **26**. c) 0.6 equiv. (*i*PrCO)$_2$O. d) –40 °C

2.7 α–Functionalised alkyl substituents

Returning to the triethylamine-catalyzed decarboxylative-[1,2]-addition reaction, a range of 3-hydroxyoxindoles was synthesized using a variety of malonic acid derivatives, with functional groups, such as esters, amides, ketones and nitriles targeted. The limitation of this procedure, as stated in the literature, is that only acids bearing electron-withdrawing substituents at the α-position are applicable in this process.

2.7.1 Alcohol and ester synthesis

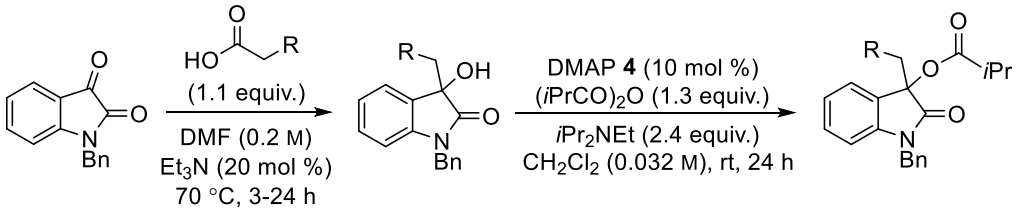
The desired α-functionalised malonic acid half esters and half amides were synthesized using cheap and available starting materials. Monomethyl malonate **149** was synthesised by partial hydrolysis of dimethyl malonate **148** with potassium hydroxide in 35% yield,[100] whilst addition of phenol **150** to Meldrum's acid **151** gave monophenyl malonate **152** in good yield.[101] Attempts to make half thioester and half amide derivatives by the same method, from Meldrum's acid and either thiophenol and aniline respectively, were not successful with full recovery of starting materials. However, methyl malonyl chloride **153** and diethylamine gave half-ester-half-amide **154**,[102] and following subsequent hydrolysis, gave malonic acid half amide **155** in moderate yield.[103] Hydrolysis of ethyl benzoylacetate **156** gave benzoyl acetic acid **157**[104] in 51% yield (Scheme 37).



Scheme 37 – Synthesis of α-functionalised carboxylic acids

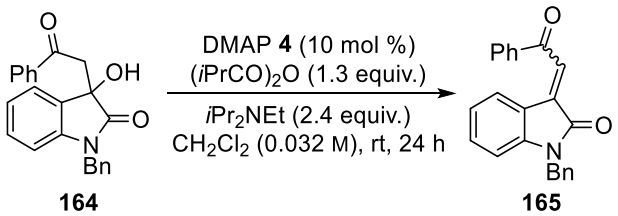
Using the newly synthesised acids, a range of 3-hydroxyoxindole derivatives, **158-162**, was synthesized in good yield (Table 12), with no reactivity observed for electron-rich or -neutral species, such as phenylacetic acid. Esterification was carried out using the standard conditions of DMAP **4** and isobutyric anhydride, with the esters obtained in moderate to excellent yield.

Table 12 – Decarboxylative addition to *N*-benzyl isatin and esterification



Entry	R'	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	CO_2Me	**158**	58	**159**	50
2	CO_2Ph	**160**	51	**161**	64
3	CO_2NEt_2	**162**	52	**163**	83
4	COPh	**164**	30	-	-

Treatment of alcohol **164** under the standard esterification conditions, led to the α,β-unsaturated product **165**, which was isolated in 87% yield. The formation of this undesired product was presumably due to α-deprotonation of the ketone, leading to elimination of the carboxylate, with none of the desired ester observed (Scheme 38).

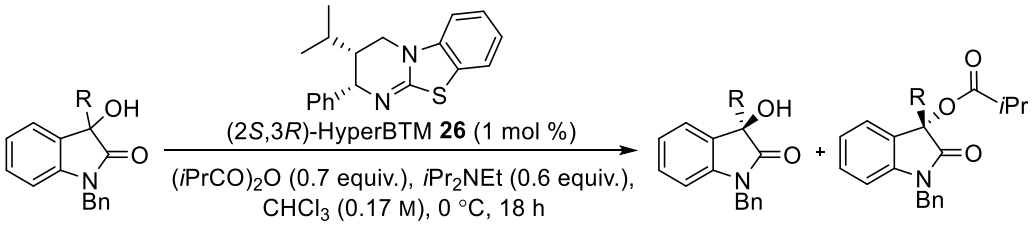


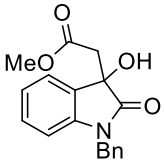
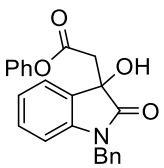
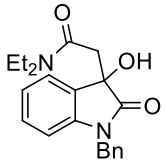
Scheme 38 – Formation of elimination product **165** upon acylation of alcohol **164**

2.7.2 KR of α-functionalized alkyl substituents

Methoxy ester bearing alcohol **158** (entry 1) required a longer reaction time at 25 h to achieve good reaction conversion, however good selectivity was observed (*s* = 19). In contrast, the KR of phenoxy ester containing alcohol **160** (entry 2) proceeded with higher conversion, thus fewer equivalents of anhydride were required for the KR, leading to the same selectivity observed (*s* = 19). The KR of amide-substituted alcohol **162** (entry 3) proceeded with only 19% conversion, therefore a higher catalyst loading (5 mol %) was required. However, a good level of selectivity was observed (*s* = 26), comparable to that of the two ester substituted substrates.

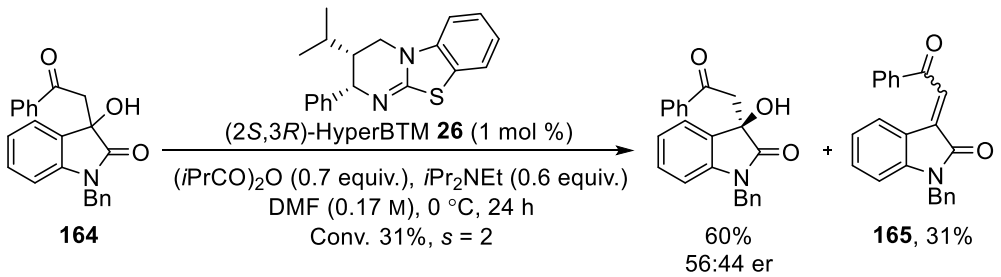
Table 13 – Kinetic resolution of α-functionalized methyl substituted alcohols



Entry		1[a]	2[b]	3[c]
Alcohol				
		158	**160**	**162**
Conv (%)		59	54	45
Alc	**er**	98:2	93:7	85:15
	Yield	31	24	48
Est	**er**	83:17	87:13	93:7
	Yield	44	38	45
s		19	19	26

a) 25 h. b) 0.6 equiv. (iPrCO)$_2$O. c) 5 mol % (2*S*,3*R*)-HyperBTM **26**.

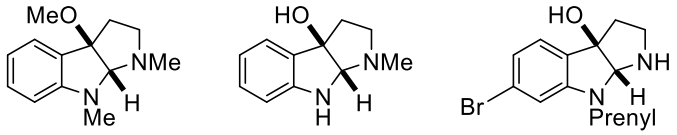
The same phenomenon in the KR of alcohol **164** was observed as with the acylation using DMAP **4**, with the undesired α,β-unsaturated product **165** obtained upon acylation. Attempted stereoablative KR using (2*S*,3*R*)-HyperBTM **26** proceeded with 31% conversion of the starting alcohol, though a longer reaction time (24 h) and DMF as solvent was required, due to alcohol insolubility issues in $CHCl_3$. However, alcohol **164** was recovered with only low enantioenrichment indicating an *s* of only 2 (Scheme 39).



Scheme 39 – Stereoablative KR of **164**

2.7.3 Synthesis of cyanomethyl substituted 3-hydroxyoxindoles

A range of cyanomethyl substituted alcohols was synthesized, using cyanoacetic acid in the same decarboxylative-[1,2]-addition method shown above. These alcohols are of high interest as the cyanomethyl group is a handle that can be used in the synthesis of natural products and bioactive compounds, such as CPC-1, Alline and Flustraminol B (Figure 23).

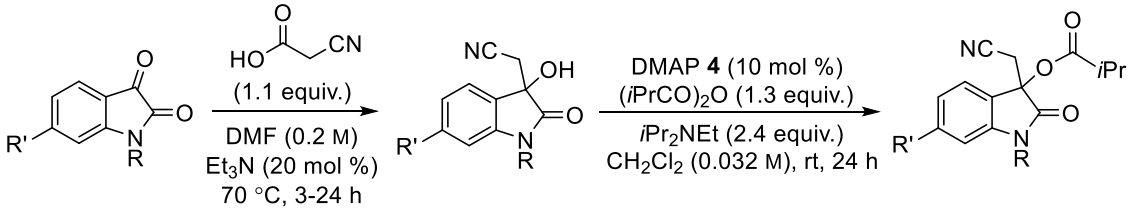


CPC-1 **Alline** **Flustraminol B**

Figure 23 – Potential natural products from cyanomethyl derivatives

A range of these cyanomethyl-substituted alcohols was synthesized in low to excellent yields. Various *N*-substituents were investigated with this cyanomethyl handle, due to natural products and bioactive compounds containing differing *N*-substituents. As a *N*-Boc group has already been shown to been easily cleaved, this was also incorporated into the scope, with Alline (Figure 3) containing a free NH group. Esterification was carried out using the standard conditions, with the esters obtained in moderate to excellent yield (Table 14).

Table 14 – Decarboxylative addition to *N*-substituted isatin derivatives and esterification

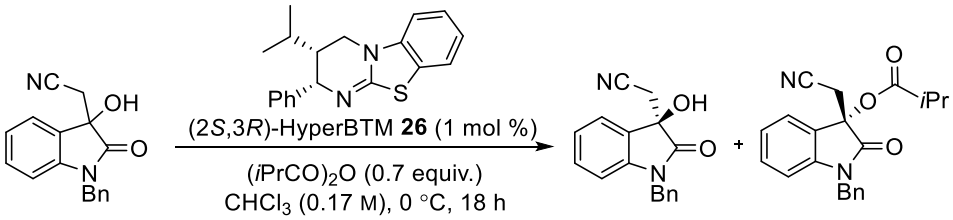


Entry	R'	N-R	Alcohol		Ester	
			No.	Yield (%)	No.	Yield (%)
1	H	Bn	**166**	73	**167**	72
2	H	Me	**168**	52	**169**	81
3	H	Allyl	**170**	76	**171**	70
4	Br	Prenyl	**172**	90	**173**	90
5	H	Boc	**174**	23	**175**	62

2.7.4 KR of cyanomethyl substituted 3-hydroxyoxindoles

Under standard conditions (entry 1), the KR of alcohol **166** (a precursor to Alline) proceeded with good conversion and moderate selectivity. Removal of base from the reaction medium (entry 2) gave a slight increase in selectivity, indicating a potential base-mediated background reaction. Birman has previously reported the use of acid in the BTM-mediated DKR of azlactones, in which the acid acts as a promoter in the reaction.[105] A further jump in selectivity was observed with the addition of isobutyric acid (0.5 equiv.). Excluding the catalyst from the reaction to test for a base-mediated background reactivity showed 25% conversion of starting material (entry 4). No reactivity was observed with the removal of base and catalyst (entry 5) or with just the addition of acid (entry 6). For other cyanomethyl derivatives, the conditions in entry 3 were used.

Table 15 – Kinetic resolution of *N*-benzyl alcohol **166** using various conditions

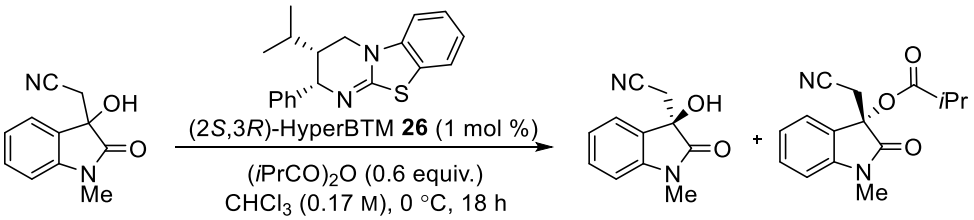


Entry	Additive (equiv.)	Conv (%)	alc er (%)	est er (%)	*s*
1	*i*Pr$_2$NEt (0.6)	55	93:7	84:16	14
2	-	55	93:7	86:14	17
3	*i*PrCO$_2$H (0.5)	55	96:4	87:13	21
4[a]	*i*Pr$_2$NEt (0.6)	25	-	-	-
5[a]	-	-	-	-	-
6[a]	*i*PrCO$_2$H (0.5)	-	-	-	-

a) no (2*S*,3*R*)-HyperBTM **26**

The KR of cyanomethyl derivatives bearing different *N*-substituents was then investigated. The KR of *N*-methyl derivative **168** (a precursor to CPC-1) gave good selectivity (*s* = 22) under the standard conditions, though conversion was high (64%) (entry 1). Removal of base and reduction in equivalents of anhydride resulted in a slight increase in selectivity (*s* = 24), and inclusion of isobutyric acid (0.5 equiv.) gave another boost in selectivity (*s* = 30) (Table 16).

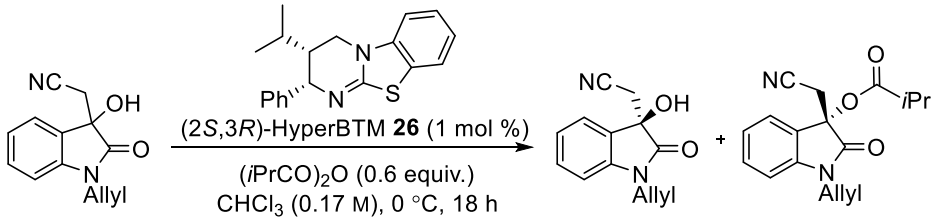
Table 16 – Kinetic resolution of *N*-methyl alcohol **168** using various conditions



Entry	Additive (equiv.)	Conv (%)	alc er (%)	est er (%)	*s*
1	*i*Pr$_2$NEt (0.6)	64	>99:1	78:22	22
2	-	58	99:1	85:15	24
3	*i*PrCO$_2$H (0.5)	59	>99:1	84:16	30

The KR of *N*-allyl example **170** proceeded with reduced selectivity relative to the *N*-methyl derivatives, with all 3 conditions producing very similar selectivity, though addition of acid had a slight positive influence (entry 3) (*s* = 15) (Table 17).

Table 17 – Kinetic resolution of *N*-allyl alcohol **170** using various conditions

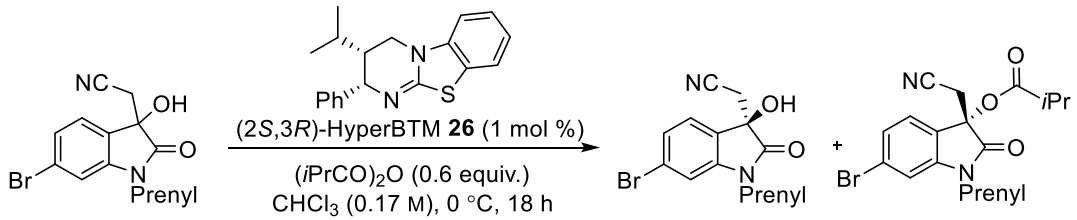


170 **(*R*)-170** **(*S*)-171**

Entry	Additive (equiv.)	Conv (%)	alc er (%)	est er (%)	*s*
1	*i*Pr$_2$NEt (0.6)	59	96:2	82:18	14
2	-	64	99:1	77:23	14
3	*i*PrCO$_2$H (0.5)	63	99:1	72:28	15

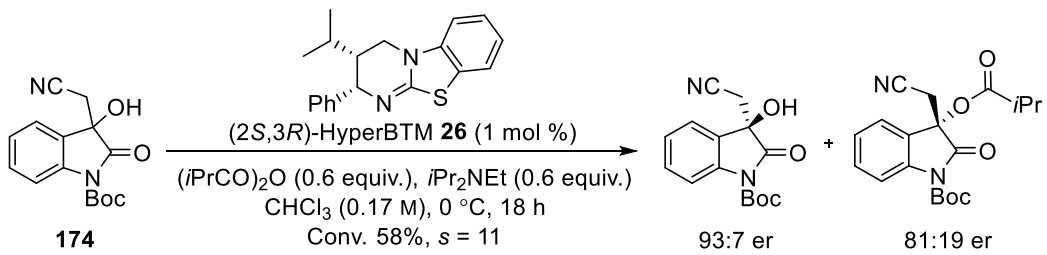
The KR of 5-Br-*N*-isoprenyl alcohol **172** (a precursor to Flustraminol B) proceeded with good selectivity in the presence of base (*s* = 23). A slight increase in selectivity was observed for the KR of alcohol **172** in the absence of base (*s* = 27), yet inclusion of isobutyric acid again resulted in significantly improved selectivity (*s* = 47) (Table 18).

Table 18 – Kinetic resolution of *N*-prenyl alcohol **172** using various conditions



Entry	Additive (equiv.)	Conv (%)	alc er (%)	est er (%)	*s*
1	*i*Pr$_2$NEt (0.6)	57	98:2	86:14	23
2	-	56	98:2	88:12	27
3	*i*PrCO$_2$H (0.5)	55	>99:1	90:10	47

As the Boc group was previously used in the KR of allyl-substituted *N*-Boc alcohol **136** with high selectivity (*s* = 108) (Table 8, entry 3), the same conditions were used for the KR of cyanomethyl-*N*-Boc alcohol **174**. Unfortunately, the KR of **174** proceeded with low selectivity (*s* = 11), and was not investigated further in the presence of acid, due to this low selectivity (Scheme 40).

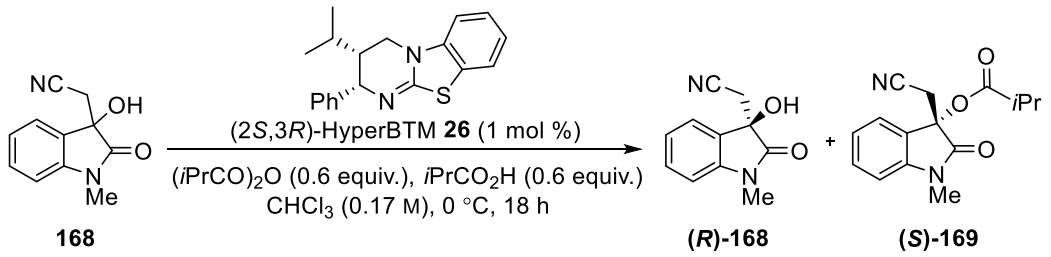


174 93:7 er 81:19 er

Scheme 40 – The KR of cyanomethyl *N*-Boc alcohol **174**

2.7.5 Measurements over time

To obtain more information about the KR of **168**, the er of both alcohol and ester, as well as conversion were monitored over time, by removing small aliquots from the reaction every 90 minutes. From Figure 24, the er of the ester starts high (95:5) as the (*S*)-enantiomer is acylated at a faster rate than its enantiomer. This leads to a rapid initial reaction rate over the first 1.5 hours (23% conversion), due to a high relative concentration of the (*S*)-enantiomer. However, as this relative concentration decreases over time, a significant reduction in rate of alcohol acylation is observed over the following 12 hours. The er of the ester will therefore decrease over time as the opposite (*R*)-enantiomer is acylated, due to the mass action effect with its higher relative concentration in the reaction medium. However, the er of the alcohol steadily increases over time as the (*S*)-enantiomer is acylated, with the slower reacting (*R*)-enantiomer remaining unreacted, leading to a steady increase in enantiopurity of the alcohol. Apart from an anomalous result at 12 hours, the selectivity factor is shown to hold quite steady over the course of the reaction (*s* = 30–32), though it appears to slightly lower near the start of the reaction, before quickly settling into a steady range. However, this may result from lower precision of measuring the er for small quantities of the ester product formed at the start of the reaction after low conversion.



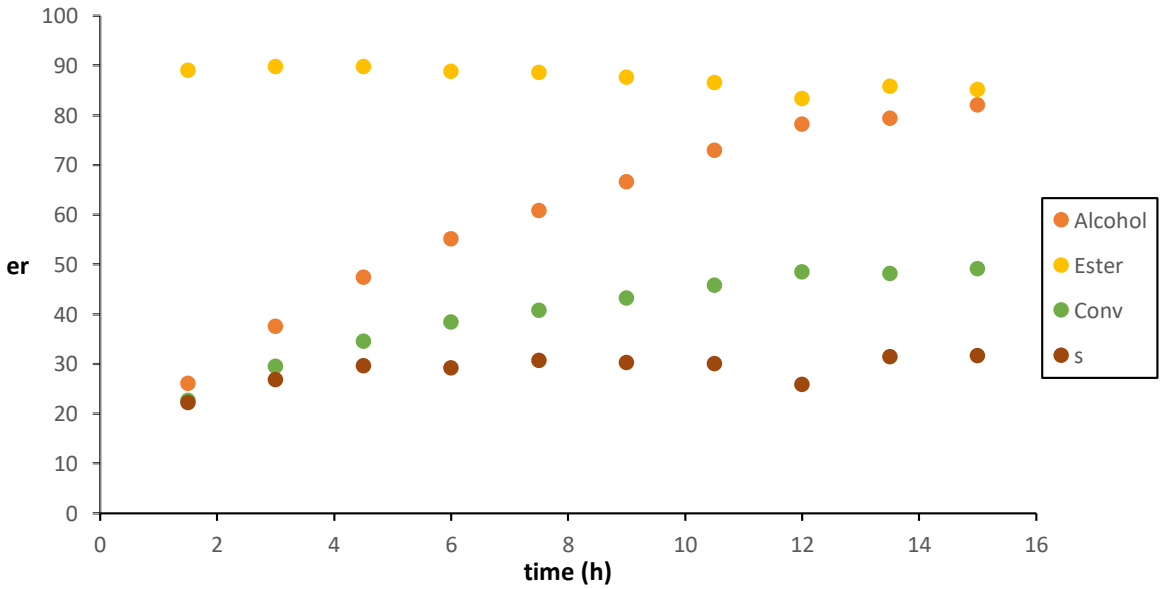


Figure 24 – KR of **168** monitored over time by HPLC

Plotting a linear regression of these results shows a strong correlation (R^2 = 0.94), with the gradient of the graph giving the selectivity factor (s = 29). Removal of the anomalous result at 12 h gives a stronger correlation (R^2 = 0.98), but has little effect on gradient, resulting in a selectivity factor of 30 (Figure 25).

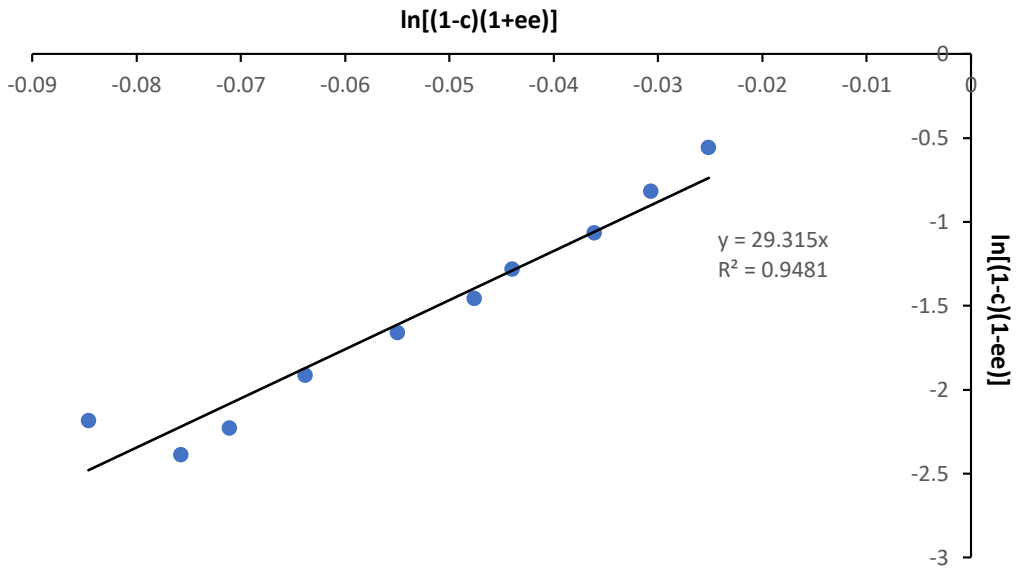


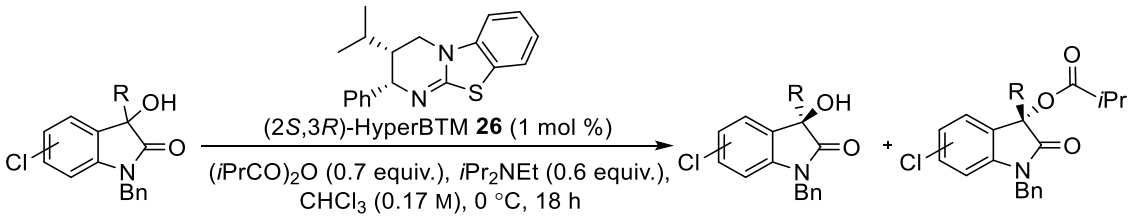
Figure 25 – Linear regression graph of KR

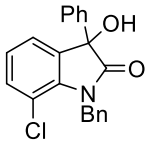
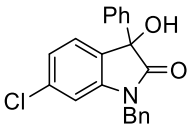
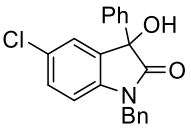
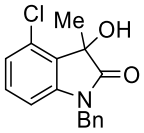
2.8 Benzenoid substitution

Further studies on the project, with regards to substitution around the benzenoid ring, were conducted in the Smith group by Dr. Mark Greenhalgh,[87] with substitution of the benzenoid ring bearing a chloro-substituent around each position of the ring was probed (Table 19). The KR of alcohol **176**, bearing a 7-chloro substituent resulted in excellent selectivity (entry 1; *s* = 140). The KR of alcohol **177**, with a 6-chloro substituent led to a lower selectivity factor (entry 2; *s* = 70), with a further reduction in selectivity seen in the KR of alcohol **178** with a 5-chloro substituent (entry 3; *s* = 44). Substitution at the 5- and 6-positions with a chloro substituent has a negative effect on selectivity when compared to the unsubstituted *N*-benzyl 3-phenyl substituted alcohol **88** (Scheme 27; *s* = 130), however, a comparable selectivity was observed for alcohol **176**, bearing the 7-chloro substituent, indicating that substitution at this position may have an overall neutral effect on selectivity. However, a 3-methyl group was required for reactivity with the 4-chloro substituent, as in contrast, no acylation was observed when a 3-phenyl substituent was incorporated in proximity to the 4-chloro substituent. The KR of 4-chloro substituted alcohol **179**, resulted in high selectivity (entry 1; *s* = 80), though a higher catalyst loading (10 mol %) and much longer reaction time of 118 h were required, but a higher selectivity was seen in comparison to the unsubstituted *N*-benzyl 3-methyl substituted alcohol **85**

(Scheme 27; *s* = 50). The increased reaction time is likely due to the increased steric effect of the 4-chloro substituent in close proximity to the tertiary alcohol centre.

Table 19 – Kinetic resolution of tertiary alcohols with benzenoid substitution



Entry		1	2[a]	3[b]	4[c]
Alcohol					
		176	**177**	**178**	**179**
Conv (%)		51	49	49	48
Alc	**er**	>90:1	93:7	93:7	93:7
	Yield	46	47	51	51
Est	**er**	97:3	96:4	94:6	97:3
	Yield	42	44	45	45
s		140	70	44	80

a) solvent: DMF. b) 2 mol % (2*S*,3*R*)-HyperBTM **26**, (0.1 M), 24 h. c) 10 mol % (2*S*,3*R*)-HyperBTM **26**, 1.5 equiv. $(i\text{PrCO})_2\text{O}$, (0.04 M), 118 h.

2.9 Structural modifications

After focusing on the KR of 3-hydroxyoxindole substrates, derivatives of the oxindole core structure were investigated to further probe the wider scope and limitations of the KR protocol, and to provide possible insight into both the structural features necessary for, and the origin of, efficient enantiodiscrimination (Figure 26). Replacement of the amide carbonyl oxygen with a sulfur to give the thioamide, as well as replacement of the amide with a thioester and ester to give the 3-hydroxybenzothiophenone and 3-hydroxybenzofuranone substrates, were synthesized. Removal of the carbonyl completely, whilst maintaining sp^2 hybridization adjacent to the carbinol centre, led to the synthesis of the corresponding indenol.

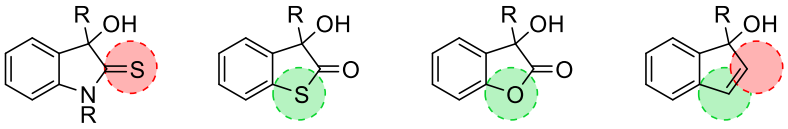
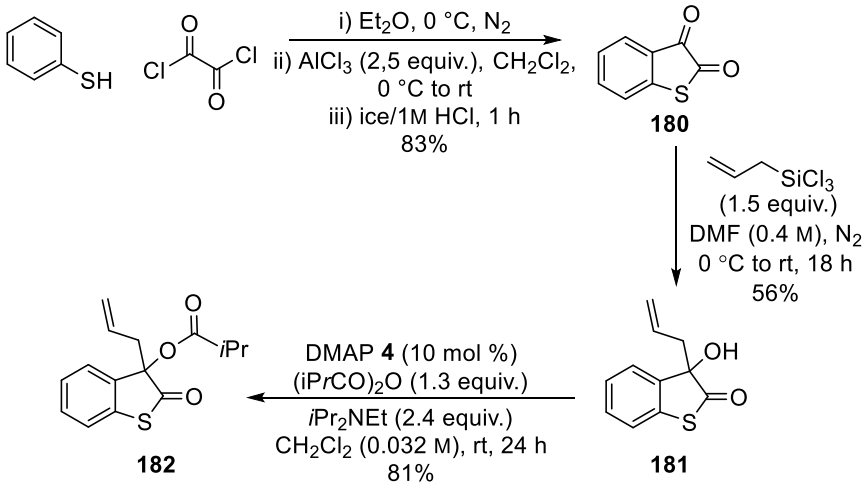


Figure 26 – Structural modifications of 3-hydroxyoxindole

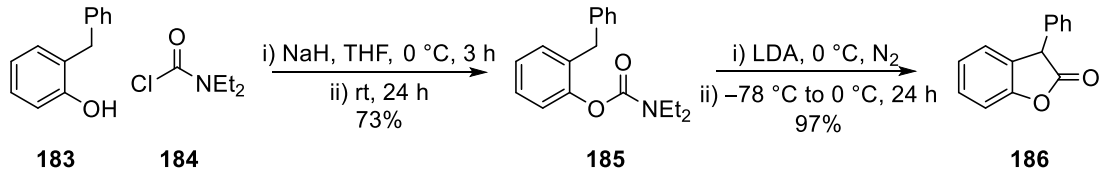
2.9.1 Alcohol and ester synthesis

To incorporate a thioester in place of an amide, benzothiophene-2,3-dione **180** was first synthesized following a procedure by Matsubara, using thiophenol and oxalyl chloride in the presence of $AlCl_3$, to give the desired dione **180** in 83% yield.[106] Organometallic additions to this dione were unsuccessful, so the organosilicon reagent, allyltrichlorosilane was used. Tertiary alcohol **181** was obtained in 56% yield. The corresponding isobutyrate ester **182** was obtained in 81% yield, in the same manner previously stated (Scheme 41).



Scheme 41 – Synthesis of benzothiophene-2,3-dione **180**, subsequent alcohol **181** and ester **182**

The synthesis of benzofuran-2,3-dione was unsuccessful under the same conditions; therefore, other methods were investigated. Following a method by Snieckus,[107] 2-benzyl phenol **183** was reacted with diethycarbamyl chloride **184** to give carbamate **185** in good yield. This was then treated with LDA to give 3-phenylbenzofuran-2-one **186** in excellent yield (Scheme 42). A variety of oxidation conditions were attempted to oxidize the 3-position to give the tertiary alcohol; i) LDA or NaH and atmospheric O_2, ii) formation of the silyl enol ether, followed by addition of an oxaziridine or iii) $P(OEt)_3$, Cs_2CO_3 and atmospheric O_2. Unfortunately, all of the above returned >90% of starting material, so an alternative synthetic route was explored.

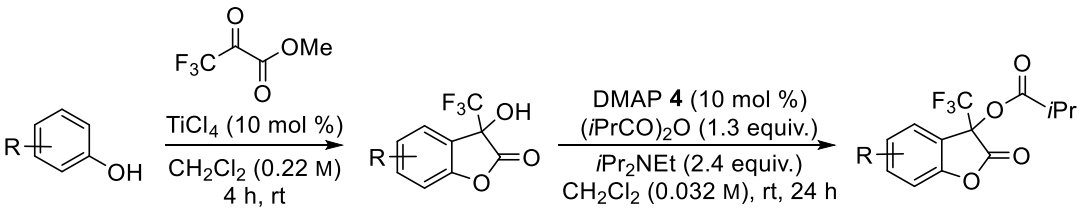


Scheme 42 – Synthesis of benzofuranone **186**

Following a method by Gasperi,[108] the reaction of phenol and pyruvate derivatives, in the presence of $TiCl_4$, led to a small set of 3-hydroxybenzofuran-2-one substrates. The reaction of 2,4-di-*tert*-butylphenol, 4-cresol and 2-naphthol with methyl trifluoromethylpyruvate gave the corresponding

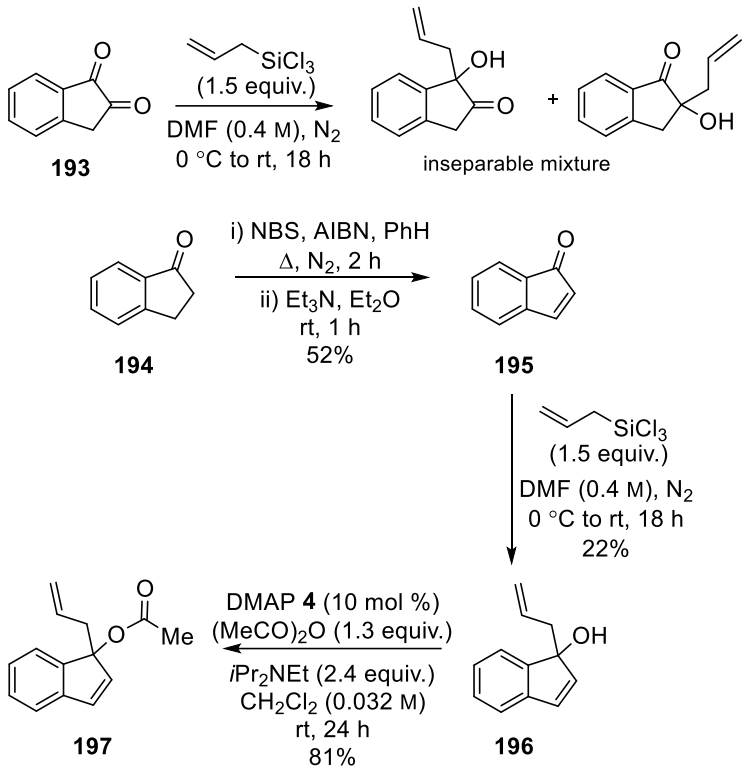
alcohols **187**, **189** and **191** in good yields. Their corresponding isobutyrate esters **188**, **190** and **192** were obtained under the same esterification conditions in high yields (Table 20). Attempts to incorporate other substituents at the 3-position, such as phenyl, methyl or ethyl, proved unsuccessful under these conditions, therefore only examples bearing CF_3 were investigated.

Table 20 – Synthesis of 3-hydroxybenzofuranones and esters



Entry	R	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	5,7-di-*t*Butyl	**187**	76	**188**	73
2	5-Methyl	**189**	62	**190**	72
3	2-Naphthyl	**191**	68	**192**	83

Attention then turned to tertiary alcohol substrates containing a ketone group, rather than amide or ester containing compounds, through an indanone core ring structure, whilst maintaining sp^2 hybridization adjacent to the carbinol centre. Attempts at synthesizing 1-allyl-1-hydroxyinden-2-one, using 1,2-indanone **193** and allyltrichlorosilane, led to an inseparable mixture of substitution products at both the 1- and 2-carbonyls. Attention then turned to the removal of the carbonyl altogether. 1-Indanone **194** was treated with AIBN and NBS to give 3-bromoindan-1-one, which upon treatment with Et_3N, gave inden-1-one **195** in an overall 52% yield. This was reacted with allyltrichlorosilane to give tertiary alcohol **196** in 22% yield. Acylation was not observed using isobutyric anhydride, however the acetate ester **197** was obtained in an 81% yield (Scheme 43).



Scheme 43 – Synthesis of 3-hydroxyinden-1-ol **196** and acetate ester **197**

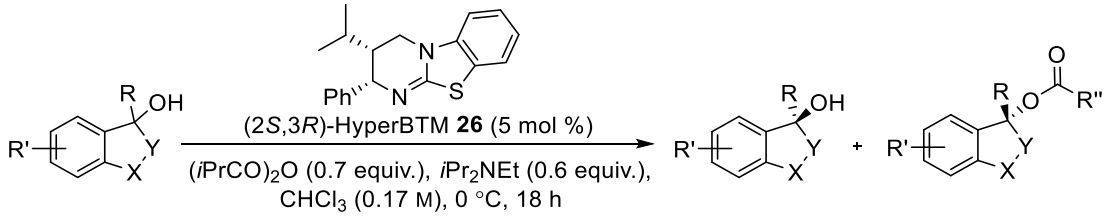
2.9.2 KR of structural derivatives

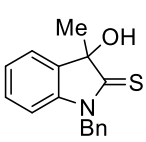
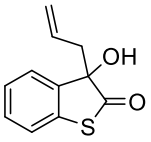
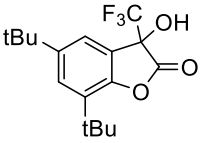
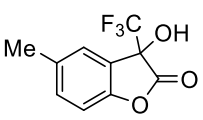
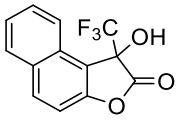
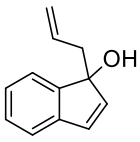
Indoline-2-thione derivative **198**,[87] with the carbonyl oxygen replaced by a sulfur, was resolved with excellent selectivity (*s* = 39), though a slight reduction in selectivity is noted in comparison to the parent C=O oxindole **85** (*s* = 50).[83] Compared to the oxindole derivative **87** (*s* = 110), the benzothiophene derivative **181**, in which the lactam nitrogen is replaced with sulfur, proceeded with good, albeit lower selectivity (entry 2; *s* = 41). In comparison, the benzofuranone series **187**, **189** and **191** required different conditions, with low selectivity (*s* = <3) and higher conversion (>65%) observed. Therefore, a reduction in reaction time (2.5 h) and temperature (–78 or –94 °C) was required. As much lower temperatures were required, a change in solvent to CH_2Cl_2 was necessary, due to $CHCl_3$ freezing at such low temperatures, with –94 °C the lowest temperature used, due to the freezing point of CH_2Cl_2.

Under the standard conditions used for the oxindole series, the KR of alcohol **187** proceeded with 51% conversion and gave a selectivity factor of 4. This poor selectivity is not too dissimilar to the selectivity obtained under the same conditions for the CF_3-substituted oxindole tertiary alcohol **144** (*s* = 10). Repeating the KR of alcohol **144** under a reduced temperature led to a significantly higher selectivity (*s* = 32), therefore a reduced temperature was explored for the benzofuranone series. However, compared to the oxindole series, poor selectivity factors were still observed for each alcohol with the benzofuranone core structure at this lower temperature; **187** (entry 3; *s* = 9), **189** (entry 4; *s* = 3) and

191 (entry 5; *s* = 4). The KR of inden-1-ol **196** using acetic anhydride as acylating agent revealed a drastic reduction in selectivity (entry 6; *s* = 5) relative to the oxindole series, suggesting the carbonyl is an important structural motif required to obtain high selectivities. During optimization studies on 3-allyl substituted oxindole **87**, acetic anhydride (0.55 equiv.) was tested in the presence of (2*S*,3*R*)-HyperBTM **26** (1 mol %) resulting in 53% conversion and *s* = 9. Therefore, there is not a very significant difference in selectivity when compared to the KR of inden-1-ol **196**, though higher catalyst and anhydride loadings were required to observe a good conversion. This would suggest that whilst the carbonyl is essential for activity, it is also beneficial for selectivity. The absolute stereochemistry of the recovered alcohol and ester products throughout this chapter have so far been based on the X-ray crystallographic analysis of the recovered (*S*)-**88** (see Section 2.1). This is also on the assumption that every substrate proceeds in the same manner, with the lowest energy TS for the fast-reacting enantiomer being stabilized by a C=O•••isothiouronium interaction between alcohol and acylated catalyst. However, the lack of carbonyl in alcohol **196**, raises the question about which enantiomer of alcohol is faster reacting, with further investigations required to fully determine the absolute configuration of recovered alcohol and ester.

Table 21 – KR of structurally modified compounds



Entry		1	2[a]	3[b,c]	4[b,d]	5[b,d]	6[e]
Alcohol							
		198[87]	**181**	**187**	**189**	**191**	**196**
Conv (%)		41	53	54	58	56	65
Alc	er	81:19	98:2	87:13	73:27	77:23	87:13
	Yield	50	33	29	31	29	30
Est	er	95:5	92:8	-	-	-	76:24
	Yield	30	41	45	49	45	39
s		39	41	9	3	4	5

a) 1 mol % (2*S*,3*R*)-HyperBTM **26**. b) (*i*PrCO$_2$)O (0.6 equiv.), *i*Pr$_2$NEt (1.0 equiv.), 2.5 h, CH_2Cl_2 [0.2 M]. c) –94 °C. d) –78 °C. e) (MeCO$_2$)O, 24 h

2.10 Computational analysis

Computations (carried out by Prof. Paul Ha-Yeon Cheong and Daniel Walden)[109] were conducted to propose intermediates and transition state (TS) structures present during the KR of *N*-benzyl-3-methyl-3-hydroxyindolin-2-one **85** under standard conditions.

Computations were conducted for the catalytic cycle of both enantiomers of alcohol **85**. Upon initial formation of the acylated catalyst, ternary complex **II** is formed, with coordination of the alcohol to the acylated catalyst. In ternary complex **II**, the isobutyrate counter-ion is hydrogen-bonded to the alcohol hydroxyl, as well as simultaneously providing a non-classical H-bond to the catalyst C(2)H. The lowest energy ternary complex for the faster reacting enantiomer **(*S*)-II,** shows a C=O•••isothiouronium interaction as the lowest energy recognition motif (ΔG = 2.6 kcal mol^{-1}), whereas a π•••isothiouronium interaction is identified as the key recognition motif in the lowest energy ternary complex for the slower reacting enantiomer **(*R*)-II,** (ΔG = 4.0 kcal mol^{-1}). These ternary complexes, **(*S*)-II** and **(*R*)-II**, are lower in energy than both the ion-pair of the isothiouronium and carboxylate (ΔG = 13.6 kcal mol^{-1}) and these as individually separated components (ΔG = 22.4 kcal mol^{-1}). This suggests that the interactions of the alcohol and isobutyrate in ternary complex **II** have a profound stabilizing effect, eclipsing the entropic effect of ordering the system. Acylation of the alcohol occurs *via* **TS-III**, and the energy difference between **TS-(*S*)-III** and **TS-(*R*)-III** (ΔΔG = 2.0 kcal mol^{-1}) equating to a selectivity factor of 50, which is in good agreement with the experimental selectivity of *s* = 50. After acylation **TS-III**, the product is released and regeneration of the catalyst is essentially barrierless, with computational studies not identifying a tetrahedral intermediate upon release, which is consistent with other computations conducted on DMAP-catalyzed acylation[23] (Figure 27).

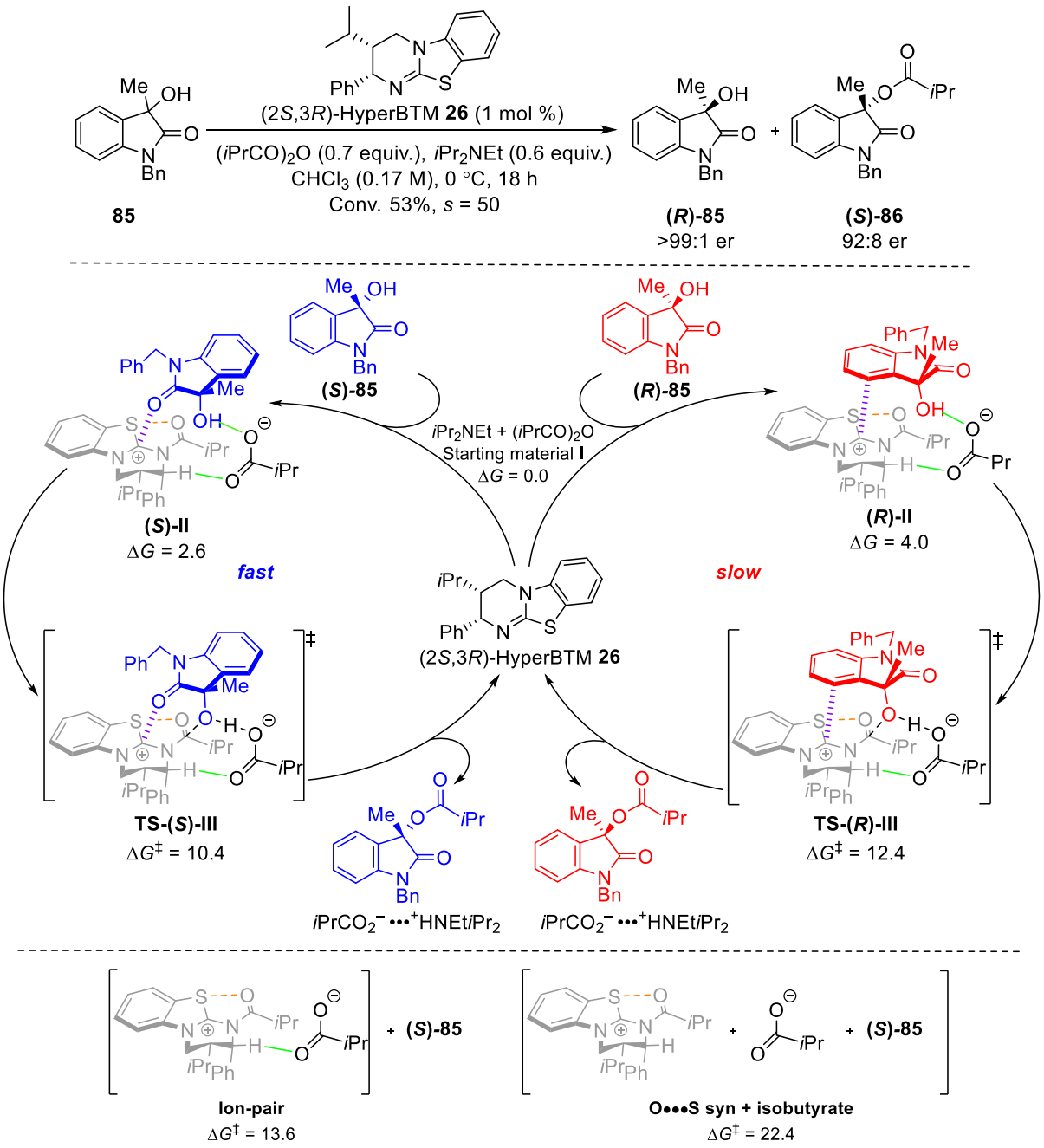
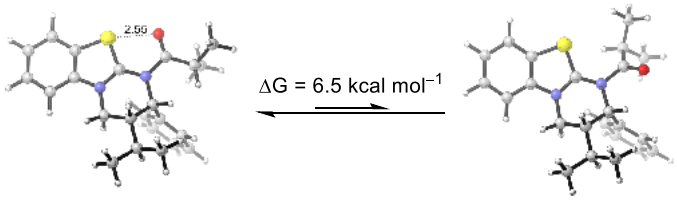


Figure 27 – Computed catalytic cycle for the acylation of alcohol **85**

There are three main interactions that are responsible for the enantiodiscrimination observed. A 1,5-*O•••S* interaction is calculated between the acyl *O* and the isothiouronium *S*, locking the acyl isothiouronium conformation. This *syn* conformation was computed to be 6.5 kcal mol^{-1} lower in energy than the corresponding *anti* conformation (Figure 28). Due to the rigidity of this locked conformation, the stereodirecting phenyl group is held in a pseudo-axial position, blocking the *Re* face and exposing the *Si* face as the single prochiral face of the acyl group.



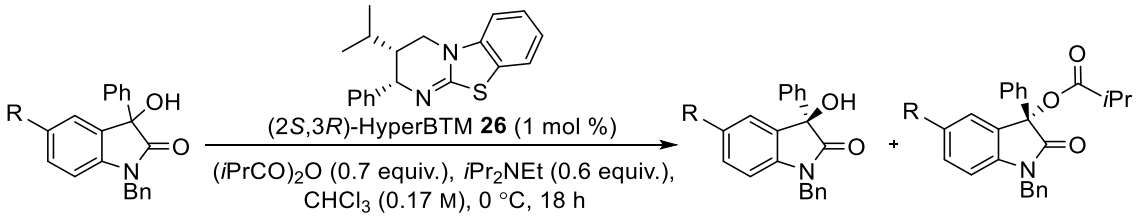
O•••S-syn ***O•••S-anti***

Figure 28 – *O•••S-syn* and *anti* geometries observed in acylated HyperBTM

Computational studies conducted identified a C=O•••isothiouronium interaction as the key recognition motif in the lowest energy transition state. It was also experimentally found that the carbonyl is important for selectivity and reactivity, with the KR of the tertiary alcohol indenol derivative **196** requiring a higher catalyst loading, with poor selectivity obtained (Table 21, entry 6; *s* = 5). Alterations to the Lewis basicity of this amide oxygen were then investigated to observe how this would affect the acylation of the TSs, with the expectation that inclusion of electron-withdrawing substituents would have a negative effect on the selectivity, due to a less favourable C=O•••isothiouronium interaction.

Further studies were conducted in the smith group by Dr. Mark Greenhalgh on a variety of 3-phenyl-3-hydroxyoxindole derivatives, bearing electronically varied substituents at the 5-position of the oxindole core.[87] The C=O stretching frequency was used as a measure of Lewis basicity of the amide oxygen. The trend observed shows that the KR of substrates bearing an electron-donating substituent such as, dimethylamino-, methoxy- and methyl-substituents of alcohols **199**, **200** and **201** gave the highest selectivities (*s* = 90–140). In comparison, the KR of electron-withdrawing chloro-, bromo- and nitro-substituted **178**, **202** and **203** in the 5-position gave a significant reduction in the selectivity factor (*s* = 11–44). A consistent trend is observed between selectivity and the donating ability of the amide for a C=O•••isothiouronium interaction, and this is consistent with the more Lewis basic amides being able to better stabilize the TS for the faster reacting enantiomer relative to the slow reacting enantiomer (Table 22).

Table 22 – Kinetic resolution of tertiary alcohols with a range of groups at the 5-position



Entry		1	2[a]	3	4	5[b]	6
R		NMe_2	OMe	Me	Cl	Br	NO_2
		199	**200**	**201**	**178**	**202**	**203**
$\nu_{C=O}$ (cm^{-1})		1697	1697	1699	1705	1709	1717
Conv (%)		47	45	47	49	49	62
Alc	er	92:8	89:11	91:9	93:7	91:9	95:54
	Yield	42	53	49	51	50	37
Est	er	98:2	98:2	97:3	94:6	93:7	78:22
	Yield	42	43	41	45	40	54
s		140	100	90	44	31	11

a) 5 mol % (2*S*,3*R*)-HyperBTM **26**. b) 2 mol % (2*S*,3*R*)-HyperBTM **26**.

A graph of the C=O stretching frequency against the natural logarithm of the selectivity factor was plotted, showing good correlation in the trend between these two factors (R^2 = 0.99) (Figure 29).

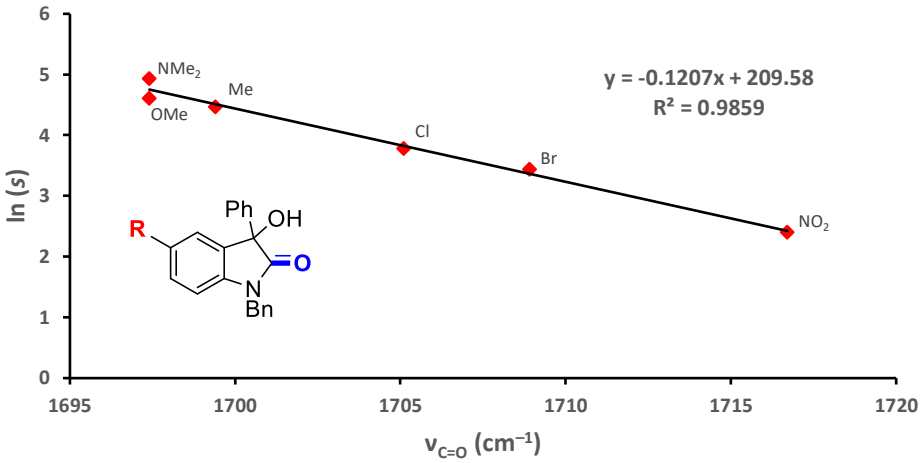


Figure 29 – Natural logarithm of *s* as a function of amide C=O stretching frequency

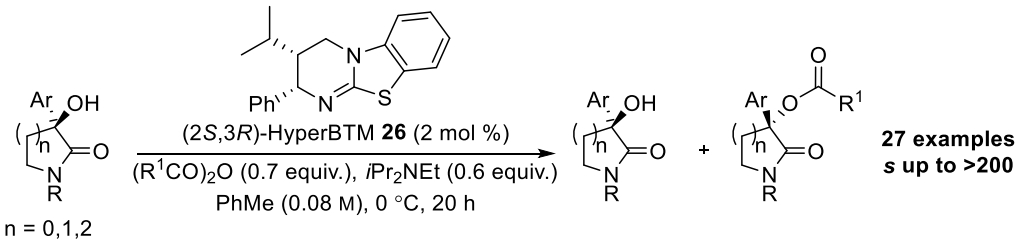
2.11 Conclusions

It has been shown that under mild reaction conditions, the acylative organocatalytic KR of 3-hydroxyoxindoles using HyperBTM and an anhydride can lead to excellent selectivity factors (*s* up to >200). This work provides only the third example of acylative organocatalytic KR of tertiary alcohols, and compared to the work conducted by Zhao, the reaction conditions implemented are significantly simplified. In comparison to this work, a significantly wider range of 3-substituted-3-hydroxyindolin-2-one substrates was investigated, with a variety of substitution patterns at the tertiary centre, as well

as around the benzenoid ring of the core structure. A range of *N*-substituents was tolerated, and that removal of the *N*-substituent can be performed. This was extended to show that modifying the structure of the oxindole core is tolerated; replacing the *N* with either an *O* or *S* gives varying selectivities, changing the C=O to a C=S still gives good selectivity, whereas removal of the carbonyl completely shuts off any selectivity. Computational studies identified a C=O•••isothiouronium interaction between the fact reacting enantiomer of the alcohol and acylated catalyst as the major stabilizing effect that dictates enantiodiscrimination. Substitution at the 5-position of the benzenoid ring with electron-donating groups had a positive effect on the selectivity factor, whereas electron-withdrawing groups had a negative effect on the selectivity factor. This trend was attributed to the donor ability of the amide carbonyl, affecting the magnitude of the stabilizing effect of the C=O•••isothiouronium interaction and thus the selectivity factor observed in the KR. Overall, the KR of tertiary alcohols still remains a significant challenge, with only very specialized substrate classes reported thus far. Therefore, using the knowledge gained from experimental and computational work, further studies will apply our method to other classes of tertiary alcohols to expand the synthetic utility of this work.

CHAPTER 3: KINETIC RESOLUTION OF 3-HYDROXYPYRROLIDINONES

This chapter describes the acylative kinetic resolution of tertiary alcohols based on a 3-aryl-3-hydroxypyrrolidin-2-one core structure, using [(2*S*,3*R*)-HyperBTM] and an anhydride to afford the recovered alcohol and corresponding ester in good to excellent levels of selectivity (*s* up to >200) (Scheme 44).



Scheme 44 – Kinetic resolution of 3-aryl-3-hydroxypyrrolidin-2-ones

3.1 Initial studies with 3-hydroxypyrrolidinones

Computational studies conducted on the KR of 3-hydroxyoxindoles identified the key stabilizing interaction in the lowest energy acylation TS between catalyst and substrate, for the faster reacting enantiomer, to be an amide carbonyl n_O•••isothiouronium interaction. In comparison, the lowest energy acylation TS for the slow reacting enantiomer included a π•••isothiouronium interaction between the benzenoid of the oxindole and catalyst as the key stabilising effect (Figure 30). Therefore, it was questioned whether benzannulation of the oxindole core structure was necessary for high selectivity, so the KR of 3-hydroxypyrollidinones was investigated.

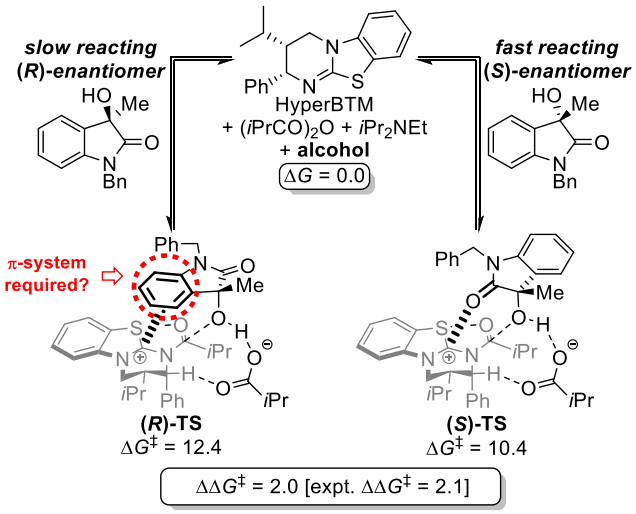


Figure 30 – Computations showing key structural motifs for the lowest energy TS for each enantiomer

3-Substituted-3-hydroxypyrrolidin-2-one derivatives possess a range of biological activities, as represented by Norsecurinamine A, an alkaloid dimer derived from the fruits of *Flueggea virosa*.[110]

Compound **A** is precursor for the synthesis of pyrrolidine base compounds for the treatment of HIV,[111] containing this core structure. Compound **B** shows mild biological activity as a 11β-HSD1 inhibitor, contributing to the conversion of cortisol in adipose tissue,[112] with bioactive compound **C** shown to be a 5-HT_{2C} antagonist,[113] amongst others containing this core structure[114] (Figure 31).

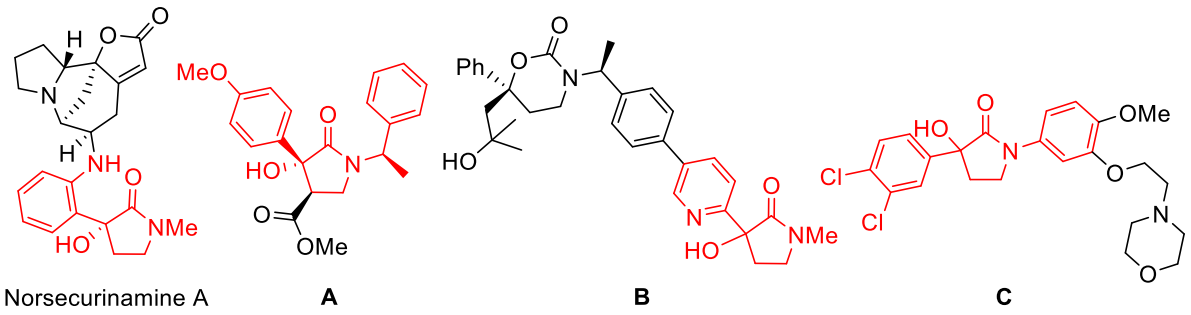
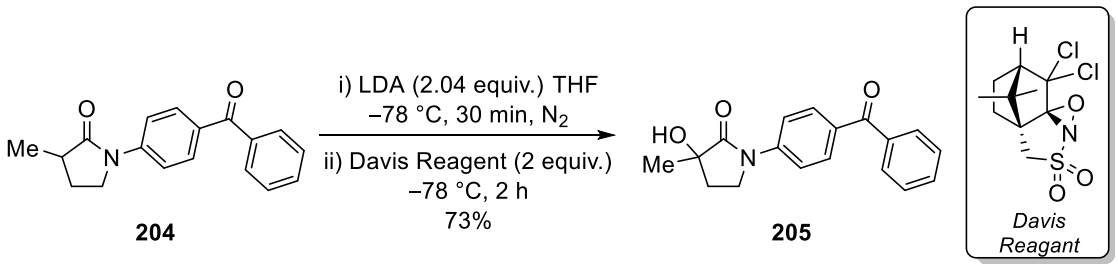


Figure 31 – Bioactive compounds and precursors containing the core pyrrolidinone structure

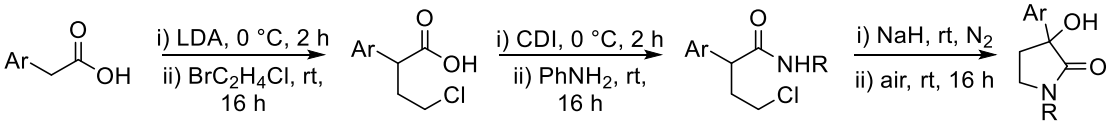
In contrast to 3-hydroxyoxindoles, there is only one example in the literature of an enantioselective method for their synthesis. Treatment of 3-methylpyrrolidin-2-one derivative **204** with LDA, led to the formation of the intermediate enolate, followed by the addition of a chiral oxaziridine, Davis reagent,[115] giving the required 3-hydroxy-3-methylpyrrolidinone derivative **205** in good yield. However, the level of enantiopurity and absolute configuration were not reported, with only the optical rotation quoted to identify any enantioselectivity (Scheme 45).[116]



Scheme 45 – Enantioselective synthesis of 3-hydroxypyrrolidinone derivative **205**

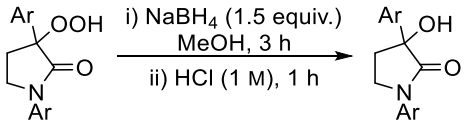
3.2 Synthesis of tertiary alcohols and esters

The desired 3-hydroxypyrrolidinone substrates were synthesised *via* a simple 3-step procedure from commercially available reagents. For example, in Scheme 3, an arylacetic acid was treated with a solution of lithium diisopropylamide (LDA), followed by addition of 1-bromo-2-chloroethane giving the α-alkylated acid in excellent yields. This was then subjected to a CDI-mediated amide coupling withan amine, giving the α-alkylated amide. The amide was treated with an excess of NaH that promotes cyclization to give the pyrrolidinone core, followed by formation of the enolate. Upon exposure to atmospheric oxygen, α-oxidation provides the required tertiary alcohols.[117] The full range of 3-aryl-3-hydroxypyrrolidinone substrates was synthesized using this synthetic route outlined below (Scheme 46).



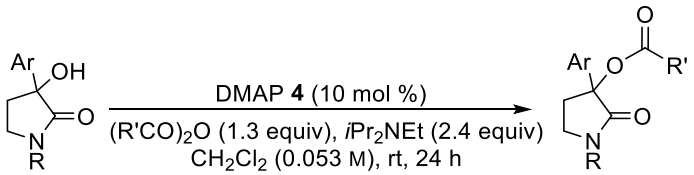
Scheme 46 – Synthetic strategy for 3-aryl-3-hydroxypyrrolidin-2-ones

In some cases, the desired tertiary alcohol was isolated alongside with an intermediate 3-aryl-3-hydroperoxypyrrolidinone, identified from the ^{1}H NMR spectra with a chemical shift for the peroxy proton at 12 ppm. Treatment of this mixture with $NaBH_4$, followed by addition of 1 M HCl led to reduction of the intermediate hydroperoxide to the desired tertiary alcohol (Scheme 47).



Scheme 47 – Reduction of intermediate hydroperoxide to desired product

Racemic samples of the esters were synthesized from the acylation of the required tertiary alcohol using DMAP **4** and an anhydride, giving the desired esters (Scheme 48).



Scheme 48 – Scheme for the esterification of 3-hydroxypyrrolidinones

3.3 Optimization

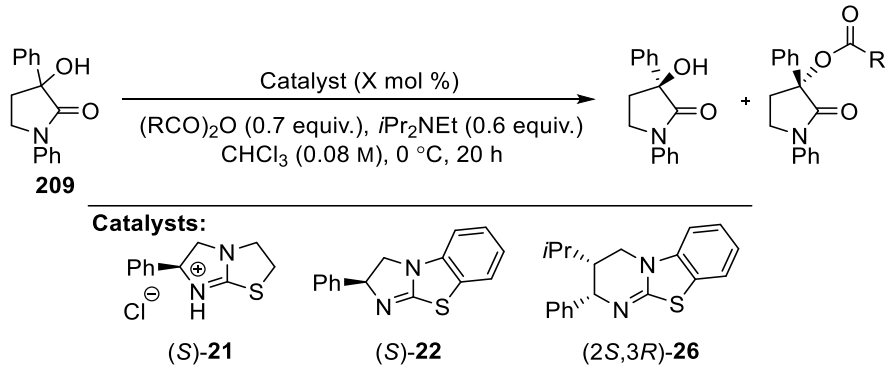
The KR of *N*-phenyl alcohol **209** was optimized by systematic variation of the catalyst, anhydride and solvent all tested, as well as testing the reproducibility of the KR protocol. Due to ease of purification after synthesis, optimization studies were conducted on **209**. Racemic samples of the isobutyrate, propionate and acetate esters (**210-212**) were synthesized following the above synthetic route in good yields (78-87%).

3.3.1 Catalyst and anhydride screen

Screening three isothiourea catalysts; tetramisole hydrochloride (*S*)-**21**, benzotetramisole (*S*)-**22** and HyperBTM (2*S*,3*R*)-**26**, at 1 mol % in the KR protocol with isobutyric anhydride, showed very little conversion (entries 1-3). Only (2*S*,3*R*)-**26** gave any selectivity and therefore, this catalyst was used in further subsequent KR reactions (entry 3). The KR using propionic anhydride with HyperBTM (2*S*,3*R*)-**26** provided a higher rate of conversion and similar selectivity (entry 4), with acetic anhydride showing a further boost in conversion with similar levels of selectivity with (2*S*,3*R*)-**26** (entry 5). Repeating the KR with 2 mol % of (2*S*,3*R*)-**26** gave 51% conversion after 20 h with good selectivity (*s* = 40) (entry 6).

The use of acetic anhydride and (2*S*,3*R*)-**26** at 2 mol % was therefore chosen for further reaction optimization.

Table 23 – Catalyst and anhydride screen

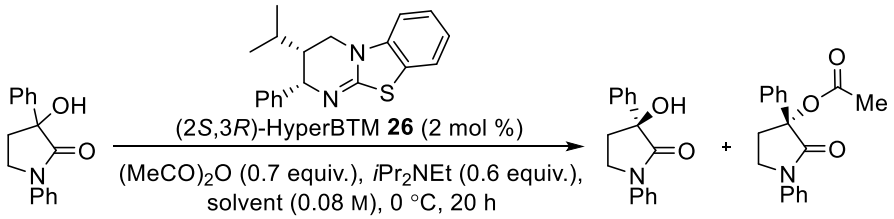


Entry	Catalyst (mol %)	R	Conv	er alc	er est	*s*
1	(*S*)-**21** (1)	*i*Pr	<1	50:50	75.5:24.5	3
2	(*S*)-**22** (1)	*i*Pr	<1	50:50	71:29	2
3	(2*S*,3*R*)-**26** (1)	*i*Pr	3	51.5:48.5	97:3	35
4	(2*S*,3*R*)-**26** (1)	Et	13	57:43	97.5:2.5	43
5	(2*S*,3*R*)-**26** (1)	Me	20	61.5:38.5	96.5:3.5	36
6	(2*S*,3*R*)-**26** (2)	Me	51	95:5	98:2	40

3.3.2 Solvent screen

A wide range of solvents was then tested in the KR protocol. The KR conducted in diethyl ether proceeds in good selectivity (*s* = 60), albeit with slightly lower conversion compared to chloroform (entry 2). The KR in toluene proceeded with good conversion and excellent selectivity (*s* = 180), with good conversion and moderate selectivity (*s* = 23) observed in dichloromethane. Various resolutions in the literature have utilised *tert*-amyl alcohol, however, a decreased rate of acylation was observed in this solvent (conv = 25%), although good selectivity was still observed (*s* = 41). The KR in dimethyl carbonate and EtOAc both proceeded with good conversion and excellent selectivity (*s* = 50 and 110), though less selective than the KR conducted in toluene. Another industrially friendly solvent, *tert*-butyl acetate was tested, and though the KR proceeded with excellent selectivity, the conversion was much lower than that in EtOAc. From this screen, toluene was chosen as the optimal solvent for the KR of 3-hydroxypyrrolidinones.

Table 24 – Solvent screen



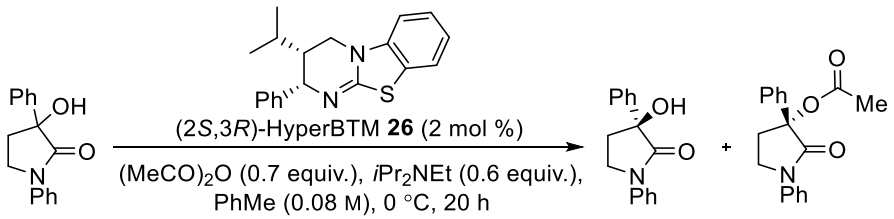
Entry	Solvent	Conv	er alc	er est	*s*
1	$CHCl_3$	51	95:5	93:7	40
2	Et_2O	43	86:14	97:3	60
3	PhMe	44	88:12	99:1	180
4	CH_2Cl_2	39	73:27	93:7	23
5	*t*-amyl alc	25	66:34	97:3	41
6[a]	DMC	50	95:5	95:5	50
7	EtOAc	48	94:6	98:2	110
8	*t*BuOAc	24	65:35	99:1	110

[a] Reaction at RT

3.3.3 Reproducibility of results

To ascertain the reliability of the optimized KR conditions, the KR of **209** was repeated 5 times. Over the 5 runs, conversion ranged between 44–49%, with *s* = 130-180 and as there is little difference at high *s*, the observed selectivities are very similar. Combined isolated yields for both alcohol and ester in each example was >85% (Table 25).

Table 25 – Reproducibility of KR under optimised conditions



Run	Conv	er alc	er est	*s*
1	44	88:12	99:1	180
2	46	92:8	98:2	130
3	46	91:9	99:1	150
4	47	93:7	99:1	170
5	49	96:4	98:2	150

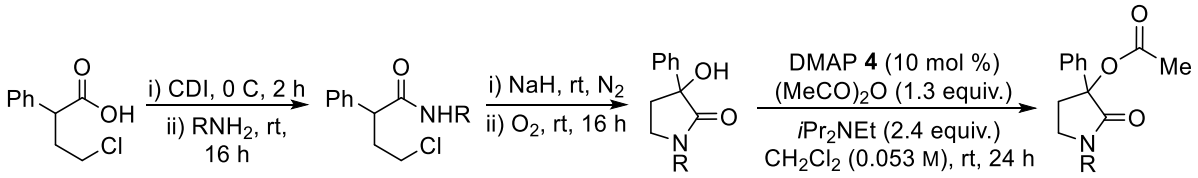
3.4 KR with various *N*-substituents

The KR of a range of 3-hydroxy-3-phenylpyrrolidinone derivatives, bearing differing *N*-substituents implemented into the core structure, was conducted under the optimized KR protocol.

3.4.1 *N*-substituent screen

Starting from 4-chloro-2-phenylbutanoic acid **207**, a range of alcohols bearing various *N*-substituents was synthesized. Initial formation of the amide *via* a CDI-mediated amide coupling, then a subsequent tandem cyclization/oxidation with NaH in the presence of O_2 gave the required alcohols. The amides were synthesized in good yields, however amide **222** was not isolated. The alcohols were obtained in moderate to excellent yields, with the corresponding esters isolated in good yields under the previously established conditions of acetic anhydride and DMAP **4** (Table 26).

Table 26 – Synthesis of various amides, alcohols and esters with varying N-substituents

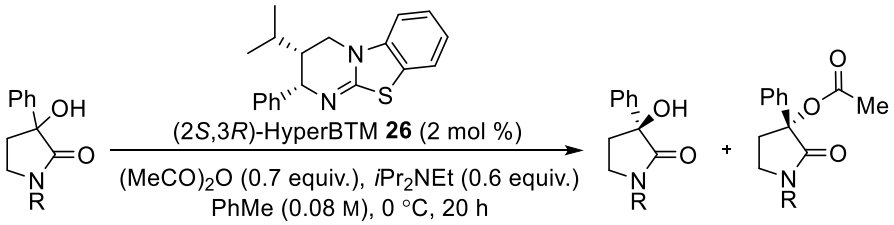


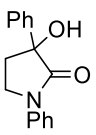
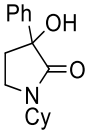
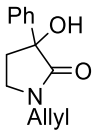
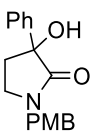
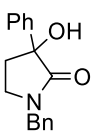
Entry	R	Amide		Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)	No.	Yield (%)
1	Phenyl	**208**	53	**209**	32	**212**	86
2	Cyclohexyl	**213**	71	**214**	62	**215**	71
3	Allyl	**216**	78	**217**	43	**218**	75
4	Benzyl[118]	**219**	71	**220**	82	**221**	94
5	4-Methoxybenzyl	**222**	– [a]	**223**	35	**224**	61

[a] Amide not isolated and taken on.

Using the previously optimized KR conditions, the KR of *N*-cyclohexyl protected alcohol **214** using acetic anhydride and (2*S*,3*R*)-HyperBTM **26** provided an excellent *s* factor (*s* = 70), giving ester **215** in high enantiopurity, though low conversion was observed (Table 27, entry 2). The KR of *N*-allyl protected alcohol **217** and *N*-benzyl protected alcohol **220** proceeded with the same level of selectivity (*s* = 110) (entries 3 and 5). *N*-4-Methoxybenzyl protected alcohol **223** was not soluble in toluene, therefore the KR was conducted in chloroform. Under these conditions, the selectivity factor obtained was 28, similar to that of *N*-benzyl protected alcohol **220** in chloroform (*s* = 32).

Table 27 – Initial kinetic resolution with various *N*-substituents



Entry	1	2	3	4	5[a]
Alcohol					
	209	**214**	**217**	**223**	**220**
Conv (%)	44	17	43	30	45
Alc er	88:12	60:40	87:13	69:31	90:10
Est er	99:1	99:1	98:2	95:5	98:2
s	180	70	110	28	110

[a] Insoluble in PhMe, KR conducted in $CHCl_3$

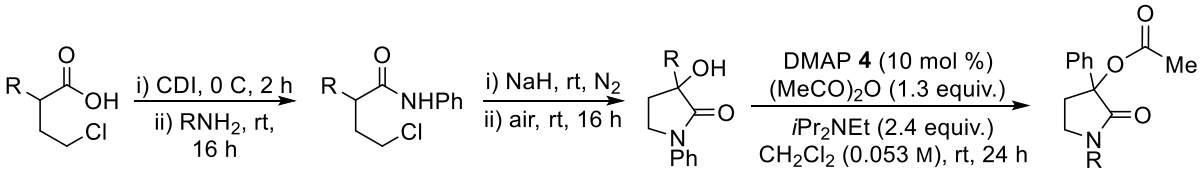
3.5 *N*-Ph subset

As the *N*-phenyl substituent provided the best conversion and gave good selectivity under the optimized conditions, a small range of substrates were synthesised to test in the KR protocol, with varying electronics at the 3-aryl group.

3.5.1 Synthesis of alcohols and esters

4-Substituted phenyl acetic acids, bearing fluoro- and methoxy- groups, as well as a 2-thienyl acetic acid and *trans*-styryl acetic acid were alkylated using LDA and 1-bromo-2-chloroethane to give the alkylated acids, followed by a CDI-mediated amide coupling with aniline to give the corresponding alkylated amides. Purification of the amides by column chromatography proved difficult in each case, therefore the crude amide was taken on for alcohol synthesis using excess sodium hydride in the presence of atmospheric O_2. Unfortunately, poor overall yields were obtained over the 2 steps (4-20%). Esters were obtained under the standard conditions giving **226-232** in good to excellent yields (Table 28).

Table 28 – Synthesis of *N*-Ph subset; alcohols and esters



Entry	R	Alcohol[a]		Ester	
		No.	Yield (%)	No.	Yield (%)
1	4-F-C_6H_4	**225**	20	**226**	89
2	4-MeO-C_6H_4	**227**	19	**228**	73
3	2-Thienyl	**229**	6	**230**	83
4	*trans*-Styryl	**231**	4	**232**	69

[a] Yields over 2 steps

3.5.2 KR of *N*-Ph subset

Compared to the parent 3-phenyl substituted alcohol (s = 180), the KR of alcohol **225** bearing electron-withdrawing 4-fluorophenyl substituted progressed with good conversion and excellent, albeit lower, selectivity (entry 1; *s* = 100), with both alcohol and ester obtained in high enantiopurity. The electron-donating 4-methoxyphenyl substituted alcohol **227** provided the same selectivity in the KR (entry 2; *s* = 100) as the 4-fluorophenyl substituted alcohol, though a slightly lower conversion was observed over the same reaction time. The KR of 2-thienyl substituted alcohol (entry 3) proceeded with excellent selectivity (*s* = >200), with the alcohol obtained in enantiopure form. Single crystal X-ray analysis of the recovered alcohol, performed by Prof. Alexandra Slawin, confirmed the absolute (*S*)-configuration (Figure 32).[119] From the obtained X-ray crystal structure of (*S*)-**229**, the absolute configuration of recovered alcohols from all other KRs was considered to be the (*S*)-enantiomr by analogy. Incorporation of the (*E*)-styryl group at the 3-position gave a lower conversion in the KR and also led to lower selectivity (entry 4; *s* = 10) (Table 29).

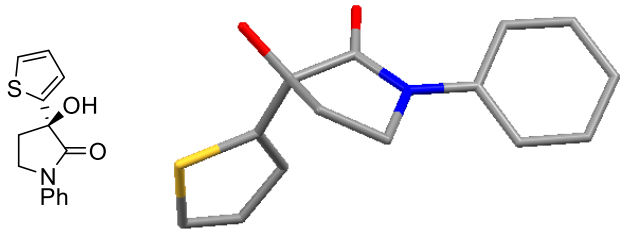
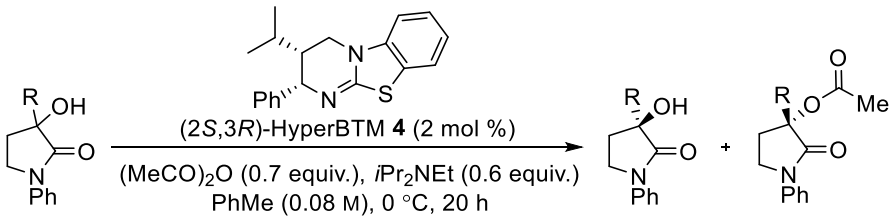
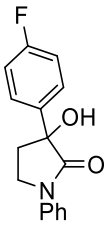
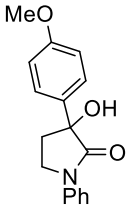
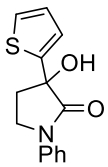
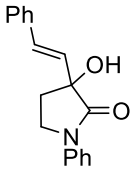


Figure 32 – X-ray crystal structure of **(*S*)-229**

Table 29 – Kinetic resolution of *N*-Ph subset



Entry		1	2	3	4
Alcohol					
		225	**227**	**229**	**231**
Conv (%)		49	41	52	25
Alc	er	95:5	84:16	>99:1	63:37
	Yield	43	49	43	59
Est	er	97:3	98:2	97:3	89:11
	Yield	41	30	39	21
s		100	100	>200	10

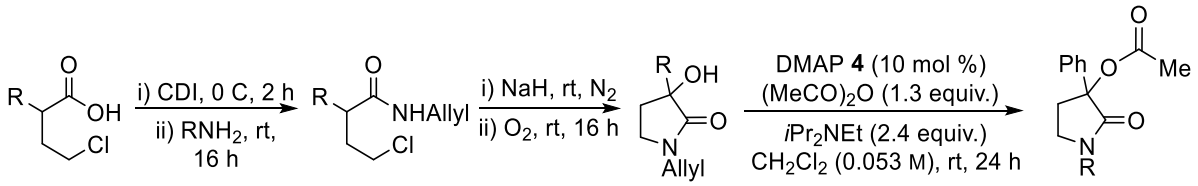
3.6 *N*-Allyl alcohols

Due to difficulties in purification and low overall yields obtained for the preparation of *N*-phenyl substituted tertiary alcohols, the wider substrate scope for the KR process was investigated using *N*-allyl substituents. To garner a direct comparison to the *N*-phenyl substrates investigated above, analogous substrates bearing an *N*-allyl substituent were then synthesized. 3-Aryl-3-hydroxypyrrolidinone derivatives containing aromatic rings with various substitution patterns and varying electronic nature, were also synthesized and investigated in the KR protocol.

3.6.1 Amide, alcohol and ester synthesis

A range of 3-aryl-3-hydroxypyrrolidinone derivatives was synthesized using the relevant aryl acetic acids, under the established three-step synthetic route. The amides were obtained in moderate yields, but a majority of the amides were taken on, due to difficulties in purification. Subsequent cyclization, following by oxidation was achieved using excess sodium hydride in the presence of atmospheric O_2, to give a range of alcohols isolated in low to moderate yields. The corresponding esters were obtained using acetic anhydride and DMAP **4** in good to excellent yields (Table 30).

Table 30 – Synthesis of *N*-allyl amides, alcohols and esters



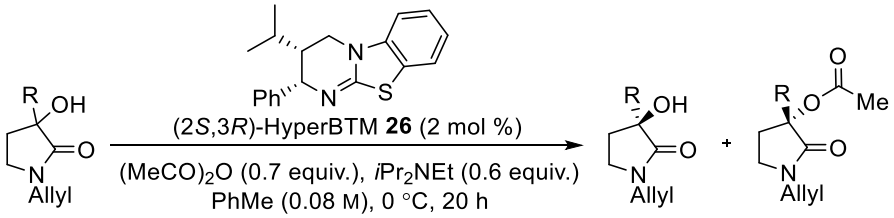
Entry	R	Amide		Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)	No.	Yield (%)
1	4-F-C_6H_4	**233**	45	**234**	63	**235**	91
2	4-MeO-C_6H_4	**236**	45	**237**	17	**238**	82
3	2-Thienyl	**239**	–[a]	**240**	9[b]	**241**	79
4	3-Thienyl	**242**	–[a]	**243**	40[b]	**244**	94
5	4-Ph-C_6H_4	**245**	–[a]	**246**	14[b]	**247**	93
6	4-Me-C_6H_4	**248**	54	**249**	17	**250**	78
7	4-Cl-C_6H_4	**251**	50	**252**	48	**253**	94
8	3-Me-C_6H_4	**254**	–[a]	**255**	11[b]	**256**	73
9	3-Cl-C_6H_4	**257**	–[a]	**258**	55[b]	**259**	79
10	2-Naphthyl	**260**	–[a]	**261**	39[b]	**262**	85
11	3,4-*di*-Cl-C_6H_3	**263**	51	**264**	36	**265**	96
12	3,4-*di*-MeO-C_6H_3	**266**	30	**267**	11	**268**	95
13	2-Me-C_6H_4	**269**	–[a]	**270**	10[b]	**271**	80
14	2-Cl-C_6H_4	**272**	–[a]	**273**	12[b]	**274**	67
15	1-Naphthyl	**275**	–[a]	**276**	8[b]	**277**	73

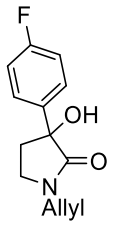
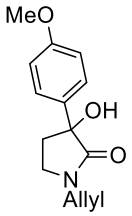
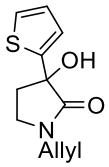
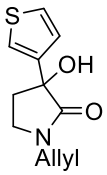
[a] Amide not isolated. [b] Yield over 2 steps

3.6.2 KR of *N*-allyl vs *N*-phenyl alcohols

The KR of 4-fluorophenyl substituted alcohol **234** proceeded with good conversion and excellent selectivity (*s* = 100), consistent with the *N*-phenyl equivalent **225** (*s* = 100). The KR of 4-methoxyphenyl substituted alcohol **237** proceeded with a reduction in selectivity (*s* = 60) in comparison to *N*-phenyl analogue **227**, though the KR required a higher catalyst loading (5 mol %), due to significantly lower conversion (26%) using 2 mol % of (2*S*,3*R*)-HyperBTM **26**. The KR of 2-thienyl substituted alcohol **240** proceeded with good conversion and excellent selectivity, *s* = 160, comparable to that of the *N*-phenyl analogue **229**. The KR of 3-thienyl substituted alcohol **243** proceeded with good conversion and excellent selectivity (*s* = 90), albeit lower than that observed for 2-thienyl substituted alcohol **240** (Table 31).

Table 31 – Kinetic resolution of *N*-allyl analogues



Entry		1	2[a]	3	4
Alcohol					
		234	**237**	**240**	**243**
Conv (%)		41	38	50	45
Alc	er	84:16	79:21	98:2	89:11
	Yield	47	59	39	47
Est	er	98:2	97:3	98:2	98:2
	Yield	38	32	42	39
s		100	60	160	90

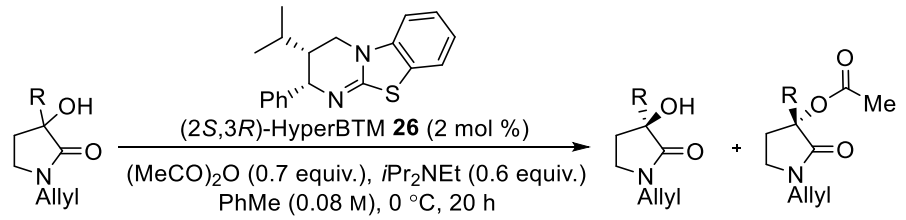
[a] 5 mol % (2*S*,3*R*)-**26**

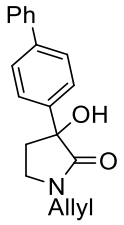
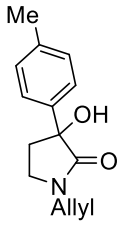
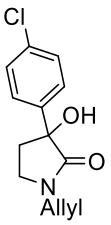
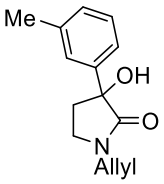
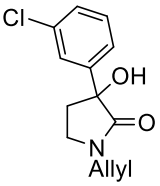
3.6.3 4- and 3-substituted aryl groups

The KR of other 4-substituted aryls at the 3-position of the pyrrolidinone were conducted, with the KR of biphenyl substituted **246** proceeding with good conversion and an excellent selectivity (s = 120). The KR of **249**, bearing an electron-donating 4-methylphenyl group at the 3-position, proceeded in good conversion and with high selectivity (*s* = 90). In contrast, the KR of electron-withdrawing 4-chlorophenyl **252** progressed with good conversion and an excellent selectivity factor of >200, with (*R*)-**253** obtained in a highly enantiopure form.

Incorporation of substituents at the 3-position of the 3-phenyl substituent had a profound effect on the selectivity of the KR when compared to 4-substitution. For the KR of 3-methylphenyl substituted alcohol **255**, a higher catalyst and anhydride loading were required to boost reactivity, compared to the 4-substituted equivalent **249**. A selectivity factor of 70 was observed for **255**, a comparable selectivity to *s* = 90 for the 4-methylphenyl substituted alcohol **249**. The KR of 3-chlorophenyl substituted alcohol **258** proceeded with similar conversion to the 4-substituted analogue **252**. However, there was a significant reduction observed in the selectivity, compared to the 4-substituted equivalent, with *s* = 31 observed, compared to the excellent *s* = >200 seen for **252**. The combined yield for the recovery of starting alcohols and ester products was greater than 86% in each case (Table 32).

Table 32 – KR of alcohols 4- and 3-substituted aryls



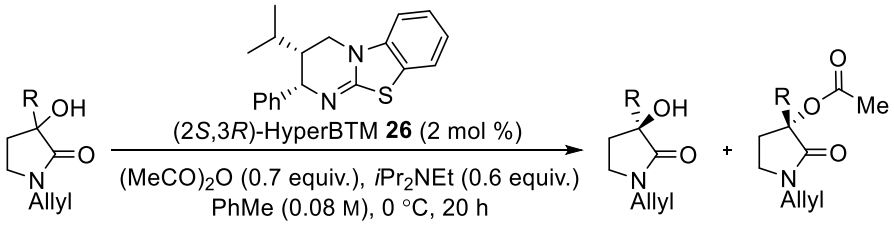
Entry		1	2	3	4[a]	5
Alcohol						
		246	**249**	**252**	**255**	**258**
Conv (%)		43	44	46	47	51
Alc	**er**	86:14	87:13	92:8	92:8	94:6
	Yield	50	46	50	49	45
Est	**er**	98:2	98:2	99:1	97:3	92:8
	Yield	37	40	44	43	46
s		120	90	>200	70	31

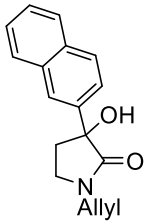
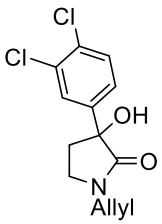
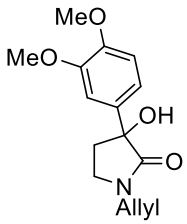
[a] 5 mol % (2*S*,3*R*)-**26**, 0.9 equiv. $(MeCO)_2O$.

3.6.4 Disubstituted aryl groups

The KR of 2-naphthyl substituted **261** required a higher catalyst (5 mol %) and anhydride loadings (0.9 equiv.) to obtain good conversion, though selectivity was surprisingly low (*s* = 24), especially when compared to the oxindole equivalent **99**, which had an excellent *s* = 180. Similarly, the KR of 3,4-dichlorophenyl substituted alcohol **264** proceeded in good conversion and selectivity (*s* = 27) under the optimized reaction conditions, with similar *s* to that for the KR of 3-chlorophenyl substituted alcohol **258**. The KR of 3,4-dimethoxyphenyl substituted alcohol **267** also required higher catalyst (5 mol %) and anhydride loadings (0.9 equiv.) to obtain moderate conversion and selectivity (*s* = 20), however the selectivity factor was still lower than alcohol **237** (Table 33).

Table 33 – KR of alcohols bearing disubstituted phenyls



Entry		1[a]	2	3[a]
Alcohol				
		261	**264**	**267**
Conv (%)		45	45	32
Alc	er	85:15	85:15	71:29
	Yield	50	47	61
Est	er	92:8	93:7	93:7
	Yield	40	38	28
s		24	27	20

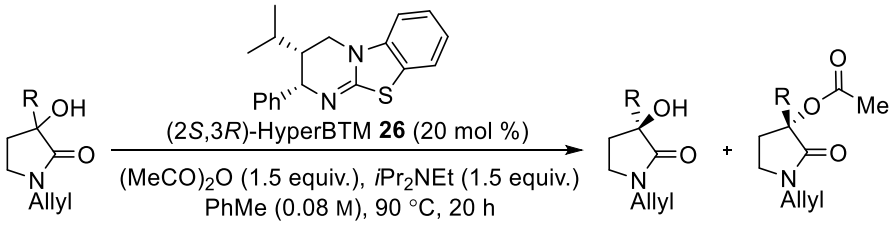
[a] 5 mol % (2*S*,3*R*)-**26**, 0.9 equiv. $(MeCO)_2O$, $CHCl_3$

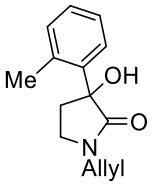
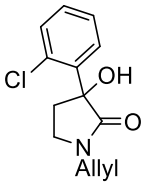
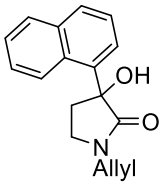
3.6.5 2-Substituted aryl groups

The KR of 3-phenyl substituted alcohols bearing substituents at the 2-position led to low conversion under the standard reaction conditions and therefore, higher catalyst and anhydride loadings, as well as an increased reaction temperature was required. For example, using 20 mol % of catalyst at 0 °C provided very low conversion for all substrates **270-276**.

Repeating these reactions at room temperature and 50 °C also gave low conversion. However, by performing the KR at 90 °C, and with 20 mol % of catalyst and 1.5 equivalents of anhydride and base, good conversions were obtained. The KR of 2-methylphenyl substituted alcohol **270** proceeded with good conversion under these conditions, however, a selectivity factor of just 6 was obtained. The KR of 2-chlorophenyl substituted **273** gave excellent conversion with a moderate selectivity obtained (*s* = 15). Considering the reaction was conducted at 90 °C, this proved to be an interesting result, with near synthetically useful levels of selectivity observed. The KR of 1-naphthyl substituted alcohol **276** proceeded in good conversion, however very poor selectivity was obtained (*s* = 3) (Table 34).

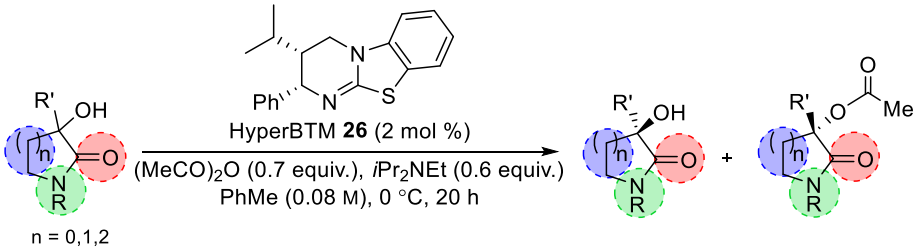
Table 34 – KR of 2-substituted phenyl bearing alcohols



Entry		1	2	3
Alcohol				
		270	**273**	**276**
Conv (%)		44	49	42
Alc	**er**	77:23	86:14	64:36
	Yield	51	47	55
Est	**er**	80:20	88:12	69:31
	Yield	40	43	38
s		6	15	3

3.7 Structural variations

Variations in the core structure of the 3-hydroxypyrollidin-2-one core were then investigated with the attempted incorporation of an alkyl substituent at the 3-position, variations at the carbonyl, *N*-substituent and varying ring sizes explored to further probe the scope and limitations of the KR protocol (Scheme 49). These variations could help to provide possible mechanistic insight of the KR, as well as lead to natural product or potential bioactive compound synthesis.[111]

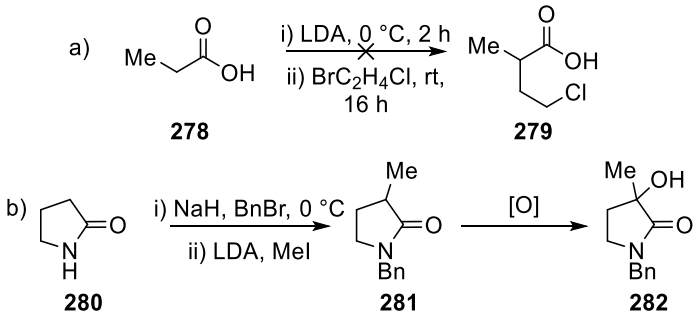


Scheme 49 – Variations in the core 3-hydroxypyrrolidinone structure

3.7.1 3-Alkyl substituent

Unfortunately, the same synthetic procedure could not be applied to alkyl acetic acids as attempted alkylation under the same conditions led to full recovery of starting materials (Scheme 50a). Alternative pathways were explored, with *N*-benzyl pyrrolidinone alkylated at the 3-position using methyl iodide giving *N*-benzyl-3-methylpyrolidinone **281**. However, attempts at oxidation were unsuccessful, with the established NaH/O_2 route giving no reaction. Formation of the enolate with

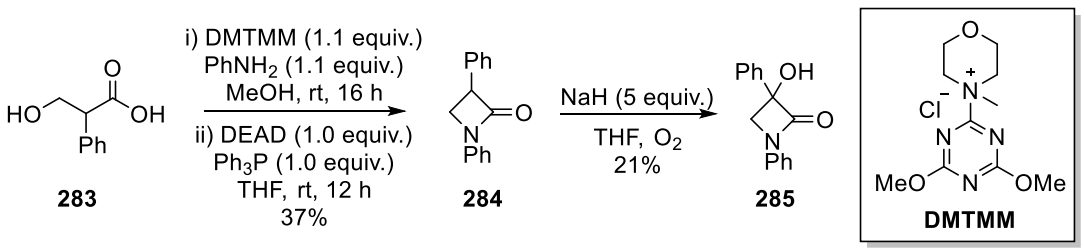
LDA or trapping the enolate as a silyl enol ether, followed by treatment with an oxaziridine, atmospheric O_2 or even a full O_2 atmosphere all proved unsuccessful, with complete recovery of starting material after work up (Scheme 50b).



Scheme 50 – Unsuccessful attempts to obtain 3-alkyl-3-hydroxypyrrolidinone derivatives

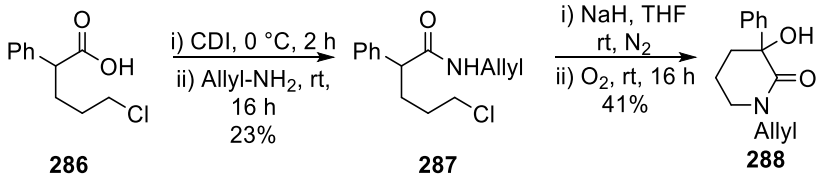
3.7.2 Alternative ring sizes

The synthesis of the 4-membered ring analogue, 3-hydroxy-1,3-diphenylazetidin-2-one **285,** was conducted. Using the conditions outlined by Cade,[120] amide coupling of tropic acid **283** and aniline using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as coupling agent gave an intermediate amide, which was subjected to a Mitsunobu reaction using diethyl diazodicarboxylate and triphenylphosphine, giving 1,3-diphenylazetidin-2-one **284** in 37% yield over both steps. Using the previously established conditions of NaH and atmospheric O_2, the successful α-oxidation of the amide led to the desired tertiary alcohol **285** in 21% yield (Scheme 51).



Scheme 51 – Synthesis of β-lactam derivative

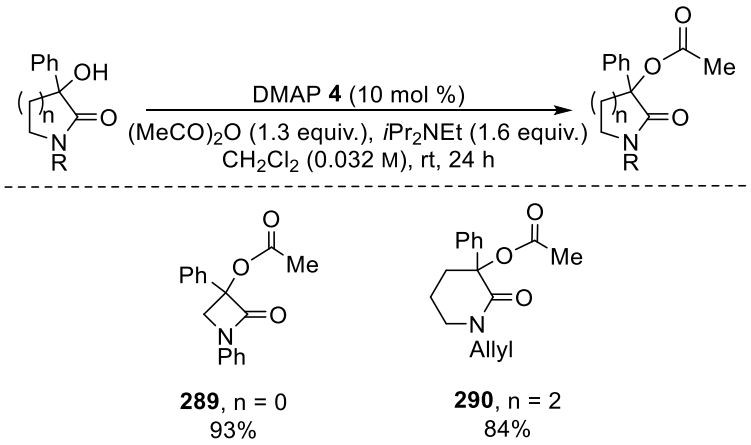
Synthesis of 1-allyl-3-hydroxy-3-phenylpiperidin-2-one **288** was conducted in the same manner as the 3-hydroxypyrrolidin-2-one tertiary alcohols. Alkylation of phenyl acetic acid using 1-bromo-3-chloropropane gave **286** in a quantitative yield. A CDI-mediated amide coupling with allylamine gave amide **287** in 23% yield, and subsequent oxidation to tertiary alcohol **288** was performed under the standard conditions, using NaH and atmospheric O_2, in 41% yield (Scheme 52).



286 **287** **288**

Scheme 52 – Synthesis of δ-lactam derivative **288**

Esterification of β-lactam derivative **285** and δ-lactam derivative **286** were performed using the standard acylation conditions of acetic anhydride and DMAP, with excellent yields obtained for both **289** and **290** (Scheme 53).



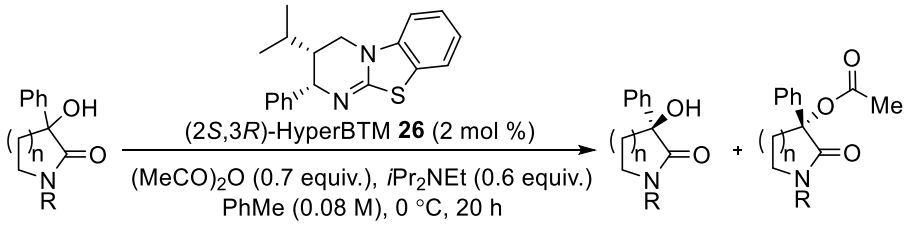
289, n = 0
93%

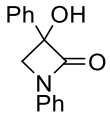
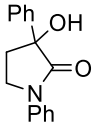
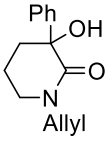
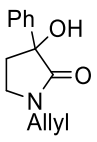
290, n = 2
84%

Scheme 53 – Esterification of tertiary alcohols of varying ring size

The KR of β-lactam alcohol **285** proceeded with high conversion of the alcohol, with s = 10. When compared to the analogous 3-hydroxypyrrolidinone **209**, the reaction proceeded with much higher conversion, and a significant reduction in selectivity in comparison to **209** (entry 1 v 2). Attempted KR of δ-lactam alcohol **288** at 0 °C gave no observed acylation, even with increased catalyst concentration (20 mol %) and anhydride loading (1.5 equiv.). Subsequent repeats at room temperature and 50 °C also led to no observable reactivity. However, an increase in reaction concentration [0.24 M], catalyst (20 mol %), anhydride and base loadings (1.5 equiv.), and reaction temperature (90 °C) for 24 h, 48% conversion of the alcohol was achieved. This led to good enantioselectivity for both alcohol and ester, with a selectivity factor of 25, which considering the KR was performed at 90 °C, is an excellent result. As a comparison, the KR of alcohol **217** was repeated at 90 °C, with other conditions remaining as previously used. This led to a very similar level of selectivity (*s* = 26), however, interestingly a much lower conversion of 19% was obtained at 90 °C when compared to the KR at 0 °C, possibly due to degradation of the catalyst at the elevated temperature.

Table 35 – KR of β- and δ-lactam derivative tertiary alcohols



Entry		1	2	3[a]	4[b]
Alcohol					
		285	**209**	**288**	**217**
Conv (%)		61	44	48	19
Alc	**er**	95:5	88:12	89:11	61:39
	Yield	32	49	51	72
Est	**er**	78:22	99:1	92:8	96:4
	Yield	54	38	40	16
s		10	180	25	26

[a] 20 mol % (2*S*,3*R*)-**26**, 1.5 equiv. $(MeCO)_2O$, 1.5 equiv. $^{i}PrNEt_2$, [0.24 M], 90 °C, 24 h.
[b] 90 °C

The proposed degradation of the catalyst was explored further in order to help explain the result of lower conversion at a high temperature. A reaction was conducted under the optimized KR conditions, in the absence of a tertiary alcohol substrate, with (2*S*,3*R*)-HyperBTM **26** (2 mol %), acetic anhydride (0.7 equiv.) and $^{i}Pr_2NEt$ (0.6 equiv.) in toluene, with an increase reaction temperature of 90 °C. Comparing the NMR spectrum of the crude reaction mixture to that of a pure sample of (2*S*,3*R*)-HyperBTM **26**, it is evident that over the course of the reaction there is significant degradation of the catalyst (Figure 33). From the crude NMR, three sets of doublets, which arise from the isopropyl group of the catalyst, can be identified between 1.25 and 0.75 ppm, possibly indicating the formation of at least three products formed upon degradation, however no degradation products could be isolated after column chromatography upon multiple attempts (Fig 4b). Assuming this is representative of the acylation reaction, this result could help to explain why such low conversion (19%) is observed in the KR of alcohol **217** at 90 °C, compared to the same reaction at 0 °C, where the conversion is observed to be 43%.

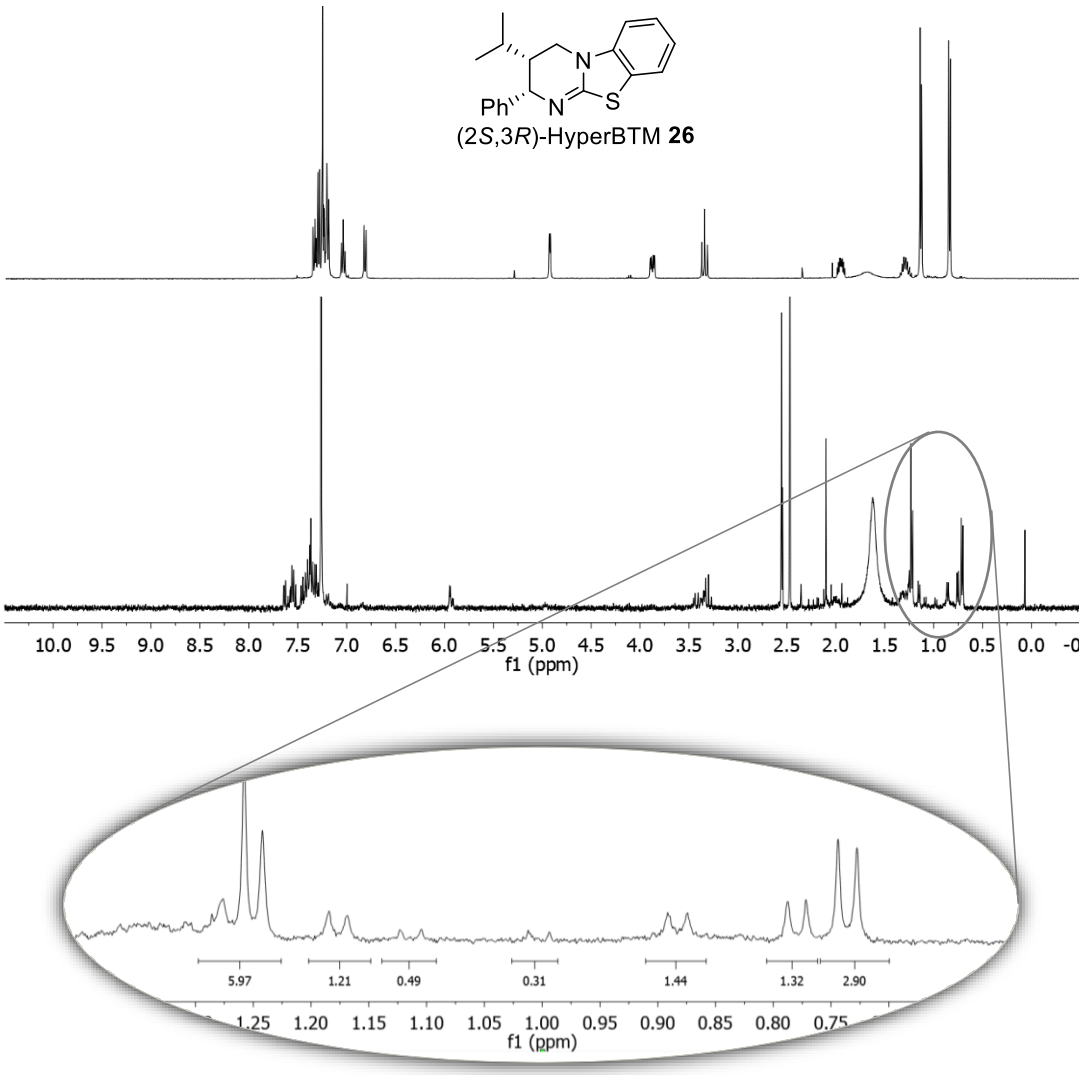


Figure 33 – NMR comparison of HyperBTM **26** and crude reaction mixture

The reaction was repeated with a higher catalyst loading (20 mol %), with reaction conditions analogous to the KR of alcohol **288**. Though the formation of other products can clearly be seen, the crude NMR shows a significant amount of (2*S*,3*R*)-HyperBTM **26** present in the reaction medium, that would be available for turnover during a KR (Figure 34). These observations back up the conversions seen in the KR of both alcohols **288** and **217**.

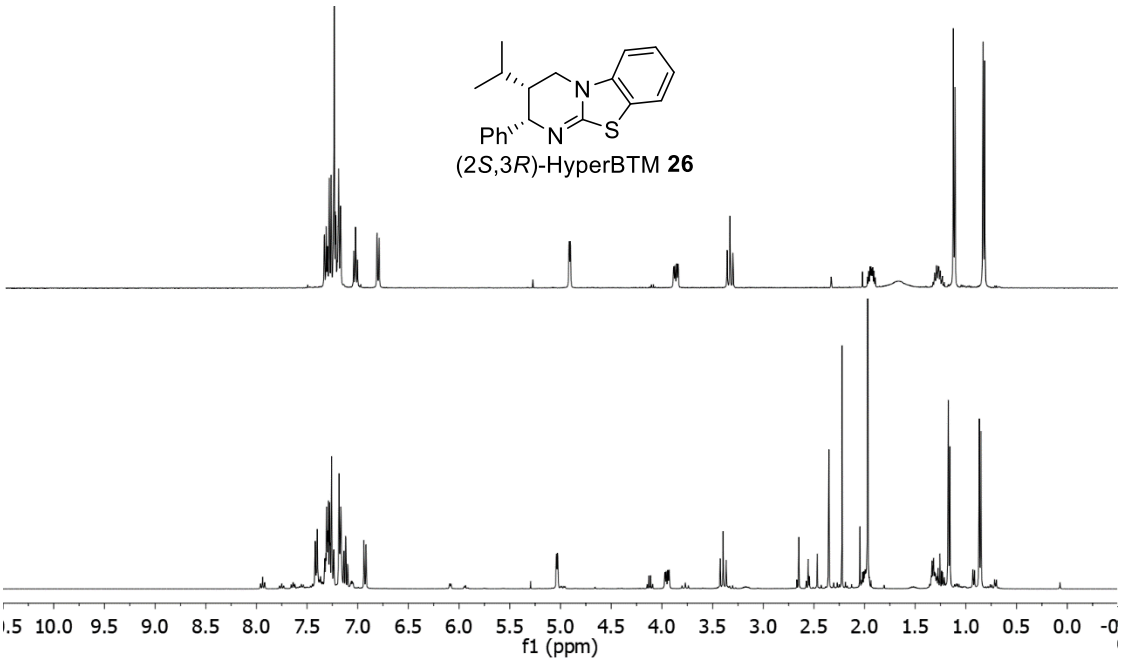


Figure 34 – HyperBTM **26** NMR vs crude NMR with higher catalyst loading

Whilst no degradation products of the catalyst could be isolated, it can be speculated how the catalyst could be deactivated to form new species. Whilst the degradation/deactivation of HyperBTM **26** has not been reported, Birman has previously shown the deactivation of (*R*)-BTM **22** in the presence of excess acetic anhydride and moisture. Upon formation of the *N*-acylated intermediate, nucleophilic attack of water forms the tetrahedral intermediate **291**. Ring opening onto sulfur forms the substituted thiophenol species **292**, and subsequent acylation of the thiol in the presence of excess anhydride gives product **293** (Figure 35).[121] This same sense of deactivation was identified in unpublished work in the Smith group from the reaction of isobutyric anhydride and (*R*)-BTM **22**.

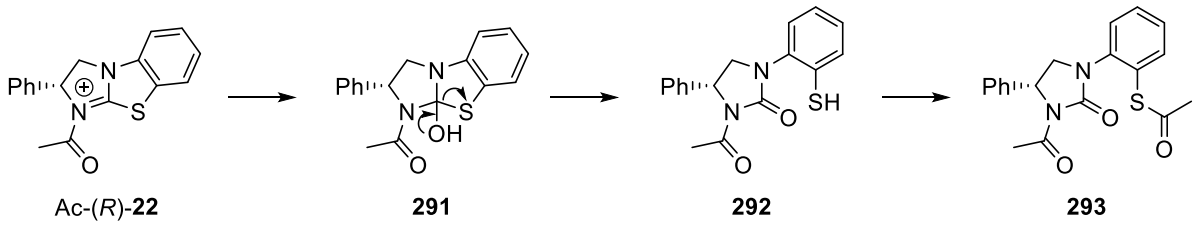


Figure 35 – Potential deactivation/degradation pathways for (*R*)-BTM **22**

However, the work conducted by Birman only identified the products formed following ring opening onto sulfur, however there is potential to ring open onto nitrogen to give a substituted benzothiazolone product. For the degradation of HyperBTM **26**, two potential pathways could then arise; pathway **A**, *via* opening of the thiazole ring, to give two potential products, thiol **295** and the acylated thiol **296**, whilst pathway **B** proceeds *via* cleavage of a carbon-nitrogen bond, external to the thiazole ring, to give the amide-benzothiazolone species **297** (Figure 36).

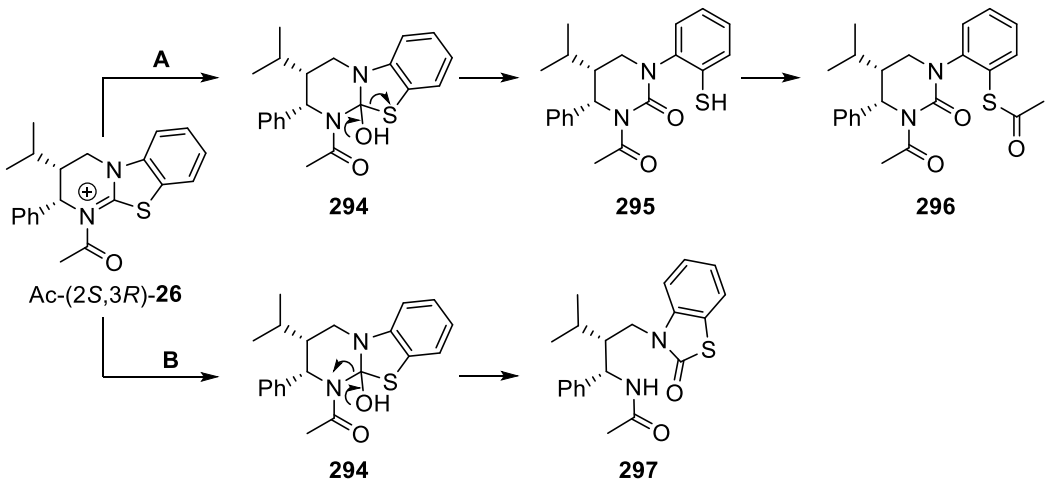
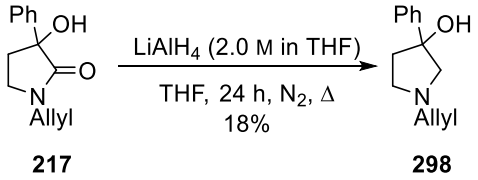


Figure 36 – Potential deactivation/degradation pathways for HyperBTM **26**

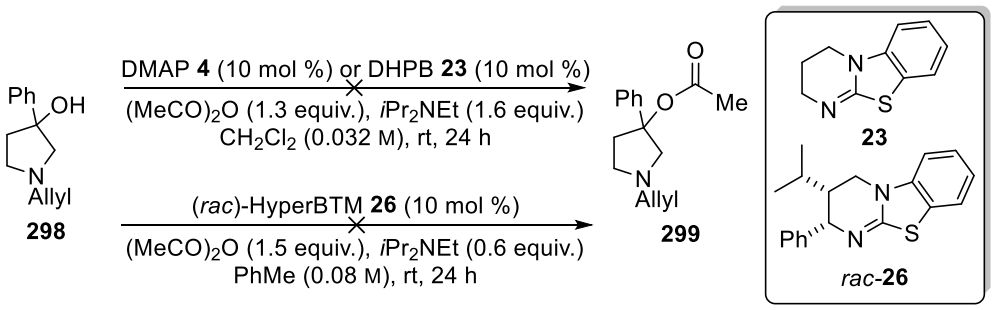
3.7.3 Carbonyl and amide variation

Removal of the amide carbonyl was accomplished by lithium aluminium hydride reduction of alcohol **217** giving 1-allyl-3-phenylpyrrolidin-3-ol **298** in a poor 18% yield (Scheme 54).[122]



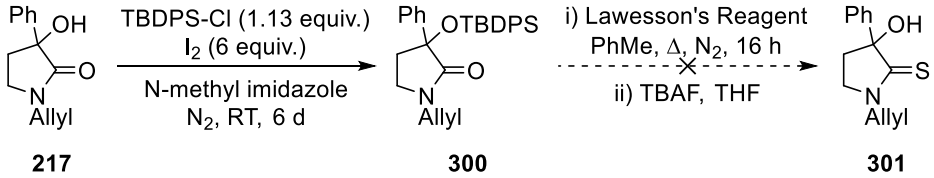
Scheme 54 – Reduction of 3-hydroxypyrrolidin-2-one to pyrrolidin-3-ol

Acylation of alcohol **298** was attempted using DMAP **4** and acetic anhydride, to give ester **299**, however no reactivity was obtained, with full recovery of starting material. Even with an increased reaction temperature of 90 °C, only starting material was recovered upon work up. The reaction was repeated using the achiral isothiourea catalyst DHPB **23**, but again, only starting material was obtained. Alcohol **217** was also subjected to the KR conditions, using racemic HyperBTM **26**, however, the complete recovery of starting material was achieved upon purification (Scheme 55). This lack of reactivity is consistent with the computations previously established in the work on the 3-hydroxyoxindole substrates, in which the amide carbonyl shown to be essential for both selectivity and reactivity.



Scheme 55 – Attempts at esterification of pyrrolidin-3-ol **298**

As previously established from computational studies conducted on the 3-hydroxyoxindole substrates, the carbonyl-catalyst interaction is considered to be important for high selectivity. To gauge this interaction further for this new substrate class, replacement of the amide carbonyl oxygen with a sulfur to give the thioamide was attempted. Protection of the 3-hydroxyl of **217** was conducted using *tert*-butyldiphenylchloro silane and iodine (6 equiv.) in *N*-methylimidazole at room temperature under nitrogen for 6 days.[123] The TBDPS-protected alcohol **300** was obtained, however after numerous purifications, the product could only be obtained in 90% purity. Consequently, this was taken on and reacted with Lawesson's reagent in toluene at reflux,[124] producing a complex mixture with none of the desired TBDPS-protected thione isolable (Scheme 56).

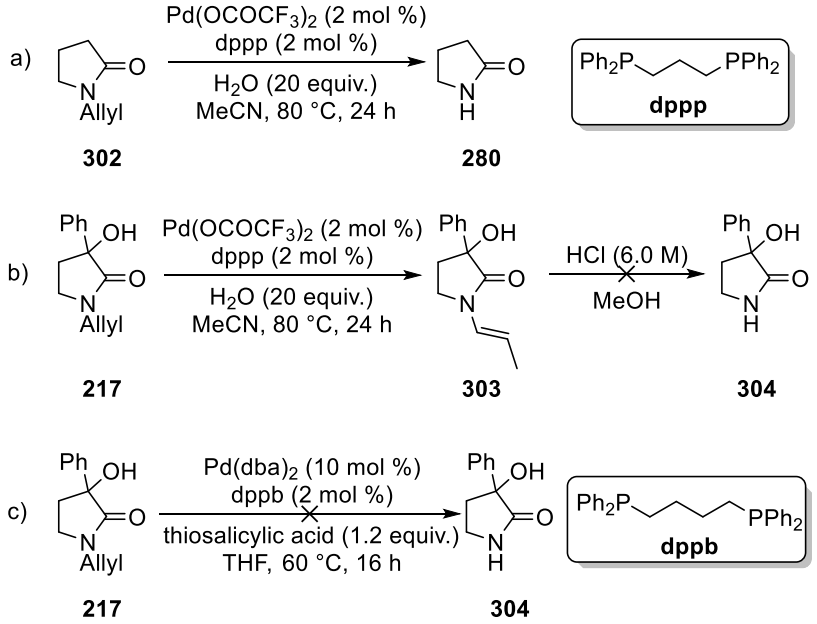


Scheme 56 – Reduction of 3-hydroxypyrrolidin-2-one to pyrrolidin-3-ol

3.7.4 Removal of *N*-substituent

Removal of the *N*-allyl group to give the unprotected 3-hydroxypyrrolidin-2-one would prove to be of synthetic use for application of the resolved products. Deallylation of *N*-allylpyrrolidin-2-one **302** to the free *N*-H pyrrolidin-2-one **280** has been shown using catalytic palladium(II) trifluoroacetate (2 mol %), 1,3-bis(diphenylphosphanyl)propane as ligand and water (20 equiv.) in acetonitrile at 80 °C.[125] However, there was no literature precedent for using this process for the deallylation of tertiary alcohol pyrrolidinone substrates. With this in mind, these conditions were utilized for the deallylation of **217**, however, the isomerised product, *N*-(*E*)-propenylpyrrolidin-2-one **303**, was the only product observed in 80% yield, with none of the desired alcohol, **304** observed. Attempts to remove the enamide by retreatment using the Pd-deallylation conditions, or 6 M HCl in MeOH were both unsuccessful, with complete recovery of starting material in each case. Conditions previously used in

the Smith group for deallylation were also implemented using **217**,[126] however no reactivity was observed in this instance (Scheme 57).



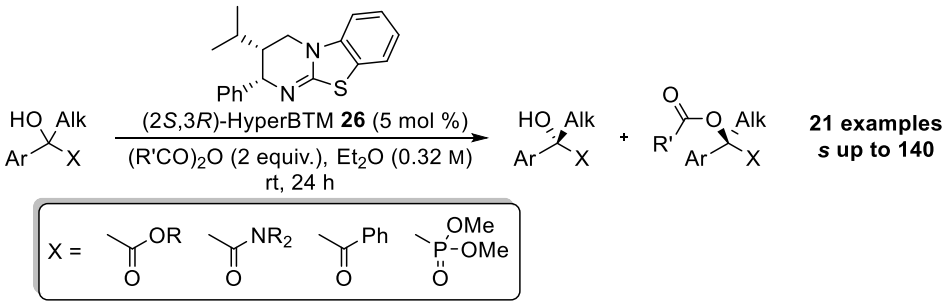
Scheme 57 – a) Literature precedent for deallylation of N-allylpyrrolidin-2-one; b) Attempts at deallylation of **217**; c) Previously used deallylation conditions in group

3.8 Conclusion

In this chapter, it has been determined that a range of 3-aryl-3-hydroxypyrrolidin-2-ones, with varying substitution patterns can effectively and selectivity be resolved, with selectivity factors up to >200 observed. Re-optimization of the previous KR conditions led to the use of HyperBTM (2 mol %), acetic anhydride as acylating agent and toluene as solvent as optimal. The 3-aryl-3-hydroxypyrrolidin-2-one core was constructed through initial enolate formation of aryl acetic acids using LDA, followed by alkylation using 1-bromo-2-chloroethane giving the α-alkylated aryl acetic acid. This was followed by a CDI-mediated amide coupling to give the amide, and using excess NaH under atmospheric O_2, a tandem cyclization/oxidation gave the desired core structure. It was determined that 2-substituted aryl groups at the 3-position are not reactive under the standard conditions, with higher catalyst (20 mol %) and anhydride loadings (1.5 equiv.) at 90 °C required for reactivity, leading to moderate selectivity. Variations in ring size were investigated with the KR of a 3-hydroxy substituted β-lactam proceeding with lower selectivity, in comparison to its pyrrolidinone analogue, whereas the KR of 3-hydroxy substituted δ-lactam gave no reactivity under the standard KR conditions. For any observable reactivity, higher catalyst (20 mol %), anhydride and base (1.5 equiv.) loadings and heating at 90 °C were required, with an impressive *s* = 25 observed at this elevated temperature.

CHAPTER 4: KINETIC RESOLUTION OF ACYCLIC TERTIARY ALCOHOLS

This chapter describes the use of an isothiourea catalyst [(2*S*,3*R*)-HyperBTM] and an anhydride as the acylating agent, for the acylative KR of acyclic tertiary α-hydroxy carbonyl derivatives, such as ester, ketone and phosphonate, to afford the recovered tertiary alcohol and corresponding ester with low to excellent levels of selectivity (*s* up to 140) (Scheme 58).



Scheme 58 – Kinetic resolution of α-hydroxy esters

4.1 Structural progression to acyclic α-hydroxy carbonyl derivatives

To obtain an overview of the scope and limitations of the developed KR protocol, the next logical approach was to investigate the KR of tertiary alcohols based on an acyclic core structure (Figure 37). Computational studies on the KR of 3-hydroxyoxindoles have already identified the carbonyl functionality as the key recognition motif between substrate and catalyst. With this in mind, a range of α-hydroxy carbonyl derivatives were to be synthesized by sequentially varying the electronic parameters of the carbonyl group, such as amide, ester, ketone and phosphonate, in order to observe how variation in this group alters the donor ability of the substrate-catalyst interaction, and the resulting effect on observed selectivity.

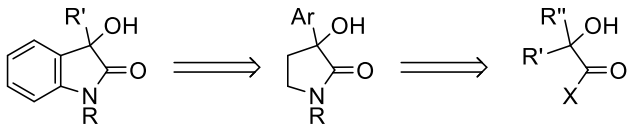


Figure 37 – Progressive structure breakdown

Thus far, there is only one manuscript in the literature, reported by Miller in 2001, for the acylative KR of acyclic tertiary alcohols, based on *N*-acylated 1,2-amino alcohols.[79] However, this work requires a complex pentapeptide catalyst and high catalyst loadings (10 mol %), a large excess of anhydride (8.5 equiv.) and base (3.4 equiv.), low temperatures for good selectivity (–23 °C) and long reaction times (3 d). The overall scope was very limited with only seven substrates tested in the KR protocol, all containing an *N*-acetyl group. Four examples which showed varied substitution on the aromatic substituent, such as 4-methyl, 4-nitro, 2-naphthyl and tetrahydronaphthyl, and one example replacing

the phenyl group with a cyclohexyl group. Finally, there is only one example deviating from methyl substitution at the carbinol centre (Figure 38).

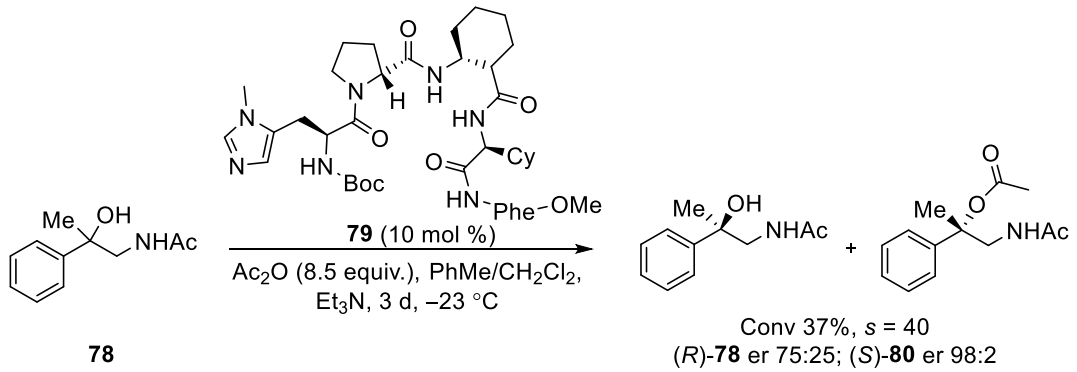
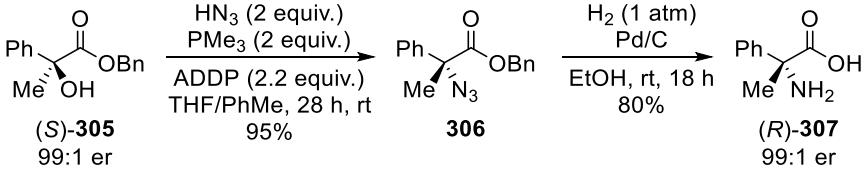


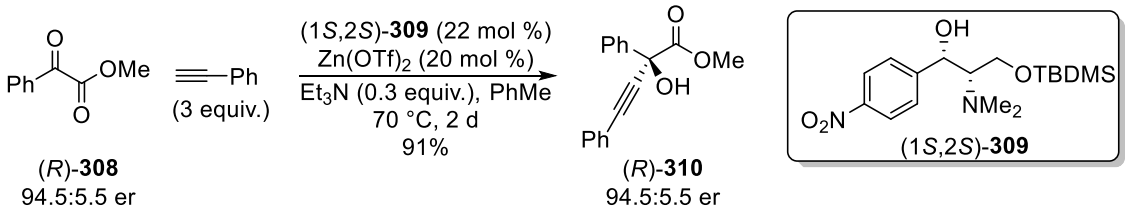
Figure 38 – Only reported acylative KR of acyclic tertiary alcohols

However, whilst there are no examples in the literature for the KR of tertiary α-hydroxy esters, there are numerous examples for the enantioselective synthesis for this class of substrate. The ability to synthesize α-hydroxy esters in highly enantiopure form is important as they serve as valuable building blocks and are present in many biologically active compounds and synthetic drugs.[127] For example, α-hydroxy esters have also been used in the synthesis of optically active unnatural amino acids by McCarthy and co-workers,[128] *via* a Mitsunobu reaction with HN_3 to give α-azido ester **306** intermediate, followed by hydrogenolysis to give the optically active α,α-disubstituted amino acid (*R*)-**307** in overall 76% yield, with complete enantiospecificity (99:1 er) (Scheme 59).



Scheme 59 – Chemical transformation of α-hydroxy ester **305** to α,α-disubstituted amino acid **307**

In 2002, Jiang and co-workers utilized a zinc catalyst for the enantioselective alkynylation of aromatic α-ketoesters, using chiral amino alcohols as ligands, enabling enantioselectivities of up to 97:3 er.[129] Methyl 2-oxo-2-phenylacetate **308** and phenylacetylene were reacted with $Zn(OTf)_2$ (20 mol %), ligand **309** (22 mol %), NEt_3 (0.3 equiv.) in toluene at 70 °C for 2 days to give the desired α-hydroxy ester **310** in excellent yield and enantioselectivity (Scheme 60). However, the scope reported was limited with only three aromatic groups, and only three alkyne substrates utilized, and this method requiring high temperatures, in addition to long reaction times and high catalyst loadings.



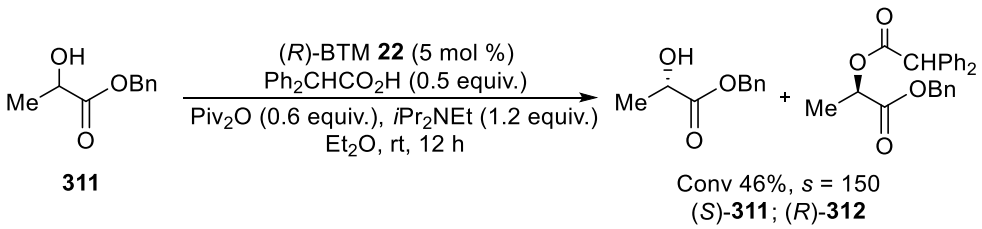
Scheme 60 – Alkynylation of α-ketoester **308**

There are numerous other examples in the literature that report variations of the asymmetric addition of dialkylzinc reagents to α-ketoesters, leading to α-hydroxy ester products with high enantioselectivity.[130]

4.1.1 KR of α-hydroxy esters

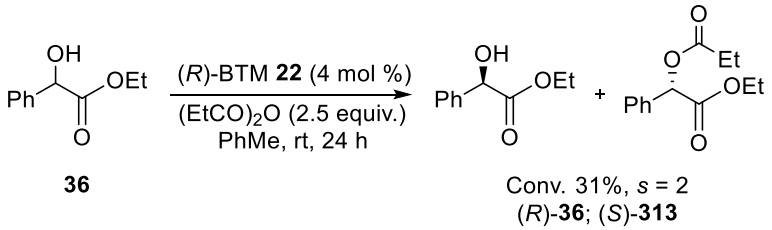
To date, there are only two examples in the literature for the KR of acyclic secondary α-hydroxy esters, with currently no examples for the KR of tertiary α-hydroxy esters.

In 2010, Shiina reported the acylative KR of 2-hydroxyalkanoates, through the use of (*R*)-BTM **22** and a mixed anhydride, formed in situ from an anhydride and a carboxylic acid, with *s* up to >200 observed.[50c] The KR of benzyl lactate **311** with (*R*)-BTM **22**, diphenylacetic acid and pivalic anhydride in the presence of Hünig's base, proceeded with excellent conversion (46%) and excellent selectivity (*s* = 150) after 12 h (Scheme 61).



Scheme 61 – KR of secondary alcohol α-hydroxy ester **311**

In the same year, Chen reported the acylative KR of a range of α-substituted secondary benzyl alcohols, with a range of functional groups at the α-position, such as nitrile, ester and trifluoromethyl groups, through the use of an anhydride and isothiourea catalyst (*R*)-BTM **22**.[131] The KR of ethyl mandelate **36** with propionic anhydride and (*R*)-BTM **22** proceeded with moderate conversion (31%) and poor selectivity (*s* = 2) (Scheme 62).

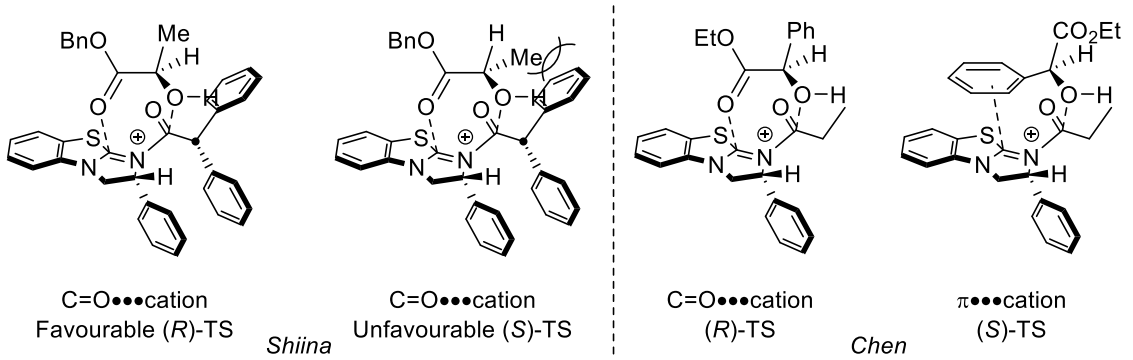


36

Conv. 31%, *s* = 2
(*R*)-**36**; (*S*)-**313**

Scheme 62 – KR of secondary alcohol α-hydroxy ester **36**

Despite the resolution of very similar substrates, there is a vast difference in the observed selectivities in these reports. The work conducted by Shiina produced excellent selectivities, as there is only one recognition motif present in the lowest energy TS (C=O•••isothiouronium), with the acylation TS for the fast reacting (*R*)-enantiomer stabilized by a C=O•••isothiouronium interaction between substrate and *N*-acylated catalyst, however the TS for the slower reacting (*S*)-enantiomer is destabilized due to a steric clash between the methyl group and the *N*-acyl group of the acylated catalyst (Figure 39). In comparison, the work conducted by Chen produced considerably lower selectivities. This is due to the lowest energy acylation TS for (*R*)-enantiomer being stabilized by a C=O•••isothiouronium interaction, whilst the lowest energy acylation TS for (*S*)-enantiomer is stabilized by a π•••isothiouronium interaction. The low selectivity can therefore be attributed to competition between these two lowest energy TSs for each enantiomer.



C=O•••cation
Favourable (*R*)-TS

Shiina

C=O•••cation
Unfavourable (*S*)-TS

C=O•••cation
(*R*)-TS

Chen

π•••cation
(*S*)-TS

Figure 39 – Competitive recognition motifs and steric effects for KR of α-hydroxy esters

An analogous interaction between substrate and catalyst has also been shown to be present for the KR of secondary alcohol α-hydroxy phosphonates, with a P=O•••isothiouronium interaction identified through computational studies as the key recognition motif between substrate and catalyst (see Section 1.3.2).

4.2 Aims and objectives

The aim of the work in this chapter describes the first example of the acylative KR of acyclic tertiary α-hydroxy carbonyl derivatives, that incorporate two or more recognition motifs at the carbinol stereocentre. Computations have previously identified the key interaction between substrate and

catalyst in the lowest energy TS for the acylative KR of 3-hydroxyoxindole as a C=O•••isothiouronium interaction. Therefore, a range of acyclic α-hydroxy carbonyl substrates, with variation in the carbonyl functionality, containing groups such as amides, ketones, phosphonates and esters, were synthesized. These substrates will be investigated in order to observe how alterations in the donating ability of the C=O group affects selectivity and reactivity. The main focus of the work will concentrate on α-hydroxy ester substrates containing two potential recognition motifs; aryl and carbonyl groups, with variation of the ester group and aryl substituents investigated. Following this, substrates with varying alkyl substituents will be investigated to gauge how the sterics of this stereocentre affects acylation efficiency and selectivity. Subsequently, a third potential recognition motif will be introduced at the carbinol stereocentre in the form of alkenyl and alkynyl substituents (Figure 40). Finally, under the optimized conditions, the KR protocol will be extended to other carbonyl functionalities, such as amide, ketone and phosphonate.

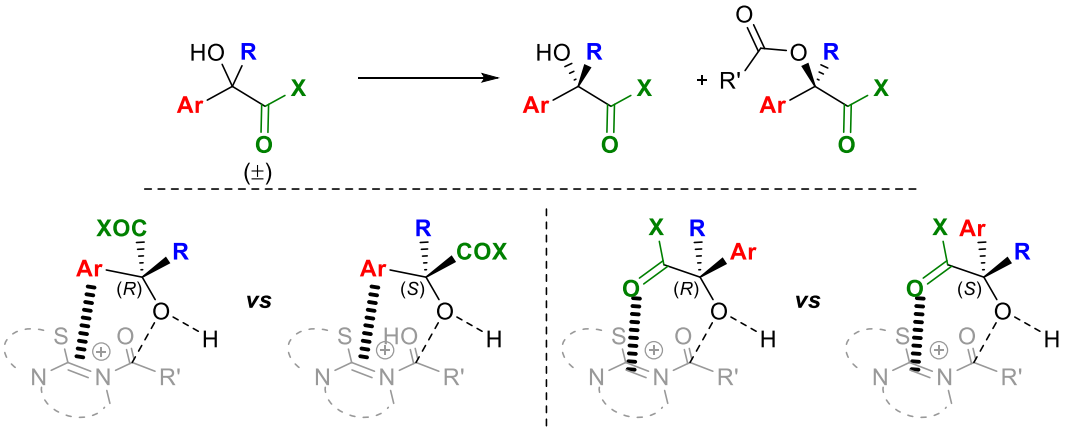
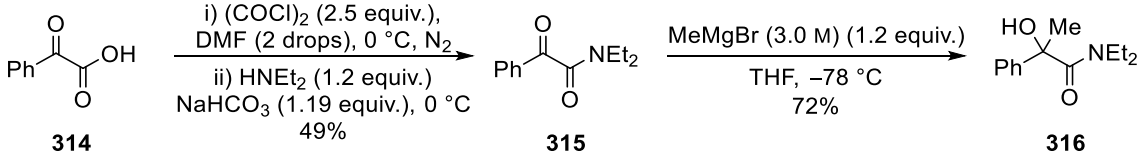


Figure 40 – Potential three recognition motifs for tertiary alcohol α-hydroxy carbonyl derivatives

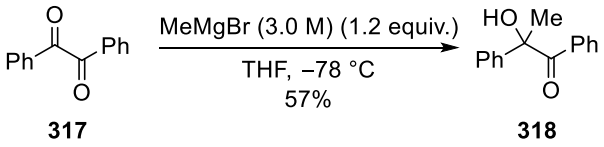
4.3 Synthesis of acyclic α-hydroxy carbonyl derivatives

As a continuation from the previous projects and to test whether our KR protocol could be extended to tertiary α-hydroxy carbonyl derivatives, a range of α-hydroxy carbonyl derivatives was synthesized. An assumption is that the aryl π-system of the alcohol could potentially act as the major interaction between substrate and catalyst, over the carbonyl substituent. Starting from phenylglyoxylic acid **314**, *N*,*N*-diethyl-2-oxo-2-phenylacetamide **315** was synthesized *via* the intermediate acid chloride, using oxalyl chloride and DMF. To this intermediate, diethylamine and sodium bicarbonate were added to give **315** in 49% overall yield. This amide was treated with methyl magnesium bromide at –78 °C to give the desired tertiary alcohol, α-hydroxy amide **316**, in 72% yield (Scheme 63).



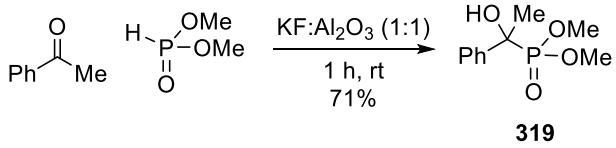
Scheme 63 – Synthesis of α-hydroxy amide **316**

The synthesis of α-hydroxy ketone **318** was achieved by the simple addition of methyl magnesium bromide to benzil **317,** giving the desired product in 57% yield (Scheme 64).



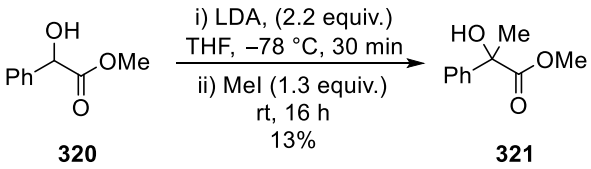
Scheme 64 – Synthesis of α-hydroxy ketone **318**

Attention then turned to the use of α-hydroxy phosphonates, in which the secondary alcohol analogues have already been investigated in KR by Shiina.[52] The tertiary alcohol analogue was synthesized from the method reported by Foucaud, treating acetophenone and dimethyl phosphite, in a 1:1 mixture of potassium fluoride and alumina, with the desired product **319** isolated in 71% yield (Scheme 65).[132]



Scheme 65 – Synthesis of α-hydroxy phosphonate **319**

A tertiary alcohol bearing an ester group as the α-functional group was also synthesized. Following a method by Ruiz, methyl mandelate **320** was added to a solution of LDA in THF at –78 °C, followed by addition of methyl iodide to give the desired α-hydroxy ester **321** in low yield (Scheme 66).[133]

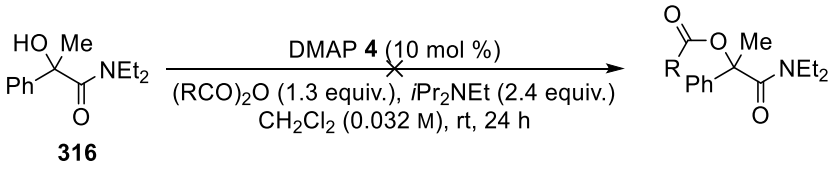


Scheme 66 – Synthesis of α-hydroxy ester **321**

4.4 Acylation of α-hydroxy carbonyl derivatives

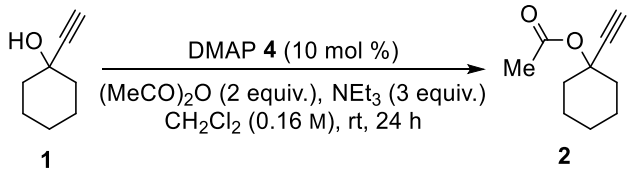
Under the conditions previously established for the esterification of 3-hydroxyoxindoles and 3-hydroxypyrrolidinones, α-hydroxy amide **316** was treated with isobutyric anhydride (1.3 equiv.), DMAP **4** (10 mol %) and *i*Pr$_2$NEt (2.4 equiv.) at room temperature for 24 h (Scheme 67). However, none of the desired ester was observed with full recovery of starting material. This reaction was repeated

using the less sterically demanding acetic anhydride, however, the same outcome was observed, with only starting material recovered. An increase in the catalyst loading to 20 mol %, temperature to 50 °C and concentration to 0.16 M again resulted in full recovery of **316**. These results were unexpected as no problems had previously been observed with the acylation of the oxindole and pyrrolidinone substrates.



Scheme 67 – Attempted acylation of α-hydroxy amide **316**

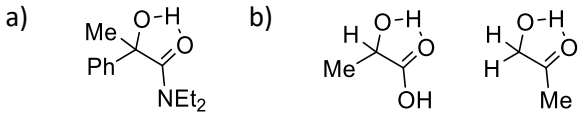
These results prompted the testing of the esterification conditions on a standard tertiary alcohol substrate previously demonstrated in the literature. The tertiary alcohol that has historically been utilized for acylation is 1-ethynylcyclohexan-1-ol **1**, as previously shown in section 1.1.2. Therefore, alcohol **1** was synthesized from lithiated trimethylsilyl acetylene and cyclohexanone in 61% yield. Under the previously used esterification conditions, only 25% conversion of **1** was observed. However, subjecting this sterically strained tertiary alcohol to the standardized conditions widely reported in the literature,[134] using acetic anhydride (2 equiv.), DMAP (10 mol %) and triethylamine (3 equiv.), over 95% conversion of the starting alcohol to the desired ester was observed (Scheme 68), with a much higher reaction concentration used for the literature conditions (0.16 M).



Scheme 68 – Acylation of **1** using standard literature procedure

These conditions were then implemented in the attempted acylation of α-hydroxy amide **316**, however, no acylation was again observed with full recovery of starting material. To try to understand why there was no observable acylation, further investigation was required. Upon analysis of the ^{1}H NMR spectrum of α-hydroxy amide **316**, the chemical shift of C(2)O*H* was seen to be at 5.46 ppm, which is higher than that observed for the 3-hydroxyoxindole and 3-hydroxypyrrolidinone substrates in previous work. This higher chemical shift may be attributed to an internal hydrogen bond between the C(2)O*H* and the carbonyl oxygen (Figure 41a). Based on their hydrogen bonding potentials,[135] hydroxyl groups are good hydrogen bond donors (α = 2.7), and amides group are excellent hydrogen bond acceptors (β = 8.3), therefore this theorized intramolecular 1,5-hydrogen bond seems very possible. This phenomenon can be further supported as intramolecular 1,5-hydrogen bonding has

been observed to be energetically favourable by computations in a range molecular structures between an α-hydroxyl and a carbonyl oxygen, such as lactic acid **322** and acetol **323** (Figure 41b).[136] This could help to explain the lack of acylation observed, as the hydroxyl is not readily available, due to the presence of this intramolecular hydrogen bond to the amide carbonyl.



316 **322** **323**

Figure 41 – a) Potential internal H-bond in alcohol **316**; b) Most stable conformers of **322** and **323** showing internal H-bond determined by computations

To try to disrupt this hydrogen bond, the reaction was repeated using solvents of different polarities; toluene, DMSO, DMF and MeCN were all tested at reaction temperatures, ranging from room temperature to 90 °C, however all of these proved unsuccessful with no conversion to the ester and only starting material recovered.

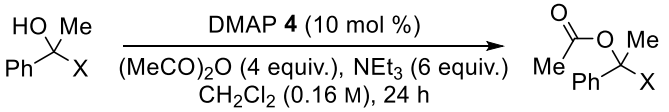
The acylation of α-hydroxy ketone **318,** α-hydroxy phosphonate **319** and α-hydroxy ester **321** was conducted using acetic anhydride (4 equiv.), DMAP (10 mol %) and NEt_3 (6 equiv.) at RT for 24 h (Table 36).

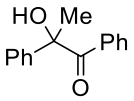
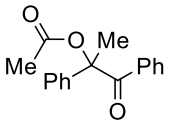
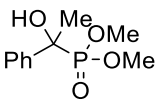
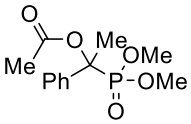
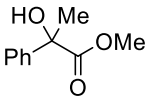
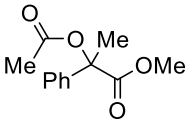
For α-hydroxy ketone **318**, only 19% conversion to the desired ester was observed, though this is significant compared to α-hydroxy amide **316**. The reaction was repeated at 50 °C, with 90% conversion to ester **324** observed. For this class of substrate to be investigated for KR, acylation must also readily occur using an isothiourea catalyst. Racemic HyperBTM **26** (10 mol %) was used to test this, in order to eliminate any matched-mismatched effect that could arise from using the enantioselective catalyst, with over 90% conversion of starting alcohol observed at 50 °C.

Acylation of α-hydroxy phosphonate **319** proceeded with only 25% conversion after 24 h. The reaction at 50 °C provided only 23% conversion to the desired ester (observed by ^{1}H NMR), with significant amounts of acetophenone and dimethyl phosphite observed in the crude ^{1}H NMR. This would indicate that α-hydroxy phosphonate **319** undergoes a retro reaction at the elevated temperature back to its precursor starting materials, with a similar retro reaction shown in the work conducted by Yao.[137] Therefore, acylation of **319** was repeated at RT with a reaction time of 3 days to provide ester **325** in 73% yield. However, using racemic HyperBTM **26** (20 mol %) and acetic anhydride, over 3 days, led to only 37% conversion to ester **325**.

Acylation of α-hydroxy ester **321** proceeded with quantitative conversion to the desired ester **326**. The reaction was repeated using racemic HyperBTM **26** (10 mol %) with full consumption of the starting alcohol observed.

Table 36 – Testing acylation conditions for various α-hydroxy carbonyl derivatives



Entry	Alcohol	Product	Conv (%) RT	RT, 3 d	50 °C	*rac* **26**
1	 **318**	 **324**	19	–	>90	>90[a]
2	 **319**	 **325**	25	74	23	37[b]
3	 **321**	 **326**	>99	–	–	>99

[a] 50 °C. [b] RT, 3 d, 20 mol %. [b] RT, 3 d, 20 mol %

From analysis of the ^{1}H NMR spectrum of these α-functionalized tertiary alcohols, the chemical shifts for C(2)O*H* are seen at 4.77 ppm for α-hydroxy ketone **318**, 3.19 ppm for α-hydroxy phosphonate **319** and 3.76 ppm for α-hydroxy ester **321** (Table 37). Based on hydrogen-bonding potentials, an amide (β = 8.3) is a better hydrogen bond acceptor than a ketone (β = 5.8), which is consistent with the hydroxyl of **318** having a lower chemical shift compared to α-hydroxy amide **316**. This indicates a higher potential for reactivity, which was observed for the acylation of **318**, though a higher temperature was required for good reactivity. Phosphonate diesters have a much higher H-bond acceptor value (β = 8.9) than ketones and slightly higher than amides. From this, it could be expected that acylation may be challenging. However, the chemical shift of the hydroxyl was much lower for **319**, than that of both ketone and amide substrates, indicating a significantly weaker internal hydrogen bond between the hydroxyl and P=O bond, potentially due to longer C-P and P=O bonds disfavouring this interaction. The H-bonding acceptor value for an ester is significantly lower (β = 5.3) than that of the other functional groups, indicating a weaker hydrogen bond between the α-hydroxyl and the carbonyl, as indicated by the reactivity observed for the acylation of α-hydroxy ester **321**.

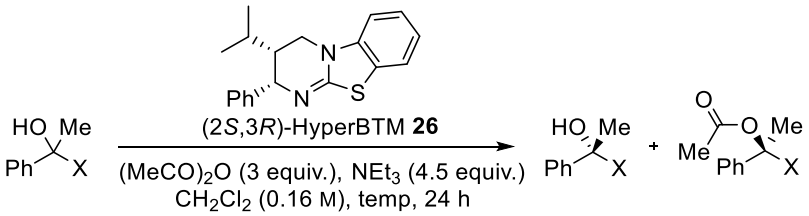
Table 37 – H-bond acceptor values and hydroxyl chemical shift values for carbonyl derivatives

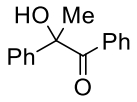
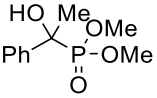
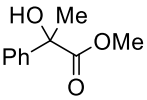
Carbonyl derivative	β	C(2)O*H* (ppm, $CDCl_3$)
Amide	8.3	5.46
Ketone	5.8	4.77
Phosphonate	8.9	3.19
Ester	5.3	3.76

4.5 Initial KR of α-hydroxy carbonyl derivatives

These α-hydroxy carbonyl derivatives were then tested in an initial KR with (2*S*,3*R*)-HyperBTM **26** (Table 38). The initial KR of α-hydroxy ketone **318** at 50 °C resulted in promising conversion of 36% obtained, however only minimal selectivity was achieved (*s* = 3). The KR of α-hydroxy phosphonate **319** required (2*S*,3*R*)-HyperBTM **26** (20 mol %) for 72 h, however low conversion (17%) and poor selectivity (s = 1.4) was achieved. The KR of α-hydroxy ester **321** was conducted with acetic anhydride (1 equiv.), NEt_3 (1.5 equiv.) and (2*S*,3*R*)-HyperBTM **26** (5 mol %) at room temperature. This led to good conversion (44%), but with poor *s* = 3. Despite poor selectivity, the facile acylation of **321** in comparison to other substrates tested showed good potential for further optimisation. Based on this, a variety of acyclic α-hydroxy ester tertiary alcohols were investigated for the acylative KR using an isothiourea catalyst and an anhydride.

Table 38 – KR of α-hydroxy benzyl esters with varied aromatics



Entry	Alcohol	Conv	Alc er	Ester er	*s*
1[a]	 **318**	36	62:38	71:29	3
2[b]	 **319**	17	52:48	58:42	1.4
3[c]	 **321**	44	67:33	72:28	3

[a] **26** (10 mol %), 50 °C. [b] **26** (20 mol %), 72 h, RT. [b] **26** (5 mol %), $(MeCO)_2O$ (1 equiv.), NEt_3 (1.5 equiv.), RT.

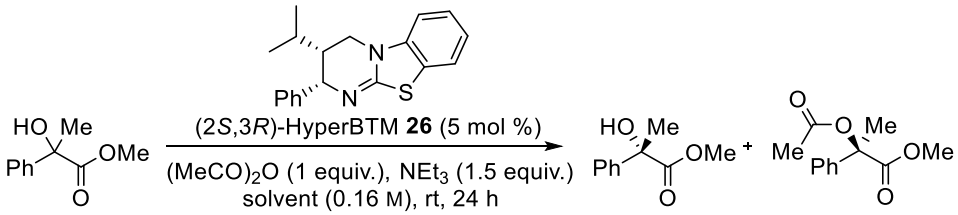
4.6 Optimization

The KR of α-hydroxy methyl ester **321** was optimized by systematic variation of the solvent, anhydride, reaction scale, catalyst and base all tested. Following this, differing substituents on the ester group will be investigated.

4.6.1 Solvent screen

To improve upon the initially observed s = 3 in CH_2Cl_2 (entry 1), the KR of α-hydroxy methyl ester **321**, in the presence of (2*S*,3*R*)-HyperBTM **26**, acetic anhydride (1 equiv.) and NEt_3 (1.5 equiv.), was tested using a variety of other solvents (Table 39). Due to previous successes in the KR of 3-hydroxyoxindoles and 3-hydroxypyrrolidinones, $CHCl_3$ and toluene were first tested in this KR protocol. The KR of **321** in $CHCl_3$ proceeded with 39% conversion, with *s* = 5 (entry 2), comparable to that in CH_2Cl_2 (entry 1). In toluene, improved selectivity (*s* = 12) was observed, in addition to good conversion (43%) (entry 3). The KR of 2-hydroxyalkanoates reported by Shiina was conducted in Et_2O, therefore this was the next tested in the KR of **321**. Pleasingly, the KR of **321** conducted in Et_2O resulted in good conversion (43%) and a higher selectivity (*s* = 15) (entry 4). Other ethereal solvents were then investigated. Interestingly, conducting the KR of **321** in THF provided no conversion to the ester (entry 5). This was repeated to confirm whether it was an anomalous result, however the same outcome was observed with no conversion of starting alcohol. The KR in 1,4-dioxane resulted in lower conversion

Table 39 – Solvent screen



Entry	Solvent	Conv	er alc	er est	*s*
1	CH_2Cl_2	44	67:33	72:28	3
2	$CHCl_3$	39	67:33	77:23	5
3	PhMe	43	78:22	88:12	12
4	Et_2O	43	80:20	89:11	15
5[a]	THF	0	-	-	-
6	1,4-Dioxane	19	59:41	88:12	8
7	MTBE	36	73:27	90:10	14
8	EtOAc	41	74:26	85:15	9
9	DMC	37	71:29	85:15	8
10	MeCN	25	58:42	76:24	3

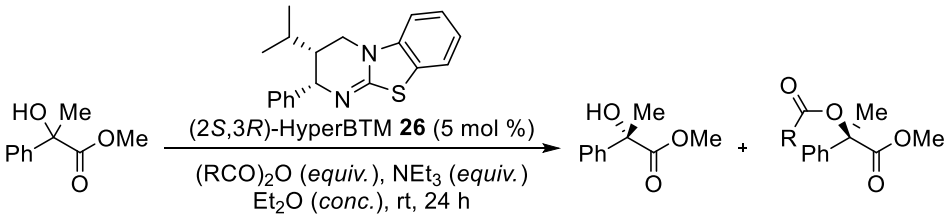
[a] Repeated twice

(19%) and selectivity (*s* = 8) compared to Et_2O (entry 6), whilst conducting the KR of **321** in *tert*-butyl methyl ether (MTBE) resulted in similar selectivity (*s* = 14) (entry 7), with a slight decrease in conversion (36%). Other solvents such as EtOAc, dimethyl carbonate and acetonitrile were also screened with lower selectivity observed (*s* = 3-9, entries 8-10). From this screen, Et_2O was chosen for further optimization.

4.6.2 Anhydride and equivalents

Racemic samples of propionate **327** and isobutyrate ester **328** were synthesized from α-hydroxy methyl ester **321**. Repeating the KR reaction of **321** with (2*S*,3*R*)-HyperBTM **26**, propionic anhydride (1 equiv.) and NEt_3 (1.5 equiv.) resulted in 46% conversion and increased selectivity (s = 24) (Table 40, entry 2). However, the use of isobutyric anhydride in the KR led to a drop in conversion (32%), but significantly improved selectivity (*s* = 60) (entry 3). Concentration was taken into consideration and reaction vessels were sealed to prevent solvent evaporation. To boost the conversion closer to 50%, an increase in anhydride (2 equiv.) and reaction concentration (0.32 M) resulted in a much higher conversion of 47%, without altering selectivity (*s* = 60) (entry 4). Therefore, the use of isobutyric anhydride (2 equiv.) and NEt_3 (3 equiv.) at a concentration of 0.32 M was chosen for further optimization.

Table 40 – Anhydride and concentration screen



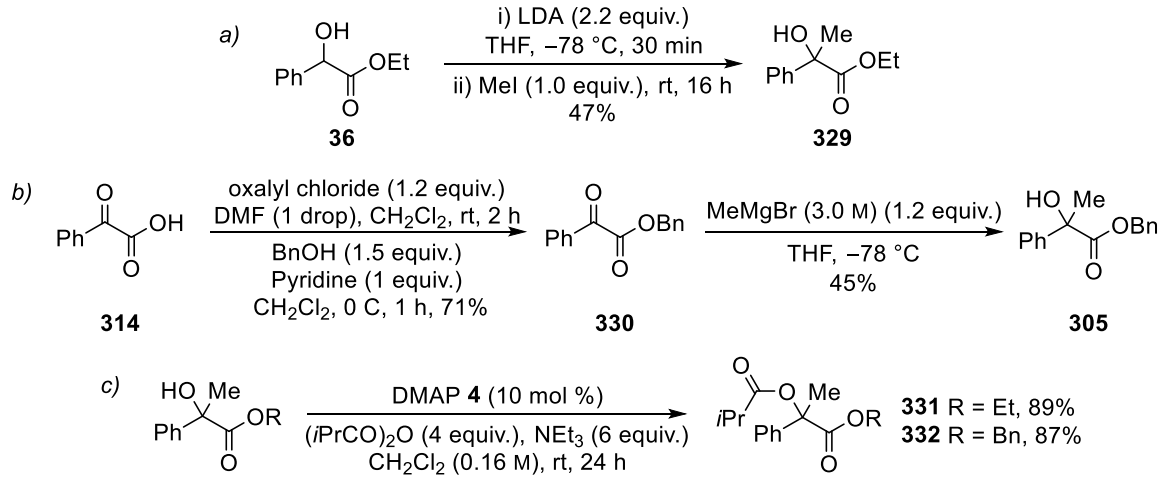
Entry	R (equiv.)	Conc. (M)	Conv	er alc	er est	*s*
1	Me (1)	0.16	43	80:20	89:11	15
2	Et (1)	0.16	46	87:13	92:8	24
3	*i*Pr (1)	0.16+	32	73:275	98:2	60
4	*i*Pr (2)	0.32	47	92:8	96:4	60

Anhydride to base ratio 1:1.5 equiv.

4.6.3 Ester variation and scale

Variation of the ester group was next investigated. Ethyl ester **329** was synthesized in the same manner as the methyl ester; by treatment of ethyl mandelate **36** with LDA, followed by MeI to give the desired α-hydroxy ethyl ester **329** in 47% yield (Scheme 69a). Purification of the benzyl ester derivative by column chromatography proved difficult, therefore an alternative synthetic route was determined for the synthesis of this substrate. Phenylglyoxylic acid **314** was subjected to oxalyl chloride and DMF (1 drop) giving the intermediate acid chloride, which was then treated with benzyl

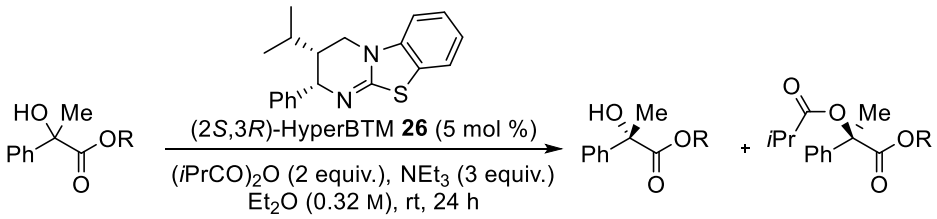
alcohol and pyridine, giving benzyl 2-oxo-2-phenylacetate **330** in 71% yield (Scheme 69b). This α-keto ester was then treated with methyl magnesium bromide resulting in the desired α-hydroxy benzyl ester **305** in 31% yield. Racemic samples of the isobutyrate esters, **331** and **332,** were synthesized from isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP (10 mol %) (Scheme 69c).



Scheme 69 – Differing synthetic routes to desired tertiary α-hydroxy esters

The KR of α-hydroxy ethyl ester **329** surprisingly proceeded with lower conversion (33%) (entry 2) compared to the methyl ester derivative **321**, albeit giving the same selectivity (*s* = 60) (entry 1). Pleasingly, the KR of α-hydroxy benzyl ester **305** proceeded with good conversion (51%), with a significant increase in selectivity (*s* = 120) (entry 3). Therefore, the benzyl esters of α-hydroxy ester variants would be used going forward.

Table 41 – KR of α-hydroxy esters with ester group variation



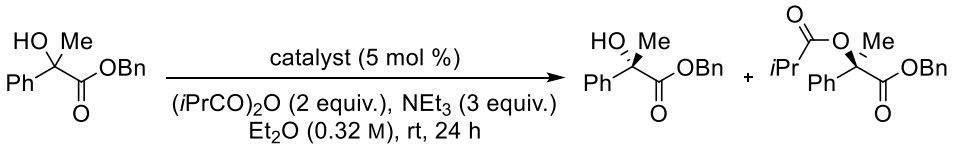
Entry	R	Conv	er alc	er est	*s*
1	Me, **321**	47	92:8	96:4	60
2	Et, **329**	33	74:26	98:2	60
3[a]	Bn, **305**	51	99:1	97:3	120

4.6.4 Catalyst, temperature and base

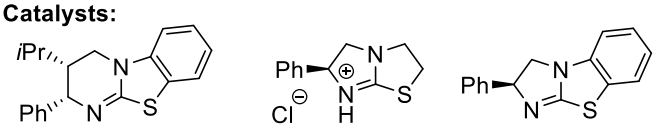
The KR of alcohol **305** was repeated using other isothiourea catalysts: tetramisole hydrochloride (*S*)-**21** and benzotetramisole (*S*)-**22** at 5 mol %, and isobutyric anhydride, with no conversion at room temperature observed, and full recovery of starting alcohol (Table 42). The temperature of the KR using (2*S*,3*R*)-HyperBTM **26** was then investigated, with the reaction repeated at 0 °C. The KR of **305**

proceeded with 41% conversion, and a slightly increased selectivity factor of 130. However, as the KR at room temperature proceeded with higher conversion and with similar levels of selectivity, subsequent reactions were carried out at room temperature for convenience. The possible operation of a base-mediated background reaction was investigated by excluding the catalyst from the reaction medium, with no conversion observed. The KR of **305** using (2*S*,3*R*)-HyperBTM **26** was again repeated in the absence of base, resulting in 49% conversion and s = 140 was observed. Therefore, as the base is not required in the reaction, further KR reactions were conducted in the absence of base. From these studies, the optimized conditions for the KR of α-hydroxy ester **305** was found to be isobutyric anhydride (2 equiv.) and (2*S*,3*R*)-HyperBTM **26** (5 mol %) in Et_2O (0.32 M) at RT for 24 h.

Table 42 – Catalyst, temperature and base screen



Catalysts:



(2*S*,3*R*)-**26** (*S*)-**21** (*S*)-**22**

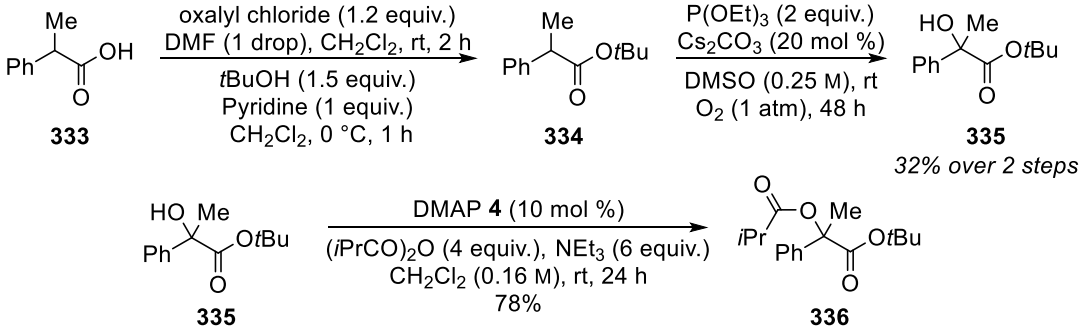
Entry	Catalyst	Conv	er alc	er est	*s*
1	(2*S*,3*R*)-**26**	51	99:1	97:3	120
2	(*S*)-**21**	<1	–	–	–
3	(*S*)-**22**	<1	–	–	–
4[a]	(2*S*,3*R*)-**26**	41	83:17	99:1	130
5[b]	(2*S*,3*R*)-**26**	49	95:5	98:2	140

[a] Reaction at 0 °C. [b] No base.

4.6.5 Varying ester group under optimized conditions

The KR of alcohols **321** and **329** bearing methyl and ethyl ester groups were repeated under these optimized conditions, as well as α-hydroxy *tert*-butyl ester. For the synthesis of the *tert*-butyl ester variant, esterification of 2-phenylpropionic acid was conducted *via* initial formation of the intermediate acid chloride using oxalyl chloride/DMF, followed by addition of *tert*-butyl alcohol and pyridine to give the required ester. However, after several attempts at purification, the ester was not obtained in a completely pure form, but was taken on for oxidation. From the method reported by Liang and co-workers,[144] this ester was treated with $P(OEt)_3$, Cs_2CO_3 in DMSO under an O_2 atmosphere for 48 h, giving the desired α-hydroxy *tert*-butyl ester **335** in 32% yield over the 2 steps (Scheme 70). A racemic sample of the isobutyrate ester **336** was synthesized from isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP (10 mol %) in 78% yield, however baseline separation was not achieved for

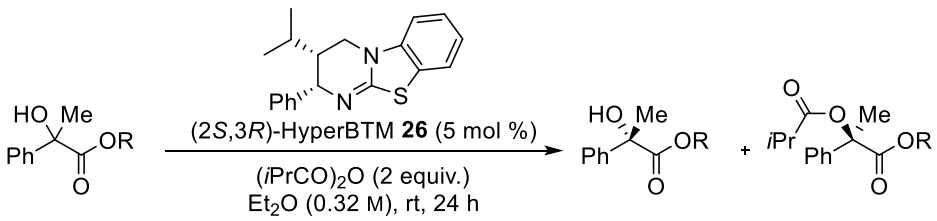
the isobutyrate ester of α-hydroxy *tert*-butyl ester **336**, therefore, the selectivity factor was determined from the conversion of the KR (by ^{1}H NMR) and enantioselectivity of recovered alcohol **335**.



Scheme 70 – Synthesis of α-hydroxy *tert*-butyl ester **336** and diester **336**

Repeating the KR of α-hydroxy methyl ester **321** under the optimized conditions resulted in 41% conversion of starting material, with a s = 70 (Table 31, entry 1). For the KR of α-hydroxy ethyl ester **329**, lower conversion was observed (32%), with a similar level of selectivity to **321** (entry 2). In comparison, the KR of α-hydroxy *tert*-butyl ester **335** proceeded with only low conversion (15%) and the alcohol recovered with low enantioenrichment (57:43 er), corresponding to *s* = 7 (Table 43).

Table 43 – KR of α-hydroxy esters with ester group variation under optimized conditions



Entry	R	Conv	er alc	er est	*s*
1	Me	41	84:16	97:3	70
2	Et	32	73:27	98:2	60
3	*t*Bu	15	57:43	–[a]	7[b]

[a] Baseline separation not achieved for ester [b] Determined by conversion by ^{1}H NMR and er of recovered alcohol

4.6.6 Determination of absolute configuration

The KR of α-hydroxy methyl ester **321** was repeated using isobutyric anhydride (3 equiv.) for 42 h to push to higher conversion in order to obtain a highly enantiopure sample of recovered alcohol. The alcohol was recovered in 93:7 er and 70% yield, and the ester in 64:36 er in 17% yield.

The absolute configuration of α-hydroxy methyl ester **321** was determined by comparison of the specific rotation to that reported in the literature. Literature values show the (*S*)-enantiomer has a positive rotation [([$[\alpha]_D^{20}$ +66 (*c* 0.08, $CHCl_3$), 98.5:1.5 er,[138] $[\alpha]_D^{20}$ +55 (*c* 1.3, $CHCl_3$) at 90.5:9.5 er,[130f] and

$[\alpha]_D^{20}$ +51 (*c* 1.3, $CHCl_3$) at 90.5:9.5 er,[139] with the (*R*)-enantiomer giving negative rotation $[\alpha]_D^{20}$ –58 (*c* 1.39, $CHCl_3$) at 96:4 er.[130a] The specific rotation of isolated α-hydroxy methyl ester **321** following KR (93:7 er) was $[\alpha]_D^{20}$ +52 (*c* 0.1, $CHCl_3$), consistent with an (*S*)-configuration.

In addition, the recovered α-hydroxy methyl ester **321** was hydrolysed to 2-hydroxy-2-phenyl propionic acid **337**,[130a] and literature values have shown the (*S*)-enantiomer of **337** with a specific rotation of $[\alpha]_D^{20}$ +35 (*c* 1.3, $CHCl_3$)[140] and $[\alpha]_D^{20}$ +71 (*c* 0.14, $CHCl_3$),[139] with the (*R*)-enantiomer of **337** having a specific rotation of $[\alpha]_D^{20}$ –33 (*c* 1.3, $CHCl_3$).[140] The specific rotation of **337** from the hydrolysis of **321** was determined to be $[\alpha]_D^{20}$ +63 (*c* 0.1, $CHCl_3$). This further demonstrates that the (*S*)-enantiomer of recovered alcohol is isolated from the KR. This assignment of configuration was therefore assumed for all subsequent alcohols recovered from the KR.

From the configuration of recovered alcohol, it can be inferred that the fast-reacting enantiomer of the alcohol has (*R*)-configuration. A simple model for the enantiodiscrimination observed in the KR process can be postulated based upon comparison of acylation transition state structures previously proposed for the KR of the 3-hydroxyoxindole series which contain a dominant C=O•••isothiouronium interaction (Chapter 2). This key interaction places the ester group over the isothiouronium ion, with the phenyl and methyl substituents at the carbinol stereocentre then positioned either above the *N*-acyl substituent or in a pseudo-axial position away from the catalyst (Figure 42a). For the slow-reacting (*S*)-enantiomer of alcohol, the larger phenyl group sits over the *N*-acyl substituent, producing an unfavourable steric contact and hence hindering the rate of acylation. In comparison, for the fast-reacting (*R*)-enantiomer of alcohol, the steric clash between the smaller methyl group and *N*-acyl substituent is diminished. However, if the phenyl group is acting as the directing group (Figure 42b), providing a π•••isothiouronium interaction, and based on the recovered alcohol, the ester group will be in a pseudo-axial position, with the methyl group sitting over the *N*-acyl substituent.

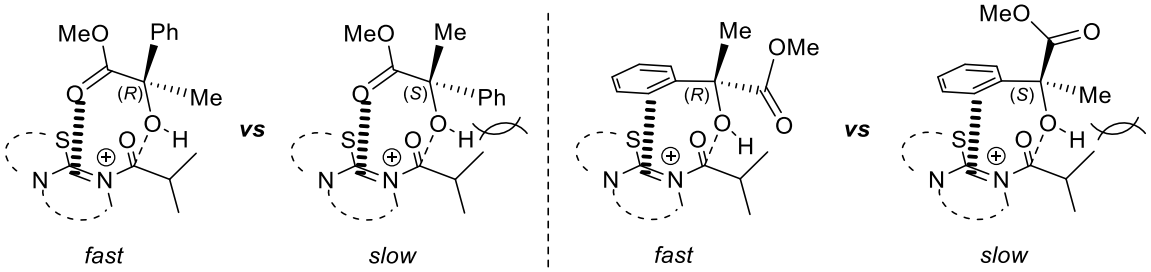


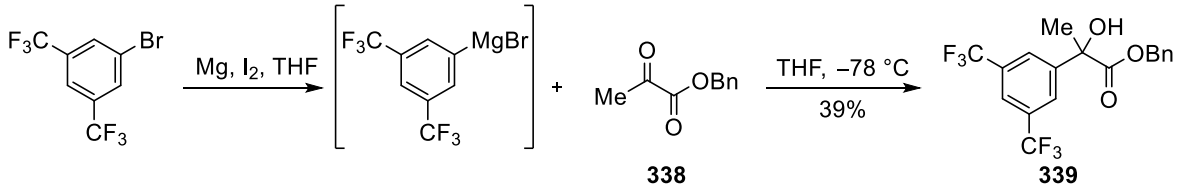
Figure 42 – Possible acylation TS with a) C=O•••isothiouronium interaction, and b) π•••isothiouronium interaction

4.7 Aryl substituents

To investigate the scope and limitations of this KR protocol, a range of α-hydroxy benzyl esters were synthesized bearing differing aromatic groups with both electron-donating and electron-withdrawing substituents, as well as heteroaromatics, incorporated at the carbinol centre.

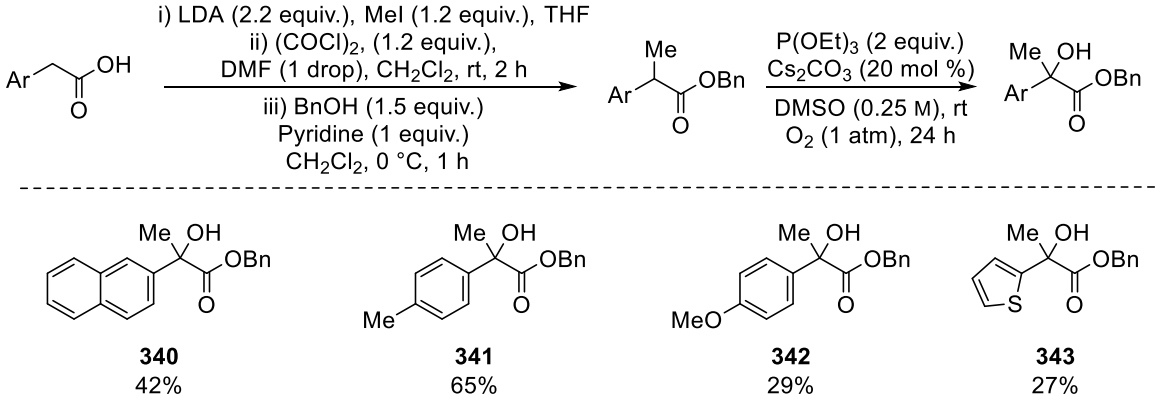
4.7.1 Alcohol and ester synthesis

A range of benzyl 2-aryl-2-hydroxypropionate derivatives were synthesized that incorporated varying electronic nature of the aryl group, either from Grignard addition to benzyl pyruvate **338**, or from a 3-step synthesis from the relevant aryl acetic acids. To 3,5-bis(trifluoromethyl)bromobenzene in THF was added magnesium turnings and an iodine crystal to give the desired Grignard reagent. This was subsequently added to benzyl pyruvate **338** giving the desired α-hydroxy ester **339** in 39% yield (Scheme 71).



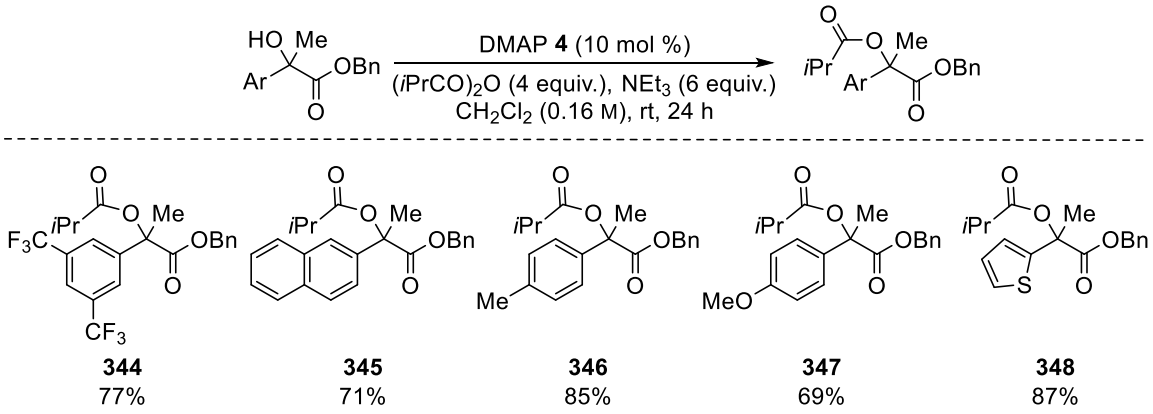
Scheme 71 – Synthesis of Grignard and subsequent α-hydroxy ester **339**

However, an alternative synthetic method was utilized to access other α-hydroxy esters bearing other aromatic groups. The relevant aryl acetic acids were methylated using an LDA solution in THF, followed by addition of methyl iodide to give the methylated acids, obtained in quantitative yield. This was followed by esterification using oxalyl chloride/DMF, then addition of BnOH/pyridine. Intermediate purification proved difficult, so were taken on for oxidation using $P(OEt)_3$, Cs_2CO_3 and an O_2 atmosphere, giving the desired α-hydroxy esters (Scheme 72).



Scheme 72 – 3-step synthesis of α-hydroxy esters

Esterification was carried out under the previously established conditions using isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP **4** (10 mol %), giving the desired esters in good to excellent yields (Scheme 73).

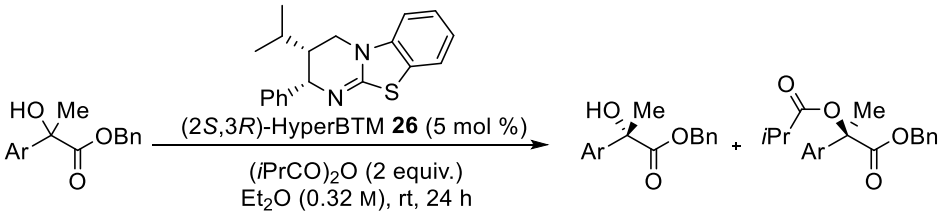


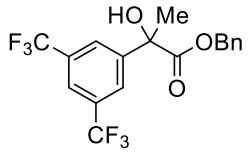
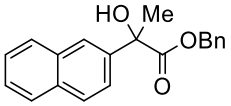
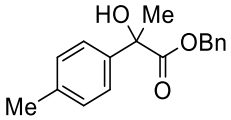
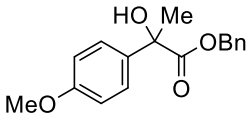
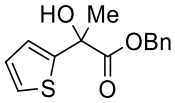
Scheme 73 – Esterification of α-hydroxy esters

4.7.2 KR of α-hydroxy esters

The KR of 2-naphthyl substituted alcohol **340** proceeded with good conversion and excellent selectivity (*s* = 70), albeit with lower selectivity than that observed for the phenyl substituted alcohol **305**. The KR of 3,5-bis(trifluoromethyl)phenyl substituted alcohol **339** under the standard conditions gave 75% conversion and therefore was repeated using just 1 equivalent of isobutyric anhydride. Under these modified conditions, 63% conversion of **339** was obtained with the recovered alcohol obtained in a high enantiopurity (98:2 er) corresponding to *s* = 12. This indicates that groups bearing electron-withdrawing substituents have a detrimental effect on the overall selectivity, as has previously been observed in Chapter 2. Conversely, the KR of the electron-donating 4-methoxyphenyl substituted alcohol **342** proceeded with a slightly lower conversion of 43%, but with increased selectivity (s = 80), which is consistent with the findings seen in Chapter 2, with regards to electron-rich vs electron-poor aromatic groups. The KR of 2-thienyl substituted alcohol **343** proceeded with good conversion and excellent selectivity (*s* = 60), whilst the KR of 4-methylphenyl substituted alcohol **342** gave *s* = 50, albeit with lower conversion (Table 44).

Table 44 – KR of α-hydroxy benzyl esters with varied aromatics



Entry	Alcohol	Conv	Alc		Ester		*s*
			er	Yield	er	Yield	
1[a]	 **339**	63	98:2	29	–[b]	53	12[c]
2	 **340**	52	99:1	41	95:5	41	70
3	 **341**	34	73:27	57	97:3	28	50
4	 **342**	43	86:14	49	98:2	35	80
5	 **343**	55	>99:1	40	91:9	49	60

[a] $(i\text{PrCO})_2\text{O}$ (1 equiv.) [b] Baseline separation not achieved for ester [c] Determined by conversion by ^{1}H NMR and er of recovered alcohol

4.8 Alkyl substituents

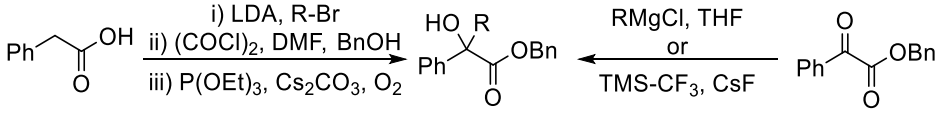
The wider substrate scope of the KR protocol was investigated through variation of the alkyl substituent at the carbinol centre. These α-hydroxy benzyl esters were synthesized by different synthetic routes, in order to incorporate various groups at the α-position, and to observe how larger alkyl groups affect the reaction conversion and selectivity.

4.8.1 Alcohol and ester synthesis

A range of α-hydroxy benzyl ester derivatives was synthesized containing a variety of alkyl substituents, with most starting from phenylacetic acid, followed by deprotonation by LDA and subsequent alkylation using the relevant alkyl bromide. The α-alkylated acids were treated with oxalyl chloride/DMF, followed by addition of benzyl alcohol/pyridine to give the benzyl esters. These esters

could not be obtained pure, so were taken on for further synthetic transformations. Treatment of these esters with $P(OEt)_3$, Cs_2CO_3 in DMSO under a O_2 atmosphere resulted in the desired α-hydroxy benzyl esters. However, this 3-step synthesis was not applicable for all alkyl substituents, therefore alternative methods were applied. Addition of *tert*-butylmagnesium chloride Grignard reagent or Ruppert-Prakash reagent (TMS-CF_3) to benzyl 2-oxo-2-phenylacetate **330**, to give the desired *tert*-butyl substituted α-hydroxy benzyl ester **357** in 32% yield and trifluoromethyl substituted α-hydroxy benzyl ester **359** in 78% yield. Racemic samples of the isobutyrate esters were synthesized under the standard conditions of isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP **4** (10 mol %) in good to excellent yields (Table 45). However, acylation of alcohols **355** and **357** bearing benzyl and *tert*-butyl groups at the carbinol centre, was not observed under these conditions, and repeating these esterifications with higher catalyst loading (20 mol %) for a prolonged reaction time (48 h), yielded the same result. Due to the lack of acylation with DMAP, benzyl substituted alcohol **355** and *tert*-butyl substituted alcohol **357** were not investigated in the KR protocol.

Table 45 – Synthesis of α-hydroxy esters and subsequent esterification



Entry	R	Alcohol		Ester	
		No.	Yield (%)	No.	Yield (%)
1	Et	**349**	35[a]	**350**	91
2	Allyl	**351**	37[a]	**352**	87
3	*n*Bu	**353**	43[a]	**354**	77
4	Benzyl	**355**	27[a]	**356**	–[b]
5	*t*Bu	**357**	32	**358**	–[b]
6	CF_3	**359**	78	**360**	92

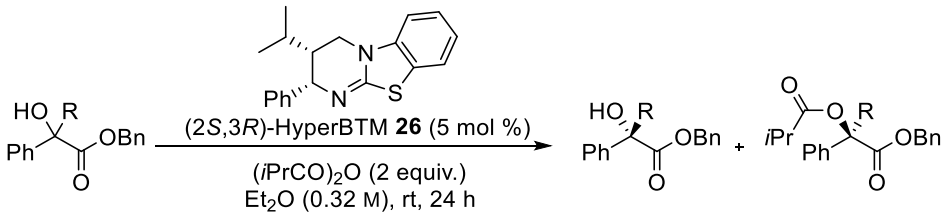
[a] Yield over 3 steps. [b] Conversion <5%

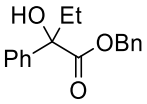
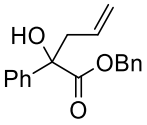
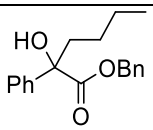
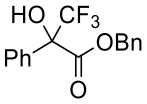
4.8.2 KR of α-hydroxy esters

Interestingly, compared to the KR of α-hydroxy benzyl ester **305**, replacement of the methyl substituent with larger alkyl substituents significantly inhibits reactivity in the KR using (2*S*,3*R*)-HyperBTM **26** and isobutyric anhydride (Table 46). The KR of ethyl substituted **349** proceeded with less than 2% conversion over the usual 24 h reaction period, with the recovered alcohol obtained effectively as a racemate, though the recovered ester was isolated with good enantioselectivity (92:8 er), corresponding to *s* = 11. Low conversion was also observed for the KR of allyl substituted **351**, with only 4% conversion, and moderate selectivity (*s* = 13). A similar result was also observed for the KR of *n*-butyl substituted **353** after less than 2% conversion (*s* = 9). The KR of trifluoromethyl substituted **359** proceeded with moderate conversion, but the trifluoromethyl substituent had an adverse effect

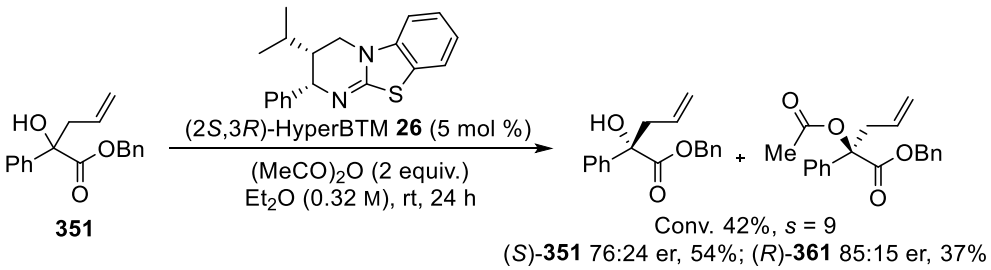
on selectivity, with the KR of **359** proceeding with *s* = 5. This huge reduction in selectivity, compared to methyl analogue **305** is surprising, but indicates that the electron-withdrawing nature of the trifluoromethyl group has a significant detrimental effect on the KR reaction. This is potentially through increased acidity of the hydroxyl proton, thus weakening the hydrogen bond between alcohol hydroxyl and carbonxylate, which facilitates acylation. This result parallels that observed for the KR of 3-hydroxy-3-trifluoromethyloxindole in Chapter 2, which produced significantly reduced selectivity compared to the methyl substituted analogue.

Table 46 – KR of α-hydroxy benzyl esters with varied alkyl substituents



Entry	Alcohol	Conv	Alcer	Alc Yield	Ester er	Ester Yield	*s*
1	 **349**	<2	51:49	92	92:8	1	11
2	 **351**	4	52:48	90	93:7	2	13
3	 **353**	<2	51:49	89	90:10	1	9
4	 **359**	26	60:40	65	80:20	20	5

Due to poor conversions observed in the KR of α-hydroxy benzyl esters bearing alternative alkyl substituents, it was postulated that using acetic anhydride, might result in an increase in reactivity. Repeating the KR of allyl-substituted alcohol **351** in the presence of acetic anhydride and (2*S*,3*R*)-HyperBTM **26** (5 mol %), resulted in much improved reactivity, with a conversion of 42% observed over a 24 h reaction period (Scheme 74). However, similar to the KR with isobutyric anhydride, a relatively low selectivity factor was observed (*s* = 9), indicating that whilst using acetic anhydride in the KR protocol helps to improve the overall reactivity of the KR, high selectivity may be challenging. This is something that could be investigated further, however due to time constraints, this is the only example of acetic anhydride utilized in this KR protocol.



Scheme 74 – KR of **351** using acetic anhydride

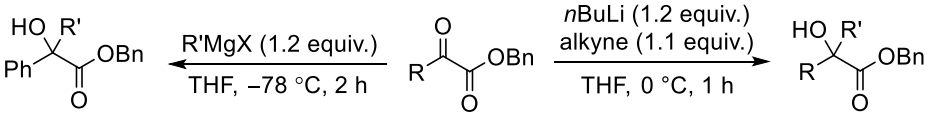
4.9 Alkenyl- and alkynyl- substituents

So far, substrates containing two potential recognition motifs - an ester carbonyl and an aryl substituent - had been tested in the KR. To expand the scope and limitations of the KR, a third recognition motif was introduced adjacent to the carbinol stereocentre, in the form of either an alkenyl substituent, giving a comparison between three sp^2 centres (aryl v carbonyl v alkenyl), or an alkynyl substituent.

4.9.1 Alcohol and ester synthesis

A small range of α-hydroxy benzyl esters containing alkenyl substituents were synthesized from the addition of vinylmagnesium chloride and isopropenylmagneisum bromide to benzyl 2-oxo-2-phenylacetate **330**, providing tertiary alcohols with three sp^2-hybridized recognition motifs at the carbinol stereocentre (Table 47). However, only moderate yields of the isolated alkenyl-substituted tertiary alcohols were obtained due to difficulties arising in purification. For the synthesis of alkyne substituted tertiary alcohols, deprotonation of cyclopropylacetylene with *n*BuLi provided the lithiated acetylene species, which was subsequently added to either benzyl 2-oxo-2-phenylacetate **330**, or benzyl pyruvate **338**, to provide alkynyl-substituted tertiary alcohols **366** and **368** in low to good yield. Racemic samples of the isobutyrate esters were synthesized under the standard conditions of isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP **4** (10 mol %) in good to excellent yield.

Table 47 – Alkenyl- or alkynyl addition to α-ketoester

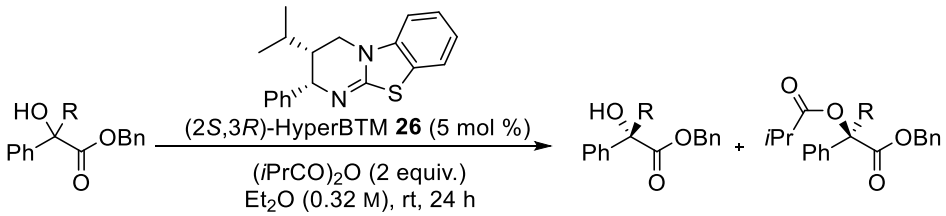


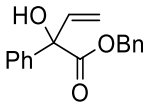
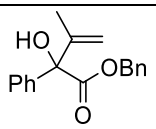
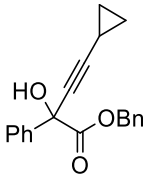
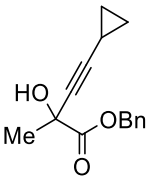
Entry	R	R'	Alcohol		Ester	
			No.	Yield (%)	No.	Yield (%)
1	Ph	Vinyl	**362**	38	**363**	90
2	Ph	Isopropenyl	**364**	42	**365**	87
3	Ph	Cyclopropylacetylynyl	**366**	71	**367**	75
4	Me	Cyclopropylacetylynyl	**368**	24	**369**	81

4.9.2 KR of α-hydroxy esters

The KR of vinyl-substituted alcohol **362** proceeded with moderate conversion and selectivity (*s* = 22), In comparison to the ethyl substituted alcohol **338**, the KR proceeded to much higher conversion, possibly due to the reduced steric hindrance of the sp^2 centre compared to the sp^3 centre in alcohol **338** (Table 48). Increasing the steric bulk at the sp^2 centre adjacent to the carbinol centre, the KR of isopropenyl-substituted **364** resulted in much lower conversion (12%), and very poor selectivity (*s* = 2) under the standard KR conditions. The KR of both alkynyl-substituted tertiary alcohols **366** and **368** resulted in >95% conversion of the starting material under the standardized conditions using 2 equivalents of isobutyric anhydride. Therefore, the amount of anhydride was reduced and the KR for

Table 48 – KR of α-hydroxy benzyl esters with varied alkyl substituents



Entry	Alcohol	Conv	Alcohol		Ester		*s*
			er	Yield	er	Yield	
1	 **362**	32	70:30	60	94:6	27	22
2	 **364**	12	52:48	77	63:37	7	2
3[a]	 **366**	47	76:24	45	80:20	40	6
4[a]	 **368**	41	55:45	48	57:43	34	2

[a] (iPrCO)$_2$O (0.55 equiv.)

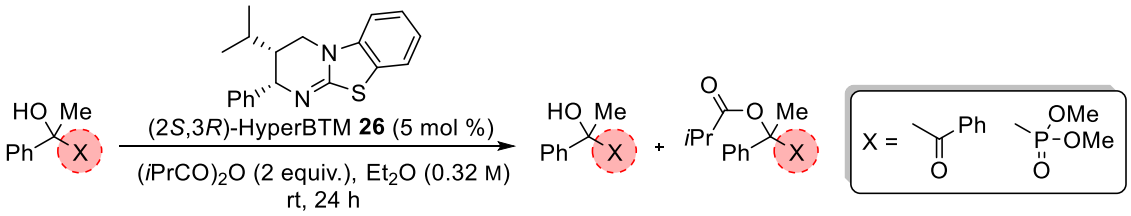
these substrates repeated. The KR of alcohol **366**, using 0.55 equivalents of isobutyric anhydride, proceeded to 47% conversion of alcohol, however only low selectivity was obtained (*s* = 6). In comparison, the KR of alcohol **368** proceeded with a similar conversion (41%), but even lower

selectivity (*s* = 2). These results could indicate that the alkyne group is potentially acting as more of a competitive recognition motif, *via* a π••••isothiouronium interaction in the TS, compared to the phenyl ring, resulting in these low selectivity factors observed.

A reduction in the reaction temperature could potentially help to improve the observed selectivity, especially for the KR of alcohol **366**, which shows semi-promising selectivity. However, due to time constraints, this was not investigated.

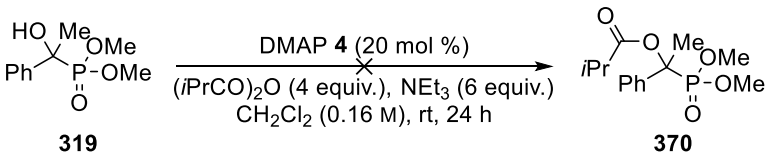
4.10 Structural variations

Poor reactivity and selectivity was previously observed in the KR of other a-hydroxy carbonyl derivatives, such as ketone and phosphonate substrates. Therefore, the KR of these substrates was re-evaluated under the conditions established for the KR of α-hydroxy esters. Variations in the core structure of the α-hydroxy benzyl esters were then investigated with the attempted incorporation of a thioester to give a direct comparison to the parent esters, as well as re-submitting the previously synthesized α-hydroxy ketone and α-hydroxy phosphonate to the optimized KR conditions used for the KR of α-hydroxy esters (Scheme 75).



Scheme 75 – Variations in the core α-hydroxy ester structure

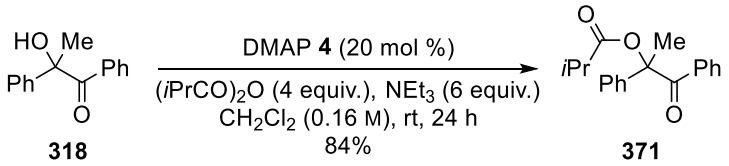
Racemic samples of the isobutyrate esters of α-hydroxy ketone **318** and α-hydroxy phosphonate **319** were required before submitting them to the optimized KR conditions. Attempts to acylate α-hydroxy phosphonate **319** with isobutyric anhydride, even with higher catalyst loadings, were unsuccessful with full recovery of starting material (Scheme 76).



319 **370**

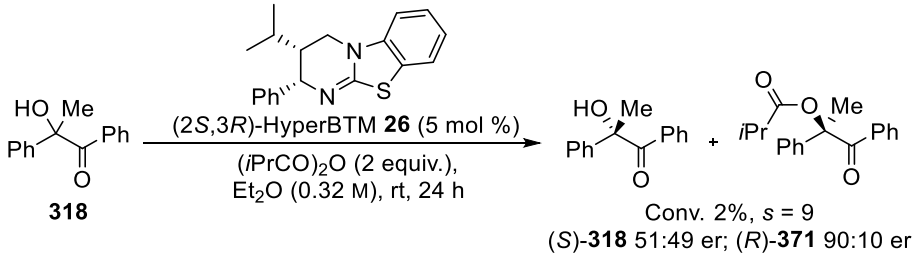
Scheme 76 – Attempted acylation of **319** with isobutyric anhydride

Treatment of alcohol **318** with isobutyric anhydride (4 equiv.), NEt_3 (6 equiv.) and DMAP (20 mol %) at room temperature resulted in good conversion, with the isobutyrate ester **371** obtained in 84% yield (Scheme 77). This was surprising as difficulty arose in the acylation of **318** with acetic anhydride, with an increased reaction temperature of 50 °C required for reactivity.



Scheme 77 – Synthesis of isobutyrate ester **371**

Under the optimized KR conditions using isobutyric anhydride (2 equiv.), (2*S*,3*R*)-HyperBTM **26** (5 mol %) in Et_2O at room temperature for 24 h, the KR of α-hydroxy ketone **318** proceeded with very low conversion (<2%), though with promising selectivity (*s* = 9) (Scheme 78).



Scheme 78 – KR of α-hydroxy ketone **318** with isobutyric anhydride

Further investigations could be conducted for the KR of α-hydroxy ketones, with variation in anhydride, as well as reaction solvent and temperature and differing substitution on the ketone substrate, potentially leading to increased conversion and selectivity.

4.11 Conclusion

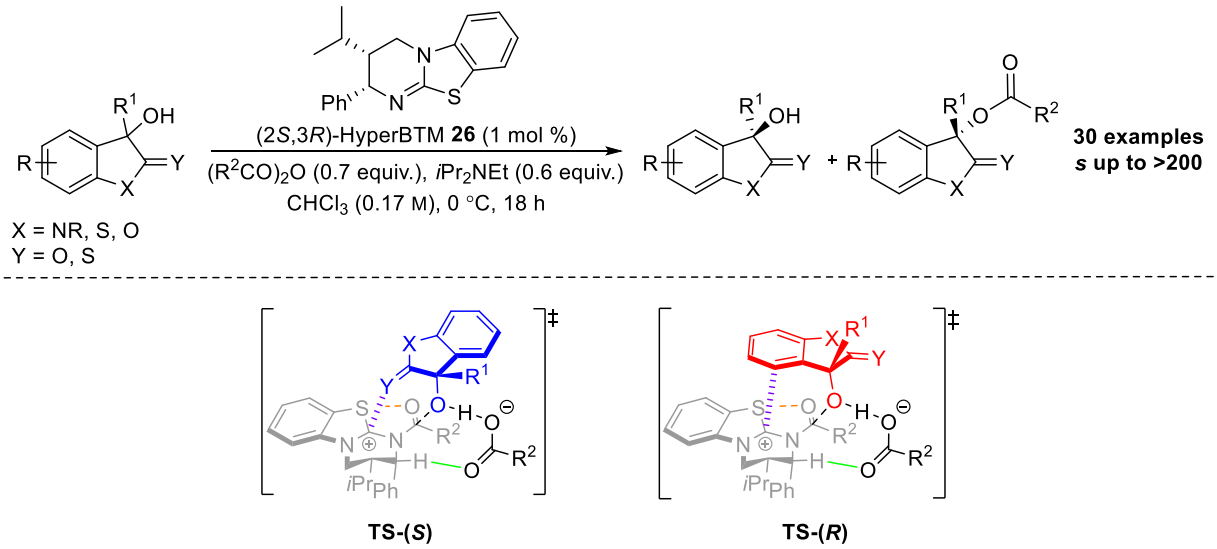
In this chapter, it has been determined that variation of the carbonyl functionality can have a profound effect on reactivity and selectivity in the acylation of various α-hydroxy carbonyl derivatives, such as amide, ketone, phosphonate and ester. Significantly better reactivity and selectivity was observed for α-hydroxy esters, compared to the analogous ketone and phosphonate substrates, leading to the conclusion that the key interaction is between C=O•••isothiouronium, as already established in previous chapters, and not an aryl π•••isothiouronium interaction. Acylation of an α-hydroxy amide was not possible, even at high temperatures and high catalyst loadings. In contrast, acylation of an α-hydroxy ketone and an α-hydroxy phosphonate was possible, however, thus far, the KR of these substrates has led to relatively low selectivity. A range of α-hydroxy esters, bearing α-aryl groups, with groups of varying electronic nature at the carbinol stereocentre can be resolved effectively with selectivity factors up to 140 obtained. Optimization of the KR system found that benzyl esters of the tertiary alcohols gave the best selectivity with (2*S*,3*R*)-HyperBTM **26** (5 mol %), isobutyric anhydride (2 equiv.) as acylating agent and diethyl ether as solvent as optimal, without the requirement of base in the reaction medium. However, though good selectivity was observed for varying the aryl substituent, changing the alkyl substituent from a methyl group to any other substituent significantly

reduces reaction conversion, with less than 5% conversion and low selectivity factors observed in some cases. Introduction of alkenyl substituents at the carbinol stereocentre resulted in higher conversion compared to the larger alkyl substituents, whereas the KR of alkynyl-substituted tertiary alcohols required fewer equivalents of anhydride, due to faster conversion, though poor selectivity factors were still observed in the KR. From the scope investigated in this KR protocol, the limitations of these substrates seem to lie with the alkyl substituent, with any variation from a methyl group significantly decreasing reaction conversion and observed selectivity, with only variations in the aryl substituent leading to good conversion and high selectivities.

CHAPTER 5: CONCLUSIONS AND FUTURE WORK

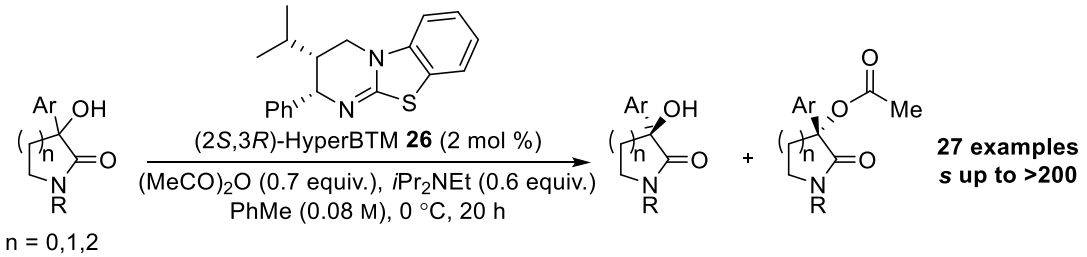
This thesis has described investigations into the acylative organocatalytic kinetic resolution of a range of heterocyclic and acyclic tertiary alcohols, through the use of an anhydride and an isothiourea catalyst.

Firstly, investigations were conducted on the acylative kinetic resolution of tertiary alcohols, with substrates containing a 3-hydroxyoxindole core structure, with selectivity factors up to > 200 observed (Scheme 79). This methodology was only the third example of an acylative kinetic resolution of tertiary alcohols, following work conducted by Miller, using a pentapeptide catalyst and Zhao, utilizing NHC redox catalysis. By comparison, the optimized isothiourea-mediated protocol utilized much simpler reaction conditions, and provided a wider scope than that reported by Zhao. A wide range of 3-substituted-3-hydroxyoxindole substrates, containing a variety of substituents at the 3-position of the oxindole core; ranging from aryl, alkyl, alkenyl and alkynyl substitution with differing electronic properties were investigated, with efficient selectivity observed between the three substituents at the carbinol centre. Notably, in some cases, addition of isobutyric acid was essential to improve the selectivity of the reaction. Various *N*-substituents of differing electronic properties, such as 4-methoxybenzyl, tosyl, 4-methoxybenzoyl and Boc group, were incorporated and tested in the KR protocol, as well as varying substitution around the benzenoid ring of the oxindole core. Tuning the electronics of the substituent at the 5-position of the oxindole core, ranging from strongly electron-donating to strongly electron-withdrawing, ring had a significant effect on the selectivity of the KR and also an effect on C=O bond stretching frequency, which was suggested to provide insight into the interactions between the substrate and catalyst that controls enantiodiscrimination. Computations found that a C=O•••isothiouronium interaction is the major interaction between the fast-reacting enantiomer of alcohol and the acylated catalyst, with the slow-reacting enantiomer being acylated *via* a TS featuring a less favourable π•••cation interaction between the benzenoid ring of the oxindole and the acylated catalyst. Structural variations of the oxindole core were also investigated with the inclusion of a thioamide, thioester, 3-hydroxybenzofuranones and removal of the carbonyl to observe the effect on the selectivity of the reaction. The results obtained were consistent with the proposed TS model, in which the presence of carbonyl is important for both reactivity and selectivity.



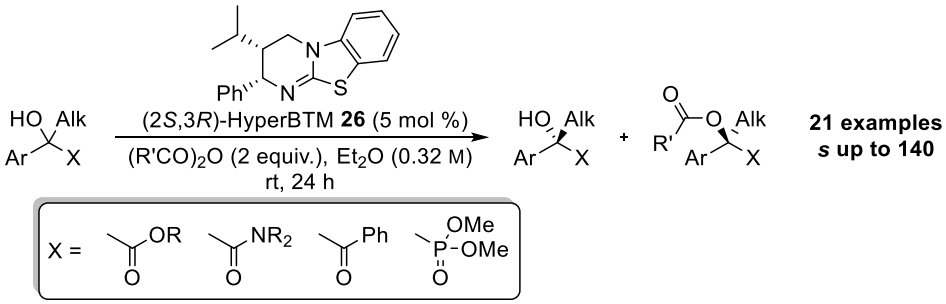
Scheme 79 – Kinetic resolution of 3-aryl-3-hydroxyoxindoles

Subsequent studies focused on expanding the protocol and substrate scope to heterocyclic compounds without a benzenoid backbone in the form of 3-hydroxypyrrolidinones. A range of 3-aryl-3-hydroxypyrrolidinone tertiary alcohols were synthesized from the alkylation of aryl acetic acids with LDA and 1-bromo-2-chloroethane, followed by subsequent amide coupling with the desired amine, and finally a tandem cyclization/oxidation reaction using NaH in the presence of atmospheric O_2. The KR protocol was reoptimized for these new substrates, with the use of acetic anhydride, (2*S*,3*R*)-HyperBTM (2 mol %) and Hünig's base in toluene at 0 °C optimal. Overall, this KR protocol proved to be effective for these substrates with selectivity factors of up to > 200 obtained in the process (Scheme 80). A range of 3-aryl-3-hydroxypyrrolidinone substrates, containing aromatic and heteroaromatic substituents of varying substitution patterns and differing electronic nature, were then investigated. It was found that 4-substituted aromatic groups at the 3-position of the pyrrolidinone core gave high selectivity factors, 3-substituted aromatic groups produced lower selectivities and an increase in reaction temperature was required for 2-substituted aromatic groups, due to poor conversion under the standard conditions. Ring contracted and expanded substrates were also demonstrated, allowing the KR of 3-hydroxyazetidin-2-one and 3-hydroxypiperidin-2-one substrates, however further structural variations proved unsuccessful.



Scheme 80 – Kinetic resolution of 3-aryl-3-hydroxypyrrolidin-2-ones

The next logical approach was to investigate the KR of acyclic tertiary alcohols with varying carbonyl functionality, such as amide, ester, ketone and phosphonate. With only one example in the literature, reported by Miller for the acylative KR of acyclic tertiary alcohols, based on *N*-acylated 1,2-amino alcohols, these substrates were of interest in the KR protocol. Investigating the KR of a α-hydroxy amide demonstrated that acylation was challenging even at high catalyst loadings and reaction temperatures. Alternative core structures were investigated and it was found that acylation of α-hydroxy esters readily occurs with an anhydride and (2*S*,3*R*)-HyperBTM **26** as catalyst, with selectivities of up to 140 observed. A range of α-aryl-α-hydroxy-α-methyl esters, bearing aromatic groups of varying electronic nature, and a heteroaromatic group, were shown to be tolerated in the KR protocol, with high selectivity factors observed, although incorporation of electron-withdrawing substituents at the carbinol centre had a negative effect on the observed selectivity factors. Some current limitations of the scope exist however, with only variation in the aryl substituent at the carbinol stereocentre accepted under these conditions. Moving from a methyl group to bulkier alkyl or alkenyl substituents inhibits acylation and also reduces selectivity (Scheme 81). Fewer equivalents of anhydride were required to obtain conversions closer to 50% for for alkynyl substituents at the carbinol centre, though poor selectivity factors obtained. Alternative functional groups, such as ketones and phosphonates, were briefly investigated with limited reactivity and selectivity observed in the kinetic resolution of these substrates.

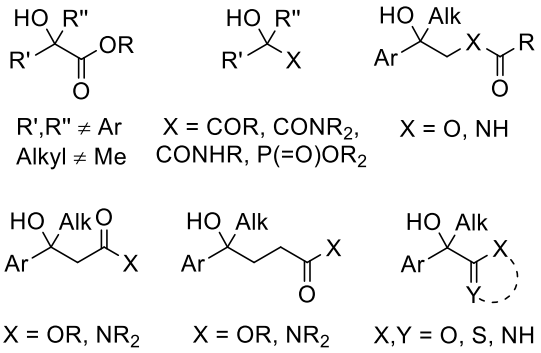


Scheme 81 – Kinetic resolution of acyclic tertiary alcohols

Repeating the kinetic resolution of an α-hydroxy ester bearing a bulkier allyl substituent at the carbinol centre using a less bulky anhydride, acetic anhydride, resulted in a significant increase in conversion, though selectivity remained poor. However, due to time constraints, these substrates were not investigated further.

To further investigate the kinetic resolution of acyclic tertiary alcohols, the reaction system could be further optimized using acetic anhydride for substrates bearing these bulkier substituents with improvements in the selectivity factor targeted through variation of the reaction conditions, such as solvent, temperature and catalyst.

The utility of this acylative kinetic resolution protocol has the potential for use in a wide variety of applications, with further investigations into the KR of acyclic tertiary alcohols, such as substrates similar to that used by Miller, as well as extension of the work conducted on the KR of α-hydroxy esters. Another potential area for investigation would be to vary the donor ability of the carbonyl for α-hydroxy carbonyl derivatives, with variation of the amide substituents to see if acylation can be achieved for this class of substrates, as well as varying the ketone group, as the KR looked to be promising for this class of substrates. Implementing an extended alkyl chain to give β- or γ-functionalized tertiary alcohols, or through incorporation of a heteroaromatic group, which may act as a recognition motif, in place of the carbonyl group, could also be investigated in our KR protocol (Scheme 82).



Scheme 82 – Extension of acyclic tertiary alcohol work

The use of isothioureas as acyl transfer catalysts has been well established in the literature for the kinetic resolution of a wide variety of secondary alcohols. The work reported in this thesis has continued the exploration of this class of catalysts, and advanced what has previously been reported with the kinetic resolution of tertiary alcohols. Most notably, this work has built upon and exceeded the work conducted by Zhao in the KR of 3-hydroxyoxindoles using NHC-catalysts, not only in scope, but also with respect to the materials required for reactivity, with only the use of an anhydride, base and catalyst needed in this developed kinetic resolution protocol. A much broader range of tertiary alcohols have been applied across the three methods outlines, all based on the premise of a C=O•••isothiouronium interaction that was identified as the key recognition motif in the acylation TS. With this in mind, a broader appreciation of this interaction could inspire the use of other catalytic methods that utilize this key stabilizing interaction to direct reactivity.

CHAPTER 6: EXPERIMENTAL

6.1 General information

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N_2) using standard vacuum line techniques. Anhydrous solvents (Et_2O, CH_2Cl_2, THF and PhMe) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 °C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

Room temperature (rt) refers to 20–25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/water and CO_2(s)/acetone baths, respectively. Temperatures of 0 °C to –78 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reaction involving heating were performed using DrySyn blocks and a contact thermocouple.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC vacuum controller, or an IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to –5 °C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and staining with aqueous $KMnO_4$ solution, followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-$20A_5$ degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-$20A_{5R}$ degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using either DAICEL CHIRALCEL OD-H

and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.

GC analyses were obtained on a Shimadzu GC consisting of a Shimadzu AOC-20i auto injector and a Shimadzu GC-2025 gas chromatograph. Analysis was performed using Shimadzu GCsolution v2.41 software and separation was achieved using the column described.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}.

^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; $^{13}C\{^{1}H\}$ 75 MHz; $^{19}F\{^{1}H\}$ 282 MHz; $^{31}P\{^{1}H\}$ 122 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 377 MHz; $^{31}P\{^{1}H\}$ 162 MHz), a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 376 MHz; $^{31}P\{^{1}H\}$ 162 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, $^{19}F\{^{1}H\}$ 470 MHz; $^{31}P\{^{1}H\}$ 203 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, $^{19}F\{^{1}H\}$ 470 MHz; $^{31}P\{^{1}H\}$ 203 MHz), or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe (^{1}H 700 MHz, $^{13}C\{^{1}H\}$ 176 MHz, ^{19}F 659 MHz; $^{31}P\{^{1}H\}$ 284 MHz) in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, J, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic and app denotes apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry (*m/z*) data were acquired by either atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University ($[A]^{+}$ or $[A]^{-}$ quoted).

6.2 General procedures

General procedure A*: Synthesis of 3-hydroxybenzofuran-2-one compounds*

Following the method described by Gasperi *et al*,[108] a pyruvate derivative (1.1 equiv) was added to a stirred solution of a phenol derivative (1 equiv) in anhydrous CH_2Cl_2 under an inert N_2 atmosphere. $TiCl_4$ (1M in CH_2Cl_2, 10 mol %) was added and the solution stirred at the desired temperature for the required time. On completion, the reaction mixture was added to cold water and the aqueous phase extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified *via* column chromatography.

General procedure B*: Esterification of alcohol with anhydrides and DMAP*

An anhydride (1.3 equiv) and DMAP (10 mol %) were added to a solution of alcohol (1 equiv) in CH_2Cl_2. Base (2.4 equiv) was added and the reaction mixture was stirred at RT for 24 h. On completion, the mixture was diluted with EtOAc and washed sequentially with HCl (2 x10 mL) and sat. aq. $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The ester products were purified by column chromatography and analysed by chiral HPLC.

General procedure C*: Kinetic resolution of tertiary alcohols with anhydrides and isothioureas*

An isothiourea catalyst (1-10 mol %) was added to a solution of alcohol (1 equiv) in the required solvent. The reaction was cooled to the required temperature and anhydride (0.6-2.0 equiv) and base (0.6-4.0 equiv) were added. The reaction mixture was stirred for the required time. On completion, the mixture was diluted with EtOAc (20 mL) and washed with HCl (2 x 10 mL) and sat. aq. $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The alcohol and ester were purified by column chromatography and analysed by chiral HPLC.

General procedure D*: Synthesis of tertiary alcohols through Grignard addition*

Following the method described by Trost *et al*,[141] a solution of *N*-protected isatin (1 equiv) was dissolved in anhydrous THF under a N_2 atmosphere and cooled to −78 °C. A Grignard reagent (1 equiv) was added dropwise and the solution stirred at −78 °C for 20 mins, then at 0 °C for 30 mins. Further Grignard reagent (0.2 equiv) was added at 0 °C and reaction monitored by TLC until completion. The reaction mixture reaction was poured into aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified *via* column chromatography.

General procedure E*: Formation of 3-hydroxy oxindoles via a catalytic decarboxylative [1,2]-addition*

Following the method described by Wang *et al*,[97] a solution of *N*-protected isatin (1 equiv) was dissolved in DMF and the corresponding acid (1.1 equiv) was added at RT, followed by addition of triethylamine (20 mol %). The mixture was stirred at 70 °C for the required time. The crude product was purified *via* column chromatography.

General procedure F*: Preparation of Grignard reagent*

Magnesium turnings (3 equiv) were added to anhydrous THF in an oven-dried multi-necked round-bottomed flask under a N_2 atmosphere. The desired bromide (2 equiv) was dissolved in anhydrous THF and 10% of this solution was added to the magnesium. The reaction was stirred at RT until the reaction temperature increased. If the reaction temperature did not increase, a small iodine crystal was added and stirred until the brown colour disappeared and temperature increased. The remaining bromide solution was added over 15 minutes and stirred for a further 2 h, then left cool and settle. The concentration of the prepared Grignard reagent was determined by titration using 2-hydroxybenzaldehyde phenylhydrazone.

General procedure G*: Preparation of α-substituted arylacetic acids*

Following a modified method outlined by Rao *et al*,[142] *n*BuLi (2.2 equiv) was added to a solution of HN^iPr_2 (2.2 equiv) in anhydrous THF in a flame-dried round-bottomed flask under a N_2 atmosphere at 0 °C. The LDA solution was stirred for 30 minutes, the arylacetic acid (1.0 equiv) was added and the reaction mixture stirred for 1 h at 0 °C. The dihaloalkane (2.2 equiv) was added and the reaction stirred overnight at RT. HCl (20 mL) was added until pH 1 was reached. The aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude α-substituted aryl acetic acid.

General procedure H*: Amidation of α-substituted arylacetic acids*

Following the method by Tam *et al*,[117] the crude acid (1 equiv) was dissolved in anhydrous THF and stirred at 0 °C under N_2. 1,1'-Carbonyldiimidazole (0.95 equiv) was added and the mixture stirred for 1 h. The desired amine (1.2 equiv) was added and the reaction mixture warmed to RT and stirred for 2 h. Et_2O (30 mL) and Na_2CO_3 (5 mL) were then added and the organic layer separated, washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

General procedure I*: Preparation of 3-hydroxy-3-aryl pyrrolidin-2-ones*

Following the method by Tam *et al*,[117] to an amide (1 equiv) in anhydrous THF (25 mL) under N_2, was added NaH (60% in mineral oil) (5 equiv) and the mixture stirred for 2 h under N_2. The reaction was then exposed to air and stirred for 16 h. On completion, NH_4Cl (30 mL) was added and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organics were combined, dried ($MgSO_4$) and

concentrated *in vacuo*. On peroxide formation, the mixture was dissolved in anhydrous MeOH (15 mL) and $NaBH_4$ (1.5 equiv) was added and the mixture stirred for 3 h. 1M HCl (10 mL) was then added and the mixture stirred for a further 1 h. The product was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

General procedure J*: Esterification of alcohol with anhydrides and DMAP*

An anhydride (4 equiv) and DMAP (10 mol %) were added to a solution of alcohol (1 equiv) in CH_2Cl_2. Base (6 equiv) was added and the reaction mixture was stirred at RT for 24 h. On completion, the mixture was diluted with EtOAc and washed sequentially with HCl (2 x10 mL) and sat. aq. $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The ester products were purified by column chromatography and analysed by chiral HPLC.

General procedure K*: Esterification of acids via an intermediate acid chloride*

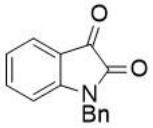
Following the method by Zhao *et al*,[143] to a solution of acid (1 equiv.) in anhydrous CH_2Cl_2 (25 mL), was added oxalyl chloride (1.2 equiv.) and a drop of DMF. The mixture was stirred for 2 h at RT before the solvent and redundant oxalyl chloride were removed under reduced pressure. After which, the relevant alcohol (2 equiv.) and pyridine (1 equiv.) were added to the resulting α-acyl chloride in CH_2Cl_2 at 0 °C and stirred for 1 h. Upon completion, the mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic phases were combined, dried over $MgSO_4$ filtered and concentrated *in vacuo*. The ester products were purified by column chromatography.

General procedure L*: Preparation of α-hydroxy esters*

Following the method by Liang *et al*,[144] the desired ester (1 equiv.), triethyl phosphite (2 equiv.) and cesium carbonate (20 mol %) were mixed under a O_2 atmosphere. DMSO [0.25 M] was added and mixture stirred under O_2 (1 atm) at RT for 24-72 h. On completion, the mixture was diluted with Et_2O and washed with brine (2 x 10 mL), extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The α -hydroxy ester products were purified by column chromatography.

6.3 Data for Chapter 2: Kinetic resolution of 3-hydroxyoxindoles

1-Benzylindoline-2,3-dione, 89

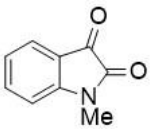


Following the method reported by Hayashi *et al*,[145] isatin (3.67 g, 25 mmol) was dissolved in DMF (125 mL) and cooled to 0 °C. NaH (1.10 g, 27.5 mmol, 60% dispersion in mineral oil), was added in portions and the reaction mixture stirred at 0 °C for 20 mins. Benzyl bromide (4.70 g, 27.5 mmol) was added dropwise and the solution then warmed to RT and stirred for 3 h. The reaction was then quenched with dropwise addition of H_2O (5 mL) and diluted with EtOAc (200 mL). The reaction was quenched with H_2O (3 x 200 mL) and brine (3 x 200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, reduced *in vacuo* and recrystallized from EtOAc/hexane, affording **89** as orange crystals (4.32 g, 18.3 mmol, 73%); mp 126-127 °C; **δ_H (400 MHz, $CDCl_3$)** 4.94 (2H, s, C*H*$_2$Ph), 6.77 (1H, app dt, *J* 8.0, 0.8 Hz, C(7)*H*), 7.09 (1H, app td, *J* 7.6, 0.8 Hz, C(5)*H*), 7.27-7.39 (5H, m, CH_2Ar*H*), 7.48 (1H, app td, *J* 7.8, 1.4 Hz, C(6)*H*), 7.62 (1H, ddd, *J* 7.4, 1.4, 0.6 Hz, C(4)*H*).

Data were in accordance with those previously reported.[145]

Lab book Reference: SMS-146

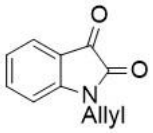
1-Methylindoline-2,3-dione, 90



Following the method outlined by Ishihara *et al*,[146] isatin (3.67 g, 25 mmol) was dissolved in DMF (60 mL) and cooled to 0 °C. NaH (1.10 g, 27.5 mmol, 60% dispersion in mineral oil) was added in portions and the reaction mixture stirred for 20 mins at 0 °C. Methyl iodide (1.71 mL, 27.5 mmol) was added dropwise and the solution then warmed to RT and stirred for 3 h. The reaction was then quenched with dropwise addition of H_2O (60 mL) and diluted with EtOAc (200 mL). The reaction mixture was then extracted with H_2O (3 x 200 mL) and brine (3 x 200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, reduced *in vacuo* and recrystallized from Et_2O, affording **90** as a red solid (3.10 g, 15.3 mmol, 61%); mp 124-125 °C; **δ_H (400 MHz, $CDCl_3$)** 3.26 (3H, s, ArC*H*$_3$), 6.88-6.92 (1H, m, C(7)*H*), 7.13 (1H, app td, *J* 7.6, 0.8 Hz, C(5)*H*), 7.58-7.64 (2H, m, C(4,6)*H*).

Lab book Reference: SMS-277

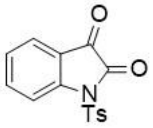
1-Allylindoline-2,3-dione, 91



Following the method outlined by Willis *et al*,[147] isatin (2.50 g, 17.2 mmol) and cesium carbonate (6.0 g, 18.9 mmol) in DMF (40 mL) were stirred for 30 mins. Allyl bromide (1.78 mL, 20.8 mmol) was added dropwise and the solution stirred for 16 h at RT. The reaction was then partitioned with addition of H_2O (100 mL) and EtOAc (150 mL), extracted and washed with H_2O (3 x 200 mL) and brine (3 x 200 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and recrystallized from Et_2O, affording **91** as a red solid (2.26 g, 12 mmol, 70%); mp 85-86 °C; δ_H (400 MHz, $CDCl_3$) 4.37 (2H, dt, *J* 5.4, 1.6 Hz, NC*H*$_2$CH=CH$_2$), 5.25-5.37 (2H, m, NCH$_2$CH=C*H*$_2$), 5.84 (1H, ddt, *J* 17.1, 10.6, 5.4 Hz, NCH$_2$C*H*=CH$_2$), 6.89 (1H, app d, *J* 8.0 Hz, C(7)*H*), 7.12 (1H, app td, *J* 7.6, 0.8 Hz, C(5)*H*), 7.51-7.66 (2H, m, C(4,6)*H*).

Lab book Reference: SMS-278

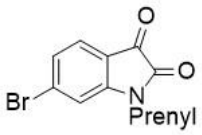
1-Tosylindoline-2,3-dione, 93



Following the method outlined by Hayashi *et al*,[145] isatin (1.83 g, 12.5 mmol) was dissolved in DMF (60 mL) and cooled to 0 °C. NaH (0.55 g, 13.8 mmol, 60% dispersion in mineral oil) was added in portions and the reaction mixture stirred for 20 mins at 0 °C. Tosyl chloride (2.61 g, 13.8 mmol) was added portionwise and the solution then warmed to RT and stirred for 3 h. The reaction was then quenched with dropwise addition of H_2O (5 mL) and diluted with EtOAc (200 mL). The reaction mixture was then extracted with H_2O (3 x 200 mL) and brine (3 x 200 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and recrystallized from Et_2O, affording **93** as a yellow powder (713 mg, 19%); mp 126-127 °C; δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, ArC*H*$_3$), 7.29 (1H, app td, *J* 7.6 Hz, C(7)*H*), 8.36 (2H, d, *J* 8.1 Hz, Ar(3,5)*H*), 7.67-7.78 (2H, m, C(5,6)*H*), 8.00 (2H, d, *J* 8.4 Hz, Ar(2,6)*H*), 8.08 (1H, d, *J* 8.3 Hz, C(4)*H*).

Lab book Reference: SMS-213

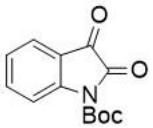
6-Bromo-1-(3-methylbut-2-en-1-yl)indoline-2,3-dione, 95



Following the method outlined by Willis *et al*,[147] 6-bromo isatin (2.33 g, 10.3 mmol) and cesium carbonate (3.6 g, 11.3 mmol) in DMF (30 mL) were stirred for 30 mins. 1-Bromo-3-methylbut-2-ene (1.45 mL, 12.5 mmol) was added dropwise and the solution stirred for 16 h at RT. The reaction was then partitioned with addition of H_2O (100 mL) and EtOAc (150 mL), extracted and washed with H_2O (3 x 200 mL) and brine (3 x 200 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and recrystallized from Et_2O, affording **95** as an orange solid (2.67 g, 9.1 mmol, 88%); mp 68-70 °C; **δ_H** (400 MHz, $CDCl_3$) 1.76 (3H, m, $CH_2CH{=}C(CH_3)_A(CH_3)_B$), 1.83 (3H, s, $CH_2CH{=}C(CH_3)_A(CH_3)_B$), 4.30 (2H, d, *J* 6.8 Hz, $CH_2CH{=}C(CH_3)_2$), 5.15 (1H, app dddt, *J* 6.8, 5.6, 2.7, 1.4 Hz, $CH_2CH{=}C(CH_3)_2$), 7.01 (1H, d, *J* 1.5 Hz, ArC(7)*H*), 7.26 (1H, dd, *J* 7.9, 1.5 Hz, ArC(5)*H*), 7.44 (1H, d, *J* 7.9 Hz, C(4)*H*).

Lab book Reference: SMS-292

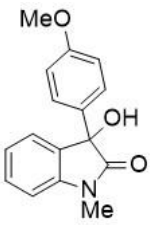
***Tert*-butyl 2,3-dioxoindoline-1-carboxylate, 96**



Following the method outlined by Steglich *et al*,[148] isatin (2.95 g, 20 mmol) was added to a solution of DMAP **4** (122 mg, 5 mol %) in anhydrous THF (100 mL) at RT. Di-*tert* butyl dicarbonate (4.80 g, 22 mmol) was slowly added and the solution stirred for 6 h. Upon completion, brine (50 mL) was added to the solution and the organic layer extracted with EtOAc (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo and recrystallized from CH_2Cl_2/hexane (1:1), affording **96** as a yellow soild (3.54 g, 14.2 mmol, 72%), mp 125-126 °C; **δ_H (400 MHz, $CDCl_3$)** 1.65 (9H, s, $C(CH_3)_3$), 7.29 (1H, app td, *J* 7.6, 0.7 Hz, C(7)*H*), 7.67-7.76 (2H, m, Ar(4,6)*H*), 8.07 (1H, app d, *J* 8.3 Hz, C(7)*H*).

Lab book Reference: SMS-348

3-Hydroxy-3-(4-methoxyphenyl)-1-methylindolin-2-one, 97

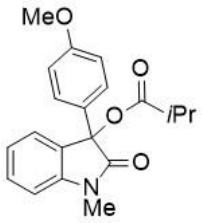


Following general procedure D, **90** (805 mg, 5 mmol) and 4-methoxyphenyl magnesium bromide (20 mL, 10 mmol, 0.5 M) in anhydrous THF (25 mL) gave, after column chromatography (eluent

CH_2Cl_2/EtOAc, 9:1; R_F 0.31), **97** as a light yellow solid (600 mg, 2.2 mmol, 44%), mp 134-136 °C; **ν_{max} (ATR)** 3352 (OH), 1699 (C=O), 1611, 1470, 1246, 1175; **δ_H (500 MHz, $CDCl_3$)** 3.20 (1H, s, O*H*), 3.24 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 6.85 (2H, AB d, C(3)ArC(3,5)*H*), 6.90 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.10 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.29-7.38 (4H, m, ArC(4,6)*H*, C(3)ArC(2,6)*H*); **δ_C (125 MHz, $CDCl_3$)** 26.5 (NCH_3), 55.3 (OCH_3), 77.6 (*C*(3)), 108.7 (Ar*C*(7)H), 114.0 (C(3)Ar*C*(3,5)H), 123.5 (Ar*C*(5)H), 124.9 (Ar*C*(4)H), 126.8 (C(3)Ar*C*(2,6)H), 129.9 (Ar*C*(6)H), 131.5 (Ar*C*(3a)), 132.1 (C(3)Ar*C*(1)), 143.5 (Ar*C*(7a)), 159.6 (C(3)Ar*C*(4)), 178.6 (*C*=O); ***m/z* (NSI)** 270 ($[M+H]^+$, 100%) $C_{16}H_{16}NO_3^+$ ($[M+H]^+$) requires 270.1125; found 270.1127 (+0.9 ppm).

Lab book Reference: SMS-312

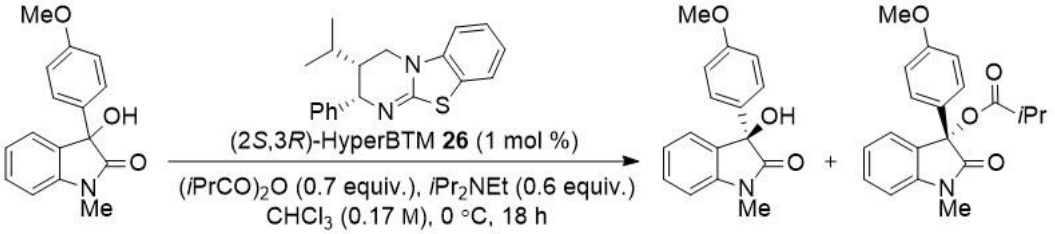
3-(4-Methoxyphenyl)-1-methyl-2-oxoindolin-3-yl isobutyrate, 98



Following general procedure B, **97** (43 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.61), **98** as a colourless oil (41 mg, 0.12 mmol, 76%); **ν_{max} (ATR)** 2974, 1738 (C=O), 1609 (C=C), 1470, 1246, 1086; **δ_H (400 MHz, $CDCl_3$)** 1.17 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.22 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.68 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 3.22 (3H, s, NCH_3), 3.78 (1H, s, OCH_3), 6.85 (2H, AB d, C(3)ArC(3,5)*H*), 6.90 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.10 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.20-7.24 (1H, m, ArC(4)*H),* 7.29 (2H, AB d, C(3)ArC(3,5)*H*), 7.39 (1H, app td, *J* 7.7, 1.3 Hz, ArC(6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.7 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.8 (CH(CH_3)$_A$(*C*H_3)$_B$), 26.7 (NCH_3), 33.7 (*C*H(CH_3)$_2$), 55.3 (OCH_3), 80.5 (*C*(3)), 108.6 (Ar*C*(7)H), 113.9 (C(3)Ar*C*(3,5)H), 122.9 (Ar*C*(5)H), 123.9 (Ar*C*(4)H), 127.9 (C(3)Ar*C*(2,6)H), 128.2 (Ar*C*(3a)), 128.4 (C(3)Ar*C*(1)), 130.1 (Ar*C*(6)H), 144.6 (Ar*C*(7a)), 160.1 (C(3)Ar*C*(4)), 174.4 (*C*(2)=O), 175.3 4 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 362 ($[M+Na]^+$, 100%) $C_{20}H_{21}NO_4Na^+$ ($[M+Na]^+$) requires 362.1363; found 362.1364 (+0.3 ppm).

Lab book Reference: SMS-315

Kinetic resolution of 97



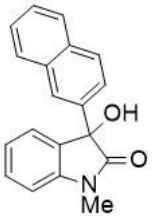
Following general procedure C, **97** (135 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (65 mg, 0.24 mmol, 48%) and ester (68 mg, 0.20 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +19 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 31.9, 36.3 min, 90:10 er.

Data for ester: $[\alpha]_D^{20}$ +153 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 9.9, 12.7 min, 98:2 er; *s* = 100.

Lab book Reference: SMS-411

3-Hydroxy-1-methyl-3-(naphthalen-2-yl)indolin-2-one, 99

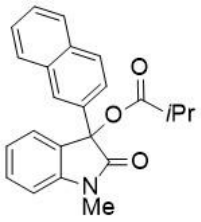


Following general procedure F, a 10% portion of 2-bromonaphthalene (2.07 g, 10 mmol) in anhydrous THF (5 mL) was added to a solution of magnesium turnings (362 mg, 15 mmol) in anhydrous THF (15 mL). A small iodine crystal was required. Upon turning colourless, the remaining 2-bromonaphthalene solution was added and reacted for a further 2 h. The concentration of the prepared Grignard reagent, 2-naphthyl magnesium bromide, was determined to be 0.3 M. Following general procedure D, **90** (805 mg, 5 mmol) and 2-naphthyl magnesium bromide (20 mL, 6 mmol, 0.3 M) in anhydrous THF (20 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc 9:1; R_F 0.33), **99** as a light yellow solid (683 mg, 2.4 mmol, 47%), mp 152-154 °C; $\boldsymbol{\nu_{max}}$ **(ATR)** 3331 (OH), 1703 (C=O),1611, 1470, 1350, 1103, 1088; $\boldsymbol{\delta_H}$ **(400 MHz, $CDCl_3$)** 3.24 (3H, s, NCH_3), 4.12 (1H, s, O*H*), 6.91 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.07 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.28-7.32 (1H, m, ArC(4)*H*), 7.32 (1H, td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.39 (1H, dd, *J* 8.6, 1.9 Hz, C(3)ArC(3)*H*), 7.43-7.50 (2H, m, C(3)ArC(6,7)*H*), 7.72 (1H, d, *J* 8.6 Hz, C(3)ArC(1)*H*), 7.75-7.80 (2H, m, C(3)ArC(5,8)*H*), 7.90 (1H, d, *J* 1.8 Hz, C(3)ArC(4)*H*); $\boldsymbol{\delta_C}$ **(100 MHz, $CDCl_3$)** 26.6 (NCH_3), 78.2 (*C*(3)), 108.8 (Ar*C*(7)H), 123.2 (Ar*C*(5)H), 123.6 (Ar*C*(4)H), 124.4 (C(3)Ar*C*H), 125.0 (C(3)Ar*C*H), 126.2 (C(3)Ar*C*H), 126.3 (C(3)Ar*C*H), 127.6 (C(3)Ar*C*H), 128.3 (C(3)Ar*C*H), 128.5 (C(3)Ar*C*H), 129.9

(Ar*C*(6)H), 131.7 (Ar*C*(3a)), 133.0 (C(3)Ar*C),* 133.1 (C(3)Ar*C*), 137.5 (C(3)Ar*C*), 143.5 (Ar*C*(7a)), 177.6 (*C*=O).

Lab book Reference: SMS-319

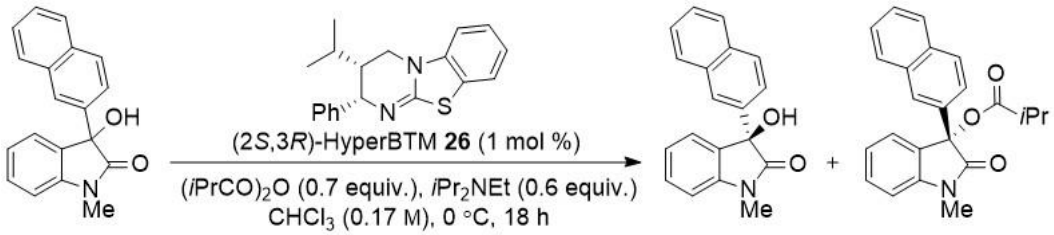
1-Methyl-3-(naphthalen-2-yl)-2-oxoindolin-3-yl isobutyrate, 100



Following general procedure B, **99** (47 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.81), **100** as a colourless oil (51 mg, 0.14 mmol, 89%); **ν_{max} (ATR)** 2974, 1726 (C=O), 1612 (C=C), 1467, 1341, 1142, 1090; **δ_H (400 MHz, $CDCl_3$)** 1.22 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.27 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.76 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 3.26 (3H, s, NCH_3), 6.96 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.11-7.14 (1H, m, ArC(5)*H*), 7.27 (1H, app d, *J* 7.4 Hz, ArC(4)*H*), 7.40-7.51 (3H, m, ArC(6)*H*, C(3)ArC(6,7)*H*), 7.61 (1H, dd, *J* 8.7, 1.8 Hz, C(3)ArC(3)*H*), 7.69 (1H, s, C(3)ArC(1)H), 7.75-7.87 (3H, m, C(3)ArC(4,5,8)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.7 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.8 (CH(CH_3)$_A$(*C*H_3)$_B$), 26.8 (N*C*H_3), 33.8 (*C*H(CH_3)$_2$), 81.0 (*C*(3)), 108.7 (Ar*C*(7)H), 123.1 (Ar*C*(5)H), 123.9 (Ar*C*(4)H), 124.0 (C(3)Ar*C*H), 125.6 (C(3)Ar*C*H), 126.3 (C(3)Ar*C*H), 126.7 (C(3)Ar*C*H), 127.6 (C(3)Ar*C*H), 128.3 (Ar*C*(3a)), 128.4 (C(3)Ar*C*H), 128.8 (C(3)Ar*C*H), 130.3 (Ar*C*(6)H), 132.8 (C(3)Ar*C),* 133.4 (C(3)Ar*C*), 133.9 (C(3)Ar*C*), 144.7 (Ar*C*(7a)), 174.1 (*C*=O), 175.3 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 382 ([M+Na]$^+$, 100%) $C_{23}H_{21}NO_3Na^+$ ([M+Na]$^+$) requires 382.1414; found 382.1414 (+0.1 ppm).

Lab book Reference: SMS-320

Kinetic resolution of 99



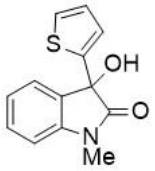
Following general procedure C, **99** (145 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography to separate alcohol (63 mg, 0.22 mmol, 43%) and ester (57 mg, 0.16 mmol, 32%).

Data for alcohol: $[\alpha]_D^{20}$ +82 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.9, 35.5 min, 99:1 er.

Data for ester: $[\alpha]_D^{20}$ +164 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.4, 46.6 min, 98:2 er; *s* = 180.

Lab book Reference: SMS-328

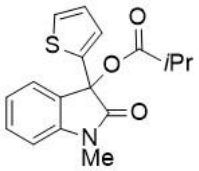
3-Hydroxy-1-methyl-3-(thiophen-2-yl)indolin-2-one, 105



Following the procedure by Cava *et al*,[86] *n*-butyl lithium (2.8 mL, 7 mmol, 2.5 M in hexanes) was added dropwise to a solution of thiophene (474 µL, 6 mmol) in anhydrous THF (25 mL) at 0 °C under N_2 and the solution stirred at RT for 1 hour. This solution was added to **90** (805 mg, 5 mmol) in anhydrous THF (25 mL) at 0 °C under N_2 and stirred for 2 h. The reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.26), **105** as a dark orange solid (468 mg, 1.7 mmol, 34%), mp 102-104 °C; **ν_{max} (ATR)** 3348 (OH), 2158, 1699 (C=O), 1612, 1470, 1346, 1092; **δ_H (500 MHz, $CDCl_3$)** 3.23 (3H, s, NC*H*$_3$), 3.42 (1H, s, O*H*), 6.89 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 6.94 (1H, dd, *J* 5.0, 3.6 Hz, C(3)ArC(4)*H*), 6.99 (1H, dd, *J* 3.6, 1.2 Hz, C(3)ArC(5)*H*), 7.15 (1H, app td, *J* 7.6, 0.9 Hz, ArC(3)*H*), 7.32 (1H, d, *J* 5.0, 1.2 Hz, C(3)ArC(5)*H*), 7.38 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.51-7.57 (1H, m, ArC(4)*H*); **δ_C (125 MHz, $CDCl_3$)** 26.6 (N*C*H$_3$), 75.4 (*C*(3)), 108.8 (Ar*C*(7)H), 123.4 (Ar*C*(5)H), 125.0 (Ar*C*(4)H), 126.0 (C(3)Ar*C*(4)H), 126.7 (C(3)Ar*C*(5)H), 126.8 (C(3)Ar*C*(3)H), 130.1 (Ar*C*(3a)), 130.3 (Ar*C*(6)H), 143.2 (C(3)Ar*C*(2)), 143.3 (Ar*C*(7a)), 178.6 (*C*=O); ***m/z* (NSI)** 263 ($[M+NH_4]^+$, 100%) $C_{13}H_{15}N_2O_2S^+$ ($[M+NH_4]^+$) requires 263.0849; found 263.0852 (+1.2 ppm).

Lab book Reference: SMS-313

1-Methyl-2-oxo-3-(thiophen-2-yl)indolin-3-yl isobutyrate, 106

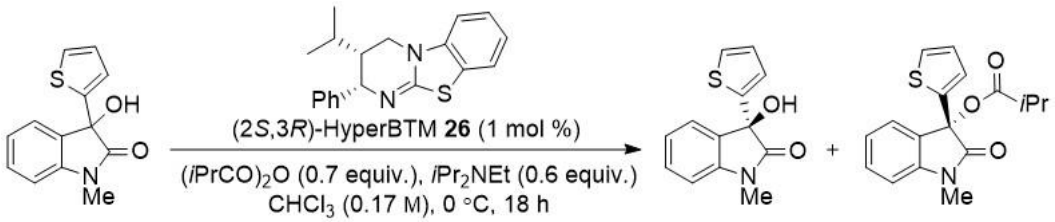


Following general procedure B, **105** (39 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.76), **106** as a yellow oil (40 mg, 0.13 mmol, 81%); **ν_{max} (ATR)** 2967, 1724 (C=O), 1612 (C=C), 1468, 1344, 1142, 1090; **δ_H (400 MHz, $CDCl_3$)** 1.15 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.20 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.65 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.24 (3H, s, NC*H*$_3$), 6.88-6.95 (3H, m, ArC(7)*H*, C(3)ArC(4,5)*H*), 7.12 (1H, app td, *J* 7.6, 0.9 Hz, ArC(3)*H*), 7.35-7.43 (3H, m, C(3)ArC(5)*H*, ArC(4,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.6 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.7

($CH(CH_3)_A(CH_3)_B$), 26.8 (NCH_3), 33.5 ($CH(CH_3)_2$), 78.5 (*C*(3)), 108.7 (Ar*C*(7)H), 122.9 (Ar*C*(5)H), 123.7 (Ar*C*(4)H), 126.5 (C(3)Ar*C*(4)H), 126.7 (C(3)Ar*C*(5)H), 127.6 (Ar*C*(3a)), 127.8 (C(3)Ar*C*(3)H), 130.5 (Ar*C*(6)H), 138.9 (C(3)Ar*C*(2)), 144.2 (Ar*C*(7a)), 172.9 (*C*(2)=O), 175.2 (*C*(=O)$CH(CH_3)_2$); ***m/z* (NSI)** 338 ($[M+Na]^+$, 100%) $C_{17}H_{17}NO_3SNa^+$ ($[M+Na]^+$) requires 338.0821; found 338.0822 (+0.2 ppm).

Lab book Reference: SMS-316

Kinetic resolution of 105



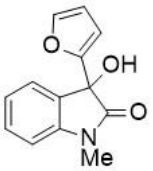
Following general procedure C, **105** (123 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (64 mg, 0.26 mmol, 52%) and ester (52 mg, 0.17 mmol, 33%).

Data for alcohol: $[\alpha]_D^{20}$ –37 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.1, 29.9 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ +239 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 7.9, 13.2 min, 90:10 er; *s* = 90.

Lab book Reference: SMS-337

3-(Furan-2-yl)-3-hydroxy-1-methylindolin-2-one, 107

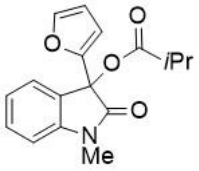


Following the procedure by Cava *et al*,[86] *n*-butyl lithium (2.8 mL, 7 mmol, 2.5 M in hexanes) was added dropwise to a solution of furan (436 µL, 6 mmol) in anhydrous THF (25 mL) at 0 °C under N_2 and the solution stirred at RT for 1 hour. This solution was added to **90** (805 mg, 5 mmol) in anhydrous THF (25 mL) at 0 °C under N_2 and stirred for 2 h. The reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.20), **107** as a brown solid (276 mg, 1.44 mmol, 24%), mp 156-158 °C; **ν_{max} (ATR)** 3360 (OH), 1699 (C=O), 1614, 1470, 1381, 1092; **δ_H (400 MHz, $CDCl_3$)** 3.23 (3H, s, NCH_3), 3.54 (1H, s, O*H*), 6.28-6.36 (2H, m, C(3)ArC(3,4)*H*), 6.87 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.14 (1H, app td, *J* 7.6, 0.8 Hz, ArC(5)*H*), 7.38 (1H, td, *J* 7.8, 1.2 Hz, ArC(6)*H*), 7.42-7.47 (1H, m, C(3)ArC(5)*H*), 7.54-7.61 (1H, m, ArC(4)*H*); **δ_C (100 MHz,**

$CDCl_3$) 26.5 (N*C*H_3), 73.4 (*C*(3)), 108.7 (Ar*C*(7)H), 109.0 (C(3)Ar*C*(3)H), 110.4 (C(3)Ar*C*(4)H), 123.4 (Ar*C*(5)H), 125.4 (Ar*C*(4)H), 128.1 (Ar*C*(3a)), 130.4 (Ar*C*(6)H), 143.6 (Ar*C*(7a)), 144.0 (C(3)Ar*C*(5)H), 151.3 (C(3)Ar*C*(2)), 178.6 (*C*=O); ***m/z* (NSI)** 252 ([M+Na]$^+$, 100%) $C_{13}H_{11}NO_3Na^+$ ([M+Na]$^+$) requires 252.0631; found 252.0631 (–0.1 ppm).

Lab book Reference: SMS-314

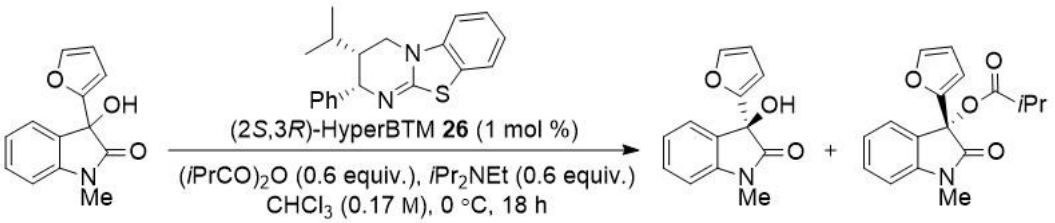
3-(Furan-2-yl)-1-methyl-2-oxoindolin-3-yl isobutyrate, 108



Following general procedure B, **107** (37 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.76), **108** as an orange oil (37 mg, 0.12 mmol, 77%); **ν_{max} (ATR)** 2974, 1728 (C=O), 1612 (C=C), 1470, 1344, 1142, 1090; **δ_H (400 MHz, $CDCl_3$)** 1.15 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.16 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$), 2.66 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.26 (1H, s, NCH_3), 6.32-6.39 (2H, m, C(3)ArC(3,4)*H*), 6.86 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.10 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.37 (1H, td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.43-7.46 (1H, m, ArC(4)*H*), 7.48 (1H, dd, *J* 1.8, 0.9 Hz, C(3)ArC(5)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.9 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 26.8 (N*C*H_3), 33.5 (*C*H(CH$_3$)$_2$), 76.3 (*C*(3)), 108.6 (Ar*C*(7)H), 110.5 (C(3)Ar*C*(3)H), 111.0 (C(3)Ar*C*(4)H), 122.9 (Ar*C*(5)H), 123.9 (Ar*C*(4)H), 125.9 (Ar*C*(3a)), 130.3 (Ar*C*(6)H), 144.1 (Ar*C*(7a)), 144.7 (C(3)Ar*C*(5)H), 147.5 (C(3)Ar*C*(2)), 171.6 (*C*(2)=O), 175.2 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 300 ([M+H]$^+$, 100%) $C_{17}H_{18}NO_3H^+$ ([M+H]$^+$) requires 300.1230; found 300.1232 (+0.6 ppm).

Lab book Reference: SMS-317

Kinetic resolution of 107



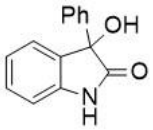
Following general procedure C, **107** (115 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (41 mg, 0.18 mmol, 36%) and ester (62 mg, 0.21 mmol, 42%).

Data for alcohol: $[\alpha]_D^{20}$ +104 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 25.0, 30.4 min, 88:12 er.

Data for ester: $[\alpha]_D^{20}$ +86 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 7.2, 13.0 min, 90:10 er *s* = 19.

Lab book Reference: SMS-323

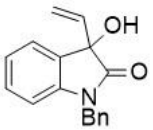
3-Hydroxy-3-phenylindolin-2-one, 109



NaH (360 mg, 9 mmol, 60% in mineral oil) was added to isatin (883 mg, 3.3 mmol) in anhydrous THF (20 mL) at 0 °C and stirred for 30 mins. Phenylmagnesium bromide (4 mL, 12 mmol, 3.0 M) was added dropwise and the reaction allowed to warm to RT. The reaction was quenched with NH_4Cl (20 mL) and extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (3 x 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give, after recrystallisation from petrol/EtOAc (1:1) (CH_2Cl_2/EtOAc, 9:1; R_F 0.38), **109** a light orange solid (481 mg, 2.14 mmol, 36%), mp 197-199 °C; **ν_{max} (ATR)** 3408 (NH), 3188 (OH), 3059, 1695 (C=O), 1616 (C=C), 1468, 1180; **δ_H (400 MHz, $(CD_3)_2CO$)** 5.56 (1H, s, O*H*), 6.99-7.06 (2H, m, ArC(5,7)*H*), 7.18-7.22 (1H, m, ArC(4)*H*), 7.26-7.37 (4H, m, ArC(6)*H*, C(3)Ar(3,4,5)*H*), 7.43-7.48 (2H, m, C(3)ArC(2,6)*H*); **δ_C (100 MHz, $(CD_3)_2CO$)** 77.7 (*C*(3)), 109.9 (Ar*C*(7)H), 122.3 (Ar*C*(5)H), 124.9 (Ar*C*(6)H), 125.6 (C(3)Ar*C*(2,6)H), 127.5 (Ar*C*(4)H), 128.0 (C(3)Ar*C*(3,5)H), 129.4 (C(3)Ar*C*(4)H), 133.5 (C(3)Ar*C*(1)), 141.7 (Ar*C*(3a)), 142.1 (Ar*C*(7a)), 178.2 (*C*=O); ***m/z* (NSI)** 243 ($[M+NH_4]^+$, 100%) $C_{14}H_{15}O_2N_2^+$ ($[M+NH_4]^+$) requires 243.1128; found 243.1129 (+0.4 ppm).

Lab book Reference: SMS-204

1-Benzyl-3-hydroxy-3-vinylindolin-2-one, 110

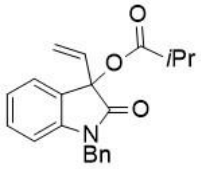


Following general procedure D, **89** (877 mg, 7.4 mmol) and vinylmagnesium bromide (10.6 mL, 7.4 mmol, 0.7 M) in anhydrous THF (50 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.29), **110** as an orange solid (931 mg, 3.33 mmol, 45%), mp 83-85 °C; **ν_{max} (ATR)** 3316 (OH), 2954, 1705 (C=O), 1612 (C=C), 1466, 1358, 1175, 968; **δ_H (400 MHz, $CDCl_3$)** 3.37 (1H, s, O*H*), 4.80 (1H, d, *J* 15.7 Hz, C$H_A$$H_B$Ph), 5.00 (1H, d, *J* 15.7 Hz, C$H_A$$H_B$Ph), 5.36 (1H, dd, *J* 10.5, 0.7 Hz, HRC=$CH_{cis}H_{trans}$), 5.46 (1H, dd, *J* 17.1, 0.7 Hz, HRC=C$H_{cis}$$H_{trans}$), 6.07 (1H, dd, *J* 17.1, 10.5 Hz, *H*RC=CH_2), 6.73 (1H, app dt, *J* 7.9, 0.8 Hz, ArC(7)*H*), 7.08 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.18-7.40 (7H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 43.9 (NCH_2Ph), 77.1 (*C*(3)), 109.7 (Ar*C*(7)H), 117.0 (HRC=CH_2), 123.4 (Ar*C*(5)H), 124.8 (Ar*C*(4)H), 127.2 (CH_2Ar*C*(2,6)H), 127.7 (CH_2Ar*C*(4)H), 128.9 (CH_2Ar*C*(3,5)H), 129.2 (CH_2Ar*C*(1)), 129.8 (Ar*C*(6)H), 135.3

(Ar*C*(3a)), 136.2 (HR*C*=CH_2), 142.5 (Ar*C*(7a)), 176.9 (C=O); ***m/z* (NSI)** 266 ([M+H]$^+$, 100%) $C_{17}H_{16}NO_2^+$ ([M+H]$^+$) requires 266.1176; found 266.1170 (–2.1 ppm).

Lab book Reference: SMS-169

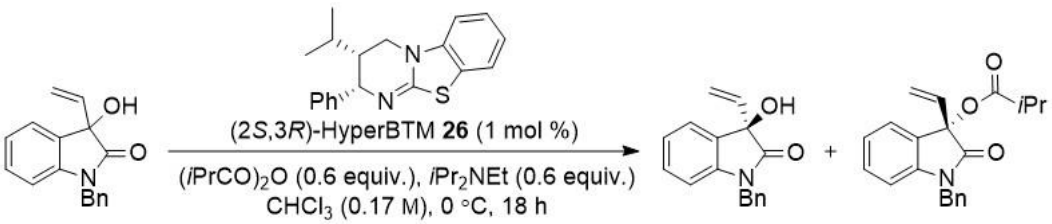
1-Benzyl-2-oxo-3-vinylindolin-3-yl isobutyrate, 111



Following general procedure B, **110** (43 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.64), **111** as an orange oil (36 mg, 0.11 mmol, 68%); **ν_{max} (ATR)** 2974, 1724 (C=O), 1614 (C=O), 1466, 1348, 1144; **δ_H (400 MHz, $CDCl_3$)** 1.18 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.19 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.67 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.86 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 5.03 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 5.28 (1H, dd, *J* 17.1, 0.7 Hz, HRC=C$H_{cis}$$H_{trans}$), 5.37 (1H, dd, *J* 10.5, 0.7 Hz, HRC=C$H_{cis}$$H_{trans}$), 6.07 (1H, dd, *J* 17.1, 10.5 Hz, *H*RC=CH_2), 6.67 (1H, app dt, *J* 7.6, 0.9 Hz, ArC(7)*H*), 7.08 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.16-7.37 (7H, m, ArC*H*); **δ_C (100 MHz, d_6-DMSO)** 18.9 (CH(*C*H_3)$_A$(CH_3)$_B$), 19.1 (CH(CH_3)$_A$(*C*H_3)$_B$), 33.3 (*C*H(CH_3)$_2$), 43.3 (N*C*H_2Ph), 80.3 (*C*(3)), 110.1 (Ar*C*(7)H), 118.9 (HRC=*C*H_2), 123.3 (Ar*C*(5)H), 123.6 (Ar*C*(6)H), 126.7 (CH-$_2$Ar*C*(1)), 127.5 (CH_2Ar*C*(2,6)H), 127.8 (CH_2Ar*C*(4)H), 129.0(CH_2Ar*C*(3,5)H), 130.3 (Ar*C*(4)H), 134.1 (HR*C*=CH_2), 136.5 (Ar*C*(3a)), 143.0 (Ar*C*(7a)), 172.9 (C=O), 174.7 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 336 ([M+H]$^+$, 100%) $C_{21}H_{22}NO_3^+$ ([M+H]$^+$) requires 336.1594; found 336.1595 (+0.2 ppm).

Lab book Reference: SMS-171

Kinetic resolution of 110



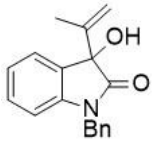
Following general procedure C, **110** (133 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.30 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.30 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (48 mg, 0.18 mmol, 36%) and ester (81 mg, 0.24 mmol, 48%).

Data for alcohol: $[\alpha]_D^{20}$ +39 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (7% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 18.7, 22.3 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ +20 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 17.1, 19.4 min, 90:10 er; *s* = 50.

Lab book Reference: SMS-178

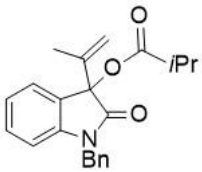
1-Benzyl-3-hydroxy-3-(prop-1-en-2-yl)indolin-2-one, 112



Following general procedure D, **89** (877 mg, 3.7 mmol) and 2-methyl prop-1-enyl magnesium bromide (23 mL, 3.7 mmol, 0.5 M) in anhydrous THF (50 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.38), **112** as a pale yellow solid (186 mg, 0.67 mmol, 18%), mp 102-104 °C; **ν_{max} (ATR)** 3327 (OH), 2954, 1697 (C=O), 1612 (C=C), 1466, 1171, 970; **δ_H (400 MHz, $CDCl_3$)** 1.60 (3H, dd, *J* 1.5, 0.8 Hz, CH_3), 3.50 (1H, s, O*H*), 4.76 (1H, d, *J* 15.6 Hz, C$H_A$$H_B$Ph), 5.05 (1H, d, *J* 15.6 Hz, C$H_A$$H_B$Ph), 5.13 (1H, pent, *J* 1.5 Hz, CH_3CR=C$H_{cis}$$H_{trans}$), 5.48 (1H, t, *J* 0.8 Hz, CH_3CR=$CH_{cis}$$H_{trans}$), 6.74 (1H, app dt, *J* 7.9, 0.7 Hz, ArC(7)*H*), 7.05 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.21 (1H, app td, *J* 7.7, 1.3 Hz, ArC(6)*H*), 7.25-7.37 (6H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 18.0 (*C*H_3), 44.0 (N*C*H_2Ph), 79.3 (*C*(3)OH), 109.6 (Ar*C*(7)H), 112.7 ((H_2*C*=C(CH_3)R), 123.3 (Ar*C*(5)H), 124.3 (Ar*C*(6)H), 127.3 (CH_2Ar*C*(2,6)H), 127.7 (CH_2Ar*C*(4)H), 128.9 (CH_2Ar*C*(3,5)H), 129.4 (H_2C=*C*(CH_3)R), 129.9 (Ar*C*(4)H), 135.4 (CH_2Ar*C*(1)), 142.8 (Ar*C*(3a)), 143.2 (Ar*C*(7a)), 177.0 (C=O); ***m/z* (NSI)** 280 ($[M+H]^+$, 100%) $C_{18}H_{18}NO_2^+$ ($[M+H]^+$) requires 280.1332; found 280.1331 (–0.4 ppm).

Lab book Reference: SMS-148

1-Benzyl-2-oxo-3-(prop-1-en-2-yl)indolin-3-yl isobutyrate, 113

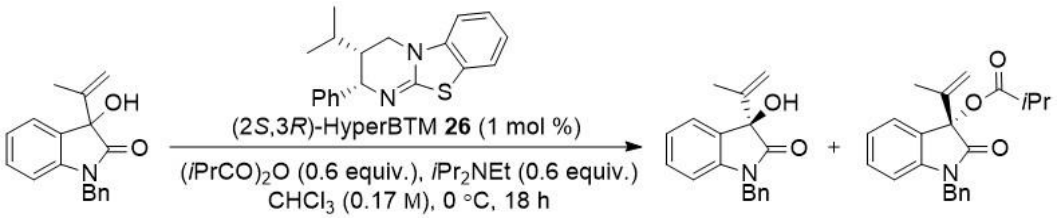


Following general procedure B, **112** (50 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **19** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.86), **113** as a yellow solid (35 mg, 0.10 mmol, 63%), mp 82-84 °C; **ν_{max} (ATR)** 2974, 1724 (C=O), 1612 (C=O), 1466, 1354, 1150, 982; **δ_H (400 MHz, $CDCl_3$)** 1.19 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.20 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.83 (3H, dd, *J* 1.5, 0.8 Hz, H_2C=C(CH_3)R), 2.67 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.82 (1H, d, *J* 15.9 Hz, NC$H_A$$H_B$Ph), 5.04-5.11 (3H, m, NC$H_A$$H_B$Ph, H_2C=C(CH_3)R)), 6.67 (1H, app dt, *J* 7.8, 0.8 Hz, ArC(7)*H*), 7.01 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.14 (1H, ddd, *J* 7.4, 1.3, 0.6 Hz, C(6)*H*), 7.19 (1H, app td, *J* 7.7, 1.3 Hz, ArC(4)*H*), 7.23-7.38 (5H, m, CH_2ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 17.6 (H_2C=C(*C*H_3)R), 18.6 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.8

($CH(CH_3)_A(CH_3)_B$), 33.8 ($CH(CH_3)_2$), 44.2 (CH_2Ph), 77.2 (*C*(3)), 109.5 (Ar*C*(7)H), 114.6 (H_2C=$C(CH_3)R$), 122.8 (Ar*C*(5)H), 123.1 (Ar*C*(4)H), 127.2 (CH_2ArC(2,6)H), 127.5 (H_2C=*C*(CH_3)R), 127.5 (CH_2ArC(4)H), 128.7 (CH_2ArC(3,5)H), 129.7 (Ar*C*(6)H), 135.8 (CH_2ArC(1)), 140.5 (Ar*C*(3a)), 143.6 (Ar*C*(7a)), 173.5 (*C*(2)=O), 174.7 (*C*(=O)$CH(CH_3)_2$); ***m/z* (NSI)** 372 ([M+Na]$^+$, 100%) $C_{22}H_{23}NO_3Na^+$ ([M+Na]$^+$) requires 372.1570; found 372.1565 (–1.4 ppm).

Lab book Reference: SMS-150

Kinetic resolution of 112



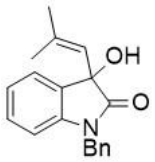
Following general procedure C, **112** (139 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) for 24 h gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (81 mg, 0.29 mmol, 58%) and ester (56 mg, 0.17 mmol, 33%).

Data for alcohol: $[\alpha]_D^{20}$ +34 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 8.3, 10.1 min, 83:17 er.

Data for ester: $[\alpha]_D^{20}$ +15 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 8.3, 11.3 min, 98:2 er; *s* = 80.

Lab book Reference: SMS-412

1-Benzyl-3-hydroxy-3-(2-methylprop-1-en-1-yl)indolin-2-one, 114

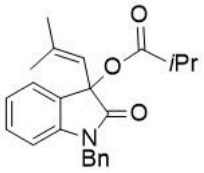


Following general procedure D, **89** (877 mg, 3.7 mmol) and 2-methyl prop-1-enyl magnesium bromide (7.4 mL, 3.7 mmol, 0.5 M) in anhydrous THF (50 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.23), **114** as a pale yellow solid (291 mg, 1.0 mmol, 27%), mp 108-110 °C; **ν_{max} (ATR)** 3339 (OH), 2966, 1697 (C=O), 1614 (C=O), 1466, 1373, 1197; **δ_H (400 MHz, $CDCl_3$)** 1.50 (3H, d, *J* 1.4 Hz, C(CH_3)$_A$(CH_3)$_B$), 1.76 (3H, d, *J* 1.4 Hz, C(CH_3)$_A$(CH_3)$_B$), 2.82 (1H, s, O*H*), 4.86 (1H, d, *J* 15.6 Hz, CH_AH_BPh), 4.94 (1H, d, *J* 15.6 Hz, CH_AH_BPh), 5.55 (1H, app sept, *J* 1.4 Hz, RC*H*=$C(CH_3)_2$), 6.73 (1H, app dt, *J* 7.9, 0.8 Hz, ArC(7)*H*), 7.05 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.20 (1H, app td, *J* 7.7, 1.3 Hz, ArC(6)*H*), 7.27-7.35 (5H, m, CH_2ArCH), 7.37 (1H, ddd, *J* 7.4, 1.3, 0.6 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 19.1 (RCH=C(CH_3)$_A$(CH_3)$_B$)), 27.0 (RCH=C(CH_3)$_A$(CH_3)$_B$)), 43.9 (NCH_2Ph), 75.9 (*C*(3)OH), 109.5 (Ar*C*(7)H), 123.4

(Ar*C*(5)H), 124.3 (R*C*H=C(CH$_3$)$_2$), 124.6 (Ar*C*(4)H), 127.4 (CH$_2$Ar*C*(2,6)H), 127.7 (CH$_2$Ar*C*(4)H), 128.8 (CH$_2$Ar*C*(3,5)H), 129.6 (Ar*C*(6)H), 131.4 (RCH=*C*(CH$_3$)$_2$), 135.5 (CH$_2$Ar*C*(1)), 138.6 (Ar*C*(3a)), 142.6 (Ar*C*(7a)), 177.5 (C=O); ***m/z* (APCI)** 292 ([M-H]$^+$, 100%) $C_{19}H_{18}NO_2^+$ ([M-H]$^+$) requires 292.1332; found 292.1331 (–0.4 ppm).

Lab book Reference: SMS-138

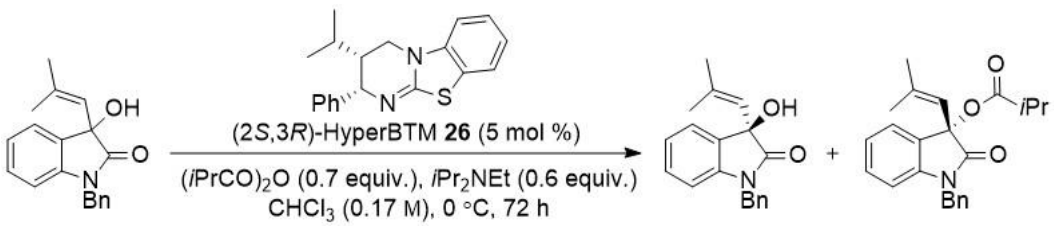
1-Benzyl-3-(2-methylprop-1-en-1-yl)-2-oxoindolin-3-yl isobutyrate, 115



Following general procedure B, **114** (41.2 mg, 0.18 mmol), isobutyric anhydride (43 µL, 0.23 mmol), DMAP **4** (2.2 mg, 0.018 mmol, 10 mol %) and *i*Pr$_2$NEt (77 µL, 0.43 mmol) in CH$_2$Cl$_2$ (2.5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.26), **115** as a colourless oil (95 mg, 0.16 mmol, 87%); **ν_{max} (ATR)** 2974, 1724 (C=O), 1614 (C=O), 1466, 1346, 1152, 980; **δ_H (400 MHz, CDCl$_3$)** 1.18 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.19 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.69 (3H, d, *J* 1.4 Hz, RCH=C(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.78 (3H, d, *J* 1.4 Hz, RCH=C(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.64 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 4.90 (1H, d, *J* 15.8 Hz, NC*H*$_A$H$_B$Ph), 4.99 (1H, d, *J* 15.8 Hz, NCH$_A$*H*$_B$Ph), 5.33-5.37 (1H, m, RCH=C(CH$_3$)$_2$), 6.64 (1H, d, *J* 7.8 Hz, ArC(7)*H*), 7.00 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.16 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.20-7.28 (2H, m, ArC(2,6)*H*), 7.33 (2H, dd, *J* 8.4, 6.8 Hz, CH$_2$ArC(3,5)*H*), 7.36-7.40 (2H, m, C(4)*H*, CH$_2$ArC(4)*H*); **δ_C (100 MHz, CDCl$_3$)** 18.6 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.9 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 19.5 (RCH=C(*C*H$_3$)$_A$(CH$_3$)$_B$), 27.6 (RCH=C(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.8 (*C*H(CH$_3$)$_2$), 44.4 (*C*H$_2$Ph), 79.7 (*C*(3)), 109.5 (Ar*C*(7)H), 120.1 (R*C*H=C(CH$_3$)$_2$), 122.8 (Ar*C*(4)H), 123.0 (Ar*C*(5)H), 127.3 (CH$_2$Ar*C*(2,6)H), 127.5 ((CH$_2$Ar*C*(4)H), 128.7 (CH$_2$Ar*C*(3,5)H), 129.5 (Ar*C*(6)H), 135.8 (CH$_2$Ar*C*(1)), 141.4 (Ar*C*(3a)), 143.0 (Ar*C*(7a)), 174.3 (*C*(2)=O), 175.0 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 386 ([M+Na]$^+$, 100%) $C_{23}H_{25}NO_3Na^+$ ([M+Na]$^+$) requires 386.1727; found 386.1720 (–1.7 ppm).

Lab book Reference: SMS-145

Kinetic resolution of 114



Following general procedure C, **114** (80 mg, 0.27 mmol), isobutyric anhydride (32 µL, 0.19 mmol), (2*S*,3*R*)-HyperBTM **26** (4 mg, 0.0135 mmol, 5 mol %) and *i*Pr$_2$NEt (29 µL, 0.16 mmol) in CHCl$_3$ (1.6 mL)

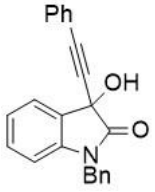
for 72 h gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (41 mg, 0.13 mmol, 51%) and ester (39 mg, 0.11 mmol, 40%).

Data for alcohol: $[\alpha]_D^{20}$ +97 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 32.6, 34.9 min, 87:13 er.

Data for ester: $[\alpha]_D^{20}$ +65 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 8.9, 17.3 min, 97:3 er; *s* = 60.

Lab book Reference: SMS-410

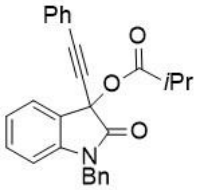
1-Benzyl-3-hydroxy-3-(phenylethynyl)indolin-2-one, 116



89 (767 mg, 3.3 mmol) was dissolved in THF (20 mL) and cooled to –78 °C. Separately, phenylacetylene (0.46 mL, 4.2 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. To the alkyne solution, *n*-butyl lithium (1.5 mL, 3.6 mmol, 2.5 M) was added dropwise and the solution stirred for 25 mins. The lithiated-alkyne solution was then transferred to the **89** solution at –78 °C, warmed to RT and stirred for a further 3 h. On completion, the solution was poured into NH_4Cl (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.60), **116** as a yellow powder (483 g, 1.42 mmol, 43%), mp 159-161 °C; **ν_{max} (ATR)** 3300 (OH), 3029, 2220 (C≡C), 1709 (C=O), 1610 (C=C); **δ_H (400 MHz, $CDCl_3$)** 3.71 (1H, s, O*H*), 4.96 (2H, s, CH_2Ph), 6.75 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.15 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.23-7.36 (9H, m, ArC*H*), 7.43-7.48 (2H, m, ArC*H*), 7.65 (1H, ddd, *J* 7.5, 1.3, 0.5 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 44.1 (*C*H_2Ph), 69.6 (*C*(3)), 85.4 (*C*≡CPh), 86.6 (C≡*C*Ph), 109.9 (Ar*C*(7)H), 121.6 (C≡CAr*C*(1)), 123.8 (Ar*C*(5)H), 124.8 (Ar*C*(4)H), 127.2 (CH_2Ar*C*(2,6)H), 127.8 (Ar*C*(4)H), 128.3 (C≡CAr*C*(2,6)H), 128.8 (CH_2Ar*C*(1)), 128.9 (CH_2Ar*C*(3,5)H), 129.1 (C≡CAr*C*(4)H), 130.4 (Ar*C*(6)H), 132.1 (C≡CAr*C*(3,5)H), 135.0 (Ar*C*(3a)), 142.2 (Ar*C*(7a)), 174.1 (*C*=O); ***m/z* (NSI)** 339 ($[M+H]^+$, 100%) $C_{23}H_{18}O_2N^+$ ($[M+H]^+$) requires 340.1332; found 340.1335 (+0.9 ppm).

Lab book Reference: SMS-202

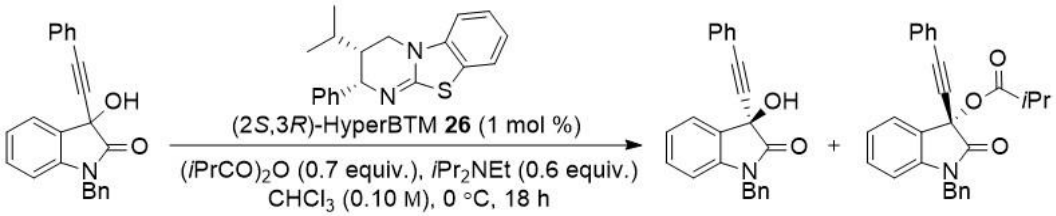
1-Benzyl-2-oxo-3-(phenylethynyl)indolin-3-yl isobutyrate, 117



Following general procedure B, **116** (54 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.80), **117** as a brown solid (38 mg, 0.09 mmol, 58%), mp 109-111 °C; **ν_{max} (ATR)** 2974, 2239(C≡C), 1728 (C=O), 1610 (C=C), 1468, 1341, 1256, 1074; **δ_H (400 MHz, $CDCl_3$)** 1.20 (3H, d, *J* 7.0 Hz CH(CH_3)$_A$(CH_3)$_B$), 1.21 (3H, d, *J* 7.0 Hz CH(CH_3)$_A$(CH_3)$_B$), 2.72 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.97 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 5.03 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 6.67 (1H, app d, *J* 7.8 Hz, C(7)*H*), 7.06 (1H, app td, *J* 7.6, 1.0 Hz, C(5)*H*), 7.22 (1H, app td, *J* 7.8, 1.3 Hz, C(6)*H*), 7.24-7.50 (11H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 18.6 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.9 (CH(CH_3)$_A$(*C*H_3)$_B$), 33.6 (*C*H(CH_3)$_2$), 44.5 (*C*H_2Ph), 73.5 (*C*(3)), 82.4 (C(3)*C*≡CPh), 87.6 (C(3)C≡*C*Ph), 110.0 (Ar*C*(7)H), 121.4 (C≡CAr*C*(1)), 123.2 (Ar*C*(4)H), 123.4 (Ar*C*(5)H), 127.1 (CH_2Ar*C*(1)), 127.2 (CH_2Ar*C*(2,6)H), 127.6 (CH_2Ar*C*(4)H), 128.2 (C≡CAr*C*(3,5)H), 128.8 (CH_2Ar*C*(3,5)H), 129.3 (C≡CAr*C*(4)H), 130.3 (Ar*C*(6)H), 132.3 (C≡CAr*C*(2,6)H), 135.3 (Ar*C*(3a)), 142.6 (Ar*C*(7a)), 170.9 (*C*(2)=O), 174.8 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 432 ([M+Na]$^+$, 100%) $C_{27}H_{23}O_3NNa^+$ ([M+Na]$^+$) requires 432.1570; found 324.1569 (–0.3 ppm).

Lab book Reference: SMS-208

Kinetic resolution of 116



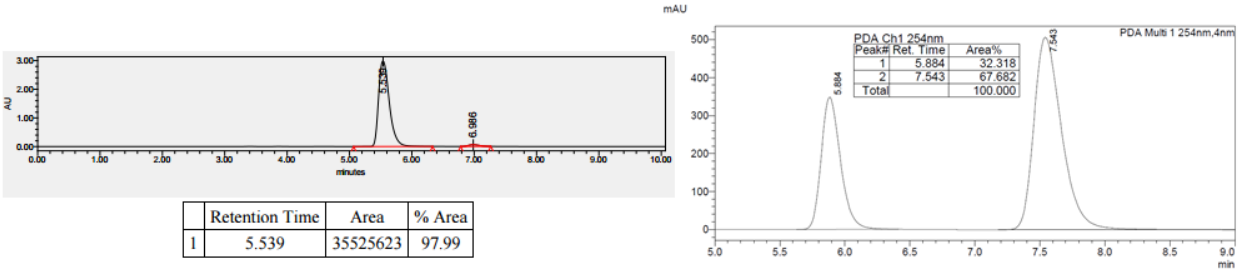
Following general procedure C, **116** (170 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (32 mg, 0.1 mmol, 19%) and ester (85 mg, 0.21 mmol, 42%).

Data for alcohol: $[\alpha]_D^{20}$ –5 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak IB (30% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 5.9, 7.5 min, 68:32 er.

Data for ester: $[\alpha]_D^{20}$ +34 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.9, 19.9 min, 64:36 er; *s* = 2.

Lab book Reference: SMS-217

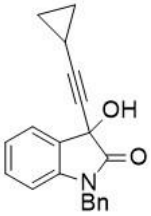
Confirmation of alcohol stereochemistry from KR of 116



	Retention Time	Area	% Area
1	5.539	35525623	97.99

Figure 43 – HPLC traces; enantioenriched (*S*)-**115** *(left)*; KR of **115** with major (*R*)-enantiomer *(right)*

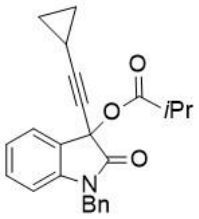
1-Benzyl-3-(cyclopropylethynyl)-3-hydroxy-indolin-2-one, 118



89 (1.54 g, 6.6 mmol) was dissolved in THF (30 mL) and cooled to –78 °C. Separately, cyclopropylacetylene (711 µL, 8.4 mmol) was dissolved in THF (15 mL) and cooled to –78 °C. To the alkyne solution, *n*-butyl lithium (2.9 mL, 7.2 mmol, 2.5 M) was added dropwise and the solution stirred for 25 mins. The lithiated-alkyne solution was then transferred to the **89** solution at –78 °C, warmed to RT and stirred for a further 3 h. On completion, the solution was poured into NH_4Cl (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.63), **118** as a yellow powder (1.48 g, 4.88 mmol, 74%), mp 170-172 °C; **ν_{max} (ATR)** 3308 (OH), 3026, 2236 (C≡C), 1707 (C=O), 1614 (C=C); **δ_H (400 MHz, $CDCl_3$)** 0.70-0.83 (4H, m, C≡C-Cyclopropyl-(CH_2)$_2$), 1.25-1.33 (1H, m, C≡C-Cyclopropyl-C*H*), 3.44 (1H, s, O*H*), 4.69 (2H, s, CH_2Ph), 6.68 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.08 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.21 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.24-7.35 (5H, m, CH_2ArC*H*), 7.51 (1H, app dd, *J* 7.4, 0.8 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** –0.34 (C≡C-Cyclopropyl-*C*H), 8.53 (C≡C-Cyclopropyl-(*C*H_2)$_A$(CH_2)$_B$), 8.56 (C≡C-Cyclopropyl-(CH_2)$_A$(*C*H_2)$_B$), 44.0 (*C*H_2Ph), 69.3 (*C*(3)), 72.0 (*C*≡C-Cyclopropyl), 91.2 (C≡*C*-Cyclopropyl), 109.8 (Ar*C*(7)H), 123.6 (Ar*C*(5)H), 124.5 (Ar*C*(4)H), 127.1 (CH_2Ar*C*(2,6)H), 127.8 (Ar*C*(4)H), 128.9 (CH_2Ar*C*(3,5)H), 129.2 (CH_2Ar*C*(1)), 130.2 (Ar*C*(6)H), 135.1 (Ar*C*(3a)), 142.1 (Ar*C*(7a)), 174.3 (*C*=O); ***m/z* (NSI)** 303 ([M+H]$^+$, 100%) $C_{20}H_{18}O_3N^+$ ([M+H]$^+$) requires 304.1332; found 304.1333 (+0.3 ppm).

Lab book Reference: SMS-203

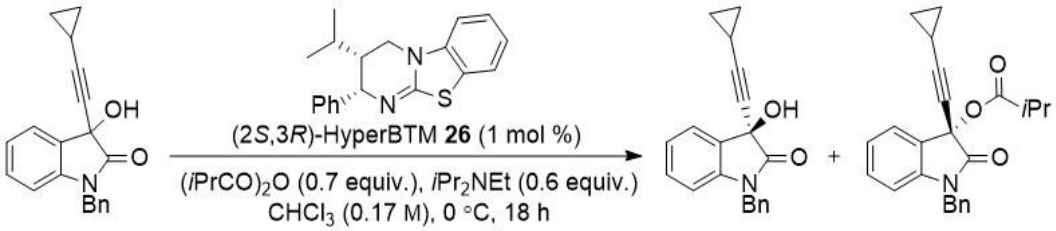
1-Benzyl-3-(cyclopropylethynyl)-2-oxo-indolin-3-yl isobutyrate, 119



Following general procedure B, **118** (48.5 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.80), **119** as a yellow solid (35 mg, 0.09 mmol, 59%), mp 68-70 °C; **ν_{max} (ATR)** 2974, 2241 (C≡C), 1732 (C=O), 1612 (C=C), 1468, 1348, 1140; **δ_H (400 MHz, $CDCl_3$)** 0.71-0.83 (4H, m, C≡C-Cyclopropyl-(CH_2)$_2$), 1.16 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.17 (3H, d, *J* 7.0 Hz CH(CH_3)$_A$(CH_3)$_B$), 1.25-1.35 (1H, m, C≡C-Cyclopropyl-C*H*), 2.67 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.92 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 5.00 (1H, d, *J* 16.0 Hz, NC$H_A$$H_B$Ph), 6.63 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.02 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.18 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.24-7.40 (6H, m, ArC(4)*H*, CH_2ArC*H*); **δ_C (100 MHz, $CDCl_3$)** –0.21 (C≡C-Cyclopropyl-*C*H), 8.61 (C≡C-Cyclopropyl-(*C*H_2)$_A$(CH_2)$_B$), 8.65 (C≡C-cyclopropyl-(CH_2)$_A$(*C*H_2)$_B$), 18.5 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.9 (CH(CH_3)$_A$(*C*H_3)$_B$), 33.5 (*C*H(CH_3)$_2$), 44.4 (*C*H_2Ph), 69.0 (*C*≡C-Cyclopropyl), 73.3 (*C*(3)), 92.5 (C≡*C*-Cyclopropyl), 109.8 (Ar*C*(7)H), 122.9 (Ar*C*(4)H), 123.5 (Ar*C*(5)H), 127.1 (CH_2Ar*C*(2,6)H), 127.5 (CH_2Ar*C*(1)), 127.6 (Ar*C*(4)H), 128.8 (CH_2Ar*C*(3,5)H), 130.0 (Ar*C*(6)H), 135.4 (Ar*C*(3a)), 142.4 (Ar*C*(7a)), 171.2 (*C*(2)=O), 174.8 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 396 ([M+Na]$^+$, 100%) $C_{24}H_{23}O_3NNa^+$ ([M+Na]$^+$) requires 396.1570; found 396.1569 (–0.3 ppm).

Lab book Reference: SMS-209

Kinetic resolution of 118



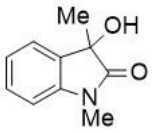
Following general procedure C, **118** (152 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (21 mg, 0.07 mmol, 14%) and ester (49 mg, 0.13 mmol, 26%).

Data for alcohol: $[\alpha]_D^{20}$ –17 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.1, 23.4 min, 90:10 er.

Data for ester: $[\alpha]_D^{20}$ +23 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.0, 23.0 min, 69:31 er; *s* = 5.

Lab book Reference: SMS-218

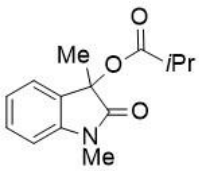
3-Hydroxy-1,3-dimethylindolin-2-one, 120[149]



Following general procedure D, **90** (600 mg, 3.7 mmol) and methylmagnesium bromide (1.5 mL, 4.4 mmol, 3.0 M) in anhydrous THF (35 mL) gave, after column chromatography (CH_2Cl_2/Et_2O 8:2, R_F 0.19), **120** as a green powder (448 mg, 2.5 mmol, 68%), mp 138-140 °C; **ν_{max} (ATR)** 3311 (OH), 2974, 1699 (C=O), 1614 (C=C), 1471, 1381; **δ_H (400 MHz, $CDCl_3$)** 1.61 (3H, s, CH_3), 3.03 (1H, s, O*H*), 3.20 (3H, s, NCH_3), 6.84 (1H, app dt, *J* 7.8, 0.8 Hz, C(7)*H*), 7.11 (1H, app td, *J* 7.3, 1.0 Hz, C(5)*H*), 7.33 (1H, app td, *J* 7.8, 1.3 Hz, C(6)*H*), 7.41 (1H, ddd, *J* 7.3, 1.3, 0.6 Hz, C(4)*H*); **δ_C (125 MHz, d_6-DMSO)** 24.9 (C(3)*C*H_3), 26.3 (N*C*H_3), 72.8 (*C*(3)), 108.9 (Ar*C*(7)H), 122.8 (Ar*C*(5)H), 123.4 (Ar*C*(6)H), 129.4 (Ar*C*(4)H), 133.4 (Ar*C*(3a)), 143.0 (Ar*C*(7a)), 178.2 (*C*=O); ***m/z* (NSI)** 200 ($[M+Na]^+$, 100%) $C_{10}H_{11}NO_2Na^+$ ($[M+Na]^+$) requires 200.0682; found 200.0682 (+0.0 ppm).

Lab book Reference: JET-729

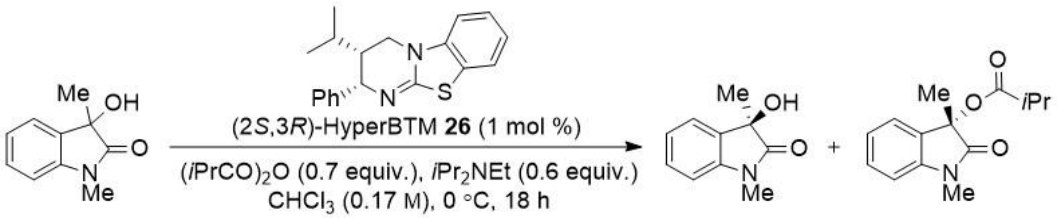
1,3-Dimethyl-2-oxoindolin-3-yl isobutyrate, 121[149]



Following general procedure B, **120** (35 mg, 0.2 mmol), isobutyric anhydride (33 µL, 0.2 mmol), DMAP **4** (2.4 mg, 0.02 mmol, 10 mol %) and *i*Pr_2NEt (42 µL, 0.24 mmol) in CH_2Cl_2 (2.0 mL) gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1; R_F 0.64), **121** as a colourless oil (38 mg, 0.16 mmol, 78%); **ν_{max} (ATR)** 2976, 1726 (C=O), 1614 (C=C), 1470, 1346, 1096; **δ_H (300 MHz, $CDCl_3$)** 1.12 (3H, d, *J* 7.0 Hz CH(CH_3)$_A$(CH$_3$)$_B$), 1.14 (3H, d, *J* 7.0 Hz CH(CH$_3$)$_A$(CH_3)$_B$), 1.60 (3H, s, CH_3), 2.57 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.24 (3H, s, NCH_3), 6.81-6.89 (1H, m, C(7)*H*), 6.99-7.08 (1H, m, C(5)*H*), 7.19 (1H, dd, *J* 7.4, 1.2 Hz, C(6)*H*), 7.27-7.34 (1H, m, C(4)*H*); **δ_C (125 MHz, d_6-DMSO)** 18.8 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 19.0 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.4 (C(3)*C*H$_3$), 26.6 (NCH$_3$), 33.0 (*C*H(CH$_3$)$_2$), 77.0 (*C*(3)), 109.2 (Ar*C*(7)H), 122.2 (Ar*C*(5)H), 122.9 (Ar*C*(6)H), 129.3 (Ar*C*(3a)), 129.9 (Ar*C*(4)H), 143.6 (Ar*C*(7a)H), 174.7 (*C*(2)=O), 174.8 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 248 ($[M+H]^+$, 100%) $C_{14}H_{18}NO_3^+$ ($[M+H]^+$) requires 248.1281; found 248.1283 (+0.7 ppm).

Lab book Reference: JET-733

Kinetic resolution of 129



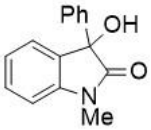
Following general procedure C, **129** (89 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1), alcohol (32 mg, 0.18 mmol, 36%) and ester (59 mg, 0.24 mmol, 48%).

Data for alcohol: $[\alpha]_D^{20}$ +52 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 13.9, 16.2 min, 96:4 er.

Data for ester: $[\alpha]_D^{20}$ +103 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 6.2, 8.2 min, 93:7 er; *s* = 39.

Lab book Reference: SMS-396

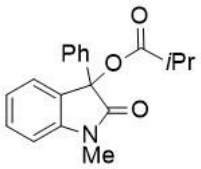
3-Hydroxy-1-methyl-3-phenylindolin-2-one, 122[149]



Following general procedure D, **90** (600 mg, 3.7 mmol) and phenylmagnesium bromide (1.5 mL, 4.4 mmol, 3.0 M) in anhydrous THF (35 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1, R_F 0.26), **122** as a yellow powder (730 mg, 3.0 mmol, 82%), mp 123-125 °C; **ν_{max} (ATR)** 3375, 2974, 1703 (C=O), 1612 (C=C), 1470, 1371; **δ_H (400 MHz, $CDCl_3$)** 3.25 (3H, s, NCH_3), 3.41 (1H, s, O*H*), 6.91 (1H, app dt, *J* 7.9, 0.7 Hz, C(7)*H*), 7.09 (1H, app td, *J* 7.5, 1.0 Hz, C(5)*H*), 7.26-7.41 (7H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 26.7 (N*C*H_3), 78.0 (*C*(3)), 108.7 (Ar*C*(7)H), 123.6 (Ar*C*(5)H), 124.9 (Ar*C*(6)H), 125.3 (C(3)Ar*C*(2,6)H), 128.3 (C(3)Ar*C*(4)H), 128.6 (C(3)Ar*C*(3,5)H), 129.9 (Ar*C*(4)H), 131.5 (C(3)Ar*C*(1)), 140.1 (Ar*C*(3a)), 143.5 (Ar*C*(7a)), 177.5 (*C*=O); ***m/z* (NSI)** 240 ($[M+H]^+$, 100%) $C_{15}H_{14}NO_2^+$ ($[M+H]^+$) requires 240.1019; found 240.1020 (+0.4 ppm).

Lab book Reference: JET-734

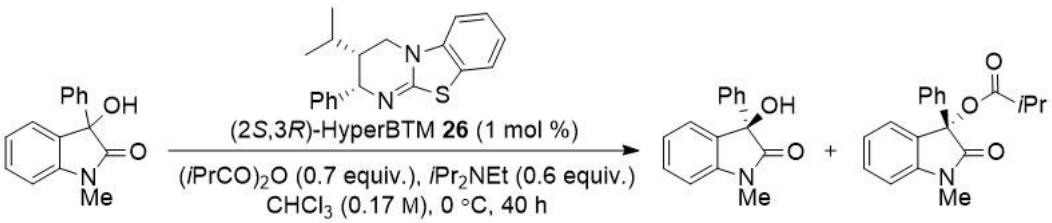
1-Methyl-2-oxo-3-phenylindolin-3-yl isobutyrate, 123



Following general procedure B, **122** (38 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.69), **123** as a colourless powder (39 mg, 0.12 mmol, 78%), mp 123-125 °C; **ν_{max} (ATR)** 2978, 1721 (C=O), 1613 (C=C). 1470, 1342, 1148**; δ_H (400 MHz, $CDCl_3$)** 1.20 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.24 (3H, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.71 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 3.24 (3H, s, NCH_3), 6.93 (1H, app dt, *J* 7.8, 0.7 Hz, C(7)*H*), 7.10 (1H, app td, *J* 7.5, 1.0 Hz, C(5)*H*), 7.10 (1H, ddd, *J* 7.3, 1.4, 0.5 Hz, C(4)*H*), 7.31-7.43 (6H, m, Ar*H*); **δ_C (125 MHz, d_6-DMSO)** 18.9 (CH(*C*H_3)$_A$(CH_3)$_B$), 19.0 (CH(CH_3)$_A$(*C*H_3)$_B$), 26.9 (CH_3), 33.4 (*C*H(CH_3)$_2$), 76.4 (*C*(3)), 109.6 (Ar*C*(7)H), 123.4 (Ar*C*(5)H), 123.8 (Ar*C*(6)H), 126.2 (C(3)Ar*C*(2,6)H), 128.6 (C(3)Ar*C*(1)), 129.1 (C(3)Ar*C*(2,6)H), 129.2 (C(3)Ar*C*(3,5)H), 129.3 (C(3)Ar*C*(4)H), 130.7 (Ar*C*(4)H), 137.2 (Ar*C*(3a)), 144.6 (Ar*C*(7a)), 173.7 (*C*(2)=O), 174.8 (*C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 332 ([M+Na]$^+$, 100%) $C_{19}H_{19}NO_3Na^+$ ([M+Na]$^+$) requires 332.1257; found 332.1259 (+0.6 ppm).

Lab book Reference: JET-740

Kinetic resolution of 122



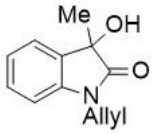
Following general procedure C, **122** (120 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) for 40 h gave, after column chromatography (CH_2Cl_2/EtOAc 9:1), alcohol (67 mg, 0.29 mmol, 57%) and ester (63 mg, 0.21 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +71 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 27.7, 30.7 min, 86:14 er.

Data for ester: $[\alpha]_D^{20}$ +223 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.8, 12.3 min, 99:1 er; *s* = 160.

Lab book Reference: SMS-399

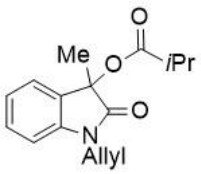
1-Allyl-3-hydroxy-3-methylindolin-2-one, 124[149]



Following general procedure D, **91** (575 mg, 3.1 mmol) and methylmagnesium bromide (1.2 mL, 3.7 mmol, 3.0 M) in anhydrous THF (30 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1, R_F 0.16), **124** as a green solid (464 mg, 2.3 mmol, 74%), mp 114-116 °C; **ν_{max} (ATR)** 3381, 2978, 1703 (C=O), 1614 (C=C), 1468, 1366, 1184; **δ_H (400 MHz, $CDCl_3$)** 1.62 (3H, s, CH_3), 2.94 (1H, br s, OH), 4.27 (1H, ddt, *J* 16.3, 5.2, 1.6 Hz, NCH_AH$_B$CH=CH$_2$), 4.37 (1H, ddt, *J* 16.3, 5.2, 1.6 Hz, NCH$_A$$H_B$CH=CH$_2$), 5.23 (2H, m, NCH$_2$CH=C$H_2$), 5.84 (1H, dddd, *J* 17.4, 10.3, 5.6, 4.9 Hz, NCH$_2$CH=CH$_2$), 6.84 (1H, dd, *J* 7.8, 0.9 Hz, C(7)H), 7.10 (1H, app td, *J* 7.5, 1.0 Hz, C(5)H), 7.29 (1H, app td, *J* 7.8, 1.3 Hz, C(6)H), 7.42 (1H, ddd, *J* 7.3, 1.4, 0.6 Hz, C(4)H); **δ_C (125 MHz, d_6-DMSO)** 25.1 (*C*H$_3$), 41.7 (N*C*H$_2$CH=CH$_2$), 72.8 (*C*(3)), 109.6 (Ar*C*(7)H), 117.1 (NCH$_2$CH=*C*H$_2$), 122.8 (Ar*C*(5)H), 123.6 (Ar*C*(6)H), 129.3 (Ar*C*(4)H), 132.4 (NCH$_2$*C*H=CH$_2$), 133.4 (Ar*C*(3a)), 142.1 (Ar*C*(7a)), 178.1 (*C*=O); ***m/z* (NSI)** 204 ([M+H]$^+$, 100%) $C_{12}H_{14}NO_2^+$ ([M+H]$^+$) requires 204.1019; found 204.1018 (–0.5 ppm).

Lab book Reference: JET-737

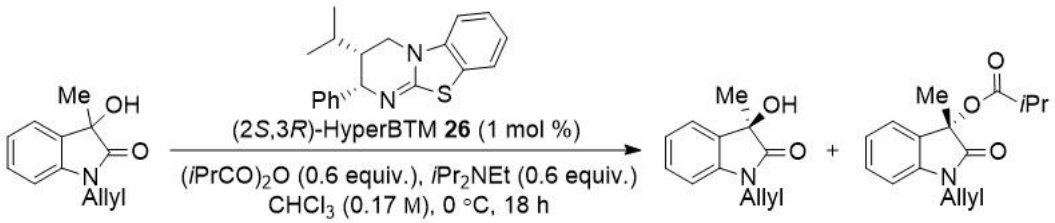
1-Allyl-3-methyl-2-oxoindolin-3-yl isobutyrate, 125



Following general procedure B, **124** (32.5 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1; R_F 0.69), **125** as a colourless oil (29 mg, 0.11 mmol, 66%); **ν_{max} (ATR)** 2978, 1724 (C=O), 1614 (C=C), 1468, 1354, 1188, 1098; **δ_H (400 MHz, $CDCl_3$)** 1.12 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.13 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$), 1.61 (3H, s, CH_3), 2.58 (1H, sept, *J* 7.0 Hz, CH(CH$_3$)$_2$), 4.30-4.42 (2H, m, NCH_2CH=CH$_2$), 5.23 (1H, dq, *J* 10.4, 1.5 Hz, NCH$_2$CH=CH$_{cis}$$H_{trans}$), 5.33 (1H, dtd, *J* 17.2, 1.8, 1.1 Hz, NCH$_2$CH=CH_{cis}H$_{trans}$), 5.86 (1H, ddt, *J* 17.2, 10.3, 5.2 Hz, NCH$_2$CH=CH$_2$), 6.83 (1H, app dt, *J* 7.9, 0.7 Hz, C(7)H), 7.02 (1H, app td, *J* 7.5, 1.0 Hz, C(5)H), 7.19 (1H, ddd, *J* 7.4, 1.3, 0.5 Hz, C(4)H), 7.26 (1H, app td, *J* 7.7, 1.3 Hz, C(6)H); **δ_C (125 MHz, d_6-DMSO)** 18.9 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 19.1 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.7 (*C*H$_3$), 33.1 (*C*H(CH$_3$)$_2$), 42.0 (N*C*H$_2$CH=CH$_2$), 77.0 (*C*(3)), 109.9 (Ar*C*(7)H), 117.3 (NCH$_2$CH=*C*H$_2$), 122.3 (Ar*C*(5)H), 123.0 (Ar*C*(6)H), 129.3 (Ar*C*(3a)), 129.8 (Ar*C*(4)H), 132.2 (NCH$_2$*C*H=CH$_2$), 142.5 (Ar*C*(7a)), 174.6 (*C*(2)=O), 174.7 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 274 ([M+H]$^+$, 100%) $C_{16}H_{20}NO_3^+$ ([M+H]$^+$) requires 274.1438; found 274.1438 (+0.1 ppm).

Lab book Reference: SMS-176

Kinetic resolution of 124



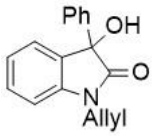
Following general procedure C, **124** (60 mg, 0.3 mmol), isobutyric anhydride (29 µL, 0.18 mmol), (2*S*,3*R*)-HyperBTM **26** (0.9 mg, 0.003 mmol, 1 mol %) and *i*Pr_2NEt (31 µL, 0.18 mmol) in $CHCl_3$ (1.8 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1), alcohol (29 mg, 0.19 mmol, 49%) and ester (34 mg, 0.13 mmol, 42%).

Data for alcohol: $[\alpha]_D^{20}$ +59 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 30.3, 35.0 min, 85:15 er.

Data for ester: $[\alpha]_D^{20}$ +48 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.3, 10.3 min, 99:1 er; *s* = 140.

Lab book Reference: SMS-395

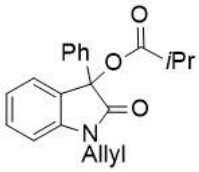
1-Allyl-3-hydroxy-3-phenylindolin-2-one, 126[149]



Following general procedure D, **91** (555 mg, 3.0 mmol) and phenylmagnesium bromide (1.2 mL, 3.6 mmol, 3.0 M) in anhydrous THF (30 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1, R_F 0.40), **126** as a yellow powder (702 mg, 2.6 mmol, 88%), mp 132-134 °C; **δ_H (400 MHz, $CDCl_3$)** 3.38 (1H, br s, O*H*), 4.28 (1H, ddt, *J* 16.4, 5.4, 1.7 Hz, C$H_A$$H_B$CH=$CH_2$), 4.46 (1H, ddt, *J* 16.4, 5.4, 1.7 Hz, CH$_A$$H_B$C=$CH_2$), 5.27 (2H, m, HRC=C$H_2$), 5.87 (1H, m, CH_2C*H*=CH_2), 6.90 (1H, app dt, *J* 7.8, 0.8 Hz, C(7)*H*), 7.08 (1H, app td, *J* 7.5, 1.0 Hz, C(5)*H*), 7.27-7.43 (7H, m, ArC*H*).

Lab book Reference: JET-739

1-Allyl-2-oxo-3-phenylindolin-3-yl isobutyrate, 127

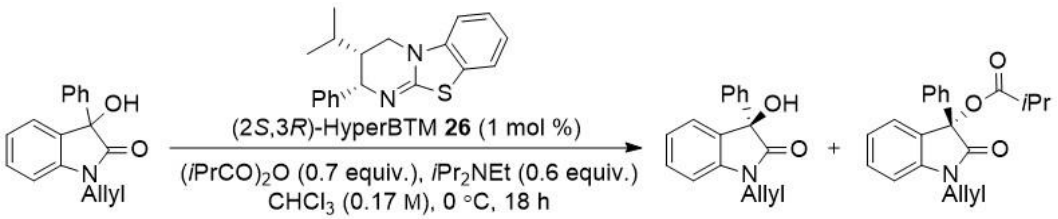


Following general procedure B, **126** (42 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.55), **127** as a yellow solid (42 mg, 0.12 mmol, 78%), mp 61-63 °C; **ν_{max} (ATR)** 2972, 1724 (C=O), 1614 (C=O), 1466, 1348, 1146; **δ_H (400 MHz, $CDCl_3$)**

1.20 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.24 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.71 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 4.35 (2H, m, NC*H*$_2$CH=CH$_2$), 5.23 (1H, dq, *J* 10.4, 1.5 Hz, NCH$_2$CH=CH$_{cis}$*H*$_{trans}$), 5.32 (1H, dq, *J* 17.2, 1.5 Hz, NCH$_2$CH=C*H*$_{cis}$H$_{trans}$), 5.86 (1H, ddt, *J* 17.2, 10.4, 5.2 Hz, NCH$_2$C*H*=CH$_2$), 6.91 (1H, app dt, *J* 7.9, 0.8 Hz, C(7)*H*), 7.08 (1H, app td, *J* 7.4, 1.0 Hz, C(5)*H*), 7.20 (1H, ddd, *J* 7.4, 1.5, 0.6 Hz, C(6)*H*), 7.31-7.39 (6H, m, Ar*H*); **δ$_C$ (125 MHz, *d*$_6$-DMSO)** 18.9 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 19.0 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.4 (*C*H(CH$_3$)$_2$), 42.3 (*C*H$_2$CH=CH$_2$), 80.8 (*C*(3)), 110.2 (Ar*C*(7)H), 117.5 (CH$_2$CH=*C*H$_2$), 123.5 (Ar*C*(5)H), 123.9 (Ar*C*(6)H), 126.1 (C(3)Ar*C*(2,6)H), 128.6 (C(3)Ar*C*(1)), 129.2 (C(3)Ar*C*(3,5)H), 129.3 (C(3)Ar*C*(4)H), 130.4 (Ar*C*(4)H), 132.0 (CH$_2$*C*H=CH$_2$), 137.3 (Ar*C*(3a)), 143.5 (Ar*C*(7a)), 173.4 (*C*(2)=O), 174.8 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 358 ([M+Na]$^+$, 100%) $C_{21}H_{21}NO_3Na^+$ ([M+Na]$^+$) requires 358.1414; found 314.1415 (+0.4 ppm).

Lab book Reference: SMS-175

Kinetic resolution of 126



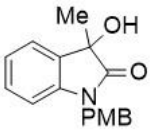
Following general procedure C, **126** (133 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in CHCl$_3$ (3 mL) gave, after column chromatography (CH$_2$Cl$_2$/EtOAc 9:1), alcohol (65 mg, 0.25 mmol, 49%) and ester (67 mg, 0.20 mmol, 40%).

Data for alcohol: [α]$_D^{20}$ +55 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T$_R$: 13.6, 15.4 min, 78% *ee.*

Data for ester: [α]$_D^{20}$ +137 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T$_R$: 11.3, 13.0 min, 96% *ee*; S = 118.6.

Lab book Reference: SMS-398

3-Hydroxy-1-(4-methoxybenzyl)-3-methylindolin-2-one, 128

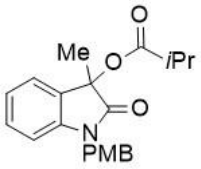


Following general procedure D, **92** (1.54 g, 3.7 mmol) and methylmagnesium bromide (1.5 mL, 4.5 mmol, 3.0 M) in anhydrous THF (25 mL) gave, after column chromatography (CH$_2$Cl$_2$:EtOAc 9:1, R$_F$ 0.18), **128** a green solid (410 g, 1.45 mmol, 37%), mp 122-124 °C; **ν$_{max}$ (ATR)** 3396 (OH), 2976, 1695 (C=O), 1612 (C=O), 1514, 1467, 1250, 1028; **δ$_H$ (400 MHz, CDCl$_3$)** 1.65 (3H, s, C*H*$_3$), 2.91 (1H, br s, O*H*),

3.76 (3H, s, OCH_3), 4.76 (1H, d, *J* 15.4 Hz, CH_AH$_B$Ph), 4.88 (1H, d, *J* 15.4 Hz, CH$_A$$H_B$Ph), 6.74 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 6.79-6.88 (2H, m, CH$_2$ArC(2,6)*H*), 7.06 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.18-7.24 (3H, m, ArC(6)*H*, CH$_2$ArC(3,5)*H*), 7.41 (1H, app ddd, *J* 7.3, 1.2, 0.4 Hz, ArC(4)*H*); **δ_C (100 MHz, CDCl$_3$)** 25.1 (*C*H$_3$), 43.2 (*C*H$_2$Ph), 55.3 (O*C*H$_3$), 73.7 (*C*(3)), 109.6 (Ar*C*(7)H), 114.2 (CH$_2$Ar*C*(2,6)H), 123.2 (Ar*C*(5)H), 123.5 (Ar*C*(6)H), 127.5 (CH$_2$Ar*C*(1)), 128.6 (CH$_2$Ar*C*(3,5)H), 129.5 (Ar*C*(4)H), 131.4 (Ar*C*(3a)), 141.9 (Ar*C*(7a)), 159.1 (CH$_2$Ar*C*(4)), 178.6 (*C*=O); ***m/z* (NSI)** 284 ([M+H]$^+$, 100%) $C_{17}H_{18}O_3N^+$ ([M+H]$^+$) requires 284.1281; found 284.1283 (+0.6 ppm).

Lab book Reference: SMS-199

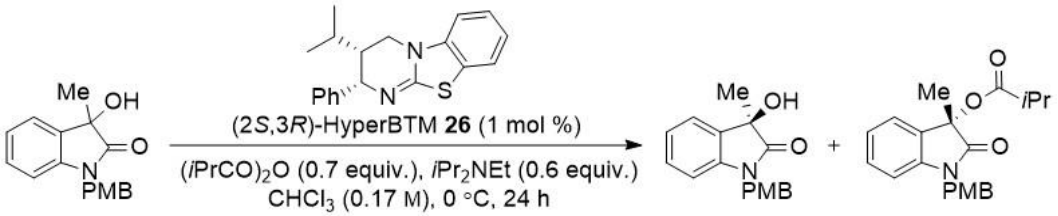
1-(4-methoxybenzyl)-3-methyl-2-oxoindolin-3-yl isobutyrate, 129



Following general procedure B, **128** (45 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH$_2$Cl$_2$ (2.5 mL) gave, after column chromatography (eluent CH$_2$Cl$_2$/EtOAc, 9:1; R_F 0.70), **129** as a green oil (42 mg, 0.12 mmol, 75%); **ν_{max} (ATR)** 2976, 1724 (C=O), 1612 (C=C), 1514, 1467, 1153, 1098; **δ_H (400 MHz, CDCl$_3$)** 1.15 (3H, d, *J* 7.0 Hz CH(CH_3)$_A$(CH$_3$)$_B$), 1.16 (3H, d, *J* 7.0 Hz CH(CH$_3$)$_A$(CH_3)$_B$), 1.64 (3H, s, CH_3), 2.61 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.77 (3H, s, OCH$_3$), 4.87 (1H, d, *J* 15.6 Hz, NCH_AH$_B$Ph), 4.92 (1H, d, *J* 15.6 Hz, NCH$_A$$H_B$Ph), 6.68 (1H, app d, *J* 7.8 Hz, C(7)*H*), 6.83-6.89 (2H, m, CH$_2$ArC(3,5)*H*), 6.99 (1H, app td, *J* 7.7, 0.9 Hz, C(5)*H*), 7.13-7.21 (2H, m, C(4,6)*H*), 7.27-7.32 (2H, m, CH$_2$ArC(2,6)*H*); **δ_C (100 MHz, CDCl$_3$)** 18.6 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.9 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 23.6 (*C*H$_3$), 33.4 (*C*H(CH$_3$)$_2$), 43.5 (*C*H$_2$Ar), 55.3 (O*C*H$_3$), 77.0 (*C*(3)), 109.6 (Ar*C*(7)H), 114.2 (CH$_2$Ar*C*(3,5)H), 121.7 (Ar*C*(4)H), 122.7 (Ar*C*(5)H), 127.7 (CH$_2$Ar*C*(1)), 128.5 (CH$_2$Ar*C*(2,6)H), 129.4 (2C, Ar*C*(6)H, Ar*C*(3a)), 142.3 (Ar*C*(7a)), 159.0 (CH$_2$Ar*C*(4)), 175.0 (*C*(=O)CH(CH$_3$)$_2$), 175.3 (*C*(2)=O); ***m/z* (NSI)** 354 ([M+H]$^+$, 100%) $C_{21}H_{24}O_4N^+$ ([M+H]$^+$) requires 354.1700; found 354.1695 (–1.4 ppm).

Lab book Reference: SMS-207

Kinetic resolution of 127



Following general procedure C, **128** (141 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in CHCl$_3$ (3 mL) for

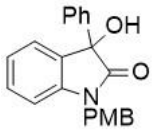
24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (61 mg, 0.22 mmol, 43%) and ester (88 mg, 0.25 mmol, 49%).

Data for alcohol: $[\alpha]_D^{20}$ +65 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (15% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.1, 15.9 min, 94:6 er.

Data for ester: $[\alpha]_D^{20}$ –9 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.4, 10.3 min, 96:4 er; *s* = 70.

Lab book Reference: SMS-245

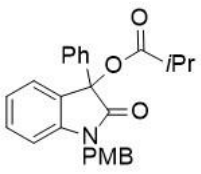
3-Hydroxy-1-(4-methoxybenzyl)-3-phenylindolin-2-one, 130



Following general procedure D, **92** (1.54 g, 3.7 mmol) and phenylmagnesium bromide (1.5 mL, 4.5 mmol, 3.0 M) in anhydrous THF (25 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.40), **130** as a yellow solid (508 g, 1.48 mmol, 40%), mp 122-124 °C; **ν_{max} (ATR)** 3364 (OH), 2972, 1699 (C=O), 1611 (C=O), 1512, 1466, 1246, 1028; **δ_H (400 MHz, $CDCl_3$)** 3.32 (1H, br s, O*H*), 3.81 (3H, s, OCH_3), 4.80 (1H, d, *J* 15.4 Hz, CH_AH_BPh), 5.01 (1H, d, *J* 15.4 Hz, CH_AH_BPh), 6.84 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 6.88-6.91 (2H, m, CH_2ArC(2,6)*H*), 7.06 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.23-7.45 (9H, m, Ar*H*); **δ_C (100 MHz, $CDCl_3$)** 43.6 (*C*H_2Ph), 55.3 (*C*H_3), 78.0 (*C*(3)), 109.8 (Ar*C*(7)H), 114.3 (CH_2Ar*C*(2,6)H), 123.5 (Ar*C*(5)H), 124.9 (Ar*C*(6)H), 125.3 (C(3)Ar*C*(2,6)H), 127.5 (CH_2Ar*C*(1)), 128.4 (Ar*C*(4)H), 128.7 (CH_2Ar*C*(3,5)H), 128.8 (C(3)Ar*C*(3,5)H), 129.8 (C(3)Ar*C*(4)H), 131.6 (Ar*C*(3a)), 140.2 (Ar*C*(7a)), 142.7 (C(3)ArC(1)), 159.2 (CH_2Ar*C*(4)), 175.0 (*C*=O); ***m/z* (NSI)** 346 ($[M+H]^+$, 100%) $C_{22}H_{20}O_3N^+$ ($[M+H]^+$) requires 346.1438; found 346.1439 (+0.4 ppm).

Lab book Reference: SMS-198

1-(4-Methoxybenzyl)-2-oxo-3-phenylindolin-3-yl isobutyrate, 131

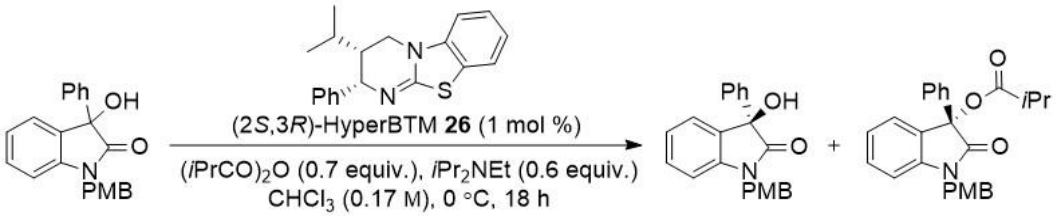


Following general procedure B, **130** (55 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.75), **131** as a yellow solid (52 mg, 0.13 mmol, 79%), mp 92-94 °C; **ν_{max} (ATR)** 2974, 1727 (C=O), 1612 (C=C), 1514, 1466, 1246, 1144; **δ_H (400 MHz, $CDCl_3$)** 1.23 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.26 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.74 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.82 (1H, d, *J* 15.6 Hz, NCH_AH_BAr), 4.92 (1H, d, *J* 15.6 Hz, NCH_AH_BAr), 6.74 (1H, app t, *J*

7.8 Hz, C(7)*H*), 6.84 (2H, m, $NCH_2ArC(3,5)H$), 7.04 (1H, app td, *J* 7.6, 0.9 Hz, C(5)*H*), 7.16-7.20 (1H, m, C(6)*H*), 7.21-7.28 (3H, m, C(4)*H*, $NCH_2ArC(2,6)H$), 7.35 (5H, s, C(3)Ar*CH*); **δ_C (100 MHz, $CDCl_3$)** 18.7 ($CH(CH_3)_A(CH_3)_B$), 18.9 ($CH(CH_3)_A(CH_3)_B$), 33.8 ($CH(CH_3)_2$), 43.8 (CH_2Ph), 55.3 (OCH_3), 80.1 (*C*(3)), 109.8 (Ar*C*(7)H), 114.1 ($CH_2ArC(3,5)H$), 123.0 (Ar*C*(5)H), 123.7 (Ar*C*(6)H), 126.4 (C(3)Ar*C*(3,5)H), 127.6 ($CH_2ArC(1)$), 128.5 (C(3)Ar*C*(1)), 128.6 ($CH_2ArC(2,6)H$), 128.7 (C(3)Ar*C*(2,6)H), 128.9 (Ar*C*(4)H), 129.9 (C(3)Ar*C*(4)H), 136.9 (Ar*C*(3a)), 143.7 (Ar*C*(7a)), 159.0 ($CH_2ArC(4)$), 174.1 (*C*(2)=O), 175.0 ($C(=O)CH(CH_3)_2$); ***m/z* (NSI)** 438 ([M+Na]$^+$, 100%) $C_{26}H_{25}O_4NNa^+$ ([M+Na]$^+$) requires 438.1676; found 438.1674 (–0.4 ppm).

Lab book Reference: SMS-206

Kinetic resolution of 130



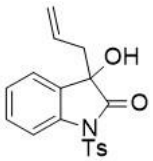
Following general procedure C, **129** (173 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (62 mg, 0.18 mmol, 36%) and ester (77 mg, 0.19 mmol, 37%).

Data for alcohol: $[\alpha]_D^{20}$ +54 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (15% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 24.7, 31.2 min, 96:4 er.

Data for ester: $[\alpha]_D^{20}$ +139 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.9, 32.4 min, 97:3 er; *s* = 90.

Lab book Reference: SMS-215

3-Allyl-3-hydroxy-1-tosylindolin-2-one, 132

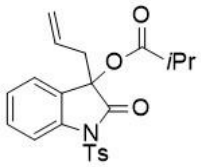


Following the procedure by Bisai *et al*,[95] **93** (601 mg, 2 mmol) was dissolved in anhydrous DMF (5 mL) under an N_2 atmosphere and cooled to 0 °C. Allyltrichlorosilane (434 µL, 3 mmol) was added dropwise over 15 mins and the reaction stirred overnight at RT. On completion, the reaction was quenched with H_2O (10 mL) and brine (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.62), **132** as an orange solid (428 mg, 1.24

mmol, 62%); **ν_{max} (ATR)** 3401 (OH), 2922, 1726 (C=O), 1609 (C=C), 1464, 1364, 1161, 1088; **δ_H (400 MHz, $CDCl_3$)** 2.42 (3H, s, $SO_2ArC(4)CH_3$), 2.52-2.68 (2H, m, $CH_2CH=CH_2$), 2.66 (1H, s, OH), 4.98-5.05 (2H, m, $CH_2CH=CH_2$), 5.47 (1H, dddd, 16.5, 10.1, 8.5, 6.4 Hz, $CH_2CH=CH_2$), 7.22 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)H), 7.31 (2H, d, *J* 8.0 Hz, $SO_2ArC(3,5)H$), 7.34-7.43 (2H, m, ArC(4,6)H), 7.91 (1H, app d, *J* 8.2 Hz, ArC(7)H), 7.94-7.99 (2H, m, $SO_2ArC(2,6)H$); **δ_C (100 MHz, $CDCl_3$)** 21.7 ($SO_2ArC(4)CH_3$), 43.7 ($CH_2CH=CH_2$), 75.6 (C(3)), 113.7 (ArC(7)H), 121.6 ($CH_2CH=CH_2$), 124.4 (ArC(4)H), 125.3 (ArC(5)H), 127.9 ($SO_2ArC(2,6)H$), 128.5 (ArC(3a)), 129.1 ($CH_2CH=CH_2$), 129.8 ($SO_2ArC(3,5)H$), 130.5 (ArC(6)H), 134.9 ($SO_2ArC(4)$), 138.6 ($SO_2ArC(1)$), 145.9 (ArC(7a)), 176.1 (C=O); ***m/z* (NSI)** 361 ($[M+NH_4]^+$, 100%) $C_{18}H_{21}N_2O_4S^+$ ($[M+NH_4]^+$) requires 361.1217; found 361.1213 (–1.0 ppm).

Lab book Reference: SMS-341

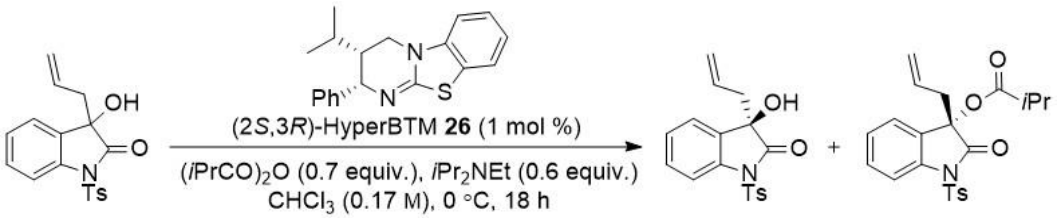
3-Allyl-2-oxo-1-tosylindolin-3-yl isobutyrate, 133



Following general procedure B, **132** (55 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and iPr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.72), **133** as a colourless oil (51 mg, 0.12 mmol, 77%), mp 69-71 °C; **ν_{max} (ATR)** 2976, 1771(C=O), 1746, 1609 (C=C), 1462, 1373, 1176, 1084; **δ_H (400 MHz, $CDCl_3$)** 1.00 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.02 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 2.40 (3H, s, $SO_2ArC(4)CH_3$), 2.46 (1H, sept, *J* 7.0 Hz, $CH(CH_3)_2$), 2.58 (1H, dd, *J* 13.6, 8.0 Hz, $CH_ACH_BCH=CH_2$), 2.73 (1H, ddt, *J* 13.5, 6.5, 1.2 Hz, $CH_ACH_BCH=CH_2$), 4.95-5.04 (2H, m, $CH_2CH=CH_2$), 5.44 (1H, dddd, *J* 16.8, 10.5, 8.1, 6.5 Hz, $CH_2CH=CH_2$), 7.11-7.17 (2H, m, ArC(4,5)H), 7.27-7.32 (2H, m, $SO_2ArC(3,5)H$), 7.32-7.40 (1H, m, ArC(6)H), 7.90 (1H, app d, *J* 8.2 Hz, ArC(7)H), 7.93-7.99 (2H, m, $SO_2ArC(2,6)H$); **δ_C (100 MHz, $CDCl_3$)** 18.2 ($CH(CH_3)_A(CH_3)_B$), 18.6 ($CH(CH_3)_A(CH_3)_B$), 21.7 ($SO_2ArC(4)CH_3$), 33.1 ($CH(CH_3)_2$), 41.2 ($CH_2CH=CH_2$), 78.3 (C(3)), 113.6 (ArC(7)H), 121.4 ($CH_2CH=CH_2$), 122.8 (ArC(4)H), 124.8 (ArC(5)H), 126.8 (ArC(3a)), 128.2 ($SO_2ArC(2,6)H$), 128.3 ($CH_2CH=CH_2$), 129.5 ($SO_2ArC(3,5)H$), 130.2 (ArC(6)H), 134.7 ($SO_2ArC(4)$), 139.3 ($SO_2ArC(1)$), 145.5 (ArC(7a)), 172.3 (C(2)=O), 174.4 (C(=O)$CH(CH_3)_2$); ***m/z* (NSI)** 431 ($[M+NH_4]^+$, 100%) $C_{22}H_{27}N_2O_5S^+$ ($[M+NH_4]^+$) requires 431.1635; found 431.1632 (–0.7 ppm).

Lab book Reference: SMS-343

Kinetic resolution of 132



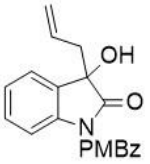
Following general procedure C, **132** (172 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5), alcohol (57 mg, 0.17 mmol, 33%) and ester (104 mg, 0.25 mmol, 50%).

Data for alcohol: $[\alpha]_D^{20}$ +3 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AS-H (2.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 27.0, 34.6 min, 90:10 er.

Data for ester: $[\alpha]_D^{20}$ +77 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.6, 20.3 min, 75:25 er; *s* = 7.

Lab book Reference: SMS-345

3-Allyl-3-hydroxy-1-(4-methoxybenzoyl)indolin-2-one, 134

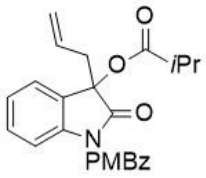


Following the procedure by Bisai *et al*,[95] **94**[150] (426 mg, 1.52 mmol) was dissolved in anhydrous DMF (5 mL) under an N_2 atmosphere and cooled to 0 °C. Allyltrichlorosilane (330 µL, 2.27 mmol) was added dropwise over 15 mins and the reaction stirred overnight at RT. On completion, the reaction was quenched with H_2O (10 mL) and brine (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.62), **134** as a pale orange solid (394 mg, 1.22 mmol, 80%), mp 100-102 °C; **ν_{max} (ATR)** 3373 (OH), 2926, 1720 (C=O), 1701 (C=O), 1685, 1603 (C=C), 1466, 1341, 1263, 1169; **δ_H (400 MHz, $CDCl_3$)** 2.72 (1H, dd, *J* 13.4, 8.9 Hz, C$H_A$$H_B$CH=$CH_2$), 2.82 (1H, ddt, *J* 13.4, 5.9, 1.2 Hz, C$H_A$$H_B$CH=$CH_2$), 2.84 (1H, s, O*H*), 3.89 (3H, s, OCH_3), 5.18-5.26 (2H, m, CH_2CH=CH_2), 5.63 (1H, dddd, *J* 16.3, 10.2, 8.9, 5.9 Hz, CH_2C*H*=CH_2), 6.92-6.97 (2H, m, C(O)ArC(3,5)*H*), 7.25 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.40 (1H, app td, *J* 7.9, 1.4 Hz, ArC(6)*H*), 7.48 (1H, app dd, *J* 7.5, 0.9 Hz, ArC(4)*H*), 7.70 (1H, app d, *J* 8.1 Hz, ArC(7)*H*), 7.73-7.77 (2H, m, C(O)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 43.8 (*C*H_2CH=CH_2), 55.6 (O*C*H_3), 76.9 (*C*(3)), 113.7 (C(O)Ar*C*(3,5)H), 115.0 (Ar*C*(7)H), 121.3 (CH_2CH=*C*H_2), 124.1 (Ar*C*(4)H), 125.1 (Ar*C*(5)H), 125.6 (C(O)Ar*C*(1)), 128.9 (Ar*C*(3a)), 130.1 (CH_2*C*H=CH_2), 130.1 (Ar*C*(6)H), 132.3 (C(O)Ar*C*(2,6)H), 140.0 (Ar*C*(7a)), 163.9

(C(O)Ar*C*(4)), 167.9 (*C*(O)ArOCH$_3$), 176.1 (*C*(2)=O); ***m/z* (NSI)** 342 ([M+H]$^+$, 100%) $C_{19}H_{18}NO_4^+$ ([M+H]$^+$) requires 324.1230; found 324.1231 (+0.2 ppm).

Lab book Reference: SMS-342

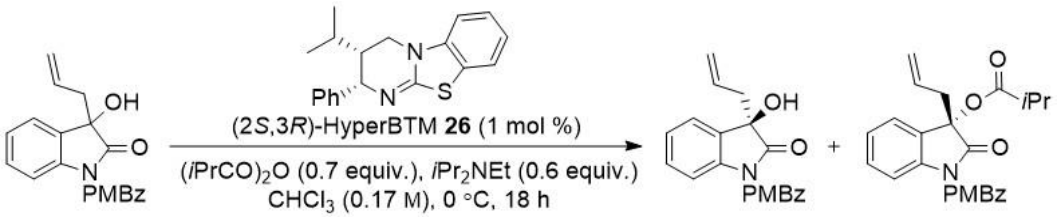
3-Allyl-1-(4-methoxybenzoyl)-2-oxoindolin-3-yl isobutyrate, 135



Following general procedure B, **134** (52 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.68), **135** as a colourless oil (53 mg, 0.13 mmol, 84%), mp 76-78 °C; **ν_{max} (ATR)** 2982, 1771(C=O), 1738, 1678, 1603 (C=C), 1472, 1263, 1161; **δ_H (400 MHz, $CDCl_3$)** 1.15 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.16 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.62 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 2.68 (1H, dd, *J* 13.3, 8.9 Hz, C*H*$_A$H$_B$CH=CH$_2$), 2.86 (1H, ddt, *J* 13.5, 6.1, 1.3 Hz, CH$_A$*H*$_B$CH=CH$_2$), 3.87 (3H, s, OC*H*$_3$), 5.09-5.18 (2H, m, CH$_2$CH=C*H*$_2$), 5.63 (1H, dddd, *J* 16.4, 10.2, 8.4, 6.1 Hz, CH$_2$C*H*=CH$_2$), 6.91-6.97 (2H, m, C(O)ArC(3,5)*H*), 7.18 (1H, app td, *J* 7.5, 1.0 Hz, ArC(5)*H*), 7.27 (1H, app dd, *J* 7.5, 0.9 Hz, ArC(4)*H*), 7.35-7.42 (1H, m, ArC(6)*H*), 7.72 (1H, app d, *J* 8.1 Hz, ArC(7)*H*), 7.84-7.89 (2H, m, C(O)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.6 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.7 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.4 (*C*H(CH$_3$)$_2$), 41.6 (*C*H$_2$CH=CH$_2$), 55.5 (OCH$_3$), 78.9 (*C*(3)), 113.5 (C(O)Ar*C*(3,5)H), 114.8 (Ar*C*(7)H), 121.3 (CH$_2$CH=*C*H$_2$), 122.6 (Ar*C*(4)H), 124.6 (Ar*C*(5)H), 125.9 (C(O)Ar*C*(1)), 126.8 (Ar*C*(3a)), 129.0 (CH$_2$*C*H=CH$_2$), 130.1 (Ar*C*(6)H), 132.6 (C(O)Ar*C*(2,6)H), 140.4 (Ar*C*(7a)), 163.8 (C(O)Ar*C*(4)), 168.2 (*C*(O)ArOCH$_3$), 173.3 (*C*(2)=O), 175.2 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 394 ([M+H]$^+$, 100%) $C_{23}H_{24}NO_5^+$ ([M+NH$_4$]$^+$) requires 394.1649; found 394.1646 (–0.8 ppm).

Lab book Reference: SMS-344

Kinetic resolution of 134



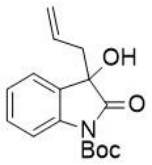
Following general procedure C, **134** (162 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5), alcohol (50 mg, 0.16 mmol, 31%) and ester (113 mg, 0.29 mmol, 57%).

Data for alcohol: $[\alpha]_D^{20}$ +13 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 47.6, 54.4 min, 90:10 er.

Data for ester: $[\alpha]_D^{20}$ –18 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 10.5, 13.8 min, 75:25 er; *s* = 8.

Lab book Reference: SMS-346

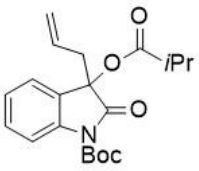
***Tert*-butyl 3-allyl-3-hydroxy-2-oxoindoline-1-carboxylate, 136**



Following the procedure by Bisai *et al*,[95] **96** (595 mg, 2.0 mmol) was dissolved in anhydrous DMF (5 mL) under an N_2 atmosphere and cooled to 0 °C. Allyltrichlorosilane (434 µL, 3 mmol) was added dropwise over 15 mins and the reaction stirred overnight at RT. On completion, the reaction was quenched with H_2O (10 mL) and brine (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.18), **136** as a pale orange solid (416 mg, 1.44 mmol, 72%); ν_{max} **(ATR)** 3455 (OH), 2980, 1775, 1730 (C=O), 1701 (C=O), 1610 (C=C), 1466, 1342, 1285, 1248, 1143; δ_H **(400 MHz, $CDCl_3$)** 1.62 (9H, s, C(CH_3)$_3$), 2.61 (1H, dd, *J* 13.4, 8.5 Hz, $CH_AH_BCH=CH_2$), 2.67-2.76 (1H, m, $CH_AH_BCH=CH_2$), 3.13 (1H, s, O*H*), 5.07-5.15 (2H, m, $CH_2CH=CH_2$), 5.63 (1H, dddd, *J* 15.2, 11.6, 8.5, 6.3 Hz, $CH_2CH=CH_2$), 7.19 (1H, app td, *J* 7.5, 0.9 Hz, ArC(5)*H*), 7.35 (1H, app td, *J* 7.9, 1.4 Hz, ArC(6)*H*), 7.40 (1H, app dd, *J* 7.4, 0.9 Hz, ArC(4)*H*), 7.82 (1H, app d, *J* 8.1 Hz, ArC(7)*H*); δ_C **(100 MHz, $CDCl_3$)** 28.1 (C(CH_3)$_3$), 43.7 ($CH_2CH=CH_2$), 75.5 (*C*(3)), 84.7 (*C*(CH_3)$_3$), 115.2 (Ar*C*(7)H), 121.1 ($CH_2CH=CH_2$), 124.0 (Ar*C*(4)H), 124.8 (Ar*C*(5)H), 128.6 (Ar*C*(3a)), 129.8 ($CH_2CH=CH_2$), 129.9 (Ar*C*(6)H), 139.2 (Ar*C*(7a)), 148.9 (N*C*(=O)OC(CH_3)$_3$), 176.5 (*C*(2)=O).

Lab book Reference: SMS-349

***Tert*-butyl 3-allyl-3-(isobutyryloxy)-2-oxoindoline-1-carboxylate, 137**

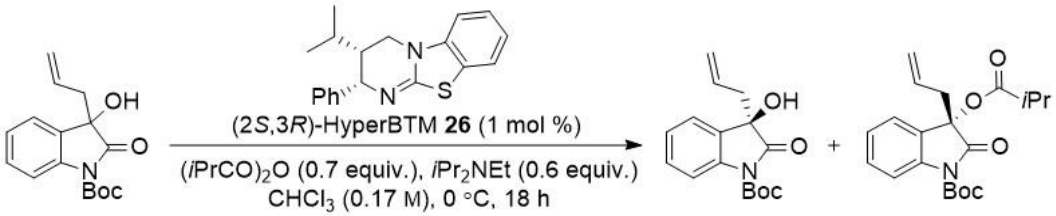


Following general procedure B, **136** (46 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.85), **137** as a colourless oil (50 mg, 0.14 mmol, 88%); ν_{max} **(ATR)** 2978, 1778 (C=O), 1728, 1611 (C=C), 1466, 1292, 1248, 1144; δ_H **(400 MHz, $CDCl_3$)** 1.12 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.13 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.58 (1H, sept, *J* 7.0

Hz, C*H*$(CH_3)_2$), 2.61 (1H, dd, *J* 13.3, 8.9 Hz, CH_AH_BCH=CH_2), 2.81 (1H, ddt, *J* 13.5, 6.1, 1.3 Hz, CH_AH_BCH=CH_2), 5.03-5.16 (2H, m, CH_2CH=CH_2), 5.60 (1H, dddd, *J* 16.8, 10.2, 8.2, 6.3 Hz, CH_2C*H*=CH_2), 7.13 (1H, app td, *J* 7.4, 0.8 Hz, ArC(5)*H*), 7.19 (1H, app dd, *J* 7.4, 1.4 Hz, ArC(4)*H*), 7.29-7.34 (1H, m, ArC(6)*H*), 7.86 (1H, app d, *J* 8.1 Hz, ArC(7)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (CH(*C*$H_3)_A(CH_3)_B$), 18.7 (CH$(CH_3)_A$(*C*$H_3)_B$), 33.4 (*C*H$(CH_3)_2$), 41.5 (*C*H_2CH=CH_2), 78.6 (*C*(3)), 115.3 (Ar*C*(7)H), 121.1 (CH_2CH=*C*H_2), 122.4 (Ar*C*(4)H), 124.4 (Ar*C*(5)H), 126.5 (Ar*C*(3a)), 128.9 (CH_2*C*H=CH_2), 129.8 (Ar*C*(6)H), 139.8 (Ar*C*(7a)), 149.0 (N*C*(=O)OC$(CH_3)_3$), 172.5 (*C*(2)=O), 174.9 (*C*(=O)CH$(CH_3)_2$); ***m/z* (NSI)** 382 ($[M+Na]^+$, 100%) $C_{20}H_{25}NO_5Na^+$ ($[M+Na]^+$) requires 382.1625; found 382.1624 (–0.2 ppm).

Lab book Reference: SMS-350

Kinetic resolution of 136



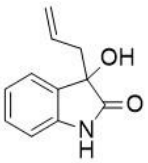
Following general procedure C, **136** (145 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5), alcohol (59 mg, 0.21 mmol, 41%) and ester (80 mg, 0.23 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ +43 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 10.3, 13.1 min, 99:1 er.

Data for ester: $[\alpha]_D^{20}$ +17 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 4.7, 7.5 min, 96:4 er; *s* = 110.

Lab book Reference: SMS-448

3-Allyl-3-hydroxyindolin-2-one, 138



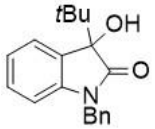
Following the method outlined by Shanahan *et al*,[151] **136** (289 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.15 µL, 15 mmol) was added dropwise. The reaction was stirred for 5 h, at which point, the reaction was made basic with $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford **138** as a pale brown solid, without further need for purification (143 mg, 0.76 mmol, 76%), mp 110-112 °C (lit 112-115 °C); **δ_H (400 MHz,**

$CDCl_3$) 2.62 (1H, dd, *J* 13.4, 8.3 Hz, CH_AH_BCH=CH_2), 2.75 (1H, *J* 13.4, 6.4, 1.2 Hz, CH_AH_BCH=CH_2), 3.03 (1H, s, O*H*), 5.10-5.17 (2H, m, CH_2CH=CH_2), 5.69 (1H, dddd, *J* 16.8, 10.2, 8.3, 6.4 Hz, CH_2C*H*=CH_2), 6.87 (1H, d, *J* 7.8 Hz, ArC(7)*H*), 7.08 (1H, td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.27 (1H, td, *J* 7.7, 1.3 Hz, ArC(6)*H*), 7.35-7.40 (1H, m, ArC(4)*H*), 7.90 (1H, s, N*H*).

Lab book Reference: SMS-459

Data in accordance with literature[152]

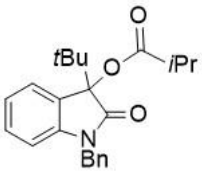
1-Benzyl-3-(*tert*-butyl)-3-hydroxyindolin-2-one, 139



Following general procedure D, **89** (0.88 g, 3.7 mmol) and *tert*-butylmagnesium chloride (3.7 mL, 3.7 mmol, 1.0 M) in anhydrous THF (25 mL) gave, after column chromatography (CH_2Cl_2/EtOAc 9:1, R_F 0.60), **139** as an orange solid (391 mg, 36 %), mp 83-85 °C[153]; **ν_{max} (ATR)** 3395 (OH), 2957, 1690 (C=O), 1466, 1358, 1179; **δ_H (400 MHz, $CDCl_3$)** 1.09 (9H, s, C(CH_3)$_3$), 2.69 (1H, s, O*H*), 4.66 (1H, d, *J* 15.7 Hz, CH_AH$_B$Ph), 5.07 (1H, d, *J* 15.7 Hz, CH$_A$$H_B$Ph), 6.71 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.03 (1H, app td, *J* 7.6, 0.7 Hz, ArC(5)*H*), 7.20 (1H, td, *J* 7.8, 1.1 Hz, ArC(6)*H*), 7.24-7.36 (5H, m, ArC*H*), 7.42 (1H, app dd, *J* 7.5, 0.6 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 24.1 (C(*C*H$_3$)$_3$), 37.9 (*C*(CH$_3$)$_3$), 44.0 (*C*H$_2$Ph), 80.8z (*C*(3)), 109.0 (Ar*C*(7)), 122.3 (Ar*C*(5)), 125.8 (Ar*C*(4)), 127.4 (CH$_2$Ar*C*(2,6)), 127.6 (CH$_2$Ar*C*(4)), 128.8 (CH$_2$Ar*C*(3,5)), 129.3 (Ar*C*(6)), 129.4 (CH$_2$Ar*C*(1)), 135.8 (Ar*C*(3a)), 143.5 (Ar*C*(7a)), 178.6 (*C*=O); ***m/z* (NSI)** 296 ([M+H]$^+$, 100%) $C_{19}H_{22}NO_2^+$ ([M+H]$^+$) requires 296.1645; found 296.1647 (+0.7 ppm).

Lab book Reference: SMS-197

1-Benzyl-3-(*tert*-butyl)-2-oxoindolin-3-yl isobutyrate, 140

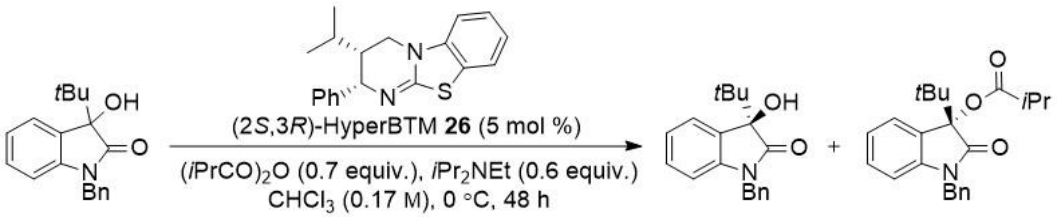


Following general procedure B, **139** (53 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) for 72 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.75), **140** as an orange oil (28 mg, 0.07 mmol, 48%); **ν_{max} (ATR)** 2972, 1722 (C=O), 1612 (C=C), 1465, 1348, 1175, 1152; **δ_H (400 MHz, $CDCl_3$)** 1.10 (9H, s, (CH_3)$_3$), 1.18 (6H, d, *J* 7.0 Hz, CH(CH_3)$_2$), 2.63 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 4.70 (1H, d, *J* 15.9 Hz, NCH_AH$_B$Ph), 5.08 (1H, d, *J* 15.9 Hz, NCH$_A$$H_B$Ph), 6.65 (1H, app d, *J* 7.6 Hz, C(7)*H*), 6.92-6.98 (1H, m, C(5)*H*), 7.13-7.19 (2H, m, C(4,6)*H*), 7.22-7.40 (5H, m, NCH$_2$Ar*CH*); **δ_C (100 MHz, $CDCl_3$)** 18.6 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.8 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 24.1 (C(*C*H$_3$)$_3$), 33.8 (*C*H(CH$_3$)$_2$), 37.6 (*C*(CH$_3$)$_3$), 44.2 (*C*H$_2$Ph),

83.5 (*C*(3)), 109.0 (Ar*C*(7)H), 121.8 (Ar*C*(5)H), 124.0 (Ar*C*(4)H), 127.0 (CH_2Ar*C*(1)), 127.3 (CH_2Ar*C*(2,6)H), 127.4 (CH_2Ar*C*(4)H), 128.7 (CH_2Ar*C*(3,5)H), 129.3 (Ar*C*(6)H), 136.1 (Ar*C*(3a)), 144.2 (Ar*C*(7a)), 174.7 (*C*(=O)CH(CH_3)$_2$), 174.9 (*C*(2)=O); ***m/z* (NSI)** 383 ([M+NH_4]$^+$, 100%) $C_{23}H_{31}O_3N_2^+$ ([M+NH_4]$^+$) requires 383.2329; found 383.2328 (–0.3 ppm).

Lab book Reference: SMS-205

Kinetic resolution of 139



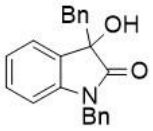
Following general procedure C, **139** (148 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (8.0 mg, 0.025 mmol, 5 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) for 48 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (87 mg, 0.30 mmol, 59%) and ester (2 mg, 0.01 mmol, 1%).

Data for alcohol: $[\alpha]_D^{20}$ +5 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.4, 23.0 min, 50:50 er.

Data for ester: $[\alpha]_D^{20}$ –34 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.8, 15.2 min, 91:9 er; *s* = 10.

Lab book Reference: SMS-219

1,3-Dibenzyl-3-hydroxyindolin-2-one, 141

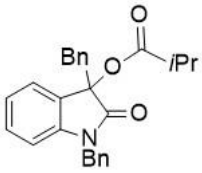


Following general procedure D, **89** (1.54 g, 6.6 mmol) and benzylmagnesium chloride (7.2 mL, 7.2 mmol, 1.0 M) in anhydrous THF (25 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.49), **141** as a cream solid (536 mg, 1.6 mmol, 25%), mp 160-162 °C; **ν_{max} (ATR)** 3318 (OH), 3030, 1707 (C=O), 1614, 1467, 1174; **δ_H (400 MHz, $CDCl_3$)** 3.04 (1H, s, O*H*), 3.30 (1H, d, *J* 12.7 Hz, C(3)CH_AH$_B$Ph), 3.42 (1H, d, *J* 12.7 Hz, C(3)CH$_A$*H$_B$*Ph), 4.45 (1H, d, *J* 16.0 Hz, NCH_AH$_B$Ph), 5.00 (1H, d, *J* 16.0 Hz, NCH$_A$*H$_B$*Ph), 6.44 (1H, app d, *J* 7.5 Hz, ArC(7)*H*), 6.68-6.75 (2H, m, ArC*H*), 6.91-6.98 (2H, m, ArC*H*), 7.05-7.22 (8H, m, ArC*H*), 7.37 (1H, app dd, *J* 7.3, 1.0 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 43.7 (C(3)*C*H_2Ph), 44.8 (N*C*H_2Ph), 77.5 (*C*(3)), 109.6 (Ar*C*(7)H), 122.9 (Ar*C*(5)H), 124.4 (Ar*C*(4)H), 126.7 (Ar*C*H), 126.9 (Ar*C*H), 127.3 (Ar*C*H), 128.1 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*), 129.1 (Ar*C*(6)H), 130.4 (Ar*C*H), 133.8

(Ar*C*), 134.9 (Ar*C*(3a)), 142.7 (Ar*C*(7a)), 177.3 (*C*=O); ***m/z* (NSI)** 330 ([M+H]$^+$, 100%) $C_{22}H_{20}NO_2^+$ ([M+H]$^+$) requires 330.1489; found 330.1492 (+1.0 ppm).

Lab book Reference: SMS-242

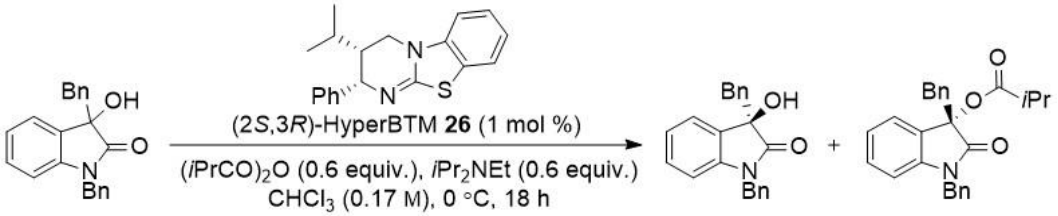
1,3-Dibenzyl-2-oxoindolin-3-yl isobutyrate, 142



Following general procedure B, **141** (53 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.91), **142** as an orange oil (74 mg, 0.12 mmol, 74%); **ν_{max} (ATR)** 2974, 1726 (C=O), 1614 (C=C), 1468, 1354, 1148; **δ_H (400 MHz, $CDCl_3$)** 1.16 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.18 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.66 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.21 (1H, d, *J* 12.9 Hz, C(3)C*H*$_A$H$_B$Ph), 3.48 (1H, d, *J* 12.9 Hz, C(3)CH$_A$*H*$_B$Ph), 4.63 (1H, d, *J* 16.1 Hz, NC*H*$_A$H$_B$Ph), 4.93 (1H, d, *J* 16.1 Hz, NCH$_A$*H*$_B$Ph), 6.40 (1H, app d, *J* 7.8 Hz, C(7)*H*), 6.84-7.01 (6H, m, Ar*CH*), 7.07-7.16 (7H, m, Ar*CH*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.9 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.6 (*C*H(CH$_3$)$_2$), 42.6 (C(3)*C*H$_2$Ph), 44.0 (NC*H*$_2$Ph), 80.2 (*C*(3)), 109.5 (Ar*C*(7)H), 122.3 (Ar*C*(5)H), 122.9 (Ar*C*(4)H), 126.7 (Ar*C*H), 126.8 (C(3)CH$_2$Ar*C*(1)), 127.2 (C(3)CH$_2$Ar*C*(4)H), 127.2 (NCH$_2$Ar*C*(4)H), 127.9 (Ar*C*H), 128.6 (Ar*C*H), 129.6 (Ar*C*(6)H), 130.9 (Ar*C*H), 132.8 (NCH$_2$Ar*C*(1)), 135.4 (Ar*C*(3a)), 143.2 (Ar*C*(7a)), 174.4 (*C*(2)=O), 174.8 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 422 ([M+Na]$^+$, 100%) $C_{26}H_{25}NO_3Na^+$ ([M+Na]$^+$) requires 422.1727; found 422.1724 (–0.6 ppm).

Lab book Reference: SMS-248

Kinetic resolution of 141



Following general procedure C, **141** (165 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.30 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) were reacted in $CHCl_3$ (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (81 mg, 0.25 mmol, 49%) and ester (70 mg, 0.18 mmol, 35%).

Data for alcohol: $[\alpha]_D^{20}$ –50 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 29.7, 32.8 min, 71:29 er.

Data for ester: $[\alpha]_D^{20}$ +32 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.0, 34.8 min, 83:17 er; *s* = 7.

Lab book Reference: SMS-267

1-Benzyl-3-hydroxy-3-(4-nitrobenzyl)indolin-2-one, 143

Following general procedure E, **89** (1.18 g, 5 mmol), 4-nitrophenylacetic acid (996 mg, 5.5 mmol) and triethylamine (140 µL, 1 mmol, 20 mol %) in DMF (25 mL) for 6 h gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.31), **143** as a beige solid (1.38 g, 3.7 mmol, 74%), mp 159-161 °C; **ν_{max} (ATR)** 3263 (OH), 1695 (C=O), 1614, 1514 (NO), 1468, 1344 (NO), 1084; **δ_H (400 MHz, $CDCl_3$)** 3.05 (1H, s, O*H*), 3.36 (1H, d, *J* 12.6 Hz, C$H_A$$H_BArNO_2$), 3.47 (1H, d, *J* 12.6 Hz, CH$_A$$H_BArNO_2$), 4.49 (1H, d, *J* 15.6 Hz, NC$H_A$$H_B$Ph), 4.92 (1H, d, *J* 15.6 Hz, NCH$_A$$H_B$Ph), 6.58 (1H, app dt, *J* 7.8, 0.8 Hz, C(7)*H*), 6.83-6.89 (2H, m, NCH_2Ar(2,6)*H*), 7.043-7.08 (2H, m, Ar(2,6)*H*NO_2), 7.08-7.24 (5H, m, C(5,6)*H,* NCH_2Ar(3,4,5)*H*), 7.35 (1H, ddd, *J* 7.3, 1.3, 0.6 Hz, C(4)*H*), 7.87i-7.93 (2H, m, Ar(3,5)*H*NO_2); **δ_C (100 MHz, $CDCl_3$)** 43.9 (N*C*H_2Ph), 44.5 (*C*H_2ArNO_2), 77.2 (*C*(3)), 109.7 (Ar*C*(7)H), 123.1 (Ar*C*(3,5)HNO_2), 123.4 (Ar*C*(5)H), 124.5 (ArC(4)H), 127.2 (NCH_2Ar*C*(2,6)H), 127.8 (NCH_2Ar*C*(4)H, 128.5 (NCH_2Ar*C*(1)), 128.6 (NCH_2Ar*C*(3,5)H), 130.3 (Ar*C*(6)H), 131.2 (Ar*C*(2,6)HNO_2), 134.8 (Ar*C*(1)NO_2), 141.6 (Ar*C*(3a)), 142.5 (Ar*C*(7a)), 147.0 (Ar*C*(4)NO_2), 177.1 (*C*=O); ***m/z* (NSI**) 375 ($[M+H]^+$, 100%) $C_{22}H_{19}N_2O_4^+$ ($[M+H]^+$) requires 375.1339; found 375.1341 (+0.3 ppm).

Lab book Reference: SMS-158

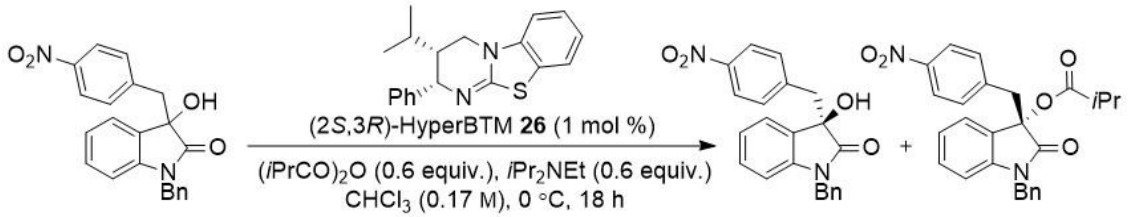
1-Benzyl-3-(4-nitrobenzyl)-2-oxoindolin-3-yl isobutyrate, 144

Following general procedure B, **143** (60 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.45), **144** as a colourless solid (46 mg, 0.10 mmol, 64%), mp 152-154 °C; **ν_{max} (ATR)** 2967, 1722 (C=O), 1604 (C=O), 1516, 1467, 1364, 1151**; δ_H (400 MHz, $CDCl_3$)** 1.17 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.18 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.66 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 3.31 (1H, d, *J* 12.7 Hz, C$H_A$$H_BArNO_2$), 3.51 (1H, d, *J* 12.7 Hz, CH$_A$$H_BArNO_2$), 4.64 (1H, d, *J* 15.9 Hz, C$H_A$$H_B$Ph), 4.87 (1H, d, *J* 15.9 Hz, CH$_A$$H_B$Ph), 6.54 (1H, app dt, *J* 7.9, 0.8 Hz, ArC(7)*H*), 6.96-7.09 (6H, m, Ar*H*), 7.15-7.22 (4H, m, Ar*H*), 7.90-7.95 (2H, m, Ar(2,6)*H*NO_2); **δ_C (100 MHz, $CDCl_3$)** 18.6

($CH(CH_3)_A(CH_3)_B$), 18.9 ($CH(CH_3)_A(CH_3)_B$), 33.6 ($CH(CH_3)_2$), 42.3 (CH_2ArNO_2), 44.1 (NCH_2Ph), 79.5 (*C*(3)), 109.6 (Ar*C*(7)H), 122.7 (ArC(5)H), 122.8 (ArC(4)H), 123.0 (Ar*C*(3,5)HNO_2), 126.2 ($NCH_2ArC(1)$), 127.1 ($NCH_2ArC(3,5)H$), 127.6 (Ar*C*(6)H), 128.6 ($NCH_2ArC(2,6)H$), 130.2 ($NCH_2ArC(4)H$), 131.6 (Ar*C*(2,6)HNO_2), 135.2 (Ar*C*(1)NO_2), 140.4 (Ar*C*(3a)), 143.1 (Ar*C*(7a)), 147.2 (Ar*C*(4)NO_2), 173.8 (*C*(2)=O), 174.6 (*C*(=O)$CH(CH_3)_2$); ***m/z*** **(NSI)** 345 ($[M+H]^+$, 100%) $C_{26}H_{25}N_2O_5^+$ ($[M+H]^+$) requires 445.1758; found 445.1750 (–1.8 ppm).

Lab book Reference: SMS-172

Kinetic resolution of 143



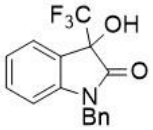
Following general procedure C, **143** (187 mg, 0.50 mmol), isobutyric anhydride (49 µL, 0.30 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.30 mmol) in $CHCl_3$ (3 mL), gave after column chromatography (eluent hexane/EtOAc, 7:3), alcohol (84 mg, 0.23 mmol, 45%) and ester (99 mg, 0.23 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ –31 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 20.5, 25.7 min, 91:9 er.

Data for ester: $[\alpha]_D^{20}$ +9 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 21.0, 28.5 min, 90:10 er; *s* = 21.

Lab book Reference: SMS-397

1-Benzyl-3-hydroxy-3-(trifluoromethyl)indolin-2-one, 145

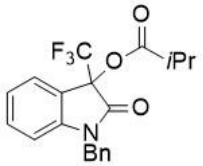


Following the method by de Frugulhetti *et al*,[98] **89** (474.2 mg, 2 mmol) was dissolved in anhydrous THF (10 mL). (Trifluoromethyl)trimethylsilane (591 µL, 4 mmol) was added, followed by cesium fluoride (31 mg, 0.2 mmol, 10 mol %) and the reaction stirred at RT for 24 h under N_2. On completion, the solution was extracted with water (20 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was then purified *via* column chromatography (eluent hexane/Et_2O, 9:1) to afford the TMS either of alcohol **145** as a yellow solid. The product was the treated with HCl (1M) in THF/H_2O (12 mL, 5:1) for 1 h.[154] The reaction mixture was then quenched with $NaHCO_3$ and the organic layer extracted

with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent hexane/Et_2O, 9:1; R_F 0.24), **145** as a pale yellow solid (363 mg, 1.1 mmol, 55%), mp 158-160 °C; **ν_{max} (ATR)** 3362 (OH), 1707 (C=O), 1614 (C=O), 1472, 1279, 1171; **δ_H (400 MHz, $CDCl_3$)** 4.01 (1H, s, O*H*), 4.76 (1H, d, *J* 15.6 Hz, C$H_A$$H_B$Ph), 5.10 (1H, d, *J* 15.6 Hz, C$H_A$$H_B$Ph), 6.75 (1H, d, *J* 7.9 Hz, ArC(7)*H*), 7.13 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.25-7.37 (6H, m, ArC*H*), 7.56 (1H, d, *J* 7.5 Hz, ArC(4)*H*); **δ_C (125 MHz, $CDCl_3$)** 44.2 (NCH_2Ph), 75.0 (q, *J* 31 Hz, *C*(3)), 110.2 (Ar*C*(7)H), 122.5 (CH_2Ar*C*(1)), 123.0 (q, *J* 285 Hz, *C*F_3), 123.8 (Ar*C*(5)H), 126.2 (Ar*C*(4)H), 127.0 (CH_2Ar*C*(2,6)H), 128.1 (CH_2Ar*C*(4)H), 129.0 (CH_2Ar*C*(3,5)H), 131.7 (Ar*C*(6)H), 134.4 (Ar*C*(3a)), 143.7 (Ar*C*(7a)), 171.5 (*C*=O); **δ_F (376 MHz, $CDCl_3$)** –79.6 (C*F*$_3$); ***m/z* (NSI)** 325 ([M+NH_4]$^+$, 100%) $C_{16}H_{12}F_3NO_2NH_4^+$ ([M+NH_4]$^+$) requires 325.1158; found 325.1162 (+0.6 ppm).

Lab book Reference: SMS-152

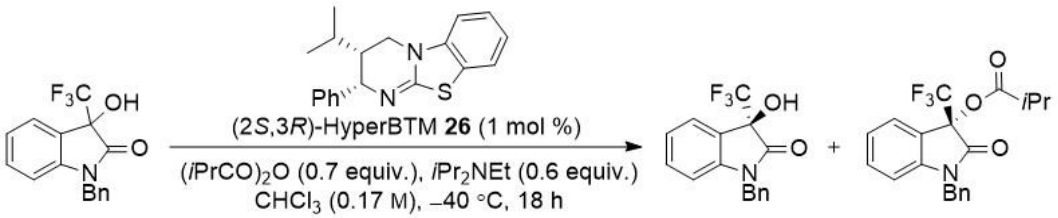
1-Benzyl-2-oxo-3-(trifluoromethyl)indolin-3-yl isobutyrate, 146



Following general procedure B, **145** (50 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent hexane/Et_2O, 9:1; R_F 0.46), **146** as a yellow oil (53 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2924, 1738 (C=O), 1614 (C=O), 1470, 1362, 1180, 980; **δ_H (400 MHz, $CDCl_3$)** 1.21 (6H, app t, *J* 7.0 Hz, CH(CH_3)$_2$), 2.73 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 4.87 (1H, d, *J* 15.9 Hz, NC$H_A$$H_B$Ph), 5.10 (1H, d, *J* 15.9 Hz, NC$H_A$$H_B$Ph), 6.69 (1H, app d, *J* 7.9 Hz, ArC(7)*H*), 7.06 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.26-7.40 (7H, m, ArC(4,6)*H*, CH_2ArC*H*); **δ_C (100 MHz, *d_6*-DMSO)** 18.7 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.8 (CH(CH_3)$_A$(*C*H_3)$_B$), 33.2 (*C*H(CH_3)$_2$), 43.9 (N*C*H_2Ph), 77.3 (q, *J* 31 Hz, *C*(3)), 110.9 (Ar*C*(7)H), 119.8 (CH_2Ar*C*(4)H), 122.2 (q, *J* 283 Hz, *C*F_3), 124.1 (Ar*C*(5)H), 124.9 (Ar*C*(4)H), 127.5 (CH_2Ar*C*(2,6)H), 128.1 (CH_2Ar*C*(1)), 129.1 (CH_2Ar*C*(3,5)H), 132.7 (Ar*C*(6)H), 135.8 (Ar*C*(3a)), 144.3 (Ar*C*(7a)), 167.3 (*C*(2)=O), 173.8 (*C*(=O)CH(CH_3)$_2$); **δ_F (376 MHz, $CDCl_3$)** –79.5 (C*F*$_3$); ***m/z* (NSI)** 395 ([M+NH_4]$^+$, 100%) $C_{20}H_{18}F_3NO_3NH_4^+$ ([M+NH_4]$^+$) requires 395.1577; found 395.1569 (–2.0 ppm).

Lab book Reference: SMS-154

Kinetic resolution of 145



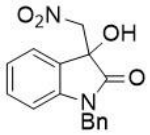
Following general procedure C, **145** (104 mg, 0.34 mmol), isobutyric anhydride (33 µL, 0.21 mmol), (2*S*,3*R*)-HyperBTM **26** (1.0 mg, 0.0034 mmol, 1 mol %) and *i*Pr$_2$NEt (36 µL, 0.21 mmol) in $CHCl_3$ (2 mL) at –40 °C gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (28 mg, 0.09 mmol, 27%) and ester (57 mg, 0.15 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ +60 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 16.0, 20.9 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ –8 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 12.8, 15.8 min, 85:15 er; *s* = 32.

Lab book Reference: SMS-157

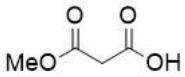
1-Benzyl-3-hydroxy-3-(nitromethyl)indolin-2-one, 147



Following the procedure outlined by Ding *et al*,[155] **89** (883 g, 3.7 mmol) was dissolved in nitromethane (50 mL). Et_2NH (5 drops) was added and the reaction stirred at RT until the solution turned pale yellow (~5 mins). Upon completion, NH_4Cl was added and the organic layer extracted, dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give **147** as a pale orange solid (1.04 g, 3.5 mmol, 94%), mp 120-122 °C, (R_F 0.53, CH_2Cl_2:EtOAc 9:1); **ν_{max} (ATR)** 3262 (OH), 2922, 1699 (C=O), 1541 (N–O), 1373 (N–O), 1238; **δ_H (400 MHz, $CDCl_3$)** 4.00 (1H, br s, O*H*), 4.84 (1H, d, *J* 15.7 Hz, CH_AH$_B$Ph), 4.90 (1H, d, *J* 13.0 Hz, CH_AH$_B$NO$_2$), 4.92 (1H, d, *J* 13.0 Hz, CH$_A$$H_BNO_2$), 5.02 (1H, d, *J* 15.7 Hz, CH$_A$$H_B$Ph), 6.76 (1H, app d, *J* 7.9 Hz, ArC(7)*H*), 7.10 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.27-7.39 (6H, m, ArC(6)*H*, CH$_2$ArC*H*), 7.42 (1H, app dd, *J* 7.6, 0.8 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 44.0 (*C*H$_2$Ph), 73.3 (*C*(3)), 78.2 (*C*H$_2$NO$_2$), 110.4 (Ar*C*(7)), 123.8 (Ar*C*(5)), 124.3 (Ar*C*(4)), 125.5 (CH$_2$Ar*C*(1)), 127.3 (CH$_2$Ar*C*(2,6)), 128.0 (CH$_2$Ar*C*(4)), 128.0 (CH$_2$Ar*C*(3,5)), 131.2 (Ar*C*(6)), 134.7 (Ar*C*(3a)), 143.1 (Ar*C*(7a)), 174.6 (*C*=O); ***m/z*** **(NSI)** 316 ($[M+NH_4]^+$, 100%) $C_{16}H_{18}N_3O_4^+$ ($[M+NH_4]^+$) requires 316.1292; found 316.1292 (+0.1 ppm).

Lab book Reference: SMS-235

3-Methoxy-3-oxopropanoic acid, 149

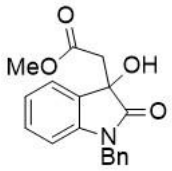


Following the method by Cho,[100] dimethyl malonate **148** (5 g, 38 mmol) was dissolved in MeCN (1 mL) and cooled to 0 °C. Water (10 mL) was added and the mixture stirred for 30 mins. Potassium hydroxide (7.6 mL, 5 M, 38 mmol) was added dropwise and the reaction mixture stirred for a further 1 h. On completion, $NaHCO_3$ (10 mL) was added to the reaction mixture, followed by EtOAc (10 mL). The aqueous layer was extracted, then acidified with conc. HCl (5 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **149** as a colourless oil (1.58 g, 13.3 mmol, 35 %). No further purification was required. **δ_H (400 MHz, $CDCl_3$)** 3.45 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 9.01 (1H, br, CO_2H).

Data were in accordance with those previously reported.[100]

Lab book Reference: SMS-160

Methyl 2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acetate, 158

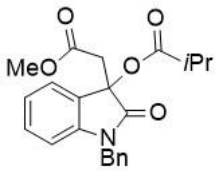


Following general procedure E, **89** (1.19 g, 5 mmol), **149** (0.65 g, 5.5 mmol) and triethylamine (140 µL, 1 mmol, 20 mol %) in DMF (25 mL) gave, after column chromatography (hexane:EtOAc 7:3, R_F 0.29), **158** as a yellow solid (906 mg, 2.9 mmol, 58%), mp 137-139 °C; **δ_H (400 MHz, $CDCl_3$)** 2.94-3.03 (2H, m, CH_2CO$_2$CH$_3$), 3.69 (3H, s, CO$_2$CH_3), 4.34 (1H, br s, O*H*), 4.85 (1H, d, *J* 15.6 Hz, NCH_AH$_B$Ph), 4.94 (1H, d, *J* 15.6 Hz, NCH$_A$$H_B$Ph), 6.72 (1H, app dt, *J* 7.8, 0.8 Hz, C(7)*H*), 7.05 (1H, app td, *J* 7.6, 1.0 Hz, C(5)*H*), 7.22 (1H, app td, *J* 7.8, 1.3 Hz, C(6)*H*), 7.25-7.36 (5H, m, NCH$_2$Ar*H*), 7.40 (1H, ddd, *J* 7.4, 1.3, 0.6 Hz, C(4)*H*).

Data were in accordance with those previously reported. [156]

Lab book Reference: SMS-166

1-Benzyl-3-(2-methoxy-2-oxoethyl)-2-oxoindolin-3-yl isobutyrate, 159

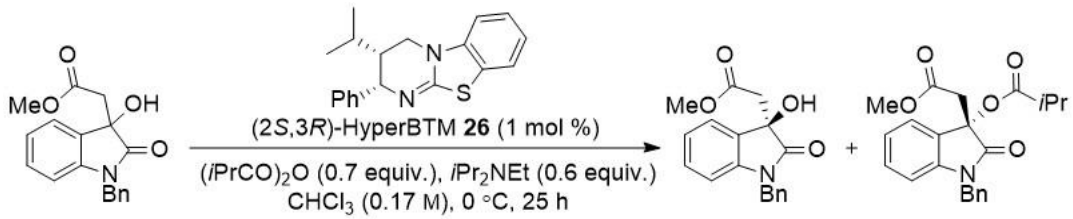


Following general procedure B, **158** (50 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.43) to afford **159** as a colourless oil (30 mg, 0.08 mmol, 50%); **ν_{max} (ATR)** 2974, 1726 (C=O), 1614 (C=O), 1467, 1352, 1146; **δ_H (400 MHz, $CDCl_3$)**

1.14 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.15 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.61 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.02 (1H, d, *J* 15.5 Hz, C*H*$_A$H$_B$CO$_2$Me), 3.23 (1H, d, *J* 15.5 Hz, CH$_A$*H*$_B$CO$_2$Me), 3.53 (3H, s, CH$_2$CO$_2$C*H*$_3$), 4.93 (1H, d, *J* 15.9 Hz, C*H*$_A$H$_B$Ph), 5.00 (1H, d, *J* 15.9 Hz, CH$_A$*H*$_B$Ph), 6.66 (1H, dd, *J* 7.9, 0.8 Hz, C(7)*H*), 7.00 (1H, app td, *J* 7.6, 0.9 Hz, C(5)*H*), 7.19 (1H, app td, *J* 7.8, 1.3 Hz, C(4)*H*), 7.24-7.29 (1H, m, ArC*H*), 7.30-7.37 (3H, m, ArC*H*), 7.39-7.44 (2H, m, ArC*H*); **δ_C (100 MHz, CDCl$_3$)** 18.5 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.8 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.6 (*C*H(CH$_3$)$_2$), 41.0 (*C*H$_2$CO$_2$Me) 44.5 (*C*H$_2$Ph), 51.8 (CO$_2$*C*H$_3$), 76.7 (*C*(3)), 109.6 (Ar*C*(7)H), 122.7 (Ar*C*(5)H), 123.5 (Ar*C*(6)H), 126.2 (CH$_2$Ar*C*(1)), 127.3 (CH$_2$Ar*C*(2,6)H), 127.6 ((CH$_2$Ar*C*(4)H), 128.8 (CH$_2$Ar*C*(3,5)H), 130.2 (Ar*C*(4)H), 135.6 (Ar*C*(3a)), 143.7 (Ar*C*(7a)), 168.2 (*C*O$_2$Me), 173.8 (*C*(2)=O), 174.5 *C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 382 ([M+H]$^+$, 100%) $C_{22}H_{24}NO_5^+$ ([M+H]$^+$) requires 382.1649; found 382.1647 (–0.5 ppm).

Lab book Reference: SMS-173

Kinetic resolution of 158



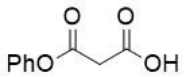
Following general procedure C, **158** (156 mg, 0.50 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.30 mmol) in CHCl$_3$ (3 mL) for 25 h gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (48 mg, 0.16 mmol, 31%) and ester (83 mg, 0.21 mmol, 44%).

Data for alcohol: $[\alpha]_D^{20}$ +16 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralpak AD-H (7% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 35.4, 39.9 min, 98:2 er.

Data for ester: $[\alpha]_D^{20}$ –30 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 12.8, 15.8 min, 83:17 er; *s* = 19.

Lab book Reference: SMS-194

3-Oxo-3-phenoxypropanoic acid, 152



Following the method by Lee *et al*,[101] a mixture of phenol **150** (1.88 g, 20 mmol) and Meldrum's acid **151** (2.88 g, 20 mmol) were stirred at 90 °C for 4 h. On completion, the mixture was cooled and partitioned with EtOAc and sat. aq. NaHCO$_3$. The aqueous layer was extracted and acidified with conc. HCl and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined extracts were dried (MgSO$_4$), filtered and

concentrated *in vacuo* to afford **152** as a cream solid (2.58 g, 14.4 mmol, 72%). No further purification was required.

δ_H (400 MHz, $CDCl_3$) 3.72 (2H, s, CH_2), 7.14-7.20 (2H, m, ArC(2,6)*H*), 7.27-7.32 (1H, m, ArC(4)*H*), 7.40-7.45 (2H, m, ArC(3,5)*H*), 11.36 (1H, br s, CO_2H).

Data were in accordance with those previously reported.[101]

Lab book Reference: SMS-162

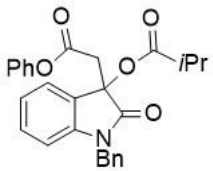
Phenyl 2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acetate, 160

Following general procedure E, **89** (1.19 g, 5 mmol), **152** (0.99 g, 5.5 mmol) and triethylamine (140 µL, 1 mmol, 20 mol %) in DMF (25 mL) gave, after column chromatography (hexane/EtOAc, 7:3; R_F 0.32), **160** as an orange solid (943 mg, 2.55 mmol, 51%), mp 121-123 °C; **ν_{max} (ATR)** 3254 (OH), 2918, 1757 (C=O), 1694 (C=O), 1607, 1466, 1348, 1184; **δ_H (400 MHz, $CDCl_3$)** 3.23 (1H, d, *J* 15.5 Hz, CH_AH$_B$CO$_2$Ph), 3.33 (1H, d, *J* 15.5 Hz, CH$_A$$H_BCO_2$Ph), 4.13 (1H, s, O*H*), 4.88 (1H, d, *J* 15.6 Hz, NCH_AH$_B$Ph), 4.94 (1H, d, *J* 15.6 Hz, NCH$_A$$H_B$Ph), 6.74 (1H, app dt, *J* 7.9, 0.7 Hz, C(7)*H*), 6.88-6.97 (2H, m, NCH$_2$Ar(2,6)*H*), 7.10 (1H, app td, *J* 7.6, 1.0 Hz, C(5)*H*), 7.18-7.37 (9H, m, C(6)*H,* NCH$_2$Ar(3,4,5)*H*, CO$_2$Ar*H*), 7.50 (1H, app dd, *J* 7.4, 0.8 Hz, C(4)*H*);

δ_C (100 MHz, $CDCl_3$) 41.7 (*C*H$_2$CO$_2$Ph), 44.0 (N*C*H$_2$Ph), 73.4 (*C*(3)), 109.7 (Ar*C*(7)H), 121.5 (NCH$_2$Ar*C*(2,6)H), 123.4 (*C*(5)H), 124.1 (*C*(4)H), 126.2 (NCH$_2$Ar*C*(4)H), 127.3 (CO$_2$Ar*C*(2,6)H), 127.7 (CO$_2$Ar*C*(4)H), 128.8 (CO$_2$Ar*C*(3,5)H), 128.9 (NCH$_2$Ar*C*(1)), 129.5 (NCH$_2$Ar*C*(3,5)H), 130.3 (Ar*C*(6)H), 135.2 (Ar*C*(3a)), 142.8 (Ar*C*(7a)), 150.1 (CO$_2$Ar*C*(1)), 168.7 (*C*O$_2$Ph), 176.3 (*C*=O); ***m/z* (NSI)** 374 ([M+H]$^+$, 100%) $C_{23}H_{20}NO_4^+$ ([M+H]$^+$) requires 374.1387; found 374.1386 (–0.2 ppm).

Lab book Reference: SMS-165

1-Benzyl-2-oxo-3-(2-oxo-2-phenoxyethyl)indolin-3-yl isobutyrate, 161

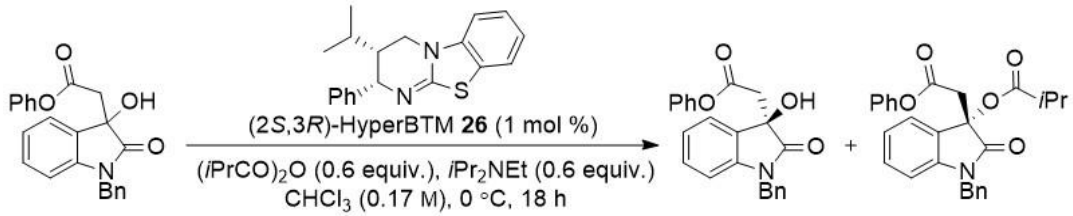


Following general procedure B, **160** (60 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.45), **161** as an orange wax (45 mg, 0.10 mmol, 64%); **ν_{max} (ATR)** 2974, 1728 (C=O), 1614 (C=O), 1467, 1354, 1140; **δ_H (400 MHz, $CDCl_3$)** 1.18 (6H, d, *J* 7.0 Hz, CH(CH_3)$_2$), 2.65 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.28 (1H, d, *J* 15.2 Hz, CH_AH$_B$CO$_2$Ph), 3.45

(1H, d, *J* 15.2 Hz, $CH_AH_BCO_2Ph$), 4.96 (2H, s, CH_2Ph), 6.68 (1H, app dt, *J* 7.9, 0.7 Hz, C(7)*H*), 6.78-6.82 (2H, m, $CO_2ArC(2,6)H$), 7.03 (1H, app dt, *J* 7.6, 1.0 Hz, C(5)*H*), 7.17-7.39 (9H, m, Ar*CH*), 7.43-7.47 (1H, m, C(6)*H*); **δ_C (125 MHz, d_6-DMSO)** 18.8 ($CH(CH_3)_A(CH_3)_B$), 19.0 ($CH(CH_3)_A(CH_3)_B$), 33.3 ($CH(CH_3)_2$), 41.6 (CH_2CO_2Ph), 43.8 (CH_2Ph), 77.0 (*C*(3)), 109.9 (Ar*C*(7)H), 121.9 (CO_2ArC(2,6)H), 123.1 (Ar*C*(5)H), 124.0 (Ar*C*(6)H), 126.3 (CH_2ArC(1)), 126.5 (CO_2ArC(4)H), 127.7 (CH_2ArC(2,6)H), 127.8 (CH_2ArC(4)H), 128.9 (CH_2ArC(3,5)H), 130.0 (CO_2ArC(3,5)H), 130.6 (Ar*C*(4)H), 136.3 (Ar*C*(3a)), 143.7 (Ar*C*(7a)), 150.4 (CO_2ArC(1)), 166.7 (CO_2Ph), 173.3 (*C*(2)=O), 174.4 *C*(=O)$CH(CH_3)_2$); ***m/z* (NSI)** 444 ($[M+H]^+$, 100%) $C_{27}H_{26}NO_5^+$ ($[M+H]^+$) requires 444.1805; found 444.1801 (–1.0 ppm).

Lab book Reference: SMS-174

Kinetic resolution of 160



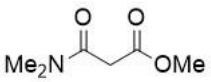
Following general procedure E, **160** (187 mg, 0.50 mmol), isobutyric anhydride (49 µL, 0.30 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.30 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3), alcohol (46 mg, 0.12 mmol, 24%) and ester (86 mg, 0.19 mmol, 38%).

Data for alcohol: $[\alpha]_D^{20}$ –2 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 24.9, 38.3 min, 93:7 er.

Data for ester: $[\alpha]_D^{20}$ +19 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 27.1, 43.1 min, 87:13 er; *s* = 19.

Lab book Reference: SMS-192

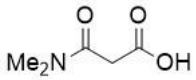
Methyl 3-(diethylamino)-3-oxopropionate, 154



Following the method by Kolarska *et al*,[157] diethylamine (1.6 mL, 15.4 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to a mixture of methyl malonyl chloride **153** (0.79 mL, 7.3 mmol) in anhydrous CH_2Cl_2 (10 mL) at 10 °C. Upon completion, the reaction was stirred at RT for 1 hour, then quenched with 2% aq. HCl solution (15 mL) and stirred for a further 5 minutes. The organic layer was then separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **154** as a yellow oil (1.26 g, 99%). Further purification was not required.

Lab book Reference: SMS-250

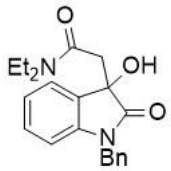
3-(Diethylamino)-3-oxopropionic acid, 155



Following the method by Pratt *et al*,[103] to **154** (1.26 g, 7.3 mmol) in methanol (50 mL), NaOH (1M, 50 mL) was added and the reaction stirred overnight at RT. Upon completion, methanol was removed *in vacuo* and the aqueous solution acidified with 20% aq. HCl solution. The mixture was then extracted with EtOAc and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **155** as a pale yellow oil (491 mg, 3.1 mmol, 43%).

Lab book Reference: SMS-251

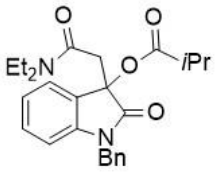
2-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)-*N*,*N*-diethylacetamide, 162



Following general procedure E, **89** (664 mg, 2.8 mmol), **155** (491 mg, 3.1 mmol) and triethylamine (78 µL, 0.6 mmol, 20 mol %) in DMF (25 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.26), **162** as a brown wax (515 mg, 1.5 mmol, 52%); **ν_{max} (ATR)** 3317 (OH), 1694, 1680 (C=O), 1616 (C=C), 1495, 1348; **δ_H (400 MHz, $CDCl_3$)** 1.04 (3H, t, *J* 7.2 Hz, (CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 1.19 (3H, t, *J* 7.2 Hz, (CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 2.63 (1H, d, *J* 15.6 Hz, CH_AH_BCONEt$_2$), 2.97 (1H, d, *J* 15.6 Hz, CH_AH_BCONEt$_2$), 3.19 (2H, dq, *J* 7.2, 1.0 Hz, (CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 3.38-3.54 (2H, m, (CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 4.88 (1H, d, *J* 15.6 Hz, CH_AH_BPh), 4.92 (1H, d, *J* 15.6 Hz, CH_AH_BPh), 6.72 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 6.93 (1H, s, O*H*), 7.02 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.19 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.24-7.36 (6H, m, Ar*H*), 7.46-7.52 (1H, m, C(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 13.0 ((CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 14.3 ((CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 37.3 (CH_2CONEt$_2$), 40.1 ((CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 42.5 ((CH_3CH_2)$_A$(CH_3CH_2)$_B$N), 43.8 (NCH_2Ph), 74.6 (*C*(3)), 109.4 (Ar*C*(7)H), 123.1 (Ar*C*(5)H), 124.4 (Ar*C*(4)H), 127.3 (NCH$_2$Ar*C*(2,6)H), 127.2 (NCH$_2$ArC(4)H), 128.8 (NCH$_2$Ar*C*(3,5)H), 129.6 (Ar*C*(6)H), 130.9 (NCH$_2$ArC(1), 135.6 (ArC(3a), 142.1 (Ar*C*(7a), 170.5 (*C*=ONEt$_2$), 176.2 (*C*(2)=O); ***m/z* (NSI)** 353 ([M+H]$^+$, 100%) $C_{21}H_{25}O_3N_2^+$ ([M+H]$^+$) requires 353.1860; found 353.1861 (+0.4 ppm).

Lab book Reference: SMS-255

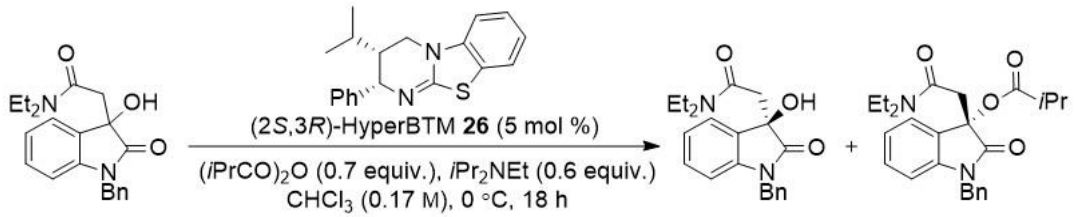
1-Benzyl-3-(2-(diethylamino)-2-oxoethyl)-2-oxoindolin-3-yl isobutyrate, 163



Following general procedure B, **162** (32 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.72), **163** as an orange oil (56 mg, 0.13 mmol, 83%); **ν_{max} (ATR)** 2972, 1726 (C=O), 1643 (C=O), 1614 (C=C), 1466, 1362, 1144; **δ_H (400 MHz, $CDCl_3$)** 1.01 (3H, t, *J* 14.9 Hz, N(CH_2CH_3)$_A$(CH_2CH_3)$_B$, 1.13-1.20 (9H, m, CH_3), 2.58 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 2.93 (1H, d, *J* 15.0 Hz, $CH_AH_BCONEt_2$), 3.16-3.41 (5H, m), 4.95 (1H, d, *J* 16.0 Hz, NCH_AH_BPh), 5.02 (1H, d, *J* 16.0 Hz, NCH_AH_BPh), 6.61 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 6.97 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.15 (1H, app td, *J* 7.8, 1.2 Hz, ArC(6)*H*), 7.22-7.27 (1H, m, Ar*H*), 7.29-7.32 (2H, m, Ar*H*), 7.36-7.40 (3H, m, Ar*H*); **δ_C (100 MHz, $CDCl_3$)** 12.9 ((CH_3CH_2)$_A$N(CH_3CH_2)$_B$), 14.4 ((CH_3CH_2)$_A$N(CH_3CH_2)$_B$), 18.5 (CH(CH_3)$_A$(CH_3)$_B$), 18.9 (CH(CH_3)$_A$(CH_3)$_B$), 33.7 (*C*H(CH_3)$_2$), 40.2 ((CH_3CH_2)$_A$N(CH_3CH_2)$_B$), 42.3 ((CH_3CH_2)$_A$N(CH_3CH_2)$_B$), 44.4 (N*C*H_2Ph), 78.1 (*C*(3)), 109.5 (Ar*C*(7)H), 122.4 (Ar*C*(5)H), 123.9 (Ar*C*(4)H), 126.8 (NCH_2ArC(1)), 127.2 (NCH_2ArC(2,6)H), 127.4 (NCH_2ArC(4)H), 128.7 (NCH_2ArC(3,5)H), 129.8 (Ar*C*(6)H), 135.8 (Ar*C*(3a)), 143.9 (Ar*C*(7a)), 166.1 (*C*(=O)CH(CH_3)$_2$), 174.5 (*C*(2)=O), 180.9 (*C*=ONEt_2); ***m/z* (NSI)** 423 ([M+H]$^+$, 100%) $C_{25}H_{31}NO_4^+$ ([M+H]$^+$) requires 423.2278; found 423.2274 (–1.0 ppm).

Lab book Reference: SMS-258

Kinetic resolution of 162



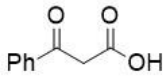
Following general procedure C, **162** (176 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (8.0 mg, 0.025 mmol, 5 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1) alcohol (85 mg, 0.24 mmol, 48%) and ester (95 mg, 0.23 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ +91 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 25.0, 30.7 min, 85:15 er.

Data for ester: $[\alpha]_D^{20}$ –41 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 32.3, 38.1 min, 93:7 er; *s* = 26.

Lab book Reference: SMS-336

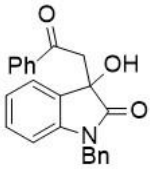
3-Oxo-3-phenylpropionic acid, 157



Following the procedure by Hara *et al*,[104] NaOH (20 mL, 1M) and ethyl benzoylacetate **156** (3.45 mL, 20 mmol) were stirred overnight at RT. The reaction mixture was washed with Et_2O (3 x 50 mL), the aqueous layer extracted and then acidified with HCl (3M) to pH 1. The white precipitate formed was filtered and dried under pressure to give **156** (1.67 g, 10.2 mmol, 51%).

Lab book Reference: SMS-253

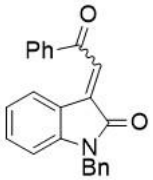
1-Benzyl-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one, 164



Following general procedure E, **89** (1.66 g, 7 mmol), **157** (1.26 g, 7.7 mmol) and triethylamine (195 µL, 1.4 mmol, 20 mol %) in DMF (35 mL) gave, after column chromatography (CH_2Cl_2:EtOAc 9:1, R_F 0.13), **164** as a cream solid (738 mg, 2.1 mmol, 30%), mp 180-182 °C; **ν_{max} (ATR)** 3337 (OH), 1695, 1647 (C=O), 1618 (C=C), 1466, 1180; **δ_H (400 MHz, $CDCl_3$)** 3.56 (1H, d, *J* 17.2 Hz, CH_AH$_B$COPh), 3.88 (1H, d, *J* 17.2 Hz, CH$_A$$H_B$COPh), 4.42 (1H, s, O*H*), 4.90 (1H, d, *J* 15.7 Hz, NCH_AH$_B$Ph), 4.98 (1H, d, *J* 15.7 Hz, NCH$_A$$H_B$Ph), 6.74 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.00 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.20 (1H, app td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.27-7.49 (8H, m, Ar*H*), 7.56-7.61 (1H, m, CH_2(C=O)ArC(4)*H*), 7.92 (2H, dd, *J* 8.4, 1.3 Hz, CH_2(C=O)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 44.0 (N*C*H_2Ph), 44.4 (CH_2CONEt_2), 74.6 (*C*(3)), 109.7 (Ar*C*(7)H), 123.1 (Ar*C*(5)H), 124.1 (Ar*C*(4)H), 127.3 (NCH_2Ar*C*(2,6)H), 127.7 (NCH_2ArC(4)H), 128.2 (CH_2(C=O)Ar*C*(2,6)H), 128.7 (CH_2(C=O)Ar*C*(3,5)H), 128.8 (NCH_2Ar*C*(3,5)H), 129.9 (Ar*C*(6)H), 130.0 (ArC(3a), 133.9 (CH_2(C=O)Ar*C*(4)H), 135.5 (NCH_2ArC(1), 136.4 (CH_2(C=O)Ar*C*(1)), 142.9 (Ar*C*(7a), 176.3 (*C*(2)=O), 198.4 (*C*=OPh); ***m/z* (NSI)** 358 ([M+H]$^+$, 100%) $C_{23}H_{20}O_3N^+$ ([M+H]$^+$) requires 358.1438; found 358.1440 (+0.6 ppm).

Lab book Reference: SMS-256

1-Benzyl-3-(2-oxo-2-phenylethylidene)indolin-2-one, 165

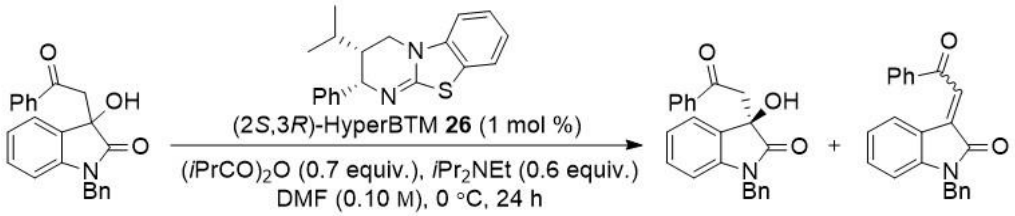


Following general procedure B, **164** (57 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.84), **165** as a red solid (47 mg, 0.14 mmol,

87%), mp 80-82 °C; **ν_{max} (ATR)** 2922, 1705 (C=O), 1661 (C=O), 1593 (C=C), 1464, 1348, 1220; **δ_H (400 MHz, $CDCl_3$)** 5.00 (2H, s, NCH_2Ph), 6.71 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.00 (1H, app td, *J* 7.7, 1.0 Hz, ArC(5)*H*), 7.23-7.38 (6H, m, Ar*H*), 7.52-7.57 (2H, m, Ar*H*), 7.61-7.67 (1H, m, Ar*H*), 7.96 (1H, s, PhC=OC*H*=C), 8.12-8.16 (2H, m, Ar*H*), 8.28-8.37 (1H, m, Ar*H*); **δ_C (100 MHz, $CDCl_3$)** 43.9 (NCH_2Ph), 109.3 (Ar*C*(7)H), 120.2 (*C*(3)), 122.9 (Ar*C*(5)H), 126.7 (PhC=O*C*H=C), 127.3 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*(4)H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 132.5 (Ar*C*(6)H), 133.9 (Ar*C*H), 135.5 (Ar*C*(3a)), 136.4 (NCH$_2$ArC(1)), 137.6 (C=OAr*C*(1)), 145.2 (Ar*C*(7a)), 168.1 (*C*(2)=O), 191.2 (Ph*C*=O); ***m/z*** **(NSI)** 340 ($[M+H]^+$, 100%) $C_{23}H_{18}O_2N^+$ ($[M+H]^+$) requires 340.1332; found 340.1334 (+0.6 ppm).

Lab book Reference: SMS-264

Kinetic resolution of 164

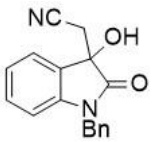


Following general procedure C, **164** (178 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in DMF (5 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1) alcohol (107 mg, 0.30 mmol, 60%) and elimination product (52 mg, 0.15 mmol, 31%).

Data for alcohol: $[\alpha]_D^{20}$ –13 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 39.9, 49.7 min, 55:45 er; *s* = 2.

Lab book Reference: SMS-434

2-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile, 166

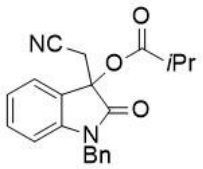


Following general procedure E, **89** (2.37 g, 10 mmol), cyanoacetic acid (0.94 g, 11 mmol) and triethylamine (280 µL, 2 mmol, 20 mol %) in DMF (50 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.19), **166** as a cream solid (2.03 g, 7.3 mmol, 73%), mp 116-118 °C; **δ_H (400 MHz, $CDCl_3$)** 2.80 (1H, d, *J* 16.5 Hz, CH_AH$_B$CN), 3.13 (1H, d, *J* 16.5 Hz, CH$_A$$H_B$CN), 3.66 (1H, s, O*H*), 4.84 (1H, d, *J* 15.6 Hz, CH_AH$_B$Ph), 4.97 (1H, d, *J* 15.6 Hz, CH$_A$$H_B$Ph), 6.79 (1H, dt, *J* 7.9, 0.8 Hz, C(7)*H*), 7.15 (1H, app td, *J* 7.9, 0.8 Hz, C(5)*H*), 7.27-7.36 (6H, m, Ar*H*), 7.66 (1H, dd, *J* 7.7, 1.1 Hz, C(4)*H*).

Data were in accordance with those previously reported.[97]

Lab book Reference: SMS-139

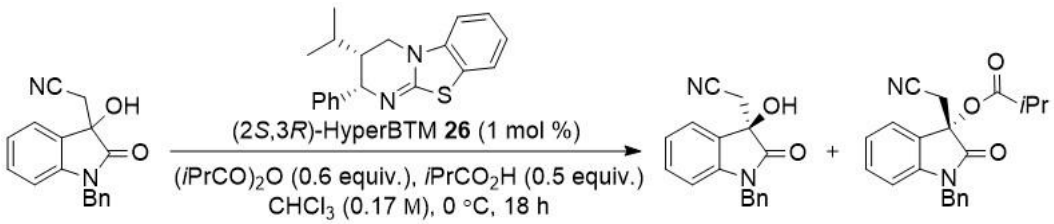
1-Benzyl-3-(cyanomethyl)-2-oxoindolin-3-yl isobutyrate, 167



Following general procedure B, **166** (41.2 mg, 0.18 mmol), isobutyric anhydride (43 µL, 0.23 mmol), DMAP **4** (2.2 mg, 0.018 mmol, 10 mol %) and *i*Pr_2NEt (77 µL, 0.43 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.26), **167** as a colourless oil (39 mg, 0.13 mmol, 72%); **ν_{max} (ATR)** 2972, 2255 (C≡N), 1728 (C=O), 1614 (C=O), 1467, 1364, 1143, 1078**; δ_H (400 MHz, $CDCl_3$)** 1.19 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.20 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.68 (1H, d, *J* 16.7 Hz, C$H_A$$H_B$CN), 2.63-2.73 (1H, m, C*H*(CH_3)$_2$), 3.20 (1H, d, *J* 16.7 Hz, $CH_A$$H_B$CN), 4.96 (2H, s, C$H_2$Ph), 6.73 (1H, d, *J* 7.9 Hz, ArC(7)*H*), 7.09 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.23-7.40 (6H, m, ArC*H*), 7.50 (1H, dd, *J* 7.5, 1.2 Hz, C(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.4 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.6 (CH(CH_3)$_A$(*C*H_3)$_B$), 26.5 (*C*H_2CN), 33.4 (*C*H(CH_3)$_2$), 44.4 (*C*H_2Ph), 74.8 (*C*(3)), 110.2 (Ar*C*(7)H), 114.7 (CH_2*C*N), 122.9 (Ar*C*(4)H), 123.5 (Ar*C*(5)H), 124.9 (CH_2Ar*C*(1)), 127.2 (CH_2Ar*C*(2,6)H), 127.8 ((CH_2Ar*C*(4)H), 128.9 (CH_2Ar*C*(3,5)H), 130.9 (Ar*C*(6)H), 134.9 (Ar*C*(3a)), 142.6 (Ar*C*(7a)), 172.2 (*C*(2)=O), 174.8 *C*(=O)CH(CH_3)$_2$); ***m/z* (NSI)** 349 ([M+H]$^+$, 100%) $C_{21}H_{21}N_2O^+$ ([M+H]$^+$) requires 349.1547; found 349.1551 (+1.2 ppm).

Lab book Reference: SMS-142

Kinetic resolution of 166



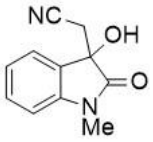
Following general procedure C, **166** (141 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.30 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mols %) and isobutyric acid (55 µL, 0.25 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent hexane/EtOAc, 4:1), alcohol (36 mg, 0.13 mmol, 25%) and ester (58 mg, 0.21 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +115 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) T_R: 18.7, 24.1 min, 95:5 er.

Data for ester: $[\alpha]_D^{20}$ +15 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (2.5% *i*PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm 30 °C) T_R: 24.1, 37.3 min, 87:13 er; *s* = 21.

Lab book Reference: SMS-244

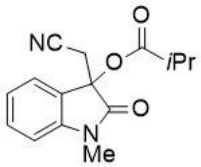
2-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)acetonitrile, 168



Following general procedure E, **90** (692 mg, 4.3 mmol), cyanoacetic acid (402 mg, 4.7 mmol) and triethylamine (120 µL, 0.86 mmol, 20 mol %) in DMF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.17), **168** as a light brown solid (447 mg, 2.2 mmol, 52%), mp 105-107 °C; **δ_H (400 MHz, $CDCl_3$)** 2.73 (1H, d, *J* 16.6 Hz, CH_AH$_B$CN), 3.07 (1H, d, *J* 16.6 Hz, CH$_A$$H_B$CN), 3.24 (3H, s, NC$H_3$), 3.42 (1H, s, O*H*), 6.71 (1H, app d, *J* 7.8 Hz, ArC(7)*H*), 7.19 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.43 (1H, td, *J* 7.8, 1.2 Hz, ArC(6)*H*), 7.67 (1H, app dd, *J* 7.5, 0.7 Hz, ArC(4)*H*).

Lab book Reference: SMS-247

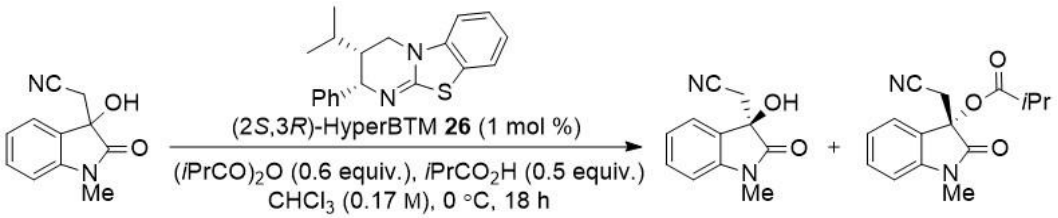
3-(Cyanomethyl)-1-methyl-2-oxoindolin-3-yl isobutyrate, 169



Following general procedure B, **168** (32 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.72), **169** as an orange oil (35 mg, 0.13 mmol, 81%); **ν_{max} (ATR)** 2974, 1724 (C=O), 1614 (C=C), 1470, 1373, 1143; **δ_H (400 MHz, $CDCl_3$)** 1.15 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.16 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$), 2.61 (1H, d, *J* 16.6 Hz, CH_AH$_B$CN), 2.64 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.14 (1H, d, *J* 16.6 Hz, CH$_A$$H_B$CN), 3.27 (3H, s, NC$H_3$), 6.91 (1H, app d, *J* 7.9 Hz, ArC(7)*H*), 7.13 (1H, app td, *J* 7.7, 0.9 Hz, ArC(5)*H*), 7.42 (1H, app td, *J* 7.8, 1.2 Hz, ArC(6)*H*), 7.50 (1H, app dd, *J* 7.4, 0.7 Hz, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.4 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.7 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 26.2 (*C*H$_2$CN), 26.8 (N*C*H$_3$), 33.4 (*C*H(CH$_3$)$_2$), 74.7 (*C*(3)), 109.0 (Ar*C*(7)H), 114.7 (*C*N), 123.0 (Ar*C*(4)H), 123.5 (Ar*C*(5)H), 124.9 (Ar*C*(3a)), 131.3 (Ar*C*(6)H), 143.5 (Ar*C*(7a)), 172.1 (*C*(2)=O), 174.4 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 290 ([M+NH$_4$]$^+$, 100%) $C_{15}H_{20}N_3O_3^+$ ([M+NH$_4$]$^+$) requires 290.1499; found 290.1500 (+0.3 ppm).

Lab book Reference: SMS-254

Kinetic resolution of 168



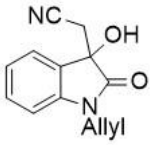
Following general procedure C, **168** (63 mg, 0.32 mmol), isobutyric anhydride (37 µL, 0.19 mmol), (2*S*,3*R*)-HyperBTM **26** (1.0 mg, 0.0032 mmol, 1 mol %) and isobutyric acid (15 µL, 0.16 mmol) in $CHCl_3$ (1.9 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (22 mg, 0.11 mmol, 35%) and ester (46 mg, 0.17 mmol, 52%).

Data for alcohol: $[\alpha]_D^{20}$ +54 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 39.1, 45.7 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ +35 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (2.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 31.5, 38.2 min, 84:16 er; *s* = 30.

Lab book Reference: SMS-274

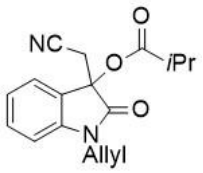
2-(1-Allyl-3-hydroxy-2-oxoindolin-3-yl)acetonitrile, 170



Following general procedure E, **91** (2.26 mg, 12 mmol), cyanoacetic acid (1.13 g, 13.2 mmol) and triethylamine (335 µL, 2.4 mmol, 20 mol %) in DMF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.20), **170** as a red/brown solid (2.07 g, 9.1 mmol, 76%), mp 83-85 °C; **ν_{max} (ATR)** 3293 (OH), 2970, 2245, 1710 (C=O), 1609 (C=C), 1466, 1179, 1078; **δ_H (400 MHz, $CDCl_3$)** 2.77 (1H, d, *J* 16.5 Hz, CH_AH$_B$CN), 3.09 (1H, d, *J* 16.5 Hz, CH$_A$$H_B$CN), 3.71 (1H, s, O*H*), 4.27 (1H, ddt, *J* 16.3, 5.2, 1.7 Hz, NCH_AH$_B$CH=CH$_2$), 4.40 (1H, ddt, *J* 16.3, 5.2, 1.7 Hz, NCH$_A$$H_B$CH=CH$_2$), 5.27 (2H, m, NCH$_2$CH=C$H_2$), 5.82 (1H, ddt, *J* 17.2, 10.4, 5.3 Hz, NCH$_2$C*H*=CH$_2$), 6.91 (1H, app d, *J* 7.9 Hz, ArC(7)*H*), 7.18 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.39 (1H, td, *J* 7.8, 1.3 Hz, ArC(6)*H*), 7.64-7.67 (1H, m, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 27.6 (*C*H$_2$CN), 42.7 (N*C*H$_2$CH=CH$_2$), 72.7 (*C*(3)), 110.1 (Ar*C*(7)H), 115.2 (*C*N), 118.4 (NCH$_2$CH=*C*H$_2$), 123.9 (Ar*C*(5)H), 124.4 (Ar*C*(4)H), 127.4 (Ar*C*(3a)), 130.4 (NCH$_2$*C*H=CH$_2$), 131.1 (Ar*C*(6)H), 142.1 (Ar*C*(7a)), 175.1 (*C*(2)=O); ***m/z* (NSI)** 246 ([M+NH$_4$]$^+$, 100%) $C_{13}H_{16}N_3O_2^+$ ([M+NH$_4$]$^+$) requires 246.1237; found 246.1237 (+0.0 ppm).

Lab book Reference: SMS-285

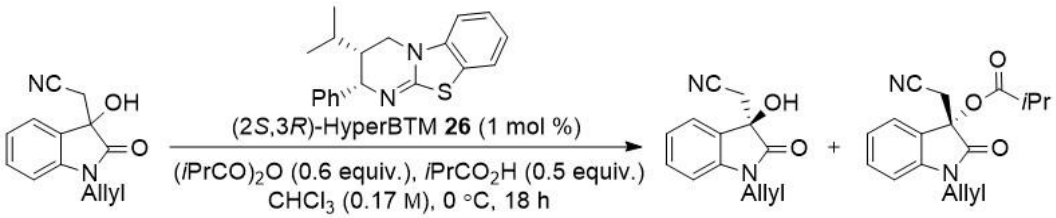
1-Allyl-3-(cyanomethyl)-2-oxoindolin-3-yl isobutyrate, 171



Following general procedure B, **170** (37 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.80), **171** as an orange oil (33 mg, 0.11 mmol, 70%); **ν_{max} (ATR)** 2980, 2255 (CN), 1730 (C=O), 1614 (C=C), 1470, 1366, 1099; **δ_H (400 MHz, $CDCl_3$)** 1.16 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.17 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$), 2.64 (1H, d, *J* 16.6 Hz, CH_AH$_B$CN), 2.64 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 3.16 (1H, d, *J* 16.6 Hz, CH$_A$*H*$_B$CN), 4.34 (1H, ddt, *J* 16.5, 5.5, 1.6 Hz, NCH_AH$_B$CH=CH$_2$), 4.42 (1H, ddt, *J* 16.5, 4.9, 1.6 Hz, NCH$_A$*H*$_B$CH=CH$_2$), 5.27 (1H, dq, *J* 10.4, 1.4 Hz, NCH$_2$CH=CH$_{cis}$*H*$_{trans}$), 5.37 (1H, dq, *J* 17.2, 1.6 Hz, NCH$_2$CH=C*H*$_{cis}$H$_{trans}$), 5.86 (1H, ddt, *J* 17.2, 10.4, 5.2 Hz, NCH$_2$C*H*=CH$_2$), 6.90 (1H, app d, *J* 7.9 Hz, ArC(7)*H*), 7.12 (1H, app td, *J* 7.6, 0.8 Hz, ArC(5)*H*), 7.37 (1H, app td, *J* 7.8, 1.2 Hz, ArC(6)*H*), 7.47-7.51 (1H, m, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.4 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.7 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 26.4 (*C*H$_2$CN), 33.4 (*C*H(CH$_3$)$_2$), 42.9 (N*C*H$_2$CH=CH$_2$), 74.7 (*C*(3)), 110.0 (Ar*C*(7)H), 114.6 (*C*N), 118.3 (NCH$_2$CH=*C*H$_2$), 122.9 (Ar*C*(4)H), 123.5 (Ar*C*(5)H), 124.9 (Ar*C*(3a)), 130.6 (NCH$_2$*C*H=CH$_2$), 130.9 (Ar*C*(6)H), 142.7 (Ar*C*(7a)), 171.8 (*C*(2)=O), 174.3 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 316 ([M+NH$_4$]$^+$, 100%) $C_{17}H_{22}N_3O_3^+$ ([M+NH$_4$]$^+$) requires 316.1656; found 316.1656 (+0.1 ppm).

Lab book Reference: SMS-287

Kinetic resolution of 170



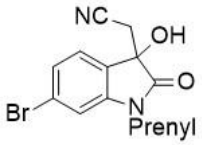
Following general procedure C, **170** (114 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and isobutyric acid (23 µL, 0.25 mmol) were reacted in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (27 mg, 0.12 mmol, 24%) and ester (71 mg, 0.24 mmol, 47%).

Data for alcohol: $[\alpha]_D^{20}$ +88 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.9, 34.4 min, 99:1 er.

Data for ester: $[\alpha]_D^{20}$ –42 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.2, 19.4 min, 79:21 er; *s* = 15.

Lab book Reference: SMS-291

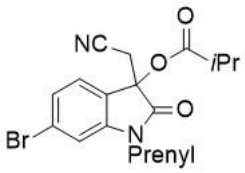
2-(6-Bromo-3-hydroxy-1-(3-methylbut-2-en-1-yl)-2-oxoindolin-3-yl)acetonitrile, 172



Following general procedure E, **95** (2.66 g, 9.1 mmol), cyanoacetic acid (850 mg, 10 mmol) and triethylamine (254 µL, 1.8 mmol, 20 mol %) in DMF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.38), **172** as a beige solid (2.39 g, 7.2 mmol, 79%), mp 122-124 °C; **δ_H (400 MHz, $CDCl_3$)** 1.74 (3H, m, $CH_2CH=C(CH_3)_A(CH_3)_B$), 1.82 (3H, s, $CH_2CH=C(CH_3)_A(CH_3)_B$), 2.71 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 3.06 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 3.74 (1H, s, O*H*), 4.23 (1H, dd, *J* 15.5, 6.8 Hz, $CH_AH_BCH=C(CH_3)_2$), 4.31 (1H, dd, *J* 15.5, 6.8 Hz, $CH_AH_BCH=C(CH_3)_2$), 5.13 (1H, tt, *J* 6.7, 1.4 Hz, $CH_2CH=C(CH_3)_2$), 7.01 (1H, d, *J* 1.6 Hz, ArC(7)*H*), 7.31 (1H, dd, *J* 7.9, 1.7 Hz, ArC(5)*H*), 7.51 (1H, d, *J* 7.9 Hz, C(4)*H*).

Lab book Reference: SMS-294

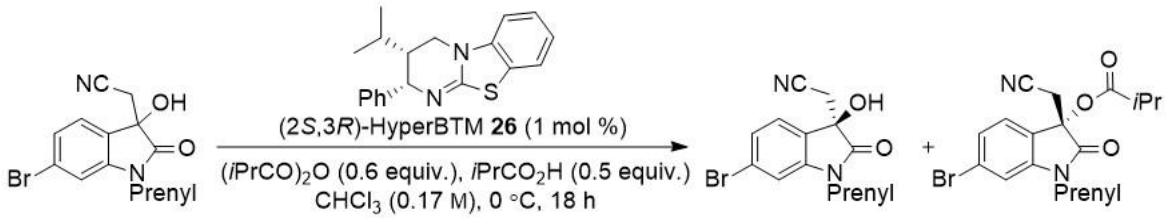
6-Bromo-3-(cyanomethyl)-1-(3-methylbut-2-en-1-yl)-2-oxoindolin-3-yl, 173



Following general procedure B, **172** (54 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.80), **173** as an orange oil (58 mg, 0.14 mmol, 90%); **ν_{max} (ATR)** 2974, 2255 (CN), 1732 (C=O), 1604 (C=C), 1485, 1371, 1141, 1007; **δ_H (400 MHz, $CDCl_3$)** 1.15 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.16 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.72-1.84 (6H, m, $CH_2CH=C(CH_3)_2$), 2.59 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 2.63 (1H, sept, *J* 7.0 Hz, $CH(CH_3)_2$), 3.13 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 4.27 (1H, dd, *J* 15.7, 6.3 Hz, $CH_AH_BCH=C(CH_3)_2$), 4.38 (1H, dd, *J* 15.7, 6.8 Hz, $CH_AH_BCH=C(CH_3)_2$), 5.16 (1H, tt, *J* 6.5, 1.4 Hz, $CH_2CH=C(CH_3)_2$), 6.99 (1H, d, *J* 1.6 Hz, ArC(7)*H*), 7.25 (1H, app dd, *J* 7.9, 1.6 Hz, ArC(5)*H*), 7.35 (1H, d, *J* 7.9 Hz, C(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.3 ($CH_2CH=C(CH_3)_A(CH_3)_B$), 18.4 ($CH(CH_3)_A(CH_3)_B$), 18.7 ($CH(CH_3)_A(CH_3)_B$), 25.7 ($CH_2CH=C(CH_3)_A(CH_3)_B$), 26.0 (CH_2CN), 33.3 ($CH(CH_3)_2$), 38.8 ($CH_2CH=C(CH_3)_2$), 74.3 (*C*(3)), 113.4 (Ar*C*(7)H), 114.5 (*C*N), 116.9 ($CH_2CH=C(CH_3)_2$), 123.9 ($CH_2CH=C(CH_3)_2$), 124.2 (Ar*C*(4)H), 125.0 (Ar*C*(6)Br), 126.2 (Ar*C*(5)H), 138.0 (Ar*C*(3a)), 144.2 (Ar*C*(7a)), 171.5 (*C*(2)=O), 174.4 (*C*(=O)$CH(CH_3)_2$); ***m/z*** **(NSI)** 422 ($[M+NH_4]^+$, 100%) $C_{19}H_{25}N_3O_3Br^+$ ($[M+NH_4]^+$) requires 422.1074; found 422.1069 (–1.1 ppm).

Lab book Reference: SMS-296

Kinetic resolution of 172



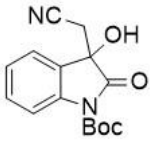
Following general procedure C, **172** (167 mg, 0.5 mmol), isobutyric anhydride (49 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and isobutyric acid (23 µL, 0.25 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (60 mg, 0.18 mmol, 36%) and ester (93 mg, 0.23 mmol, 46%).

Data for alcohol: $[\alpha]_D^{20}$ +68 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 28.0, 38.1 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ –36 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralcel OD-H (2.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 19.3, 36.8 min, 90:10 er; *s* = 47.

Lab book Reference: SMS-300

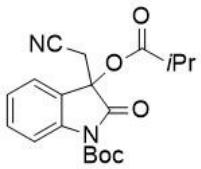
***Tert*-butyl 3-(cyanomethyl)-3-hydroxy-2-oxoindoline-1-carboxylate, 174**



Following general procedure E, **96** (1.49 g, 6.0 mmol), cyanoacetic acid (554 mg, 6.6 mmol) and triethylamine (168 µL, 1.2 mmol, 20 mol %) in DMF (40 mL) gave, after column chromatography (eluent hexane/EtOAc, 7:3; R_F 0.24), **174** as a red oil (402 mg, 1.4 mmol, 23%); **ν_{max} (ATR)** 3431 (OH), 2980, 2257 (CN), 1788 (C=O), 1732, 1611 (C=C), 1468, 1293, 1248, 1113; **δ_H (400 MHz, $CDCl_3$)** 1.63 (9H, s, C(CH_3)$_3$), 2.76 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 3.07 (1H, d, *J* 16.6 Hz, CH_AH_BCN), 3.65 (1H, br s, O*H*), 7.27 (1H, app td, *J* 7.6, 0.9 Hz, ArC(5)*H*), 7.44 (1H, app td, *J* 8.0, 1.4 Hz, ArC(6)*H*), 7.69 (1H, app dd, *J* 7.5, 1.0 Hz, ArC(4)*H*), 7.87 (1H, app d, *J* 8.2 Hz, ArC(7)*H*); **δ_C (100 MHz, $CDCl_3$)** 27.9 (CH_2CN), 28.0 (C(CH_3)$_3$), 72.3 (*C*(3)), 85.7 (*C*(CH_3)$_3$), 114.9 (CH_2CN), 115.7 (Ar*C*(7)H), 124.2 (Ar*C*(4)H), 125.6 (Ar*C*(5)H), 126.2 (Ar*C*(3a)), 131.3 (Ar*C*(6)H), 139.1 (Ar*C*(7a)), 148.5 (N*C*(=O)OC(CH_3)$_3$), 174.0 (*C*(2)=O); ***m/z* (NSI)** 306 ($[M+NH_4]^+$, 100%) $C_{15}H_{20}N_3O_4^+$ ($[M+NH_4]^+$) requires 306.1448; found 306.1451 (–0.9 ppm).

Lab book Reference: SMS-356

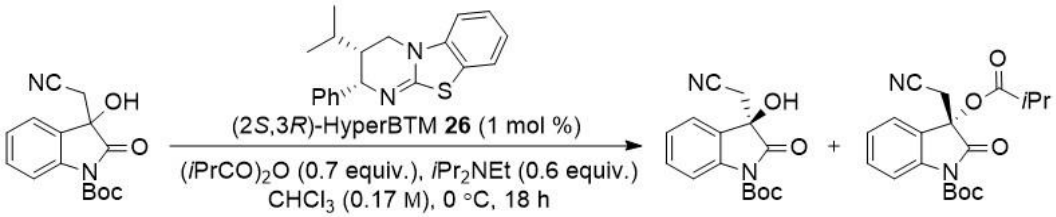
***Tert*-butyl 3-(cyanomethyl)-3-(isobutyryloxy)-2-oxoindoline-1-carboxylate, 175**



Following general procedure B, **174** (46 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.83), **175** as an orange oil (36 mg, 0.10 mmol, 62%); **ν_{max} (ATR)** 2978, 2255 (CN), 1776 (C=O), 1734, 1609 (C=C), 1468, 1346, 1249, 1142; **δ_H (400 MHz, $CDCl_3$)** 1.16 (6H, d, *J* 7.0 Hz, CH(CH_3)$_2$), 1.64 (9H, s, C(CH_3)$_3$), 2.65 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 2.69 (1H, d, *J* 16.6 Hz, C$H_A$$H_B$CN), 3.14 (1H, d, *J* 16.6 Hz, C$H_A$$H_B$CN), 7.24 (1H, app td, *J* 7.6, 1.0 Hz, ArC(5)*H*), 7.45 (1H, m, ArC(6)*H*), 7.53 (1H, app dd, *J* 7.5, 1.0 Hz, ArC(4)*H*), 7.93 (1H, app d, *J* 8.2 Hz, ArC(7)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.3 (CH(CH_3)$_A$(CH_3)$_B$), 18.6 (CH(CH_3)$_A$(CH_3)$_B$), 26.7 (*C*H_2CN), 28.1 (C(CH_3)$_3$), 33.3 (*C*H(CH_3)$_2$), 74.3 (*C*(3)), 85.3 (*C*(CH_3)$_3$), 114.3 (CH$_2$*C*N), 115.8 (Ar*C*(7)H), 122.7 (Ar*C*(4)H), 123.9 (Ar*C*(3a)), 125.3 (Ar*C*(5)H), 131.3 (Ar*C*(6)H), 139.7 (Ar*C*(7a)), 148.5 (N*C*(=O)OC(CH$_3$)$_3$), 170.3 (*C*(2)=O), 174.9 (*C*(=O)CH(CH$_3$)$_2$); ***m/z* (NSI)** 376 ([M+NH_4]$^+$, 100%) $C_{19}H_{26}N_3O_5^+$ ([M+NH_4]$^+$) requires 376.1867; found 376.1868 (+0.3 ppm).

Lab book Reference: SMS-362

Kinetic resolution of 174



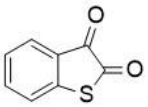
Following general procedure C, **174** (144 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (45 mg, 0.15 mmol, 31%) and ester (90 mg, 0.25 mmol, 51%).

Data for alcohol: $[\alpha]_D^{20}$ +111 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.9, 21.2 min, 93:7 er.

Data for ester: $[\alpha]_D^{20}$ +20 (*c* 1.0, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 10.0, 12.0 min, 85:15 er; *s* = 11.

Lab book Reference: SMS-364

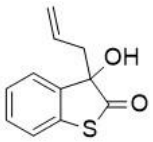
Benzo[b]thiophene-2,3-dione, 180



Following the procedure by Matsubara *et al*,[106] thiophenol (1.02 mL, 10 mmol) in anhydrous Et_2O (20 mL) was cooled to 0 °C under a N_2 atmosphere. Oxalyl chloride (0.96 mL, 11 mmol) was added dropwise at 0 °C and the reaction stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in anhydrous CH_2Cl_2 (20 mL). Aluminium chloride (4.66 g, 25 mmol) was added portionwise at 0 °C and the reaction mixture stirred at RT for 16 h. An ice/1 M HCl mixture was added dropwise until the mixture turned clear and was stirred for 1 h. The phases were then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were then combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give, after recrystallization from hexane, **180** as an orange solid (1.36 g, 8.3 mmol, 83%), mp 118-120 °C; **δ_H (400 MHz, $CDCl_3$)** 7.38 (1H, td, *J* 7.5, 0.9 Hz, ArC(5)*H*), 7.43 (1H, d, *J* 7.8 Hz, ArC(4)H), 7.69 (1H, td, *J* 7.7, 1.4 Hz, ArC(6)*H*), 7.83 (1H, d, *J* 7.6, 1.3 Hz, ArC(7)*H*).

Lab book Reference: SMS-370

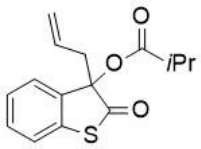
3-Allyl-3-hydroxybenzo[b]thiophen-2(3H)-one, 181



Following the procedure by Bisai *et al*,[95] **180** (328 mg, 2.0 mmol) was dissolved in anhydrous DMF (5 mL) under an N_2 atmosphere and cooled to 0 °C. Allyltrichlorosilane (434 µL, 3 mmol) was added dropwise over 15 mins and the reaction stirred overnight at RT. On completion, the reaction was quenched with H_2O (10 mL) and brine (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.69), **181** as a red oil (231 mg, 1.12 mmol, 56%); **ν_{max} (ATR)** 3412 (OH), 3069, 1701 (C=O), 1593, 1450, 1059, 901; **δ_H (400 MHz, $CDCl_3$)** 2.58-2.74 (2H, m, C*H*$_2$CH=CH$_2$), 3.25 (1H, s, O*H*), 5.06-5.17 (2H, m, CH$_2$CH=C*H*$_2$), 5.62 (1H, dddd, *J* 16.8, 10.2, 8.3, 6.5 Hz, CH$_2$C*H*=CH$_2$), 7.25-7.42 (4H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 45.2 (*C*H$_2$CH=CH$_2$), 84.2 (*C*(3)), 121.3 (CH$_2$CH=*C*H$_2$), 123.4 (Ar*C*(6)H), 125.3 (Ar*C*(7)H), 126.8 (Ar*C*(5)H), 129.5 (CH$_2$*C*H=CH$_2$), 129.9 (Ar*C*(4)H), 133.2 (Ar*C*(3a)), 137.0 (Ar*C*(7a)), 206.9 (*C*=O); ***m/z* (NSI)** 229 ([M+Na]$^+$, 100%) $C_{11}H_{10}O_4SNa^+$ ([M+Na]$^+$) requires 229.0294; found 229.0294 (+0.0 ppm).

Lab book Reference: SMS-371

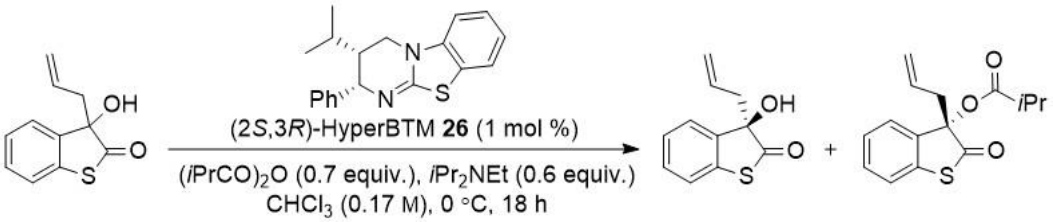
3-Allyl-2-oxo-2,3-dihydrobenzo[b]thiophen-3-yl isobutyrate, 182



Following general procedure B, **181** (33 mg, 0.16 mmol), isobutyric anhydride (40 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.83), **182** as an orange oil (36 mg, 0.13 mmol, 81%); **ν_{max} (ATR)** 2976, 1717 (C=O), 1593, 1468, 1451, 1148; **δ_H (400 MHz, $CDCl_3$)** 1.14 (3H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.15 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.61 (1H, sept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 2.68 (1H, ddt, *J* 13.7, 7.9, 0.9 Hz, C*H*$_A$H$_B$CH=CH$_2$), 2.75 (1H, ddt, *J* 13.7, 6.7, 1.3 Hz, CH$_A$*H*$_B$CH=CH$_2$), 5.07 (1H, app dq, *J* 17.0, 1.4 Hz, CH$_2$CH=C*H*$_{cis}$H$_{trans}$), 5.11-5.16 (1H, m, CH$_2$CH=CH$_{cis}$*H*$_{trans}$), 5.64 (1H, dddd, *J* 16.9, 10.2, 7.8, 6.7 Hz, CH$_2$C*H*=CH$_2$), 7.16-7.26 (2H, m, ArC*H*), 7.30-7.37 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.7 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 33.2 (*C*H(CH$_3$)$_2$), 42.9 (*C*H$_2$CH=CH$_2$), 86.2 (*C*(3)), 121.1 (CH$_2$CH=*C*H$_2$), 123.5 (2C, Ar*C*(6)H, Ar*C*(7)H), 126.4 (Ar*C*(5)H), 128.7 (Ar*C*(4)H), 129.6 (CH$_2$*C*H=CH$_2$), 134.3 (Ar*C*(3a)), 135.1 (Ar*C*(7a)), 174.8 (C(=O)CH(CH$_3$)$_2$), 201.9 (*C*=O); ***m/z* (NSI)** 294 ([M+NH$_4$]$^+$, 100%) $C_{15}H_{20}NO_3S^+$ ([M+NH$_4$]$^+$) requires 294.1158; found 294.1159 (+0.2 ppm).

Lab book Reference: SMS-372

Kinetic resolution of 181



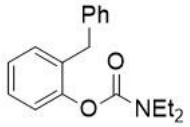
Following general procedure C, **181** (103 mg, 0.5 mmol), isobutyric anhydride (58 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (1.6 mg, 0.005 mmol, 1 mol %) and *i*Pr$_2$NEt (52 µL, 0.3 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (34 mg, 0.17 mmol, 33%) and ester (56 mg, 0.20 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +76 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.1, 9.8 min, 98:2 er.

Data for ester: $[\alpha]_D^{20}$ –47 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (2.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 4.9, 7.2 min, 92:8 er; *s* = 41.

Lab book Reference: SMS-374

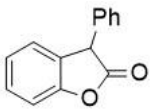
2-Benzylphenyl diethylcarbamate, 185



Following the procedure by Snieckus *et al*,[107] to flame-dried glassware, anhydrous hexane (10 mL) was slowly added to NaH (1.04 g, 26 mmol, 60% in mineral oil) and stirred for 10 minutes. The hexanes were then carefully cannulated out leaving crystalline NaH. 2-Benzyl phenol **183** (3.69 g, 20 mmol) in THF (100 mL) was added at 0 °C *via* cannula with stirring. After complete addition, the reaction was left to stir at RT for 3 h. The reaction was then cooled to 0 °C and diethylcarbamyl chloride **184** (5.9 mL, 26 mmol) was added dropwise and the reaction left to stir at RT for 24 h. The reaction was monitored by TLC until complete consumption of starting phenol. The reaction was then quenched with NH_4Cl (25 mL) at 0 °C. The organic layer was separated and concentrated *in vacuo*. Distilled water (50 mL) was then added and the organic layers extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by Kugelrohr distillation to give **185** as a pale yellow oil (4.14 g, 14.2 mmol, 73%); **ν_{max} (ATR)** 2972, 2479, 1711 (CO), 1416, 1271, 1215, 1152; **δ_H (400 MHz, $CDCl_3$)** 1.18 (6H, app q, *J* 6.7 Hz, $N(CH_2CH_3)_2$), 3.35 (4H, dq, *J* 14.1, 7.0 Hz, $N(CH_2CH_3)_2$), 3.98 (2H, s, ArC(2)CH_2Ph), 7.12-7.32 (9H, m, ArC*H*).

Lab book reference: SMS-366

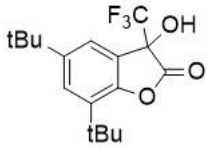
3-Phenylbenzofuran-2(3H)-one, 186



Following the procedure by Snieckus *et al*,[107] a solution of diisopropylamine (3.08 mL. 22 mmol) and *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexane) in THF (20 mL) under a N_2 atmosphere was stirred at 0 °C for 1 h. This solution was then cooled to –78 °C, and a solution of **185** (2.84 g, 10 mmol) in THF (40 mL) was added dropwise over 1 h. The mixture was warmed to 0 °C and stirred for 24 h. Upon completion, sat. NH_4Cl (30 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the organic extracts combined, washed with brine (3 x 20 mL), dried (Na_2SO_4) filtered and conc. *in vacuo*. The residue was dissolved in toluene (30 mL) and *p*-toluenesulfonic acid (5.17 g, 30 mmol) was added and the mixture was heated at reflux for 1 h. The mixture was then cooled, conc. *in vacuo* and extracted with hot hexanes. The extract was passed through charcoal and the product recrystallized from $CHCl_3$ to give **186** as a white crystalline solid (2.03 g, 9.7 mmol, 97%), mp 96-98 °C; **δ_H (400 MHz, $CDCl_3$)** 4.90 (1H, s, C(3)*H*), 7.15-7.26 (5H, m, ArC*H*), 7.31-7.40 (4H, m, ArC*H*).

Lab book reference: SMS-368

5,7-Di-*tert*-butyl-3-hydroxy-3-(trifluoromethyl)benzofuran-2(3*H*)-one, 187

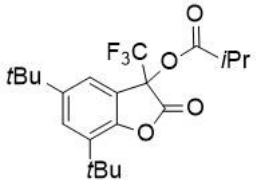


Following general procedure A, 2,4-di-*tert*-butyl phenol (412.3 mg, 2 mmol), methyl 3-trifluoromethyl pyruvate (225 µL, 2.2 mmol) and $TiCl_4$ (0.4 mL, 0.2 mmol, 10 mol %) in anhydrous CH_2Cl_2 (10 mL) gave, after column chromatography (eluent hexane/Et_2O, 9:1; R_F 0.26), **187** as a colourless solid (500 mg, 1.52 mmol, 76%), mp 74-76 °C; **δ_H (400 MHz, $CDCl_3$)** 1.36 (9H, s, $(CH_3)_3$), 1.43 (9H, s, $(CH_3)_3$), 3.55 (1H, s, O*H*), 7.42-7.43 (1H, m, C(4)*H*), 7.50 (1H, d, *J* 2.1 Hz, C(6)*H*); **δ_F (376 MHz, $CDCl_3$)** –79.8 (CF_3).

Data were in accordance with those previously reported.[108]

Lab book Reference: SMS-71

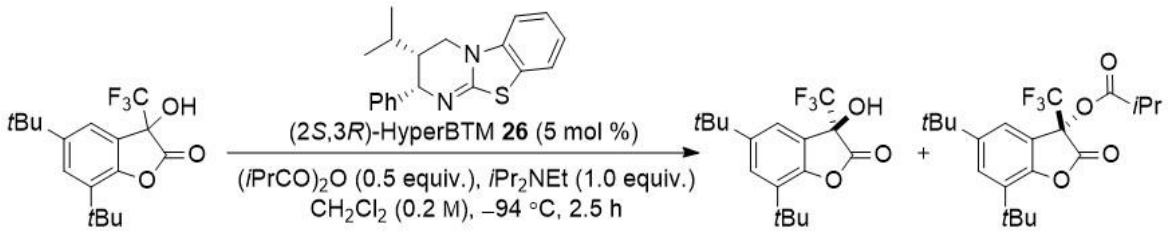
5,7-Di-*tert*-butyl-2-oxo-3-(trifluoromethyl)-2,3-benzofuran-3-yl isobutyrate, 188



Following general procedure B, **187** (165 mg, 0.5 mmol), isobutyric anhydride (108 µL, 0.65 mmol), DMAP **4** (6 mg, 0.05 mmol, 10 mol %) and *i*Pr_2NEt (210 µL, 1.2 mmol) in CH_2Cl_2 (5 mL) gave, after column chromatography (eluent hexane/Et_2O, 95:5; R_F 0.32), **188** as a colourless oil (146 mg, 0.37 mmol, 73%); **ν_{max} (ATR)** 2963, 1827 (C=O), 1759 (C=O), 1483, 1186, 1091, 997; **δ_H (400 MHz, $CDCl_3$)** 1.17 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.20 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.31 (9H, s, $(CH_3)_3$), 1.42 (9H, s, $(CH_3)_3$), 2.71 (1H, sept, *J* 7.0 Hz, $CH(CH_3)_2$), 7.20 (1H, dq, *J* 2.1, 0.9 Hz, C(6)*H*), 7.46 (1H, d, *J* 2.1 Hz, C(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.3 ($CH(CH_3)_A(CH_3)_B$), 18.5 ($CH(CH_3)_A(CH_3)_B$), 29.5 ($(CH_3)_3$), 31.5 ($(CH_3)_3$), 33.3 ($CH(CH_3)_2$), 34.5 ($C(CH_3)_3$), 34.9 ($C(CH_3)_3$), 75.9 (q, *J* 33 Hz, *C*(3)CF_3), 118.7 (Ar*C*(4)H), 118.9 (Ar*C*(^{t}Bu), 121.5 (q, *J* 283 Hz, *C*F_3), 127.1 (Ar*C*(6)H), 134.1 (Ar*C*(^{t}Bu), 148.1 (Ar*C*(3a)), 150.9 (Ar*C*(7a)), 166.3 (*C*(2)=O), 174.0 (CH_3CH_2(*C*=O)); **δ_F (376 MHz, $CDCl_3$)** –77.8 (CF_3); ***m/z* (NSI)** 418 ($[M+NH_4]^+$, 100%) $C_{21}H_{27}F_3O_4NH_4^+$ ($[M+NH_4]^+$) requires 418.2200; found 418.2185 (–1.1 ppm).

Lab book Reference: SMS-84

Kinetic resolution of 187



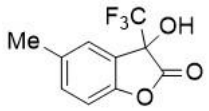
Following general procedure C, **187** (165 mg, 0.5 mmol), isobutyric anhydride (46 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (7.7 mg, 0.025 mmol, 5 mol %) and *i*Pr$_2$NEt (178 µL, 0.5 mmol) in CH_2Cl_2 (5 mL) at –94 °C gave, after column chromatography (eluent hexane/Et_2O, 7:3), alcohol (48 mg, 0.15 mmol, 29%) and ester (92 mg, 0.19 mmol, 0.23 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ +53 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 7.8, 9.2 min, 87:13 er; *s* = 9.

Data for ester: $[\alpha]_D^{20}$ –12 (*c* 0.1, $CHCl_3$).

Lab book Reference: SMS-115

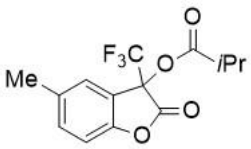
3-Hydroxy-5-methyl-3-(trifluoromethyl)benzofuran-2(3H)-one, 189



Following general procedure A, cresol (216 mg, 2 mmol), methyl 3-trifluoromethyl pyruvate (194 µL, 1.8 mmol) and $TiCl_4$ (0.4 mL, 0.2 mmol, 10 mol %) in anhydrous CH_2Cl_2 (10 mL) for 96 h gave, after column chromatography (eluent hexane/Et_2O, 4:1; R_F 0.26), **189** as a light brown solid (137 mg, 1.24 mmol, 62%), mp 82-84 °C; ν_{max} (ATR) 3429 (OH), 2916, 1794 (C=O), 1483, 1188, 1169; **δ_H (400 MHz, $CDCl_3$)** 2.40 (3H, d, *J* 0.8 Hz, C*H*$_3$), 3.58 (1H, s, O*H*, br), 7.08 (1H, d, *J* 8.3 Hz, C(7)*H*), 7.32 (1H, ddt, *J* 8.3, 1.9, 0.8 Hz, C(6)*H*), 7.37 (1H, dd, *J* 1.9 Hz, 0.8 Hz, C(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (*C*H$_3$), 74.8 (*C*(3), q, *J* 33.6 Hz), 111.3 (Ar*C*(7)H), 120.4 (Ar*C*(5)CH$_3$), 122.2 (*C*F$_3$, q, *J* 287 Hz), 126.5 (Ar*C*(4)H), 133.5 (Ar*C*(6)H), 135.5 (Ar*C*(3a)), 152.2 (Ar*C*(7a)), 170.3 (*C*=O)); **δ_F (376 MHz, $CDCl_3$)** –79.7 (C*F*$_3$); ***m/z* (NSI)** 250 ($[M+NH_4]^+$, 100%) $C_{10}H_7F_3O_3NH_4^+$ ($[M+NH_4]^+$) requires 250.0686; found 250.0685 (–0.2 ppm).

Lab book Reference: SMS-129

5-Methyl-2-oxo-3-(trifluoromethyl)-2,3-dihydrobenzofuran-3-yl isobutyrate, 190

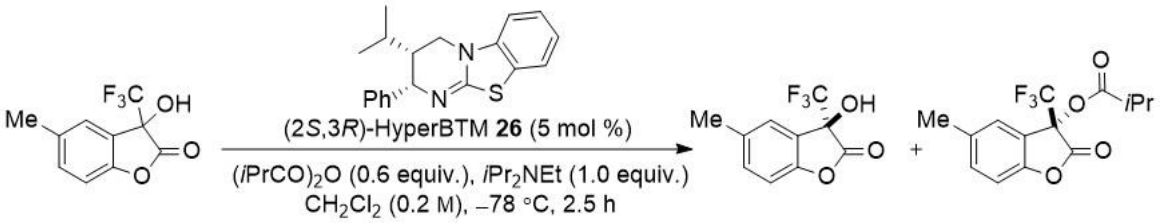


Following general procedure B, **189** (41.2 mg, 0.18 mmol), isobutyric anhydride (43 µL, 0.23 mmol), DMAP **4** (2.2 mg, 0.018 mmol, 10 mol %) and *i*Pr$_2$NEt (77 µL, 0.43 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent hexane/Et_2O, 7:3; R_F 0.58), **190** as a colourless oil (39 mg, 72%); ν_{max}

(ATR) 2980, 1821 (C=O), 1759 (C=O), 1622, 1489, 1188, 1090, 1001; **δ_H (400 MHz, $CDCl_3$)** 1.18 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.21 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 2.37 (3H, s, C(5)CH_3), 2.71 (1H, sept, *J* 7.0 Hz, $CH(CH_3)_2$), 7.08 (1H, d, *J* 8.3 Hz, C(7)*H*), 7.19 (1H, s, C(4)*H*), 7.31 (1H, ddd, *J* 8.3, 1.9, 0.8 Hz, C(6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.3 ($CH(CH_3)_A(CH_3)_B$), 18.4 ($CH(CH_3)_A(CH_3)_B$), 21.1 (C(5)CH_3), 33.3 ($CH(CH_3)_2$), 76.2 (q, *J* 33 Hz, *C*(3)CF_3), 111.3 (Ar*C*(7)H), 118.9 (Ar*C*(5)CH_3), 121.4 (q, *J* 283 Hz, CF_3), 124.9 (Ar*C*(4)H), 133.6 (Ar*C*(6)H), 135.1 (Ar*C*(3a)), 152.9 (Ar*C*(7a)), 166.1 (*C*(2)=O), 174.1 (*C*(=O)$CH(CH_3)_2$); **δ_F (376 MHz, $CDCl_3$)** –77.7 (CF_3); ***m/z* (NSI)** 320 ($[M+NH_4]^+$, 100%) $C_{14}H_{13}F_3O_4NH_4^+$ ($[M+NH_4]^+$) requires 320.1104; found 320.1108 (+1.2 ppm).

Lab book Reference: SMS-140

Kinetic resolution of 189



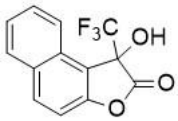
Following general procedure C, **189** (94 mg, 0.41 mmol), isobutyric anhydride (43 µL, 0.25 mmol), (2*S*,3*R*)-HyperBTM **26** (6.2 mg, 0.02 mmol, 5 mol %) and *i*Pr_2NEt (73 µL, 0.41 mmol) in CH_2Cl_2 (2 mL) at –78 °C gave, after column chromatography (eluent hexane/Et_2O, 7:3), alcohol (29 mg, 0.13 mmol, 31%) and ester (61 mg, 0.20 mmol, 49%).

Data for alcohol: $[\alpha]_D^{20}$ +24 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.0, 22.7 min, 73:27 er; *s* = 3.

Data for ester: $[\alpha]_D^{20}$ –8 (*c* 0.1, $CHCl_3$).

Lab book Reference: SMS-141

1-Hydroxy-1-(trifluoromethyl)naphtho[2,1-b]furan-2(1H)-one, 191

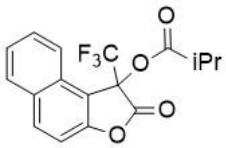


Following general procedure A, 2-naphthol (412.3 mg, 2 mmol), methyl 3-trifluoromethyl pyruvate (184 µL, 1.8 mmol) and $TiCl_4$ (0.4 mL, 0.2 mmol, 10 mol %) in anhydrous CH_2Cl_2 (10 mL) gave, after column chromatography (eluent hexane/Et_2O, 5:1; R_F 0.23), **191** as a light brown solid (328 mg, 1.36 mmol, 68%), mp 116-118 °C; **δ_H (400 MHz, $CDCl_3$)** 3.75 (1H, br s, O*H*), 7.39 (1H, d, *J* 8.9 Hz, C(8)*H*), 7.53 (1H, ddd, *J* 8.3, 6.9, 1.3, C(5)*H*), 7.64 (1H, ddd, *J* 8.3, 6.9, 1.3, C(6)*H*), 7.92 (1H, d, *J* 8.3, C(4)*H*), 8.05 (1H, d, *J* 8.9 Hz, C(9)*H*), 8.12 (1H, d, *J* 8.6, C(7)*H*); **δ_F (376 MHz, $CDCl_3$)** –77.6 (CF_3).

Data were in accordance with those previously reported.[108]

Lab book Reference: SMS-130

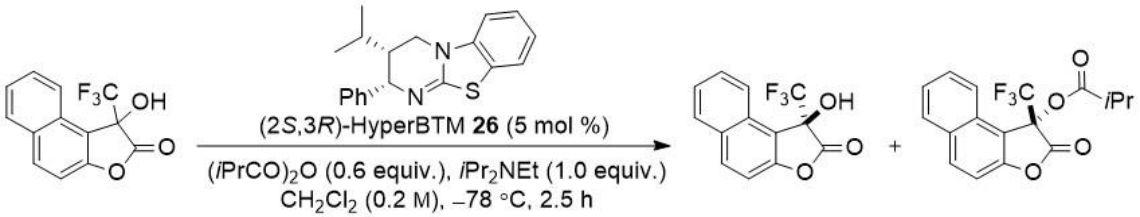
2-Oxo-1-(trifluoromethyl)-1,2-dihydronaphtho[2,1-b]furan-1-yl isobutyrate, 192



Following general procedure B, **191** (67 mg, 0.25 mmol), isobutyric anhydride (54 µL, 0.33 mmol), DMAP **4** (3 mg, 0.025 mmol, 10 mol %) and *i*Pr_2NEt (105 µL, 0.6 mmol) in CH_2Cl_2 (2.5 mL) gave, after column chromatography (eluent hexane/Et_2O, 7:3; R_F 0.50), **192** as a colourless oil (71 mg, 0.21 mmol, 83%); **ν_{max} (ATR)** 2980, 1829 (C=O), 1755 (C=O), 1581, 1525, 1182, 1094, 988; **δ_H (500 MHz, $CDCl_3$)** 1.16 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.20 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.77 (1H, sept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 7.41 (1H, d, *J* 8.9 Hz, *C*(8)H), 7.50 (1H, ddd, *J* 8.1, 6.9, 1.3 Hz, *C*(5)H), 7.61 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, *C*(6)H), 7.89-7.97 (2H, m, *C*(4,9)H), 8.04 (1H, d, *J* 8.8 Hz, *C*(7)H); **δ_C (125 MHz, $CDCl_3$)** 18.4 (CH(CH_3)$_A$(*C*H_3)$_B$), 18.7 (CH(*C*H_3)$_A$(CH_3)$_B$), 33.4 (*C*H(CH_3)$_2$), 78.2 (q, *J* 34 Hz, C(3)CF_3), 111.1 (Ar*C*(3b)), 111.7 (Ar*C*(8)H), 121.9 (q, *J* 285 Hz, *C*F_3), 122.5 (Ar*C*(9)H), 122.5 (Ar*C*(3a)),125.5 (Ar*C*(5)H), 128.8 (Ar*C*(6)H), 129.6 (Ar*C*(4)H), 131.3 (Ar*C*(7a)), 134.6 (Ar*C*(7)H), 154.1 (Ar*C*(9a)), 166.5 (*C*(2)=O), 174.0 (*C*(=O)CH(CH_3)$_2$); **δ_F (470 MHz, $CDCl_3$)** –75.3 (C*F*$_3$); ***m/z* (NSI)** 356 ([M+NH_4]$^+$, 100%) $C_{17}H_{13}F_3O_4NH_4^+$ ([M+NH_4]$^+$) requires 356.1104; found 356.1107 (+0.8 ppm).

Lab book Reference: SMS-136

Kinetic resolution of 191



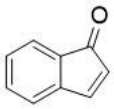
Following general procedure C, **191** (134 mg, 0.5 mmol), isobutyric anhydride (46 µL, 0.3 mmol), (2*S*,3*R*)-HyperBTM **26** (7.7 mg, 0.025 mmol, 5 mol %) and *i*Pr_2NEt (178 µL, 0.5 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C gave, after column chromatography (eluent hexane/Et_2O, 7:3), alcohol (39 mg, 0.15 mmol, 29%) and ester (78 mg, 0.23 mmol, 45%).

Data for alcohol: $[\alpha]_D^{20}$ +41 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 19.0, 23.0 min, 77:23 er; *s* = 4.

Data for ester: $[\alpha]_D^{20}$ +5 (*c* 0.1, $CHCl_3$).

Lab book Reference: SMS-137

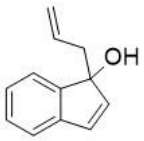
1*H*-Inden-1-one, 195



Following the procedure by Marrocchi,[158] a solution of indan-1-one **194** (1.32 g, 10 mmol), *N*-bromo succinimide (1.79 g, 10 mmol) and AIBN (13.5 mg, 0.08 mmol) in benzene (20 mL) was refluxed under a N_2 atmosphere for 2.5 h. This solution was then cooled, the succinimide removed by filtration and the crude solution concentrated *in vacuo* to give, after column chromatography (Petrol:Et_2O, 85:15, R_F 0.34), 3-bromoindanone. Then, following the procedure by Suryanarayan,[159] 3-bromoindanone was dissolved in Et_2O (20 mL) and Et_3N (4.2 mL, 57 mmol) was added dropwise at RT over 10 mins and the reaction stirred for 1 h. On completion, the reaction was quenched with cold H_2O. The organic layer was separated, washed with 1M HCl (3 x 10 mL), brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo to give **195** as a dark brown oil, without further need for purification (680 mg, 5.2 mmol, 52%); **δ_H (400 MHz, $CDCl_3$)** 5.80 (1H, d, *J* 5.9 Hz, C(2)*H*), 6.98 (1H, d, *J* 7.1 Hz, C(4)*H*), 7.12-7.18 (1H, m, C(6)*H*), 7.23-7.29 (1H, m, C(5)*H*), 7.32-7.36 (1H, m, C(7)*H*), 7.49 (1H, dd, *J* 6.0, 0.8 Hz, C(3)*H*).

Lab book reference: SMS-408

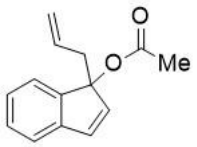
1-Allyl-1*H*-inden-1-ol, 196



Following the procedure by Bisai,[95] **195** (595 mg, 2.0 mmol) was dissolved in anhydrous DMF (5 mL) under an N_2 atmosphere and cooled to 0 °C. Allyltrichlorosilane (434 µL, 3 mmol) was added dropwise over 15 mins and the reaction stirred overnight at RT. The reaction was quenched with H_2O (10 mL) and brine (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined and washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give, after column chromatography (eluent Petrol/Et_2O, 4:1; R_F 0.24), **196** as a pale yellow powder (307 mg, 1.78 mmol, 22%); **ν_{max} (ATR)** 3264 (OH), 1641 (C=C), 1375, 1049, 1032; **δ_H (400 MHz, $CDCl_3$)** 1.92 (1H, s, O*H*), 2.55 (1H, ddt, *J* 13.7, 7.0, 1.2 Hz, C$H_A$$H_B$CH=$CH_2$), 2.73 (1H, ddt, *J* 13.7, 7.7, 1.1 Hz, $CH_A$$H_B$CH=$CH_2$), 5.06-5.16 (2H, m, CH_2CH=CH_2), 5.80 (1H, ddt, *J* 17.2, 10.2, 7.3 Hz, CH_2C*H*=CH_2), 6.31 (1H, d, *J* 5.7 Hz, ArC(2)*H*), 6.66 (1H, dd, *J* 5.7, 0.5 Hz, ArC(3)*H*), 7.16-7.28 (3H, m, ArC*H*), 7.37-7.41 (1H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 42.2 (*C*H_2CH=CH_2), 84.0 (*C*(1)), 118.8 (CH_2CH=*C*H_2), 121.6 (Ar*C*H), 122.1 (Ar*C*H), 126.3 (Ar*C*H), 128.6 (Ar*C*H), 131.3 (Ar*C*(3)H), 133.4 (CH_2*C*H=CH_2), 141.1 (Ar*C*(2)H), 141.9 (Ar*C*(7a)), 148.9 (Ar*C*(3a)); ***m/z* (EI+)** 172 ([M], 100%) $C_{12}H_{12}O$ ([M]) requires 172.0888; found 172.0892 (+2.3 ppm).

Lab book Reference: SMS-425

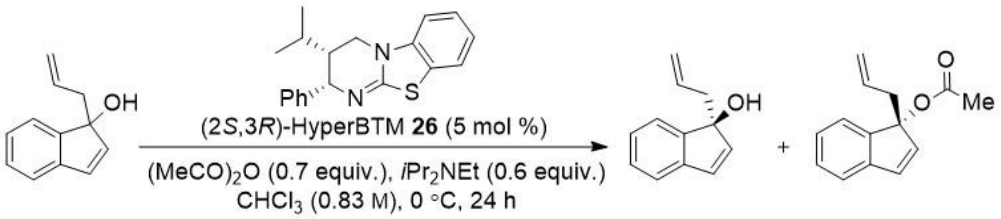
1-Allyl-1H-inden-1-yl acetate, 197



Following general procedure B, **196** (28 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (0.4 mL) gave, after column chromatography (eluent Petrol/Et_2O, 4:1; R_F 0.49), **197** as an yellow oil (36 mg, 0.13 mmol, 81%); **ν_{max} (ATR)** 3073, 1732 (C=O), 1641 (C=C), 1431, 1366, 1229, 1011; **δ_H (400 MHz, $CDCl_3$)** 2.02 (3H, s, CH_3), 2.76 (1H, ddt, *J* 13.8, 7.1, 1.2 Hz, C$H_A$$H_B$CH=$CH_2$), 2.90 (1H, ddt, *J* 13.8, 7.3, 1.1 Hz, $CH_A$$H_B$CH=$CH_2$), 4.99-5.10 (2H, m, CH_2CH=CH_2), 5.65 (1H, ddt, *J* 17.5, 10.3, 7.2 Hz, CH_2C*H*=CH_2), 6.57 (1H, d, *J* 5.7 Hz, ArC(2)*H*), 6.73 (1H, d, *J* 5.7 Hz, ArC(3)*H*), 7.14-7.30 (3H, m, ArC*H*), 7.35-7.43 (1H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 21.8 (*C*H_3), 40.0 (*C*H_2CH=CH_2), 89.7 (*C*(1)), 118.8 (CH_2CH=*C*H_2), 121.7 (Ar*C*H), 122.5 (Ar*C*H), 126.1 (Ar*C*H), 128.7 (Ar*C*H), 132.2 (CH_2*C*H=CH_2), 132.5 (Ar*C*(3)H), 137.3 (Ar*C*(2)H), 142.0 (Ar*C*(7a)), 145.0 (Ar*C*(3a)), 169.9 (*C*=O); ***m/z* (NSI)** 232 ([M+NH_4]$^+$, 100%) $C_{14}H_{18}NO_2^+$ ([M+NH_4]$^+$) requires 232.1332; found 232.1333 (+0.4 ppm).

Lab book Reference: SMS-431

Kinetic resolution of 196



Following general procedure C, **196** (86 mg, 0.5 mmol), acetic anhydride (34 µL, 0.35 mmol), (2*S*,3*R*)-HyperBTM **26** (8 mg, 0.025 mmol, 5 mol %) and *i*Pr_2NEt (52 µL, 0.3 mmol) in $CHCl_3$ (0.6 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 4:1), alcohol (26 mg, 0.15 mmol, 30%) and ester (54 mg, 0.26 mmol, 51%).

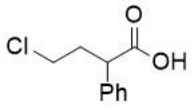
Data for alcohol: $[\alpha]_D^{20}$ +11 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 5.2, 6.2 min, 87:13 er.

Data for ester: $[\alpha]_D^{20}$ –7 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak IB (0.1% *i*PrOH:hexane, flow rate 1.5 mL min^{-1}, 254 nm, 30 °C) T_R: 6.0, 6.4 min, 70:30 er; *s* = 5.

Lab book Reference: SMS-438

6.4 Data for Chapter 3: Kinetic resolution of 3-hydroxypyrrolidinones

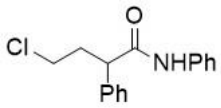
4-Chloro-2-phenylbutanoic acid, 207



Following general procedure G, *n*BuLi (4.4 mL, 11 mmol, 2.5 M in hexanes), HN^iPr_2 (1.55 mL, 11 mmol), phenylacetic acid (1.02 g, 5 mmol) and 1-bromo-2-chloroethane (914 µL, 11 mmol) in anhydrous THF (25 mL) gave **207** as an orange solid (893 mg, 4.85 mmol, 97%). The crude was taken on without further purification; **δ_H (400 MHz, $CDCl_3$)** 2.17-2.29 (1H, m, C(3)H_AH_B), 2.45-2.57 (1H, m, C(3)H_AH_B), 3.36 (1H, ddd, *J* 11.1, 8.2, 5.3 Hz, C(4)H_AH_B), 3.55 (1H, dt, *J* 11.5, 5.9 Hz, C(4)H_AH_B), 3.92 (1H, dd, *J* 8.2, 7.0 Hz, C(4)H_AH_B), 7.27-7.41 (5H, m, ArC*H*).

Lab book Reference: SMS-512

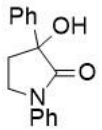
4-Chloro-*N*,2-diphenylpropanamide, 208



Following general procedure H, **207** (990 mg, 5 mmol), 1,1'-carbonyldiimidazole (770 mg, 4.75 mmol) and aniline (449 µL, 6 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.26), **208** as a pale yellow solid (683 mg, 2.60 mmol, 53%), mp 102-104 °C; **ν_{max} (ATR)** 3258 (NH), 2953, 1661 (C=O), 1597 (C=C), 1543, 1443, 1329; **δ_H (400 MHz, $CDCl_3$)** 2.28 (1H, dddd, *J* 14.5, 7.8, 6.8, 4.9 Hz, C(3)H_AH_B), 2.70 (1H, dddd, *J* 14.5, 7.8, 6.8, 4.9 Hz, C(3)H_AH_B), 3.44 (1H, ddd, *J* 11.1, 8.0, 4.5 Hz, C(4)H_AH_B), 3.65 (1H, ddd, *J* 11.5, 6.7, 5.0 Hz, C(4)H_AH_B), 3.92 (1H, t, *J* 7.4 Hz, C(2)*H*), 7.07-7.14 (1H, m, NHArC(4)*H*), 7.26-7.50 (9H, m, Ar*C*H); **δ_C (100 MHz, $CDCl_3$)** 35.7 (*C*(3)H), 43.2 (*C*(4)H), 50.5 (*C*(2)H), 120.0 (NHAr*C*(3,5)H), 124.5 (NHAr*C*(4)H),127.9 (C(2)Ar*C*(4)H), 128.1 (NHAr*C*(2,6)H), 129.0 (C(2)Ar*C*(3,5)H), 129.3 (C(2)Ar*C*(2,6)H), 137.7 (NHArC(1)), 138.3 (C(2)ArC(1)), 172.4 (*C*=O); ***m/z* (NSI)** 274 ($[M+H]^+$, 100%) $C_{16}H_{17}ONCl^+$ ($[M+H]^+$) requires 274.0993; found 274.0995 (+0.7 ppm).

Lab book Reference: SMS-535

3-Hydroxy-1,3-diphenylpyrrolidin-2-one, 209

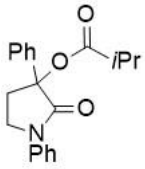


Following general procedure I, **208** (683 mg, 2.6 mmol) and NaH (530 mg, 13.23 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.32), **209** as a yellow solid (208 mg, 0.83 mmol, 32%), mp 81-83 °C; **ν_{max} (ATR)** 3358 (OH), 3059, 1676 (C=O), 1591, 1489, 1292; **δ_H (400 MHz, $CDCl_3$)** 2.50-2.63 (2H, m, C(4)*H*), 3.73 (1H, ddd, *J* 9.7, 8.2, 7.0 Hz,

C(5)H_AH_B), 3.86 (1H, ddd, *J* 9.8, 7.9, 3.4 Hz, C(5)H_AH_B), 4.26 (1H, s O*H*), 7.21-7.27 (1H, m, ArC*H*), 7.29-7.39 (3H, m, ArC*H*), 7.40-7.49 (4H, m, ArC*H*), 7.70-7.77 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 35.4 (*C*(4)H), 44.5 (*C*(5)H), 79.4 (*C*(3)), 119.9 (NAr*C*(2,6)H), 125.2 (NAr*C*(4)H), 125.3 (C(3)Ar*C*(2,6)H), 128.1 (C(3)Ar*C*(4)H), 128.7 (C(3)Ar*C*(3,5)H), 129.0 (NAr*C*(3,5)H), 139.0 (NAr*C*(1)), 142.0 (C(3)Ar*C*(1)), 174.7 (*C*=O); ***m/z*** **(NSI)** 254 ([M+H]$^+$, 100%) $C_{16}H_{16}O_2N^+$ ([M+H]$^+$) requires 254.1176; found 254.1175 (–0.2 ppm).

Lab book Reference: SMS-556

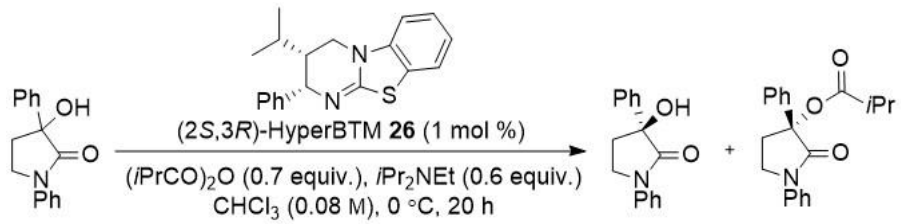
2-Oxo-1,3-diphenylpyrrolidin-3-yl propionate, 210



Following general procedure B, **209** (41 mg, 0.16 mmol), isobutyric anhydride (41 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.76), **210** as a clear oil (45 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2970, 1736 (C=O), 1697 (C=O), 1597, 1499, 1400, 1146; **δ_H (400 MHz, $CDCl_3$)** 1.24 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH$_3$)$_B$), 1.25 (3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$), 2.72 (1H, hept, *J* 7.0 Hz, C*H*(CH$_3$)$_2$), 2.86-2.96 (1H, m, C(4)*H*), 3.89 (1H, dt, *J* 9.6, 8.0 Hz, C(5)H_AH_B), 4.04 (1H, ddd, *J* 9.6, 7.1, 5.0 Hz, C(5)H_AH_B), 7.14-7.20 (1H, m, NArC(4)*H*), 7.32-7.42 (5H, m, C(3)ArC(3,4,5)*H*, NArC(3,5)*H*), 7.53-7.57 (2H, m, C(3)ArC(2,6)*H*), 7.65-7.76 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.82 (CH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.85 (CH(CH$_3$)$_A$(*C*H$_3$)$_B$), 30.9 (*C*(4)H), 34.2 (*C*H(CH$_3$)$_2$), 44.6 (*C*(5)H), 83.2 (*C*(3)), 120.0 (NAr*C*(2,6)H), 125.1 (C(3)Ar*C*(4)H), 125.3 (C(3)Ar*C*(2,6)H), 128.6 (NAr*C*(4)H), 128.8 (C(3)Ar*C*(3,5)H), 128.9 (NAr*C*(3,5)H), 138.7 (NAr*C*(1)), 139.7 (C(3)Ar*C*(1)), 170.6 (*C*(2)=O), 176.1 (*C*(=O)CH(CH$_3$)$_2$); ***m/z*** **(NSI)** 324 ([M+H]$^+$, 100%) $C_{18}H_{18}NO_3^+$ ([M+H]$^+$) requires 324.1594; found 324.1596 (+0.6 ppm).

Lab book Reference: SMS-567

Kinetic resolution of 209



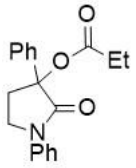
Following general procedure C, **209** (51 mg, 0.2 mmol), isobutyric anhydride (23 µL, 0.14 mmol), (2*S*,3*R*)-HyperBTM **26** (0.6 mg, 0.002 mmol, 1 mol %) and *i*Pr_2NEt (21 µL, 0.12 mmol) in $CHCl_3$ (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (47 mg, 0.18 mmol, 92%) and ester (1 mg, 0.004 mmol, 2%).

Data for alcohol: $[\alpha]_D^{20}$ +7 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.3, 27.5 min, 52:48 er.

Data for ester: $[\alpha]_D^{20}$ +15 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.2, 26.6 min, 97:3 er; *s* = 35.

Lab book Reference: SMS-909

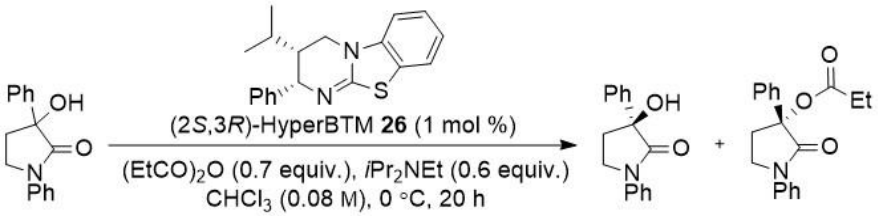
2-Oxo-1,3-diphenylpyrrolidin-3-yl propionate, 211



Following general procedure B, **209** (41 mg, 0.16 mmol), propionic anhydride (30 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.76), **211** as a brown oil (39 mg, 0.13 mmol, 78%); **ν_{max} (ATR)** 2980, 1740 C=O), 1703 (C=O), 1597, 1494, 1400; **δ_H (400 MHz, $CDCl_3$)** 1.19 (3H, t, *J* 7.5 Hz, CH_2CH_3), 2.42-2.59 (2H, m, CH_2CH_3), 2.86-2.99 (2H, m, C(4)*H*), 3.89 (1H, dt, *J* 9.6, 8.0 Hz, C(5)H_AH_B), 4.03 (1H, td, *J* 9.2, 3.3 Hz, C(5)H_AH_B), 7.15-7.20 (1H, m, NArC(4)*H*), 7.31-7.42 (5H, m, C(3)ArC(3,4,5)*H*, NArC(3,5)*H*), 7.53-7.58 (2H, m, C(3)ArC(2,6)*H*), 7.65-7.71 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 8.9 (CH_2CH_3), 27.9 (CH_2CH_3), 31.0 (*C*(4)H), 44.7 (*C*(5)H), 83.4 (*C*(3)), 120.0 (NAr*C*(2,6)H), 125.2 (C(3)Ar*C*(4)H), 125.3 (C(3)Ar*C*(2,6)H), 128.6 (NAr*C*(4)H), 128.8 (C(3)Ar*C*(3,5)H), 128.9 (NAr*C*(3,5)H), 138.5 (NAr*C*(1)), 139.1 (C(3)Ar*C*(1)), 170.0 (*C*(2)=O), 173.5 (*C*(=O)$CH(CH_3)_2$); ***m/z* (NSI)** 310 ($[M+H]^+$, 100%) $C_{19}H_{20}NO_3^+$ ($[M+H]^+$) requires 310.1438; found 310.1439 (+0.4 ppm).

Lab book Reference: SMS-904

Kinetic resolution of 209



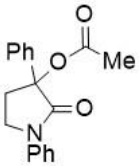
Following general procedure C, **209** (51 mg, 0.2 mmol), propionic anhydride (18 µL, 0.14 mmol), (2*S*,3*R*)-HyperBTM **26** (0.6 mg, 0.002 mmol, 1 mol %) and *i*Pr_2NEt (21 µL, 0.12 mmol) in $CHCl_3$ (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (42 mg, 0.17 mmol, 83%) and ester (7 mg, 0.02 mmol, 11%).

Data for alcohol: $[\alpha]_D^{20}$ +17 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.3, 27.6 min, 57:43 er.

Data for ester: $[\alpha]_D^{20}$ +6 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.2, 40.2 min, 97:3 er; *s* = 35.

Lab book Reference: SMS-913

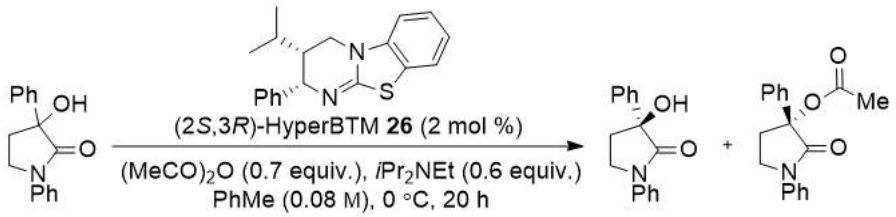
2-Oxo-1,3-diphenylpyrrolidin-3-yl acetate, 212



Following general procedure B, **209** (41 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.62), **212** as a clear oil (41 mg, 0.14 mmol, 86%); **ν_{max} (ATR)** 3055, 1740 (C=O), 1701 (C=O), 1495, 1371, 1223; **δ_H (400 MHz, $CDCl_3$)** 2.20 (3H, s, CH_3), 2.87-3.01 (2H, m, C(4)*H*), 3.88 (1H, dt, *J* 9.6, 8.0 Hz, C(5)H_AH_B), 4.01 (1H, td, *J* 9.2, 3.0 Hz, C(5)H_AH_B), 7.15-7.21 (1H, m, ArC*H*), 7.31-7.42 (5H, m, ArC*H*), 7.53-7.59 (2H, m, ArC*H*), 7.65-7.71 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 30.9 (*C*(4)H), 44.7 (*C*(5)H), 83.7 (*C*(3)), 120.0 (NAr*C*(2,6)H), 125.2 (NAr*C*(4)H), 125.4 (C(3)Ar*C*(2,6)H), 128.7 (C(3)Ar*C*(4)H), 128.8 (C(3)Ar*C*(3,5)H), 128.9 (NAr*C*(3,5)H), 138.2 (NAr*C*(1)), 139.1 (C(3)Ar*C*(1)), 169.9 (*C*(=O)CH_3), 170.0 (*C*(2)=O); ***m/z* (NSI)** 296 ($[M+H]^+$, 100%) $C_{18}H_{18}NO_3^+$ ($[M+H]^+$) requires 296.1281; found 296.1283 (+0.6 ppm).

Lab book Reference: SMS-592

Kinetic resolution of 209



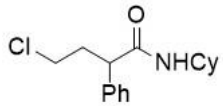
Following general procedure C, **209** (51 mg, 0.2 mmol), acetic anhydride (14 µL, 0.14 mmol), (2*S*,3*R*)-HyperBTM **26** (1.2 mg, 0.004 mmol, 2 mol %) and *i*Pr_2NEt (21 µL, 0.12 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (25 mg, 0.12 mmol, 49%) and ester (27 mg, 0.09 mmol, 38%).

Data for alcohol: $[\alpha]_D^{20}$ +151 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.2, 27.7 min, 88:12 er.

Data for ester: $[\alpha]_D^{20}$ +14 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 31.3, 37.5 min, 99:1 er; *s* = 180.

Lab book Reference: SMS-629

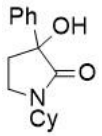
4-Chloro-*N*-cyclohexyl-2-phenylbutanamide, 213



Following general procedure H, **207** (990 mg, 5 mmol), 1,1'-carbonyldiimidazole (770 mg, 4.75 mmol) and cyclohexylamine (449 µL, 6 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.26), **213** as a white solid (995 mg, 3.55 mmol, 71%), mp 95-97 °C; **ν_{max} (ATR)** 3290 (NH), 2930, 1634 (C=O), 1545 (C=C), 1445, 1244; **δ_H (400 MHz, $CDCl_3$)** 0.87-1.17 (3H, m, cyclohexyl-C*H*), 1.22-1.40 (2H, m, cyclohexyl-C*H*), 1.52-1.70 (3H, m, cyclohexyl-C*H*), 1.72-1.80 (1H, m, cyclohexyl-C*H*), 1.85-1.94 (1H, m, cyclohexyl-C*H*), 2.18 (1H, dtd, *J* 14.6, 7.1, 5.0 Hz, C(3)H_AH_B), 2.59 (1H, dtd, *J* 14.7, 7.5, 5.1 Hz, C(3)H_AH_B), 3.41 (1H, ddd, *J* 11.0, 7.7, 5.0 Hz, C(4)H_AH_B), 3.57 (1H, ddd, *J* 11.1, 7.5, 5.0 Hz, C(4)H_AH_B), 3.62 (1H, t, *J* 7.4 Hz, C(2)*H*), 3.73 (1H, dddd, *J* 14.6, 10.7, 8.1, 3.9 Hz, NH-cyclohexyl-C(1)*H*), 5.28 (1H, d, *J* 7.7 Hz, N*H*), 7.25-7.37 (5H, m, Ar*C*H); **δ_C (100 MHz, $CDCl_3$)** 24.7 (NH-cyclohexyl-C(2)H), 24.8 (NH-cyclohexyl-C(6)H), 25.5 (NH-cyclohexyl-C(4)H), 32.8 (NH-cyclohexyl-C(3)H), 33.0 (NH-cyclohexyl-C(5)H), 35.9 (*C*(3)H), 43.3 (*C*(4)H), 48.4 (NH-cyclohexyl-C(1)H), 49.7 (*C*(2)H), 127.5 (Ar*C*(4)H), 128.0 (Ar*C*(2,6)H), 129.0 (Ar*C*(3,5)H), 139.0 (ArC(1)), 171.4 (*C*=O); ***m/z* (NSI)** 280 ($[M+H]^+$, 100%) $C_{16}H_{23}ONCl^+$ ($[M+H]^+$) requires 280.1463; found 280.1465 (+0.8 ppm).

Lab book Reference: SMS-539

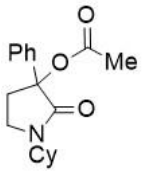
1-Cyclohexyl-3-hydroxy-3-phenylpyrrolidin-2-one, 214



Following general procedure I, **213** (995 mg, 3.55 mmol) and NaH (710 mg, 17.8 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOA,c 9:1; R_F 0.35), **214** a white solid (565 mg, 2.18 mmol, 62%), mp 108-110 °C; **ν_{max} (ATR)** 3350 (OH), 2934, 1663 (C=O), 1653, 1283, 1260; **δ_H (400 MHz, $CDCl_3$)** 1.01-1.16 (1H, m, N-cyclohexyl-C*H*), 1.28-1.46 (4H, m, N-cyclohexyl-C*H*), 1.60-1.85 (5H, m, N-cyclohexyl-C*H*), 2.23-2.38 (2H, m, C(4)*H*), 3.15 (1H, dt, *J* 9.8, 7.4 Hz, C(5)H_AH_B), 3.35 (1H, ddd, *J* 9.8, 8.3, 3.2 Hz, C(5)H_AH_B), 3.95 (1H, ddt, *J* 11.5, 7.5, 3.7 Hz, N-cyclohexyl-C(1)*H*), 4.48 (1H, s, O*H*), 7.17-7.28 (3H, m, ArC*H*), 7.30-7.35 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 25.35 (N-cyclohexyl-*C*(2)H), 25.41 (N-cyclohexyl-*C*(4,6)H), 29.7 (N-cyclohexyl-*C*(3)H), 30.5 (N-cyclohexyl-*C*(5)H), 36.4 (*C*(4)H), 39.3 (*C*(5)H), 51.3 (N-cyclohexyl-*C*(1)H), 79.0 (*C*(3)), 125.1 (Ar*C*(2,6)H), 127.5 (Ar*C*(4)H), 128.3 (Ar*C*(3,5)H), 142.8 (Ar*C*(1)), 174.4 (*C*=O); ***m/z* (NSI)** 260 ($[M+H]^+$, 100%) $C_{16}H_{22}O_2N^+$ ($[M+H]^+$) requires 260.1645; found 260.1646 (+0.4 ppm).

Lab book Reference: SMS-563

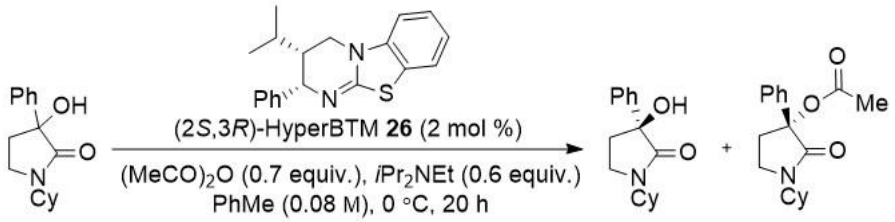
1-Cyclohenxyl-2-oxo-3-phenylpyrrolidin-3-yl acetate, 215



Following general procedure B, **214** (42 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.44), **215** as a clear oil (33 mg, 0.11 mmol, 71%); **ν_{max} (ATR)** 2930, 1738 (C=O), 1694 (C=O), 1429, 1287, 1231; **δ_H (400 MHz, $CDCl_3$)** 1.04-1.17 (1H, m, N-cyclohexyl-C*H*), 1.28-1.53 (4H, m, N-cyclohexyl-C*H*), 1.62-1.71 (2H, m, N-cyclohexyl-C*H*), 1.74-1.90 (3H, m, N-cyclohexyl-C*H*), 2.16 (3H, s, CH_3), 2.64-2.78 (2H, m, C(4)*H*), 3.36 (1H, dt, *J* 9.6, 7.7 Hz, C(5)H_AH_B), 3.57 (1H, td, *J* 9.3, 3.3 Hz, C(5)$H_A$$H_B$), 3.97 (1H, ddd, *J* 11.5, 9.3, 3.5 Hz, N-cyclohexyl-C(1)*H*), 7.28-7.39 (3H, m, ArC*H*), 7.44-7.49 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 25.3 (N-cyclohexyl-*C*(2)H), 25.4 (N-cyclohexyl-*C*(4)H), 25.5 (N-cyclohexyl-*C*(6)H), 29.3 (N-cyclohexyl-*C*(3)H), 30.3 (N-cyclohexyl-*C*(5)H), 32.0 (*C*(4)H), 39.5 (*C*(5)H), 51.4 (N-cyclohexyl-*C*(1)H), 84.0 (*C*(3)), 125.0 (Ar*C*(2,6)H), 128.3 (Ar*C*(4)H), 128.6 (Ar*C*(3,5)H), 139.4 (Ar*C*(1)), 169.9 (*C*(=O)CH_3), 170.0 (*C*(2)=O); ***m/z* (NSI)** 302 ($[M+H]^+$, 100%) $C_{18}H_{24}NO_3^+$ ($[M+_4]^+$) requires 302.1751; found 302.1752 (+0.4 ppm).

Lab book Reference: SMS-594

Kinetic resolution of 214



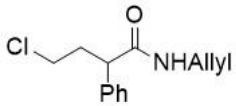
Following general procedure C, **214** (62 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.14 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (50 mg, 0.19 mmol, 80%) and ester (11 mg, 0.04 mmol, 15%).

Data for alcohol: $[\alpha]_D^{20}$ +72 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 27.1, 32.4 min, 60:40 er.

Data for ester: $[\alpha]_D^{20}$ +28 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.5, 42.7 min, 99:1 er; *s* = 70.

Lab book Reference: SMS-920

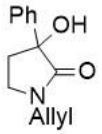
_N_-Allyl-4-chloro-2-phenylbutanamide, 216



Following general procedure H, **207** (990 mg, 5 mmol), 1,1'-carbonyldiimidazole (770 mg, 4.75 mmol) and allylamine (449 µL, 6 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 4:1; R_F 0.27), **216** as a white solid (863 mg, 3.87 mmol, 78%), mp 65-67 °C; **ν_{max} (ATR)** 3264 (NH), 3086, 1649 (C=O), 1634 (C=C), 1566, 1425; **δ_H (400 MHz, $CDCl_3$)** 2.21 (1H, dddd, *J* 14.6, 7.8, 6.9, 5.0 Hz, C(3)H_AH_B), 2.63 (1H, dddd, *J* 14.6, 7.8, 6.9, 5.0 Hz, C(3)H_AH_B), 3.41 (1H, ddd, *J* 11.0, 7.8, 5.0 Hz, C(4)H_AH_B), 3.59 (1H, ddd, *J* 11.0, 6.8, 5.1 Hz, C(4)H_AH_B), 3.75 (1H, t, *J* 7.5 Hz, C(2)*H*), 3.78-3.92 (2H, m, NHCH_2CH=CH_2), 5.00-5.09 (2H, m, NHCH_2CH=CH_2), 5.77 (1H, ddt, *J* 17.0, 10.7, 5.4 Hz, NHCH_2C*H*=CH_2), 7.28-7.40 (5H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 35.7 (*C*(3)H), 41.9 (NH*C*H_2CH=CH_2), 43.2 (*C*(4)H), 49.6 (*C*(2)H), 116.1 (NHCH_2CH=*C*H_2), 127.7 (Ar*C*(4)H), 128.1 (Ar*C*(3,5)H), 129.1 (Ar*C*(2,6)H), 134.1 (NHCH_2*C*H=CH_2), 138.8 (ArC(1)), 172.4 (*C*=O); ***m/z* (NSI)** 238 ($[M+H]^+$, 100%) $C_{13}H_{17}ONCl^+$ ($[M+H]^+$) requires 238.0993; found 238.0997 (+1.5 ppm).

Lab book Reference: SMS-534

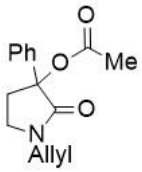
1-Allyl-3-hydroxy-3-phenylpyrrolidin-2-one, 217



Following general procedure I, **216** (863 mg, 3.87 mmol) and NaH (774 mg, 19.35 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.12), **217** as a white solid (362 mg, 1.67 mmol, 43%), mp 68-70 °C; **ν_{max} (ATR)** 3321 (OH), 2990, 1676 (C=O), 1643, 1443, 1271; **δ_H (400 MHz, $CDCl_3$)** 2.26-2.44 (2H, m, C(4)*H*), 3.23 (1H, dt, *J* 9.9, 7.2 Hz, C(5)H_AH_B), 3.34 (1H, ddd, *J* 9.9, 8.3, 3.9 Hz, C(5)H_AH_B), 3.86 (1H, dd, *J* 15.1, 6.1 Hz, NCH_AH_BCH=CH_2), 3.98 (1H, dd, *J* 15.1, 6.1 Hz, NCH_AH_BCH=CH_2), 4.70 (1H, s O*H*), 5.18-5.24 (2H, m, NCH_2CH=CH_2), 5.73 (1H, ddt, *J* 17.2, 9.8, 6.1 Hz, NCH_2C*H*=CH_2), 7.21-7.32 (3H, m, ArC*H*), 7.34-7.39 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 36.2 (*C*(4)H), 43.1 (*C*(5)H), 45.8 (N*C*H_2CH=CH_2), 78.7 (*C*(3)), 118.5 (NCH_2CH=*C*H_2), 125.2 (Ar*C*(2,6)H), 127.6 (Ar*C*(4)H), 128.4 (Ar*C*(3,5)H), 131.9 (NCH_2*C*H=CH_2), 142.7 (Ar*C*(1)), 174.9 (*C*=O); ***m/z* (NSI)** 218 ($[M+H]^+$, 100%) $C_{13}H_{16}O_2N^+$ ($[M+H]^+$) requires 218.1176; found 218.1172 (–1.6 ppm).

Lab book Reference: SMS-554

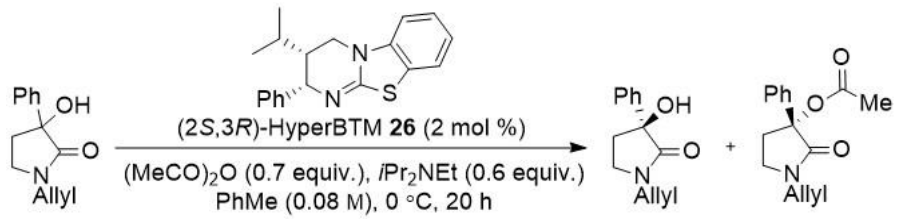
1-Allyl-2-oxo-3-phenylpyrrolidin-3-yl acetate, 218



Following general procedure B, **217** (35 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2.0 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.39 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent Petrol/Et_2O, 7:3; R_F 0.32), **218** as a clear oil (31 mg, 0.12 mmol, 75%); **ν_{max} (ATR)** 2982, 1738 (C=O), 1697 (C=O), 1643 (C=C), 1493, 1368, 1275; **δ_H (400 MHz, $CDCl_3$)** 2.17 (3H, s, CH_3), 2.76 (1H, td, *J* 7.6, 3.4 Hz, C(4)*H*), 3.40 (1H, dt, *J* 9.8, 7.7 Hz, C(5)H_AH_B), 3.53 (1H, ddd, *J* 9.8, 7.9, 4.6 Hz, C(5)H_AH_B), 3.92 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.00 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.19-5.28 (2H, m, CH_2CH=CH_2), 5.75 (1H, ddt, *J* 17.1, 10.2, 6.0 Hz, NCH_2CH=CH_2), 7.29-7.41 (3H, m, ArC*H*), 7.47-7.51 (2H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 31.7 (*C*(4)H), 43.1 (*C*(5)H), 46.0 (N*C*H_2CH=CH_2), 83.4 (*C*(3)), 118.5 (NCH_2CH=*C*H_2), 125.1 (Ar*C*(2,6)H), 128.4 (Ar*C*(4)H), 128.7 (Ar*C*(3,5)H), 131.7 (NCH_2*C*H=CH_2), 139.1 (Ar*C*(1)), 170.0 (*C*(=O)CH_3), 170.5 (*C*(2)=O); ***m/z* (NSI)** 260 ($[M+H]^+$, 100%) $C_{15}H_{18}NO_3^+$ ($[M+H]^+$) requires 260.1281; found 260.1283 (+0.7 ppm).

Lab book Reference: SMS-581

Kinetic resolution of 217



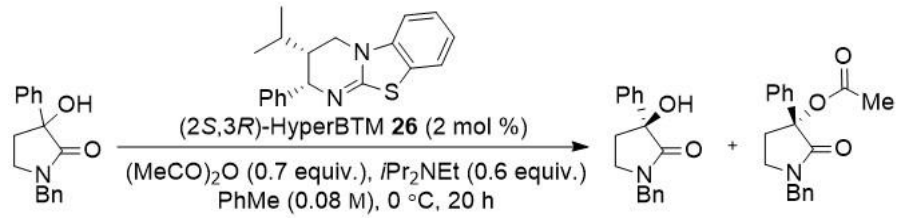
Following general procedure C, **217** (52 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.14 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (27 mg, 0.12 mmol, 52%) and ester (24 mg, 0.09 mmol, 39%).

Data for alcohol: $[\alpha]_D^{20}$ +31 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.9, 23.7 min, 87:13 *er.*

Data for ester: $[\alpha]_D^{20}$ +105 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.8, 26.6 min, 98:2 er; *s* = 110.

Lab book Reference: SMS-658

Kinetic resolution of 220



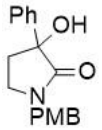
Following general procedure C, **220** (71 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.14 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (31 mg, 0.12 mmol, 48%) and ester (30 mg, 0.10 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +78 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 36.8, 40.3 min, 90:10 er.

Data for ester: $[\alpha]_D^{20}$ +103 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.5, 34.1 min, 98:2 er; *s* = 110.

Lab book Reference: SMS-657

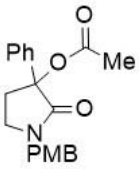
3-Hydroxy-1-(4-methoxybenzyl)-3-phenylpyrrolidin-2-one, 223



Following general procedure H, **207** (550 mg, 2.78 mmol), 1,1'-carbonyldiimidazole (428 mg, 2.64 mmol) and 4-methoxybenzylamine (435 µL, 3.33 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3; R_F 0.32), an inseparable mixture of 4-chloro-*N*-(4-methoxybenzyl)-2-phenylbutanamide **222** and 3-phenyldihydrofuran-2(3H)-one (1.0:0.7, 550 mg, (amide: 323 mg, 1.02 mmol)). Following general procedure I, this mixture and NaH (204 mg, 5.1 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.11), **223** as a white solid (105 mg, 0.35 mmol, 35%), mp 120-122 °C; **ν_{max} (ATR)** 3401 (OH), 2953, 1674 (C=O), 1610 (C=C), 1514, 1296, 1240; **δ_H (400 MHz, $CDCl_3$)** 2.32-2.45 (2H, m, C(4)*H*), 3.17 (1H, dt, *J* 10.0, 7.4 Hz, C(5)H_AH_B), 3.29 (1H, ddd, *J* 9.9, 8.4, 3.4 Hz, C(5)H_AH_B), 3.33 (1H, s, O*H*), 3.81 (3H, s, ArOCH_3), 4.48 (1H, d, *J* 14.4 Hz, NCH_AH_BAr), 4.54 (1H, d, *J* 14.4 Hz, NCH_AH_BAr), 6.86-6.91 (2H, m, NCH_2ArC(3,5)*H*), 7.19-7.24 (2H, m, NCH_2ArC(2,6)*H*), 7.26-7.39 (5H, m, C(3)Ar*CH*); **δ_C (100 MHz, $CDCl_3$)** 35.8 (*C*(4)H), 42.7(*C*(5)H), 46.7 (NCH_2Ar), 55.3 (OCH_3), 78.7 (C(3)), 114.2 (NCH_2Ar*C*(3,5)H), 125.0 (C(3)Ar*C*(2,6)H), 127.8 (NCH_2Ar*C*(1)), 127.9 (C(3)Ar*C*(4)H), 128.6 (C(3)Ar*C*(3,5)H), 129.7 (NCH_2Ar*C*(2,6)H), 142.5 (C(3)Ar*C*(1)), 159.3 (NCH_2Ar*C*(4)), 174.8 (*C*=O); ***m/z* (NSI)** 298 ($[M+H]^+$, 100%) $C_{18}H_{20}O_3N^+$ ($[M+H]^+$) requires 298.1438; found 298.1439 (+0.4 ppm).

Lab book Reference: SMS-574

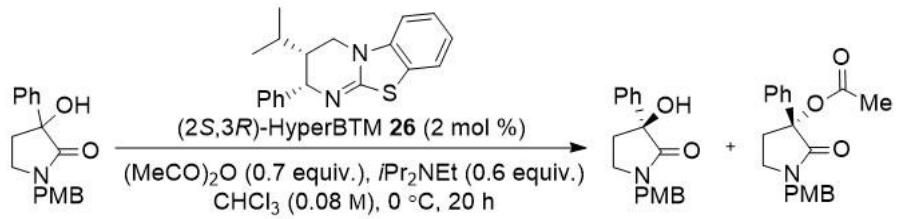
1-(4-Methoxybenzyl)-2-oxo-3-phenylpyrrolidin-3-yl acetate, 224



Following general procedure B, **223** (30 mg, 0.10 mmol), acetic anhydride (13 µL, 0.13 mmol), DMAP **4** (1.3 mg, 0.010 mmol, 10 mol %) and *i*Pr_2NEt (44 µL, 0.24 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.45), **224** as a clear oil (20 mg, 0.06 mmol, 61%); **ν_{max} (ATR)** 2934, 1738 (C=O), 1697 (C=O), 1611, 1512, 1231; **δ_H (500 MHz, $CDCl_3$)** 2.19 (3H, s, CH_3), 2.66-2.78 (2H, m, C(4)*H*), 3.26 (1H, dt, *J* 9.7, 7.3 Hz, C(5)H_AH_B), 3.40 (1H, td, *J* 9.6, 2.7 Hz, C(5)H_AH_B), 3.80 (3H, s, ArOCH_3), 4.39 (1H, d, *J* 14.6 Hz, NCH_AH_BAr), 4.53 (1H, d, *J* 14.6 Hz, NCH_AH_BAr), 6.84-6.88 (2H, m, NCH_2ArC(3,5)*H*), 7.15-7.20 (2H, m, NCH_2ArC(2,6)*H*), 7.31-7.40 (3H, m, C(3)ArC*H*), 7.46-7.50 (2H, m, C(3)ArC*H*); **δ_C (125 MHz, $CDCl_3$)** 21.6 (*C*H_3), 31.4 (*C*(4)H), 42.7 (*C*(5)H), 46.7 (N*C*H_2Ar), 55.3 (O*C*H_3), 83.4 (C(3)), 114.1 (NCH_2Ar*C*(3,5)H), 125.1 (C(3)Ar*C*(2,6)H), 127.8 (NCH_2Ar*C*(1)), 128.4 (C(3)Ar*C*(4)H), 128.7 (C(3)Ar*C*(3,5)H), 129.5 (NCH_2Ar*C*(2,6)H), 139.1 (C(3)Ar*C*(1)), 159.2 (NCH_2Ar*C*(4)), 170.0 (*C*(=O)CH_3), 170.6 (*C*(2)=O); ***m/z* (NSI)** 340 ($[M+H]^+$, 100%) $C_{20}H_{22}NO_4^+$ ($[M+H]^+$) requires 340.1543; found 340.1543 (–0.1 ppm).

Lab book Reference: SMS-596

Kinetic resolution of 223



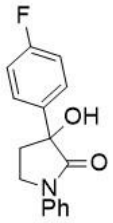
Following general procedure C, **223** (71 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.14 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (43 mg, 0.15 mmol, 61%) and ester (22 mg, 0.06 mmol, 27%).

Data for alcohol: $[\alpha]_D^{20}$ +144 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 22.1, 28.2 min, 69:31 er.

Data for ester: $[\alpha]_D^{20}$ +21 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 30.3, 51.3 min, 95:5 er; *s* = 28.

Lab book Reference: SMS-603

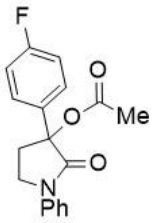
3-(4-Fluorophenyl)-3-hydroxy-1-phenylpyrrolidin-2-one, 225



Following general procedure G, *n*BuLi (4.4 mL, 11 mmol, 2.5 M in hexanes), HN^iPr_2 (1.55 mL, 11 mmol), 4-fluorophenylacetic acid (770 mg, 5 mmol) and 1-bromo-2-chloroethane (914 µL, 11 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(4-fluorophenyl)butanoic acid, which was taken on. Following general procedure H, the acid (836 mg, 3.87 mmol), 1,1'-carbonyldiimidazole (597 mg, 3.68 mmol) and aniline (424 µL, 4.65 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure 4-chloro-2-(4-fluorophenyl)-*N*-phenylbutanamide. Following general procedure I, amide (152 mg, 0.52 mmol) and NaH (104 mg, 2.6 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.29), **225** as a yellow solid (266 mg, 0.98 mmol, 20%), mp 102-104 °C; **ν_{max} (ATR)** 3334 (OH), 2951, 1674 (C=O), 1595, 1219; **δ_H (400 MHz, $CDCl_3$)** 2.48-2.63 (2H, m, C(4)*H*), 3.47 (1H, s, O*H*), 3.71 (1H, ddd, *J* 9.8, 8.6, 6.8 Hz, C(5)H_AH_B), 3.89 (1H, ddd, *J* 9.8, 8.3, 2.8 Hz, C(5)H_AH_B), 7.00-7.07 (2H, m, C(3)ArC(3,5)*H*), 7.20-7.25 (1H, m, NArC(4)*H*), 7.38-7.46 (4H, m, NArC(3,5)*H*, C(3)ArC(2,6)*H*), 7.66-7.74 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.3 (*C*(4)H), 44.4 (*C*(5)H), 78.9 (*C*(3)), 115.6 (d, *J* 21.5 Hz, C(3)Ar*C*(3,5)H), 119.8 (NAr*C*(2,6)H), 125.4 (NAr*C*(4)H), 127.2 (d, *J* 8.2 Hz, C(3)Ar*C*(2,6)H), 129.1 (NAr*C*(3,5)H), 137.7 (d, *J* 3.2 Hz, C(3)Ar*C*(1)), 138.8 (NAr*C*(1)), 162.5 (d, *J* 247.1 Hz, C(3)Ar*C*(4)F), 174.2 (*C*=O); **δ_F (376 MHz, $CDCl_3$)** -113.9 (C(3)ArC(4)*F*); ***m/z* (NSI)** 272 ($[M+H]^+$, 100%) $C_{16}H_{15}NO_3F^+$ ($[M+H]^+$) requires 272.1081; found 272.1083 (+0.6 ppm).

Lab book Reference: SMS-624

3-(4-Fluorophenyl)-2-oxo-1-phenylpyrrolidin-3-yl acetate, 226

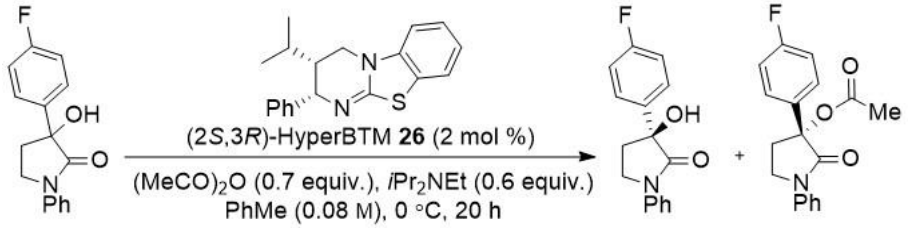


Following general procedure B, **225** (44 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.65), **226** as a clear oil (45 mg, 0.14 mmol, 89%); **ν_{max} (ATR)** 3064, 1741 (C=O), 1701 (C=O), 1597, 1494, 1304, 1219; **δ_H (400 MHz, $CDCl_3$)** 2.19 (3H, s, CH_3), 2.86-3.00 (2H, m, C(4)*H*), 3.86 (1H, dt, *J* 9.6, 8.0 Hz, C(5)H_AH_B), 4.00 (1H, ddd, *J* 9.6, 8.5, 3.4 Hz,

C(5)H_AH_B), 7.08 (2H, ddt, *J* 8.8, 6.8, 2.7 Hz, C(3)ArC(3,5)*H*), 7.16-7.21 (1H, m, NArC(4)*H*), 7.35-7.41 (2H, m, NArC(3,5)*H*), 7.53-7.59 (2H, m, C(3)ArC(2,6)*H*), 7.64-7.69 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 30.8 (*C*(4)H), 44.6 (*C*(5)H), 83.1 (*C*(3)), 115.7 (d, *J* 21.6 Hz, C(3)Ar*C*(3,5)H), 120.0 (NAr*C*(2,6)H), 125.3 (NAr*C*(4)H), 127.5 (d, *J* 8.3 Hz, C(3)Ar*C*(2,6)H), 129.0 (NAr*C*(3,5)H), 133.9 (d, *J* 3.1 Hz, C(3)Ar*C*(1)), 139.0 (NAr*C*(1)), 162.8 (d, *J* 248.2 Hz, C(3)Ar*C*(4)F), 169.7 (*C*(2)=O), 169.9 (*C*=O(CH_3)); **δ_F (376 MHz, $CDCl_3$)** -113.0 (C(3)ArC(4)*F*); ***m/z* (ASAP)** 314 ([M+H^+], 80%) $C_{18}H_{17}FNO_3^+$ ([M+H^+]) requires 314.1187; found 314.1183 (–1.3 ppm).

Lab book Reference: SMS-642

Kinetic resolution 225



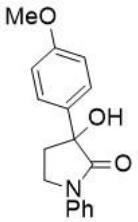
Following general procedure C, **225** (54 mg, 0.2 mmol), acetic anhydride (14 µL, 0.14 mmol), (2*S*,3*R*)-HyperBTM **26** (1.3 mg, 0.004 mmol, 2 mol %) and *i*Pr_2NEt (21 µL, 0.12 mmol) in PhMe (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (23 mg, 0.09 mmol, 43%) and ester (26 mg, 0.08 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +239 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.0, 14.4 min, 95:5 er.

Data for ester: $[\alpha]_D^{20}$ –48 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 27.6, 32.8 min, 97:3 er; *s* = 100.

Lab book Reference: SMS-647

3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpyrrolidin-2-one, 227

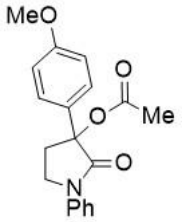


Following general procedure G, *n*BuLi (4.4 mL, 11 mmol, 2.5 M in hexanes), HN^iPr_2 (1.55 mL, 11 mmol), 4-methoxyphenylacetic acid (831 mg, 5 mmol) and 1-bromo-2-chloroethane (914 µL, 11 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(4-methoxyphenyl)butanoic acid, which was taken on. Following general procedure H, the acid (1.12 g, 4.91 mmol), 1,1'-carbonyldiimidazole (757 mg, 4.67 mmol) and aniline (539 µL, 5.90 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure 4-chloro-2-(4-methoxyphenyl)-*N*-phenylbutanamide. Following

general procedure I, amide (726 mg, 2.39 mmol) and NaH (479 mg, 11.97 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.15), **227** as a clear oil (269 mg, 0.95 mmol, 19%); **ν_{max} (ATR)** 3347 (OH), 2953, 1680 (C=O), 1597, 1494, 1294; **δ_H (400 MHz, $CDCl_3$)** 2.50-2.60 (2H, m, C(4)*H*), 3.64-3.71 (1H, m, C(5)H_AH_B), 3.75 (1H, s, O*H*), 3.78 (3H, s, OCH_3), 3.83 (1H, ddd, *J* 9.8, 6.7, 4.2 Hz, C(5)H_AH_B), 6.83-6.88 (2H, m, C(3)ArC(3,5)*H*), 7.17-7.23 (1H, m, NArC(4)*H*), 7.33-7.38 (2H, m, C(3)ArC(2,6)*H*), 7.38-7.43 (2H, m, NArC(3,5)*H*), 7.67-7.73 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.3 (*C*(4)H), 44.4 (*C*(5)H), 55.3 (O*C*H_3), 79.0 (*C*(3)), 114.0 (C(3)Ar*C*(3,5)H), 119.8 (NAr*C*(2,6)H), 125.2 (NAr*C*(4)H), 126.7 (C(3)Ar*C*(2,6)H), 129.0 (NAr*C*(3,5)H), 133.8 (C(3)Ar*C*(1)), 139.0 (NAr*C*(1)), 159.4 (C(3)Ar*C*(4)), 174.7 (*C*=O); ***m/z* (NSI)** 284 ([M+H]$^+$, 100%) $C_{17}H_{18}NO_3^+$ ([M+H]$^+$) requires 284.1281; found 284.1284 (+1.0 ppm).

Lab book Reference: SMS-625

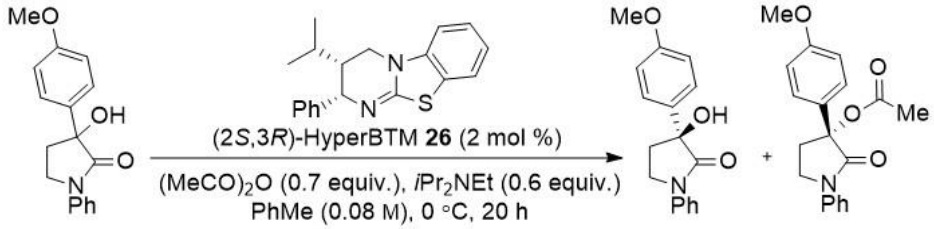
3-(4-Methoxyphenyl)-2-oxo-1-phenylpyrrolidin-3-yl acetate, 228



Following general procedure B, **227** (28 mg, 0.10 mmol), acetic anhydride (13 µL, 0.13 mmol), DMAP **4** (1.3 mg, 0.01 mmol, 10 mol %) and *i*Pr_2NEt (44 µL, 0.24 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.57), **228** as a clear oil (24 mg, 0.07 mmol, 73%); **ν_{max} (ATR)** 2936, 1737 (C=O), 1701 (C=O), 1597, 1494, 1304, 1221; **δ_H (400 MHz, $CDCl_3$)** 2.17 (3H, s, CH_3), 2.88-2.98 (2H, m, C(4)*H*), 3.79 (3H, s, OCH_3), 3.81-3.87 (1H, m, C(5)H_AH_B), 3.96 (1H, ddd, *J* 9.6, 6.6, 4.9 Hz, C(5)H_AH_B), 6.88-6.93 (2H, m, C(3)ArC(3,5)*H*), 7.13-7.19 (1H, m, NArC(4)*H*), 7.33-7.40 (2H, m, NArC(3,5)*H*), 7.48-7.54 (2H, m, C(3)ArC(2,6)*H*), 7.63-7.69 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 30.7 (*C*(4)H), 44.5 (*C*(5)H), 55.3 (O*C*H_3), 83.3 (*C*(3)), 114.1 (C(3)Ar*C*(3,5)H), 119.9 (NAr*C*(2,6)H), 125.1 (NAr*C*(4)H), 127.1 (C(3)Ar*C*(2,6)H), 128.9 (NAr*C*(3,5)H), 129.7 (C(3)Ar*C*(1)), 139.2 (NAr*C*(1)), 159.9 (C(3)Ar*C*(4)), 170.0 (*C*(2)=O), 170.1 (*C*=O(CH$_3$)); ***m/z* (ASAP)** 326 ([M$^+$], 100%) $C_{19}H_{19}NO_4^+$ ([M$^+$]) requires 325.1309; found 325.1317 (+2.5 ppm).

Lab bok Reference: SMS-638

Kinetic resolution of 228



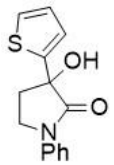
Following general procedure C, **227** (57 mg, 0.2 mmol), acetic anhydride (14 µL, 0.14 mmol), (2*S*,3*R*)-HyperBTM **26** (1.3 mg, 0.004 mmol, 2 mol %) and *i*Pr_2NEt (21 µL, 0.12 mmol) in PhMe (2.5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (28 mg, 0.10 mmol, 49%) and ester (19 mg, 0.06 mmol, 30%).

Data for alcohol: $[\alpha]_D^{20}$ +212 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.8, 33.1 min, 84:16 er.

Data for ester: $[\alpha]_D^{20}$ –23 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.6, 31.7 min, 98:2 er; *s* = 100.

Lab book Reference: SMS-648

3-Hydroxy-1-phenyl-3-(thiophen-2-yl)pyrrolidin-2-one, 229

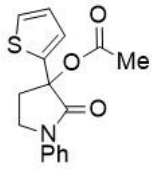


Following general procedure G, *n*BuLi (4.4 mL, 11 mmol, 2.5 M in hexanes), HN^iPr_2 (1.55 mL, 11 mmol), 2-thiopheneacetic acid (710 mg, 5 mmol) and 1-bromo-2-chloroethane (914 µL, 11 mmol) in anhydrous THF (25 mL) gave 4-chloro-2-(thiophen-2-yl)butanoic acid, which was taken on. Following general procedure H, the acid (842 mg, 4.45 mmol), 1,1'-carbonyldiimidazole (686 mg, 4.23 mmol) and aniline (488 µL, 5.34 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure 4-chloro-N-phenyl-2-(thiophen-2-yl)butanamide, which was taken on. Following general procedure I, amide (279 mg, 1 mmol) and NaH (204 mg, 5.1 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.31), **229** as an orange solid (82 mg, 0.32 mmol, 6%), mp 83-85 °C; **ν_{max} (ATR)** 3343 (OH), 1678 (C=O), 1489, 1408, 1294; **δ_H (400 MHz, $CDCl_3$)** 2.58-2.67 (1H, m, C(4)H_AH_B), 2.74 (1H, ddd, *J* 12.7, 6.3, 2.0 Hz, C(4)H_AH_B), 3.75 (1H, s, O*H*), 3.76-3.90 (2H, m, C(5)*H*), 6.95 (1H, dd, *J* 5.1, 3.6 Hz, C(3)ArC(3)*H*), 7.05 (1H, dd, *J* 3.6, 1.2 Hz, C(3)ArC(5)*H*), 7.18-7.23 (1H, m, NArC(4)*H*), 7.30 (1H, dd, *J* 5.1, 1.2 Hz, C(3)ArC(4)*H*), 7.37-7.43 (2H, m, NArC(3,5)*H*), 7.65-7.71 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.3 (*C*(4)H), 44.4 (*C*(5)H), 76.7 (*C*(3)), 119.9 (NAr*C*(2,6)H), 124.5 (C(3)Ar*C*(5)H), 125.3 (NAr*C*(4)H), 125.9 (C(3)Ar*C*(4)H),

126.9 (C(3)Ar*C*(3)H), 129.0 (NAr*C*(3,5)H), 138.9 (NAr*C*(1)), 144.9 (C(3)Ar*C*(1), 173.1 (*C*=O); ***m/z* (NSI)** 260 ([M+H]$^+$, 100%) $C_{14}H_{14}NO_3S^+$ ([M+H]$^+$) requires 260.0740; found 260.0737 (–1.1 ppm).

Lab book Reference: SMS-618

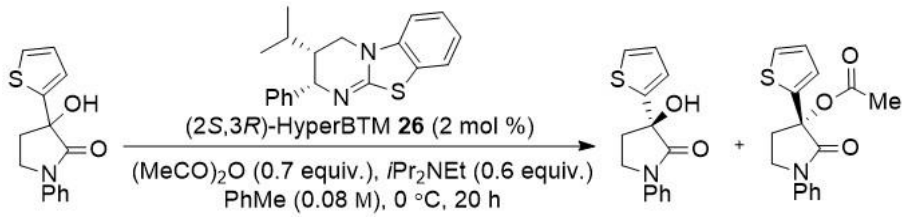
2-Oxo-1-phenyl-3-(thiophen-2-yl)pyrrolidin-3-yl acetate, 230



Following general procedure B, **229** (26 mg, 0.10 mmol), acetic anhydride (13 µL, 0.13 mmol), DMAP **4** (1.3 mg, 0.01 mmol, 10 mol %) and *i*Pr$_2$NEt (44 µL, 0.24 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.45), **230** as a clear oil (25 mg, 0.08 mmol, 83%); **ν_{max} (ATR)** 3071, 1740 (C=O), 1701 (C=O), 1497, 1304, 1215; **δ_H (500 MHz, $CDCl_3$)** 2.19 (3H, s, CH_3), 2.97-3.12 (2H, m, C(4)*H*), 3.90 (1H, td, *J* 9.2, 7.2 Hz, C(5)H_AH_B), 3.99 (1H, td, *J* 9.1, 2.6 Hz, C(5)H$_A$*H*$_B$), 7.02 (1H, dd, *J* 5.1, 3.7 Hz, C(3)ArC(4)*H*), 7.17-7.23 (1H, m, NArC(4)*H*), 7.28-7.30 (1H, m, C(3)ArC(3)*H*), 7.37-7.43 (3H, m, NArC(3,5)*H*, C(3)ArC(5)*H*), 7.65-7.70 (2H, m, NArC(2,6)*H*); **δ_C (125 MHz, $CDCl_3$)** 21.6 (*C*H$_3$), 31.7 (*C*(4)H), 44.5 (*C*(5)H), 81.5 (*C*(3)), 120.0 (NAr*C*(2,6)H), 125.2 (NAr*C*(4)H), 125.9 (C(3)Ar*C*(2)H), 126.8 (C(3)Ar*C*(3)H), 127.1 (C(3)Ar*C*(4)H), 128.9 (NAr*C*(3,5)H), 139.0 (NAr*C*(1)), 140.1 (C(3)Ar*C*(1), 168.8 (*C*(2)=O), 169.9 (*C*=O(CH$_3$)); ***m/z* (NSI)** 302 ([M+H]$^+$, 100%) $C_{16}H_{16}NO_3S^+$ ([M+H]$^+$) requires 302.0845; found 302.0842 (–1.1 ppm).

Lab book Reference: SMS-626

Kinetic resolution of 229



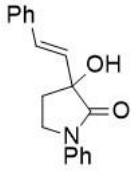
Following general procedure C, **229** (46 mg, 0.18 mmol), acetic anhydride (12 µL, 0.12 mmol), (2*S*,3*R*)-HyperBTM **26** (1.2 mg, 0.0036 mmol, 2 mol %) and *i*Pr$_2$NEt (19 µL, 0.11 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (20 mg, 0.08 mmol, 43%) and ester (21 mg, 0.07 mmol, 39%).

Data for alcohol: $[\alpha]_D^{20}$ +205 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 31.0, 34.1 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ –53 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.0, 27.3 min, 97:3 er; *s* = >200.

Lab book Reference: SMS-645

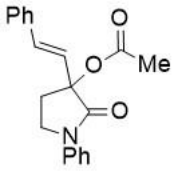
(*E*)-3-Hydroxy-1-phenyl-3-styrylpyrrolidin-2-one, 231



Following general procedure G, *n*BuLi (4.4 mL, 11 mmol, 2.5 M in hexanes), HN^iPr_2 (1.55 mL, 11 mmol), *trans*-styrylacetic acid (710 mg, 5 mmol) and 1-bromo-2-chloroethane (914 µL, 11 mmol) in anhydrous THF (25 mL) gave (*E*)-2-(2-chloroethyl)-4-phenylbut-3-enoic acid, which was taken on. Following general procedure H, the acid (825 mg, 3.68 mmol), 1,1'-carbonyldiimidazole (568 mg, 3.50 mmol) and aniline (403 µL, 4.42 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure (*E*)-2-(2-chloroethyl)-N,4-diphenylbut-3-enamide, which was taken on. Following general procedure I, amide (359 mg, 1.2 mmol) and NaH (240 mg, 6 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3; R_F 0.18), **231** as an orange solid (60 mg, 0.21 mmol, 4%), mp 135-137 °C; **ν_{max} (ATR)** 3397)OH), 3026, 1668 (C=O), 1595 (C=C), 1485, 1411, 1294; **δ_H (400 MHz, $CDCl_3$)** 2.44 (1H, dt, *J* 12.7, 8.8 Hz, C(4)H_AH_B), 2.52 (1H, ddd, *J* 12.7, 6.3, 2.4 Hz, C(4)H_AH_B), 3.23 (1H, s, O*H*), 3.75-3.89 (2H, m, C(5)*H*), 6.33 (1H, d, *J* 16.1 Hz, C(3)C*H*=CHAr), 6.72 (1H, d, *J* 16.1 Hz, C(3)CH=C*H*Ar), 7.18-7.34 (4H, m, NArC(4)*H*, C(3)ArC(3,4,5)*H*), 7.35-7.45 (4H, m, NArC(3,5)*H*, C(3)ArC(2,6)*H*), 7.67-7.73 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 33.1 (*C*(4)H), 44.3 (*C*(5)H), 77.7 (C(3)), 119.7 (NAr*C*(2,6)H), 125.2 (NAr*C*(4)H), 126.8 (C(3)CH=CHAr*C*(2,6)H), 128.0 (C(3)*C*H=CHAr), 128.2 (C(3)CH=CHAr*C*(4)H), 128.6 (C(3)CH=CHAr*C*(3,5)H), 129.1 (NAr*C*(3,5)H), 130.8 (C(3)CH=*C*HAr), 135.9 (C(3)CH=CHAr*C*(1)), 139.0 (NAr*C*(1)), 173.8 (*C*=O); ***m/z* (ASAP)** 280 ([M+H$^+$], 100%) $C_{18}H_{18}NO_2^+$ ([M+H$^+$]) requires 280.1332; found 280.1339 (+2.5 ppm).

Lab book Reference: SMS-636

(*E*)-2-Oxo-1-phenyl-3-styrylpyrrolidin-3-yl acetate, 232

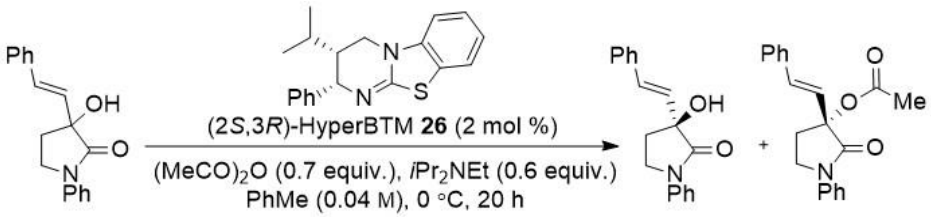


Following general procedure B, **231** (45 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.75), **232** as a clear oil (35 mg, 0.11 mmol, 69%); **ν_{max} (ATR)** 3028, 1738 (C=O), 1699 (C=O), 1597 (C=C), 1493, 1402, 1219; **δ_H (400 MHz, $CDCl_3$)** 2.18 (3H, s, CH_3), 2.74-2.82 (2H, m, C(4)*H*), 3.81-3.94 (2H, m, C(5)*H*), 6.41 (1H, d, *J* 16.2 Hz, C(3)C*H*=CHAr), 6.84 (1H, d, *J* 16.2 Hz, C(3)CH=C*H*Ar), 7.15-7.21 (1H, m, NArC(4)*H*), 7.24-7.34 (3H, m, C(3)CH=CHArC(3,4,5)*H*), 7.36-7.43 (4H, m, NArC(3,5)*H*, C(3)CH=CHArC(2,6)*H*), 7.64-7.70 (2H, m, NArC(2,6)*H*); **δ_C (100 MHz,**

$CDCl_3$) 21.6 (*C*H_3), 30.1 (*C*(4)H), 44.4 (*C*(5)H), 82.8 (C(3)), 120.0 (NAr*C*(2,6)H), 124.9 (C(3)*C*H=CHAr), 125.2 (NAr*C*(4)H), 127.0 (C(3)CH=CHAr*C*(2,6)H), 128.5 (C(3)CH=CHAr*C*(4)H), 128.6 (C(3)CH=CHAr*C*(3,5)H), 129.0 (NAr*C*(3,5)H), 132.6 (C(3)CH=*C*HAr), 135.6 (C(3)CH=CHAr*C*(1)), 139.1 (NAr*C*(1)), 169.4 (*C*(2)=O), 170.0 (*C*=O(CH_3)); ***m/z* (ASAP)** 322 ([M+H^+], 90%) $C_{20}H_{20}NO_3^+$ ([M+H^+]) requires 322.1438; found 322.1429 (–2.8 ppm).

Lab book Reference: SMS-627

Kinetic resolution of 231



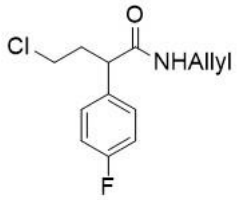
Following general procedure C, **231** (59 mg, 0.21 mmol), acetic anhydride (15 µL, 0.15 mmol), (2*S*,3*R*)-HyperBTM **26** (1.3 mg, 0.0042 mmol, 2 mol %) and *i*Pr_2NEt (22 µL, 0.13 mmol) in PhMe (5 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (35 mg, 0.12 mmol, 59%) and ester (14 mg, 0.04 mmol, 21%).

Data for alcohol: $[\alpha]_D^{20}$ +64 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 28.2, 37.7 min, 63:37 er.

Data for ester: $[\alpha]_D^{20}$ +29 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.8, 47.8 min, 89:11 er; *s* = 10.

Lab book Reference: SMS-646

***N*-Allyl-4-chloro-2-(4-fluorophenyl)butanamide, 233**

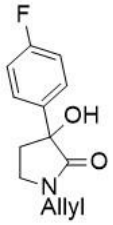


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 4-fluorophenylacetic acid (1.54 g, 10 mmol) and 1-bromo-2-chloroethane (1.83 mL, 22 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(4-fluorophenyl)butanoic acid, which was taken on. Following general procedure H, **acid** (2.16 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3;, R_F 0.47), **233** as an off white solid (1.35 g, 4.5 mmol, 45%), mp 53-55 °C; **ν_{max} (ATR)** 3269 (NH), 2914, 1649 (C=O), 1508, 1425, 1227; **δ_H (400 MHz, $CDCl_3$)** 2.10-2.20 (1H, m, C(3)H_AH_B), 2.57 (1H, dtd, *J* 15.0, 7.7, 4.8 Hz, C(3)H_AH_B), 3.38 (1H, ddd, *J* 11.1, 7.8, 4.7 Hz, C(4)H_AH_B), 3.58 (1H, ddd, *J*

11.6, 7.0, 4.8 Hz, C(4)H_AH_B), 3.70 (1H, t, *J* 7.5 Hz, C(2)*H*), 3.77-3.92 (2H, m, NCH_2CH=CH_2), 5.00-5.10 (2H, m, NCH_2CH=CH_2), 5.60 (1H, s, N*H*), 5.70-5.81 (1H, m, NCH_2C*H*=CH_2), 7.00-7.07 (2H, m, ArC(3,5)*H*), 7.28-7.34 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(3)H), 42.0 (NCH_2CH=CH_2), 43.1 (*C*(4)H), 48.8 (*C*(2)H), 115.9 (d, *J* 21.6 Hz, Ar*C*(3,5)H), 116.3 (NCH_2CH=*C*H_2), 129.6 (d, *J* 8.0 Hz, Ar*C*(2,6)H), 133.9 (NCH_2*C*H=CH_2), 134.5 (d, *J* 3.2 Hz, Ar*C*(1)), 162.2 (d, *J* 246.0 Hz, Ar*C*(4)F), 172.1 (C=O); **δ_F (376 MHz, $CDCl_3$)** -114.6 (ArC(4)*F*); ***m/z* (NSI)** 256 ([M+H]$^+$, 100%) $C_{13}H_{16}NOFCl^+$ ([M+H]$^+$) requires 256.0899; found 256.0901 (+0.8 ppm).

Lab book Reference: SMS-664

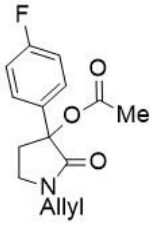
1-Allyl-3-(4-fluorophenyl)-3-hydroxypyrrolidin-2-one, 234



Following general procedure I, to **233** (1.35 g, 4.5 mmol) and NaH (902 mg, 22.6 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.29), **234** as a white solid (663 mg, 2.82 mmol, 63%), mp 68-70 °C; **ν_{max} (ATR)** 3294 (OH), 2988, 1672 (C=O), 1504, 1211; **δ_H (400 MHz, $CDCl_3$)** 2.27 (1H, ddd, *J* 13.1, 7.3, 3.9 Hz, C(4)H_AH_B), 2.38 (1H, ddd, *J* 13.1, 8.3, 6.9 Hz, C(4)H_AH_B), 3.21 (1H, dt, *J* 10.0, 7.1 Hz, C(5)H_AH_B), 3.36 (1H, ddd, *J* 10.0, 8.4, 3.9 Hz, C(5)H_AH_B), 3.88 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 3.97 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.61 (1H, s, O*H*), 5.16-5.24 (2H, m, NCH_2CH=CH_2), 5.71 (1H, ddt, *J* 17.4, 9.8, 6.1 Hz, NCH_2C*H*=CH_2), 6.90-6.98 (2H, m, ArC(3,5)*H*), 7.27-7.33 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 36.2 (*C*(4)H), 43.1 (*C*(5)H), 45.9 (NCH_2CH=CH_2), 78.3 (*C*(3)), 115.2 (d, *J* 21.5 Hz, Ar*C*(3,5)H), 118.7 (NCH_2CH=*C*H_2), 127.1 (d, *J* 8.2 Hz, Ar*C*(2,6)H), 131.7 (NCH_2C*H*=CH_2), 138.4 (d, *J* 3.0 Hz, Ar*C*(1)), 162.2 (d, *J* 246.0 Hz, Ar*C*(4)F), 174.8 (C=O); **δ_F (376 MHz, $CDCl_3$)** -114.9 (ArC(4)*F*); ***m/z* (NSI)** 236 ([M+H]$^+$, 100%) $C_{13}H_{15}NO_2F^+$ ([M+H]$^+$) requires 236.1081; found 236.1082 (+0.3 ppm).

Lab book Reference: SMS-670

1-Allyl-3-(4-fluorophenyl)-2-oxopyrrolidin-3-yl acetate, 235

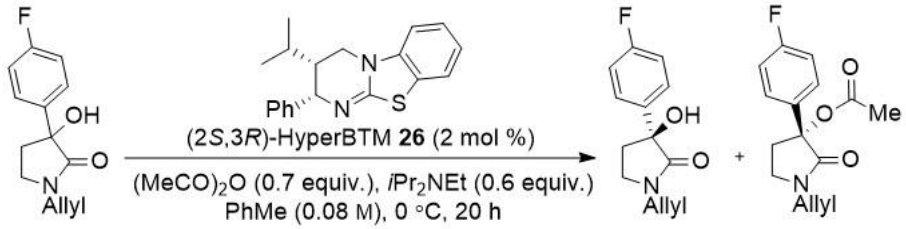


Following general procedure B, **234** (35 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column

chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.37), **235** as a colourless oil (40 mg, 0.15 mmol, 91%); **ν_{max} (ATR)** 2984, 1741 (C=O), 1697 (C=O), 1508, 1225; **δ_H (400 MHz, $CDCl_3$)** 2.16 (3H, s, CH_3), 2.70-2.82 (2H, m, C(4)*H*), 3.37 (1H, dt, *J* 9.8, 7.7 Hz, C(5)H_AH_B), 3.53 (1H, ddd, *J* 9.8, 7.6, 4.8 Hz, C(5)H_AH_B), 3.91 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 3.99 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.20-5.27 (2H, m, $NCH_2CH=CH_2$), 5.74 (1H, ddt, *J* 17.1, 10.2, 6.0 Hz, $NCH_2CH=CH_2$), 7.03-7.10 (2H, m, ArC(3,5)*H*), 7.46-7.52 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.5 (CH_3), 31.5 (*C*(4)H), 43.0 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 82.8 (*C*(3)), 115.6 (d, *J* 21.6 Hz, Ar*C*(3,5)H), 118.6 ($NCH_2CH=CH_2$), 127.2 (d, *J* 8.3 Hz, Ar*C*(2,6)H), 131.6 ($NCH_2CH=CH_2$), 134.8 (d, *J* 3.1 Hz, Ar*C*(1)), 162.7 (d, *J* 247.7 Hz, Ar*C*(4)F), 169.9 (*C*=O(CH_3)), 170.3 (*C*(2)=O); **δ_F (376 MHz, $CDCl_3$)** -113.6 (ArC(4)*F*); ***m/z* (NSI)** 278 ([M+H^+], 100%) $C_{15}H_{17}NO_3F$ ([M+H^+]) requires 278.1187; found 278.1188 (+0.4 ppm).

Lab book Reference: SMS-674

Kinetic resolution of 234



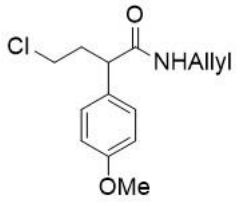
Following general procedure C, **234** (57 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (27 mg, 0.11 mmol, 47%) and ester (25 mg, 0.09 mmol, 38%).

Data for alcohol: $[\alpha]_D^{20}$ +41 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.8, 18.9 min, 84:16 er.

Data for ester: $[\alpha]_D^{20}$ –14 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.6, 22.3 min, 98:2 er; *s* = 100.

Lab book Reference: SMS-684

***N*-Allyl-4-chloro-2-(4-methoxyphenyl)butanamide, 236**

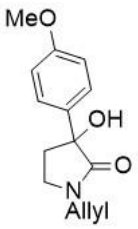


Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), 4-methoxyphenylacetic acid (2.49 g, 15 mmol) and 1-bromo-2-chloroethane (2.90 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(4-methoxyphenyl)butanoic acid, which was taken on.

Following general procedure H, the acid (2.78 g, 12.2 mmol), 1,1'-carbonyldiimidazole (1.87 g, 11.6 mmol) and allylamine (1.1 mL, 14.6 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3; R_F 0.35), **236** as yellow crystals (1.83 g, 6.8 mmol, 45%), mp 42-44 °C; **ν_{max} (ATR)** 3298 (NH), 2959, 1767, 1651 (C=O), 1510, 1248; **δ_H (400 MHz, $CDCl_3$)** 2.15 (1H, dddd, *J* 14.6, 8.2, 6.6, 5.0 Hz, C(3)H_AH_B), 2.56 (1H, dddd, *J* 14.7, 8.0, 6.7, 5.2 Hz, C(3)H_AH_B), 3.37 (1H, ddd, *J* 11.0, 8.1, 5.0 Hz, C(4)H_AH_B), 3.55 (1H, ddd, *J* 11.5, 6.5, 5.20 Hz, C(4)H_AH_B), 3.63-3.69 (1H, m, C(2)*H*), 3.74-3.88 (5H, m, ArC(4)CH_3, NCH_2CH=CH_2), 4.98-5.06 (2H, m, $NCH_2CH=CH_2$), 5.68-5.79 (2H, m, N*H*, $NCH_2CH=CH_2$), 6.84-6.89 (2H, m, ArC(3,5)*H*), 7.21-7.25 (2H, m, ArC(3,5)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.7 (*C*(3)H), 41.9 (N*C*H_2CH=CH_2), 43.2 (*C*(4)H), 48.7 (*C*(2)H), 55.3 (O*C*H_3), 114.4 (Ar*C*(3,5)H), 116.1 ($NCH_2CH=CH_2$), 129.2 (Ar*C*(2,6)H), 130.7 (Ar*C*(1)), 134.7 ($NCH_2CH=CH_2$), 159.0 (Ar*C*(4)), 172.7 (*C*=O); ***m/z* (NSI)** 268 ($[M+H]^+$, 100%) $C_{14}H_{19}NO_2Cl^+$ ($[M+H]^+$) requires 268.1099; found 268.1099 (+0.1 ppm).

Lab book Reference: SMS-663

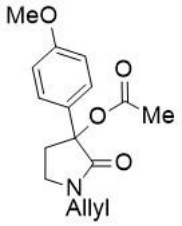
1-Allyl-3-hydroxy-3-(4-methoxyphenyl)pyrrolidin-2-one, 237



Following general procedure I, **236** (1.83 g, 6.8 mmol) and NaH (1.36 g, 34.1 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.12), **237** as a white solid (280 mg, 1.13 mmol, 17%), mp 88-90 °C; **ν_{max} (ATR)** 3294 (OH), 2938, 1674 (C=O), 1607, 1512, 1246; **δ_H (400 MHz, $CDCl_3$)** 2.32-2.46 (2H, m, C(4)*H*), 3.22 (1H, dt, *J* 9.9, 7.4 Hz, C(5)H_AH_B), 3.35 (1H, ddd, *J* 9.9, 7.9, 3.8 Hz, C(5)H_AH_B), 3.73 (1H, s, O*H*), 3.78 (3H, s, O*C*H_3), 3.93 (1H, ddt, *J* 15.2, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 4.01 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 5.18-5.26 (2H, m, $NCH_2CH=CH_2$), 5.75 (1H, ddt, *J* 17.3, 9.9, 6.1 Hz, $NCH_2CH=CH_2$), 6.80-6.88 (2H, m, ArC(3,5)*H*), 7.28-7.34 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(4)H), 43.2 (*C*(5)H), 45.9 (N*C*H_2CH=CH_2), 55.3 (O*C*H_3), 78.3 (C(3)), 113.9 (Ar*C*(3,5)H), 118.6 ($NCH_2CH=CH_2$), 126.5 (Ar*C*(2,6)H), 131.8 ($NCH_2CH=CH_2$), 134.4 (Ar*C*(1)), 159.2 (Ar*C*(4)), 174.9 (*C*=O); ***m/z* (NSI)** 248 ($[M+H]^+$, 100%) $C_{14}H_{18}NO_3^+$ ($[M+H]^+$) requires 248.1281; found 284.1282 (+0.3 ppm).

Lab book Reference: SMS-669

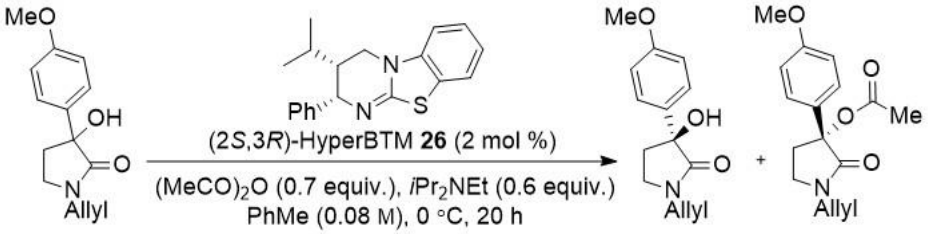
1-Allyl-3-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl acetate, 238



Following general procedure B, **237** (40 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.29), **238** as a colourless oil (24 mg, 0.13 mmol, 82%); **ν_{max} (ATR)** 2934, 1738 (C=O), 1697 (C=O), 1512, 1231, 1179; **δ_H (400 MHz, $CDCl_3$)** 2.15 (3H, s, CH_3), 2.70-2.84 (2H, m, C(4)*H*), 3.35 (1H, dt, *J* 9.7, 7.7 Hz, C(5)H_AH_B), 3.50 (1H, ddd, *J* 9.7, 8.2, 3.9 Hz, C(5)H$_A$*H*$_B$), 3.80 (3H, s, OCH_3), 3.90 (1H, ddt, *J* 15.3, 6.1, 1.3 Hz, NCH_AH_BCH=CH$_2$), 3.98 (1H, ddt, *J* 15.2, 5.8, 1.4 Hz, NCH$_A$*H*$_B$CH=CH$_2$), 5.18-5.26 (2H, m, NCH$_2$CH=CH_2), 5.67-5.79 (1H, m, NCH$_2$C*H*=CH$_2$), 6.86-6.94 (2H, m, ArC(3,5)*H*), 7.42-7.45 (2H, m, NArC(3,5)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H$_3$), 31.4 (*C*(4)H), 43.0 (*C*(5)H), 45.9 (N*C*H$_2$CH=CH$_2$), 55.3 (O*C*H$_3$), 83.0 (C(3)), 114.0 (Ar*C*(3,5)H), 118.4 (NCH$_2$CH=*C*H$_2$), 126.7 (Ar*C*(2,6)H), 130.7 (Ar*C*(1)), 131.8 (NCH$_2$*C*H=CH$_2$), 159.7 (Ar*C*(4)), 170.1 (*C*(=O)CH3), 170.7 (*C*=O); ***m/z* (NSI)** 312 ([M+Na$^+$], 100%) $C_{16}H_{19}NO_4Na$ ([M+Na$^+$]) requires 312.1206; found 312.1209 (+0.9 ppm).

Lab book Reference: SMS-673

Kinetic resolution of 237



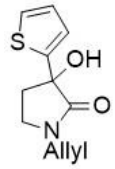
Following general procedure C, **237** (59 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (3.8 mg, 0.012 mmol, 5 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (35 mg, 0.14 mmol, 59%) and ester (22 mg, 0.08 mmol, 32%).

Data for alcohol: $[\alpha]_D^{20}$ +18 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 37.8, 41.9 min, 71:29 er.

Data for ester: $[\alpha]_D^{20}$ +28 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 30.3, 45.8 min, 97:3 er; *s* = 60.

Lab book Reference: SMS-714

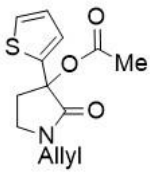
1-Allyl-3-hydroxy-3-(thiophen-2-yl)pyrrolidin-2-one, 240



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 2-thiopheneacetic acid (1.42 g, 10 mmol) and 1-bromo-2-chloroethane (1.82 mL, 22 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(thiophen-2-yl)butanoic acid, which was taken on. Following general procedure H, the acid (1.89 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (25 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(thiophen-2-yl)butanamide. Following general procedure I, amide (559 mg, 2.3 mmol) and NaH (460 mg, 11.5 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.29), **240** as a colourless oil (209 mg, 0.93 mmol, 9%); **ν_{max} (ATR)** 3327 (OH), 2949, 1674 (C=O), 1271; **δ_H (400 MHz, $CDCl_3$)** 2.43-2.59 (2H, m, C(4)*H*), 3.26-3.40 (2H, m, C(5)*H*), 3.89 (1H, ddd, *J* 15.2, 6.1, 1.3 Hz, $NCH_AH_BCH=CH_2$), 3.98 (1H, ddt, *J* 15.2, 6.1, 1.3 Hz, $NCH_AH_BCH=CH_2$), 4.25 (1H, s, O*H*), 5.15-5.24 (2H, m, $NCH_2CH=CH_2$), 5.72 (1H, ddt, *J* 16.6, 10.6, 6.1 Hz, $NCH_2CH=CH_2$), 6.93 (1H, dd, *J* 5.1, 3.6 Hz, ArC(4)*H*), 7.01 (1H, dd, *J* 3.6, 1.2 Hz, ArC(5)*H*), 7.26 (1H, dd, *J* 5.1, 1.2 Hz, ArC(3)*H*); **δ_C (100 MHz, $CDCl_3$)** 36.1 (*C*(4)H), 42.9 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 76.3 (*C*(3)), 118.7 ($NCH_2CH=CH_2$), 124.1 (Ar*C*(5)H), 125.5 (Ar*C*(3)H), 126.8 (Ar*C*(4)H), 131.6 ($NCH_2CH=CH_2$), 145.7 (Ar*C*(2)), 173.7 (*C*=O); ***m/z* (NSI)** 224 ($[M+H]^+$, 100%) $C_{11}H_{14}NO_2S^+$ ($[M+H]^+$) requires 224.0740; found 224.0739 (–0.3 ppm).

Lab book Reference: SMS-671

1-Allyl-2-oxo-3-(thiophen-2-yl)pyrrolidin-3-yl acetate, 241

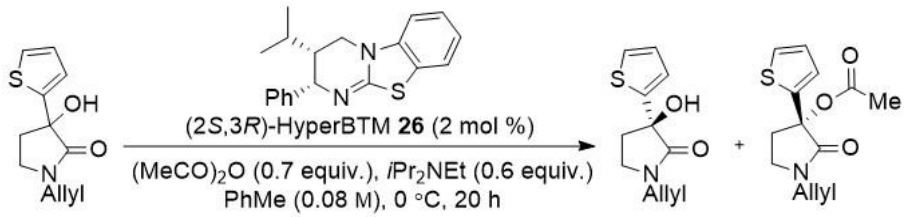


Following general procedure B, **240** (36 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and iPr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.46), **241** as a colourless oil (34 mg, 0.13 mmol, 79%); **ν_{max} (ATR)** 2982, 1740 (C=O), 1699 (C=O), 1435, 1223; **δ_H (400 MHz, $CDCl_3$)** 2.13 (3H, s, CH_3), 2.79-2.93 (2H, m, C(4)*H*), 3.36 (1H, td, *J* 9.7, 7.7 Hz, C(5)H_AH_B), 3.49 (1H, ddd, *J* 9.6, 9.0, 2.9 Hz, C(5)H_AH_B), 3.88 (1H, ddt, *J* 15.3, 6.1, 1.3 Hz, $NCH_AH_BCH=CH_2$), 3.98 (1H, ddt, *J* 15.3, 5.8, 1.4 Hz, $NCH_AH_BCH=CH_2$), 5.16-5.25 (2H, m, $NCH_2CH=CH_2$), 5.66-77 (1H, m, $NCH_2CH=CH_2$), 6.99 (1H, dd, *J* 5.1, 3.7 Hz, ArC(4)*H*), 7.20 (1H, dd, *J* 3.7, 1.2 Hz, ArC(5)*H*), 7.34 (1H, dd, *J* 5.1, 1.2 Hz, ArC(3)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.5 (CH_3),

32.2 (*C*(4)H), 42.8 (*C*(5)H), 45.9 (N*C*H$_2$CH=CH$_2$), 81.3 (*C*(3)), 118.4 (NCH$_2$CH=*C*H$_2$), 125.4 (Ar*C*(5)H), 126.69 (Ar*C*(3)H), 126.74 (Ar*C*(4)H), 131.6 (NCH$_2$*C*H=CH$_2$), 141.0 (Ar*C*(2)), 169.5 (*C*(2)=O), 169.9 (*C*=O(CH$_3$)); ***m/z* (NSI)** 266 ([M+H]$^+$, 100%) $C_{13}H_{16}NO_3S^+$ ([M+H]$^+$) requires 266.0845; found 266.0847 (+0.6 ppm).

Lab book Reference: SMS-675

Kinetic resolution of 240



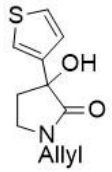
Following general procedure C, **240** (54 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH$_2$Cl$_2$/EtOAc, 9:1), alcohol (21 mg, 0.09 mmol, 39%) and ester (27 mg, 0.10 mmol, 42%).

Data for alcohol: $[\alpha]_D^{20}$ +42 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 58.7, 65.8 min, 98:2 er.

Data for ester: $[\alpha]_D^{20}$ –33 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 19.6, 28.8 min, 98:2 er; *s* = 160.

Lab book Reference: SMS-685

1-Allyl-3-hydroxy-3-(thiophen-3-yl)pyrrolidin-2-one, 243

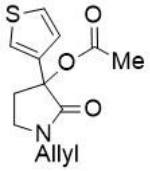


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (3.1 mL, 22 mmol), 3-thiopheneacetic acid (1.42 g, 10 mmol) and 1-bromo-2-chloroethane (1.82 mL, 22 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(thiophen-3-yl)butanoic acid, which was taken on. Following general procedure H, the acid (1.89 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure 4-chloro-*N*-phenyl-2-(thiophen-3-yl)butanamide. Following general procedure I, amide (1.23 g, 5.1 mmol) and NaH (1.02 g, 25.5 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH$_2$Cl$_2$/EtOAc, 4:1; R_F 0.14), **243** as a yellow oil (459 mg, 2.06 mmol, 40%); **ν_{max} (ATR)** 3345 (OH), 2964, 1674 (C=O), 1416, 1271; **δ_H (400 MHz, CDCl$_3$)** 2.38-2.54 (2H, m, C(4)*H*), 3.23-3.33 (1H, m, C(5)*H*), 3.32 (1H, s, O*H*), 3.37 (1H, ddd, *J* 9.9, 8.4, 2.9 Hz,

C(5)H_AH_B), 3.94 (1H, ddt, *J* 15.2, 6.1, 1.1 Hz, NCH_AH_BCH=CH_2), 4.01 (1H, ddt, *J* 15.1, 6.2, 1.1 Hz, NCH_AH_BCH=CH_2), 5.18-5.26 (2H, m, NCH_2CH=CH_2), 5.75 (1H, ddt, *J* 16.5, 10.4, 6.1 Hz, NCH_2C*H*=CH_2), 7.14 (1H, dd, *J* 5.0, 1.4 Hz, ArC(4)*H*), 7.28 (1H, dd, *J* 3.0, 1.4 Hz, ArC(2)*H*), 7.32 (1H, dd, *J* 5.0, 3.0 Hz, ArC(5)*H*); **δ_C (100 MHz, $CDCl_3$)** 34.9 (*C*(4)H), 42.9 (*C*(5)H), 45.9 (NCH_2CH=CH_2), 76.3 (*C*(3)), 118.7 (NCH_2CH=*C*H_2), 121.5 (Ar*C*(2)H), 125.5 (Ar*C*(4)H), 126.8 (Ar*C*(5)H), 131.7 (NCH_2*C*H=CH_2), 143.0 (Ar*C*(3)), 173.7 (*C*=O); ***m/z* (NSI)** 224 ([M+H]$^+$, 100%) $C_{11}H_{14}NO_2S^+$ ([M+H]$^+$) requires 224.0740; found 224.0738 (–0.8 ppm).

Lab book Reference: SMS-750

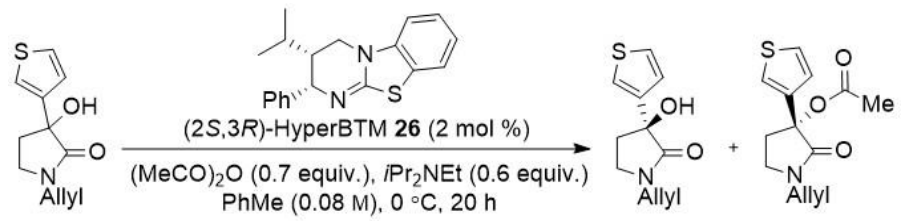
1-Allyl-2-oxo-3-(thiophen-3-yl)pyrrolidin-3-yl acetate, 244



Following general procedure B, **243** (36 mg, 0.16 mmol), acetic anhydride (21 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.30), **244** as a colourless oil (40 mg, 0.15 mmol, 94%); **ν_{max} (ATR)** 2978, 1730 (C=O), 1697 (C=O), 1423, 1240; **δ_H (400 MHz, $CDCl_3$)** 2.13 (3H, s, CH_3), 2.75-2.82 (2H, m, C(4)*H*), 3.34 (1H, q, *J* 8.6 Hz, C(5)H_AH_B), 3.49 (1H, dt, *J* 11.3, 6.1 Hz, C(5)H_AH_B), 3.90 (1H, dd, *J* 15.2, 6.0 Hz, NCH_AH_BCH=CH_2), 3.98 (1H, dd, *J* 15.4, 5.8 Hz, NCH_AH_BCH=CH_2), 5.17-5.26 (2H, m, NCH_2CH=CH_2), 5.73 (1H, ddt, *J* 16.2, 10.9, 5.9 Hz, NCH_2C*H*=CH_2), 7.23 (1H, d, *J* 5.1, ArC(4)*H*), 7.31-7.35 (1H, m, ArC(2)*H*), 7.42 (1H, s, ArC(5)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.5 (*C*H_3), 31.4 (*C*(4)H), 42.9 (*C*(5)H), 45.9 (NCH_2CH=CH_2), 81.3 (*C*(3)), 118.4 (NCH_2CH=*C*H_2), 122.5 (Ar*C*(2)H), 125.7 (Ar*C*(4)H), 126.6 (Ar*C*(5)H), 131.7 (NCH_2*C*H=CH_2), 139.9 (Ar*C*(3)), 170.0 (*C*=O(CH_3)), 170.1 (*C*(2)=O); ***m/z* (NSI)** 266 ([M+H]$^+$, 100%) $C_{13}H_{16}NO_3S^+$ ([M+H]$^+$) requires 266.0844; found 266.0847 (+1.3 ppm).

Lab book Reference: SMS-754

Kinetic resolution of 243



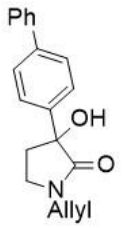
Following general procedure C, **243** (54 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (25 mg, 0.11 mmol, 47%) and ester (25 mg, 0.09 mmol, 39%).

Data for alcohol: $[\alpha]_D^{20}$ +269 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 25.7, 32.3 min, 89:11 er.

Data for ester: $[\alpha]_D^{20}$ +9 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.8, 24.0 min, 98:2 er; *s* = 90.

Lab book Reference: SMS-760

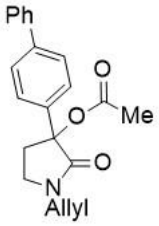
3-([1,1'-Biphenyl]-4-yl)-1-allyl-3-hydroxypyrrolidin-2-one, 246



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 2-([1,1'-biphenyl]-4-yl)acetic acid (2.12 g, 10 mmol) and 1-bromo-2-chloroethane (1.82 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-([1,1'-biphenyl]-4-yl)-4-chlorobutanoic acid, which was taken on. Following general procedure H, the acid (2.74 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure 2-([1,1'-biphenyl]-4-yl)-*N*-allyl-4-chlorobutanamide. Following general procedure I, amide (1.60 g, 5.1 mmol) and NaH (1.02 g, 25.5 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.17), **246** as a cream wax (403 mg, 1.37 mmol, 14%); **ν_{max} (ATR)** 3325 (OH), 2984, 1686 (C=O), 1277; **δ_H (400 MHz, $CDCl_3$)** 2.38-2.53 (2H, m, C(4)*H*), 3.31 (1H, dt, *J* 10.0, 7.2 Hz, C(5)H_AH_B), 3.42 (1H, ddd, *J* 10.0, 8.3, 3.8 Hz, C(5)H_AH_B), 3.84 (1H, br s, O*H*), 3.97 (1H, ddt, *J* 15.1, 6.1, 1.2 Hz, NCH_AH_BCH=CH_2), 4.06 (1H, ddt, *J* 15.1, 6.2, 1.2 Hz, NCH_AH_BCH=CH_2), 5.23-5.30 (2H, m, $NCH_2CH=CH_2$), 5.79 (1H, ddt, *J* 16.6, 10.3, 6.1 Hz, $NCH_2CH=CH_2$), 7.32-7.37 (1H, m, ArC(4)PhC(4)*H*), 7.39-7.48 (4H, m, ArC(4)PhC(2,3,5,6)*H*), 7.53-7.58 (4H, m, ArC(2,3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 36.1 (*C*(4)H), 43.2 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 78.7 (*C*(3)), 118.7 ($NCH_2CH=CH_2$), 125.6 (ArC(4)Ph*C*(2,6)H), 127.1 (Ar*C*(2,6)H), 127.2 (Ar*C*(3,5)H), 127.4 (ArC(4)Ph*C*(4)H), 128.8 (ArC(4)Ph*C*(3,5)H), 131.8 ($NCH_2CH=CH_2$), 140.6 (ArC(4)Ph*C*(1)), 140.7 (Ar*C*(4)), 141.5 (Ar*C*(1)), 174.9 (*C*=O); ***m/z* (NSI)** 294 ($[M+H]^+$, 100%) $C_{19}H_{20}NO_2^+$ ($[M+H]^+$) requires 294.1489; found 294.1490 (+0.5 ppm).

Lab book Reference: SMS-718

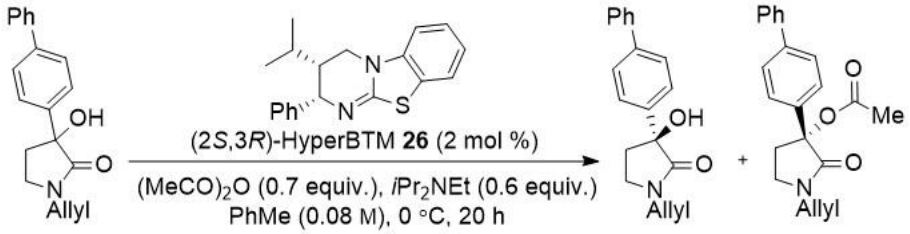
3-([1,1'-Biphenyl]-4-yl)-1-allyl-2-oxopyrrolidin-3-yl acetate, 247



Following general procedure B, **246** (47 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.38), **247** as a white solid (34 mg, 0.15 mmol, 93%), mp 86-88 °C; **ν_{max} (ATR)** 3080, 1748 (C=O), 1694 (C=O), 1233; **δ_H (400 MHz, $CDCl_3$)** 2.19 (3H, s, CH_3), 2.74-2.88 (2H, m, C(4)*H*), 3.44 (1H, dt, *J* 9.8, 7.7 Hz, C(5)H_AH_B), 3.56 (1H, ddd, *J* 9.7, 8.5, 3.9 Hz, C(5)H_AH_B), 3.93 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.02 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.20-5.30 (2H, m, NCH_2CH=CH_2), 5.77 (1H, ddt, *J* 17.1, 10.1, 6.0 Hz, NCH_2CH=CH_2), 7.33-7.36 (1H, m, ArC(4)PhC(4)*H*), 7.41-7.47 (2H, m, ArC(4)PhC(3,5)*H*), 7.54-7.63 (6H, m, ArC(4)PhC(2,6)*H*, ArC(2,3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (CH_3), 36.1 (*C*(4)H), 43.2 (*C*(5)H), 46.0 (N*C*H_2CH=CH_2), 83.3 (*C*(3)), 118.6 (NCH_2CH=*C*H_2), 125.6 (ArC(4)Ph*C*(2,6)H), 127.2 (Ar*C*(2,6)H), 127.45 (Ar*C*(3,5)H), 127.54 (ArC(4)Ph*C*(4)H), 128.8 (ArC(4)Ph*C*(3,5)H), 131.7 (NCH_2*C*H=CH_2), 137.9 (ArC(4)Ph*C*(1)), 140.5 (Ar*C*(4)), 141.4 (Ar*C*(1)), 170.0 *C*=OCH_3), 170.5 (*C*(2)=O); ***m/z* (NSI)** 358 ([M+Na]$^+$, 100%) $C_{21}H_{21}NO_3Na^+$ ([M+Na]$^+$) requires 358.1414; found 358.1415 (+0.4 ppm).

Lab book Reference: SMS-729

Kinetic resolution of 246



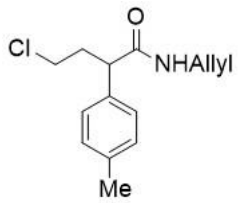
Following general procedure C, **246** (71 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (36 mg, 0.12 mmol, 50%) and ester (30 mg, 0.09 mmol, 37%).

Data for alcohol: $[\alpha]_D^{20}$ +64 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 35.8, 48.9 min, 86:!4 er.

Data for ester: $[\alpha]_D^{20}$ +83 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 33.3, 43.6 min, 98:2 er; *s* = 120.

Lab book Reference: SMS-736

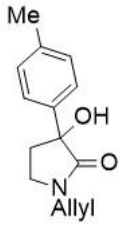
_N_-Allyl-4-chloro-2-(_p_-tolyl)butanamide, 248



Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), *p*-tolylacetic acid (2.25 g, 15 mmol) and 1-bromo-2-chloroethane (2.75 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(*p*-tolyl)butanoic acid, which was taken on. Following general procedure H, acid (3.05 g, 14.4 mmol), 1,1'-carbonyldiimidazole (2.22 g, 13.68 mmol) and allylamine (1.3 mL, 17.28 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.45), **248** as a yellow solid (2.05 g, 8.15 mmol, 54%), mp 53-55 °C; **ν_{max} (ATR)** 3289 (NH), 2922, 1639 (C=O), 1555, 1510, 1234; **δ_H (400 MHz, $CDCl_3$)** 2.17 (1H, dddd, *J* 13.4, 7.9, 6.6, 5.4 Hz, C(3)H_AH_B), 2.32 (3H, s, CH_3), 2.56 (1H, dtd, *J* 14.5, 7.5, 5.5 Hz, C(3)H_AH_B), 3.37 (1H, ddd, *J* 11.0, 7.8, 5.3 Hz, C(4)H_AH_B), 3.49-3.53 (1H, m, C(4)H_AH_B), 3.69-3.87 (3H, m, C(2)*H*, $NCH_2CH{=}CH_2$), 4.97-5.06 (2H, m, $NCH_2CH{=}CH_2$), 5.66-5.79 ($NCH_2CH{=}CH_2$), 6.33 (1H, s, N*H*), 7.13 (2H, d, *J* 7.9 Hz, ArC(3,5)*H*), 7.22 (2H, d, *J* 8.1 Hz, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (CH_3), 35.8 (*C*(3)H), 41.9 ($NCH_2CH{=}CH_2$), 43.2 (*C*(4)H), 49.1 (*C*(2)H), 115.9 ($NCH_2CH{=}CH_2$), 127.9 (Ar*C*(2,6)H), 129.6 (Ar*C*(3,5)H), 134.6 ($NCH_2CH{=}CH_2$), 135.8 (Ar*C*(4)), 137.2 (Ar*C*(4)), 172.8 (*C*=O); ***m/z* (NSI)** 252 ($[M+H]^+$, 100%) $C_{14}H_{19}NOCl^+$ ($[M+H]^+$) requires 252.1150; found 252.1150 (+0.4 ppm).

Lab book Reference: SMS-680

1-Allyl-3-hydroxy-3-(_p_-tolyl)pyrrolidin-2-one, 249

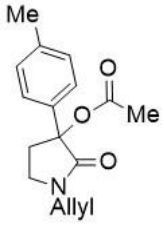


Following general procedure I, **248** (2.05 g, 8.15 mmol) and NaH (1.63 mg, 40.75 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.20), **249** as a white solid (321 mg, 1.39 mmol, 17%), mp 71-73 °C; **ν_{max} (ATR)** 3329 (OH), 2918, 1659 (C=O), 1275; **δ_H (400 MHz, $CDCl_3$)** 2.33 (3H, s, CH_3), 2.34-2.39 (2H, m, C(4)*H*), 3.25 (1H, dt, *J* 9.9, 7.4 Hz, C(5)H_AH_B), 3.36 (1H, ddd, *J* 9.9, 8.1, 3.0 Hz, C(5)H_AH_B), 3.68 (1H, s, O*H*), 3.95 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, $NCH_AH_BCH{=}CH_2$), 4.02 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, $NCH_AH_BCH{=}CH_2$), 5.20-5.27 (2H, m, $NCH_2CH{=}CH_2$), 5.76 (1H, ddt, *J* 17.4, 9.9, 6.1 Hz, $NCH_2CH{=}CH_2$), 7.10-7.17 (2H, m, ArC(3,5)*H*), 7.25-7.30 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (CH_3), 36.0 (*C*(4)H), 43.0 (*C*(5)H), 45.9 ($NCH_2CH{=}CH_2$), 78.6

(*C*(3)), 118.6 ($NCH_2CH=CH_2$), 125.1 (Ar*C*(2,6)H), 129.2 (Ar*C*(3,5)H), 131.8 ($NCH_2CH=CH_2$), 137.6 (Ar*C*(4)), 139.4 (Ar*C*(4)), 174.9 (*C*=O); ***m/z* (NSI)** 232 ($[M+H]^+$, 100%) $C_{14}H_{18}NO_2^+$ ($[M+H]^+$) requires 232.1332; found 232.1333 (+0.4 ppm).

Lab book Reference: SMS-686

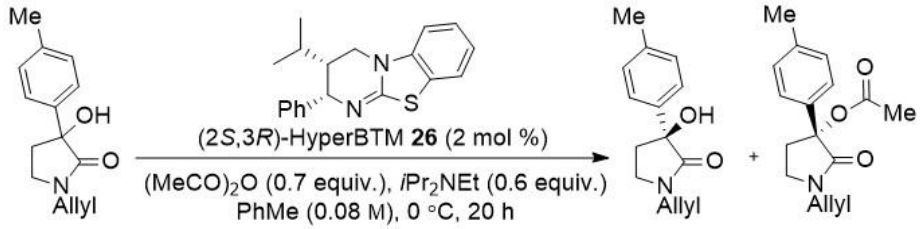
1-Allyl-2-oxo-3-(*p*-tolyl)pyrrolidin-3-yl acetate, 250



Following general procedure B, **249** (37 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.20), **250** as a colourless oil (34 mg, 0.12 mmol, 78%); **ν_{max} (ATR)** 2974, 1744 (C=O), 1625 (C=O), 1229; **δ_H (400 MHz, $CDCl_3$)** 2.15 (3H, s, C(=O)CH_3), 2.34 (3H, s, ArC(4)CH_3), 2.69-2.82 (2H, m, C(4)*H*), 3.37 (1H, dt, *J* 9.7, 7.7 Hz, C(5)H_AH_B), 3.51 (1H, ddd, *J* 9.7, 7.7, 4.6 Hz, C(5)H_AH_B), 3.90 (1H, ddt, *J* 15.3, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 3.99 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, $NCH_AH_BCH=CH_2$), 5.18-5.27 (2H, m, $NCH_2CH=CH_2$), 5.74 (1H, ddt, *J* 17.0, 10.2, 6.0 Hz, $NCH_2CH=CH_2$), 7.18 (2H, d, *J* 8.0 Hz, ArC(3,5)*H*), 7.36-7.41 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (ArC(4)CH_3), 21.6 (C(=O)CH_3), 31.5 (*C*(4)H), 43.1 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 83.3 (*C*(3)), 118.4 ($NCH_2CH=CH_2$), 125.1 (Ar*C*(2,6)H), 129.4 (Ar*C*(3,5)H), 131.8 ($NCH_2CH=CH_2$), 135.9 (Ar*C*(4)), 138.3 (Ar*C*(4)), 170.1 (*C*=O(CH_3)), 170.6 (*C*(2)=O); ***m/z* (NSI)** 274 ($[M+H^+]$, 100%) $C_{16}H_{20}NO_3$ ($[M+H^+]$) requires 274.1438; found 274.1441 (+1.2 ppm).

Lab book Reference: SMS-692

Kinetic resolution of 249



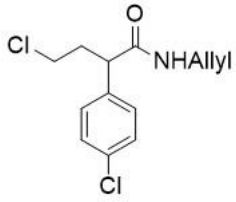
Following general procedure C, **249** (56 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (26 mg, 0.11 mmol, 46%) and ester (23 mg, 0.10 mmol, 40%).

Data for alcohol: $[\alpha]_D^{20}$ +140 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 23.1, 27.4 min, 87:13 er.

Data for ester: $[\alpha]_D^{20}$ +27 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.9, 31.0 min, 98:2 er; *s* = 90.

Lab book Reference: SMS-698

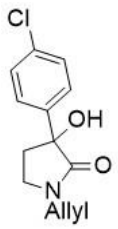
_N_-Allyl-4-chloro-2-(4-chlorophenyl)butanamide, 251



Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), 4-chlorophenylacetic acid (2.55 g, 15 mmol) and 1-bromo-2-chloroethane (2.75 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-phenylbutanoic, which was taken on. Following general procedure H, the acid (3.60 g, 15.5 mmol), 1,1'-carbonyldiimidazole (2.39 g, 14.7 mmol) and allylamine (1.4 mL, 18.6 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.45), **251** as a cream solid (2.02 g, 7.45 mmol, 50%), mp 70-72 °C; **ν_{max} (ATR)** 3296 (NH), 2970, 1639 (C=O), 1555, 1489, 1261; **δ_H (400 MHz, $CDCl_3$)** 2.06 (1H, dtd, *J* 14.6, 7.2, 4.8 Hz, C(3)H_AH_B), 2.45 (1H, dtd, *J* 14.9, 7.6, 4.9 Hz, C(3)H_AH_B), 3.29 (1H, ddd, *J* 11.1, 7.8, 4.8 Hz, C(4)H_AH_B), 3.46 (1H, ddd, *J* 11.6, 7.0, 4.9 Hz, C(4)H_AH_B), 3.65 (1H, t, *J* 7.5 Hz, C(2)*H*), 3.66-3.80 (2H, m, $NCH_2CH{=}CH_2$), 4.91-5.00 (2H, m, $NCH_2CH{=}CH_2$), 5.65 (1H, ddt, *J* 16.9, 10.7, 5.4 Hz, $NCH_2CH{=}CH_2$), 5.99-6.10 (1H, s, N*H*), 7.16-7.24 (4H, m, ArC(2,3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.8 (*C*(3)H), 42.0 ($NCH_2CH{=}CH_2$), 43.0 (*C*(4)H), 48.8 (*C*(2)H), 116.2 ($NCH_2CH{=}CH_2$), 129.1 (Ar*C*(3,5)H), 129.4 (Ar*C*(2,6)H), 133.5 (ArC(4)), 133.9 ($NCH_2CH{=}CH_2$), 137.3 (Ar*C*(1)), 172.1 (*C*=O); ***m/z* (NSI)** 272 ($[M+H]^+$, 100%) $C_{13}H_{16}NOCl_2^+$ ($[M+H]^+$) requires 272.0603; found 272.0606 (+0.9 ppm).

Lab book Reference: SMS-682

1-Allyl-3-(4-chlorophenyl)-3-hydroxypyrrolidin-2-one, 252

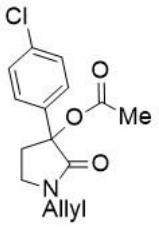


Following general procedure I, **251** (2.02 g, 7.45 mmol) and NaH (1.49 mg, 37.25 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.24), **252** as a white solid (898 mg, 3.58 mmol, 48%), mp 76-78 °C; **ν_{max} (ATR)** 3202 (OH), 2876, 1668 (C=O),

1489, 1271; **δ_H (400 MHz, $CDCl_3$)** 2.29 (1H, ddd, *J* 13.1, 7.3, 3.8 Hz, C(4)H_AH_B), 2.41 (1H, ddd, *J* 13.2, 8.4, 7.0 Hz, C(4)H_AH_B), 3.25 (1H, dt, *J* 10.0, 7.1 Hz, C(5)H_AH_B), 3.40 (1H, ddd, *J* 10.0, 8.5, 3.8 Hz, C(5)H_AH_B), 3.92 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 4.00 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.23 (1H, s, O*H*), 5.20-5.27 (2H, m, $NCH_2CH=CH_2$), 5.74 (1H, ddt, *J* 17.7, 9.7, 6.2 Hz, $NCH_2CH=CH_2$), 7.24-7.31 (4H, m, ArC(2,3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 36.1 (*C*(4)H), 43.1 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 78.4 (*C*(3)), 118.8 ($NCH_2CH=CH_2$), 126.7 (Ar*C*(3,5)H), 128.8 (Ar*C*(2,6)H), 131.6 ($NCH_2CH=CH_2$), 133.6 (Ar*C*(4)), 141.4 (Ar*C*(4)), 174.5 (*C*=O); ***m/z* (NSI)** 252 ($[M+H]^+$, 100%) $C_{13}H_{15}NO_2Cl^+$ ($[M+H]^+$) requires 252.0786; found 252.0784 (–0.7 ppm).

Lab book Reference: SMS-688

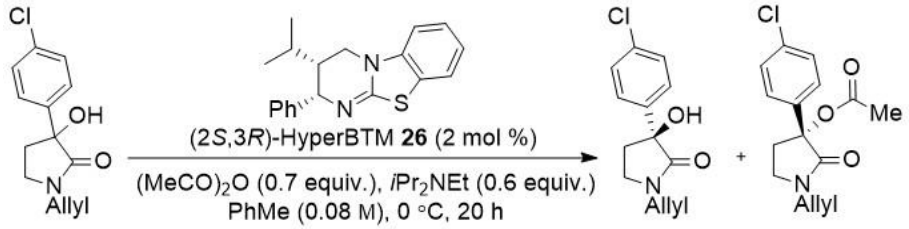
1-Allyl-3-(4-chlorophenyl)-2-oxopyrrolidin-3-yl acetate, 253



Following general procedure B, **252** (40 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.29), **253** as a colourless oil (44 mg, 0.15 mmol, 94%); **ν_{max} (ATR)** 2974, 1742 (C=O), 1686 (C=O), 1371, 1223; **δ_H (400 MHz, $CDCl_3$)** 2.16 (3H, s, CH_3), 2.69-2.81 (2H, m, C(4)*H*), 3.38 (1H, dt, *J* 9.8, 7.6 Hz, C(5)H_AH_B), 3.53 (1H, ddd, *J* 9.8, 7.3, 5.1 Hz, C(5)H_AH_B), 3.91 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 3.99 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.20-5.29 (2H, m, $NCH_2CH=CH_2$), 5.74 (1H, ddt, *J* 17.1, 10.2, 6.1 Hz, $NCH_2CH=CH_2$), 7.32-7.37 (2H, m, ArC(2,6)*H*), 7.41-7.47 (2H, m, ArC(3,5)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.5 (*C*H_3), 31.5 (*C*(4)H), 43.1 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 82.8 (*C*(3)), 118.7 ($NCH_2CH=CH_2$), 126.7 (Ar*C*(3,5)H), 128.8 (Ar*C*(3,5)H), 131.6 ($NCH_2CH=CH_2$), 134.5 (Ar*C*(1)), 137.5 (Ar*C*(1)), 169.9 (*C*=O(CH_3)), 170.1 (*C*(2)=O); ***m/z* (NSI)** 294 ($[M+H]^+$, 100%) $C_{15}H_{17}NO_3Cl^+$ ($[M+H]^+$) requires 294.0891; found 294.0896 (+1.5 ppm).

Lab book Reference: SMS-694

Kinetic resolution of 252



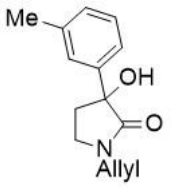
Following general procedure C, **252** (60 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (30 mg, 0.12 mmol, 50%) and ester (31 mg, 0.11 mmol, 44%).

Data for alcohol: $[\alpha]_D^{20}$ +112 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.4, 21.2 min, 92:8 er.

Data for ester: $[\alpha]_D^{20}$ +16 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 19.7, 31.2 min, 99:1 er; *s* = >200.

Lab book Reference: SMS-700

1-Allyl-3-hydroxy-3-(*m*-tolyl)pyrrolidin-2-one, 255

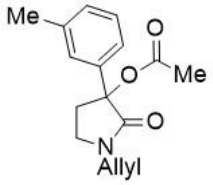


Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), *m*-tolylacetic acid (2.25 g, 15 mmol) and 1-bromo-2-chloroethane (2.74 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(*m*-tolyl)butanoic acid, which was taken on. Following general procedure H, acid (3.18 g, 15 mmol), 1,1'-carbonyldiimidazole (2.31 g, 14.25 mmol) and allylamine (1.35 mL, 18 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(*m*-tolyl)butanamide. Following general procedure I, amide (2.13 g, 8.47 mmol) and NaH (1.69 g, 42.3 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.23), **255** as a yellow oil (210 mg, 0.91 mmol, 11%); **ν_{max} (ATR)** 3347 (OH), 2918, 1674 (C=O), 1418, 1269; **δ_H (400 MHz, $CDCl_3$)** 2.33 (3H, s, ArC(3)CH_3), 2.34-2.46 (2H, m, C(4)*H*), 3.26 (1H, dt, *J* 9.9, 7.3 Hz, C(5)H_AH_B), 3.36 (1H, ddd, *J* 9.9, 8.1, 3.8 Hz, C(5)H_AH_B), 3.87 (1H, s, O*H*), 3.93 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 4.02 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 5.19-5.28 (2H, m, $NCH_2CH=CH_2$), 5.70-5.82 (1H, m, $NCH_2CH=CH_2$), 7.05-7.10 (1H, m, ArC(5)*H*), 7.13-7.17 (1H, m, ArC(6)*H*), 7.18-7.23 (2H, m, ArC(2,4)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (ArC(3)CH_3), 36.1 (*C*(4)H), 43.1 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 78.7 (*C*(3)), 118.6 ($NCH_2CH=CH_2$), 122.1

(Ar*C*(6)H), 125.8 (Ar*C*(2)H), 128.4 (Ar*C*(4)H), 128.6 (Ar*C*(5)H), 131.9 (NCH$_2$*C*H=CH$_2$), 138.1 (Ar*C*(3)), 142.5 (Ar*C*(1)), 174.9 (*C*=O); ***m/z* (NSI)** 232 ([M+H]$^+$, 100%) $C_{14}H_{18}NO_2^+$ ([M+H]$^+$) requires 232.1332; found 232.1332 (+0.0 ppm).

Lab book Reference: SMS-730

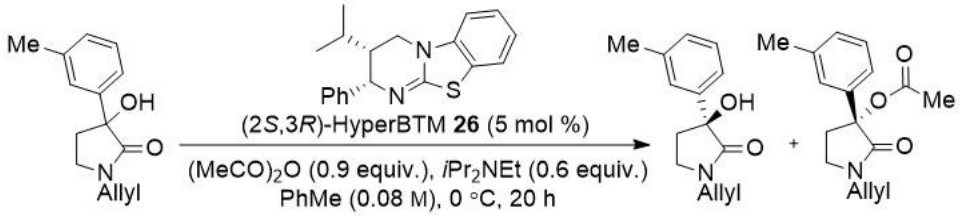
1-Allyl-2-oxo-3-(*m*-tolyl)pyrrolidin-3-yl acetate, 256



Following general procedure B, **255** (37 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.38 mmol) in CH$_2$Cl$_2$ (3 mL) gave, after column chromatography (eluent CH$_2$Cl$_2$/EtOAc, 9:1; R_F 0.35), **256** as a colourless oil (32 mg, 0.12 mmol, 73%); **ν_{max} (ATR)** 2918, 1736 (C=O), 1697 (C=O), 1437, 1231; **δ_H (400 MHz, CDCl$_3$)** 2.17 (C=OC*H*$_3$), 2.37 (3H, s, ArC(3)C*H*$_3$), 2.70-2.82 (2H, m, C(4)*H*), 3.35-3.44 (1H, m, C(5)*H*$_A$H$_B$), 3.53 (1H, ddd, *J* 9.7, 7.5, 5.0 Hz, C(5)H$_A$*H*$_B$), 3.92 (1H, dd, *J* 15.2, 6.2 Hz, NC*H*$_A$H$_B$CH=CH$_2$), 4.01 (1H, dd, *J* 15.2, 5.9 Hz, NCH$_A$*H*$_B$CH=CH$_2$), 5.20-5.30 (2H, m, NCH$_2$CH=C*H*$_2$), 5.76 (1H, ddt, *J* 16.2, 10.2, 6.0 Hz, NCH$_2$C*H*=CH$_2$), 7.10-7.17 (1H, m, ArC(5)*H*), 7.23-7.29 (2H, m, ArC(4,6)*H*), 7.31 (1H, s, ArC(2)*H*); **δ_C (100 MHz, CDCl$_3$)** 21.6 (C=O*C*H$_3$), 21.7 (ArC(3)*C*H$_3$), 31.8 (*C*(4)H), 43.1 (*C*(5)H), 46.0 (N*C*H$_2$CH=CH$_2$), 83.4 (*C*(3)), 118.5 (NCH$_2$CH=*C*H$_2$), 122.1 (Ar*C*(6)H), 125.8 (Ar*C*(2)H), 128.6 (Ar*C*(4)H), 129.2 (Ar*C*(5)H), 131.8 (NCH$_2$*C*H=CH$_2$), 138.4 (Ar*C*(3)), 139.0 (Ar*C*(1)), 170.0 (*C*=OCH$_3$), 174.9 (*C*(2)=O); ***m/z* (NSI)** 274 ([M+H]$^+$, 100%) $C_{16}H_{20}NO_3^+$ ([M+H]$^+$) requires 274.1438; found 274.1439 (+0.5 ppm).

Lab book Reference: SMS-737

Kinetic resolution of 255



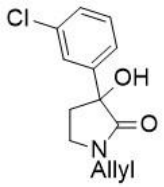
Following general procedure C, **255** (55 mg, 0.24 mmol), acetic anhydride (22 µL, 0.216 mmol), (2*S*,3*R*)-HyperBTM **26** (3.8 mg, 0.012 mmol, 5 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH$_2$Cl$_2$/EtOAc, 9:1), alcohol (27 mg, 0.12 mmol, 49%) and ester (28 mg, 0.10 mmol, 43%).

Data for alcohol: $[\alpha]_D^{20}$ +221 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 37.3, 41.8 min, 92:8 er.

Data for ester: $[\alpha]_D^{20}$ +27 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 13.3, 21.9 min, 97:3 er; *s* = 70.

Lab book Reference: SMS-761

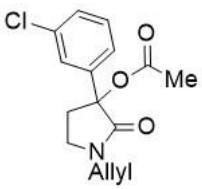
1-Allyl-3-(3-chlorophenyl)-3-hydroxypyrrolidin-2-one, 258



Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), 3-chlorophenylacetic acid (2.55 g, 15 mmol) and 1-bromo-2-chloroethane (2.74 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(3-chlorophenyl)butanoic acid, which was taken on. Following general procedure H, acid (3.48 g, 15 mmol), 1,1'-carbonyldiimidazole (2.31 g, 14.25 mmol) and allylamine (1.35 mL, 18 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(3-chlorophenyl)butanamide. Following general procedure I, amide (2.65 g, 9.77 mmol) and NaH (1.95 g, 48.9 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.38), **258** as a yellow solid (1.35 g, 5.38 mmol, 55%), mp 58-60 °C; **ν_{max} (ATR)** 3316 (OH), 2962, 1686 (C=O), 1414, 1273; **δ_H (400 MHz, $CDCl_3$)** 2.34 (1H, ddd, *J* 13.2, 7.3, 3.6 Hz, C(4)H_AH_B), 2.44 (1H, ddd, *J* 13.2, 8.4, 7.3 Hz, C(4)H_AH_B), 3.30 (1H, dt, *J* 10.1, 7.2 Hz, C(5)H_AH_B), 3.42 (1H, ddd, *J* 10.0, 8.6, 3.6 Hz, C(5)H_AH_B), 3.63 (1H, s, O*H*), 3.98 (1H, ddt, *J* 15.2, 6.1, 1.1 Hz, NCH_AH_BCH=CH_2), 4.04 (1H, ddt, *J* 15.1, 6.2, 1.2 Hz, NCH_AH_BCH=CH_2), 5.22-5.31 (2H, m, $NCH_2CH=CH_2$), 5.78 (1H, *J* 17.3, 9.9, 6.2 Hz, $NCH_2CH=CH_2$), 7.21-7.32 (3H, m, ArC(4,5,6)*H*), 7.38-7.43 (1H, m, ArC(2)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(4)H), 43.0 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 78.4 (*C*(3)), 119.0 ($NCH_2CH=CH_2$), 123.2 (Ar*C*(6)H), 125.2 (Ar*C*(2)H), 128.1 (Ar*C*(4)H), 129.9 (Ar*C*(5)H), 131.6 ($NCH_2CH=CH_2$), 134.6 (Ar*C*(3)), 144.7 (Ar*C*(1)), 174.9 (*C*=O); ***m/z* (NSI)** 252 ($[M+H]^+$, 100%) $C_{13}H_{15}NO_2Cl^+$ ($[M+H]^+$) requires 252.0786; found 252.0787 (+0.5 ppm).

Lab book Reference: SMS-748

1-Allyl-3-(3-chlorophenyl)-2-oxopyrrolidin-3-yl acetate, 259

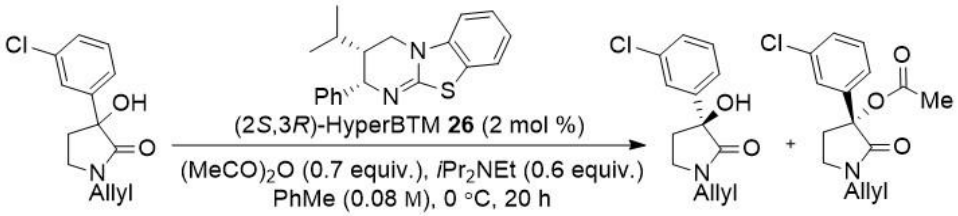


Following general procedure B, **258** (40 mg, 0.16 mmol), acetic anhydride (21 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and iPr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.37), **259** as a colourless oil (37 mg, 0.13 mmol, 79%);

ν_{max} (ATR) 2968, 1748 (C=O), 1686 (C=O), 1416, 1221; **δ_H (500 MHz, $CDCl_3$)** 2.18 (3H, s, CH_3), 2.67-2.79 (2H, m, C(4)H), 3.40 (1H, dt, J 9.8, 7.7 Hz, C(5)H_AH_B), 3.55 (1H, td, J 9.5, 3.4 Hz, C(5)H_AH_B), 3.91 (1H, dd, J 15.2, 6.3 Hz, NCH_AH_BCH=CH_2), 3.97-4.04 (1H, m, NCH_AH_BCH=CH_2), 5.22-5.29 (2H, m, $NCH_2CH=CH_2$), 5.75 (1H, m, $NCH_2CH=CH_2$), 7.28-7.32 (2H, m, ArC(4,5)H), 7.32-7.37 (1H, m, ArC(6)H), 7.46-7.52 (1H, m, ArC(2)H); **δ_C (125 MHz, $CDCl_3$)** 21.5 (CH_3), 31.7 (C(4)H), 43.1 (C(5)H), 46.1 ($NCH_2CH=CH_2$), 82.9 (C(3)), 118.8 ($NCH_2CH=CH_2$), 123.2 (ArC(6)H), 125.5 (ArC(2)H), 128.6 (ArC(4)H), 130.0 (ArC(5)H), 131.8 ($NCH_2CH=CH_2$), 134.7 (ArC(3)), 134.7 (ArC(1)), 169.8 (C=OCH_3), 170.0 (C(2)=O); ***m/z* (NSI)** 294 ($[M+H]^+$, 100%) $C_{15}H_{17}NO_3Cl^+$ ($[M+H]^+$) requires 294.0891; found 294.0894 (+0.9 ppm).

Lab book Reference: SMS-752

Kinetic resolution of 258



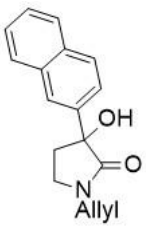
Following general procedure C, **258** (60 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr_2NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (27 mg, 0.11 mmol, 45%) and ester (32 mg, 0.11 mmol, 46%).

Data for alcohol: $[\alpha]_D^{20}$ +126 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 33.9, 38.2 min, 94:6 er.

Data for ester: $[\alpha]_D^{20}$ +43 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.2, 23.1 min, 92:8 er; *s* = 31.

Lab book Reference: SMS-767

1-Allyl-3-hydroxy-3-(naphthalen-2-yl)pyrrolidin-2-one, 261



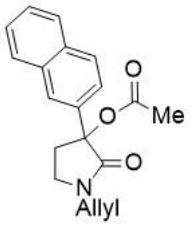
Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), 2-(naphthalen-2-yl)acetic acid (2.79 g, 15 mmol) and 1-bromo-2-chloroethane (2.74 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(naphthalene-2-yl)butanoic acid, which was taken on. Following general procedure H, the acid (3.72 g, 15 mmol), 1,1'-carbonyldiimidazole (2.31 g, 14.25 mmol) and allylamine (1.35 mL, 18 mmol) in anhydrous THF (50 mL) gave, after column

chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(naphthalen-2-yl)butanamide. Following general procedure I, amide (3.14 g, 10.9 mmol) and NaH (2.18 g, 54.5 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.26), **261** as a yellow solid (1.15 g, 4.30 mmol, 39%), mp 74-76 °C; **ν_{max} (ATR)** 3347 (OH), 2986, 1676 (C=O), 1422, 1275; **δ_H (400 MHz, $CDCl_3$)** 2.45-2.57 (2H, m, C(4)*H*), 3.31 (1H, dt, *J* 10.0, 7.4 Hz, C(5)H_AH_B), 3.42 (1H, ddd, *J* 10.0, 7.5, 4.3 Hz, C(5)H_AH_B), 3.48 (1H, s, O*H*), 4.01 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 4.10 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 5.24-5.32 (2H, m, $NCH_2CH=CH_2$), 5.82 (1H, ddt, *J* 17.0, 10.1, 6.1 Hz, $NCH_2CH=CH_2$), 7.45-7.51 (2H, m, ArC(6,7)*H*), 7.53 (1H, dd, *J* 8.6, 1.9 Hz, ArC(3)*H*), 7.77-7.83 (3H, m, ArC(4,5,8)*H*), 7.84 (1H, s, ArC(1)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(4)H), 43.0 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 79.0 (*C*(3)), 118.5 ($NCH_2CH=CH_2$), 123.4 (Ar*C*(3)H), 123.8 (Ar*C*(1)H), 126.25 (Ar*C*(6)H), 126.31 (Ar*C*(7)H), 127.6 (Ar*C*(5)H), 128.3 (Ar*C*(8)H), 128.7 (Ar*C*(4)H), 131.8 ($NCH_2CH=CH_2$), 132.9 (2C, Ar*C*(4a, 8a)), 139.6 (Ar*C*(2)), 174.6 (*C*=O);

***m/z* (NSI)** 268 ($[M+H]^+$, 100%) $C_{17}H_{18}NO_2^+$ ($[M+H]^+$) requires 268.1332; found 268.1333 (+0.4 ppm).

Lab book Reference: SMS-747

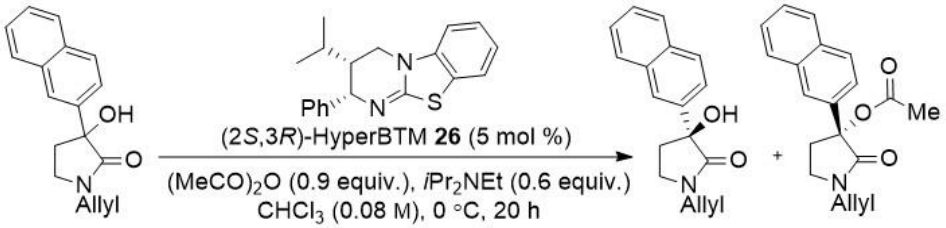
1-Allyl-3-(naphthalene-2-yl)-2-oxopyrrolidin-3-yl acetate, 262



Following general procedure B, **261** (43 mg, 0.16 mmol), acetic anhydride (21 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.29), **262** as a white solid (42 mg, 0.14 mmol, 85%); **ν_{max} (ATR)** 2907, 1734 (C=O), 1688 (C=O), 1447, 1225; **δ_H (400 MHz, $CDCl_3$)** 2.21 (3H, s, CH_3), 2.79-2.92 (2H, m, C(4)*H*), 3.45 (1H, dt, *J* 9.8, 7.6 Hz, C(5)H_AH_B), 3.57 (1H, ddd, *J* 9.8, 8.1, 4.3 Hz, C(5)H_AH_B), 3.95 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.04 (1H, ddt, *J* 15.2, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.21-5.31 (1H, m, $NCH_2CH=CH_2$), 5.71-5.84 (1H, m, $NCH_2CH=CH_2$), 7.46-7.52 (2H, m, ArC(6,7)*H*), 7.63 (1H, dd, *J* 8.7, 1.9 Hz, ArC(3)*H*), 7.79-7.90 (3H, m, ArC(4,5,8)*H*), 7.94 (1H, d, *J* 1.8 Hz, ArC(1)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H_3), 31.7 (*C*(4)H), 43.2 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 83.6 (*C*(3)), 118.6 ($NCH_2CH=CH_2$), 123.2 (Ar*C*(3)H), 124.2 (Ar*C*(1)H), 126.4 (Ar*C*(6)H), 126.5 (Ar*C*(7)H), 127.6 (Ar*C*(5)H), 128.4 (Ar*C*(8)H), 128.7 (Ar*C*(4)H), 131.8 ($NCH_2CH=CH_2$), 132.9 (Ar*C*(8a)), 133.1 (Ar*C*(4a)), 136.2 (Ar*C*(1)), 170.0 (*C*=OCH_3), 170.4 (*C*(2)=O); ***m/z* (NSI)** 310 ($[M+H]^+$, 100%) $C_{19}H_{20}NO_3^+$ ($[M+H]^+$) requires 310.1438; found 310.1440 (+0.7 ppm).

Lab book Reference: SMS-751

Kinetic resolution of 261



Following general procedure C, **261** (64 mg, 0.24 mmol), acetic anhydride (22 µL, 0.22 mmol), (2*S*,3*R*)-HyperBTM **26** (3.8 mg, 0.012 mmol, 5 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (32 mg, 0.12 mmol, 50%) and ester (30 mg, 0.10 mmol, 40%).

Data for alcohol: $[\alpha]_D^{20}$ +57 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.0, 23.6 min, 85:15 er.

Data for ester: $[\alpha]_D^{20}$ +37 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 58.1, 67.2 min, 92:8 er; *s* = 24.

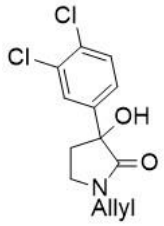
Lab book Reference: SMS-762

***N*-Allyl-4-chloro-2-(3,4-dichlorophenyl)butanamide, 263**

Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (4.6 mL, 33 mmol), 3,4-dichlorophenylacetic acid (3.06 g, 15 mmol) and 1-bromo-2-chloroethane (2.75 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-phenylbutanoic acid, which was taken on. Following general procedure H, the acid (3.31 g, 12.5 mmol), 1,1'-carbonyldiimidazole (1.93 g, 11.88 mmol) and allylamine (1.12 mL, 15 mmol) in anhydrous THF (20 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.45), **263** as an off white solid (2.35 g, 7.69 mmol, 51%), mp 63-65 °C; **ν_{max} (ATR)** 3289 (NH), 2968, 1637 (C=O), 1539, 1472; **δ_H (400 MHz, $CDCl_3$)** 2.14 (1H, dtd, *J* 14.6, 7.4, 4.5 Hz, C(3)H_AH_B), 2.54 (1H, dtd, *J* 15.1, 7.0, 4.5 Hz, C(3)H_AH_B), 3.37-3.45 (1H, m, C(4)H_AH_B), 3.57 (1H, ddd, *J* 11.7, 7.4, 4.5 Hz, C(4)H_AH_B), 3.67 (1H, t, *J* 7.5 Hz, C(2)*H*), 3.76-3.94 (2H, m, NCH_2CH=CH_2), 5.03-5.14 (2H, m, NCH$_2$CH=CH_2), 5.68 (2H, m, N*H*CH$_2$C*H*=CH$_2$), 7.21 (1H, dd, *J* 8.3, 2.1 Hz, ArC(6)*H*), 7.41 (1H, d, *J* 8.3 Hz, ArC(5)*H*), 7.46 (1H, d, *J* 2.1 Hz, ArC(2)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(3)H), 42.1 (N*C*H$_2$CH=CH$_2$), 42.8 (*C*(4)H), 48.7 (*C*(2)H), 116.7 (NCH$_2$CH=*C*H$_2$), 127.3 (Ar*C*(6)H), 130.0 (Ar*C*(2)H), 130.9 (Ar*C*(5)H), 131.9 (Ar*C*(3)), 133.0 (Ar*C*(4)), 133.7 (NCH$_2$*C*H=CH$_2$), 138.9 (Ar*C*(1)), 171.2 (*C*=O); ***m/z* (NSI)** 306 ([M+H]$^+$, 100%) $C_{13}H_{15}NOCl_3^+$ ([M+H]$^+$) requires 306.0214; found 306.0216 (+0.7 ppm).

Lab book Reference: SMS-681

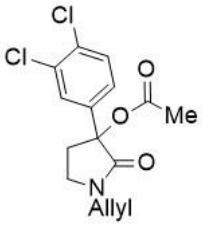
1-Allyl-3-(3,4-dichlorophenyl)-3-hydroxypyrrolidin-2-one, 264



Following general procedure I, **263** (2.35 g, 7.69 mmol) and NaH (1.54 mg, 38.45 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.30), **264** as a white solid (788 mg, 2.76 mmol, 36%), mp 66-68 °C; **ν_{max} (ATR)** 3312 (OH), 2980, 1684 (C=O), 1385, 1279; **δ_H (400 MHz, $CDCl_3$)** 2.23 (1H, ddd, *J* 13.3, 7.6, 4.4 Hz, C(4)H_AH_B), 2.39 (1H, ddd, *J* 13.4, 8.3, 6.2 Hz, C(4)H_AH_B), 3.26 (1H, ddd, *J* 10.1, 7.5, 6.3 Hz, C(5)H_AH_B), 3.42 (1H, ddd, *J* 10.1, 8.3, 4.4 Hz, C(5)H_AH_B), 3.91 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NCH_AH_BCH=CH_2), 3.98 (1H, ddt, *J* 15.0, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.83 (1H, s, O*H*), 5.19-5.27 (2H, m, $NCH_2CH=CH_2$), 5.67-5.78 (1H, m, $NCH_2CH=CH_2$), 7.13 (1H, dd, *J* 8.4, 2.2 Hz, ArC(6)*H*), 7.34 (1H, d, *J* 8.4 Hz, ArC(5)*H*), 7.46 (1H, d, *J* 2.2 Hz, ArC(2)*H*); **δ_C (100 MHz, $CDCl_3$)** 36.2 (*C*(4)H), 43.2 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 78.2 (*C*(3)), 119.0 ($NCH_2CH=CH_2$), 124.7 (Ar*C*(6)H), 127.5 (Ar*C*(2)H), 130.3 (Ar*C*(5)H), 131.4 ($NCH_2CH=CH_2$), 131.7 (Ar*C*(1)), 132.5 (Ar*C*(3)), 143.0 (Ar*C*(4)), 174.2 (*C*=O); ***m/z* (NSI)** 286 ($[M+H]^+$, 100%) $C_{13}H_{14}NO_2Cl_2^+$ ($[M+H]^+$) requires 286.0396; found 286.0399 (+1.0 ppm).

Lab book Reference: SMS-687

1-Allyl-3-(3,4-dichlorophenyl)-2-oxopyrrolidin-3-yl acetate, 265

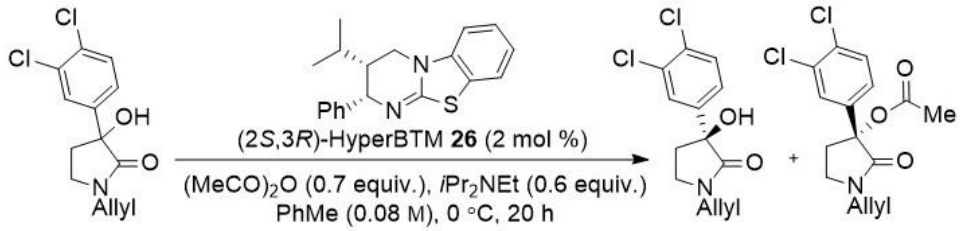


Following general procedure B, **264** (46 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.35), **265** as a colourless oil (50 mg, 0.15 mmol, 96%); **ν_{max} (ATR)** 2907, 1744 (C=O), 1686 (C=O), 1375, 1221; **δ_H (400 MHz, $CDCl_3$)** 2.17 (3H, s, CH_3), 2.65-2.79 (2H, m, C(4)*H*), 3.39 (1H, dt, *J* 9.9, 7.5 Hz, C(5)H_AH_B), 3.55 (1H, ddd, *J* 9.9, 8.3, 4.4 Hz, C(5)H_AH_B), 3.91 (1H, ddt, *J* 15.2, 6.3, 1.3 Hz, NCH_AH_BCH=CH_2), 4.00 (1H, ddt, *J* 15.1, 5.9, 1.4 Hz, NCH_AH_BCH=CH_2), 5.22-5.29 (2H, m, $NCH_2CH=CH_2$), 5.68-5.80 (1H, m, $NCH_2CH=CH_2$), 7.32 (1H, dd, *J* 8.5, 2.2 Hz, ArC(6)*H*), 7.45 (1H, d, *J* 8.5 Hz, ArC(5)*H*), 7.60 (1H, d, *J* 2.2 Hz, ArC(6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.5 (CH_3), 31.5 (*C*(4)H), 43.1 (*C*(5)H), 46.1 ($NCH_2CH=CH_2$), 82.4 (*C*(3)), 118.9 ($NCH_2CH=CH_2$), 124.6 (Ar*C*(6)H), 127.6 (Ar*C*(2)H), 130.6 (Ar*C*(5)H), 131.4 ($NCH_2CH=CH_2$), 132.7 (Ar*C*(1)), 133.0 (Ar*C*(3)), 139.3 (Ar*C*(4)), 169.6 (*C*=O(CH_3)),

169.7 (*C*(2)=O); ***m/z* (NSI)** 328 ([M+H$^+$], 100%) $C_{15}H_{16}NO_3Cl_2$ ([M+H$^+$]) requires 328.0502; found 328.0506 (+1.3 ppm).

Lab book Reference: SMS-693

Kinetic resolution of 264



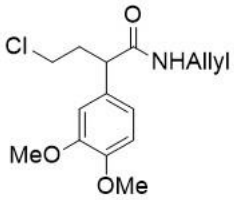
Following general procedure C, **264** (68 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (32 mg, 0.11 mmol, 47%) and ester (29 mg, 0.09 mmol, 38%).

Data for alcohol: $[\alpha]_D^{20}$ +43 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AS-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 9.0, 23.0 min, 85:15 er.

Data for ester: $[\alpha]_D^{20}$ +92 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 15.8, 26.6 min, 93:7 er; *s* = 27.

Lab book Reference: SMS-699

***N*-Allyl-4-chloro-2-(3,4-dimethoxyphenyl)butanamide, 266**

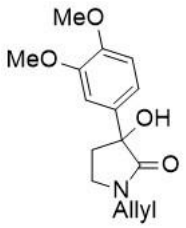


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (1.55 mL, 22 mmol), 3,4-dimethoxyphenyl acetic acid (1.96 g, 10 mmol) and 1-bromo-2-chloroethane (1.82 mL, 22 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-phenylbutanoic acid, which was taken on. Folllowing general procedure H, the acid (2.58 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.34), **266** as a yellow solid (877 mg, 2.95 mmol, 30%), mp 65-67 °C; **ν_{max} (ATR)** 3322 (NH), 2916, 1638 (C=O), 1516, 1227, 1142; **δ_H (400 MHz, $CDCl_3$)** 2.11 (1H, dddd, *J* 13.3, 8.1, 6.6, 5.0 Hz, C(3)H_AH_B), 2.44-2.55 (1H, m, C(3)H_AH_B), 3.32 (1H, ddd, *J* 11.0, 8.0, 4.9 Hz, C(4)H_AH_B), 3.50 (1H, ddd, *J* 11.4, 6.4, 5.2 Hz, C(4)H_AH_B), 3.59-3.65 (1H, m, C(2)*H*), 3.73-3.82 (8H, m, NCH_2CH=CH_2, ArC(3)OCH_3, ArC(4)OCH_3), 4.92-5.00 (2H, m, NCH$_2$CH=CH_2), 5.64-5.74 (1H, m, NCH$_2$C*H*=CH$_2$), 5.99 (1H, t, *J* 5.7 Hz, N*H*), 6.73-6.82 (2H, m, ArC(2,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.8 (*C*(3)H), 41.8 (N*C*H$_2$CH=CH$_2$),

43.2 (*C*(4)H), 49.0 (*C*(2)H), 55.8 (ArC(3)O*C*H$_3$, ArC(4)O*C*H$_3$), 110.7 (Ar*C*(2)H), 111.3 (Ar*C*(5)H), 115.9 (NCH$_2$CH=*C*H$_2$), 120.4 (Ar*C*(6)H), 131.2 (Ar*C*(1)), 134.1 (NCH$_2$*C*H=CH$_2$), 148.4 (Ar*C*(4)), 149.2 (Ar*C*(3)), 172.6 (*C*=O); ***m/z* (NSI)** 298 ([M+H]$^+$, 100%) $C_{15}H_{21}NO_3Cl^+$ ([M+H]$^+$) requires 298.1204; found 298.1209 (+1.5 ppm).

Lab book Reference: SMS-696

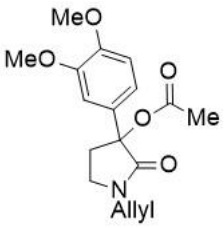
1-Allyl-3-(3,4-dimethoxyphenyl)-3-hydroxypyrrolidin-2-one, 267



Following general procedure I, **266** (877 mg, 2.95 mmol) and NaH (590 mg, 14.76 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.09), **267** as a white solid (291 mg, 1.05 mmol, 11%), mp 106-108 °C; **ν_{max} (ATR)** 3292 (OH), 2983, 1674 (C=O), 1508, 1263, 1136; **δ_H (400 MHz, $CDCl_3$)** 2.34-2.47 (2H, m, C(4)*H*), 3.25 (1H, dt, *J* 9.9, 7.4 Hz, C(5)*H*$_A$H$_B$), 3.35 (1H, ddd, *J* 9.9, 7.6, 3.9 Hz, C(5)H$_A$*H*$_B$), 3.55 (1H, s, O*H*), 3.85 (3H, s, ArC(4)OC*H*$_3$), 3.86 (3H, s, ArC(3)OC*H*$_3$), 3.92 (1H, ddt, *J* 15.1, 6.1, 1.3 Hz, NC*H*$_A$H$_B$CH=CH$_2$), 4.05 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH$_A$*H*$_B$CH=CH$_2$), 5.20-5.26 (2H, m, NCH$_2$CH=C*H*$_2$), 5.74 (1H, ddt, *J* 17.0, 9.7, 6.1 Hz, NCH$_2$C*H*=CH$_2$), 6.78 (1H, *J* 8.4 Hz, ArC(5)*H*), 6.83 (1H, *J* 8.3, 2.1 Hz, ArC(6)*H*), 7.03 (1H, *J* 2.1 Hz, ArC(2)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.9 (*C*(4)H), 43.0 (*C*(5)H), 45.9 (NC*H*$_2$CH=CH$_2$), 55.9 (ArC(3)O*C*H$_3$, ArC(4)O*C*H$_3$), 78.4 (*C*(3)), 108.8 (Ar*C*(2)H), 110.8 (Ar*C*(5)H), 117.1 (Ar*C*(6)H), 118.6 (NCH$_2$CH=*C*H$_2$), 131.8 (NCH$_2$C*H*=CH$_2$), 134.9 (Ar*C*(1)), 148.7 (Ar*C*(3)), 149.1 (Ar*C*(4)), 174.8 (*C*=O); ***m/z* (NSI)** 278 ([M+H]$^+$, 100%) $C_{15}H_{20}NO_4^+$ ([M+H]$^+$) requires 278.1387; found 278.1389 (+0.8 ppm).

Lab book Reference: SMS-703

1-Allyl-3-(3,4-dimethoxyphenyl)-2-oxopyrrolidin-3-yl acetate, 268

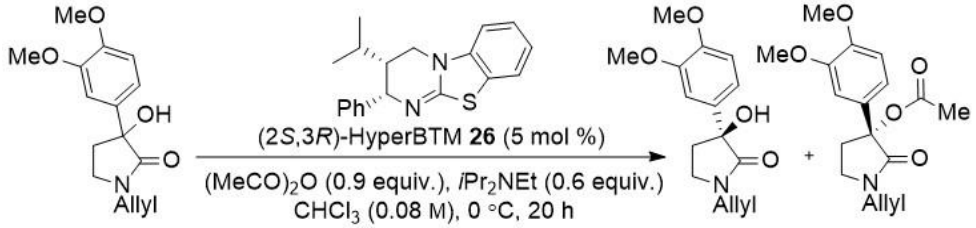


Following general procedure B, **267** (44 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr$_2$NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.26), **268** as a yellow oil (49 mg, 0.15 mmol, 95%); **ν_{max} (ATR)** 2936, 1740 (C=O), 1697 (C=O), 1516, 1231, 1022; **δ_H (400 MHz, $CDCl_3$)** 2.15 (3H, s, C*H*$_3$), 2.70-2.86 (2H, m, C(4)*H*), 3.36 (1H, dt, *J* 9.7, 7.7 Hz, C(5)*H*$_A$H$_B$), 3.49 (1H, td, *J* 9.2, 3.0 Hz, C(5)H$_A$*H*$_B$), 3.87

(3H, s, ArC(4)OCH_3), 3.90 (3H, s, ArC(3)OCH_3), 3.89-4.00 (2H, m, NCH_2CH=CH$_2$), 5.18-5.25 (2H, m, NCH$_2$CH=CH_2), 5.68-5.79 (1H, m, NCH$_2$CH=CH$_2$), 6.84 (1H, *J* 8.5 Hz, ArC(5)*H*), 7.02 (1H, *J* 8.4, 2.2 Hz, ArC(6)*H*), 7.12 (1H, *J* 2.2 Hz, ArC(2)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (*C*H$_3$), 31.4 (*C*(4)H), 43.1 (*C*(5)H), 45.9 (N*C*H$_2$CH=CH$_2$), 55.9 (ArC(3)O*C*H$_3$), 56.0 (ArC(4)O*C*H$_3$), 83.1 (*C*(3)), 109.2 (Ar*C*(2)H), 110.8 (Ar*C*(5)H), 117.5 (Ar*C*(6)H), 118.4 (NCH$_2$CH=*C*H$_2$), 131.0 (NCH$_2$C*H*=CH$_2$), 131.0 (Ar*C*(1)), 149.1 (Ar*C*(3)), 149.3 (Ar*C*(4)), 170.0 (*C*=OCH$_3$), 170.5 (*C*=O); ***m/z* (NSI)** 342 ([M+Na]$^+$, 100%) $C_{17}H_{21}NO_5Na$ ([M+Na]$^+$) requires 342.1312; found 342.1314 (+0.6 ppm).

Lab book Reference: SMS-706

Kinetic resolution of 267



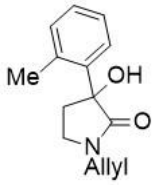
Following general procedure C, **267** (67 mg, 0.24 mmol), acetic anhydride (22 µL, 0.22 mmol), (2*S*,3*R*)-HyperBTM **26** (3.8 mg, 0.012 mmol, 5 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in $CHCl_3$ (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1), alcohol (41 mg, 0.15 mmol, 61%) and ester (21 mg, 0.07 mmol, 28%).

Data for alcohol: $[\alpha]_D^{20}$ +40 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 47.7, 64.4 min, 71:29 er.

Data for ester: $[\alpha]_D^{20}$ –8 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.7, 23.4 min, 93:7 er; *s* = 20.

Lab book Reference: SMS-734

1-Allyl-3-hydroxy-3-(*o*-tolyl)pyrrolidin-2-one, 270



Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (4.6 mL, 33 mmol), *o*-tolylacetic acid (2.25 g, 15 mmol) and 1-bromo-2-chloroethane (2.74 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(*o*-tolyl)butanoic acid, which was taken on. Following general procedure H, acid (3.18 g, 15 mmol), 1,1'-carbonyldiimidazole (2.31 g, 14.25 mmol) and allylamine (1.35 mL, 18 mmol) in anhydrous THF (50 mL) gave, after column chromatopgraphy (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(*o*-tolyl)butanamide. Following general procedure I, amide (2.13 g, 8.47

mmol) and NaH (1.69 g, 42.3 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.26), **270** as a yellow solid (201 mg, 0.87 mmol, 10%), mp 56-58 °C; **ν_{max} (ATR)** 3292 (OH), 2957, 1667 (C=O), 1456, 1271; **δ_H (400 MHz, $CDCl_3$)** 2.34-2.44 (2H, m, C(4)*H*), 2.45 (3H, s, ArC(3)CH_3), 3.18 (1H, dt, *J* 9.9, 7.2 Hz, C(5)H_AH_B), 3.35 (1H, ddd, *J* 9.9, 7.9, 4.3 Hz, C(5)H_AH_B), 3.55 (1H, s, O*H*), 3.95 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.08 (1H, ddt, *J* 15.1, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 5.21-5.30 (2H, m, NCH_2CH=CH_2), 5.73-5.84 (1H, m, NCH_2CH=CH_2), 7.06-7.13 (1H, m, ArC(4)*H*), 7.15-7.21 (3H, m, ArC(3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 20.6 (ArC(3)CH_3), 34.7 (*C*(4)H), 43.1 (*C*(5)H), 45.9 (NCH_2CH=CH_2), 79.9 (*C*(3)), 118.7 (NCH_2CH=CH_2), 125.5 (Ar*C*(4)H), 125.8 (Ar*C*(6)H), 127.9 (Ar*C*(5)H), 131.8 (NCH_2CH=CH_2), 132.8 (Ar*C*(3)H), 136.5 (Ar*C*(2)), 139.5 (Ar*C*(1)), 175.1 (*C*=O); ***m/z* (NSI)** 232 ($[M+H]^+$, 100%) $C_{14}H_{18}NO_2^+$ ($[M+H]^+$) requires 232.1332; found 232.1333 (+0.4 ppm).

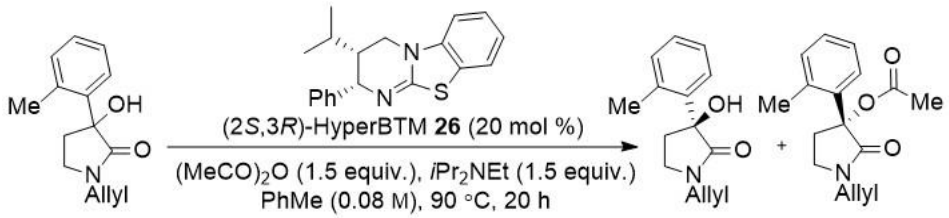
Lab book Reference: SMS-731

1-Allyl-2-oxo-3-(*o*-tolyl)pyrrolidin-3-yl acetate, 271

Following general procedure B, **270** (47 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.33), **271** as a colourless oil (35 mg, 0.13 mmol, 80%); **ν_{max} (ATR)** 2986, 1742 (C=O), 1701 (C=O), 1263, 1231; **δ_H (400 MHz, $CDCl_3$)** 2.14 (3H, s, C=OCH_3), 2.43-2.50 (1H, m, C(4)H_AH_B), 2.50 (3H, s, ArC(3)CH_3), 2.98 (1H, ddd, *J* 13.1, 9.9, 7.0 Hz, C(4)H_AH_B), 3.19-3.28 (1H, m, C(5)H_AH_B), 3.50 (1H, td, *J* 9.8, 2.7 Hz, C(5)H_AH_B), 4.00-4.15 (2H, m, NCH_2CH=CH_2), 5.22-5.36 (2H, m, NCH_2CH=CH_2), 5.76-5.89 (1H, m, NCH_2CH=CH_2), 7.11-7.20 (2H, m, ArC(4,6)*H*), 7.21-7.25 (2H, m, ArC(3,5)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.2 (ArC(2)CH_3), 21.5 (C=OCH_3), 31.5 (*C*(4)H), 43.0 (*C*(5)H), 46.0 (NCH_2CH=CH_2), 85.7 (*C*(3)), 118.5 (NCH_2CH=CH_2), 125.8 (Ar*C*(4)H), 126.0 (Ar*C*(6)H), 128.5 (Ar*C*(5)H), 131.8 (NCH_2CH=CH_2), 132.6 (Ar*C*(3)H), 137.0 (2C, Ar*C*(1,2)), 170.1 (*C*=OCH_3), 170.7 (*C*(2)=O); ***m/z* (NSI)** 274 ($[M+H]^+$, 100%) $C_{16}H_{20}NO_3^+$ ($[M+H]^+$) requires 274.1438; found 274.1438 (+0.1 ppm).

Lab book Reference: SMS-738

Kinetic resolution of 270



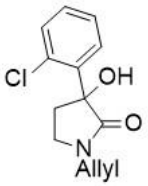
Following general procedure C, **270** (55 mg, 0.24 mmol), acetic anhydride (36 µL, 0.36 mmol), (2*S*,3*R*)-HyperBTM **26** (15 mg, 0.048 mmol, 20 mol %) and *i*Pr_2NEt (63 µL, 0.36 mmol) in PhMe (3 mL) at 90 °C gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (28 mg, 0.12 mmol, 51%) and ester (26 mg, 0.09 mmol, 40%).

Data for alcohol: $[\alpha]_D^{20}$ +33 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 9.8, 11.7 min, 74:26 er.

Data for ester: $[\alpha]_D^{20}$ +11 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.3, 16.1 min, 80:20 er; *s* = 6.

Lab book Reference: SMS-907

1-Allyl-3-(2-chlorophenyl)-3-hydroxypyrrolidin-2-one, 273

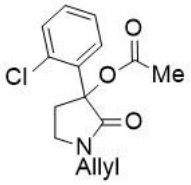


Following general procedure G, *n*BuLi (13.2 mL, 33 mmol, 2.5 M in hexanes), HN^iPr_2 (4.6 mL, 33 mmol), 2-chlorophenylacetic acid (2.55 g, 15 mmol) and 1-bromo-2-chloroethane (2.74 mL, 33 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(2-chlorophenyl)butanoic acid, which was taken on. Folowing general procedure H, acid (3.48 g, 15 mmol), 1,1'-carbonyldiimidazole (2.31 g, 14.25 mmol) and allylamine (1.35 mL, 18 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(3-chlorophenyl)butanamide. Following general procedure I, amide (2.13 g, 7.86 mmol) and NaH (1.57 g, 39.3 mmol, 60% in mineral oil) in anhydrous THF (50 mL)gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.21), **272** as a white solid (228 mg, 0.91 mmol, 12%), mp 101-103 °C; **ν_{max} (ATR)** 3300 (OH), 2955, 1672 (C=O), 1441, 1265; **δ_H (400 MHz, $CDCl_3$)** 2.29 (1H, ddd, *J* 13.8, 8.3, 3.8 Hz, C(4)H_AH_B), 2.61 (1H, dddd, *J* 13.9, 8.8, 6.2, 1.4 Hz, C(4)H_AH_B), 3.25 (1H, s, O*H*), 3.41 (1H, ddd, *J* 9.8, 8.9, 3.8 Hz, C(5)H_AH_B), 3.53 (1H, ddd, *J* 9.8, 8.3, 6.2 Hz, C(5)H_AH_B), 3.93 (1H, ddt, *J* 15.1, 6.4, 1.3 Hz, NCH_AH_BCH=CH_2), 4.08 (1H, ddt, *J* 15.1, 6.0, 1.3 Hz, NCH_AH_BCH=CH_2), 5.23-5.33 (2H, m, $NCH_2CH=CH_2$), 5.80 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, $NCH_2CH=CH_2$), 7.21-7.30 (2H, m, ArC(5,6)*H*), 7.33-7.40 (1H, m, ArC(4)*H*), 7.65-7.71 (1H, m, ArC(3)*H*); **δ_C (100 MHz, $CDCl_3$)** 33.0 (*C*(4)H), 43.7 (*C*(5)H), 45.9 ($NCH_2CH=CH_2$), 79.3 (*C*(3)), 118.7 ($NCH_2CH=CH_2$), 126.7

(Ar*C*(6)H), 127.8 (Ar*C*(3)H), 129.3 (Ar*C*(5)H), 130.8 (Ar*C*(4)H), 131.6 (Ar*C*(2)), 131.7 ($NCH_2CH=CH_2$), 139.4 (Ar*C*(1)), 173.6 (*C*=O); ***m/z* (NSI)** 252 ($[M+H]^+$, 100%) $C_{13}H_{15}NO_2Cl^+$ ($[M+H]^+$) requires 252.0786; found 252.0788 (+0.9 ppm).

Lab book Reference: SMS-749

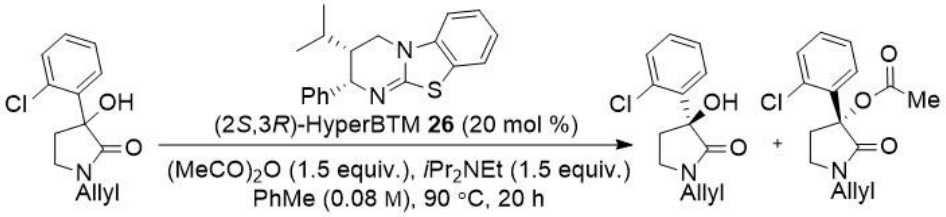
1-Allyl-3-(3-chlorophenyl)-2-oxopyrrolidin-3-yl acetate, 274



Following general procedure B, **273** (40 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.39), **274** as a colourless oil (32 mg, 0.11 mmol, 67%); **ν_{max} (ATR)** 2963, 1734 (C=O), 1699 (C=O), 1423, 1234; **δ_H (400 MHz, $CDCl_3$)** 2.16 (3H, s, CH_3), 2.68 (1H, ddd, *J* 14.2, 8.6, 3.7 Hz, C(4)H_AH_B), 2.93 (1H, ddd, *J* 14.2, 9.7, 5.7 Hz, C(4)H_AH_B), 3.25-3.32 (1H, m, C(5)H_AH_B), 3.55 (1H, td, *J* 9.7, 3.7 Hz, C(5)H_AH_B), 4.05 (2H, ddt, *J* 6.1, 2.7, 1.4 Hz, NCH_2CH=CH_2), 5.26 (1H, dq, *J* 10.2, 1.3 Hz, $NCH_2CH=CH_{cis}H_{trans}$), 5.32 (1H, dq, *J* 17.1, 1.5 Hz, $NCH_2CH=CH_{cis}H_{trans}$), 5.82 (1H, ddt, *J* 17.1, 10.2, 6.1 Hz, $NCH_2CH=CH_2$), 7.26-7.31 (2H, m, ArC(5,6)*H*), 7.43-7.46 (1H, m, ArC(4)*H*), 7.46-7.50 (1H, m, ArC(3)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.4 (CH_3), 31.0 (*C*(4)H), 43.4 (*C*(5)H), 46.3 ($NCH_2CH=CH_2$), 84.5 (*C*(3)), 118.7 ($NCH_2CH=CH_2$), 126.8 (Ar*C*(6)H), 128.2 (Ar*C*(3)H), 129.7 (Ar*C*(5)H), 131.67 (Ar*C*(4)H), 131.7 ($NCH_2CH=CH_2$), 133.4 (Ar*C*(2)), 136.6 (Ar*C*(1)), 169.5 (*C*=OCH_3), 170.0 (*C*(2)=O); ***m/z* (NSI)** 294 ($[M+H]^+$, 100%) $C_{15}H_{17}NO_3Cl^+$ ($[M+H]^+$) requires 294.0891; found 294.0894 (+0.9 ppm).

Lab book Reference: SMS-753

Kinetic resolution of 273



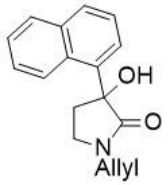
Following general procedure C, **273** (60 mg, 0.24 mmol), acetic anhydride (36 µL, 0.36 mmol), (2*S*,3*R*)-HyperBTM **26** (15 mg, 0.048 mmol, 20 mol %) and *i*Pr_2NEt (36 µL, 0.36 mmol) in PhMe (3 mL) at 90 °C gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (28 mg, 0.11 mmol, 47%) and ester (30 mg, 0.10 mmol, 43%).

Data for alcohol: $[\alpha]_D^{20}$ +19 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.9, 20.6 min, 86:14 er.

Data for ester: $[\alpha]_D^{20}$ +62 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 15.4, 25.7 min, 88:12 er; *s* = 15.

Lab book Reference: SMS-917

1-Allyl-3-hydroxy-3-(naphthalen-1-yl)pyrrolidin-2-one, 276



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 2-(naphthalen-1-yl)acetic acid (1.86 g, 10 mmol) and 1-bromo-2-chloroethane (1.83 mL, 22 mmol) in anhydrous THF (50 mL) gave 4-chloro-2-(naphthalene-1-yl)butanoic acid, which was taken on. Following general procedure H, acid (2.48 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 12 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3), impure *N*-allyl-4-chloro-2-(naphthalen-1-yl)butanamide. Following general procedure I, amide (1.60 mg, 5.58 mmol) and NaH (1.12 g, 27.9 mmol, 60% in mineral oil) in anhydrous THF (50 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.29), **276** as a colourless oil (216 mg, 0.81 mmol, 8%); **ν_{max} (ATR)** 3345 (OH), 2988, 1676 (C=O), 1267; **δ_H (400 MHz, $CDCl_3$)** 2.65 (1H, dt, *J* 12.7, 8.7 Hz, C(4)H_AH_B), 2.81 (1H, ddd, *J* 12.7, 6.7, 2.1 Hz, C(4)H_AH_B), 3.14 (1H, ddd, *J* 9.9, 8.7, 6.7 Hz, C(5)H_AH_B), 3.36 (1H, ddd, *J* 10.0, 8.8, 2.1 Hz, C(5)H_AH_B), 3.53 (1H, s, O*H*), 4.06 (1H, ddt, *J* 15.1, 6.1, 1.2 Hz, NCH_AH_BCH=CH_2), 4.13 (1H, ddt, *J* 15.0, 6.2, 1.2 Hz, NCH_AH_BCH=CH_2), 5.25-5.33 (2H, m, NCH_2CH=CH_2), 5.84 (1H, ddt, *J* 16.3, 10.1, 6.2 Hz, NCH_2CH=CH_2), 7.27 (1H, dd, *J* 7.1, 1.2 Hz, ArC(2)*H*), 7.30-7.35 (1H, m, ArC(7)*H*), 7.46-7.56 (2H, m, ArC(3,6)*H*), 7.78 (1H, d, *J* 8.1 Hz, ArC(5)*H*), 7.84-7.89 (1H, m, ArC(8)*H*), 8.46-8.51 (1H, m, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 35.7 (*C*(4)H), 43.2 (*C*(5)H), 45.9 (NCH_2CH=CH_2), 80.3 (*C*(3)), 118.8 (NCH_2CH=CH_2), 123.8 (Ar*C*(2)H), 124.6 (Ar*C*(4)H), 125.7 (Ar*C*(6)H), 126.0 (Ar*C*(3)H), 126.2 (Ar*C*(7)H), 129.1 (Ar*C*(8)H), 129.4 (Ar*C*(5)H), 130.7 (Ar*C*(8a)), 131.6 (NCH_2CH=CH_2), 134.9 (Ar*C*(4a)), 136.6 (Ar*C*(1)), 175.1 (*C*=O); ***m/z* (NSI)** 268 ($[M+H]^+$, 100%) $C_{17}H_{18}NO_2^+$ ($[M+H]^+$) requires 268.1332; found 268.1335 (+1.1 ppm).

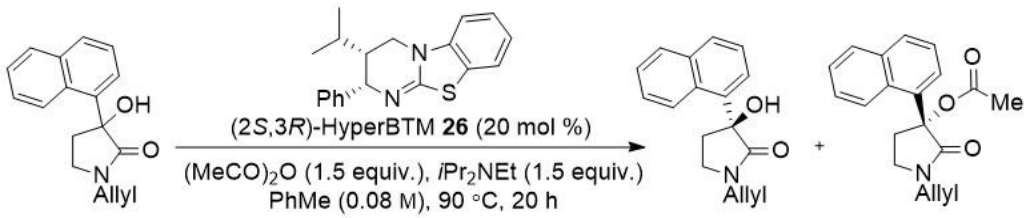
Lab book Reference: SMS-704

1-Allyl-3-(naphthalene-1-yl)-2-oxopyrrolidin-3-yl acetate, 277

Following general procedure B, **276** (43 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 4:1; R_F 0.53), **277** as a colourless oil (36 mg, 0.12 mmol, 73%); **ν_{max} (ATR)** 2986, 1740 (C=O), 1697 (C=O), 1229, 1094; **δ_H (400 MHz, $CDCl_3$)** 2.16 (3H, s, CH_3), 2.73-2.84 (1H, m, C(4)H_AH_B), 3.16-3.26 (1H, m, C(4)H_AH_B, C(5)H_AH_B), 3.48-3.58 (1H, m, C(5)H_AH_B), 4.07 (1H, ddt, *J* 15.2, 6.2, 1.3 Hz, NCH_AH_BCH=CH_2), 4.16 (1H, ddt, *J* 15.1, 5.6, 1.3 Hz, NCH_AH_BCH=CH_2), 5.27 (1H, dq, *J* 10.2, 1.2 Hz, $NCH_2CH=CH_{cis}H_{trans}$), 5.34 (1H, dq, *J* 17.1, 1.5 Hz, $NCH_2CH=CH_{cis}H_{trans}$), 5.85 (1H, ddt, *J* 17.0, 10.2, 6.0 Hz, $NCH_2CH=CH_2$), 7.37-7.41 (1H, m, ArC(7)*H*), 7.46 (1H, dd, *J* 7.3, 1.3 Hz, ArC(2)*H*), 7.49-7.58 (2H, m, ArC(3,6)*H*), 7.84 (1H, d, *J* 8.1 Hz, ArC(5)*H*), 7.87-7.92 (1H, m, ArC(8)*H*), 8.20-8.25 (1H, m, ArC(4)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.6 (CH_3), 32.2 (*C*(4)H), 43.1 (*C*(5)H), 46.0 ($NCH_2CH=CH_2$), 85.9 (*C*(3)), 118.5 ($NCH_2CH=CH_2$), 124.6 (Ar*C*(2)H), 124.8 (Ar*C*(4)H), 125.7 (Ar*C*(6)H), 125.8 (Ar*C*(4)H), 126.2 (Ar*C*(3)H), 129.3 (Ar*C*(8)H), 130.0 (Ar*C*(5)H), 130.7 (Ar*C*(8a)), 131.8 ($NCH_2CH=CH_2$), 134.2 (Ar*C*(1)), 134.9 (Ar*C*(4a)), 170.3 ($C=OCH_3$), 170.6 (*C*(2)=O); ***m/z* (NSI)** 310 ($[M+H]^+$, 100%) $C_{19}H_{20}NO_3^+$ ($[M+H]^+$) requires 310.1438; found 310.1440 (+0.7 ppm).

Lab book Reference: SMS-707

Kinetic resolution of 276



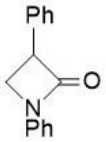
Following general procedure C, **276** (64 mg, 0.24 mmol), acetic anhydride (36 µL, 0.36 mmol), (2*S*,3*R*)-HyperBTM **26** (15 mg, 0.048 mmol, 20 mol %) and *i*Pr_2NEt (63 µL, 0.36 mmol) in PhMe (3 mL) at 90 °C gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (35 mg, 0.13 mmol, 55%) and ester (28 mg, 0.09 mmol, 38%).

Data for alcohol: $[\alpha]_D^{20}$ +119 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.5, 33.1 min, 64:36 er.

Data for ester: $[\alpha]_D^{20}$ +69 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.9, 22.1 min, 69:31 er; *s* = 3.

Lab book Reference: SMS-918

1,3-Diphenylazetidin-2-one, 284

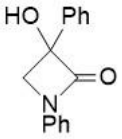


Following the procedure by Cade *et al*,[120] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (1.52 g, 5.5 mmol) was added to a magnetically stirred solution of tropic acid (841 mg, 5 mmol) and aniline (502 µL, 5.5 mmol) in MeOH (50 mL) at RT. The reaction mixture was stirred overnight, then concentrated *in vacuo*. The residue was treated with water (30 mL) and extracted with EtOAc (2 x 75 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent hexane/EtOAc, 1:1; R_F 0.20), impure 3-hydroxy-*N*,2-diphenylpropanamide. Diethyl diazodicarboxylate (662 µL, 4.22 mmol) was added to a magnetically stirred solution of triphenylphosphine (1.11 g, 4.22 mmol) and the amide (1.02 g, 4.22 mmol) in THF (50 mL) under a N_2 atmosphere at RT. The solution was stirred for 12 h, then concentrated *in vacuo*. The residue was purified to give, after column chromatography (eluent hexane/EtOAc, 5:1; R_F 0.30), **284** as a white solid (410 mg, 1.84 mmol, 37%), mp 101-103 °C; **δ_H (400 MHz, $CDCl_3$)** 3.69 (1H, dd, *J* 5.8, 2.9 Hz, C(4)H_AH_B), 4.07 (1H, t, *J* 5.9 Hz, C(3)*H*), 4.52 (1H, dd, *J* 5.9, 2.9 Hz, C(4)H_AH_B), 7.11-7.16 (1H, m, ArC*H*), 7.28-7.41 (7H, m, ArC*H*), 7.42-7.47 (2H, m, ArC*H*).

Data were in accordance with those previously reported.

Lab book Reference: SMS-770

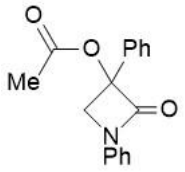
3-Hydroxy-1,3-diphenylazetidin-2-one, 285



Following general procedure I, **284** (410 mg, 1.84 mmol) and NaH (368 mg, 9.19 mmol, 60% in mineral oil) in anhydrous THF (25 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.30), **285** as a yellow wax (91 mg, 0.38 mmol, 21%); **ν_{max} (ATR)** 3354 (OH), 3032, 1721 (C=O), 1597, 1495, 1383, 1150; **δ_H (400 MHz, $CDCl_3$)** 3.94 (1H, d, *J* 5.8 Hz, C(4)H_AH_B), 4.00 (1H, d, *J* 5.8 Hz, C(4)H_AH_B), 4.09 (1H, s, O*H*), 7.12-7.17 (1H, m, C(3)ArC(4)*H*), 7.32-7.42 (7H, m, NArC(2,3,4,5,6)*H*, C(3)ArC(3,5)*H*), 7.51-7.58 (1H, m, C(3)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 56.4 (*C*(4)H), 84.4 (*C*(3)), 117.6 (NAr*C*(2,6)H), 124.7 (C(3)Ar*C*(4)H), 125.6 (C(3)Ar*C*(2,6)H), 128.8 (NAr*C*(4)H), 128.9 (NAr*C*(3,5)H), 129.3 (C(3)Ar*C*(3,5)H), 137.6 (C(3)Ar*C*(1)), 138.2 (NAr*C*(1)), 166.7 (*C*=O); ***m/z* (NSI)** 240 ($[M+H]^+$, 100%) $C_{15}H_{14}NO_2^+$ ($[M+H]^+$) requires 240.1019; found 240.1021 (+0.8 ppm).

Lab book Reference: SMS-772

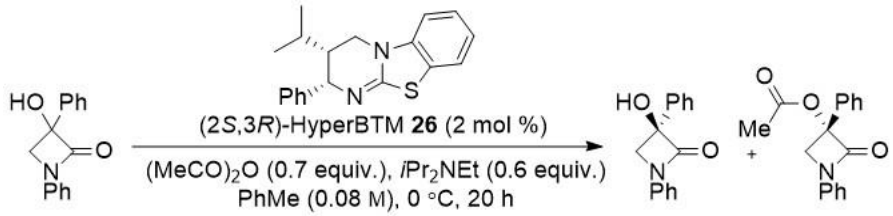
2-Oxo-1,3-diphenylazetidin-3-yl acetate, 289



Following general procedure B, **285** (24 mg, 0.10 mmol), acetic anhydride (13 µL, 0.13 mmol), DMAP **4** (1.25 mg, 0.01 mmol, 10 mol %) and *i*Pr$_2$NEt (44 µL, 0.24 mmol) in CH_2Cl_2 (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.86), **289** as a colourless oil (26 mg, 0.093 mmol, 93%); **ν_{max} (ATR)** 3061, 1741 (C=O), 1599, 1497, 1387, 1219; **δ_H (700 MHz, $CDCl_3$)** 2.16 (3H, s, CH_3), 4.26 (1H, d, *J* 6.7 Hz, C(4)H_AH_B), 4.40 (1H, d, *J* 6.7 Hz, C(4)H_AH_B), 7.15 (1H, t, *J* 7.3 Hz, C(3)ArC(4)*H*), 7.35-7.44 (7H, m, NArC(2,3,4,5,6)*H*, C(3)ArC(3,5)*H*), 7.62-7.65 (1H, m, C(3)ArC(2,6)*H*); **δ_C (176 MHz, $CDCl_3$)** 21.2 (*C*H_3), 52.2 (*C*(4)H), 86.4 (*C*(3)), 116.9 (NAr*C*(2,6)H), 124.7 (C(3)Ar*C*(4)H), 126.8 (C(3)Ar*C*(2,6)H), 128.8 (NAr*C*(3,5)H), 129.2 (NAr*C*(4)H), 129.3 (C(3)Ar*C*(3,5)H), 134.2 (C(3)Ar*C*(1)), 137.5 (NAr*C*(1)), 162.5 (*C*(2)=O), 169.8 (*C*=OCH$_3$); ***m/z* (NSI)** 282 ([M+H]$^+$, 100%) $C_{17}H_{16}NO_3^+$ ([M+H]$^+$) requires 282.1125; found 282.1128 (+1.2 ppm).

Lab book Reference: SMS-773

Kinetic resolution of 285



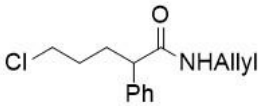
Following general procedure C, **285** (57 mg, 0.24 mmol), acetic anhydride (17 µL, 0.17 mmol), (2*S*,3*R*)-HyperBTM **26** (1.5 mg, 0.0048 mmol, 2 mol %) and *i*Pr$_2$NEt (25 µL, 0.144 mmol) in PhMe (3 mL) gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (18 mg, 0.08 mmol, 32%) and ester (36 mg, 0.13 mmol, 54%).

Data for alcohol: $[\alpha]_D^{20}$ +212 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.1, 28.9 min, 95:5 er.

Data for ester: $[\alpha]_D^{20}$ +27 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 31.5, 54.8 min, 78:22 er; *s* = 10.

Lab book Reference: SMS-807

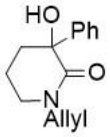
_N_-Allyl-5-chloro-2-phenylpentanamide, 287



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), $HN^{i}Pr_2$ (3.1 mL, 22 mmol), phenylacetic acid (1.36 g, 10 mmol) and 1-bromo-3-chloropropane (2.18 mL, 22 mmol) in anhydrous THF (50 mL) gave 5-chloro-2-phenylpentanoic acid, which was taken on. Following general procdure H, acid (2.12 g, 10 mmol), 1,1'-carbonyldiimidazole (1.54 g, 9.5 mmol) and allylamine (898 µL, 18 mmol) in anhydrous THF (50 mL) gave, after column chromatography (eluent Petrol/EtOAc, 7:3; R_F 0.30), **287** as a white solid (583 mg, 2.32 mmol, 23%), mp 55-57 °C; **ν_{max} (ATR)** 3300 (NH), 2930, 1634 (C=O), 1533, 1233; **δ_H (400 MHz, $CDCl_3$)** 1.60-1.84 (2H, m, C(4)*H*), 1.89-2.00 (1H, m, C(3)H_AH_B), 2.28 (1H, dddd, *J* 13.3, 10.5, 7.1, 5.3 Hz, C(3)H_AH_B), 3.38 (1H, t, *J* 7.6 Hz, C(2)*H*), 3.45-3.56 (2H, m, C(5)*H*), 3.74-3.88 (2H, m, $NCH_2CH=CH_2$), 4.96-5.06 (2H, m, $NCH_2CH=CH_2$), 5.67-5.80 (2H, m, N*H*, $NCH_2CH=CH_2$), 7.24-7.37 (5H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 30.5 (*C*(3)H), 30.8 (*C*(4)H), 41.9 ($NCH_2CH=CH_2$), 44.8 (*C*(5)H), 52.6 (*C*(2)H), 116.1 ($NCH_2CH=CH_2$), 127.5 (Ar*C*(4)H), 127.9 (Ar*C*(2,6)H), 129.0 (Ar*C*(3,5)H), 134.1 ($NCH_2CH=CH_2$), 139.5 (Ar*C*(1)), 172.9 (*C*=O); ***m/z* (NSI)** 252 ($[M+H]^+$, 100%) $C_{14}H_{19}NOCl^+$ ($[M+H]^+$) requires 252.1150; found 252.1152 (+0.9 ppm).

Lab book Reference: SMS-764

1-Allyl-3-hydroxy-3-phenylpiperidin-2-one, 288

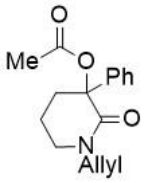


Following general procedure I, to **287** (583 mg, 2.32 mmol) in anhydrous THF (50 mL) under N_2 was added NaH (464 mg, 11.6 mmol, 60% in mineral oil) and the mixture stirred for 2 h under N_2. The reaction was then exposed to air and stirred for 16 h. On completion, NH_4Cl (30 mL) was added and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude was then purified via column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.24) to afford **288** as a white solid (218 mg, 0.94 mmol, 41%), mp 58-60 °C; **ν_{max} (ATR)** 3464 (OH), 2938, 1622 (C=O), 1492, 1267, 1105; **δ_H (400 MHz, $CDCl_3$)** 1.57-1.70 (1H, m, C(5)H_AH_B), 1.74-1.84 (1H, m, C(5)H_AH_B), 2.17 (1H, td, *J* 13.0, 3.7 Hz, C(4)H_AH_B), 2.25-2.33 (1H, m, C(4)H_AH_B), 3.29-3.42 (2H, m, C(6)*H*), 3.97-4.06 (2H, m, $NCH_AH_BCH=CH_2$, O*H*) 4.22 (1H, ddt, *J* 14.8, 6.1, 1.3 Hz, $NCH_AH_BCH=CH_2$), 5.22-5.31 (2H, m, $NCH_2CH=CH_2$), 5.87 (1H, ddt, *J* 17.6, 9.6, 6.2 Hz, $NCH_2CH=CH_2$), 7.24-7.41 (5H, m, ArC*H*); **δ_C (100 MHz, $CDCl_3$)** 18.7 (*C*(5)H), 35.4 (*C*(4)H), 47.5 (*C*(6)H), 50.0 ($NCH_2CH=CH_2$), 75.4 (*C*(3)), 118.5 ($NCH_2CH=CH_2$), 126.0 (Ar*C*(2,6)H), 127.7 (Ar*C*(4)H), 128.3

(Ar*C*(3,5)H), 132.2 ($NCH_2C\mathit{H}=CH_2$), 144.7 (Ar*C*(1)), 172.6 (*C*=O); ***m/z* (NSI)** 232 ($[M+H]^+$, 100%) $C_{14}H_{18}NO_2^+$ ($[M+H]^+$) requires 232.1332; found 232.1331 (–0.5 ppm).

Lab book Reference: SMS-813

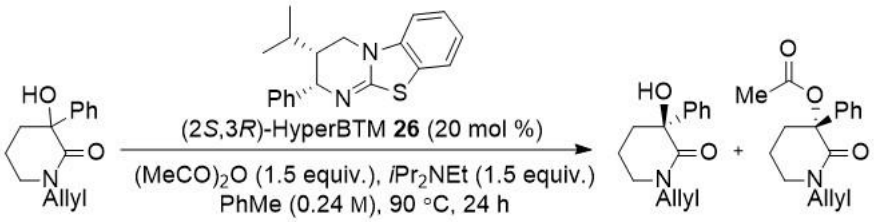
1-Allyl-2-oxo-3-phenylpiperidin-3-yl acetate, 290



Following general procedure B, **288** (37 mg, 0.16 mmol), acetic anhydride (20 µL, 0.21 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and *i*Pr_2NEt (70 µL, 0.38 mmol) were reacted in CH_2Cl_2 (3 mL) to give the crude product, which was product was purified by column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.44) to afford **290** as a colourless oil (37 mg, 0.13 mmol, 84%); **ν_{max} (ATR)** 2940, 1736 (C=O), 1659 (C=O), 1489, 1370, 1233; **δ_H (400 MHz, $CDCl_3$)** 1.62-1.82 (2H, m, C(5)*H*), 2.11-2.20 (4H, s, CH_3, C(4)H_AH_B), 2.86 (1H, ddd, *J* 13.5, 12.6, 4.0 Hz, C(4)H_AH_B), 3.24-3.32 (1H, m, C(6)H_AH_B), 3.54 (1H, td, *J* 12.0, 4.6 Hz, C(6)H_AH_B), 4.12 (1H, ddt, *J* 14.9, 6.3, 1.3 Hz, $NCH_ACH_BCH=CH_2$), 4.20 (1H, ddt, *J* 14.9, 5.8, 1.4 Hz, $NCH_ACH_BCH=CH_2$), 5.22-5.34 (2H, m, $NCH_2CH=CH_2$), 5.83-5.95 (1H, m, $NCH_2CH=CH_2$), 7.28-7.39 (3H, m, ArC(3,4,5)*H*), 7.41-7.47 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 19.7 (*C*(5)H), 21.7 (CH_3), 34.4 (*C*(4)H), 47.3 (*C*(6)H), 50.1 ($NCH_2CH=CH_2$), 83.3 (*C*(3)), 117.9 ($NCH_2CH=CH_2$), 126.7 (Ar*C*(2,6)H), 128.2 (Ar*C*(4)H), 128.3 (Ar*C*(3,5)H), 132.7 ($NCH_2CH=CH_2$), 141.8 (Ar*C*(1)), 168.0 (*C*=OCH_3), 170.4 (*C*(2)=O); ***m/z* (NSI)** 274 ($[M+H^+]$, 100%) $C_{16}H_{20}NO_3$ ($[M+H^+]$) requires 274.1438; found 274.1439 (+0.5 ppm).

Lab book Reference: SMS-817

Kinetic resolution of 288



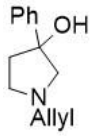
Following general procedure C, **288** (55 mg, 0.24 mmol), acetic anhydride (34 µL, 0.36 mmol), (2*S*,3*R*)-HyperBTM **26** (15 mg, 0.048 mmol, 20 mol %) and *i*Pr_2NEt (63 µL, 0.36 mmol) in PhMe (1 mL) at 90 °C for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (16 mg, 0.11 mmol, 44%) and ester (30 mg, 0.11 mmol, 44%).

Data for alcohol: $[\alpha]_D^{20}$ +67 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (0.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 58.5, 67.7 min, 89:11 er.

Data for ester: $[\alpha]_D^{20}$ –112 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (2.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.0, 29.4 min, 92:8 er; *s* = 25.

Lab book Reference: SMS-832

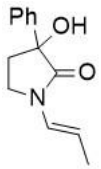
1-Allyl-3-phenylpyrrolidin-3-ol, 298



Following the procedure by Ma *et al*,[122] **217** (550 mg, 2.53 mmol) was dissolved in anhydrous THF (50 mL). $LiAlH_4$ (3.04 mL, 6.08 mmol, 2.0 M in THF) was added in portions. The reaction mixture was then heated under reflux for 24 h. Upon completion, H_2O (1 mL) was added, followed by 1M NaOH (1 mL) and H_2O (5 mL). The organic layer was extracted with EtOAc (3 x 10 mL), dired ($MgSO_4$), filtered and concentrated *in vacuo*, to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.15), **298** as a colourless oil (93 mg, 0.46 mmol, 18%); **ν_{max} (ATR)** 3366 (OH), 2801, 1643, 1447, 1263; **δ_H (400 MHz, $CDCl_3$)** 2.21 (1H, dddd, *J* 14.1, 7.9, 6.2, 1.4 Hz, C(4)H_AH_B), 2.33-2.42 (1H, m, C(4)H_AH_B), 2.57 (1H, td, *J* 9.4, 6.2 Hz, C(5)H_AH_B), 2.68 (1H, d, *J* 10.0 Hz, C(2)H_AH_B), 3.06 (1H, d, *J* 10.0 Hz, C(2)H_AH_B), 3.14-3.24 (3H, m, C(5)H_AH_B, $NCH_2CH{=}CH_2$), 3.63 (1H, s, O*H*), 5.13 (1H, ddt, *J* 10.2, 1.9, 1.0 Hz, $NCH_2CH{=}CH_{cis}H_{trans}$), 5.22 (1H, dq, *J* 17.1, 1.5 Hz, $NCH_2CH{=}CH_{cis}H_{trans}$), 5.93 (1H, ddt, *J* 16.7, 10.2, 6.5 Hz, $NCH_2CH{=}CH_2$), 7.22-7.29 (1H, m, ArC(4)*H*), 7.31-7.37 (1H, m, ArC(3,5)*H*), 7.48-7.53 (1H, m, ArC(2,6)*H*); **δ_C (176 MHz, $CDCl_3$)** 42.0 (*C*(4)H), 52.9 (*C*(5)H), 58.8 ($NCH_2CH{=}CH_2$), 68.6 (*C*(2)H), 80.7 (*C*(3)), 117.6 ($NCH_2CH{=}CH_2$), 125.2 (C(3)Ar*C*(3,5)H), 127.0 (C(3)Ar*C*(4)H), 128.2 (NAr*C*(2,6)H), 135.1 ($NCH_2CH{=}CH_2$), 144.5 (C(3)Ar*C*(1)); ***m/z* (NSI)** 204 ($[M+H]^+$, 100%) $C_{13}H_{18}NO^+$ ($[M+H]^+$) requires 204.1383; found 204.1382 (–0.4 ppm).

Lab book Reference: SMS-774

(*E*)-3-Hydroxy-3-phenyl-1-(prop-1-en-1-yl)pyrrolidin-2-one, 303



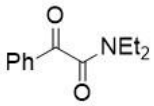
Following the procedure by Tokunga *et al*,[125] palladium (II) trifluoroacetate (1.33 mg, 0.004 mmol, 1 mol%), 1,3-bis(diphenylphosphino)propane (3.3 mg, 0.008 mmol, 2 mol%), degassed MeCN (0.4 mL) and water (144 µL, 20 equiv.) were added to a flame dried Schlenk under N_2 and stirred for 10 mins. **217** (86 mg, 0.4 mmol) was then added and the reaction mixture heated at 80 C for 24 h. The reaction mixture was concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.47), **303** as a pale yellow soild (69 mg, 0.32 mmol, 80%); **ν_{max} (ATR)** 3358 (OH), 2959, 1678 (C=O), 1667 (C=C), 1418, 1283; **δ_H (400 MHz, $CDCl_3$)** 1.77 (3H, d, *J* 6.7, 1.6 Hz, $NCH{=}CHCH_3$), 2.41-2.57 (2H, m,

C(4)*H*), 3.36 (1H, dt, *J* 10.2, 7.6 Hz, C(5)H_AH_B), 3.45 (1H, s, O*H*), 3.59 (1H, ddd, *J* 10.2, 7.9, 3.9 Hz, C(5)H_A*H*$_B$), 5.09-5.19 (1H, m, NCH=C*H*CH_3), 6.93 (1H, dd, *J* 14.4, 1.6 Hz, NC*H*=$CHCH_3$), 7.26-7.39 (5H, m, ArC*H*); **δ_C (176 MHz, $CDCl_3$)** 15.3 (NCH=CH*C*H_3), 35.4 (*C*(4)*H*), 41.7 (*C*(5)*H*), 79.0 (*C*(3)), 109.0 (NCH=*C*HCH_3), 124.3 (N*C*H=$CHCH_3$), 125.0 (Ar*C*(2,6)H), 128.1 (Ar*C*(4)H), 128.7 (Ar*C*(3,5)H), 142.2 (Ar*C*(1)), 172.7 (*C*=O); ***m/z*** **(NSI)** 21 ($[M+H]^+$, 100%) $C_{13}H_{16}NO_2^+$ ($[M+H]^+$) requires 218.1176; found 218.1174 (–0.7 ppm).

Lab book Reference: SMS-803

6.5 Data for Chapter 4: Kinetic resolution of acyclic tertiary alcohols

***N,N*-Diethyl-2-oxo-2-phenylacetamide, 315**

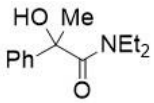


Following the procedure outlined by Sivagura,[160] phenylglyoxylic acid **314** (1.50 g, 10 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to 0 °C under a N_2 atmosphere. Oxalyl chloride (2.2 mL, 25 mmol) was added slowly, then DMF (2 drops) was added. The reaction was stirred for 15 mins, then warmed to RT and stirred for 3 h. The reaction concentrated *in vacuo* at 25 °C and taken on without further purification. Following the procedure outlined by Heaney,[161] a solution of diethylamine (1.24 mL, 12 mmol) and $NaHCO_3$ (1.00 g, 11.9 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and stirred for 1 h. 2-Oxo-2-phenylacetylchloride (1.68 g, 10 mmol) in CH_2Cl_2 (10 mL) was added, the reaction mixture warmed to rt and stirred for 1 h. The reaction mixture was poured into aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give, after column chromatography (eluent Petrol/EtOAc, 7:3; R_F 0.29), **315** as a yellow oil (1.00 g, 4.9 mmol, 49%); **δ_H (400 MHz, $CDCl_3$)** 1.10 (3H, t, *J* 7.1 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 1.24 (3H, t, *J* 7.2 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 3.19 (2H, d, *J* 7.1 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 3.52 (2H, q, *J* 7.2 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 7.43-7.46 (2H, m, ArC(3,5)*H*), 7.56-7.61 (1H, m, ArC(4)*H*), 7.87-7.91 (2H, m, ArC(2,6)*H*);

Data is in accordance with the literature.[162]

Lab book Reference: SMS-925

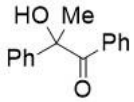
***N,N*-Diethyl-2-hydroxy-2-phenylpropanamide, 316**



Following general procedure D, **315** (1.00 g, 4.9 mmol) and methylmagnesium bromide (2 mL, 6 mmol, 3.0 M) in anhydrous THF (50 mL) gave, after column chromatography (Petrol:EtOAc, 9:1; R_F 0.33), **316** as an off yellow solid (777 mg, 3.5 mmol, 72%), mp 70-72 °C; **ν_{max} (ATR)** 3343 (OH), 2972, 1593 (C=O), 1445, 1366; **δ_H (400 MHz, $CDCl_3$)** 0.64 (3H, t, *J* 6.9 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 1.12 (3H, t, *J* 6.9 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 1.78 (3H, s, C(2)$CH_3$), 2.98 (2H, d, *J* 6.4 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 3.36 (2H, dq, *J* 11.8, 6.5 Hz, $N(CH_2CH_3)_A(CH_2CH_3)_B$), 5.46 (1H, s, O*H*), 7.22-7.29 (1H, m, ArC(4)*H*), 7.30-7.37 (4H, m, ArC(2,3,5,6)*H*).

Lab book Reference: SMS-926

2-Hydroxy-1,2-diphenylpropan-1-one, 318

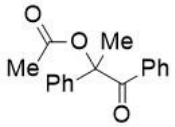


Following general procedure D, benzil **317** (2.10 g, 10 mmol) and methylmagnesium bromide (4 mL, 12 mmol, 3.0 M) in anhydrous THF (50 mL) gave, after column chromatography (CH_2Cl_2:EtOAc, 9:1; R_F 0.45), **318** as a white solid (1.28 g, 5.7 mmol, 57%), mp 49-51 °C; **ν_{max} (ATR)** 3437 (OH), 2995, 1667 (C=O), 1595, 1445; **δ_H (400 MHz, $CDCl_3$)** 1.90 (3H, s, C(2)C*H*$_3$), 4.77 (1H, s, O*H*), 7.27-7.35 (3H, m, C(2)ArC(3,4,5)*H*), 7.36-7.42 (2H, m, C=OArC(3,5)*H*), 7.43-7.48 (3H, m, C(2)ArC(2,6)*H*, C=OArC(4)*H*), 7.66-7.70 (2H, m, C=OArC(2,6)*H*).

Data is in accordance with the literature.[163]

Lab book Reference: SMS-941

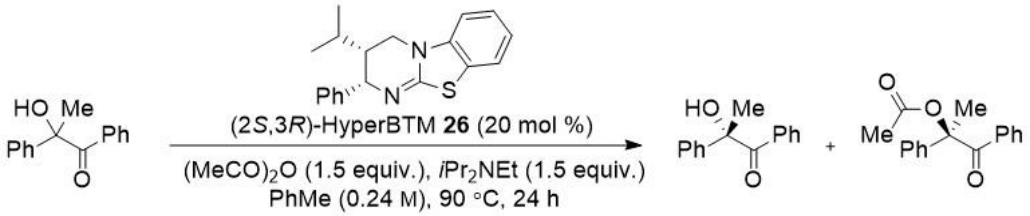
1-Oxo-1,2-diphenylpropan-2-yl acetate, 324



Following general procedure J, **318** (36 mg, 0.16 mmol), acetic anhydride (61 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) at 50 °C to give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 9:1; R_F 0.29) to afford **324** as a yellow oil (37 mg, 0.13 mmol, 84%); **ν_{max} (ATR)** 3026, 1738 (C=O), 1690 (C=O), 1447, 1368, 1211; **δ_H (400 MHz, $CDCl_3$)** 1.95 (3H, s, C*H*$_3$), 2.00 (C=OC*H*$_3$), 7.23-7.29 (2H, m, C(2)ArC(3,5)*H*), 7.29-7.34 (1H, m, C(2)ArC(4)*H*), 7.36-7.42 (3H, m, C=OArC(3,4,5)*H*), 7.52-7.56 (2H, m, C(2)ArC(2,6)*H*), 7.68-7.73 (2H, m, C=OArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.4 (*C*H$_3$), 26.8 (C=O*C*H$_3$), 87.1 (*C*(2)C=OPh), 124.2 (C(2)Ar*C*(2,6)H), 128.0 (C(2)Ar*C*(4)H), 128.1 (C(2)Ar*C*(3,5)H), 129.0 (C=OAr*C*(3,5)H), 129.1 (C=OAr*C*(2,6)H), 132.2 (C=OAr*C*(4)H), 135.0 (C=OAr*C*(1)), 140.3 (C(2)Ar*C*(1)), 169.5 (*C*=OCH$_3$), 196.8 (*C*=OPh); ***m/z* (NSI)** 286 ($[M+NH_4]^+$, 100%) $C_{17}H_{20}NO_3^+$ ($[M+NH_4]^+$) requires 286.1438; found 286.1440 (+0.8 ppm).

Lab book Reference: SMS-972

Kinetic resolution of 318



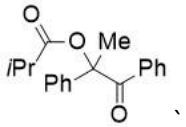
Following general procedure C, **318** (55 mg, 0.24 mmol), acetic anhydride (34 µL, 0.36 mmol), (2*S*,3*R*)-HyperBTM **26** (15 mg, 0.048 mmol, 20 mol %) and *i*Pr_2NEt (63 µL, 0.36 mmol) in PhMe (1 mL) at 90 °C for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (24 mg, 0.11 mmol, 44%) and ester (26 mg, 0.10 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +26 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.1, 13.5 min, 62:38 er.

Data for ester: $[\alpha]_D^{20}$ +386 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 6.1, 7.9 min, 71:29 er; *s* = 3.

Lab book Reference: SMS-991

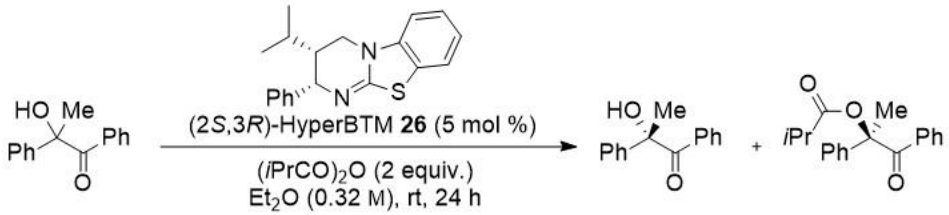
1-Oxo-1,2-diphenylpropan-2-yl isobutyrate, 371



Following general procedure J, **318** (36 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (4 mg, 0.032 mmol, 20 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.34) to afford **371** as a yellow oil (40 mg, 0.13 mmol, 84%); **ν_{max} (ATR)** 2938, 1730 (C=O), 1682 (C=O), 1447, 1261, 1117; **δ_H (400 MHz, $CDCl_3$)** 0.97 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.06 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.92 (3H, s, CH_3), 2.51 (C=OC*H*(CH_3)$_2$), 7.21-7.26 (2H, m, C(2)ArC(3,5)*H*), 7.30-7.43 (4H, m, C(2)ArC(4)*H*, C=OArC(3,4,5)*H*), 7.53-7.58 (2H, m, C(2)ArC(2,6)*H*), 7.62-7.67 (2H, m, C=OArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (C=OCH(CH_3)$_A$(CH_3)$_B$), 18.6 (C=OCH(CH_3)$_A$(CH_3)$_B$), 26.8 (C(2)*C*H_3), 34.3 (C=O*C*H(CH_3)$_2$), 86.6 (*C*(2)), 124.2 (C(2)Ar*C*(2,6)H), 127.9 (C(2)Ar*C*(3,5)H), 128.0 (C(2)Ar*C*(4)H), 129.0 (C=OAr*C*(3,5)H), 129.2 (C=OAr*C*(2,6)H), 132.0 (C=OAr*C*(4)H), 135.3 (C=OAr*C*(1)), 140.5 (C(2)Ar*C*(1)), 175.5 (*C*=OCH(CH_3)$_2$)), 197.3 (*C*(1)=OPh); ***m/z* (NSI)** 314 ($[M+NH_4]^+$, 100%) $C_{19}H_{24}NO_3^+$ ($[M+NH_4]^+$) requires 314.1751; found 314.1755 (+1.4 ppm).

Lab book Reference: SMS-1143

Kinetic resolution of 318



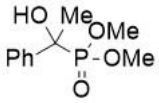
Following general procedure C, **318** (72 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.36 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), alcohol (65 mg, 0.29 mmol, 90%) and ester (1 mg, 0.003 mmol, 1%).

Data for alcohol: $[\alpha]_D^{20}$ +38 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.1, 13.4 min, 51:49 er.

Data for ester: $[\alpha]_D^{20}$ +166 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 7.7, 11.5 min, 90:10 er; *s* = 9.

Lab book Reference: SMS-1156

Dimethyl (1-hydroxy-1-phenylethyl)phosphonate, 319

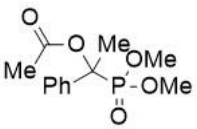


Following the procedure outlined by Foucaud,[132] a mixture of potassium fluoride (2.50 g) and alumina (2.50 g) were added slowly to a mixture of dimethyl phosphite (917 µL, 10 mmol) and acetophenone (1.17 mL, 10 mmol). This was stirred for 1 h at RT, and then CH_2Cl_2 (20 mL) was added. The solid was filtered and the organic layer concentrated in vacuo, to give, without further purification (eluent CH_2Cl_2/MeOH, 9:1; R_F 0.43), **319** as a white powder (1.54 g, 0.71 mmol, 71%), mp 124-126 °C; **δ_H (400 MHz, $CDCl_3$)** 1.81 (3H, d, *J* 15.5 Hz, C(2)CH_3), 3.19 (1H, br s, O*H*), 3.60 (3H, d, *J* 10.3 Hz, P=O(OCH_3)$_A$(OCH_3)$_B$), 3.74 (3H, d, *J* 10.2 Hz, P=O(OCH_3)$_A$(OCH_3)$_B$), 7.27-7.33 (1H, m, ArC(4)*H*), 7.34-7.42 (2H, m, ArC(2,6)*H*), 7.58-7.63 (2H, m, ArC(3,5)*H*); **δ_P (162 MHz, $CDCl_3$)** 26.1 (*P*=O$(OCH_3)_2$).

Data is in accordance with the literature.[164]

Lab book Reference: SMS-883

1-(Dimethoxphosphoryl)-1-phenylethyl acetate, 325

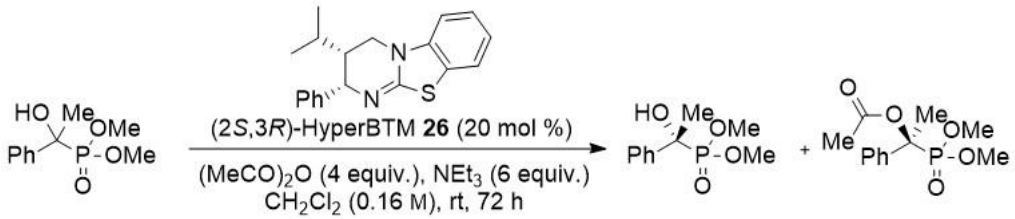


Following general procedure J, **319** (37 mg, 0.16 mmol), acetic anhydride (61 µL, 0.64 mmol), DMAP **19** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) for 3

days to give the crude product, which was product was purified by column chromatography (eluent CH_2Cl_2/EtOAc, 9:1; R_F 0.50) to afford **325** as a yellow oil (30 mg, 0.11 mmol, 69%); **ν_{max} (ATR)** 2957, 1749 (C=O), 1449, 1371, 1219, 1022; **δ_H (400 MHz, $CDCl_3$)** 2.15 (3H, s, C=OCH_3), 2.18 (3H, d, *J* 15.9 Hz, CH_3), 3.62 (3H, d, *J* 10.5 Hz, P=O(OCH_3)$_A$(OCH$_3$)$_B$), 3.68 (3H, d, *J* 10.5 Hz, P=O(OCH$_3$)$_A$(OCH_3)$_B$), 7.27-7.33 (1H, m, ArC(4)*H*), 7.34-7.44 (4H, m, ArC(2,3,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 20.4 (C=OCH_3), 22.1 (CH_3), 54.3 (d, *J* 7.1 Hz, P=O(OCH_3)$_A$(OCH$_3$)$_B$), 54.4 (d, *J* 7.1 Hz, P=O(OCH$_3$)$_A$(OCH_3)$_B$), 81.5 (d, *J* 7.1 Hz, *C*P=O(OCH$_3$)$_2$), 126.3 (d, *J* 4.9 Hz, Ar*C*(2,6)H), 128.0 (d, *J* 3.3 Hz, Ar*C*(4)H), 128.8 (d, *J* 2.7 Hz, Ar*C*(3,5)H), 137.4 (d, *J* 3.6 Hz, Ar*C*(1)), 168.8 (*C*=O); **δ_P (162 MHz, $CDCl_3$)** 22.1 (*P*=O(OCH$_3$)$_2$). ***m/z* (NSI)** 273 ([M+H$^+$], 100%) $C_{12}H_{18}O_5P$ ([M+H$^+$]) requires 273.0886; found 273.0889 (+1.0 ppm).

Lab book Reference: SMS-884

Kinetic resolution of 319



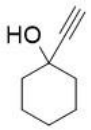
Following general procedure C, **319** (37 mg, 0.16 mmol), acetic anhydride (61 µL, 0.64 mmol), (2*S*,3*R*)-HyperBTM **26** (9.8 mg, 0.032 mmol, 20 mol %) and NEt_3 (133 µL, 0.96 mmol) in CH_2Cl_2 (1 mL) for 72 h gave, after column chromatography (eluent CH_2Cl_2/MeOH, 9:1), alcohol (12 mg, 0.10 mmol, 65%) and ester (13 mg, 0.05 mmol, 12%).

Data for alcohol: $[\alpha]_D^{20}$ +91 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 22.3, 27.1 min, 52:48 er.

Data for ester: $[\alpha]_D^{20}$ +16 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.5, 14.1 min, 58:42 er; *s* = 1.

Lab book Reference: SMS-995

1-Ethynylcyclohexan-1-ol, 1



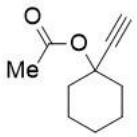
Following the procedure outlined by Lasemi,[165] to trimethylsilylacetylene (1.4 mL, 10 mmol) in anhydrous Et_2O (20 mL) was added *n*BuLi (4 mL, 10 mmol, 2.5 M) at 0 °C and the reaction stirred for 1 h. This solution was transferred to a solution of cyclohexanone (1.1 mL, 9.8 mmol) in Et_2O (10 mL) at 0 °C, then warmed to RT and stirred overnight. H_2O (10 mL) was added and the organic layer extracted with Et_2O (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. This was then taken further

without further purifcaiton. The TMS-ethynynl alcohol was treated with K_2CO_3 (30 mmol) in MeOH (20 mL) and THF (20 mL). The solid was dissolved in H_2O/EtOAc (1:1, 50 mL), the organic layer separated, dried ($MgSO_4$), and concentrated *in vacuo*, to give, after column chromatography (eluent Petrol/EtOAc, 9:1; R_F 0.29), **1** as a yellow oil (742 mg, 5.97 mmol, 61%); **ν_{max} (ATR)** 3404 (OH), 2933, 2247, 1726, 1447, 1256; **δ_H (400 MHz, $CDCl_3$)** 1.16-1.28 (1H, m, C(4)H_AH_B), 1.46-1.61 (5H, m, C(3,5)*H*, C(4)H_AH_B), 1.63-1.72 (2H, m, C(2,6)H_AH_B), 1.83-1.94 (2H, m, C(2,6)H_AH_B), 2.19 (1H, s, O*H*), 2.46 (1H, s, RC≡C*H*).

Data is in accordance with the literature.[162]

Lab book Reference: SMS-948

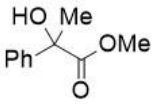
1-Ethynylcyclohexyl acetate, 2



Following general procedure J, **1** (20 mg, 0.16 mmol), acetic anhydride (61 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 9:1; R_F 0.33) to afford **2** as a yellow oil (37 mg, 0.13 mmol, 84%); **ν_{max} (ATR)** 3286, 2936, 2112, 1740 (C=O), 1447, 1225; **δ_H (400 MHz, $CDCl_3$)** 1.27-1.39 (1H, m, C(4)H_AH_B), 1.47-1.55 (1H, m, C(4)H_AH_B), 1.58-1.68 (4H, m, C(3,5)*H*), 1.80-1.89 (2H, m, C(2,6)H_AH_B), 2.05 (3H, s, C=OCH_3), 2.09-2.17 (2H, m, C(2,6)H_AH_B), 2.60 (1H, s, RC≡C*H*).

Lab book Reference: SMS-965

Methyl 2-hydroxy-2-phenypropanoate, 321



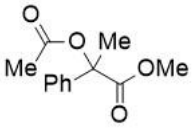
Following the procedure outlined by Ruiz,[133] *n*BuLi (8.8 mL, 22 mmol, 2.5 M) was added to a solution of HN^iPr_2 (3.1 mL, 22 mmol) in anhydrous THF (50 mL) under a N_2 atmosphere at 0 °C. The LDA solution was stirred for 30 minutes, cooled to –78 °C and methyl mandelate **320** (1.66 g, 10 mmol) was added and the reaction mixture stirred for 15 mins. Methyl iodide (623 µL, 10 mmol) was added and the reaction mixture stirred overnight at RT. HCl (20 mL) was added until pH 1 was reached. The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give, after column chromatography (Petrol/EtOAc, 4:1; R_F 0.28), **321** as a yellow oil (242 mg, 1.3 mmol, 13%); **ν_{max} (ATR)** 3493 (OH), 2955, 1724 (C=O), 1447, 1250,

1144; **δ_H (400 MHz, $CDCl_3$)** 1.79 (3H, s, C(2)CH_3), 3.76 (1H, s, O*H*), 3.78 (3H, s, OCH_3), 7.27-7.32 (1H, m, ArC(4)*H*), 7.33-7.39 (2H, m, ArC(3,5)*H*), 7.53-7.57 (2H, m, ArC(2,6)*H*).

Data is in accordance with the literature.[133]

Lab book Reference: SMS-996

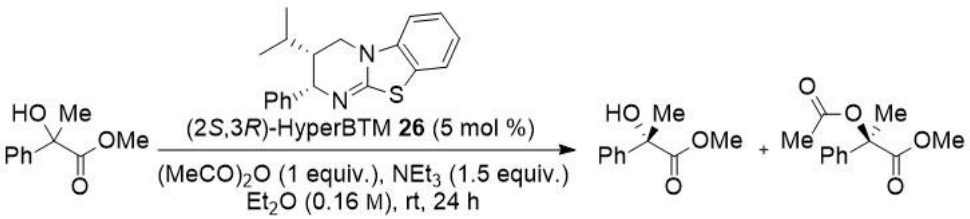
Methyl 2-acetoxy-2-phenylpropanoate, 326



Following general procedure J, **321** (29 mg, 0.16 mmol), acetic anhydride (61 µL, 0.64 mmol), DMAP **19** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 4:1; R_F 0.32) to afford **326** as a colourless oil (31 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2953, 1736 (C=O), 1371, 1253, 1221; **δ_H (400 MHz, $CDCl_3$)** 1.95 (3H, s, C(2)CH_3), 2.21 (3H, s, C=OCH_3), 3.69 (3H, s, OCH_3), 7.30-7.41 (3H, m, ArC(3,4,5)*H*), 7.49-7.54 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.4 (C=O*C*H_3), 24.1 (C(2)*C*H_3), 52.8 (O*C*H_3), 87.1 (*C*(2)), 124.7 (Ar*C*(2,6)H), 128.3 (Ar*C*(4)H), 128.6 (Ar*C*(3,5)H), 139.7 (Ar*C*(1)), 169.9 (*C*=OCH_3), 171.4 (*C*(1)=O); ***m/z* (NSI)** 240 ($[M+NH_4]^+$, 100%) $C_{12}H_{18}NO_4^+$ ($[M+NH_4]^+$) requires 240.1230; found 240.1232 (+0.7 ppm).

Lab book Reference: SMS-997

Kinetic resolution of 321



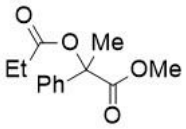
Following general procedure C, **321** (29 mg, 0.32 mmol), acetic anhydride (15 µL, 0.16 mmol), (2*S*,3*R*)-HyperBTM **26** (2.5 mg, 0.008 mmol, 50 mol %) and NEt_3 (34 µL, 0.24 mmol) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (14 mg, 0.16 mmol, 49%) and ester (26 mg, 0.12 mmol, 36%).

Data for alcohol: $[\alpha]_D^{20}$ +66 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.4, 12.9 min, 80:20 er.

Data for ester: $[\alpha]_D^{20}$ +172 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak IC (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 16.6, 19.9 min, 90:10 er; *s* = 15.

Lab book Reference: SMS-1005

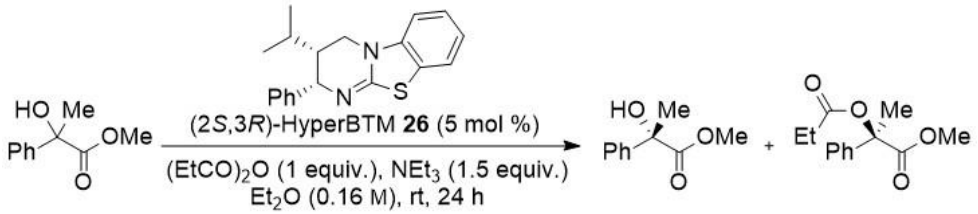
Methyl 2-phenyl-2-(propionyloxy)propanoate, 327



Following general procedure J, **321** (29 mg, 0.16 mmol), propionic anhydride (82 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.75) to afford **327** as a colourless oil (27 mg, 0.11 mmol, 71%); **ν_{max} (ATR)** 2951, 1740 (C=O), 1261, 1177, 1119; **δ_H (400 MHz, $CDCl_3$)** 1.22 (3H, t, *J* 7.6 Hz, C=OCH$_2$C*H*$_3$), 1.95 (3H, s, C(2)C*H*$_3$), 2.41-2.58 (2H, m, C=OC*H*$_2$CH$_3$), 3.69 (3H, s, OC*H*$_3$), 7.30-7.35 (1H, m, ArC(4)*H*), 7.35-7.40 (2H, m, ArC(3,5)*H*), 7.49-7.54 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 9.1 (C=OCH$_2$*C*H$_3$), 24.1 (C(2)*C*H$_3$), 28.0 (C=O*C*H$_2$CH$_3$), 52.7 (O*C*H$_3$), 81.4 (*C*(2)), 124.7 (Ar*C*(2,6)H), 128.2 (Ar*C*(4)H), 128.6 (Ar*C*(3,5)H), 139.9 (Ar*C*(1)), 171.4 (*C*=OCH$_2$CH$_3$), 173.3 (*C*(1)=O); ***m/z* (NSI)** 254 ([M+NH$_4$]$^+$, 100%) $C_{13}H_{20}NO_4^+$ ([M+NH$_4$]$^+$) requires 254.1387; found 254.1389 (+0.8 ppm).

Lab book Reference: SMS-1009

Kinetic resolution of 321



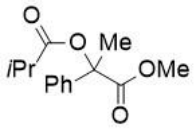
Following general procedure C, **321** (29 mg, 0.32 mmol), propionic anhydride (20 µL, 0.16 mmol), (2*S*,3*R*)-HyperBTM **26** (2.5 mg, 0.008 mmol, 50 mol %) and NEt_3 (34 µL, 0.24 mmol) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (18 mg, 0.20 mmol, 61%) and ester (20 mg, 0.09 mmol, 27%).

Data for alcohol: $[\alpha]_D^{20}$ +48 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.4, 12.9 min, 87:13 er.

Data for ester: $[\alpha]_D^{20}$ +159 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (0.5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 27.4, 48.6 min, 92:8 er; *s* = 24.

Lab book Reference: SMS-1015

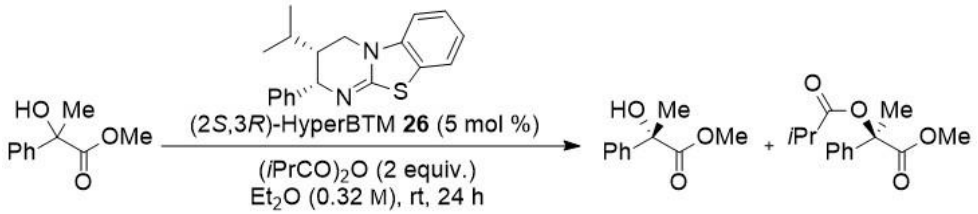
Methyl 2-(isobutyryloxy)-2-phenylpropanoate, 328



Following general procedure J, **321** (29 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent CH_2Cl_2/EtOAc, 95:5; R_F 0.75) to afford **328** as a colourless oil (37 mg, 0.15 mmol, 92%); **ν_{max} (ATR)** 2976, 1740 (C=O), 1260, 1153, 1119; **δ_H (400 MHz, $CDCl_3$)** 1.26 (6H, app t, *J* 7.2 Hz, C=OCH(CH_3)$_2$), 1.94 (3H, s, C(2)CH_3), 2.71 (1H, m, C=OC*H*(CH$_3$)$_2$), 3.68 (3H, s, OCH_3), 7.30-7.35 (1H, m, ArC(4)*H*), 7.35-7.40 (2H, m, ArC(3,5)*H*), 7.50-7.54 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.8 (C=OCH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.9 (C=OCH(CH$_3$)$_A$(*C*H$_3$)$_B$), 24.0 (C(2)*C*H$_3$), 34.3 (C=O*C*H(CH$_3$)$_2$), 52.7 (O*C*H$_3$), 81.3 (*C*(2)), 124.7 (Ar*C*(2,6)H), 128.2 (Ar*C*(4)H), 128.6 (Ar*C*(3,5)H), 140.0 (Ar*C*(1)), 171.4 (*C*(1)=O), 175.8 (*C*=OCH(CH$_3$)$_2$); ***m/z* (NSI)** 268 ([M+NH$_4$]$^+$, 100%) $C_{14}H_{22}NO_4^+$ ([M+NH$_4$]$^+$) requires 268.1543; found 268.1546 (+1.0 ppm).

Lab book Reference: SMS-1010

Kinetic resolution of 321



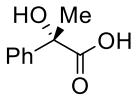
Following general procedure C, **321** (58 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (25 mg, 0.14 mmol, 43%) and ester (31 mg, 0.12 mmol, 39%).

Data for alcohol: $[\alpha]_D^{20}$ +52 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (2% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.4, 12.9 min, 84:16 er.

Data for ester: $[\alpha]_D^{20}$ +164 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (0.5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 16.9, 20.8 min, 97:3 er; *s* = 70.

Lab book Reference: SMS-1138

(*S*)-2-Hydroxy-2-phenylpropanoic acid, 337

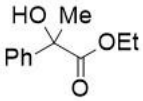


Following the procedure outlined by Zhou,[130i] a solution of (*S*)-**321** (31 mg, 0.17 mmol) in a NaOH solution (0.07 g, 2 mL H_2O, 6 mL MeOH) was refluxed for 4 h. This was then cooled to RT and acidified with 1M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **337** as a white solid (26 mg, 0.16 mmol, 91%); **δ_H (400 MHz, $CDCl_3$)** 1.83 (3H, s, C(2)C*H*$_3$), 7.29-7.41 (3H, m, ArC(2,4,6)*H*), 7.55-7.61 (2H, m, ArC(3,5)*H*).

Data for acid: $[\alpha]_D^{20}$ +63 (*c* 0.1, $CHCl_3$); lit: $[\alpha]_D^{20}$ +35 (*c* 1.3, $CHCl_3$);[140] $[\alpha]_D^{20}$ +71 (*c* 0.14, $CHCl_3$).[139]
Data is in accordance with the literature.[166]

Lab book Reference: SMS-1169

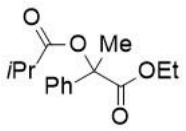
Ethyl 2-hydroxy-2-phenylpropanoate, 329



Following the procedure outlined by Ruiz,[133] *n*BuLi (17.6 mL, 44 mmol, 2.5 M) was added to a solution of HN^iPr_2 (6.2 mL, 44 mmol) in anhydrous THF (50 mL) under a N_2 atmosphere at 0 °C. The LDA solution was stirred for 30 minutes, cooled to –78 °C and ethyl mandelate **36** (3.60 g, 20 mmol) was added and the reaction mixture stirred for 15 mins. Methyl iodide (1.25 mL, 20 mmol) was added and the reaction mixture stirred overnight at RT. HCl (20 mL) was added until pH 1 was reached. The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give, after column chromatography (Petrol/EtOAc, 4:1; R_F 0.41), **329** as a yellow oil (1.82 g, 4.7 mmol, 47%); **ν_{max} (ATR)** 3501 (OH), 2982, 1721 (C=O), 1447, 1244, 1144; **δ_H (400 MHz, $CDCl_3$)** 1.25 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.79 (3H, s, C(2)C*H*$_3$), 3.92 (1H, br s, O*H*), 4.15-4.30 (2H, m, OCH_2CH_3), 7.26-7.31 (1H, m, ArC(4)*H*), 7.32-7.38 (2H, m, ArC(2,6)*H*), 7.55-7.60 (2H, m, ArC(3,5)*H*).
Data is in accordance with the literature.[144]

Lab book Reference: SMS-1022

Ethyl 2-(isobutyryloxy)-2-phenylpropanoate, 331

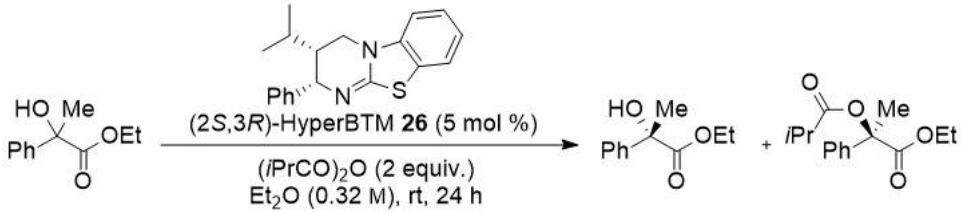


Following general procedure J, **329** (29 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent

CH_2Cl_2/EtOAc, 95:5; R_F 0.65) to afford **331** as a colourless oil (38 mg, 0.14 mmol, 89%); **ν_{max} (ATR)** 2976, 1736 (C=O), 1449, 1258, 1117; **δ_H (400 MHz, $CDCl_3$)** 1.18 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.25 (3H, d, *J* 7.0 Hz, $C{=}OCH(CH_3)_A(CH_3)_B$), 1.27 (3H, d, *J* 7.0 Hz, $C{=}OCH(CH_3)_A(CH_3)_B$), 1.94 (3H, s, C(2)CH_3), 2.71 (1H, hept, *J* 7.0 Hz, $C{=}OCH(CH_3)_2$), 4.08 (1H, dq, *J* 10.8, 7.1 Hz, $OCH_AH_BCH_3$), 4.20 (1H, dq, *J* 10.8, 7.1 Hz, $OCH_AH_BCH_3$), 7.29-7.34 (1H, m, ArC(4)*H*), 7.34-7.40 (2H, m, ArC(3,5)*H*), 7.50-7.55 (2H, m, ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 13.9 ($C{=}OCH_2CH_3$), 18.8 ($C{=}OCH(CH_3)_A(CH_3)_B$), 18.9 ($C{=}OCH(CH_3)_A(CH_3)_B$), 24.0 (C(2)CH_3), 34.3 ($C{=}OCH(CH_3)_2$), 61.6 (OCH_2CH_3), 81.3 (*C*(2)), 124.7 (Ar*C*(2,6)H), 128.1 (Ar*C*(4)H), 128.5 (Ar*C*(3,5)H), 140.2 (Ar*C*(1)), 170.8 (*C*(1)=O), 175.7 ($C{=}OCH(CH_3)_2$); ***m/z* (NSI)** 287 ([M+Na]$^+$, 100%) $C_{15}H_{20}O_4Na^+$ ([M+Na]$^+$) requires 287.1254; found 287.1256 (+0.8 ppm).

Lab book Reference: SMS-1027

Kinetic resolution of 329



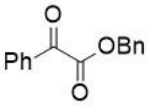
Following general procedure C, **329** (62 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.018 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (37 mg, 0.19 mmol, 60%) and ester (21 mg, 0.08 mmol, 25%).

Data for alcohol: $[\alpha]_D^{20}$ +100 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 13.7, 15.0 min, 73:27 er.

Data for ester: $[\alpha]_D^{20}$ +34 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (1% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 12.9, 17.6 min, 98:2 er; *s* = 60.

Lab book Reference: SMS-1139

Benzyl 2-oxo-2-phenylacetate, 330

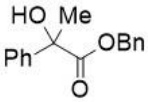


Following general procedure K, phenylglyoxylic acid **314** (3.00 g, 20 mmol), oxalyl chloride (2.09 mL, 24 mmol), DMF (1 drop), benzyl alcohol (3.12 mL, 30 mmol) and pyridine (1.61 mL, 20 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), **330** as a yellow oil (3.42 g, 14.3 mmol, 71%); **ν_{max} (ATR)** 3065, 1732 (C=O), 1686 (C=O), 1595, 1450, 1292, 1192, 1171; **δ_H (400 MHz, $CDCl_3$)** 5.42 (2H, s, OCH_2Ph), 7.34-7.53 (7H, m, C(2)ArC(3,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.62-7.68 (1H, m, C(2)ArC4)*H*), 7.94-8.00 (2H, m, C(2)ArC(2,6)*H*);

Data is in accordance with the literature.[143]

Lab book Reference: SMS-1120

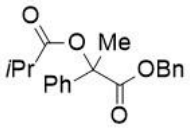
Benzyl 2-hydroxy-2-phenypropanoate, 305



Following general procedure K, 2-phenylpropionic acid **333** (2.73 mL, 20 mmol), oxalyl chloride (2.09 mL, 24 mmol), DMF (1 drop), benzyl alcohol (3.12 mL, 30 mmol) and pyridine (1.61 mL, 20 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.54), the impure product as a colourless oil. Following general procedure L, the impure ester (2.15 g, 8.95 mmol), triethyl phosphite (3.1 mL, 17.9 mmol), cesium carbonate (583 mg, 1.79 mmol, 20 mol %) in DMSO (36 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.14) to afford **305** as a colourless oil (1.59 g, 6.2 mmol, 31%); **ν_{max} (ATR)** 3503 (OH), 3032, 1722 (C=O), 1447, 1234, 1142; **δ_H (400 MHz, $CDCl_3$)** 1.82 (3H, s, C(2)CH_3), 3.79 (1H, s, O*H*), 5.17 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.24 (1H, d, *J* 12.4 Hz, OCH_AH_BPh), 7.23-7.27 (2H, m, OCH_2ArC(2,6)*H*), 7.29-7.38 (6H, m, C(2)Ar(3,4,5)*H*, OCH_2ArC(3,4,5)*H*), 7.53-7.58 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 26.6 (C(2)*C*H_3), 67.9 (O*C*H_2Ph), 75.8 (*C*(2)), 125.2 (C(2)Ar*C*(2,6)H), 127.8 (C(2)Ar*C*(4)H), 127.9 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (C(2)Ar*C*(3,5)H), 135.1 (OCH_2Ar*C*(1)), 142.6 (C(2)Ar*C*(1)), 175.5 (*C*=O); ***m/z* (NSI)** 279 ([M+Na]$^+$, 100%) $C_{16}H_{16}O_3Na^+$ ([M+Na]$^+$) requires 279.0992; found 279.0992 (+0.1 ppm).

Lab book Reference: SMS-1035

Benzyl 2-(isobutyryloxy)-2-phenylpropanoate, 332

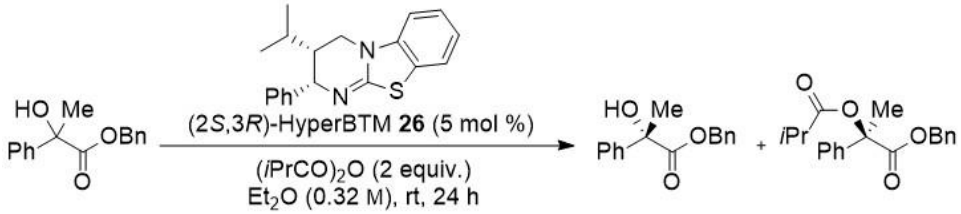


Following general procedure J, **305** (41 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.43) to afford **332** as a colourless oil (45 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2974, 1736 (C=O), 1449, 1256, 1113; **δ_H (400 MHz, $CDCl_3$)** 1.18 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.20 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.97 (3H, s, C(2)CH_3), 2.67 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 5.06 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.16 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 7.17-7.22 (2H, m, OCH_2ArC(2,6)*H*), 7.26-7.38 (6H, m, C(2)Ar(3,4,5)*H*, OCH_2ArC(3,4,5)*H*), 7.48-7.53 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.76 (C=OCH(*C*H_3)$_A$(CH_3)$_B$), 18.79 (C=OCH(CH_3)$_A$(*C*H_3)$_B$), 23.8 (C(2)*C*H_3), 34.3 (C=O*C*H(CH_3)$_2$), 67.2 (O*C*H_2Ph), 81.3 (*C*(2)), 124.8 (C(2)Ar*C*(2,6)H), 128.1 (OCH_2Ar*C*(2,3,5,6)H), 128.4 (OCH_2Ar*C*(4)H, C(2)Ar*C*(4)H), 128.5 (C(2)Ar*C*(3,5)H), 135.4 (OCH_2Ar*C*(1)), 139.9 (C(2)Ar*C*(1)), 170.7 (*C*(1)=O), 175.7

(*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 349 ([M+Na]$^+$, 100%) $C_{20}H_{22}O_4Na^+$ ([M+Na]$^+$) requires 349.1410; found 349.1411 (+0.3 ppm).

Lab book Reference: SMS-1036

Kinetic resolution of 305



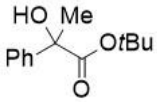
Following general procedure C, **305** (82 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), alcohol (35 mg, 0.14 mmol, 43%) and ester (46 mg, 0.14 mmol, 44%).

Data for alcohol: $[\alpha]_D^{20}$ +5 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.1, 34.6 min, 95:5 er.

Data for ester: $[\alpha]_D^{20}$ +22 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.6, 17.4 min, 98:2 er; *s* = 140.

Lab book Reference: SMS-1046

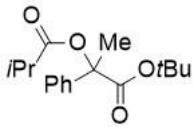
***Tert*-butyl 2-hydroxy-2-phenylpropanoate, 335**



Following general procedure K, 2-phenylpropionic acid **333** (1.37 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), *tert*-butyl alcohol (1.44 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1), the impure ester **334** as a colourless oil (1.79 g). Following general procedure L, the impure **334** (1.86 g, 9 mmol), triethyl phosphite (3.09 mL, 18 mmol), cesium carbonate (635 mg, 1.8 mmol, 20 mol %) in DMSO (36 mL) under a O_2 atmosphere was stirred for 48 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.16) to afford **335** as a colourless oil (644 mg, 2.9 mmol, 32%); **ν_{max} (ATR)** 3503 (OH), 2980, 1715 (C=O), 1447, 1369, 1256, 1140; **δ_H (400 MHz, $CDCl_3$)** 1.44 (9H, s, C(*C*H$_3$)$_3$), 1.74 (1H, s, C(2)CH$_3$), 3.89 (1H, s, O*H*), 7.25-7.30 (1H, m, C(2)ArC(4)*H*), 7.32-7.37 (2H, m, C(2)Ar(3,5)*H*), 7.54-7.59 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 26.7 (C(2)*C*H$_3$), 27.8 (OC(*C*H$_3$)$_3$), 75.6 (*C*(2)), 83.0 (O*C*(CH$_3$)$_3$), 125.2 (Ar*C*(2,6)H), 127.5 (Ar*C*(4)H), 128.2 (Ar*C*(3,5)H), 143.3 (C(2)Ar*C*(1)), 174.9 (*C*=O); ***m/z* (NSI)** 245 ([M+Na]$^+$, 100%) $C_{13}H_{18}O_3Na^+$ ([M+Na]$^+$) requires 245.1148; found 245.1150 (+0.8 ppm).

Lab book Reference: SMS-1104

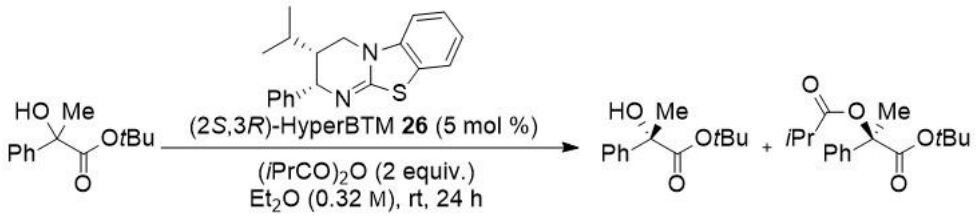
***Tert*-butyl 2-(isobutyryloxy)-2-phenylpropanoate, 336**



Following general procedure J, **335** (36 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.31) to afford **336** as a colourless oil (36 mg, 0.12 mmol, 78%); **ν_{max} (ATR)** 2976, 1734 (C=O), 1448, 1368, 1277, 1119; **δ_H (400 MHz, $CDCl_3$)** 1.25 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.28 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.37 (9H, s, C(CH_3)$_3$), 1.89 (1H, s, C(2)CH_3), 2.69 (1H, hept, *J* 7.0 Hz, CH(CH_3)$_2$), 7.28-7.33 (1H, m, C(2)ArC(4)*H*), 7.34-7.40 (2H, m, C(2)Ar(3,5)*H*), 7.50-7.55 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.8 (CH(CH_3)$_A$(CH_3)$_B$), 19.1 (CH(CH_3)$_A$(CH_3)$_B$), 23.9 (C(2)CH_3), 27.6 (OC(CH_3)$_3$), 34.3 (CH(CH_3)$_2$), 81.7 (*C*(2)), 81.8 (OC(CH_3)$_3$), 124.7 (Ar*C*(2,6)H), 127.8 (Ar*C*(4)H), 128.3 (Ar*C*(3,5)H), 140.7 (C(2)Ar*C*(1)), 169.7 (*C*(1)=O), 175.4 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 310 ([M+NH_4]$^+$, 100%) $C_{17}H_{28}NO_4^+$ ([M+NH_4]$^+$) requires 310.2013; found 310.2016 (+1.0 ppm).

Lab book Reference: SMS-1115

Kinetic resolution of 335



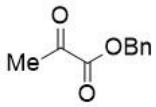
Following general procedure C, **335** (72 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (56 mg, 0.25 mmol, 78%) and ester (10 mg, 0.04 mmol, 11%).

Data for alcohol: $[\alpha]_D^{20}$ +6 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OJ-H (1% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 11.3, 17.9 min, 57:43 er; *s* = 7.

Data for ester: $[\alpha]_D^{20}$ –5 (*c* 0.1, $CHCl_3$).

Lab book Reference: SMS-1150

Benzyl pyruvate, 338

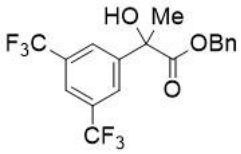


Following the procedure outlined by Yao,[167] to a solution pyruvic acid (695 µL, 10 mmol), benzyl alcohol (2.08 mL, 10 mmol) and pyridine (2.01 mL, 25 mmol) in THF (10 mL) was added dropwise mesyl chloride (929 µL, 12 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was warmed to RT and stirred and monitored by TLC until completion. The reaction was then quenched with water (20 mL), and extracted with Et_2O (3 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), **338** as a yellow oil (1.02 g, 5.7 mmol, 57%); **ν_{max} (ATR)** 3034, 1728 (C=O), 1497, 1454, 1290, 1265, 1130; **δ_H (400 MHz, $CDCl_3$)** 2.45 (3H, s, CH_3), 5.26 (2H, s, OC*H*$_2$Ph), 7.32-7.46 (5H, m, OCH_2ArC(2,3,4,5,6)*H*).

Data is in accordance with the literature.[167]

Lab book Reference: SMS-1155

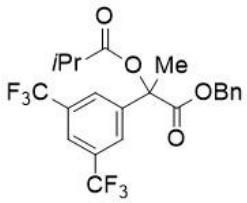
Benzyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxypropanoate, 339



Following general procedure F, a 10% portion of 1-bromo-3,5-bis(trifluoromethyl)benzene (1.74 mL, 10 mmol) in anhydrous THF (5 mL) was added to a solution of magnesium turnings (362 mg, 15 mmol) in anhydrous THF (15 mL). A small iodine crystal was required. Upon turning colourless, the remaining 1-bromo-3,5-bis(trifluoromethyl)benzene solution was added and reacted for a further 2 h. The concentration of the prepared Grignard reagent, 2-naphthyl magnesium bromide, was determined to be 0.33 M. Following general procedure D, **338** (890 mg, 5 mmol) and (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (18 mL, 6 mmol, 0.33 M) in anhydrous THF (20 mL) gave, after column chromatography (Petrol/Et_2O, 9:1; R_F 0.11), **339** as a light yellow solid (767 mg, 1.95 mmol, 39%); **ν_{max} (ATR)** 3495 (OH), 2967, 1732 (C=O), 1371, 1275, 1124; **δ_H (400 MHz, $CDCl_3$)** 1.82 (3H, s, C(2)CH_3), 3.99 (1H, s, O*H*), 5.19 (1H, d, *J* 12.0 Hz, OCH_AH_BPh), 5.26 (1H, d, *J* 12.0 Hz, OCH_AH_BPh), 7.22-7.26 (2H, m, OCH_2ArC(3,5)*H*), 7.32-7.37 (3H, m, OCH_2Ar(2,4,6)*H*), 7.81 (1H, s, C(2)ArC(4)*H*), 8.06 (2H, s, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 27.5 (C(2)*C*H_3), 68.9 (O*C*H_2Ph), 75.2 (*C*(2)), 121.9 (m, C(2)Ar*C*(4)H), 123.2 (q, *J* 273 Hz, 2 x *C*F_3), 126.0 (OCH_2Ar*C*(2,6)H), 128.2 (OCH_2Ar*C*(3,5)H), 128.9 (OCH_2Ar*C*(4)H), 131.6 (q, *J* 33 Hz, C(2)Ar*C*(3,5)H), 134.3 (OCH_2Ar*C*(1)), 145.0 (C(2)Ar*C*(1)), 174.2 (*C*=O); **δ_F (376 MHz, $CDCl_3$)** –62.8 (2 x C*F*$_3$); ***m/z* (NSI)** Structure confirmed from mass spec analysis of **344.**

Lab book Reference: SMS-1052

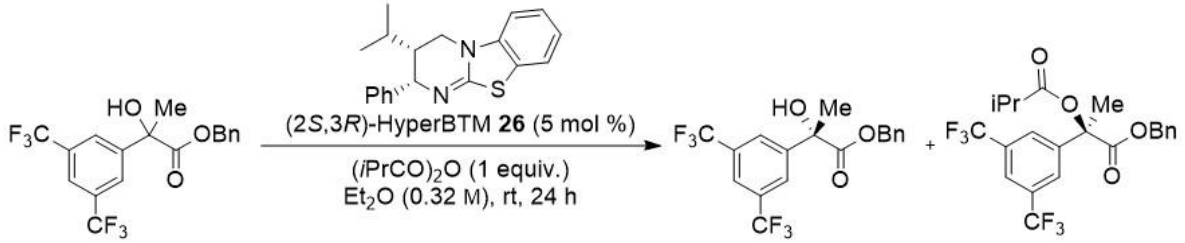
Benzyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-(isobutyryloxy)propanoate, 344



Following general procedure J, **339** (63 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.43) to afford **344** as a colourless oil (57 mg, 0.12 mmol, 77%); **ν_{max} (ATR)** 2978, 1744 (C=O), 1373, 1277, 1126; **δ_H (400 MHz, $CDCl_3$)** 1.20 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.21 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.99 (3H, s, C(2)CH_3), 2.71 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 5.10 (1H, d, *J* 12.1 Hz, OC*H*$_A$H$_B$Ph), 5.16 (1H, d, *J* 12.1 Hz, OCH$_A$*H*$_B$Ph), 7.17-7.21 (2H, m, OCH_2ArC(3,5)*H*), 7.27-7.32 (3H, m, OCH_2ArC(2,4,6)*H*), 7.83 (1H, s, C(2)ArC(4)*H*), 7.94 (2H, s, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.67 (C=OCH(*C*H_3)$_A$(CH_3)$_B$), 18.71 (C=OCH(CH_3)$_A$(*C*H_3)$_B$), 24.1 (C(2)*C*H_3), 34.1 (C=O*C*H(CH_3)$_2$), 68.0 (O*C*H_2Ph), 80.3 (*C*(2)), 122.3 (m, C(2)Ar*C*(4)H), 123.1 (q, *J* 273 Hz, 2 x *C*F_3), 125.3 (m, C(2)Ar*C*(2,6)H), 128.4 (OCH_2Ar*C*(3,5)H), 128.5 (OCH_2Ar*C*(2,6)H), 128.6 (OCH_2Ar*C*(4)H), 131.9 (q, *J* 34 Hz, C(2)Ar*C*(3,5)H), 134.7 (OCH_2Ar*C*(1)), 142.5 (C(2)Ar*C*(1)), 169.4 (*C*(1)=O), 174.2 (*C*=OCH(CH_3)$_2$); **δ_F (376 MHz, $CDCl_3$)** –62.9 (2 x C*F*$_3$); ***m/z* (NSI)** 480 ([M+NH_4]$^+$, 100%) $C_{22}H_{24}NO_4F_6^+$ ([M+NH_4]$^+$) requires 480.1604; found 480.1593 (–2.3 ppm).

Lab book Reference: SMS-1056

Kinetic resolution of 339



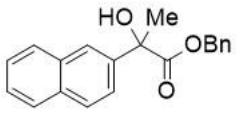
Following general procedure C, **339** (125 mg, 0.32 mmol), isobutyric anhydride (53 µL, 0.32 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (0.5 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/EtOAc, 9:1), alcohol (36 mg, 0.09 mmol, 29%) and ester (78 mg, 0.17 mmol, 53%).

Data for alcohol: $[\alpha]_D^{20}$ +47 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 8.9, 11.3 min, 98:2 er; *s* = 12

Data for ester: $[\alpha]_D^{20}$ +28 (*c* 0.1, $CHCl_3$).

Lab book Reference: SMS-1088

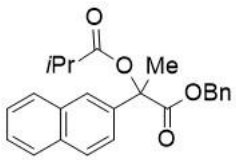
Benzyl 2-hydroxy-2-(naphthalene-2-yl)propanoate, 340



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 2-(naphthalen-2-yl)acetic acid (1.86 g, 10 mmol) and iodomethane (1.37 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-(naphthalen-2-yl)propanoic acid, which was taken on. Following general procedure K, the acid (2.00 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.54), the impure ester as a colourless oil. Following general procedure L, the impure ester (2.41 g, 8.3 mmol), triethyl phosphite (2.84 mL, 16.6 mmol), cesium carbonate (586 mg, 1.66 mmol, 20 mol %) in DMSO (33 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.16) to afford **340** as a colourless oil (1.07 g, 4.2 mmol, 42%); **ν_{max} (ATR)** 3489 (OH), 2982, 1724 (C=O), 1454, 1233, 1126; **δ_H (400 MHz, $CDCl_3$)** 1.92 (3H, s, C(2)CH_3), 3.82 (1H, br s, O*H*), 5.20 (1H, d, *J* 12.3 Hz, OC$H_A$$H_B$Ph), 5.25 (1H, d, *J* 12.3 Hz, OC$H_A$$H_B$Ph), 7.24-7.29 (2H, m, OCH_2ArC(2,6)*H*), 7.30-7.35 (3H, m, OCH_2ArC(3,4,5)*H*), 7.47-7.52 (2H, m, C(2)ArC(6,7)*H*), 7.66 (1H, dd, *J* 8.7, 1.9 Hz, C(2)ArC(3)*H*), 7.79-7.86 (3H, m, C(2)ArC(4,5,8)*H*), 8.02 (1H, d, *J* 1.8 Hz, C(2)ArC(1)*H*); **δ_C (100 MHz, $CDCl_3$)** 26.6 (C(2)*C*H_3), 68.0 (O*C*H_2Ph), 76.0 (*C*(2)), 123.5 (C(2)Ar*C*(3)H), 124.2 (C(2)Ar*C*(1)H), 126.26 (C(2)Ar*C*(6)H), 126.28 (C(2)Ar*C*(7)H), 127.5 (C(2)Ar*C*(5)H), 128.08 (OCH_2Ar*C*(2,6)H), 128.13 (C(2)Ar*C*(8)H), 128.4 (OCH_2Ar*C*(4)H), 128.5 (C(2)Ar*C*(4)H), 128.6 (OCH_2Ar*C*(3,5)H), 132.8 (C(2)Ar*C*(8a)), 133.0 (C(2)Ar*C*(4a)), 135.1 (OCH_2Ar*C*(1)), 140.0 (C(2)Ar*C*(2)H), 175.5 (*C*=O); ***m/z* (NSI)** 329 ($[M+Na]^+$, 100%) $C_{20}H_{18}O_3Na^+$ ($[M+Na]^+$) requires 329.1148; found 329.1144 (–1.3 ppm).

Lab book Reference: SMS-1091

Benzyl 2-(isobutyryloxy)-2-(naphthalen-2-yl)propanoate, 345

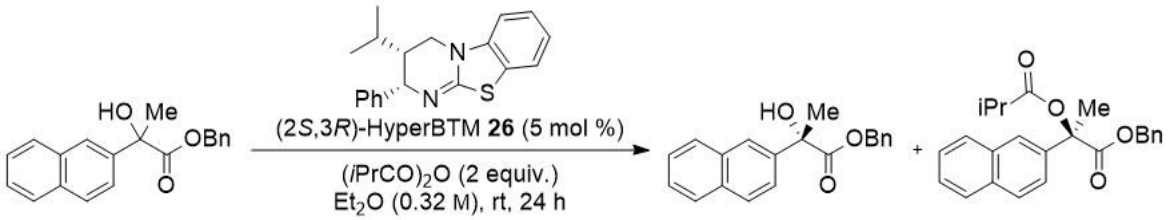


Following general procedure J, **340** (49 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.39) to afford **344** as a colourless oil (43 mg, 0.11 mmol, 71%); **ν_{max} (ATR)** 2974, 1736 (C=O), 1373, 1256, 1110; **δ_H (400 MHz, $CDCl_3$)** 1.22 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.24 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.06 (3H, s, C(2)CH_3), 2.73 (1H, hept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 5.06 (1H, d, *J* 12.3

Hz, OC*H*$_A$H$_B$Ph), 5.18 (1H, d, *J* 12.3 Hz, OCH$_A$*H*$_B$Ph), 7.17-7.22 (2H, m, OCH$_2$ArC(2,6)*H*), 7.23-7.29 (3H, m, OCH$_2$ArC(3,4,5)*H*), 7.47-7.53 (2H, m, C(2)ArC(6,7)*H*), 7.62 (1H, dd, *J* 8.7, 1.9 Hz, C(2)ArC(3)*H*), 7.78-7.87 (3H, m, C(2)ArC(4,5,8)*H*), 7.94 (1H, d, *J* 1.8 Hz, C(2)ArC(1)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.8 (2C, CH(*C*H$_3$)$_2$), 23.9 (C(2)*C*H$_3$), 34.3 (*C*H(CH$_3$)$_2$), 67.4 (O*C*H$_2$Ph), 81.4 (*C*(2)), 122.7 (C(2)Ar*C*(3)H), 124.0 (C(2)Ar*C*(1)H), 126.4 (C(2)Ar*C*(6)H), 126.5 (C(2)Ar*C*(7)H), 127.5 (C(2)Ar*C*(5)H), 128.19 (C(2)Ar*C*(8)H), 128.27 (OCH$_2$Ar*C*(2,6)H), 128.33 (OCH$_2$Ar*C*(4)H), 128.35 (OCH$_2$Ar*C*(3,5)H), 128.39 (C(2)Ar*C*(4)H), 132.9 (C(2)Ar*C*(8a)), 133.0 (C(2)Ar*C*(4a)), 135.3 (OCH$_2$Ar*C*(1)), 137.2 (C(2)Ar*C*(2)H), 170.7 (*C*(1)=O), 175.7 (*C*=OCH(CH$_3$)$_2$); ***m/z* (NSI)** 394 ([M+NH$_4$]$^+$, 100%) $C_{24}H_{28}NO_4^+$ ([M+NH$_4$]$^+$) requires 394.2013; found 394.2008 (–1.2 ppm).

Lab book Reference: SMS-1113

Kinetic resolution of 340



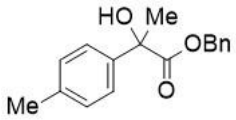
Following general procedure C, **340** (98 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et$_2$O (1 mL) for 24 h gave, after column chromatography (eluent CH$_2$Cl$_2$/Et$_2$O, 9:1), alcohol (40 mg, 0.13 mmol, 41%) and ester (49 mg, 0.13 mmol, 41%).

Data for alcohol: $[\alpha]_D^{20}$ +17 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 21.6, 29.5 min, 98:2 er.

Data for ester: $[\alpha]_D^{20}$ +89 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 17.5, 51.6 min, 95:5 er; *s* = 70.

Lab book Reference: SMS-1125

Benzyl 2-hydroxy-2-(*p*-tolyl)propanoate, 341

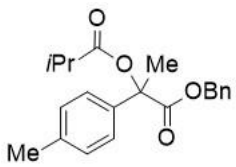


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (3.1 mL, 22 mmol), *p*-tolylacetic acid (1.51 g, 10 mmol) and methyl iodide (1.37 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-phenylhexanoic acid, which was taken on. Following general procedure K, the acid (1.64 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH$_2$Cl$_2$ (25 mL) gave, after column chromatography (eluent Petrol/Et$_2$O, 9:1), the impure ester as a colourless oil. Following general procedure L, the impure ester

(1.97 g, 7.75 mmol), triethyl phosphite (2.66 mL, 15.5 mmol), cesium carbonate (547 mg, 1.55 mmol, 20 mol %) in DMSO (31 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.08) to afford **341** as a colourless oil (1.36 g, 5.0 mmol, 65%); **ν_{max} (ATR)** 3507 (OH), 2982, 1724 (C=O), 1454, 1234, 1143; **δ_H (400 MHz, $CDCl_3$)** 1.82 (3H, s, C(2)CH_3), 2.37 (3H, s, C(2)ArC(4)CH_3), 3.67 (1H, s, O*H*), 5.17 (1H, d, *J* 12.4 Hz, OC$H_A$$H_B$Ph), 5.25 (1H, d, *J* 12.4 Hz, OCH$_A$$H_B$Ph), 7.15-7.20 (2H, m, C(2)ArC(3,5)*H*), 7.25-7.30 (2H, m, OCH_2ArC(2,6)*H*), 7.33-7.39 (3H, m, OCH_2ArC(3,4,5)*H*), 7.44-7.48 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (C(2)ArC(4)*C*H_3), 26.6 (C(2)*C*H_3), 67.9 (O*C*H_2Ph), 75.7 (*C*(2)), 125.2 (C(2)Ar*C*(2,6)H), 128.0 (OCH_2Ar*C*(2,6)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (OCH_2Ar*C*(3,5)H), 129.0 (C(2)Ar*C*(3,5)H), 135.2 (OCH_2Ar*C*(1)), 137.6 (C(2)Ar*C*(1)), 139.8 (C(2)Ar*C*(4)), 175.6 (*C*=O); ***m/z* (NSI)** 293 ([M+Na]$^+$, 100%) $C_{17}H_{18}O_3Na^+$ ([M+Na]$^+$) requires 293.1148; found 293.1148 (–0.1 ppm).

Lab book Reference: SMS-1140

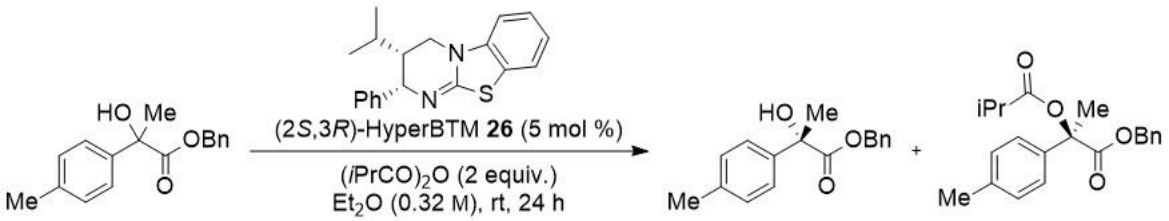
Benzyl 2-(isobutyryloxy)-2-(*p*-tolyl)propanoate, 346



Following general procedure J, **341** (43 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.19) to afford **346** as a colourless oil (46 mg, 0.14 mmol, 85%); **ν_{max} (ATR)** 2974, 1736 (C=O), 1456, 1258, 1155, 1099; **δ_H (400 MHz, $CDCl_3$)** 1.17 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.18 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.95 (3H, s, C(2)CH_3), 2.35 (3H, s, C(2)ArC(4)CH_3), 2.65 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 5.04 (1H, d, *J* 12.3 Hz, OC$H_A$$H_B$Ph), 5.15 (1H, d, *J* 12.3 Hz, OCH$_A$$H_B$Ph), 7.14-7.18 (2H, m, C(2)ArC(3,5)*H*), 7.19-7.22 (2H, m, OCH_2ArC(2,6)*H*), 7.27-7.31 (3H, m, OCH_2ArC(3,4,5)*H*), 7.37-7.42 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.76 (C=OCH(*C*H_3)$_A$(CH_3)$_B$), 18.79 (C=OCH(CH_3)$_A$(*C*H_3)$_B$), 21.1 (C(2)ArC(4)*C*H_3), 23.7 (C(2)*C*H_3), 34.2 (C=O*C*H(CH_3)$_2$), 67.2 (O*C*H_2Ph), 81.2 (*C*(2)), 124.2 (C(2)Ar*C*(2,6)H), 128.1 (OCH_2Ar*C*(4)H), 128.2 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 129.2 (C(2)Ar*C*(3,5)H), 135.4 (OCH_2Ar*C*(1)), 137.0 (C(2)Ar*C*(4)), 138.0 (C(2)Ar*C*(1)), 170.9 (*C*(1)=O), 175.8 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 358 ([M+NH_4]$^+$, 100%) $C_{21}H_{28}NO_4^+$ ([M+NH_4]$^+$) requires 358.2013; found 358.2016 (+0.9 ppm).

Lab book Reference: SMS-1146

Kinetic resolution of 341



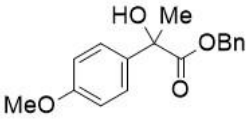
Following general procedure C, **341** (86 mg, 0.32 mmol), isobutyric anhydride (106 μL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (49 mg, 0.18 mmol, 57%) and ester (31 mg, 0.09 mmol, 28%).

Data for alcohol: $[\alpha]_D^{20}$ +5 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 14.2, 16.2 min, 73:27 er.

Data for ester: $[\alpha]_D^{20}$ +49 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.4, 17.9 min, 97:3 er; *s* = 50.

Lab book Reference: SMS-1149

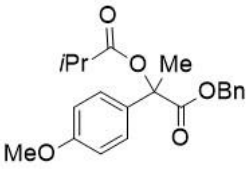
Benzyl 2-hydroxy-2-(4-methoxyphenyl)propanoate, 342



Following general procedure F, a 10% portion of 4-bromoanisole (1.24 mL, 10 mmol) in anhydrous THF (5 mL) was added to a solution of magnesium turnings (362 mg, 15 mmol) in anhydrous THF (15 mL). A small iodine crystal was required. Upon turning colourless, the remaining 4-bromoanisole solution was added and reacted for a further 2 h. The concentration of the prepared Grignard reagent, 4-methoxyphenyl magnesium bromide, was determined to be 0.3 M. Following general procedure D, benzyl pyruvate (890 mg, 5 mmol) and 4-methoxyphenyl magnesium bromide (20 mL, 6 mmol, 0.3 M) in anhydrous THF (20 mL) gave, after column chromatography (Petrol/Et_2O, 9:1; R_F 0.11), **342** as a colourless oil (412 mg, 1.44 mmol, 29%); **ν_{max} (ATR)** 3491 (OH), 2936, 1724 (C=O), 1608, 1510, 1248; **δ_H (400 MHz, $CDCl_3$)** 1.78 (3H, s, C(2)CH_3), 3.73 (1H, s, O*H*), 3.80 (3H, s, C(2)ArC(4)OCH_3), 5.15 (1H, d, *J* 12.4 Hz, OC$H_A$$H_B$Ph), 5.22 (1H, d, *J* 12.4 Hz, OC$H_A$$H_B$Ph), 6.84-6.88 (2H, m, C(2)ArC(3,5)*H*), 7.22-7.27 (2H, m, OCH_2ArC(2,6)*H*), 7.31-7.36 (3H, m, OCH_2ArC(3,4,5)*H*), 7.42-7.47 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 26.6 (C(2)*C*H_3), 55.3 (ArC(4)O*C*H_3), 67.8 (O*C*H_2Ph), 75.4 (*C*(2)), 113.6 (C(2)Ar*C*(3,5)H), 126.5 (C(2)Ar*C*(2,6)H), 127.9 (OCH_2Ar*C*(2,6)H), 128.4 (OCH_2Ar*C*(4)H), 128.5 (OCH_2Ar*C*(3,5)H), 134.7 (OCH_2Ar*C*(1)), 135.7 (C(2)Ar*C*(1)), 159.2 (C(2)Ar*C*(4)), 175.7 (*C*=O); ***m/z* (NSI)** 309 ($[M+Na]^+$, 100%) $C_{17}H_{18}O_4Na^+$ ($[M+Na]^+$) requires 309.1097; found 309.1097 (–0.1 ppm).

Lab book Reference: SMS-1053

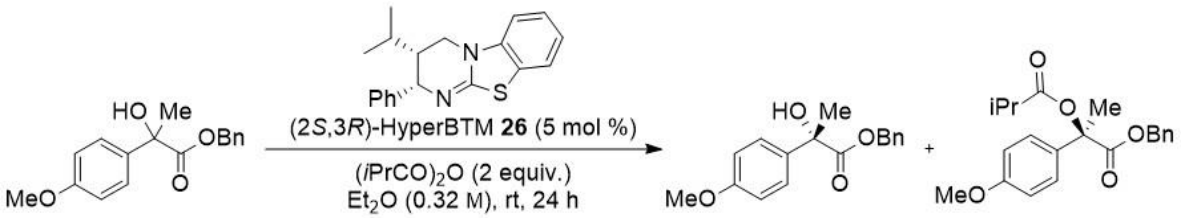
Benzyl 2-(isobutyryloxy)-2-(4-methoxyphenyl)propanoate, 347



Following general procedure J, **342** (46 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 4:1; R_F 0.34) to afford **347** as a colourless oil (39 mg, 0.11 mmol, 69%); **ν_{max} (ATR)** 2972, 1736 (C=O), 1611, 1572, 1456, 1250; **δ_H (400 MHz, $CDCl_3$)** 1.17 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.18 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.96 (3H, s, C(2)CH_3), 2.64 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 3.81 (3H, s, C(2)ArC(4)OCH_3), 5.05 (1H, d, *J* 12.3 Hz, OCH_AH$_B$Ph), 5.14 (1H, d, *J* 12.3 Hz, OCH$_A$$H_B$Ph), 6.85-6.90 (2H, m, C(2)ArC(3,5)*H*), 7.18-7.22 (2H, m, OCH_2ArC(2,6)*H*), 7.27-7.32 (3H, m, OCH_2ArC(3,4,5)*H*), 7.41-7.46 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.75 (C=OCH(CH_3)$_A$(CH_3)$_B$), 18.80 (C=OCH(CH_3)$_A$(CH_3)$_B$), 23.5 (C(2)CH_3), 34.2 (C=O*C*H(CH_3)$_2$), 55.3 (ArC(4)OCH_3), 67.2 (OCH_2Ph), 81.0 (*C*(2)), 113.8 (C(2)Ar*C*(3,5)H), 126.3 (C(2)Ar*C*(2,6)H), 128.1 (OCH_2Ar*C*(2,6)H), 128.4 (OCH_2Ar*C*(3,4,5)H), 131.9 (OCH_2Ar*C*(1)), 135.4 (C(2)Ar*C*(1)), 159.4 (C(2)Ar*C*(4)), 170.9 (*C*(1)=O), 175.8 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 374 ([M+NH_4]$^+$, 100%) $C_{21}H_{28}NO_5^+$ ([M+NH_4]$^+$) requires 374.1962; found 371.1963 (+0.3 ppm).

Lab book Reference: SMS-1057

Kinetic resolution of 342



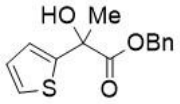
Following general procedure C, **342** (92 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), alcohol (45 mg, 0.16 mmol, 49%) and ester (39 mg, 0.11 mmol, 35%).

Data for alcohol: $[\alpha]_D^{20}$ +22 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 18.1, 20.3 min, 86:14 er.

Data for ester: $[\alpha]_D^{20}$ +64 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.1, 31.9 min, 98:2 er; *s* = 80.

Lab book Reference: SMS-1071

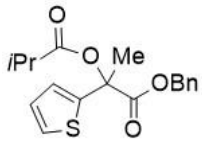
Benzyl 2-hydroxy-2-(thiophene-2-yl)propanoate, 343



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), 2-thiopheneacetic acid (1.42 g, 10 mmol) and iodomethane (1.37 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-(thiophen-2-yl)propanoic acid, which was taken on. Following general procedure K, the acid (1.54 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.63), the impure ester as a dark red oil. Following general procedure L, the impure ester (1.83 g, 7.6 mmol), triethyl phosphite (2.62 mL, 15.3 mmol), cesium carbonate (539 mg, 1.53 mmol, 20 mol %) in DMSO (30 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.09) to afford **343** as a colourless oil (708 mg, 2.7 mmol, 27%); **ν_{max} (ATR)** 3495 (OH), 2984, 1724 (C=O), 1454, 1258, 1225, 1134; **δ_H (400 MHz, $CDCl_3$)** 1.85 (3H, s, C(2)CH_3), 4.02 (1H, s, O*H*), 5.19 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.26 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 6.95 (1H, dd, *J* 5.1, 3.6 Hz, C(2)ArC(4)*H*), 7.05 (1H, dd, *J* 3.6, 1.2 Hz, C(2)ArC(3)*H*), 7.23 (1H, dd, *J* 5.1, 1.2 Hz, C(2)ArC(5)*H*), 7.27-7.31 (2H, m, OCH_2ArC(2,6)*H*), 7.32-7.39 (3H, m, OCH_2ArC(3,4,5)*H*); **δ_C (100 MHz, $CDCl_3$)** 27.8 (C(2)*C*H_3), 68.3 (O*C*H_2Ph), 74.4 (*C*(2)), 124.2 (C(2)Ar*C*(3)H), 125.2 (C(2)Ar*C*(5)H), 127.0 (C(2)Ar*C*(4)H), 128.0 (OCH_2Ar*C*(2,6)H), 128.6 (OCH_2Ar*C*(4)H), 128.7 (OCH_2Ar*C*(3,5)H), 134.9 (OCH_2Ar*C*(1)), 147.4 (C(2)Ar*C*(2)), 174.5 (*C*=O); ***m/z* (NSI)** 285 ($[M+Na]^+$, 100%) $C_{14}H_{14}O_3SNa^+$ ($[M+Na]^+$) requires 285.0556; found 285.0555 (–0.3 ppm).

Lab book Reference: SMS-1092

Benzyl 2-(isobutyryloxy)-2-(thiophene-2-yl)propanoate, 348

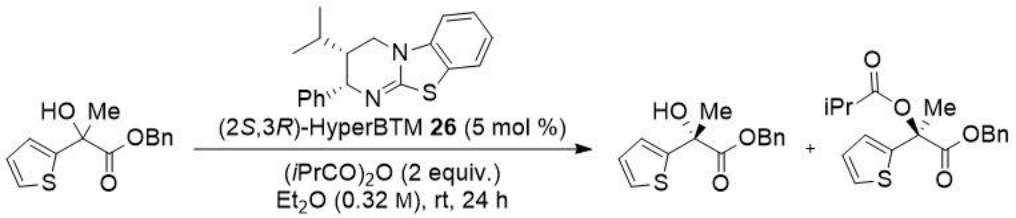


Following general procedure J, **343** (42 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.26) to afford **348** as a colourless oil (46 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2974, 1736 (C=O), 1456, 1456, 1260, 1113; **δ_H (400 MHz, $CDCl_3$)** 1.15 (6H, app d, *J* 7.0 Hz, CH(CH_3)$_2$), 2.06 (3H, s, C(2)CH_3), 2.60 (1H, hept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 5.11 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.17 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 6.96 (1H, dd, *J* 5.1, 3.7 Hz, C(2)ArC(4)*H*), 7.09 (1H, dd, *J* 3.7, 1.2 Hz, C(2)ArC(3)*H*), 7.24-7.35 (6H, m, C(2)ArC(5)*H*, OCH_2ArC(2,3,4,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.6 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.7 (CH(CH_3)$_A$(*C*H_3)$_B$), 24.2 (C(2)*C*H_3), 34.1 (O*C*H_2Ph), 67.5 (O*C*H_2Ph), 79.7 (*C*(2)), 124.9 (C(2)Ar*C*(3)H), 125.8

(C(2)Ar*C*(5)H), 126.7 (C(2)Ar*C*(4)H), 128.18 (OCH_2Ar*C*(2,6)H), 128.24 (OCH_2Ar*C*(4)H), 128.4 (OCH_2Ar*C*(3,5)H), 135.2 (OCH_2Ar*C*(1)), 143.0 (C(2)Ar*C*(2)), 169.8 (*C*(1)=O), 175.6 (*C*=OCH$(CH_3)_2$); ***m/z* (NSI)** 350 ($[M+NH_4]^+$, 100%) $C_{18}H_{24}NO_4S^+$ ($[M+ NH_4]^+$) requires 350.1421; found 350.1425 (+1.3 ppm).

Lab book Reference: SMS-1114

Kinetic resolution of 343



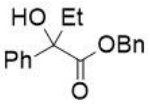
Following general procedure C, **343** (84 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), alcohol (34 mg, 0.13 mmol, 40%) and ester (52 mg, 0.16 mmol, 49%).

Data for alcohol: $[\alpha]_D^{20}$ +99 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.3, 33.2 min, >99:1 er.

Data for ester: $[\alpha]_D^{20}$ +76 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.7, 15.5 min, 91:9 er; *s* = 60.

Lab book Reference: SMS-1126

Benzyl 2-hydroxy-2-phenylbutanoate, 349

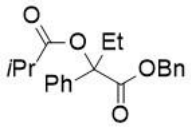


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), phenylacetic acid (1.36 g, 10 mmol) and bromoethane (1.62 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-phenylbutanoic acid, which was taken on. Following general procedure K, the acid (1.64 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.63), the impure ester as a colourless oil. Following general procedure L, the impure ester (1.98 g, 7.8 mmol), triethyl phosphite (2.67 mL, 15.6 mmol), cesium carbonate (550 mg, 1.56 mmol, 20 mol %) in DMSO (31 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.16) to afford **349** as a colourless oil (945 mg, 3.5 mmol, 35%); **ν_{max} (ATR)** 3516 (OH), 2968, 1721 (C=O), 1497, 1449, 1225, 1142; **δ_H (400 MHz, $CDCl_3$)** 0.89 (3H, t, *J* 7.3 Hz, C(2)CH_2CH_3), 2.05 (1H, dq, *J* 14.5, 7.3 C(2)$CH_AH_BCH_3$), 2.26 (1H, dq, *J* 14.5, 7.3 C(2)$CH_AH_BCH_3$), 3.77 (1H, s, O*H*), 5.15 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.25 (1H, d, *J* 12.3 Hz, OCH_AH_BPh),

7.24-7.37 (8H, m, $OCH_2ArC(2,3,4,5,6)H$, $C(2)ArC(3,4,5)H$), 7.57-7.62 (2H, m, $C(2)ArC(2,6)H$); **δ_C (100 MHz, $CDCl_3$)** 8.0 ($C(2)CH_2CH_3$), 32.5 ($C(2)CH_2CH_3$), 68.0 (OCH_2Ph), 78.8 ($C(2)$), 125.7 ($C(2)ArC(2,6)H$), 127.7 ($C(2)ArC(4)H$), 128.1 ($OCH_2ArC(2,6)H$), 128.2 ($OCH_2ArC(3,5)H$), 128.5 ($OCH_2ArC(4)H$), 128.6 ($C(2)ArC(3,5)H$), 135.1 ($OCH_2ArC(1)$), 141.6 ($C(2)ArC(1)$), 175.3 (C=O); ***m/z* (NSI)** 293 ($[M+Na]^+$, 100%) $C_{17}H_{18}O_3Na^+$ ($[M+Na]^+$) requires 293.1148; found 293.1148 (–0.1 ppm).

Lab book Reference: SMS-1090

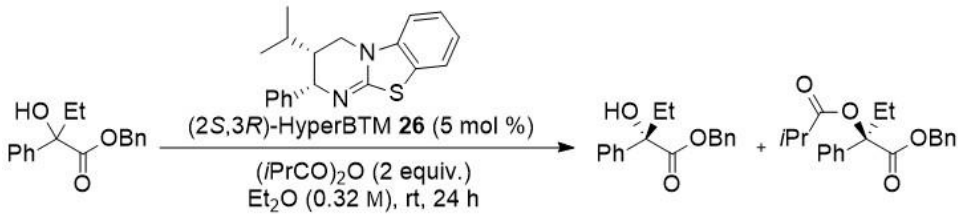
Benzyl 2-(isobutyryloxy)-2-phenylbutanoate, 350



Following general procedure J, **349** (43 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.30) to afford **350** as a colourless oil (50 mg, 0.15 mmol, 91%); **ν_{max} (ATR)** 2974, 1736 (C=O), 1449, 1234, 1128; **δ_H (400 MHz, $CDCl_3$)** 0.64 (3H, t, *J* 7.5 Hz, $C(2)CH_2CH_3$), 1.20 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 1.23 (3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$), 2.38 (1H, dq, *J* 15.0, 7.5 Hz, $C(2)CH_AH_BCH_3$), 2.65-2.78 (2H, m, $C(2)CH_AH_BCH_3$, $CH(CH_3)_2$), 5.03 (1H, d, *J* 12.4 Hz, OCH_AH_BPh), 5.14 (1H, d, *J* 12.4 Hz, OCH_AH_BPh), 7.14-7.19 (2H, m, $OCH_2ArC(3,5)H$), 7.25-7.38 (6H, m, $C(2)Ar(3,4,5)H$, $OCH_2ArC(2,4,6)H$), 7.47-7.51 (2H, m, $C(2)ArC(2,6)H$); **δ_C (100 MHz, $CDCl_3$)** 6.9 ($C(2)CH_2CH_3$), 18.9 ($CH(CH_3)_A(CH_3)_B$), 19.0 ($CH(CH_3)_A(CH_3)_B$), 28.1 ($C(2)CH_2CH_3$), 34.3 ($CH(CH_3)_2$), 67.1 (OCH_2Ph), 84.0 ($C(2)$), 125.1 ($C(2)ArC(3,5)H$), 127.9 ($C(2)ArC(4)H$), 128.1 (3C, $OCH_2ArC(2,4,6)H$), 128.3 ($OCH_2ArC(3,5)H$), 128.4 ($C(2)ArC(2,6)H$), 135.4 ($OCH_2ArC(1)$), 137.7 ($C(2)ArC(1)$), 170.7 ($C(1)=O$), 175.7 ($C=OCH(CH_3)_2$); ***m/z* (NSI)** 358 ($[M+NH_4]^+$, 100%) $C_{21}H_{28}NO_4^+$ ($[M+NH_4]^+$) requires 358.2013; found 358.2016 (+0.9 ppm).

Lab book Reference: SMS-1112

Kinetic resolution of 349



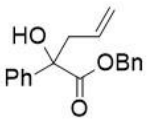
Following general procedure C, **349** (86 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent CH_2Cl_2/Et_2O, 9:1), alcohol (79 mg, 0.29 mmol, 92%) and ester (1 mg, 0.003 mmol, 1%).

Data for alcohol: $[\alpha]_D^{20}$ +3 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.6, 30.3 min, 51:49 er.

Data for ester: $[\alpha]_D^{20}$ –44 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.7, 15.5 min, 92:8 er; *s* = 11.

Lab book Reference: SMS-1134

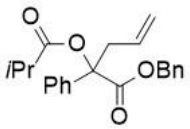
Benzyl 2-hydroxy-2-phenylpent-4-enoate, 351



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^iPr_2 (3.1 mL, 22 mmol), phenylacetic acid (1.36 g, 10 mmol) and allyl bromide (1.90 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-phenylpent-4-enoic acid, which was taken on. Following general procedure K, the acid (1.76 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1), the impure ester as a colourless oil. Following general procedure L, the impure ester (1.79 g, 6.73 mmol), triethyl phosphite (2.3 mL, 13.5 mmol), cesium carbonate (476 mg, 1.35 mmol, 20 mol %) in DMSO (27 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.11) to afford **351** as a colourless oil (1.04 g, 3.7 mmol, 37%); **ν_{max} (ATR)** 3503 (OH), 3034, 1724 (C=O), 1497, 1449, 1263; **δ_H (400 MHz, $CDCl_3$)** 2.79 (1H, ddt, *J* 14.0, 6.5, 1.3 Hz, C(2)C$H_A$$H_B$CH=$CH_2$), 3.00 (1H, ddt, *J* 14.0, 7.6, 0.9 Hz, C(2)C$H_A$$H_B$CH=$CH_2$), 3.77 (1H, br s, O*H*), 5.08-5.17 (3H, m, C(2)CH_2CH=CH_2, OC$H_A$$H_B$Ph), 5.23 (1H, d, *J* 12.2 Hz, OC$H_A$$H_B$Ph), 5.77 (1H, dddd, *J* 17.0, 10.3, 7.6, 6.6 Hz, C(2)CH_2C*H*=CH_2), 7.24-7.39 (8H, m, C(2)ArC(3,4,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.58-7.64 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 44.0 (C(2)*C*H_2CH=CH_2), 68.1 (O*C*H_2Ph), 78.1 (*C*(2)), 119.5 (C(2)CH_2CH=*C*H_2), 125.6 (C(2)Ar*C*(2,6)H), 127.9 (C(2)Ar*C*(4)H), 128.2 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.56 (OCH_2Ar*C*(4)H), 128.62 (C(2)Ar*C*(3,5)H), 132.2 (C(2)CH_2*C*H=CH_2), 135.0 (OCH_2Ar*C*(1)), 141.2 (C(2)Ar*C*(1)), 174.5 (*C*=O); ***m/z* (NSI)** 305 ([M+Na]$^+$, 100%) $C_{18}H_{18}O_3Na^+$ ([M+Na]$^+$) requires 305.1148; found 305.1150 (+0.6 ppm).

Lab book Reference: SMS-1108

Benzyl 2-(isobutyryloxy)-2-phenylpent-4-enoate, 352

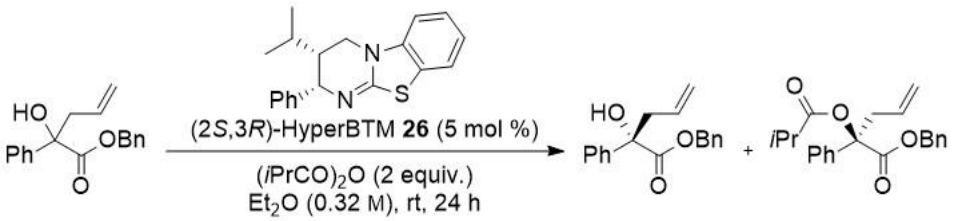


Following general procedure J, **351** (45 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to

give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.30) to afford **352** as a colourless oil (49 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2976, 1736 (C=O), 1449, 1229, 1150; **δ_H (400 MHz, $CDCl_3$)** 1.18 (3H, d, *J* 7.0 Hz, C=OCH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.20 (3H, d, *J* 7.0 Hz, C=OCH(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.97 (3H, s, C(2)C*H*$_3$), 2.67 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH$_3$)$_2$), 3.16 (1H, ddt, *J* 15.1, 5.7, 1.5 Hz, C(2)C*H*$_A$H$_B$CH=CH$_2$), 3.47 (1H, app dd, *J* 15.1, 8.7 Hz, C(2)CH$_A$*H*$_B$CH=CH$_2$), 4.94-5.02 (2H, m, C(2)CH$_2$CH=C*H*$_2$), 5.04 (1H, d, *J* 12.3 Hz, OC*H*$_A$H$_B$Ph), 5.17 (1H, d, *J* 12.3 Hz, OCH$_A$*H*$_B$Ph), 5.46 (1H, dddd, *J* 17.0, 10.1, 8.7, 5.7 Hz, C(2)CH$_2$C*H*=CH$_2$), 7.15-7.21 (2H, m, OCH$_2$ArC(3,5)*H*), 7.26-7.38 (6H, m, C(2)Ar(3,4,5)*H*, OCH$_2$ArC(2,4,6)*H*), 7.47-7.53 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.8 (C=OCH(*C*H$_3$)$_A$(CH$_3$)$_B$), 19.0 (C=OCH(CH$_3$)$_A$(*C*H$_3$)$_B$), 34.2 (C=O*C*H(CH$_3$)$_2$), 39.8 (C(2)*C*H$_2$CH=CH$_2$), 67.3 (O*C*H$_2$Ph), 82.5 (*C*(2)), 119.1 (C(2)CH$_2$CH=*C*H$_2$), 125.1 (C(2)Ar*C*(2,6)H), 128.11 (C(2)Ar*C*(4)H), 128.14 (OCH$_2$Ar*C*(2,6)H), 128.2 (OCH$_2$Ar*C*(4)H), 128.4 (OCH$_2$Ar*C*(3,5)H), 128.5 (C(2)Ar*C*(3,5)H), 131.3 (C(2)CH$_2$*C*H=CH$_2$), 135.3 (OCH$_2$Ar*C*(1)), 137.6 (C(2)Ar*C*(1)), 170.4 (*C*(1)=O), 175.4 (*C*=OCH(CH$_3$)$_2$); ***m/z* (NSI)** 370 ([M+NH$_4$]$^+$, 100%) $C_{20}H_{28}NO_4^+$ ([M+NH$_4$]$^+$) requires 370.2013; found 370.2015 (+0.6 ppm).

Lab book Reference: SMS-1117

Kinetic resolution of 351



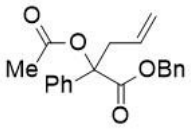
Following general procedure C, **351** (90 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 20 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (81 mg, 0.29 mmol, 90%) and ester (2 mg, 0.006 mmol, 2%).

Data for alcohol: $[\alpha]_D^{20}$ +38 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.3, 31.3 min, 52:48 er.

Data for ester: $[\alpha]_D^{20}$ +110 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 10.5, 14.5 min, 93:7 er; *s* = 13.

Lab book Reference: SMS-1135

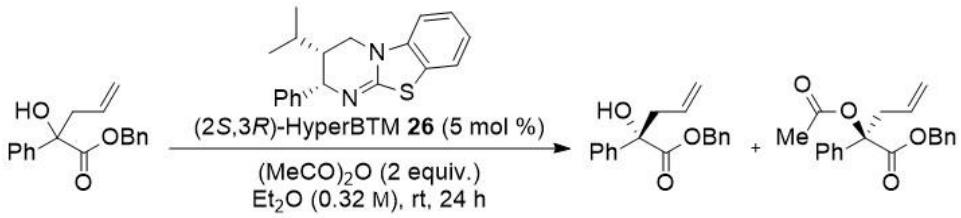
Benzyl 2-acetoxy-2-phenylpent-4-enoate, 361



Following general procedure J, **351** (40 mg, 0.14 mmol), acetic anhydride (53 µL, 0.56 mmol), DMAP **4** (1.7 mg, 0.014 mmol, 10 mol %) and NEt_3 (117 µL, 0.84 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.30) to afford **361** as a colourless oil (34 mg, 0.11 mmol, 75%); **ν_{max} (ATR)** 2953, 1743 (C=O), 1732, 1252, 1219, 1043; **δ_H (400 MHz, $CDCl_3$)** 2.18 (3H, s, C=OCH_3), 3.15 (1H, ddt, *J* 15.0, 5.8, 1.5 Hz, C(2)CH_AH$_B$CH=CH_2), 3.46 (1H, app dd, *J* 15.0, 8.6 Hz, C(2)CH$_A$$H_B$CH=$CH_2$), 4.95-5.05 (2H, m, C(2)CH_2CH=CH_2), 5.11 (1H, d, *J* 12.4 Hz, OCH_AH$_B$Ph), 5.14 (1H, d, *J* 12.3 Hz, OCH$_A$$H_B$Ph), 5.42 (1H, dddd, *J* 17.1, 10.1, 8.7, 5.8 Hz, C(2)CH_2C*H*=CH_2), 7.14-7.19 (2H, m, OCH$_2$ArC(3,5)*H*), 7.26-7.39 (6H, m, C(2)Ar(3,4,5)*H*, OCH$_2$ArC(2,4,6)*H*), 7.46-7.51 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 21.1 (C=O*C*H$_3$), 39.8 (C(2)*C*H$_2$CH=CH$_2$), 67.8 (O*C*H$_2$Ph), 83.1 (*C*(2)), 119.1 (C(2)CH$_2$CH=*C*H$_2$), 125.1 (C(2)Ar*C*(2,6)H), 127.9 (C(2)Ar*C*(4)H), 128.2 (OCH$_2$Ar*C*(2,6)H), 128.4 (OCH$_2$Ar*C*(3,5)H), 128.5 (C(2)Ar*C*(3,5)H, OCH$_2$Ar*C*(4)H), 131.3 (C(2)CH$_2$*C*H=CH$_2$), 135.4 (OCH$_2$Ar*C*(1)), 137.3 (C(2)Ar*C*(1)), 169.5 (*C*=OCH$_3$), 170.3 (*C*(1)=O); ***m/z* (NSI)** 342 ([M+NH$_4$]$^+$, 100%) $C_{20}H_{24}NO_4^+$ ([M+NH$_4$]$^+$) requires 342.1700; found 342.1702 (+0.6 ppm).

Lab book Reference: SMS-1167

Kinetic resolution of 351



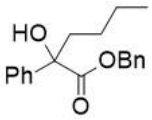
Following general procedure C, **351** (90 mg, 0.32 mmol), acetic anhydride (61 µL, 0.64 mmol) and HyperBTM **PS85** (5 mg, 0.016 mmol, 20 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (49 mg, 0.17 mmol, 54%) and ester (38 mg, 0.12 mmol, 37%).

Data for alcohol: $[\alpha]_D^{20}$ +51 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.3, 31.3 min, 76:24 er.

Data for ester: $[\alpha]_D^{20}$ +121 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.9, 18.7 min, 85:15 er; *s* = 9.

Lab book Reference: SMS-1168

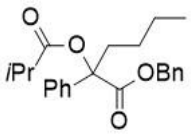
Benzyl 2-hydroxy-2-phenylhexanoate, 353



Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), $HN^{i}Pr_2$ (3.1 mL, 22 mmol), phenylacetic acid (1.36 g, 10 mmol) and *n*-butyl bromide (1.90 mL, 22 mmol) in anhydrous THF (50 mL) gave 2-phenylhexanoic acid, which was taken on. Following general procedure K, the acid (1.92 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1), the impure ester as a colourless oil. Following general procedure L, the impure ester (2.33 g, 8.26 mmol), triethyl phosphite (2.83 mL, 16.5 mmol), cesium carbonate (582 mg, 1.65 mmol, 20 mol %) in DMSO (33 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.09) to afford **353** as a colourless oil (1.28 g, 4.3 mmol, 43%); **ν_{max} (ATR)** 3503 (OH), 2957, 1722 (C=O), 1497, 1456, 1213, 1144; **δ_H (400 MHz, $CDCl_3$)** 0.85 (3H, t, *J* 7.2 Hz, C(6)H_3), 1.10-1.21 (1H, m, C(4)H_AH_B), 1.29 (2H, hex, *J* 7.1 Hz, C(5)H_2), 1.34-1.45 (1H, m, C(4)H_AH_B), 2.02 (1H, ddd, *J* 13.7, 11.9, 4.3 Hz, C(3)H_AH_B), 2.20 (1H, ddd, *J* 13.7, 11.6, 4.4 Hz, C(3)H_AH_B), 3.73 (1H, br s, O*H*), 5.15 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.26 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 7.24-7.38 (8H, m, C(2)ArC(3,4,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.58-7.63 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 14.0 (*C*(6)H), 22.8 (*C*(5)H), 25.8 (*C*(4)H), 39.3 (*C*(3)H), 68.0 (OCH_2Ph), 78.4 (*C*(2)), 125.6 (C(2)Ar*C*(2,6)H), 127.7 (C(2)Ar*C*(4)H), 128.1 (OCH_2Ar*C*(3,5)H), 128.2 (OCH_2Ar*C*(3,5)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (C(2)Ar*C*(2,6)H), 135.1 (OCH_2Ar*C*(1)), 141.8 (C(2)Ar*C*(1)), 174.5 (*C*=O); ***m/z* (NSI)** 321 ([M+Na]$^+$, 100%) $C_{19}H_{22}O_3Na^+$ ([M+Na]$^+$) requires 321.1461; found 321.1462 (+0.3 ppm).

Lab book Reference: SMS-1109

Benzyl 2-(isobutyryloxy)-2-phenylhexanoate, 354

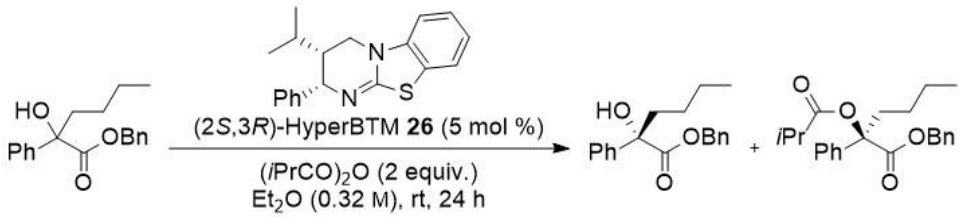


Following general procedure J, **353** (48 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.21) to afford **354** as a colourless oil (45 mg, 0.12 mmol, 77%); **ν_{max} (ATR)** 2961, 1736 (C=O), 1466, 1225, 1152; **δ_H (400 MHz, $CDCl_3$)** 0.78 (3H, t, *J* 7.3 Hz, C(6)H_3), 0.89-1.09 (2H, m, C(4)H_2), 1.13-1.28 (8H, m, CH(CH_3)$_2$, C(5)H_2), 2.34 (1H, ddd, *J* 14.6, 12.0, 4.6 Hz, C(3)H_AH_B), 2.62-2.75 (3H, m, C*H*$(CH_3)_2$, C(3)H_AH_B), 5.02 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.14 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 7.13-7.19 (2H, m, OCH_2ArC(2,6)*H*), 7.28-7.37 (6H, m, OCH_2ArC(3,4,5,)*H*, C(2)ArC(3,4,5)*H*), 7.48-7.53 (2H, m,

C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 13.9 (*C*(6)H), 18.9 (CH(*C*H_3)$_A$(CH_3)$_B$), 19.0 (CH(CH_3)$_A$(*C*H_3)$_B$), 22.5 (*C*(5)H), 24.8 (*C*(4)H), 34.3 (CH(*C*H_3)$_2$), 34.7 (*C*(3)H), 67.1 (O*C*H_2Ph), 83.7 (*C*(2)), 125.0 (C(2)Ar*C*(3,5)H), 127.9 (C(2)Ar*C*(4)H), 128.1 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.4 (3C, OCH_2Ar*C*(4)H, (C(2)Ar*C*(2,6)H), 135.4 (OCH_2Ar*C*(1)), 138.1 (C(2)Ar*C*(1)), 170.9 (*C*(1)=O), 175.9 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 386 ([M+NH_4]$^+$, 100%) $C_{23}H_{32}NO_4^+$ ([M+NH_4]$^+$) requires 386.2326; found 386.2324 (–0.5 ppm).

Lab book Reference: SMS-1118

Kinetic resolution of 353



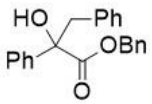
Following general procedure C, **353** (96 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (85 mg, 0.28 mmol, 89%) and ester (1 mg, 0.003 mmol, 1%).

Data for alcohol: $[\alpha]_D^{20}$ +23 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (0.5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 55.1, 60.6 min, 51:49 er.

Data for ester: $[\alpha]_D^{20}$ +63 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (0.5% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C) T_R: 30.9, 35.4 min, 90:10 er; *s* = 9.

Lab book Reference: SMS-1136

Benzyl 2-hydroxy-2,3-diphenylpropanoate, 355

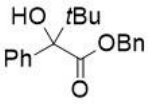


Following general procedure G, *n*BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes), HN^{i}Pr$_2$ (3.1 mL, 22 mmol), phenylacetic acid (1.36 g, 10 mmol) and benzyl bromide (2.62 mL, 22 mmol) in anhydrous THF (50 mL) gave 2,3-diphenylpropionic acid, which was taken on. Following general procedure K, the acid (2.26 g, 10 mmol), oxalyl chloride (1.05 mL, 12 mmol), DMF (1 drop), benzyl alcohol (1.06 mL, 15 mmol) and pyridine (0.81 mL, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) gave, after column chromatography (eluent Petrol/Et_2O, 9:1), the impure ester as a colourless oil. Following general procedure L, the impure ester (2.21 g, 7 mmol), triethyl phosphite (2.4 mL, 14 mmol), cesium carbonate (494 mg, 1.4 mmol, 20 mol %) in DMSO (28 mL) under a O_2 atmosphere was stirred for 24 h, to give after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.13) to afford **355** as a colourless oil (488 g, 1.47 mmol, 21%); **ν_{max} (ATR)** 3524 (OH), 3032, 1728 (C=O), 1497, 1454, 1260, 1196; **δ_H (400 MHz, $CDCl_3$)** 3.22 (1H, d, *J* 13.6 Hz,

C(3)H_AH_BPh), 3.61 (1H, d, *J* 13.6 Hz, C(3)H_AH_BPh), 3.64 (1H, br s, O*H*), 5.12 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 5.16 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 7.13-7.28 (7H, m, C(2)ArC(3,4,5)*H*, C(3)ArC(3,4,5)*H*, OCH_2ArC(4)*H*), 7.30-7.41 (6H, m, C(3)Ar(2,6)*H*, OCH_2ArC(2,3,5,6)*H*), 7.68-7.73 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 45.8 (*C*(3)H), 68.1 (O*C*H_2Ph), 78.8 (*C*(2)), 125.8 (C(2)Ar*C*(2,6)H), 126.9 (C(3)Ar*C*(4)H), 127.9 (C(2)Ar*C*(4)H), 128.1 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.5 (C(3)Ar*C*(2,6)H), 128.6 (OCH_2Ar*C*(4)H), 128.7 (C(2)Ar*C*(3,5)H), 130.6 (C(3)Ar*C*(3,5)H), 134.8 (OCH_2Ar*C*(1)), 138.6 (C(3)Ar*C*(1)), 141.5 (C(2)Ar*C*(1)), 74.8 (*C*=O); ***m/z* (NSI)** 355 ([M+Na]$^+$, 100%) $C_{22}H_{20}O_3Na^+$ ([M+Na]$^+$) requires 355.1305; found 355.1309 (+1.2 ppm).

Lab book Reference: SMS-1110

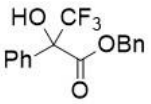
Benzyl 2-hydroxy-3,3-dimethyl-2-phenylbutanoate, 357



Following general procedure D, **330** (1.20 g mg, 5 mmol) and *tert*-butylmagnesium chloride (33 mL, 6 mmol, 0.18 M) in anhydrous THF (25 mL) gave, after column chromatography (Petrol/Et_2O, 9:1; R_F 0.32), **357** as a colourless oil (471 mg, 1.58 mmol, 32%); **ν_{max} (ATR)** 3509 (OH), 2959, 1713 (C=O), 1447, 1202, 1173; **δ_H (400 MHz, $CDCl_3$)** 1.04 (9H, s, C(2)C(CH_3)$_3$), 3.77 (1H, br s, O*H*), 5.32 (2H, s, OCH_2Ph), 7.29-7.35 (3H, m, OCH_2ArC(2,6)*H*, C(2)ArC(4)*H*), 7.37-7.45 (5H, m, OCH_2Ar(3,4,5)*H*, C(2)ArC(3,5)*H*), 7.73-7.78 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 25.8 (C(2)C(*C*H_3)$_3$), 39.2 (C(2)*C*(CH_3)$_3$), 68.2 (O*C*H_2Ph), 83.1 (*C*(2)), 127.3 (C(2)Ar*C*(2,6)H), 127.48 (OCH_2Ar*C*(2,6)H), 127.53 (C(2)Ar*C*(4)H), 128.7 (3C, OCH_2Ar*C*(4)H, C(2)Ar*C*(3,5)H), 128.8 (OCH_2Ar*C*(3,5)H), 134.9 (OCH_2Ar*C*(1)), 139.1 (C(2)Ar*C*(1)), 174.8 (*C*=O); ***m/z* (NSI)** 321 ([M+Na]$^+$, 100%) $C_{19}H_{22}O_3Na^+$ ([M+Na]$^+$) requires 321.1461; found 321.1461 (–0.0 ppm).

Lab book Reference: SMS-1060

Benzyl 3,3,3-trifluoro-2-hydroxy-2-phenylpropanoate, 359

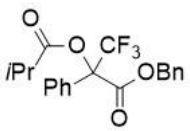


Following the method by de Frugulhetti *et al*,[98] **330** (1.28 g, 5.34 mmol) was dissolved in anhydrous THF (10 mL). (Trifluoromethyl)trimethylsilane (1.48 mL, 10.7mmol) was added, followed by cesium fluoride (81 mg, 0.53 mmol, 10 mol %) and the reaction stirred at RT for 24 h under N_2. On completion, the solution was extracted with water (20 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was then purified *via* column chromatography (eluent hexane/Et_2O, 9:1) to afford the TMS-protected alcohol as a yellow oil. The product was the treated with HCl (1M) in THF/H_2O (12 mL,

5:1) for 1 h.[154] The reaction mixture was then quenched with $NaHCO_3$ and the organic layer extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.21), **359** as a pale yellow solid (1.28 g, 4.1 mmol, 78%); **ν_{max} (ATR)** 3483 (OH), 3036, 1736 (C=O), 1452, 1279, 1163; **δ_H (400 MHz, $CDCl_3$)** 4.33 (1H, s, O*H*), 5.35 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 5.41 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 7.33-7.44 (8H, m, C(2)Ar(3,4,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.75-7.81 (2H, m, C(2)ArC(2,6*H*); **δ_C (100 MHz, $CDCl_3$)** 69.8 (OCH_2Ph), 77.9 (*C*(2)), 123.0 (q, *J* 286 Hz, *C*F_3), 126.8 (C(2)Ar*C*(2,6)H), 128.2 (OCH_2Ar*C*(2,6)H), 128.4 (OCH_2Ar*C*(3,5)H), 128.8 (OCH_2Ar*C*(4)H), 129.0 (C(2)Ar*C*(2,6)H), 129.6 (C(2)Ar*C*(4)H), 132.7 (C(2)Ar*C*(1)), 133.9 (OCH_2Ar*C*(1)), 168.9 (*C*=O); **δ_F (376 MHz, $CDCl_3$)** –76.1 (C*F*$_3$); ***m/z* (NSI)** 333 ($[M+Na]^+$, 100%) $C_{16}H_{13}O_3F_3Na^+$ ($[M+Na]^+$) requires 333.0709; found 333.0712 (+0.9 ppm).

Lab book Reference: SMS-1137

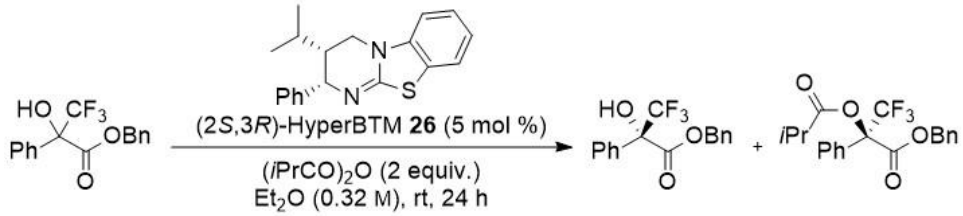
Benzyl 3,3,3-trifluoro-2-(isobutyryloxy)-2-phenylpropanoate, 360



Following general procedure J, **359** (50 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 4:1; R_F 0.66) to afford **360** as a colourless oil (56 mg, 0.15 mmol, 92%); **ν_{max} (ATR)** 2978, 1755 (C=O), 1452, 1273, 1177, 1020; **δ_H (400 MHz, $CDCl_3$)** 1.19 (3H, d, *J* 7.0 Hz, C=OCH(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.21 (3H, d, *J* 7.0 Hz, C=OCH(CH$_3$)$_A$(C*H*$_3$)$_B$), 2.76 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH$_3$)$_2$), 5.23 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 5.27 (1H, d, *J* 12.2 Hz, OCH_AH_BPh), 7.25-7.44 (8H, m, C(2)Ar(3,4,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.54-7.59 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.5 (C=OCH(*C*H$_3$)$_A$(CH$_3$)$_B$), 18.6 (C=OCH(CH$_3$)$_A$(*C*H$_3$)$_B$), 34.0 (C=O*C*H(CH$_3$)$_2$), 68.3 (O*C*H$_2$Ph), 80.6 (*C*(2)), 122.2 (q, *J* 286 Hz, *C*F_3), 126.6 (C(2)Ar*C*(2,6)H), 128.4 (OCH_2Ar*C*(2,6)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (OCH_2Ar*C*(3,5)H, C(2)Ar*C*(4)H), 129.6 (C(2)Ar*C*(3,5)H), 131.1 (C(2)Ar*C*(1)), 134.4 (OCH_2Ar*C*(1)), 164.5 (*C*(1)=O), 173.7 (*C*=OCH(CH$_3$)$_2$); **δ_F (376 MHz, $CDCl_3$)** –73.7 (C*F*$_3$); ***m/z* (NSI)** 398 ($[M+NH_4]^+$, 100%) $C_{20}H_{23}NO_4F_3^+$ ($[M+NH_4]^+$) requires 398.1574; found 398.1569 (–1.2 ppm).

Lab book Reference: SMS-1145

Kinetic resolution of 359



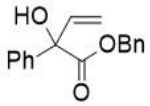
Following general procedure C, **359** (100 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (65 mg, 0.21 mmol, 65%) and ester (24 mg, 0.06 mmol, 20%).

Data for alcohol: $[\alpha]_D^{20}$ –39 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 23.5, 31.7 min, 60:40 er.

Data for ester: $[\alpha]_D^{20}$ +44 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 9.1, 15.8 min, 80:20 er; *s* = 5.

Lab book Reference: SMS-1148

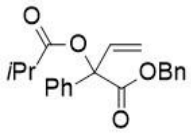
Benzyl 2-hydroxy-2-phenylbut-3-enoate, 362



Following general procedure D, **330** (1.32 g mg, 5.5 mmol) and vinylmagnesium chloride (4.12 mL, 6 mmol, 1.6 M) in anhydrous THF (25 mL) gave, after column chromatography (Petrol/Et_2O, 9:1; R_F 0.19), **362** as a colourless oil (560 mg, 2.09 mmol, 38%); **ν_{max} (ATR)** 3501 (OH), 3304, 1724 (C=O), 1449, 1233, 1150; **δ_H (400 MHz, $CDCl_3$)** 3.86 (1H, s, O*H*), 5.20 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.26 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.34 (1H, dd, *J* 10.5, 1.2 Hz, $RCH{=}CH_{cis}H_{trans}$), 5.63 (1H, dd, *J* 17.0, 1.2 Hz, $RCH{=}CH_{cis}H_{trans}$), 6.44 (1H, dd, *J* 17.0, 10.5 Hz, $RCH{=}CH_2$), 7.22-7.27 (2H, m, $OCH_2ArC(3,5)H$), 7.28-7.37 (6H, m, $OCH_2ArC(2,4,6)H$, C(2)ArC(3,4,5)*H*), 7.48-7.53 (2H, m, C(2)ArC(2,6)*H*)); **δ_C (100 MHz, $CDCl_3$)** 68.2 (OCH_2Ph), 78.5 (*C*(2)), 116.0 ($C(2)CH{=}CH_2$), 126.1 (C(2)Ar*C*(2,6)H), 128.0 ($OCH_2ArC(2,6)H$), 128.1 (C(2)Ar*C*(4)H), 128.4 ($OCH_2ArC(3,5)H$), 128.5 ($OCH_2ArC(4)H$), 128.6 (C(2)Ar*C*(3,5)H), 134.9 ($OCH_2ArC(1)$), 137.6 ($C(2)CH{=}CH_2$), 141.0 (C(2)Ar*C*(1)), 174.0 (*C*=O); ***m/z* (NSI)** 291 ($[M+Na]^+$, 100%) $C_{17}H_{16}O_3Na^+$ ($[M+Na]^+$) requires 291.0992; found 291.0990 (–0.6 ppm).

Lab book Reference: SMS-1085

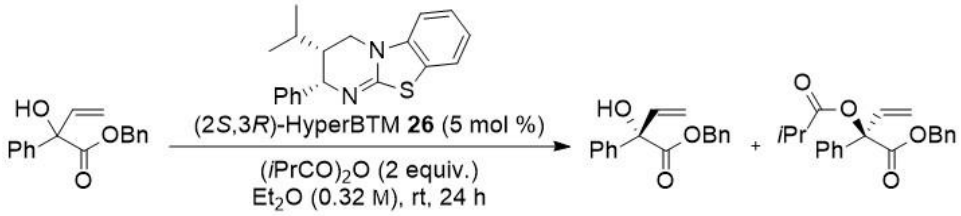
Benzyl 2-(isobutyryloxy)-2-phenylbut-3-enoate, 363



Following general procedure J, **362** (43 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.27) to afford **363** as a colourless oil (49 mg, 0.14 mmol, 90%); **ν_{max} (ATR)** 2974, 1740 (C=O), 1449, 1233, 1140, 1049; **δ_H (400 MHz, $CDCl_3$)** 1.19 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 1.20 (3H, d, *J* 7.0 Hz, CH(CH_3)$_A$(CH_3)$_B$), 2.69 (1H, hept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 5.08 (1H, d, *J* 12.3 Hz, OCH_AH$_B$Ph), 5.11 (1H, dd, *J* 17.5, 0.6 Hz, C(2)CH=CH$_{cis}$$H_{trans}$), 5.19 (1H, d, *J* 12.3 Hz, OCH$_A$$H_B$Ph), 5.33 (1H, dd, *J* 10.9, 0.6 Hz, C(2)CH=CH_{cis}H$_{trans}$), 6.88 (1H, dd, *J* 17.5, 10.8 Hz, C(2)C*H*=CH_2), 7.17-7.24 (2H, m, OCH_2ArC(3,5)*H*), 7.27-7.37 (6H, m, OCH_2ArC(2,4,6)*H*, C(2)ArC(3,4,5)*H*), 7.48-7.54 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.69 (CH(*C*H_3)$_A$(CH_3)$_B$), 18.72 (CH(CH_3)$_A$(*C*H_3)$_B$), 34.0 (*C*H(CH_3)$_2$), 67.5 (O*C*H_2Ph), 82.5 (*C*(2)), 117.4 (C(2)CH=*C*H_2), 126.1 (C(2)Ar*C*(2,6)H), 128.2 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.35 (C(2)Ar*C*(4)H), 128.39 (3C, OCH_2Ar*C*(4)H, C(2)Ar*C*(3,5)H), 135.2 (OCH_2Ar*C*(1)), 137.1 (C(2)*C*H=CH_2), 138.1 (C(2)Ar*C*(1)H), 169.7 (*C*(1)=O), 174.0 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 356 ([M+NH_4]$^+$, 100%) $C_{21}H_{26}NO_4^+$ ([M+NH_4]$^+$) requires 356.1856; found 356.1858 (+0.5 ppm).

Lab book Reference: SMS-1111

Kinetic resolution of 362



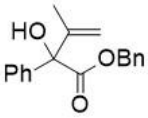
Following general procedure C, **362** (86 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (52 mg, 0.19 mmol, 60%) and ester (29 mg, 0.09 mmol, 27%).

Data for alcohol: $[\alpha]_D^{20}$ +22 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 26.2, 37.5 min, 70:30 er.

Data for ester: $[\alpha]_D^{20}$ +10 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 12.5, 17.8 min, 94:6 er; *s* = 22.

Lab book Reference: SMS-1123

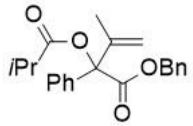
Benzyl 2-hydroxy-3-methyl-2-phenylbut-3-enoate, 364



Following general procedure D, **330** (1.20 g mg, 5 mmol) and isopropenylmagnesium bromide (10.5 mL, 6 mmol, 0.5 M) in anhydrous THF (25 mL) gave, after column chromatography (Petrol/Et_2O, 9:1; R_F 0.12), **364** as a colourless oil (592 mg, 2.1 mmol, 42%); **ν_{max} (ATR)** 3501 (OH), 3034, 1724 (C=O), 1449, 1219, 1065; **δ_H (400 MHz, $CDCl_3$)** 1.78 (3H, dd, *J* 1.3, 0.7 Hz, C(2)C(CH_3)=CH_2), 3.88 (1H, s, O*H*), 4.90-4.92 (1H, m, C(2)C(CH_3)=$CH_{cis}H_{trans}$), 5.09-5.12 (1H, m, C(2)C(CH_3)=$CH_{cis}H_{trans}$), 5.25 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 5.31 (1H, d, *J* 12.3 Hz, OCH_AH_BPh), 7.22-7.27 (8H, m, C(2)ArC(3,4,5)*H*, OCH_2ArC(2,3,4,5,6)*H*), 7.56-7.60 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 19.1 (C(2)C(CH_3)=CH_2), 68.2 (OCH_2Ph), 81.8 (*C*(2)), 115.1 (C(2)C(CH_3)=CH_2), 127.0 (C(2)Ar*C*(2,6)H), 127.9 (C(2)Ar*C*(4)H), 128.0 (OCH_2Ar*C*(2,6)H), 128.2 (OCH_2Ar*C*(3,5)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (C(2)Ar*C*(3,5)H), 134.8 (OCH_2Ar*C*(1)), 139.4 (C(2)Ar*C*(1)H), 145.4 (C(2)*C*(CH3)=CH_2), 174.0 (*C*=O); ***m/z* (NSI)** 305 ($[M+Na]^+$, 100%) $C_{14}H_{22}O_4Na^+$ ($[M+Na]^+$) requires 305.1148; found 305.1151 (+0.9 ppm).

Lab book Reference: SMS-1129

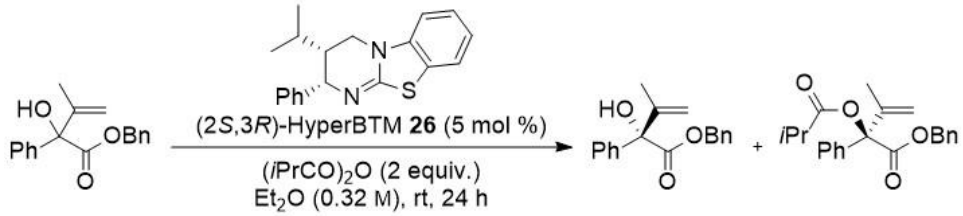
Benzyl 2-(isobutyryloxy)-3-methyl-2-phenylbut-3-enoate, 365



Following general procedure J, **364** (45 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.42) to afford **365** as a colourless oil (49 mg, 0.14 mmol, 87%); **ν_{max} (ATR)** 2974, 1740 (C=O), 1449, 1223, 1184, 1144; **δ_H (400 MHz, $CDCl_3$)** 1.13 (3H, app t, *J* 6.8 Hz, CH(CH_3)$_2$), 1.62 (3H, dd, *J* 1.2, 0.6 Hz, C(2)C(CH_3)=CH_2), 2.62 (1H, hept, *J* 7.0 Hz, C*H*(CH_3)$_2$), 5.11-5.18 (2H, m, OCH_2Ph), 5.19 (1H, app pent, *J* 1.3 Hz, C(2)C(CH_3)=$CH_{cis}H_{trans}$), 5.56 (1H, app s, C(2)C(CH_3)=$CH_{cis}H_{trans}$), 7.23-7.27 (2H, m, C(2)ArC(3,5)*H*), 7.27-7.37 (6H, m, OCH_2ArC(2,3,4,5,6)*H*, C(2)ArC(4)*H*), 7.48-7.54 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** 18.7 (CH(*C*H_3)$_2$), 19.4 (C(2)C(*C*H_3)=CH_2), 34.2 (*C*H(CH_3)$_2$), 67.3 (OCH_2Ph), 84.6 (*C*(2)), 115.4 (C(2)C(CH_3)=CH_2), 127.0 (C(2)Ar*C*(2,6)H), 127.9 (OCH_2Ar*C*(2,6)H), 128.0 (C(2)Ar*C*(4)H), 128.2 (OCH_2Ar*C*(4)H), 128.3 (OCH_2Ar*C*(3,5)H), 128.4 (C(2)Ar*C*(3,5)H), 135.3 (OCH_2Ar*C*(1)), 137.5 (C(2)Ar*C*(1)H), 141.8 (C(2)*C*(CH3)=CH_2), 168.5 (*C*(1)=O), 174.9 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 370 ($[M+NH_4]^+$, 100%) $C_{22}H_{28}NO_4^+$ ($[M+NH_4]^+$) requires 370.2013; found 370.2015 (+0.6 ppm).

Lab book Reference: SMS-1142

Kinetic resolution of 364



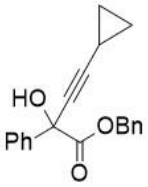
Following general procedure C, **364** (90 mg, 0.32 mmol), isobutyric anhydride (106 µL, 0.64 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (69 mg, 0.25 mmol, 77%) and ester (8 mg, 0.02 mmol, 7%).

Data for alcohol: $[\alpha]_D^{20}$ +24 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 19.4, 26.0 min, 52:48 er.

Data for ester: $[\alpha]_D^{20}$ +12 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 10.2, 11.9 min, 63:37 er; *s* = 2.

Lab book Reference: SMS-1147

Benzyl 4-cyclopropyl-2-hydroxy-2-phenybut-3-ynoate, 366

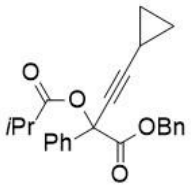


330 (1.20 g, 5 mmol) was dissolved in THF (25 mL) and cooled to –78 °C. Separately, cyclopropylacetylene (508 µL, 6 mmol) was dissolved in THF (15 mL) and cooled to –78 °C. To the alkyne solution, *n*BuLi (2.2 mL, 5.5 mmol, 2.5 M) was added dropwise and the solution stirred for 25 mins. The lithiated-alkyne solution was then transferred to the α-keto ester solution at –78 °C, warmed to RT and stirred for a further 3 h. On completion, the solution was poured into NH_4Cl (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.17), **366** as a yellow oil (1.09 g, 3.55 mmol, 71%); **ν_{max} (ATR)** 3487 (OH), 3032, 2237 (C≡C), 1730 (C=O), 1450, 1227, 1067; **δ_H (400 MHz, $CDCl_3$)** 0.73-0.87 (4H, m, C≡C-Cyclopropyl-(CH_2)$_2$), 1.37 (1H, tt, *J* 8.1, 5.1 Hz, C≡C-Cyclopropyl-C*H*), 4.18 (1H, s, O*H*), 5.13 (1H, d, *J* 12.5 Hz, OC$H_A$$H_B$Ph), 5.29 (1H, d, *J* 12.5 Hz, OCH$_A$$H_B$Ph), 7.16-7.22 (2H, m, OCH$_2$ArC(2,6)*H*), 7.29-7.40 (6H, m, OCH$_2$ArC(3,4,5,)*H*, C(2)ArC(3,4,5)*H*), 7.66-7.70 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** –0.34 (C≡C-Cyclopropyl-*C*H), 8.53 (C≡C-Cyclopropyl-(*C*H$_2$)$_2$), 68.3 (O*C*H$_2$Ph), 73.1 (*C*(2)), 73.3 (*C*≡C-Cyclopropyl), 90.8 (C≡*C*-Cyclopropyl), 126.4 (C(2)Ar*C*(2,6)H), 127.5 (OCH$_2$Ar*C*(2,6)H), 128.28 (OCH$_2$Ar*C*(3,5)H), 128.31 (OCH$_2$Ar*C*(4)H), 128.5 (C(2)Ar*C*(2,6)H), 128.6 (C(2)Ar*C*(4)H), 135.1

(C(2)Ar*C*(1)), 139.6 (OCH_2Ar*C*(1)), 171.9 (*C*=O); ***m/z* (NSI)** 329 ([M+Na]$^+$, 100%) $C_{20}H_{18}O_3Na^+$ ([M+Na]$^+$) requires 329.1148; found 329.1149 (+0.3 ppm).

Lab book Reference: SMS-1152

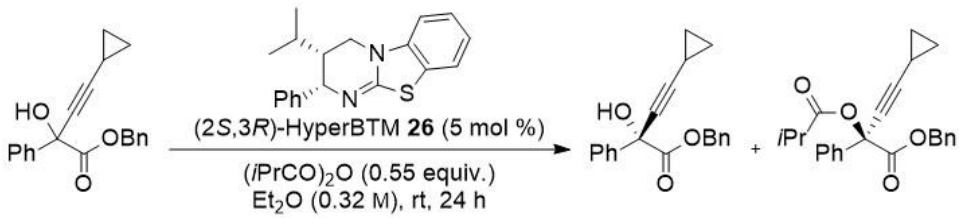
Benzyl 4-cyclopropyl-2-(isobutyryloxy)-2-phenylbut-3-ynoate, 367



Following general procedure J, **366** (49 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 4:1; R_F 0.32) to afford **367** as a colourless oil (45 mg, 0.12 mmol, 75%); **ν_{max} (ATR)** 2974, 2245 (C≡C), 1744 (C=O), 1450, 1213, 1136; **δ_H (400 MHz, $CDCl_3$)** 0.72-0.84 (4H, m, C≡C-Cyclopropyl-(CH_2)$_2$), 1.21 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.22 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.33-1.41 (1H, m, C≡C-Cyclopropyl-C*H*), 2.67 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 5.12 (2H, app s, OCH_2Ph), 7.16-7.21 (2H, m, OCH_2ArC(2,6)*H*), 7.20-7.30 (3H, m, C(2)ArC(3,4,5)*H*), 7.30-7.39 (3H, m, OCH_2ArC(3,4,5,)*H*), 7.68-7.75 (2H, m, C(2)ArC(2,6)*H*); **δ_C (100 MHz, $CDCl_3$)** –0.23 (C≡C-Cyclopropyl-*C*H), 8.54 (C≡C-Cyclopropyl-(CH_2)$_2$), 18.6 (C=OCH(CH_3)$_A$(CH_3)$_B$), 18.8 (C=OCH(CH_3)$_A$(CH_3)$_B$), 34.0 (C=O*C*H(CH_3)$_2$), 67.8 (OCH_2Ph), 70.8 (*C*≡C-Cyclopropyl), 76.6 (*C*(2)), 92.5 (C≡*C*-Cyclopropyl), 126.4 (C(2)Ar*C*(2,6)H), 127.7 (OCH_2Ar*C*(2,6)H), 128.1 (OCH_2Ar*C*(4)H), 128.4 (4C, OCH_2Ar*C*(3,5)H, C(2)Ar*C*(2,6)H), 129.0 (C(2)Ar*C*(4)H), 135.2 (C(2)Ar*C*(1)), 136.6 (OCH_2Ar*C*(1)), 167.6 (*C*(1)=O), 175.0 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 394 ([M+NH_4]$^+$, 100%) $C_{24}H_{28}NO_4^+$ ([M+NH_4]$^+$) requires 394.2013; found 394.2008 (–1.2 ppm).

Lab book Reference: SMS-1153

Kinetic resolution of 366



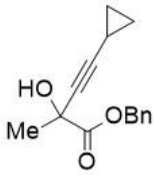
Following general procedure C, **366** (98 mg, 0.32 mmol), isobutyric anhydride (29 µL, 0.18 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (44 mg, 0.14 mmol, 45%) and ester (48 mg, 0.13 mmol, 40%).

Data for alcohol: $[\alpha]_D^{20}$ +29 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 33.9, 48.9 min, 76:24 er.

Data for ester: $[\alpha]_D^{20}$ –10 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 20.7, 23.4 min, 80:20 er; *s* = 6.

Lab book Reference: SMS-1164

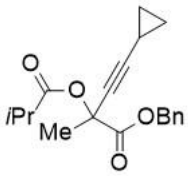
Benzyl 4-cyclopropyl-2-hydroxy-2-methylbut-3-ynoate, 368



338 (1.02 g, 5 mmol) was dissolved in THF (25 mL) and cooled to –78 °C. Separately, cyclopropylacetylene (508 µL, 6 mmol) was dissolved in THF (15 mL) and cooled to –78 °C. To the alkyne solution, *n*BuLi (2.2 mL, 5.5 mmol, 2.5 M) was added dropwise and the solution stirred for 25 mins. The lithiated-alkyne solution was then transferred to the pyruvate solution at –78 °C, warmed to RT and stirred for a further 3 h. On completion, the solution was poured into NH_4Cl (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with water (2 x 30 mL) and brine (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give, after column chromatography (eluent Petrol/Et_2O, 9:1; R_F 0.14), **368** as a yellow oil (294 mg, 1.21 mmol, 24%); **ν_{max} (ATR)** 3466 (OH), 3009, 2245 (C≡C), 1736 (C=O), 1454, 1238, 1132; **δ_H (400 MHz, $CDCl_3$)** 0.63-0.67 (2H, m, C≡C-Cyclopropyl-(CH_2)$_A$(CH_2)$_B$), 0.73-0.79 (2H, m, C≡C-Cyclopropyl-(CH_2)$_A$(CH_2)$_B$), 1.20 (1H, m, C≡C-Cyclopropyl-C*H*), 1.65 (3H, s, C(2)CH_3), 3.39 (1H, s, O*H*), 5.23 (1H, d, *J* 12.4 Hz, OCH_AH$_B$Ph), 5.29 (1H, d, *J* 12.4 Hz, OCH$_A$$H_B$Ph), 7.32-7.41 (5H, m, OCH_2ArC(2,3,4,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** –0.63 (C≡C-Cyclopropyl-*C*H), 8.25 (C≡C-Cyclopropyl-(*C*H_2)$_2$), 27.2 (C(2)*C*H_3), 68.0 (O*C*H_2Ph), 68.1 (*C*(2)), 74.8 (*C*≡C-Cyclopropyl), 88.3 (C≡*C*-Cyclopropyl), 127.9 (OCH_2Ar*C*(2,6)H), 128.5 (OCH_2Ar*C*(4)H), 128.6 (OCH_2Ar*C*(3,5)H), 135.2 (OCH_2Ar*C*(1)), 172.8 (*C*=O); ***m/z* (NSI)** 262 ([M+NH_4]$^+$, 100%) $C_{15}H_{20}NO_3^+$ ([M+NH_4]$^+$) requires 262.1438; found 262.1441 (+1.3 ppm).

Lab book Reference: SMS-1159

Benzyl 4-cyclopropyl-2-(isobutyryloxy)-2-methylbut-3-ynoate, 369

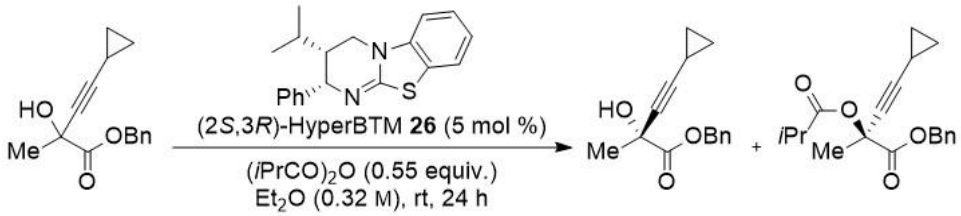


Following general procedure J, **368** (49 mg, 0.16 mmol), isobutyric anhydride (106 µL, 0.64 mmol), DMAP **4** (2 mg, 0.016 mmol, 10 mol %) and NEt_3 (133 µL, 0.96 mmol) were reacted in CH_2Cl_2 (1 mL) to

give the crude product, which was product was purified by column chromatography (eluent Petrol/EtOAc, 4:1; R_F 0.35) to afford **369** as a colourless oil (41 mg, 0.13 mmol, 81%); **ν_{max} (ATR)** 2974, 2253 (C≡C), 1742 (C=O), 1456, 1223, 1113; **δ_H (400 MHz, $CDCl_3$)** 0.69-0.74 (2H, m, C≡C-Cyclopropyl-(CH_2)$_A$(CH_2)$_B$), 0.76-0.83 (2H, m, C≡C-Cyclopropyl-(CH_2)$_A$(CH_2)$_B$), 1.149 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.153 (3H, d, *J* 7.0 Hz, C=OCH(CH_3)$_A$(CH_3)$_B$), 1.26-1.33 (1H, m, C≡C-Cyclopropyl-C*H*), 1.77 (3H, s, C(2)CH_3), 2.57 (1H, hept, *J* 7.0 Hz, C=OC*H*(CH_3)$_2$), 5.19 (1H, d, *J* 12.3 Hz, OC$H_A$$H_B$Ph), 5.23 (1H, d, *J* 12.3 Hz, OCH$_A$$H_B$Ph), 7.31-7.41 (5H, m, OCH_2ArC(2,3,4,5,6)*H*); **δ_C (100 MHz, $CDCl_3$)** –0.44 (C≡C-Cyclopropyl-*C*H), 8.43 (C≡C-Cyclopropyl-(CH_2)$_2$), 18.6 (C=OCH(CH_3)$_A$(CH_3)$_B$), 18.7 (C=OCH(CH_3)$_A$(CH_3)$_B$), 25.8 (C(2)CH_3), 33.7 (C=OCH(CH_3)$_2$), 67.6 (OCH_2Ph), 71.2 (*C*≡C-Cyclopropyl), 72.7 (*C*(2)), 90.3 (C≡*C*-Cyclopropyl), 128.1 (OCH_2Ar*C*(2,6)H), 128.3 (OCH_2Ar*C*(4)H), 128.5 (4C, OCH_2Ar*C*(3,5)H), 135.4 (OCH_2Ar*C*(1)), 168.9 (*C*(1)=O), 175.3 (*C*=OCH(CH_3)$_2$); ***m/z* (NSI)** 332 ([M+NH_4]$^+$, 100%) $C_{19}H_{26}NO_4^+$ ([M+NH_4]$^+$) requires 332.1856; found 332.1860 (+1.1 ppm).

Lab book Reference: SMS-1162

Kinetic resolution of 368



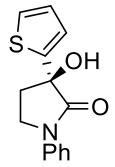
Following general procedure C, **368** (78 mg, 0.32 mmol), isobutyric anhydride (29 µL, 0.18 mmol) and (2*S*,3*R*)-HyperBTM **26** (5 mg, 0.016 mmol, 5 mol %) in Et_2O (1 mL) for 24 h gave, after column chromatography (eluent Petrol/Et_2O, 9:1), alcohol (37 mg, 0.15 mmol, 48%) and ester (34 mg, 0.11 mmol, 34%).

Data for alcohol: $[\alpha]_D^{20}$ +34 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralpak AD-H (1% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 35.7, 43.3 min, 55:45 er.

Data for ester: $[\alpha]_D^{20}$ +106 (*c* 0.1, $CHCl_3$); Chiral HPLC Chiralcel OD-H (0.5% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C) T_R: 11.2, 13.5 min, 43:57 er; *s* = 2.

Lab book Reference: SMS-1165

6.6 X-ray crystallograhic data for (*S*)-229



(S)-**229**

A. Crystal Data

Empirical Formula	$C_{14}H_{13}NO_2S$
Formula Weight	259.32
Crystal Colour, Habit	colourless, prism
Crystal Dimensions	0.100 x 0.050 x 0.030 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 11.6568(3) Å b = 17.3147(6) Å c = 18.5363(6) Å V = 3741.3(2) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	12
D_{calc}	1.381 g/cm^3
F_{000}	1632.00
μ(MoKα)	2.519 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB P200
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Temperature	-180.0 °C
Detector Aperture	83.8 x 70.0 mm
Data Images	572 exposures
Pixel Size	0.172 mm
$2\theta_{max}$	56.7°
No. of Reflections Measured	Total: 21983 Unique: 7763 (R_{int} = 0.0385) Parsons quotients (Flack x parameter): 2502
Corrections	Lorentz-polarization Absorption (trans. factors: 0.819 - 0.992)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXT Version 2014/4)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ \sigma^2(Fo^2) + (0.0461 \cdot P)^2 + 0.3766 \cdot P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	56.7°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	7763
No. Variables	535
Reflection/Parameter Ratio	14.51
Residuals: R_1 (I>2.00□(I))	0.0370
Residuals: R (All reflections)	0.0490
Residuals: wR_2 (All reflections)	0.0874
Goodness of Fit Indicator	1.047
Flack parameter (Parsons' quotients = 2502)	-0.02(3)
Max Shift/Error in Final Cycle	0.008
Maximum peak in Final Diff. Map	0.30 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.45 $e^-/Å^3$

Table 49 – Atomic coordinates and B_{iso}/B_{eq} and occupancy

Atom	x	y	z	B_{eq}
S13	0.06232(6)	0.75131(4)	0.58957(4)	1.631(13)
S33	-0.14170(15)	0.37089(12)	0.57538(11)	0.90(3)
S36	0.0384(5)	0.2928(3)	0.5484(3)	3.90(13)
S53	-0.1414(3)	0.5541(3)	0.8669(2)	1.11(5)
S56	0.0126(2)	0.55276(19)	0.97892(15)	1.88(4)
O2	0.32095(17)	0.59287(11)	0.72493(10)	1.49(4)
O3	0.12027(16)	0.58567(11)	0.63553(11)	1.26(3)
O22	0.21688(16)	0.43974(11)	0.62285(10)	1.38(3)
O23	-0.00805(17)	0.44045(11)	0.68652(10)	1.36(3)
O42	0.14800(16)	0.45905(11)	0.80359(11)	1.46(4)
O43	0.02705(17)	0.59983(12)	0.77245(10)	1.52(4)
N1	0.41757(19)	0.61762(14)	0.61822(12)	1.19(4)
N21	0.23567(19)	0.32285(13)	0.68338(12)	1.08(4)
N41	0.26252(19)	0.53715(13)	0.87608(12)	1.10(4)
C2	0.3232(2)	0.61040(16)	0.66102(15)	1.15(5)
C3	0.2171(2)	0.62970(16)	0.61518(14)	1.12(5)
C4	0.2616(2)	0.61415(17)	0.53857(14)	1.25(5)
C5	0.3867(2)	0.63947(18)	0.54330(15)	1.45(5)

C6	0.5347(2)	0.60883(17)	0.63878(16)	1.44(5)
C7	0.5652(3)	0.55836(18)	0.69414(17)	1.89(5)
C8	0.6806(3)	0.5466(2)	0.7092(2)	2.58(7)
C9	0.7663(3)	0.5841(2)	0.6705(2)	2.78(7)
C10	0.7343(3)	0.6349(2)	0.61662(19)	2.62(6)
C11	0.6194(3)	0.64773(19)	0.60059(17)	1.87(5)
C12	0.1874(2)	0.71382(16)	0.62547(14)	1.12(5)
C14	0.0991(3)	0.84310(18)	0.61550(16)	1.63(5)
C15	0.2006(3)	0.84484(18)	0.65044(17)	1.74(5)
C16	0.2516(3)	0.77072(16)	0.65614(16)	1.58(5)
C22	0.1772(2)	0.38358(16)	0.65517(14)	1.06(5)
C23	0.0476(2)	0.37054(16)	0.66819(14)	1.14(5)
C24	0.0466(2)	0.30952(17)	0.72744(15)	1.31(5)
C25	0.1587(2)	0.26544(17)	0.71708(16)	1.45(5)
C26	0.3562(2)	0.31132(16)	0.68130(14)	1.11(5)
C27	0.4313(2)	0.37112(17)	0.66441(15)	1.31(5)
C28	0.5486(3)	0.35719(18)	0.66465(16)	1.59(5)
C29	0.5914(3)	0.28511(18)	0.68157(16)	1.74(5)
C30	0.5173(3)	0.22593(18)	0.69833(15)	1.68(5)
C31	0.3997(3)	0.23849(18)	0.69865(15)	1.54(5)
C32	-0.0052(2)	0.34253(15)	0.59830(15)	1.11(5)
C33	-0.1199(15)	0.3617(12)	0.5708(11)	0.6(3)
C34	-0.1384(3)	0.31476(18)	0.50017(16)	1.88(5)
C35	-0.0402(3)	0.27477(18)	0.49130(16)	1.90(6)
C36	0.0603(6)	0.2757(4)	0.5468(3)	1.69(12)
C42	0.1688(2)	0.51963(16)	0.83559(14)	1.13(5)
C43	0.0854(2)	0.58840(17)	0.83830(15)	1.25(5)
C44	0.1642(2)	0.65510(17)	0.86048(16)	1.45(5)
C45	0.2592(3)	0.61624(16)	0.90439(16)	1.44(5)
C46	0.3554(2)	0.48686(16)	0.89307(15)	1.22(5)
C47	0.3759(3)	0.42004(18)	0.85258(16)	1.69(5)
C48	0.4649(3)	0.3712(2)	0.87261(17)	2.27(6)
C49	0.5325(3)	0.38714(19)	0.93210(17)	2.01(6)
C50	0.5125(2)	0.45373(18)	0.97162(15)	1.61(5)
C51	0.4249(2)	0.50401(17)	0.95202(15)	1.32(5)
C52	-0.0060(2)	0.56857(16)	0.89295(15)	1.36(5)
C53	-0.1232(12)	0.5560(10)	0.8738(10)	1.0(3)
C54	-0.1861(3)	0.53187(19)	0.9455(2)	2.59(7)
C55	-0.1093(3)	0.53270(19)	0.99920(18)	2.75(7)
C56	0.0167(19)	0.5595(12)	0.9683(11)	5.9(4)

$B_{eq} = 8/3\ \theta^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\theta + 2U_{13}(aa^*cc^*)\cos\theta + U_{23}(bb^*cc^*)\cos\theta)$

Table 50 – Atomic coordinates and B_{iso} involving hydrogen atoms

Atom	x	y	z	B_{iso}
H3	0.143(3)	0.5314(8)	0.633(2)	5.0(11)
H4A	0.25534	0.55873	0.52603	1.499
H4B	0.21906	0.64503	0.50243	1.499
H5A	0.43473	0.61177	0.50767	1.738
H5B	0.39453	0.69580	0.53562	1.738
H7	0.50785	0.53233	0.72121	2.264
H8	0.70150	0.51214	0.74689	3.093
H9	0.84503	0.57510	0.68085	3.338
H10	0.79182	0.66149	0.59009	3.146
H11	0.59878	0.68304	0.56356	2.248
H14	0.05340	0.88746	0.60634	1.955
H15	0.23415	0.89064	0.66915	2.088
H16	0.32322	0.76169	0.67904	1.900
H23	0.023(3)	0.458(2)	0.7324(11)	3.9(9)
H24A	-0.02023	0.27467	0.72206	1.576
H24B	0.04366	0.33390	0.77571	1.576
H25A	0.18973	0.24762	0.76393	1.743
H25B	0.14758	0.22023	0.68515	1.743
H27	0.40261	0.42096	0.65283	1.569
H28	0.60013	0.39783	0.65301	1.912
H29	0.67184	0.27637	0.68164	2.088
H30	0.54671	0.17625	0.70973	2.014
H31	0.34884	0.19759	0.71066	1.844
H33A	-0.17300	0.39641	0.59220	0.687
H34	-0.20425	0.31438	0.47001	2.261
H35	-0.03181	0.24438	0.44896	2.279
H36	0.13122	0.24887	0.55016	2.030
H43	0.078(3)	0.594(2)	0.7312(14)	4.7(10)
H44A	0.19618	0.68140	0.81754	1.745
H44B	0.12217	0.69337	0.89010	1.745
H45A	0.33359	0.64263	0.89704	1.729
H45B	0.24048	0.61645	0.95649	1.729
H47	0.32950	0.40824	0.81191	2.031
H48	0.47959	0.32609	0.84497	2.724
H49	0.59211	0.35272	0.94576	2.418
H50	0.55898	0.46509	1.01237	1.927
H51	0.41255	0.55003	0.97881	1.588
H53	-0.15643	0.56106	0.82722	1.214
H54	-0.26498	0.51897	0.94990	3.112
H55	-0.12526	0.51971	1.04797	3.298
H56	0.08646	0.56701	0.99380	7.052

Table 51 – Anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S13	0.0201(3)	0.0195(4)	0.0224(4)	0.0028(3)	-0.0061(3)	-0.0017(3)
S33	0.0075(7)	0.0117(7)	0.0150(6)	0.0029(6)	-0.0042(6)	-0.0038(5)
S36	0.0493(18)	0.0498(18)	0.0492(17)	0.0003(7)	-0.0001(7)	0.0006(7)
S53	0.0076(11)	0.0192(12)	0.0155(13)	-0.0037(9)	-0.0016(10)	0.0005(8)
S56	0.0195(9)	0.0315(12)	0.0203(10)	0.0008(8)	0.0055(8)	0.0022(8)
O2	0.0249(11)	0.0189(11)	0.0130(10)	-0.0026(9)	-0.0019(9)	0.0027(9)
O3	0.0146(9)	0.0145(11)	0.0189(10)	-0.0025(8)	0.0006(8)	0.0003(8)
O22	0.0172(10)	0.0156(11)	0.0198(10)	-0.0020(8)	-0.0018(8)	0.0045(9)
O23	0.0182(10)	0.0127(11)	0.0207(10)	0.0027(9)	-0.0007(9)	-0.0042(8)
O42	0.0183(10)	0.0164(11)	0.0207(10)	-0.0016(9)	-0.0010(9)	-0.0050(8)
O43	0.0173(10)	0.0247(12)	0.0158(10)	0.0028(9)	-0.0004(9)	0.0035(9)
N1	0.0150(11)	0.0167(13)	0.0136(11)	-0.0010(10)	-0.0030(9)	-0.0000(10)
N21	0.0137(11)	0.0118(12)	0.0153(11)	0.0005(10)	-0.0001(9)	0.0026(10)
N41	0.0150(11)	0.0132(12)	0.0136(11)	-0.0004(10)	0.0008(10)	-0.0010(9)
C2	0.0197(13)	0.0098(14)	0.0144(13)	-0.0001(11)	-0.0010(11)	-0.0011(11)
C3	0.0149(13)	0.0134(14)	0.0143(13)	-0.0021(11)	-0.0008(11)	0.0018(11)
C4	0.0175(14)	0.0184(16)	0.0116(13)	-0.0000(12)	-0.0019(11)	0.0013(11)
C5	0.0187(14)	0.0229(17)	0.0135(14)	-0.0021(13)	-0.0020(11)	0.0013(12)
C6	0.0173(14)	0.0188(16)	0.0187(14)	0.0028(12)	-0.0048(12)	-0.0088(12)
C7	0.0252(16)	0.0182(17)	0.0283(16)	0.0027(14)	-0.0124(14)	-0.0065(13)
C8	0.0346(18)	0.0222(18)	0.041(2)	0.0076(15)	-0.0219(16)	-0.0096(15)
C9	0.0230(17)	0.034(2)	0.048(2)	0.0093(15)	-0.0179(16)	-0.0201(17)
C10	0.0197(16)	0.043(2)	0.0369(19)	-0.0029(16)	-0.0014(14)	-0.0173(17)
C11	0.0174(14)	0.0301(18)	0.0236(16)	-0.0002(13)	-0.0012(12)	-0.0065(14)
C12	0.0148(13)	0.0152(14)	0.0124(13)	-0.0005(11)	0.0014(11)	0.0034(11)
C14	0.0248(15)	0.0172(16)	0.0199(15)	0.0024(13)	0.0036(13)	0.0022(12)
C15	0.0248(16)	0.0142(15)	0.0272(17)	-0.0040(13)	-0.0010(13)	0.0001(12)
C16	0.0186(14)	0.0182(16)	0.0234(15)	-0.0036(13)	-0.0029(13)	0.0011(12)
C22	0.0170(13)	0.0117(14)	0.0116(13)	-0.0002(11)	-0.0017(11)	-0.0017(11)
C23	0.0144(13)	0.0130(14)	0.0158(13)	0.0013(12)	0.0012(11)	-0.0027(11)
C24	0.0176(14)	0.0183(15)	0.0140(13)	-0.0036(12)	0.0014(11)	0.0006(12)
C25	0.0226(15)	0.0144(16)	0.0182(14)	-0.0006(12)	0.0024(12)	0.0045(12)
C26	0.0166(13)	0.0171(14)	0.0086(12)	0.0014(12)	-0.0024(11)	-0.0017(11)
C27	0.0173(13)	0.0152(15)	0.0171(14)	0.0026(12)	-0.0001(12)	0.0003(12)
C28	0.0186(14)	0.0217(16)	0.0202(15)	0.0012(12)	-0.0016(12)	-0.0016(12)
C29	0.0179(14)	0.0299(18)	0.0183(15)	0.0075(13)	-0.0013(12)	-0.0011(13)
C30	0.0263(15)	0.0214(17)	0.0160(14)	0.0104(13)	-0.0001(13)	0.0036(12)
C31	0.0264(15)	0.0179(16)	0.0141(14)	0.0047(13)	-0.0006(12)	0.0019(12)
C32	0.0157(13)	0.0121(14)	0.0144(13)	-0.0022(11)	-0.0003(11)	0.0015(11)
C34	0.0279(16)	0.0219(17)	0.0217(15)	-0.0040(14)	-0.0080(14)	0.0024(13)
C35	0.0376(18)	0.0216(17)	0.0129(14)	-0.0018(14)	-0.0013(13)	-0.0003(12)
C42	0.0169(13)	0.0159(15)	0.0103(13)	-0.0013(12)	0.0029(11)	0.0008(11)
C43	0.0161(13)	0.0173(15)	0.0142(13)	-0.0013(12)	0.0011(11)	0.0012(11)
C44	0.0206(15)	0.0164(15)	0.0182(14)	-0.0009(12)	0.0026(12)	0.0017(12)
C45	0.0218(14)	0.0137(15)	0.0193(14)	-0.0025(12)	0.0004(12)	-0.0030(12)

C46	0.0135(13)	0.0190(15)	0.0140(13)	-0.0018(12)	0.0032(11)	0.0009(11)
C47	0.0211(15)	0.0266(17)	0.0166(14)	0.0036(13)	-0.0001(12)	-0.0045(13)
C48	0.0299(17)	0.0304(19)	0.0260(16)	0.0117(15)	-0.0015(14)	-0.0070(15)
C49	0.0204(15)	0.0271(18)	0.0290(16)	0.0055(13)	0.0007(13)	0.0046(14)
C50	0.0139(13)	0.0304(18)	0.0167(14)	-0.0048(13)	0.0008(12)	0.0023(12)
C51	0.0175(14)	0.0174(15)	0.0155(14)	-0.0043(12)	0.0013(12)	0.0004(12)
C52	0.0183(14)	0.0129(15)	0.0202(14)	0.0020(12)	0.0036(12)	-0.0011(11)
C53	0.013(3)	0.012(3)	0.013(3)	0.0000(13)	0.0006(13)	-0.0006(13)
C54	0.0233(16)	0.0195(18)	0.056(2)	-0.0028(14)	0.0177(16)	-0.0075(16)
C55	0.062(2)	0.0225(19)	0.0200(16)	0.0097(17)	0.0133(17)	0.0018(14)
C56	0.074(5)	0.075(5)	0.074(5)	-0.0011(14)	0.0004(14)	0.0006(14)

The general temperature factor expression:
$\exp(-2\theta^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 52 – Fragment Analysis

Fragment 1 –					
	S(13)	O(2)	O(3)	N(1)	C(2)
	C(3)	C(4)	C(5)	C(6)	C(7)
	C(8)	C(9)	C(10)	C(11)	C(12)
	C(14)	C(15)	C(16)		
Fragment 2 –					
	S(33)	S(36)			
Fragment 3 –					
	S(53)				
Fragment 4 –					
	S(56)				
Fragment 5 –					
	O(22)	O(23)	N(21)	C(22)	C(23)
	C(24)	C(25)	C(26)	C(27)	C(28)
	C(29)	C(30)	C(31)	C(32)	C(33)
	C(34)	C(35)	C(36)		
Fragment 6 –					
	O(42)	O(43)	N(41)	C(42)	C(43)
	C(44)	C(45)	C(46)	C(47)	C(48)
	C(49)	C(50)	C(51)	C(52)	C(53)
	C(54)	C(55)	C(56)		

Table 53 – Bond lengths (Å)

Atom	Atom	Distance	Atom	Atom	Distance
S13	C12	1.729(3)	S13	C14	1.715(3)
S33	S36	2.548(6)	O2	C2	1.223(3)
O3	C3	1.414(3)	O22	C22	1.232(3)
O23	C23	1.415(3)	O42	C42	1.229(3)
O43	C43	1.411(3)	N1	C2	1.362(4)
N1	C5	1.484(4)	N1	C6	1.425(3)
N21	C22	1.358(4)	N21	C25	1.478(4)
N21	C26	1.420(4)	N41	C42	1.360(3)

N41	C45	1.467(4)	N41	C46	1.424(4)
C2	C3	1.537(4)	C3	C4	1.535(4)
C3	C12	1.509(4)	C4	C5	1.525(4)
C6	C7	1.394(4)	C6	C11	1.389(4)
C7	C8	1.389(5)	C8	C9	1.392(5)
C9	C10	1.382(5)	C10	C11	1.391(4)
C12	C16	1.361(4)	C14	C15	1.349(4)
C15	C16	1.418(4)	C22	C23	1.547(4)
C23	C24	1.524(4)	C23	C32	1.514(4)
C24	C25	1.526(4)	C26	C27	1.392(4)
C26	C31	1.397(4)	C27	C28	1.389(4)
C28	C29	1.380(4)	C29	C30	1.376(4)
C30	C31	1.388(4)	C32	C33	1.469(18)
C32	C36	1.684(7)	C33	C34	1.56(2)
C34	C35	1.348(4)	C35	C36	1.559(7)
C42	C43	1.538(4)	C43	C44	1.532(4)
C43	C52	1.509(4)	C44	C45	1.530(4)
C46	C47	1.400(4)	C46	C51	1.393(4)
C47	C48	1.389(4)	C48	C49	1.383(4)
C49	C50	1.386(4)	C50	C51	1.390(4)
C52	C53	1.429(15)	C52	C56	1.43(2)
C53	C54	1.574(18)	C54	C55	1.339(5)
C55	C56	1.64(2)			

Table 54 – Bond lengths involving hydrogens (Å)

Atom	Atom	Distance	Atom	Atom	Distance
O3	H3	0.978(17)	O23	H23	0.98(2)
O43	H43	0.98(3)	C4	H4A	0.990
C4	H4B	0.990	C5	H5A	0.990
C5	H5B	0.990	C7	H7	0.950
C8	H8	0.950	C9	H9	0.950
C10	H10	0.950	C11	H11	0.950
C14	H14	0.950	C15	H15	0.950
C16	H16	0.950	C24	H24A	0.990
C24	H24B	0.990	C25	H25A	0.990
C25	H25B	0.990	C27	H27	0.950
C28	H28	0.950	C29	H29	0.950
C30	H30	0.950	C31	H31	0.950
C33	H33A	0.950	C34	H34	0.950
C35	H35	0.950	C36	H36	0.950
C44	H44A	0.990	C44	H44B	0.990
C45	H45A	0.990	C45	H45B	0.990
C47	H47	0.950	C48	H48	0.950
C49	H49	0.950	C50	H50	0.950
C51	H51	0.950	C53	H53	0.950
C54	H54	0.950	C55	H55	0.950
C56	H56	0.950			

Table 55 – Bond angles (°)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C12	S13	C14	91.68(14)	C2	N1	C5	111.9(2)
C2	N1	C6	127.4(2)	C5	N1	C6	120.7(2)
C22	N21	C25	112.3(2)	C22	N21	C26	126.5(2)
C25	N21	C26	121.2(2)	C42	N41	C45	112.6(2)
C42	N41	C46	126.6(2)	C45	N41	C46	120.8(2)
O2	C2	N1	127.2(3)	O2	C2	C3	124.9(2)
N1	C2	C3	107.9(2)	O3	C3	C2	112.2(2)
O3	C3	C4	114.9(2)	O3	C3	C12	107.6(2)
C2	C3	C4	101.6(2)	C2	C3	C12	109.0(2)
C4	C3	C12	111.3(2)	C3	C4	C5	102.6(2)
N1	C5	C4	102.3(2)	N1	C6	C7	120.6(3)
N1	C6	C11	119.5(3)	C7	C6	C11	119.8(3)
C6	C7	C8	119.2(3)	C7	C8	C9	121.5(3)
C8	C9	C10	118.4(3)	C9	C10	C11	121.1(3)
C6	C11	C10	119.9(3)	S13	C12	C3	120.5(2)
S13	C12	C16	110.6(2)	C3	C12	C16	128.7(2)
S13	C14	C15	112.0(2)	C14	C15	C16	112.5(3)
C12	C16	C15	113.2(3)	O22	C22	N21	127.6(2)
O22	C22	C23	123.9(2)	N21	C22	C23	108.5(2)
O23	C23	C22	111.1(2)	O23	C23	C24	114.6(2)
O23	C23	C32	107.1(2)	C22	C23	C24	102.8(2)
C22	C23	C32	108.1(2)	C24	C23	C32	113.0(2)
C23	C24	C25	104.4(2)	N21	C25	C24	103.7(2)
N21	C26	C27	121.6(2)	N21	C26	C31	118.7(2)
C27	C26	C31	119.7(3)	C26	C27	C28	119.3(3)
C27	C28	C29	120.9(3)	C28	C29	C30	119.9(3)
C29	C30	C31	120.3(3)	C26	C31	C30	119.9(3)
C23	C32	C33	126.5(8)	C23	C32	C36	121.4(3)
C33	C32	C36	111.8(9)	C32	C33	C34	107.5(12)
C33	C34	C35	104.7(7)	C34	C35	C36	123.5(3)
C32	C36	C35	92.3(4)	O42	C42	N41	128.0(3)
O42	C42	C43	123.5(2)	N41	C42	C43	108.5(2)
O43	C43	C42	112.6(2)	O43	C43	C44	114.5(2)
O43	C43	C52	105.8(2)	C42	C43	C44	102.3(2)
C42	C43	C52	107.0(2)	C44	C43	C52	114.5(2)
C43	C44	C45	104.2(2)	N41	C45	C44	103.9(2)
N41	C46	C47	121.1(2)	N41	C46	C51	119.1(2)
C47	C46	C51	119.8(3)	C46	C47	C48	119.2(3)
C47	C48	C49	121.2(3)	C48	C49	C50	119.5(3)
C49	C50	C51	120.4(3)	C46	C51	C50	119.9(3)
C43	C52	C53	122.9(8)	C43	C52	C56	123.4(9)
C53	C52	C56	113.8(12)	C52	C53	C54	106.0(11)
C53	C54	C55	108.3(6)	C54	C55	C56	109.9(8)
C52	C56	C55	101.9(13)				

Table 56 – Bond angles involving hydrogens (°)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C3	O3	H3	107(2)	C23	O23	H23	108(2)
C43	O43	H43	111.5(18)	C3	C4	H4A	111.2
C3	C4	H4B	111.2	C5	C4	H4A	111.2
C5	C4	H4B	111.2	H4A	C4	H4B	109.1
N1	C5	H5A	111.3	N1	C5	H5B	111.3
C4	C5	H5A	111.3	C4	C5	H5B	111.3
H5A	C5	H5B	109.2	C6	C7	H7	120.4
C8	C7	H7	120.4	C7	C8	H8	119.2
C9	C8	H8	119.2	C8	C9	H9	120.8
C10	C9	H9	120.8	C9	C10	H10	119.5
C11	C10	H10	119.5	C6	C11	H11	120.0
C10	C11	H11	120.0	S13	C14	H14	124.0
C15	C14	H14	124.0	C14	C15	H15	123.7
C16	C15	H15	123.7	C12	C16	H16	123.4
C15	C16	H16	123.4	C23	C24	H24A	110.9
C23	C24	H24B	110.9	C25	C24	H24A	110.9
C25	C24	H24B	110.9	H24A	C24	H24B	108.9
N21	C25	H25A	111.0	N21	C25	H25B	111.0
C24	C25	H25A	111.0	C24	C25	H25B	111.0
H25A	C25	H25B	109.0	C26	C27	H27	120.3
C28	C27	H27	120.3	C27	C28	H28	119.6
C29	C28	H28	119.5	C28	C29	H29	120.1
C30	C29	H29	120.1	C29	C30	H30	119.9
C31	C30	H30	119.9	C26	C31	H31	120.0
C30	C31	H31	120.0	C32	C33	H33A	126.3
C34	C33	H33A	126.3	C33	C34	H34	127.7
C35	C34	H34	127.7	C34	C35	H35	118.2
C36	C35	H35	118.2	C32	C36	H36	133.9
C35	C36	H36	133.8	C43	C44	H44A	110.9
C43	C44	H44B	110.9	C45	C44	H44A	110.9
C45	C44	H44B	110.9	H44A	C44	H44B	108.9
N41	C45	H45A	111.0	N41	C45	H45B	111.0
C44	C45	H45A	111.0	C44	C45	H45B	111.0
H45A	C45	H45B	109.0	C46	C47	H47	120.4
C48	C47	H47	120.4	C47	C48	H48	119.4
C49	C48	H48	119.4	C48	C49	H49	120.3
C50	C49	H49	120.3	C49	C50	H50	119.8
C51	C50	H50	119.8	C46	C51	H51	120.0
C50	C51	H51	120.0	C52	C53	H53	127.0
C54	C53	H53	127.0	C53	C54	H54	125.9
C55	C54	H54	125.9	C54	C55	H55	125.0
C56	C55	H55	125.0	C52	C56	H56	129.0
C55	C56	H56	129.0				

Table 57 – Torsion Angles (°) (Those having bond angles > 160 or < 20 degrees are excluded.)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C12	S13	C14	C15	-0.7(2)	C14	S13	C12	C3	-174.57(19)
C14	S13	C12	C16	0.63(19)	C2	N1	C5	C4	-21.4(3)
C5	N1	C2	O2	179.8(3)	C5	N1	C2	C3	-1.2(3)
C2	N1	C6	C7	30.5(4)	C2	N1	C6	C11	-153.0(3)
C6	N1	C2	O2	-2.2(5)	C6	N1	C2	C3	176.8(2)
C5	N1	C6	C7	-151.6(2)	C5	N1	C6	C11	24.8(4)
C6	N1	C5	C4	160.4(2)	C22	N21	C25	C24	-17.2(3)
C25	N21	C22	O22	-178.8(2)	C25	N21	C22	C23	-0.4(3)
C22	N21	C26	C27	15.6(4)	C22	N21	C26	C31	-166.1(2)
C26	N21	C22	O22	-0.1(4)	C26	N21	C22	C23	178.3(2)
C25	N21	C26	C27	-165.8(2)	C25	N21	C26	C31	12.4(3)
C26	N21	C25	C24	164.0(2)	C42	N41	C45	C44	-14.2(3)
C45	N41	C42	O42	178.3(2)	C45	N41	C42	C43	-4.3(3)
C42	N41	C46	C47	18.7(4)	C42	N41	C46	C51	-159.9(2)
C46	N41	C42	O42	-3.3(4)	C46	N41	C42	C43	174.0(2)
C45	N41	C46	C47	-163.0(2)	C45	N41	C46	C51	18.4(4)
C46	N41	C45	C44	167.3(2)	O2	C2	C3	O3	-34.5(4)
O2	C2	C3	C4	-157.8(2)	O2	C2	C3	C12	84.6(3)
N1	C2	C3	O3	146.4(2)	N1	C2	C3	C4	23.1(3)
N1	C2	C3	C12	-94.5(2)	O3	C3	C4	C5	-156.44(19)
O3	C3	C12	S13	-50.5(3)	O3	C3	C12	C16	135.2(2)
C2	C3	C4	C5	-35.0(2)	C2	C3	C12	S13	-172.43(19)
C2	C3	C12	C16	13.3(4)	C4	C3	C12	S13	76.3(3)
C4	C3	C12	C16	-97.9(3)	C12	C3	C4	C5	80.9(2)
C3	C4	C5	N1	34.5(3)	N1	C6	C7	C8	175.1(2)
N1	C6	C11	C10	-175.0(2)	C7	C6	C11	C10	1.4(4)
C11	C6	C7	C8	-1.3(4)	C6	C7	C8	C9	0.1(5)
C7	C8	C9	C10	0.9(5)	C8	C9	C10	C11	-0.8(5)
C9	C10	C11	C6	-0.4(5)	S13	C12	C16	C15	-0.4(3)
C3	C12	C16	C15	174.3(2)	S13	C14	C15	C16	0.7(3)
C14	C15	C16	C12	-0.2(4)	O22	C22	C23	O23	-40.7(3)
O22	C22	C23	C24	-163.7(2)	O22	C22	C23	C32	76.5(3)
N21	C22	C23	O23	140.8(2)	N21	C22	C23	C24	17.8(3)
N21	C22	C23	C32	-102.0(2)	O23	C23	C24	C25	-148.05(19)
O23	C23	C32	C33	-24.1(3)	O23	C23	C32	C36	162.81(18)
C22	C23	C24	C25	-27.4(2)	C22	C23	C32	C33	-143.9(2)
C22	C23	C32	C36	43.0(3)	C24	C23	C32	C33	103.1(3)
C24	C23	C32	C36	-70.0(3)	C32	C23	C24	C25	88.9(2)
C23	C24	C25	N21	27.5(3)	N21	C26	C27	C28	178.6(2)
N21	C26	C31	C30	-178.8(2)	C27	C26	C31	C30	-0.6(4)
C31	C26	C27	C28	0.4(4)	C26	C27	C28	C29	-0.2(4)
C27	C28	C29	C30	0.1(4)	C28	C29	C30	C31	-0.3(4)
C29	C30	C31	C26	0.5(4)	C23	C32	C33	C34	-176.0(5)
C23	C32	C36	C35	177.9(2)	C33	C32	C36	C35	3.8(9)
C36	C32	C33	C34	-2.4(14)	C32	C33	C34	C35	-0.5(13)

C33	C34	C35	C36	3.9(8)	C34	C35	C36	C32	-4.9(5)
O42	C42	C43	O43	-38.2(4)	O42	C42	C43	C44	-161.7(2)
O42	C42	C43	C52	77.7(3)	N41	C42	C43	O43	144.3(2)
N41	C42	C43	C44	20.9(3)	N41	C42	C43	C52	-99.8(2)
O43	C43	C44	C45	-150.6(2)	O43	C43	C52	C53	6.9(3)
O43	C43	C52	C56	-174.1(2)	C42	C43	C44	C45	-28.4(2)
C42	C43	C52	C53	-113.5(3)	C42	C43	C52	C56	65.6(3)
C44	C43	C52	C53	134.0(2)	C44	C43	C52	C56	-47.0(3)
C52	C43	C44	C45	86.9(3)	C43	C44	C45	N41	26.5(3)
N41	C46	C47	C48	-177.7(2)	N41	C46	C51	C50	176.9(2)
C47	C46	C51	C50	-1.7(4)	C51	C46	C47	C48	0.8(4)
C46	C47	C48	C49	0.7(4)	C47	C48	C49	C50	-1.3(5)
C48	C49	C50	C51	0.4(4)	C49	C50	C51	C46	1.1(4)
C43	C52	C53	C54	176.5(5)	C43	C52	C56	C55	-176.1(4)
C53	C52	C56	C55	3.0(15)	C56	C52	C53	C54	-2.6(15)
C52	C53	C54	C55	0.9(12)	C53	C54	C55	C56	0.8(7)
C54	C55	C56	C52	-2.3(13)					

Table 58 – Possible hydrogen bonds

Donor	H	Acceptor	D...A	D-H	H...A	D-H...A
O3	H3	O22	2.776(3)	0.978(17)	1.81(2)	167(3)
O23	H23	O42	2.850(3)	0.98(2)	1.96(3)	150(3)
O43	H43	O3	2.772(3)	0.98(3)	1.84(3)	157(3)

Table 59 – Intramolecular contacts less than 3.60 Å

Atom	Atom	Distance	Atom	Atom	Distance
S13	O3	3.067(2)	S13	C4	3.454(3)
O2	O3	2.869(3)	O2	C4	3.542(3)
O2	C5	3.546(3)	O2	C6	2.972(3)
O2	C7	2.965(4)	O2	C12	3.195(3)
O2	C16	3.430(3)	O3	N1	3.524(3)
O3	C16	3.571(3)	O22	O23	2.875(3)
O22	C24	3.575(3)	O22	C25	3.552(4)
O22	C26	2.959(3)	O22	C27	2.873(3)
O22	C32	3.121(3)	O23	N21	3.496(3)
O23	C33	2.86(2)	O42	O43	2.874(3)
O42	C44	3.560(4)	O42	C45	3.547(3)
O42	C46	2.971(3)	O42	C47	2.887(4)
O42	C52	3.092(3)	O43	N41	3.522(3)
O43	C53	2.678(17)	N1	C12	3.161(4)
N1	C16	3.357(4)	N21	C32	3.238(3)
N21	C36	3.355(7)	N41	C52	3.192(4)
N41	C56	3.36(2)	C2	C7	3.024(4)
C2	C16	2.900(4)	C4	C16	3.480(4)
C5	C11	2.917(4)	C5	C12	3.062(4)
C5	C16	3.467(4)	C6	C9	2.797(4)
C7	C10	2.776(5)	C8	C11	2.763(5)

C22	C27	2.975(4)	C22	C36	3.063(7)
C24	C36	3.404(7)	C25	C31	2.868(4)
C25	C32	3.206(4)	C25	C36	3.364(7)
C26	C29	2.779(4)	C27	C30	2.778(4)
C28	C31	2.763(4)	C42	C47	2.983(4)
C42	C53	3.533(15)	C42	C56	3.11(2)
C44	C56	3.11(2)	C45	C51	2.879(4)
C45	C52	3.206(4)	C45	C56	3.22(2)
C46	C49	2.787(4)	C47	C50	2.783(4)
C48	C51	2.770(4)			

Table 60 – Intramolecular contacts less than 3.60 Å involving hydrogens

Atom	Atom	Distance	Atom	Atom	Distance
S13	H4B	3.055	S13	H15	3.465
S13	H16	3.469	O2	H3	2.89(4)
O2	H7	2.419	O2	H16	3.044
O3	H4A	2.611	O3	H4B	2.910
O22	H23	3.05(3)	O22	H27	2.259
O23	H24A	2.948	O23	H24B	2.550
O23	H33A	2.708	O42	H43	2.81(4)
O42	H47	2.297	O43	H44A	2.565
O43	H44B	2.934	O43	H53	2.461
N1	H3	3.54(4)	N1	H4A	2.745
N1	H4B	3.192	N1	H7	2.633
N1	H11	2.602	N1	H16	2.950
N21	H23	3.53(3)	N21	H24A	3.179
N21	H24B	2.824	N21	H27	2.644
N21	H31	2.588	N21	H36	3.037
N41	H43	3.57(3)	N41	H44A	2.831
N41	H44B	3.172	N41	H47	2.647
N41	H51	2.595	N41	H56	3.040
C2	H3	2.56(3)	C2	H4A	2.773
C2	H4B	3.237	C2	H5A	3.126
C2	H5B	2.877	C2	H7	2.775
C2	H16	2.641	C3	H5A	3.241
C3	H5B	2.786	C3	H16	2.855
C4	H3	2.65(4)	C5	H11	2.612
C5	H16	3.370	C6	H5A	2.696
C6	H5B	2.931	C6	H8	3.256
C6	H10	3.261	C7	H9	3.284
C7	H11	3.267	C8	H10	3.243
C9	H7	3.282	C9	H11	3.268
C10	H8	3.240	C11	H5A	2.826
C11	H5B	3.002	C11	H7	3.268
C11	H9	3.273	C12	H3	3.204(15)
C12	H4A	3.352	C12	H4B	2.599
C12	H5B	2.950	C12	H14	3.406

C12	H15	3.213	C14	H16	3.194
C16	H5B	3.074	C16	H14	3.205
C22	H23	2.64(3)	C22	H24A	3.223
C22	H24B	2.856	C22	H25A	3.103
C22	H25B	2.903	C22	H27	2.706
C22	H36	3.085	C23	H25A	3.229
C23	H25B	2.869	C23	H33A	2.966
C23	H36	3.190	C24	H23	2.59(4)
C24	H36	3.588	C25	H31	2.511
C25	H36	3.124	C26	H25A	2.707
C26	H25B	2.899	C26	H28	3.256
C26	H30	3.268	C27	H29	3.264
C27	H31	3.269	C28	H30	3.243
C29	H27	3.265	C29	H31	3.253
C30	H28	3.240	C31	H25A	2.735
C31	H25B	2.966	C31	H27	3.272
C31	H29	3.255	C32	H23	3.21(3)
C32	H24A	2.583	C32	H24B	3.341
C32	H25B	3.201	C32	H34	3.358
C32	H35	3.263	C33	H24A	3.388
C33	H35	3.206	C33	H36	3.540
C34	H36	3.469	C35	H33A	3.214
C36	H24A	3.382	C36	H25B	2.922
C36	H33A	3.532	C36	H34	3.462
C42	H43	2.55(3)	C42	H44A	2.839
C42	H44B	3.220	C42	H45A	3.086
C42	H45B	2.921	C42	H47	2.724
C42	H56	3.193	C43	H45A	3.231
C43	H45B	2.882	C43	H53	2.865
C43	H56	2.906	C44	H43	2.81(3)
C44	H56	3.042	C45	H51	2.533
C45	H56	2.743	C46	H45A	2.710
C46	H45B	2.865	C46	H48	3.262
C46	H50	3.266	C47	H49	3.270
C47	H51	3.275	C48	H50	3.249
C49	H47	3.270	C49	H51	3.265
C50	H48	3.247	C51	H45A	2.817
C51	H45B	2.902	C51	H47	3.276
C51	H49	3.267	C52	H43	3.19(3)
C52	H44A	3.365	C52	H44B	2.628
C52	H45B	3.214	C52	H54	3.312
C52	H55	3.302	C53	H43	3.60(3)
C53	H55	3.290	C53	H56	3.311
C54	H56	3.356	C55	H53	3.272
C56	H44B	2.997	C56	H45B	2.797
C56	H53	3.303	C56	H54	3.375
H3	H4A	2.422	H3	H4B	3.242

H4A	H5A	2.309	H4A	H5B	2.880
H4B	H5A	2.581	H4B	H5B	2.310
H5A	H11	2.501	H5B	H11	2.447
H5B	H16	3.010	H7	H8	2.333
H8	H9	2.342	H9	H10	2.335
H10	H11	2.333	H14	H15	2.408
H15	H16	2.469	H23	H24A	3.227
H23	H24B	2.312	H24A	H25A	2.610
H24A	H25B	2.277	H24B	H25A	2.276
H24B	H25B	2.856	H25A	H31	2.273
H25B	H31	2.425	H25B	H36	2.558
H27	H28	2.337	H28	H29	2.324
H29	H30	2.325	H30	H31	2.336
H33A	H34	2.698	H34	H35	2.379
H35	H36	2.671	H43	H44A	2.600
H43	H44B	3.454	H43	H53	3.314
H44A	H45A	2.278	H44A	H45B	2.857
H44B	H45A	2.620	H44B	H45B	2.278
H44B	H56	2.942	H45A	H51	2.391
H45B	H51	2.349	H45B	H56	2.106
H47	H48	2.337	H48	H49	2.329
H49	H50	2.336	H50	H51	2.337
H53	H54	2.702	H54	H55	2.441
H55	H56	2.787			

Table 61 – Intermolecular contacts less than 3.60 Å

Atom	Atom	Distance	Atom	Atom	Distance
S53	S56	2.745(5)	S56	S53	2.745(5)
O2	O22	3.476(3)	O2	O42	3.400(3)
O2	O43	3.539(3)	O2	N41	3.040(3)
O2	C30[1]	3.300(4)	O2	C42	2.994(3)
O2	C43	3.459(3)	O2	C44	3.289(3)
O2	C45	3.428(3)	O3	O22	2.776(3)
O3	O23	3.075(3)	O3	O43	2.772(3)
O3	C22	3.580(3)	O3	C50[2]	3.477(3)
O22	O2	3.476(3)	O22	O3	2.776(3)
O22	O42	3.461(3)	O22	C2	3.282(3)
O22	C3	3.292(3)	O22	C4	3.440(3)
O23	O3	3.075(3)	O23	O42	2.850(3)
O23	O43	3.212(3)	O42	O2	3.400(3)
O42	O22	3.461(3)	O42	O23	2.850(3)
O42	N21	3.402(3)	O42	C22	3.065(3)
O42	C23	3.165(3)	O42	C24	3.177(3)
O43	O2	3.539(3)	O43	O3	2.772(3)
O43	O23	3.212(3)	O43	C9[3]	3.589(4)
O43	C25[4]	3.598(4)	N21	O42	3.402(3)
N41	O2	3.040(3)	C2	O22	3.282(3)

C3	O22	3.292(3)	C4	O22	3.440(3)
C4	C46[2]	3.492(4)	C4	C51[2]	3.389(4)
C7	C28	3.531(4)	C9	O43[5]	3.589(4)
C14	C24[4]	3.420(4)	C15	C49[1]	3.544(4)
C16	C29[1]	3.530(4)	C22	O3	3.580(3)
C22	O42	3.065(3)	C23	O42	3.165(3)
C24	O42	3.177(3)	C24	C14[6]	3.420(4)
C25	O43[6]	3.598(4)	C28	C7	3.531(4)
C29	C16[7]	3.530(4)	C30	O2[7]	3.300(4)
C30	C35[8]	3.578(4)	C31	C35[8]	3.597(4)
C34	C54[9]	3.502(5)	C35	C30[10]	3.578(4)
C35	C31[10]	3.597(4)	C42	O2	2.994(3)
C43	O2	3.459(3)	C44	O2	3.289(3)
C45	O2	3.428(3)	C46	C4[11]	3.492(4)
C49	C15[7]	3.544(4)	C50	O3[11]	3.477(3)
C51	C4[11]	3.389(4)	C54	C34[12]	3.502(5)

Symmetry Operators:

(1) -X+1,Y+1/2,-Z+1/2+1	(2) -X+1/2,-Y+1,Z+1/2-1
(3) X-1,Y,Z	(4) -X,Y+1/2,-Z+1/2+1
(5) X+1,Y,Z	(6) -X,Y+1/2-1,-Z+1/2+1
(7) -X+1,Y+1/2-1,-Z+1/2+1	(8) X+1/2,-Y+1/2,-Z+1
(9) -X+1/2-1,-Y+1,Z+1/2-1	(10) X+1/2-1,-Y+1/2,-Z+1
(11) -X+1/2,-Y+1,Z+1/2	(12) -X+1/2-1,-Y+1,Z+1/2

Table 62 – Intermolecular contacts less than 3.60 Å involving hydrogens

Atom	Atom	Distance	Atom	Atom	Distance
S13	H5A[1]	3.329	S13	H5B[1]	3.170
S13	H10[2]	3.516	S13	H11[1]	3.087
S13	H24A[3]	3.549	S13	H24B[3]	3.132
O2	H27	3.399	O2	H30[4]	2.435
O2	H43	2.83(3)	O2	H44A	2.722
O2	H45A	3.308	O2	H47	3.582
O3	H9[2]	3.322	O3	H23	3.06(3)
O3	H43	1.84(3)	O3	H50[5]	3.217
O22	H3	1.81(2)	O22	H4A	2.769
O22	H45B[5]	3.272	O22	H51[5]	3.072
O22	H56[5]	3.315	O23	H3	2.56(3)
O23	H9[2]	2.895	O23	H43	2.95(4)
O42	H3	3.40(4)	O42	H14[6]	3.136
O42	H23	1.96(3)	O42	H24B	2.538
O43	H3	3.15(4)	O43	H9[2]	2.751
O43	H23	2.56(3)	O43	H24A[3]	3.030
O43	H25B[3]	3.018	N1	H27	3.469
N1	H30[4]	3.373	N21	H47	3.010
N41	H4A[7]	3.244	C2	H27	3.411
C2	H30[4]	3.056	C2	H43	3.15(3)

C2	H44A	3.482	C3	H43	2.76(3)
C5	H14^{8}	3.419	C6	H30^{4}	3.186
C6	H31^{4}	3.463	C6	H55^{5}	2.984
C7	H27	3.137	C7	H28	2.911
C7	H30^{4}	3.007	C7	H31^{4}	3.151
C7	H55^{5}	3.108	C8	H28	2.933
C8	H31^{4}	3.026	C8	H53^{9}	2.908
C8	H55^{5}	3.267	C9	H25A^{4}	3.123
C9	H31^{4}	3.242	C9	H53^{9}	3.067
C9	H55^{5}	3.331	C10	H25A^{4}	3.081
C10	H31^{4}	3.517	C10	H50^{10}	3.541
C10	H55^{5}	3.225	C11	H48^{4}	3.448
C11	H55^{5}	3.060	C12	H24A^{3}	3.591
C12	H43	3.13(3)	C14	H5A^{1}	3.081
C14	H11^{1}	3.350	C14	H24A^{3}	3.364
C14	H24B^{3}	2.619	C15	H24A^{3}	3.388
C15	H24B^{3}	3.165	C15	H49^{4}	3.007
C16	H24A^{3}	3.518	C16	H29^{4}	3.138
C16	H44A	3.429	C16	H48^{4}	3.277
C16	H49^{4}	2.984	C22	H3	2.622(16)
C22	H47	3.431	C23	H3	3.07(2)
C24	H14^{6}	3.560	C24	H44B^{6}	3.558
C26	H35^{11}	2.909	C26	H47	2.962
C26	H48	3.367	C27	H7	3.114
C27	H35^{11}	2.933	C27	H47	3.049
C27	H48	3.482	C27	H56^{5}	3.345
C28	H7	3.244	C28	H8	3.563
C28	H33A^{9}	3.577	C28	H35^{11}	2.899
C28	H48	3.480	C28	H55^{5}	3.165
C29	H16^{12}	2.798	C29	H35^{11}	2.860
C29	H44A^{12}	3.059	C29	H45A^{12}	2.996
C29	H48	3.373	C30	H16^{12}	3.001
C30	H35^{11}	2.836	C30	H44A^{12}	3.441
C30	H45A^{12}	2.868	C30	H48	3.254
C31	H34^{11}	3.476	C31	H35^{11}	2.866
C31	H48	3.244	C32	H44B^{6}	2.928
C32	H51^{5}	3.087	C33	H29^{2}	3.507
C33	H44B^{6}	3.004	C33	H50^{5}	3.267
C33	H51^{5}	3.329	C33	H54^{13}	3.331
C34	H36^{14}	3.049	C34	H44B^{6}	2.931
C34	H51^{5}	3.545	C34	H54^{13}	3.229
C35	H44B^{6}	2.781	C35	H45A^{5}	3.301
C35	H51^{5}	3.387	C36	H34^{11}	3.172
C36	H44B^{6}	2.815	C36	H45A^{5}	3.351
C36	H45B^{5}	3.418	C36	H51^{5}	3.285
C42	H23	2.77(3)	C43	H23	3.07(3)
C43	H24A^{3}	3.497	C43	H25B^{3}	3.574

C44	H24A[3]	3.073	C44	H29[4]	2.945
C45	H29[4]	3.298	C45	H30[4]	3.267
C46	H4A[7]	2.892	C46	H4B[7]	3.174
C47	H4A[7]	3.579	C47	H4B[7]	3.195
C47	H7	3.475	C48	H4B[7]	3.235
C48	H11[12]	3.545	C48	H16[12]	3.258
C49	H4B[7]	3.257	C49	H5B[12]	3.472
C49	H15[12]	3.306	C49	H16[12]	3.434
C49	H54[9]	3.300	C50	H3[7]	3.51(4)
C50	H4A[7]	3.288	C50	H4B[7]	3.246
C50	H54[9]	2.857	C51	H3[7]	3.50(4)
C51	H4A[7]	2.735	C51	H4B[7]	3.217
C52	H14[6]	3.184	C52	H23	3.55(3)
C52	H25B[3]	3.423	C53	H8[2]	3.207
C53	H14[6]	3.051	C53	H15[6]	3.240
C53	H23	3.56(3)	C53	H25B[3]	3.060
C53	H34[15]	3.503	C54	H14[6]	3.093
C54	H15[6]	3.288	C54	H33A[15]	3.411
C54	H34[15]	2.988	C54	H50[2]	3.421
C55	H5A[7]	3.228	C55	H14[6]	3.252
C55	H28[7]	3.096	C55	H33A[15]	3.304
C55	H34[15]	3.468	C56	H4A[7]	3.521
C56	H5A[7]	3.106	C56	H14[6]	3.384
C56	H27[7]	3.564	C56	H35[3]	3.554
H3	O22	1.81(2)	H3	O23	2.56(3)
H3	O42	3.40(4)	H3	O43	3.15(4)
H3	C22	2.622(16)	H3	C23	3.07(2)
H3	C50[5]	3.51(4)	H3	C51[5]	3.50(4)
H3	H23	2.64(5)	H3	H27	3.597
H3	H43	2.24(5)	H3	H50[5]	3.249
H3	H51[5]	3.252	H4A	O22	2.769
H4A	N41[5]	3.244	H4A	C46[5]	2.892
H4A	C47[5]	3.579	H4A	C50[5]	3.288
H4A	C51[5]	2.735	H4A	C56[5]	3.521
H4A	H45B[5]	3.296	H4A	H51[5]	2.853
H4A	H56[5]	2.915	H4B	C46[5]	3.174
H4B	C47[5]	3.195	H4B	C48[5]	3.235
H4B	C49[5]	3.257	H4B	C50[5]	3.246
H4B	C51[5]	3.217	H4B	H11[1]	3.511
H5A	S13[8]	3.329	H5A	C14[8]	3.081
H5A	C55[5]	3.228	H5A	C56[5]	3.106
H5A	H14[8]	2.526	H5A	H55[5]	3.267
H5A	H56[5]	3.116	H5B	S13[8]	3.170
H5B	C49[4]	3.472	H5B	H14[8]	3.526
H5B	H48[4]	3.484	H5B	H49[4]	2.743
H7	C27	3.114	H7	C28	3.244
H7	C47	3.475	H7	H27	2.613

H7	H28	2.860	H7	H30[4]	2.873
H7	H31[4]	3.546	H7	H47	3.430
H8	C28	3.563	H8	C53[9]	3.207
H8	H15[12]	2.722	H8	H28	2.888
H8	H31[4]	3.358	H8	H53[9]	2.383
H9	O3[9]	3.322	H9	O23[9]	2.895
H9	O43[9]	2.751	H9	H23[9]	3.052
H9	H25A[4]	3.184	H9	H25B[4]	3.534
H9	H33A[9]	3.510	H9	H43[9]	2.894
H9	H50[10]	3.390	H9	H53[9]	2.724
H10	S13[9]	3.516	H10	H25A[4]	3.097
H10	H49[10]	3.008	H10	H50[10]	3.147
H11	S13[8]	3.087	H11	C14[8]	3.350
H11	C48[4]	3.545	H11	H4B[8]	3.511
H11	H14[8]	3.419	H11	H48[4]	3.138
H11	H55[5]	3.536	H14	O42[3]	3.136
H14	C5[1]	3.419	H14	C24[3]	3.560
H14	C52[3]	3.184	H14	C53[3]	3.051
H14	C54[3]	3.093	H14	C55[3]	3.252
H14	C56[3]	3.384	H14	H5A[1]	2.526
H14	H5B[1]	3.526	H14	H11[1]	3.419
H14	H23[3]	3.353	H14	H24B[3]	2.631
H14	H53[3]	3.463	H14	H54[3]	3.515
H15	C49[4]	3.306	H15	C53[3]	3.240
H15	C54[3]	3.288	H15	H8[4]	2.722
H15	H24B[3]	3.535	H15	H29[4]	3.573
H15	H48[4]	3.529	H15	H49[4]	3.012
H15	H53[3]	3.087	H15	H54[3]	3.152
H16	C29[4]	2.798	H16	C30[4]	3.001
H16	C48[4]	3.258	H16	C49[4]	3.434
H16	H29[4]	2.596	H16	H30[4]	2.956
H16	H44A	3.274	H16	H48[4]	2.593
H16	H49[4]	2.968	H23	O3	3.06(3)
H23	O42	1.96(3)	H23	O43	2.56(3)
H23	C42	2.77(3)	H23	C43	3.07(3)
H23	C52	3.55(3)	H23	C53	3.56(3)
H23	H3	2.64(5)	H23	H9[2]	3.052
H23	H14[6]	3.353	H23	H43	2.43(5)
H23	H53	3.262	H24A	S13[6]	3.549
H24A	O43[6]	3.030	H24A	C12[6]	3.591
H24A	C14[6]	3.364	H24A	C15[6]	3.388
H24A	C16[6]	3.518	H24A	C43[6]	3.497
H24A	C44[6]	3.073	H24A	H43[6]	3.324
H24A	H44A[6]	2.712	H24A	H44B[6]	2.778
H24B	S13[6]	3.132	H24B	O42	2.538
H24B	C14[6]	2.619	H24B	C15[6]	3.165
H24B	H14[6]	2.631	H24B	H15[6]	3.535

H25A	C9[12]	3.123	H25A	C10[12]	3.081
H25A	H9[12]	3.184	H25A	H10[12]	3.097
H25A	H47	3.344	H25B	O43[6]	3.018
H25B	C43[6]	3.574	H25B	C52[6]	3.423
H25B	C53[6]	3.060	H25B	H9[12]	3.534
H25B	H34[11]	3.408	H25B	H44B[6]	3.471
H25B	H53[6]	2.767	H27	O2	3.399
H27	N1	3.469	H27	C2	3.411
H27	C7	3.137	H27	C56[5]	3.564
H27	H3	3.597	H27	H7	2.613
H27	H35[11]	3.513	H27	H47	3.077
H27	H55[5]	3.401	H27	H56[5]	2.958
H28	C7	2.911	H28	C8	2.933
H28	C55[5]	3.096	H28	H7	2.860
H28	H8	2.888	H28	H33A[9]	2.875
H28	H35[11]	3.464	H28	H55[5]	2.432
H29	C16[12]	3.138	H29	C33[9]	3.507
H29	C44[12]	2.945	H29	C45[12]	3.298
H29	H15[12]	3.573	H29	H16[12]	2.596
H29	H33A[9]	3.216	H29	H35[11]	3.410
H29	H44A[12]	2.252	H29	H44B[12]	3.098
H29	H45A[12]	2.737	H30	O2[12]	2.435
H30	N1[12]	3.373	H30	C2[12]	3.056
H30	C6[12]	3.186	H30	C7[12]	3.007
H30	C45[12]	3.267	H30	H7[12]	2.873
H30	H16[12]	2.956	H30	H35[11]	3.373
H30	H44A[12]	3.041	H30	H45A[12]	2.491
H31	C6[12]	3.463	H31	C7[12]	3.151
H31	C8[12]	3.026	H31	C9[12]	3.242
H31	C10[12]	3.517	H31	H7[12]	3.546
H31	H8[12]	3.358	H31	H34[11]	3.412
H31	H35[11]	3.420	H31	H53[6]	3.333
H33A	C28[2]	3.577	H33A	C54[13]	3.411
H33A	C55[13]	3.304	H33A	H9[2]	3.510
H33A	H28[2]	2.875	H33A	H29[2]	3.216
H33A	H44B[6]	3.580	H33A	H50[5]	3.116
H33A	H54[13]	3.103	H33A	H55[13]	2.883
H34	C31[14]	3.476	H34	C36[14]	3.172
H34	C53[13]	3.503	H34	C54[13]	2.988
H34	C55[13]	3.468	H34	H25B[14]	3.408
H34	H31[14]	3.412	H34	H36[14]	2.240
H34	H44B[6]	3.468	H34	H54[13]	2.931
H35	C26[14]	2.909	H35	C27[14]	2.933
H35	C28[14]	2.899	H35	C29[14]	2.860
H35	C30[14]	2.836	H35	C31[14]	2.866
H35	C56[6]	3.554	H35	H27[14]	3.513
H35	H28[14]	3.464	H35	H29[14]	3.410

H35	H30[14]	3.373	H35	H31[14]	3.420
H35	H44B[6]	3.285	H35	H45A[5]	3.177
H35	H56[6]	3.311	H36	C34[11]	3.049
H36	H34[11]	2.240	H36	H44B[6]	3.298
H36	H45A[5]	3.428	H36	H45B[5]	3.269
H43	O2	2.83(3)	H43	O3	1.84(3)
H43	O23	2.95(4)	H43	C2	3.15(3)
H43	C3	2.76(3)	H43	C12	3.13(3)
H43	H3	2.24(5)	H43	H9[2]	2.894
H43	H23	2.43(5)	H43	H24A[3]	3.324
H44A	O2	2.722	H44A	C2	3.482
H44A	C16	3.429	H44A	C29[4]	3.059
H44A	C30[4]	3.441	H44A	H16	3.274
H44A	H24A[3]	2.712	H44A	H29[4]	2.252
H44A	H30[4]	3.041	H44B	C24[3]	3.558
H44B	C32[3]	2.928	H44B	C33[3]	3.004
H44B	C34[3]	2.931	H44B	C35[3]	2.781
H44B	C36[3]	2.815	H44B	H24A[3]	2.778
H44B	H25B[3]	3.471	H44B	H29[4]	3.098
H44B	H33A[3]	3.580	H44B	H34[3]	3.468
H44B	H35[3]	3.285	H44B	H36[3]	3.298
H45A	O2	3.308	H45A	C29[4]	2.996
H45A	C30[4]	2.868	H45A	C35[7]	3.301
H45A	C36[7]	3.351	H45A	H29[4]	2.737
H45A	H30[4]	2.491	H45A	H35[7]	3.177
H45A	H36[7]	3.428	H45B	O22[7]	3.272
H45B	C36[7]	3.418	H45B	H4A[7]	3.296
H45B	H36[7]	3.269	H47	O2	3.582
H47	N21	3.010	H47	C22	3.431
H47	C26	2.962	H47	C27	3.049
H47	H7	3.430	H47	H25A	3.344
H47	H27	3.077	H48	C11[12]	3.448
H48	C16[12]	3.277	H48	C26	3.367
H48	C27	3.482	H48	C28	3.480
H48	C29	3.373	H48	C30	3.254
H48	C31	3.244	H48	H5B[12]	3.484
H48	H11[12]	3.138	H48	H15[12]	3.529
H48	H16[12]	2.593	H49	C15[12]	3.007
H49	C16[12]	2.984	H49	H5B[12]	2.743
H49	H10[16]	3.008	H49	H15[12]	3.012
H49	H16[12]	2.968	H49	H54[9]	3.327
H50	O3[7]	3.217	H50	C10[16]	3.541
H50	C33[7]	3.267	H50	C54[9]	3.421
H50	H3[7]	3.249	H50	H9[16]	3.390
H50	H10[16]	3.147	H50	H33A[7]	3.116
H50	H54[9]	2.534	H51	O22[7]	3.072
H51	C32[7]	3.087	H51	C33[7]	3.329

H51	C34[7]	3.545	H51	C35[7]	3.387
H51	C36[7]	3.285	H51	H3[7]	3.252
H51	H4A[7]	2.853	H53	C8[2]	2.908
H53	C9[2]	3.067	H53	H8[2]	2.383
H53	H9[2]	2.724	H53	H14[6]	3.463
H53	H15[6]	3.087	H53	H23	3.262
H53	H25B[3]	2.767	H53	H31[3]	3.333
H54	C33[15]	3.331	H54	C34[15]	3.229
H54	C49[2]	3.300	H54	C50[2]	2.857
H54	H14[6]	3.515	H54	H15[6]	3.152
H54	H33A[15]	3.103	H54	H34[15]	2.931
H54	H49[2]	3.327	H54	H50[2]	2.534
H55	C6[7]	2.984	H55	C7[7]	3.108
H55	C8[7]	3.267	H55	C9[7]	3.331
H55	C10[7]	3.225	H55	C11[7]	3.060
H55	C28[7]	3.165	H55	H5A[7]	3.267
H55	H11[7]	3.536	H55	H27[7]	3.401
H55	H28[7]	2.432	H55	H33A[15]	2.883
H56	O22[7]	3.315	H56	C27[7]	3.345
H56	H4A[7]	2.915	H56	H5A[7]	3.116
H56	H27[7]	2.958	H56	H35[3]	3.311

Symmetry Operators:

(1) X+1/2-1,-Y+1/2+1,-Z+1
(2) X-1,Y,Z
(3) -X,Y+1/2,-Z+1/2+1
(4) -X+1,Y+1/2,-Z+1/2+1
(5) -X+1/2,-Y+1,Z+1/2-1
(6) -X,Y+1/2-1,-Z+1/2+1
(7) -X+1/2,-Y+1,Z+1/2
(8) X+1/2,-Y+1/2+1,-Z+1
(9) X+1,Y,Z
(10) -X+1/2+1,-Y+1,Z+1/2-1
(11) X+1/2,-Y+1/2,-Z+1
(12) -X+1,Y+1/2-1,-Z+1/2+1
(13) -X+1/2-1,-Y+1,Z+1/2-1
(14) X+1/2-1,-Y+1/2,-Z+1
(15) -X+1/2-1,-Y+1,Z+1/2
(16) -X+1/2+1,-Y+1,Z+1/2

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