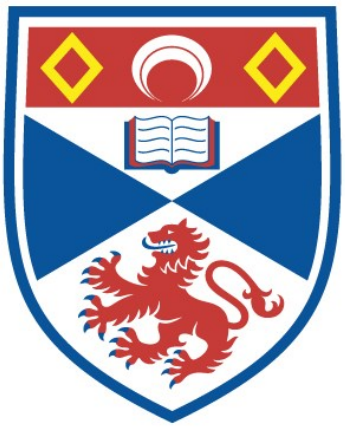
ENANTIOSELECTIVE ISOTHIOUREA CATALYSIS VIA C(1)-AMMONIUM ENOLATE INTERMEDIATES: APPLICATIONS AND MECHANISTIC STUDIES

Calum McLaughlin

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



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Enantioselective Isothiourea Catalysis via C(1)-Ammonium Enolate Intermediates: Applications and Mechanistic Studies

Calum McLaughlin

University of
St Andrews

This thesis is submitted in partial fulfilment for the degree of Doctor of Philosophy (PhD) at the University of St Andrews

September 2020

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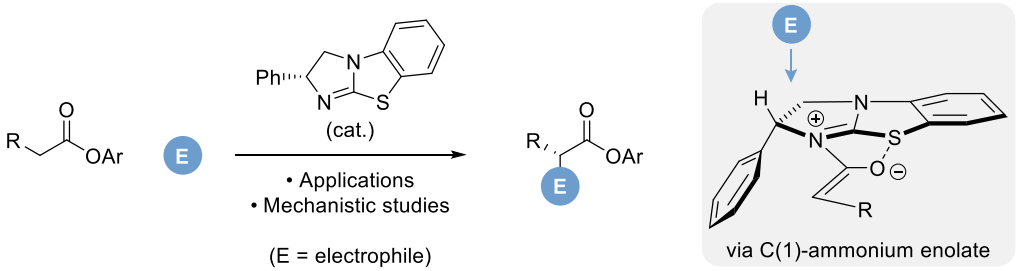
Abstract

The absolute stereochemistry of organic compounds can have a profound influence on the conformation, properties, and function of molecules. Therefore, sustainable synthetic methods that enable the catalytic, stereoselective preparation of enantioenriched compounds is a central research goal in chemistry.

Catalytically generated C(1)-ammonium enolate intermediates, derived from chiral tertiary amine Lewis base catalysts such as isothioureas, have emerged as synthetically useful intermediates for the enantioselective synthesis of α-functionalised carbonyl compounds at the carboxylic acid oxidation level, motifs that are found in many biologically relevant molecules. Despite the widespread application of C(1)-ammonium enolates in the synthesis of chiral heterocycles, there is typically a requirement for relatively high catalyst loadings, stoichiometric additives and/or auxiliary base for effective reactivity in the formation of acyclic α-functionalised products. In addition, a fundamental mechanistic understanding of these processes, governed by intermolecular catalyst turnover via an aryloxide, remains elusive and compatible electrophiles are limited to alkene and carbonyl derivatives.

The research goals of this thesis targeted the development of novel methodologies in isothiourea catalysis via C(1)-ammonium enolates using aryloxide catalyst turnover in reaction with alternative electrophiles, specifically looking to address the previous limitations of sustainability and mechanistic understanding (Scheme I). Herein, we report the base-free enantioselective α-functionalisation of esters via a Michael addition reaction of aryl esters to vinyl bis-sulfones enabled by a multifunctional aryloxide (Chapter 2). Using $^{19}F\{^{1}H\}$ NMR reaction monitoring, a thorough mechanistic investigation was carried out to interrogate this methodology, enabling a large amount of mechanistic information to be collected, including elucidation of the turnover limiting step (Chapter 3). We also report the regio-, diastereo- and enantioselective dearomatisation of pyridinium salts using isothiourea catalysis via C(1)-ammonium enolate intermediates for the synthesis of 1,4-dihydropyridine heterocyclic motifs (Chapter 4). An enantioselective

nucleophilic aromatic substitution protocol was also targeted, however, attempts to render both inter- and intramolecular variations of this transformation enantioselective proved challenging (Chapter 5).



Scheme I.

PhD Publications

The work described in this thesis has formed the basis for the following peer-reviewed publications.

1. "Base-free Enantioselective C(1)-Ammonium Enolate Catalysis Exploiting Aryloxides: A Synthetic and Mechanistic Study", **C. McLaughlin**, A. M. Z. Slawin, A. D. Smith, *Angew. Chem.* **2019**, *131*, 15255-15263; *Angew. Chem. Int. Ed.* **2019**, *58*, 15111-15119.
2. "Generation and Reactivity of C(1)-Ammonium Enolates Using Isothiourea Catalysis", **C. McLaughlin**, A. D. Smith, *Chem. Eur. J.* **2020**, DOI: 10.1002/chem.202002059.
3. "Enantioselective Dearomatisation of Pyridinium Salts via C(1)-Ammonium Enolates", **C. McLaughlin**, L. J. Barber, A. M. Z. Slawin, A. D. Smith, *Manuscript in preparation*.

Abbreviations

Ac	Acetyl
aq.	Aqueous
Ar	Aryl
ASAP	Atmospheric solids analysis probe
atm	Atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bpy	Bipyridine
BTM	Benzotetramisole
Bu	Butyl
Bz	Benzoyl
C	Celsius
CAN	Cerium ammonium nitrate
Cat.	Catalyst
COD	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
d1	Relaxation delay
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT	Density functional theory
DHP	Dihydropyridine
DHPB	3,4-Dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine
DIBAL	Di-iso-butylaluminium
DIPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
DMAP	4-Dimethylaminopyridine
DMC	Dimethyl carbonate

DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
Equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
FDA	Food and drug administration
FTIR	Fourier transform infrared spectroscopy
g	Grams
GC	Gas chromatography
h	Hours
HBTM	HomoBTM
HMBC	Heteronuclear multiple-bond correlation
HMDS	Hexamethyldisilazane
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
i	Iso
IPA	Isopropanol
IR	Infrared
J	Coupling constant
KIE	Kinetic isotope effect
KR	Kinetic resolution
LB	Lewis base
LED	Light emitting diode
Lit.	Literature
LG	Leaving group
M	Molar
MVK	Methyl vinyl ketone

Me	Methyl
Mes	Mesityl
MHz	Megahertz
min	Minutes
mL	Millilitres
mol	Moles
mp	Melting point
MS	Molecular sieves
Ms	Methane sulfonyl
μL	Microlitres
NBO	Natural bond orbital
NFSI	*N*-Fluorobenzenesulfonimide
NHC	N-Heterocyclic carbene
NMR	Nuclear magnetic resonance
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
app	apparent
NOESY	Nuclear Overhauser effect spectroscopy
Ns	Number of scans
NSI	Nanospray ionisation
Nuc	Nucleophile
PCC	Pyridinium chlorochromate
Petrol	Petroleum ether 40-60 °C
Ph	Phenyl
Pin	Pinacol
ppm	Parts per million
Pr	Propyl
PS-BEMP	Polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Quant.	Quantitative
PTC	Phase transfer catalyst

RAMP	(*R*)-1-Amino-2-methoxymethylpyrrolidine
RPKA	Reaction progress kinetic analysis
RT	Room temperature
s	Seconds
s	Selectivity factor
SAMP	(*S*)-1-Amino-2-methoxymethylpyrrolidine
sat.	Saturated
S_NAr	Nucleophilic aromatic substitution
SOMO	Singly occupied molecular orbital
t	Tertiary
TBDMS	*Tert*-butyl dimethyl silyl
TBME	*Tert*-butyl methyl ether
Temp.	Temperature
Tert	Tertiary
Tf	Trifluoromethane sulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Tetramisole
TOCSY	Total correlation spectroscopy
Tol	Tolyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	Tosyl
TS	Transition state
UV-Vis	Ultraviolet-visible spectroscopy
VTNA	Variable time normalisation analysis
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
ZPE	Zero point energy
δ	Chemical shift

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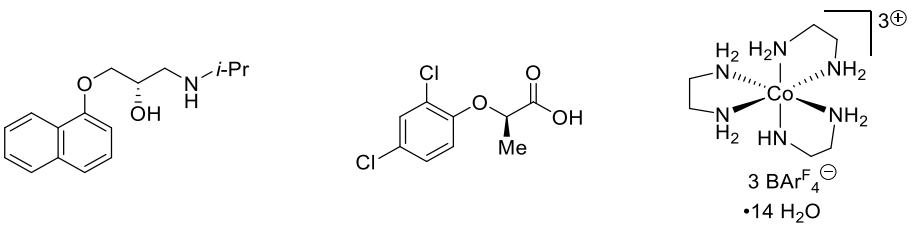
Chapter 1. Introduction

1.1. Chirality

Chirality is a fundamental property of a three-dimensional object that renders it non-superimposable upon its mirror image.[1] Enantiomers, the two non-superimposable forms of a chiral molecule, were first found to be composed of tetrahedral carbon centres, although nitrogen, phosphorous and sulfur atoms can also exhibit point chirality. Additionally, allenes,[2] rotationally hindered biaryls and helices can show axial chirality,[3],[4] and unsymmetrical rotationally restricted non-coplanar rings can be planar chiral.[5] While opposite enantiomers of a chiral structure exhibit identical chemical and physical properties, they differ in their spatial arrangement. Consequently, the absolute configuration of a chiral molecule can have a considerable influence on its behaviour when placed in a chiral environment. This is now well known in the scientific community and is of high interest for many research areas. This is profound in biological systems where opposite enantiomers can interact with receptors differently and enantiomeric discrimination occurs.[6] For example, (*S*)-Propranolol **1** (Figure 1), a β-adrenoceptor blocker, is almost 100 times more potent than the (*R*)-enantiomer.[7] The FDA encourage the development of single enantiomer drugs over racemates and advise the evaluation of safety and activity of both enantiomers.[8] Similarly, there is a drive toward increasing the number of single enantiomer pesticides in the agrochemical industry in order to lessen the detrimental effects of the non-target enantiomer;[9] for example (*R*)-Dichlorprop **2** is the active herbicide whilst the (*S*)-enantiomer is inactive.[10]



1
(*S*)-Propranolol
β-adrenoceptor blocker

2
(*R*)-Dichlorprop
herbicide

3
(Δ)-[Co(1,2-ethylenediamine)$_3$]$^{3+}$
chiral-at-metal complex
(Ar^F: 3,5-(CF$_3$)$_2$C$_6$H$_3$)

Figure 1. Examples of chiral compounds.

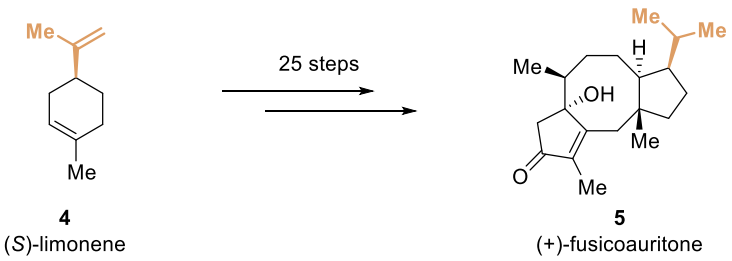
Aside from biological applications, enantiopure molecules are sought after in materials science. The synthesis of optically active chiral macromolecules such as polymers has received significant attention with respect to the relationship of stereochemistry to conformation, properties and function.[11] Applications of optically active polymers include chiral stationary phases, optoelectronics and catalysts for asymmetric synthesis.[12,13] In inorganic coordination chemistry, tetrahedral and octahedral metal complexes exhibit propeller chirality where the dissymmetric arrangement of non-chiral ligands renders the metal centre stereogenic.[14] For example, chiral-at-metal cobalt catalyst **3** has a "right-handed" twist (Δ) and can catalyse enantioselective reactions.[15] The demand for chiral molecules has enhanced significantly over the previous two decades; especially for pharmaceuticals where two thirds of prescribed drugs are chiral.[16] Therefore, synthetic methods that allow control of absolute configuration of chiral compounds for the synthesis of enantioenriched, spatially well-defined structures is a central research goal in chemistry.

1.2. Asymmetric Synthesis

1.2.1. First Generation Asymmetric Synthesis: Chiral Pool

The first generation of asymmetric synthesis enabled the preparation of enantioenriched molecules using starting materials from the chiral pool.[17] The three major classes of natural origin precursors used were amino acids,[18] sugars and terpenes.[19],[20] In 2007, the 5,8,5-fused tricyclic diterpene (+)-fusicoauritone **5** was concisely prepared in twenty-five steps from the naturally occurring monoterpene (*S*)-limonene **4** (Scheme 1).[21] Advantageously, all the stereochemical information of the starting material is transferred to the product, with the absolute configuration within (*S*)-limonene **4** used to direct the subsequent diastereoselective reactions. Whilst there is a wide range of starting materials to choose from, chiral pool synthesis is normally designed to 'best-fit' around the natural precursors. For example, in this publication 44% of steps involved redox reactions and 8% were protecting group manipulations. In 2010, it was proposed all steps in an ideal synthesis should be constructive bond-forming reactions and redox and protecting

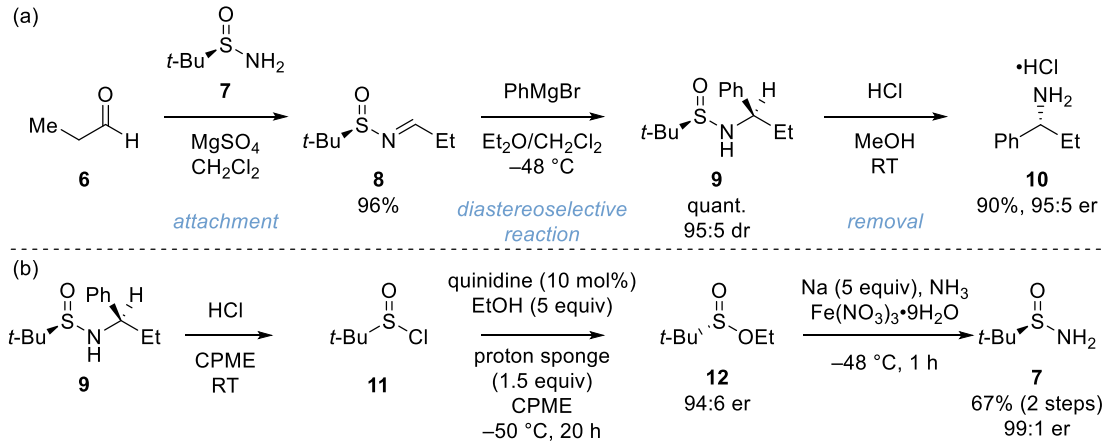
group steps should be minimised.[22] To address these drawbacks, new approaches have been targeted.



Scheme 1. Chiral pool total synthesis of (+)-fusicoauritone.

1.2.2. Second Generation Asymmetric Synthesis: Chiral Auxiliaries

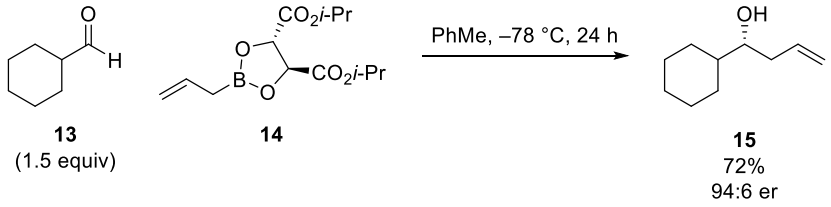
The second-generation of asymmetric synthesis to emerge was the chiral auxiliary approach.[23] The strategy involves (i) the attachment of an enantiopure auxiliary to the starting material, (ii) a diastereoselective reaction and (iii) the removal and recycling of the auxiliary to leave the product with a high enantiomeric ratio (er). This overcomes some of the limitations of chiral pool synthesis as stereogenic centres can be created and starting materials more suited to the synthetic target can be employed. Evans, Myers and Ellman have pioneered the use of chiral oxazolidinone, pseudoephedrine and *tert*-butyl sulfinamide auxiliaries respectively for alkylation, aldol and Diels-Alder reactions,[24–28] with a representative example of an Ellman's auxiliary approach for the asymmetric synthesis of α-branched amines described in Scheme 2a.[29] Condensation of the auxiliary *tert*-butanesulfinamide **7** onto aldehyde **6** provides *tert*-butanesulfinimine **8**. Subsequent diastereoselective Grignard addition, followed by auxiliary removal under acidic conditions, affords the enantioenriched hydrochloride amine salt **10**. The auxiliary can be recycled through a two-step procedure (Scheme 2b).[30] Dynamic kinetic resolution of **11**, formed during acid deprotection, using quinidine and ethanol provided enantiomerically enriched sulfinate ester **12**. Addition of sodium amide allowed the *tert*-butanesulfinamide auxiliary **7** to be recovered in high yield and enantiomeric ratio.



Scheme 2. Ellman's auxiliary sequence.

1.2.3. Third Generation Asymmetric Synthesis: Chiral Reagents

The development of chiral reagents established the third generation of asymmetric synthesis. It was potentially more attractive than the auxiliary approach as no additional "attachment" and "removal" reactions were required, enabling the direct asymmetric functionalisation of achiral substituents. Boron reagents have been demonstrated as some of the most useful chiral reagents. Chiral boron enolates developed by Patterson for asymmetric aldol protocols,[31] and allyl- and crotyl boron reagents reported by Brown and Roush have been widely applied for the direct construction of new stereogenic centres, as indicated in Scheme 3 for the asymmetric synthesis of alcohol **15**.[32,33]

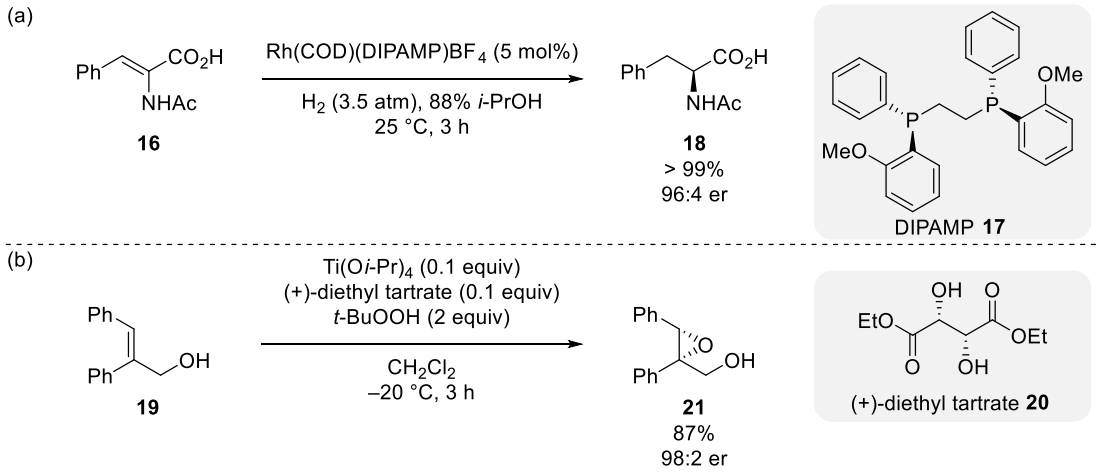


Scheme 3. Roush's direct asymmetric allylation of aldehydes.

1.3. Asymmetric Catalysis

Whilst the preparation of enantiomerically enriched compounds using a variety of traditional methods has been achievable for some time, these processes require stoichiometric reagents. Protocols that enable the catalytic conversion of achiral substrates to enantioenriched chiral products would have enormous economic advantages. Early insights into asymmetric catalysis utilised transition metal catalysts bearing chiral ligands. In 1968, Knowles reported the first catalytic

asymmetric hydrogenation and by 1975 had developed the rhodium-catalysed asymmetric hydrogenation of enamides (Scheme 4a).[34],[35] Independently, Noyori reported the catalytic asymmetric hydrogenation of enamides using novel ruthenium-BINAP complexes, which exhibited significantly improved substrate scope.[36] Complementary to these advances in alkene reduction, Sharpless reported the seminal titanium tetraisopropoxide-catalysed asymmetric epoxidation of allylic alcohols in 1980 (Scheme 4b),[37] and the osmium-catalysed asymmetric dihydroxylation of alkenes eight years postliminary.[38] The Sharpless oxidation of alkenes remains one of the most utilised reactions when chiral epoxides and diols are required. In 2001, the importance of these discoveries was highlighted when Knowles, Noyori and Sharpless received the Nobel Prize in chemistry for contributions to "chirally catalysed reactions".[39]



Scheme 4. (a) Knowles' enantioselective alkene reduction and (b) Sharpless' enantioselective alkene epoxidation.

Following these leading breakthroughs, the field of asymmetric catalysis has expanded dramatically over the last four decades and is now one of the most explored areas in synthetic chemistry. A plethora of complementary metal and organic catalysts now exist to carry out enantioselective transformations over a broad range of substrates (Figure 2). Whilst not all these methods can be discussed in detail, notable contributions include metal complexes such as Jacobsen's salen derived manganese catalyst **22** for the enantioselective epoxidation of alkenes,[40] and Noyori and Ikariya's catalyst **23** developed for enantioselective transfer hydrogenation.[41] Organocatalysis has emerged as an attractive method for

enantioselective synthesis and is now recognised as the third major discipline of catalysis alongside transition metal and enzymatic catalysis.[42] Selected examples of organocatalysts include phase transfer catalysts such as Maruoka's C_2-symmetric chiral spiro ammonium salts **24**, which have been shown to be effective chiral counter ions.[43],[44] Chiral Brønsted base catalysts including guanidine **25** and cyclopropenimine **26** are proposed to form a chiral environment around a substrate anion formed from deprotonation by the chiral base.[45],[46] Chiral Brønsted acids, e.g. phosphoric acid catalysts derived from BINOL **27** and hydrogen-bond donor thioureas **28**,[47],[48] can activate a range of electrophiles and a suite of these acids now exist over a wide pK_a range.

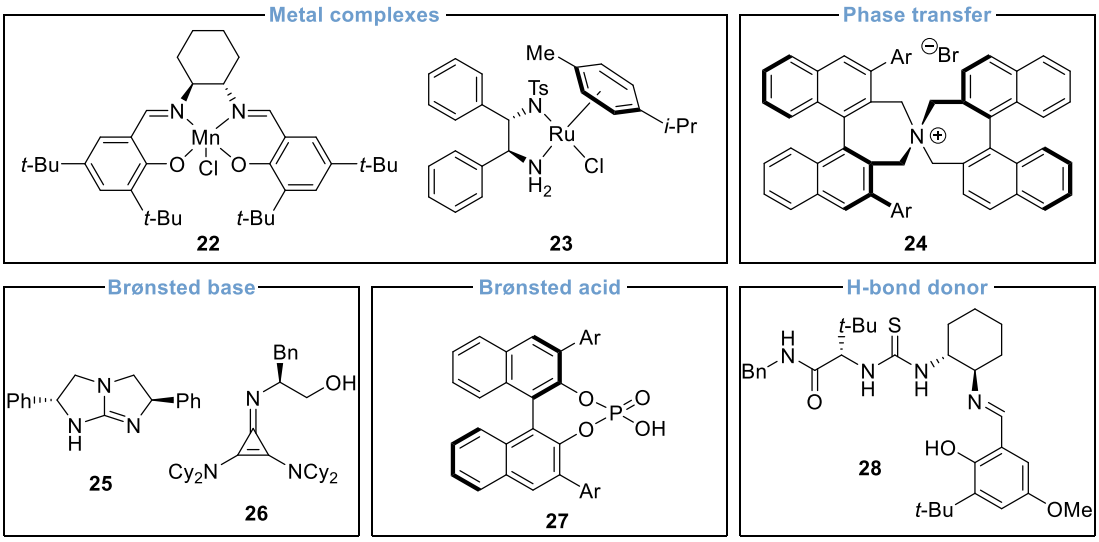
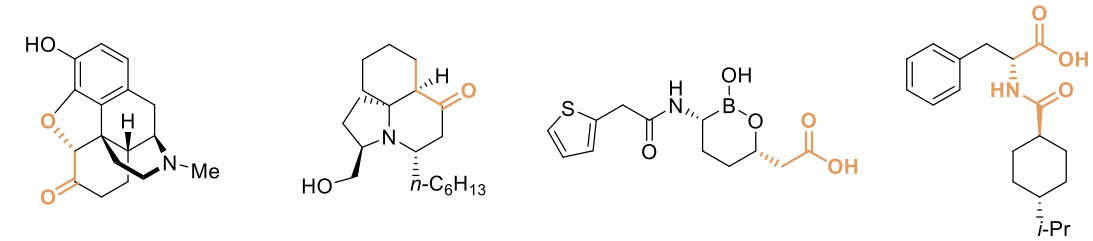


Figure 2. Selected catalysts for enantioselective transformations.

1.4. Enantioselective α-Functionalisation of Carbonyl Compounds

The stereodefined α-functionalised carbonyl motif is an important class of functional group found in many biologically relevant molecules (Figure 3). At the aldehyde/ketone oxidation level, the α-functionalised ketone functionality is prevalent in many medicines and natural products. Hydromorphone **29** is a semi-synthetic opioid approved for severe pain relief,[49] whilst the naturally occurring marine alkaloid (−)-Cylindricine C **30**, isolated from ascidian *Calenlina cylindrica*, exhibits promising cytotoxic activity and its tricyclic structure includes an α-functionalised ketone moiety.[50] It is not surprising that there is a wealth of biologically relevant molecules based on α-functionalised carbonyls at the carboxylic

acid oxidation level when the number of amino acids is considered. α-Functionalised carboxylic acids and derivatives are found in many designer medicines. Two examples include Vaborbactam **31** and Nateglinide **32**,[51],[52] which are treatments for bacterial infections and type 2 diabetes, respectively.



29
Hydromorphone
treatment for severe pain

30
(–)-cylindricine C
marine natural product

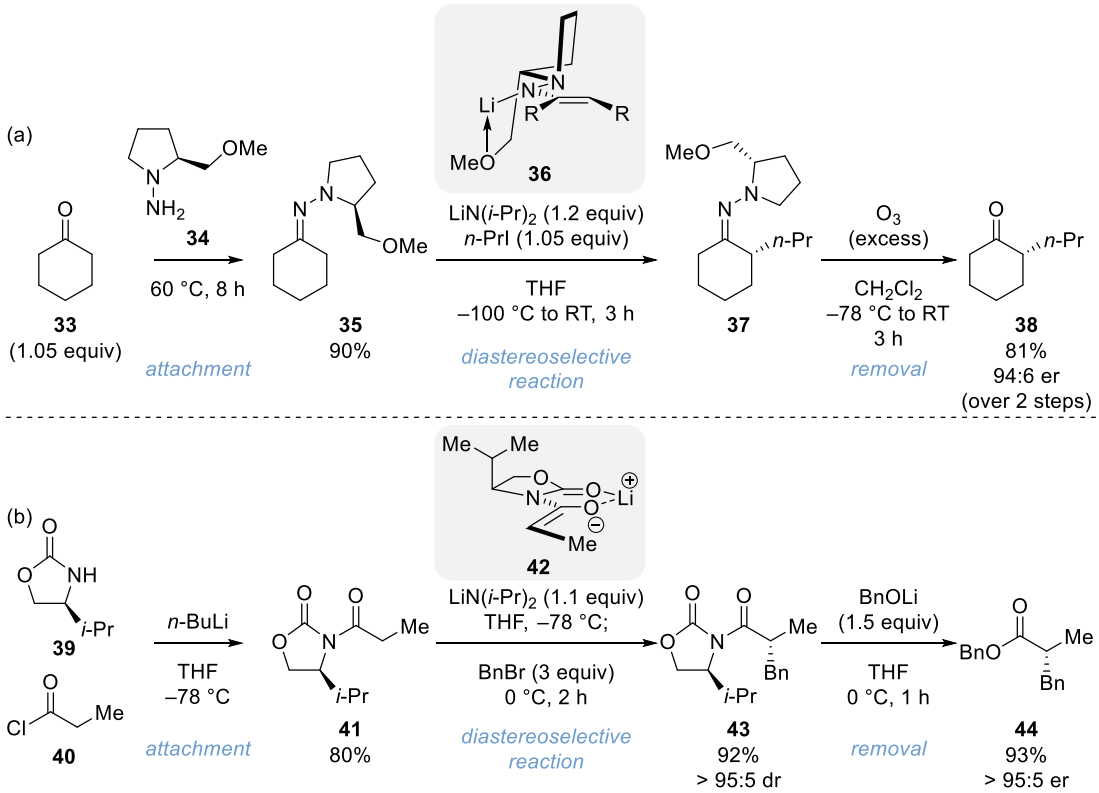
31
Vaborbactam
treatment for bacterial infections

32
Nateglinide
type 2 diabetes treatment

Figure 3. α-Functionalised carbonyl containing molecules.

Consequently, the α-functionalisation of carbonyl compounds has been a long-standing goal in organic chemistry; synthetic methods that enable the efficient, stereoselective synthesis of α-functionalised carbonyl compounds are highly sought after. Typically, these methods involve the coupling of an enolate equivalent with an electrophilic partner. Traditional methods used chiral auxiliary approaches to impart stereoselectivity (Scheme 5). For example, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) **34**, and the (*R*)-enantiomer RAMP, synthesised in four steps from (*S*)-proline and six steps from (*R*)-glutamic acid respectively, were developed by Enders for aldehyde and ketone functionalisation (Scheme 5a).[53] This three-step procedure involves condensation of the hydrazine **34** with ketone **33** to give hydrazone **35**.[54] Following deprotonation to give the lithium azaenolate, alkylation with a suitable electrophile affords product **37**. The auxiliary can be oxidatively cleaved to give the product **38** in high enantiomeric purity, whilst the nitrosamine by-product can be reduced with $LiAlH_4$ to enable recovery of the chiral auxiliary. The stereoselectivity of the reaction can be rationalised by transition state assembly **36**; selective formation of the $(E)_{C\text{-}C}$-azaenolate through deprotonation of the $(Z)_{C\text{-}N}$ hydrazone and subsequent alkylation on the lower, sterically less-hindered *Re* face.

Evans reported the use of an oxazolidinone auxiliary **39**, derived from (*S*)-valinol, for the enantioselective synthesis of α-functionalised carboxylic acid derivatives through a three-step auxiliary sequence (Scheme 5b).[25] Attachment of the auxiliary proceeds via deprotonation of the carbamate and reaction with acyl chloride **40** to yield *N*-acyl oxazolidinone **41**. Subsequent alkylation of the (*Z*)-lithium enolate occurs through transition state **42**, where the C(4)-substituent of the auxiliary dictates the diastereofacial selection, to give alkylated product **43** with high levels of diastereoselectivity. The auxiliary can be cleaved through various transformations to give enantioenriched α-alkylated esters (peroxide), acids (hydrogenolysis) and primary alcohols ($LiAlH_4$). Whilst these established auxiliary-mediated methods are robust and remain highly utilised in total synthesis, recent advances have focused on the catalytic generation and functionalisation of enolates.

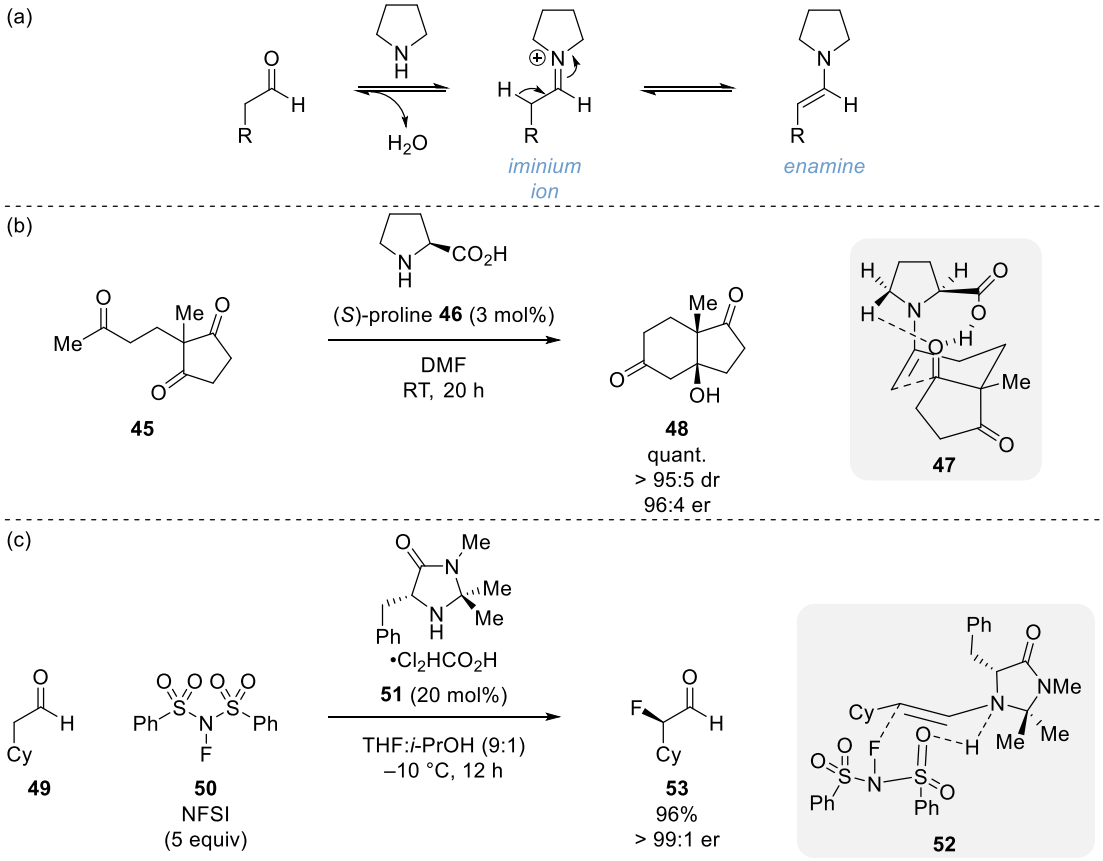


Scheme 5. (a) SAMP auxiliary for the α-alkylation of ketones and (b) Evans oxazolidinone auxiliary for the α-alkylation of esters.

Lewis basic secondary amines have been established as broadly applicable, efficient organocatalysts for the enantioselective α-functionalisation of aldehydes.[55] This protocol involves the catalytic generation of a nucleophilic enamine intermediate through the condensation of a secondary amine catalyst and an aldehyde or ketone

via deprotonation of the preformed an iminium ion (Scheme 6a). The first example of asymmetric enamine catalysis was reported independently by Hajos and Parrish, and Wienchert, Sauer and Eder in 1971: a proline catalysed intramolecular aldol reaction (Scheme 6b).[56–58] Triketone **45** could be converted to bicycle **48** catalysed by only 3 mol% (*S*)-proline **46**. Houk later proposed the reaction proceeded via a six-membered "chair-like" transition state **47** which includes favourable COO−H···O and additional non-classical NC−H···O hydrogen bond contacts.[59]

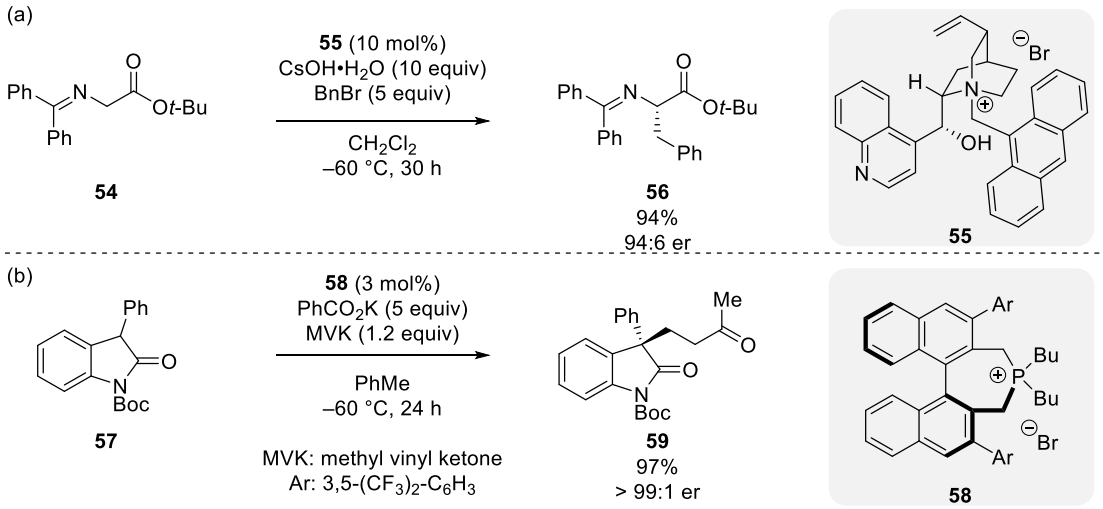
Following this exceptional breakthrough, Barbas, Lerner and List demonstrated the broad applicability of enamine activation of aldehydes and ketones through enantioselective α-functionalisation processes such as intermolecular aldol,[60] Mannich and Michael addition.[61,62] Since then, novel effective enamine catalysts have been developed. Most notably, imidazolidinone catalysts by MacMillan and prolinol catalysts by Jørgensen are some of the most general catalysts for α-functionalisation of carbonyl compounds.[63] For example, MacMillan and co-workers employed imidazolidinone enamine catalyst **51** for the first organocatalytic enantioselective α-fluorination of aldehydes using NFSI **50** as an electrophilic fluorine source, giving α-fluorinated aldehydes in excellent yields and er (Scheme 6c).[64] This methodology has been extended through the development of single occupied molecular orbital (SOMO) activation. This approach involves the single electron oxidation of the enamine to form a 3π-electron radical cation electrophile, which can react via single electron pathways. MacMillan and co-workers introduced the methodology in 2006 by reporting the enantioselective α-allylation of aldehydes with excellent enantioselectivity.[65] The novel reactivity of SOMO catalysis has been exploited for α-arylation,[66] vinylation and halogenation protocols,[67,68] establishing it as one of the newest branches of organocatalysis. More recently, MacMillan and co-workers have extended the single electron reactivity of enamines to radicals generated in situ by photocatalysis.[69] This has led to the advent of photoredox organocatalysis catalysis, which has been applied with a broad range of radicals for enamine alkylation,[70] trifluoromethylation and amination reactions.[71],[72]



Scheme 6. Enantioselective α-functionalisation of aldehydes/ketones via secondary amine organocatalysis.

Catalytic methods have also been developed for enantioselective α-functionalisation at the carboxylic acid oxidation level. One approach involves the use of phase transfer organocatalysts, which have been demonstrated as efficient catalysts in various enantioselective transformations of esters.[43] The benchmark reaction catalysed by phase transfer catalyst **55** is the enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **54**, allowing access to amino acid derivatives in high enantiopurity (Scheme 7).[73] Marouka and co-workers have also reported the enantioselective α-alkylation, by Michael addition, of 3-aryloxindole substrates **57** using an axially chiral phosphonium catalyst **58**.[74] Whilst many cinchona alkaloid and binaphthyl-derived onium salt catalysts have been demonstrated to catalyse a variety of enantioselective transformations such as alkylation, Michael addition, aldol and C-X bond forming processes, these reactions are commonly limited to specific glycine Schiff base imine ester substrates. In cases where other model substrates are used, generally α-tertiary esters and amides are employed to form all-carbon quaternary centres. The formation of enolisable tertiary

stereogenic centres from secondary carboxylic acid derivatives is limited due to product racemisation under the strong basic reaction conditions.

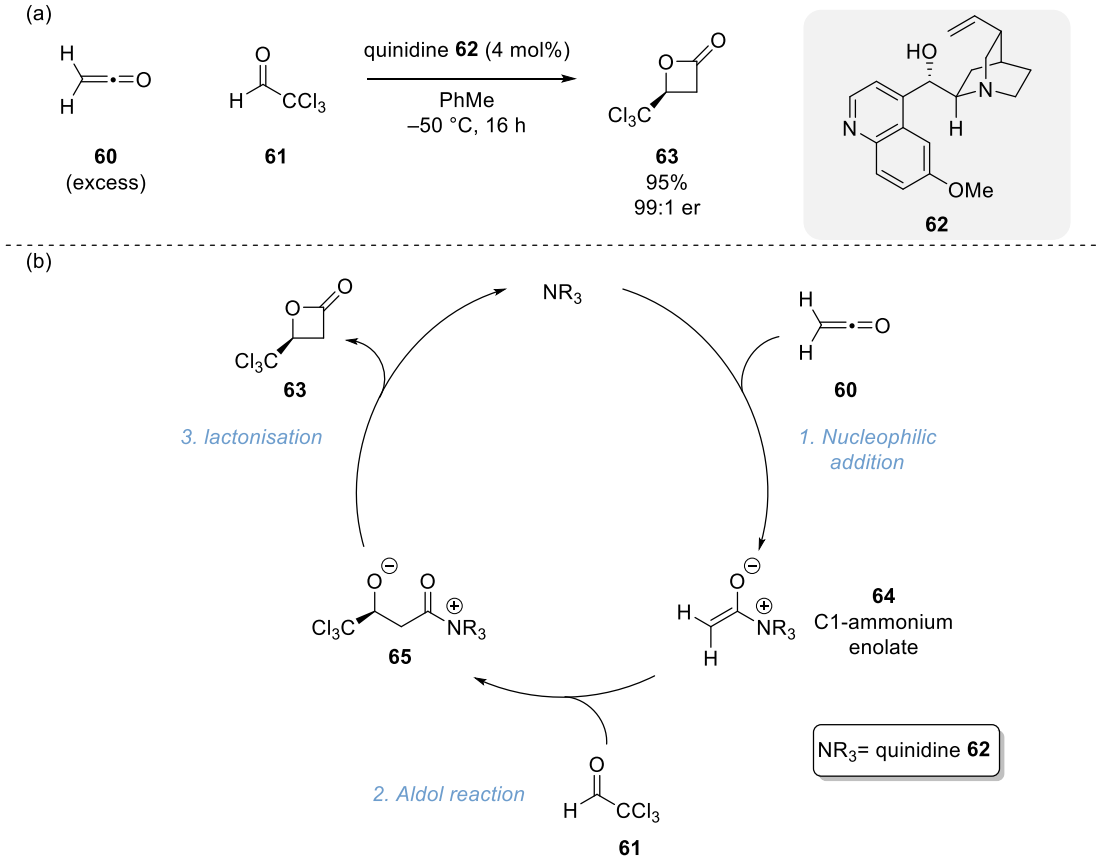


Scheme 7. Enantioselective α-functionalisation at the carboxylic acid oxidation level via phase transfer organocatalysis.

1.5. C(1)-Ammonium Enolates

1.5.1. From Ketenes

C(1)-Ammonium enolate intermediates,[75],[76] derived from chiral tertiary amine Lewis base catalysts[77–81] have emerged as synthetically useful intermediates for the enantioselective synthesis of α-functionalised carbonyl compounds at the carboxylic acid oxidation level. Early studies on C(1)-ammonium enolates focussed on ketene dimerisation reactions.[82],[83] However, it was not until the seminal publication of Wynberg that the fundamental reactivity of C(1)-ammonium enolates was established. In 1982, Wynberg and co-workers reported the aldol-lactonisation of a C(1)-ammonium enolate, derived from ketene **60** and quinidine **62**, and chloral **61** to form β-lactone **63** in excellent yield and er (Scheme 8a).[84] The mechanism proceeds via addition of quinidine **62** to ketene **60** to form the C(1)-ammonium enolate **64**. Aldol reaction onto chloral and subsequent lactonisation proceeds to form β-lactone **63** and release the Lewis base catalyst (Scheme 8b). It is noted that use of highly reactive aldehydes and excess ketene is required in this process due to competing ketene dimerisation. C(1)-Ammonium enolates generated from ketenes have been applied in reactions with a range of electrophilic partners in β-lactone and lactam formation,[85],[86] α-halogenation,[87] and formal [4+2] cycloaddition reactions.[88]

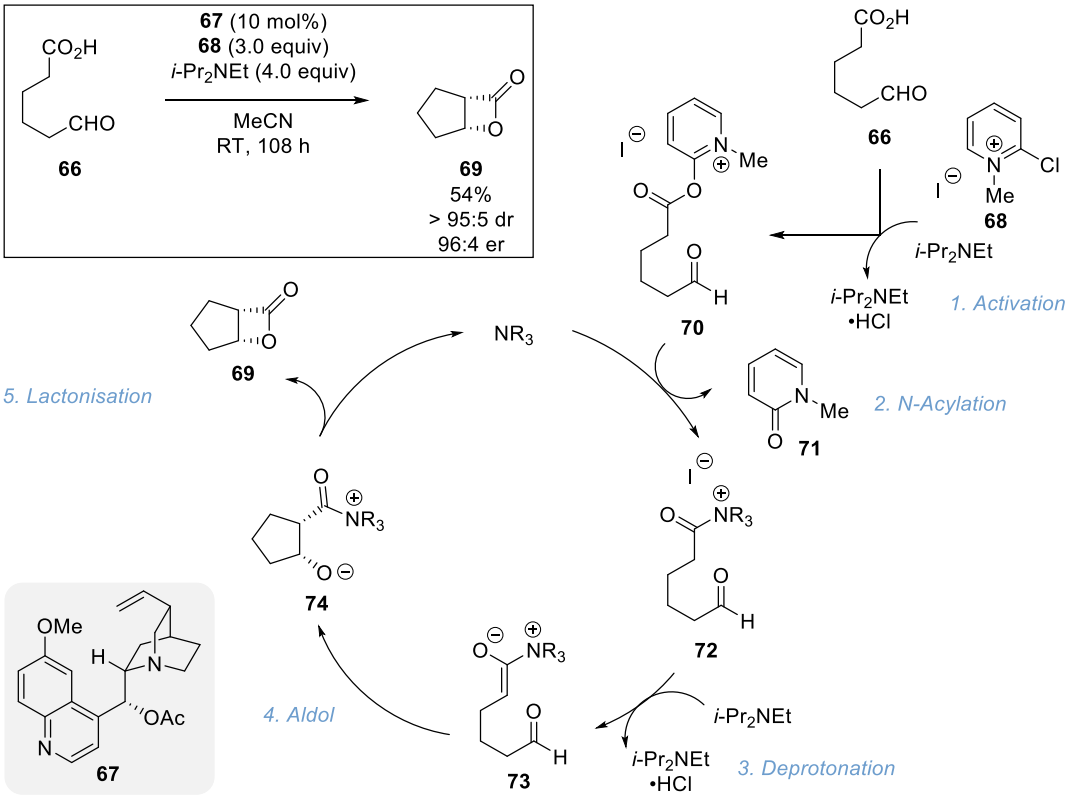


Scheme 8. (a) Catalytic enantioselective aldol-lactonisation via a C(1)-ammonium enolate and (b) proposed mechanism.

1.5.2. From Carboxylic Acids

Whilst C(1)-ammonium enolates derived from ketenes have received widespread application in reactions with electrophiles, ketenes are unstable to long-term storage and are prone to dimerisation. Alternative strategies that allow more practical access to C(1)-ammonium enolates from readily available, stable starting materials were sought. In 2001, Romo and co-workers reported the first Lewis base-catalysed aldol-lactonisation of carboxylic acid substrates. Reaction of aldehyde-acids **66**, activated using Mukaiyama[89] reagent **68**, catalysed by *O*-acetyl quinine **67** gave *cis*-bicyclic β-lactones **69** in high er (Scheme 9, inset).[90] Mechanistically, this reaction was proposed to proceed via activation of carboxylic acid **66** with reagent **68** to afford activated ester **70** in situ (Scheme 9). Acylation of the tertiary amine catalyst by activated ester to form acyl ammonium intermediate **72**, followed by deprotonation generates enolate **73**. Intramolecular aldol reaction gives intermediate **74** which undergoes lactonisation to afford product **69** and regenerates the Lewis base catalyst. Romo and co-workers have since extended this methodology for the

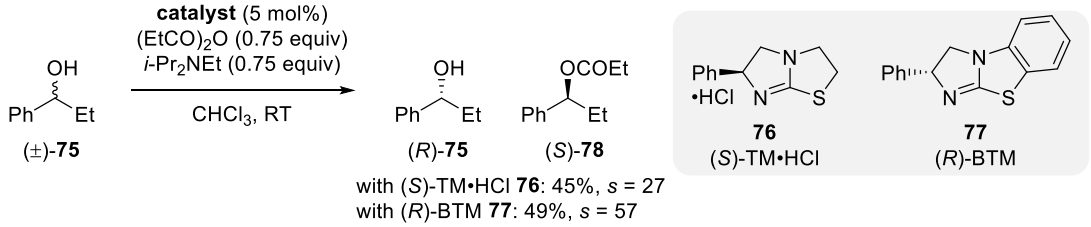
diastereoselective aldol-lactonisation of enantiopure aldehyde-acids.[91] Less reactive keto-acid substrates have also been reported to undergo aldol-lactonisation procedure using planar chiral DMAP catalysts;[92] the synthetic utility of this methodology was further demonstrated in the synthesis of various natural products.[93] Dikshit later reported an aza-aldol-lactonisation using amino acid-derived aldehyde-acids.[94]



Scheme 9. Catalytic asymmetric aldol-lactonisation of carboxylic acid-aldehydes and proposed mechanism.

1.5.3. Using Isothioureas

In 2006, Birman and co-workers reported the use of commercially available medicinal and veterinary drug tetramisole (TM)[95] **76** as an efficient acyl transfer catalyst for the kinetic resolution (KR) of secondary alcohols (Scheme 10).[96] During this study it was also reported that the benzannulated derivative benzotetramisole (BTM) **77** demonstrated even greater enantioselectivity. The isothiourea catalysts were shown to be more selective for the KR of secondary alcohols compared to the corresponding amidine catalysts.



Scheme 10. KR of benzylic secondary alcohols catalysed by isothioureas.

Okamoto and co-workers concurrently reported the synthesis of achiral DHPB **79** and showcased its superior catalytic ability compared to the five-membered ring isothioureas **76** and **77** (Figure 4).[97] Encouraged by this enhanced reactivity of DHPB, Birman developed HomoBTM (HBTM) **80** for enantioselective acyl transfer reactions of aryl-cycloalkanols which proceeded at temperatures as low as −55 °C with 2 mol% catalyst loading.[98] However only moderate enantioselectivities were obtained for secondary benzylic alcohols with HBTM. Birman and Smith independently showed that introduction of an alkyl group in the C(3) position of the HBTM framework led to a greater increase in reactivity through the synthesis of HBTM-2 **81** and HyperBTM **82.**[99],[100]

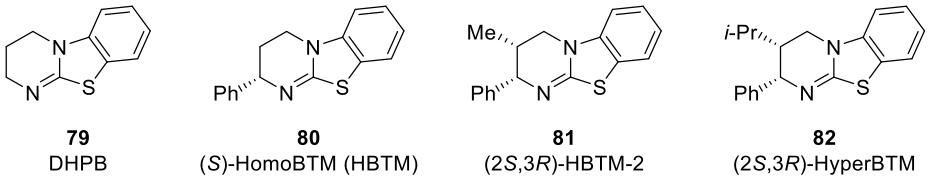
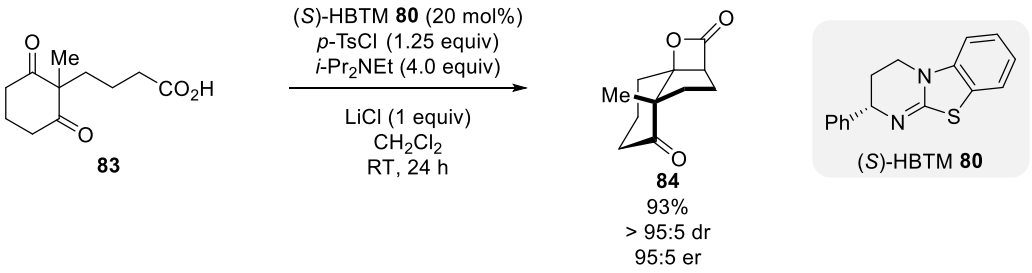


Figure 4. Isothiourea Lewis base catalysts.

In 2010, Romo and co-workers demonstrated the first catalytic generation of an ammonium enolate derived from an isothiourea organocatalyst (Scheme 11).[101] Using *para*-toluene sulfonyl chloride to activate the carboxylic acid, isothiourea **80** catalysed the transformation of a range of keto-acids such as **83** into tricyclic β-lactones **84** in high yield with excellent stereoselectivity.

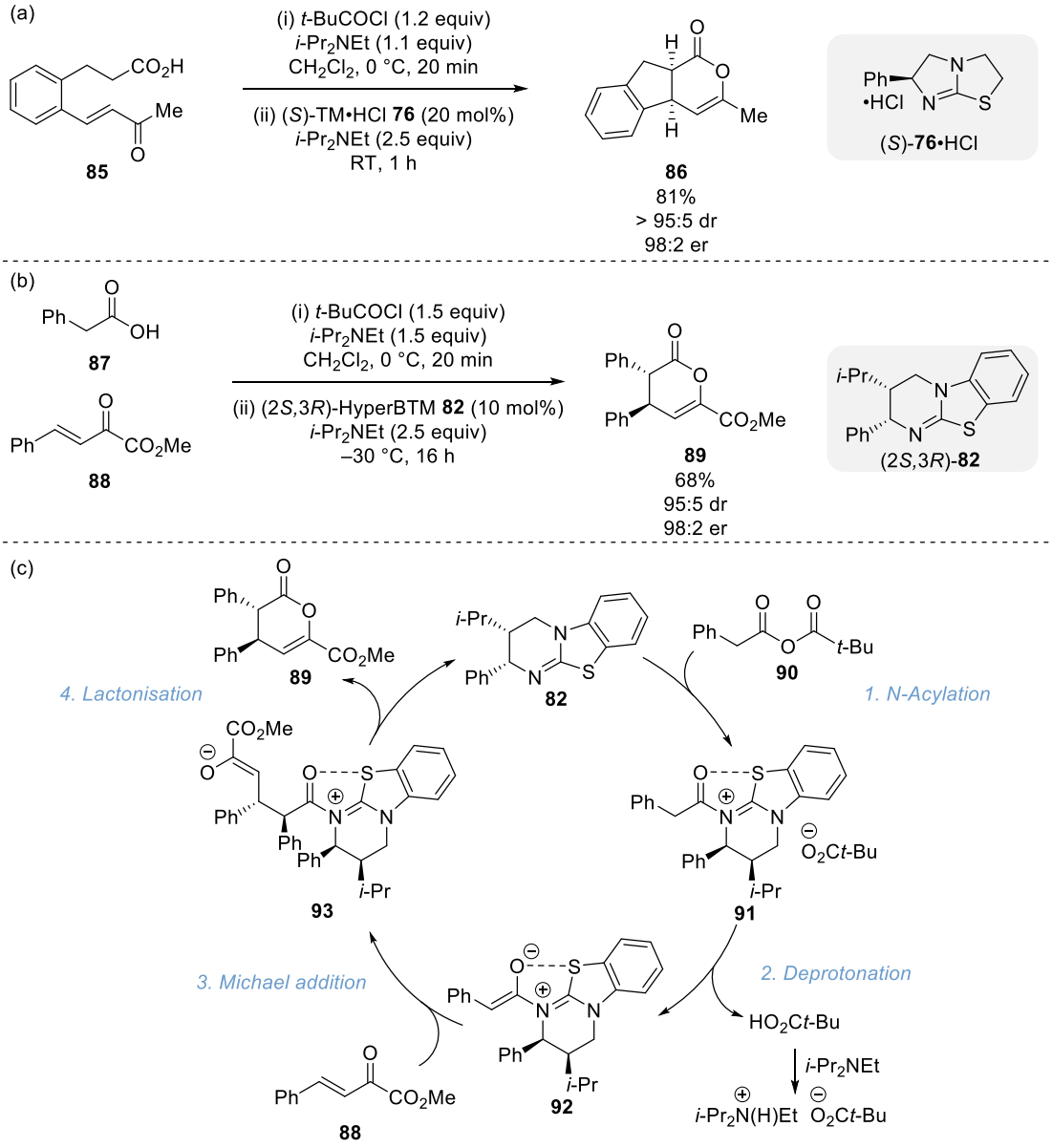


Scheme 11. First example of isothiourea catalysis via C(1)-ammonium enolates.

Following the precedent set by Romo for ammonium enolates derived from carboxylic acids, Smith and co-workers reported the functionalisation of carboxylic acids in an enantioselective Michael addition-lactonisation protocol (Scheme 12).[102] Enone-acid **85** was activated with pivaloyl chloride and treated with TM **76** to promote intramolecular Michael addition-lactonisation to form indane **86** in high diastereo- and enantioselectivity (Scheme 12a). This protocol was also successfully extended to challenging intermolecular systems (Scheme 12b). Aryl acetic acid **87** and α-keto-β,γ-unsaturated ester **88** were transformed to *anti*-dihydropyranone **89** in high dr and er catalysed by HyperBTM **82**. The proposed mechanism (Scheme 12c) involves the initial acylation of HyperBTM with the mixed anhydride **90** to form acyl ammonium ion **91**. Deprotonation by the pivalate counterion affords (*Z*)-ammonium enolate **92** and generates pivalic acid,[103] which is mopped up by the excess mild auxiliary base. Stereoselective Michael addition to acceptor **88** and intramolecular lactonisation affords product **89** and regenerates the catalyst.

The high enantiocontrol observed in isothiourea catalysis via C(1)-ammonium enolates is proposed to be governed by selective formation of the (*Z*)-enolate and a 1,5-O···S non-bonded interaction between the enolate oxygen anion and sulfur atom of the catalyst (Figure 5). Computational studies by Smith and Cheong disclosed O···S distances (~2.5–2.8 Å) to be notably lower than the van der Waals radii (3.4 Å), consistent with a substantial interaction.[104],[105] Although the exact nature of this interaction is unknown, it has been rationalised as either n_O to $\sigma^*_{C\text{-}S}$ delocalisation process,[106] or as an electrostatic attraction between anionic oxygen and partially cationic sulfur atom. This interaction lowers the conformational freedom of the intermediate and leads to a rigid coplanar structure enforcing elevated levels of enantiocontrol. The stereodirecting phenyl substituent effectively blocks the *Si* face of the enolate, with preferential reaction with an electrophile occurring on the less hindered *Re* face. Further evidence for this interaction can be found throughout the literature. Romo and co-workers found transition states of a Diels Alder-lactonisation reaction containing S···O interactions were of lower energy.[107] Further NBO analysis suggested multiple interactions were involved, including n_S to $\sigma^*_{C\text{-}H}$/ $\sigma_{C\text{-}H}$ which destabilised the opposite conformation. Birman and Houk have also

reported computational investigations which show a conformational preference for close O···S contacts.[108],[109] Outside isothiourea catalysis, Nagao and co-workers exploited 1,5-O···S interactions of a sulfonium ion and amide oxygen to develop an asymmetric Pummerer reaction.[110] Furthermore, 1,4- and 1,5-O···S interactions have been taken advantage of in medicinal chemistry for the design of conformationally rigid drug molecules.[111]



Scheme 12. Isothiourea-catalysed (a) intramolecular and (b) intermolecular Michael addition-lactonisation and (c) proposed mechanism.

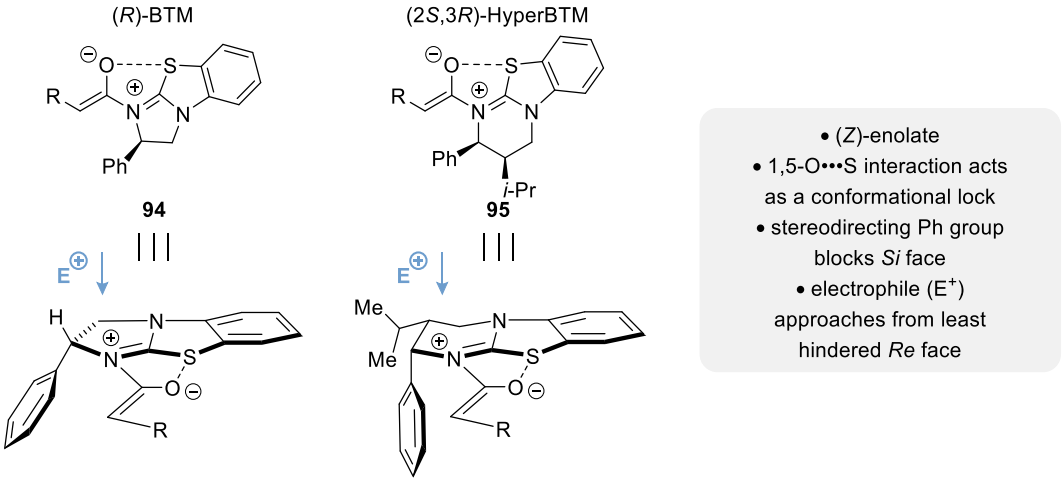


Figure 5. Stereochemical rationale for isothiourea catalysis via C(1)-ammonium enolates.

The Michael addition/lactonisation strategy has found widespread application for the synthesis of chiral heterocycles in formal cycloaddition processes with high stereocontrol (Figure 6).[76,112] Complex polycyclic ring systems **96**-**99** can be efficiently constructed in intramolecular formal [4+2] cycloaddition processes. Intermolecular processes have been developed for the synthesis of trifluoromethyl-, trichloromethyl-, phosphonate-, 3,5,6-substituted and fused-heterocyclic dihydropyranones (**101**-**106**). This has been extended to ketimines and saccharin-derived Michael acceptors in Michael addition/lactamisation processes for the synthesis of dihydropyridinones **107** and **108**. In addition to carbon-carbon bonding forming reactions, α-amination of carboxylic acids has been achieved using diazene Michael acceptors for the synthesis of 1,3,4-oxadiazin-6-ones **109**. The formal [3+2] cycloaddition using oxaziridine electrophiles enabled the enantioselective preparation of oxazolidine-4-ones **100**, whilst enantioenriched β-lactams **105** and perfluoroalkyl-substituted β-lactones **110** can be prepared in formal [2+2] cycloadditions with the corresponding imine or ketone. Higher order enantioselective formal [8+2] cycloadditions have also been reported by Pericàs and co-workers employing an immobilised polystyrene-supported catalyst. In all cases, the heterocyclic lactone/lactam product can be ring opened with an appropriate nucleophile to give the corresponding acyclic derivative. This post-functionalisation method can also be employed in situ where the cyclic product is unstable.

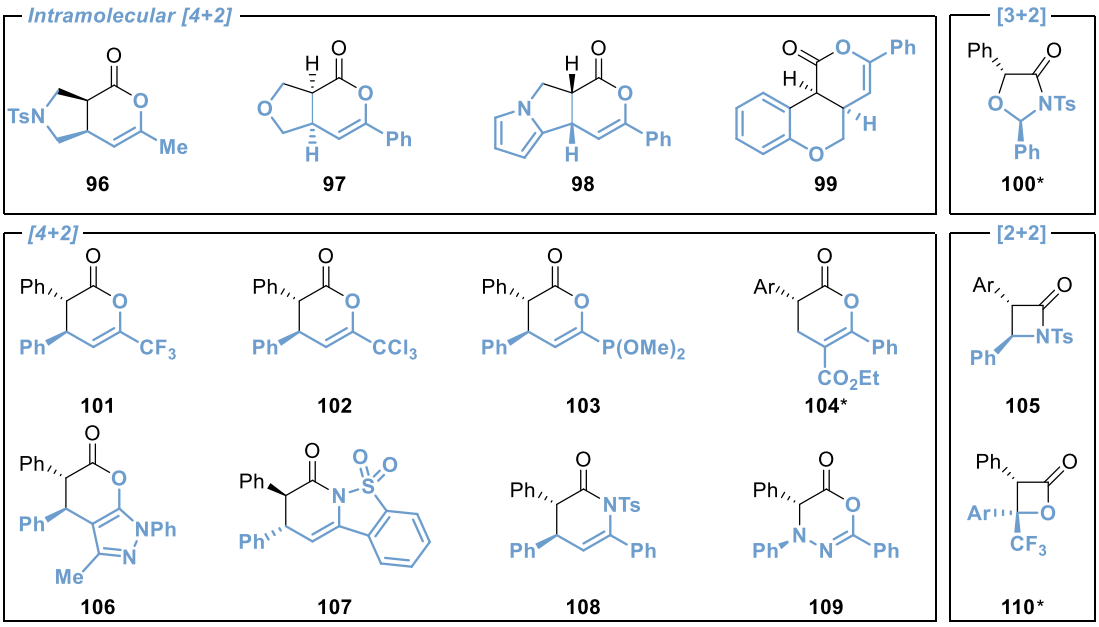
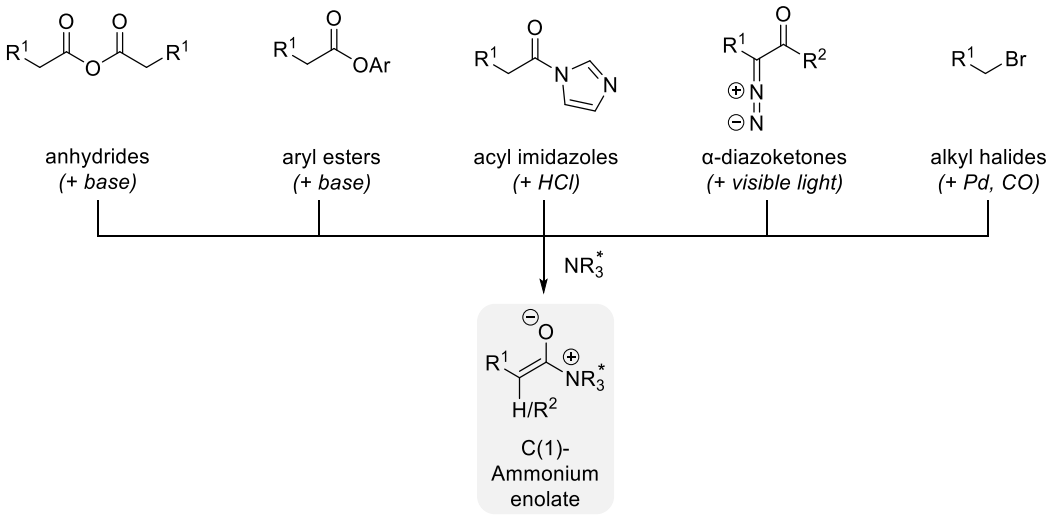


Figure 6. Isothiourea-catalysed formal cycloaddition products.
(*: from the corresponding homoanhydride)

Whilst these impressive strategies employing carboxylic acid precursors have been applied for the synthesis of a range of chiral heterocycles, a major limitation is the use of a stoichiometric reagent required for substrate activation (often multiple equivalents), and the common use of super-stoichiometric amounts of auxiliary base. In addition, the by-products generated from these processes (such as pivalic acid anhydride from pivaloyl chloride) can be difficult to separate from the desired products. Recent developments have reported the use of alternative starting materials for ammonium enolate generation (Scheme 13). In 2014, Smith and co-workers reported the use of homoanhydrides as efficient ammonium enolate precursors for the Michael addition/lactonisation methodology.[113] The carboxylic acid by-product from this procedure was easily removed by basic aqueous work-up. The use of aryl esters in the Michael addition/lactonisation approach has also been reported.[114] This procedure avoids using two equivalents of the carboxylic acid precursor in the case of homoanhydrides. Smith and co-workers reported the development of an alternative method of generating C(1)-ammonium enolates from bench stable *N*-acyl imidazoles under acidic conditions..[115] In situ protonation of the *N*-acyl imidazole enables significantly enhanced catalyst acylation (utilising the recognised "imidazolium" effect) whilst the expected imidazole by-product is non-toxic and water soluble and can be readily removed from the reaction mixture. In

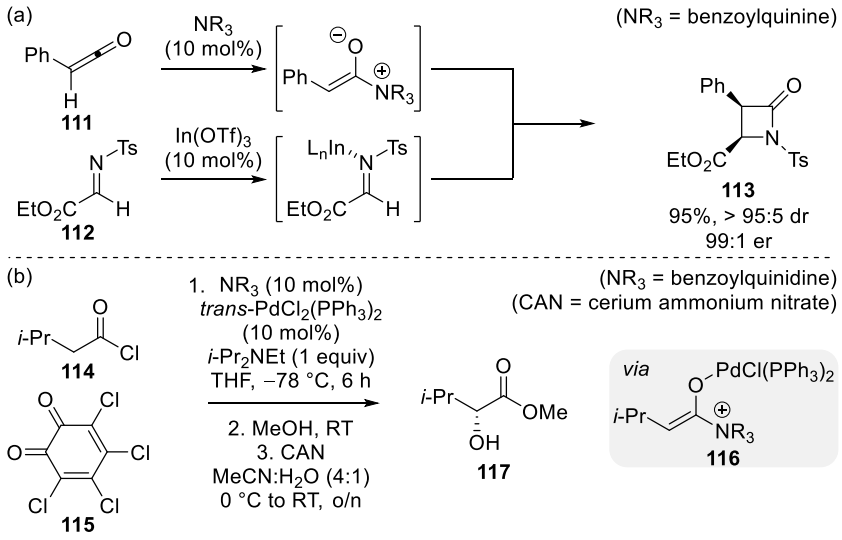
2019, Song and co-workers developed an elegant method to generate isothiouronium enolates from α-diazoketones for the first time in combination with visible light photoactivation.[116] Excitation of the diazoketone initiates nitrogen extrusion to generate the α-keto carbene intermediate which can undergo [1,2]-migration to afford the ketene intermediate. Significantly, this allows access to disubstituted ketenes, and therefore disubstituted ammonium enolates, which previously had seen limited examples of reactivity using C(1)-ammonium enolates. Gong and co-workers have also reported the seminal catalytic generation of C(1)-ammonium enolates from feedstock chemicals (alkyl halides) and carbon monoxide (CO).[117] The authors demonstrated this protocol in a one-pot palladium catalysed carbonylation-Michael addition/lactonisation cascade for the formation of a range of dihydropyridones.



Scheme 13. C(1)-Ammonium enolate precursors.

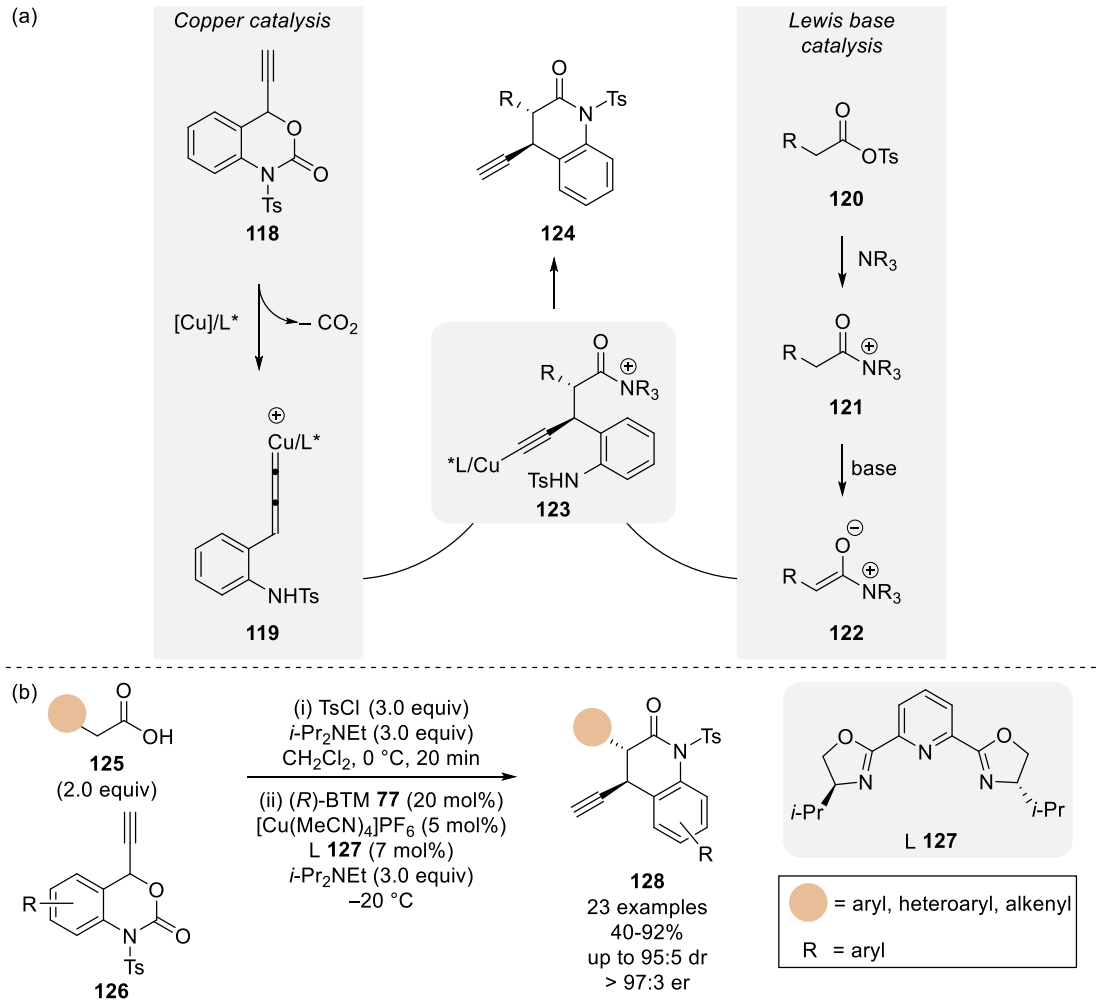
The unification of C(1)-ammonium enolate intermediates with catalytically generated reaction partners in cooperative or synergistic processes has been targeted in the pursuit of novel reactivity modes. In 2002, in a pioneering contribution, Lectka and co-workers introduced this concept in the diastereo- and enantioselective synthesis of β-lactams through dual Lewis base/Lewis acid catalysis (Scheme 14a).[118,119] A cinchona alkaloid-based Lewis base catalyst was employed for the in situ generation of the C(1)-ammonium enolate intermediate from a ketene precursor, whilst an achiral Lewis acid catalyst ($In(OTf)_3$) was proposed to increase the electrophilicity of the imine electrophile. Subsequently, Lectka, and others, have

demonstrated the utility of C(1)-ammonium enolates combined with various metal Lewis acids.[120–123] In another significant development, Leckta demonstrated the advantageous use of nickel, palladium and platinum Lewis acid catalysts in the reaction of C(1)-ammonium enolates with *o*-chloranil **115** for enantioselective α-hydroxylation, with palladium giving optimal results (Scheme 14b).[124,125] In this case, rather than simple coordination to the electrophile to increase reactivity, it is proposed that the Lewis acid cocatalyst complexes to the C(1)-ammonium enolate. This leads to stabilisation of this intermediate, increasing its concentration in the reaction mixture, therefore enhancing the rate of reaction.



Scheme 14. Enantioselective dual tertiary amine/metal catalysis by Leckta.

Transition metals are capable of catalysing a broad range of transformations and have shown to be compatible with various organocatalysts in dual catalytic processes.[126–128] Inspired by the work of Lectka, Snaddon and co-workers reported the first synergistic isothiourea/transition metal catalysis process involving C(1)-ammonium enolates intermediates in 2016 (discussed in section 1.5.4).[129] Building on this precedent, Gong and co-workers demonstrated the combination of an isothiourea Lewis base and copper catalytic cycles for the enantioselective α-propargylation of carboxylic acids (Scheme 15a).[130] Uniting the transient C(1)-ammonium enolate **122** simultaneously with the known decarboxylative generation



Scheme 15. Dual copper/isothiourea-catalysed decarboxylative formal [4+2] cycloaddition for the synthesis of 3,4-dihydroquinolin-2-one derivatives.

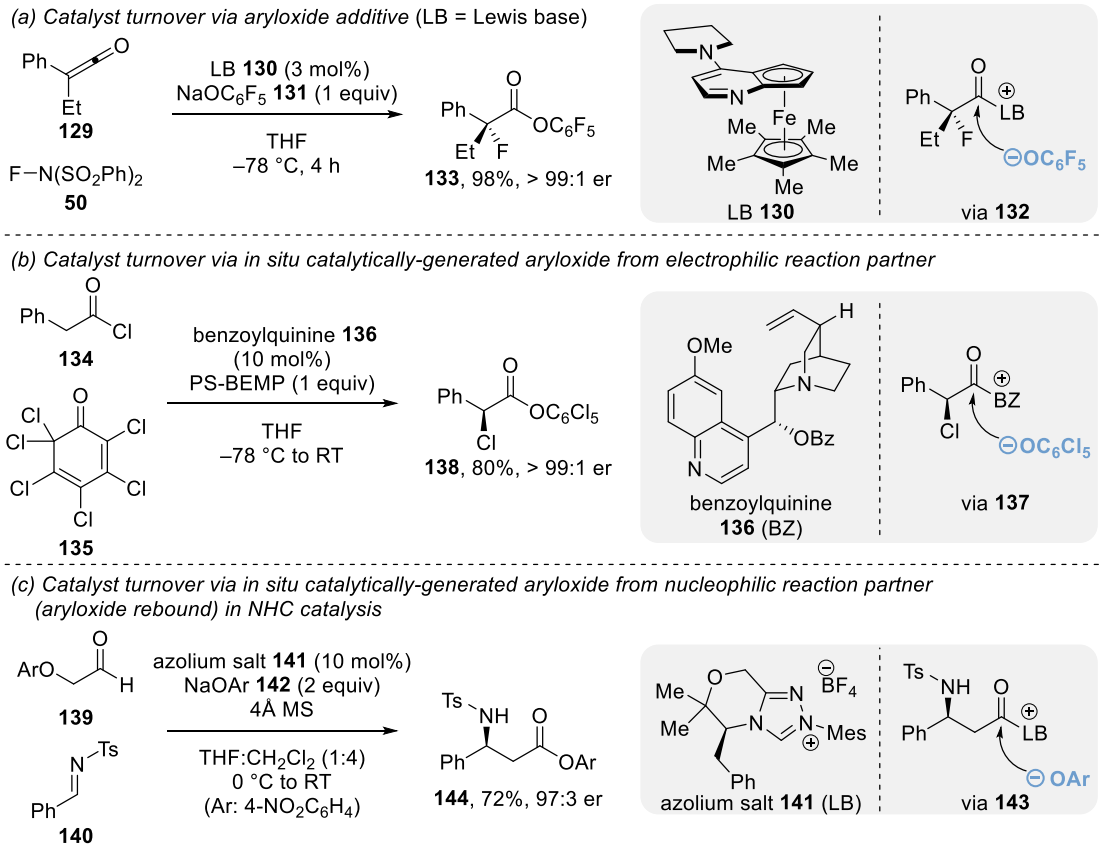
of an electrophilic copper-allenylidene complex **119** from propargylic ester derivatives **118** would enable the formation of intermediate acyl ammonium **123**, which could undergo lactamisation to form 3,4-dihydroquinolin-2-ones **124**. Using a chiral copper complex generated in situ from [Cu(MeCN)$_4$]PF$_6$] and pyridinyl bis(oxazoline) ligand **127**, the authors reported the formal [4+2] annulation of a range of carboxylic acids **125** and 4-ethynyl dihydrobenzooxazinones **126** to give the 3,4-dihydroquinolin-2-one products **128** with excellent stereoselectivities (Scheme 15b). Lower diastereoselectivities were observed when achiral ligands were used, or when the opposite enantiomer of isothiourea was employed, indicating the matched chirality of each catalyst is crucial for stereocontrol. Wu and co-workers have also developed a related α-propargylation/lactamisation cascade using pivaloyl chloride activation,[131] whilst Gong and co-workers extended this cooperative Lewis base-copper catalysis strategy for the α-amination of esters.[132]

Although powerful in concept, catalyst turnover by lactonisation/lactamisation has limitations in terms of atom economy. When using carboxylic acid starting materials, pre-treatment with stoichiometric amounts of activating agent and base is required to generate a reactive mixed anhydride in situ prior to catalyst acylation. Following deprotonation, the leaving group plays no further role in the catalytic cycle and is removed at the end of the reaction, leading to substantial waste. In addition, a key limitation is the requirement of intramolecular cyclisation by a proximal nucleophile, leading to the formation of cyclic α-functionalised lactone/lactam products. To overcome these shortfalls, recent work has focused on a novel catalyst turnover method.

1.5.4. Catalyst Turnover via Aryloxide

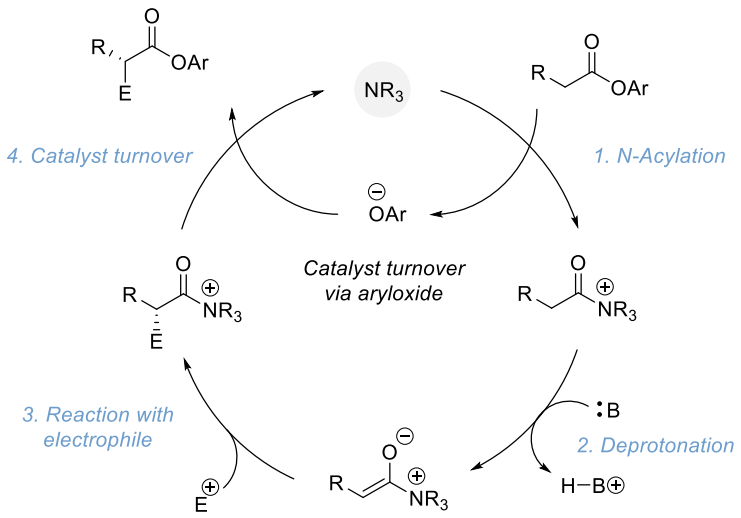
Catalyst turnover via aryloxide relies on the intermolecular addition of an aryloxide nucleophile to the post-reaction acyl ammonium ion to complete the catalytic cycle. One method to achieve this is the inclusion of a stoichiometric aryloxide as an additive. In 2014, Fu and co-workers utilised sodium pentafluorophenolate **131** as a catalyst turnover agent for the enantioselective fluorination of ketenes using planar chiral DMAP catalyst **130** via a C(1)-ammonium enolate intermediate (Scheme 16a).[133] However, this approach requires the aryloxide to be compatible with other reagents, or, as in this case, the dropwise addition of reagents to avoid side reactions. Alternatively, the aryloxide can be catalytically generated in situ from a reaction partner. This was first established in conjunction with C(1)-ammonium enolate intermediates in a series of elegant manuscripts by Leckta and co-workers for enantioselective halogenation.[134–139] Reaction of the C(1)-ammonium enolate (generated from ketenes) with a polyhalogenated quinone electrophile **135** gave the acyl ammonium/aryloxide ion pair, with the aryloxide used for catalyst turnover (Scheme 16b). Scheidt and co-workers have developed a related "aryloxide rebound" concept in an NHC-catalysed formal Mannich process.[140] Opposite to Lectka's strategy, in this case the aryloxide is generated from the nucleophilic reaction partner. Using α-aryloxyaldehydes **139** as azolium enolate precursors, the aryloxide generated in situ can react with the post-reaction acyl azolium ion to affect catalyst

turnover (Scheme 16c). It was proposed this approach could be translated to reactions of C(1)-ammonium enolates through use of aryl ester enolate precursors.



Scheme 16. Catalyst turnover via aryloxide.

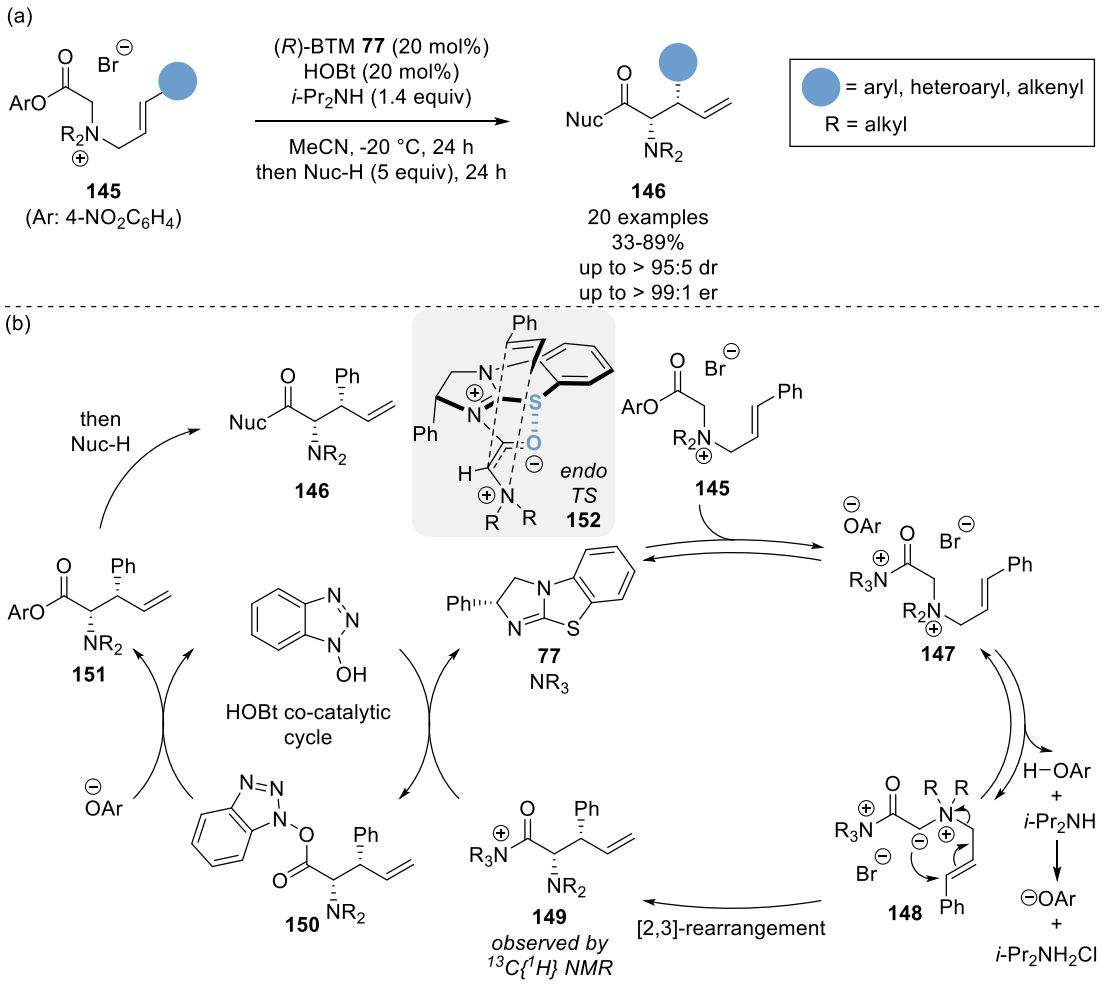
When using electron deficient aryl esters as C(1)-ammonium enolate precursors, the aryloxide anion, released upon acylation of the Lewis base in the first step, can react with the post-reaction acyl ammonium ion to form the product and regenerate the catalyst (Scheme 17).[141] This approach presents a new opportunity for the formation of acyclic α-functionalised products at the carboxylic acid oxidation level, significantly broadening the potential applicability of ammonium enolates in enantioselective catalysis.



Scheme 17. Aryloxide catalyst turnover in isothiourea catalysis via C(1)-ammonium enolates.

In 2014, Smith and co-workers reported the isothiourea-promoted intramolecular [2,3]-sigmatropic rearrangement of allylic quaternary ammonium salts **145** to give stereodefined *syn* α-amino acid derivatives **146** bearing two contiguous stereogenic centres in excellent yield and stereoselectivity (Scheme 18a).[142] Key to the success of this protocol was the addition of hydroxybenzotriazole (HOBt) as co-catalyst to achieve enhanced diastereo- and enantioselectivities (61% yield, 92:8 dr and 98:2 er without HOBt, vs 76% yield, > 95:5 dr and > 99:1 er with HOBt). Various nucleophiles such as amines, alcohols and hydrides could be employed to give the corresponding amide, ester or alcohol products. To circumvent the need for salt isolation, a one-pot allylic alkylation/[2,3]-rearrangement protocol was also developed, although the products were isolated in diminished yield and enantioselectivity. Thorough experimental and computational studies were also carried out to probe the reaction mechanism (Scheme 18b).[105] Through ^{13}C and ^{15}N isotopic-labelling experiments and in situ $^{13}C\{^{1}H\}$ NMR, post-rearrangement intermediate **149** was identified as a resting state form of the catalyst in the absence of HOBt. The addition of HOBt was found to shift the catalyst speciation toward the free catalyst, leading to increased catalyst concentration in the reaction mixture. Therefore, the beneficial effect of HOBt was proposed to originate from a higher concentration of free catalyst, enabling the enantioselective pathway to better outcompete the racemic background reaction. The reaction mechanism is proposed to proceed by direct and reversible *N*-acylation of the catalyst **77** by *para*-nitrophenyl ester ammonium salt **145** to give acyl

ammonium ion intermediate **147** and release *para*-nitrophenoxide. Reversible deprotonation yields ammonium ylide **148** which undergoes irreversible [2,3]-sigmatropic rearrangement, which is both stereo- and product determining, to give post-rearrangement isothiouronium **149**. Catalyst turnover is achieved by addition of HOBt to give HOBt-ester **150** in a secondary co-catalytic cycle, rebound of *para*-nitrophenoxide gives the ester product **151** which is subsequently converted to the corresponding amide by addition of a nucleophile. The observed stereoselectivity can be rationalised by an *endo* pre-transition state assembly **152** where the ammonium ylide exhibits the stabilizing n_O to $\sigma^*_{C\text{-}S}$ interaction and an additional π-cation interaction between the allylic C(3)-aryl substituent and the acyl isothiouronium ion. The rearrangement occurs from the opposite face to the stereodirecting phenyl unit of the catalyst. This methodology was extended to the enantioselective [2,3]-rearrangement of (*Z*)-3-fluoro-3-arylprop-2-ene containing

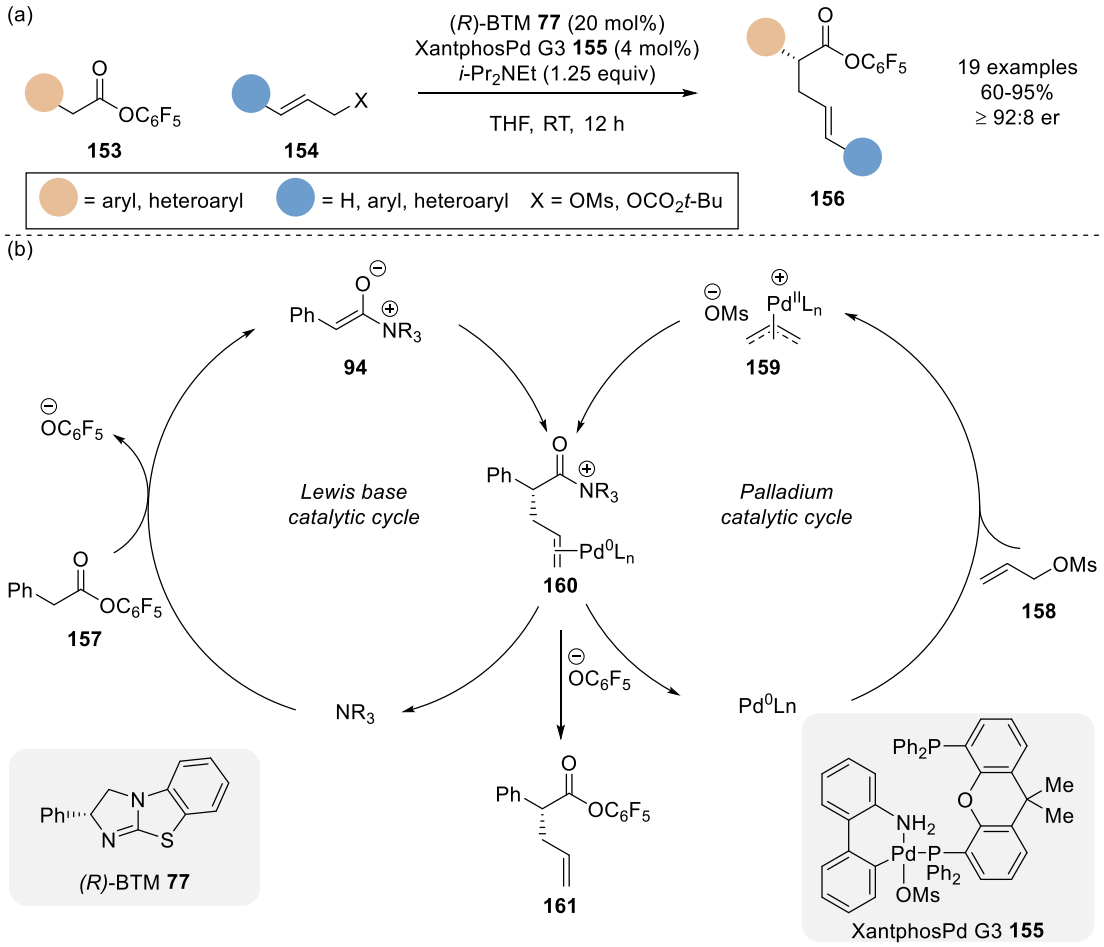


Scheme 18. (a) Isothiourea-catalysed asymmetric [2,3]-sigmatropic rearrangement of allylic ammonium ylides and (b) the proposed mechanism.

quaternary ammonium salts, enabling the synthesis of a range of β-fluoro-β-aryl-α-aminopentenamides containing a stereogenic fluorocarbon centre in high diastereo- and enantioselectivity.[143] Song and co-workers later reported the first catalytic asymmetric [2,3]-rearrangement of propargylic ammonium salt substrates, leading to the enantioselective formation of allenyl α-amino amides in good yields with excellent enantioselectivity.[144] To avoid salt isolation, Smith and co-workers reported the development of a tandem palladium-catalysed allylic amination of allylic phosphates with glycine aryl ester derivatives followed by a [2,3]-rearrangement of intermediate allowed direct access to a range of α-amino acid derivatives.[145]

Snaddon and co-workers applied the aryloxide catalyst turnover strategy for the enantioselective α-allylation of esters enabled by dual isothiourea/palladium catalysis.[129] In the presence of both (*R*)-BTM **77** and XantphosPd G3 **155**, a range of pentafluorophenyl esters **153** underwent enantioselective α-allylation with various allylic electrophiles **154** to give the corresponding linear α-functionalised ester products **156** with excellent enantiocontrol (Scheme 19a). The nature of the allylic leaving group had a marked effect on reactivity and enantioselectivity; allylic esters and chlorides gave the allylation products with poor enantioselectivity, whilst mesylate and *tert*-butylcarbonate leaving groups gave the products in high yield and er. Pentafluorophenyl esters were found to be optimal for this dual-catalytic system, allowing the products to be isolated in higher yield (due to increased chromatographic stability) and in shorter reaction times compared to other electron deficient aryl esters. The reaction mechanism (Scheme 19b) for this process is proposed to involve the union of C(1)-ammonium enolate **94** intermediate from the Lewis base nucleophilic catalytic cycle (left) and the π-(allyl)Pd(II) electrophile **159** generated from the palladium cycle (right). Critical to the success of merging these catalytic cycles is the reagent compatibility of each process; variation of either allylic nucleofuge, palladium catalyst, Lewis base or electron deficient aryl ester has a substantial effect on the reaction outcome. Building on this precedent, the protocol has been extended to using pyrrole 2-acetic acid pentafluorophenyl ester for the synthesis of α-alkylated pyrroles.[146] Snaddon and co-workers have also broadened

the scope of the electrophilic component; a range of electron-withdrawing group-,[147] B(pin)- and silicon-substituted allylic partners bearing useful functional handles has been enabled through modification of the palladium catalyst system.[148],[149]

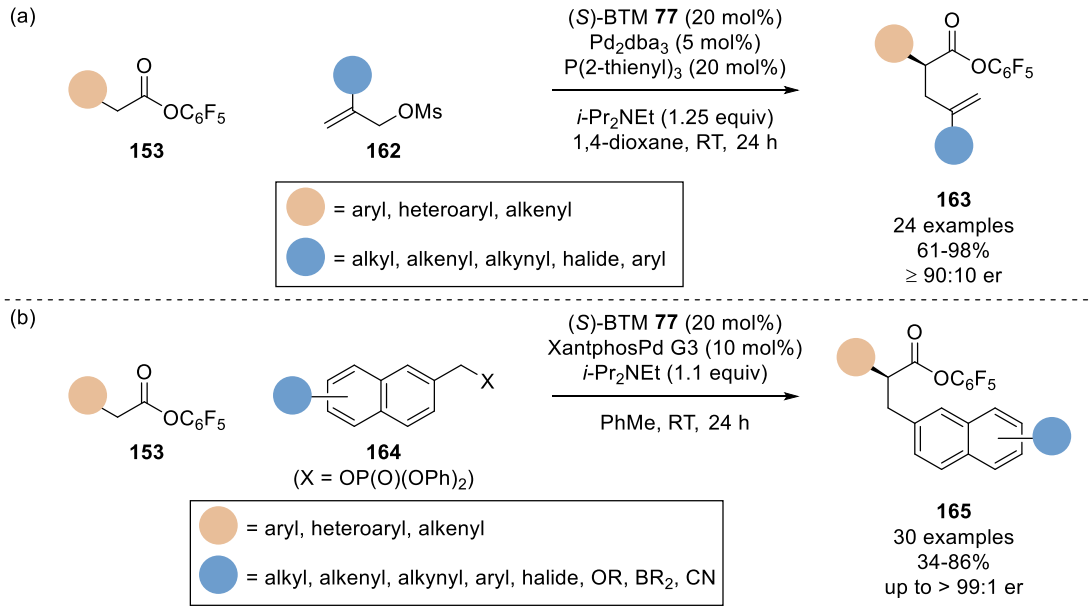


Scheme 19. (a) Cooperative palladium/isothiourea catalysis for the enantioselective α-allylation of pentafluorophenyl esters and (b) proposed mechanism.

In the previous case the linear allylated products were observed. Snaddon and co-workers postulated modulation of the palladium catalyst-ligand system from a bidentate Xantphos ligand to a monodentate phosphine ligand would relieve steric congestion around the metal centre and engage 2-substituent allyl partners. Indeed, a range of 2-substituted allylic mesylates **162** underwent reaction with the corresponding pentafluorophenyl esters **153** using a monodentate, sterically undemanding 2-thienyl phosphine ligand to give a range of branched α-allylated esters **163** (Scheme 20a).[150] The product esters could be isolated, or also be derivatised in situ by addition of an appropriate nucleophile (amine or hydride) at the end of the reaction to give the corresponding amide or primary alcohol product.

DFT studies were carried out to determine the nature of the transition state. This revealed a relatively low barrier (12.2 kcal mol^{-1}) for an outer-sphere attack of the enolate onto the π(allyl)Pd complex, whereas an inner-sphere attack of a palladium-ligated (*Z*)-enolate was found to be highly disfavoured (29.8 kcal mol^{-1}).

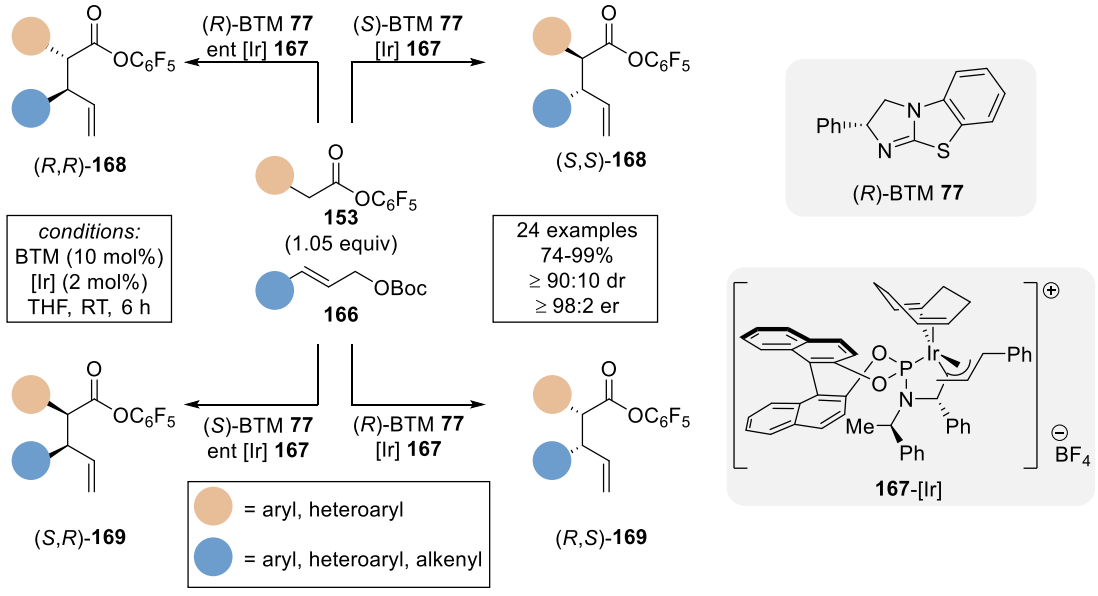
Snaddon and co-workers later extended the scope of this methodology to benzylic electrophiles.[151] Traditionally these are more challenging reaction partners due to the high energy of oxidative addition which requires dearomatisation of the arene unit. Critical to the success of this protocol was the identity of the nucleofuge (X): screening benzylic leaving groups revealed tosylate, acetate, *tert*-butylcarbonate were all unreactive, with only diphenylphosphate proving productive. Various benzylic phosphates underwent reaction with pentafluorophenyl esters in toluene catalysed by BTM and Xantphos palladium (Scheme 20b). Notably a wide range of functional groups are tolerated under the reaction conditions including bromide, alkyne and boron functionality. However, the electrophilic partner was limited to π-extended naphthyl groups. Monocyclic benzene-derived electrophiles were unreactive presumably due to higher dearomatisation energy.



Scheme 20. Dual palladium/isothiourea-catalysed (a) enantioselective α-allylation using 2-substituted allyl electrophiles and (b) enantioselective α-benzylation.

While Snaddon and co-workers have varied the palladium catalyst to address reactivity challenges, Hartwig and co-workers sought to access complementary

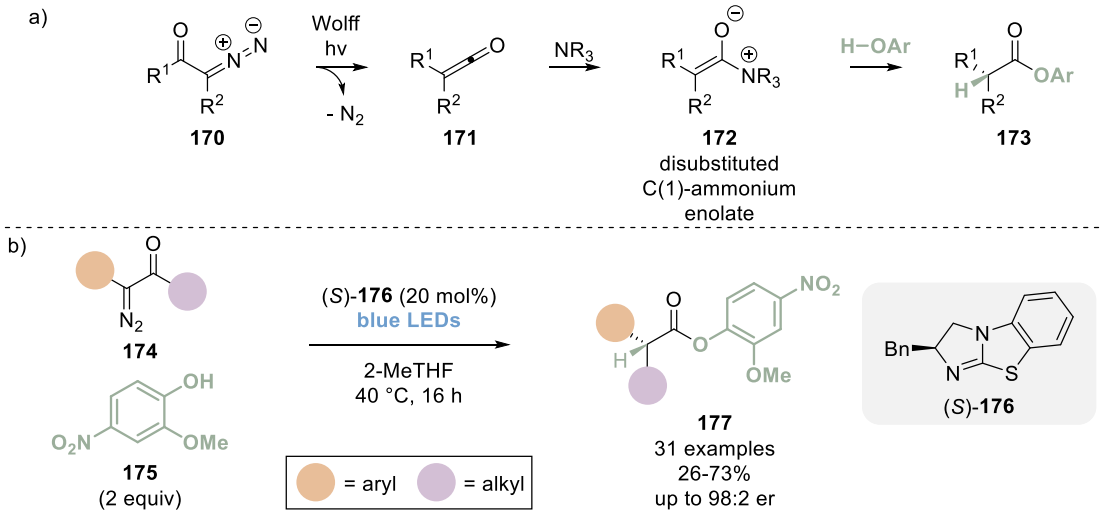
reactivity through use of an alternative metal catalyst. The authors reported a related dual catalytic protocol using cooperative isothiourea/iridium catalysis, enabling exclusive formation of the branched allylated product. The enantioselective α-allylation of pentafluorophenyl esters **153** was achieved, giving exclusively the branched allylated products (Scheme 21).[152] This stereodivergent protocol allows access to all four product stereoisomers through predictable pairing of chiral catalyst antipodes. Using each of the four different catalyst enantiomer combinations, each product stereoisomer could be isolated in high yield and in excellent dr and er, exemplifying the high control each catalyst exhibits over the substrates. BTM **77** governs the absolute configuration of the C(2)-carbon, whilst the metalacyclic iridium complex [Ir] **167** determines the geometry, facial selectivity and regioselectivity of the allyl electrophile, and therefore, the absolute configuration at C(3).



Scheme 21. Dual iridium/isothiourea-catalysed stereodivergent α-allylation of pentafluorophenyl esters.

Han and co-workers have reported the enantioselective protonation of C(1)-ammonium enolates generated from α-diazoketones through a visible-light-induced ketene formation (Scheme 22).[153] The transformation is proposed to proceed through Wolff rearrangement of α-diazoketones **170** to give disubstituted ketene **171** which can be intercepted by a Lewis base to give disubstituted ammonium enolate **172**. Protonation and catalyst turnover by a corresponding phenol gives access to

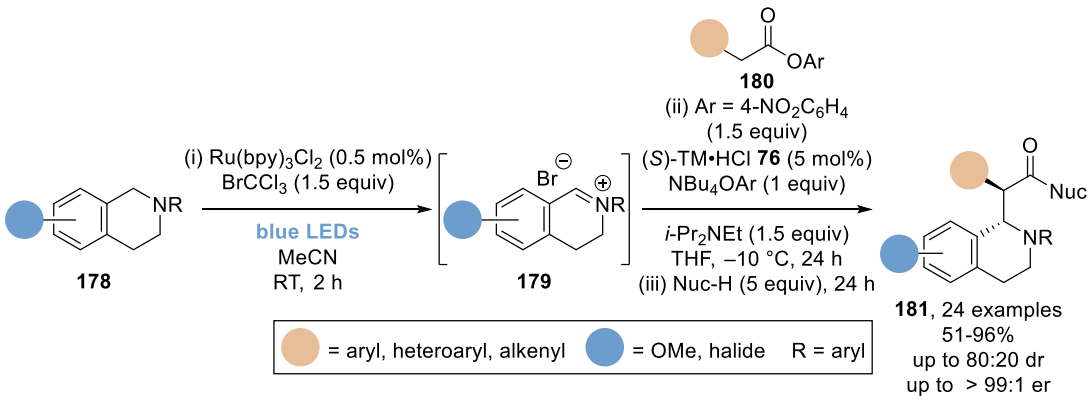
α,α-disubstituted carboxylic esters (Scheme 22a). A range of α-aryl-α-diazoalkylketones **174** smoothly underwent the rearrangement/enantioselective protonation sequence when treated with phenol **175** and isothiourea catalyst **176** under blue LED irradiation to give the corresponding α-alkyl-α-aryl-ester products (Scheme 22b). Substitution in the 2-position with an electron-donating group, and an electron-withdrawing group in the 4-position of the phenol is required for high enantioselectivities.



Scheme 22. Enantioselective protonation of a disubstituted C(1)-ammonium enolate generated from α-diazoketones.

In 2018, using *para*-nitrophenyl esters **180** as C(1)-ammonium enolate precursors, Smith and co-workers reported the isothiourea-catalysed addition to tetrahydroisoquinoline-derived iminium ions **179** (Scheme 23).[154] An appropriate amine nucleophile was added at the end of the catalytic reaction to convert the less stable *para*-nitrophenyl ester product to the corresponding amide **181**. During the optimisation of this process it was found that addition of stoichiometric tetra *n*-butylammonium *para*-nitrophenoxide gave increased yields and enantioselectivities. This is proposed to increase polarity of the reaction mixture whilst also enhancing the rate of catalyst turnover. Also noteworthy was the effect that the iminium counterion had on enantioselectivity. Small, coordinating halides (Br^-, Cl^-) gave higher enantioselectivities than larger, non-coordinating anions such as BF_4^-, PF_6^- and BPh_4^-. The iminium bromide ions could also be generated in situ via photoredox catalysis using $BrCCl_3$ and $Ru(bpy)_3Cl_2$, allowing for the development of a one-pot

sequential strategy. Using this sequential photoredox/Lewis base-catalysed procedure, a range of *para*-nitrophenyl esters **180** could be converted to the β-amino amide products **181** in good yield with high enantioselectivity, however, low diastereoselectivity was observed (~ 75:25 dr). Despite the low diastereoselectivity, this process overcomes some of the challenges associated with aryloxide catalyst turnover such as compatibility of nucleophilic (aryloxide, Lewis base catalyst) and electrophilic species (iminium ion) within the reaction mixture.



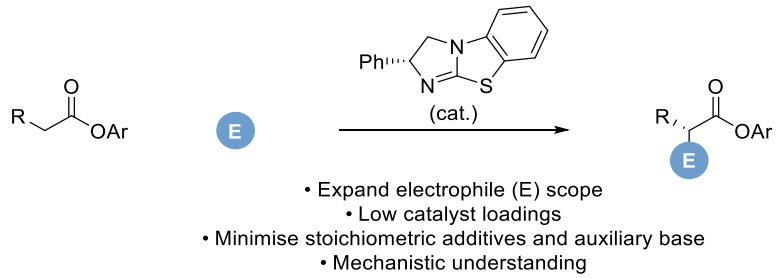
Scheme 23. Enantioselective addition of C(1)-ammonium enolates to iminium ion electrophiles.

1.6. Proposed Work

These impressive methodologies using aryloxide catalyst turnover have significantly broadened the scope of isothiourea catalysis via C(1)-ammonium enolates, showcasing the reactivity in dual-catalytic processes and with alternative electrophiles for the enantioselective α-functionalisation of acylic esters. However, in all these previous processes there is a typical requirement for relatively high catalyst loadings (often 20 mol%), stoichiometric additives and/or excess stoichiometric auxiliary base (necessary to neutralise acidic by-products) for effective reactivity. In addition, the mechanism of these processes had not been investigated experimentally to identify key features such as reaction intermediates, orders with respect to each component and the turnover-limiting step.

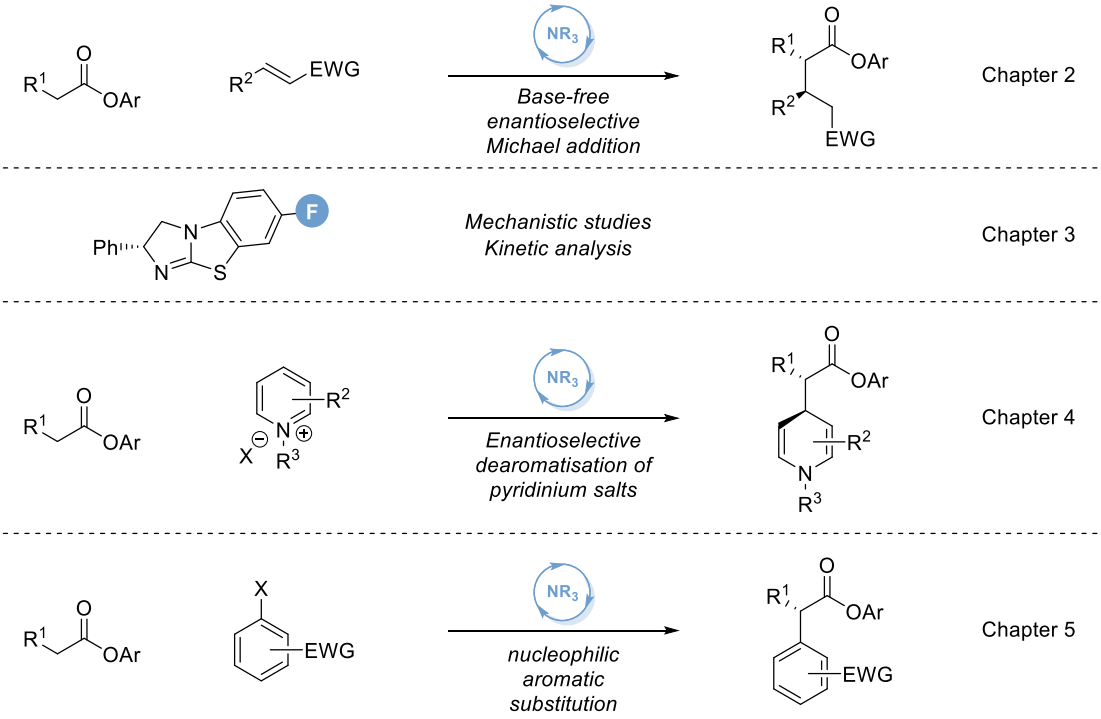
The proposed work of this PhD was to develop novel methods for the enantioselective α-functionalisation of esters through the identification of new electrophilic partners (Scheme 24). In addition, it was hoped to develop processes which use low catalyst loadings of organocatalyst and minimise the amount of

auxiliary base and additives required for effective catalysis. It was envisaged that a thorough mechanistic investigation could be carried out on the developed methodologies to advance the collective understanding of the field. It was recognised that one of the most challenging aspects of this work would be reagent compatibility. In particular, identification of electrophiles that could react with a catalytically-generated C(1)-ammonium enolate, but be unreactive, or react reversibly, with the nucleophilic aryloxide and catalyst would be required. In addition, the tertiary α-functionalised products possessing acidic α-protons may be labile to epimerisation and hence may impact the stereochemical integrity of the product under the reaction conditions.



Scheme 24. Proposed work.

Targets for this thesis, depicted in Scheme 25, include the development of a base free Michael addition protocol (Chapter 2), a mechanistic study into C(1)-ammonium catalysis involving aryloxide promoted catalyst turnover (Chapter 3), the enantioselective nucleophilic dearomatisation of pyridinium salts (Chapter 4) and enantioselective nucleophilic aromatic substitution reactions (Chapter 5).

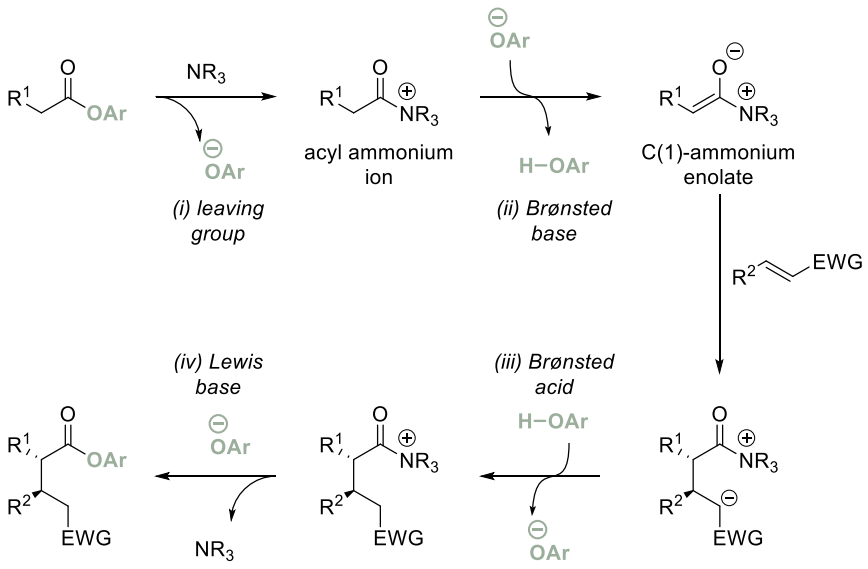


Scheme 25. Thesis targets.

Chapter 2. Base-Free Enantioselective Michael Addition via C(1)-Ammonium Enolates

2.1. Introduction

To address some of the limitations identified in Section 1.6, we envisaged the development of a base-free and proton neutral Lewis base-catalysed strategy for the enantioselective functionalisation of electron-deficient aryl esters through a Michael addition reaction (Scheme 26). Addition of an isothiourea Lewis base to an aryl ester would initially generate an acyl ammonium aryloxide ion pair, with deprotonation of the acyl ammonium by the aryloxide generating the reactive C(1)-ammonium enolate. Enantioselective Michael addition to a suitable acceptor, followed by proton transfer from the in situ generated phenol, and subsequent aryloxide turnover would deliver α-alkylated ester products containing two tertiary, contiguous stereogenic centres. This approach would circumvent the previous necessity for the addition of an auxiliary base but would require the aryloxide to fulfil the role of proton shuttle within the catalytic cycle.



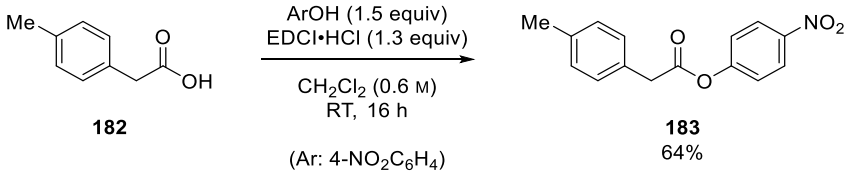
Scheme 26. Proposed base-free isothiourea catalysis via C(1)-ammonium enolates.

2.2. Results and Discussion

2.2.1. Ester Synthesis

To attempt the Michael addition reaction, a suitable activated aryl acetic acid ester was required. Previous work has demonstrated that the aryloxide catalyst turnover

concept could be affected with a range of electron deficient aryl esters using isothiourea catalysts. Smith and co-workers have employed *para*-nitrophenol esters in [2,3]-rearrangement and ammonium enolate methodologies,[142],[154] whilst α-allylation processes by Snaddon and Hartwig utilised pentafluorophenol esters.[129],[152] During reaction optimisation, Snaddon and co-workers also demonstrated tetrafluorophenol esters gave high yields (75%) and enantioselectivity (97:3 er), whilst trichlorophenol esters gave 37% yield and 70:30 er. It was initially proposed that *para*-nitrophenol esters could be employed for initial exploration of the proposed process (Scheme 27). Ester **183** was efficiently prepared from *para*-tolyl acetic acid **182** and *para*-nitrophenol using EDCI in good yield on a multigram scale (5.0 g, 34 mmol).

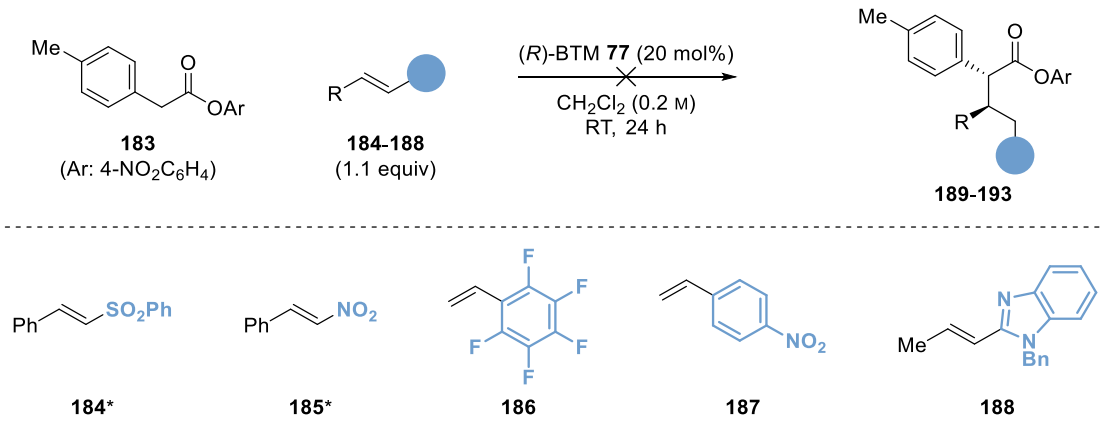


Scheme 27. Synthesis of para-nitrophenyl ester.

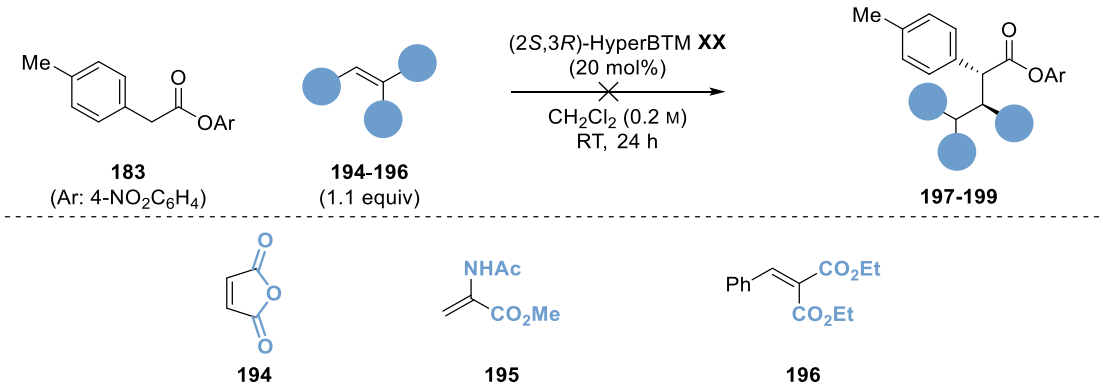
2.2.2. Electrophile Screen

Initially, a range of readily available, structurally simple Michael acceptors bearing one electron-withdrawing group were targeted for reaction with ester **183**. Vinyl sulfone **184**, β-nitrostyrene **185**, pentafluorostyrene **186** and 4-nitrostyrene **187** are commercially available, whilst alkenyl benzimidazole **188** was synthesised according to literature procedures.[155] Applying each of these substrates under the model reaction conditions ((*R*)-BTM **77**, dichloromethane, room temperature) led to no formation of product with only starting materials observed in each case (Scheme 28).

A source of this lack of reactivity was postulated as insufficient electrophilicity of the Michael acceptor. Therefore, electrophiles bearing two electron-withdrawing groups (Scheme 29) were tested in reactions with the ammonium enolate. Unfortunately, commercially available electrophiles maleic anhydride **194**, methyl acetamidoacrylate **195** and diethyl benzylidenemalonate **196** were also unreactive under the catalytic conditions, with only starting materials returned.



Scheme 28. Screen of electrophiles bearing one electron-withdrawing group.
(*: using HyperBTM)



Scheme 29. Screen of electrophiles bearing two electron-withdrawing groups.

It was evident that simply screening different electrophiles was not the best method to continue with and that a more systematic approach was required. Mayr and co-workers have extensively investigated the relative reactivity of electrophiles using kinetic analysis (Figure 7). Study of reactions of electrophiles with reference carbanion nucleophiles (such as sulfur ylides, pyridinium ylides, enolates with known nucleophile-specific parameters N and s_N) has allowed for the calculation of the empirical electrophilicity parameter E for a wide range of electrophiles using Equation 1 by determining the rate constant for each reaction.[156],[157] With this data, the authors have complied a general reactivity scale for various electrophiles to compare relative electrophilicities. Significantly, electrophiles that had not shown any reactivity in isothiourea catalysis via C(1)-ammonium enolates, such as vinyl sulfone **184** and diethyl benzylidenemalonate **196**, are found at the lower end of Mayr's reactivity series.[158],[159] However, despite β-nitrostyrene **185** and maleic anhydride **194** being significantly more electrophilic,[160],[161] these were also

unreactive. As discussed in Section 1.5.4, C(1)-ammonium enolates have been demonstrated to react with tetrahydroisoquinoline-derived iminium ions. Mayr and co-workers have calculated the electrophilicity parameter of *N*,*N*-dimethyl iminium ions such as **202** to be –9.3.[162] It was proposed that reaction with an electrophile of similar electrophilicity may lead to the desired reactivity. Two Michael acceptors identified as suitable candidates were benzylidene malononitrile **201** (E = –9.4)[163] and vinyl bis-sulfone **200** (E = –12.9).[164]

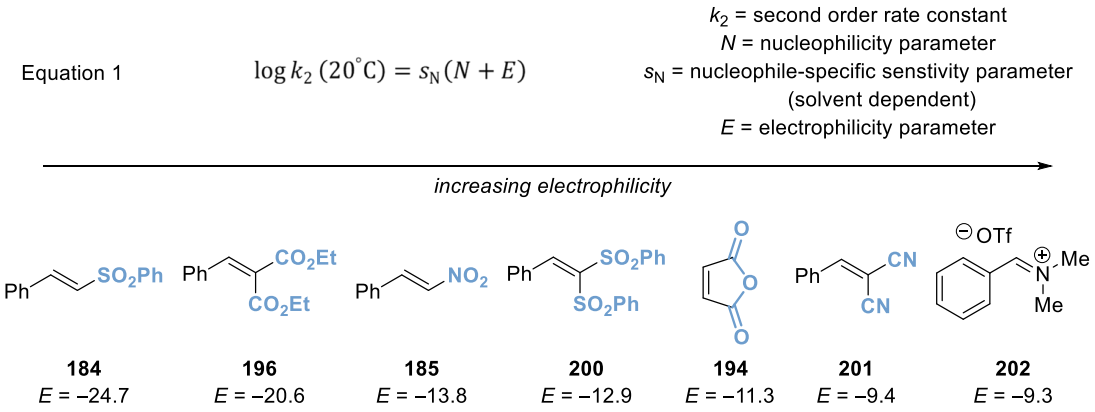
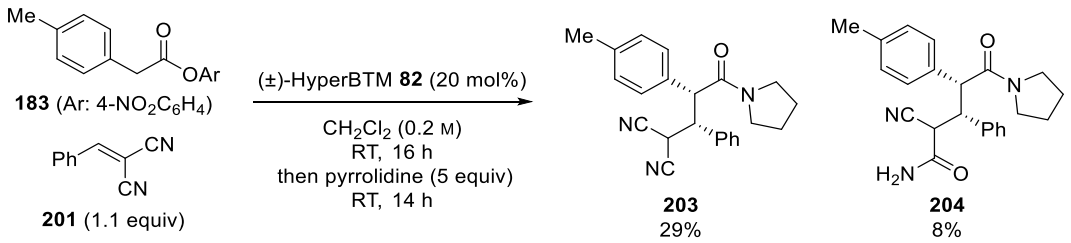


Figure 7. Mayr reactivity scale of selected electrophiles.

2.2.3. Reaction Using Benzylidene Malononitrile

Firstly, the reaction using benzylidene malononitrile **201** as the electrophile was attempted under the model catalysis conditions (Scheme 30). Pleasingly, reactivity was observed, giving product **203** in 29% yield, following conversion of the product ester to the corresponding amide in situ. Additionally, 8% of amide **204** was isolated, presumably formed via hydrolysis of one of the nitrile groups. However, the reaction could not be reproduced after multiple attempts, with the addition of pyrrolidine leading to product decomposition in each case.

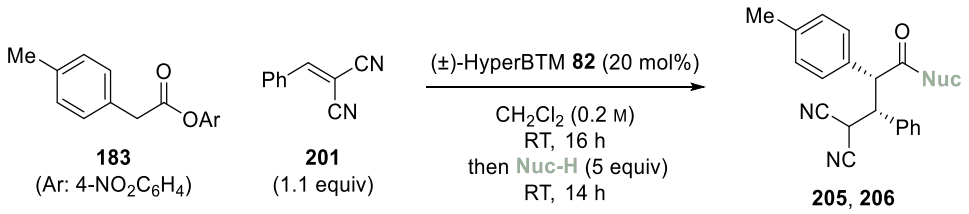


Scheme 30. Initial catalytic reaction using benzylidene malononitrile.

It was decided to try alternative nucleophiles at the end of the reaction to try and limit product decomposition (Table 1). Carrying out the same catalysis reaction and

adding either benzylamine (entry 1) or morpholine (entry 2) at the end of the reaction also gave no product at the end of the reaction and resulted in decomposition of the *para*-nitrophenyl ester product.

Table 1. Use of alternative nucleophiles with benzylidene malononitrile.

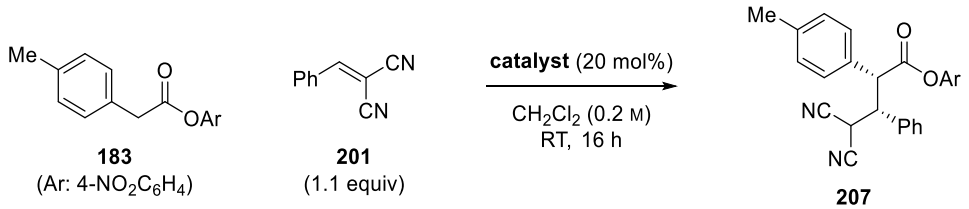


Entry	Nucleophile	Yield[a] (%)
1	Benzylamine	0
2	Morpholine	0

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard.

It was decided to avoid adding a nucleophile at the end of the catalytic reaction and attempt to isolate the ester products. Reaction using (2*S*,3*R*)-HyperBTM **82** as the Lewis base allowed ester product **207** to be isolated in 31% yield with moderate enantioinduction (72:28 er, Table 2, entry 1). The relative and absolute configuration was assigned by analogy to previously reported related reactions.[102] Employing (*R*)-BTM **77** lead to an increase in enantioselectivity (84:16 er), with a similar yield (28%) of product **207** obtained (entry 2). In both cases, the remainder of the crude reaction mixture was unreacted starting materials.

Table 2. Catalyst study using benzylidene malononitrile.

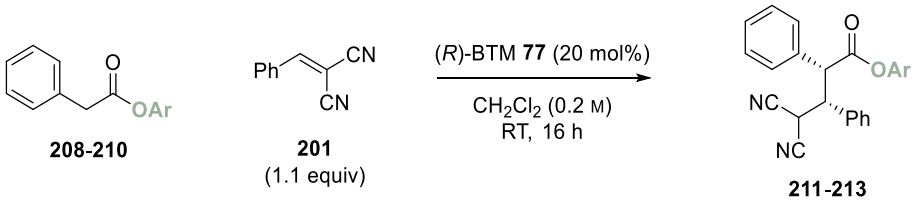


Entry	Catalyst	Yield (%)	dr	er[a]
1	(2*S*,3*R*)-HyperBTM **82**	31	nd	72:28
2	(*R*)-BTM **77**	28	nd	84:16

[a] Determined by chiral HPLC analysis.

As the success of this reaction would require the aryloxide to fulfil multiple roles (leaving group, Brønsted base, Brønsted acid, Lewis base) it was decided to next vary the aryl ester component in an attempt to increase the yield of product (Table 3). However, reactions using pentafluoro phenyl **208** (entry 1), tetrafluoro phenyl **209** (entry 2) and trichloro phenyl **210** (entry 3) esters gave lower conversion to product (< 20%).

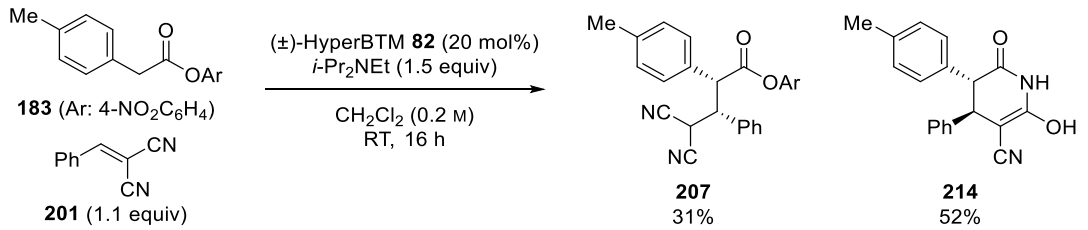
Table 3. Aryloxide study using benzylidene malononitrile.



Entry	Ar	Yield[a] (%)
1	C_6F_5 **208**	19
2	2,3,5,6-C_6F_4H **209**	18
3	2,4,6-$C_6Cl_3H_2$ **210**	12

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard.

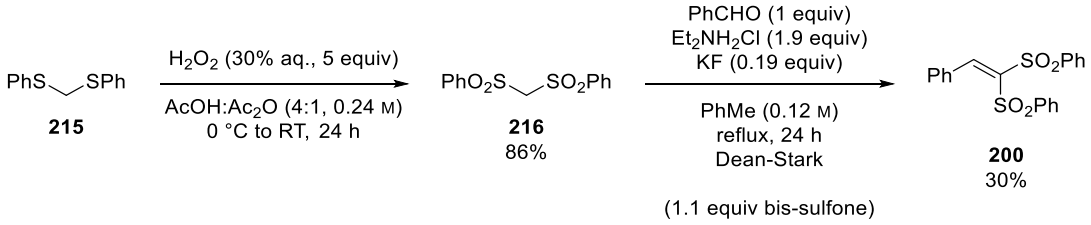
Up to this stage, the yields were limited around 20-30%, approximately the same as the amount of catalyst present, potentially consistent with the isothiourea being deactivated through protonation and being unable to perform multiple cycles. To test this hypothesis, a reaction with an additional 1.5 equivalents of an auxiliary base (*i*-Pr_2NEt, Hunig's base) was attempted (Scheme 31). Interestingly, a similar amount of product was observed (31%). Additionally, 52% of cyclised product **214** was isolated following column chromatography. It was proposed this could form through deprotonation of the acidic proton adjacent to the nitrile groups in structure **207**, and subsequent cyclisation/hydrolysis to give the cyclised product. At this stage it was recognised the development of a base-free methodology using benzylidene malononitrile **201** would be challenging, having exhausted most options for the optimisation of the reaction using this electrophile. Therefore, it was decided to explore the use of vinyl bis-sulfone **200**.



Scheme 31. Reaction in the presence of auxiliary base.

2.2.4. Reaction Optimisation of Vinyl Bis-Sulfones

Although not commercially available, vinyl bis-sulfone **200** was readily prepared using a procedure reported by Alexakis and co-workers (Scheme 32).[165] Aqueous hydrogen peroxide-mediated oxidation of bis(phenylthio)methane **215** in acetic acid and acetic anhydride gave the corresponding bis(phenylsulfonyl)methane **216** in excellent 86% yield after recrystallisation. The reaction could be carried out on a 50 mmol scale to afford 12 g of the bis-sulfone. Subsequent Knoevenagel condensation using diethylammonium chloride and catalytic potassium fluoride gave vinyl bis-sulfone **200** in low 30% yield.

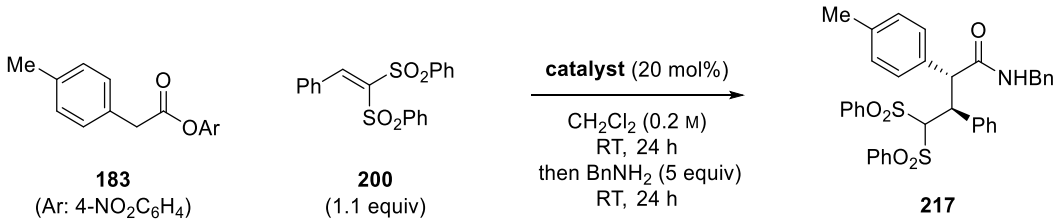


Scheme 32. Synthesis of vinyl bis-sulfone electrophile.

Employing vinyl bis-sulfone **200** under catalysis conditions using (2*S*,3*R*)-HyperBTM catalyst **82** showed conversion of the starting materials to the product (Table 4). The reaction was stopped after 24 h by the addition of benzylamine to convert the aryl ester to the corresponding benzyl amide product **217**. ^{1}H NMR analysis of the crude reaction mixture indicated the reaction had proceeded in good yield (60%) with good diastereoselectivity (80:20 dr). Purification by flash column chromatography enabled separation of the diastereoisomers, with the major diastereoisomer isolated with excellent enantioselectivity (98:2 er, entry 1). Following this result, it was decided to screen alternative isothiourea catalysts in an attempt to increase the yield and diastereoselectivity of this Michael addition reaction. Encouragingly, changing the catalyst from HyperBTM **82** (entry 1) to (*S*)-

TM·HCl **76** led to an increase in yield (entry 2), with amide **217** formed in 67% yield with high diastereoselectivity (90:10 dr) and exceptional enantioselectivity (> 99:1 er). BTM **77** gave the product in improved yield (78%, entry 3), whilst maintaining high dr (85:15) and er (> 99:1).

Table 4. Catalyst study.

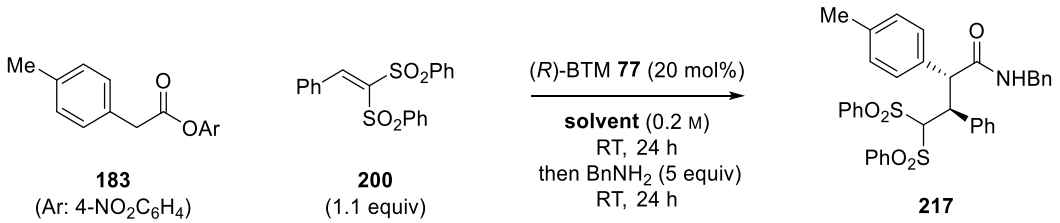


Entry	Catalyst	Yield[a] (%)	dr[b]	er[c]
1	(2*S*,3*R*)-HyperBTM **82**	60	80:20	98:2
2[d]	(*S*)-TM·HCl **76**	67	90:10	< 1:99
3	**(*R*)-BTM 77**	**78**	**85:15**	**> 99:1**

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] 1.0 equiv *i*-Pr$_2$NEt added.

The use of various solvents was next investigated (Table 5). In comparison to dichloromethane (entry 1), reactions in THF and DMF both gave amide **217** in comparable yield with excellent stereoselectivity (entries 2,3). However, when the reaction was performed in chloroform, the product was obtained in significantly diminished yield (45%), albeit in high dr and er (entry 4). Notably, the diastereo- and enantioselectivity remained high despite variation of the Lewis base catalyst and reaction solvent (≥ 85:15 dr, ≥ 99:1 er).

Table 5. Solvent study.

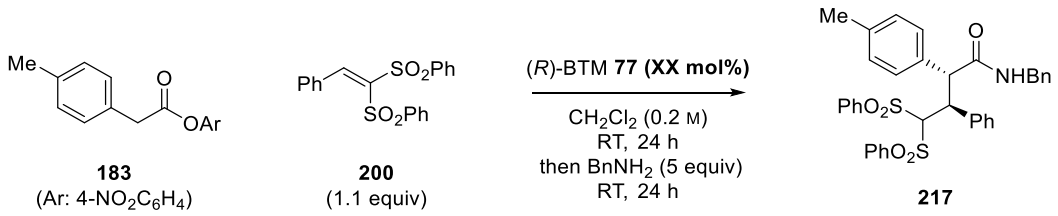


Entry	Solvent	Yield[a] (%)	dr[b]	er[c]
1	**CH_2Cl_2**	**78**	**85:15**	**> 99:1**
2	THF	69	85:15	> 99:1
3	DMF	74	90:10	99:1
4	$CHCl_3$	45	90:10	> 99:1

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Generally, one limitation in organocatalytic reactions is the requirement for high catalyst loadings (e.g. 20 mol%) compared to transition metal mediated processes. With this protocol proving robust, it was decided to probe if the catalyst loading could be lowered (Table 6). Gratifyingly, 15 mol% of (*R*)-BTM gave approximately the same result (78%, 90:10 dr, > 99:1 er, entry 2). Lowering the catalyst loading to 10 mol% resulted in only a small drop in yield (to 62%), whilst maintaining exceptional stereoselectivities (entry 3). Carrying out the reaction at 5 mol% gave a useful yield of 54% (entry 4). However, reaction at 1 mol% gave only 14% product (entry 5). It was decided to proceed with 5 mol% organocatalyst and attempt to increase the yield through variation of other reaction parameters.

Table 6. Catalyst loading study.

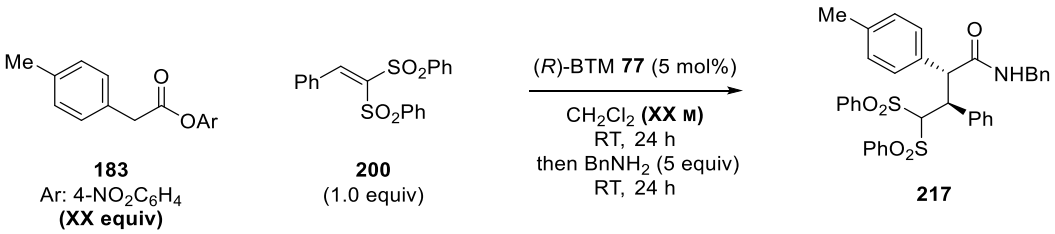


Entry	Catalyst Loading (mol%)	Yield[a] (%)	dr[b]	er[c]
1	20	78	85:15	> 99:1
2	15	78	90:10	> 99:1
3	10	62	90:10	> 99:1
4	**5**	**54**	**90:10**	**> 99:1**
5	1	14	90:10	> 99:1

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

It was proposed the yield of amide product could be increased through variation of the reaction stoichiometry and concentration (Table 7). Indeed, increasing the reaction concentration to 0.3 M led to an improved yield of amide **217** (70%) without affecting the stereoselectivity of the reaction. Increasing both the equivalents of ester **183** (1.5 equiv) and concentration (0.5 M) gave amide **217** in excellent yield with no change in stereoselectivity (entry 3). Although increasing the concentration further to 0.8 M gave approximately the same result and had the advantage of using less solvent, the reaction was heterogeneous at this concentration. Therefore, it was decided to proceed using 0.5 M that would be more broadly applicable. The diastereoisomers were separable by flash column chromatography, with the major diastereoisomer isolated in 75% yield.

Table 7. Stoichiometry and concentration study.

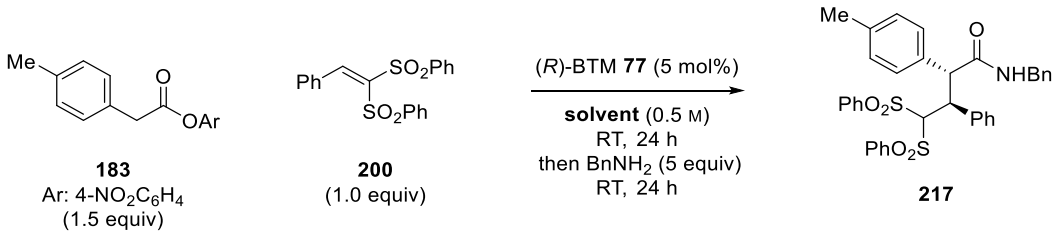


Entry	183 (equiv)	Concentration (M)	Yield[a] (%)	dr[b]	er[c]
1[d]	1.0	0.2	54	90:10	> 99:1
2	1.0	0.3	70	90:10	> 99:1
3	**1.5**	**0.5**	**86 (75)**	**90:10**	**> 99:1**
4	1.5	0.8	87	90:10	> 99:1

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] 1.1 equivalents **200**.

Pleasingly, this process requires no additional auxiliary base for effective catalysis. To further explore the sustainability of the protocol, the use of alternative, industrially preferable solvents was next investigated (Table 8).[166] Whilst *tert*-butylmethylether (TBME) gave amide **217** in lower yield (entry 2), reactions carried out in dimethylcarbonate (DMC), and ester solvents such as iso-propyl acetate and ethyl acetate gave the product in excellent yields and stereoselectivities (entries 3-5). 2-Methyl tetrahydrofuran (2-MeTHF) was also amenable for this transformation, although amide **217** was formed in lower diastereoselectivity. (entry 6).

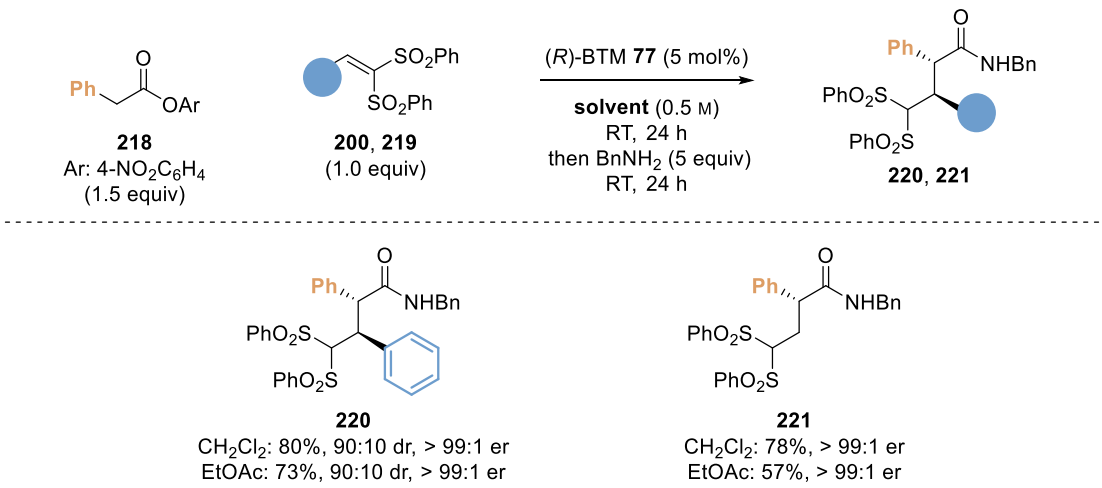
Table 8. Industrially preferable solvent study.



Entry	Solvent	Yield[a] (%)	dr[b]	er[c]
1	CH_2Cl_2	86	90:10	> 99:1
2	TBME	37	90:10	> 99:1
3	DMC	85	90:10	98:2
4	*i*-PrOAc	89	90:10	> 99:1
5	EtOAc	92	90:10	> 99:1
6	2-MeTHF	63	80:20	> 99:1

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

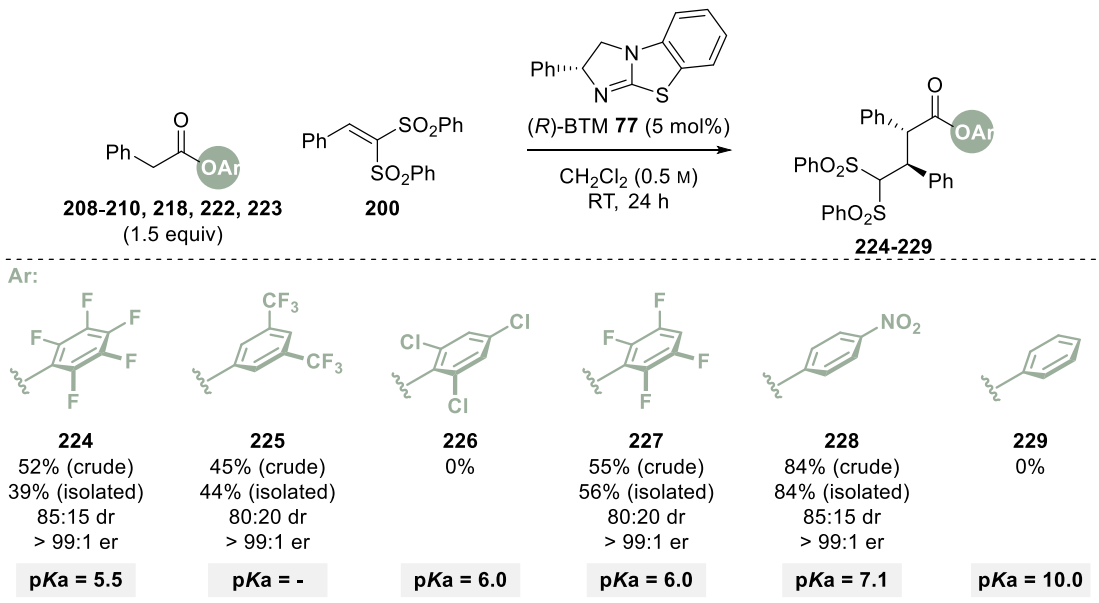
To finalise the optimisation of the reaction solvent, the generality of the protocol in dichloromethane and ethyl acetate was probed on selected substrates through variation of the aryl ester and vinyl bis-sulfone components (Scheme 33). Whilst ethyl acetate proved superior in the model optimised system, dichloromethane was found to be the most general solvent on extension to the synthesis of alternative substrates. Amide **220** was formed in slightly diminished yield in ethyl acetate (73%) compared to dichloromethane (80%), with the same diastereoselectivity (90:10 dr). A substantial drop in yield was observed for the synthesis of amide **221** (78% vs 57%). The decreased yield for reactions in ethyl acetate is proposed to be due to the heterogeneity of the reaction mixture, whereas reactions in dichloromethane are homogeneous. Encouragingly, the enantioselectivities remained excellent across the board (all ≥ 99:1 er).



Scheme 33. Substrate scope comparing dichloromethane and ethyl acetate.

Key to the success of this strategy is the multiple roles that the aryloxide is required to perform within the catalytic cycle. It must be an effective leaving group to promote *N*-acylation; act as a Brønsted base and a Brønsted acid (as the corresponding phenol); before finally acting as a Lewis base. The steric and electronic effects of the aryloxide leaving group were examined to gain insight into the subtle effects that could alter its nucleophilicity, nucleofugality and basicity (Scheme 34).[167–169] ^{1}H NMR yields of the crude reaction mixtures were obtained to measure the efficiency of the reaction with each ester. The esters were also isolated without in situ derivatisation to determine the stability of the product esters. Although isolable, the esters proved unstable to HPLC analysis, therefore, all products were converted to the corresponding benzylamide to determine the enantiopurity. Using *para*-nitrophenyl ester **218** allowed ester product **228** to be isolated in high yield, dr and er (84%, 85:15 dr, > 99:1 er). Reaction of pentafluorophenyl ester **208** gave product **224** in lower yield (39%), although excellent stereocontrol was maintained (85:15 dr, > 99:1 er). The use of tetrafluorophenyl ester **209** gave product **227** in 56% yield, whilst 3,5-bis(trifluoromethyl) ester **222** gave product **225** in 44% yield. Interestingly, the reaction of both 2,4,6-trichlorophenyl ester **210** and the parent phenyl ester **223** showed no reactivity. In general, the crude and isolated yields of the ester products are comparable. However, in the case of pentafluorophenyl ester, the isolated yield is slightly lower than the crude yield, presumably due to a small amount of product decomposition. The yields obtained using these aryl esters can be correlated to some extent with the pK_a of the corresponding phenol. *para*-Nitrophenol (pK_a 7.1 in

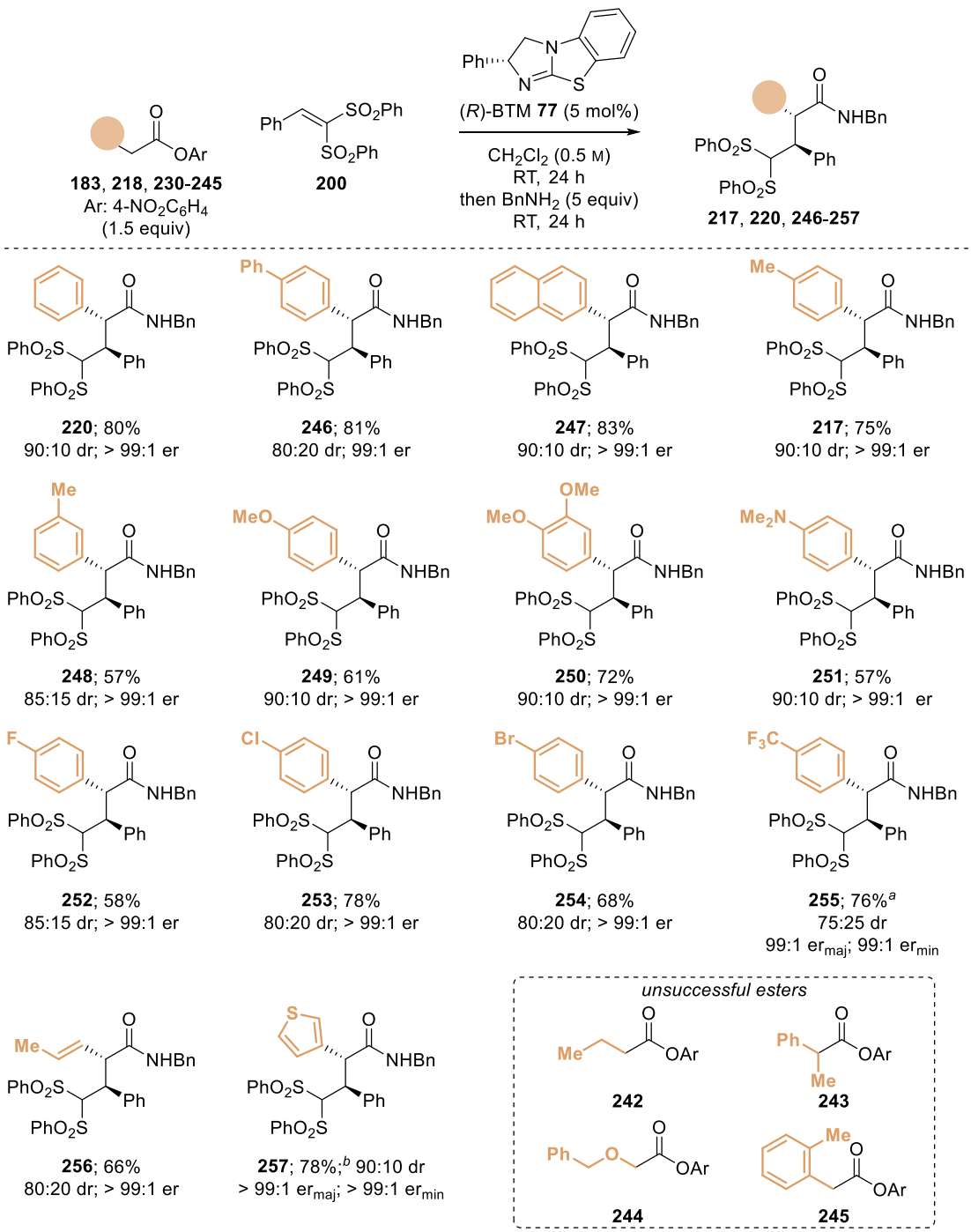
H_2O)[170] appears to be the optimal choice, implying it is an efficient leaving group but is also capable of the desired amphoteric behaviour and promoting catalyst turnover. Pentafluorophenol (pK_a 5.53) and tetrafluorophenol (pK_a 6.0) have lower pK_a values,[171] meaning the corresponding aryloxides are less Brønsted basic, presumably resulting in lower concentrations of the reactive ammonium enolate. 2,4,6-Trichlorophenol esters have been previously shown to acylate isothiourea catalysts in C(1)-ammonium enolate and α,β-unsaturated acyl ammonium processes, meaning that the aryloxide is a competent leaving group.[114,172,173] 2,4,6-Trichlorophenol has a comparable pK_a (5.99) to tetrafluorophenol, which suggests the aryloxide should also be able to operate as a Brønsted base in this process. Therefore, the lack of reactivity using 2,4,6-trichlorophenol ester is presumably due to the steric demands of the *ortho*-chloro substituents attenuating the nucleophilicity of the aryloxide. The ester derived from phenol is expected to be significantly less electrophilic than the other esters tested and the lack of reactivity in this case is most likely a consequence of the ester not efficiently acylating the catalyst. A careful balance of leaving group ability, amphoteric behaviour and steric effects within this series indicates that *para*-nitrophenol is the most effective aryl ester for this application.



Scheme 34. Aryloxide study.

2.2.5. Reaction Scope and Limitations

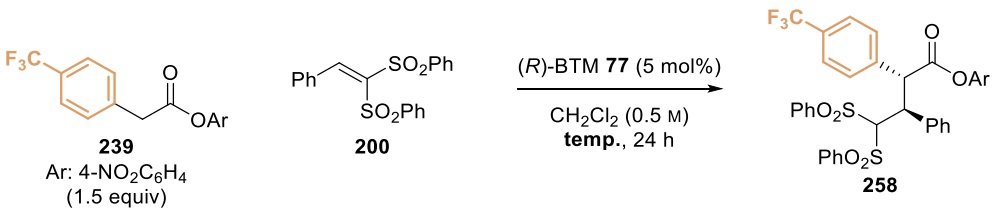
The generality of the Michael addition protocol was next investigated by exploring the scope of the ester component (Scheme 35). For simplicity, since the product esters were unstable to HPLC analysis, all products were converted to the corresponding benzylamide in situ with the addition of benzylamine at the end of the catalytic reaction. The product diastereoisomers were separable by column chromatography in each case and the quoted yield refers to the isolated yield of the major diastereoisomer. Firstly, a range of substituted arylacetic *para*-nitrophenyl esters with different steric and electronic properties was explored. Electron-neutral phenyl, 4-biphenyl and 2-naphthyl groups provided the corresponding amide products **220**, **246** and **247** in high yield and diastereoselectivity, with exceptional enantiocontrol (all ≥ 99:1 er). Electron-donating aryl substituents (such as 4-tolyl, 4-methoxyphenyl and 4-dimethylaminophenyl) gave the corresponding amide products **217**, **249**-**251** in good yield and with high diastereoselectivity (~ 90:10 dr). Halogen-substituted aryl rings gave amides **252**-**254** in good yield and er, although in reduced dr (~ 80:20 dr). Introduction of the electron-withdrawing 4-trifluoromethylphenyl group gave product **255** with diminished diastereoselectivity (75:25 dr), albeit still in high yield (76%) and enantiopurity for both diastereoisomers (both 99:1 er). Having demonstrated a range of substituted aryl rings were compatible with the optimised conditions, attention was turned to other classes of ester. Pleasingly, alkenyl substituents were tolerated, with amide **256** obtained in 66% yield and with good stereoselectivity (80:20 dr, > 99:1 er). Heteroarylacetic esters were also compatible, with 3-thienyl amide **257** obtained in high yield and dr; both diastereoisomers were obtained in > 99:1 er. Unfortunately, alkyl, α,α-disubstituted, benzyloxy and *ortho*-substituted aryl esters **242**-**245** were unreactive in this protocol, only returning starting materials in each case.



Scheme 35. Aryl ester reaction scope.
([a]: isolated > 95:5 dr. [b] combined yield of separable diastereoisomers.).

Studies were undertaken to probe the low diastereoselectivity observed for aryl esters substituted with an electron-withdrawing group, such as trifluoromethyl substituted ester **239**. Firstly, the effect of temperature was investigated on the diastereoselectivity of the reaction of ester **239** with vinyl bis-sulfone **200** (Table 9). Reactions carried out at lower temperatures (0, –40, –78 °C) gave ester **258** in lower yields but with similar diastereomeric ratios (60:40-80:20 dr).

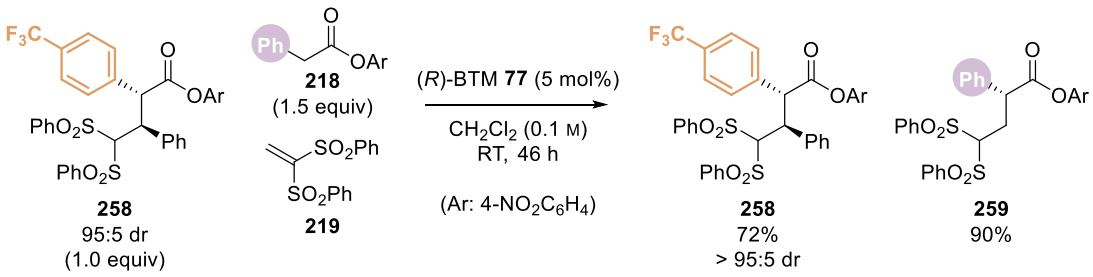
Table 9. Effect of temperature on diastereoselectivity.



Entry	Temp. (°C)	Yield[a] (%)	dr[b]
1	RT	quant.	75:25
2	0	68	80:20
3	–40	27	60:40
4	–78	16	60:40

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

To determine if product epimerisation was occurring under the reaction conditions, a sample of the major diastereomer of the *para*-nitrophenyl ester product **258** (> 95:5 dr) was exposed to the on-going reaction of ester **218** and electrophile **219** (Scheme 36). No product epimerisation was observed, with ester **258** remaining in high dr. Whilst epimerisation of the post-Michael addition acyl ammonium ion cannot be ruled out, these results indicate the observed diastereomeric ratio is representative of the diastereoselectivity of the reaction and is derived from the orientation of the electrophile on approach to the ammonium enolate rather than product epimerisation.



Scheme 36. Epimerisation study.

The relative and absolute configuration of the major (2*R*,3*S*)-diastereoisomer **217** was determined by single crystal X-ray crystallography with all other products assigned

by analogy (Figure 8). The relative and absolute configuration within the minor (2*R*,3*R*)-diastereoisomer **257** was also determined by single crystal X-ray crystallography. This is consistent with high enantiocontrol at C(2) for both diastereoisomers, which are epimeric at C(3). Interestingly, the relative configuration within the major diastereoisomer obtained using these bis-sulfone electrophiles is opposite to that observed in previous isothiourea catalysis employing intramolecular catalyst turnover processes (Scheme 12)[102] and in the intermolecular addition to iminium ions (Scheme 23).[154] This difference can presumably be rationalised due to the two highly sterically demanding sulfone groups of this series of electrophile, resulting in a different pre-transition state organisation for this reaction.

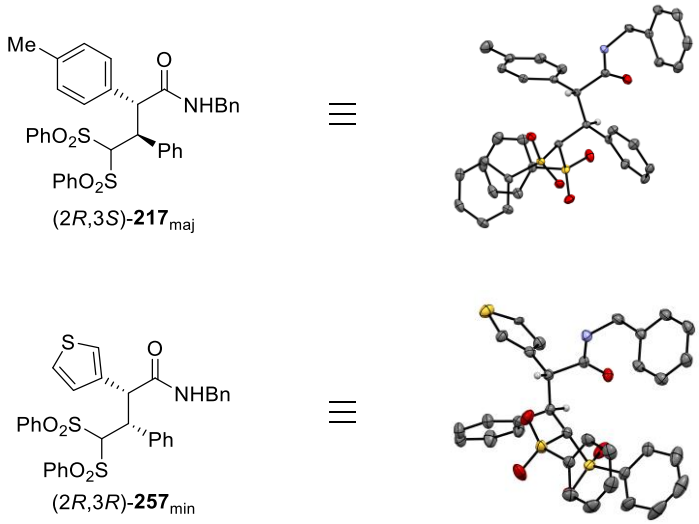
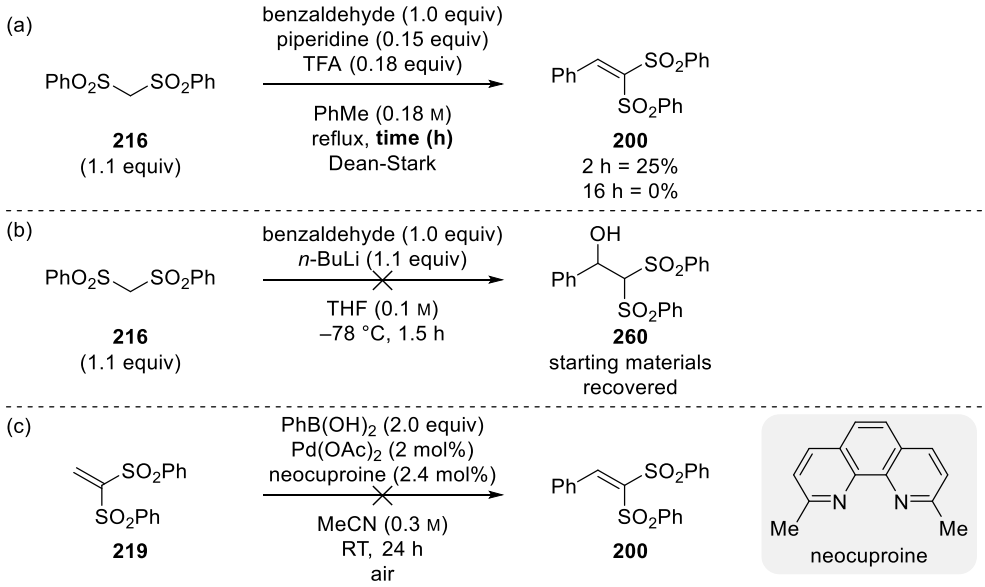


Figure 8. X-Ray crystal structures of major and minor diastereoisomers.

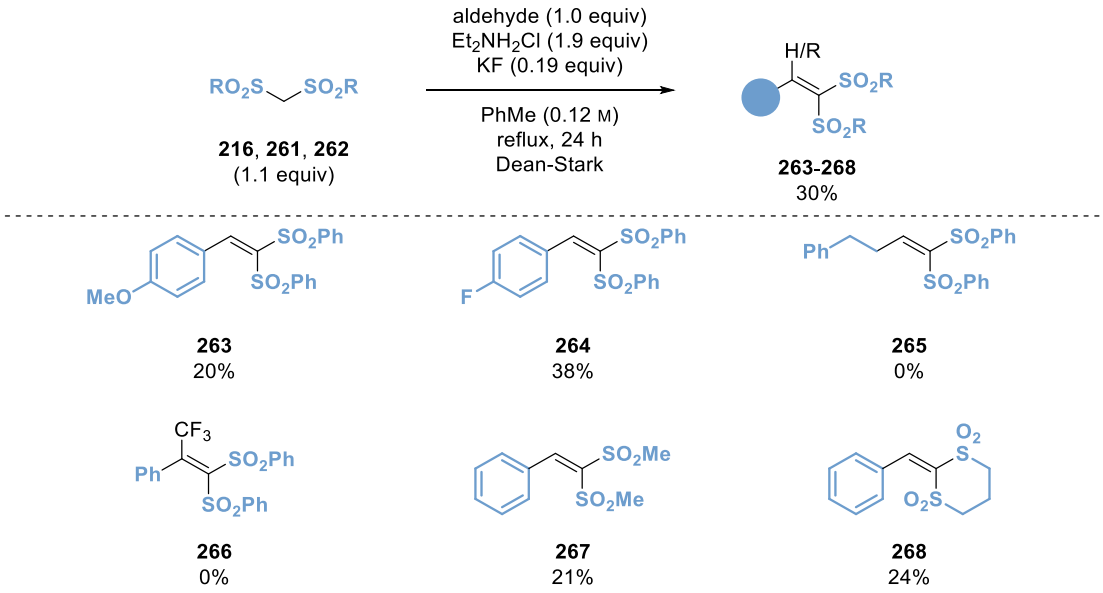
Next, attention was turned to probing the scope of the vinyl-bis sulfone component. Before proceeding, it was decided to attempt to improve the yield of the current vinyl-bis sulfone synthesis due to the low yield previously obtained in Scheme 32. Alternative conditions using piperidine and trifluoroacetic acid (TFA) - presumably via in situ iminium ion formation - were initially promising, with 25% yield in two hours. However, when the reaction time was extended, only starting materials were recovered (Scheme 37). An alternative two-step addition-elimination sequence was then attempted. Cossy and co-workers have previously reported the addition of dimethylsulfone to benzaldehyde using *n*-butyl lithium,[174] whilst Hu and co-

workers have added α-fluoro bis(phenylsulfonyl)methane to aldehydes.[175] However, treatment of bis(phenylsulfonyl)methane **216** with *n*-BuLi and benzaldehyde only resulted in the unproductive formation of a white precipitate. Following work up, only starting materials were isolated. It was proposed the white solid was the deprotonated form of the bis(phenylsulfonyl)methane **216**. Performing the reaction to reflux also failed to give any of the desired product, returning only starting material. Alternatively, based on a procedure by Larhed and co-workers who reported the addition of aryl boronic acids to vinyl sulfones,[176] palladium-catalysed addition of phenyl boronic acid to vinyl bis-sulfone **219** gave no product.



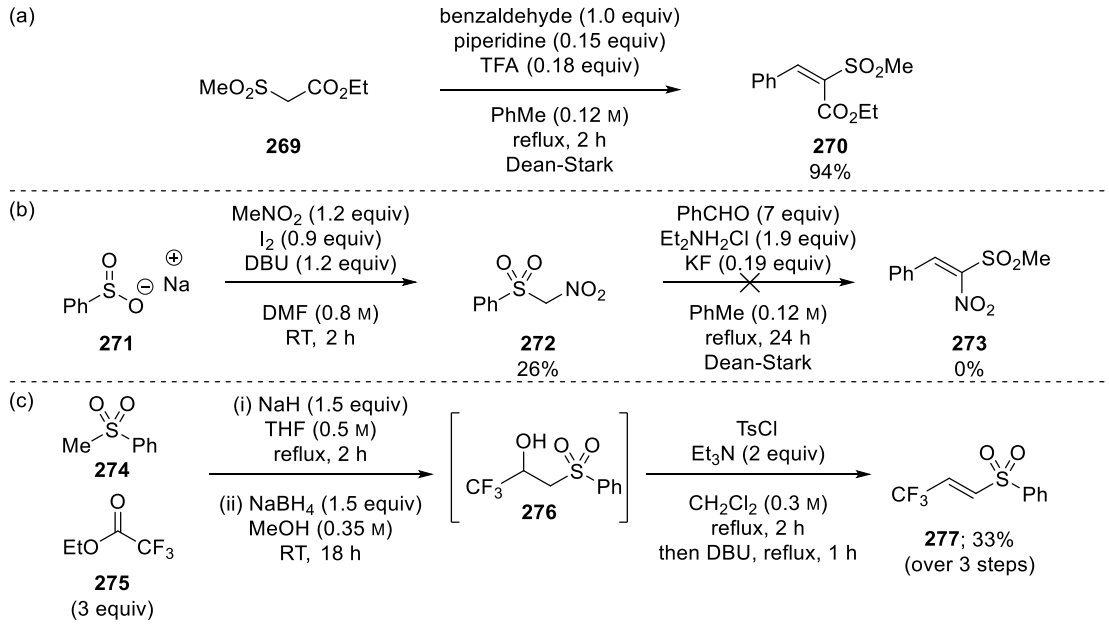
Scheme 37. Attempted alternative synthesis of vinyl bis-sulfone.

Following these efforts, the synthesis of a variety of vinyl bis-sulfones was carried out using the original conditions. 4-Methoxyphenyl vinyl bis-sulfone **263** was synthesised from 4-methoxybenzaldehyde in low yield, whilst using *para*-fluoro-benzaldehyde gave the corresponding Michael acceptor **264** in moderate yield (Scheme 38). ^{1}H NMR of the crude reaction mixture indicated that alkyl-substituted alkene **265** could be formed, however, this could not be isolated from impurities, whilst trifluoromethylated substrate **266** could not be accessed through this method from trifluoroacetophenone. Hydrogen peroxide-mediated oxidation of bis(methylthiol)methane and subsequent condensation gave methyl sulfone **267**, and the same procedure could be applied for the synthesis of sulfone **268** from dithiane.



Scheme 38. Synthesis of vinyl bis-sulfones.

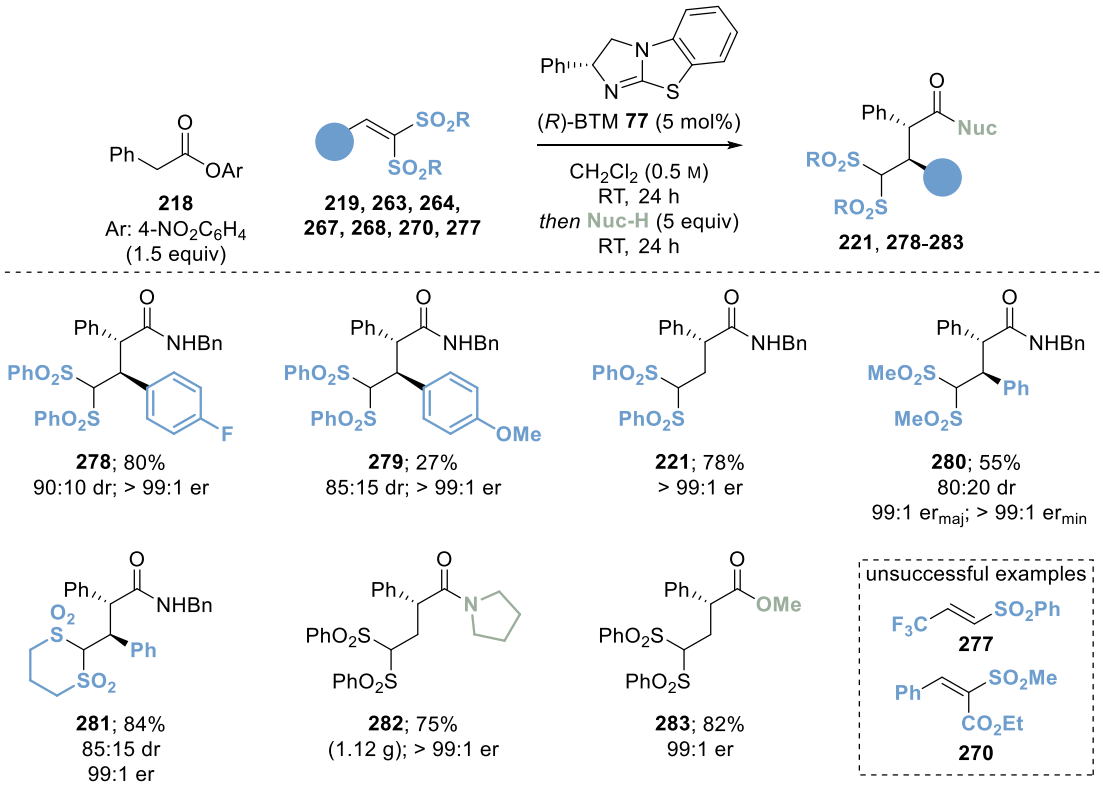
It was of interest to synthesise a range of disubstituted electrophiles bearing only one sulfone group to enable assessment of a reactivity scale. Following a procedure from Mayr and co-workers, 1,1-ester,sulfone-substituted alkene **270** was efficiently prepared as a single isomer using catalytic piperidine and TFA (Scheme 39).[177] It was hoped that 1,1-nitro,sulfone alkene **273** could also be accessed. Treatment of benzene sulfinic acid sodium salt **271** with iodine and nitromethane gave ((nitromethyl)sulfonyl)benzene **272** in low yield (26%).[178] Subjecting **272** to the condensation conditions gave no product and only starting materials remained. In addition to 1,1-disubstituted alkenes, it was proposed introduction of an electron-withdrawing group at the 2-position may allow for reaction with mono-sulfone Michael acceptors. Following a procedure by Eguchi and co-workers,[179] addition of ethyl trifluoroacetate **275** to a stirred solution of sodium hydride and (methylsulfonyl)benzene **274** gave the crude ketone. Reduction using sodium borohydride gave the corresponding alcohol **276**. Subsequent tosylation-elimination afforded trifluoromethyl-substituted vinyl sulfone **277** in 33% yield over 3 steps.



Scheme 39. Synthesis of vinyl bis-sulfones.

Having synthesised a range of electrophiles, their applicability in catalysis was tested (Scheme 40). Firstly, the effect of the β-substituent was examined: the use of an electrophile bearing a 4-fluorophenyl substituent gave amide **278** in excellent yield, dr and er. However, substitution with an electron-donating 4-methoxyphenyl gave amide **279** in lower yield. These results are in agreement with Mayr's electrophilicity scale where the 4-methoxyphenyl vinyl bis-sulfone is calculated to be less electrophilic (E = -13.9) than the parent phenyl substituted vinyl bis-sulfone (E = -12.9).[164] Whilst the electrophilicity parameter of the *para*-fluoro-vinyl bis-sulfone has not been calculated, a comparison can be drawn to data for β-nitrostyrene Michael acceptors: *para*-bromo subtituted β-nitrostyrene (E = -13.4) is more electrophilic than β-nitrostyrene (E = -13.8).[160] Using the commercially available unsubstituted bis(phenylsulfonyl)ethylene electrophile **219** provided a single enantiomer of amide **221** in high yield (78%). The scope of the electrophile was extended to alkyl sulfone groups, with methyl sulfone giving amide **280** in acceptable yield (55%). The use of a cyclic bis-sulfone allowed access to amide **281** in excellent yield, dr and er but required acetonitrile as the reaction solvent due to the insolubility of the electrophile in dichloromethane. Unfortunately, Michael acceptors bearing a single sulfone group (**270**, **277**) were unreactive, presumably due to the lower electrophilicity of these acceptors. This result is not unexpected; as discussed

in Section 2.2.2, these Michael acceptors are significantly less electrophilic (E = -24.7 for phenyl *trans*-styryl sulfone **184**).[158] To further exemplify product diversity, the addition of alternative nucleophiles at the end of the reaction was investigated. Using unsubstituted bis-sulfone **219**, addition of pyrrolidine gave tertiary amide **282** in high yield and er (75%, > 99:1 er) on a 3 mmol scale (1.12 g of product). Alternatively, addition of methanol provided methyl ester product **283** in excellent yield and er.

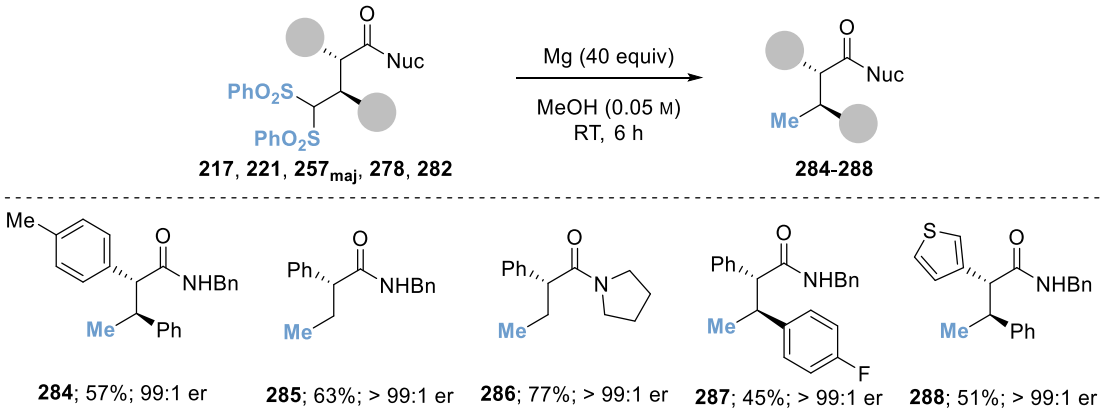


Scheme 40. Vinyl bis-sulfone and nucleophile reaction scope.

2.2.6. Product Derivatisations

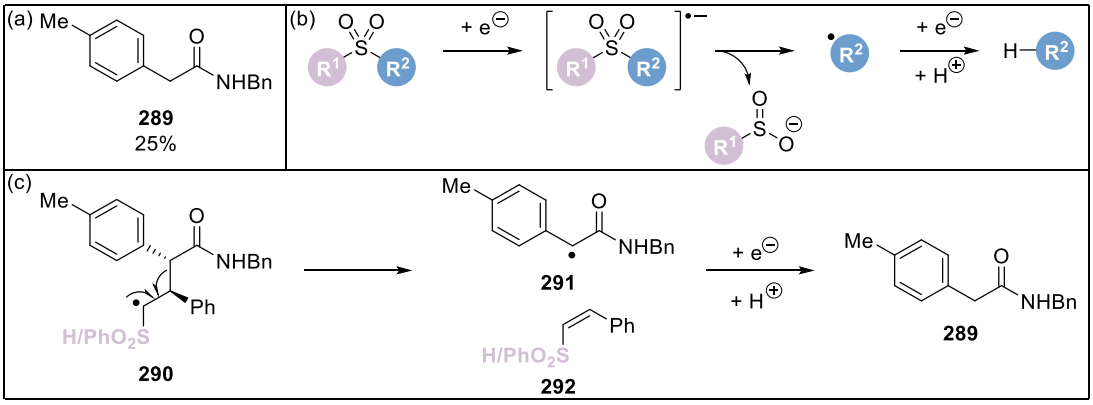
Having demonstrated the scope and limitations of this protocol, it was proposed that the sulfone functional handle in the product could be exploited to carry out further manipulations. Following a procedure developed by Williams and co-workers,[180] initial studies focused on desulfonylation using magnesium turnings in methanol at room temperature (Scheme 41). Desulfonylation of 2-tolyl-3-phenyl substituted amide gave product **284** in good yield (57%), whilst maintaining stereointegrity (> 95:5 dr, 99:1 er). Desulfonylation of pyrrolidinyl and benzyl-amides containing a single stereogenic centre was also successful, providing amides **285** and **286** in good

yield (63% and 77%). Desulfonylation of 4-fluorophenyl and thienyl amides was also successful, allowing access to single enantiomers of products **287** and **288** in moderate yield.



Scheme 41. Product derivatisation via desulfonylation.

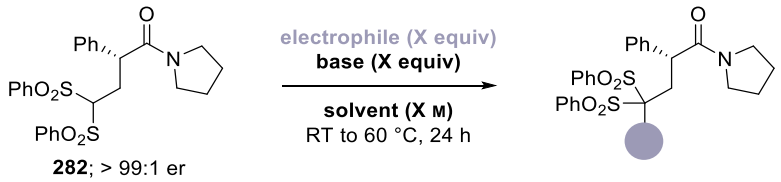
It is noted that the yields for the synthesis of amides **284**, **287** and **288** containing two stereogenic centres are lower than that for the products containing a single stereogenic centre. Indeed, in the synthesis of **284**, it was noted that 25% of amide **289** was recovered (Scheme 42a). It is the proposed the desulfonylation reaction proceeds via a single electron reduction pathway (Scheme 42b).[181] Reduction of the sulfone group to a radical anion is mediated by the magnesium/methanol mixture, although alternative conditions such as sodium amalgam can also be employed. Subsequent homolysis of the sulfur-R^2 bond to give the more stabilised radical group ($R^2 > R^1$) and the corresponding sulfinate anion. The R^2 radical can then be reduced further before protonation. In the reactions to form amides **284**, **287** and **288**, it is proposed the yield is lower due to competing styrene formation (Scheme 42c). The radical generated after desulfonylation **290** can undergo styrene formation and giving α-amide radical **291**. Subsequent reduction and protonation gives **289**, which is observed after the reaction.



Scheme 42. (a) By-product observed during desulfonylation, (b) general reaction mechanism and (c) proposed mechanism for the formation of 289.

Alternatively, it was hoped to exploit the pro-nucleophilic nature of the bis-sulfone moiety to allow further functionalisation (Table 10). Initial attempts to alkylate substrate **282** employed allyl bromide in combination with sodium hydride as base, however, low conversion to product was observed when the reaction was carried out in DMF (entry 1). Pre-stirring the substrate and base at 60 °C before the addition of the electrophile also gave low conversion to product (entry 2), whilst attempting the reaction in THF gave even poorer results (entry 3). It was noted that when sodium hydride was added to the reaction bubbles formed, indicating the release of hydrogen and therefore that deprotonation was occurring. It was decided to attempt the reaction with an alternative electrophile. Disappointingly, use of 1-iodopentane as the electrophile gave no reactivity, with starting materials returned. It was considered that the counterion of the nucleophile generated in situ could be important for the reactivity with the electrophile. However, reactions using a combination of benzyl bromide and potassium *tert*-butoxide, or benzoyl chloride and triethylamine also gave no conversion to product.

Table 10. Attempted product derivatisations.

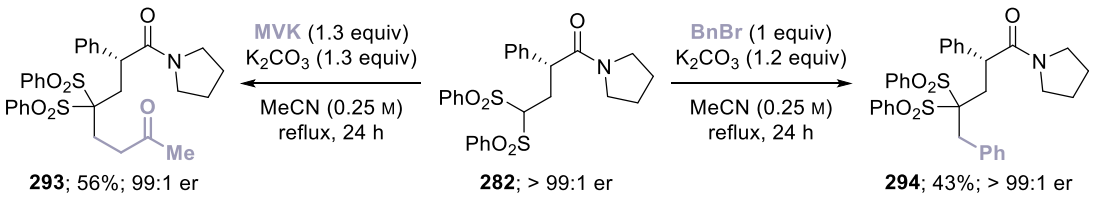


282; > 99:1 er

Entry	Electrophile (equiv)	Base (equiv)	Solvent (M)	Yield[a] (%)
1	Allyl bromide (2.0)	NaH (2.0)	DMF (0.1)	14
2[b]	Allyl bromide (2.0)	NaH (2.0)	DMF (0.1)	15
3	Allyl bromide (1.5)	NaH (1.2)	THF (0.1)	9
4	1-iodopentane (1.05)	NaH (1.2)	THF (0.3)	0
5	Benzyl bromide (1.1)	*t*-BuOK (1.5)	DMF (0.1)	0
6	Benzoyl chloride (1)	Et_3N (2.2)	$CHCl_3$ (0.2)	0

[a] Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Stirred at 60 °C for 1 h before addition of electrophile.

It was proposed the acidity of the α-amide proton and competitive deprotonation may be the problem and that use of a weaker inorganic base may enable the desired reactivity. Pleasingly, treatment of substrate **282** with methyl vinyl ketone (MVK) and potassium carbonate in acetonitrile gave chain extended amide **293** in good yield whilst maintaining enantiopurity (Scheme 43). These conditions were also utilised for alkylation with benzyl bromide to give enantiopure amide **294** in moderate yield.



293; 56%; 99:1 er

282; > 99:1 er

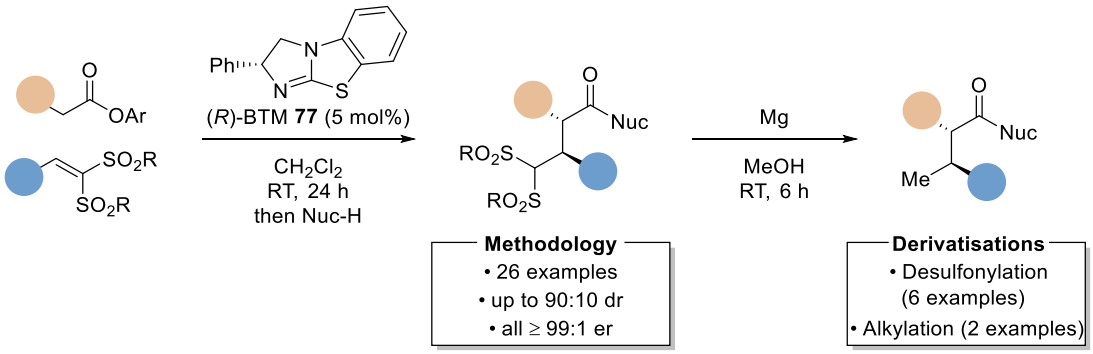
294; 43%; > 99:1 er

Scheme 43. Product derivatisation via alkylation.

2.3. Conclusions

In conclusion, a base-free and proton-neutral enantioselective Michael addition of aryl ester pronucleophiles to vinyl bis-sulfones has been developed (Scheme 44). This protocol, which can be carried out in environmentally benign solvents, allows for the formation of α-alkylated products in excellent yield and with excellent

diastereo- and enantioselectivity using low catalyst loadings (26 examples, up to 90:10 dr and ≥ 99:1 er). Notably, no auxiliary base is required for this Michael addition process, with the key role of the aryloxide to act firstly as a leaving group, then a Brønsted base, a Brønsted acid and finally a Lewis base to promote catalyst turnover. The functional products can be deprotected upon treatment with Mg in MeOH to form α-alkylated amides without loss of stereointegrity. The next section will discuss the mechanistic investigations conducted to interrogate the mechanism of this protocol.



Scheme 44. Base-free enantioselective isothiourea catalysis via C(1)-ammonium enolates exploiting aryloxides.

Chapter 3. Mechanistic Analysis of Base-Free Enantioselective Isothiourea Catalysis via C(1)-Ammonium Enolates

3.1. Introduction

Having demonstrated the reaction development and scope, further studies sought to provide mechanistic insight into this methodology through an extensive kinetic investigation. The treatment of reaction kinetics involves the study of product formation during a chemical reaction over time through experimental measurement of macroscopic parameters. This enables establishment of a relationship between concentration of reactants (and products) and the rate of reaction. Typically, kinetic analysis involves performing reactions at multiple different concentrations of a reactant to determine the order of the reaction with respect to the reactant, and therefore, give the overall order of the reaction. This provides useful mechanistic information, i.e. a first order reaction involves only one species in the rate-limiting step (step with highest energy transition state), whilst reaction inhibition can also be identified. The knowledge of a chemical transformation gained through kinetic understanding can enable chemists to control/manipulate the outcome of the reaction through judicious variation of reaction parameters. In combination with other experimental observations, potential reaction mechanisms can be proposed, verified or discounted.

Simple reaction mechanisms involving only one chemical step can be efficiently interpreted using mathematical expressions to solve for rate constants. However, complex processes involving more than one elementary step produce complex rate law equations which are difficult to analyse. These challenges are even more pronounced when a catalytic system is under investigation, where multiple catalytic species are present, which can be on or off-cycle species, and catalyst deactivation can occur. Modern analysis methods have been developed to allow facile data extraction of complex, catalytic reactions involving multiple components under standard conditions.

In 2005, Blackmond described reaction progress kinetic analysis (RPKA) as a tool to enable mechanistic investigation.[182] This protocol involves three sets of analytical

experiments: (i) "same excess", (ii) "different [catalyst]" and (iii) "different excess" followed by subsequent graphical interrogation of the data. Figure 9 shows representative examples of each of these experiments for a general catalytic reaction ($A + B \rightarrow P$). "Same excess" experiments are used to check for product inhibition and catalyst deactivation in a reaction. Multiple reactions are performed at different starting concentrations. This means that each reaction will, at some stage, have the same concentration of reaction substrate components but different concentrations of product and catalyst turnover numbers. Curves of rate against [substrate] can be plotted and if the profiles overlay no reaction inhibition is present (Figure 9a). "Different [catalyst]" experiments are employed to elucidate the order of the reaction with respect to the catalyst. Multiple reactions are carried out using different concentrations of catalyst and plots of rate/$[cat]_T^{\gamma}$ against [substrate] are constructed. Variation of γ will allow the plots to overlay when γ is the correct order in catalyst (Figure 9b). For this analysis to be accurate the catalyst concentration is required to remain approximately constant throughout the reaction and not undergo deactivation. "Different excess" analysis involves performing multiple reactions with varying concentration of one component, whilst the concentration of all other reactants remains the same, enabling the reaction order with respect to the component to be determined. Plots of rate/$[B]^{\beta}$ against [A] are constructed, with the profiles overlaying when β is set to the correct reaction order (Figure 9c). Overall, a wealth of information can be gained efficiently using RPKA. However, this method requires rate data for the y-axis of plots to extract the information on reaction orders. This can either be obtained directly by isothermal calorimetry (ITC) which measures instantaneous heat flow, a technique not suitable for many reactions. Alternatively, rate data can be obtained by differentiating the experimental temporal concentration versus time data collected using an appropriate technique such as FTIR spectroscopy. Thus, this method requires manipulation of each data point of a reaction profile. Since many measurements are normally required in order to collect dense, accurate data, errors can accumulate through this data processing method.

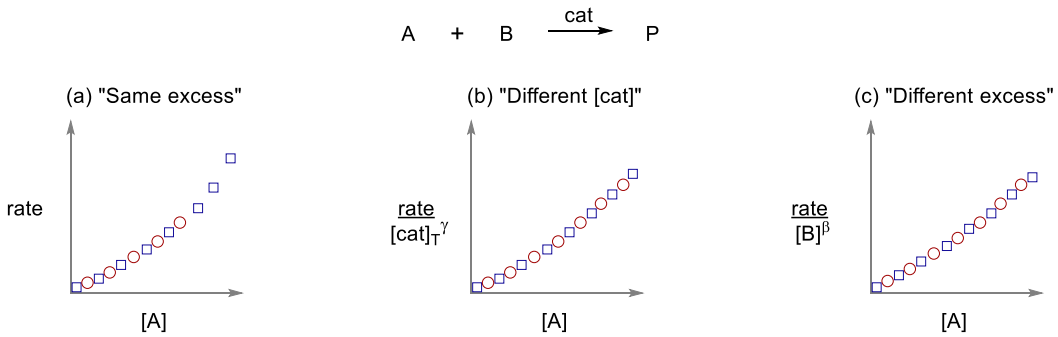


Figure 9. Reaction progress kinetic analysis.

More recently, Burés reported the complementary variable time normalisation analysis (VTNA) method for the elucidation of reaction orders.[183,184] This protocol directly utilises reaction concentration data, which is more readily obtained from analytical techniques such as from NMR, IR, UV, HPLC, GC. The method is most effective if the concentration of every reaction component (including catalyst) can be assessed at each time point of the reaction profile. The process normalises the time axis of reaction profile traces using equation 2, where α, β and γ are arbitrarily set integers corresponding to the reaction order of each component (Figure 10). Equation 2 is used if the catalyst concentration remains constant over a reaction time course. If catalyst concentration changes over the reaction course, then it can be treated in the same way as reagents A and B. Through performing multiple different experiments whilst varying the starting concentration of only one of the reaction components at a time, reaction profiles can be constructed. Time normalisation of the x-axis will give overlay of all the reaction curves when α, β and γ are set to the correct order. The slope of the line corresponds to k_{obs} of the reaction. This visual analysis technique allows facile elucidation of reaction orders of any component in a reaction mixture.

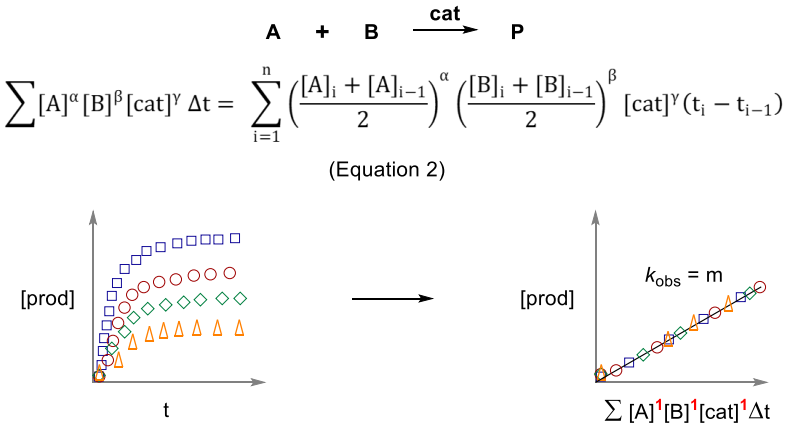


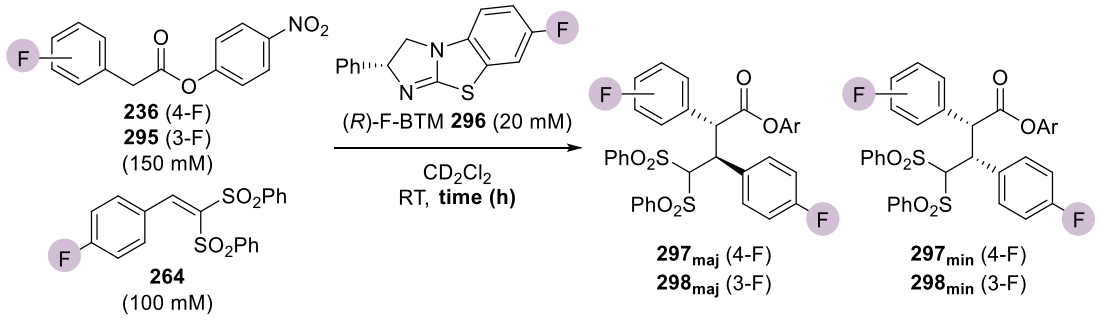
Figure 10. Variable time normalisation analysis.

3.2. Results and Discussion

3.2.1. Developing a Suitable System for Reaction Monitoring

Initial studies looked to develop a system that would enable quantitative reaction monitoring via in situ $^{19}F\{^1H\}$ NMR spectroscopy. Ideally, the reaction would reach high conversion (≥ 80%) within ~5 h. This would mean the reaction is slow enough to be able to obtain reliable data during the early stages of the reaction, but fast enough to reach high conversion in an appropriate time period. Using ^{19}F-labelled ester **236**, ^{19}F-labelled electrophile **264** and ^{19}F-BTM **296** in CD_2Cl_2 under model reaction conditions gave only 56% conversion to products **297**$_{maj}$ and **297**$_{min}$ in 21 h (Table 11, entry 1). Increasing the catalyst loading to 20 mol% also gave inadequate conversion, with 49% product observed in 7 h (entry 2). Using the more electron-withdrawing 3-fluoro substituted ester **295** (σ_m = +0.34 vs σ_p = +0.05) gave slightly improved conversion, with product **298** formed in 61% in 8 h.

Table 11. Optimisation.



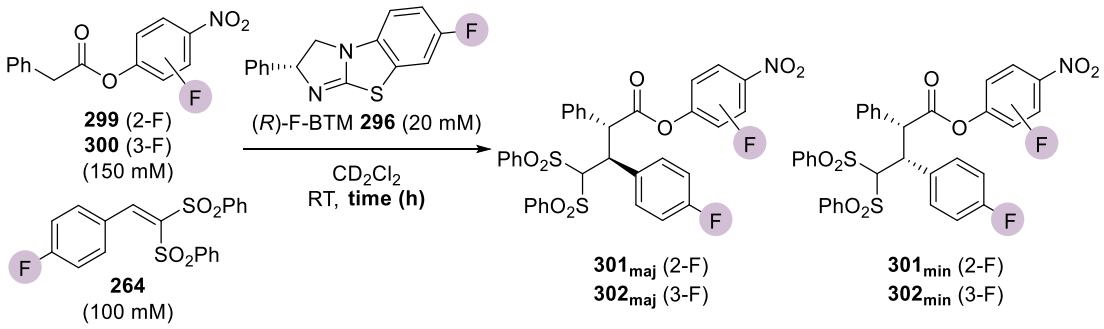
Entry	Ester	Time (h)	Conversion to Product[a]
1[b]	4-F	21	56
2	4-F	7	49
3	3-F	8	61

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis. [b] 5 mM catalyst.

It was decided to investigate the use of an alternative ester with the fluorine tag on the aryloxide rather than the aryl acetic component in an attempt to find a reaction with higher conversion to product in the desired timeframe. As discussed in Section 2.2.4, subtle variation of the electronic and steric properties of the aryloxide can have a significant effect on its ability to fulfil the multiple roles within the catalytic cycle. Although substitution of an electronegative fluorine may be expected to increase the rate of catalyst acylation and protonation (as the corresponding phenol), it was considered this may also slow down the deprotonation and catalyst turnover steps. The small size of a fluorine atom would be unlikely to have a significant effect on the ability of the aryloxide to act as a Lewis base. Substitution on the aryloxide component would advantageously allow monitoring of the concentration of the free aryloxide/phenol over the reaction course. Pleasingly, the reaction of 2-fluoro-4-nitrophenol ester **299** gave 74% conversion to product in substantially shorter reaction time- only 2 hours (Table 12, entry 1). In addition, 3-fluoro-4-nitrophenol ester **299** also demonstrated appropriate conversion to product (entry 2). Analysis of the ^{19}F NMR peaks of each reaction revealed the substrate and product peaks derived

from the 2-fluoro-4-nitrophenol ester **301** were better separated in the NMR spectrum and would be the preferred substrate for analysis.

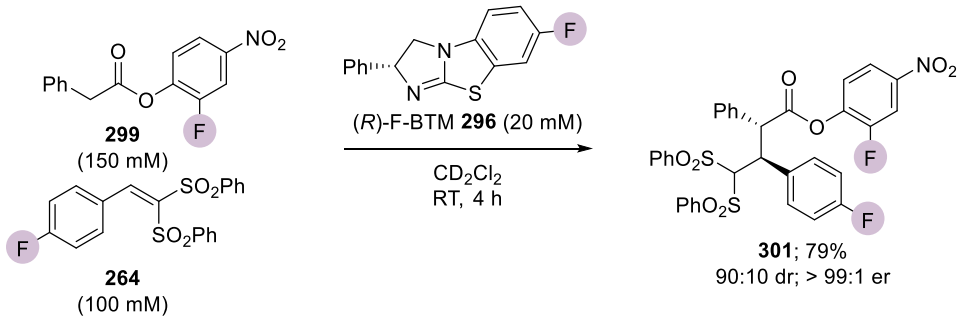
Table 12. Optimisation.



Entry	Ester	Time (h)	Conversion to Product[a]
1	2-F	2	74
2	3-F	2	78

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis.

A batch reaction of 2-fluoro ester **299** was carried out to confirm the reaction proceeded catalytically with similar stereoselectivity to the model system (Scheme 45). Encouragingly, product **301** was formed in 79% yield with excellent diastereo- and enantioselectivity (90:10 dr and > 99:1 er).



Scheme 45. Batch reaction.

Next, attention turned to ^{19}F{^{1}H} NMR spectroscopy for reaction monitoring: firstly, the use of a suitable internal standard was investigated. It was decided a compound containing an Ar(C)-F bond would be most appropriate for comparison to each of the reaction components. 1,3-Difluorobenzene **303** was found to be most applicable, chemically inert standard which had no effect on the reaction time by monitoring

through ^{1}H NMR spectroscopy. In the $^{19}F\{^{1}H\}$ NMR spectrum, the chemical shift of standard **303** did not overlay with any of the reaction components, however, it was noticed that the integration values of vinyl-bis sulfone **264** and 1,3-difluorobenzene **303** were significantly lower than expected when compared to ester **299**, indicating these signals did not have sufficient delay to fully relax under the standard NMR parameters. Therefore, the $^{19}F\{^{1}H\}$ NMR parameters were optimised to allow full relaxation of all fluorine nuclei under observation. The number of scans (ns) and relaxation delay (d1) were systematically varied (Figure 11). The standard parameters, ns = 64 and d1 = 1 s, gave integration values of 0.72 and 0.35 for the vinyl bis-sulfone **264** and standard **303**, respectively normalised against ester **299** (expected values 1.50 and 1.0). Increasing the delay time to 10 s gave the integral of sulfone **264** to almost the required value (0.95), although the internal standard integral remained significantly off. By increasing d1 from 10 through to 60 s, it was found that the integral of the standard remained approximately constant for delay times of 30 s and above. It was decided to minimise the number of scans per measurement (ns = 2) as this would give a more accurate integral at a specific time period. The optimal $^{19}F\{^{1}H\}$ NMR parameters were therefore chosen to be d1 = 30 s and ns = 2. In an additional experiment, these conditions were found to be appropriate for the integrals of catalyst **296** by comparison to the internal standard. Finally, the independent stability of each of the components in deuterated dichloromethane was investigated; ester **299**, vinyl bis-sulfone **264** and catalyst **296** were stored in separate stock solutions and monitored by ^{1}H and $^{19}F\{^{1}H\}$ NMR. Ester **299** was found to be stable for 3 days before small amounts of hydrolysis was observed, whilst vinyl bis-sulfone **264** and catalyst **296** were both stable for 14 days without degradation. No reaction occurred when both ester **299** and vinyl bis-sulfone **264** were mixed in solution, meaning each could be combined before addition of the catalyst to start the reaction.

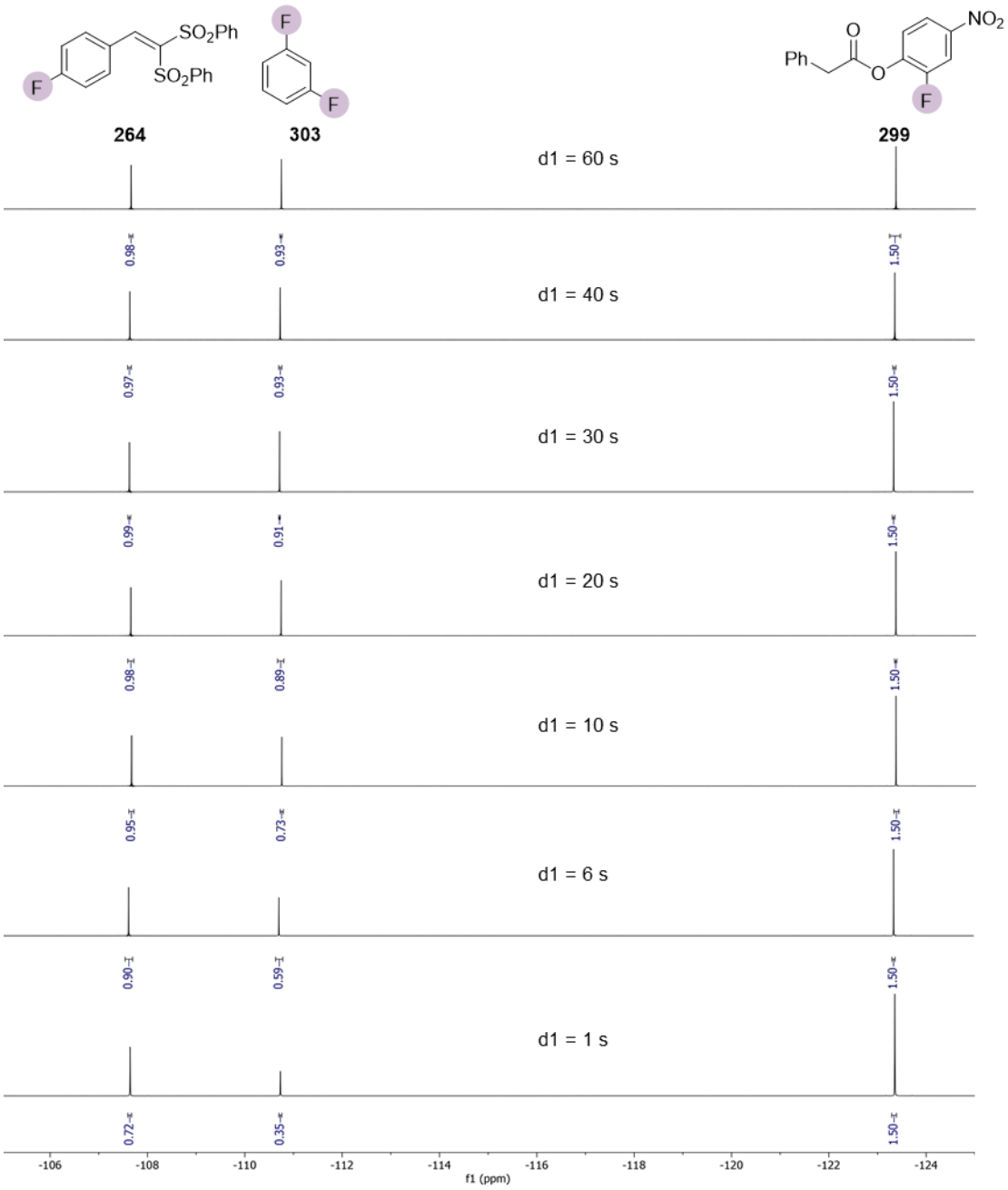


Figure 11. Optimisation of $^{19}F\{^{1}H\}$ NMR parameters.

3.2.2. Quantitative $^{19}F\{^{1}H\}$ NMR Reaction Monitoring

With a suitable system in place, primary studies set out to investigate the reaction speciation with the goal of identifying the catalyst resting state and any potential reaction intermediates. The typical overlay of reaction spectra is shown in Figure 12 and the benefits of using $^{19}F\{^{1}H\}$ NMR are clearly noticeable where only one peak per component (two peaks per product) is observed. Each component can be clearly identified: ^{19}F-labelled electrophile **264** (δ_F −107.64 ppm), 1,3-difluorobenzene (δ_F −110.73 ppm) **303**, ^{19}F-BTM **296** (δ_F −122.26 ppm) and ^{19}F-labelled ester **299** (δ_F −123.36 ppm). During the course of the reaction, both diastereoisomeric reaction products

301$_{maj}$ and **301**$_{min}$, each containing two distinct ^{19}F-environments, were observed and were distinguishable from the starting components.

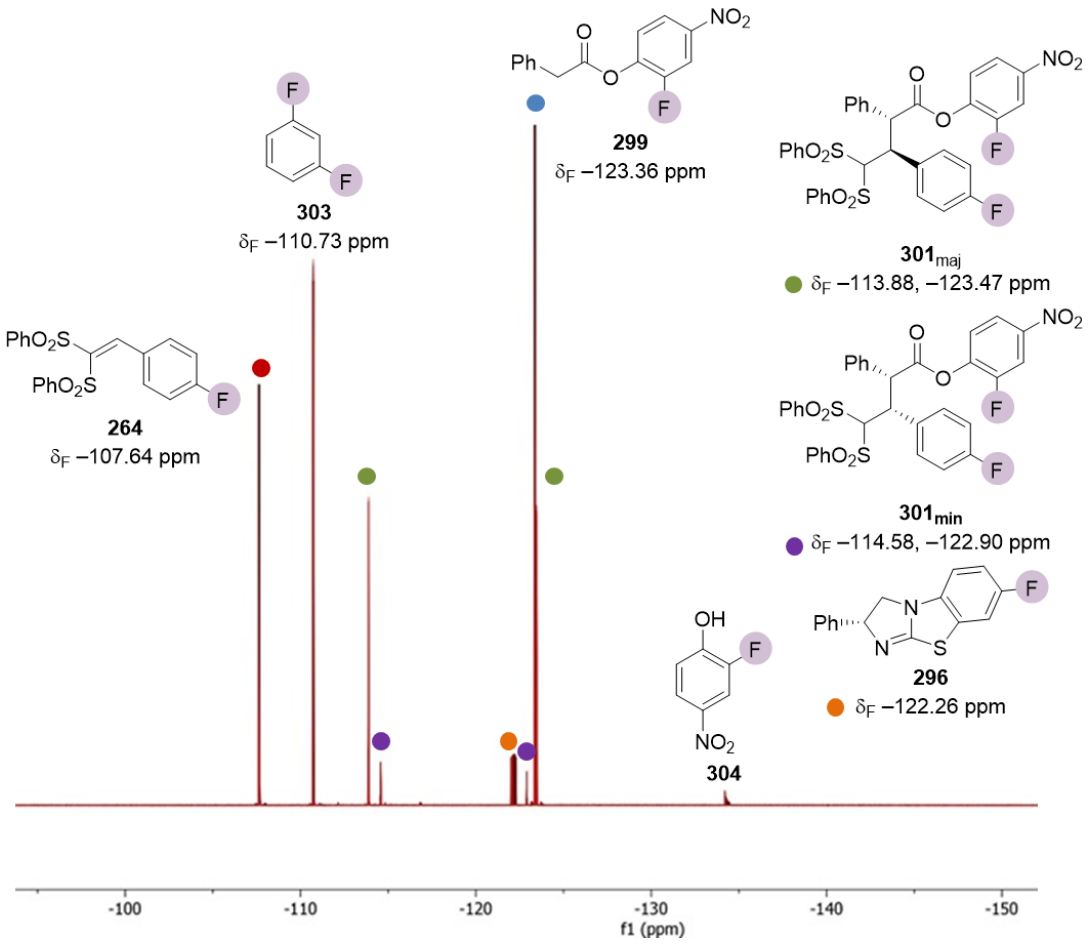


Figure 12. Superimposed reaction spectra for standard reaction conditions.

Monitoring the reaction over time revealed the ^{19}F chemical shift of ^{19}F-BTM **296** underwent a downfield shift (δ_F −122.26 to δ_F −121.99 ppm) during the reaction, indicative of partial protonation, and hence deactivation, of the catalyst (Figure 13). To account for this observation, ^{19}F-BTM·HCl **306** was synthesised as a standard (δ_F −115.64 ppm), allowing the concentration of free catalyst (18-16 mM) to be calculated as a function of δ_F (Equation 3, Figure 14).[185] These studies are consistent with the dominant catalyst resting state being the free catalyst throughout the reaction protocol. It is proposed that slow partial hydrolysis of ester **299** to phenylacetic acid and 2-fluoro-4-nitrophenol **304** during the reaction could be the source of catalyst protonation. Consistent with this hypothesis, a small quantity of 2-fluoro-4-nitrophenol was observed to form over the reaction course (< 5%, Figure 12).

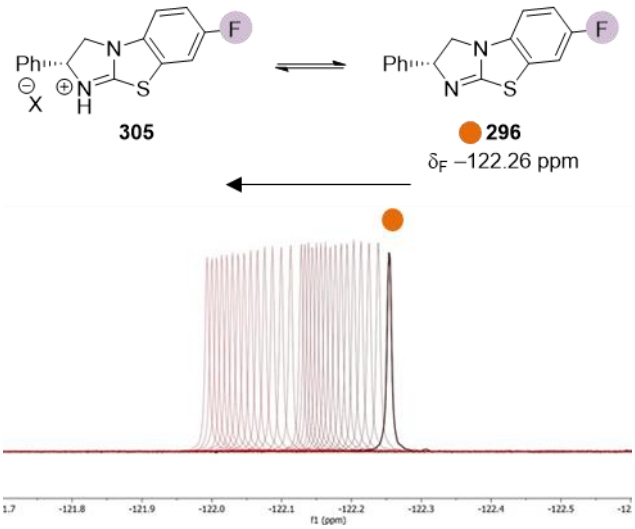
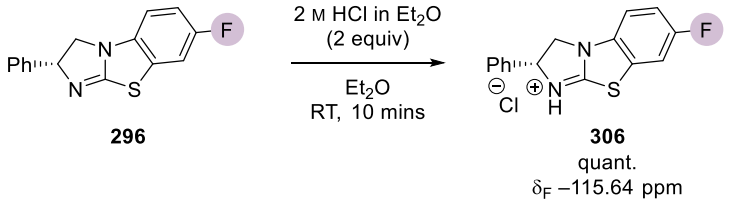


Figure 13. Catalyst protonation.



(Equation 3) $$[cat]_{free} = [cat]_{measured} \; x \; \frac{\delta_{measured} - \delta_{protonated}}{\delta_{free} - \delta_{protonated}}$$

Figure 14. Synthesis of protonated (*R*)-F-BTM and calculation of free catalyst concentration.

Having quantified each component, the temporal data can be used to plot the reaction profile (Figure 15). It is observed that concurrent consumption of ester **299** and vinyl bis-sulfone **264** is accompanied by the simultaneous formation of the major and minor diastereoisomers of product **301**. The diastereomeric ratio remained approximately constant over the reaction course; this is further evidence that the diastereoselectivity is kinetically derived. It is noted the concentration of catalyst remains almost constant, with only a minimal amount of deactivation through protonation occurring over the reaction course. The monitored reaction was repeated in triplicate to ensure this data was reliable and consistent before commencing detailed studies.

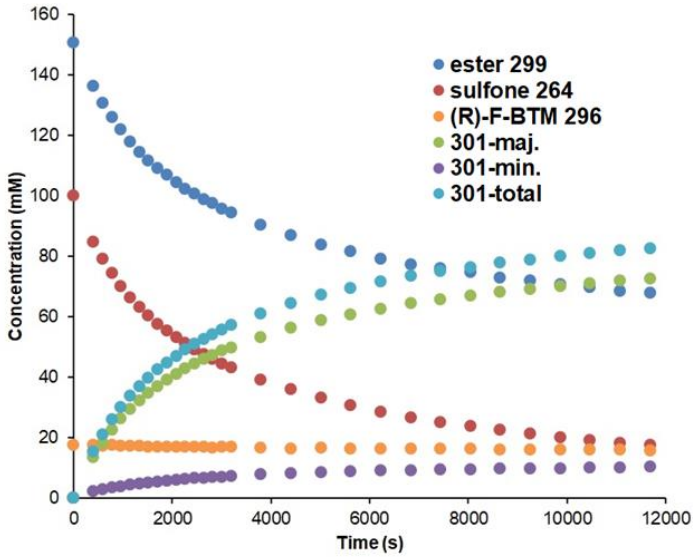
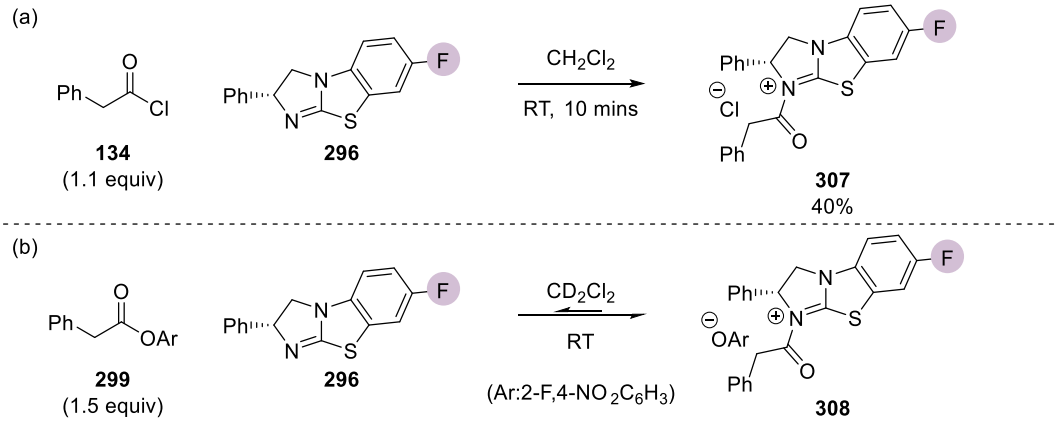


Figure 15. Reaction profile.

3.2.3. Identification of Catalytic Intermediates

Two unknown peaks A (δ_F approx. −111.36 ppm, 0.24-0.38 mM) and B (δ_F −112.14 ppm, 0.16-0.84 mM) were observed during the analysis. It was proposed these could be potential pre- and post-Michael addition acyl ammonium intermediates. In an attempt to identify these, an acyl ammonium salt of the starting ester **307** was synthesised in moderate yield through reaction of (*R*)-F-BTM **296** and phenyl acetyl chloride **134** (δ_F −111.52 ppm) (Scheme 46a). To account for the difference in counterion (chloride in this case), reaction of (*R*)-F-BTM **296** and *para*-nitrophenyl ester **299** enabled observation of a new signal, which was assumed to be the corresponding 2-fluoro-4-nitrophenoxide (δ_F −111.70 ppm) counterion **308**, with the observed signal corresponding to the fluorine tag on the isothiouronium core (Scheme 46b).



Scheme 46. Synthesis of acyl ammoniums.

The isothiouronium ^{19}F chemical shifts of chloride (δ_F −111.52 ppm) **307** and 2-fluoro-4-nitrophenoxide (δ_F −111.70 ppm) **308** salts were then compared to the reaction mixture (Figure 16). However, neither corresponded to unknown A or unknown B. On closer inspection, peak A underwent a downfield shift (δ_F −111.45 to −111.12 ppm) over the course of the reaction and concentration increased gradually (0.24-0.38 mM). This gradual downfield shift is most consistent with protonation over the reaction course. Potential structures that could undergo drift of chemical shift are the catalyst or aryloxide, but both had already been identified in the reaction mixture. Therefore, a reasonable proposal for the identity of A could not be provided.

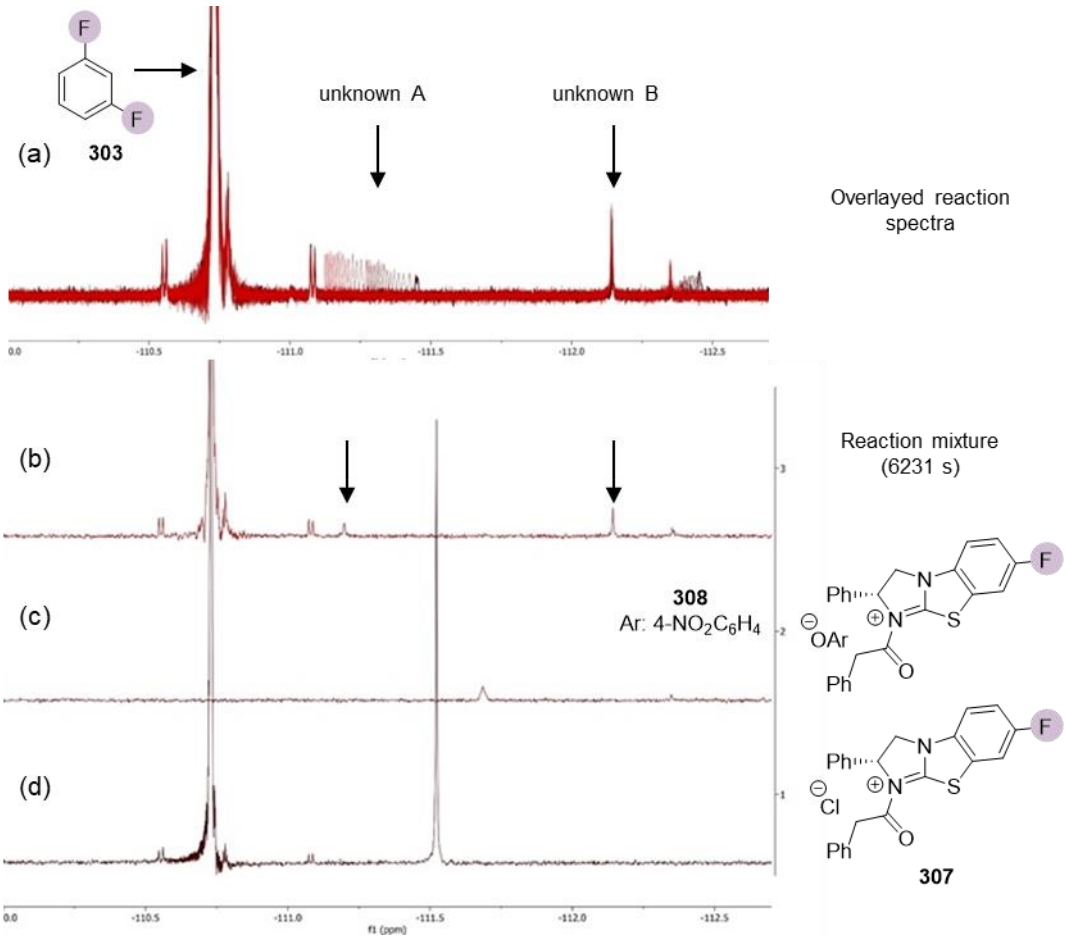
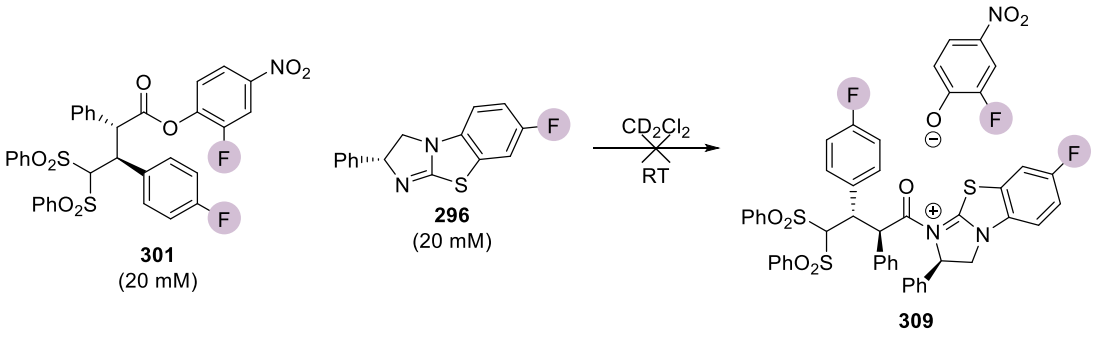


Figure 16. Attempted identification of reaction intermediates.

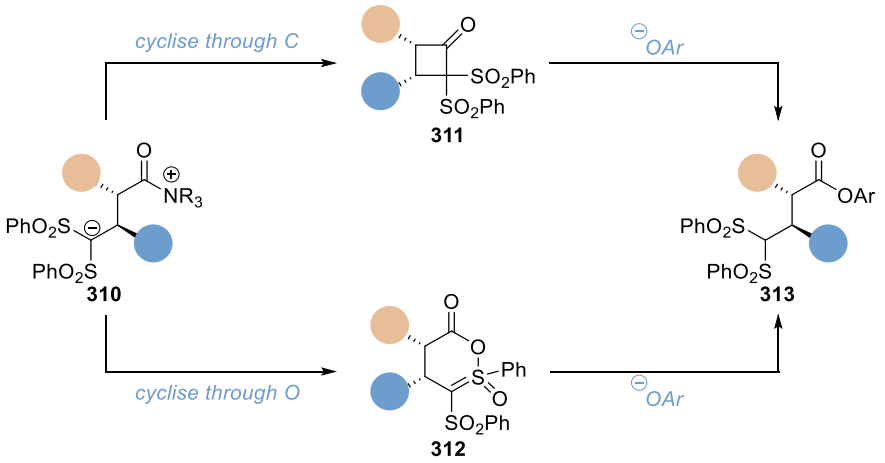
Unknown peak B increased in concentration over the course of the reaction (0.16-0.84 mM) and its chemical shift remained approximately constant. Peak B could potentially be a post-Michael addition acyl ammonium species. Formation of this intermediate in isolation was attempted by addition of catalyst to the product, but observation of the mixture by ^1H NMR showed no catalyst acylation (Scheme 47).

This is most likely a consequence of catalyst turnover being irreversible in the catalytic cycle, with nucleophilic addition of catalyst **296** to product **301** inhibited by the α-substitution present in the product. This observation is consistent with previous work with α-substituted aryl esters in which the catalyst turnover step was also found to be irreversible.[105]



Scheme 47. Attempted observation of the post-Michael addition acyl ammonium.

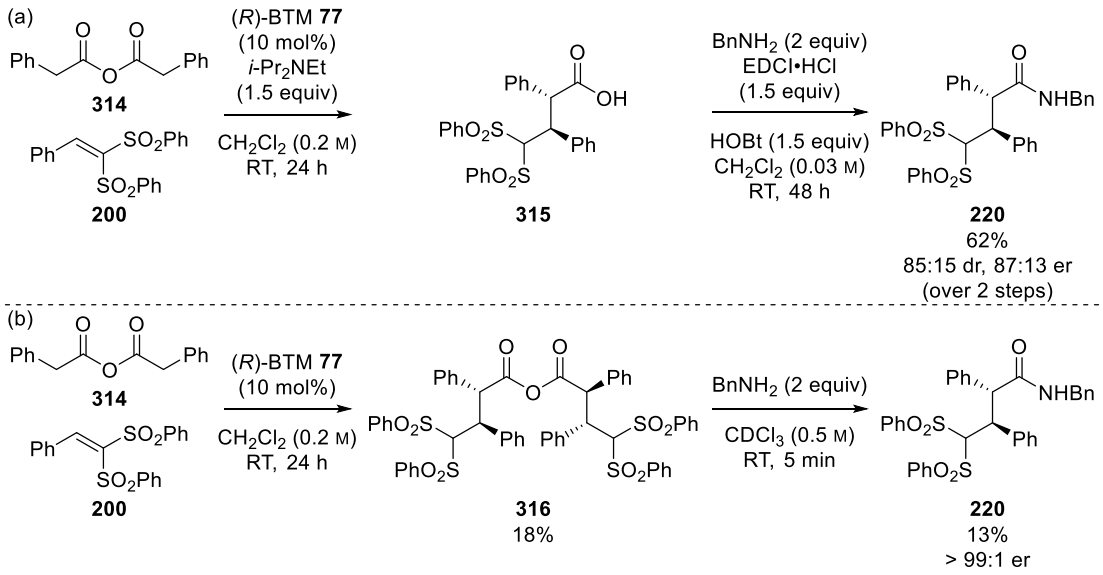
Whilst no significant quantities of other intermediates were detected during the analysis of this reaction, an alternative intramolecular catalyst turnover event to form a reactive, short-lived intermediate, which is subsequently intercepted by the aryloxide to form the product, cannot be ruled out. Such mechanistic alternatives (Scheme 48) could involve cyclisation through the carbanion of intermediate **310** to give cyclobutanone **311**. Alternatively, cyclisation through the sulfone oxygen would generate a six-membered ring species **312**. The aryloxide could ring open either intermediate to deliver product **313**. Indeed, cyclobutanones



Scheme 48. Potential alternative catalyst turnover intermediates and pathways.

have been observed as key intermediates in secondary amine-catalysed Michael addition of enamines to nitrostyrene Michael acceptors.[186]

To probe this hypothesis, it was proposed a reaction using an anhydride ammonium enolate precursor may allow one of the intermediates to be isolated as there are no examples of carboxylate-promoted catalyst turnover in isothiourea catalysis via C(1)-ammonium enolates. To this end, reaction of homoanhydride **314** with vinyl bis-sulfone **200** was carried out in the presence of Hünig's base (Scheme 17). Interestingly, following column chromatographic purification using 50% methanol in ethyl acetate, carboxylic acid product **315** was isolated. However, acid **315** was only partially soluble in most organic solvents and excess solvent impurities could not be removed. Consequently, EDCI-mediated amide coupling with benzylamine afforded the benzyl amide **220** in 62% over two steps with high levels of stereoselectivity. To further investigate this, the reaction of homoanhydride **314** and vinyl bis-sulfone **200** was undertaken in the absence of auxiliary base, which led to approximately 60% conversion of both starting materials. Purification using less polar conditions (70% ethyl acetate in petrol) indicated a single product from the reaction that was not the carboxylic acid. ^{1}H NMR indicated the presence of three aliphatic protons and multiple aromatic signals, but the structure was not conclusively elucidated until X-ray analysis was performed. To our surprise, the isolated product was identified as C_2-symmetric homoanhydride **316** (Figure 17). It is proposed if the mixed anhydride of the product is formed this may be more susceptible to hydrolysis, or that the post-Michael addition acyl ammonium intermediate may be long lived and may be hydrolysed. Treatment of **316** with benzylamine gave benzyl amide **220** in 13% yield with excellent enantioselectivity (> 99:1 er).



Scheme 49. Reaction using homoanhydride with no base.

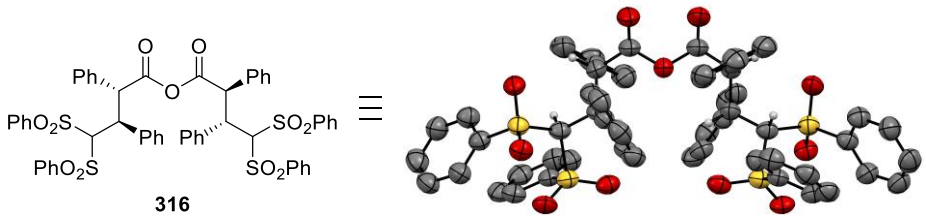
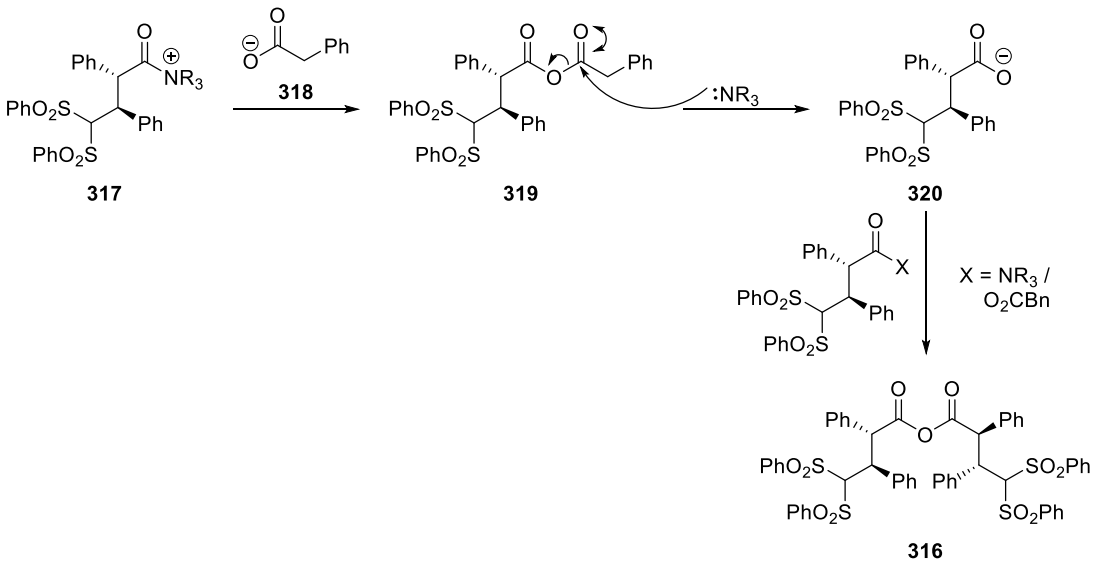


Figure 17. X-Ray crystal structure of homoanhydride Michael addition product.

The formation of homoanhydride **316** is tentatively proposed to proceed via carboxylate mediated catalyst turnover of post-Michael addition acyl ammonium **317** to give mixed anhydride product **319** (Scheme 50). At this stage, regioselective *N*-acylation of the isothiourea at the least hindered side of the anhydride could occur, giving carboxylate **320** which could then add to an equivalent of acyl ammonium **317** or mixed anhydride **319**, forming product **316**. It is recognised that the first step could also involve the addition of the carboxylic anion **318** to one of the proposed reactive intermediates proposed in Scheme 48, such as cyclobutanone **311**. It is postulated that this is the first evidence of carboxylate mediated intermolecular catalyst turnover in isothiourea catalysis via C(1)-ammonium enolates.

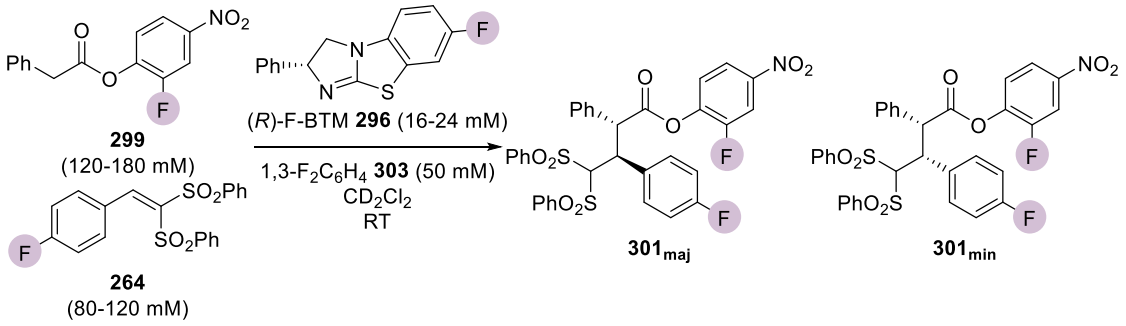


Scheme 50. Proposed mechanism for the formation of the homoanhydride product.

3.2.4. Kinetic Analysis

Having established a reliable method for determining the temporal concentration of the reaction components, information concerning their reaction orders was sought. Kinetic analysis was carried out using the Burés' variable time normalisation analysis (VTNA) protocol described earlier.[183] Seven different reactions, each with varying concentrations (± 20%) of ester **299** (120-180 mM), electrophile **264** (80-120 mM) and catalyst ^{19}F-**296** (16-24 mM) were performed (Table 13). The procedure for each experiment used stock solutions and involved addition of ester **299**, vinyl bis-sulfone **264**, 1,3-difluorobenzene **303** and CD_2Cl_2 to an oven dried NMR tube, which was loaded into an NMR spectrometer at room temperature. The sample was locked to CD_2Cl_2, shimmed and an initial $^{19}F\{^1H\}$ spectrum acquired to find the initial concentrations of the components. The sample was removed from the spectrometer and (*R*)-F-BTM **296** was added to start the reaction and this time was noted. The sample was returned to the NMR spectrometer, locked to CD_2Cl_2 and shimmed before the kinetics loop was initiated. Each kinetics loop involved 15 measurements (1 every 3 mins) then 15 subsequent measurements (1 every 10 mins).

Table 13. Variable time normalisation analysis.



Entry	299 (mM)	264 (mM)	296 (mM)
1	150	100	20
2	**180**	100	20
3	150	**120**	20
4	150	100	**24**
5	**120**	100	20
6	150	**80**	20
7	150	100	**16**

Table 14 shows an example of the concentration data extracted from the standard reaction conditions for the first ten time points using ester **299** [150 mM], vinyl bis-sulfone **264** [100 mM] and catalyst **296** [20 mM]. The amount of free catalyst at each time point was calculated using equation 3. The data was then processed using equation 4 (Table 15).

Table 14. Concentration data of reaction ester **299** [150 mM], vinyl bis-sulfone **264** [100 mM], catalyst **296** [20 mM].

Time (s)	[**299**]	[**264**]	[**301**$_{maj}$]	[**301**$_{min}$]	[**301**$_{total}$]	[**296**]	**296** δ_F	[**296**]$_{free}$
0	150.57	100.00	0.00	0.00	0.00	-	-	-
408	136.13	84.56	13.31	2.13	15.44	17.56	−122.25	17.56
594	130.67	79.05	18.17	2.78	20.95	17.34	−122.24	17.29
780	125.81	74.20	22.38	3.42	25.80	17.46	−122.23	17.38
967	121.71	70.03	26.09	3.88	29.97	17.23	−122.21	17.13
1153	117.65	66.32	29.31	4.37	33.68	17.36	−122.20	17.22
1339	114.49	63.15	32.11	4.74	36.85	17.25	−122.19	17.09
1525	111.65	60.24	34.64	5.13	39.76	17.11	−122.19	16.92
1711	108.91	57.60	36.95	5.45	42.40	17.22	−122.18	17.01
1898	106.70	55.19	39.08	5.73	44.81	17.09	−122.17	16.87

Visual analysis of the data was achieved by plotting the temporal concentration of product **301** (sum of both diastereoisomers) against a time normalised axis of $\sum$[**299**]$^{\alpha}$ [**264**]$^{\beta}$ [**296**]$^{\gamma}$ Δt. This assumes the same rate-limiting step for formation of both diastereoisomers. Subsequent variation of α, β and γ at integer and half-integer values from 0 to 2 was carried out to achieve best overlay. To exemplify, graphs of [**301**] against $\sum$[**299**]$^{\alpha}$ Δt are shown in Figure 18. It can be clearly seen that the profiles overlap when α = 1, indicating the reaction is first order with respect to ester **299**.

Table 15. Processed data of reaction ester **299** [150 mM], vinyl bis-sulfone **264** [100 mM], catalyst **296** [20 mM].

(Equation 4)

$$\sum_{i=i}^{n}\left(\frac{[\mathbf{299}]_i + [\mathbf{299}]_{i-1}}{2}\right)^{\alpha}\left(\frac{[\mathbf{264}]_i + [\mathbf{264}]_{i-1}}{2}\right)^{\beta}\left(\frac{[\mathbf{296}]_i + [\mathbf{296}]_{i-1}}{2}\right)^{\gamma}(t_i - t_{i-1})$$

Time (s)	[299]	[264]	[301$_{total}$]	[296]$_{free}$	$\sum$[299]$^{\alpha}$[264]$^{\beta}$[296]$^{\gamma}\Delta$t
0	150.57	100.00	0.00	17.56	-
408	136.13	84.56	15.44	17.56	94770484.26
594	130.67	79.05	20.95	17.29	130142014.56
780	125.81	74.20	25.80	17.38	161828918.32
967	121.71	70.03	29.97	17.13	190623611.40
1153	117.65	66.32	33.68	17.22	216687347.92
1339	114.49	63.15	36.85	17.09	240665962.16
1525	111.65	60.24	39.76	16.92	262733196.06
1711	108.91	57.60	42.40	17.01	283242185.57
1898	106.70	55.19	44.81	16.87	302502224.92

$\alpha = 1$, $\beta = 1$, $\gamma = 1$

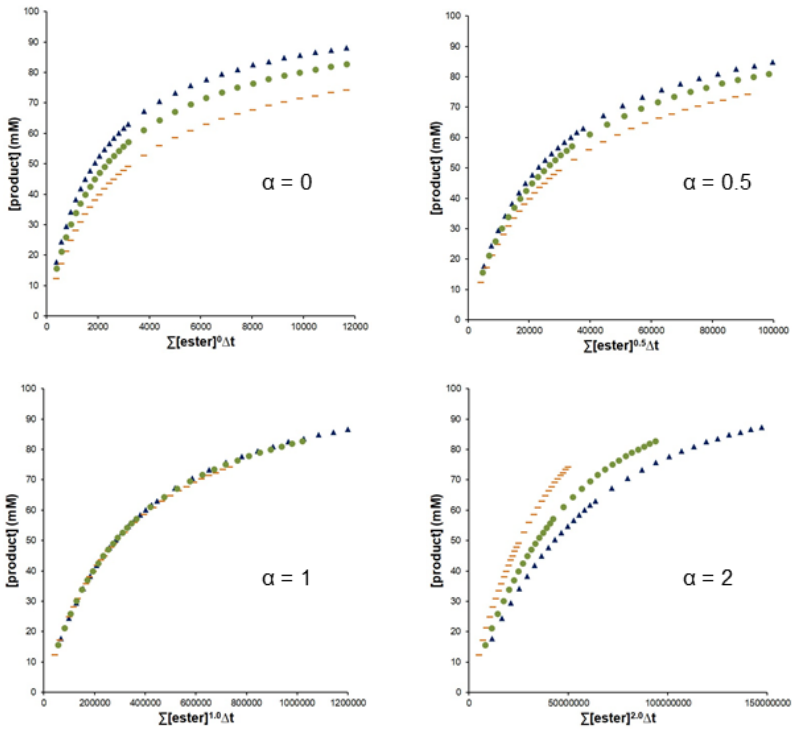


Figure 18. Variation of α = 0, 0.5, 1, 2 for the ester component.

The same procedure was applied for vinyl bis-sulfone **264** and (*R*)-F-BTM **296**; variation of β and γ gave best overlay when both β and γ = 1. The combined profiles are shown in Figure 19 where all seven plots overlay.

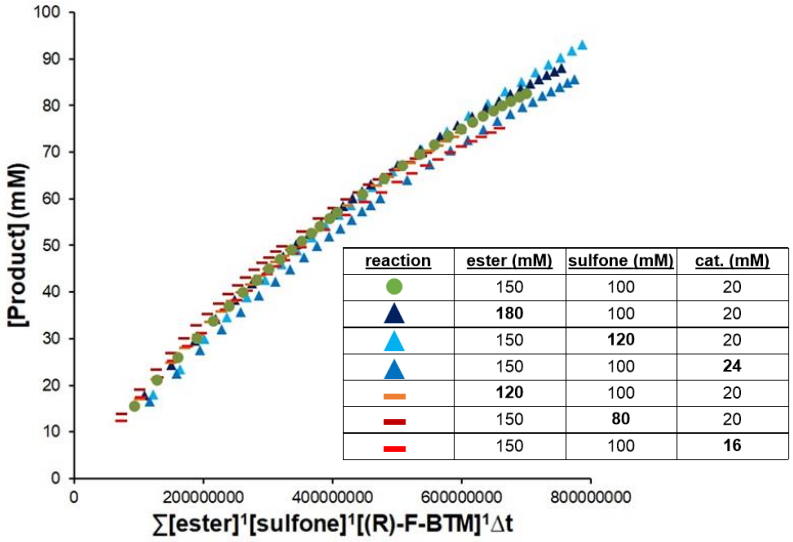


Figure 19. Variable time normalisation analysis, $\alpha = 1$, $\beta = 1$, and $\gamma = 1$.

3.2.5. Product Inhibition

Although reasonable overlay had been achieved, the observed curvature in Figure 19 indicates an additional variable, which has an effect of reducing the reaction rate over time, remained unaccounted for. As catalyst deactivation through protonation had already been included in the kinetic analysis, the potential for product inhibition was considered. Consistent with this hypothesis, incorporation of the product concentration into the time normalization approach $\sum[\mathbf{299}]^1[\mathbf{264}]^1[\mathbf{296}]^1[\mathbf{301}]^\delta \Delta t$, and arbitrarily setting $\delta = -0.2$ as a proxy for product inhibition improved the linearity of the plot (Figure 20).

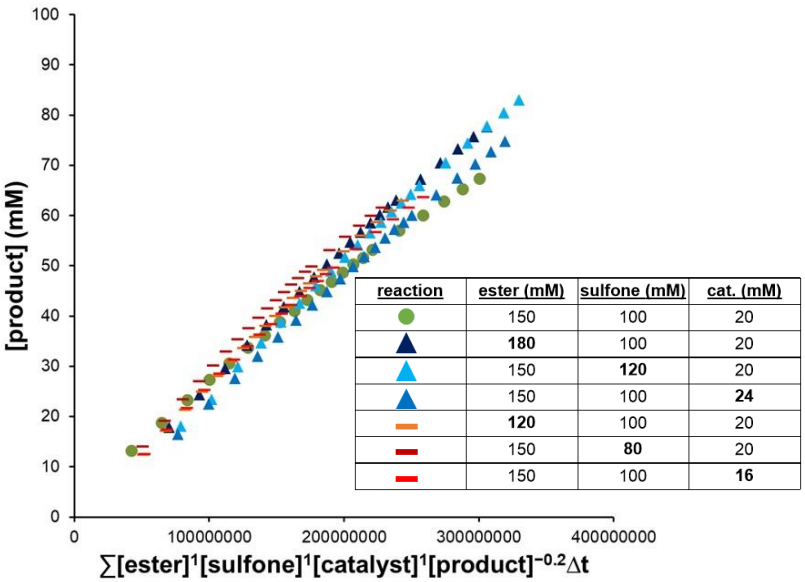


Figure 20. Variable time normalisation analysis with product inhibition included, $\alpha = 1$, $\beta = 1$, $\gamma = 1$ and $\delta = -0.2$.

To investigate the potential for product inhibition, a series of control reactions were untaken and compared to the standard reaction profile (Figure 21). Reactions with 20 mM product **301** added at the start of the reaction were carried out in triplicate, with the displayed profile an average of these three runs. It is clearly noticeable that the observed rate of consumption of vinyl bis-sulfone **264** is reduced in comparison to the standard reaction. Using the VTNA approach, where the gradient of the straight line = k_{obs}, the magnitude of k_{obs} was calculated to be 0.86 the magnitude of k_{obs} of the standard reaction. It was proposed the cause of the product inhibition could be the acidic proton adjacent to the bis-sulfone functionality. Consistent with this hypothesis, the addition of 20 mM of saturated bis-sulfone **321** at the start of the reaction resulted in a similar retardation of the reaction rate. Using an identical protocol to that described above, the magnitude of k_{obs} was calculated to be 0.80 the magnitude of k_{obs} of the standard reaction.

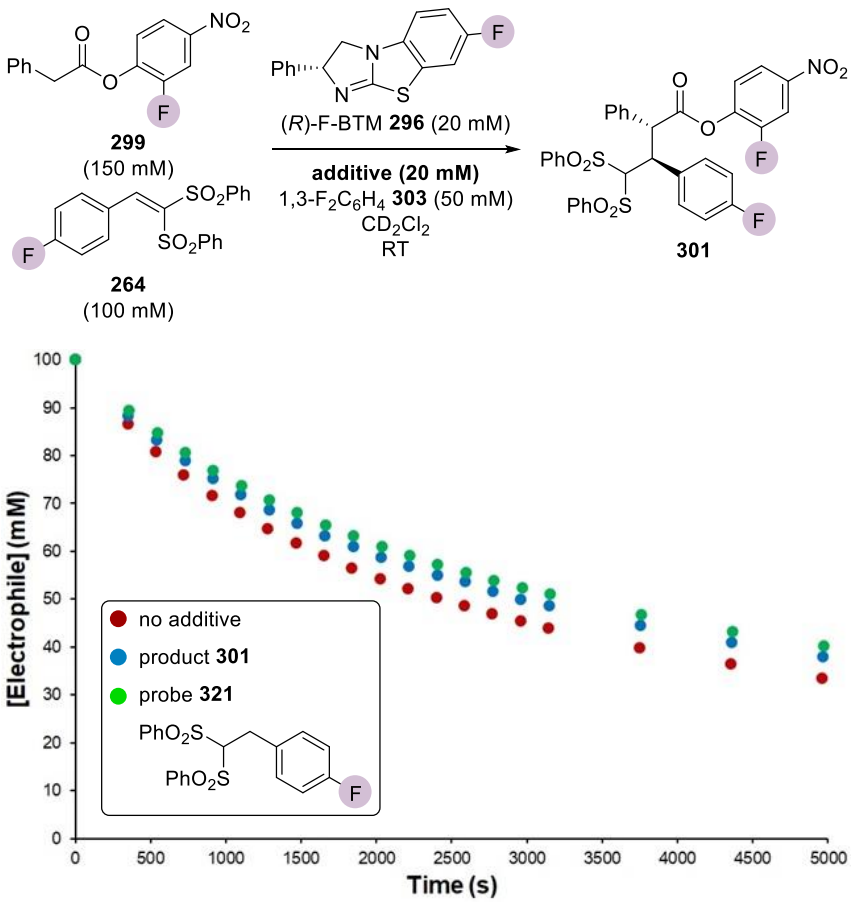
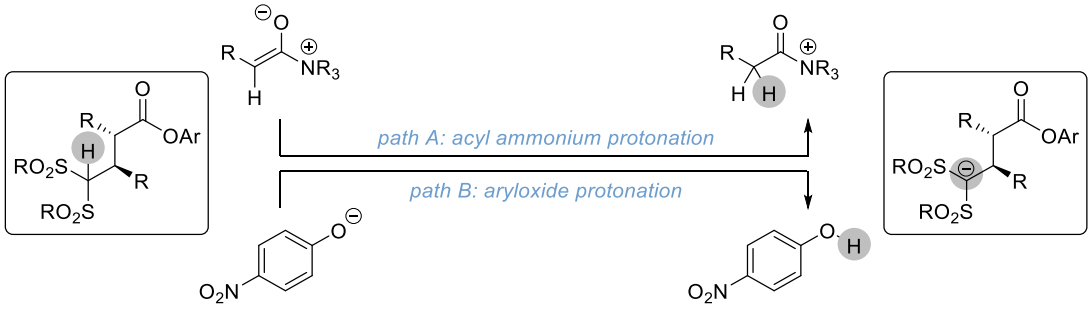


Figure 21. Product inhibition study.

Based on these results, it is postulated that the product may inhibit the reaction by decreasing the concentration of either the C(1)-ammonium enolate intermediate or aryloxide, thus retarding the rate of Michael addition or catalyst turnover, respectively (Scheme 51).

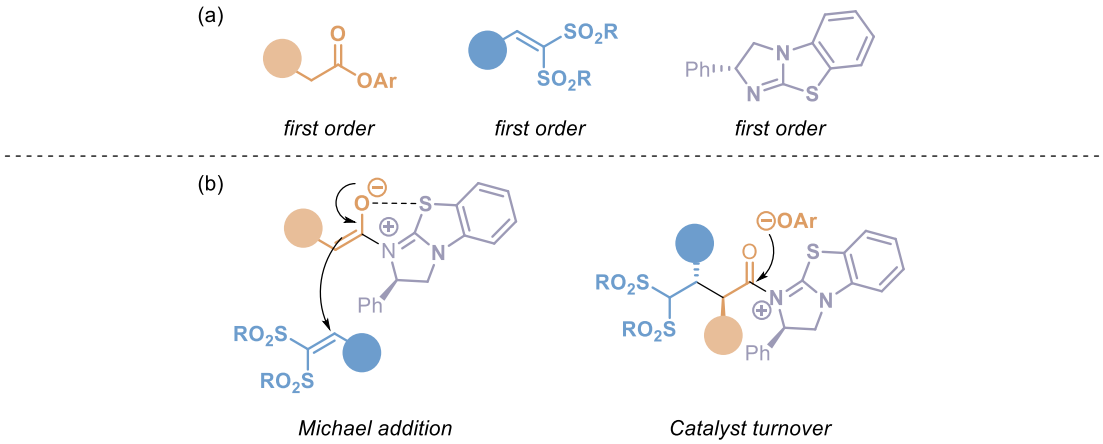


Scheme 51. Proposed product inhibition pathways.

3.2.6. Isotope Experiment

In the kinetic analysis described so far, the reaction order with respect to each component – ester **299**, vinyl bis-sulfone **264** and catalyst **296** – was determined to be first order. These results indicate each of the three reactants are involved in the

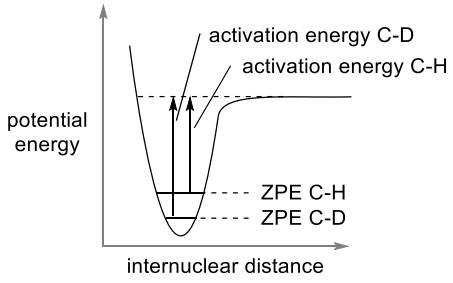
turnover-limiting step of the reaction. We envisaged two possible mechanistic scenarios: (i) rate-limiting Michael addition or (ii) rate-limiting catalyst turnover (Scheme 52). To discern between these possibilities, it was proposed an isotope experiment could be conducted.



Scheme 52. Proposed rate-limiting steps.

Substitution of one isotope for another can provide information on which bonds have been broken, formed or undergo a change in hybridisation during the rate-limiting step of a chemical reaction. Kinetic isotope effects (KIEs) are observed when the substituted atom has been involved in, or is proximal to, a bond-breaking, bond-forming or rehybridisation event during the rate-limiting step of a reaction, leading to a change in rate of reaction. Replacing hydrogen with deuterium or tritium often leads to a large isotope effect that can be measured experimentally. This is because KIEs are based upon the difference in mass of the isotopes under study, with deuterium double the mass of hydrogen. Isotope effects involving other elements do exist but are smaller and challenging to observe due to smaller percentage difference in isotopic mass. KIEs are expressed as a ratio of rate constants, eg for hydrogen KIE = k_H/k_D. The magnitude of the KIE provides detail about the reaction mechanism. If $k_H/k_D = 1$, the isotopically altered position does not change during the rate-limiting step. A normal isotope effect is observed when $k_H/k_D > 1$, whilst when $k_H/k_D < 1$ it is referred to as an inverse KIE. KIEs can be expressed as either primary or secondary, when the effect involves a bond-breaking/forming event or rehybridisation event, respectively.

The fundamental basis of an observed KIE can be most simply visualised by the case of breaking of a C-H bond.[187] The bond dissociation energy of a covalent bond can be related to the vibrational degrees of freedom that a molecule has, with each normal vibration mode having a unique frequency. As depicted in Figure 22, the Morse potential for a C-H stretch shows how the potential energy varies with internuclear separation. The energy minimum is where the overlap of bonding orbitals is greatest and nuclear repulsion is minimised. The energies of the vibrations are quantised using equation 5 and separated as rungs. The lowest energy vibration is known as the zero point energy (n = 0); at ambient temperature the ZPE is the most populated vibrational level. A deeper potential energy well means the bond is stronger due to larger bond dissociation energy, with stronger bonds having higher vibrational frequencies. As used in IR spectroscopy, the frequency of a stretching vibration can be described by the classical equation 6 through modelling a bond as a spring connecting two masses, where k is the force constant that relates to the strength of the bond. Deuterium has a larger reduced mass than for hydrogen, therefore, the C-D bond has a lower stretching frequency and hence a lower ZPE. Consequently, the activation energy for breaking a C-D bond is larger.



Equation 5

$$e_n = \left(n + \frac{1}{2}\right) hv$$

Equation 6

$$v = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}} \quad \text{where} \quad m_r = \frac{m_1 m_2}{m_1 + m_2}$$

Figure 22. Morse potential for a C-H/C-D stretch.

Although this explanation is intuitive, in most reactions the bond which is breaking is not fully dissociated at the transition state of the RDS. We can construct reaction coordinate diagrams in which the ZPE of the reactants and activated complex are compared (Figure 23); in this situation partial bonding remains between C and H/D. The ZPE difference in the activated complex is smaller than the ZPE difference in the reactants. The activation energy for the C-D bonds remains higher than that for a C-H bond, however, it is reduced in absolute value compared to the activation energy

for a fully-dissociated bond, accounting for the residual bonding in the transition state.

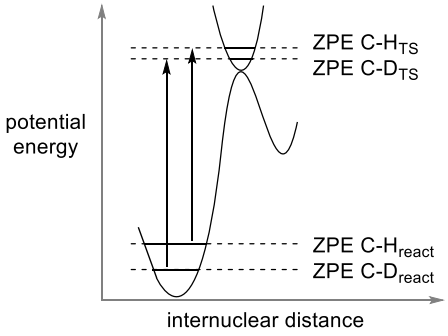


Figure 23. Morse potential for a C-H/C-D activated complex.

Secondary KIEs can be observed when a bond substituted with an isotope undergoes a change in hybridisation, such as sp^2 to sp^3. As with the above case, the ZPE of the reactants and the transition state must be considered. For a rehybridisation event, the vibrational modes which undergo the largest changes going from the reactants to products will have the greatest contribution to the KIE. It is predicted that C-H/D stretching vibrations would contribute to give a large KIE value. However, in the case of hybridisation changes the observed KIE values are substantially smaller (~ 0.8 to 0.9), therefore this must be due to other vibrations. When going from sp^2 to sp^3 hybridised orbitals, the in-plane bending motions have a similar IR frequency (Figure 24). The in-plane and out-of-plane bend for sp^3 hybridised orbitals are degenerate, however, for an sp^2 hybrid orbital the out-of-plane bend is significantly lower frequency due to the lack of steric hindrance out of the plane of the alkene. Therefore, there is a significant difference in ZPE between C-D and C-H out-of-plane bending motion on going from sp^2 to sp^3.

As before, this difference in zero point energies can be depicted in the form of a reaction coordinate diagram (Figure 25). Going from sp^2 to sp^3, the activated complex develops more sp^3 character, and hence the force constant is greater at the activated complex than at the reactants. The ZPE difference between C-H and C-D therefore increases, with a larger activation energy for C-H rehybridisation. Therefore, the reaction proceeds faster for a substrate containing a C-D bond than one containing a C-H bond and an inverse secondary KIE is observed.

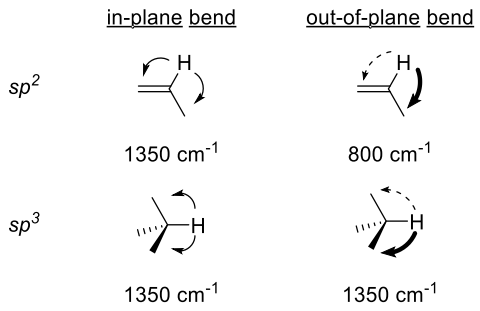


Figure 24. Bending vibrational modes considered in secondary KIE.

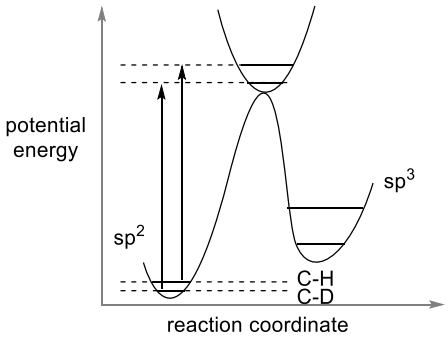
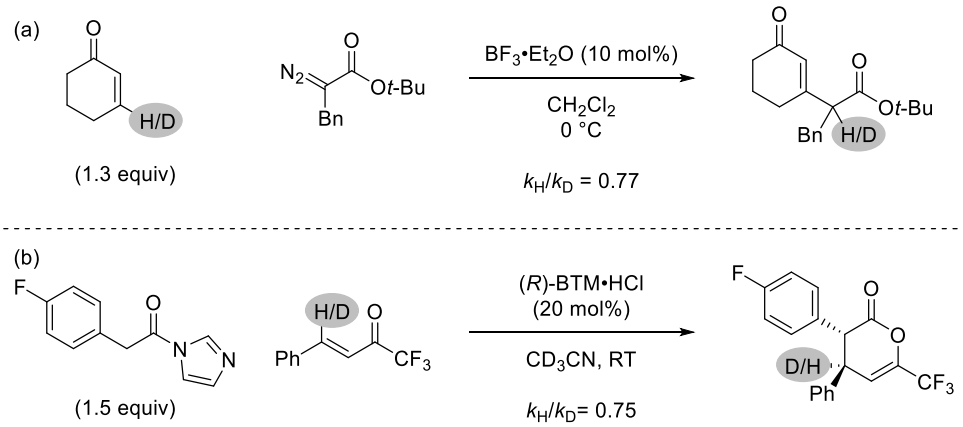


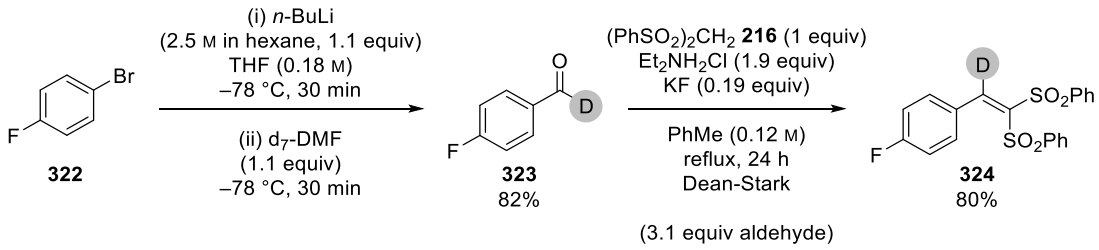
Figure 25. Out-of-plane bending vibrations for the rehybridisation of sp^2 to sp^3.

It was hoped to exploit the change in hybridisation of vinyl bis-sulfone electrophile **264** from sp^2 to sp^3 during the Michael addition step in attempt to probe if this is the rate-limiting step of the reaction. The change in hybridisation of an sp^2-hybridised Michael acceptor to an sp^3-hybridised product has previously been used to probe the turnover-limiting step of Michael addition reactions through the observation of an inverse secondary kinetic isotope effect (Scheme 53). Ryu and co-workers conducted a competition experiment between the protio- and deutero- cyclohexenone isotopologues on reaction with diazoacetate derivatives (Scheme 53a).[188] A significant inverse secondary KIE was observed (k_H/k_D = 0.77) which enabled the authors to conclude that the Michael addition step was rate-limiting. Smith and co-workers have also utilised isotope experiments to delineate the reaction mechanism of a formal [4+2] cycloaddition of acyl imidazoles and trifluoromethyl enones.[115] Kinetic analysis found the catalyst, *N*-acyl imidazole and enone to be first order. During subsequent isotope experiments, an inverse secondary kinetic isotope effect was observed (k_H/k_D = 0.75), indicating the Michael addition step was turnover-limiting (Scheme 53b).



Scheme 53. Out-of-plane bending vibrations for the rehybridisation of sp^2 to sp^3.

To this end, deuterated vinyl bis-sulfone **324** was prepared according to literature procedures (Scheme 54). 1-Bromo-4-fluorobenzene **322** was treated with *n*-BuLi in THF at −78 °C for 30 minutes. Addition of d_7-dimethylformamide to the in situ generated aryl lithium, and subsequent acidic work-up using sulfuric acid gave deuterated aldehyde **323** in high yield.[105] Knoevenagel condensation of the aldehyde with bis(phenylsulfonyl)methane gave deuterated vinyl bis-sulfone **324** in 80% yield.



Scheme 54. Synthesis of deutero-vinyl bis-sulfone.

With deuterated electrophile **324** in hand, it was observed that the protio- and deuteron- isotopologues had different fluorine chemical shifts (δ_F) in d_2-dichloromethane (Figure 26).

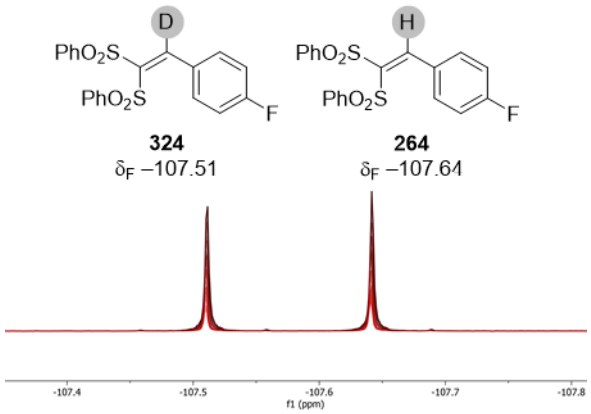
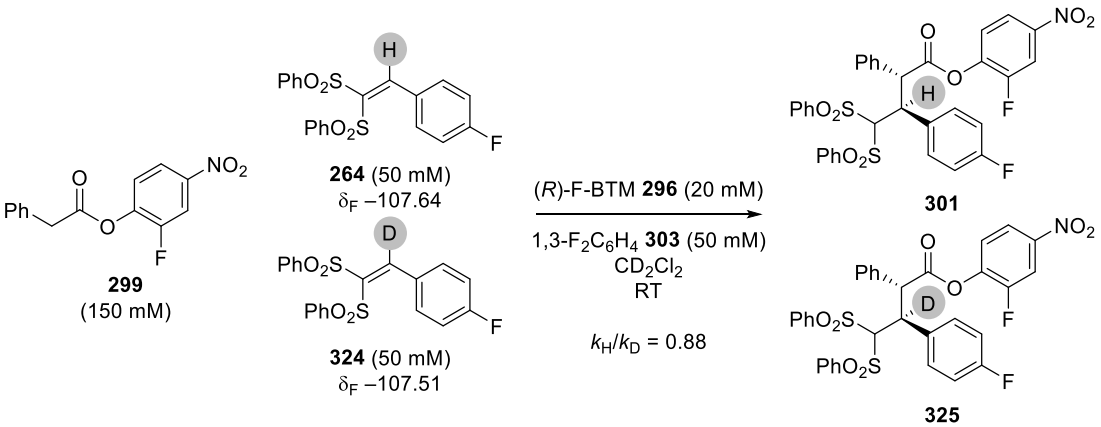


Figure 26. $^{19}F\{^{1}H\}$ Chemical shifts of deutero- and protio-vinyl bis-sulfones.

It was proposed this could be exploited in a direct competition experiment between enantioselective addition of ester **299** to a 50:50 ratio of isotopologues C(2)-H **264** (δ_F −107.64 ppm) and C(2)-D **324** (δ_F −107.51 ppm). Monitoring the relative rates of consumption of C(2)-H **264** and C(2)-D **324** in triplicate gave a kinetic isotope effect k_H/k_D = 0.88 (Scheme 55, Figure 27). For comparison, a similar KIE (k_H/k_D = 0.89) was observed in separate independent parallel kinetic experiments using C(2)-H **264** and C(2)-D **324** (see experimental section). This information is consistent with the Michael addition being kinetically significant in this protocol and contrasts the intramolecular catalyst turnover approach in formal [4+2] cycloadditions.[103] In this previous work, the process was found to be zero order in electrophile, with deprotonation of the acyl ammonium ion identified as the turnover-limiting step through a significant primary kinetic isotope effect. This is consistent with two mechanistically distinct scenarios being operative in these reactions.



Scheme 55. Isotope experiment via competition.

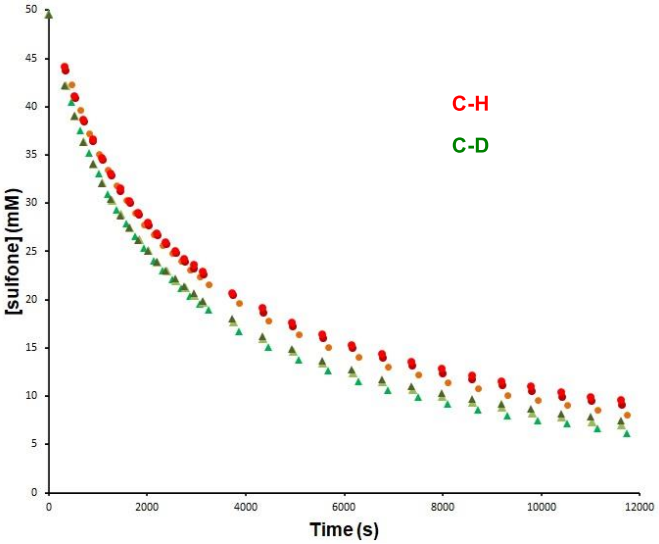
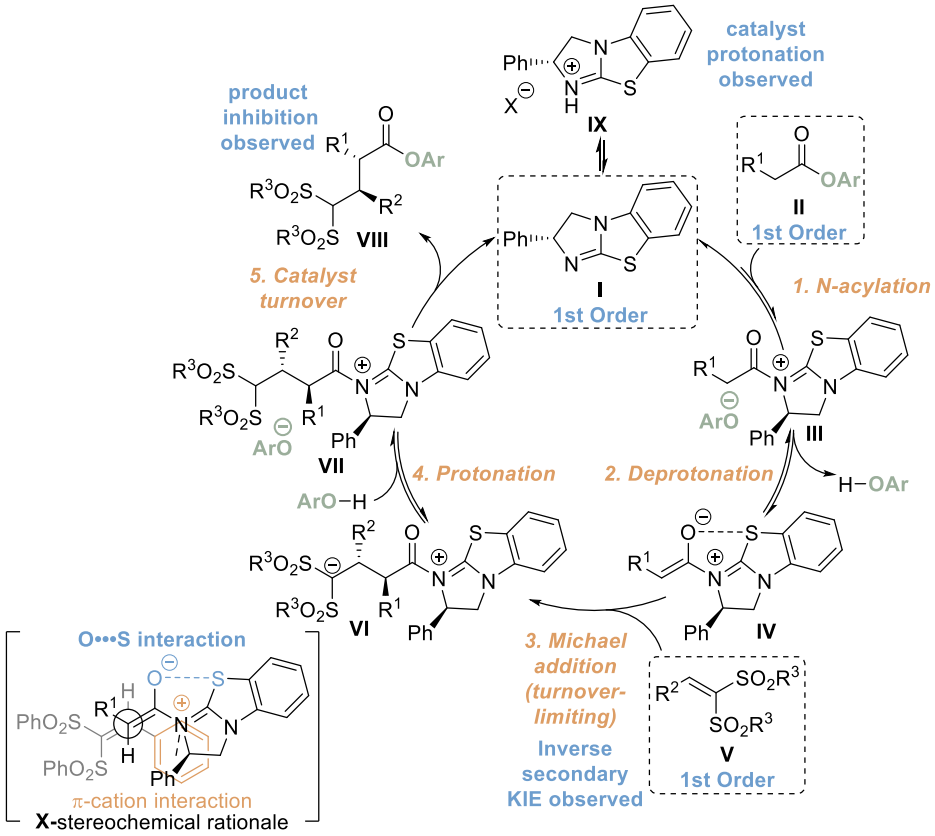


Figure 27. Reaction profile of isotope experiments via competition.

3.2.7. Proposed Mechanism

Taking all the mechanistic information into account, the following mechanism is proposed (Scheme 56). The catalytic cycle starts by reversible *N*-acylation of free base BTM catalyst **I** with ester **II** to form acyl ammonium ion pair **III**. Reversible deprotonation of the acyl ammonium by the aryloxide counterion affords the nucleophilic ammonium enolate **IV** and releases *para*-nitrophenol. It is proposed that a 1,5-O···S interaction (characterised as n_O to $\sigma^*_{C\text{-}S}$) lowers the rotational freedom of this intermediate, with the stereodirecting phenyl group blocking the *Si* face of the enolate intermediate. Turnover rate-limiting Michael addition to the electrophile **V** on the *Re* face of the enolate leads to intermediate **VI**. Protonation by the *para*-nitrophenol released in step two gives acyl ammonium ion-pair **VII**. Addition of the aryloxide anion forms the product **VIII** and regenerates catalyst **I**, which is in equilibrium with the catalytically inactive protonated-BTM **IX**. Critical to the success of this protocol is the aryloxide's ability to act as the leaving group, Brønsted base, Brønsted acid (as the corresponding phenol) and nucleophile to turnover the catalyst, enabling the reaction to be carried out in the absence of auxiliary base. The observed diastereoselectivity can be rationalised tentatively by a favoured open pre-transition state assembly **X** where gauche interactions are minimized about the forming C–C bond,[189] while allowing a potentially favourable π-cation interaction between the β-substituent of the bis-sulfone electrophile and the isothiouronium

cation.[190,191] Inhibition of the reaction by the product has also been observed. It is proposed the acidic proton adjacent to the sulfone groups can protonate either the C(1)-ammonium enolate intermediate or aryloxide, therefore limiting the rate of Michael addition or catalyst turnover, respectively.



Scheme 56. Proposed mechanism.

3.3. Conclusions

Mechanistic investigations using quantitative reaction monitoring via in situ $^{19}F\{^{1}H\}$ NMR spectroscopy have enabled detailed investigation of the reaction protocol. Substitution of a fluorine tag on the aryloxide component of the aryl ester enabled the development of a system which went to high conversion within 3 h, enabling efficient NMR analysis. Variable time normalisation analysis in combination with an observed inverse secondary KIE identified the Michael addition as the turnover-limiting step. In addition, catalyst protonation and product inhibition were observed during the analysis. It is hoped that this mechanistic study will advance the collective understanding of enantioselective isothiourea catalysis via C(1)-ammonium enolates and aid future reaction design.

Chapter 4. Enantioselective Dearomatisation of Pyridinium Salts via C(1)-Ammonium Enolates

4.1. Introduction

While impressive recent advances, described in section 1.5.4, broaden the compatibility of C(1)-ammonium enolate intermediates in dual catalytic processes and with alternative electrophilic components, the electrophiles employed are generally limited to alkenes and carbonyl derivatives (Figure 28). More appealing would be the expansion of compatible electrophiles to incorporate desirable functionality for use in the synthesis of high value target molecules.

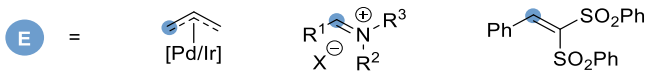
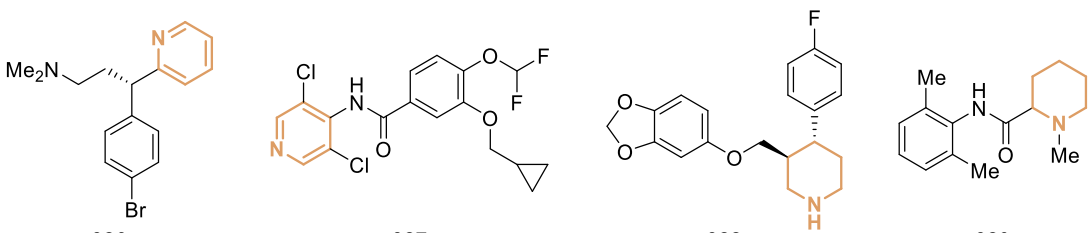


Figure 28. Compatible electrophiles in isothiourea catalysis via C(1)-ammonium enolates using aryloxide catalyst turnover.

Nitrogen-containing heterocycles are an important structural motif prevalent in a diverse range of biologically relevant compounds,[192] agrochemicals,[193] and dyes.[194] Their importance is readily quantified as 59% of US FDA approved small-molecule drugs contain a nitrogen heterocycle, with these heterocycles commonly incorporated into molecules to improve physicochemical properties.[192] In particular, Lewis basic piperidine and pyridine heterocycles are the two most prevalent in unique small-molecule drugs; 134 out of 640 pharmaceuticals contain either a piperidine or pyridine ring, including the billion dollar antidepressant medicine Paroxetine **328** (Figure 29).



326 Dexbrompheniramine antihistamine

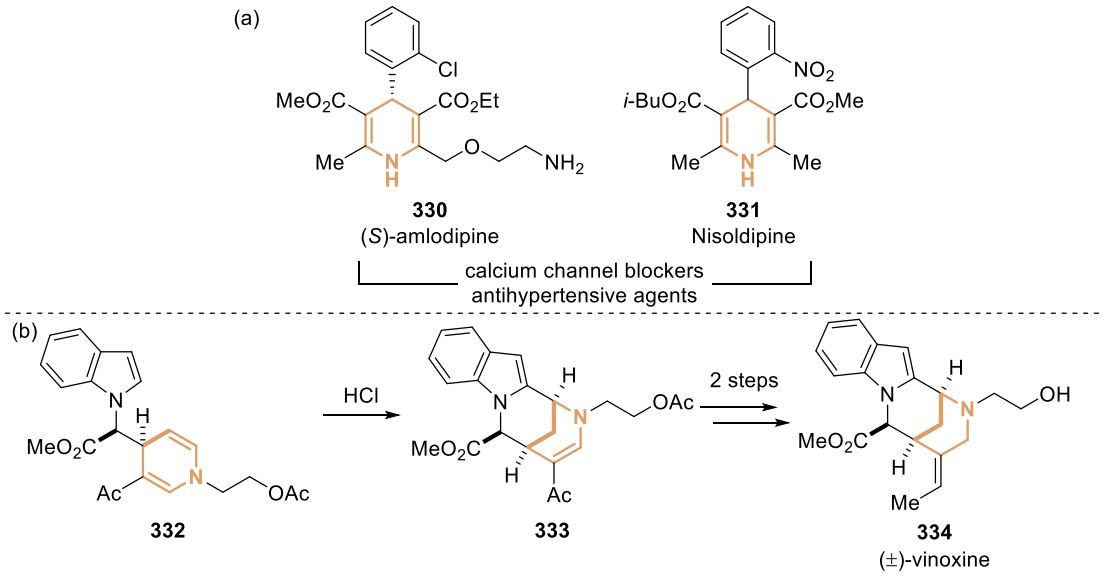
327 Romflumilast treatmend for COPD

328 Paroxetine antidepressant

329 Mepivacaine anesthetic

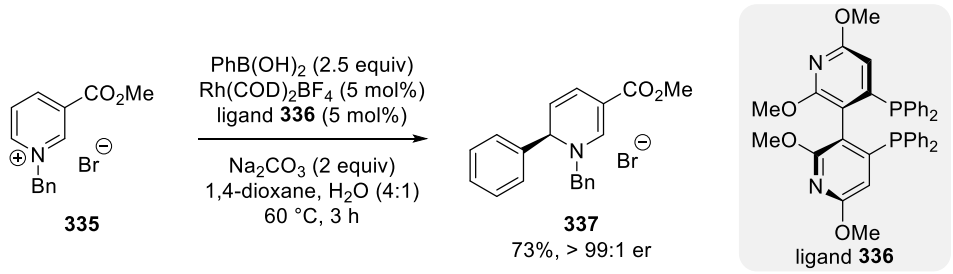
Figure 29. Examples of pyridine and piperidine medicines.

1,4-Dihydropyridines (DHPs) are a privileged class of heterocycle widely found in pharmaceuticals as potent calcium channel blockers for the treatment of hypertension (Scheme 57a).[195] Although a less common fragment in terms of total number of commercial medicines (10 small-molecule drugs), incorporation of 1,4-DHP units is of increasing interest for structural diversity in the treatment of cardiorenal diseases,[196] cancer and asthma.[197] Additionally, 1,4-DHPs can serve as versatile intermediates in contemporary organic synthesis en route to pyridines and piperidines. 1,4-DHPs can also be exploited for the efficient construction of complex polycyclic architectures and have been used in the synthesis of various natural products, such as the indole alkaloid vinoxine **334**, highlighted in Scheme 57b.[198] Therefore, direct and mild methods for the efficient preparation of DHPs are highly sought after.



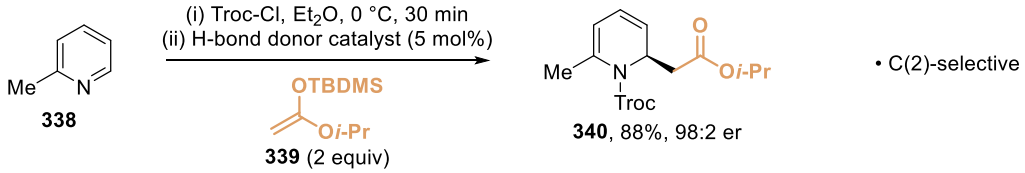
Scheme 57. 1,4-DHPs as (a) commercial medicines and (b) synthetic intermediates.

Nucleophilic dearomatisation of electron deficient pyridines with carbon nucleophiles is a powerful method for the enantioselective synthesis of DHPs. Although early dearomatisation methods utilised stoichiometric chiral auxiliaries and preformed nucleophiles to impart stereoselectivity,[199] recent advances have focused on the development of catalytic enantioselective protocols. Transition metal-catalysed dearomatisation reactions of pyridines has been achieved using various nucleophiles (cyanide, alkyne, aryl zinc)[200–202] typically yielding the C(2) or C(6)-addition products, as exemplified in Scheme 58.[203]



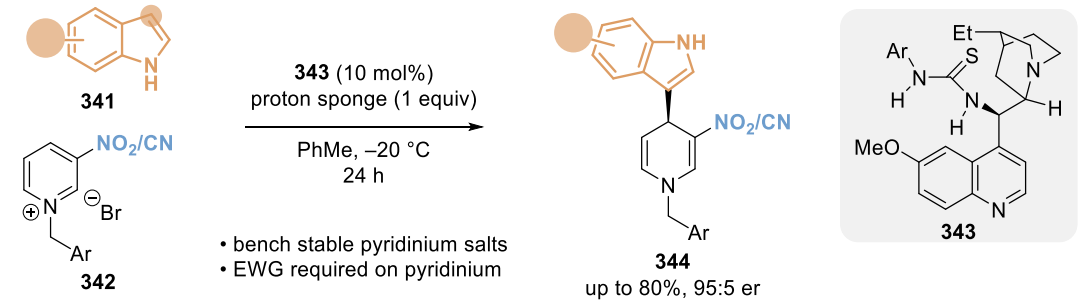
Scheme 58. Transition metal-catalysed enantioselective dearomatisation of pyridinium salts.

Organocatalysis has emerged as an effective strategy for the dearomatisation of pyridines. In 2015, Mancheño and co-workers disclosed the enantioselective dearomatisation of in situ generated *N*-acyl pyridinium intermediates using silyl ketene acetal nucleophiles via anion-binding catalysis to give enantioenriched 1,2-DHPs (Scheme 59).[204] Significantly, substitution on the carbon framework of the pyridine ring with an electron-withdrawing group was not required in this process.



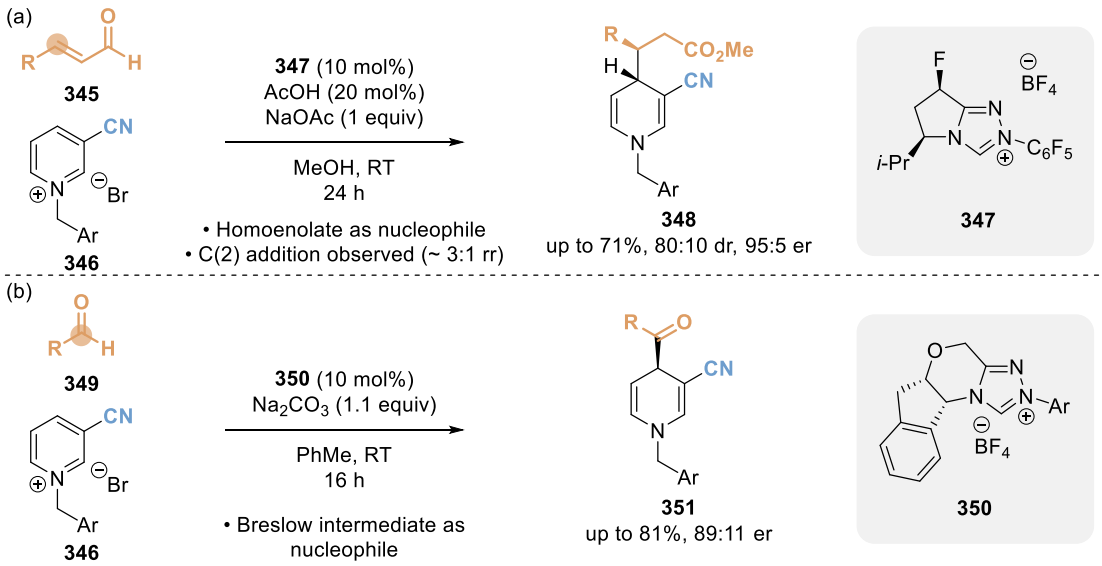
Scheme 59. C(2)-Selective dearomatisation by Mancheño.

N-Alkyl pyridinium salts are bench stable solids and can be conveniently prepared in one step from the corresponding, widely available, pyridine precursor and alkylating agent. Building on the work of Mancheño, Bernardi and co-workers reported a complementary approach for the regioselective C(4)-dearomatisation of 3-nitro and -nitrile substituted pyridinium salts for the synthesis of enantioenriched 1,4-DHPs using indole nucleophiles (Scheme 60).[205] Bifunctional catalyst **343** bearing a basic tertiary amine group and hydrogen-bond donor thiourea functionality were required to achieve high enantioselectivities.



Scheme 60. C(4)-Selective dearomatisation by Bernardi.

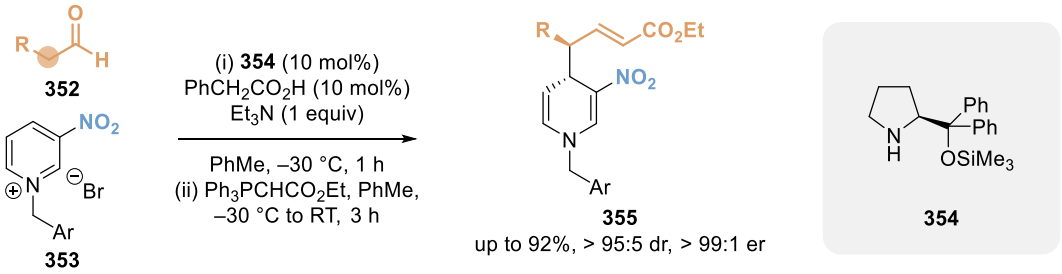
N-heterocyclic carbene catalysis has also been employed for the synthesis of enantioenriched 1,4-DHPs through the addition of Breslow intermediate nucleophiles to pyridinium salts (Scheme 61). Rovis and co-workers reported the addition of Breslow intermediate-derived homoenolate nucleophiles to 3-nitrile substituted pyridinium salts using NHC catalyst **347** (Scheme 61a).[206] In this case, small amounts of C(2)-addition was also observed (~3:1 regioisomeric ratio) whilst one example using a 3-acyl substituted pyridinium gave the corresponding product in lower er (75:25). In a related protocol, Massi and co-workers subsequently employed the in situ generated Breslow intermediates as acyl anion equivalents in the addition to 3-nitrile pyridinium salts (Scheme 61b).[207] 3-Bromo, nitro, amide and ester substituted pyridiniums were also attempted, however, in all these cases low conversion to product was observed (< 10%).



Scheme 61. C(4)-Selective dearomatisation via NHC organocatalysis.

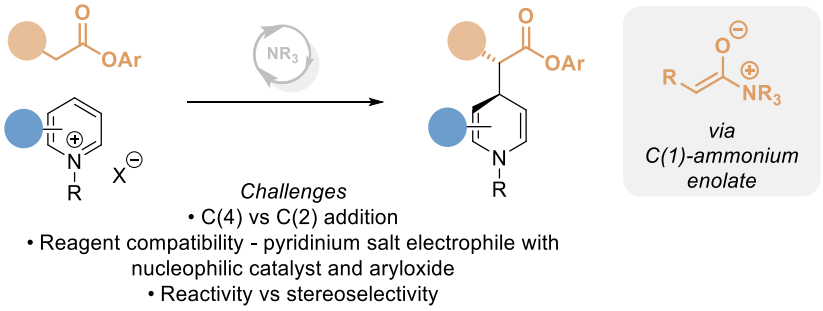
Bernardi and co-workers have reported the regioselective addition of catalytically generated enamine nucleophiles to 3-nitro substituted pyridinium salts for the

synthesis of 1,4-DHPs (Scheme 62).[208] In this case, Wittig homologaton of the aldehyde products to the corresponding α,β-unsaturated ester was required due to the instability of the aldehyde functionality. In a similar observation to previous examples, when the nitro electron-withdrawing group was changed to a nitrile, the diastereo- and enantioselectivity of the reaction dropped (~70:30 dr and ~70:30 er). In general, substitution of an electron-withdrawing group in the 3-position is required to activate the pyridine nucleus for the synthesis of 1,4-DHPs. This renders the pyridinium salt more electrophilic for nucleophilic addition while also stabilising the DHP product.



Scheme 62. C(4)-Selective dearomatisation via secondary amine catalysis.

We envisaged a complementary approach through the addition of a catalytically generated C(1)-ammonium enolate intermediate to pyridinium salts for the enantioselective synthesis of α-functionalised esters bearing nitrogen heterocycle functionality (Scheme 63). The key challenges in the development of this process would be control of regioselectivity (C4 vs C2 addition), compatibility of the reagents (nucleophilic catalyst and aryloxide with pyridinium electrophile) and achieving sufficient reactivity whilst maintaining stereoselectivity.

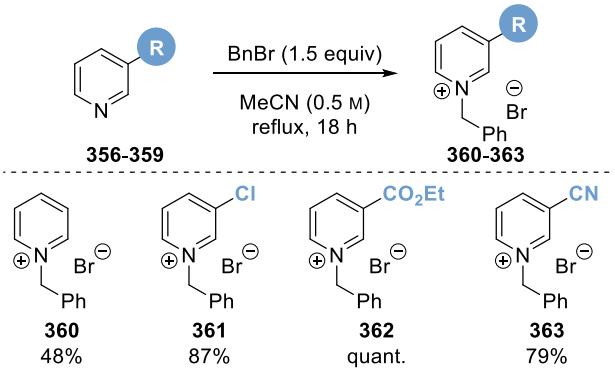


Scheme 63. Proposed dearomatisation of pyridinium salts via C(1)-ammonium enolate addition.

4.2. Results and Discussion

4.2.1. Reaction Optimisation

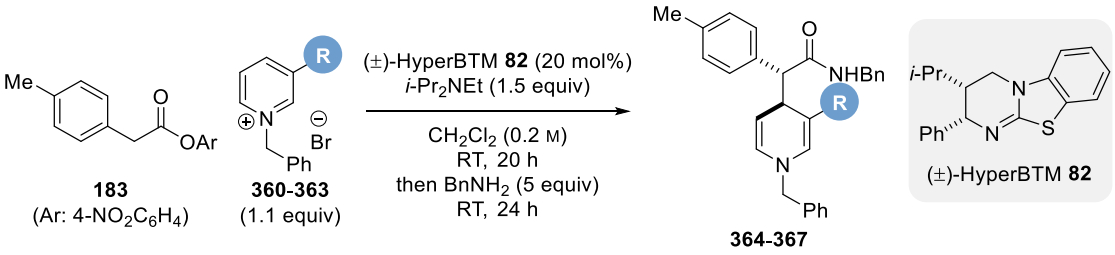
Preliminary investigations looked to probe the reactivity of various pyridinium salts using isothiourea catalysts via generation of a C(1)-ammonium enolate. To this end, a range of 3-substituted *N*-benzyl pyridinium salts **360**-**363** were prepared through simple *N*-alkylation of commercially available pyridines with benzyl bromide in acetonitrile (Scheme 64). The pyridinium salts were easily isolated through precipitation using diethyl ether and subsequent filtration.



Scheme 64. Synthesis of pyridinium salts.

With a range of pyridinium electrophiles prepared, these were then subjected to catalytic conditions using racemic HyperBTM **82** and *para*-tolyl ester **183** in an initial search for reactivity (Table 16). Not surprisingly, considering the previous organocatalytic dearomatisation methods discussed in Section 4.1, unsubstituted pyridinium salt **360** gave no conversion to product in reactions carried out either with or without auxiliary Hunig's base, with only starting materials remaining by ^{1}H NMR analysis of the crude reaction mixture (entries 1,2). Whilst 3-chloro substituted pyridinium showed no reactivity without base (entry 3), the reaction with base showed a small amount of conversion to product (< 10%, entry 4). 3-Ester substituted pyridinium **362** gave conversion to product both with and without base, albeit in low yield (entries 5,6). Encouragingly, the pyridinium substituted with a nitrile group provided an initial hit in the presence of base, giving 47% of the desired product by ^{1}H NMR analysis of the crude reaction mixture. In contrast to the previous work in the Michael addition of vinyl bis-sulfones, limited reactivity was observed when no auxiliary base was used (entry 7, < 10%).

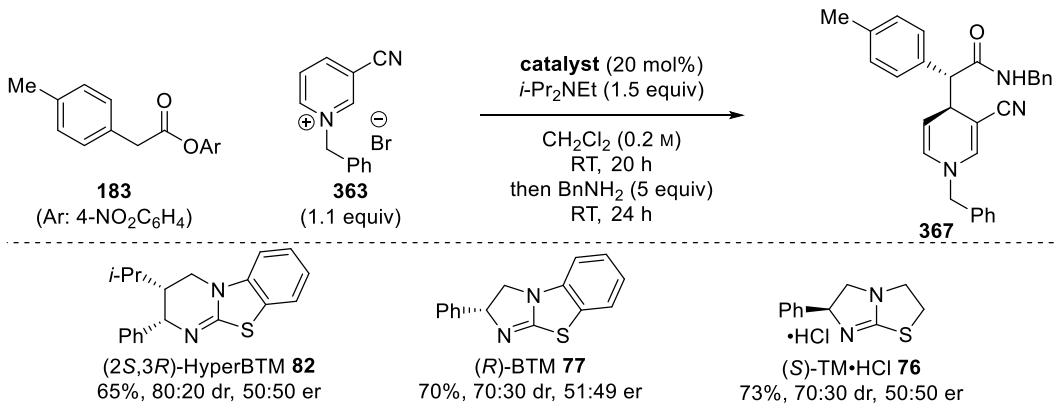
Table 16. Probing the reactivity of various pyridinium salts.



Entry	R	Base (Y/N)	Yield[a] (%)
1	H	N	0
2	H	Y	0
3	Cl	N	0
4	Cl	Y	< 10
5	CO_2Et	N	< 10
6	CO_2Et	Y	14
7	CN	N	< 10
8	CN	Y	47

[a] Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard.

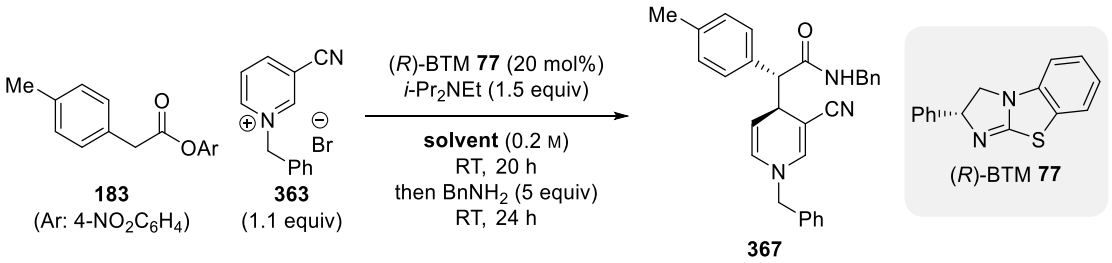
Reactions with various enantiopure isothiourea catalysts were then carried out to determine the stereoselectivity of the reaction using 3-nitrile pyridinium salt **363** (Scheme 65). However, although reactions with (2*S*,3*R*)-HyperBTM **82**, (*R*)-BTM **77** and (*S*)-TM·HCl **76** gave promising reactivity, each gave racemic product.



Scheme 65. Catalyst study.

Attention was then turned to varying the reaction solvent in the pursuit of rendering the protocol enantioselective (Table 17). Using (*R*)-BTM **77** as catalyst, which had been the optimal catalyst in the previous work described in chapter 2, reactions carried out in chloroform, DMF, acetonitrile and THF gave 1,4-DHP product **367** in good yield with moderate diastereoselectivity, but no enantioselectivity (entries 2-5). Promisingly, performing the reaction in toluene afforded the product in 74% yield in 85:15 dr and 65:35 er (entry 6). Interestingly, reactions in toluene using (*S*)-TM·HCl **76** and (2*S*,3*R*)-HyperBTM **82** gave racemic product (entries 7,8).

Table 17. Solvent study.

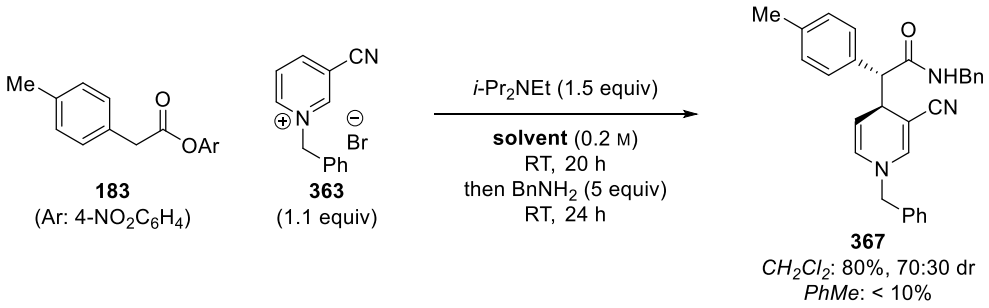


Entry	Solvent	Yield[a] (%)	dr[b]	er[c]
1	CH_2Cl_2	70	70:30	51:49
2	$CHCl_3$	78	75:25	52:48
3	DMF	65	70:30	50:50
4	MeCN	70	75:25	50:50
5	THF	75	75:25	50:50
6	PhMe	74	85:15	65:35
7[d]	PhMe	65	80:20	48:52
8[e]	PhMe	78	80:20	52:48

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] (*S*)-TM·HCl as catalyst. [e] (2*S*,3*R*)-HyperBTM as catalyst.

To gain insight into the higher enantioselectivity observed for the reaction carried out in toluene, control reactions without the isothiourea catalyst present were performed in both dichloromethane and toluene to determine if a base mediated

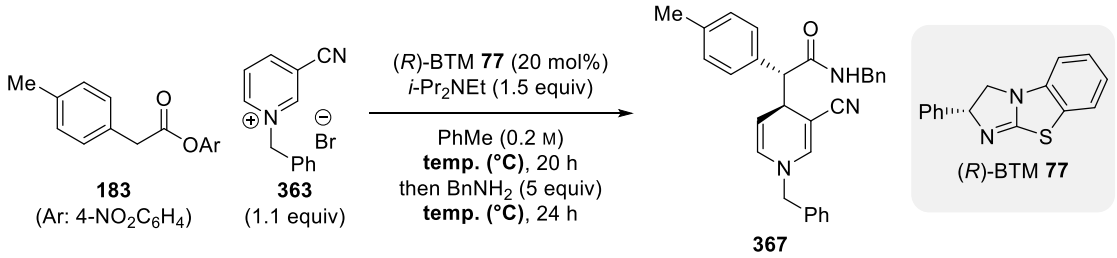
background reaction was occurring in either solvent (Scheme 66). Interestingly, 80% of product was observed in the case of dichloromethane with maintained dr (70:30), whilst in toluene < 10% conversion of starting materials to product was observed.



Scheme 66. Control reactions without the isothiourea catalyst present.

Encouraged by these initial results in toluene, further efforts were undertaken to improve the enantioselectivity of this process. Firstly, the effect of temperature on the reaction was studied (Table 18). Going from room temperature (entry 1) to 0 °C gave a lower product yield (48%) with similar diastereoselectivity (90:10 dr) and improved enantioselectivity (82:18 er). Performing the reaction at −10 °C gave similar results to 0 °C; however, at −40 °C no reactivity was observed.

Table 18. Temperature study.

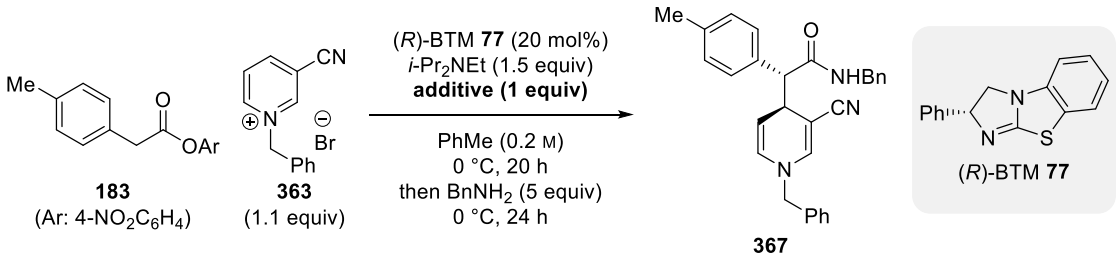


Entry	Temp. (°C)	Yield[a] (%)	dr[b]	er[c]
1	RT	74	85:15	65:35
2	0	48	90:10	82:18
3	-10	46	85:15	82:18
4	-40	0	-	-

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Previous work in isothiourea catalysis has demonstrated the beneficial effect of additives on enantioselectivity, for example HOBt aids catalyst turnover (Section 1.5.4, Scheme 18) and tetra *n*-butylammonium *para*-nitrophenoxide aids both catalyst turnover and increases the polarity of the reaction media (Section 1.5.4, Scheme 23). In an attempt to increase the enantiomeric ratio from moderate to high, reactions were carried out using one equivalent of hydroxybenzotriazole (HOBt) (Table 19, entry 1), tetra *n*-butylammonium *para*-nitrophenoxide (entry 2) and tetra *n*-butylammonium bromide (entry 3). However, no improvement in enantioselectivity was observed in each case.

Table 19. Additive study.



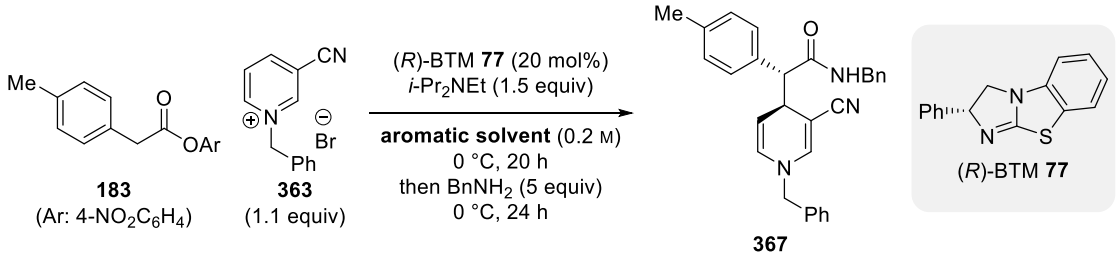
Entry	Additive	Yield[a] (%)	dr[b]	er[c]
1	HOBt	48	80:20	51:49
2	*n*-Bu$_4$NOAr	50	80:20	80:20
3	*n*-Bu$_4$NBr	41	80:20	71:29

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Up to this stage, the largest discriminating factor on the enantioselectivity of the reaction had been the use of toluene as the reaction solvent. It was decided to carry out a set of reactions using various aromatic solvents of differing substitution to investigate the subtle differences of molecular solvent structure (electronic and steric properties) on enantioselectivity. In comparison to toluene (Table 20, entry 1, 82:18 er), performing the reaction in disubstituted solvent xylenes gave the product in lower diastereomeric ratio and significantly lower er (entry 2), whilst using trisubstituted mesitylene inhibited the reaction and gave only 19% product (entry 3). Monosubstituted aromatic solvents such as anisole, chloro- and fluorobenzene all

afforded 1,4-DHP with moderate enantioselectivity (entries 4-6); however, these ers were significantly lower than toluene. It is interesting that although toluene is the best solvent for enantioselectivity, other aromatic solvents give some level of enantioinduction. The optimal solvent in previous organocatalytic dearomatisation methods (Discussed in Section 4.1) using bifunctional, secondary amine and NHC catalysts was also toluene. Considering this, solvent interactions may be important in distinguishing between diastereomeric transition states. Alternatively, solubility could also be an important factor to rationalise the enhancement of the reaction in toluene. In this protocol it was observed that the pyridinium salt, ester and catalyst were all less soluble in toluene compared to dichloromethane. We have also previously shown that negligible base-mediated background reaction occurs in toluene (Scheme 66). Possibly, there is an added phase transfer benefit of including the catalyst in the reaction, although this is just speculation based on experimental observations and further work would be required to confirm this hypothesis.

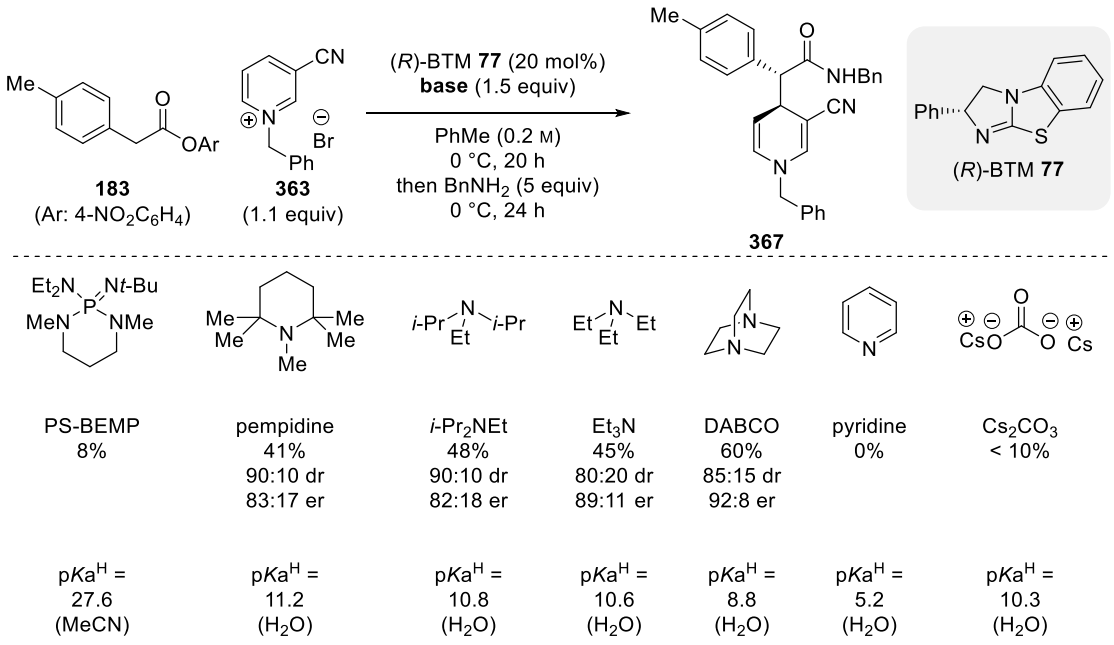
Table 20. Aromatic solvent study.



Entry	Ar Solvent	Yield[a] (%)	dr[b]	er[c]
1	PhMe	48	90:10	82:18
2	Xylenes	71	75:25	57:43
3	Mesitylene	19	-	-
4	Anisole	54	95:5	68:32
5	Chlorobenzene	61	90:10	73:27
6	Fluorobenzene	59	90:10	72:28

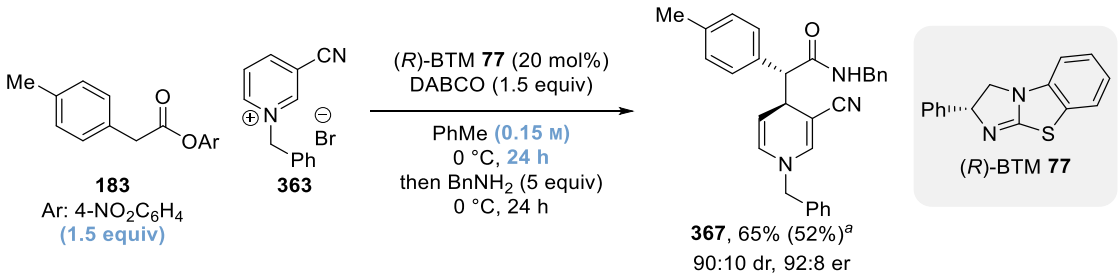
[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

With the enantioselectivity remaining at moderate levels, attention was turned to investigating the effect of the auxiliary base on the reaction (Scheme 67). Carrying out the reaction with one of the strongest organic bases recorded, polymer-supported (PS) BEMP,[209] led to minimal product formation and resulted in the decomposition of starting material. Use of an inorganic base caesium carbonate was also unproductive, returning only starting materials. However, a selection of organic amine bases did afford the desired 1,4-DHP with some interesting results. The strongest amine base tested, Pempidine (pentamethylpiperidine), gave similar results compared to Hunig's base (41%, 90:10 dr, 83:17 er). Interestingly, use of a slightly weaker base, triethylamine, gave the product in similar yield (45%) with improved enantioselectivity (89:11 er). To our delight, performing the reaction in the presence of DABCO gave the product in good yield (60%) with the highest enantioselectivity (92:8 er). Finally, use of a significantly weaker base, pyridine, led to no product formation. Overall, these results demonstrate that the identity of the auxiliary base has a significant effect on the outcome of the reaction. A careful balance is required for this reaction: use of a weaker amine base leads to improved enantioselectivity,[210,211] however, too weak and no reactivity will be observed. A situation where the amine plays a secondary beneficial role, such as acting as a nucleophile by adding to the pyridinium salt cannot be ruled out.



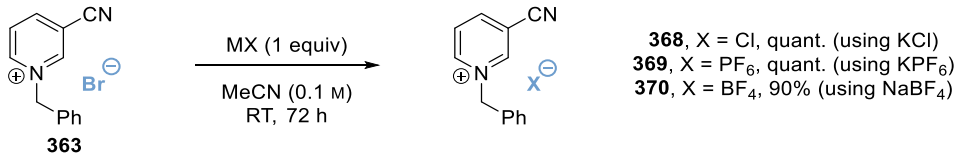
Scheme 67. Auxiliary base study.

Further refinement of the reaction conditions through switching the stoichiometry, increasing the equivalents of *para*-nitrophenyl ester **183**, lowering the reaction concentration and extending the reaction time to 24 h led to the optimised reactions conditions as shown in Scheme 68, which gave 1,4-DHP **367** in 65% yield with excellent stereoselectivity (90:10 dr, 92:8 er). Following flash column chromatography, the 1,4-DHP could be isolated in 52% yield as a single major diastereoisomer.



Scheme 68. Optimised reaction conditions.
(Isolated yield in parenthesis. a: isolated as a single major diastereoisomer)

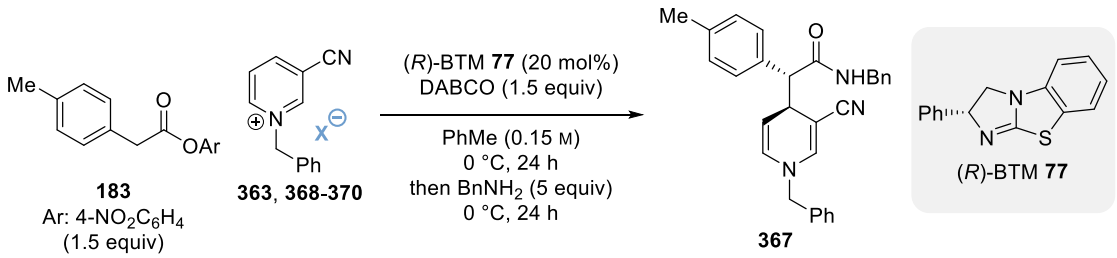
With an optimised protocol developed, we first looked to probe the effect of the counter-ion of the pyridinium salt to determine is significance towards the reaction outcome. The synthesis of substrates bearing alternative counter-ions was targeted through a counter-ion switch approach (Scheme 69). Model bromide substrate **363** was treated with potassium chloride, potassium hexafluorophosphate and sodium tetrafluoroborate, respectively, to yield the corresponding Cl, PF_6 and BF_4 counter-ion compounds after filtration and concentration.



Scheme 69. Synthesis of pyridiniums with less coordinating counter-ions.

Subjecting the various substrates to the catalytic conditions provided the results outlined in Table 21. The pyridinium substrate bearing the chloride counter-ion **368** gave the 1,4-DHP product **367** in 58% yield with excellent stereoselectivity, consistent with the bromide analogue. However, substrates containing PF_6 and BF_4 counter-anions were less reactive, giving the product in reduced yield and er. This is most likely a result of the reduced solubility of these substrates in toluene.

Table 21. Counter-ion study.



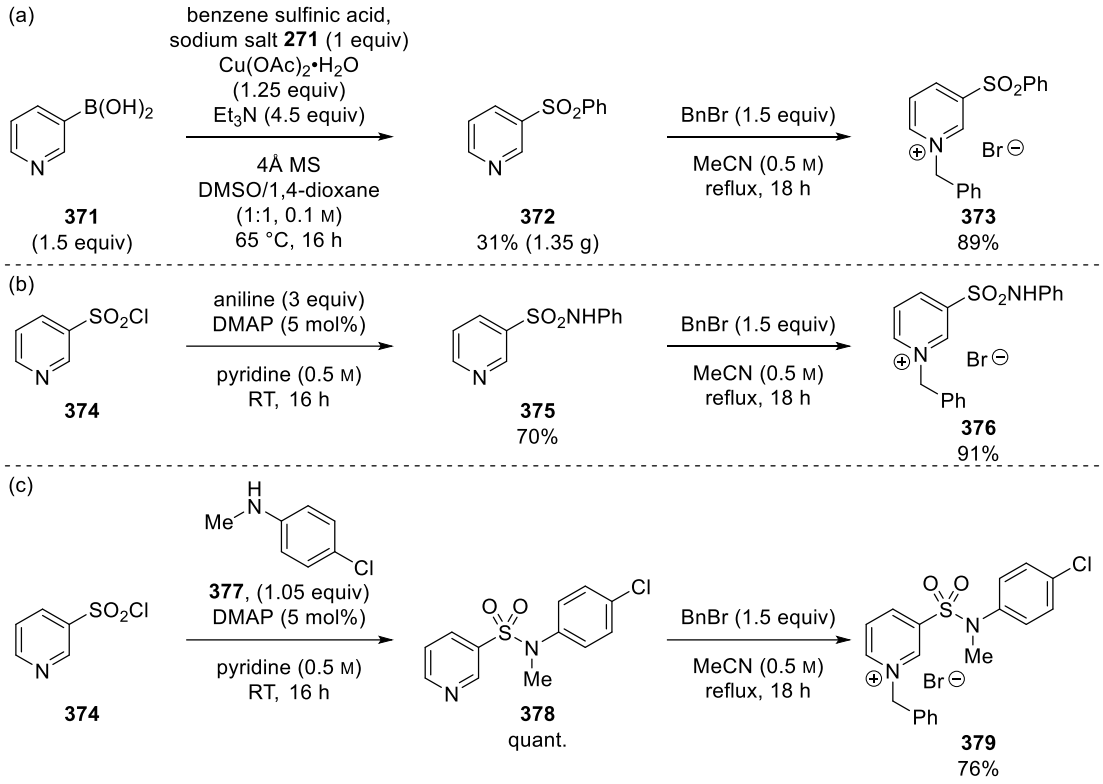
Entry	X	Yield[a] (%)	dr[b]	er[c]
1	Br	65	90:10	92:8
2	Cl	58	90:10	92:8
3	PF_6	22	nd	84:16
4	BF_4	14	nd	85:15

[a] Combined yield of diastereoisomers. Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

4.2.2. Reaction Scope and Limitations

We then looked to explore the scope and limitations of the developed methodology. Previous organocatalytic dearomatisation protocols have been shown to be sensitive to changes in the electron-withdrawing group, resulting in reduced reactivity and/or stereoselectivity. With this in mind, initial investigations looked to explore the scope of the pyridinium nucleus. Various pyridinium salts had been previously synthesised in the initial stages of the project (Scheme 64). 3-Sulfone substituted pyridinium salts have not been previously used in the dearomatisation of pyridinium salts. With sulfone electron-withdrawing groups proving amenable to isothiourea catalysis in the previous project (Chapters 2 and 3), pyridinium salts bearing sulfur (VI) substituents were proposed to be promising. Therefore, the preparation of these was targeted in a bid to develop a complementary protocol. 3-Phenyl sulfonyl substituted pyridinium **373** was synthesised through a two-step procedure: initial coupling of 3-pyridyl boronic acid **371** with benzene sulfinic acid sodium salt was carried out using stoichiometric copper acetate to afford 3-phenyl sulfonyl pyridine **372** on multigram scale, albeit in moderate yield.[212] Subsequent benzylation using benzyl bromide afforded the desired pyridinium salt **373** in 89%

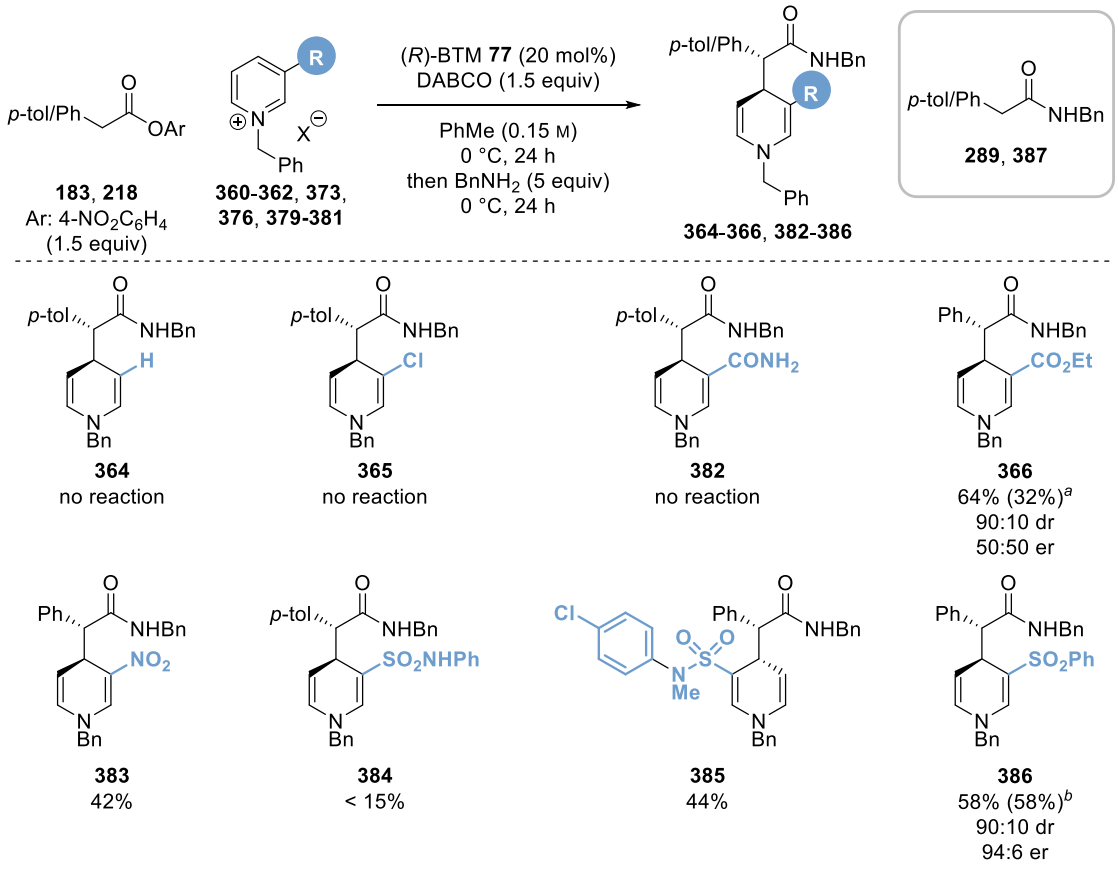
yield (Scheme 70a). 3-Pyridyl sulfonyl chloride **374** was used to access secondary and tertiary sulfonamides **376** and **379** in high yields through the reaction with the corresponding aniline. Benzylation, using the conditions previously described, afforded pyridinium salts in high yield (Scheme 70b, c).



Scheme 70. Synthesis of further pyridinium salts.

The pyridinium salts bearing various 3-substituents were then subjected to the optimised catalytic conditions (Scheme 71). Not unexpectedly, unsubstituted and 3-chloro substituted pyridinium salts **360** and **361** were unreactive, returning only starting materials, whilst primary amide substituted pyridinium **380** also returned starting material. 3-Ethyl ester substituted pyridinium salt **362** gave 64% conversion to product **366**. However, separation of the 1,4-DHP from reaction by-products (amide **387**, catalyst, unreacted pyridinium salt by-products) was challenging during chromatography, with only 32% isolated yield of **366**, which was subsequently found to be racemic through HPLC analysis. Employing the more electron-withdrawing nitro substituent, pyridinium **381** gave full conversion of starting materials, however, 1,4-DHP **383** could not be isolated from the multiple by-products in the crude reaction material. Secondary sulfonamide pyridinium **376** gave low conversion to product. To probe if the acidic sulfonamide N-H was inhibiting the

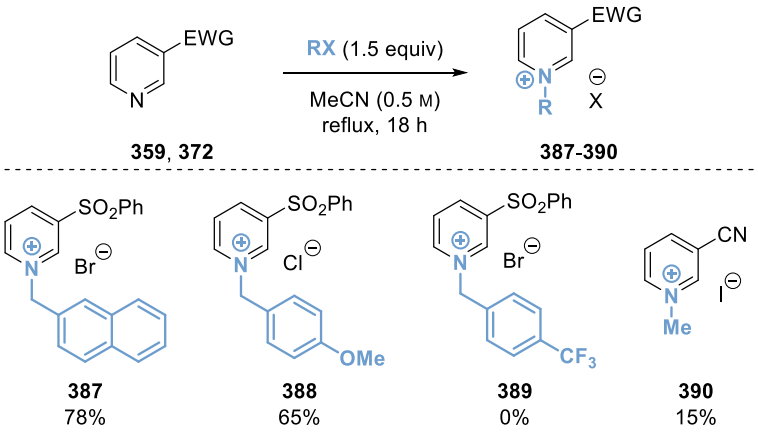
reaction, tertiary sulfonamide **379** was subjected to the catalytic conditions and, encouragingly, product **385** was formed in 44% conversion. However, product isolation from reaction by-products again proved challenging. Finally, a significant breakthrough was observed when 3-sulfone substituted pyridinium **373** was used, forming 1,4-DHP **386** in 58% yield with high diastereo- and enantioselectivity (90:10 dr, 94:6 er). Consistent with previous dearomatisation procedures, changes in electron-withdrawing group had a substantial effect on the reaction outcome. It is possible that further reaction optimisation for each electron-withdrawing group may enable these to be synthesised with high enantioselectivity, however, this was not carried out due to the time constraints of the project and COVID-19.



Scheme 71. Pyridinium 3-position scope.
(isolated yields in parenthesis. a: isolated > 95:5 dr. b: isolated 92:8 dr)

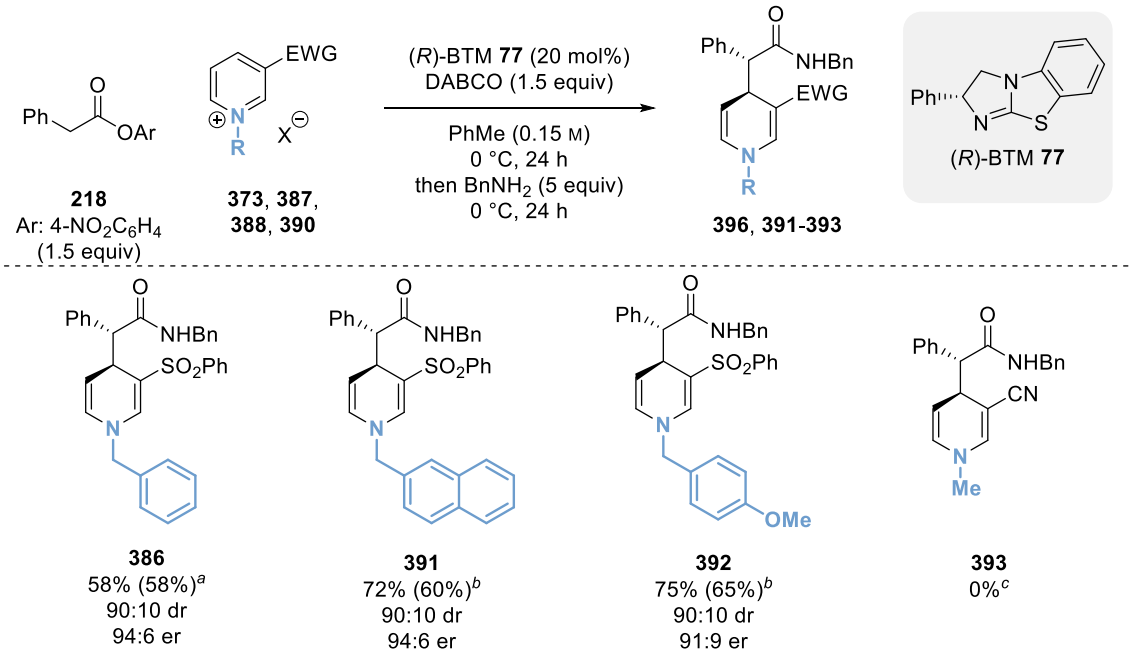
Next, the scope of the nitrogen substituent was investigated to determine the importance of the *N*-benzyl group (Scheme 72). To this end, the synthesis of a range of *N*-substituted pyridinium salts was targeted. Using the appropriate alkyl halide, 2-naphthyl and 4-methoxyphenyl substituted sulfonyl pyridinium salts **387** and **388** were synthesised in good yield. However, the 4-trifluoromethyl substituted

analogue **389** could not be isolated from the starting materials, and multiple attempts to precipitate and recrystallise the salt using various solvents were unsuccessful. Methyl substituted pyridinium **390** was also synthesised, albeit in low yield (15%).



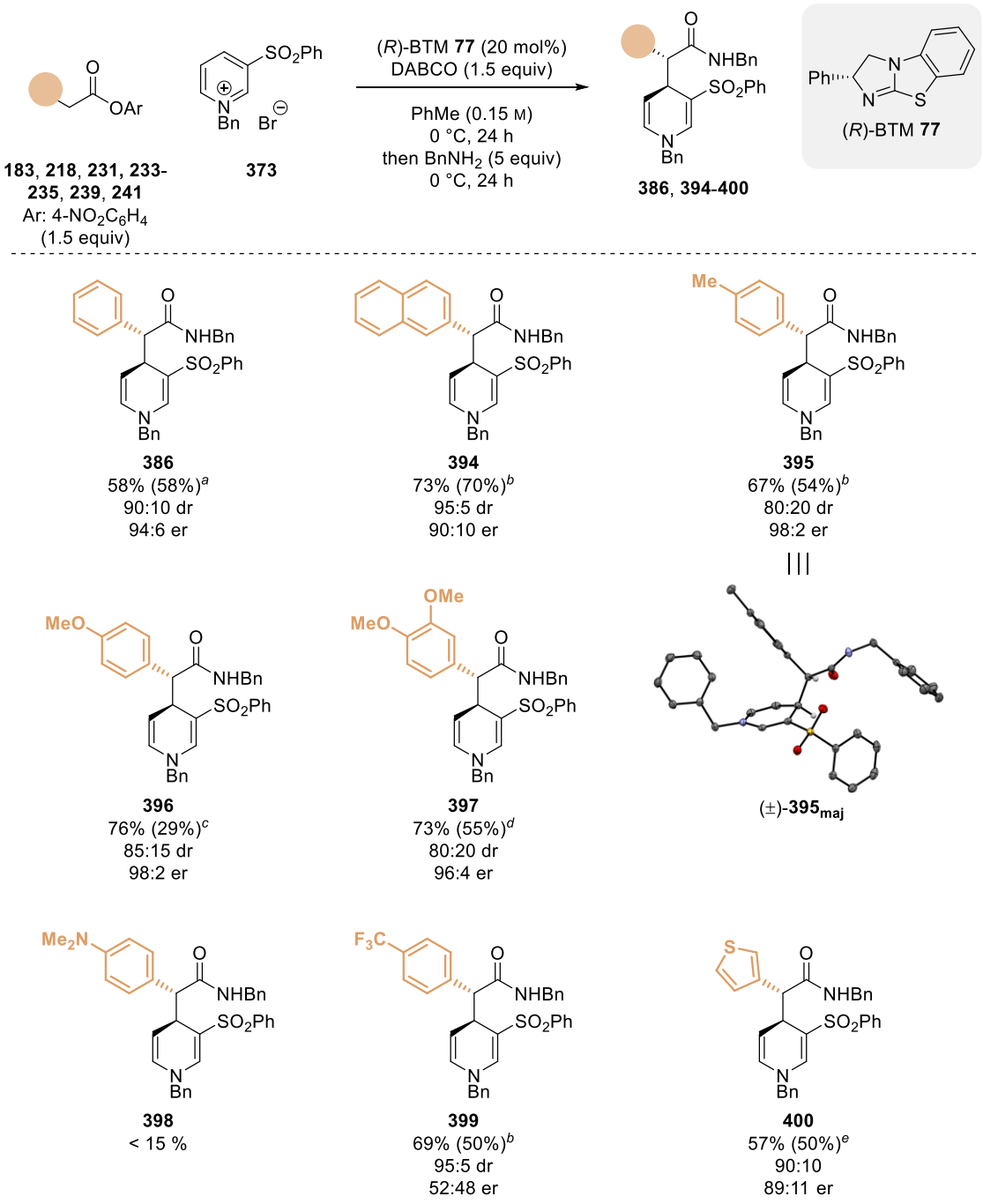
Scheme 72. Synthesis of various *N*-substituted pyridinium salts.

The various *N*-substituted pyridinium salts were then subjected to the catalytic reaction conditions (Scheme 73). Both 2-naphthyl and 4-methoxy-pyridinium salts gave the corresponding 1,4-DHP **391** and **392** in good isolated yields with excellent stereocontrol. However, methyl substituted nitrile pyridinium **390** showed no conversion to product. This result suggests an *N*-benzyl substituent is critical for reactivity. There are multiple ways to rationalise this result: it could be due to (i) the critical formation of a pyridinium ylide species in the reaction mixture, with **390** not exhibiting the required p*K*a value; (ii) alkylation of the isothiourea catalyst inhibiting the catalytic reaction since *N*-methyl pyridinium salts can be used for the alkylation of various nucleophiles;[213] or (iii) stabilising π-cation or π-π interactions in the transition state involving the benzyl group. Further investigation would be required to probe these possibilities.

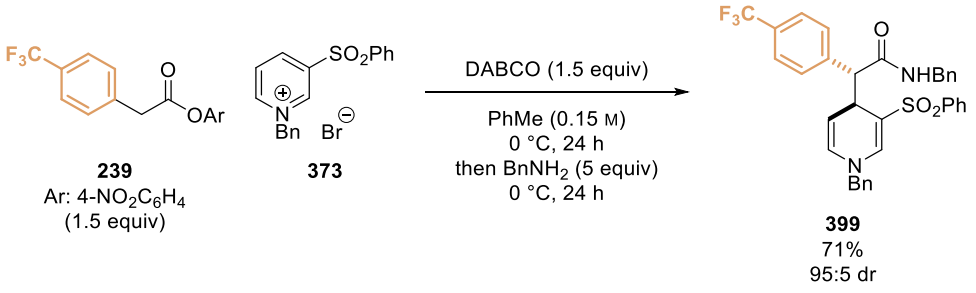


Scheme 73. *N*-substituent scope.
(isolated yields in parenthesis; a: isolated 92:8 dr; b: isolated 94:6 dr; c: *i*-Pr$_2$NEt as base.)

Next, a range of aryl esters were utilised in the catalysis (Scheme 74). Reaction of 2-naphthyl ester **231** gave the corresponding 1,4-DHP **394** in excellent yield, diastereo- and enantioselectivity (70%, 95:5 dr and 90:10 er). Electron-donating groups were also tolerated to the methodology: 4-tolyl 1,4-DHP **395** was formed in 54% isolated yield with good diastereoselectivity (80:20 dr) and excellent enantiocontrol (98:2 er). The relative configuration of the major diastereoisomer **395** was determined by single crystal X-ray crystallography, with the absolute configuration assigned by analogy to the known stereochemical outcome of BTM **77** in C(1)-ammonium enolate chemistry. All other products were assigned by analogy. Interestingly, the relative configuration observed within the major diastereoisomer is consistent with previous isothiourea catalysed processes, opposite to that at C(3) using the vinyl bis-sulfone electrophiles. 4-Methoxy and 3,4-dimethoxy esters **233** and **234** were also productive, furnishing the 1,4-DHP's **396** and **397** with high stereocontrol. However, the isolated yields in these cases were reduced compared to the conversion observed by ^{1}H NMR of the crude reaction mixture. This was due to difficult isolation of the products from the reaction by-products. Unfortunately, *para*-dimethylamino gave < 15% conversion to product, returning only starting materials. Electron-withdrawing groups proved incompatible with the dearomatisation methodology: *para*-trifluoromethyl phenyl



Scheme 74. Aryl ester scope.
(isolated yields in parenthesis; [a]: 92:8 dr, [b]: > 95:5 dr, [c]: 90:10 dr, [d] 95:5 dr, [e] 93:7 dr.)

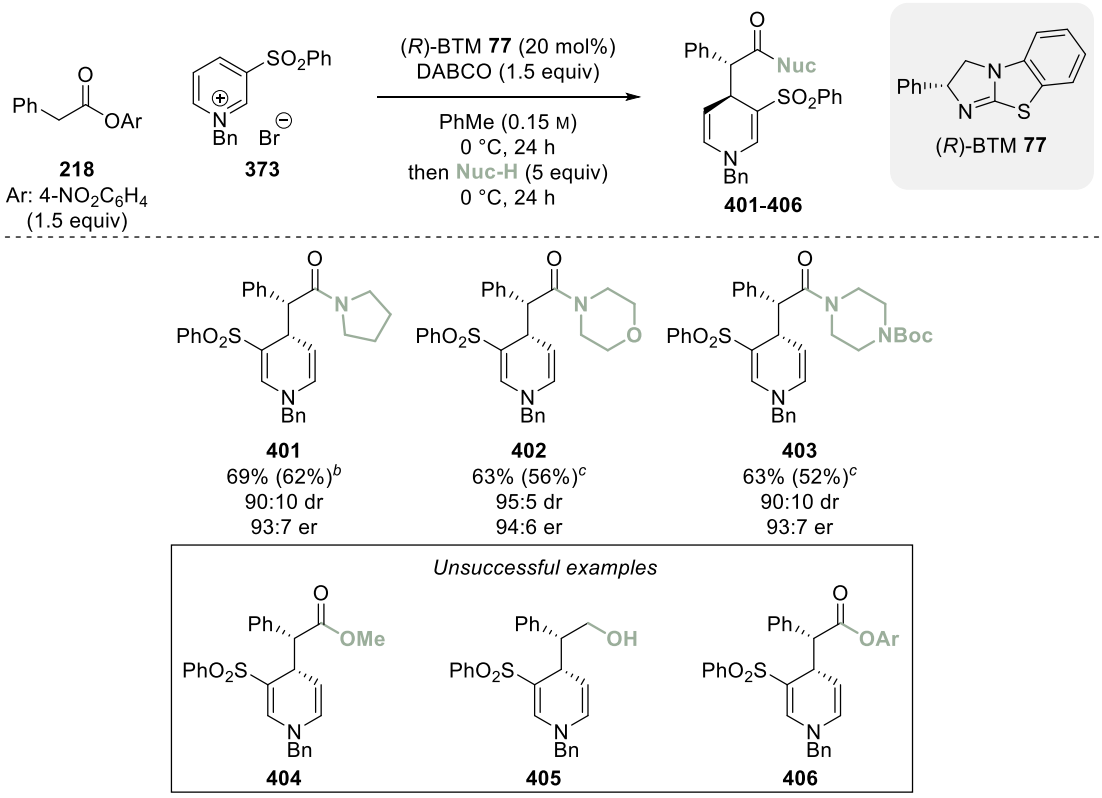


Scheme 75. Control reaction without isothiourea catalyst using ester 239.

substituted ester **239** gave racemic product **399**. This suggests there is a narrow reactivity window for the aryl ester component: it requires sufficient acidity for deprotonation to generate the reactivity nucleophilic C(1)-ammonium enolate, whilst also not being so acidic that a racemic background reaction takes place. A significant base-promoted background reaction was confirmed by carrying out a reaction with no catalyst present affording the product in 71% yield in the same diastereomeric ratio (95:5 dr, Scheme 75). Finally, use of 3-thiophenyl ester **241** demonstrated that heterocyclic esters can be used, giving 1,4-DHP **400** in good yield with high stereocontrol.

To demonstrate the synthetic utility of the dearomatisation protocol, a range of nucleophiles were added at the end of the catalytic reactions allowing access to various carbonyl motifs (Scheme 76). Amine nucleophiles were demonstrated to be generally applicable: addition of pyrrolidine, morpholine and *N*-Boc piperazine enabled access to amides **401**-**403** in good yield with high diastereo- and enantioselectivities. Unfortunately, ester **404** and alcohol **405** could not be accessed, with the respective reactions using methanol and $LiAlH_4$ leading to decomposition of the reaction components. Direct isolation of the *para*-nitrophenyl ester was also attempted, but **406** decomposed during column chromatography.

During the synthesis of pyrrolidinyl amide **401**, the C(6) regioisomer **407** was observed by ^{1}H NMR analysis of the crude reaction mixture and was isolated in 4% yield (Figure 30). The identity of **407** was confirmed through 2D NMR techniques (^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC). Regioisomer **407** exhibits a distinct change in ^{1}H and ^{13}C chemical shifts at the highlighted position compared to the analogous C(4)H of major diastereomer **401**. In regioisomer **407**, the ^{1}H signal is significantly more deshielded compared to the C(4) product, whilst the ^{13}C shift also lies further downfield (~ 60 ppm) which is characteristic of a carbon atom attached to a heteroatom. Considering this new evidence, the ^{1}H NMR spectra of previous crude reaction mixtures were analysed to determine if significant amounts of regioisomers were formed in these cases. However, in general, limited amounts were observed in all cases (< 5%).



Scheme 76. Nucleophile scope.
(isolated yields in parenthesis; isolated in [a]: 92:8 dr, [b]: 93:7 dr, [c]: > 95:5 dr.)

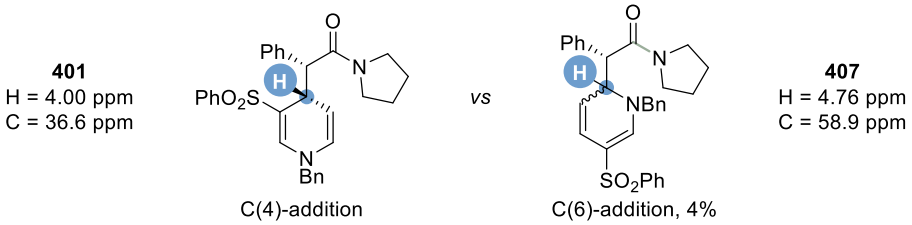
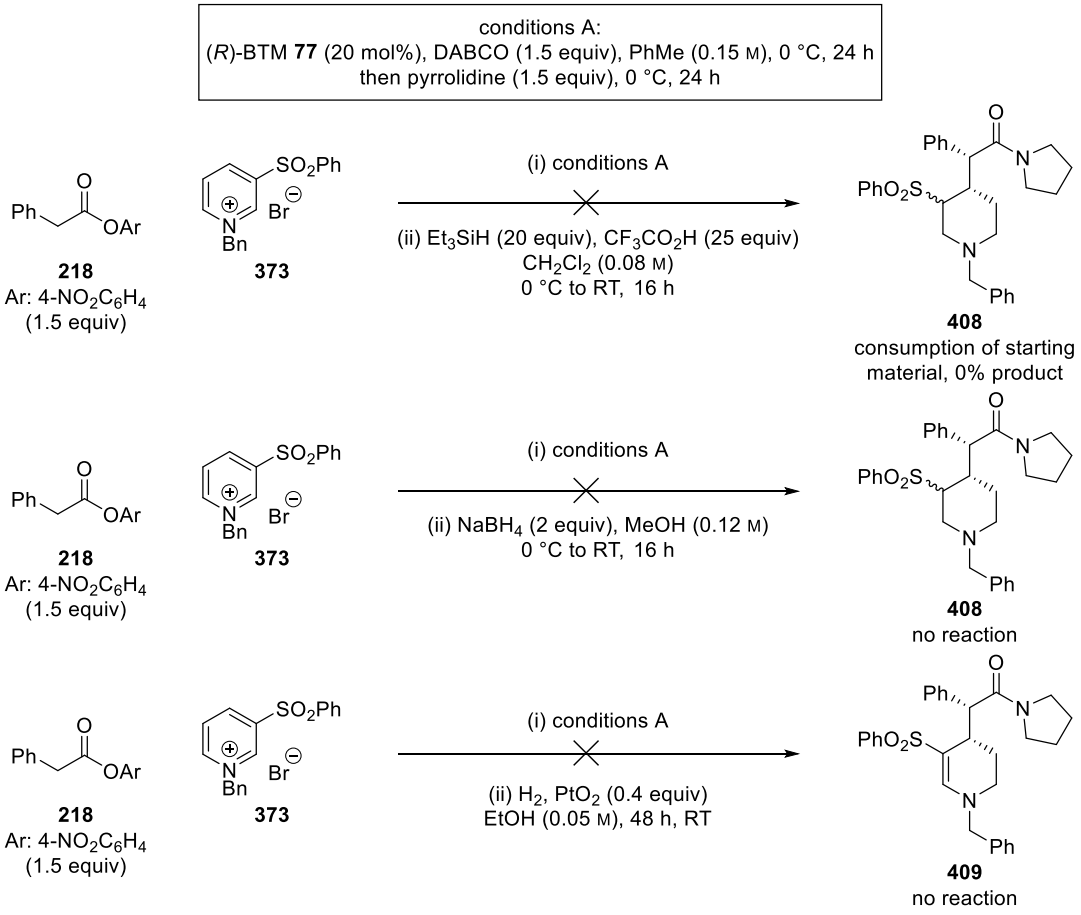


Figure 30. Observation of C(6)-addition.

4.2.3. Product Derivatisations

Whilst enantioenriched 1,4-DHPs are privileged structural architectures, they are also important synthetic intermediates. To demonstrate the utility of the methodology, a series of derivatisation experiments were carried out in an attempt to reduce the 1,4-DHPs to piperidines (Scheme 77). To avoid chromatographic purification of the inherently less stable 1,4-DHPs, a two-step procedure was proposed. After the catalytic reaction and subsequent aqueous work-up, the crude 1,4-DHP was treated with triethylsilane and trifluoroacetic acid, as previously reported.[206] In this reaction, whilst all the crude material was consumed, no reduction product was observed. These reduction conditions were also employed on the isolated 1,4-DHP after column chromatography to determine if use of the crude

material was the problem, however, this also gave none of the desired piperidine. Next, attention was turned to alternative reducing conditions using sodium borohydride.[208] However, in this case no reduction was observed and starting material remained. In an alternative strategy, hydrogenation of the crude DHP was attempted using PtO_2 catalyst, which had been previously used in the reduction of DHPs.[214] However, no conversion of the starting material was observed. Although the sulfone functional group enables the dearomatisation to occur, it seems the 1,4-DHP product is quite stable to reduction conditions. Hydrogenation under pressure using an autoclave may be a future solution to this problem.

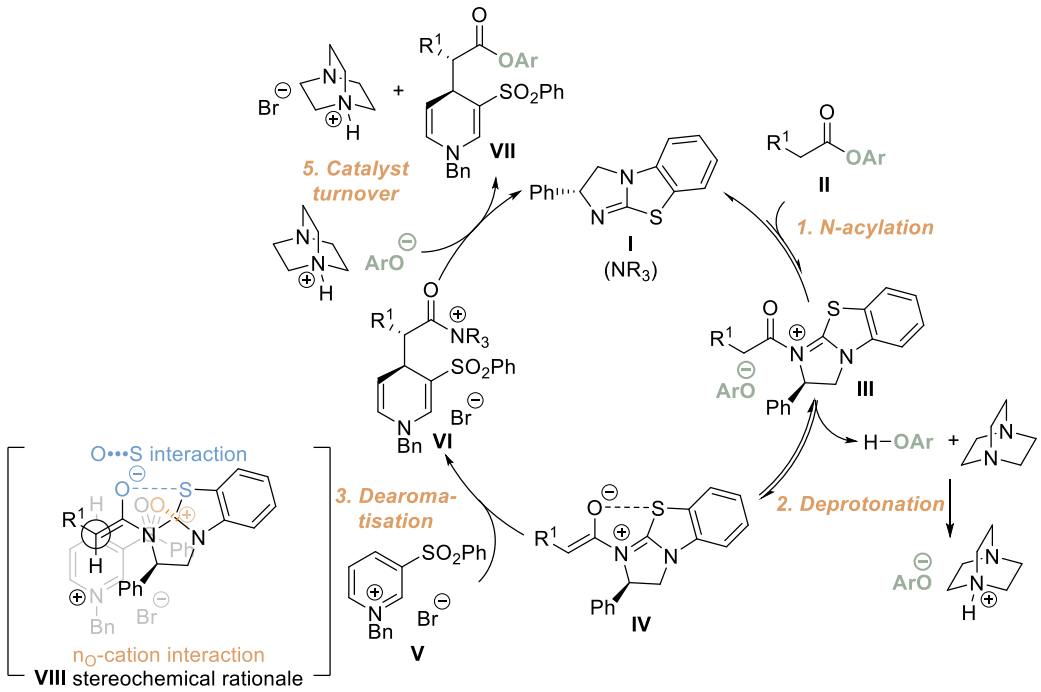


Scheme 77. Product derivatisation attempts.

4.2.4. Proposed Mechanism

A simplified reaction mechanism can be proposed analogous to similar isothiourea-catalysed processes via C(1)-ammonium enolate intermediates using aryl ester precursors (Scheme 78). Acylation of the Lewis base isothiourea catalyst **I** by the aryl ester **II** affords acyl ammonium ion pair **III**, which can be deprotonated by the

aryloxide to form C(1)-ammonium enolate **IV**. The phenol released from step two can be deprotonated by the DABCO auxiliary base regenerating the aryloxide, however, elucidation of the exact role of DABCO in this process would require further investigation. Regioselective addition of the C(1)-ammonium enolate to the 4-position of the benzyl pyridinium **V** generates acyl ammonium **VI**. Catalyst turnover can be achieved through addition of the aryloxide to intermediate **VI** to reform BTM **I** and generate the product **VII**. The observed diastereoselectivity can be rationalised tentatively by pre-transition state assembly **VIII** which allows for a potentially favourable n_O-cation interaction between the sulfone oxygen atom and isothiouronium cation. A similar C=O···isothiouronium interaction has been observed in the acylative kinetic resolution of tertiary alcohols.[215]



Scheme 78. Proposed mechanism.

4.3. Conclusions

A procedure for the regio-, diastereo- and enantioselective dearomatisation of pyridinium salts using isothiourea catalysis via C(1)-ammonium enolates has been developed. This significantly broadens the scope of compatible electrophiles in isothiourea catalysis via C(1)-ammonium enolates from alkene and carbonyl derivatives, enabling the synthesis of enantioenriched 1,4-DHP hetereocyclic motifs. This protocol required extensive optimisation to achieve high enantioselectivities

alongside synthetically useful product yields. Key factors in the optimisation included the use of toluene as the reaction solvent, DABCO as the auxiliary base and carrying out the reaction at low temperature (0 °C). The developed methodology was used for the synthesis of 14 enantioenriched 1,4-DHPs in good yield with excellent stereocontrol (up to 70% isolated yield, 95:5 dr, 98:2 er). However, some of the isolated yields were lower than the observed reaction conversion due to the instability of the 1,4-DHPs and challenging separation from reaction by-products. Derivatisations of the 1,4-DHPs were also attempted, however, none of these were successful.

Chapter 5. Enantioselective Nucleophilic Aromatic Substitution via C(1)-Ammonium Enolates

5.1. Introduction

5.1.1. α-Arylation

The α-aryl carbonyl motif is an integral structural component of many biologically active compounds. For example, α-arylpropanoic acids such as Naproxen **410**, Ketoprofen **411**, Ibuprofen **412** and Flurbiprofen **413** (Figure 31) are a class of non-steroidal anti-inflammatory drugs with analgesic and antipyretic effects.[216] Therefore, the development of novel protocols for the α-arylation of carbonyl derivatives is of significant interest.

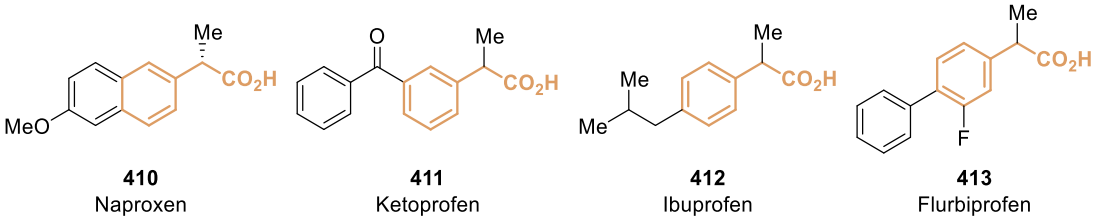
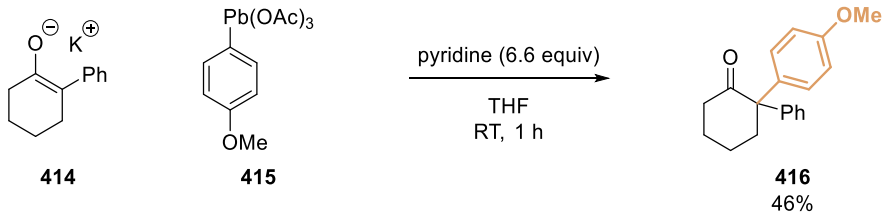


Figure 31. α-Arylpropanoic acid non-steroidal anti-inflammatory drugs.

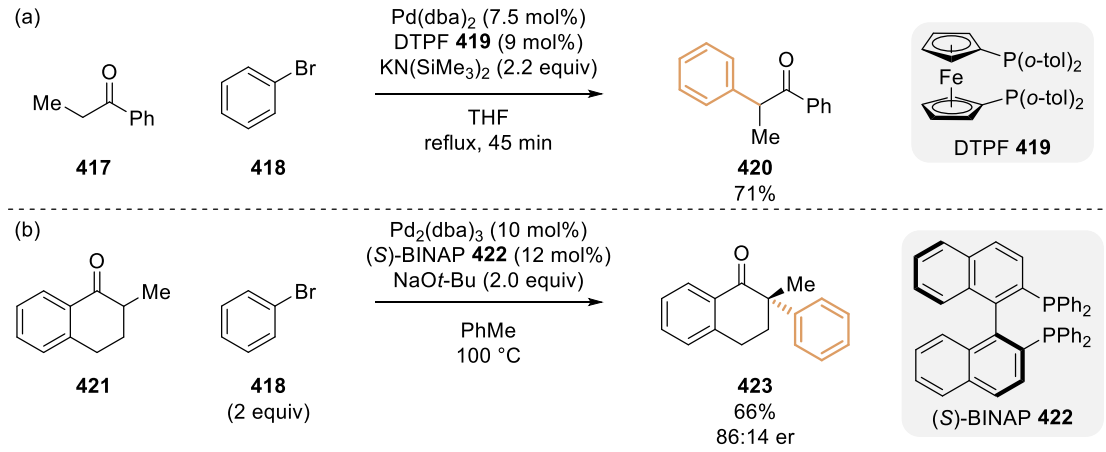
Early methods for the α-arylation of carbonyl groups involved the treatment of preformed metal enolates with electrophiles. In 1997, Pinhey reported the α-arylation of preformed potassium enolate **414** with lead triacetate electrophile **415** to give α-arylated ketone **416** in moderate yield (Scheme 79).[217]



Scheme 79. Early α-arylation method using a preformed potassium enolate.

The development of more general and catalytic protocols were required and over the last twenty years many transition metal-catalysed methods have been reported. One method that allows for facile α-arylation is the Buchwald-Hartwig enolate arylation (Scheme 80a).[218],[219] This involves the palladium-catalysed coupling of aryl halides and carbonyl-containing/carbonyl equivalent compounds to give α-arylated

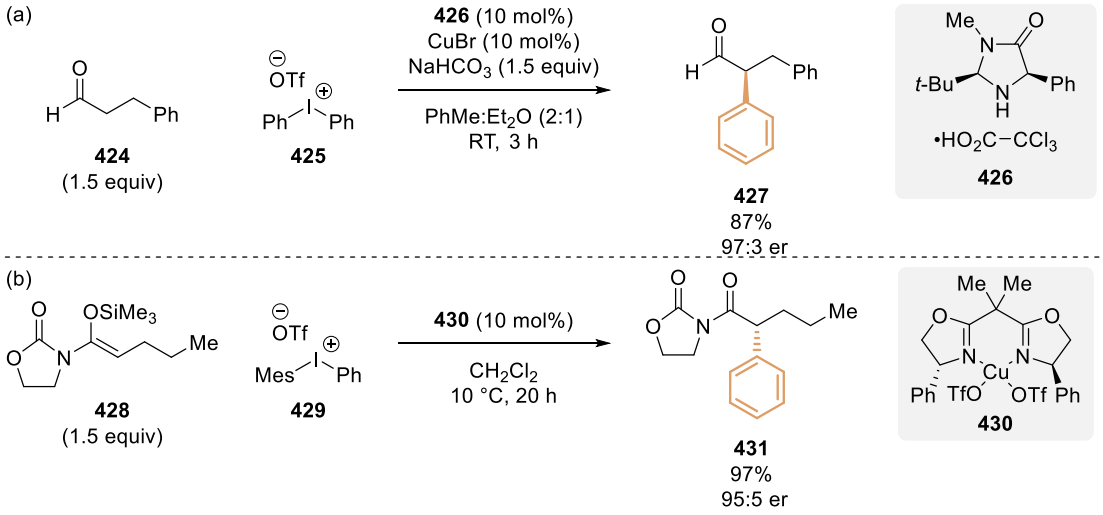
carbonyl products. The reaction is high yielding and functional group tolerant. Notably, a wide range of enolate equivalent precursors can be employed: aldehydes, ketones, esters, amides, nitriles, malonates, nitroalkanes and sulfones can all be used to form secondary, tertiary and quaternary carbon centres. More challenging is the enantioselective α-arylation of carbonyls. The Buchwald-Hartwig approach can be carried out asymmetrically by employing chiral phosphine ligands to give products in high yield and er (Scheme 80b).[220],[221] However, this process is limited to cyclic ketone and lactone substrates such as **421**, and only quaternary centres can be formed with high enantioselectivity, presumably because of the potential for product racemisation and bis-arylation under the basic reaction conditions. An alternative enantioselective umpolung approach developed by Fu described the nickel-catalysed cross-coupling of α-halocarbonyls with aryl silicon or boron reagents that allows for the formation of tertiary stereogenic centres.[222],[223] However, this protocol had to be carried out in a glovebox.



Scheme 80. Palladium-catalysed Buchwald-Hartwig enolate arylation.

MacMillan and co-workers reported the α-arylation of aldehydes via combined enamine and copper catalysis (Scheme 81a).[224] Aldehyde **424** was treated with catalyst **426**, copper bromide and diaryl iodonium electrophile **425** to give α-aryl aldehyde **427** in good yield and high er, with product configuration governed by the chiral organocatalyst. An additional complementary method which allows for the formation of tertiary α-aryl carbonyl compounds was reported by Gaunt and co-workers.[225] Silyl ketenimide **428** underwent α-arylation when subjected to copper catalyst **430** with iodonium salt **429** to afford α-aryl product **431** in excellent yield

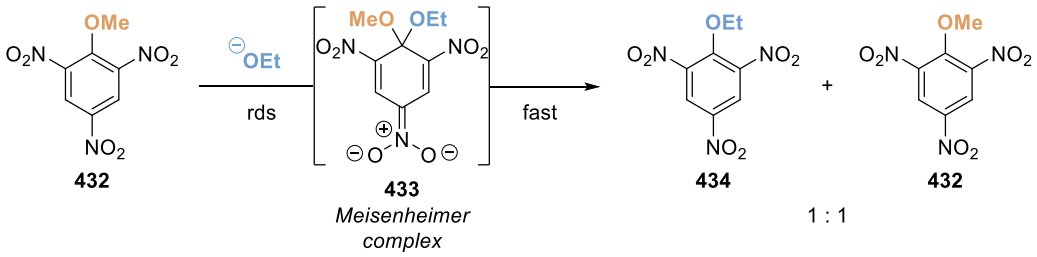
and enantioselectivity (Scheme 81b). In this case, the enantioselectivity is determined by the chiral copper-(II)-bisoxazoline complex. Despite recent advancements, the significant limitations of existing protocols necessitate the development of novel catalytic enantioselective α-arylation methods.



Scheme 81. Enantioselective α-arylation via (a) combined enamine and copper catalysis, and (b) copper catalysis.

5.1.2. Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution (S_NAr) is a fundamental reaction in organic synthesis, proposed to proceed via the rate-limiting addition of a nucleophile onto an electron deficient arene via an anionic Meisenheimer complex, followed by fast re-aromatisation through elimination of the leaving group. This was first reported by Meisenheimer in 1902, who observed a 1:1 mixture of products **432** and **434** from the reaction of methoxy trinitrobenzene **432** and ethoxide (Scheme 82).[226] Indeed, stabilised Meisenheimer complexes bearing strong electron-withdrawing groups (nitro) with poor leaving groups (fluoride) have been characterised as reaction intermediates.[227] This general addition-elimination reaction mechanism has been widely accepted, taught to undergraduate students and found in textbooks.[228]

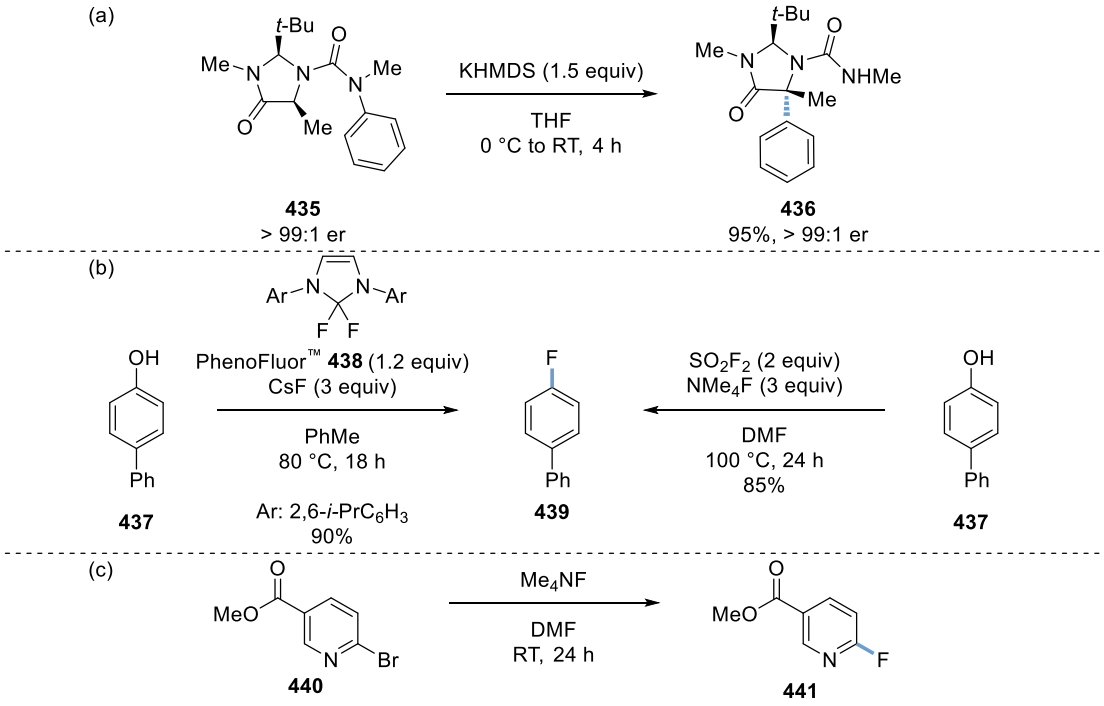


Scheme 82. The first nucleophilic aromatic substitution reaction.

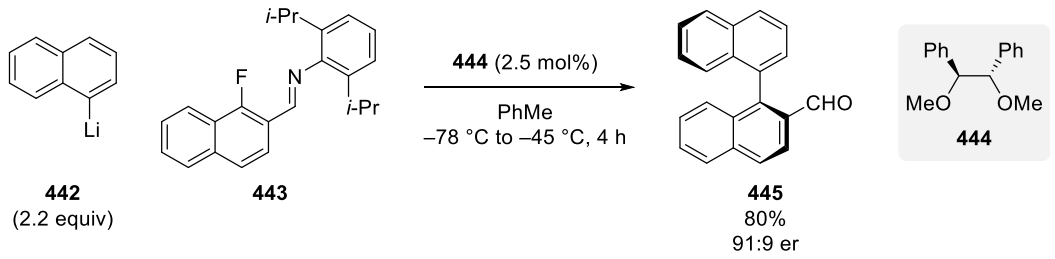
Recently, several reactions have been reported which are proposed to proceed via a concerted S_NAr mechanism at the sp^2-hybridised carbon centre. Clayden and co-workers reported the diastereoselective α-arylation of enantiopure amino acids through an intramolecular rearrangement of imidazolidinone **435** under basic conditions (Scheme 83a).[229] Electron deficient, neutral and electron rich aromatic rings undergo the arylation in excellent yield and enantioselectivity. During mechanistic studies, no Meisenheimer intermediate was detectable. Hammett analysis was used to measure the sensitivity of the reaction to varying electronics, and gave a ρ value of 4.5, significantly lower than the calculated value for a stepwise S_NAr process (ρ = 8.6) indicating a concerted mechanism. The groups of Ritter and Sanford have developed methods for the deoxyfluorination of phenols using PhenoFluor™ and tetramethylammonium fluoride, respectively (Scheme 83b).[230],[231] In each case, mechanistic studies (DFT calculations, Hammett analysis) implicate a concerted nucleophilic aromatic substitution mechanism without the formation of a Meisenheimer intermediate. Jacobsen and co-workers have carried out $^{12}C/^{13}C$ isotope studies and computational analyses to demonstrate that many S_NAr reactions, such as the example in Scheme 83c proceed through a concerted mechanism, and that stepwise mechanisms are predicted primarily only for reactions of substrates bearing strong electron-withdrawing groups and fluoride as a leaving group.[232]

There are only limited reports of enantioselective S_NAr processes: Tomioka and co-workers reported the first catalytic enantioselective nucleophilic aromatic substitution reaction of fluoronaphthylimine **443** using naphthyllithium **442** to give chiral biaryl aldehyde **445** (Scheme 84).[233] This process consists of an enantioselective addition of the chiral Lewis base-bound naphthyllithium

nucleophile, followed by point-to-axial chirality transfer during fluoride elimination. Finally, hydrolysis of the imine upon reaction work-up generates the product.

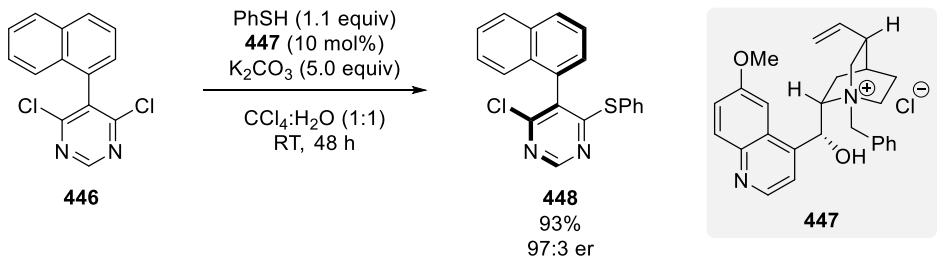


Scheme 83. Concerted SNAr reactions.



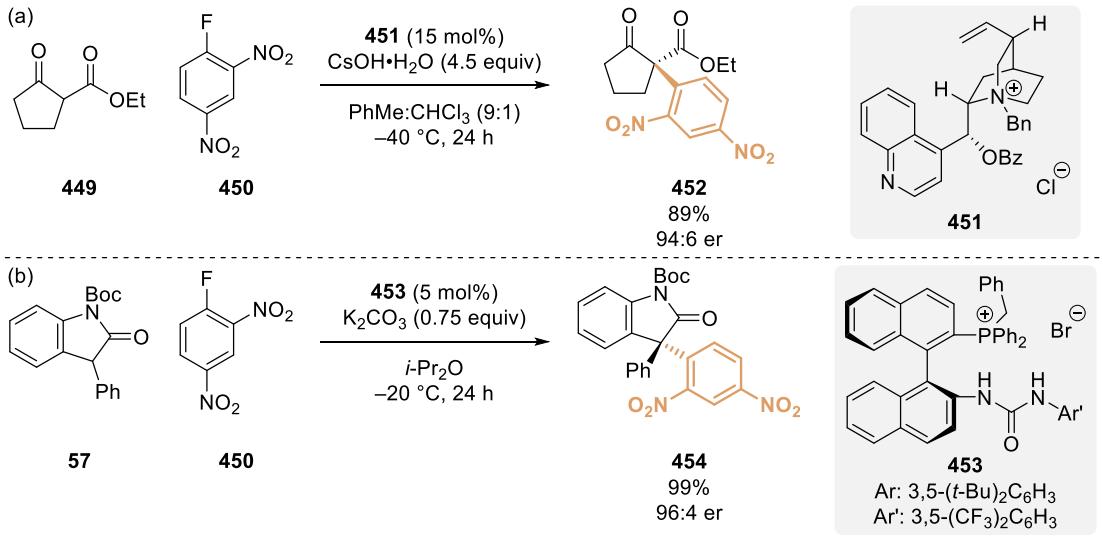
Scheme 84. The first catalytic enantioselective SNAr reaction.

In 2014, M. D. Smith and co-workers reported the nucleophilic aromatic substitution using thiols for the desymmetrisation of dichloropyrimidine **446** to give axially chiral biaryl **448** in excellent yield and er using chiral quaternary ammonium PTC **447** (Scheme 85).[234] The thiophenol is deprotonated and then directed by the chiral counter ion PTC to the prochiral electrophile to generate axially chiral **448**.



Scheme 85. Catalytic enantioselective SNAr of dichloropyrimidines.

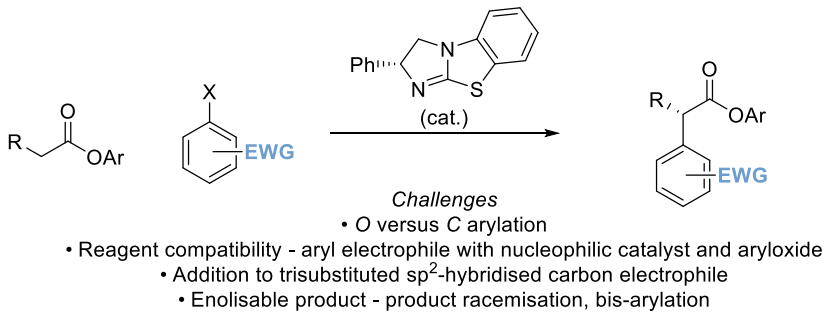
There are two examples of catalytic enantioselective SNAr reactions that generate point chirality. Firstly, Jørgensen reported the nucleophilic aromatic substitution of dinitrofluorobenzene **450** with 1,3-dicarbonyl compounds **449** using quaternary ammonium PTC **451** (Scheme 86a).[235] Quaternary stereocentres were formed in high yields and er. In a similar protocol, Marouka reported the SNAr reaction of dinitrofluorobenzene **450** with oxoindole **57** using phosphonium PTC **453** to yield quaternary stereogenic centres **454** in high yield and er (Scheme 86b).[236]



Scheme 86. Catalytic enantioselective SNAr reactions of dinitrofluorobenzene.

Currently, all the catalytic enantioselective SNAr protocols for the generation of point chiral products employ phase transfer organocatalysis and are limited to the formation of products containing quaternary stereocentres. The proposed project was to develop a novel enantioselective nucleophilic aromatic substitution of aryl electrophiles with C(1)-ammonium enolate nucleophiles using isothiourea catalysis allowing for the synthesis of α-arylated ester derivatives (Scheme 87). For the proposed work to be successful there would be significant challenges to overcome. Most commonly, heteroatom nucleophiles are employed in nucleophilic aromatic

substitution reactions. There are examples of carbon-based nucleophiles utilised in SNAr processes; however, the majority of these are 1,3-dicarbonyl species.[237] In this respect, the enolate derivative can undergo addition through either carbon versus oxygen atom. This regioselectivity would need to be controlled for the protocol to be successful. In relation to this, whilst the aryl electrophile is required to be reactive enough to undergo reaction with the C(1)-ammonium enolate, it must avoid side reactions with the heteroatomic nucleophilic catalyst and aryloxide. Thus, reagent compatibility will also be crucial. Previous work has shown that C(1)-ammonium enolates add to mono β-substituted Michael acceptors. Since the aryl electrophile requires a leaving group for elimination, the C(1)-ammonium enolate is required to add to a challenging tri-substituted sp^2-hybridised carbon atom. Finally, the products contain an enolisable tertiary stereogenic centre, which could potentially undergo racemisation or subsequent enolate formation and bis-arylation. Overall, whilst the development of this protocol would be very challenging, the potential for catalytic enantioselective synthesis of valuable products would be of significant interest.



Scheme 87. Proposed work.

5.2. Results and Discussion

5.2.1. Intermolecular SNAr

First, identification of a suitable electrophilic aromatic partner was required for the development of the SNAr process. It is well known that nucleofuge-substituted heteroaromatics such as pyridine and diazines readily undergo nucleophilic aromatic substitution.[238],[239] Diazines such as C4- and C2-pyrimidines, C4- and C3-pyridazines and C2-pyrazines (Figure 32) have been shown to be amongst the most reactive heteroaromatic electrophiles for SNAr. Heteroaromatics bearing only one

nitrogen atom such as C4- and C2-pyridines also react efficiently with nucleophiles. In all these cases, the built-up negative charge can be delocalised onto an electronegative nitrogen atom. C5-pyrimidines and C3-pyridines react slowly in nucleophilic aromatic substitution processes; this is a consequence of the negative charged build up not being delocalised onto nitrogen.

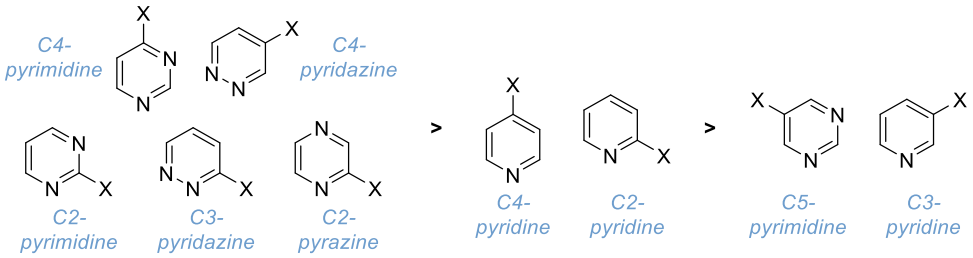
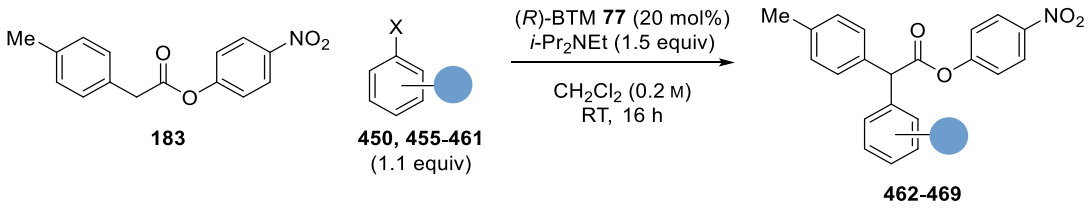
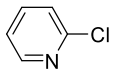
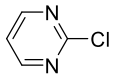
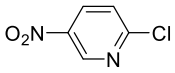
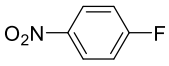
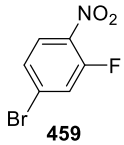
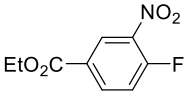
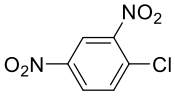
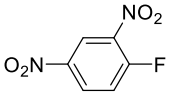


Figure 32. Reactivity scale of heteroaryl electrophiles in SNAr.

Based on these considerations, a range of electrophiles were screened (Table 22). Aryl ester **183** and 2-chloropyridine **455** were subjected to the model reaction conditions: isothiourea (*R*)-BTM **77** and Hünig's base in dichloromethane at room temperature (entry 1).[240] The reaction conditions were chosen based upon the previous external catalyst turnover protocols developed within the Smith group, although it was recognised the SNAr system could require significantly different conditions. After 16 hours at room temperature no product was observed, and starting materials remained. Reaction with the more reactive 2-chloropyrimidine **456** was also trialled; again, no product was detected (entry 2). Additional reactions of these electrophiles with TM·HCl **76** and HyperBTM **82** catalysts in various solvents (THF, PhMe, DMF) between RT and 60 °C also gave no product, with only small amounts of ester hydrolysis observed.[95],[241] To increase the electrophilicity of the arylation reagent, the introduction of an electron-withdrawing substituent was investigated. Therefore, a reaction with 2-chloro-5-nitropyridine **457** was attempted (entry 3); however, once again only starting materials were observed. At this stage, it was recognised heteroaromatic electrophiles were either not electrophilic enough or incompatible with isothiourea catalysis via C(1)-ammonium enolates. As an alternative, it was decided to utilise electron-deficient benzene derivatives as the electrophile, as these had been shown previously to participate in nucleophilic aromatic substitution reactions with enolate nucleophiles.[235],[236] Reaction using

Table 22. Study of various electrophiles.



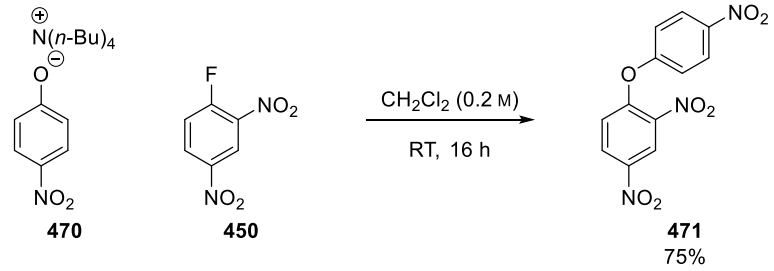
Entry	Electrophile	Ester Remaining (%)	Electrophile Remaining (%)	Product (%)
1	 **455**	85	90	0
2	 **456**	80	81	0
3	 **457**	88	97	0
4	 **458**	88	87	0
5	 **459**	99	85	0
6	 **460**	80	86	0
7	 **461**	90	65	0
8	 **450**	42	0	0

[a] yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

1-fluoro-4-nitrobenzene **458** (entry 4) also yielded no product. It was hoped introduction of a second electron-withdrawing group would provide reactivity.

However, reactions with 1-fluoro-2-nitro-5-bromobenzene **459**, ester substituted **460** and 1-chloro-2,4-dinitrobenzene **461** (entries 5-7) gave no reaction. Interestingly, on reaction with Sanger's reagent (1-fluoro-2,4-dinitrobenzene) **450** full consumption of the electrophile was observed (entry 8).[242] In addition, 58% of the ester had been consumed. A complex reaction mixture containing numerous aromatic peaks was observed by ^{1}H NMR, and TLC analysis indicated multiple spots. However, no product could be isolated from this mixture.

To gain an understanding of the reaction, a series of control experiments were conducted to determine the compatibility of the various reaction components. Reaction of tetrabutylammonium *para*-nitrophenoxide **470** and dinitrofluorobenzene **450** gave biaryl ether product **471** in 75% yield (Scheme 88), resulting from S$_N$Ar of **450** by the phenoxide.

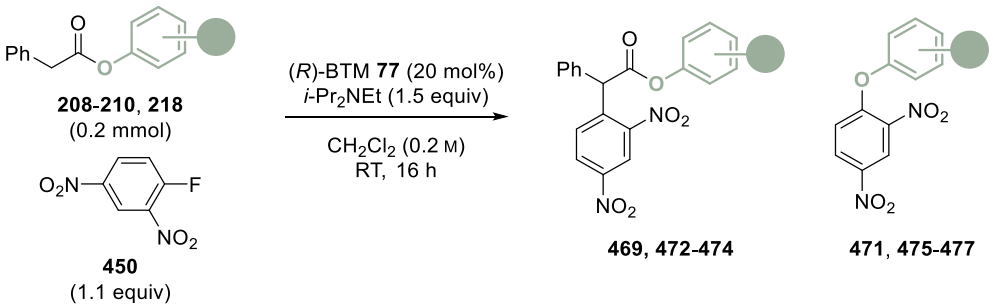


470 **450** **471** 75%

Scheme 88. Control reaction of the aryloxide and dinitrofluorobenzene.

Correspondingly, even at this early stage the incompatibility of the aryloxide and the electrophile was apparent and could adversely impact the success of the methodology. Subsequently, an aryl ester study was undertaken. It was hoped that screening a range of alternative aryl ester starting materials may lead to a reduction in the aryloxide S$_N$Ar side reaction. To this end, various aryl esters were applied in the S$_N$Ar reaction (Table 23). However, inspection of the ^{1}H NMR of the crude reaction mixture of the reaction between electrophile **450** and ester **218** showed 41% S$_N$Ar by-product (entry 1). Reaction of pentafluorophenyl **208**, tetrafluorophenyl **209** and trichlorophenyl **210** esters (entries 2-4) were attempted. Although lower amounts of the phenoxide S$_N$Ar by-product were observed by ^{1}H NMR analysis of the crude material, in all cases none of the desired *C*-arylated product was detected.

Table 23. Aryl ester study.

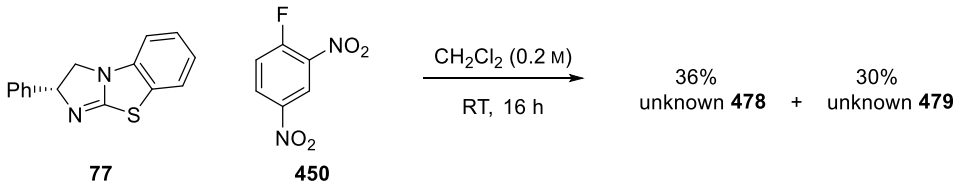


Entry	OAr	Ester Remaining (%)	Electrophile Remaining (%)	Product (%)	OAr S_NAr (%)
1	4-$NO_2C_6H_4$ (**218**)	40	0	0	41
2	C_6F_5 (**208**)	40	0	0	35
3	2,3,5,6-F_4C_6H (**209**)	50	22	0	23
4	2,4,6-$Cl_3C_6H_2$ (**210**)	70	37	0	20

[a] yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene internal standard.

A final stoichiometric control reaction between (*R*)-BTM **77** and electrophile **450** was carried out (Scheme 89). Unexpectedly, full consumption of the electrophile occurred. ^{1}H NMR of the reaction mixture indicated the formation of two unknown products **478** and **479** in 36% and 30% yield respectively, whilst 31% of BTM **77** remained. The reaction mixture was concentrated and purified by column chromatography to afford one of the unknown products in 31% isolated yield. ^{1}H NMR (Figure 33) showed the presence of three alkyl peaks similar to BTM **77** and two sets of three aromatic signals corresponding to two dinitrobenzene moieties. ^{1}H, ^{1}H-COSY spectra showed the presence of coupling between the three alkyl peaks and indicated the two dinitrobenzene rings were remote. HMBC revealed multiple bond correlations between alkyl C(2)*H* and a carbonyl carbon, whilst NOESY spectra showed alkyl C(2)*H* also coupled through space to aromatic C(6')*H*. IR data suggested the presence of a carbonyl group and HRMS indicated an extra oxygen

atom had been incorporated. From this data, it was proposed the product from the reaction was urea **478**.



Scheme 89. Control reaction of BTM and dinitrofluorobenzene.

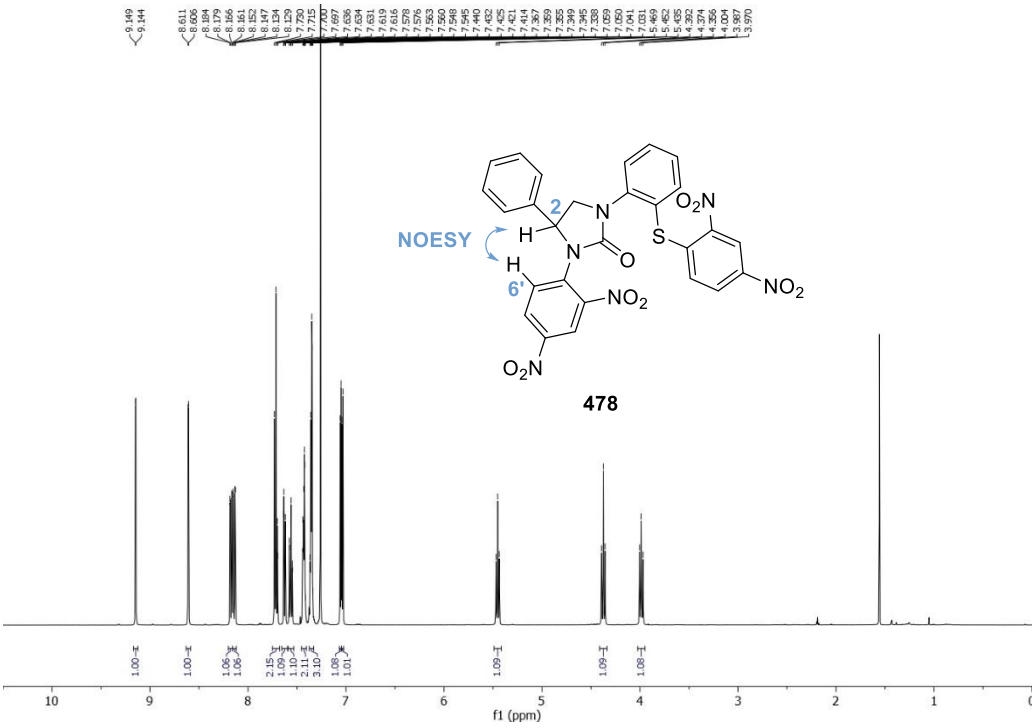
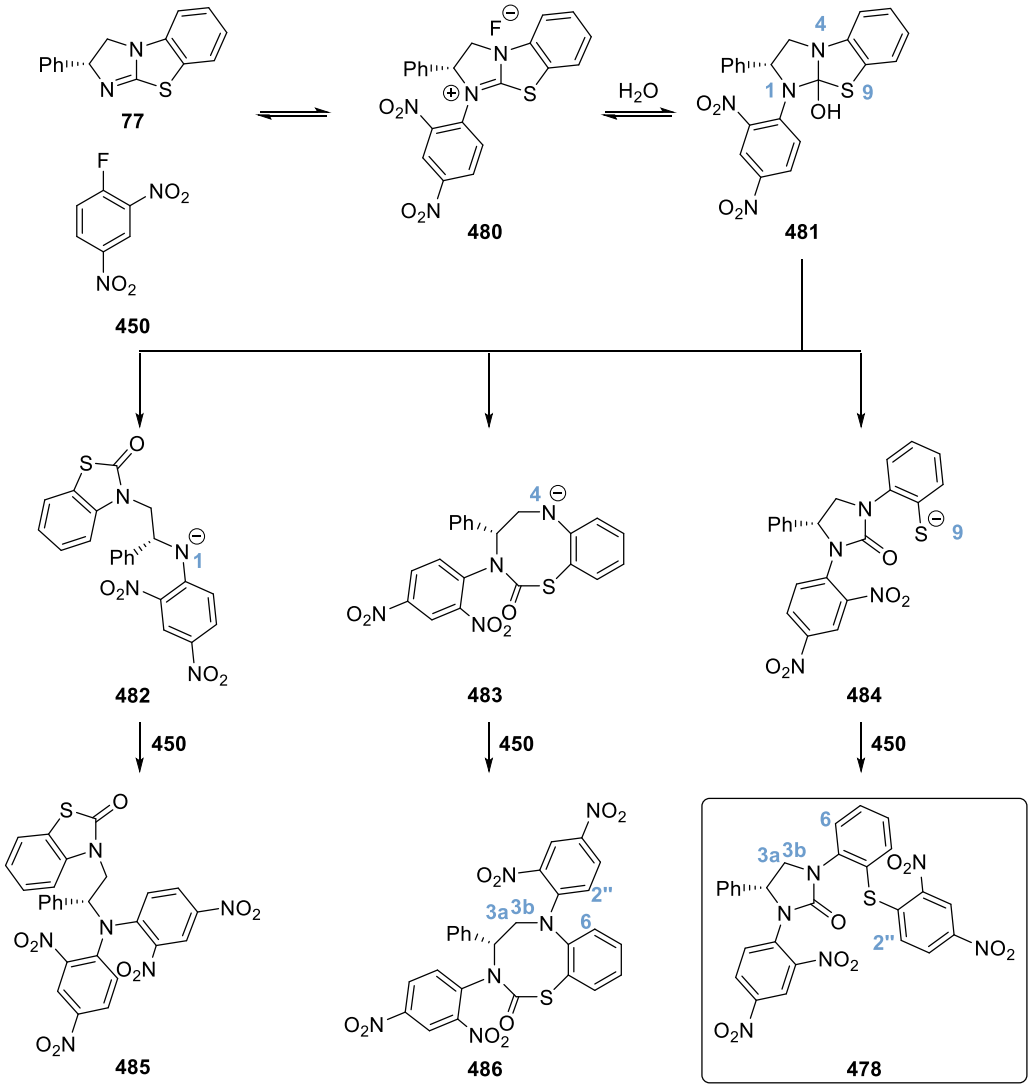


Figure 33. ^{1}H NMR of unknown product and proposed structure.

Mechanistically, this could have formed through initial *N*-arylation of the catalyst to form isothiouronium **480** (Scheme 90). At this stage, water could add to form tetrahedral intermediate **481**. Breakdown of this tetrahedral species through fragmentation could give either **482**, **483** or **484**, followed by addition of another equivalent of **450** would lead to **485**, **486** or **478** respectively. Based on the ^{1}H NMR spectrum, product **485** was ruled out because the dinitrobenzene peaks are non-equivalent. Considering the IR and 2D-NMR information, product **478** best matched the experimental data. IR data suggested the presence of a urea carbonyl group at 1720 cm^{-1}, whereas a urethane would be expected to have a lower carbonyl stretching frequency. NOESY through space correlations between C(3)$H^{A}H^{B}$ and C(2'')*H* were very weak, which would have been expected to be significant for product **486**.

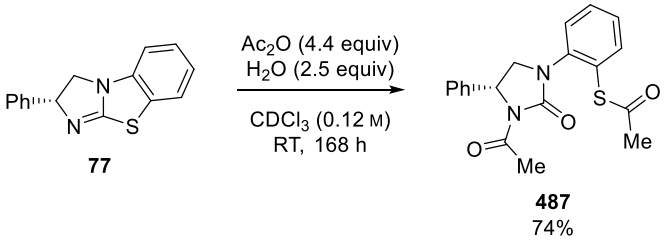
NOESY correlations were also observed from C(3)H^AH^B to C(6)*H*, which would be unexpected for **486**. Finally, one dinitrobenzene ring contains protons that are significantly more shielded than the other, indicating contrasting electronic characteristics of the *ipso* substituent in each. This is suggestive of an *S*-linked and an *N*-linked dinitrobenzene ring. Unfortunately, unknown **479** could not be isolated. However, BTM **77** was recovered in 51% yield, which is higher than what was expected based on the composition of the crude reaction mixture. Following multiple unsuccessful attempts to isolate unknown **479**, its structure was proposed to be intermediate **480**. It is postulated that intermediate **480** could revert to catalyst **77** and starting material **450** when subjected to silica.



Scheme 90. Proposed mechanism for the formation of 478.

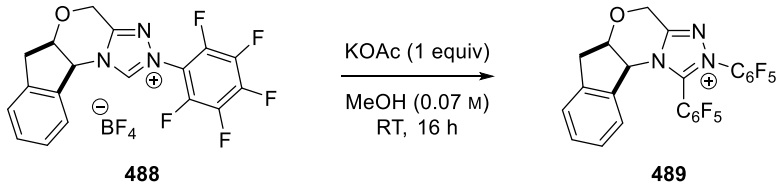
Birman and co-workers observed similar water-mediated decomposition of (*R*)-BTM **77** whilst carrying out the KR of secondary benzylic alcohols (Scheme 91).[96],[243]

When reactions were carried out in an ice-bath, or when water was intentionally added to the reaction mixture, ring opening of (*R*)-BTM **77** ensued to give degradation product **487**. The authors stated that catalyst degradation could be "effectively suppressed by utilising dry chloroform and adding a drying agent, such as sodium sulfate or carbonate".[96] However, on inspection of the supplementary data of the paper, the conversion and selectivity factor (*s*) were the same for reactions with and without sodium sulfate, whereas the addition of molecular sieves (MS) gave lower conversion and *s* value. The lower values observed in the presence of MS may be due to the presence of water in the MS if these were not properly activated.



Scheme 91. Water-mediated decomposition of BTM observed by Birman.

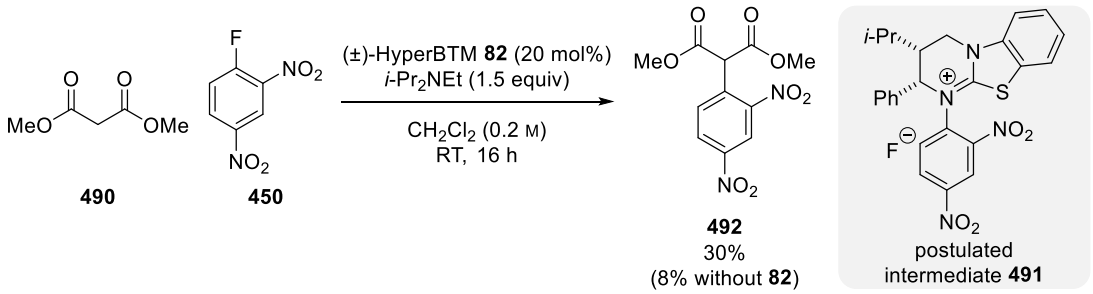
Catalyst decomposition has been previously reported in other Lewis base-catalysed processes. Evidence for SNAr decomposition of NHC catalysts was reported by Rovis in 2013.[244] When NHC precatalyst **488** was treated with base to form the carbene in situ, trace by-product **489** was observed (Scheme 92). It was proposed to have formed through SNAr of the NHC onto precatalyst **488**. Further studies to prevent catalyst decomposition for SNAr were carried out. Control reactions with sodium sulfate and MS respectively in combination with various catalysts gave similar results in comparison to reaction without desiccants, although further drying agents of varying capacity were not investigated.



Scheme 92. SNAr decomposition of an NHC precatalyst observed by Rovis.

5.2.2. Exploiting Catalyst Arylation

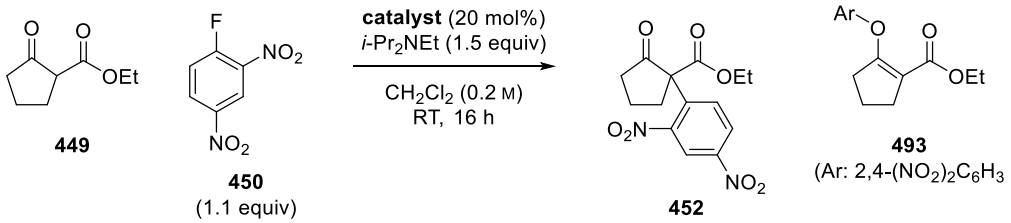
On the assumption that catalyst arylation was being observed to make a chiral *N*-aryl isothiouronium intermediate **491**, it was proposed that this species could be employed as a chiral arylating agent in the presence of an additional nucleophile as outlined in Scheme 93. An initial reaction was carried out using a symmetrical nucleophile to validate the hypothesis. Dimethyl malonate **490** was subjected to electrophile **450** and HyperBTM **82** at room temperature to give 30% of product **492**. Encouragingly, only an 8% yield was achieved without HyperBTM **82** present, consistent with this process being promoted by the isothiourea.



Scheme 93. Reaction of dimethyl malonate and dinitrofluorobenzene.

The use of an unsymmetrical enolate nucleophile was next probed to allow the formation of chiral products. A catalyst study was carried out using 1,3-dicarbonyl nucleophile **449** and electrophile **450**. In all cases, both *C*- and *O*-arylated products **452** and **493** were observed (Table 24). While TM **76** and BTM **77** gave the products in low yields (entries 1 and 2), HyperBTM **82** and DHPB **79** gave **452** and **493** in moderate yield in 70:30 ratio in favour of the desired *C*-arylated product (entries 3 and 4). Unexpectedly, DMAP reversed the selectivity, giving *O*-arylation preferentially in good yield (entry 5). DABCO gave the best yield of 77% in 75:25 selectivity (entry 6), whilst reaction using DBN gave poor yields (entry 7). Importantly, reactions in the absence of isothiourea but using Hünig's base gave only 10% yield (entry 8). Given the reactivity of DABCO, reactions with various cinchona alkaloids were also carried out, however, in all cases poor yields (14-28%) with similar selectivities (70:30) were obtained.

Table 24. Catalyst study.

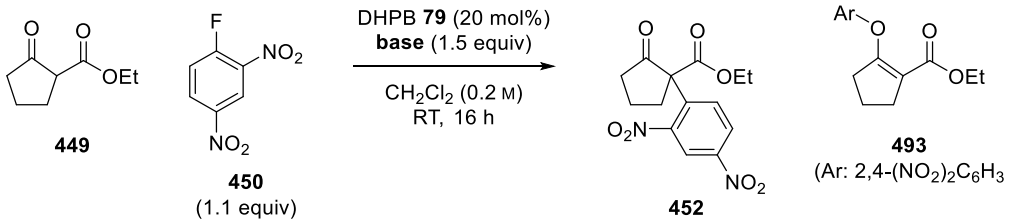


Entry	Catalyst	Yield (%)	452:493
1	BTM **77**	34	70:30
2	TM **76**	22	70:30
3	HyperBTM **82**	54	70:30
4	DHPB **79**	58	70:30
5	DMAP	66	15:85
6	DABCO	77	75:25
7	DBN	24	60:40
8	n/a	10	80:20

[a] yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Next, by using DHPB as a model isothiourea catalyst, the influence of the auxiliary base was investigated in an attempt to increase the *C*- to *O*-arylation ratio (Table 25). In comparison to Hünig's base (entry 1), triethylamine gave a lower yield (41%) with similar selectivity (75:25, entry 2). Inorganic bases potassium phosphate, caesium carbonate and potassium hydroxide gave the highest yields, albeit with lower *C*-selectivity (entries 3-5), whilst potassium fluoride and sodium carbonate gave lower conversion to product (entries 6 and 7). Diisopropylamine gave similar yield and selectivity (entry 8) to Hünig's base, and reaction without base gave no product (entry 9).

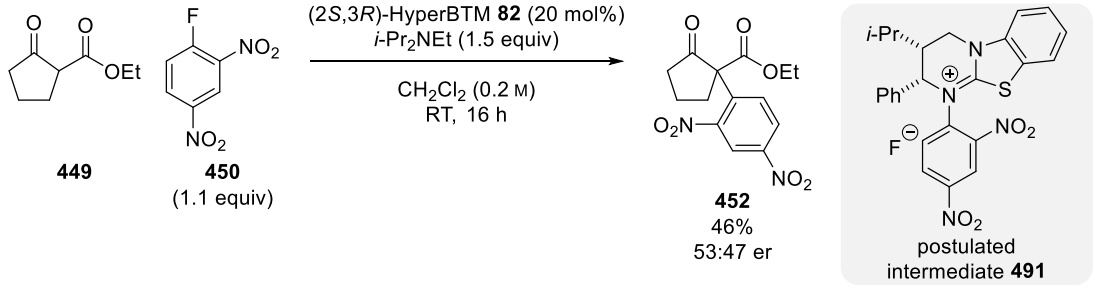
Table 25. Base study.



Entry	Base	Yield (%)	452:493
1	*i*-Pr$_2$NEt	58	70:30
2	Et$_3$N	41	75:25
3	K$_3$PO$_4$	74	50:50
4	Cs$_2$CO$_3$	71	55:45
5	KOH	61	40:60
6	KF	42	70:30
7	Na$_2$CO$_3$	36	70:30
8	*i*-Pr$_2$NH	57	70:30
9	n/a	0	-

[a] yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

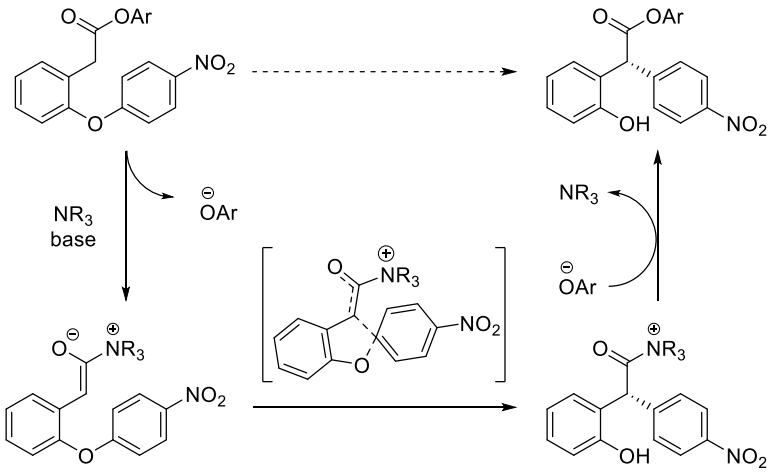
Although the yield and selectivity achieved were moderate at this point, it was decided to determine if any enantioinduction was occurring with the present system before proceeding further. Therefore, a reaction catalysed by (2*S*,3*R*)-HyperBTM **82** was carried out and yielded product **452** in 46% yield (Scheme 94). Disappointingly, the product was essentially racemic (53:47 er). It was rationalised no rigid transition state was being formed to allow for any enantioselectivity to be achieved. In addition, the nucleophile has no aryl ring fragment to form potential interactions with the postulated intermediate **491**. Alternatively, the catalyst could simply be acting as a Brønsted base, or the formation of salt **491** may lead to a favourable increase in the polarity of the reaction mixture.



Scheme 94. Determination of er of product 452.

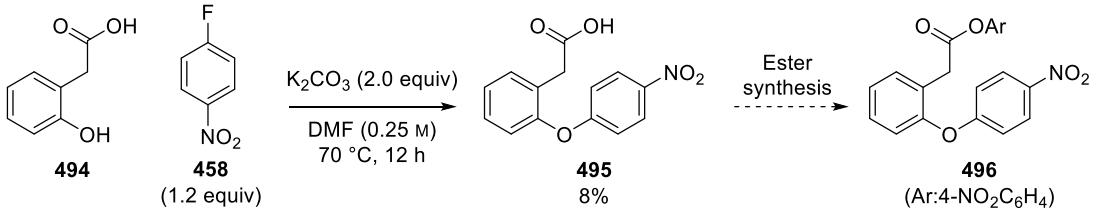
5.2.3. Intramolecular SNAr

With the intermolecular system proving challenging, the development of an intramolecular Smiles rearrangement was proposed to simplify the process and limit any competitive side reactions.[245] The aryl ester depicted in Scheme 95 was identified as the model substrate, which could be quickly accessed. It was envisioned that upon treatment with isothiourea catalyst and base, the ammonium enolate could be formed. Nucleophilic aromatic substitution of dinitrophenol moiety using the enolate nucleophile via a five-membered transition state would afford an acyl ammonium intermediate, which could react with the aryloxide to afford the product and release the Lewis base catalyst.



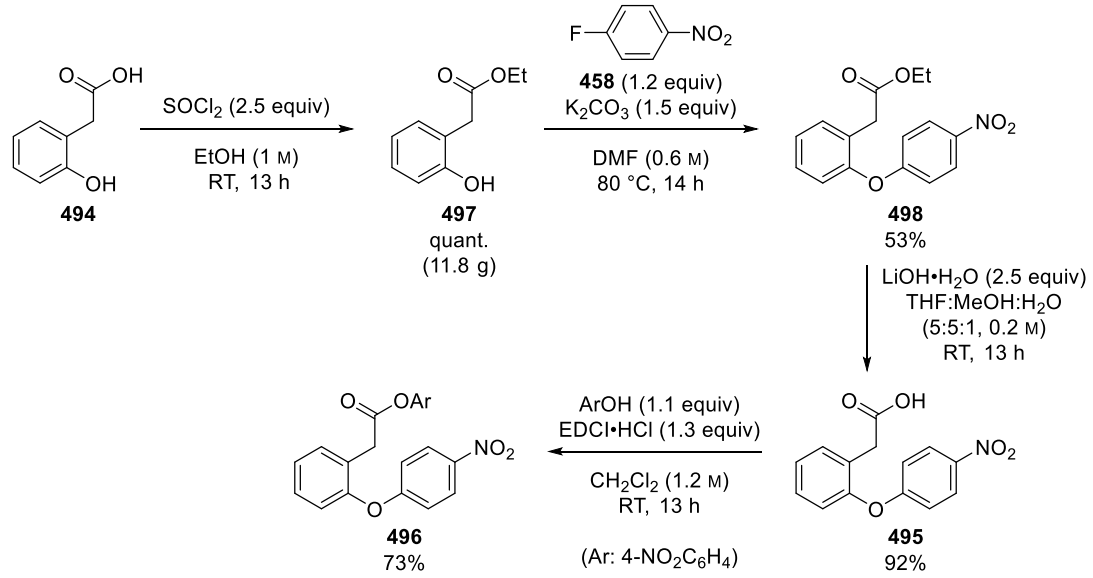
Scheme 95. Proposed intramolecular SNAr reaction.

It was hoped substrate **496** could be synthesised from carboxylic acid **494** via SNAr then aryl ester formation (Scheme 96). However, when acid **494** was treated with fluoronitrobenzene **458** under basic conditions only 8% of product **495** was observed.



Scheme 96. Attempted synthesis of substrate 496 via SNAr then esterification.

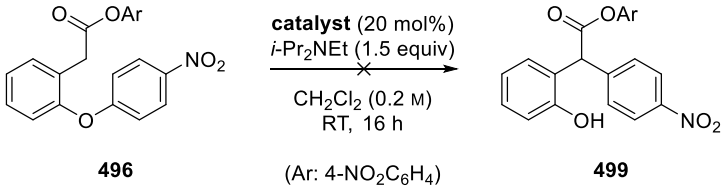
It was recognised a more elaborate synthesis involving protecting group strategies was required. To this end, ethyl ester **497** was prepared using thionyl chloride in ethanol from acid **494** (Scheme 97). Subsequent SNAr reaction of phenol **497** with fluoronitrobenzene **458** afforded ether **498** in good yield. Ester hydrolysis under basic conditions and *para*-nitrophenyl ester synthesis gave substrate **496** in 36% yield in four steps.



Scheme 97. Synthesis of substrate 496.

With the model substrate in hand, the catalytic enantioselective SNAr reaction was attempted (Table 26). Exposure of aryl ester **496** to BTM **77**, TM **76** and HyperBTM **82** under the standard reaction conditions (entries 1-3) led to no product formation. Reactions in DMF were also attempted, however, only substrate **496** and acid **495**, resulting from hydrolysis, were observed.

Table 26. Initial SNAr reactions of substrate 496.

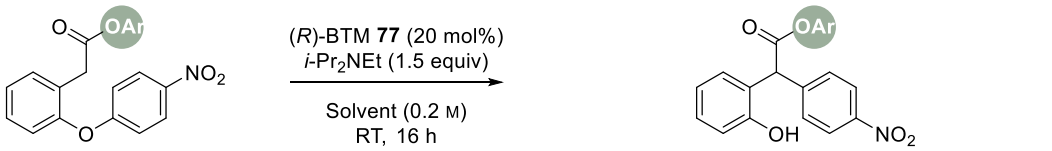


496 **499**

Entry	Catalyst	496 Remaining (%)	499 (%)
1	BTM **77**	90	0
2	TM·HCl **76**	89	0
3	HyperBTM **82**	92	0

[a] yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene internal standard.

To determine if the lack of reactivity was inherent with the aryloxide, trichloro-**500** and tetrafluoro-**501** were prepared using the same route and subjected to the reaction conditions (Scheme 98). However, again only starting materials were observed.



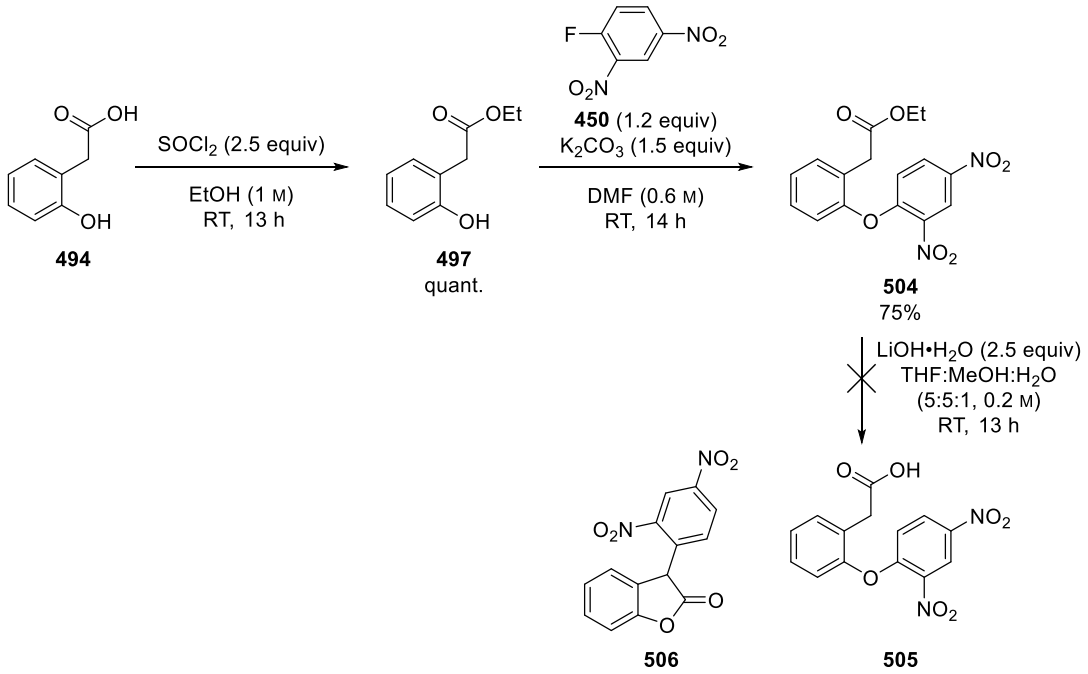
500 (Ar: 2,4,6-$Cl_3C_6H_2$)
501 (Ar: 2,3,5,6-F_4C_6H)

502 (Ar: 2,4,6-$Cl_3C_6H_2$): starting material recovered
503 (Ar: 2,3,5,6-F_4C_6H): starting material recovered

Scheme 98. SNAr reactions of substrates 498 and 499.

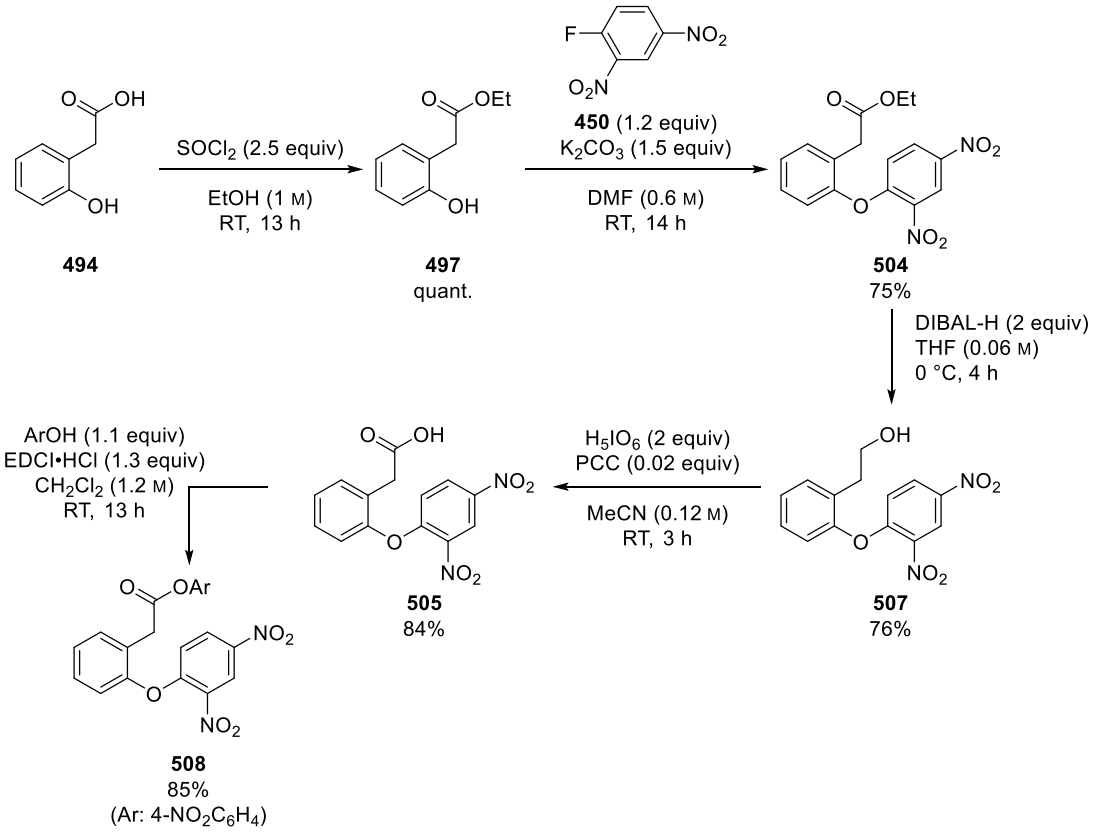
It was postulated the nitroarene was insufficiently electrophilic for the SNAr reaction to occur. Consequently, it was decided to synthesise the dinitro-ester analogue by employing the same route (Scheme 99). Ethyl ester **497** was treated with dinitrofluorobenzene **450** at room temperature to give ester **504** in 75% yield. Disappointingly, when ester **504** was treated with lithium hydroxide, the expected product was not observed. Instead, side product **506** was isolated, which was proposed to have formed through SNAr, followed by lactonisation. Although problematic, this result was promising as it indicated the desired SNAr reaction had occurred under basic conditions. Alternative conditions for the hydrolysis of ethyl

ester **504** were attempted (Me_3SiI,[246] Me_3SiOK,[247] LiCl + Et_3N),[248] however, all resulted in recovery of starting material or cyclised product **506**.

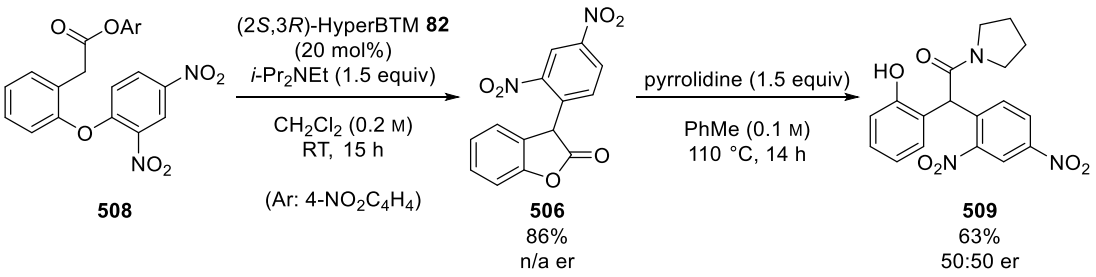


Scheme 99. Attempted synthesis of a dinitro substrate.

Therefore, it was decided to carry out a reduction-oxidation strategy to synthesise substrate **508** (Scheme 100). Reduction of ester **504** using DIBAL-H afforded alcohol **507** in 75% yield, and subsequent oxidation gave carboxylic acid **505**.[249] Esterification using EDCI and *para*-nitrophenol furnished substrate **508**. With the more electrophilic substrate in hand, activated ester **508** was treated with HyperBTM **82** and Hunig's base (Scheme 101). Encouragingly, full consumption of starting material was observed, and following purification by flash chromatography product **506** was isolated in 86% yield. However, benzofuranone **506** proved unstable to HPLC conditions and therefore the er could not be obtained. Following a procedure by Snape and co-workers,[250] benzofuranone **506** was reacted with pyrrolidine to afford amide **509**. Derivatisation to product **509** enabled determination of the er; however, this was determined to be racemic. It is noted that the ring opening reaction required forcing conditions, and racemisation could have occurred at this stage.



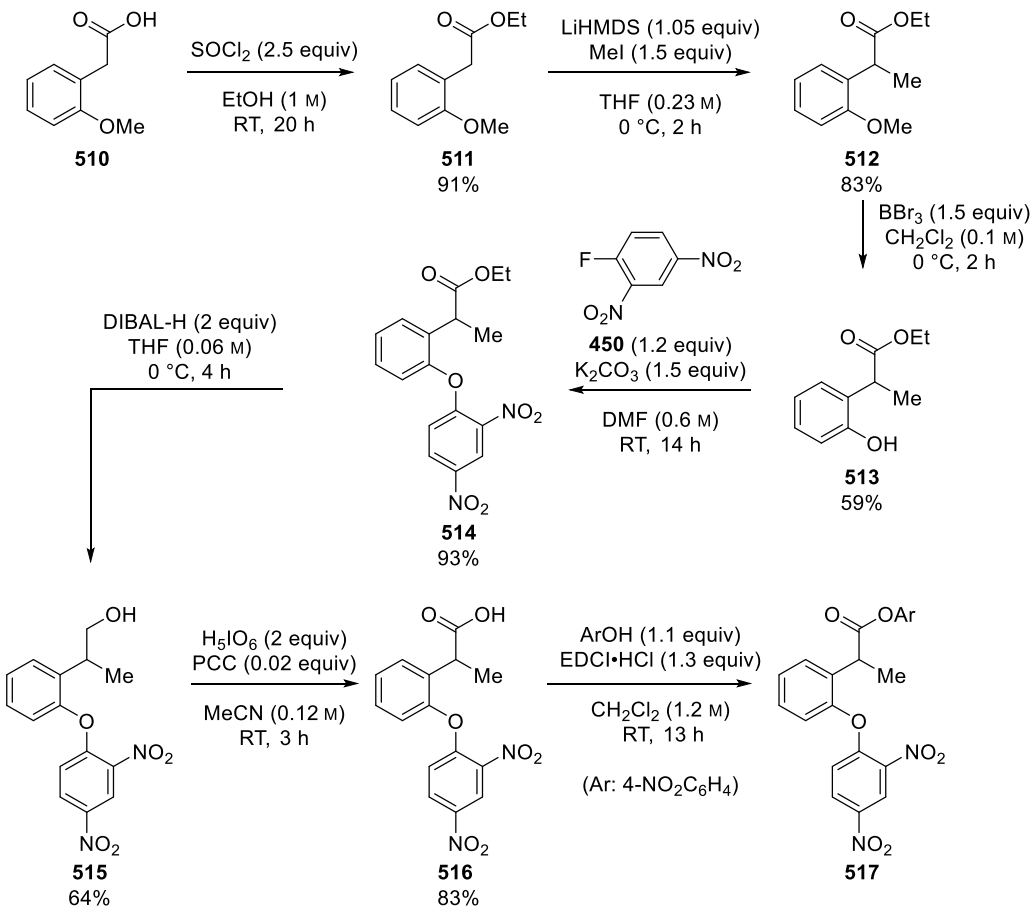
Scheme 100. Revised synthesis of ester 508.



Scheme 101. SNAr-ring opening of aryl ester 506.

In a further attempt to develop an enantioselective SNAr reaction, it was proposed that formation of a quaternary centre could prevent any post-reaction racemisation. Although the formation of quaternary stereogenic centres has been a long-standing limitation in isothiourea catalysis via C(1)-ammonium enolates, the intramolecular nature of this process may make this transformation more feasible. Consequently, it was proposed that ester **517** would be a suitable substrate for optimisation (Scheme 102). To this end, carboxylic acid **510** was efficiently converted to ethyl ester **511**. Methylation of ester **511** with methyl iodide afforded α-methyl ester **512**. Facile methoxy deprotection of **512** using boron tribromide gave phenol **513**. Subsequent

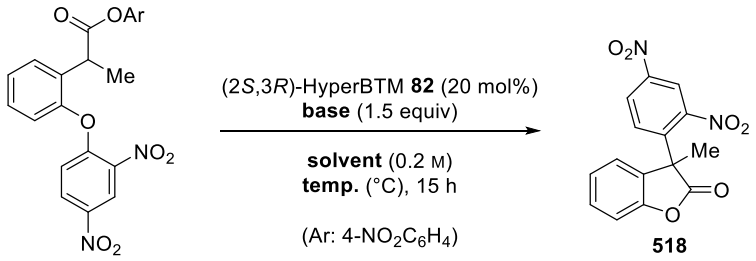
SNAr with dinitrofluorobenzene, reduction, oxidation and *para*-nitrophenyl ester synthesis gave substrate **517**.



Scheme 102. Synthesis of aryl ester 517.

Ester **517** was then subjected to the model reaction conditions (Table 27) and, encouragingly, 7% product was observed (entry 1). Variation of the base and solvent was then investigated. Reaction with caesium carbonate gave only 6% product (entry 2), whilst changing the solvent to DMF afforded the product in 45% yield at 40 °C (entry 3). Pleasingly, increasing the temperature to 80 °C gave a 75% yield, however the product was obtained in only 58:42 er (entry 4). Conducting a control reaction under these conditions in the absence of catalyst resulted in quantitative yield (entry 5), and a subsequent reaction without either catalyst or base gave 60% yield (entry 6).

Table 27. S_NAr reaction of aryl ester 517.



Entry	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	*i*-Pr$_2$NEt	CH_2Cl_2	RT	7
2	Cs_2CO_3	CH_2Cl_2	RT	6
3	*i*-Pr$_2$NEt	DMF	40	45
4	*i*-Pr$_2$NEt	DMF	80	75 (58:42)
5[a]	*i*-Pr$_2$NEt	DMF	80	quant
6[a]	n/a	DMF	80	60

[a] Reaction without isothiourea catalyst. [b] er in brackets.

5.3. Conclusions

In conclusion, a novel catalytic enantioselective nucleophilic aromatic substitution reaction has been investigated. The intermolecular process proved challenging and a range of aryl electrophiles were attempted; however, no reactivity was observed with heteroaromatic derivatives. Promisingly, conversion of starting material was detected on reaction with dinitrofluorobenzene **450**. However, subsequent control reactions revealed side reactions between the electrophile and aryloxide, and the electrophile and catalyst gave by-products **471** and **478** which were potentially having an adverse effect on the success of the catalytic protocol. Despite achieving an understanding of this process, no product was observed.

It was hoped to exploit catalyst arylation by adding an external nucleophile to the in situ generated isothiouronium intermediate. This was demonstrated in a reaction of 1,3-dicarbonyl and electrophile, which gave the arylated product in 37% yield. Disappointingly, no enantioselectivity was observed. Future work in the pursuit for enantioselectivity could use an indanone-derived nucleophile bearing an aromatic

ring, which could potentially pick up favourable interactions with the salt intermediate.

It was proposed the development of an intramolecular process would limit the side reactions and allow for product formation. When subjected to the isothiourea catalysis conditions, mononitro substrate **496** was unreactive, however, dinitro substrate **508** gave product **506** in 86% yield. Upon derivatisation, it was demonstrated the product was racemic. Subsequent studies with tertiary substrate **517** gave product **518** in high yield in 58:42 er. However, it was demonstrated a significant background reaction was occurring and as such this project was abandoned.

Chapter 6. Conclusions and Outlook

6.1. Conclusions

The primary goals of this PhD research were to develop new applications of enantioselective isothiourea catalysis via C(1)-ammonium enolates using intermolecular aryloxide catalyst turnover and to achieve a fundamental understanding of this catalyst turnover methodology through mechanistic studies.

A base-free Michael addition protocol using *para*-nitrophenyl esters as C(1)-ammonium enolate precursors to vinyl bis-sulfones has been developed (Chapter 2). This new reactivity enables the synthesis of enantioenriched α-functionalised esters and amides with exceptional diastereo- and enantioselectivity (26 examples, up to 90:10 dr, all $\geq$ 99:1 er). Enabled by the multifunctional aryloxide, which performs multiple roles, no auxiliary base was required for effective reactivity whilst low catalyst loadings were employed (5 mol%), overcoming previous limitations in this area of enantioselective organocatalysis. The synthetic utility of the methodology was also demonstrated: the products can be deprotected using magnesium turnings, and also extended through alkylation under basic conditions, furnishing functionalised α-alkylated products whilst maintaining stereointegrity.

The base-free protocol described in Chapter 2 was used as a representative example for extensive mechanistic investigations to gain a fundamental understanding of the catalyst turnover via aryloxide methodology (Chapter 3). Quantitative reaction monitoring was achieved using in situ $^{19}F\{^{1}H\}$ NMR spectroscopy, which enabled detailed investigation of the reaction course. Kinetic investigations using variable time normalisation analysis, combined with an observed inverse secondary KIE, identified the Michael addition as the turnover-limiting step in this process. Additionally, catalyst protonation and product inhibition were observed during the analysis. This mechanistic study has provided a wealth of information for intermolecular catalyst turnover via aryloxide in isothiourea catalysis via C(1)-ammonium enolates. It is hoped that this increased knowledge will advance the collective understanding of practitioners within the field and wider community and aid future reaction design.

The addition of catalytically generated C(1)-ammonium enolates to pyridinium salts has also been developed (Chapter 4), enabling the diastereo- and enantioselective synthesis of 1,4-DHP heterocyclic motifs through regioselective dearomatisation. This is the first application describing the addition of C(1)-ammonium enolates generated from aryl ester precursors to an electrophile other than an alkene or carbonyl derivative, broadening the scope of compatible electrophiles. This enabled the synthesis of a range of enantioenriched 1,4-DHPs (14 examples. up to 70% isolated yield, 95:5 dr, 98:2 er).

In attempts to further extend the scope of compatible electrophiles in isothiourea catalysis via C(1)-ammonium enolates, and to tackle a long-standing challenge in organic chemistry, the enantioselective α-arylation of esters was attempted via a nucleophilic aromatic substitution approach (Chapter 5). However, both inter- and intramolecular protocols proved significantly challenging, with the requirement for highly reactive aromatic electrophiles leading to problems of reagent compatibility and racemic background reaction. In addition, examples of C(1)-ammonium enolates adding to di-substituted alkenes are rare, which could be another factor why this process was unsuccessful.

6.2. Outlook

Whilst Chapters 2 and 4 demonstrate new reactivity of C(1)-ammonium enolates in base-free reactions and in the addition to heteroaromatic pyridinium rings, a significant limitation associated with this chemistry is the requirement to use highly reactive electrophiles. Only Michael acceptors bearing two electron-withdrawing groups (vinyl bis-sulfones) or pyridinium salts (which are already electron-deficient), further substituted with an electron-withdrawing group in the 3-position, demonstrated reactivity. Clearly, a general solution to enable the widespread application of C(1)-ammonium enolates in combination with a variety of electrophiles remains elusive.

During the mechanistic analysis of the base-free Michael addition protocol (Chapter 3), no significant quantities of reaction intermediates were observed in reaction monitoring. This demonstrates that the concentration of reactive C(1)-ammonium

enolate species is consistently very low over the course of the reaction, an observation also found in other isothiourea-catalysed processes.[105,251] This may be one explanation as to why there is a limited reactivity window for the reaction of C(1)-ammonium enolates with electrophiles. To increase the concentration of reactive intermediate in the reaction mixture and potentially make reaction with other electrophiles more viable, methods to stabilise the C(1)-ammonium enolate intermediate could be utilised. In 2020, we reported the synthesis of novel isochalcogenourea catalysts and demonstrated the increased activity of the selenium analogue **520** in various catalytic processes compared to HyperBTM **82**, whilst isourea **519** was catalytically inactive (Figure 34a).[252] These results were rationalised by the increased strength of the 1,5-O···chalcogen interaction, leading to increased stabilisation of reactive intermediates. Use of isoselenourea catalyst **520** may enable reaction of C(1)-ammonium enolates with less-reactive electrophiles. Additionally, the catalyst structure could be modified to increase the strength of the 1,5-O···chalcogen interaction, such as introduction of an electron-withdrawing group *para* to the sulfur/selenium atom (Figure 34b). Alternatively, this could be achieved through substitution of a methoxy group in the *meta* position relative to the sulfur atom. This would have the dual effect of increasing the nucleophilicity of the nitrogen atom, as well as acting as an electron-withdrawing group (σ_{meta} = 0.12). As described in Section 1.5.3, Lectka and co-workers have used metal Lewis acids to stabilise C(1)-ammonium enolates using ketene precursors. This approach could be extrapolated to aryloxide catalyst turnover, although whether the 1,5 O···chalcogen interaction would be maintained in this case is unknown (Figure 34b).

Another possible reason why the C(1)-ammonium enolate only reacts with very reactive electrophiles could be due to the positive charge residing on the catalyst-based nitrogen atom of this intermediate. Whilst this positive charge is beneficial as it increases the acidity of the protons in the α-position of the preceding acyl ammonium intermediate, enabling deprotonation to form the C(1)-ammonium enolate, the positive charge also results in the C(1)-ammonium enolate being less nucleophilic. Since the reactivity of isothioureas is predicated on activation by *N*-acylation, it is hard to find a solution to this problem.

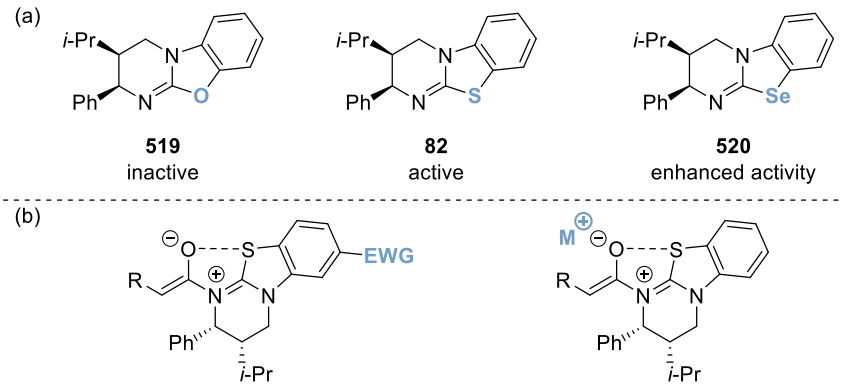
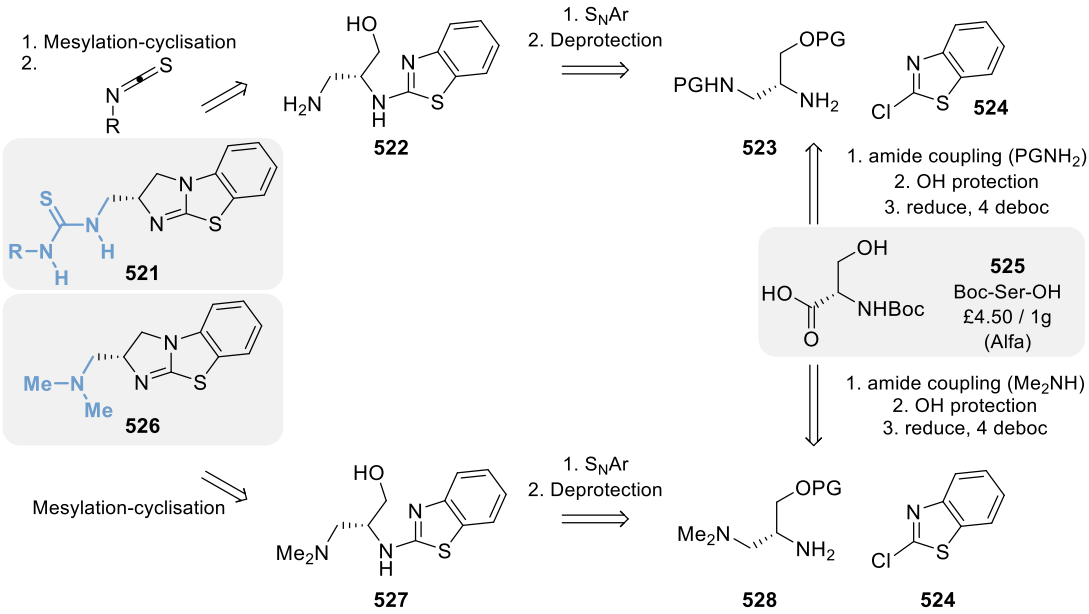


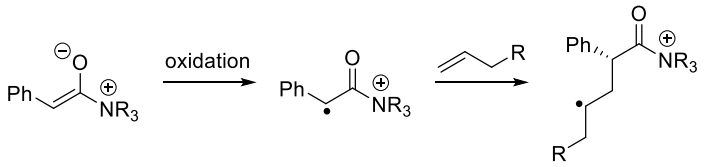
Figure 34. Methods to increase the stabilisation of catalytic intermediates.

In isothiourea catalysis enantioselectivity is achieved through steric blocking of one catalyst face, forcing the electrophile to approach from the opposite less hindered face. In an alternative approach, the blocking phenyl unit could be replaced with a directing group to (i) achieve enantioselectivity and (ii) to increase the electrophilicity of an electrophilic partner. For example, a hydrogen bond donor group (e.g. a thiourea) could be utilised to increase the electrophilicity of previously unreactive carbonyl derived electrophiles (Scheme 103). Alternatively, a Brønsted basic group could be used to deprotonate the C(1)-ammonium enolate. This would have the dual effect of increasing the concentration of C(1)-ammonium enolate (more deprotonation due to intramolecular proximity) whilst also the ammonium group could activate electrophiles through a hydrogen bond interaction. The synthesis of these bifunctional catalysts could be achieved through modification of the established synthetic route to BTM **77**. For the hydrogen-bonding bifunctional catalyst, the thiourea functionality could be incorporated through the known reaction of an amine with an isothiocyanate, whilst the mesylation-cyclisation procedure from the synthesis of BTM could be used to gain access from amino-alcohol **522**. Known S_NAr and deprotection reactions would allow this intermediate to be accessed from amine **523** and 2-chlorobenzothioazole. Following known literature procedures, **523** could be accessed from cheap amino acid **525**. A similar protocol could be used to access Brønsted basic catalyst **526**. If successful, these preliminary bifunctional catalyst proposals could be extended to take advantage of other non-covalent interaction-electrophile combinations (such as halogen bonds).



Scheme 103. Retrosynthesis of potential bifunctional catalysts.

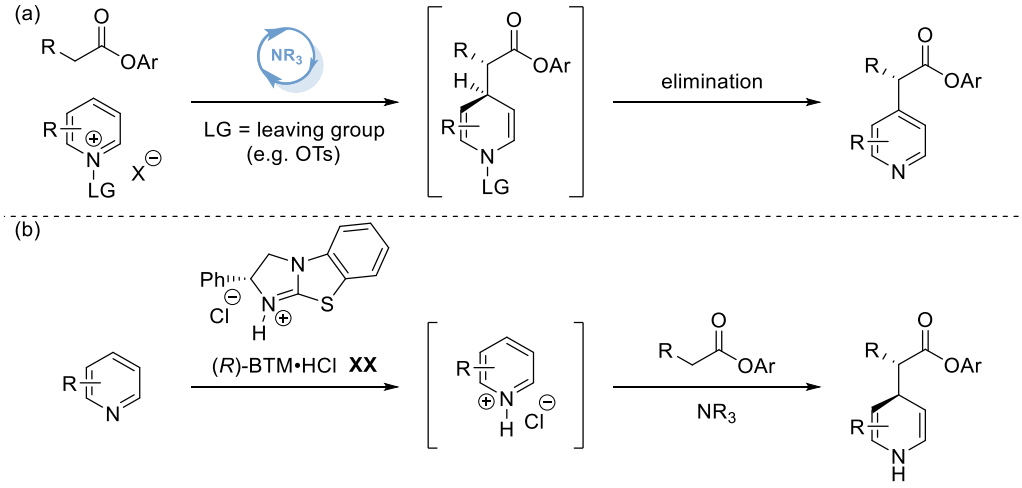
These proposals look to advance the reactivity of C(1)-ammonium enolates in polar chemistry. However, over the last decade the area of photocatalysis has emerged as a popular research area, enabling novel reactivity modes to be accessed through single electron transformations. Translation of isothiourea catalysis via C(1)-ammonium enolates into the area of radical chemistry is an exciting prospect, which would enable novel reactions with alternative electrophiles. This could be achieved through use of an excited state photocatalyst which oxidises the C(1)-ammonium enolate to give a radical intermediate, or using a stoichiometric oxidising agent, which could then be utilised in reactions with electrophiles such as alkenes (Scheme 104). One potential problem in realising this idea would be competing oxidation and deactivation of the tertiary amine catalyst.



Scheme 104. Potential radical reactivity of C(1)-ammonium enolates.

Finally, the addition of C(1)-ammonium enolates to pyridinium salts was disclosed in Chapter 5, enabling the synthesis of 1,4-DHPs. This new reactivity open avenues to new reactions for further investigation. Incorporation of a rearomatisation step after the initial formation of the 1,4-DHP would enable the enantioselective α-

arylation of esters. This would involve the use of a pyridinium salt bearing a leaving group on the nitrogen atom. Following the dearomatisation step, base-mediated elimination could afford the α-arylated product (Scheme 105a). Alternatively, a dual-catalytic process could be developed using BTM·HCl as catalyst and pyridine substrates. Activation of the pyridine through protonation using BTM·HCl would generate the pyridinium ion in situ, circumventing the necessity to isolate the corresponding pyridinium salt (Scheme 105b). However, currently only benzyl substituted pyridinium salts were reactive in the established protocol. Therefore, further understanding would be required to enable these methods to be developed.



Scheme 105. Potential new dearomatisation strategies.

Chapter 7. Experimental

7.1. General Experimental

All reagents and solvents were obtained from commercial suppliers and were used as received without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods. Tetramisole(TM)·HCl **76** was purchased from Sigma-Aldrich, benzotetramisole (BTM) **77** and HyperBTM **82** were prepared in house.[103,240] All diastereomeric ratios (drs) of crude reaction mixtures analysed by ^{1}H NMR are reported to the nearest multiple of 5.

7.1.1. Purification of Solvents

Anhydrous solvents (Et_2O, CH_2Cl_2, THF and PhMe) were obtained after passing through an alumina column (Mbraun SPS-800). Anhydrous MeOH and MeCN were purchased from Sigma-Aldrich and used without further purification. Petrol is defined as petroleum ether 40-60 °C. EtOAc, Et_2O, CH_2Cl_2 and petrol for purification purposes were used as obtained from suppliers without further purification.

7.1.2. Purification of Reagents

Dry Hunig's base was obtained by distillation over KOH and transferred to and stored in a screw-top vial over KOH and purged with and stored under nitrogen. Diethylammonium chloride was purchased from Sigma Aldrich and washed with EtOH, dried in vacuo and stored under N_2 prior to use.

7.1.3. Experimental Details

Reactions were carried out in flame-dried glassware under an inert atmosphere (N_2) using standard vacuum line techniques. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using an ice/water and CO_2(s)/acetone baths, respectively. Temperatures of 0 °C and −40 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reactions involving heating were performed using DrySyn blocks, sand, 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. In vacuo refers to the use of a Schlenk line manifold and high vacuum pump.

7.1.4. Purification of Products

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/or staining with either aqueous $KMnO_4$ solution or ethanolic Vanillin 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. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Kieselgel 60 silica. Purification of catalysis products using a gradient between 0-10% Et_2O in CH_2Cl_2 was carried out using a stock solution of 10% Et_2O in CH_2Cl_2, diluted appropriately with CH_2Cl_2.

7.1.5. Analysis of Products

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

Optical rotations $[\alpha]_D^{20}$ 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.

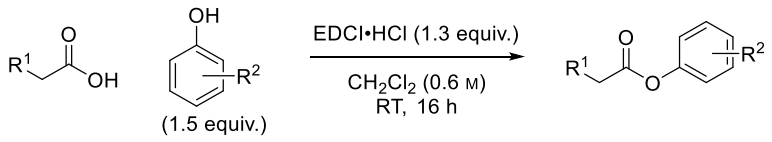
Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}.

^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra were acquired on either a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 377 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), 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), or a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, ^{19}F 470 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 single quantum coherence (HSQC), 2D ^{1}H-^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), 2D ^{1}H total correlation spectroscopy (TOCSY) and 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), where necessary.

High resolution mass spectrometry (HRMS) data were acquired by either electrospray ionisation (ESI), electron impact (EI), atmospheric solids analysis probe (ASAP), or nanospray ionisation (NSI) at either the University of St Andrews Mass Spectrometry Facility or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

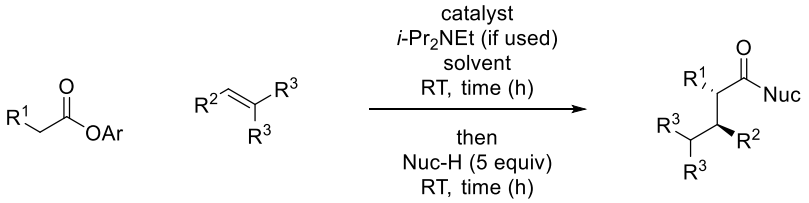
7.2. General Procedures

7.2.1. General procedure A: Synthesis of Esters



The appropriate acetic acid (1.0 equiv) and EDCI·HCl (1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (0.6 M) and the reaction mixture was stirred at room temperature. After 10 mins, the appropriate phenol (1.5 equiv) was added and the reaction stirred at room temperature for 16 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 ×). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography.

7.2.2. General procedure B: Optimisation of the Isothiourea-Catalysed Michael Addition Protocol



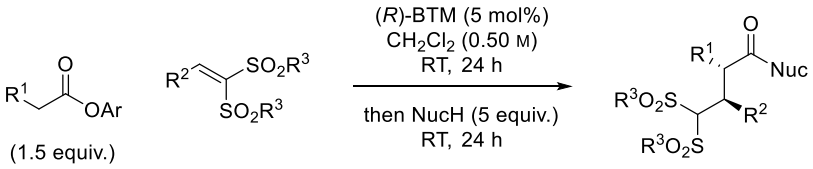
The appropriate ester, electrophile (if solid) and catalyst were weighed into a flame dried 4 mL screw top vial. The vial was capped and purged before the addition of the appropriate solvent, electrophile (if liquid) and *i*-Pr_2NEt (if used) and the reaction was stirred at room temperature for the appropriate time.

No nucleophile added: A solution of 1,3,5-trimethoxybenzene (0.33 equiv) internal standard in $CHCl_3$ (1 mL) was added and the reaction was concentrated under reduced pressure, before ^1H NMR analysis of the crude reaction mixture. If required, the crude product was purified by flash column chromatography.

With nucleophile: The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at room temperature for the appropriate time. The reaction mixture was diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine

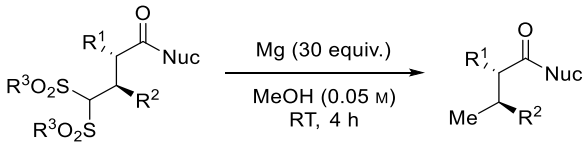
(10 mL), dried over $MgSO_4$ and filtered. A solution of 1,3,5-trimethoxybenzene (0.33 equiv) internal standard in $CHCl_3$ (1 mL) was added and the reaction was concentrated under reduced pressure, before ^1H NMR analysis of the crude reaction mixture. The crude product was purified by flash column chromatography.

7.2.3. General Procedure C: Isothiourea-Catalysed Enantioselective Michael addition to Vinyl Bis-Sulfones



The appropriate ester (1.5 equiv), vinyl bis-sulfone (1.0 equiv) and (*R*)-BTM (5 mol%) were weighed into a flame dried 4 mL screw top vial. The vial was capped and purged before the addition of CH_2Cl_2 (0.5 M) and the reaction was stirred at room temperature for 24 h. The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at room temperature for a further 24 h. The reaction mixture was diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered. A solution of 1,3,5-trimethoxybenzene (0.33 equiv) internal standard in $CHCl_3$ (1 mL) was added and the reaction was concentrated under reduced pressure, before ^1H NMR analysis of the crude reaction mixture. The crude product was purified by flash column chromatography.

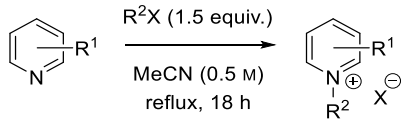
7.2.4. General Procedure D: Desulfonylation of Products



Magnesium turnings were activated by vigorous stirring with shards of glass at room temperature for 1 h under N_2. The activated Mg turnings (10 equiv) were added to MeOH (0.05 M) in a Schlenk flask and stirred at room temperature for 0.5 h. The appropriate substrate (1.0 equiv) was added and the reaction was stirred at room temperature for 1 h. Further activated Mg turnings (20 equiv) were added in two portions and the reaction was stirred at room temperature for 3 h. The reaction

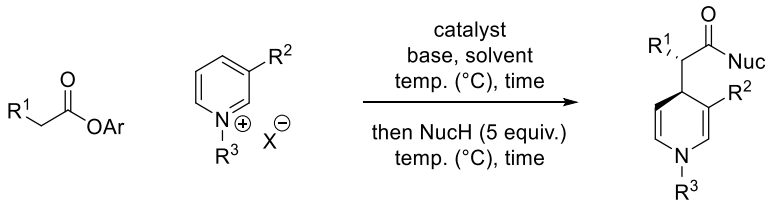
mixture was poured into 1 M aq. HCl (10 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography.

7.2.5. General Procedure E: Pyridinium Salt Synthesis



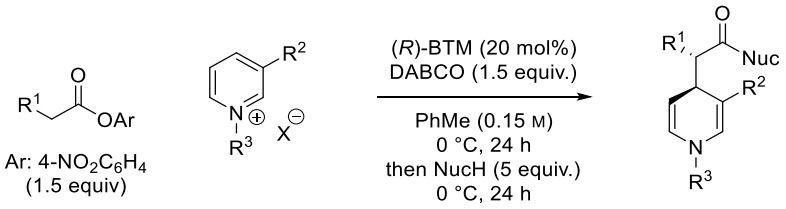
The appropriate electrophile (1.5 equiv) was added to the appropriate pyridine (1.0 equiv) in MeCN (0.5 M) and the reaction was refluxed for 18 h. The reaction mixture was cooled to 0 °C and cold Et_2O was added with stirring until a precipitate formed. The solid was filtered, washed with cold Et_2O and dried in vacuo.

7.2.6. General Procedure F: Optimisation of the Dearomatisation Protocol



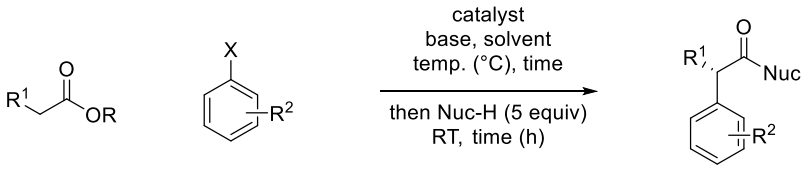
The appropriate ester, pyridinium salt, base (if solid) and catalyst were dissolved in solvent. The appropriate base (if liquid) was added, and the reaction was stirred at the stated temperature for the required time. The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at the stated temperature for the required time. The reaction mixture was quenched with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography.

7.2.7. General Procedure G: Isothiourea-catalysed dearomatisation of Pyridinium Salts



The appropriate ester (1.5 equiv), electrophile (1.0 equiv), DABCO (1.5 equiv) and catalyst (20 mol%) were weighed into a 20 mL test tube. The test tube was sealed, purged, lowered into a cryostat bath at 0 °C. PhMe (0.15 M) was added and the reaction was stirred at 0 °C for 24 h. The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at 0 °C for a further 24 h. The reaction mixture was quenched with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.

7.2.8. General procedure H: Optimisation of the S_NAr Protocol



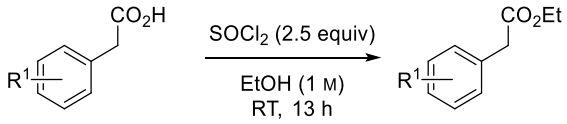
The appropriate ester, electrophile (if solid), base (if solid) and catalyst were weighed into a flame dried 4 mL screw top vial. The vial was capped and purged before the addition of the appropriate solvent, electrophile (if liquid) and base (if liquid) and the reaction was stirred at at the stated temperature for the required time.

No nucleophile added: A solution of 1,3,5-trimethoxybenzene (0.33 equiv) internal standard in $CHCl_3$ (1 mL) was added and the reaction was concentrated under reduced pressure, before ^1H NMR analysis of the crude reaction mixture. If required, the crude product was purified by flash column chromatography.

With nucleophile: The appropriate nucleophile (5.0 equiv) was added and the reaction was stirred at room temperature for the appropriate time. The reaction mixture was diluted with 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL).

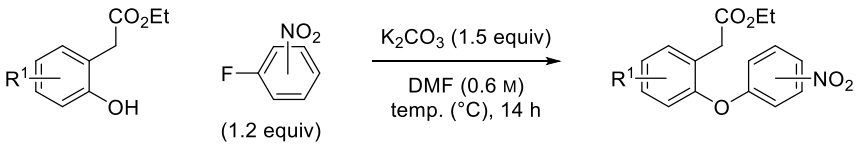
The organic layer was washed successively with 1 M NaOH (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. A solution of 1,3,5-trimethoxybenzene (0.33 equiv) internal standard in $CHCl_3$ (1 mL) was added and the reaction was concentrated under reduced pressure, before ^1H NMR analysis of the crude reaction mixture. The crude product was purified by flash column chromatography.

7.2.9. General procedure I: Intramolecular S_NAr Ester Synthesis



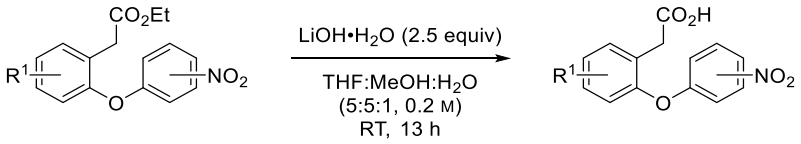
Thionyl chloride (2.5 equiv) was added dropwise to a stirred solution of the appropriate carboxylic acid (1.0 equiv) in EtOH (1.0 M) at 0 °C and the reaction was stirred at room temperature for 13 h. The reaction mixture was concentrated under reduced pressure before being diluted with CH_2Cl_2 and washed successively with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

7.2.10. General procedure J: Intramolecular S_NAr Ether Synthesis



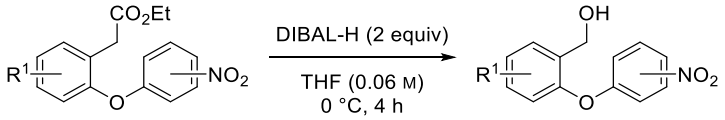
The appropriate phenol (1.0 equiv), fluoronitrobenzene (1.2 equiv) and potassium carbonate (1.5 equiv) were combined in DMF (0.6 M) and the reaction was stirred at room temperature or 70 °C for 14 h. The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure before being diluted with EtOAc and washed successively with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.

7.2.11. General procedure K: Intramolecular S_NAr Ester Hydrolysis



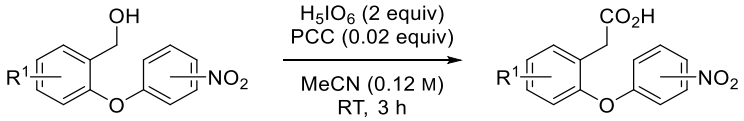
Lithium hydroxide monohydrate (2.5 equiv) was added to a stirred solution of the appropriate ester (1.0 equiv) in THF, MeOH and H_2O (5:5:1, 0.2 M) at room temperature and the reaction was stirred for 13 h. The reaction mixture was concentrated under reduced pressure before being diluted with H_2O and washed with EtOAc. The aqueous layer was acidified to pH 1, extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

7.2.12. General procedure L: Intramolecular S_NAr Ester Reduction



The appropriate aryl ester (1.0 equiv) was dissolved THF (0.06 M) and the reaction mixture was cooled to 0 °C. DIBAL-H (1 M in hexane, 2.0 equiv) was added dropwise and the reaction was stirred at 0 °C for 4 h. The reaction mixture was diluted with H_2O, acidified to pH=1 with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

7.2.13. General procedure M: Intramolecular S_NAr Alcohol Oxidation



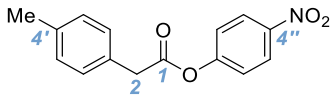
Periodic acid (2.0 equiv) was dissolved in MeCN (0.16 M) and the reaction mixture was stirred vigorously at room temperature for 15 min, then cooled to 0 °C. A solution of the appropriate alcohol (1.0 equiv) in MeCN (0.62 M) was added, followed by a solution of PCC (0.02 equiv) in MeCN (0.5 M), and the reaction was stirred at room temperature for 3 h. The reaction mixture was diluted EtOAc and washed

successively with H_2O:brine (1:1), sat. aq. $NaHSO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

7.3. Synthesis of Aryl Esters

4-Nitrophenyl 2-([1,1'-biphenyl]-4-yl)acetate **230** was prepared in house.[154]

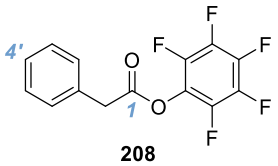
4''-Nitrophenyl 2-(4'-tolyl)acetate (**183**)



183

Following general procedure A, using 2-(*p*-tolyl)acetic acid (5.00 g, 34 mmol, 1.0 equiv), EDCI·HCl (8.40 g, 44 mmol, 1.3 equiv), 4-nitrophenol (7.00 g, 50 mmol, 1.5 equiv) and CH_2Cl_2 (56 mL, 0.6 M) for 22 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.58), the title compound (5.81 g, 64%) as a colourless solid with spectroscopic data in accordance with the literature.[253] **mp** 60-62 °C {Lit.[154] 60-62 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.39 (3H, s, CH_3), 3.88 (2H, s, C(2)H_2), 7.22 (2H, d, *J* 8.0, ArC(3',5')*H*), 7.24 – 7.32 (4H, m, ArC(2',6')*H* and ArC(2'',6'')*H*), 8.27 (2H, d, *J* 9.2, ArC(3'',5'')*H*). (LNB ref: CM261, CM344, CM382)

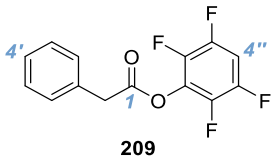
Perfluorophenyl 2-phenylacetate (**208**)



208

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.5 g, 13 mmol, 1.3 equiv), pentafluorophenol (2.76 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in Petrol (50% 5 CV, 50-70% 8 CV), R_f 0.77 at 100% CH_2Cl_2] the title compound (1.93 g, 64%) as a colourless solid with spectroscopic data in accordance with the literature.[254] **mp** 28-30 °C {no Lit. mp}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.97 (2H, s, C(2)H_2), 7.30 – 7.36 (1H, m, C(4')*H*), 7.35 – 7.42 (4H, m, C(2',6')*H* and C(3',5')*H*); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ_F: −163.56 – −161.63 (m), −157.79 (t, *J* 21.8), −153.83 – −151.75 (m). (LNB ref: CM438)

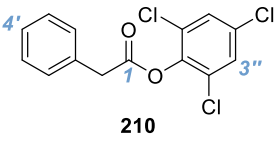
2'',3'',5'',6''-Tetrafluorophenyl 2-phenylacetate (**209**)



209

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 2,3,5,6-tetrafluorophenol (2.50 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in Petrol (50% 5 CV, 40-60% 7 CV), R_f 0.77 at 100% CH_2Cl_2], the title compound (1.74 g, 61%) as a colourless solid with spectroscopic data in accordance with the literature.[129] **mp** 44-46 °C {Lit.[129] 45-46 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.98 (2H, s, C(2)H_2), 6.99 (1H, tt, *J* 9.9, 7.1, C(4'')*H*), 7.30 – 7.36 (1H, m, C(4')*H*), 7.36 – 7.44 (4H, m, C(3',5')*H* and C(2',6')*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −153.29 – −152.61 (m), −139.27 – −138.69 (m). (LNB ref: CM439)

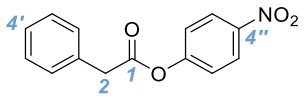
2'',4'',6''-Trichlorophenyl 2-phenylacetate (**210**)



210

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 2,4,6-trichlorophenol (2.96 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by column chromatography (0 to 20% Et_2O in Petrol; R_f 0.66 at 20% Et_2O in Petrol), the title compound (1.20 g, 38%) as a colourless solid with spectroscopic data in accordance with the literature.[129] **mp** 42-44 °C {no Lit mp}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.97 (2H, s, C(2)H_2), 7.29 – 7.35 (1H, m, C(4')*H*), 7.35 (2H, s, C(3'',5'')*H*), 7.36 – 7.39 (2H, m, C(3',5')*H*), 7.39 – 7.44 (2H, m, C(2',6')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.7 (*C*(2)H_2), 127.7 (*C*(4')H), 128.7 (*C*(3'',5'')H), 128.8 (*C*(3',5')H), 129.7 (*C*(2',6')H) and (*C*(2'',6'')), 132.2 (*C*(4'')), 132.6 (*C*(1')), 143.0 (*C*(1'')), 167.8 (*C*(1)=O). (LNB ref: CM440)

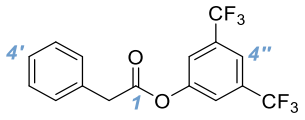
4''-Nitrophenyl 2-phenylacetate (**218**)



218

Following general procedure A, using phenylacetic acid (5.44 g, 40 mmol, 1.0 equiv), EDCI·HCl (9.97 g, 52 mmol, 1.3 equiv), 4-nitrophenol (8.35 g, 60 mmol, 1.5 equiv) and CH_2Cl_2 (67 mL, 0.6 M) for 21 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.6), the title compound (7.28 g, 71%) as a colourless solid with spectroscopic data in accordance with the literature.[255] **mp** 58-60 °C {Lit.[154] 58-60 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.90 (2H, s, C(2)H_2), 7.26 (2H, d, *J* 9.2, ArC(2',6')*H*), 7.28 – 7.46 (5H, m, ArC*H*), 8.25 (2H, d, *J* 9.2, C(3'',5'')*H*). (LNB ref: CM401, CM535)

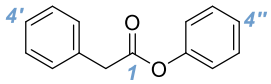
3'',5''-Bis(trifluoromethyl)phenyl 2-phenylacetate (**222**)



222

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 3,5-bis(trifluoromethyl)phenol (2.3 mL, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in Petrol (30% 5 CV, 30-50% 5 CV), R_f 0.82 at 100% CH_2Cl_2], the title compound (1.79 g, 51%) as a colourless solid. **mp** < 25 °C; **ν_{max}** (solid, cm^{-1}) 1772 (C=O), 1369, 1275, 1103; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.92 (2H, s, C(2)H_2), 7.31 – 7.48 (5H, m, C(4')*H*, C(2',6')*H*, C(3',5')*H*), 7.59 (2H, s, C(2'',6'')*H*), 7.76 (1H, s, C(4'')*H*); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F: −62.9 (s); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 41.3 (*C*(2)H_2), 119.9 (hept, $^3J_{C\text{-}F}$ 3.7 (*C*(4'')H), 122.5 (q, $^3J_{C\text{-}F}$ 4.0, *C*(2'',6'')H), 122.9 (q, $^1J_{C\text{-}F}$ 272.9, *C*F_3), 127.9 (*C*(4')H), 129.1 (*C*(3',5')H), 129.5 (*C*(2',6')H), 132.6 (*C*(1')), 133.1 (q, $^2J_{C\text{-}F}$ 34.0, *C*(3'',5''), 151.3 (*C*(1'')), 169.3 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{16}H_{11}F_6O_2$ $[M+H]^+$ found 349.0660, requires 349.0658 (+0.6 ppm). (LNB ref: CM441)

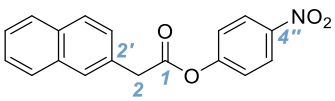
Phenyl 2-phenylacetate (**223**)



223

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), phenol (1.4 mL, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 24 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in Petrol (40% 5 CV, 40-80% 12 CV), R_f 0.64 at 100% CH_2Cl_2], the title compound (0.47 g, 22%) as a colourless solid with spectroscopic data in accordance with the literature.[256] **mp** 38-39 °C {Lit.[257] 38.9-39.3 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.87 (2H, s, C(2)H_2), 7.02 – 7.11 (2H, m, C(2'',6'')*H*), 7.22 (1H, tt, *J* 6.9, 1.0, C(4'')*H*), 7.28 – 7.33 (1H, m, C(4')*H*), 7.33 – 7.45 (6H, m, C(2',6')*H*, C(3',5')*H* and C(3'',5'')*H*). (LNB ref: CM437)

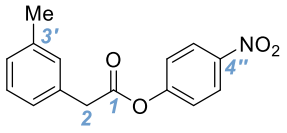
4''-Nitrophenyl 2-(naphthalen-2'-yl)acetate (**231**)



231

Following general procedure A, using 2-naphthylacetic acid (1.86 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in Petrol (50% 5 CV, 50-75% 10 CV), R_f 0.68 at 100% CH_2Cl_2] the title compound (2.21 g, 72%) as a colourless solid. **mp** 96-98 °C {Lit. 95-97 °C}; **ν_{max}** (solid, cm^{-1}) 1755 (C=O), 1612 (ArC=C), 1589 (ArC=C), 1514 (C-NO_2), 1487, 1350 (C-NO_2), 1115 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.09 (2H, s, C(2)H_2), 7.28 (2H, d, *J* 9.3, C(2'',6'')*H*), 7.45 – 7.62 (3H, m, ArC*H*), 7.79 – 7.97 (4H, m, ArC*H*), 8.27 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 41.7 (*C*(2)H_2), 122.5 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H), 126.3 (ArCH), 126.6 (ArCH), 127.2 (ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.4 (ArCH), 128.8 (ArCH), 130.2 (*C*(2')), 132.8 (*C*(8'a)), 133.6 (*C*(4'a)), 145.5 (*C*(4'')), 155.5 (*C*(1'')), 169.2 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{18}H_{13}NO_4$ $[M]^+$ found 307.0841, requires 307.0839 (+0.6 ppm). (LNB ref: CM490)

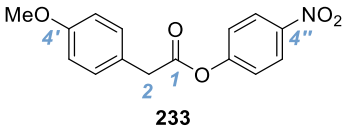
4''-Nitrophenyl 2-(3'-tolyl)acetate (**232**)



232

Following general procedure A, using *m*-tolylphenylacetic acid (1.50 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (70% 5 CV, 70-100% 10 CV, 100% 4 CV), R_f 0.65 at 100% CH_2Cl_2] the title compound (1.74 g, 64%) as a yellow oil with spectroscopic data in accordance with the literature.[154] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.39 (3H, s, CH_3), 3.87 (2H, s, C(2)H_2), 7.14 – 7.18 (2H, m, C(4')*H* and C(6')*H*), 7.20 (1H, s, C(2')*H*), 7.27 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.24 – 7.32 (1H, m, C(5')*H*), 8.26 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 21.5 (CH_3), 41.4 (*C*(2)H_2), 122.5 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H) 126.4 (*C*(6')H), 128.5 (*C*(4')H), 128.9 (*C*(5')H), 130.2 (*C*(2')H), 132.6 (*C*(1')), 138.7 (*C*(3')), 145.4 (*C*(4'')), 155.6 (*C*(1'')), 169.3 (*C*=O). (LNB ref: CM424)

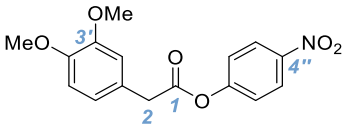
4''-Nitrophenyl 2-(4'-methoxyphenyl)acetate (**233**)



233

Following general procedure A, using 4-methoxyphenylacetic acid (0.66 g, 4 mmol, 1.0 equiv), EDCI·HCl (1.0 g, 5.2 mmol, 1.3 equiv), 4-nitrophenol (0.84 g, 6 mmol, 1.5 equiv) and CH_2Cl_2 (6.7 mL, 0.6 M) for 21 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.56), the title compound (0.61 g, 53%) as a colourless solid with spectroscopic data in accordance with the literature.[154] **mp** 89-91 °C {Lit.[154] 88-90 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, CH_3), 3.84 (2H, s, C(2)H_2), 6.92 (2H, d, *J* 8.7, C(3',5')*H*), 7.25 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.29 (2H, d, *J* 8.8, C(2',6')*H*), 8.24 (2H, d, *J* 9.2, C(3'',5'')*H*). (LNB ref: CM402)

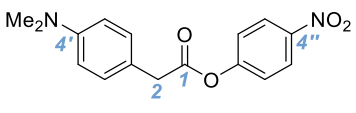
4''-Nitrophenyl 2-(3',4'-dimethoxyphenyl)acetate (**234**)



234

Following general procedure A, using 3,4-methoxyphenylacetic acid (3.9 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.00 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.2 g, 30 mmol, 1.5 equiv) and CH_2Cl_2 (34 mL, 0.6 M) for 20 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (70% 5 CV, 70-80% 7 CV), R_f 0.40 at 100% CH_2Cl_2] the title compound (3.1 g, 49%) as a colourless solid with spectroscopic data in accordance with the literature.[258] **mp** 77-79 °C {Lit.[258] 126-128 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.86 (2H, s, C(2)H_2), 3.91 (3H, s, C(4')OCH_3), 3.92 (3H, s, C(3')OCH_3), 6.89 (1H, d, *J* 8.2, C(5')*H*), 6.91 (1H, d, *J* 1.9, C(2')*H*), 6.94 (1H, dd, *J* 8.1, 2.0, C(6')*H*), 7.28 (2H, d, *J* 9.2, C(2'',6'')*H*), 8.27 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 40.9 (*C*(2)H_2), 56.0 (C(3')OCH_3), 56.0 (C(4')OCH_3), 111.4 (*C*(5')H), 112.4 (*C*(2')H), 121.7 (*C*(6')H), 122.5 (*C*(2'',6'')H), 125.1 (*C*(1')), 125.3 (*C*(3'',5'')H), 145.4 (*C*(4'')), 148.6 (*C*(4')OCH_3), 149.2 (*C*(3')OCH_3), 155.5 (*C*(1'')), 169.5 (*C*(1)=O). The observed melting point was significantly lower than the one reported. However, I am satisfied that the structure of the compound is correct and of high purity based on the other characterisation data. Therefore, I am confident the observed melting point is accurate for the named compound when it is synthesised and purified as described. (LNB ref: CM550)

4''-Nitrophenyl 2-(4'-(dimethylamino)phenyl)acetate (**235**)

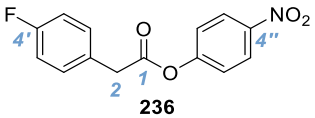


235

Following general procedure A, using 4-(dimethylamino)phenylacetic acid (3.6 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.00 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.2 g, 30 mmol, 1.5 equiv) and CH_2Cl_2 (34 mL, 0.6 M) for 20 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-90% 7 CV), R_f 0.55 at 100% CH_2Cl_2] the title compound (2.55 g, 42%) as an orange

solid. **mp** 93-95 °C; ν_{max} (solid, cm^{-1}) 2893 (C-H), 2808 (C-H), 1749 (C=O), 1612 (ArC=C), 1589 (ArC=C), 1519 (C-NO_2), 1483, 1342 (C-NO_2), 1227 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.96 (6H, s, NCH_3), 3.79 (2H, s, C(2)H_2), 6.74 (2H, d, *J* 8.8, C(3',5')*H*), 7.24 (2H, d, *J* 8.7, C(2',6')*H*), 7.25 (2H, d, *J* 9.2, C(2'',6'')*H*), 8.24 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.5 (*C*(2)H_2), 40.7 (NCH_3), 112.9 (*C*(3',5')H), 120.2 (*C*(1)), 122.5 (*C*(2'',6'')H), 125.2 (*C*(3'',5'')H), 130.1 (*C*(2',6')H), 145.4 (*C*(4'')), 150.1 (*C*(4')), 155.8 (*C*(1'')), 169.9 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{16}H_{17}N_2O_4$ $[M+H]^+$ found 301.1183, requires 301.1183. (LNB ref: CM551)

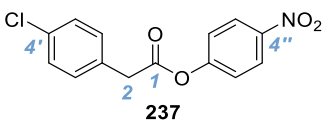
4''-Nitrophenyl 2-(4'-fluorophenyl)acetate (**236**)



236

Following general procedure A, using 4-fluorophenylacetic acid (3.10 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.00 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.20 g, 30 mmol, 1.5 equiv) and CH_2Cl_2 (33 mL, 0.6 M) for 24 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (20% 5 CV, 20-100% 20 CV, 100% 5 CV), R_f 0.68 at 100% CH_2Cl_2] the title compound (3.72 g, 68%) as a colourless solid. **mp** 79-81 °C; ν_{max} (solid, cm^{-1}) 1748 (C=O), 1520, 1510, 1344 (C-NO_2), 1240 (C-F), 1126 (C-O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.88 (2H, s, C(2)H_2), 7.07 (2H, t, *J* 8.6, C(3',5')*H*), 7.26 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.34 (2H, dd, *J* 8.5, 5.3, C(2',6')*H*), 8.25 (2H, d, *J* 9.1, C(3'',5'')*H*); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F: −114.6 (s); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.5 (*C*(2)H_2), 115.9 (d, $^2J_{C\text{-}F}$ 21.6, *C*(3',5')H), 122.4 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H), 128.5 (d, $^4J_{C\text{-}F}$ 3.3, *C*(1')), 131.1 (d, $^3J_{C\text{-}F}$ 8.1 *C*(2',6')H), 145.5 (*C*(4'')), 155.4 (*C*(1'')), 162.4 (d, $^1J_{C\text{-}F}$ 246.4, *C*(4')F), 169.1 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{14}H_{11}FNO_4$ $[M+H]^+$ found 276.0678, requires 276.0667 (+4.0 ppm). (LNB ref: CM532)

4''-Nitrophenyl 2-(4'-chlorophenyl)acetate (**237**)

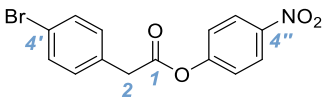


237

Following general procedure A, using 4-chlorophenylacetic acid (1.71 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.00 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.20 g, 30 mmol, 1.5

equiv) and CH_2Cl_2 (34 mL, 0.6 M) for 20 h gave, after purification by column chromatography (CH_2Cl_2; R_f 0.71) the title compound (3.77 g, 77%) as a colourless solid. **mp** 70-72 °C; **ν_{max}** (solid, cm^{-1}) 1761 (C=O), 1591 (ArC=C), 1519, 1490, 1409, 1340 (C-NO_2), 1211, 1117 (C-O), 759 (C-Cl); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.88 (2H, s, C(2)H_2), 7.26 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.31 (2H, d, *J* 8.5, C(2',6')*H*), 7.36 (2H, d, *J* 8.5, C(3',5')*H*), 8.25 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.7 (*C*(2)H_2), 122.4 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H), 129.2 (*C*(3',5')H), 130.8 (*C*(2',6')H), 131.2 (*C*(1')), 133.9 (*C*(4')), 145.6 (*C*(4'')), 155.4 (*C*(1'')), 168.8 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{14}H_{11}ClNO_4$ $[M+H]^+$ found 292.0379, requires 292.0371 (+2.7 ppm). (LNB ref: CM548)

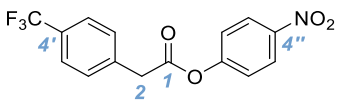
4''-Nitrophenyl 2-(4'-bromophenyl)acetate (**238**)



238

Following general procedure A, using 4-bromophenylacetic acid (2.20 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 17 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (40% 5 CV, 40-80% 15 CV), R_f 0.42 at 60% CH_2Cl_2 in petrol] the title compound (2.30 g, 69%) as a colourless solid with spectroscopic data in accordance with the literature.[253] **mp** 84-86 °C {Lit.[154] 82-84 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.86 (2H, s, C(2)H_2), 7.20 – 7.28 (4H, m, C(2',6')*H* and C(2'',6'')*H*), 7.51 (2H, d, *J* 8.4, C(3',5')*H*), 8.25 (2H, d, *J* 9.1, C(3'',5'')*H*). (LNB ref: CM422)

4''-Nitrophenyl 2-(4'-(trifluoromethyl)phenyl)acetate (**239**)

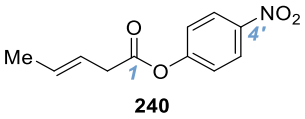


239

Following general procedure A, using 4-(trifluoromethyl)phenylacetic acid (1.63 g, 8 mmol, 1.0 equiv), EDCI·HCl (2.00 g, 10.4 mmol, 1.3 equiv), 4-nitrophenol (1.67 g, 12 mmol, 1.5 equiv) and CH_2Cl_2 (13 mL, 0.6 M) for 21 h gave, after purification by by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (40% 5 CV, 50-60% 6 CV), R_f 0.72 at 100% CH_2Cl_2] the title compound (1.41 g, 54%) as a colourless

solid with spectroscopic data in accordance with the literature.[154] **mp** 71-73 °C {Lit.[154] 65-67 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.98 (2H, s, C(2)H_2), 7.27 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.51 (2H, d, *J* 8.1, C(2',6')*H*), 7.65 (2H, d, *J* 8.1, C(3',5')*H*), 8.26 (2H, d, *J* 9.1, C(3'',5'')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −62.6 (s). (LNB ref: CM403, CM530)

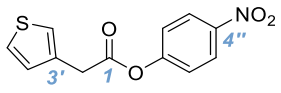
4'-Nitrophenyl (*E*)-pent-3-enoate (**240**)



240

Following general procedure A, using 3-pentenoic acid (1.0 mL, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.10 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 2 CV, 50-100% 14 CV), R_f 0.65 at 100% CH_2Cl_2] the title compound (1.11 g, 50%) as a colourless solid with spectroscopic data in accordance with the literature.[154] **mp** 49-51 °C {Lit.[154] 34-36 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.75 (3H, dd, *J* 6.2, 1.2, C(5)H_3), 3.31 (2H, d, *J* 6.8, C(2)H_2), 5.55 – 5.69 (1H, m, C(3)*H*), 5.69 – 5.77 (1H, m, C(4)*H*), 7.28 (2H, d, *J* 9.1, C(2',6')*H*), 8.27 (2H, d, *J* 9.1, C(3',5')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 18.1 (*C*(5)H_3), 38.1 (*C*(2)H_2), 121.4 (*C*(3)H), 122.6 (*C*(2',6')H), 125.3 (*C*(3',5')H), 131.1 (*C*(4')H), 145.4 (*C*(4')), 155.6 (*C*(1')), 169.8 (*C*(1)). (LNB ref: CM426)

4''-Nitrophenyl 2-(thiophen-3'-yl)acetate (**241**)

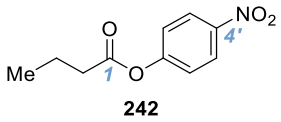


241

Following general procedure A, using 3-thiophene acetic acid (1.42 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.10 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (40-100% 21 CV), R_f 0.62 at 100% CH_2Cl_2] the title compound (1.73 g, 66%) as a colourless solid with spectroscopic data in accordance with the literature.[154] **mp** 55-57 °C {Lit.[154] 55-57 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.95 (2H, s, C(2)H_2), 7.13 (1H, dd, *J* 5.0, 1.2,

C(4')*H*), 7.24 – 7.30 (3H, m, C(2'',6'')*H* and C(2')*H*), 7.36 (1H, dd, *J* 4.9, 3.0, C(5')*H*), 8.26 (2H, d, *J* 9.1, C(3'',5'')*H*). (LNB ref: CM448)

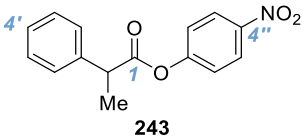
4'-Nitrophenyl butyrate (**242**)



242

Following general procedure A, using butyric acid (0.91 mL, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-100% 10 CV, 100% 8 CV)), R_f 0.60 at 100% CH_2Cl_2] the title compound (0.83 g, 40%) as a colourless oil with spectroscopic data in accordance with the literature.[259] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.06 (3H, t, *J* 7.4, C(4)H_3), 1.80 (2H, app hept., *J* 7.4, C(3)H_2), 2.59 (2H, t, *J* 7.4, C(2)H_2), 7.28 (2H, d, *J* 9.2, C(2',6')*H*), 8.27 (2H, d, *J* 9.2, C(3',5')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 13.7 (*C*(4)H_3), 18.4 (*C*(3)H_2), 36.2 (*C*(2)H_2), 122.6 (*C*(2',6')H), 125.3 (*C*(3',5')H), 145.3 (*C*(4')), 155.6 (*C*(1')), 171.3 (*C*(1)). (LNB ref: CM427)

4''-Nitrophenyl 2-phenylpropanoate (**243**)

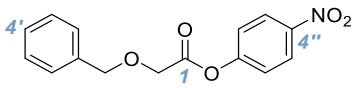


243

Following general procedure A, using 2-phenyl propanoic acid (1.4 mL, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.10 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-60% 6 CV), R_f 0.59 at 100% CH_2Cl_2] the title compound (1.65 g, 61%) as a colourless solid with spectroscopic data in accordance with the literature.[260] **mp** 49-51 °C {no Lit. mp}. **1H NMR** (500 MHz, $CDCl_3$) δ_H: 1.64 (3H, d, *J* 7.2, C(3)H_3), 4.00 (1H, q, *J* 7.1, C(2)*H*), 7.18 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.29 – 7.37 (1H, m, C(4')*H*), 7.37 – 7.48 (4H, m, C(2',6')*H* and C(3',5')*H*), 8.23 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 18.5 (*C*(3)H_3), 45.8 (*C*(2)H), 122.4 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H), 127.6 (*C*(2',6')H),

127.8 (*C*(4')H), 129.1 (*C*(3',5')H), 139.4 (*C*(1')), 145.4 (*C*(4'')), 155.7 (*C*(1'')), 172.3 (*C*(1)=O). (LNB ref: CM488)

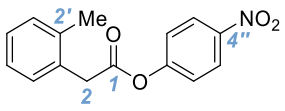
4''-Nitrophenyl 2-(benzyloxy)acetate (**244**)



244

Following general procedure A, using benzyloxyacetic acid (1.4 mL, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 24 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (60% 5 CV, 60-90% 11 CV), R_f 0.47 at 100% CH_2Cl_2] the title compound (1.49 g, 52%) as a colourless solid. **mp** 54-55 °C; **ν_{max}** (solid, cm^{-1}) 2903 (C-H), 1784 (C=O), 1616 (ArC=C), 1589 (ArC=C), 1522 (C-NO_2), 1489, 1344 (C-NO_2), 1202, 1107 (C-O), 860, 742; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.39 (2H, s, C(2)H_2), 4.73 (2H, s, BnCH_2), 7.31 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.34 – 7.38 (1H, m, C(4')*H*), 7.38 – 7.45 (4H, m, C(2',6')*H* and C(3',5')*H*), 8.28 (2*H*, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 67.0 (*C*(2)H_2), 73.8 (BnCH_2), 122.4 (*C*(2'',6'')H), 125.4 (*C*(3'',5'')H), 128.3 (*C*(2',6')H), 128.5 (*C*(4')H), 128.8 (*C*(3',5')H), 136.7 (*C*(1')), 145.6 (*C*(4'')), 154.9 (*C*(1'')), 168.2 (*C*=O); **HRMS** (ESI$^+$) $C_{15}H_{13}NNaO_5$ $[M+Na]^+$ found 310.0678, requires 310.0686 (−2.6 ppm). (LNB ref: CM436)

4''-Nitrophenyl 2-(2'-tolyl)acetate (**245**)



245

Following general procedure A, using *o*-tolylphenylacetic acid (1.50 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.50 g, 13 mmol, 1.3 equiv), 4-nitrophenol (2.09 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-85% 13 CV), R_f 0.67 at 100% CH_2Cl_2] the title compound (1.41 g, 52%) as a colourless solid with spectroscopic data in accordance with the literature.[154] **mp** 42 °C {no Lit. mp}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, CH_3), 3.93 (2H, s, C(2)H_2), 7.19 – 7.29 (3H, m, C(3')*H*, C(4')*H*, C(5')*H*), 7.27 (2H, d, *J* 7.1, C(2'',6'')*H*), 7.28 – 7.33 (1H, m, C(6')*H*),

8.25 (2H, d, *J* 9.2, C(3'',5'')*H*); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ_C: 19.8 (*C*H_3), 39.3 (*C*(2)H_2), 122.5 (*C*(2'',6'')H), 125.3 (*C*(3'',5'')H), 126.5 (*C*(5')H), 128.1 (*C*(4')H), 130.3 (*C*(6')H), 130.8 (*C*(3')H), 131.5 (*C*(2')), 137.0 (*C*(1')), 145.4 (*C*(4'')), 155.5 (*C*(1'')), 169.1 (*C*=O). (LNB ref: CM425)

7.4. Experimental for Chapter 2

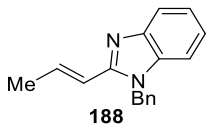
Phenyl *trans*-styryl sulfone **184** and benzylidene malononitrile **201** were purchased from Sigma Aldrich, *trans*-β-nitrostyrene **185**, 2,3,4,5,6-pentafluorostyrene **186**, 4-nitrostyrene **187** and diethyl benzylidenemalonate **196** were purchased from Alfa Aesar, maleic anhydride **194** was purchased from VWR, methyl 2-acetamidoacrylate **195** was purchased from TCI.

Reactions in Schemes 28, 29, 30, 31 and Tables 1, 2, 3 were carried out according to general procedure B.

Reactions in Tables 4, 5, 6, 7, 8 were carried out according to general procedure B.

7.4.1. Electrophile screen

(*E*)-1-Benzyl-2-(prop-1-en-1-yl)-1H-benzo[d]imidazole (**188**)

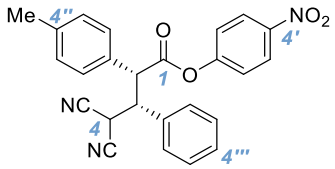


188

Following the procedure of Terada and co-workers.[155] A suspension of crotonic acid (861 mg, 10 mmol, 1.0 equiv), 1,2-phenylenediamine (1.10 g, 10 mmol, 1.0 equiv) and polyphosphoric acid (4.0 g) was stirred at 180 °C for 12 h. The reaction mixture was allowed to cool to room temperature, diluted with sat. aq. $NaHCO_3$ and the organics were extracted with EtOAc (4 ×). The organic layer was dried over $MgSO_4$, filtered concentrated under reduced pressure. The crude product was purified by flash column chromatography (50 to 85 % EtOAc in petrol; R_f 0.29 at 80% EtOAc in petrol). Et_2O was added to the product and filtered to give (*E*)-2-(prop-1-en-1-yl)-1*H*-benzo[*d*]imidazole (481 mg, 30%) as a colourless solid with spectroscopic data in accordance with the literature.[155] **mp** 194-196 °C {no Lit. mp}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.97 (3H, dd, *J* 6.7, 1.7, C*H*$_3$), 6.52 (1H, dq, *J* 16.0, 1.6, CH_3CHC*H*), 6.77 (1H, dq, *J* 16.0, 6.7, CH_3C*H*CH), 7.18 – 7.27 (2H, m, ArC*H*), 7.39 (1H, app s, ArC*H*), 7.72

(1H, s, ArC*H*), 9.89 (1H, s, N*H*). (CM734). Sodium hydride (60% suspension in oil, 86 mg, 3.6 mmol, 1.2 equiv) was added to a stirred solution of (*E*)-1-benzyl-2-(prop-1-en-1-yl)-1*H*-benzo[*d*]imidazole (475 mg, 3 mmol, 1.0 equiv) in DMF (15 mL, 0.2 M) at 0 °C and the reaction was allowed to stir at 0 °C for 30 mins. Benzyl bromide (0.7 mL, 6 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 48 h. The reaction mixture was diluted with sat. aq. NH_4Cl and the organics were extracted with EtOAc (4 ×). The organic layer was washed with brine, dried over $MgSO_4$, filtered concentrated under reduced pressure. The crude product was purified by flash column chromatography (0 to 75 % EtOAc in petrol; R_f 0.31 at 60% EtOAc in petrol) to give the title compound (471 mg, 40%) as a white solid with spectroscopic data in accordance with the literature.[155] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.96 (3H, dd, *J* 6.9, 1.8, C*H*$_3$), 5.39 (2H, s, C*H*$_2$), 6.44 (1H, dq, *J* 15.4, 1.7, CH$_3$CHC*H*), 7.01 – 7.11 (2H, m, ArC*H*), 7.11 – 7.25 (4H, m, ArCH and CH$_3$C*H*CH), 7.25 – 7.36 (3H, m, ArCH), 7.65 – 7.78 (1H, m, ArC*H*). (CM735)

4'''-Nitrophenyl 4,4-dicyano-3-phenyl-2-(*p*-tolyl)butanoate (**207**)

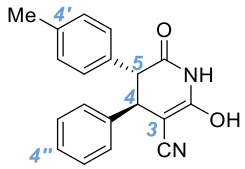


207

Following general procedure B, using 4-nitrophenyl 2-(*p*-tolyl)acetate **183** (54.2 mg, 0.20 mmol, 1.0 equiv), benzylidene malononitrile (33.9 mg, 0.22 mmol, 1.1 equiv), BTM (10.1 mg, 0.04 mmol, 20 mol%) and CH_2Cl_2 (1 mL, 0.20 M) at room temperature for 16 h. Purification by flash column chromatography (0 to 40 % EtOAc in petrol; R_f 0.31 at 30% EtOAc in petrol) gave the title compound (24 mg, 28%) as a white solid. **mp** 70-71 °C; **HPLC**: Chiralcel OD-H, (99:1 hexane: IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 87.5 min, t_R (minor): 102.1 min, 84:16 er; ν_{max} (film, cm^{-1}) 2901, 2050 (CN), 1759 (C=O), 1521, 1344, 1121; **^{1}H NMR** (500 MHz, CD_3CN) δ_H: 2.40 (3H, s, C*H*$_3$), 4.06 (1H, d, *J* 4.6, C(4)*H*), 4.22 (1H, dd, *J* 12.2, 4.6, C(3)*H*), 4.61 (1H, d, *J* 12.2, C(2)*H*), 6.75 (2H, d, *J* 9.1, C(2',6')*H*), 7.37 (2H, d, *J* 8.0, C(3'',5'')*H*), 7.47 – 7.60 (5H, m, C(2'',6'')*H*, C(3''',5''')*H*, C(4''')*H*), 7.68 (2H, d, *J* 6.9, C(2''',6''')*H*), 8.10 (2H, d, *J* 9.1, C(3',5')*H*); **^{13}C{^{1}H} NMR** (126 MHz, CD_3CN) δ_C: 21.2 (*C*H$_3$), 29.0 (*C*(4)H), 48.2 (*C*(3)H),

54.5 (*C*(2)H), 112.7 (*C*N), 113.2 (*C*N), 123.0 (*C*(2',6')H), 126.2 (*C*(3',5')H), 129.6 (*C*(2'',6'')H, *C*(2''',6''')H), 130.2 (*C*(3''',5''')H), 130.4 (*C*(4''')H), 131.1 (*C*(1'')), 131.3 (C(3'',5'')H), 136.7 (*C*(1''')), 140.6 (*C*(4'')), 146.7 (*C*(1')), 155.7 (*C*(4')), 169.9 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{25}H_{20}N_3O_4$ [M+H]$^+$ found 426.1455, requires 426.1448 (+1.6 ppm). (LNB ref: CM249, CM257, CM277)

2-Hydroxy-6-oxo-4-phenyl-5-(*p*-tolyl)-1,4,5,6-tetrahydropyridine-3-carbonitrile (**214**)



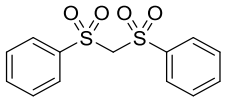
214

Following general procedure B, using 4-nitrophenyl 2-(*p*-tolyl)acetate **183** (54.2 mg, 0.20 mmol, 1.0 equiv), benzylidene malononitrile (33.9 mg, 0.22 mmol, 1.0 equiv), HyperBTM (12.3 mg, 0.04 mmol, 20 mol%), *i*-Pr$_2$NEt (52 μL, 0.3 mmol, 1.5 equiv) and CH_2Cl_2 (1 mL, 0.20 M) at room temperature for 16 h gave, after purification by column chromatography (10 to 100 % EtOAc in petrol, then 0 to 40% MeOH in EtOAc) to give the title compound (31 mg, 52%) as a white solid. **mp** 226 °C; **ν_{max}** (film, cm^{-1}) 3032, 2922, 2322, 2189, 1568, 1396; **^{1}H NMR** (400 MHz, MeOD) δ_H: 2.15 (3H, s, C*H*$_3$), 3.95 (1H, d, *J* 11.9, C(4)*H*), 4.05 (1H, d, *J* 11.9, C(5)*H*), 6.89 (2H, d, *J* 7.9, C(3',5')*H*), 7.13 (2H, d, *J* 8.1, C(2',6')*H*), 7.18 – 7.26 (3H, m, C(3'',5'')*H*, C(4'')*H*), 7.30 (2H, d, *J* 6.6, C(2'',6'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, MeOD) δ_C: 21.0 (*C*H$_3$), 49.9 (*C*(4)H), 57.4 (*C*(5)H), 114.0 (*C*N), 114.3 (*C*(3)), 129.2 (*C*(4'')H), 129.4 (*C*(3'',5'')H), 129.6 (*C*(2'',6'')H), 129.7 (*C*(3',5')H), 130.3 (*C*(2',6')H), 136.8 (*C*(1')), 137.3 (*C*(1'')), 137.4 (*C*(4')), 180.2 (*C*(6)=O), (*C*(2) was not observed despite measurements with increased relaxation delay); **HRMS** (ESI$^-$) $C_{19}H_{15}N_2O_2$ [M−H]$^-$ found 303.1135, requires 303.1139 (−1.3 ppm). (LNB ref: CM253, CM255, CM258)

7.4.2. Synthesis of vinyl bis-sulfones

1,1-Bis(phenylsulfonyl)ethylene **219** was purchased from Sigma-Aldrich.

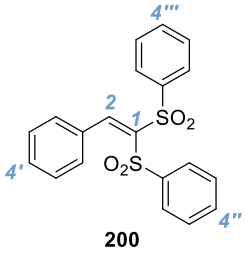
Bis(phenylsulfonyl)methane (**216**)



216

Following the procedure of Alexakis and co-workers.[165] 30% Hydrogen peroxide (26 mL, 250 mmol, 5.0 equiv) was added to bis(phenylthio)methane (11.6 g, 50 mmol, 1.0 equiv) in acetic acid (167 mL, 0.3 M) and acetic anhydride (45 mL, 1.1 M) and the reaction was stirred at 0 °C for 2 h then at room temperature for 24 h. H_2O (5 × 70 mL) was added and the precipitate was filtered, washed with H_2O and recrystallised in PhMe to give the title compound (12.3 g, 86%) as white crystalline needles with spectroscopic data in accordance with the literature.[261] **mp** 118-120 °C (PhMe) {Lit.[261] 121-122 °C (PhMe)}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.74 (2H, s, C*H*$_2$), 7.44 – 7.68 (4H, m, C(3,5)*H*), 7.72 (2H, tt, *J* 7.1, 1.2, C(4)*H*), 7.96 (4H, dd, *J* 8.5, 1.2, C(2,6)*H*); (LNB ref: CM498, CM504, CM515, CM568, CM572)

(2-Phenylethene-1,1-diyldisulfonyl)dibenzene (**200**)

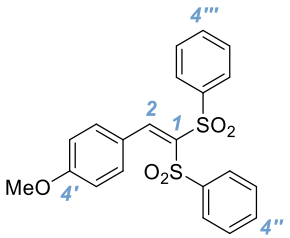


200

Following the procedure of Alexakis and co-workers.[165] Benzaldehyde (1.5 mL, 15.0 mmol, 1.0 equiv), bis(phenylsulfonyl)methane **216** (4.89 g, 16.5 mmol, 1.1 equiv), diethylammonium chloride (3.12 g, 28.5 mmol, 1.9 equiv), potassium fluoride (131 mg, 2.2 mmol, 0.15 equiv) and PhMe (122 mL, 0.12 M) were combined and the reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (25 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was stirred in CH_2Cl_2/Et_2O (1:4, 10 mL) for 5 mins. The precipitate was filtered and

washed with Et_2O. The crude product was purified by column chromatography (20 to 45% EtOAc in petrol; R_f 0.40 at 40% EtOAc in petrol) to give the title compound (1.72 g, 30%) as a colourless solid with spectroscopic data in accordance with the literature.[165] **mp** 174-176 °C {Lit.[262] 175 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.26 – 7.33 (2H, m, C(3'',5'')*H*), 7.36 (2H, t, *J* 7.4, C(3',5')*H*), 7.40 – 7.53 (4H, m, C(4')*H*, C(2',6')*H* and C(4'')*H*), 7.54 – 7.64 (4H, m, C(2'',6'')*H* and C(3''',5''')*H*), 7.66 – 7.74 (1H, m, C(4''')*H*), 8.02 – 8.11 (2H, m, C(2''',6''')*H*), 8.67 (1H, s, C(2)*H*). (LNB ref: CM276, CM343, CM351, CM366, CM413, CM442, CM472, CM473, CM514, CM516, CM571)

(2-(4'-Methoxyphenyl)ethene-1,1-diyldisulfonyl)dibenzene (**263**)

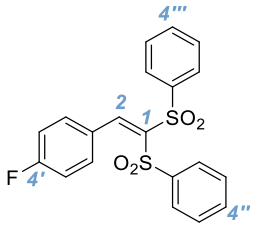


263

Following the procedure of Mayr and co-workers.[164] 4-Methoxybenzaldehyde (5.1 mL, 42.2 mmol, 7.4 equiv), bis(phenylsulfonyl)methane **216** (1.70 g, 5.7 mmol, 1.0 equiv), diethylammonium chloride (1.19 g, 10.8 mmol, 1.9 equiv) and potassium fluoride (50 mg, 0.86 mmol, 0.15 equiv) were combined and PhMe (46 mL, 0.12 M) was added. The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10 to 50% EtOAc in petrol; R_f 0.40 at 40% EtOAc in petrol) to give the title compound (456 mg, 20%) as a yellow solid with spectroscopic data in accordance with the literature.[164] **mp** 162 °C {Lit.[164] 123.0-123.9 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.86 (3H, s, CH_3), 6.90 (2H, d, *J* 8.9, C(3',5')*H*), 7.37 (2H, t, *J* 7.9, C(3'',5'')*H*), 7.51 (1H, t, *J* 7.5, C(4'')*H*), 7.56 (2H, t, *J* 7.7, C(3''',5''')*H*), 7.65 (1H, t, *J* 7.4, C(4''')*H*), 7.78 – 7.84 (4H, m, C(2'',6'')*H* and C(2',6')*H*), 8.02 (2H, d, *J* 7.3, C(2''',6''')*H*), 8.57 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 55.7 (CH_3), 114.2 (*C*(3',5')H), 122.6 (*C*(1')), 127.8 (*C*(2'',6'')H), 128.7 (*C*(2''',6''')H), 128.9 (*C*(3'',5'')H), 129.1 (*C*(3''',5''')H), 133.7 (*C*(4''')H), 133.9 (*C*(4'')H), 135.5 (*C*(2',6')H), 138.9

(*C*(1)), 140.7 (*C*(1''')), 140.8 (C(1'')), 151.6 (*C*(2)), 163.4 (*C*(4')). The observed melting point was significantly higher than the one reported. However, I am satisfied that the structure of the compound is correct and of high purity based on the other characterisation data. Therefore, I am confident the observed melting point is accurate for the named compound when it is synthesised and purified as described. (LNB ref: CM417)

(2-(4'-Fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene (**264**)

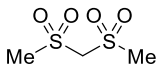


264

4-Fluorobenzaldehyde (7.5 mL, 70 mmol, 7.0 equiv), bis(phenylsulfonyl)methane **216** (2.96 g, 10 mmol, 1.0 equiv), diethylammonium chloride (2.10 g, 19 mmol, 1.9 equiv) and potassium fluoride (87 mg, 1.5 mmol, 0.15 equiv) were combined and PhMe (81 mL, 0.12 M) was added. The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 40% EtOAc in petrol; R_f 0.40 at 40% EtOAc in petrol) which precipitated following purification. The solid was filtered and washed with petrol to give the title compound (1.50 g, 38%) as a colourless solid. **mp** 150-152 °C; ν_{max} (solid, cm^{-1}) 1595 (ArC=C), 1574 (ArC=C), 1506 (ArC=C), 1308 (SO_2), 1142 (SO_2), 1082, 756 (C-F); **^{1}H NMR** (500 MHz, $CDCl_3$) δH: 7.07 (2H, t, *J* 8.6, C(3',5')*H*), 7.34 (2H, t, *J* 7.9, C(3'',5'')*H*), 7.52 (1H, t, *J* 7.5, C(4'')*H*), 7.56-7.66 (6H, m, C(3''',5''')*H*, C(2',6')*H* and C(2'',6'')*H*), 7.69 (1H, t, *J* 7.4, C(4''')*H*), 8.04 (2H, d, *J* 7.5, C(2''',6''')*H*), 8.60 (1H, s, C(2)*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −106.4 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 115.8 (d, $^2J_{C\text{-}F}$ 22.0, *C*(3',5')H), 126.5 (d, $^4J_{C\text{-}F}$ 3.3, *C*(1')), 128.0 (*C*(2'',6'')H), 128.9 (*C*(3'',5'')H), 129.0 (*C*(2''',6''')H), 129.2 (*C*(3''',5''')H), 133.6 (d, $^3J_{C\text{-}F}$ 9.0, *C*(2',6')H), 134.2 (*C*(4''')H), 134.2 (*C*(4'')H), 139.9 (*C*(1''')), 140.3 (*C*(1'')), 143.9 (*C*(1)), 150.7 (*C*(2)H), 164.6 (d, $^1J_{C\text{-}F}$ 254.9,

C(4')); **HRMS** (ASAP$^+$) $C_{20}H_{16}FO_4S_2$ $[M+H]^+$ found 403.0467, requires 403.0469 (−0.5 ppm). (LNB ref: CM543, CM630, CM673)

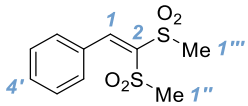
Bis(methylsulfonyl)methane (**261**)



261

Following the procedure of Mallah and co-workers.[263] 30% Hydrogen peroxide (14.4 mL, 140 mmol, 10 equiv) was added to bis(methylthio)methane (1.4 mL, 14 mmol, 1.0 equiv) in acetic acid (11 mL, 1.25 M) at 0 °C. The reaction was stirred at 55 °C for 31 h and then allowed to cool, diluted with water and extracted with CH_2Cl_2. The organics were combined, washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (799 mg, 33%) as a colourless solid with spectroscopic data in accordance with the literature.[264] **mp** 144 °C {no Lit. mp}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.26 (6H, s, C*H*$_3$), 4.44 (2H, s, C*H*$_2$). (LNB ref: CM505)

(2,2-Bis(methylsulfonyl)vinyl)benzene (**267**)

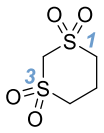


267

Benzaldehyde (3.2 mL, 31.5 mmol, 7.0 equiv), bis(methylsulfonyl)methane **261** (775 mg, 4.5 mmol, 1.0 equiv), diethylammonium chloride (937 mg, 8.6 mmol, 1.9 equiv) and potassium fluoride (39 mg, 0.68 mmol, 0.15 equiv) were combined and PhMe (36 mL, 0.12 M) was added. The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Et_2O (20 mL) was added and the precipitate was filtered and washed with Et_2O. The crude product was purified by column chromatography (0 to 45% EtOAc in petrol; R_f 0.30 at 40% EtOAc in petrol) to give the title compound (215 mg, 21%) as a colourless solid with spectroscopic data in accordance with the literature.[265] **mp** 134 °C {Lit.[265] 136-137 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.30 (3H,

s, C(1'')*H*$_3$), 3.40 (3H, s, C(1''')*H*$_3$), 7.43 – 7.56 (3H, m, C(3',5')*H* and C(4')*H*), 7.65 – 7.71 (2H, m, C(2',6')*H*), 8.45 (1H, s, C(1)*H*). (LNB ref: CM518)

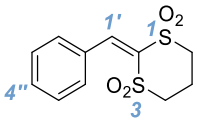
1,3-Dithiane 1,1,3,3-tetraoxide (**262**)



262

30% Hydrogen peroxide (22 mL, 210 mmol, 15 equiv) was added to dithiane (1.68 g, 14 mmol, 1.0 equiv) in acetic acid (11 mL, 1.25 M) at 0 °C and the reaction was stirred at 55 °C for 30 h. The reaction was allowed to cool, and the precipitate was filtered and washed with H_2O then pentane to give the title compound (1.99 g, 78%) as a colourless solid with spectroscopic data in accordance with the literature.[266] **mp** > 300 °C (dec) {Lit.[266] 309-312 °C}; **^{1}H NMR** (400 MHz, DMSO) δ_H: 2.21 – 2.31 (2H, m, C(5)*H*$_2$), 3.35 – 3.42 (4H, m, C(4,6)*H*$_2$), 5.25 (2H, s, C(2)*H*$_2$). (LNB ref: CM506, 569)

2-Benzylidene-1,3-dithiane 1,1,3,3-tetraoxide (**268**)

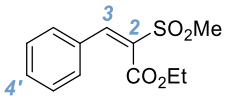


268

Benzaldehyde (5 mL, 49 mmol, 7.0 equiv), 1,3-dithiane 1,1,3,3-tetraoxide **262** (1.3 g, 7.0 mmol, 1.0 equiv), diethylammonium chloride (1.46 g, 13.3 mmol, 1.9 equiv) and potassium fluoride (61 mg, 1.05 mmol, 0.15 equiv) were combined and PhMe (57 mL, 0.07 M) was added. The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (50 to 80% EtOAc in petrol; R_f 0.38 at 80% EtOAc in petrol) to give the title compound (451 mg, 24%) as a colourless solid. **mp** 190 °C; **ν_{max}** (solid, cm^{-1}) 2926 (C-H), 1593 (C=C), 1327 (SO_2), 1315, 1134 (SO_2), 923, 754; **^{1}H NMR** (500 MHz, DMSO) δ_H: 2.15 – 2.45 (2H, m, C(5)*H*$_2$), 3.52 – 3.87 (4H, m, C(4,6)*H*$_2$), 7.48 (2H, t, *J* 7.5, C(3'',5'')*H*), 7.55 (1H, t, *J* 7.4, C(4'')*H*), 7.64 (2H, d, *J* 7.4, C(2'',6'')*H*), 8.28 (1H, s, C(1')*H*); **^{13}C{^{1}H} NMR**

(126 MHz, DMSO) δ_C: 17.3 (*C*(5)H_2), 50.9 (*C*(3)H_2), 53.6 (*C*(6)H_2), 127.8 (*C*(3'',5'')H), 130.3 (*C*(1'')), 131.8 (*C*(4'')H), 131.9 (*C*(2'',6'')H, 141.5 (*C*(2)), 145.9 (*C*(1')); **HRMS** (ASAP$^+$) $C_{11}H_{13}O_4S_2$ $[M+H]^+$ found 273.0258, requires 273.0250 (+2.9 ppm). (LNB ref: CM524)

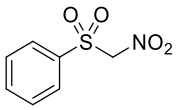
Ethyl (*E*)-2-(methylsulfonyl)-3-phenylacrylate (**270**)



270

Following the procedure of Mayr and co-workers.[177] Ethyl methylsulfonyl acetate (1.1 mL, 8 mmol, 1.0 equiv) and benzaldehyde (0.8 mL, 8 mmol, 1.0 equiv) were combined in PhMe (65 mL, 0.12 M) before the addition of (0.12 mL, 1.2 mmol, 0.15 equiv) and trifluoroacetic acid (0.11 mL, 1.44 mmol, 0.18 equiv). The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and and quenched with 2 M HCl (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organics were combined, washed with sat. aq. $NaHCO_3$ (200 mL) and water (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, EtOAc in petrol (5% 5 CV, 5-45% 20 CV, 45% 5 CV), R_f 0.41 at 40% EtOAc in petrol] to give the title compound (1.1 g, 94%) as a colourless solid with spectroscopic data in accordance with the literature.[177] **mp** 54-56 °C {Lit.[267] 53-55 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.2, CH_2CH_3), 3.24 (3H, s, SO_2CH_3), 4.34 (2H, q, *J* 7.1, CH_2CH_3), 7.31 – 7.58 (5H, m, C(2',6')*H*, C(3',5')*H* and C(4')*H*), 7.82 (1H, s, C(3)*H*). (LNB ref: CM531)

((Nitromethyl)sulfonyl)benzene (**272**)

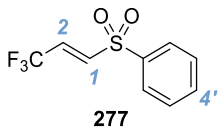


272

Following the procedure of Prakash and co-workers.[268] DBU (5.4 mL, 36 mmol, 1.2 equiv) was added to nitromethane (1.95 mL, 36 mmol, 1.2 equiv) in DMF (36 mL, 0.83 M) at 0 °C and stirred for 10 min. Benzenesulfinic acid sodium salt (4.9 g, 30

mmol, 1 equiv) and iodine (6.85 g, 27 mmol, 0.9 equiv) were added and the reaction was stirred at room temperature for 1 h. The reaction mixture was quenched with sat. aq. Na_2SO_3 until the reaction mixture turned bright yellow and then acidified to pH = 1 with conc. HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organics were combined and washed with 2 M NaOH (4 × 100 mL) [note: sodium nitro(phenylsulfonyl)methide goes into the aqueous layer]. The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL), acidified to pH = 1 using 2 M HCl and extracted with CH_2Cl_2 (3 × 100 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallised from CH_2Cl_2/petrol to give the title compound (1.57 g, 26%) as a pale yellow solid with spectroscopic data in accordance with the literature.[268] **mp** 75-76 °C {Lit.[269] 76-77 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 5.61 (2H, s, C*H*$_2$), 7.62 – 7.70 (2H, m, C(3,5)*H*), 7.76 – 7.84 (1H, m, C(4)*H*), 7.97 (2H, dd, *J* 8.5, 1.2, C(2,6)*H*). (CM544)

(*E*)-((3,3,3-Trifluoroprop-1-en-1-yl)sulfonyl)benzene (**277**)



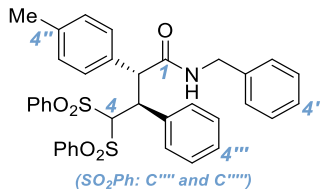
277

Sodium hydride (60% suspension in oil, 540 mg, 22.5 mmol, 1.5 equiv) was added portion wise to methyl phenyl sulfone (2.3 g, 15 mmol, 1.0 equiv) in THF (30 mL, 0.5 M) at 0 °C and stirred at 0 °C for 10 mins. Ethyl trifluoroacetate (5.4 mL, 45 mmol, 3.0 equiv) was added dropwise at 0 °C and the reaction was heated at reflux for 2 h. The reaction mixture was poured into brine (375 mL) and extracted with Et_2O (4 × 150 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude 1,1,1-trifluoro-3-(phenylsulfonyl)propan-2-one (4.4 g). Sodium borohydride (993 mg, 26.2 mmol, 1.5 equiv) was added to crude 1,1,1-trifluoro-3-(phenylsulfonyl)propan-2-one (4.4 g, 17.5 mmol, 1.0 equiv) in MeOH (50 mL, 0. 35 M) at room temperature and the reaction was stirred for 18 h. The reaction mixture was poured into brine (480 mL) and extracted with Et_2O (3 × 240 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and recrystallised from Et_2O/hexane to give 1,1,1-trifluoro-3-(phenylsulfonyl)propan-2-ol (2.35 g, 53%). Triethylamine (2.6 mL, 18.6 mmol, 2.0

equiv) and tosyl chloride (1.77 g, 9.3 mmol, 1.0 equiv) were added to 1,1,1-trifluoro-3-(phenylsulfonyl)propan-2-ol (2.35 g, 9.3 mmol, 1.0 equiv) in CH_2Cl_2 (32 mL, 0.29 M) and the reaction was heated at reflux for 2 h. The reaction was cooled to rt, DBU was added (1.4 mL, 9.3 mmol, 1.0 equiv) and the reaction was heated at reflux for 1 h. The reaction mixture was allowed to cool to rt, poured into sat. aq. $NaHCO_3$ (300 mL), extracted with CH_2Cl_2 (3 × 150 mL). The organics were combined, washed with 1 M HCl (2 × 150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 50% EtOAc in petrol; R_f 0.30 at 20% EtOAc in petrol) to give the title compound (1.18 g, 33% over 3 steps) as a colourless solid with spectroscopic data in accordance with the literature.[270] **mp** 69-70 °C {Lit.[271] 66-66.5 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.83 (1H, dq, *J* 15.2, 6.1, C(2)*H*), 7.03 (1H, dq, *J* 15.2, 1.7, C(1)*H*), 7.62 (2H, t, *J* 7.7, C(3',5')*H*), 7.68 – 7.79 (1H, tt, *J* 7.2, 1.6, C(4')*H*), 7.93 (2H, dd, *J* 8.4, 1.3, C(2',6')*H*). (CM500, CM502, CM503)

7.4.3. Catalysis products

(2*R*,3*S*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(*p*-tolyl)butanamide (**217**)

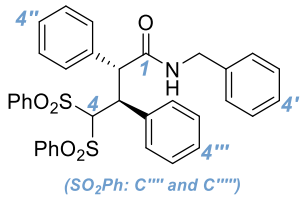


217

Following general procedure C, using 4-nitrophenyl 2-(*p*-tolyl)acetate **183** (81 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 5% Et_2O in CH_2Cl_2; R_f 0.26 at 3% Et_2O in CH_2Cl_2) gave the title compound (94 mg, 75%, single major diastereoisomer) as a colourless solid. **mp** 208-210 °C; $\mathbf{[\alpha]_D^{20}}$ −11.2 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 13.8 min, t_R (major): 20.7 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3389 (CON-H), 2914 (C-H), 1676 (C=ONH), 1524 (C=ONH), 1508 (ArC=C), 1323 (SO_2), 1144

(SO_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s, C*H*$_3$), 3.80 (1H, dd, *J* 15.0, 4.2, NC*H*^{A}H^{B}Ph), 4.40 (1H, dd, *J* 15.0, 7.4, NCH^A*H*^{B}Ph), 4.64 (1H, d, *J* 11.7, C(2)*H*), 4.71 (1H, dd, *J* 11.7, 1.7, C(3)*H*), 4.75 (1H, d, *J* 1.8, C(4)*H*), 5.67 (1H, dd, *J* 7.1, 4.3, N*H*), 6.58 (2H, d, *J* 7.0, C(2',6')*H*), 7.07 – 7.13 (2H, m, C(3',5')*H*), 7.14 – 7.17 (1H, m, C(4')*H*), 7.15 – 7.20 (2H, broad-m, C(3'',5'')*H*), 7.29 – 7.35 (7H, m, C(3'''',5'''')*H*, C(2'',6'')*H*, C(3''',5''')*H* and C(4''')*H*), 7.34 – 7.39 (2H, m, C(3'''',5'''')*H*), 7.41 (2H, dd, *J* 8.5, 1.0, C(2'''',6'''')*H*), 7.46 (2H, dd, *J* 8.5, 1.0, C(2'''',6'''')*H*), 7.51 (1H, t, *J* 7.4, C(4'''')H), 7.57 (1H, t, *J* 7.4, C(4'''')*H*), 7.80 (2H, dd, *J* 8.0, 2.0, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 21.4 (C*H*$_3$), 43.5 (NC*H*$_2$Ph), 47.7 (*C*(3)H), 57.5 (*C*(2)H), 82.9 (*C*(4)H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (*C*(4''')H), 128.2 (*C*(3''',5''')H), 128.5 (*C*(2'''',6'''')H), 128.6 (*C*(3',5')H), 128.7 (*C*(3'''',5'''')H), 128.8 (*C*(2'',6'')H), 129.1 (*C*(2'''',6'''')H), 129.2 (*C*(3'''',5'''')H), 130.1 (*C*(3'',5'')H), 131.4 (*C*(2''',6''')H), 133.9 (*C*(4'''')H), 134.0 (*C*(1'')), 134.3 (*C*(4'''')H), 134.6 (*C*(1''')), 137.7 (*C*(1')), 138.2 (*C*(1'''')), 138.4 (*C*(4'')), 141.4 (*C*(1'''')), 170.9 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{36}H_{34}NO_5S_2$ $[M+H]^+$ found 624.1866, requires 624.1873 (−1.1 ppm). (LNB ref: CM284, CM334, CM338, CM419, CM476)

(2*R*,3*S*)-*N*-Benzyl-2,3-diphenyl-4,4-bis(phenylsulfonyl)butanamide (**220**)

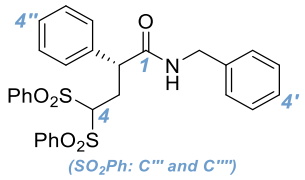


220

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 6% Et_2O in CH_2Cl_2; R_f 0.30 at 5% Et_2O in CH_2Cl_2) gave the title compound (98 mg, 80%, single major diastereoisomer) as a colourless solid. **mp** 236 °C; **$[\alpha]_D^{20}$** −17.5 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.2 min, t_R (major): 38.3 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 3277 (CON-H), 2872 (C-H), 1638 (C=O), 1522 (ArC=C), 1448, 1312 (SO_2), 1136 (SO_2), 729; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ_H: 3.81 (1H, dd, *J* 15.1, 4.3, NC*H*$_2$Ph), 4.41 (1H, dd, *J* 15.1, 7.4, NC*H*$_2$Ph), 4.71 (1H, d, *J* 11.7, C(2)*H*), 4.72 (1H, d, *J* 1.7, C(4)*H*), 4.78 (1H, dd, *J* 11.7, 1.6, C(3)*H*), 5.78 (1H, dd, *J* 7.0, 4.4, N*H*), 6.58 (2H, d, *J* 7.1, C(2',6')*H*), 7.13 (2H, t, *J* 7.2, C(3',5')*H*), 7.18 (1H, t, *J* 7.2, C(4')*H*), 7.32 (2H, t, *J* 7.1, C(3'''',5'''')*H*), 7.34 – 7.36 (2H, m, C(3''',5''')*H*), 7.36 – 7.45 (10H, m, ArC*H*), 7.46 – 7.50 (2H, m, C(2'''',6'''')*H*), 7.52 (1H, t, *J* 7.4, C(4'''')*H*), 7.60 (1H, t, *J* 7.4, C(4'''')*H*), 7.66 – 7.99 (2H, m, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH_2Ph), 47.6 (*C*(3)H), 57.9 (*C*(2)H), 82.7 (*C*(4)H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (*C*(3''',5''')H), 128.2 (*C*(4''')H), 128.4 (*C*(2'''',6'''')H), 128.5 (*C*(4'')H), 128.6 (*C*(3',5')H), 128.8 (*C*(3'''',5'''')H), 129.0 (*C*(2'''',6'''')H and 2 ArCH), 129.3 (*C*(3'''',5'''')H), 129.5 (2xArCH), 131.5 (*C*(2''',6''')H), 133.9 (*C*(4'''')H), 134.3 (*C*(4'''')H), 134.5 (*C*(1''')), 137.1 (*C*(1'')), 137.6 (*C*(1')), 138.2 (*C*(1'''')), 141.3 (*C*(1'''')), 170.7 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{35}H_{32}NO_5S_2$ $[M+H]^+$ found 610.1712, requires 610.1716 (−0.6 ppm). (LNB ref: CM474, CM428)

(*R*)-*N*-Benzyl-2-phenyl-4,4-bis(phenylsulfonyl)butanamide (**221**)

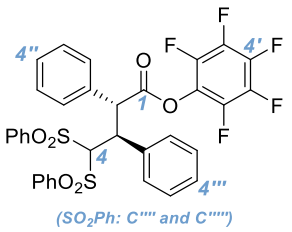


221

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene **219** (62 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product. Purification by flash column chromatography (0 to 5% Et_2O in CH_2Cl_2; R_f 0.35 at 5% Et_2O in CH_2Cl_2) gave the title compound (83 mg, 78%) as a colourless solid. **mp** 128-129 °C; $[\alpha]_D^{20}$ −34.0 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.7 min, t_R (major): 24.6 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3383 (N-H), 2905 (C-H), 1655 (C=O), 1539, 1447, 1335 (SO_2), 1308, 1150 (SO_2), 1076, 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.70 (1H, ddd, *J* 15.5, 9.4, 4.5, C(3)*H*$_A$H$_B$), 2.80 – 2.93 (1H, m, C(3)H^A*H*^{B}), 4.16 (1H, dd, *J* 9.3, 6.9, C(2)*H*), 4.30 (1H, dd, *J* 14.9, 5.7, NC*H*^{A}H^{B}Ph), 4.35 – 4.49 (2H, m, NCH^A*H*^{B}Ph

and C(4)*H*), 5.74 (1H, app t, *J* 5.5, N*H*), 7.06 – 7.12 (2H, m, C(2',6')*H*), 7.14 (2H, dd, *J* 7.4, 1.9, C(2'',6'')*H*), 7.21 – 7.33 (6H, m, (C(3',5')*H*, C(4')*H*, C(3'',5'')*H*, C(4'')*H*), 7.51 (2H, t, *J* 7.9, C(3'''',5'''')*H*), 7.56 (2H, t, *J* 7.9, C(3''',5''')*H*), 7.63 – 7.69 (1H, m, C(4'''')*H*), 7.67 – 7.73 (1H, m, C(4''')*H*), 7.73 – 7.78 (2H, m, C(2'''',6'''')*H*), 7.87 – 7.94 (2H, m, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.3 (*C*(3)H), 43.8 (NCH^{A}H^{B}Ph), 49.6 (*C*(2)H), 80.5 (*C*(4)H), 127.6 (*C*(2',6')H), 127.6 (*C*(4')H or *C*(4'')H), 128.3 (*C*(4')H or *C*(4'')H), 128.4 (*C*(2'',6'')H), 128.8 (*C*(3',5')H or *C*(3'',5'')H), 129.2 (*C*(3''',5''')H), 129.3 (*C*(3'''',5'''')H), 129.5 (*C*(3',5')H or *C*(3'',5'')H), 129.7 (*C*(2'''',6'''')H), 129.7 (*C*(2''',6''')H), 134.7 (*C*(4'''')H), 134.8 (*C*(4''')H), 137.2 (*C*(1'')), 137.4 (*C*(1'''')), 138.0 (*C*(1') or *C*(1''')), 138.0 (*C*(1') or *C*(1''')), 171.7 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{29}H_{28}NO_5S_2$ $[M+H]^+$ found 534.1394, requires 534.1403 (−1.7 ppm). (LNB ref: CM429, CM475, CM615, CM618,)

Perfluorophenyl (2*R*,3*S*)-2,3-diphenyl-4,4-bis(phenylsulfonyl)butanoate (**224**)

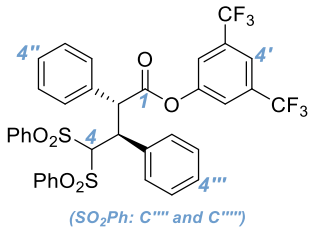


224

Following general procedure C, using perfluorophenyl 2-phenylacetate **208** (91 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (50 to 75% Et_2O in petrol; R_f 0.30 at 70% Et_2O in petrol) gave the title compound (54 mg, 39%, single major diastereoisomer) as a colourless solid. **mp** 232-233 °C; $[\alpha]_D^{20}$ −58.0 (*c* 0.5, $CHCl_3$); **HPLC**: [determined by conversion to amide **220** using benzylamine] Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.2 min, t_R (major): 38.3 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 1782 (C=O), 1520 (ArC=C), 1447, 1339 (SO_2), 1146 (SO_2), 1076, 995 (C-F), 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.72 (1H, s, C(4)*H*), 4.95 (1H, d, *J* 12.4, C(3)*H*), 5.50 (1H, d, *J* 12.4, C(2)*H*), 7.21 (2H, d, *J* 7.9, C(2'''',6'''')*H*), 7.22 – 7.29 (4H, m, C(3'''',5'''')*H* and C(3'''',5'''')*H*), 7.31 – 7.44 (5H, m, C(3''',5''')*H*, C(4''')*H* and C(2'''',6'''')*H*), 7.45 – 7.55 (5H, m, C(3'',5'')*H*, C(4'')*H*, C(4'''')*H* and C(4'''')*H*), 7.59 (2H, broad-s, C(2'',6'')*H*), 7.84

(2H, d, *J* 7.4, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −163.1 – −161.2 (m), −157.7 (t, *J* 21.8), −153.5 – −151.9 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 46.2 (*C*(3)H), 54.8 (*C*(2)H), 82.3 (*C*(4)H), 124.4 – 124.9 (m, C(1')), 128.4 (*C*(2'''',6'''')H), 128.5 (*C*(3''',5''')H), 128.8 (*C*(4''')H and *C*(2'''',6'''')H), 128.9 (*C*(3''',5''')H or *C*(3'''',5'''')H), 129.2 (*C*(3''',5''')H or *C*(3'''',5'''')H), 129.5 (*C*(4'')H), 130.0 (*C*(2'',6'')H and *C*(3'',5'')H), 130.7 (*C*(2''',6''')H), 133.5 (*C*(1''')), 134.1 (*C*(4'''')H and *C*(4'''')H), 134.7 (*C*(1'')), 136.5 – 136.9 (m, Ar*C*F), 138.4 – 140.1 (m, 2 Ar*C*F), 138.6 (*C*(1'''')), 140.1 (*C*(1'''')), 140.3 – 142.2 (m, 2 Ar*C*F), 168.2 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{34}H_{27}F_5NO_6S_2$ $[M+NH_4]^+$ found 704.1182, requires 704.1194 (−1.7 ppm). (LNB ref: CM593, CM598)

3',5'-Bis(trifluoromethyl)phenyl(2*R*,3*S*)-2,3-diphenyl-4,4-bis(phenylsulfonyl)butanoate (**225**)

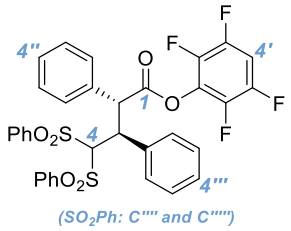


225

Following general procedure C, using 3,5-bis(trifluoromethyl)phenyl 2-phenylacetate **222** (104 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (45 to 70% Et_2O in petrol; R_f 0.27 at 65% Et_2O in petrol) gave the title compound (64 mg, 44%, single major diastereoisomer) as a colourless solid. **mp** 192-193 °C; **$[\alpha]_D^{20}$** −18.5 (*c* 0.2, $CHCl_3$); **HPLC**: [determined by conversion to amide **220** using benzylamine] Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.2 min, t_R (major): 38.3 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 1763 (C=O), 1335 (SO_2), 1277, 1157 (SO_2), 1115 (C-F), 1080, 910, 682; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.69 (1H, s, C(4)*H*), 4.78 (1H, d, *J* 12.4, C(3)*H*), 5.39 (1H, d, *J* 12.3, C(2)*H*), 6.81 (2H, s, C(2',6')*H*), 7.28 – 7.33 (6H, m, C(2'''',6'''')*H*, C(3'''',5'''')*H* and C(3'''',5'''')*H*), 7.37 – 7.44 (3H, m, C(3''',5''')*H* and C(4''')*H*), 7.45 (2H, d, *J* 8.0, C(2'''',6'''')*H*), 7.46 – 7.56 (5H, m, C(2'',6'')*H* or C(3'',5'')*H*, C(4'')*H*, C(4'''')*H* and C(4'''')*H*), 7.59 (2H, s, C(2'',6'')*H* or C(3'',5'')*H*), 7.63 (1H, s,

C(4')*H*), 7.89 (2H, d, *J* 6.8, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −63.0 (s); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 47.8 (*C*(3)H), 55.6 (*C*(2)H), 82.0 (*C*(4)H), 120.0 (*C*(4')H), 122.4 (*C*(2',6')H), 122.7 (q, $^1J_{C\text{-}F}$ 272.8, *C*F_3), 128.5 (2 ArCH), 128.6 (2 ArCH), 128.7 (2 ArCH), 128.9 (2 ArCH), 129.0 (*C*(4''')H), 129.3 (*C*(2'',6'')H or *C*(3'',5'')H and 2 ArCH), 129.4 (*C*(4'')H), 130.0 (*C*(2'',6'')H or *C*(3'',5'')H), 131.4 (*C*(2''',6''')H), 132.9 (q, $^2J_{C\text{-}F}$ 34.1, *C*(3',5')CF_3), 133.8 (*C*(1''')), 134.2 (*C*(4''''')H), 134.3 (*C*(4''')H), 134.8 (*C*(1'')), 138.3 (*C*(1''')), 140.5 (*C*(1''''')), 150.8 (*C*(1')), 170.4 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{36}H_{26}F_6NaO_6S_2$ $[M+Na]^+$ found 755.0958, requires 755.0967 (−1.2 ppm). (LNB ref: CM595, CM600)

2',3',5',6'-Tetrafluorophenyl (2*R*,3*S*)-2,3-diphenyl-4,4-bis(phenylsulfonyl)butanoate (**227**)

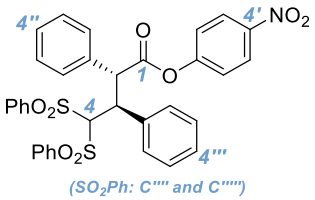


227

Following general procedure C, using 2,3,5,6-tetrafluorophenyl 2-phenylacetate **209** (85 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (50 to 75% Et_2O in petrol; R_f 0.30 at 70% Et_2O in petrol) gave the title compound (75 mg, 56%, single major diastereoisomer) as a colourless solid. **mp** 247-249 °C; **$[\alpha]_D^{20}$** −56.0 (*c* 0.5, $CHCl_3$); **HPLC**: [determined by conversion to amide **220** using benzylamine] Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 30 °C) t_R (minor): 19.2 min, t_R (major): 38.3 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 1778 (C=O), 1524 (ArC=C), 1485, 1339 (SO_2), 1284, 1146 (SO_2), 1107 (C-F), 1076, 910, 721; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.73 (1H, s, C(4)*H*), 4.95 (1H, d, *J* 12.4, C(3)*H*), 5.50 (1H, d, *J* 12.4, C(2)*H*), 6.79 – 6.94 (1H, m, C(4')*H*), 7.22 (2H, d, *J* 7.9, C(2'''',6'''')*H*), 7.23 – 7.28 (4H, m, C(3'''',5'''')*H* and C(3''''',5''''')*H*), 7.32 – 7.42 (5H, m, C(3''',5''')*H*, C(4''')*H* and C(2''''',6''''')*H*), 7.44 – 7.53 (5H, m, C(2'',6'')*H* or C(3'',5'')*H*, C(4'')*H*, C(4'''')*H* and C(4''''')*H*), 7.59 (2H, s, C(2'',6'')*H* or C(3'',5'')*H*), 7.85 (2H, d, *J* 7.5, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −153.3 – −151.1 (m), −141.1 – −137.6 (m); **^{13}C{^{1}H} NMR**

(126 MHz, $CDCl_3$) δ_C: 46.2 (*C*(3)H), 54.8 (*C*(2)H), 82.4 (*C*(4)H), 103.4 (t, *J* 22.8, *C*(4')H), 128.4 (*C*(2''',6''')H), 128.5 (2 ArCH), 128.8 (*C*(4''')H), 128.8 (2 ArCH), 128.9 (2 ArCH), 129.2 (4 ArCH), 129.4 (*C*(4'')H), 130.0 (2 ArCH), 130.7 (*C*(2''',6''')H), 133.6 (*C*(1''')), 134.1 (*C*(4''')H and *C*(4''''')H), 134.8 (*C*(1'')), 138.6 (*C*(1''')), 139.1 – 141.7 (m, *C*(3',5')), 140.2 (*C*(1''''')), 143.9 – 147.3 (m, C(2',6')), 168.1 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{34}H_{24}F_4NaO_6S_2$ $[M+Na]^+$ found 691.0830, requires 691.0843 (−1.9 ppm). (LNB ref: CM594, CM599)

4'-Nitrophenyl (2*R*,3*S*)-2,3-diphenyl-4,4-bis(phenylsulfonyl)butanoate (**228**)

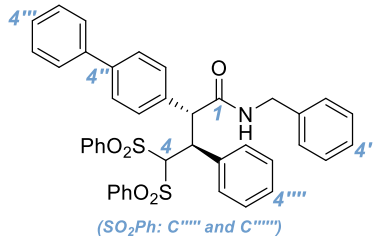


228

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (80 to 100% CH_2Cl_2 in petrol; R_f 0.30 at 90% CH_2Cl_2 in petrol) gave the title compound (108 mg, 84%, 95:5 dr) as a colourless solid. **mp** 211 °C (dec) then 223 °C; $[\alpha]_D^{20}$ −41.9 (*c* 1.0, $CHCl_3$); **HPLC**: [determined by conversion to amide **220** using benzylamine] Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.2 min, t_R (major): 38.3 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 1759 (C=O), 1529, 1348 (SO_2), 1128 (SO_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.69 (1H, d, *J* 1.4, C(4)*H*), 4.87 (1H, d, *J* 12.4, C(3)*H*), 5.40 (1H, d, *J* 12.4, C(2)*H*), 6.63 (2H, d, *J* 9.1, C(2',6')*H*), 7.18 – 7.32 (6H, m, ArC*H*), 7.34 – 7.45 (5H, m, ArC*H*), 7.46 – 7.54 (5H, m, C(3'',5'')*H*, C(4'')*H*, C(4''')*H* and C(4''''')*H*), 7.61 (2H, broad-s, C(2'',6'')*H*), 7.90 (2H, d, *J* 6.3, C(2''',6''')*H*), 8.09 (2H, d, *J* 9.1, C(3',5')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: δ c (126 MHz, $CDCl_3$) 47.2 (*C*(3)H), 55.5 (*C*(2)H), 82.0 (*C*(4)H), 122.3 (*C*(2',6')H), 125.2 (*C*(3',5')H), 128.4 (2 ArCH), 128.5 (2 ArCH), 128.7 (2 ArCH), 128.8 (*C*(4''')H), 128.9 (2 ArCH), 129.2 (*C*(3'',5'')H and 2 ArCH), 129.4 (*C*(4'')H), 130.0 (2 ArCH), 131.2 (*C*(2''',6''')H), 133.9 (*C*(1''')), 134.2 (*C*(4''')H) or (*C*(4''''')H)), 134.2 (*C*(4''')H) or (*C*(4''''')H)), 135.0 (*C*(1'')), 138.4 (*C*(1''')), 140.3 (*C*(1''''')), 145.5 (*C*(4')), 155.0 (*C*(1')), 170.1

(*C*(1)=O); **HRMS** could not be obtained for this compound due to instability and was obtained after conversion to amide **220**. (LNB ref: CM592)

(2*R*,3*S*)-2-([1'',1'''-Biphenyl]-4''-yl)-*N*-benzyl-3-phenyl-4,4-bis(phenylsulfonyl)butan-amide (**246**)

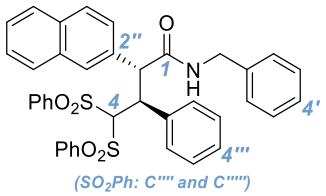


246

Following general procedure C, using 4-nitrophenyl 2-([1,1'-biphenyl]-4-yl)acetate **230** (100 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (0 to 4.5% Et_2O in CH_2Cl_2; R_f 0.28 at 4% Et_2O in CH_2Cl_2) gave the title compound (111 mg, 81%, single major diastereoisomer) as a colourless solid. **mp** 232-234 °C; $[\alpha]_D^{20}$ +50.2 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 12.8 min, t_R (major): 26.9 min, 99:1 er; ν_{max} (solid, cm^{-1}) 3302 (CON-H), 3030 (ArC-H), 1647 (C=ONH), 1518 (ArC=C), 1447, 1327 (SO_2), 1146 (SO_2), 1076; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.81 (1H, dd, *J* 15.1, 4.2, NC*H*^{A}H^{B}Ph), 4.42 (1H, dd, *J* 15.0, 7.4, NCH^A*H*^{B}Ph), 4.75 (1H, d, *J* 11.5, C(2)*H*), 4.79 – 4.85 (2H, m, C(3)*H* and C(4)*H*), 5.81 (1H, dd, *J* 7.2, 4.4, N*H*), 6.58 (2H, d, *J* 7.2, C(2',6')*H*), 7.12 (2H, t, *J* 7.2, C(3',5')*H*), 7.13 – 7.20 (1H, m, C(4')*H*), 7.26 (2H, t, *J* 7.9, 2 ArC*H*), 7.30 – 7.37 (5H, m, C(3'''',5'''')*H*, C(4'''')*H* and 2 ArC*H*), 7.39 (2H, d, *J* 7.5, 2 ArC*H*), 7.41 – 7.48 (4H, m, C(4''''')*H* and 3 ArC*H*), 7.50 – 7.68 (9H, m, C(4''''')*H* and 8 ArC*H*), 7.79 – 7.90 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.6 (*C*(3)H), 57.6 (*C*(2)H), 82.8 (*C*(4)H), 127.1 (2 ArC*H*), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.0 (2 ArCH), 128.1 (2 ArC*H*), 128.3 (4 ArCH), 128.4 (2 ArCH), 128.6 (*C*(3',5')H), 128.8 (2 ArCH), 129.0 (2 ArCH), 129.2 (2 ArCH), 129.2 (2 ArCH), 131.4 (*C*(2'''',6'''')H), 133.9 (*C*(4'''')H), 134.3 (*C*(4''''')H), 134.5 (*C*(1'''')), 136.0

(*C*(1'')), 137.6 (*C*(1')), 138.2 (Ar*C*), 140.4 (Ar*C*), 141.2 (Ar*C*), 141.5 (Ar*C*), 170.7 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{41}H_{36}NO_5S_2$ $[M+H]^+$ found 686.2017, requires 686.2029 (−1.7 ppm). (LNB ref: CM580)

(2*R*,3*S*)-*N*-Benzyl-2-(naphthalen-2''-yl)-3-phenyl-4,4-bis(phenylsulfonyl)butan-amide (**247**)

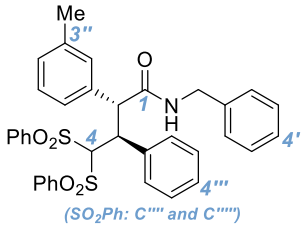


247

Following general procedure C, using 4-nitrophenyl 2-(naphthalen-2-yl)acetate **231** (92 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 4% Et_2O in CH_2Cl_2; R_f 0.30 at 3% Et_2O in CH_2Cl_2) gave the title compound (109 mg, 83%, single major diastereoisomer) as a colourless solid. **mp** 151-152 °C; $[\alpha]_D^{20}$ +36.4 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 16.4 min, t_R (major): 30.1 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3391 (CON-H), 3287 (CON-H), 3061 (C-H), 2916 (C-H), 1655 (C=O), 1535 (C=O), 1497 (ArC=C), 1329 (SO_2), 1144 (SO_2), 1078, 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.79 (1H, dd, *J* 15.1, 4.3, NC*H*^{A}H^{B}Ph), 4.41 (1H, dd, *J* 15.0, 7.4, NCH^A*H*^{B}Ph), 4.68 (1H, broad-s, C(4)*H*), 4.84 (1H, dd, *J* 11.8, 1.0, C(3)*H*), 4.90 (1H, d, *J* 11.7, C(2)*H*), 5.82 (1H, dd, *J* 7.1, 4.4, N*H*), 6.59 (2H, d, *J* 7.2, C(2',6')*H*), 7.05 – 7.13 (4H, m, C(3',5')*H* and 2 ArC*H*), 7.15 (1H, t, *J* 7.3, C(4')*H*), 7.22 (2H, broad-s, ArC*H*), 7.29 – 7.43 (8H, m, C(3''',5''')*H* and 6 ArC*H*), 7.45 – 7.54 (2H, m, ArC*H*), 7.56 – 7.62 (2H, m, ArC*H*), 7.81 (2H, broad-s, ArC*H*), 7.85 – 7.93 (3H, m, C(2''',6''')*H* and ArC*H*), 8.01 (1H, broad-s, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.8 (*C*(3)H), 57.8 (*C*(2)H), 82.9 (*C*(4)H), 126.8 (ArCH), 126.9 (ArCH), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 127.9 (ArCH), 128.3 (5 ArCH), 128.4 (2 ArCH), 128.6 (*C*(3',5')H), 128.7 (2 ArCH), 128.8 (2 ArCH), 129.2 (4 ArCH), 131.4 (*C*(2''',6''')H), 133.2 (quat.-Ar*C*), 133.5 (quat.-Ar*C*), 133.8

(ArCH), 134.2 (ArCH), 134.5 (*C*(1''')), 134.5 (*C*(1'')), 137.6 (*C*(1')), 138.1 (*C*(1'''')), 141.2 (*C*(1''''')), 170.6 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{39}H_{34}NO_5S_2$ $[M+H]^+$ found 660.1863, requires 660.1873 (−1.5 ppm). (LNB ref: CM519)

(2*R*,3*S*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(*m*-tolyl)butanamide (**248**)

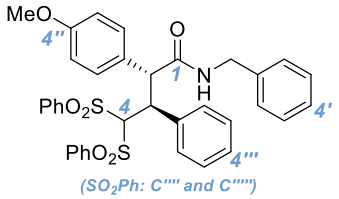


248

Following general procedure C, using 4-nitrophenyl 2-(*m*-tolyl)acetate **232** (81 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (0 to 4% Et_2O in CH_2Cl_2; R_f 0.36 at 3% Et_2O in CH_2Cl_2) gave the title compound (71 mg, 57%, single major diastereoisomer) as a colourless solid. **mp** 216 °C; $[\alpha]_D^{20}$ −12.4 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 21.4 min, t_R (major): 28.8 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3273 (CON-H), 3059, 2868 (C-H), 1639 (C=O), 1551 (ArC=C), 1447, 1310 (SO_2), 1134 (SO_2), 1076, 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.37 (3H, s, CH_3), 3.78 (1H, dd, *J* 15.0, 4.2, NCH^AH^{B}Ph), 4.40 (1H, dd, *J* 15.0, 7.4, NCH^AH^BPh), 4.67 (1H, d, *J* 12.0, C(2)*H*), 4.69 – 4.76 (2H, m, C(3)*H* and C(4)*H*), 5.72 (1H, dd, *J* 7.0, 4.3, N*H*), 6.57 (2H, d, *J* 7.2, C(2',6')*H*), 7.11 (2H, t, *J* 7.2, C(3',5')*H*), 7.14 – 7.18 (1H, m, C(4')*H*), 7.21 (3H, broad-s, ArC*H*), 7.28 – 7.39 (8H, m, C(3'''',5'''')*H*, C(3''',5''')*H*, C(4''')*H*, ArC*H* and C(3'''',5'''')*H*), 7.44 (4H, app t, *J* 8.0, C(2'''',6'''')*H* and C(2''''',6''''')*H*), 7.50 (1H, t, *J* 7.4, C(4''''')*H*), 7.56 (1H, t, *J* 7.4, C(4'''')*H*), 7.77 – 7.86 (2H, m, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 21.7 (*C*H_3), 43.5 (NCH^{A}H^{B}Ph), 47.7 (*C*(3)H), 57.7 (*C*(2)H), 82.7 (*C*(4)H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (*C*(4''')H and *C*(3''',5''')H or *C*(3'''',5'''')H), 128.5(*C*(2'''',6'''')H), 128.6 (*C*(3',5')H), 128.8 (*C*(3''',5''')H or *C*(3'''',5'''')H), 128.9 (*C*(2'''',6'''')H), 129.0 (ArCH), 129.3 (*C*(3'''',5''')H), 129.3 (3 ArCH), 131.4 (*C*(2''',6''')H), 133.9 (*C*(4''''')H), 134.3 (*C*(4'''')H), 134.6 (*C*(1''')), 137.0 (*C*(1'')), 137.7 (*C*(1')), 138.2

(*C*(1''''')) and Ar*C*), 139.1 (*C*(3'')H), 141.5 (*C*(1''''')), 170.7 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{36}H_{34}NO_5S_2$ $[M+H]^+$ found 624.1863, requires 624.1873 (−1.6 ppm). (LNB ref: CM477)

(2*R*,3*S*)-*N*-Benzyl-2-(4''-methoxyphenyl)-3-phenyl-4,4-bis(phenylsulfonyl)butan-amide (**249**)

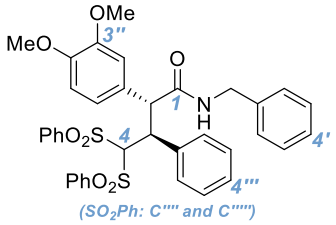


249

Following general procedure C, using 4-nitrophenyl 2-(4-methoxyphenyl)acetate **233** (86 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 5% Et_2O in CH_2Cl_2; R_f 0.32 at 5% Et_2O in CH_2Cl_2) gave the title compound (78 mg, 61%, single major diastereoisomer) as a colourless solid. **mp** 100 °C (dec) then 196 °C; $[\alpha]_D^{20}$ +1.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 23.0 min, t_R (major): 35.3 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3287 (CON-H), 1643 (C=O), 1508 (ArC=C), 1329 (SO_2), 1252 (Ar-O-CH_3), 1150 (SO_2), 1076 (Ar-O-CH_3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.79 (1H, dd, *J* 15.0, 4.2, NC*H*^{A}H^{B}Ph), 3.86 (3H, s, OC*H*$_3$), 4.39 (1H, dd, *J* 15.0, 7.4, NCH^A*H*^{B}Ph), 4.63 (1H, d, *J* 11.7, C(2)*H*), 4.68 (1H, dd, *J* 11.7, 1.6, C(3)*H*), 4.75 (1H, d, *J* 1.6, C(4)*H*), 5.70 (1H, dd, *J* 7.2, 4.3, N*H*), 6.56 (2H, d, *J* 7.0, C(2',6')*H*), 6.89 (2H, broad-s, C(3'',5'')*H*), 7.11 (2H, t, *J* 7.2, C(3',5')*H*), 7.16 (1H, t, *J* 7.2, C(4')*H*), 7.28 – 7.35 (7H, m, C(2'',6'')*H*, C(3''',5''')*H*, C(4''')*H* and C(3'''',5'''')*H*), 7.35 – 7.40 (2H, m, C(3'''',5'''')*H*), 7.45 (2H, d, *J* 7.4, C(2'''',6'''')*H*), 7.48 (2H, d, *J* 7.3, C(2''',6''')*H*), 7.51 (1H, t, *J* 7.5, C(4'''')*H*), 7.57 (1H, t, *J* 7.4, C(4''')*H*), 7.73 – 7.87 (2H, m, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.4 (NCH^{A}H^{B}Ph), 47.8 (*C*(3)H), 55.6 (OCH_3), 57.0 (*C*(2)H), 82.8 (*C*(4)H), 114.8 (*C*(3'',5'')H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (*C*(4''')H, and *C*(3''',5''')H or *C*(3'''',5'''')H), 128.5 (*C*(2'''',6'''')H), 128.6 (*C*(3',5')H), 128.8 (*C*(3''',5''')H or *C*(3'''',5'''')H), 128.9 (*C*(1'')), 129.1 (*C*(2''',6''')H), 129.3 (*C*(3'''',5'''')H and *C*(2'',6'')H),

131.5 (*C*(2''',6''')H), 133.9 (*C*(4'''')H), 134.3 (*C*(4'''')H), 134.5 (*C*(1''')), 137.7 (*C*(1')), 138.2 (*C*(1'''')), 141.3 (*C*(1'''')), 159.8 (*C*(4'')), 171.0 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{36}H_{34}NO_6S_2$ $[M+H]^+$ found 640.1812, requires 640.1822 (−1.6 ppm). (LNB ref: CM479)

(2*R*,3*S*)-*N*-Benzyl-2-(3'',4''-dimethoxyphenyl)-3-phenyl-4,4-bis(phenylsulfonyl)butanamide (**250**)

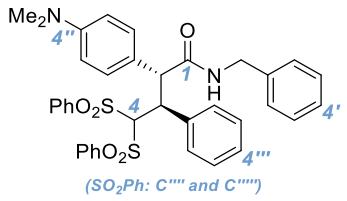


250

Following general procedure C, using 4-nitrophenyl 2-(3,4-dimethoxyphenyl)acetate **234** (95 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 20% Et_2O in CH_2Cl_2; R_f 0.29 at 10% Et_2O in CH_2Cl_2) gave the title compound (97 mg, 72%, single major diastereoisomer) as a colourless solid. **mp** 162 °C; $[\alpha]_D^{20}$ −4.7 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 14.6 min, t_R (major): 26.0 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3265 (CON-H), 3063 (C-H), 1645 (C=ONH), 1508 (ArC=C), 1447, 1325 (SO_2), 1263 (Ar-O-CH_3), 1140 (SO_2), 1026 (Ar-O-CH_3), 685; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.82 (1H, dd, *J* 15.0, 4.2, NC*H*^{A}H^{B}Ph), 3.88 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.39 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.67 (1H, d, *J* 11.6, C(2)*H*), 4.82 (1H, d, *J* 11.8, C(3)*H*), 4.85 (1H, s, C(4)*H*), 5.66 – 5.86 (1H, m, N*H*), 6.59 (2H, d, *J* 7.2, C(2',6')*H*), 6.89 (1H, broad s, ArC*H*), 7.12 (3H, t, *J* 7.2, C(3',5')*H* and ArC*H*), 7.14 – 7.17 (1H, m, C(4')*H*), 7.18 (1H, broad s, ArC*H*), 7.23 – 7.35 (7H, m, C(3''',5''')*H*, C(4''')*H*, C(3'''',5'''')*H* and C(3'''',5'''')*H*), 7.40 (2H, d, *J* 7.8, C(2'''',6'''')*H*), 7.44 (2H, d, *J* 8.1, C(2''',6''')*H*), 7.44 – 7.54 (2H, m, C(4'''')*H* and C(4'''')*H*), 7.76 (2H, d, *J* 7.2, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.7 (*C*(3)H), 56.2 (2 OCH_3), 57.1 (*C*(2)H), 82.9 (*C*(4)H), 111.1 (*C*(2'')H and *C*(5'')H), 122.8 (*C*(6'')H), 127.3 (*C*(2',6')H and *C*(4')H)), 128.1 (*C*(3''',5''')H and *C*(4''')H), 128.4 (*C*(2'''',6'''')H), 128.5 (*C*(3',5')H), 128.8

(*C*(3'''',5'''')H or *C*(3''''',5''''')H), 129.0 (*C*(2''',6''')H), 129.0 (*C*(3''',5''')H or *C*(3''''',5''''')H), 129.4 (*C*(1'')), 131.4 (*C*(2''',6''')H), 133.9 (*C*(4''''')H), 134.2 (*C*(4''')H), 134.5 (*C*(1''')), 137.7 (*C*(1')), 138.2 (*C*(1''''')), 141.1 (*C*(1''''')), 149.3 (*C*(3'') or *C*(4'')), 149.9 (*C*(3'') or *C*(4'')), 170.9 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{37}H_{36}NO_7S_2$ $[M+H]^+$ found 670.1917, requires 670.1928 (−1.6 ppm). (LNB ref: CM582, CM587)

(2*R*,3*S*)-*N*-Benzyl-2-(4''-(dimethylamino)phenyl)-3-phenyl-4,4-bis(phenylsulfonyl)-butanamide (**251**)

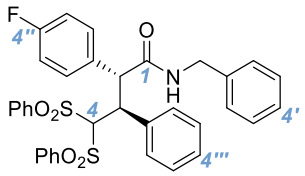


251

Following general procedure C, using 4-nitrophenyl 2-(4-(dimethylamino)phenyl)acetate **235** (90 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 5.5% Et_2O in CH_2Cl_2; R_f 0.30 at 5% Et_2O in CH_2Cl_2) gave the title compound (75 mg, 57%, single major diastereoisomer) as a colourless solid. **mp** 260 °C (dec); $[\alpha]_D^{20}$ +23.4 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 13.0 min, t_R (major): 25.6 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3395 (CON-H), 2903 (C-H), 1676 (C=ONH), 1608 (C=ONH), 1517 (ArC=C), 1447, 1327 (SO_2), 1144 (SO_2), 740 (CH_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.00 (6H, s, N(C*H*$_3$)$_2$), 3.76 (1H, dd, *J* 15.1, 4.2, NC*H*$_2$Ph), 4.42 (1H, dd, *J* 15.1, 7.5, NC*H*$_2$Ph), 4.57 (1H, d, *J* 11.7, C(2)*H*), 4.69 (1H, dd, *J* 11.7, 1.7, C(3)*H*), 4.89 (1H, d, *J* 1.7, C(4)*H*), 5.69 (1H, dd, *J* 7.3, 4.3, N*H*), 6.57 (2H, d, *J* 7.1, C(2',6')*H*), 6.68 (2H, broad-s, C(2'',6'')*H*), 7.02 – 7.13 (2H, m, C(3',5')*H*), 7.13 – 7.19 (1H, m, C(4')*H*), 7.27 – 7.33 (7H, m, C(3'',5'')*H*, C(3''',5''')*H*, C(4''')*H* and C(3'''',5'''')*H*), 7.35 (2H, t, *J* 7.8, C(3'''',5'''')*H*), 7.44 – 7.51 (5H, m, C(2''',6''')*H*, C(2''''',6''''')*H*, and (C(4''''')*H*), 7.56 (1H, t, *J* 7.4, C(4''')*H*), 7.80 (2H, dd, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 40.8 (N(*C*H$_3$)$_2$), 43.3 (NCH$_2$Ph), 47.7 (*C*(3)H), 56.9

(*C*(2)H), 82.8 (*C*(4)H), 113.1 (*C*(2'',6'')H), 124.1 (*C*(1'')), 127.1 (*C*(4')H), 127.2 (*C*(2',6')H), 128.0 (*C*(4''')H), 128.1 (*C*(3''',5''')H or *C*(3'''',5'''')H), 128.5 (*C*(3',5')H), 128.6 (*C*(3''',5''')H or *C*(3'''',5'''')H, and *C*(3'',5'')H), 128.7 (*C*(2'''',6'''')H), 129.1 (*C*(2''',6''')H), 129.2 *C*(3'''',5'''')H), 131.4 (*C*(2''',6''')H), 133.8 (*C*(4'''')H), 134.1 *C*(4''')H), 134.9 (*C*(1''')), 137.9 (*C*(1')), 138.3 (*C*(1'''')), 141.5 (*C*(1'''')), 150.7 (*C*(4'')), 171.3 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{37}H_{37}N_2O_5S_2$ $[M+H]^+$ found 653.2131, requires 653.2138 (−1.1 ppm). (LNB ref: CM583)

(2*R*,3*S*)-*N*-Benzyl-2-(4''-fluorophenyl)-3-phenyl-4,4-bis(phenylsulfonyl)butanamide (**252**)

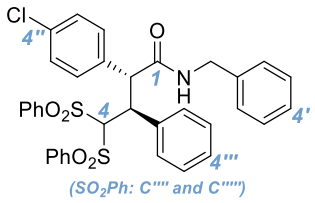


252

Following general procedure C, using 4-nitrophenyl 2-(4-fluorophenyl)acetate **236** (83 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (0 to 4% Et_2O in CH_2Cl_2; R_f 0.30 at 3% Et_2O in CH_2Cl_2) gave the title compound (73 mg, 58%, single major diastereoisomer) as a colourless solid. **mp** 248-249 °C; $[\alpha]_D^{20}$ −14.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 26.0 min, t_R (major): 35.0 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3296 (CON-H), 1641 (C=ONH), 1555 (C=ONH), 1504 (ArC=C), 1329 (SO_2), 1311 (C-F), 1150 (SO_2), 730 (C-F); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.77 (1H, dd, *J* 15.0, 4.3, NC*H*^{A}H^{B}Ph), 4.35 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.62 (1H, d, *J* 1.2, C(4)*H*), 4.65 – 4.79 (2H, m, C(3)*H* and C(2)*H*), 5.74 (1H, dd, *J* 6.9, 4.5, N*H*), 6.54 (2H, d, *J* 7.3, C(2',6')*H*), 7.04 (2H, broad-t, *J* 7.1, C(3'',5'')*H*), 7.11 (2H, t, *J* 7.3, C(3',5')*H*), 7.14 – 7.18 (1H, m, C(4')*H*), 7.28 – 7.35 (5H, m, C(3''',5''')*H*, C(4''')*H* and C(3'''',5'''')*H*), 7.36 – 7.40 (2H, m, C(3'''',5'''')*H*), 7.40 – 7.44 (4H, m, C(2'',6'')*H* and C(2'''',6'''')*H*), 7.47 (2H, dd, *J* 8.4, 1.1, C(2'''',6'''')*H*), 7.52 (1H, t, *J* 7.4, C(4'''')*H*), 7.58 (1H, t, *J* 7.4, C(4''')*H*), 7.81 (2H,

d, *J* 7.1, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −112.91 – −112.66 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.9 (*C*(3)H), 57.0 (*C*(2)H), 82.8 (*C*(4)H), 116.3 (d, $^2J_{C\text{-}F}$ 19.2, *C*(3'',5'')H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (*C*(3''',5''')H), 128.3 (*C*(4''')H), 128.4 (*C*(2'''',6'''')H), 128.6 (*C*(3',5')H), 128.9 (*C*(3'''',5'''')H), 129.0 (*C*(2''',6''')H), 129.3 (*C*(3''',5''')H), 130.7 (*C*(2'',6'')H), 131.5 (*C*(2''',6''')H), 132.8 (d, $^4J_{C\text{-}F}$ 3.0, *C*(1'')), 134.1 (*C*(4'''')H), 134.2 (*C*(1''')), 134.4 (*C*(4''')H), 137.5 (*C*(1')), 138.1 (*C*(1''')), 141.2 (*C*(1'''')), 162.8 (d, $^1J_{C\text{-}F}$ 248.4, *C*(4'')), 170.7 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{35}H_{31}FNO_5S_2$ [M+H]$^+$ found 628.1613, requires 628.1622 (−1.4 ppm). (LNB ref: CM555, CM721)

(2*R*,3*S*)-*N*-Benzyl-2-(4''-chlorophenyl)-3-phenyl-4,4-bis(phenylsulfonyl)butanamide (**253**)

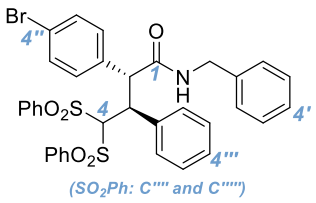


253

Following general procedure C, using 4-nitrophenyl 2-(4-chlorophenyl)acetate **237** (88 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (0 to 3% Et_2O in CH_2Cl_2; R_f 0.31 at 2% Et_2O in CH_2Cl_2) gave the title compound (101 mg, 78%, single major diastereoisomer) as a colourless solid. **mp** 186-188 °C; **$[\alpha]_D^{20}$** +4.7 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 15.7 min, t_R (major): 22.7 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 3298 (CON-H), 1645 (C=ONH), 1558 (C=ONH), 1489, 1447, 1321 (SO_2), 1152 (SO_2), 1130, 681 (C-Cl); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.78 (1H, dd, *J* 15.0, 4.3, NC*H*^{A}H^{B}Ph), 4.35 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.62 (1H, s, C(4)*H*), 4.70 (2H, s, C(2)*H* and C(3)*H*), 5.82 (1H, dd, *J* 7.1, 4.4, N*H*), 6.33 – 6.69 (2H, m, C(2',6')*H*), 7.08 – 7.14 (2H, m, C(3',5')*H*), 7.14 – 7.21 (1H, m, C(4')*H*), 7.27 – 7.42 (13H, m, 13 ArC*H*),7.45 (2H, dd, *J* 8.5, 1.3, C(2''',6''')*H*), 7.53 (1H, tt, *J* 7.3, 1.3, C(4'''')*H*), 7.58 (1H, tt, *J* 7.4, 1.3, C(4''')*H*),

7.79 (2H, dd, *J* 7.9, 1.2, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.8 (*C*(3)H), 57.1 (*C*(2)H), 82.9 (*C*(4)H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.2 (2 ArCH), 128.3 (*C*(4''')H), 128.5 (*C*(3',5')H), 128.6 (2 ArCH), 128.9 (2 ArCH), 129.0 (2 ArCH), 129.3 (2 ArCH), 129.5 (2 ArCH), 130.4 (2 ArCH), 131.4 (*C*(2''',6''')H), 134.1 (*C*(4'''')H), 134.2 (*C*(1''')), 134.4 (*C*(4''')H), 134.6 (*C*(1'')), 135.6 (*C*(4'')), 137.5 (*C*(1')), 138.2 (*C*(1'''') or *C*(1''''')), 141.1 (*C*(1'''') or *C*(1''''')), 170.4 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{35}H_{31}ClNO_5S_2$ $[M+H]^+$ found 644.1319, requires 644.1327 (−1.2 ppm). (LNB ref: CM590)

(2*R*,3*S*)-*N*-Benzyl-2-(4'-bromophenyl)-3-phenyl-4,4-bis(phenylsulfonyl)butanamide (**254**)

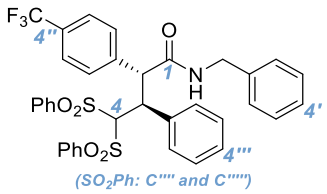


254

Following general procedure C, using 4-nitrophenyl 2-(4-bromophenyl)acetate **238** (101 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (0 to 4% Et_2O in CH_2Cl_2; R_f 0.30 at 3% Et_2O in CH_2Cl_2) gave the title compound (94 mg, 68%, single major diastereoisomer) as a colourless solid. **mp** 268-270 °C; $[\alpha]_D^{20}$ +12.2 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 14.8 min, t_R (major): 23.9 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3298 (CON-H), 1645 (C=ONH), 1560 (C=ONH), 1483, 1447, 1310 (SO_2), 1132 (SO_2), 1074, 581 (C-Br); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.79 (1H, dd, *J* 15.0, 4.3, NC*H*^{A}H^{B}Ph), 4.36 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.62 (1H, d, *J* 1.1, C(4)*H*), 4.67 (1H, d, *J* 11.7, C(2)*H*), 4.70 (1H, dd, *J* 11.8, 1.3, C(3)*H*), 5.78 (1H, dd, *J* 7.0, 4.4, N*H*), 6.57 (2H, d, *J* 7.2, C(2',6')*H*), 7.12 (2H, t, *J* 7.3, C(3',5')*H*), 7.17 (1H, t, *J* 7.3, C(4)*H*), 7.27 – 7.33 (2H, m, C(3''',5''')*H*), 7.32 – 7.37 (5H, m, C(2'',6'')*H*, C(4''')*H* and C(3'''',5'''')*H*), 7.37 – 7.41 (4H, m, C(3'''',5'''')*H* and C(2'''',6'''')*H*), 7.45 (2H, dd, *J* 8.4, 1.1, C(2'''',6'''')*H*),

7.48 (2H, app broad-d, *J* 6.9, C(3'',5'')*H*), 7.54 (1H, t, *J* 7.3, C(4'''')*H*), 7.58 (1H, t, *J* 7.4, C(4'''')*H*), 7.79 (2H, d, *J* 7.1, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.7 (*C*(3)H), 57.2 (*C*(2)H), 82.8 (*C*(4)H), 122.7 (*C*(4'')), 127.2 (*C*(2',6')H), 127.4 (*C*(4')H), 128.3 (*C*(3''',5''')H), 128.3 (*C*(4)H), 128.4 (*C*(2'''',6'''')H), 128.6 (*C*(3',5')H), 128.9 (*C*(3'''',5'''')H or *C*(3'''',5'''')H), 129.0 (*C*(2'''',6'''')H), 129.3 (*C*(3'''',5'''')H or *C*(3'''',5'''')H), 130.7 (*C*(2'',6'')H), 131.4 (*C*(2''',6''')H), 132.5 (*C*(3'',5'')H), 134.1 (*C*(4'''')H), 134.1 (*C*(1''')), 134.4 (*C*(4''')H), 136.1 (*C*(1'')), 137.4 (*C*(1')), 138.1 (*C*(1'''')), 141.1 (*C*(1'''')), 170.3 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{35}H_{31}BrNO_5S_2$ [M+H]$^+$ found 688.0815, requires 688.0822 (−1.0 ppm). (LNB ref: CM482, CM722)

(2*R*,3*S*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(4''-(trifluoromethyl)phenyl)-butanamide (**255$_{maj}$**)

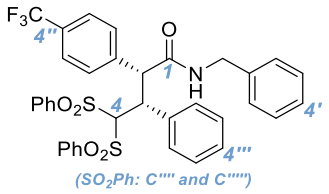


255$_{maj}$

Following general procedure C, using 4-nitrophenyl 2-(4-(trifluoromethyl)phenyl)acetate **239** (98 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (75:25 dr). Purification by flash column chromatography (0 to 3% Et_2O in CH_2Cl_2; R_f 0.29 at 3% Et_2O in CH_2Cl_2) gave the title compound (103 mg, 76%, > 95:5 dr) as a colourless solid. **mp** 224-225 °C; **$[\alpha]_D^{20}$** −11.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 7.9 min, t_R (major): 12.6 min, 99:1 er; **ν_{max}** (solid, cm^{-1}) 3296 (CON-H), 1651 (C=ONH), 1562 (ArC=C), 1447, 1323 (SO_2), 1128 (SO_2), 1067 (C-F), 681; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.80 (1H, dd, *J* 15.0, 4.3, NC*H*^{A}H^{B}Ph), 4.37 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.54 (1H, app s, C(4)*H*), 4.78 (2H, app s, C(2)*H* and C(3)*H*), 5.82 (1H, dd, *J* 7.1, 4.4, N*H*), 6.57 (2H, d, *J* 7.1, C(2',6')H), 7.12 (2H, t, *J* 7.2, C(3',5')*H*), 7.17 (1H, t, *J* 7.3, C(4')*H*), 7.28 – 7.32 (5H, m, C(4''')*H*, C(2'''',6'''')*H* and C(3'''',5'''')*H*), 7.32 – 7.38 (4H, m, C(3''',5''')*H* and C(3'''',5'''')*H*), 7.40

– 7.44 (2H, m, C(2''',6''')*H*), 7.52 (1H, tt, *J* 5.9, 2.5, C(4''''')*H*), 7.57 (1H, t, *J* 7.4, C(4''')*H*), 7.61 (4H, broad-s, C(2'',6'')*H* and C(3'',5'')*H*), 7.80 (2H, d, *J* 7.1, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −62.6 (s); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.6 (NCH^AH^BPh), 47.8 (*C*(3)H), 57.7 (*C*(2)H), 82.9 (*C*(4)H), 124.0 (q, $^1J_{C\text{-}F}$ 272.2, CF_3), 126.2 (*C*(3'',5'')H), 127.2 (*C*(2',6')H), 127.4 (*C*(4')H), 128.3 (*C*(2''',6''')H and 2 ArCH), 128.4 (*C*(4''')H), 128.6 (*C*(3',5')H), 128.9 (2 ArCH), 128.9 (*C*(2''',6''')H), 129.3 (2 ArCH), 129.5 (*C*(2'',6'')H), 130.8 (q, $^2J_{C\text{-}F}$ 32.7, *C*(4'')), 131.3 (*C*(2''',6''')H), 134.0 (*C*(1''')), 134.2 (*C*(4''''')H), 134.5 (*C*(4''')H), 137.3 (*C*(1')), 138.1 (*C*(1''')), 140.9 (*C*(1''''')), 141.2 (*C*(1'')), 170.0 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{36}H_{31}F_3NO_5S_2$ $[M+H]^+$ found 678.1581, requires 678.1590 (−1.3 ppm). (LNB ref: CM480-b-3-f1)

(2*R*,3*R*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(4''-(trifluoromethyl)phenyl)-butanamide (**255$_{min}$**)

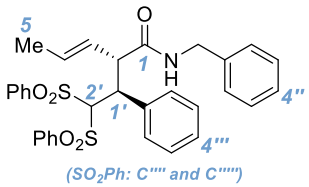


255$_{min}$

Following general procedure C, using 4-nitrophenyl 2-(4-(trifluoromethyl)phenyl)acetate **239** (98 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (75:25 dr). Purification by flash column chromatography (0 to 3% Et_2O in CH_2Cl_2; R_f 0.38 at 3% Et_2O in CH_2Cl_2) gave the title compound (19 mg, 14%, single minor diastereoisomer) as a colourless solid. **mp** 96-98 °C; **$[\alpha]_D^{20}$** −50.2 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 12.7 min, t_R (major): 32.6 min, 99:1 er; **ν_{max}** (solid, cm^{-1}) 3385 (CON-H), 1661 (C=O), 1533, 1447, 1323 (SO_2), 1157, 1121 (SO_2), 1067 (C-F), 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.34 (1H, dd, *J* 14.8, 5.6, NCH^AH^BPh), 4.60 (1H, dd, *J* 14.8, 6.2, NCH^AH^BPh), 4.76 (1H, dd, *J* 11.6, 2.9, C(3)*H*), 4.91 (1H, d, *J* 11.6, C(2)*H*), 6.03 (1H, d, *J* 2.9, C(4)*H*), 6.20 (1H, app t, *J* 5.8, N*H*), 7.08 – 7.15 (3H, m, C(3''',5''')*H* and C(4''')*H*), 7.18 (2H, dd, *J* 6.7, 2.6, C(2',6')*H*),

7.22 – 7.27 (5H, m, C(3',5')*H*, C(4')*H* and C(2'',6'')*H*), 7.25 – 7.30 (2H, m, C(3'''',5'''')*H*), 7.29 – 7.32 (2H, m, C(3'''',5'''')*H*), 7.38 (2H, d, *J* 8.3, C(3'',5'')*H*), 7.38 – 7.43 (2H, m, C(2''',6''')*H*), 7.48 (1H, t, *J* 7.5, C(4'''')*H*), 7.52 (1H, t, *J* 7.5, C(4'''')*H*), 7.55 (2H, dd, *J* 8.5, 1.1, C(2'''',6'''')*H*), 7.56 – 7.60 (2H, m, C(2'''',6'''')*H*); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ_F: −62.6. (s); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 44.1 (NCH^AH^BPh), 48.5 (*C*(3)H), 56.6 (*C*(2)H), 83.0 (*C*(4)H), 124.0 (q, $^1J_{C\text{-}F}$ 271.8, CF_3), 125.6 (q, $^3J_{C\text{-}F}$ 3.4, *C*(3'',5'')H), 127.8 (*C*(2',6')H), 127.8 (*C*(4')H), 128.1 (*C*(3''',5''')H), 128.1 (*C*(4''')H), 128.7 (2 ArCH), 128.8 (4 ArCH), 128.9 (2 ArCH), 129.0 (2 ArCH), 129.1 (2 ArCH), 129.9 (q, $^2J_{C\text{-}F}$ 32.2, *C*(4'')), 131.1 (*C*(2''',6''')H), 133.5 (*C*(1''')), 133.9 (*C*(4'''')H), 134.1 (*C*(4'''')H), 137.8 (*C*(1')), 139.2 (*C*(1'''')), 140.8 (*C*(1'''')), 142.2 (*C*(1'')), 172.2 (*C*(1)=O); **HRMS** (ESI^-) $C_{36}H_{29}F_3NO_5S_2$ $[M-H]^-$ found 676.1442, requires 676.1445 (−0.4 ppm). (LNB ref: CM480-b-3-f2)

(*S*,*E*)-*N*-Benzyl-2-((*S*)-1'-phenyl-2',2'-bis(phenylsulfonyl)ethyl)pent-3-enamide (**256**)

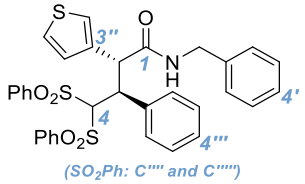


256

Following general procedure C, using 4-nitrophenyl (*E*)-pent-3-enoate **240** (66 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (0 to 4.5% Et_2O in CH_2Cl_2; R_f 0.28 at 5% Et_2O in CH_2Cl_2) gave the title compound (76 mg, 66%, single major diastereoisomer) as a colourless solid. **mp** 169-170 °C; $\mathbf{[\alpha]_D^{20}}$ −74.9 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 33.6 min, t_R (major): 40.8 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3265 (CON-H), 1637 (C=ONH), 1560 (C=C), 1447, 1310 (SO_2), 1150 (SO_2), 980; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.78 (3H, dd, *J* 6.5, 1.4, C(5)H_3), 3.87 (1H, dd, *J* 15.0, 4.4, NCH^AH^BPh), 4.01 – 4.15 (1H, m, C(2)*H*), 4.21 (1H, dd, *J* 11.4, 1.7, C(1')*H*), 4.34 (1H, dd, *J* 15.0, 7.1, NCH^AH^BPh), 5.09 – 5.24 (1H, m, C(3)*H*), 5.28 (1H, d, *J* 1.6, C(2')H), 5.60 – 5.71 (1H, m, N*H*), 5.95 – 6.14 (1H, m, C(4)*H*), 6.62 (2H, d, *J* 6.8, C(2'',6'')*H*), 7.07 – 7.17 (3H, m,

C(3'',5'')*H* and C(4'')*H*), 7.20 (2H, t, *J* 7.5, C(3''',5''')*H*), 7.26 (1H, t, *J* 7.2, C(4''')*H*), 7.40 – 7.45 (2H, m, C(3'''',5'''')*H*), 7.45 – 7.50 (2H, m, C(3''''',5''''')*H*), 7.55 – 7.65 (4H, m, C(2''',6''')*H*, C(4'''')*H* and C(4''''')*H*), 7.70 – 7.78 (4H, m, C(2'''',6'''')*H* and C(2''''',6''''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 18.3 (*C*(5)H_3), 43.3 (NCH^AH^BPh), 46.8 (*C*(1')H), 56.2 (*C*(2)H), 84.1 (*C*(2')H), 127.3 (*C*(4'')H), 127.3 (*C*(2'',6'')H), 128.0 (*C*(4''')H), 128.1 (*C*(3''',5''')H), 128.6 (*C*(3'',5'')H), 128.8 (*C*(2'''',6'''')H or *C*(2''''',6''''')H), 128.9 (*C*(3''''',5''''')H), 129.0 (*C*(3)H), 129.2 (*C*(3'''',5'''')H), 129.2 (*C*(2''',6''')H or *C*(2''''',6''''')H), 131.4 (*C*(2''',6''')H), 132.8 (*C*(4)H), 134.2 (*C*(4''''')H), 134.2 (*C*(1''')), 134.5 (*C*(4'''')H), 137.6 (*C*(1'')), 138.4 (*C*(1'''')), 141.2 (*C*(1''''')), 171.2 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{32}H_{32}NO_5S_2$ $[M+H]^+$ found 574.1706, requires 574.1716 (−1.7 ppm). (LNB ref: CM483)

(2*R*,3*S*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(thiophen-3''-yl)butanamide (**257$_{maj}$**)

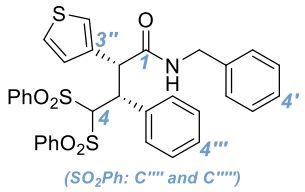


257$_{maj}$

Following general procedure C, using 4-nitrophenyl 2-(thiophen-3-yl)acetate **241** (79 mg, 0.30 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (77 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 4.5% Et_2O in CH_2Cl_2; R_f 0.36 at 4% Et_2O in CH_2Cl_2) gave the title compound (89 mg, 72%, single major diastereomer) as a colourless solid. **mp** 222 °C (dec) then 250 °C; **$[\alpha]_D^{20}$** −21.8 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 13.5 min, t_R (major): 23.8 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 3292 (CON-H), 1645 (C=ONH), 1553 (ArC=C), 1447, 1310 (SO_2), 1150 (SO_2), 1076; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.83 (1H, dd, *J* 15.0, 4.3, NCH^AH^{B}Ph), 4.38 (1H, dd, *J* 15.0, 7.3, NCH^A*H*^{B}Ph), 4.69 (1H, dd, *J* 11.6, 1.9, C(3)*H*), 4.74 (1H, d, *J* 1.9, C(4)*H*), 4.88 (1H, d, *J* 11.6, C(2)*H*), 5.70 (1H, dd, *J* 7.0, 4.5, N*H*), 6.57 (2H, d, *J* 7.2, C(2',6')*H*), 7.07 – 7.11 (1H, m, C(4'')*H*), 7.10 – 7.14 (2H, m, C(3',5')*H*), 7.14 – 7.18 (1H,

m, C(4')*H*), 7.29 – 7.44 (9H, m, C(3''',5''')*H*, C(2'')*H*, C(5'')*H*, C(4''')*H*, C(3'''',5'''')*H*, C(3''''',5''''')*H*), 7.45 – 7.51 (4H, m, C(2'''',6'''')*H* and C(2''''',6''''')*H*), 7.51 – 7.54 (1H, m, C(4''''')*H*), 7.54 – 7.59 (1H, m, C(4'''')*H*), 7.79 (2H, d, *J* 6.8, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^AH^BPh), 47.9 (*C*(3)H), 53.5 (*C*(2)H), 82.7 (*C*(4)H), 124.5 (*C*(2'')H), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 127.3 (*C*(5'')H), 127.6 (*C*(4'')H), 128.2 (*C*(3''',5''')H), 128.3 (*C*(4''')H), 128.5 (*C*(3',5')H), 128.6 (*C*(2''''',6''''')H), 128.9 (*C*(3'''',5'''')H or *C*(3''''',5''''')H), 129.0 (*C*(2'''',6'''')H), 129.3 (*C*(3'''',5'''')H or *C*(3''''',5''''')H), 131.4 (*C*(2''',6''')H), 134.0 (*C*(4''''')H), 134.3 (*C*(4'''')H), 134.3 (*C*(1''')), 137.6 (*C*(1')), 137.8 (*C*(1'')), 138.2 (*C*(1'''')), 141.3 (*C*(1''''')), 170.4 (*C*(1)=O); **HRMS** (NSI^+) $C_{33}H_{30}NO_5S_3$ $[M+H]^+$ found 616.1271, requires 616.1281 (−1.6 ppm). (LNB ref: CM491, CM641)

(2*R*,3*R*)-*N*-Benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(thiophen-3-yl)butanamide (**257$_{min}$**)

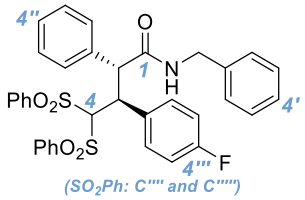


257$_{min}$

Following general procedure C, using 4-nitrophenyl 2-(thiophen-3-yl)acetate **241** (157 mg, 0.60 mmol, 1.5 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (154 mg, 0.40 mmol, 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 10 mol%) and CH_2Cl_2 (0.8 mL, 0.50 M) at room temperature for 24 h, then benzylamine (218 μL, 2.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 4.5% Et_2O in CH_2Cl_2; R_f 0.36 at 4% Et_2O in CH_2Cl_2) then (0 to 55% EtOAc in petrol; R_f 0.31 at 50% EtOAc in petrol) gave the title compound (16 mg, 6%, single minor diastereoisomer) as a colourless solid. **mp** 232-233 °C; $[\alpha]_D^{20}$ −72 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 19.7 min, t_R (major): 31.8 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3366 (N-H), 1659 (C=O), 1530 (C=O), 1447, 1335 (SO_2), 1142 (SO_2), 1076, 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.40 (1H, dd, *J* 14.9, 5.6, NCH^AH^BPh), 4.60 (1H, dd, *J* 14.9, 6.1, NCH^AH^BPh), 4.69 (1H, dd, *J* 11.5, 2.9, C(3)*H*), 5.00 (1H, d, *J* 11.5, C(2)*H*), 6.14 (1H, d, *J* 2.8, C(4)*H*), 6.17 (1H, t, *J* 5.7, N*H*), 6.84 (1H, d, *J* 5.0, C(4'')*H*), 6.86 (1H, d, *J* 1.8, C(2'')*H*),

7.10 (1H, dd, *J* 4.9, 3.0, C(5)*H*), 7.13 – 7.17 (3H, m, C(3''',5''')*H* and C(4''')*H*), 7.19 – 7.22 (2H, m, C(2',6')*H*), 7.26 (3H, broad-s, C(3',5')*H* and C(4')*H*), 7.27 – 7.33 (4H, m, C(3'''',5'''')*H* and C(3''''',5''''')*H*), 7.41 – 7.45 (2H, m, C(2''',6''')*H*)), 7.44 – 7.48 (1H, m, C(4'''')*H*), 7.51 (1H, t, *J* 7.5, C(4''')*H*), 7.56 (2H, d, *J* 7.6, C(2''''',6''''')*H*), 7.60 (2H, d, *J* 7.7, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.9 (N*C*H^{A}H^{B}Ph), 48.2 (*C*(3)H), 52.0 (*C*(2)H), 82.9 (*C*(4)H), 123.6 (*C*(2'')H), 126.1 (*C*(5'')H), 126.9 (*C*(4'')H), 127.7 (*C*(2',6')H and *C*(4')H), 127.8 (*C*(4''')H), 127.9 (*C*(3''',5''')H), 128.7 (*C*(2'''',6'''')H), 128.8 (*C*(2''''',6''''')H), 128.8 (2 ArCH), 128.9 (2 ArCH), 129.0 (2 ArCH), 131.0 (*C*(2''',6''')H), 133.8 (*C*(4''''')H), 134.0 (*C*(4'''')H), 134.4 (*C*(1''')), 138.0 (*C*(1')), 138.3 (*C*(3'')), 139.2 (*C*(1''''')), 140.9 (*C*(1'''')), 172.7 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{33}H_{29}NNaO_5S_3$ $[M+Na]^+$ found 638.1086, requires 638.1100 (−2.2 ppm). (LNB ref: CM491, CM641)

(2*R*,3*S*)-*N*-Benzyl-3-(4'''-fluorophenyl)-2-phenyl-4,4-bis(phenylsulfonyl)butanamide (**278**)

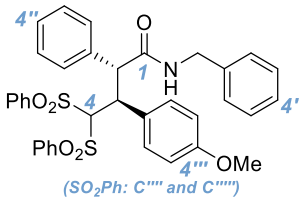


278

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (80 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (90:10 dr). Purification by flash column chromatography (0 to 3.5% Et_2O in CH_2Cl_2; R_f 0.35 at 3% Et_2O in CH_2Cl_2) gave the title compound (100 mg, 80%, single major diastereoisomer) as a colourless solid. **mp** 239-241 °C; $[\alpha]_D^{20}$ −21.2 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 31.7 min, t_R (minor): 43.2 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3344 (N-H), 1670 (C=O), 1508, 1447, 1335 (SO_2), 1223, 1145 (SO_2), 1076, 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.77 (1H, dd, *J* 15.0, 4.2, NC*H*^{A}H^{B}Ph), 4.43 (1H, dd, *J* 15.0, 7.6, NCH^A*H*^{B}Ph), 4.53 – 4.69 (2H, m, C(2)*H* and C(4)*H*), 4.74 (1H, dd, *J* 11.8, 1.7, C(3)*H*), 5.81 (1 H, dd, *J* 7.1, 4.3, N*H*), 6.59 (2H, d, *J* 7.1, C(2',6')*H*), 6.99 (2H, t, *J* 8.6,

C(3''',5''')*H*), 7.14 (2H, t, *J* 7.1, C(3',5')*H*), 7.16 – 7.22 (1H, m, C(4')*H*), 7.31 (2H, t, *J* 7.9, C(3'''',5'''')*H*), 7.33 – 7.46 (11H, m, 11 ArC*H*), 7.51 (1H, t, *J* 7.4, C(4'''')*H*), 7.58 (1H, t, *J* 7.3, C(4''''')*H*), 7.81 (2 H, dd, *J* 8.5, 5.3, C(2''',6''')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −115.7 – −112.7 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 46.9 (*C*(3)H), 57.9 (*C*(2)H), 82.3 (*C*(4)H), 115.1 (d, $^2J_{C\text{-}F}$ 21.3, *C*(3''',5''')H), 127.2 (*C*(2',6')H), 127.4 (*C*(4')H), 128.4 (2 ArCH), 128.6 (2 ArCH), 128.7 (*C*(4'')H), 128.8 (2 ArCH), 128.9 (2 ArCH), 129.4 (2 ArCH), 129.5 (4 ArCH), 130.3 (d, $^4J_{C\text{-}F}$ 3.1, *C*(1''')), 133.3 (d, $^3J_{C\text{-}F}$ 8.1, *C*(2''',6''')H), 134.0 (*C*(4'''')H), 134.4 (*C*(4''''')H), 136.9 (*C*(1'')), 137.6 (*C*(1')), 138.1 (*C*(1''''')), 141.2 (*C*(1'''')), 162.7 (d, $^1J_{C\text{-}F}$ 247.1, *C*(4''')), 170.5 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{35}H_{31}FNO_5S_2$ $[M+H]^+$ found 628.1614, requires 628.1622 (−1.3 ppm). (LNB ref: CM564, CM628, CM642)

(2*R*,3*S*)-*N*-Benzyl-3-(4'''-methoxyphenyl)-2-phenyl-4,4-bis(phenylsulfonyl)butan-amide (**279**)

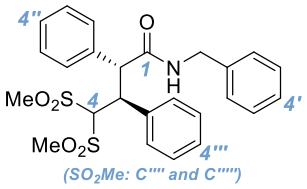


279

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), (2-(4-methoxyphenyl)ethene-1,1-diyldisulfonyl)dibenzene **263** (83 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (0 to 5.5% Et_2O in CH_2Cl_2; R_f 0.33 at 5% Et_2O in CH_2Cl_2) then (0 to 60% EtOAc in petrol; R_f 0.37 at 60% EtOAc in petrol) gave the title compound (35 mg, 27%, single minor diastereoisomer) as a colourless solid. **mp** 230 °C (dec) then 268 °C; $[\alpha]_D^{20}$ −46.4 (*c* 0.3, CH_2Cl_2); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 16.8 min, t_R (major): 33.8 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3302 (N-H), 2920 (C-H), 1647 (C=O), 1558 (ArC=C), 1512 (ArC=C), 1447, 1339 (SO_2), 1258 (Ar-O-CH_3), 1150 (SO_2), 1080, 1034, 733; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.79 (1H, dd, *J* 15.1, 4.1, NC*H*^{A}H^{B}Ph), 3.85 (3H, s, OC*H*$_3$), 4.45 (1H, dd, *J* 15.0, 7.5,

NCH^{A}*H*^{B}Ph), 4.61 – 4.73 (3H, m, C(4)*H*, C(2)*H* and C(3)*H*), 5.66 – 5.80 (1H, m, N*H*), 6.58 (2H, d, *J* 6.8, C(2',6')*H*), 6.87 (2H, d, *J* 8.8, C(3''',5''')*H*), 7.07 – 7.20 (3H, m, C(3',5')*H* and C(4')*H*), 7.30 (2H, d, *J* 8.2, C(2'''',6'''')*H*), 7.32 – 7.43 (9H, m, ArC*H*), 7.46 (2H, d, *J* 7.3, C(2'''',6'''')*H*), 7.50 (1H, t, *J* 7.4, C(4'''')*H*), 7.58 (1H, t, *J* 7.3, C(4'''')*H*), 7.75 (2H, d, *J* 8.7, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 43.5 (NCH^{A}H^{B}Ph), 47.0 (*C*(3)H), 55.3 (OCH_3), 58.1 (*C*(2)H), 82.5 (*C*(4)H), 113.6 (*C*(3''',5''')H), 126.3 (*C*(1''')), 127.2 (*C*(2',6')H), 127.3 (*C*(4')H), 128.4 (*C*(3'''',5'''')H or *C*(3'''',5'''')H), 128.5 (*C*(3',5')H and *C*(4'')H), 128.8 (*C*(2'''',6'''')H), 129.1 (*C*(2'''',6'''')H), 129.3 (*C*(3'''',5'''')H or *C*(3'''',5'''')H), 129.5 (*C*(2'',6'')H and *C*(3'',5'')H), 132.7 (*C*(2''',6''')H), 133.9 (*C*(4'''')H), 134.3 (*C*(4'''')H), 137.1 (*C*(1'')), 137.7 (*C*(1')), 138.2 (*C*(1'''')), 141.4 (*C*(1'''')), 159.4 (*C*(4''')), 170.8 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{36}H_{34}NO_6S_2$ $[M+H]^+$ found 640.1814, requires 640.1822 (−1.2 ppm). (LNB ref: CM523, CM725)

(2*R*,3*S*)-*N*-Benzyl-4,4-bis(methylsulfonyl)-2,3-diphenylbutanamide (**280**)

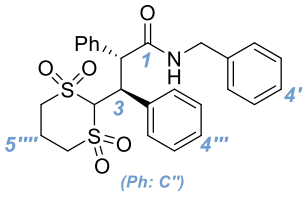


280

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), (2,2-bis(methylsulfonyl)vinyl)benzene **267** (52 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (80:20 dr). Purification by flash column chromatography (0 to 4.5% Et_2O in CH_2Cl_2; R_f 0.30 at 4% Et_2O in CH_2Cl_2) then (0 to 45% EtOAc in petrol; R_f 0.26 at 40% EtOAc in petrol) gave the title compound (53 mg, 55%, 80:20 dr) as a colourless solid. **mp** 151-153 °C; $[\alpha]_D^{20}$ −46.4 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor diastereomer): 24.4 and 49.6 min, t_R (major diastereomer): 33.3 and 59.9 min, 80:20 dr, > 99:1 er_{min} and 99:1 er_{maj}; ν_{max} (solid, cm^{-1}) 3302 (N-H), 1651 (C=O), 1545, 1497, 1454, 1331, 1304 (SO_2), 1142, 1123, 960, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.64 (3H, s, $SO_2C(1'''')H_3$), 2.65 (3H, s, $SO_2C(1'''')H_3$), 3.85 (1H, dd, *J* 15.1, 4.4, NC*H*^{A}H^{B}Ph), 4.03 (1H, s, C(4)*H*), 4.43

(1H, dd, *J* 15.1, 7.3, NCH$_A$*H*$_B$Ph), 4.60 (1H, d, *J* 12.1, C(2)*H*), 5.04 (1H, dd, *J* 12.0, 2.2, C(3)*H*), 5.76 – 5.88 (1H, m, N*H*), 6.62 (2H, d, *J* 7.3, C(2',6')*H*), 7.06 – 7.17 (3H, m, C(3',5')*H* and C(4')*H*), 7.37 – 7.42 (4H, m, C(4'')*H*, C(3''',5''')*H* and C(4''')*H*), 7.45 (2H, t, *J* 7.5, C(3'',5'')*H*), 7.68 (2H, broad-s, C(2'',6'')*H*), 7.77 (2H, broad-s, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 42.4 ($SO_2C(1'''')H_3$), 43.4 (NCH^{A}H^{B}Ph), 44.2 ($SO_2C(1'''')H_3$), 47.4 (*C*(3)H), 56.2 (*C*(2)H), 83.3 (*C*(4)H), 127.3 (*C*(2',6')H), 127.3 (*C*(4')H), 128.6 (*C*(3',5')H), 128.8 (*C*(4'')H), 128.8 (*C*(3''',5''')H), 128.9 (*C*(4''')H), 129.2 (*C*(2'',6'')H), 129.7 (*C*(3''',5''')H), 130.8 (*C*(2''',6''')H), 134.7 (*C*(1''')), 136.6 (*C*(1'')), 137.8 (*C*(1')), 170.3 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{25}H_{28}NO_5S_2$ $[M+H]^+$ found 486.1395, requires 486.1403 (−1.6 ppm). Selected data for minor diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.51 (3H, s, $SO_2C(1'''')H_3$), 2.84 (3H, s, $SO_2C(1'''')H_3$), 4.23 (1H, dd, *J* 15.0, 5.6, NC*H*^{A}H^{B}Ph), 4.55 (1H, dd, *J* 15.0, 6.5, NCH$_A$*H*$_B$Ph), 4.59 (2H, app s, C(3)*H* and C(4)*H*), 5.61 (1H, app s, C(2)*H*), 6.10 (1H, t, *J* 5.8, N*H*), 7.19 – 7.24 (3H, m, ArC*H*), 7.27 – 7.32 (3 H, m, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 42.1 ($SO_2C(1'''')H_3$), 43.8 (NCH^{A}H^{B}Ph), 44.6 ($SO_2C(1'''')H_3$), 48.7 (*C*(3)H), 55.5 (*C*(2)H), 83.5 (*C*(4)H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 134.3 (*C*(1'')), 137.7 (*C*(1''')), 138.2 (*C*(1')), 172.5 (*C*(1)=O). (LNB ref: CM528)

(2*R*,3*S*)-*N*-Benzyl-2,3-diphenyl-3-(1'''',1'''',3'''',3''''-tetraoxido-1'''',3''''-dithian-2''''-yl)propanamide (**281**)

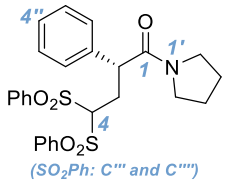


281

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 2-benzylidene-1,3-dithiane 1,1,3,3-tetraoxide **268** (54 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and MeCN (0.4 mL, 0.50 M) at room temperature for 24 h, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h, gave crude product (85:15 dr). Purification by flash column chromatography (50 to 100% EtOAc in petrol; R_f 0.28 at 70% EtOAc in petrol) then (0 to 25% Et_2O in CH_2Cl_2; R_f 0.40 at 20% Et_2O in CH_2Cl_2) gave the title compound (84 mg, 84%, single

major diastereoisomer) as a colourless solid. **mp** 176 °C (dec) then 261 °C; **$[\alpha]_D^{20}$** −69.2 (*c* 0.25, CH_2Cl_2); **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 27.3 min, t_R (major): 40.2 min, 99:1 er; **ν_{max}** (solid, cm^{-1}) 3305 (N-H), 1647 (C=O), 1554, 1496, 1339 (SO_2), 1292, 1146 (SO_2), 1107, 698; **^{1}H NMR** (400 MHz, CD_3CN) δ_H: 1.98 – 2.15 (2H, m, C(5'''')*H*ax and C(5'''')*Heq*), 2.50 – 2.69 (1H, m, C(4'''')*Hax*), 2.72 – 2.83 (1H, m, C(6'''')*Hax*), 2.93 – 3.14 (2H, m, C(4'''')*Heq* and, C(6'''')*Heq*), 3.83 (1H, dd, *J* 15.6, 5.3, NCH_AH_BPh), 4.01 (1H, s, C(2'''')*H*), 4.21 (1H, dd, *J* 15.6, 7.1, NCH_AH_BPh), 4.79 (1H, d, *J* 12.3, C(2)*H*), 4.86 (1H, dd, *J* 12.3, 1.7, C(3)*H*), 6.58 (2H, dd, *J* 7.9, 1.5, C(2',6')*H*), 6.97 – 7.14 (3H, m, C(3',5')*H* and C(4')*H*), 7.18 (1H, app t, *J* 5.6, N*H*), 7.30 – 7.43 (4H, m, C(4'')*H*, C(3''',5''')*H* and C(4''')*H*), 7.47 (2H, t, *J* 7.3, C(3'',5'')*H*), 7.60 (2H, d, *J* 7.1, C(2'',6'')*H*), 7.67 – 7.71 (2H, m, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, CD_3CN) δ_C: 18.2 (*C*(5'''')H_2), 43.1 (NCH_AH_BPh), 45.6 (*C*(3)H), 51.8 (C(6'''')H_2), 52.7 (*C*(4'''')H_2), 56.0 (*C*(2)H), 83.7 (*C*(2'''')H), 127.4 (*C*(2',6')H), 127.5 (*C*(4')H), 129.1 (*C*(3',5')H and *C*(3''',5''')H), 129.3 (*C*(4''')H), 129.4 (*C*(4'')H), 129.8 (*C*(2'',6'')H), 130.2 (*C*(3'',5'')H), 132.2 (*C*(2''',6''')H), 135.8 (*C*(1''')), 138.0 (*C*(1'')), 139.7 (*C*(1')), 171.6 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{26}H_{28}NO_5S_2$ $[M+H]^+$ found 498.1398, requires 498.1403 (−1.0 ppm). (LNB ref: CM534)

(*R*)-2-Phenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1'-yl)butan-1-one (**282**)

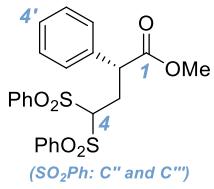


282

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (1.16 g, 4.5 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene **219** (925 mg, 3.0 mmol, 1.0 equiv), (*R*)-BTM (37.8 mg, 0.15 mmol, 5 mol%) and CH_2Cl_2 (6.0 mL, 0.50 M) at room temperature for 24 h, then pyrrolidine (1.25 mL, 15.0 mmol, 5.0 equiv) for 24 h, after purification by flash column chromatography (0 to 25% Et_2O in CH_2Cl_2; R_f 0.38 at 30% Et_2O in CH_2Cl_2) gave the title compound (1.12 g, 75%) as a colourless solid. **mp** 74-76 °C; **$[\alpha]_D^{20}$** −56.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (90:10 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 33.7 min, t_R (major): 39.1 min, > 99:1 er; **ν_{max}**

(solid, cm^{-1}) 1632 (C=O), 1329 (SO_2), 1310, 1152 (SO_2), 1078, 725, 687; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.67 – 1.85 (3H, m, C(3')H^AH^B and C(4')H^A), 1.85 – 2.03 (1H, m, C(4')H^B), 2.57 – 2.67 (1H, m, C(3)H^A), 2.67 – 2.77 (1H, m, C(3)H^B), 3.00 – 3.14 (1H, m, C(5')H^A), 3.29 – 3.39 (1H, m, C(2')H^A), 3.41 – 3.52 (1H, m, C(2')H^B), 3.53 – 3.69 (1H, m, C(5')H^B), 4.17 – 4.41 (1H, m, C(2)*H*), 4.45 (1H, dd, *J* 7.5, 5.3, C(4)*H*), 7.06 – 7.15 (2H, m, C(2'',6'')*H*), 7.17 – 7.25 (3H, m, C(3'',5'')*H* and C(4'')*H*), 7.50 (2H, t, *J* 7.9, C(3'''',5'''')*H*), 7.57 (2H, t, *J* 7.9, C(3''',5''')*H*), 7.62 – 7.67 (1H, m, C(4''')*H*), 7.67 – 7.73 (1H, m, C(4'''')*H*), 7.78 (2H, d, *J* 7.4, C(2'''',6'''')*H*), 7.94 (2H, d, *J* 7.3, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.2 (*C*(3')H^AH^B), 26.0 (*C*(4')H^AH^B), 30.5 (*C*(3)H^AH^B), 46.2 (*C*(2')H^AH^B), 46.3 (*C*(5')H^AH^B), 47.4 (*C*(2)H), 80.7 (*C*(4)H), 127.8 (*C*(4'')H), 128.4 (*C*(2'',6'')H), 129.2 (*C*(3''',5''')H), 129.3 (*C*(3'',5'')H and (*C*(3'''',5'''')H), 129.6 (*C*(2''',6''')H), 129.7 (*C*(2'''',6'''')H), 134.6 (*C*(4'''')H), 134.7 (*C*(4''')H), 137.0 (*C*(1'')), 137.4 (*C*(1'''')), 138.4 (*C*(1''')), 169.9 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{26}H_{28}NO_5S_2$ $[M+H]^+$ found 498.1395, requires 498.1403 (−1.6 ppm). (LNB ref: CM613, CM617, CM625, CM698)

Methyl (*R*)-2-phenyl-4,4-bis(phenylsulfonyl)butanoate (**283**)

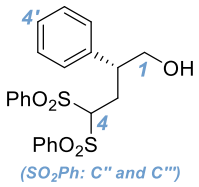


283

Following general procedure C, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.3 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene **219** (62 mg, 0.2 mmol, 1.0 equiv), (*R*)-BTM (2.5 mg, 0.01 mmol, 5 mol%) and CH_2Cl_2 (0.4 mL, 0.50 M) at room temperature for 24 h, then MeOH (3 mL) and DMAP (4.9 mg, 0.04 mmol, 0.2 equiv) for 24 h, after purification by flash column chromatography (0 to 3% Et_2O in CH_2Cl_2; R_f 0.4 at 3% Et_2O in CH_2Cl_2) then (0 to 50% EtOAc in petrol; R_f 0.3 at 30% EtOAc in petrol) gave the title compound (75 mg, 82%) as a colourless solid. **mp** 96-98 °C; **$[\alpha]_D^{20}$** −58.0 (*c* 0.5, $CHCl_3$); **HPLC**: determined by conversion to the corresponding alcohol; **ν_{max}** (solid, cm^{-1}) 1730 (C=O), 1447, 1331 (SO_2), 1310, 1159, 1146 (SO_2), 1078, 685; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.55 – 2.85 (2H, m, C(3)H_2), 3.63 (3H, s, CH_3), 4.24 (1H, dd, *J* 8.4, 3.9, C(4)*H*), 4.28 (1H, dd, *J* 10.1, 6.3, C(2)*H*), 7.08 (2H, dd, *J* 7.7, 1.6, C(2',6')*H*),

7.18 – 7.34 (3H, m, C(3',5')*H* and C(4')*H*), 7.51 (2H, t, *J* 7.9, C(3''',5''')*H*), 7.59 (2H, t, *J* 7.9, C(3'',5'')*H*), 7.64 – 7.69 (1H, m, C(4''')*H*), 7.69 – 7.72 (1H, m, C(4'')*H*), 7.73 (2H, dd, *J* 8.4, 1.1, C(2''',6''')*H*), 7.95 (2H, dd, *J* 8.4, 1.1, C(2'',6'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 28.9 (*C*(3)H_2), 48.3 (*C*(2)H), 52.6 (*C*H_3), 80.3 (*C*(4)H), 128.2 (*C*(4')H), 128.4 (*C*(2',6')H), 129.3 (*C*(3'',5'')H), 129.3 (*C*(3''',5''')H), 129.4 (*C*(3',5')H), 129.6 (*C*(2''',6''')H), 129.8 (*C*(2'',6'')H), 134.7 (*C*(4''')H), 134.9 (*C*(4'')H), 136.1 (*C*(1')), 137.3 (*C*(1''')), 138.0 (*C*(1'')), 173.1 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{23}H_{22}NaO_6S_2$ $[M+Na]^+$ found 481.0739, requires 481.0750 (−2.3 ppm). (LNB ref: CM643)

(*R*)-2-Phenyl-4,4-bis(phenylsulfonyl)butan-1-ol (**S1**)



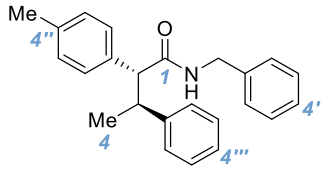
S1

DIBAL-H (1 M in hexane, 0.2 mL, 0.2 mmol, 2.0 equiv) was added dropwise to methyl (*R*)-2-phenyl-4,4-bis(phenylsulfonyl)butanoate **283** (46 mg, 0.1 mmol, 1.0 equiv) in THF (2 mL, 0.06 M) at 0 °C and the reaction was stirred at 0 °C for 4 h. The reaction mixture was quenched with water (10 mL), acidified to pH = 3 using 1 M HCl (few drops) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0 to 75% EtOAc in petrol; R_f 0.25 at 60% EtOAc in petrol) to give the title compound (26 mg, 60%) as a white gum. $[\alpha]_D^{20}$ −18.6 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 21.5 min, t_R (minor): 27.4 min, 99:1 er; ν_{max} (film, cm^{-1}) 3545 (O-H), 2918 (C-H), 1584, 1495, 1447, 1327, 1310, 1150 (SO_2), 1078, 729, 684; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.51 (1H, ddd, *J* 15.6, 10.5, 2.9, C(3)*H*^{A}H^B), 2.62 (1H, ddd, *J* 15.5, 8.8, 5.4, C(3)H^A*H*^{B}), 3.27 – 3.40 (1H, m, C(2)*H*), 3.65 – 3.83 (2H, m, C(1)*H*^{A}*H*^{B}), 4.39 (1H, dd, *J* 8.8, 2.8, C(4)*H*), 7.03 (2H, dd, *J* 6.6, 2.9, C(2',6')*H*), 7.23 – 7.32 (3H, m, C(3',5')*H* and C(4')*H*), 7.45 – 7.53 (2H, m, C(3'',5'')*H*), 7.58 (2H, t, *J* 7.8, C(3''',5''')*H*), 7.64 – 7.69 (1H, m, C(4'')*H*), 7.69 – 7.75 (3H, m, C(2'',6'')*H* and C(4''')*H*), 7.95 (2H, dd, *J* 8.5, 1.2, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (101MHz, $CDCl_3$) δ_C:

28.3 (*C*(3)H^{A}H^B), 46.1 (*C*(2)H), 67.4 (*C*(1)H^{A}H^B), 81.0 (*C*(4)H), 127.7 (*C*(4')H), 128.3 (*C*(2',6')H), 129.2 (2 ArCH), 129.2 (2 ArCH), 129.3 (2 ArCH), 129.5 (*C*(2'',6'')H), 129.9 (*C*(2''',6''')H), 134.6 (*C*(4'')H), 134.8 (*C*(4''')H), 137.7 (*C*(1'')), 138.0 (*C*(1''')), 139.0 (*C*(1')); **HRMS** (ESI$^+$) $C_{22}H_{22}NaO_5S_2$ [M+Na]$^+$ found 453.0790, requires 453.0801 (−2.4 ppm). (LNB ref: CM713, 715)

7.4.4. Derivatisation products

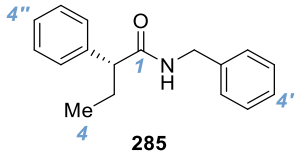
N-Benzyl-3-phenyl-2-(4''-tolyl)butanamide (**284**)



284

Following general procedure D, using activated magnesium turnings (200 mg, 8.24 mmol, 40 equiv), (2*R*,3*S*)-*N*-benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(*p*-tolyl)butanamide **217** (125 mg, 0.2 mmol, 1.0 equiv), and MeOH (4.2 mL, 0.05 M) at room temperature for 6 h gave after column chromatography (0 to 50% EtOAc in petrol; R_f 0.54 at 40% EtOAc in petrol) then (0 to 4% Et_2O in CH_2Cl_2; R_f 0.44 at 3% Et_2O in CH_2Cl_2) the title compound (39 mg, 57%) as a colourless solid. **mp** 140 °C; $[\alpha]_D^{20}$ −2.6 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 6.8 min, t_R (major): 12.2 min, 99:1 er; ν_{max} (solid, cm^{-1}) 3306 (CON-H), 3030 (ArC-H), 2920 (C-H), 1645 (C=ONH), 1545 (C=ONH), 1512, 1493, 1452, 1030, 694; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.04 (3H, d, *J* 7.0, C(4)*H*$_3$), 2.35 (3H, s, ArC*H*$_3$), 3.29 (1H, d, *J* 10.9, C(2)*H*), 3.49 – 3.64 (1H, m, C(3)*H*), 3.88 (1H, dd, *J* 15.0, 4.5, NC*H*^{A}H^{B}Ph), 4.38 (1H, dd, *J* 15.0, 7.0, NCH^A*H*^{B}Ph), 5.40 (1H, broad-s, N*H*), 6.64 (2H, d, *J* 6.6, C(2',6')*H*), 7.09 – 7.19 (5H, m, C(3',5')*H*, C(4')*H* and C(3'',5'')*H*), 7.26 – 7.30 (1H, m, C(4''')*H*), 7.29 – 7.37 (4H, m, C(3''',5''')*H* and C(2''',6''')*H*), 7.37 (2H, d, *J* 7.9, C(2'',6'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 19.9 (*C*(4)H$_3$), 21.3 (ArCH$_3$), 43.1 (*C*(3)H), 43.3 (NCH^{A}H^{B}Ph), 62.0 (*C*(2)H), 126.6 (*C*(4''')H), 127.1 (*C*(4')H), 127.4 (*C*(2',6')H), 127.7 (*C*(2''',6''')H), 128.5 (*C*(3',5')H), 128.5 (*C*(2'',6'')H), 128.7 (*C*(3''',5''')H), 129.4 (*C*(3'',5'')H), 135.7 (*C*(1'')), 137.2 (*C*(4'')), 138.2 (*C*(1')), 145.5 (*C*(1''')), 172.4 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{24}H_{26}NO$ [M+H]$^+$ found 344.2012, requires 344.2009 (+0.9 ppm). (LNB ref: CM389, CM591)

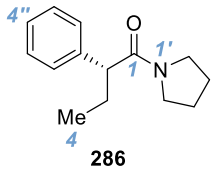
(*R*)-*N*-Benzyl-2-phenylbutanamide (**285**)



285

Following general procedure D, using activated magnesium turnings (252 mg, 10.3 mmol, 40 equiv), (*R*)-*N*-benzyl-2-phenyl-4,4-bis(phenylsulfonyl)butanamide **221** (120 mg, 0.225 mmol, 1.0 equiv), and MeOH (5.2 mL, 0.05 M) at room temperature for 6 h gave after column chromatography (0 to 40% EtOAc in petrol; R_f 0.29 at 30% EtOAc in petrol) the title compound (36 mg, 63%) as a beige solid with spectroscopic data in accordance with the literature.[272] **mp** 76-78 °C {Lit.[273] 77-78 °C}; $\boldsymbol{[\alpha]_D^{20}}$ −20.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralcel OJ-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 9.1 min, t_R (major): 10.2 min, > 99:1 er; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 0.90 (3H, t, *J* 7.4, C(4)H_3), 1.76 – 1.90 (1H, m, C(3)H^AH^B), 2.15 – 2.33 (1H, m, C(3)H^AH^B), 3.26 (1H, t, *J* 7.6, C(2)*H*), 4.35 (1H, dd, *J* 14.9, 5.7, NCH^AH^BPh), 4.45 (1H, dd, *J* 14.9, 5.9, NCH^AH^BPh), 5.73 (1H, s, N*H*), 7.14 (2H, d, *J* 6.7, C(2',6')*H*), 7.20 – 7.29 (4H, m, C(3',5')*H*, C(4')*H* and C(4'')*H*), 7.29 – 7.36 (4H, m, C(2'',6'')*H* and C(3'',5'')*H*). (LNB ref: CM623, CM624)

(*R*)-2-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (**286**)

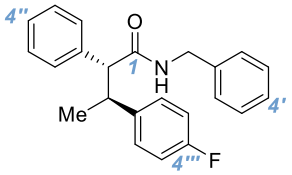


286

Following general procedure D, using activated magnesium turnings (252 mg, 10.3 mmol, 40 equiv), (*R*)-2-phenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1-yl)butan-1-one **282** (124 mg, 0.25 mmol, 1.0 equiv), and MeOH (5.2 mL, 0.05 M) at room temperature for 6 h gave after column chromatography (0 to 75% EtOAc in petrol; R_f 0.35 at 70% EtOAc in petrol) the title compound (42 mg, 77%) as a peach solid. **mp** 42-44 °C; $\boldsymbol{[\alpha]_D^{20}}$ −41.2 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak AD-H, (98:2 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 13.4 min, t_R (major): 16.6 min, > 99:1 er; $\boldsymbol{\nu_{max}}$ (solid, cm^{-1}) 2959 (C-H), 2870 (C-H), 1627 (C=O), 1454, 1423, 1337, 744, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 0.86 (3H, t, *J* 7.4, C(4)H_3), 1.66 – 1.83 (4H, m, C(3)*H*,

C(3')H^AH^B and C(4')H^AH^B), 1.83 – 1.95 (1H, m, C(3')H^AH^B), 2.03 – 2.18 (1H, m, C(3)*H*), 3.12 – 3.29 (1H, m, C(2')H^AH^B), 3.34 – 3.42 (1H, m, C(5')H^AH^B), 3.44 (1H, t, *J* 7.4, C(2)*H*), 3.47 – 3.58 (2H, m, C(2')H^AH^B and C(5')H^AH^B), 7.19 – 7.24 (1H, m, C(4'')*H*), 7.27 – 7.34 (4H, m, C(2'',6'')*H* and C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 12.6 (*C*(4)H_3), 24.3 (*C*(4')H^AH^B), 26.2 (*C*(3')H^AH^B), 28.0 (*C*(3)H^AH^B), 46.0 (*C*(5')H^AH^B), 46.4 (*C*(2')H^AH^B), 52.8 (*C*(2)H), 126.9 (*C*(4'')H), 128.3 (*C*(2'',6'')H), 128.7 (*C*(3'',5'')H), 140.2 (*C*(1'')), 171.9 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{14}H_{20}NO$ $[M+H]^+$ found 218.1533, requires 218.1539 (−2.8 ppm). (LNB ref: CM621, CM622)

(2*R*,3*S*)-*N*-Benzyl-3-(4'''-fluorophenyl)-2-phenylbutanamide (**287**)

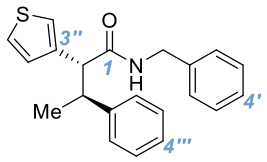


287

Following general procedure D, using activated magnesium turnings (200 mg, 8.24 mmol, 40 equiv), (2*R*,3*S*)-*N*-benzyl-3-(4-fluorophenyl)-2-phenyl-4,4-bis(phenylsulfonyl)butanamide **278** (126 mg, 0.20 mmol, 1.0 equiv), and MeOH (4.2 mL, 0.05 M) at room temperature for 5 h gave after column chromatography (0 to 30% EtOAc in petrol; R_f 0.63 at 50% EtOAc in petrol) the title compound (31 mg, 45%) as a colourless solid. **mp** 158-160 °C;**$[\alpha]_D^{20}$** −18.0 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AD-H, (95:5 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 35.3 min, t_R (minor): 40.6 min, > 99:1 er; **ν_{max}** (solid, cm^{-1}) 3285 (CON-H), 2988 (C-H), 2922 (C-H), 1649 (C=O), 1558, 1508, 1221 (C-F), 831, 696; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.02 (3H, d, *J* 7.1, C(4)H_3), 3.27 (1H, d, *J* 10.9, C(2)*H*), 3.60 (1H, dq, *J* 11.0, 7.1, C(3)*H*), 3.85 (1H, dd, *J* 15.0, 4.5, NC$H^A$$H^B$Ph), 4.42 (1H, dd, *J* 15.0, 7.2, NCH^AH^BPh), 5.39 – 5.71 (1H, m, N*H*), 6.66 (2H, dd, *J* 7.6, 1.6, C(2',6')*H*), 6.99 (2H, t, *J* 8.7, C(3''',5''')*H*), 7.11 – 7.22 (3H, m, C(3',5')*H* and C(4')*H*), 7.27 – 7.34 (3H, m, C(4'')*H* and C(2''',6''')*H*), 7.33 – 7.38 (2H, m, C(3'',5'')*H*), 7.42 – 7.50 (2H, m, C(2'',6'')*H*); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ_F: −116.6 (s); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 19.9 (*C*(4)H_3), 42.5 (C(3)*H*), 43.3 (NCH^AH^BPh), 62.5 (*C*(2)H), 115.4 (d, $^2J_{C\text{-}F}$ 21.1, *C*(3''',5''')H), 127.3 (*C*(2',6')H and *C*(4')H), 127.6 (*C*(4'')H), 128.5 (*C*(3',5')H and *C*(2'',6'')H), 128.8 (*C*(3'',5'')H), 129.2 (d, $^3J_{C\text{-}F}$ 7.8, *C*(2''',6''')H), 138.1 (*C*(1')), 138.5 (*C*(1'')), 141.0 (d, $^4J_{C\text{-}F}$ 3.0, *C*(1''')), 161.7 (d, $^1J_{C\text{-}F}$

244.1, *C*(4'")), 172.0 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{23}H_{22}FNNaO$ $[M+Na]^+$ found 370.1566, requires 370.1578 (−3.2 ppm). (LNB ref: CM652, CM653)

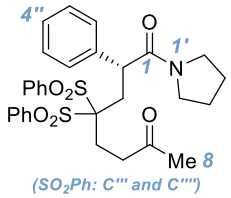
(2*R*,3*S*)-*N*-Benzyl-3-phenyl-2-(thiophen-3''-yl)butanamide (**288**)



288

Following general procedure D, using activated magnesium turnings (200 mg, 8.24 mmol, 40 equiv), (2*R*,3*S*)-*N*-benzyl-3-phenyl-4,4-bis(phenylsulfonyl)-2-(thiophen-3-yl)butanamide **257**$_{maj}$ (123 mg, 0.20 mmol, 1.0 equiv), and MeOH (4.2 mL, 0.05 M) at room temperature for 6 h gave after column chromatography (0 to 35% EtOAc in petrol; R_f 0.63 at 50% EtOAc in petrol) the title compound (34 mg, 51%) as a colourless solid. **mp** 126-128 °C; $[\alpha]_D^{20}$ −12.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 6.9 min, t_R (major): 11.8 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 3250 (CON-H), 2968 (C-H), 1641 (C=O), 1560, 1493, 1452, 1229, 1080, 1028, 762, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.09 (3H, dd, *J* 4.5, 2.2, C(4)*H*$_3$), 3.45 – 3.61 (2H, m, C(2)*H* and C(3)*H*), 3.93 (1H, dd, *J* 15.0, 4.6, NC*H*^{A}H^{B}Ph), 4.35 (1H, dd, *J* 15.0, 6.8, NCH^A*H*^{B}Ph), 5.48 (1H, s, N*H*), 6.66 (2H, dd, *J* 7.7, 1.6, C(2',6')*H*), 7.08 – 7.19 (3H, m, C(3',5')*H* and C(4')*H*), 7.21 – 7.28 (3H, m, ArC*H*), 7.29 – 7.37 (5H, m, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 19.8 (*C*(4)H$_3$), 43.3 (NCH^{A}H^{B}Ph), 43.5 (*C*(3)H), 57.6 (*C*(2)H), 122.5 (ArCH), 125.9 (ArCH), 126.7 (ArCH), 127.2 (ArCH), 127.4 (*C*(2',6')H), 127.7 (2 ArCH), 127.8 (ArCH), 128.6 (2 ArCH), 128.7 (2 ArCH), 138.0 (*C*(1')), 139.1 (*C*(3'')), 145.2 (*C*(1''')), 171.9 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{21}H_{21}NNaOS$ $[M+Na]^+$ found 358.1227, requires 358.1236 (−2.5 ppm). (LNB ref: CM650, CM651)

(*R*)-2-Phenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1-yl)octane-1,7-dione (**293**)

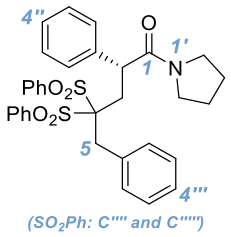


293

(*R*)-2-Phenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1-yl)butan-1-one **282** (124 mg, 0.25 mmol, 1.0 equiv), potassium carbonate (45 mg, 0.32 mmol, 1.3 equiv) and methyl vinyl ketone (27 μL, 0.32 mmol, 1.3 equiv) were heated at reflux in MeCN (1 mL, 0.25 M) for 24 h. The reaction was allowed to cool to room temperature, diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organics were combined, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 30% EtOAc in CH_2Cl_2; R_f 0.27 at 30% EtOAc in CH_2Cl_2) to give the title compound (80 mg, 56%) as a colourless solid. **mp** 80-82 °C; $\mathbf{[\alpha]_D^{20}}$ +7.6 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 22.6 min, t_R (major): 44.9 min, 99:1 er; ν_{max} (solid, cm^{-1}) 1714 (C=O, ketone), 1634, C=O amide), 1433, 1308 (SO_2), 1138 (SO_2), 1076, 721; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.69 – 1.76 (1H, m, C(4')H^AH^B), 1.76 – 1.90 (2H, m, C(3')H^AH^B and C(4')H^AH^B), 1.93 – 2.00 (1H, m, C(3')H^AH^B), 2.01 (3H, s, C(8)H_3), 2.24 – 2.39 (2H, m, C(3)H^AH^B and C(5)H^AH^B), 2.44 (1H, ddd, *J* 15.5, 10.6, 4.8, C(5)H^AH^B), 2.62 (1H, ddd, *J* 19.0, 10.8, 4.8, C(6)H^AH^B), 2.83 (1H, ddd, *J* 19.0, 10.6, 4.7, C(6)H^AH^B), 3.22 – 3.35 (2H, m, C(2')H^AH^B and C(5')H^AH^B), 3.39 – 3.49 (1H, m, C(5')H^AH^B), 3.58 (1H, dd, *J* 15.5, 8.0, C(3)H^AH^B), 3.70 – 3.81 (1H, m, C(2')H^AH^B), 4.58 (1H, dd, *J* 7.9, 2.2, C(2)*H*), 7.24 (1H, t, *J* 7.4, C(4'')*H*), 7.30 (2H, t, *J* 7.4, C(3'',5'')*H*), 7.37 (2H, d, *J* 7.3, C(2'',6'')*H*), 7.55 (4H, t, *J* 7.9, C(3''',5''')*H* and C(3'''',5'''')*H*), 7.65 – 7.71 (2H, m, C(4''')*H* and C(4'''')*H*), 7.95 (2H, d, *J* 7.5, C(2''',6''')*H*), 8.04 (2H, d, *J* 7.5, C(2''',6''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.0 (*C*(5)H^AH^B), 24.3 (*C*(4')H^AH^B), 26.1 (*C*(3')H^AH^B), 30.0 (*C*(8)H_3), 35.3 (*C*(3)H^AH^B), 38.3 (*C*(6)H^AH^B), 44.8 (*C*(2)H), 46.4 (*C*(2')H^AH^B), 46.5 (*C*(5')H^AH^B), 91.2 (*C*(4)), 127.5 (*C*(4'')H), 128.2 (*C*(2'',6'')H), 128.9 (*C*(3''',5''')H and *C*(3'''',5'''')H), 129.1 (*C*(3'',5'')H), 131.3 (*C*(2'''',6'''')H), 131.4 (*C*(2''',6''')H), 134.8 (*C*(4''')H), 134.8 (*C*(4'''')H),

137.1 (*C*(1'''')), 137.5 (*C*(1''')), 140.1 (*C*(1'')), 170.6 (*C*(1)=O), 206.2 (*C*(7)=O); **HRMS** (ESI$^+$) $C_{30}H_{33}NNaO_6S_2$ $[M+Na]^+$ found 590.1625, requires 590.1642 (−2.9 ppm). (LNB ref: CM710, CM711)

(*R*)-2,5-Diphenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1'-yl)pentan-1-one (**294**)



294

(*R*)-2-Phenyl-4,4-bis(phenylsulfonyl)-1-(pyrrolidin-1-yl)butan-1-one **282** (124 mg, 0.25 mmol, 1.0 equiv), potassium carbonate (42 mg, 0.30 mmol, 1.2 equiv) and benzyl bromide (30 μL, 0.25 mmol, 1.0 equiv) were heated at reflux in MeCN (1 mL, 0.25 M) for 24 h. The reaction was allowed to cool to room temperature, diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organics were combined, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 75% EtOAc in petrol; R_f 0.50 at 70% EtOAc in petrol) then (0 to 12% Et_2O in CH_2Cl_2; R_f 0.30 at 10% Et_2O in CH_2Cl_2) to give the title compound (63 mg, 43%) as a colourless solid. **mp** 94-96 °C; $[\alpha]_D^{20}$ +17.4 (*c* 0.16, $CHCl_3$); **HPLC**: Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 21.5 min, t_R (minor): 29.9 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 1630 (C=O), 1445, 1433, 1312 (SO_2), 1150 (SO_2), 1134, 1074, 908, 723, 687; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.64 – 1.74 (1H, m, C(4')H^AH^B), 1.74 – 1.84 (2H, m, C(3')H^AH^B and C(4')H^AH^B), 1.84 – 1.98 (1H, m, C(3')H^AH^B), 2.57 (1H, dd, *J* 15.6, 3.0, C(3)H^AH^B), 3.14 – 3.26 (1H, m, C(2')H^AH^B), 3.27 – 3.35 (1H, m, C(5')H^AH^B), 3.45 (2H, app d, *J* 5.7, C(5)H^AH^B), 3.47 – 3.55 (1H, m, C(5')H^AH^B), 3.62 – 3.73 (2H, m, C(3)H^AH^B and C(2')H^AH^B), 4.81 (1H, dd, *J* 6.7, 2.9, C(2)*H*), 6.96 (2H, d, *J* 7.4, C(2''',6''')*H*), 7.06 (2H, t, *J* 7.7, C(3''',5''')*H*), 7.15 (1H, t, *J* 7.4, C(4''')*H*), 7.20 – 7.26 (1H, m, C(4'')*H*), 7.30 (2H, t, *J* 7.4, C(3'',5'')*H*), 7.39 – 7.42 (2H, m, C(2'',6'')*H*), 7.42 – 7.46 (2H, m, C(3'''',5'''')*H*), 7.46 – 7.50 (2H, m, C(3'''',5'''')*H*), 7.58 – 7.63 (1H, m, C(4'''')*H*), 7.61 – 7.67 (1H, m, C(4'''')*H*), 7.77 (2H, dd, *J* 8.4, 1.0, C(2'''',6'''')*H*), 7.92 (2H, dd, *J* 8.5, 1.1, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$)

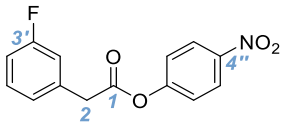
δ_C: 24.3 (*C*(4')H^{A}H^B), 26.1 (*C*(3')H^{A}H^B), 36.6 (*C*(3)H^{A}H^B), 37.6 (*C*(5)H$_2$), 45.0 (*C*(2)H), 46.3 (*C*(2')H^{A}H^B), 46.4 (*C*(5')H^{A}H^B), 92.6 (*C*(4)), 127.3 (*C*(4'')H), 127.5 (*C*(4''')H), 128.3 (*C*(3''',5''')H), 128.6 (*C*(2'',6'')H), 128.7 (*C*(3'''',5'''')H or *C*(3''''',5''''')H), 128.9 (*C*(3'''',5'''')H or *C*(3''''',5''''')H), 128.9 (*C*(3'',5'')H), 131.6 (*C*(2'''',6'''')H and *C*(2''''',6''''')H), 131.9 (*C*(2''',6''')H), 133.0 (*C*(1''')), 134.4 (*C*(4''''')H), 134.5 (*C*(4'''')H), 137.8 (*C*(1'''')), 137.8 (*C*(1'''')), 141.0 (*C*(1'')), 171.0 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{33}H_{34}NO_5S_2$ $[M+H]^+$ found 588.1861, requires 588.1873 (−2.0 ppm). (LNB ref: CM638, CM639)

7.5. Experimental for Chapter 3

7.5.1. Synthesis of Fluorinated Compounds

(*R*)-F-BTM **296** was prepared in house.[115]

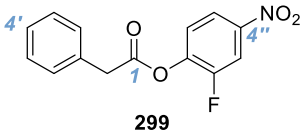
4''-Nitrophenyl 2-(3'-fluorophenyl)acetate (**295**)



295

Following general procedure A, using 3-fluorophenylacetic acid (3.1 g, 20 mmol, 1.0 equiv), EDCI·HCl (5.0 g, 26 mmol, 1.3 equiv), 4-nitrophenol (4.2 g, 30 mmol, 1.5 equiv) and CH_2Cl_2 (34 mL, 0.6 M) for 20 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-70% 7 CV), R_f 0.72 at 100% CH_2Cl_2] the title compound (3.03 g, 55%) as a white solid. **mp** 58-60 °C; **ν_{max}** (film, cm^{-1}) 3113 (ArC-H), 1767 (C=O), 1616 (ArC=C), 1589 (ArC=C), 1519 (C-NO_2), 1487, 1344 (C-NO_2), 1207 (C-F), 1115 (C-O), 762 (C-F); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 3.93 (2H, s, C(2)*H*$_2$), 7.02 – 7.09 (1H, m, C(4')*H*), 7.13 (1H, app dt, $^3J_{H\text{-}F}$ 9.5, *J* 1.9, C(2')*H*), 7.18 (1H, d, *J* 7.6, C(6')*H*), 7.29 (2H, d, *J* 9.1, C(2'',6'')*H*), 7.38 (1H, app td, *J* 8.0, $^4J_{H\text{-}F}$ 6.0, C(5')*H*), 8.28 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: -112.5 – -112.3 (m, C(3')*F*); **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ_C: 41.0 (d, $^4J_{C\text{-}F}$ 1.2, (*C*(2)H$_2$), 114.9 (d, $^2J_{C\text{-}F}$ 21.0, *C*(4')H), 116.5 (d, $^2J_{C\text{-}F}$ 22.0, *C*(2')H), 122.5 (*C*(2'',6'')H), 125.2 (d, $^4J_{C\text{-}F}$ 2.9, *C*(6')H), 125.4 (*C*(3'',5'')H), 130.5 (d, $^3J_{C\text{-}F}$ 8.3, *C*(5')H), 134.9 (d, $^3J_{C\text{-}F}$ 7.8, *C*(1')), 145.5 (*C*(4'')), 155.3 (*C*(1'')), 163.0 (d, $^1J_{C\text{-}F}$ 246.7, *C*(3')), 168.7 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{14}H_{11}FNO_4$ $[M+H]^+$ found 276.0667, requires 276.0667. (LNB ref: CM557)

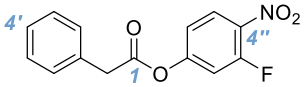
2''-Fluoro-4''-nitrophenyl 2-phenylacetate (**299**)



299

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.5 g, 13 mmol, 1.3 equiv), 2-fluoro-4-nitrophenol (2.36 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-60% 4 CV), R_f 0.61 at 100% CH_2Cl_2], the title compound (2.15 g, 78%) as a colourless solid. **mp** 51-53 °C; ν_{max} (solid, cm^{-1}) 1774 (C=O), 1523(ArC=C), 1493 (C-NO_2), 1350 (C-NO_2), 1265, 1092, 891, 810, 721, 694; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ_H: 3.97 (2H, s, C(2)H_2), 7.22 – 7.50 (6H, m, C(2',6')*H*, C(3',5')*H*, C(4')*H* and C(6'')*H*), 7.78 – 8.38 (2H, m, C(3'')*H* and C(5'')*H*); **^{19}F{^{1}H} NMR** (470 MHz, CD_2Cl_2) δ_F: −123.3 (s); **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ_C: 41.0 (*C*(2)H_2), 113.4 (d, $^2J_{C\text{-}F}$ 23.7, *C*(3'')H), 120.7 (d, $^4J_{C\text{-}F}$ 3.6, *C*(5'')H), 124.9 (*C*(6'')H), 128.2 (*C*(4')H), 129.3 (*C*(3',5')H), 129.9 (*C*(2',6')H), 133.2 (*C*(1')), 144.1 (d, $^2J_{C\text{-}F}$ 12.9, (*C*(1'')), 146.4 (d, $^3J_{C\text{-}F}$ 7.3, *C*(4'')), 154.1 (d, $^1J_{C\text{-}F}$ 254.2, *C*(2'')), 168.8 (*C*(1)=O); **HRMS** (EI^+) $C_{14}H_{10}FNO_4$ $[M]^+$ found 275.0590, requires 275.0588 (+0.7 ppm). (LNB ref: CM620, CM689)

3''-Fluoro-4''-nitrophenyl 2-phenylacetate (**300**)

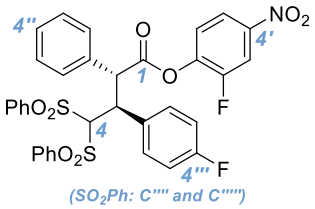


300

Following general procedure A, using phenylacetic acid (1.36 g, 10 mmol, 1.0 equiv), EDCI·HCl (2.5 g, 13 mmol, 1.3 equiv), 3-fluoro-4-nitrophenol (2.36 g, 15 mmol, 1.5 equiv) and CH_2Cl_2 (17 mL, 0.6 M) for 72 h gave, after purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, CH_2Cl_2 in petrol (50% 5 CV, 50-75% 7 CV), R_f 0.61 at 100% CH_2Cl_2], the title compound (1.87 g, 68%) as a yellow oil. ν_{max} (film, cm^{-1}) 3062 (ArC-H), 1767 (C=O), 1600 (ArC=C), 1528 (ArC=C), 1489, 1342 (C-NO_2), 1265 (C-F), 1096 (C-O); **^{1}H NMR** (500 MHz, CD_2Cl_2) δ_H: 3.92 (2H, s, C(2)H_2), 7.10 (1H, d, *J* 9.1, C(6'')*H*), 7.16 (1H, d, *J* 11.6, C(2'')*H*), 7.37 (5H, m, C(2',6')*H*, C(3',5')*H* and C(4')*H*), 8.12 (1H, app t, *J* 8.7, C(5'')*H*); **^{19}F{^{1}H} NMR** (470 MHz, CD_2Cl_2) δ_F: –114.3

(Ar*F*); **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ_C: 41.6 (*C*(2)H_2), 112.6 (d, $^{2}J_{C\text{-}F}$ 23.9, *C*(2'')H), 118.5 (d, $^{4}J_{C\text{-}F}$ 3.9, *C*(6'')H), 127.7 (*C*(5'')H), 128.2 (*C*(4')H), 129.3 (*C*(3',5')H), 129.9 (*C*(2',6')H), 133.2 (*C*(1')), 135.3 (*C*(4'')), 156.1 (d, $^{3}J_{C\text{-}F}$ 10.6, *C*(1'')), 156.6 (d, $^{1}J_{C\text{-}F}$ 265.6, *C*(3'')), 169.4 (*C*(1)=O); **HRMS** (EI$^+$) $C_{14}H_{10}FNO_4$ $[M]^+$ found 275.0588, requires 275.0588. (LNB ref: CM619)

2'-Fluoro-4'-nitrophenyl (2*R*,3*S*)-3-(4'''-fluorophenyl)-2-phenyl-4,4-bis(phenylsulfonyl)butanoate (**301**)

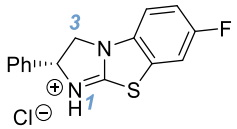


301

Following general procedure C, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (25 mg, 0.09 mmol, 1.5 equiv), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24 mg, 0.06 mmol, 1.0 equiv), (*R*)-F-BTM (3.2 mg, 0.012 mmol, 20 mol%) and CD_2Cl_2 (0.6 mL, 0.10 M) at room temperature for 3 h gave crude product (90:10 dr). Purification by flash column chromatography (50 to 95% CH_2Cl_2 in petrol; R_f 0.37 at 70% CH_2Cl_2 in petrol) gave the title compound (32 mg, 79%, > 95:5 dr) as a colourless solid. **mp** 190-192 °C; $[\alpha]_D^{20}$ −42.0 (*c* 1.0, $CHCl_3$); **HPLC**: [determined by conversion to amide **278** using benzylamine] Chiralpak AD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 31.7 min, t_R (minor): 44.5 min, > 99:1 er; ν_{max} (solid, cm^{-1}) 1759 (C=O), 1531 (C-NO_2), 1508, 1499, 1447, 1352 (SO_2), 1325 (C-NO_2), 1215, 1157, 1143, 1072, 721; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.67 (1H, d, *J* 1.5, C(4)*H*), 4.90 (1H, d, *J* 11.5, C(3)*H*), 5.41 (1H, d, *J* 12.4, C(2)*H*), 6.78 (1H, dd, *J* 9.1, 7.2, C(6')*H*), 7.09 (2H, t, *J* 8.6, C(3''',5''')*H*), 7.21 (2H, d, *J* 7.2, C(2'''',6'''')*H*), 7.24 – 7.32 (4H, m, C(3'''',5'''')*H* and C(3''''',5''''')*H*), 7.41 (2H, d, *J* 7.4, C(2''''',6''''')*H*), 7.46 – 7.55 (5H, m, C(4'''')*H*, C(4''''')*H*, C(3'',5'')*H* and C(4'')*H*), 7.58 (2H, broad-s, C(2'',6'')*H*), 7.82 – 7.97 (4H, m, C(2''',6''')*H*, C(3')*H* and C(5')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −122.7 – −122.3 (m), −113.0 (tt, *J* 8.4, 5.2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 46.0 (*C*(3)H), 55.4 (*C*(2)H), 81.8 (*C*(4)H), 113.0 (d, $^{2}J_{C\text{-}F}$ 23.3, *C*(3')H), 115.4 (d, $^{2}J_{C\text{-}F}$ 21.4, *C*(3''',5''')H), 120.1 (d, $^{4}J_{C\text{-}F}$ 3.6, *C*(5')H), 124.1 (*C*(6')H), 128.4 (*C*(2'''',6'''')H), 128.7

(*C*(2'''',6'''')H), 128.9 (*C*(3'''',5'''')H), 129.3 (*C*(3''',5''')H), 129.5 (*C*(2'',6'')H), 129.6 (d, $^{4}J_{C\text{-}F}$ 3.1, *C*(1''')), 130.0 (*C*(3'',5'')H and *C*(4'')H), 132.9 (d, $^{3}J_{C\text{-}F}$ 8.2, *C*(2''',6''')H), 134.3 (*C*(4''')H and *C*(4'''')H), 134.7 (*C*(1'')), 138.4 (*C*(1''')), 140.3 (*C*(1'''')), 143.1 (d, $^{2}J_{C\text{-}F}$ 13.1, *C*(1')), 146.0 (d, $^{3}J_{C\text{-}F}$ 7.0, *C*(4')), 153.5 (d, $^{1}J_{C\text{-}F}$ 256.4, *C*(2')), 162.9 (d, $^{1}J_{C\text{-}F}$ 248.3, *C*(4''')), 168.8 (*C*(1)=O); **HRMS** (ESI^{+}) $C_{34}H_{25}F_2NNaO_8S_2$ [M+Na]$^{+}$ found 700.0870, requires 700.0882 (−1.7 ppm). Selected data for minor diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 5.29 (1H, d, *J* 10.8), 5.92 (1H, d, *J* 3.1); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −121.9 (t, *J* 8.2), −113.8 – −113.7 (m). (LNB ref: CM627, CM628)

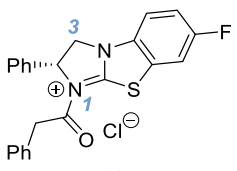
(*R*)-7-Fluoro-2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazol-1-ium chloride (**306**)



306

Following the procedure of Smith and co-workers.[115] 2 M HCl in Et_2O (0.37 mL, 0.74 mmol, 2.0 equiv) was added to (*R*)-F-BTM (100 mg, 0.37 mmol, 1.0 equiv) in Et_2O (5 mL, 0.074 M) at room temperature. The reaction mixture was allowed to stir for 10 mins at room temperature then concentrated in vacuo to give the titled compound (113 mg, quant.) as a colourless solid with spectroscopic data in accordance with the literature.[115] **mp** 130 °C {Lit.[115] 128-130 °C }; **^{1}H NMR** (500 MHz, DMSO) δ_H: 4.38 (1H, dd, *J* 10.6, 8.3, C(3)H^AH^B), 4.96 (1H, t, *J* 10.8, C(2)*H*), 5.95 (1H, dd, *J* 10.8, 8.3, C(3)H^AH^B), 7.36 – 7.51 (4H, m, 4 ArC*H*), 7.54 – 7.64 (3H, m, 3 ArC*H*), 8.00 (1H, dd, *J* 8.7, 2.5, C(8)*H*), 11.24 (1H, broad-s, N*H*); **^{19}F NMR** (471 MHz, DMSO) δ_F: −117.0 – −116.9 (m). (LNB ref: CM666)

(*R*)-7-Fluoro-2-phenyl-1-(2-phenylacetyl)-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazol-1-ium chloride (**307**)

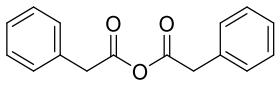


307

Following the procedure of Smith and co-workers.[115] Phenylacetyl chloride (36 μL, 0.28 mmol, 1.1 equiv) was added dropwise to (*R*)-F-BTM (67.6 mg, 0.25 mmol, 1.0

equiv) in CH_2Cl_2 (5 mL, 0.05 M) at room temperature and the reaction was allowed to stir for 10 mins. The reaction mixture was concentrated in vacuo, Et_2O was added and the precipitate filtered and washed with Et_2O to give the titled compound (84 mg, 40%) as a pale-yellow solid with spectroscopic data in accordance with the literature.[115] **mp** 208-210 °C (decomp) {Lit.[115] 221-223 °C}; **^{1}H NMR** (400 MHz, DMSO) δ_H: 3.29 – 3.32 (1H, d, PhC*H*^{A}H^{B}C=O), 4.06 (1H, d, *J* 17.1, PhCH^A*H*^{B}C=O), 4.85 (1H, dd, *J* 11.7, 6.3, C(3)*H*^{A}H^B), 5.42 (1H, app t, *J* 11.2, C(3)H^A*H*^{B}), 6.66 (1H, dd, *J* 10.5, 6.3, C(2)*H*), 6.84 – 7.08 (2H, m, ArC*H*), 7.10 – 7.41 (3H, m, ArC*H*), 7.42 – 7.63 (3H, m, ArC*H*), 7.74 (1H, td, *J* 9.1, 2.7, C(6)*H*), 7.77 – 7.83 (2H, m, ArC*H*), 7.98 (1H, dd, *J* 9.0, 4.4, C(8)*H*), 8.26 (1H, dd, *J* 8.6, 2.6, C(5)*H*); **^{19}F{^{1}H} NMR** (377 MHz, DMSO) δ_F: −113.1 (s). (LNB ref: CM683)

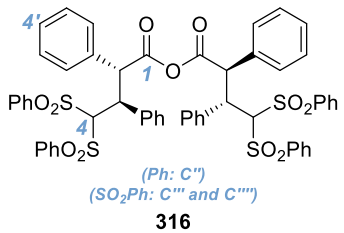
2-Phenylacetic anhydride (**314**)



314

Following the procedure of Smith and co-workers.[113] DCC (4.5 g, 22 mmol, 0.55 equiv) was added to phenylacetic acid (5.4 g, 40 mmol, 1.0 equiv) in PhMe (108 mL, 0.37 M) and stirred at room temperature for 15 mins. The reaction mixture was filtered through celite, concentrated under reduced pressure and recrystallised from Et_2O to give the title compound (5.4 g, 53%) as a white solid with spectroscopic data in accordance with the literature.[113] **mp** 73-74 °C {Lit.[274] 72-72.5 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.72 (4H, s, C(2)H_2), 7.16 – 7.24 (4H, m, ArC*H*), 7.28 – 7.38 (6H, m, ArC*H*). (LNB ref: CM567)

(2*R*,3*S*)-2,3-Diphenyl-4,4-bis(phenylsulfonyl)butanoic anhydride (**316**)

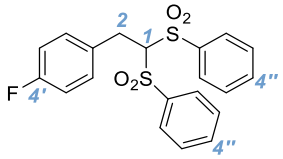


316

2-Phenylacetic anhydride **314** (25.4 mg, 0.1 mmol, 1.0 equiv), (2-phenylethene-1,1-diyldisulfonyl)dibenzene **200** (38.4 mg, 0.1 mmol, 1.0 equiv) and (*R*)-BTM (2.5 mg,

0.01 mmol, 10 mol%) were weighed into a flame dried 4 mL screw top vial. The vial was capped and purged before the addition of CH_2Cl_2 (1 mL, 0.1 M) and the reaction was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure and purified by flash column chromatography (0 to 3% CH_2Cl_2 in Et_2O; R_f 0.21 at 20% CH_2Cl_2 in Et_2O, then 0 to 75% EtOAc in petrol, R_f 0.32 at 70% EtOAc in petrol) to give the title compound (18 mg, 18%) as a colourless solid. **mp** 132 °C; **ν_{max}** (solid, cm^{-1}) 1817 ($C{=}O_{anhydride}$), 1748 ($C{=}O_{anhydride}$), 1497, 1447, 1331 (SO_2), 1153, 1146, 1078, 1036, 683; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.55 (2H, d, *J* 1.3, C(4)*H*), 4.74 (2H, d, *J* 12.3, C(3)*H*), 5.01 (2H, d, *J* 12.3, C(2)*H*), 7.13 (4H, d, *J* 7.5, ArC*H*), 7.18 – 7.24 (10H, m, C(3''',5''')*H*, C(3'''',5'''')*H* and 2 ArC*H*), 7.27 – 7.37 (16H, m, C(3'',5'')*H*, C(4'')*H* and 10 ArC*H*), 7.38 – 7.43 (2H, m, ArC*H*), 7.41 – 7.49 (4H, m, C(4''')*H* and C(4'''')*H*), 7.61 – 7.72 (4H, m, C(2'',6'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 45.8 (*C*(3)H), 56.3 (*C*(2)H), 82.2 (*C*(4)H), 128.3 (ArCH), 128.5 (ArCH), 128.8 (ArCH), 129.1 (ArCH), 129.2 (ArCH), 129.9 (ArCH), 130.7 (*C*(2'',6'')H), 133.6 (*C*(1'')), 134.0 (*C*(4''')H), 134.0 (*C*(4'''')H), 134.2 (*C*(1')), 138.7 (*C*(1'''')), 140.2 (*C*(1''')), 165.4 (*C*(1)=O); **HRMS** (ESI^-) $C_{28}H_{23}O_6S_2$ $[M(carboxylic\ acid)\text{-}H]^-$ found 519.0948, requires 519.0942 (+1.2 ppm). Structure confirmed by X-ray analysis (see Section 7.8). (LNB ref: CM604, CM610)

(2-(4'-Fluorophenyl)ethane-1,1-diyldisulfonyl)dibenzene (**321**)

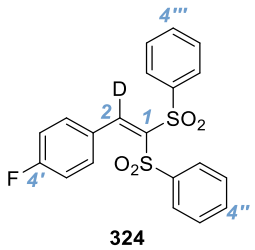


321

Following the procedure of Wang and co-workers.[275] Bis(phenylsulfonyl)methane **216** (593 mg, 2 mmol, 1.0 equiv), potassium carbonate (304 mg, 2.2 mmol, 1.1 equiv), triethylbenzylammonium chloride (91 mg, 0.4 mmol, 20 mol%) and 4-fluorobenzyl bromide (0.3 mL, 454 mg, 2.4 mmol, 1.2 equiv) were combined in MeCN (10 mL, 0.2 M) and the reaction was heated at 70 °C for 25 h. The reaction mixture was allowed to cool to room temperature, filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (0 to 45% EtOAc in petrol; R_f 0.28 at 40% EtOAc in petrol) to give the title compound (503 mg, 62%) as a

colourless solid. **mp** 148-150 °C; **ν_{max}** (solid, cm^{-1}) 1510 (ArC=C), 1447, 1314 (SO_2), 1227, 1157 (SO_2), 1146, 1082, 744, 685; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.51 (2H, d, *J* 5.5, C(2)H_2), 4.67 (1H, t, *J* 5.5, C(1)*H*), 6.88 (2H, t, *J* 8.6, C(3',5')*H*), 7.01 (2H, dd, *J* 8.6, 5.3, C(2',6')*H*), 7.54 (4H, t, *J* 7.9, C(3'',5'')*H*), 7.68 (2H, t, *J* 7.5, C(4'')*H*), 7.86 (4 H, dd, *J* 8.4, 1.1, C(2'',6'')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −115.2 – −114.8 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 30.7 (*C*(2)H_2), 85.4 (*C*(1)H), 115.7 (d, $^2J_{C\text{-}F}$ 21.5, *C*(3',5')H), 129.3 (*C*(3'',5'')H), 129.6 (*C*(2'',6'')H), 130.5 (d, $^3J_{C\text{-}F}$ 8.1, *C*(2',6')H), 132.1 (d, $^4J_{C\text{-}F}$ 3.2, *C*(1')), 134.8 (*C*(4'')H), 138.1 (*C*(1'')), 162.0 (d, $^1J_{C\text{-}F}$ 246.3, *C*(4')); **HRMS** (ESI^+) $C_{20}H_{17}FNaO_4S_2$ $[M+Na]^+$ found 427.0436, requires 427.0444 (−1.9 ppm). (LNB ref: CM714)

(2-(4'-Fluorophenyl)ethene-1,1-diyldisulfonyl-2-d)dibenzene (**324**)

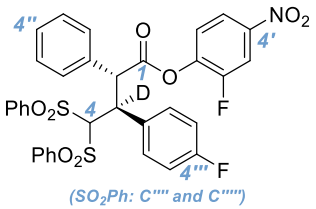


324

1-Bromo-4-fluorobenzene (3.8 mL, 35 mmol, 1.0 equiv) in THF (200 mL, 0.175 M) was cooled to −78 °C and 2.5 M solution of *n*-BuLi in hexane (15.4 mL, 38.5 mmol, 1.1 equiv) was added dropwise and allowed to stir at −78 °C for 30 min. d_7-Dimethylformamide (3 mL, 38.5 mmol, 1.1 equiv) was added and the reaction was stirred at −78 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl (150 mL) and conc. H_2SO_4 (3 drops) and allowed to warm to room temperature. The reaction mixture was extracted with Et_2O (3 × 150 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure (> 100 mbar). The crude product was purified by column chromatography (0 to 30% Et_2O in petrol; R_f 0.27 at 20% Et_2O in petrol) to give *α*-deuterio-4-fluoro-benzaldehyde [D1] **323** (3.59 g, 82%) as a clear liquid with spectroscopic data in accordance with the literature.[105] **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 7.22 (2H, t, *J* 8.6, C(3,5)*H*), 7.82 – 7.96 (2H, m, C(2,6)*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −102.3 (tt, *J* 8.2, 5.4). *α*-Deuterio-4-fluoro-benzaldhyde [D1] (3.88 g, 31 mmol, 3.1 equiv), (bis(phenylsulfonyl)methane **216** (2.96 g, 10 mmol, 1.0 equiv), diethylammonium chloride (2.1 g, 19 mmol, 1.9 equiv) and potassium fluoride (87 mg, 1.5 mmol, 0.15 equiv) were combined and PhMe (81 mL, 0.12 M) was

added. The reaction was heated at reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled and concentrated under reduced pressure, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 40% EtOAc in petrol; R_f 0.40 at 40% EtOAc in petrol) which precipitated following purification. The solid was filtered and washed with petrol to give the title compound (1.13 g, 80%) as a colourless solid**. mp** 150-152 °C; **ν_{max}** (solid, cm^{-1}) 1603 (C=C), 1562 (ArC=C), 1502 (ArC=C), 1447, 1306 (SO_2), 1236, 1144, 1084, 756, 687; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 7.07 (2H, t, *J* 8.6, C(3',5')*H*), 7.35 (2H, t, *J* 7.9, C(3''',5''')*H*), 7.52 (1H, t, *J* 7.5, C(4''')*H*), 7.59 (2H, t, *J* 7.8, C(3'',5'')*H*), 7.61 – 7.66 (4H, m, C(2',6')*H* and C(2''',6''')*H*), 7.69 (1H, t, *J* 7.5, C(4'')*H*), 8.03 (2H, dd, *J* 8.5, 1.1, C(2'',6'')*H*); **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ_F: −106.2 (s); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 115.8 (d, $^2J_{C\text{-}F}$ 21.9, *C*(3',5')H), 126.5 (d, $^4J_{C\text{-}F}$ 3.2, *C*(1')), 128.0 (*C*(2''',6''')H), 128.9 (*C*(3''',5''')H), 129.0 (*C*(2'',6'')H), 129.2 (*C*(3'',5'')H), 133.7 (d, $^3J_{C\text{-}F}$ 9.0, *C*(2',6')H), 134.1 (*C*(4'')H), 134.2 (*C*(4''')H), 139.9 (*C*(1'')), 140.3 (*C*(1''')), 143.8 (*C*(1)), 150.3 (t, $^1J_{C\text{-}D}$ 24.2 *C*(2)-D), 164.7 (d, $^1J_{C\text{-}F}$ 255.0, C(4')); **HRMS** (ESI$^+$) $C_{20}H_{15}DFO_4S_2$ $[M+H]^+$ found 404.0524, requires 404.0531 (−1.7 ppm). (LNB ref: CM672)

2'-Fluoro-4'-nitrophenyl (2*R*,3*S*)-3-(4'''-fluorophenyl)-2-phenyl-4,4-bis(phenylsulfonyl)butanoate-3-d (**325**)



325

Following general procedure C, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (83 mg, 0.3 mmol, 1.5 equiv), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl-2-d)dibenzene **324** (81 mg, 0.2 mmol, 1.0 equiv), (*R*)-F-BTM (10.8 mg, 0.04 mmol, 20 mol%) and CD_2Cl_2 (0.6 mL, 0.33 M) at room temperature for 5 h gave crude product (88:12 dr). Purification by flash column chromatography (50 to 95% CH_2Cl_2 in petrol; R_f 0.37 at 70% CH_2Cl_2 in petrol) gave the title compound (69 mg, 51%, > 95:5 dr) as a

colourless solid. **mp** 186-188 °C; $[\alpha]_D^{20}$ −39.8 (*c* 1.0, $CHCl_3$); ν_{max} (solid, cm^{-1}) 1763 (C=O), 1531 (C-NO_2), 1510, 1354 (SO_2), 1327, 1265, 1229, 1157, 1113, 1078, 910, 723; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.67 (1H, s, C(4)*H*), 5.40 (1H, s, C(2)*H*), 6.78 (1H, dd, *J* 9.1, 7.2, C(6')*H*), 7.09 (2H, t, *J* 8.7, C(3''',5''')*H*), 7.21 (2H, dd, *J* 8.4, 1.1, C(2'''',6'''')*H*), 7.24 – 7.30 (4H, m, C(3'''',5'''')*H* and C(3'''',5'''')*H*), 7.41 (2H, dd, *J* 8.4, 1.0, C(2''',6''')*H*), 7.46 – 7.53 (5H, m, C(3'',5'')*H*, C(4'')*H*, C(4''')*H* and C(4'''')*H*), 7.59 (2H, broad-s, C(2'',6'')*H*), 7.88 (2H, dd, *J* 8.7, 5.2, C(2''',6''')*H*), 7.90 – 7.95 (2H, m, C(3')*H* and C(5')*H*); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −122.7 – −122.3 (m), −113.3 – −112.6 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 45.7 (t, $^1J_{C\text{-}D}$ 18.4, *C*(3)D), 55.3 (*C*(2)H), 81.7 (*C*(4)H), 113.0 (d, $^2J_{C\text{-}F}$ 23.3, *C*(3')H), 115.4 (d, $^2J_{C\text{-}F}$ 21.4, *C*(3''',5''')H), 120.1 (d, $^4J_{C\text{-}F}$ 3.6, *C*(5')H), 124.1 (*C*(6')H), 128.4 (*C*(2'''',6'''')H), 128.7 (*C*(2''',6''')H), 128.9 (*C*(3''',5''')H or *C*(3'''',5'''')H), 129.3 (*C*(3''',5''')H or *C*(3'''',5'''')H), 129.5 (*C*(2'',6'')H and *C*(4'')H), 129.6 (*C*(1''')), 130.0 (*C*(3'',5'')H), 132.9 (d, $^3J_{C\text{-}F}$ 8.2, *C*(2''',6''')H), 134.3 (*C*(4''')H and *C*(4'''')H), 134.7 (*C*(1'')), 138.4 (*C*(1'''')), 140.2 (*C*(1''')), 143.1 (d, $^2J_{C\text{-}F}$ 13.0, *C*(1')), 146.0 (d, $^3J_{C\text{-}F}$ 7.1, *C*(4')), 153.5 (d, $^1J_{C\text{-}F}$ 256.4, *C*(2')), 162.9 (d, $^1J_{C\text{-}F}$ 248.3, *C*(4''')), 168.8 (*C*(1)=O); **HRMS** (ESI^+) $C_{34}H_{24}DF_2NNaO_8S_2$ $[M+Na]^+$ found 701.0927, requires 701.0945 (−2.6 ppm). (LNB ref: CM723)

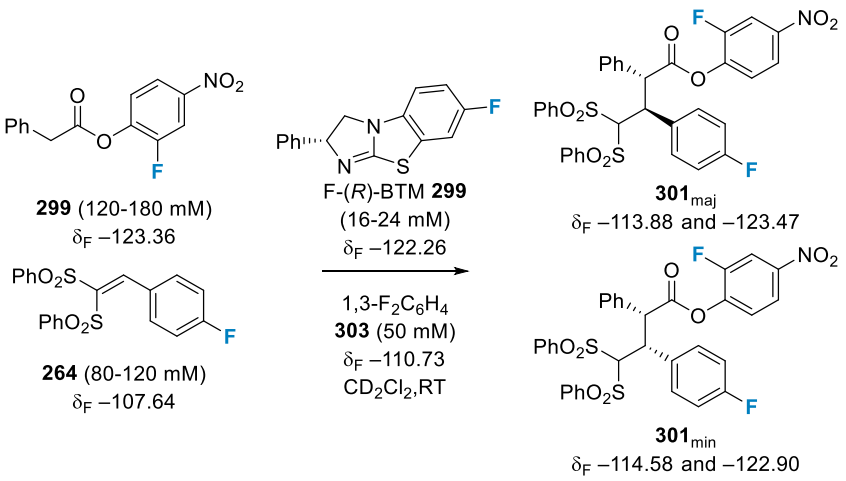
7.5.2. Quantitative Reaction Monitoring by ^{19}F{^{1}H} NMR

<u>General considerations</u>

The following stock solutions were prepared at the start of the day of the experiment: 0.9 M 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (495.4 mg, 1.8 mmol in 2 mL CD_2Cl_2), 0.3 M (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (241.5 mg, 0.6 mmol in 2 mL CD_2Cl_2), 0.12 M (*R*)-F-BTM (64.9 mg, 0.24 mmol in 2 mL CD_2Cl_2) and 0.3 M 1,3-difluorobenzene (59 μL, 0.6 mmol in 2 mL CD_2Cl_2). The reagents were added to the NMR tube using a 100 μL Hamilton Gastight microsyringe. Experiments were collected at 470 MHz and implemented using Bruker Topsin software. NMR experiment parameters: ^{19}F{^{1}H} spectra, 80 ppm sweep width (−90 to −170 ppm), number scans (ns) = 2, spectral centre (o1p) = −130 ppm, dummy scans (ds) = 2, d1 relaxation delay = 30 s. Data was processed using MestReNova software. The spectra were phase and baseline corrected in MestReNova. The time of each

measurement is the timestamp taken from the Bruker software plus the time between the addition of the catalyst and the first spectra measurement finishing. Each spectrum was processed manually. The internal standard (1,3-difluorobenzene **303**) was referenced to −110.730 ppm and integrated as 1000. The same integral range was used throughout for each species: 1,3-difluorobenzene (−110.7 to −110.763 ppm), vinyl bis-sulfone **264** (−107.60 to −107.683 ppm), ester **299** (−123.33 to −123.397 ppm), product major diastereoisomer **301**$_{maj}$ (−113.842 to −113.919 ppm) and product minor diastereoisomer **301**$_{min}$ (−114.547 to −114.605 ppm). No integral range was set for the catalyst as this peak shifted downfield over the course of the reaction. Raw concentration and processed data (using equation 4) for the reactions can be found in the supplementary data file attached with this thesis, or in the published article.[276]

General Procedure



Using the stock solutions, 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (19.8 – 29.7 mg, 0.072 – 0.0108 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (19.3 - 29.0 mg, 0.048 - 0.072 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), and CD_2Cl_2 (0.6 mL) were added to an oven dried NMR tube, which was loaded into an NMR spectrometer at room temperature. The sample was locked to CD_2Cl_2, shimmed and an initial $^{19}F\{^1H\}$ spectrum acquired. The sample was removed from the spectrometer and (*R*)-F-BTM (2.6 – 3.9 mg, 0.0096 - 0.014 mmol) was added to start the reaction and this time was noted. The sample was returned to the NMR spectrometer, locked to CD_2Cl_2 and shimmed before the kinetics loop was initiated: 15 measurements (one every 3 mins) then 15 measurements (one every 10 mins).

7.5.3. Variable Time Normalisation Analysis (VTNA)

Standard reaction conditions: 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM and 50 mM 1,3-difluorobenzene internal standard **303**.

Three additional reactions were carried where one of the components was increased in concentration (120%), and three further reactions where one of the components was decreased in concentration (80%).

Entry 1 (standard conditions): 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Entry 2: 180 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (29.7 mg, 0.108 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Entry 3: 150 mM ester **299**, 120 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (29.0 mg, 0.072 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Entry 4: 150 mM ester **299**, 100 mM sulfone **264**, 24 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (3.9 mg, 0.036 mmol).

Entry 5: 120 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (19.8 mg, 0.072 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Entry 6: 150 mM ester **299**, 80 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-

1,1-diyldisulfonyl)dibenzene **264** (19.3 mg, 0.048 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

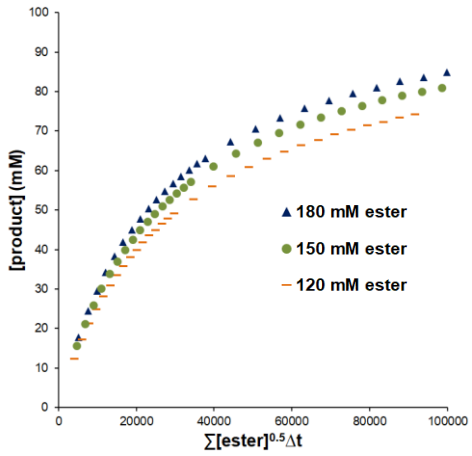
Entry 7: 150 mM ester **299**, 100 mM sulfone **264**, 16 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL and (*R*)-F-BTM (2.6 mg, 0.0096 mmol).

Normalised time axis plots

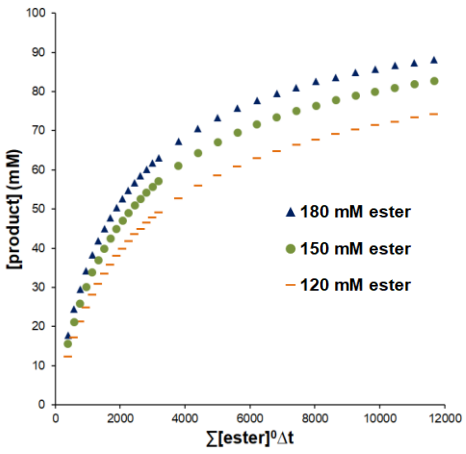
Visual analysis of the data was carried out by varying α, β and γ between 0 and 2 for each component.

Ester **299**

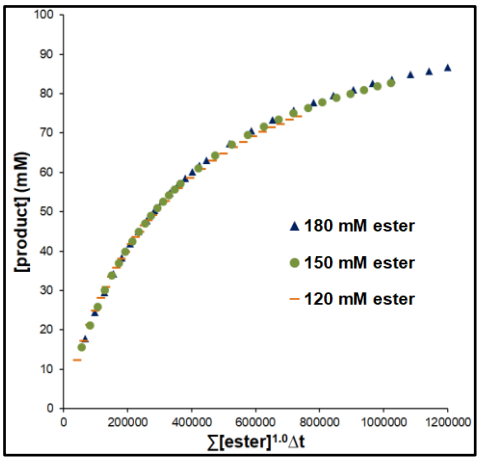
$\alpha = 0$



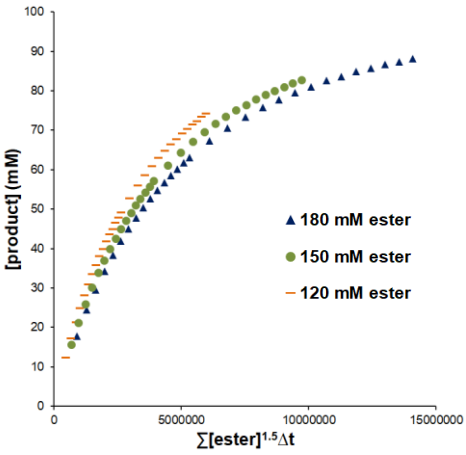
$\alpha = 0.5$



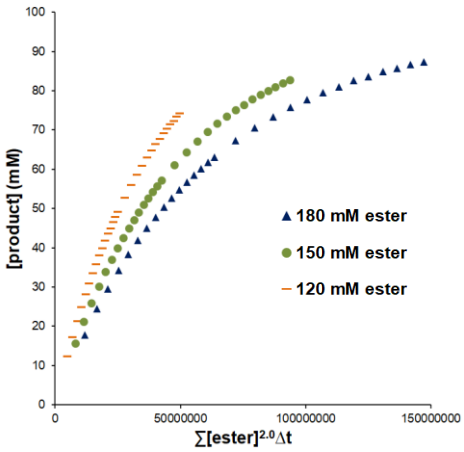
$\alpha = 1$



$\alpha = 1.5$

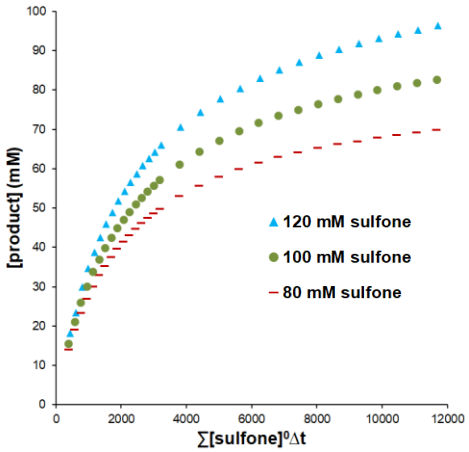


$\alpha = 2$

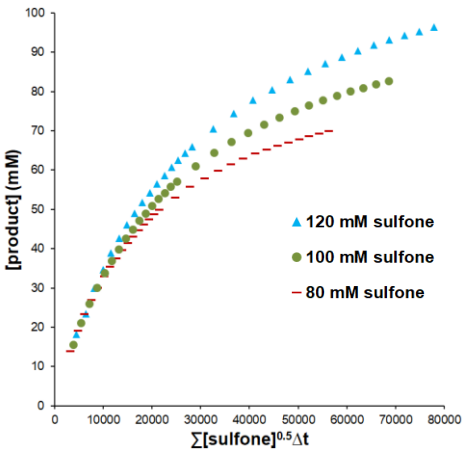


Vinyl bis-sulfone **264**

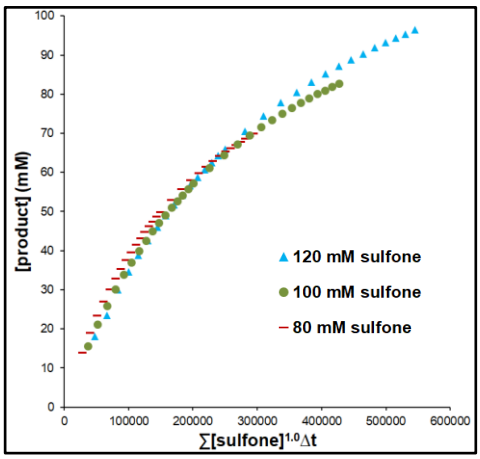
β = 0



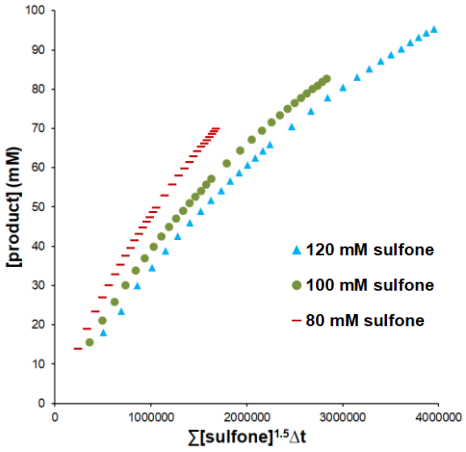
β = 0.5



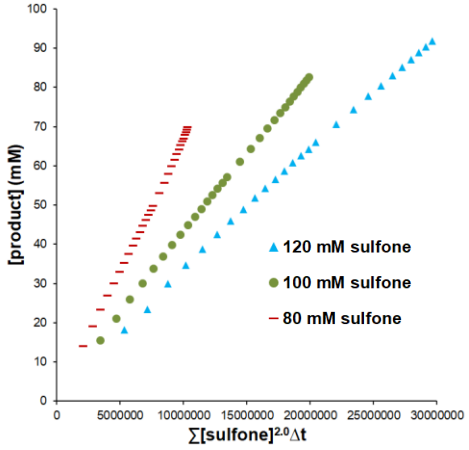
β = 1



β = 1.5

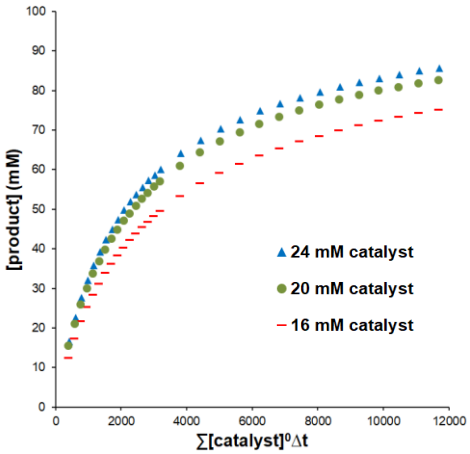


β = 2

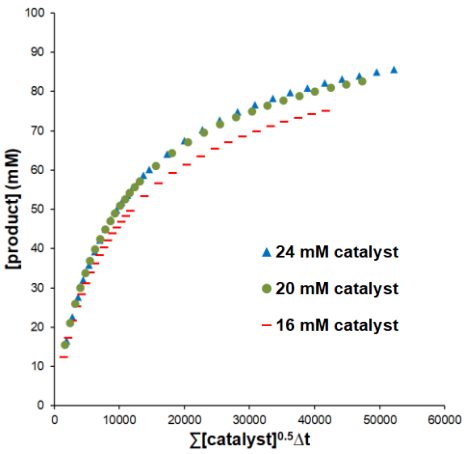


(*R*)-F-BTM **296**

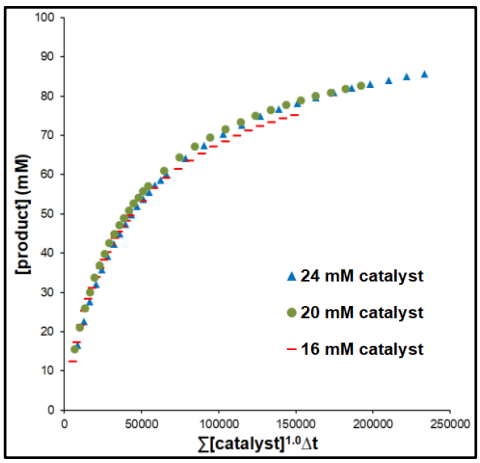
$\gamma = 0$



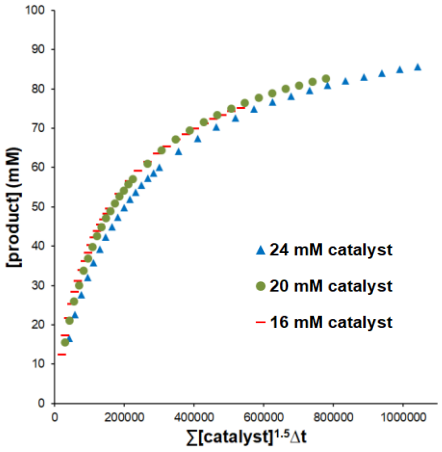
$\gamma = 0.5$



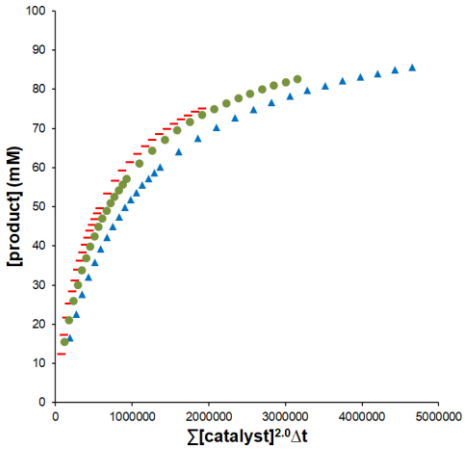
$\gamma = 1$



$\gamma = 1.5$

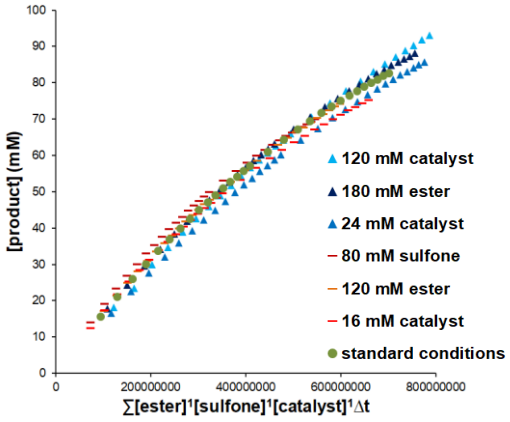


$\gamma = 2$



Overlayed spectra

$\alpha = 1$, $\beta = 1$, and $\gamma = 1$



7.5.4. Product Inhibition

Additive = product

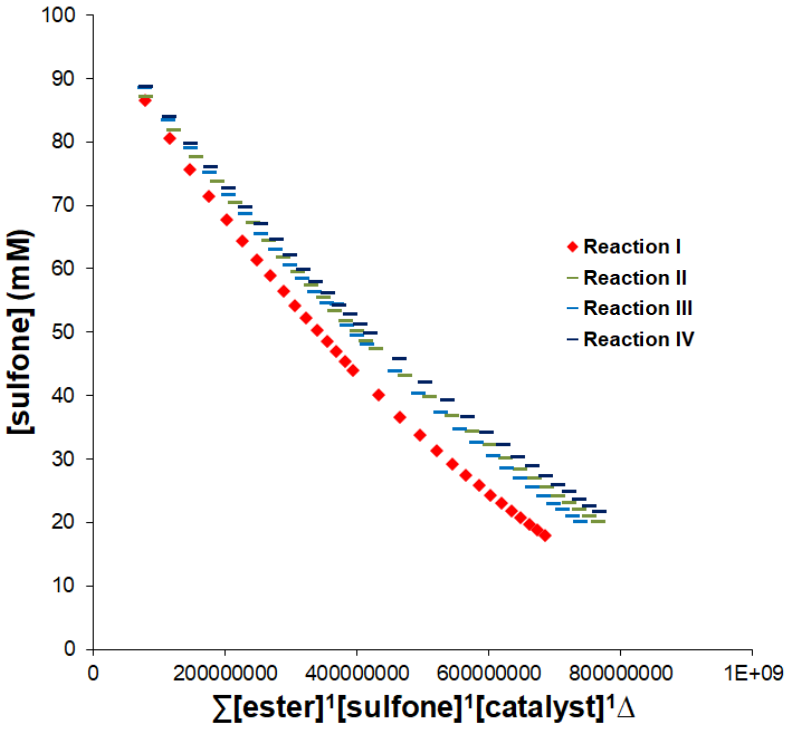
Standard reaction conditions: 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM and 50 mM 1,3-difluorobenzene **303** internal standard.

Reaction I (standard conditions): 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

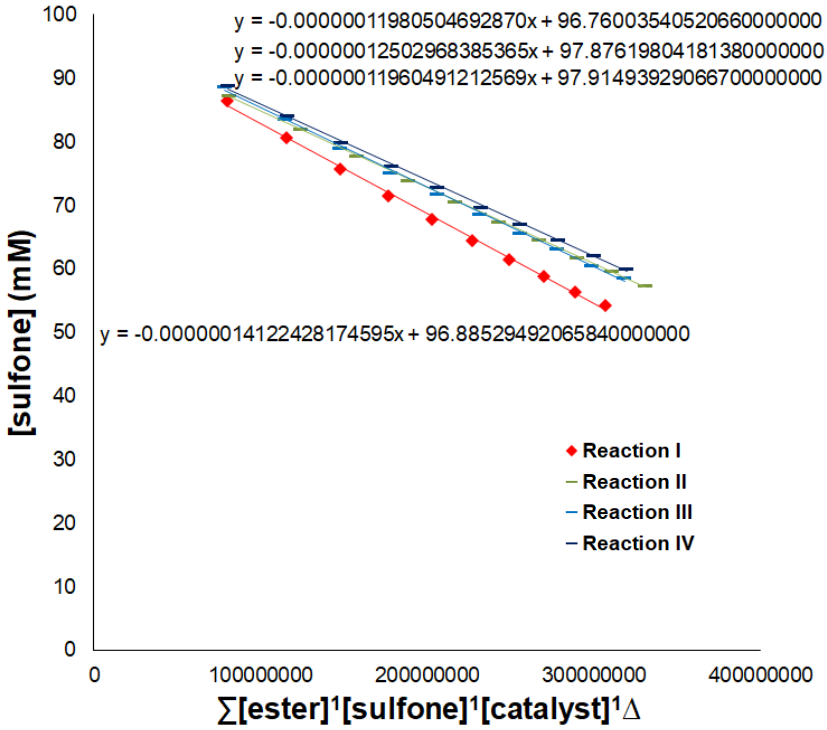
Reaction II, III, IV: 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, 20 mM product **301** using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), product **301** (8.1 mg, 0.012 mmol) CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Normalised time axis plots

$\alpha = 1$, $\beta = 1$, and $\gamma = 1$



Taking the first ten values and finding k_{obs} from the gradient of the line:



Reaction	k_{obs}	Reaction	k_{obs}
II	$1.198050469287 \times 10^{-7}$	I	$1.4122428174595 \times 10^{-7}$
III	$1.2502968385365 \times 10^{-7}$		
IV	$1.1960491212569 \times 10^{-7}$		
Average II-IV	$1.21479880969347 \times 10^{-7}$		

k_{obs} (II-IV) / k_{obs} (I) = 0.86

Therefore, reactions II-IV containing product have approximately k_{obs} 0.86 magnitude of k_{obs} of the standard reaction.

Additive = probe **321**

Reaction V (standard conditions): 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM

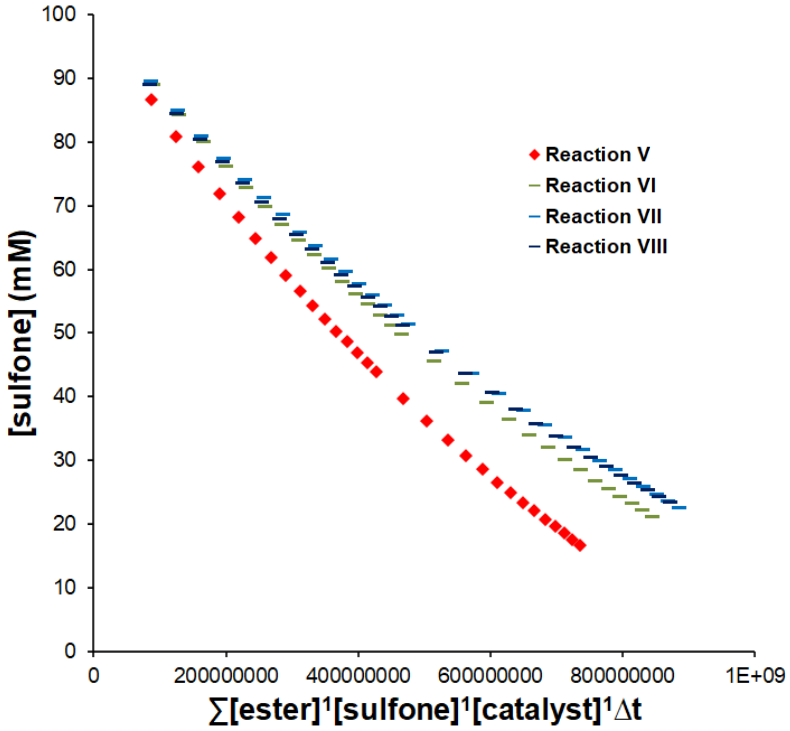
Reaction VI: 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, 20 mM probe **321**

Reaction VII: 150 mM ester **299**, 100 mM sulfone **264**, 20 mM (*R*)-F-BTM, 20 mM probe **321**

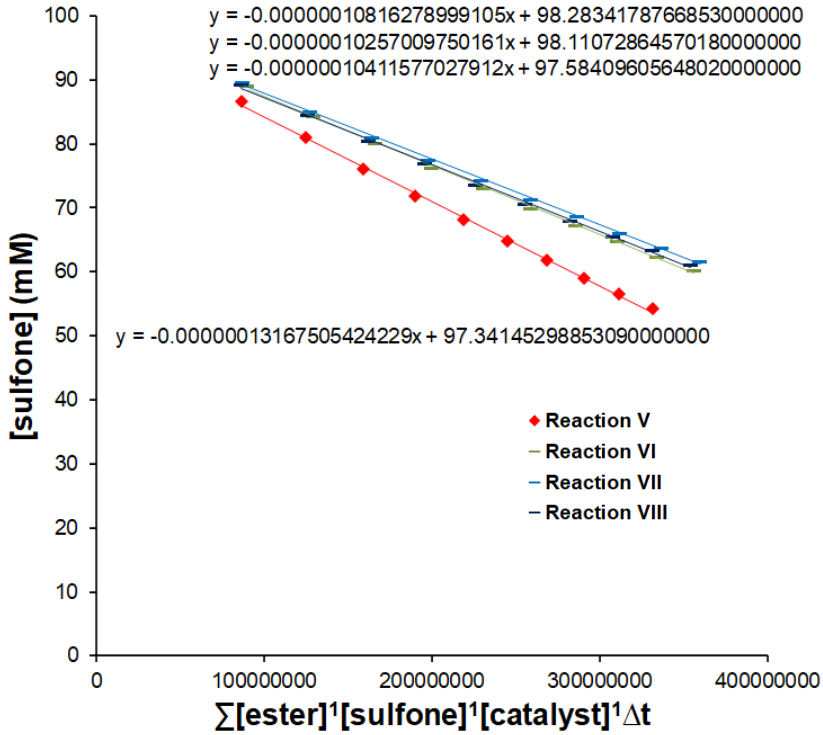
Reaction VIII: 150 mM ester **299**, 100 mM electrophile **264**, 20 mM (*R*)-F-BTM, 20 mM probe **321**, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.1 mg, 0.06 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), probe **321** (4.8 mg, 0.012 mmol) CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Normalised time axis plots

$\alpha = 1$, $\beta = 1$, and $\gamma = 1$



Taking the first ten values and finding k_{obs} from the gradient of the line:



Reaction	k_{Obs}	Reaction	k_{Obs}
VI	$1.0816278999105 \times 10^{-7}$	V	$1.3167505424229 \times 10^{-7}$
VII	$1.0257009750161 \times 10^{-7}$		
VIII	$1.0411577027912 \times 10^{-7}$		
Average VI-VIII	$1.04949552590593 \times 10^{-7}$		

k_{Obs} (VI-VIII) / k_{Obs} (V) = 0.80

Therefore, reactions V-VIII containing have approximately k_{obs} 0.80 magnitude of k_{obs} of the standard reaction.

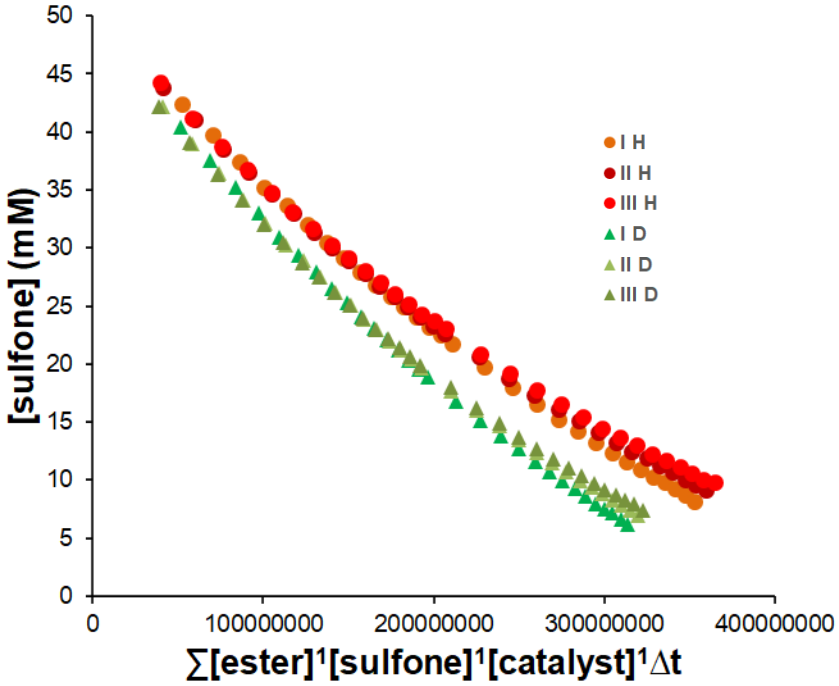
7.5.5. Isotope Experiment by Competition

The following stock solutions were prepared at the start of the day of the experiment: 0.3 M (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl-2-d)dibenzene **324** (242.1 mg, 0.6 mmol in 2 mL CD_2Cl_2). The same integral range was used throughout for C(2)-D **70** (−107.475 to −107.552 ppm). The δ_F difference between C(2)-H **264** and C(2)-D **324** allowed the consumption of each starting material to be followed. The KIE experiment was carried out in triplicate and the results averaged.

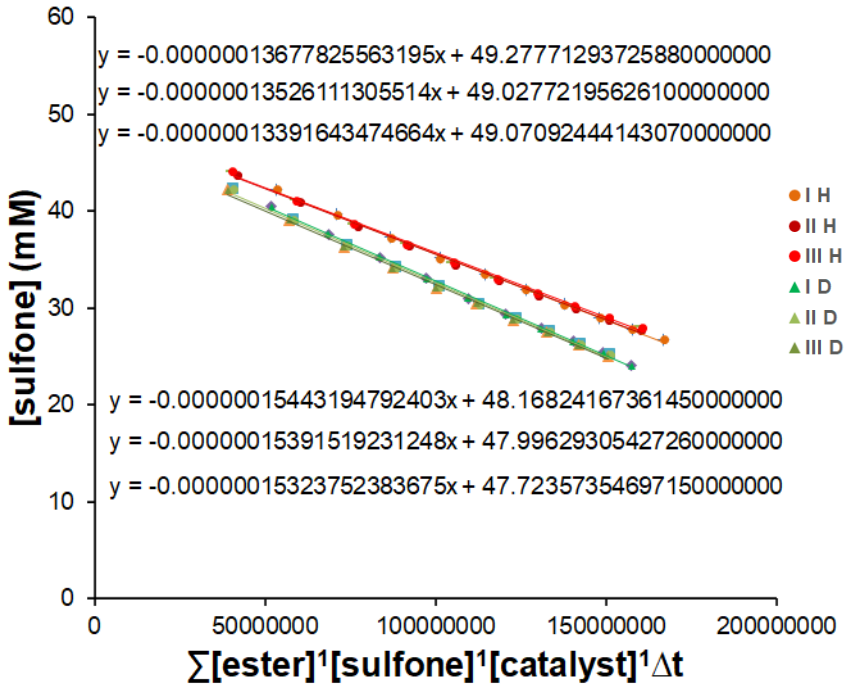
Reaction I,II,III: 150 mM ester **299**, 50 mM C(2)-H electrophile **264**, 50 mM C(2)-D electrophile **324**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (12.1 mg, 0.03 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl-2-d)dibenzene **324** (12.1 mg, 0.03 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Normalised time axis plots

$\alpha = 1$, $\beta = 1$, and $\gamma = 1$



Taking the first ten values and finding k_{obs} from the gradient of the line:



Reaction	k_H	k_D	k_H/k_D
I	1.3677825563195x10^{-7}	1.5443194792403 x10^{-7}	0.885686268098072
II	1.3526111305514E-07	1.5391519231248E-07	0.878802872042233
III	1.3391643474664E-07	1.5323752383675E-07	0.87391411316008
			0.88

k_H / k_D = 0.88

7.5.6. Isotope Experiment by Parallel Reactions

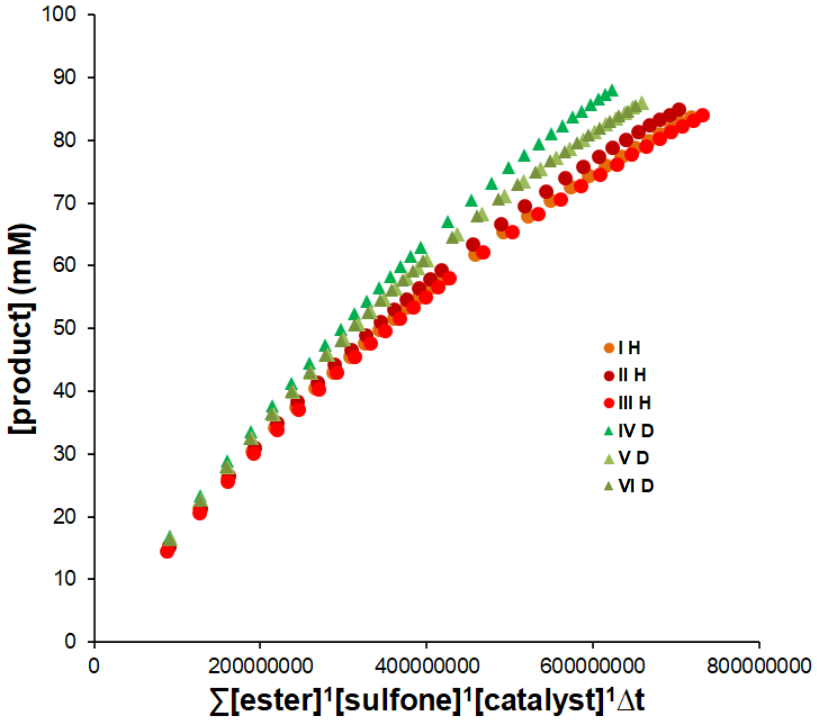
The KIE experiment was carried out in triplicate and the results averaged.

Reaction I,II,III: 150 mM ester **299**, 100 mM C(2)-H electrophile **264**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl)dibenzene **264** (24.2 mg, 0.03 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

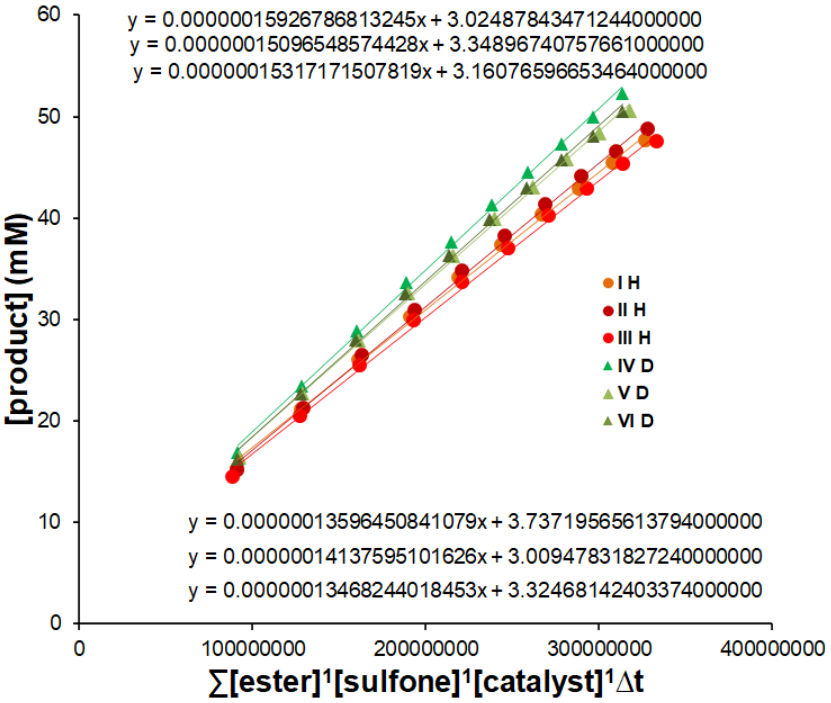
Reaction IV,V,VI: 150 mM ester **299**, 100 mM C(2)-D electrophile **324**, 20 mM (*R*)-F-BTM, using 2-fluoro-4-nitrophenyl 2-phenylacetate **299** (24.8 mg, 0.09 mmol), (2-(4-fluorophenyl)ethene-1,1-diyldisulfonyl-2-d)dibenzene **324** (24.2 mg, 0.03 mmol), 1,3-difluorobenzene **303** (2.9 μL, 0.03 mmol), CD_2Cl_2 (0.6 mL) and (*R*)-F-BTM (3.2 mg, 0.012 mmol).

Normalised time axis plots

$\alpha = 1$, $\beta = 1$, and $\gamma = 1$



Taking the first ten values and finding k_{obs} from the gradient of the line:



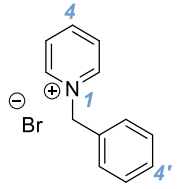
Reaction	k_H	Reaction	k_D
I	$1.3596450841079 \times 10^{-7}$	IV	$1.5926786813245 \times 10^{-7}$
II	$1.4137595101626 \times 10^{-7}$	V	$1.5096548574428 \times 10^{-7}$
III	$1.3468244018453 \times 10^{-7}$	VI	$1.5317171507819 \times 10^{-7}$
Average	$1.37340966537193 \times 10^{-7}$	Average	$1.54468356318307 \times 10^{-7}$
k_H/k_D	0.8891 = 0.89		

7.6. Experimental for Chapter 4

Tables 16, 17, 18, 19, 20, and Schemes 65, 66, 67 were carried out according to general procedure F.

7.6.1. Pyridinium Salt Synthesis

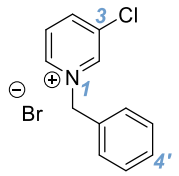
1-Benzylpyridin-1-ium bromide (**360**)



360

Benzyl bromide (2.2 mL, 18.3 mmol, 1.0 equiv) was slowly added to pyridine (1.5 mL, 18.7 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL, 6.1 M) and the reaction was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo to give the title compound (2.19 g, 48%) as a cream solid with spectroscopic data in accordance with the literature.[277] **mp** 66-70 °C {Lit.[278] 66-70 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.34 (2H, s, C*H*$_2$), 7.33 – 7.42 (3H, m, C(3',5')*H* and C(4')*H*), 7.63 – 7.72 (2H, m, C(2',6')*H*), 8.02 (2H, t, *J* 7.2, C(3,5)*H*), 8.41 (1H, tt, *J* 7.9, 1.3, C(4)*H*), 9.59 (2H, d, *J* 5.5, C(2,6)*H*). (LNB ref: CM280)

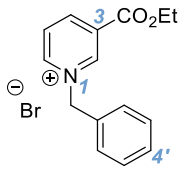
1-Benzyl-3-chloropyridin-1-ium bromide (**361**)



361

Following general procedure E, using benzyl bromide (1.1 mL, 9 mmol, 1.5 equiv), 3-chloropyridine (0.6 mL, 6 mmol, 1.0 equiv) and MeCN (12 mL, 0.5 M) for 18 h gave, the title compound (1.48 g, 87%) as a beige solid. **mp** 126-130 °C; **ν_{max}** (solid): 3003 (C-H), 2930 (C-H), 1620, 1491, 1452, 1206, 1187, 741, 714, 671; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.44 (2H, s, CH_2), 7.29 – 7.42 (3H, m, C(3',5')*H* and C(4')*H*), 7.76 (2H, dd, *J* 6.7, 2.9, C(2',6')*H*), 8.09 (1H, dd, *J* 8.4, 6.1, C(5)*H*), 8.38 (1H, ddd, *J* 8.4, 1.8, 1.1, C(4)*H*), 9.58 – 9.92 (2H, m, C(2)*H* and C(6)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 64.2 (*C*H_2), 129.0 (*C*(5)H), 129.8 (*C*(3',5')H), 130.0 (*C*(2',6')H), 130.3 (*C*(4')H), 132.6 (*C*(1')), 135.8 (*C*(3)), 143.9 (*C*(2)H or *C*(6)H), 144.0 (*C*(2)H or *C*(6)H), 145.2 (*C*(4)H); **HRMS** (ESI$^+$) $C_{12}H_{11}ClN$ $[M-Br]^+$ found 204.0571, requires 204.0575 (−2.0 ppm). (LNB ref: CM307)

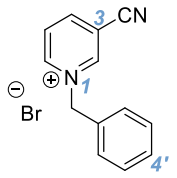
1-Benzyl-3-(ethoxycarbonyl)pyridin-1-ium bromide (**362**)



362

Following general procedure E, using benzyl bromide (2.7 mL, 22.5 mmol, 1.5 equiv), ethyl nicotinate (2.0 mL, 5 mmol, 1.0 equiv) and MeCN (30 mL, 0.5 M) for 18 h. Upon completion, the reaction mixture was concentrated in vacuo to give the title compound (4.80 g, quant.) as a beige solid with spectroscopic data in accordance with the literature.[279] **mp** 140-144 °C {no Lit. mp}; **^{1}H NMR** (400 MHz, acetone) δ_H: 1.41 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 4.48 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.49 (2H, s, CH_2), 7.21 – 7.64 (3H, m, C(3',5')*H* and C(4')*H*), 7.87 (2H, dd, *J* 6.7, 3.0, C(2',6')*H*), 8.42 (1H, dd, *J* 7.8, 6.4, C(5)*H*), 9.12 (1H, app dt, *J* 8.1, 1.5, C(4)*H*), 10.01 (1H, s, C(2)*H*), 10.09 (1H, app dt, *J* 6.2, 1.2, C(6)*H*). (LNB ref: CM295, CM409)

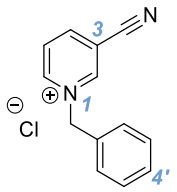
1-Benzyl-3-cyanopyridin-1-ium bromide (**363**)



363

Following general procedure E, using benzyl bromide (5.0 mL, 42 mmol, 1.5 equiv), 3-pyridine carbonitrile (2.9 g, 28 mmol, 1.0 equiv) and MeCN (56 mL, 0.5 M) for 18 h gave the title compound (6.10 g, 79%) as a beige solid with spectroscopic data in accordance with the literature.[280] **mp** 144-148 °C {Lit.[280] 151-153 °C}; **^{1}H NMR** (500 MHz, D_2O) δ_H: 5.91 (2H, s, CH_2), 7.38 – 7.60 (5H, m, C(2',6')*H*, C(3',5')*H* and C(4')*H*), 8.26 (1H, app t, *J* 14.4, C(5)*H*), 8.93 (1H, d, *J* 8.2, C(4)*H*), 9.21 (1H, d, *J* 6.3, C(6)*H*), 9.46 (1H, s, C(2)*H*). (LNB ref: CM293, CM316, CM388)

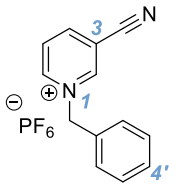
1-Benzyl-3-cyanopyridin-1-ium chloride (**368**)



368

1-Benzylpyridin-1-ium bromide **363** (138 mg, 0.5 mmol, 1.0 equiv) and potassium chloride (37 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL. 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (115 mg, quant.) as a beige solid. **mp** 130-132 °C; **ν_{max}** (solid): 2992 (C-H), 2918 (C-H), 1632, 1493, 1470, 1443, 1206, 1142, 721, 675; **^{1}H NMR** (500 MHz, DMSO) δ_H: 5.94 (2H, s, CH_2), 7.19 – 7.50 (3H, m, C(3',5')*H* and C(4')*H*), 7.62 (2H, dd, *J* 7.3, 2.1, C(2',6')*H*), 8.38 (1H, dd, *J* 7.9, 6.4, C(5)*H*), 9.13 (1H, app dt, *J* 8.0, 1.2, C(4)*H*), 9.48 (1H, d, *J* 6.3, C(6)*H*), 10.06 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 63.9 (*C*H_2), 113.3 (*C*(3)), 113.9 (C(3)*C*N), 128.9 (*C*(5)H), 129.2 (*C*(2',6')H), 129.3 (*C*(3',5')H), 129.6 (*C*(4')H), 133.4 (*C*(1)), 148.1 (*C*(6)H), 149.0 (*C*(4)H or *C*(6)H), 149.1 (*C*(4)H or *C*(6)H); **HRMS** (ESI$^+$) $C_{13}H_{11}N_2$ $[M-Cl]^+$ found 195.0914, requires 195.0917 (−1.5 ppm). (LNB ref: CM387)

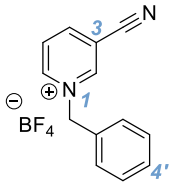
1-Benzyl-3-cyanopyridin-1-ium hexafluorophosphate(V) (**369**)



369

1-Benzylpyridin-1-ium bromide **363** (138 mg, 0.5 mmol, 1.0 equiv) and potassium hexafluorophosphate (92 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL. 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (170 mg, quant.) as a peach solid. **mp** 118-120 °C; **ν_{max}** (solid): 1502, 1495, 1458, 1447, 1200, 1140, 825 (P-F); **^{1}H NMR** (500 MHz, DMSO) δ_H: 5.87 (2H, s, CH_2), 7.35 – 7.52 (3H, m, C(3',5')*H* and C(4')*H*), 7.58 (2H, dd, *J* 7.4, 2.0, C(2',6')*H*), 8.36 (1H, dd, *J* 8.0, 6.4, C(5)*H*), 9.11 (1H, app dt, *J* 8.1, 1.3, C(4)*H*), 9.39 (1H, d, *J* 6.3, C(6)*H*), 9.97 (1H, s, C(2)*H*); **^{19}F{^{1}H} NMR** (470 MHz, DMSO) δ_F: -70.1 (d, *J* 711.3); **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 64.2 (*C*H_2), 113.4 (*C*(3)), 113.9 (C(3)*C*N), 128.9 (*C*(5)H), 129.2 (*C*(2',6')H), 129.2 (*C*(3',5')H), 129.7 (*C*(4')H), 133.4 (*C*(1')), 148.1 (*C*(6)H), 149.0 (*C*(2)H), 149.2 (*C*(4)H); **^{31}P{^{1}H} NMR** (202 MHz, DMSO) δ_P: -144.2 (sept, *J* 711.3); **HRMS** (ESI$^+$) $C_{13}H_{11}N_2$ $[M-PF_6]^+$ found 195.0912, requires 195.0917 (−2.6 ppm). (LNB ref: CM385)

1-Benzyl-3-cyanopyridin-1-ium tetrafluoroborate (**370**)

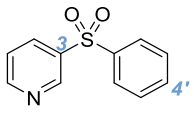


370

1-Benzylpyridin-1-ium bromide **363** (138 mg, 0.5 mmol, 1.0 equiv) and sodium tetrafluoroborate (55 mg, 0.5 mmol, 1.0 equiv) were combined in MeCN (5 mL. 0.1 M) and the reaction was stirred at room temperature for 72 h. The reaction mixture was filtered, washing with MeCN, and concentrated in vacuo to give the title compound (127 mg, 90%) as a white gum. **ν_{max}** (film): 3088 (ArC-H), 1634, 1497 (ArC=C), 1456, 1206, 1024, 723, 675; **^{1}H NMR** (500 MHz, DMSO) δ_H: 5.88 (2H, s, CH_2), 7.41 – 7.51 (3H, m, C(3',5')*H* and C(4')*H*), 7.58 (2H, dd, *J* 7.4, 2.0, C(2',6')*H*), 8.36 (1H,

dd, *J* 8.0, 6.4, C(5)*H*), 9.11 (1H, d, *J* 8.1, C(4)*H*), 9.40 (1H, d, *J* 6.3, C(6)*H*), 9.98 (1H, s, C(2)*H*); **^{19}F{^{1}H} NMR** (471 MHz, CD_3CN) –151.9, –151.8; **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 64.1 (*C*H_2), 113.4 (*C*(3)), 113.9 (*C*N), 128.9 (*C*(5)H), 129.2 (*C*(2',6')H and *C*(3',5')H), 129.7 (*C*(4')H), 133.4 (*C*(1')), 148.1 (*C*(4)H), 149.0 (*C*(2)H or *C*(6)H), 149.2 (*C*(2)H or *C*(6)H); **HRMS** (ESI$^+$) $C_{13}H_{11}N_2$ $[M-BF_4]^+$ found 195.0914, requires 195.0917 (−1.5 ppm). (LNB ref: CM386, CM756)

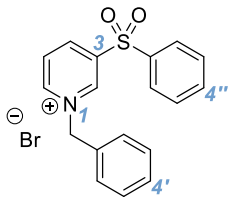
3-(Phenylsulfonyl)pyridine (**372**)



372

Flame-dried 4 Å molecular sieves, benzenesulfinic acid, sodium salt (3.28 g, 20 mmol, 1.0 equiv), 3-pyridine boronic acid (3.69 g, 30 mmol, 1.5 equiv), copper(II) acetate monohydrate (1.25 g, 6.25 mmol, 1.25 equiv), triethylamine (12.5 mL, 90 mmol, 4.5 equiv), DMSO (100 mL, 0.2 M) and 1,4-dioxane were combined in a flame-dried 500 mL round bottom flask. The flask was sealed, and the reaction was stirred at 65 °C for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with brine (200 mL) and NH_4OH (12 mL), and extracted with EtOAc:$CHCl_3$ (3:1, 3 × 200 mL). The organic layers were combined, wash with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude purified by flash column chromatography (0-100% EtOAc in petrol; R_f 0.26 at 60% EtOAc in petrol then 0-8% Et_2O in CH_2Cl_2; R_f 0.4 at 10% Et_2O in CH_2Cl_2) to give the title compound (1.35 g, 31%) as a white solid with spectroscopic data in accordance with the literature.[281] **mp** 100-102 °C {Lit.[281] 120-122 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.45 (1H, ddd, *J* 8.1, 4.9, 0.8, C(5)*H*), 7.50 – 7.58 (2H, m, C(3',5')*H*), 7.58 – 7.69 (1H, m, C(4')*H*), 7.90 – 8.05 (2H, m, C(2',6')*H*), 8.22 (1H, ddd, *J* 8.1, 2.3, 1.7, C(4)*H*), 8.79 (1H, dd, *J* 4.9, 1.6, C(6)*H*), 9.15 (1H, d, *J* 1.8, C(2)*H*). (LNB ref: CM446, CM748, CM759, CM811, CM822, CM845)

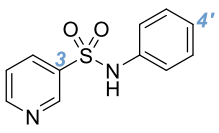
1-Benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide (**373**)



373

Following general procedure E, using benzyl bromide (0.8 mL, 7.0 mmol, 1.5 equiv), 3-(phenylsulfonyl)pyridine **372** (1.03 g, 4.7 mmol, 1.0 equiv) and MeCN (29 mL, 0.16 M) for 18 h. Upon completion, the reaction mixture was concentrated in vacuo, diluted with Et_2O and filtered to give the title compound (1.64 g, 89%) as a peach solid. **mp** 172-174 °C; ν_{max} (solid): 2995 (C-H), 1489, 1450, 1333 (SO_2), 1315, 1176, 1146 (SO_2), 1122, 870, 596; **^{1}H NMR** (500 MHz, DMSO) δ_H: 5.99 (2H, s, CH_2), 7.40 – 7.51 (3H, m, C(3',5')*H* and C(4')*H*), 7.59 (2H, dd, *J* 7.5, 1.9, C(2',6')*H*), 7.74 (2H, t, *J* 7.8, C(3'',5'')*H*), 7.83 (1H, t, *J* 7.5, C(4'')*H*), 8.14 (2H, dd, *J* 8.4, 1.1, C(2'',6'')*H*), 8.37 (1H, dd, *J* 8.1, 6.2, C(5)*H*), 9.17 (1H, d, *J* 8.6, C(4)*H*), 9.39 (1H, d, *J* 6.1, C(6)*H*), 10.05 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 63.9 (*C*H_2), 128.4 (*C*(2'',6'')H), 129.2 (*C*(2',6')H), 129.3 (*C*(3',5')H), 129.6 (*C*(4')H), 129.9 (*C*(5)H), 130.2 (*C*(3'',5'')H), 133.6 (*C*(1')), 135.4 (*C*(4'')H), 138.3 (*C*(1'')), 141.4 (*C*(3)), 144.5 (*C*(4)H or *C*(6)H), 144.6 (*C*(4)H or *C*(6)H), 149.0 (*C*(6)H); **HRMS** (ESI$^+$) $C_{18}H_{16}NO_2S$ $[M-Br]^+$ found 310.0890, requires 310.0896 (−1.9 ppm). (LNB ref: CM730, CM751, CM752, CM769, CM824)

N-Phenylpyridine-3-sulfonamide (**375**)

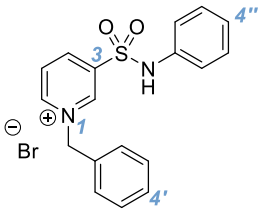


375

Aniline (1.1 mL, 12 mmol, 3.0 equiv) and DMAP (21 mg, 0.2 mmol, 0.05 equiv) were added to 3-pyridine sulfonyl chloride (0.5 mL, 4 mmol, 1.0 equiv) in pyridine (8 mL, 0.5 M) at room temperature and the reaction was stirred for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1},

EtOAc in petrol (30% 5 CV, 30-65% 21 CV), R_f 0.42 at 40% EtOAc in petrol] to give the title compound (660 mg, 70%) as a white solid with spectroscopic data in accordance with the literature.[282] **mp** 140-142 °C {Lit.[282] 141-143 °C}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.82 (1H, s, N*H*), 7.04 – 7.12 (2H, m, C(2',6')*H*), 7.14 – 7.21 (1H, m, C(4')*H*), 7.23 – 7.32 (2H, m, C(3',5')*H*), 7.38 (1H, ddd, *J* 8.1, 4.9, 0.8, C(5)*H*), 8.00 (1H, ddd, *J* 8.1, 2.3, 1.7, C(4)*H*), 8.76 (1H, dd, *J* 4.9, 1.6, C(6)*H*), 8.97 (1H, dd, *J* 2.3, 0.6, C(2)*H*). (LNB ref: CM445)

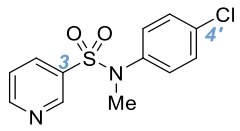
1-Benzyl-3-(*N*-phenylsulfamoyl)pyridin-1-ium bromide (**376**)



376

Following general procedure E, using benzyl bromide (0.4 mL, 3.0 mmol, 1.5 equiv), *N*-phenylpyridine-3-sulfonamide **375** (468 mg, 2.0 mmol, 1.0 equiv) and MeCN (5 mL, 0.4 M) for 18 h gave, the title compound (738 mg, 91%) as a white solid. **mp** 198-200 °C; **ν_{max}** (solid): 3007, 2938, 2876, 2828, 1626, 1595 (ArC=C), 1479, 1421, 1358 (SO_2N), 1153 (SO_2N), 1124, 939, 750, 677; **^{1}H NMR** (400 MHz, DMSO) δ_H: 5.95 (2H, s, CH_2), 7.09 (2H, dd, *J* 8.5, 1.1, C(2'',6'')*H*), 7.12 – 7.21 (1H, m, C(4'')*H*), 7.27 (2H, t, *J* 7.6, C(3'',5'')*H*), 7.35 – 7.52 (5H, m, C(2',6')*H*, C(3',5')*H* and C(4')*H*), 8.38 (1H, dd, *J* 8.2, 6.1, C(5)*H*), 8.86 (1H, app dt, *J* 8.2, 1.2, C(4)*H*), 9.43 (1H, d, *J* 6.1, C(6)*H*), 9.62 (1H, s, C(2)*H*), 10.98 (1H, s, N*H*); **^{13}C{^{1}H} NMR** (101 MHz, DMSO) δ_C: 63.7 (*C*H_2), 121.8 (*C*(2'',6'')H), 125.8 (*C*(4'')H), 128.8 (*C*(2',6')H), 129.3 (*C*(3',5')H), 129.5 (*C*(4')H), 129.6 (*C*(3'',5'')H), 129.9 (*C*(5)H), 133.7 (*C*(1')), 135.7 (*C*(1'')), 139.6 (*C*(3)), 143.1 (*C*(2)H), 143.3 (*C*(4)H), 148.9 (*C*(6)H); **HRMS** (ESI$^+$) $C_{18}H_{17}N_2O_2S$ $[M-Br]^+$ found 325.0996, requires 325.1005 (−2.8 ppm). (LNB ref: CM731)

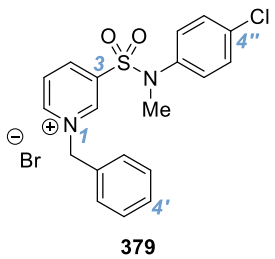
N-(4'-Chlorophenyl)-*N*-methylpyridine-3-sulfonamide (**378**)



378

4-Chloro-*N*-methylaniline (0.5 mL, 4.2 mmol, 1.05 equiv) was added to 3-pyridine sulfonyl chloride (0.5 mL, 4 mmol, 1.0 equiv) and DMAP (21 mg, 0.2 mmol, 0.05 equiv) in pyridine (8 mL, 0.5 M) at 0 °C and the reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by purification by Biotage® Isolera™ 4 [SNAP KP-Sil 50 g, 100 mL min^{-1}, EtOAc in petrol (0% 4 CV, 0-70% 23 CV), R_f 0.29 at 60% EtOAc in petrol] to give the title compound (1.13 g, quant.) as a cream solid. **mp** 68-70 °C; **ν_{max}** (solid): 1570 (ArC=C), 1485, 1414, 1342 (SO_2N), 1325, 1176 (SO_2N), 1157, 1088, 1053, 868, 750, 702; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.19 (3H, s, C*H*$_3$), 7.03 (2H, d, *J* 8.7, C(2',6')*H*), 7.29 (2 H, d, *J* 8.8, C(3',5')*H*), 7.42 (1H, dd, *J* 8.0, 4.8, C(5)*H*), 7.79 (1H, app dt, *J* 8.0, 1.9, C(4)*H*), 8.80 (1H, d, *J* 2.1, C(2)*H*), 8.81 (1H, dd, *J* 4.8, 1.5, C(6)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 38.3 (*C*H$_3$), 123.7 (*C*(5)H), 127.9 (*C*(2',6')H), 129.5 (*C*(3',5')H), 133.0 (*C*(3)), 133.8 (*C*(4')), 135.5 (*C*(4)H), 139.4 (*C*(1')), 148.5 (*C*(2)H), 153.7 (*C*(6)H); **HRMS** (ESI$^+$) $C_{12}H_{12}ClN_2O_2S$ $[M+H]^+$ found 283.0300, requires 283.0308 (−2.8 ppm). (LNB ref: CM743)

1-Benzyl-3-(*N*-(4''-chlorophenyl)-*N*-methylsulfamoyl)pyridin-1-ium bromide (**379**)

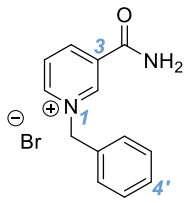


379

Following general procedure E, using benzyl bromide (0.4 mL, 3.0 mmol, 1.5 equiv), *N*-(4'-chlorophenyl)-*N*-methylpyridine-3-sulfonamide **378** (566 mg, 2.0 mmol, 1.0 equiv) and MeCN (5 mL, 0.4 M) for 18 h gave, the title compound (686 mg, 76%) as a peach solid. **mp** 158-160 °C; **ν_{max}** (solid): 3015, 1636, 1479, 1373 (SO_2N), 1364, 1190,

1146 (SO_2N), 1061, 881, 741; **^{1}H NMR** (400 MHz, DMSO) δ_H: 3.26 (3H, s, NCH_3), 5.98 (2H, s, CH_2), 7.25 (2H, d, *J* 8.8, C(2'',6'')*H*), 7.41 (2H, d, *J* 8.8, C(3'',5'')*H*), 7.45 – 7.50 (3H, m, C(3',5')*H* and C(4')*H*), 7.50 – 7.55 (2H, m, C(2',6')*H*), 8.40 (1H, dd, *J* 8.0, 6.2, C(5)*H*), 8.73 (1H, d, *J* 8.3, C(4)*H*), 9.47 – 9.55 (2H, m, C(2)*H* and C(6)*H*); **^{13}C{^{1}H} NMR** (101 MHz, DMSO) δ_C: 38.7 (NCH_3), 63.6 (NCH_2), 129.0 (*C*(2',6')H), 129.1 (*C*(2'',6'')H), 129.2 (*C*(3',5')H), 129.5 (*C*(3'',5'')H), 129.5 (*C*(4')H), 129.9 (*C*(5)H), 133.0 (*C*(4'')), 133.6 (*C*(1')), 136.5 (*C*(3)), 138.6 (*C*(1'')), 143.7 (*C*(2)H), 144.2 (*C*(4)H), 148.8 (*C*(6)H); **HRMS** (ESI$^+$) $C_{19}H_{18}ClN_2O_2S$ $[M-Br]^+$ found 373.0762, requires 373.0772 (−2.7 ppm). (LNB ref: CM749)

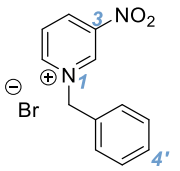
1-Benzyl-3-carbamoylpyridin-1-ium bromide (**380**)



380

Following general procedure E, using benzyl bromide (1.8 mL, 15 mmol, 1.5 equiv), nicotinamide (1.22 g, 10 mmol, 1.0 equiv) and MeCN (20 mL, 0.5 M) for 18 h. The reaction mixture was filtered, washing with Et_2O, to give the title compound (2.7 g, 92%) as a white solid with spectroscopic data in accordance with the literature.[280] **mp** 215-217 °C {Lit.[280] 214-215 °C}; **^{1}H NMR** (400 MHz, D_2O) δ_H: 5.87 (2H, s, CH_2), 7.48 (5H, s, C(2',6')*H*, C(3',5')*H* and C(4')*H*), 8.16 (1H, dd, *J* 8.0, 6.3, C(5)*H*), 8.87 (1H, app dt, *J* 8.1, 1.4, C(4)*H*), 9.04 (1H, d, *J* 6.2, C(6)*H*), 9.33 (1H, s, C(2)*H*). (LNB ref: CM408)

1-Benzyl-3-nitropyridin-1-ium bromide (**381**)

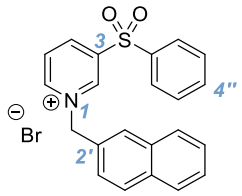


381

Following general procedure E, using benzyl bromide (5.0 mL, 42 mmol, 1.5 equiv), 3-nitropyridine (3.48 g, 28 mmol, 1.0 equiv) and MeCN (56 mL, 0.5 M) for 18 h gave the title compound (4.59 g, 56%) as a dark yellow solid. **mp** 148-150 °C; **ν_{max}** (solid,

cm^{-1}) 2984 (C-H), 2926 (C-H), 1639, 1528 (C-NO_2), 1489, 1352 (C-NO_2), 1180, 750, 696; **^{1}H NMR** (400 MHz, DMSO) δ_H: 6.09 (2H, s, CH_2), 7.37 – 7.51 (3H, m, C(3',5')*H* and C(4')*H*), 7.63 (2H, dd, *J* 7.6, 1.9, C(2',6')*H*), 8.44 (1H, dd, *J* 8.6, 6.1, C(5)*H*), 9.36 (1H, ddd, *J* 8.6, 2.2, 1.0, C(4)*H*), 9.56 (1H, d, *J* 6.1, C(6)*H*), 10.38 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (101 MHz, DMSO) δ_C: 63.8 (*C*H_2), 129.1 (*C*(2',6')H), 129.2 (*C*(5)H), 129.2 (*C*(3',5')H), 129.6 (*C*(4')H), 133.7 (*C*(1')), 140.2 (*C*(4)H), 142.5 (*C*(2)H), 146.7 (*C*(3)), 149.2 (*C*(6)H); **HRMS** (ESI$^+$) $C_{12}H_{11}NO_2$ [M−Br]$^+$ found 215.0813, requires 215.0815 (−0.9 ppm). (LNB ref: CM294, CM317)

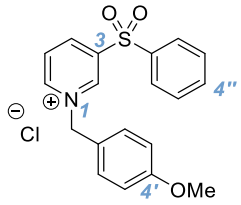
1-(Naphthalen-2'-ylmethyl)-3-(phenylsulfonyl)pyridin-1-ium bromide (**387**)



387

Following general procedure E, using 2-(bromomethyl)naphthalene (332 mg, 1.5 mmol, 1.5 equiv), 3-(phenylsulfonyl)pyridine **372** (219 mg, 1.0 mmol, 1.0 equiv) and MeCN (6.2 mL, 0.16 M) for 72 h gave, the title compound (346 mg, 78%) as a white solid. **mp** 142-144 °C; **ν_{max}** (solid): 2986 (C-H), 2901 (C-H), 1634, 1474, 1329 (SO_2), 1150 (SO_2), 1126, 1080, 831, 766; **^{1}H NMR** (500 MHz, DMSO) δ_H: 6.16 (2H, s, CH_2), 7.51 – 7.62 (2H, m, C(6')*H* and C(7')*H*), 7.66 (1H, d, *J* 8.5, C(3')*H*), 7.73 (2H, t, *J* 7.8, C(3'',5'')*H*), 7.83 (1H, t, *J* 7.4, C(4'')*H*), 7.88 – 7.98 (2H, m, C(5')*H* and C(8')*H*), 8.00 (1H, d, *J* 8.5, C(4')*H*), 8.09 – 8.25 (3H, m, C(1')*H* and C(2'',6'')*H*), 8.36 (1H, dd, *J* 8.0, 6.3, C(5)*H*), 9.17 (1H, d, *J* 8.2, C(4)*H*), 9.43 (1H, d, *J* 6.1, C(6)*H*), 10.09 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 64.1 (*C*H_2), 126.1 (*C*(3')H), 127.0 (ArCH), 127.3 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.4 (*C*(2'',6'')H), 129.0 (ArCH), 129.1 (ArCH), 129.9 (*C*(5)H), 130.2 (*C*(3'',5'')H), 130.9 (Ar*C*), 132.7 (Ar*C*), 133.0 (Ar*C*), 135.4 (*C*(4'')H), 138.3 (*C*(1'')), 141.4 (*C*(3)), 144.5 (*C*(4)H), 144.7 (*C*(2)H), 149.1 (*C*(6)H); **HRMS** (ESI$^+$) $C_{22}H_{18}NO_2S$ [M−Br]$^+$ found 360.1042, requires 360.1053 (−3.0 ppm). (LNB ref: CM817)

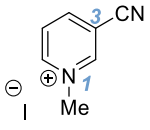
1-(4'-Methoxybenzyl)-3-(phenylsulfonyl)pyridin-1-ium chloride (**388**)



388

Following general procedure E, using 4-methoxybenzyl chloride (0.20 mL, 1.5 mmol, 1.5 equiv), 3-(phenylsulfonyl)pyridine **372** (219 mg, 1.0 mmol, 1.0 equiv) and MeCN (6.2 mL, 0.16 M) for 72 h gave, after recrystallisation from CH_2Cl_2/Et_2O, the title compound (273 mg, 65%) as a white solid. **mp** 136-138 °C; ν_{max} (solid): 3051 (C-H), 2901 (C-H), 1628, 1610, 1516, 1447, 1337, 1252, 1175 (SO_2), 1152, 1112, 1014, 868; **^{1}H NMR** (500 MHz, DMSO) δ_H: 3.76 (3H, s, OC*H*$_3$), 5.93 (2H, s, C*H*$_2$), 7.00 (2H, d, *J* 8.6, C(3',5')*H*), 7.59 (2H, d, *J* 8.6, C(2',6')*H*), 7.73 (2H, t, *J* 7.8, C(3'',5'')*H*), 7.83 (1H, t, *J* 7.4, C(4'')*H*), 8.15 (2H, d, *J* 7.5, C(2,6)*H*), 8.34 (1H, dd, *J* 7.9, 6.4, C(5)*H*), 9.13 (1H, d, *J* 8.2, C(4)*H*), 9.40 (1H, d, *J* 6.1, C(6)*H*), 10.04 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ_C: 55.3 (OCH$_3$), 63.5 (*C*H$_2$), 114.6 (*C*(3',5')H), 125.4 (*C*(1')), 128.4 (*C*(2'',6'')H), 129.8 (*C*(5)H), 130.2 (*C*(3'',5'')H), 131.2 (*C*(2',6')H), 135.4 (*C*(4'')H), 138.3 (*C*(1'')), 141.3 (*C*(3)), 144.3 (*C*(2)H or *C*(4)H), 144.3 (*C*(2)H or *C*(4)H), 148.8 (*C*(6)H), 160.2 (*C*(4)); **HRMS** (ESI$^+$) $C_{19}H_{18}NO_3S$ $[M-Cl]^+$ found 340.0991, requires 340.1002 (−3.2 ppm). (LNB ref: CM815)

3-Cyano-1-methylpyridin-1-ium iodide (**390**)



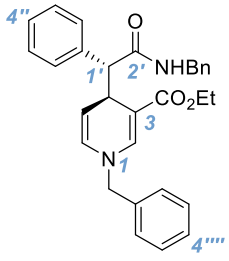
390

Following general procedure E, using methyl iodide (0.9 mL, 15.0 mmol, 1.5 equiv), 3-pyridinecarbonitrile **359** (1.04 g, 10 mmol, 1.0 equiv) and MeCN (20 mL, 0.5 M) for 18 h gave the title compound (376 mg, 15%) as a yellow solid with spectroscopic data in accordance with the literature.[283] **mp** 196-198 °C (decomp.) {No Lit mp}; **^{1}H NMR** (400 MHz, DMSO) δ_H: 4.37 (3H, s, C*H*$_3$), 8.34 (1H, dd, *J* 8.0, 6.4, C(5)*H*), 9.07 (1H, d, *J* 8.2, C(4)*H*), 9.25 (1H, d, *J* 6.2, C(6)*H*), 9.74 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (101 MHz,

DMSO) δ_C: 48.6 (*C*H_3), 112.1 (*C*(3)), 113.9 (*C*N), 128.0 (*C*(5)H), 148.1 (*C*(4)H), 149.1 (*C*(6)H), 149.8 (*C*(2)H). (LNB ref: CM341)

7.6.2. Catalysis Products

Ethyl (*R*)-1-benzyl-4-((*R*)-2'-(benzylamino)-2'-oxo-1'-phenylethyl)-1,4-dihydropyridine-3-carboxylate (**366**)

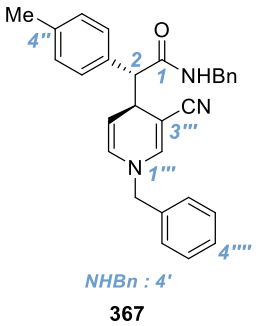


366

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77.2 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(ethoxycarbonyl)pyridin-1-ium bromide **362** (64.4 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (64%, 90:10 dr). Purification by flash column chromatography (0 to 40 % EtOAc in petrol; R_f 0.40 at 40% EtOAc in petrol) gave the title compound (30 mg, 32%, > 95:5 dr) as a yellow gum. **HPLC**: Chiralcel OD-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R: 10.2 min and 18.0 min, 50:50 er; ν_{max} (film, cm^{-1}) 3323 (N-H), 3028, 2926 (C-H), 1672 (C(=O)OR), 1651 (C(=O)NH), 1581, 1495, 1452, 1265, 1204, 1163, 1072, 1026, 731, 696; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.28 (3H, t, *J* 7.1, $CO_2CH^AH^BCH_3$), 3.96 (1H, d, *J* 3.6, C(1')*H*), 4.06 (2H, s, NCH_2Ph), 4.15 – 4.26 (2H, m, $CO_2CH^AH^BCH_3$), 4.41 (2H, dd, *J* 5.7, 2.0, $CONHCH^AH^BPh$), 4.49 (1H, app t, *J* 4.2, C(4)*H*), 5.19 (1H, dd, *J* 8.0, 4.8, C(5)*H*), 5.70 (1H, dd, *J* 8.2, 1.1, C(6)*H*), 5.77 (1H, t, *J* 5.4, N*H*), 6.69 (2H, dd, *J* 6.5, 2.9, C(2'''',6'''')*H*), 7.01 (1H, d, *J* 1.6, C(2)*H*), 7.17 – 7.22 (2H, m, C(2''',6''')*H*), 7.22 – 7.33 (11H, m, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.7 ($CO_2CH^AH^BCH_3$), 36.9 (*C*(4)H), 43.6 ($CONHCH^AH^BPh$), 56.9 (*C*(1')H), 57.4 (NCH_2Ph), 59.7 ($CO_2CH^AH^BCH_3$), 98.5 (*C*(3)), 105.9 (*C*(5)H), 126.9 (*C*(2'''',6'''')H), 127.1 (ArCH), 127.4 (ArCH), 127.7 (C(4'''')*H*), 127.8 (2 ArCH), 127.9 (2 ArCH), 128.7 (2 ArCH), 128.9 (2 ArCH), 129.5 (C(6)*H*), 130.9 (*C*(2'',6'')H), 136.8 (*C*(1'''')), 137.2 (*C*(1'')), 138.6 (*C*(1''')), 143.0 (*C*(2)H),

168.2 (*C*O$_2$Et), 172.6 (*C*ONH); **HRMS** (ESI$^+$) $C_{30}H_{29}N_2O_3$ [M−H]$^+$ found 465.2161, requires 465.2184 (−4.9 ppm). (LNB ref: CM740, CM750, CM754)

N-Benzyl-2-(1'''-benzyl-3'''-cyano-1''',4'''-dihydropyridin-4'''-yl)-2-(*p*-tolyl)acetamide (**367**)

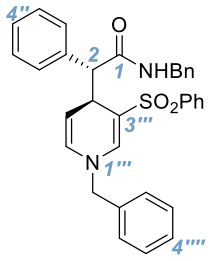


367

Following general procedure G, using 4-nitrophenyl 2-(*p*-tolyl)acetate **183** (81.4 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-cyanopyridin-1-ium bromide **363** (55 mg, 0.20 mmol, 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.30 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave the crude product (65%, 90:10 dr). Purification by flash column chromatography (0 to 50% EtOAc in petrol; R_f 0.30 at 40% EtOAc in petrol then 100% Et$_2$O; R_f 0.70 at 100% Et$_2$O) gave the title compound (45 mg, 52%, single major diastereoisomer) as a yellow foam. $[\alpha]_D^{20}$ −229.6 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak AD-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 25.5 min, t_R (major): 31.7 min, 92:8 er; ν_{max} (film, cm^{-1}) 3312 (C(O)N-H), 2920 (C-H), 2189 (C≡N), 1670 (C=C-N), 1649 (C=O), 1589, 1510, 1412, 1180, 1121, 1028, 729, 696; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, C*H*$_3$), 3.71 (1H, d, *J* 4.1, C(2)*H*), 4.06 (2H, s, N(1''')C*H*$_2$Ph), 4.33 – 4.46 (3H, m, C(4''')*H* and NHC*H*$_2$Ph), 4.99 (1H, dd, *J* 8.2, 4.2, C(5''')*H*), 5.47 – 5.92 (2H, m, C(6''')*H* and N*H*), 6.40 (1H, d, *J* 1.4, C(2''')*H*), 6.76 (2H, d, *J* 6.0, C(2'''',6'''')*H*), 7.15 (2H, d, *J* 7.8, C(3'',5'')*H*), 7.18 (2H, d, *J* 7.1, C(2',6')*H*), 7.21 – 7.33 (8H, m, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 21.4 (*C*H$_3$), 37.1 (*C*(4''')H), 43.8 (NHCH$_2$Ph), 57.2 (N(1''')CH$_2$Ph), 57.5 (*C*(2)H), 80.8 (*C*(3''')CN), 104.3 (*C*(5''')H), 121.2 (*C*N), 126.9 (*C*(2'''')H), 127.5 (*C*(4')H), 127.8 (*C*(2')H), 128.0 (*C*(4'''')H), 128.8 (*C*(3')H), 128.9 (*C*(3'''')H), 129.2 (*C*(3'')H), 129.5 (*C*(6''')H), 130.7 (*C*(2'')H), 133.0 (*C*(1'')), 136.2 (*C*(1'''')), 137.2 (*C*(4'')), 138.3 (*C*(1')), 144.1 (*C*(2''')H), 171.7

(*C*(1)); **HRMS** (ESI$^+$) $C_{29}H_{27}N_3NaO$ $[M+Na]^+$ found 456.2040, requires 456.2046 (−1.3 ppm). (LNB ref: CM298-b-4-f2, CM378, CM390)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-phenylacetamide (**386**)

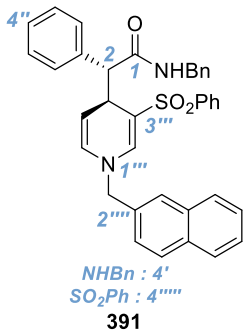


386

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (58%, 90:10 dr). Purification by flash column chromatography (0 to 5% Et_2O in CH_2Cl_2; R_f 0.35 at 5% Et_2O in CH_2Cl_2) gave the title compound (62 mg, 58%, 92:8 dr) as a white foam. $[\alpha]_D^{20}$ −471 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 12.2 min, t_R (major): 14.6 min, 94:6 er; ν_{max} (film, cm^{-1}) 3360 (N-H), 1666 (C=O), 1582, 1510 (C=C), 1495, 1281, 1136 (SO_2), 1086 (SO_2), 723, 688, 594; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.01 (2H, s, N(1''')CH_2Ph), 4.17 (1H, dd, *J* 5.0, 3.1, C(4''')*H*), 4.29 – 4.49 (3H, m, C(2)*H* and NHCH_2Ph), 5.09 (1H, dd, *J* 7.9, 5.1, C(5''')*H*), 5.56 – 5.76 (2H, m, N*H* and C(6''')*H*), 6.64 (2H, dd, *J* 7.6, 1.6, C(2'''',6'''')*H*), 7.08 (1H, d, *J* 1.2, C(2''')*H*), 7.17 (2H, d, *J* 6.9, C(2',6')*H*), 7.20 – 7.27 (4H, m, C(3'''',5'''')*H* and 2 ArC*H*), 7.26 – 7.30 (4H, m, C(3',5')*H* and 2 ArC*H*), 7.30 – 7.34 (1H, m, C(4'')*H*), 7.34 – 7.41 (2H, m, C(2'',6'')*H*), 7.52 (2H, t, *J* 7.5, C(3'''',5'''')*H*), 7.57 – 7.62 (1H, m, C(4'''')*H*), 7.85 – 7.94 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.2 (*C*(4''')H), 43.6 (NHCH_2Ph), 57.2 (*C*(2)H), 57.5 (N(1''')CH_2Ph), 105.3 (*C*(5''')H), 105.5 (*C*(3''')), 127.0 (*C*(2''',6''')H), 127.4 (ArCH), 127.5 (ArCH), 127.5 (*C*(2'''',6'''')H), 127.7 (*C*(2',6')H), 127.9 (2 ArCH), 128.7 (2 ArCH), 128.9 (2 ArCH), 129.2 (*C*(3'''',5'''')H), 129.8 (*C*(6''')H), 131.5 (*C*(2'',6'')H), 132.7 (*C*(4'''')H), 135.9 (*C*(1'''')), 136.2 (*C*(1'')), 138.4 (*C*(1')),

141.0 (*C*(1'''')), 142.9 (*C*(2''')H), 172.6 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{33}H_{30}N_2NaO_3S$ $[M+Na]^+$ found 557.1863, requires 557.1869 (−1.1 ppm). (LNB ref: CM774)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-(naphthalen-2''''-ylmethyl)-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-phenylacetamide (**391**)

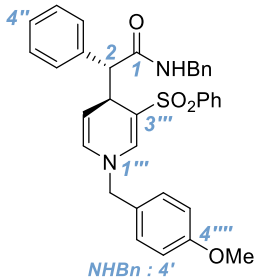


391

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77.2 mg, 0.30 mmol, 1.5 equiv), 1-(naphthalen-2-ylmethyl)-3-(phenylsulfonyl)pyridin-1-ium bromide **387** (88.1 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (72%, 90:10 dr). Purification by flash column chromatography (0 to 5.5% Et_2O in CH_2Cl_2; R_f 0.32 at 5% Et_2O in CH_2Cl_2) gave the title compound (70 mg, 60%, 94:6 dr) as a yellow/white foam. $[\alpha]_D^{20}$ −417 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 16.8 min, t_R (minor): 20.8 min, 94:6 er; ν_{max} (film, cm^{-1}) 3343 (C(O)N-H), 3055, 1664, 1584, 1508, 1414, 1279, 1134 (SO_2), 1086, 1043, 816; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.16 (2H, s, N(1''')CH^AH^B), 4.18 – 4.24 (1H, m, C(4''')*H*), 4.37 – 4.45 (3H, m, NCH^AH^BPh and C(2)*H*), 5.12 (1H, dd, *J* 7.8, 5.2, C(5''')*H*), 5.65 – 5.86 (2H, m, C(6''')*H* and N*H*), 6.74 (1H, d, *J* 8.4, C(3'''')*H*), 7.19 (3H, app d, *J* 8.7, C(2',6')*H* and C(2''')*H*), 7.22 – 7.34 (6H, m, C(3',5')*H*, C(4')*H*, C(3'',5'')*H* and C(4'')*H*), 7.35 – 7.41 (3H, m, C(2'',6'')*H* and C(1'''')*H*), 7.49 – 7.57 (4H, m, C(6'''')*H*, C(7'''')*H* and C(3'''',5'''')*H*), 7.61 (1H, t, *J* 7.3, C(4'''')*H*), 7.75 (1H, d, *J* 8.5, C(4'''')*H*), 7.76 – 7.80 (1H, m, C(8'''')*H*), 7.82 – 7.89 (1H, m, C(5'''')*H*), 7.94 (2H, d, *J* 7.7, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.2 (*C*(4''')H), 43.5 (NCH^{A}H^{B}Ph), 57.2 (*C*(2)H), 57.7 (N(1''')CH^{A}H^B), 105.3 (*C*(5)H), 105.6 (*C*(3)), 125.0 (*C*(3'''')H), 126.4 (ArCH), 126.5 (ArCH), 126.6 (ArCH), 127.4 (ArCH), 127.4 (ArCH), 127.5 (*C*(2'''',6'''')H), 127.6 (*C*(2',6')H), 127.8 (2 ArCH and ArCH), 127.9 (ArCH), 128.7 (*C*(3',5')H), 129.0

(*C*(4'''')H), 129.2 (*C*(3'''',5'''')H), 129.7 (*C*(6''')H), 131.4 (*C*(2'',6'')H), 132.7 (*C*(4'''')H), 133.0 (*C*(4''''a)), 133.2 (*C*(2'''')), 133.2 (*C*(8''''a)), 136.1 (*C*(1'')), 138.3 (*C*(1')), 141.0 (*C*(1'''')), 142.8 (*C*(2''')H), 172.5 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{37}H_{32}N_2NaO_3S$ $[M+Na]^+$ found 607.2012, requires 607.2026 (−2.3 ppm). (LNB ref: CM827)

(*R*)-N-Benzyl-2-((*R*)-1'''-(4''''-methoxybenzyl)-3'''-(phenylsulfonyl)-1''',4'''-dihydro-pyridin-4'''-yl)-2-phenylacetamide (**392**)

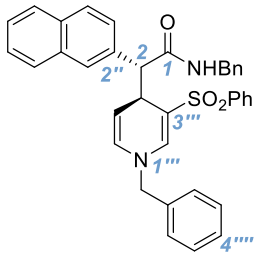


392

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77.2 mg, 0.30 mmol, 1.5 equiv), 1-(4-methoxybenzyl)-3-(phenylsulfonyl)pyridin-1-ium bromide **388** (84.1 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (75%, 90:10 dr). Purification by flash column chromatography (0 to 7.5% Et_2O in CH_2Cl_2; R_f 0.33 at 7% Et_2O in CH_2Cl_2) gave the title compound (73 mg, 65%, 94:6 dr) as a yellow/white foam. $[\alpha]_D^{20}$ −423 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 14.8 min, t_R (minor): 17.4 min, 91:9 er; ν_{max} (film, cm^{-1}) 3346 (C(O)N-H), 1664, 1582, 1510, 1414, 1281, 1246, 1134, 1086, 1026; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.81 (3H, s, OCH_3), 3.93 (2H, s, N(1''')CH_2Ph), 4.16 (1H, dd, *J* 5.1, 3.1, C(4''')*H*), 4.33 – 4.43 (3H, m, C(2)*H* and CH^AH^BPh), 5.08 (1H, dd, *J* 7.9, 5.1, C(5''')*H*), 5.64 (1H, dd, *J* 7.9, 1.3, C(6''')*H*), 5.69 (1H, app t, *J* 5.7, N*H*), 6.58 (2H, d, *J* 8.7, C(2'''',6'''')*H*), 6.76 (2H, d, *J* 8.7, C(3'''',5'''')*H*), 7.06 (1H, d, *J* 1.1, C(2''')*H*), 7.11 – 7.19 (2H, m, C(2',6')*H*), 7.21 – 7.34 (6H, m, C(4')*H*, C(3'',5'')*H* and C(4')*H*), 7.34 – 7.40 (2H, m, C(2'',6'')*H*), 7.51 (2H, t, *J* 7.4, C(3'''',5'''')*H*), 7.54 – 7.61 (1H, m, C(4'''')*H*), 7.84 – 7.94 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 36.3 (*C*(4''')H), 43.6 (CH^AH^BPh), 55.4 (OCH_3), 56.9 (N(1)CH_2Ph), 57.2 (*C*(2)H), 105.1 (*C*(5''')H), 105.2 (*C*(3''')), 127.3 (ArCH), 127.4 (ArCH), 127.4 (2 ArCH), 127.6 (*C*(2',6')H), 127.7 (*C*(1'''')),

127.9 (2 ArCH), 128.5 (*C*(2'''',6'''')H), 128.7 (2 ArCH), 129.1 (*C*(3'''',5'''')H), 129.6 (*C*(6''')H), 131.5 (*C*(2'',6'')H), 132.7 (*C*(4'''')H), 136.2 (*C*(1'')), 138.4 (*C*(1')), 141.1 (*C*(1'''')), 142.7 (*C*(2''')H), 159.3 (*C*(4'''')), 172.5 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{34}H_{32}N_2NaO_4S$ [M+Na]$^+$ found 587.1959, requires 587.1975 (−2.7 ppm). (LNB ref: CM828)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(naphthalen-2''-yl)acetamide (**394**)

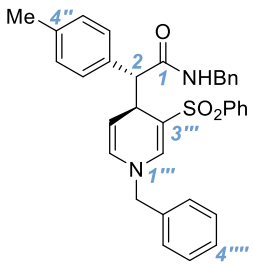


394

Following general procedure G, using 4-nitrophenyl 2-(naphthalen-2-yl)acetate **231** (92 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (73%, 95:5 dr). Purification by flash column chromatography (0 to 4.5 % Et_2O in CH_2Cl_2; R_f 0.31 at 4% Et_2O in CH_2Cl_2) gave the title compound (82 mg, 70%, 94:6 dr) as a pale yellow solid. **mp** 70-74 °C; $[\alpha]_D^{20}$ −457 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 22.4 min, t_R (major): 40.7 min, 90:10 er; ν_{max} (solid, cm^{-1}) 3329 (N-H), 3059, 1666, 1659, 1584, 1506, 1418, 1281, 1217, 1136 (SO_2), 1085, 721, 688; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.91 (2H, s, N(1)CH_2Ph), 4.25 (1H, dd, *J* 5.0, 2.9, C(4''')*H*), 4.33 – 4.50 (2H, m, NHCH^AH^BPh), 4.59 (1H, d, *J* 2.9, C(2)*H*), 5.20 (1H, dd, *J* 7.9, 5.1, C(5''')*H*), 5.63 (1H, dd, *J* 8.0, 1.3, C(6''')*H*), 5.70 (1H, app t, *J* 5.8, N*H*), 6.29 (2H, d, *J* 7.3, C(2'''',6'''')*H*), 6.74 (2H, t, *J* 7.8, C(3'''',5'''')*H*), 6.99 – 7.08 (2H, m, C(4'''')*H* and C(2''')*H*), 7.14 – 7.18 (2H, m, C(2',6')*H*), 7.20 – 7.29 (3H, m, C(3',5')*H* and C(4')*H*), 7.47 – 7.57 (5H, m, C(1'')*H*, C(3'')*H*, C(3'''',5'''')*H* and 1 ArC*H*), 7.58 – 7.63 (1H, m, C(4'''')*H*), 7.73 (1H, d, *J* 8.5, C(4'')*H*), 7.81 – 7.86 (2H, m, 2 ArC*H*), 7.88 (1H, d, *J* 7.7, 1 ArC*H*), 7.91 – 7.95 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.3 (*C*(4''')H), 43.6 (NHCH^{A}H^{B}Ph),

57.2 (*C*(2)H), 57.4 (N(1)*C*H$_2$Ph), 105.4 (*C*(5''')H), 105.5 (*C*(3''')H), 126.1 (2 Ar*C*H), 126.6 (*C*(2'''',6'''')H), 127.2 (*C*(4'')H), 127.5 (1 Ar*C*H), 127.5 (*C*(2'''',6'''')H), 127.7 (2 Ar*C*H), 127.7 (1 Ar*C*H), 127.8 (1 Ar*C*H), 128.4 (1 Ar*C*H), 128.6 (*C*(3'''',5'''')H), 128.7 (2 Ar*C*H), 129.2 (3 Ar*C*H), 129.9 (*C*(6''')H), 130.7 (1 Ar*C*H), 132.8 (*C*(4'''')H), 132.8 (1 Ar*C*), 133.2 (1 Ar*C*), 133.9 (*C*(1'')), 135.5 (*C*(1'''')), 138.3 (*C*(1')), 140.9 (*C*(1''''')), 142.9 (*C*(2''')H), 172.6 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{37}H_{32}N_2NaO_3S$ [M+Na]$^+$ found 607.2023, requires 607.2026 (−0.5 ppm). (LNB ref: CM760, CM765)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(4''-tolyl)acetamide (**395**)

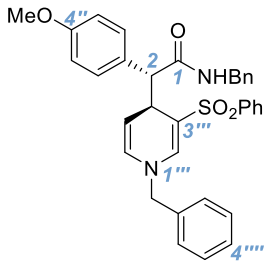


395

Following general procedure G, using 4-nitrophenyl 2-(*p*-tolyl)acetate **183** (81.4 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (67%, 80:20 dr). Purification by flash column chromatography (0 to 5.5 % Et$_2$O in CH_2Cl_2; R_f 0.40 at 5% Et$_2$O in CH_2Cl_2) gave the title compound (59 mg, 54%, > 95:5 dr) as a pale yellow solid. **mp** 160-162 °C; $[\alpha]_D^{20}$ −449 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1}, 220 nm, 30 °C) t_R (major): 17.6 min, t_R (minor): 20.3 min, 98:2 er; ν_{max} (solid, cm^{-1}) 3346 (CON-H), 2999 (C-H), 1661 (C=O), 1584, 1543, 1419, 1271, 1134 (SO_2), 1084, 723, 590; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.40 (3H, s, C*H*$_3$), 4.04 (2H, s, NC*H*$_2$Ph), 4.16 (1H, dd, *J* 4.8, 3.2, C(4''')*H*), 4.34 – 4.43 (3H, m, C(2)H and CONHC*H*^{A}*H*^{B}Ph), 5.07 (1H, dd, *J* 7.9, 5.1, C(5''')*H*), 5.60 – 5.73 (2H, m, N*H* and C(6''')*H*), 6.68 (2H, d, *J* 6.6, C(2'''',6'''')*H*), 7.08 (1H, s, C(2''')*H*), 7.10 (2H, d, *J* 7.9, C(3'',5'')*H*), 7.17 (2H, d, *J* 7.1, C(2',6')*H*), 7.20 – 7.33 (8H, m, C(4')*H*, C(2'',6'')*H*, C(3'''',5'''')*H* C(4'''')*H* and C(3',5')*H*), 7.52 (2H, t, *J* 7.6, C(3'''',5'''')*H*), 7.58 (1H, t, *J* 7.4,

C(4''''')*H*), 7.82 – 7.94 (2H, m, C(2'''',6''''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 21.5 (CH_3), 36.1 (C(4''')*H*), 43.6 (CONHCH^AH^BPh), 56.8 (*C*(2)H), 57.4 (NCH_2Ph), 105.3 (*C*(5''')H), 105.7 (*C*(3''')), 127.1 (*C*(2'''',6''''')H), 127.4 (*C*(4')H), 127.5 (*C*(2'''',6''''')H), 127.7 (*C*(2',6')H), 127.9 (*C*(4''''')H), 128.7 (*C*(3'',5'')H and 2 ArCH), 128.8 (2 ArCH), 129.2 (*C*(3'''',5'''')H), 129.8 (*C*(6''')H), 131.4 (*C*(2'',6'')H), 132.7 (*C*(4''''')H), 133.2 (*C*(1'')), 135.9 (*C*(1''''')), 136.8 (*C*(4'')), 138.4 (*C*(1')), 141.0 (*C*(1''''')), 142.8 (*C*(2''')H), 172.8 (*C*=O); **HRMS** (ESI$^+$) $C_{34}H_{32}N_2NaO_3S$ $[M+Na]^+$ found 571.2019, requires 571.2026 (−1.2 ppm). (LNB ref: CM736)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(4''-methoxyphenyl)acetamide (**396**)

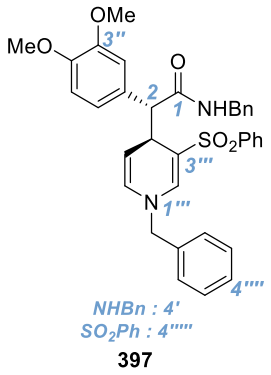


396

Following general procedure G, using 4-nitrophenyl 2-(4-methoxyphenyl)acetate **233** (86.2 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (76%, 85:15 dr). Purification by flash column chromatography (0 to 5.5 % Et_2O in CH_2Cl_2; R_f 0.36 at 6% Et_2O in CH_2Cl_2) gave the title compound (33 mg, 29%, single major diastereoisomer) as a beige foam. $[\alpha]_D^{20}$ −200 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IB, (90:10 hexane: IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 79.4 min, t_R (minor): 87.9 min, 98:2 er; ν_{max} (film, cm^{-1}) 3348 (CON-H), 2959, 2932, 1668, 1653, 1584, 1508, 1452, 1418, 1283, 1246, 1176, 1136 (SO_2), 1086, 1028; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.84 (3H, s, OCH_3), 4.06 (2H, s, N(1''')CH_2), 4.13 – 4.17 (1H, m, C(4''')*H*), 4.37 (1H, d, *J* 3.1, C(2)*H*), 4.39 (2H, d, *J* 5.8, NCH_2Ph), 5.06 (1H, dd, *J* 7.9, 5.0, C(5''')*H*), 5.59 – 5.71 (2H, m, N*H* and C(6''')*H*), 6.60 – 6.68 (2H, m, C(2'''',6''''')*H*), 6.82 (2H, d, *J* 8.5, C(3'',5'')*H*), 7.09 (1H, s, C(2''')*H*), 7.17 (2H, d, *J* 7.4, C(2',6')*H*), 7.20 – 7.34 (8H, m,

C(3',5')*H*, C(4')*H*, C(2'',6'')*H*, C(3''',5''')*H* and C(4''')*H*), 7.52 (2H, t, *J* 7.6, C(3'''',5'''')*H*), 7.59 (1H, t, *J* 7.4, C(4'''')*H*), 7.90 (2H, d, *J* 7.7, C(2'''',6'''') *H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.2 (*C*(4''')H), 43.6 (NCH_2Ph), 55.3 (OCH_3), 56.3 (*C*(2)H), 57.6 (N(1''')CH_2Ph), 105.3 (*C*(5''')H), 105.6 (*C*(3''')), 113.5 (*C*(3'',5'')H), 127.0 (*C*(2''',6''')H), 127.5 (*C*(4')H), 127.5 (2 ArCH), 127.7 (2 ArCH), 128.0 (*C*(4''')H), 128.2 (*C*(1'')), 128.7 (2 ArCH), 128.8 (2 ArCH), 129.2 (*C*(3'''',5'''')H), 129.8 (*C*(6''')H), 132.6 (*C*(2'',6'')H), 132.8 (*C*(4'''')H), 136.0 (*C*(1''')), 138.4 (*C*(1')), 141.0 (*C*(1'''')), 142.9 (*C*(2''')H), 159.0 (*C*(4'')), 172.9 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{34}H_{32}N_2NaO_4S$ $[M+Na]^+$ found 587.1965, requires 587.1975 (−1.7 ppm). (LNB ref: CM757)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(3'',4''-dimethoxyphenyl)acetamide (**397**)

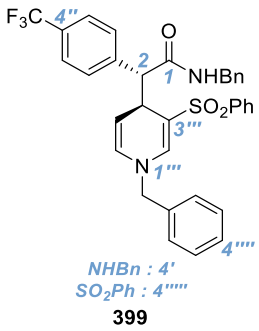


397

Following general procedure G, using 4-nitrophenyl 2-(3,4-dimethoxyphenyl)acetate **234** (95 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (73%, 80:20 dr). Purification by flash column chromatography (0 to 8.5 % Et_2O in CH_2Cl_2; R_f 0.33 at 8% Et_2O in CH_2Cl_2) gave the title compound (65 mg, 55%, 95:5 dr) as a white solid. **mp** 122-124 °C; $[\alpha]_D^{20}$ −470 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IA, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 31.2 min, t_R (minor): 44.3 min, 96:4 er; ν_{max} (solid, cm^{-1}) 3372 (C(O)N-H), 3063, 2924 (C-H), 1666 (C=O), 1582, 1516, 1454, 1422, 1273, 1260, 1234, 1155, 1132, 1086, 1022, 772; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.68 (3H, s, C(3'')OCH_3), 3.90 (3H, s, C(4'')OCH_3), 4.08 (2H, s, N(1''')CH_2Ph), 4.15 (1H, dd, *J* 4.9, 3.2, C(4''')*H*), 4.32 (1H, dd,

J 14.9, 5.6, NC*H*^{A}H^{B}Ph), 4.38 (1H, d, *J* 3.1, C(2)*H*), 4.46 (1H, dd, *J* 14.9, 6.2, NCH^{A}*H*^{B}Ph), 5.10 (1H, dd, *J* 7.9, 5.0, C(5''')*H*), 5.67 (1H, dd, *J* 8.0, 1.2, C(6''')*H*), 5.77 (1H, app t, *J* 5.7, N*H*), 6.66 (2H, dd, *J* 6.5, 2.8, C(2'''',6'''')*H*), 6.78 (1H, d, *J* 8.2, C(5'')*H*), 6.87 (1H, d, *J* 2.0, C(2'')*H*), 6.95 (1H, dd, *J* 8.2, 2.0, C(6'')*H*), 7.10 (1H, d, *J* 1.4, C(2''')*H*), 7.13 – 7.20 (2H, m, C(2',6')*H*), 7.21 – 7.32 (6H, m, C(3',5')*H*, C(4')*H*, C(3'''',5'''')*H* and C(4'''')*H*), 7.52 (2H, t, *J* 7.5, C(3'''',5'''')*H*), 7.56 – 7.62 (1H, m, C(4'''')*H*), 7.80 – 7.93 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.2 (*C*(4''')H), 43.5 (NCH^{A}H^{B}Ph), 55.8 (OCH_3), 55.8 (OCH_3), 56.7 (*C*(2)H), 57.6 (N(1''')CH_2Ph), 105.5 (*C*(5''')H), 105.7 (*C*(3''')), 110.5 (*C*(5'')H), 114.2 (*C*(2'')H), 124.1 (*C*(6'')H), 126.8 (*C*(2'''',6'''')H), 127.4 (*C*(2'''',6'''')H), 127.5 (*C*(4')H), 127.7 (*C*(2',6')H), 128.0 (*C*(4'''')H), 128.6 (*C*(1'')), 128.7 (*C*(3',5')H or *C*(3'''',5'''')H), 128.9 (*C*(3',5')H or *C*(3'''',5'''')H), 129.2 (*C*(3'''',5'''')H), 129.7 (*C*(6''')H), 132.7 (*C*(4'''')H), 135.9 (*C*(1'''')), 138.5 (*C*(1')), 140.9 (*C*(1'''')), 142.9 (*C*(2''')H), 148.1 (*C*(3'')OCH_3), 148.4 (*C*(4'')OCH_3), 172.7 (*C*(1)=O); **HRMS** (ESI^{+}) $C_{35}H_{34}N_2NaO_5S$ $[M+Na]^{+}$ found 617.2071, requires 617.2081 (−1.6 ppm). (LNB ref: CM810)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(4''-(trifluoromethyl)phenyl)acetamide (**399**)

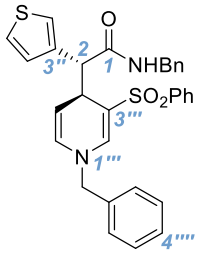


399

Following general procedure G, using 4-nitrophenyl 2-(4-(trifluoromethyl)phenyl)acetate **239** (98 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (69%, 95:5 dr). Purification by flash column chromatography (0 to 3.5% Et_2O in CH_2Cl_2; R_f 0.32 at 3% Et_2O in CH_2Cl_2) gave the title compound (60 mg, 50%, > 95:5 dr) as a pale yellow solid. **mp** 62-64 (decomp) then 160-162 °C; **HPLC**: Chiralpak AS-H, (85:15 hexane: IPA, flow rate 1.0 mLmin^{-1},

211 nm, 30 °C) t_R (minor): 13.1 min, t_R (major): 30.0 min, 52:48 er; ν_{max} (solid, cm^{-1}) 3343 (N-H), 1666 (C=O), 1582, 1531, 1418, 1323 (SO_2), 1136 (SO_2), 1111 (C-F), 1086, 1067, 723, 688, 590; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.00 (2H, s, N(1)CH_2Ph), 4.13 (1H, dd, *J* 5.0, 3.0, C(4''')*H*), 4.31 – 4.44 (2H, m, NHCH^AH^BPh), 4.45 (1H, d, *J* 3.0, C(2)*H*), 5.11 (1H, dd, *J* 7.9, 5.1, C(5''')*H*), 5.55 – 5.77 (2H, m, N*H* and C(6''')*H*), 6.69 (2H, dd, *J* 7.8, 1.5, C(2'''',6'''')*H*), 7.09 (1H, d, *J* 1.3, C(2''')*H*), 7.16 – 7.20 (2H, m, C(2',6')*H*), 7.22 – 7.34 (6H, m, C(3',5')*H*, C(4')*H*, C(3'''',5'''')*H* and C(4'''')*H*), 7.47 – 7.57 (6H, m, C(2'',6'')*H*, C(3'',5'')*H* and C(3''''',5''''')*H*), 7.58 – 7.64 (1H, m, C(4''''')*H*), 7.88 (2H, dd, *J* 8.3, 1.2, C(2''''',6''''')*H*); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: -62.1; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.7 (*C*(4''')H), 43.7 (NHCH^AH^BPh), 56.9 (*C*(2)H), 57.5 (N(1)CH_2Ph), 104.8 (*C*(5''')H), 105.3 (*C*(3''')), 124.4 (q, $^1J_{C\text{-}F}$ 272.1, *C*F_3), 124.7 (app d, $^3J_{C\text{-}F}$ 3.6, *C*(3'',5'')H), 127.2 (*C*(2'''',6'''')H), 127.5 (*C*(2''''',6''''')H), 127.6 (*C*(4')H), 127.7 (*C*(2',6')H), 128.3 (*C*(4''')H), 128.8 (*C*(3',5')H or *C*(3'''',5'''')H), 129.0 (*C*(3',5')H or *C*(3'''',5'''')H), 129.3 (*C*(3''''',5''''')H), 129.5 (app d, $^2J_{C\text{-}F}$ 32.3, *C*(4'')), 129.9 (*C*(6''')H), 131.7 (*C*(2'',6'')H), 132.9 (*C*(4''''')H), 135.4 (*C*(1'''')), 138.1 (*C*(1')), 140.4 (*C*(1'')), 140.7 (*C*(1''''')), 142.8 (*C*(2''')H), 171.7 (*C*(1)=O); **HRMS** (ESI$^-$) $C_{34}H_{28}F_3N_2O_3S$ $[M-H]^-$ found 601.1787, requires 601.1778 (+1.4 ppm). (LNB ref: CM758, CM764)

(*R*)-*N*-Benzyl-2-((*R*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-(thiophen-3''-yl)acetamide (**400**)

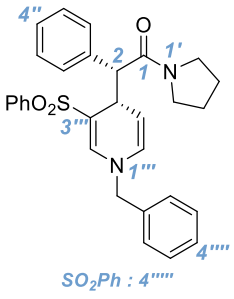


400

Following general procedure G, using 4-nitrophenyl 2-(thiophen-3-yl)acetate **241** (79 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then benzylamine (109 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (57%, 90:10 dr). Purification by flash column chromatography (0 to 5% Et_2O in CH_2Cl_2; R_f

0.35 at 5% Et_2O in CH_2Cl_2) gave the title compound (54 mg, 50%, 93:7 dr) as a white foam. $[\alpha]_D^{20}$ −399 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 15.4 min, t_R (minor): 19.4 min, 89:11 er; ν_{max} (film, cm^{-1}) 3362 (N-H), 1666 (C=O), 1585, 1526 (ArC=C), 1450, 1418, 1283, 1136 (SO_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.93 – 4.21 (3H, m, N(1''')C*H*$_2$Ph and C(4''')*H*), 4.40 (2H, dd, *J* 5.8, 2.2, NHC*H*^{A}*H*^{B}Ph), 4.53 (1H, d, *J* 3.3, C(2)*H*), 5.01 (1H, dd, *J* 7.9, 5.0, C(5''')*H*), 5.72 (1H, dd, *J* 8.0, 1.3, C(6''')*H*), 5.83 (1H, app t, *J* 5.6, N*H*), 6.84 (2H, dd, *J* 7.1, 2.2, C(2'''',6'''')*H*), 7.07 (1H, dd, *J* 4.9, 1.2, C(4'')*H*), 7.12 (1H, d, *J* 1.4, C(2''')*H*), 7.15 – 7.21 (3H, m, C(2',6')*H* and C(5'')*H*), 7.22 – 7.25 (1H, m, C(4')*H*), 7.27 – 7.35 (6H, m, C(3',5')*H*, C(2'')*H*, C(3'''',5'''')*H* and C(4'''')*H*), 7.52 (2H, t, *J* 7.6, C(3''''',5''''')*H*), 7.55 – 7.62 (1H, m, C(4''''')*H*), 7.85 – 7.91 (2H, m, C(2''''',6''''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.1 (*C*(4''')H), 43.6 (NHCH^AH^BPh), 53.0 (*C*(2)H), 57.6 (N(1)CH_2Ph), 105.1 (*C*(5''')H), 106.0 (*C*(3''')), 124.7 (*C*(5'')H), 125.8 (*C*(2'')H), 127.2 (*C*(2'''',6'''')H), 127.5 (*C*(2''''',6''''')H), 127.6 (*C*(2',6')H), 128.1 (*C*(4')H), 128.8 (2 ArCH), 129.0 (2 ArCH), 129.2 (2 ArCH), 129.8 (*C*(4'')H or *C*(6''')H), 129.8 (*C*(4'')H or *C*(6''')H), 132.8 (*C*(4''''')H), 136.0 (*C*(1'''')), 136.4 (*C*(3'')), 138.4 (*C*(1')), 140.9 (*C*(1''''')), 142.6 (*C*(2''')H), 171.9 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{31}H_{28}N_2NaO_3S_2$ $[M+Na]^+$ found 563.1425, requires 563.1434 (−1.6 ppm). (LNB ref: CM772)

(*R*)-2-((*S*)-1'''-Benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2-phenyl-1-(pyrrolidin-1'-yl)ethan-1-one (**401**)

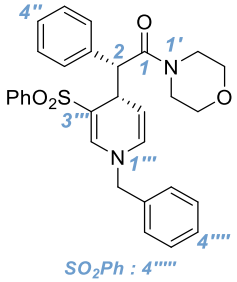


401

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then pyrrolidine (84 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (69%, 90:10 dr).

Purification by flash column chromatography (0 to 15% Et_2O in CH_2Cl_2; R_f 0.27 at 10% Et_2O in CH_2Cl_2) gave the title compound (62 mg, 62%, 94:6 dr) as a white foam. $[\alpha]_D^{20}$ −614 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak AS-H, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (minor): 11.1 min, t_R (major): 18.2 min, 93:7 er; ν_{max} (film, cm^{-1}) 2872 (C-H), 1668, 1627, 1579, 1418, 1288, 1136 (SO_2), 1086, 1022, 876; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.59 – 1.73 (2H, m, C(3')*H*^{A}H^B and C(4')*H*^{A}H^B), 1.75 – 1.90 (2H, m, C(3')H^A*H*^{B} and C(4')H^A*H*^{B}), 2.72 – 2.80 (1H, m, C(2')*H*^{A}H^B), 3.31 – 3.44 (2H, m, C(2')H^A*H*^{B} and C(5')*H*^{A}H^B), 3.47 – 3.55 (1H, m, C(5')H^A*H*^{B}), 3.92 – 4.06 (3H, m, N(1''')C*H*$_2$Ph and C(4''')*H*), 4.45 (1H, d, *J* 2.2, C(2)*H*), 5.35 (1H, dd, *J* 7.9, 5.2, C(5''')*H*), 5.54 (1H, dd, *J* 8.0, 1.3, C(6''')*H*), 6.50 – 6.66 (2H, m, C(2'''',6'''')*H*), 7.14 (1H, d, *J* 1.1, C(2''')*H*), 7.18 – 7.25 (3H, m, C(3'''',5'''')*H* and C(4'''')*H*), 7.25 – 7.33 (5H, m, C(2'',6'')*H*, C(3'',5'')*H* and C(4'')*H*), 7.51 (2H, t, *J* 7.5, C(3'''',5'''')*H*), 7.54 – 7.63 (1H, m, C(4'''')*H*), 7.81 – 7.94 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.2 (*C*(3')H^{A}H^B or *C*(4')H^{A}H^B), 26.1 (*C*(3')H^{A}H^B or *C*(4')H^{A}H^B), 36.6 (*C*(4''')H), 45.9 (*C*(5')H^{A}H^B), 46.7 (*C*(2')H^{A}H^B), 56.2 (*C*(2)H), 57.4 (N(1''')*C*H$_2$Ph), 105.0 (*C*(3''')), 106.9 (*C*(5''')H), 126.9 (*C*(4'')H), 127.0 (*C*(2'''',6'''')H), 127.3 (*C*(2'''',6'''')H), 127.8 (*C*(3'',5'')H or *C*(3'''',5'''')H), 127.8 (*C*(4'''')H), 128.9 (*C*(3'',5'')H or *C*(3'''',5'''')H), 129.1 (*C*(6''')H), 129.2 (*C*(3'''',5'''')H), 130.9 (*C*(2'',6'')H), 132.6 (*C*(4'''')H), 135.9 (*C*(1'')), 136.0 (*C*(1''')), 141.5 (*C*(1'''')), 143.3 (*C*(2)H), 171.8 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{30}H_{30}N_2NaO_3S$ $[M+Na]^+$ found 521.1864, requires 521.1869 (−1.0 ppm). (LNB ref: CM830)

(*R*)-2-((*S*)-1'''-Benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-1-morpholino-2-phenylethan-1-one (**402**)

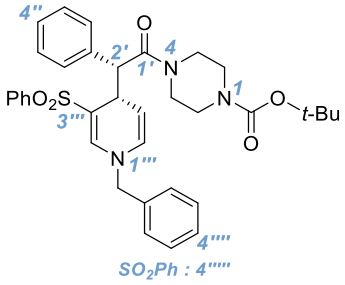


402

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6

mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then morpholine (88 μL, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (63%, 95:5 dr). Purification by flash column chromatography (6 to 12% Et_2O in CH_2Cl_2; R_f 0.28 at 10% Et_2O in CH_2Cl_2 then 30 to 55% EtOAc in petrol; R_f 0.34 at 60% EtOAc in petrol) gave the title compound (58 mg, 56%, > 95:5 dr) as a pale yellow foam. $\boldsymbol{[\alpha]_D^{20}}$ −346 (*c* 0.5, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R (major): 14.0 min, t_R (minor): 19.2 min, 94:6 er; $\boldsymbol{\nu_{max}}$ (film, cm^{-1}) 1633, 1581, 1418, 1275, 1215, 1136, 1113, 1086; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.90 – 3.00 (1H, m, C(3')H^AH^B), 3.08 – 3.17 (1H, m, C(2')H^AH^B), 3.22 – 3.31 (1H, m, C(2')H^AH^B), 3.37 – 3.53 (3H, m, C(3')H^AH^B, C(5')H^AH^B and C(6')H^AH^B), 3.62 – 3.69 (1H, m, C(5')H^AH^B), 3.69 – 3.77 (1H, m, C(6')H^AH^B), 3.94 – 4.05 (3H, m, NCH_2Ph and C(4''')*H*), 4.54 (1H, d, *J* 2.3, C(2)*H*), 5.29 (1H, dd, *J* 8.0, 5.2, C(5''')*H*), 5.53 (1H, dd, *J* 8.0, 1.5, C(6''')*H*), 6.59 (2H, dd, *J* 7.7, 1.7, C(2'''',6'''')*H*), 7.17 (1H, d, *J* 1.1, C(2''')*H*), 7.19 – 7.25 (5H, m, C(3'''',5'''')*H*, C(4'''')*H* and C(2'',6'')*H*), 7.27 – 7.34 (3H, m, C(3'',5'')*H* and C(4'')*H*), 7.46 – 7.54 (2H, m, C(3'''',5'''')*H*), 7.56 – 7.61 (1H, m, C(4'''')*H*), 7.85 – 7.93 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.7 (*C*(4''')H), 42.2 (*C*(6')H_2), 46.5 (*C*(2')H_2), 54.3 (*C*(2)H), 57.4 (NCH_2Ph), 66.2 (*C*(3')H_2), 66.8 (*C*(5')H_2), 104.8 (*C*(3''')), 106.8 (*C*(5''')H), 127.0 (*C*(2'''',6'''')H), 127.2 (Ar*C*H), 127.4 (*C*(2'''',6'''')H), 127.9 (Ar*C*H), 128.0 (2 Ar*C*H), 128.9 (2 Ar*C*H), 129.2 (*C*(3'''',5'''')H), 129.3 (*C*(6''')H), 130.6 (*C*(2'',6'')H), 132.7 (*C*(4'''')H), 135.9 (*C*(1'''')), 136.1 (*C*(1'')), 141.3 (*C*(1'''')), 143.3 (*C*(2''')H), 171.8 (*C*(1)=O); **HRMS** (ESI$^+$) $C_{30}H_{30}N_2NaO_4S$ $[M+Na]^+$ found 537.1806, requires 537.1818 (−2.2 ppm). (LNB ref: CM841)

tert-Butyl-4-((*R*)-2'-((*S*)-1'''-benzyl-3'''-(phenylsulfonyl)-1''',4'''-dihydropyridin-4'''-yl)-2'-phenylacetyl)piperazine-1-carboxylate (**403**)

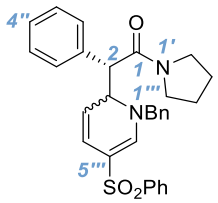


403

Following general procedure G, using 4-nitrophenyl 2-phenylacetate **218** (77 mg, 0.30 mmol, 1.5 equiv), 1-benzyl-3-(phenylsulfonyl)pyridin-1-ium bromide **373** (78.0 mg, 0.20 mmol. 1.0 equiv), (*R*)-BTM (10.1 mg, 0.04 mmol, 20 mol%), DABCO (33.6 mg, 0.3 mmol, 1.5 equiv) and PhMe (1.3 mL, 0.15 M) for 24 h at 0 °C, then 1-Boc-piperazine (186 mg, 1.0 mmol, 5.0 equiv) for 24 h at 0 °C, gave crude product (63%, 90:10 dr). Purification by flash column chromatography (25 to 50% EtOAc in petrol; R_f 0.40 at 50% EtOAc in petrol then 6 to 10% Et_2O in CH_2Cl_2; R_f 0.29 at 10% Et_2O in CH_2Cl_2) gave the title compound (64 mg, 52%, > 95:5 dr) as a pale yellow foam. $[\alpha]_D^{20}$ −437 (*c* 1.0, $CHCl_3$); **HPLC**: Chiralpak IB, (80:20 hexane: IPA, flow rate 1.0 mLmin^{-1}, 220 nm, 30 °C) t_R (major): 12.1 min, t_R (minor): 17.7 min, 93:7 er; ν_{max} (film, cm^{-1}) 2970, 1691, 1668, 1638, 1581, 1416, 1367, 1284, 1187, 1136, 1086; **^{1}H NMR** (500 MHz, CD_3CN) δ_H: 1.38 (9H, s, C(CH_3)$_3$), 2.42 – 2.55 (1H, broad-m, C(2)H^AH^B), 2.96 – 3.10 (2H, m, C(6)H^AH^B and C(3)H^AH^B), 3.10 – 3.16 (1H, m, C(3)H^AH^B), 3.16 – 3.22 (1H, m, C(2)H^AH^B), 3.24 – 3.34 (1H, m, C(5)H^AH^B), 3.37 – 3.46 (1H, m, C(6)H^AH^B), 3.58 – 3.69 (1H, m, C(5)H^AH^B), 3.88 (1H, dd, *J* 5.1, 2.3, C(4''')*H*), 4.09 (1H, d, *J* 15.7, NCH^AH^BPh), 4.14 (1H, d, *J* 15.7, NCH$^AH^B$Ph), 4.31 (1H, d, *J* 2.3, C(2')*H*), 5.12 (1H, dd, *J* 8.0, 5.1, C(5''')*H*), 5.61 (1H, dd, *J* 8.0, 1.3, C(6''')*H*), 6.67 (1H, dd, *J* 6.6, 2.9, C(2'''',6'''')*H*), 7.10 (2H, dd, *J* 8.1, 1.2, C(2'',6'')*H*), 7.20 (1H, d, *J* 1.1, C(2''')*H*), 7.22 – 7.30 (5H, m, C(3'',5'')*H*, C(3'''',5'''')*H* and C(4'''')*H*), 7.30 – 7.35 (1H, m, C(4'')*H*), 7.61 (2H, tt, *J* 6.8, 1.6, C(3''''',5''''')*H*), 7.63 – 7.69 (1H, m, C(4''''')*H*), 7.85 – 7.94 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, CD_3CN) δ_C: 28.4 (C(CH_3)$_3$), 37.4 (*C*(4''')H), 42.2 (*C*(5)H_2), 43.3 (*C*(2)H_2 or *C*(5)H_2), 44.4 (*C*(2)H_2 or *C*(5)H_2), 46.2 (*C*(3)H_2), 54.9 (*C*(2')H), 57.5 (NCH_2Ph), 80.2 (*C*(CH_3)$_3$), 105.8 (*C*(3''')), 106.7 (*C*(5''')H), 127.9 (*C*(2'''',6'''')H), 128.0 (*C*(4'')H), 128.0

(*C*(2'''',6'''')H), 128.4 (*C*(4'''')H), 128.8 (2 ArCH), 129.6 (2 ArCH), 130.3 (*C*(3'''',5'''')H), 130.4 (*C*(6''')H), 131.2 (*C*(2'',6'')H), 133.7 (*C*(4'''')H), 137.1 (*C*(1'')), 137.8 (*C*(1'''')), 142.9 (*C*(1'''')), 144.1 (*C*(2''')H), 155.2 (*C*=O$_{carbamate}$), 171.8 (*C*(1')=O); **HRMS** (ESI$^+$) $C_{35}H_{39}N_3NaO_5S$ [M+Na]$^+$ found 636.2491, requires 636.2503 (−1.9 ppm). (LNB ref: CM842)

(*S*)-2-(1'''-Benzyl-5'''-(phenylsulfonyl)-1''',2'''-dihydropyridin-2'''-yl)-2-phenyl-1-(pyrrolidin-1'-yl)ethan-1-one (**407**)



407

The reaction for **401** also gave the title compound (4 mg, 4%) as a pale yellow gum. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.69 – 1.80 (2H, m, C(3')*H*^{A}H^B and C(4')*H*^{A}H^B), 1.80 – 1.94 (2H, m, C(3')H^A*H*^{B} and C(4')H^A*H*^{B}), 2.91 – 3.02 (1H, m, C(2')*H*^{A}H^B), 3.07 – 3.17 (1H, m, C(2')H^A*H*^{B}), 3.30 – 3.43 (1H, m, C(5')*H*^{A}H^B), 3.43 – 3.53 (1H, m, C(5')H^A*H*^{B}), 3.67 (1H, d, *J* 9.4, C(2)*H*), 4.38 – 4.52 (2H, m, C(3''')*H* and N(1''')C*H*^{A}H^{B}Ph), 4.73 (1H, ddd, *J* 9.4, 5.9, 1.5, C(2''')*H*), 4.98 (1H, d, *J* 15.3, CH^A*H*^{B}Ph), 6.23 (1H, dd, *J* 9.2, 1.1, C(4''')*H*), 7.07 – 7.13 (2H, m, C(2'',6'')*H*), 7.17 (2H, d, *J* 6.4, C(2'''',6'''')*H*), 7.20 – 7.24 (3H, m, C(3'',5'')*H* and C(4'')*H*), 7.27 – 7.32 (3H, m, C(3'''',5'''')*H* and C(4'''')*H*), 7.35 (1H, s, C(6''')*H*), 7.43 – 7.57 (3H, m, C(3'''',5'''')*H* and C(4'''')*H*), 7.78 – 7.90 (2H, m, C(2'''',6'''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.3 (*C*(3')H$_2$ or *C*(4')H$_2$), 26.1 (*C*(3')H$_2$ or *C*(4')H$_2$), 46.4 (*C*(2')H$_2$ or *C*(5')H$_2$), 46.4 (*C*(2')H$_2$ or *C*(5')H$_2$), 53.1 (*C*(2)H), 58.9 (*C*(2''')H), 59.7 (N(1''')CH$_2$Ph), 110.4 (*C*(5''')), 111.4 (*C*(3''')H), 120.3 (*C*(4''')H), 126.5 (*C*(2'''',6'''')H), 127.3 (*C*(2'''',6'''')H), 127.7 (*C*(4'')H or *C*(4'''')H), 128.0 (*C*(4'')H or *C*(4'''')H), 128.6 (2 ArCH), 129.0 (2 ArCH), 129.1 (2 ArCH), 129.7 (*C*(2'',6'')H), 132.0 (*C*(4'''')H), 133.8 (*C*(1'')), 137.6 (*C*(1'''')), 143.2 (*C*(6''')H), 144.3 (*C*(1'''')), 169.9 (*C*(1)=O). (LNB ref: CM830)

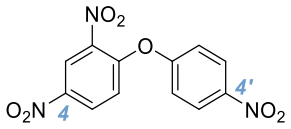
7.7. Experimental for Chapter 5

2-Chloropyridine **455**, 2-chloropyrimidine **456**, 2-chloro-5-nitropyridine **457** and 1-fluoro-4-nitrobenzene **458** were purchased from Sigma Aldrich. 1-Fluoro-2,4-dinitrobenzene **450**, 4-bromo-1-fluoro-2-nitrobenzene **459**, and 1-chloro-2,4-dinitrobenzene **461** were purchased from Alfa Aesar. Ethyl 4-fluoro-3-nitrobenzoate **460** was purchased from Apollo.

Tables 22, 23, 24, 25, 26, 27, and Schemes 98, 101 were carried out according to general procedure H.

7.7.1. Intermolecular S_NAr

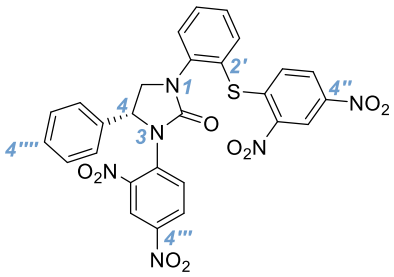
2,4-Dinitro-1-(4'-nitrophenoxy) benzene (**471**)



471

1-Fluoro-2,4-dinitrobenzene (37.2 mg, 0.20 mmol, 1.0 equiv), tetrabutylammonium *p*-nitrophenoxide (76.1 mg, 0.20 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1 mL, 0.2 M) and the reaction stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed successively with H_2O (2 × 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5 to 40% EtOAc in petrol; 70:30 R_f 0.41 at 30% EtOAc in petrol) to give the title compound (43 mg, 75%) as a beige solid. **mp** 84–85 °C; **ν_{max}** (solid, cm^{-1}) 3111, 3082, 2922, 2853, 1605, 1584, 1520, 1476, 1339, 1261, 1248, 872; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.23 (2H, d, *J* 9.2, C(2',6')*H*), 7.26 (1H, d, *J* 9.1, C(6)*H*), 8.34 (2H, d, *J* 9.2, C(3',5')*H*), 8.47 (1H, dd, *J* 9.1, 2.7, C(5)*H*), 8.91 (1H, d, *J* 2.7, C(3)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 119.6 (*C*(2',6')H), 121.6 (*C*(6)H), 122.5 (*C*(3)H), 126.6 (*C*(3',5')H), 129.3 (*C*(5)H), 141.1 (ArC), 143.4 (ArC), 145.2 (ArC), 153.5 (ArC), 159.5 (ArC); **HRMS** (ASAP$^+$) $C_{12}H_8N_3O_7$ $[M+H]^+$ found 306.0366, requires 306.0357 (+2.9 ppm). (LNB ref: CM018, CM023)

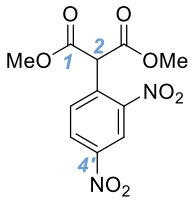
(*R*)-3-(2''',4'''-Dinitrophenyl)-1-(2'-((2'',4''-dinitrophenyl)thio)phenyl)-4-phenylimidazolidin-2-one (**478**)



478

1-Fluoro-2,4-dinitrobenzene (55.8 mg, 0.30 mmol, 1.0 equiv) and (*R*)-BTM (75.7 mg, 0.30 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.5 mL, 0.2 M) and the reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (20 to 70% EtOAc in petrol; R_f 0.33 at 60% EtOAc in petrol) then (0 to 5% Et_2O in CH_2Cl_2; R_f 0.57 at 5% Et_2O in CH_2Cl_2) to give the title compound (56 mg, 31%) as a yellow solid. **mp** 102 °C (decomp), 150 °C; ν_{max} (solid, cm^{-1}) 1720 (C=O), 1593 (ArCH), 1517 (C-NO_2), 1335 (C-NO_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.99 (1H, d, *J* 8.5, C(5)H^A), 4.37 (1H, app t, *J* 9.0, C(5)H^B), 5.45 (1H, app t, *J* 8.4, C(4)*H*), 7.04 (1H, d, *J* 5.0, ArC(6'')*H*), 7.05 (1H, d, *J* 4.9, ArC(6''')*H*), 7.33 – 7.37 (3H, m, ArC(3'''',4'''',5'''')*H*), 7.40 – 7.45 (2H, m, ArC(2'''',6'''')*H*), 7.56 (1H, td, *J* 7.7, 1.4, ArC(4')*H*), 7.60 – 7.66 (1H, m, ArC(6')*H*), 7.68 – 7.75 (2H, m, ArC(3')*H* and ArC(5')*H*), 8.14 (1H, dd, *J* 9.1, 2.5, ArC(5'')*H*), 8.17 (1H, dd, *J* 9.0, 2.6, ArC(5''')*H*), 8.61 (1H, d, *J* 2.6, ArC(3''')*H*), 9.15 (1H, d, *J* 2.5, ArC(3'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 55.9 (*C*(5)H^AH^B), 59.6 (*C*(4)H), 121.5 (Ar*C*(3'')H), 121.7 (Ar*C*(3''')H), 123.7 (Ar*C*(6''')H), 127.1 (Ar*C*(2'''',6'''')H), 127.3 (Ar*C*(5''')H), 127.5 (Ar*C*(5'')H), 128.7 (Ar*C*(2')S), 129.6 (Ar*C*(6'')H), 129.7 (Ar*C*(4'''')H), 129.7 (Ar*C*(3'''',5'''')H), 130.6 (Ar*C*(4')H), 131.0 (Ar*C*(6')H), 133.4 (Ar*C*(5')H), 136.6 (Ar*C*(1'')), 136.9 (Ar*C*(1'''')), 138.4 (Ar*C*(3')H), 142.3 (Ar*C*(1')N), 143.5 (Ar*C*(4''')NO_2), 143.9 (Ar*C*(2''')NO_2), 144.2 (Ar*C*(2'')NO_2), 144.9 (Ar*C*(4'')NO_2), 146.1 (Ar*C*(1'')S), 155.3 (*C*=O); **HRMS** (NSI^+) $C_{27}H_{22}N_7O_9S$ $[M+NH_4]^+$ found 620.1186, requires 620.1194 (−1.3 ppm). (LNB ref: CM241-r-4-f1)

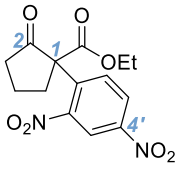
Dimethyl 2-(2',4'-dinitrophenyl)malonate (**492**)



492

1-Fluoro-2,4-dinitrobenzene (40.9 mg, 0.22 mmol, 1.1 equiv) and (±)-HyperBTM (12.3 mg, 0.04 mmol, 20 mol%) were dissolved in CH_2Cl_2 (1 mL, 0.2 M). *i*-Pr_2NEt (52 μL, 0.30 mmol, 1.5 equiv) and dimethylmalonate (23 μL, 0.20 mmol, 1.0 equiv) were added and the reaction stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 × 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20-100% EtOAc in petrol; R_f 0.16 at 30% EtOAc in petrol) to give the title compound (18 mg, 30%) as a peach solid. **mp** 68–70 °C; **ν_{max}** (solid, cm^{-1}) 3078, 2960, 1751, 1728, 1531, 1344; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.83 (6H, s, OC*H*$_3$), 5.41 (1H, s, C(2)*H*), 7.81 (1H, d, *J* 8.6, C(6')*H*), 8.49 (1H, dd, *J* 8.6, 2.4, C(5')*H*), 8.91 (1H, d, *J* 2.4, C(3')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 53.8 (O*C*H$_3$), 54.0 (*C*(2)H, 120.8 (*C*(3')H), 127.6 (Ar*C*H), 133.4 (Ar*C*H), 134.2 (Ar*C*), 147.8 (Ar*C*), 149.1 (Ar*C*), 166.7 (*C*(1)=O); **HRMS**: (ASAP$^+$) $C_{11}H_{11}N_2O_8$ $[M+H]^+$ found 299.0521, requires 299.0510 (+3.7 ppm). (LNB ref: CM085)

Ethyl 1-(2',4'-dinitrophenyl)-2-oxocyclopentane-1-carboxylate (**452**)

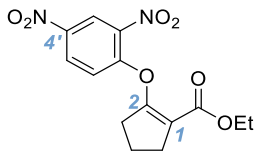


452

1-Fluoro-2,4-dinitrobenzene (40.9 mg, 0.22 mmol, 1.1 equiv) and (2*S*,3*R*)-HyperBTM (12.3 mg, 0.04 mmol, 20 mol%) were dissolved in CH_2Cl_2 (1 mL, 0.2 M). *i*-Pr_2NEt (52 μL, 0.30 mmol, 1.5 equiv) and ethyl 2-oxocyclopentane-1-carboxylate (30 μL, 0.20 mmol, 1.0 equiv) were added and the reaction stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol, R_f 0.32) to give the title compound

(30 mg, 46%) as a peach solid with spectroscopic data in accordance with the literature.[235] **mp** 94–96 °C {No Lit mp}; **HPLC**: Chiralcel OD-H (92:8 hexane: IPA, flow rate 1.00 mLmin^{-1}, 254 nm, 30 °C) t_R (major): 33.0 min, t_R (minor): 41.7 min, 53:47 er; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.21 (3H, t, *J* 7.1, C*H*$_3$), 1.95 – 2.10 (1H, m, C*H*$_2$), 2.22 – 2.46 (2H, m, C*H*$_2$), 2.45 – 2.59 (1H, m, C*H*$_2$), 2.67 – 2.81 (1H, m, C*H*$_2$), 3.16 – 3.27 (1H, m, C*H*$_2$), 4.19 (1H, q, *J* 7.1, OC*H*^{A}H^B), 4.20 (1H, q, *J* = 7.2 Hz, OCH^A*H*^{B}), 7.48 (1H, d, *J* 8.7, C(6')*H*), 8.41 (1H, dd, *J* 8.7, 2.5, C(5')*H*), 8.86 (1H, d, *J* 2.5, C(3')*H*). (LNB ref: CM087, CM105-b-3-f3, CM107, CM108, CM109, CM118, CM125, CM129, CM134, CM135)

Ethyl 2-(2',4'-dinitrophenoxy)cyclopent-1-ene-1-carboxylate (**493**)

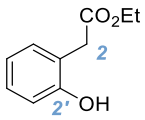


493

1-Fluoro-2,4-dinitrobenzene (40.9 mg, 0.22 mmol, 1.1 equiv) and (2*S*,3*R*)-HyperBTM (12.3 mg, 0.04 mmol, 20 mol%) were dissolved in anhydrous CH_2Cl_2 (1 mL, 0.2 M). *i*-Pr_2NEt (52 μL, 0.30 mmol, 1.5 equiv) and ethyl 2-oxocyclopentane-1-carboxylate (30 μL, 0.20 mmol, 1.0 equiv) were added and the reaction stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol, R_f 0.35) to give the title compound (11 mg, 17%) as a beige solid with spectroscopic data in accordance with the literature.[235] **mp** 62–64 °C {No Lit mp}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.08 (3H, t, *J* 7.1, C*H*$_3$), 2.06 (2H, p, *J* 7.7, C(4)*H*$_2$), 2.64 – 2.82 (4H, m, C(3)*H*$_2$ and C(5)*H*$_2$), 4.04 (2H, q, *J* 7.1, OC*H*$_2$), 7.21 (1H, d, *J* 9.2, C(6')*H*), 8.39 (1H, dd, *J* 9.2, 2.8, C(5')*H*), 8.85 (1H, d, *J* 2.7, C(3')*H*). (LNB ref: CM087, CM105-b-3-f1, CM107, CM108, CM109, CM118, CM125, CM129, CM134, CM135)

7.7.2. Intramolecular S_NAr

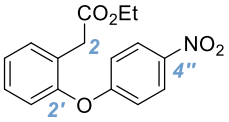
Ethyl 2-(2'-hydroxyphenyl)acetate (**497**)



497

Following general procedure I, using 2-(2-hydroxyphenyl)acetic acid (10.04 g, 66 mmol, 1.0 equiv), thionyl chloride (12 mL, 165 mmol, 2.5 equiv), EtOH (66 mL, 1.0 M) for 13 h gave, after purification by flash column chromatography (30% EtOAc in petrol, R_f 0.30) the title compound (11.8 g, quant.) as an orange oil with spectroscopic data in accordance with the literature.[284] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.2, CH_3), 3.67 (2H, s, C(2)H_2), 4.20 (2H, q, *J* 7.2, OCH_2), 6.88 (1H, td, *J* 7.4, 1.2, C(5')*H*), 6.96 (1H, dd, *J* 8.1, 1.1, C(3')*H*), 7.10 (1H, dd, *J* 7.5, 1.5, C(6')*H*), 7.20 (1H, td, *J* 7.8, 1.7, C(4')*H*), 7.63 (1H, s, O*H*). (LNB ref: CM090, CM092, CM102, CM182)

Ethyl 2-(2'-(4''-nitrophenoxy)phenyl)acetate (**498**)

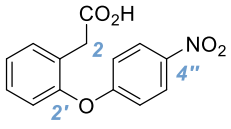


498

Following general procedure J, using ethyl 2-(2-hydroxyphenyl)acetate **497** (4.00 g, 22.2 mmol, 1.0 equiv), potassium carbonate (4.60 g, 33.30 mmol, 1.5 equiv) and 1-fluoro-4-nitrobenzene (3.96 g, 26.2 mmol, 1.2 equiv) and DMF (40 mL, 0.56 M) at 80 °C for 14 h gave, after purification by flash column chromatography (5 to 40% EtOAc in petrol; R_f 0.44 at 30% EtOAc in petrol) to give the title compound (3.54 g, 53%) as a colourless oil. ν_{max} (film, cm^{-1}) 2982, 1732 (C=O), 1514, 1485, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.14 (3H, t, *J* 7.1, CH_3), 3.62 (2H, s, C(2)H_2), 4.02 (2H, q, *J* 7.1, OCH_2), 6.95 – 7.04 (3H, m, C(2'',6'')*H* and C(3')*H*), 7.20 – 7.28 (1H, m, C(5')*H*), 7.34 (1H, td, *J* 7.8, 1.8, C(4')*H*), 7.39 (1H, dd, *J* 7.5, 1.6, C(6')*H*), 8.19 (1H, d, *J* 9.3, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 14.2 (*C*H_3), 35.9 (*C*(2)H_2), 61.1 (O*C*H_2), 117.0 (*C*(2'',6'')H), 120.8 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (*C*(3'',5'')H), 127.2 (*C*(1')), 129.3 (Ar*C*H), 132.3 (Ar*C*H), 142.8 (*C*(4'')), 153.0 (*C*(2')), 163.1 (*C*(1'')), 170.9 (*C*(1)=O); **HRMS** (ASAP$^+$)

$C_{16}H_{16}NO_5$ $[M+H]^+$ found 302.1022, requires 302.1023 (−0.3 ppm). (CM091, CM093, CM094, CM097, CM110)

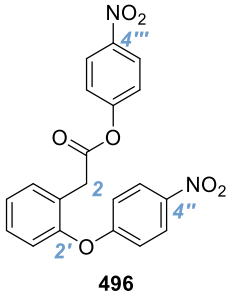
2-(2'-(4''-Nitrophenoxy)phenyl)acetic acid (**495**)



495

Following general procedure K, using ethyl 2-(2-(4-nitrophenoxy)phenyl)acetate **498** (1.60 g, 5.31 mmol, 1.0 equiv), lithium hydroxide monohydrate (1.11 g, 26.6 mmol, 5.0 equiv), MeOH (15 mL, 0.35 M), THF (15 mL, 0.35 M) and H_2O (3 mL, 1.8 M) to give the title compound (1.34 g, 92%) as an off-white solid. **mp** 120-121 °C; **ν_{max}** (film, cm^{-1}) 3082-2324 (br, O-H), 1699 (C=O), 1504, 1485, 1238; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.64 (2H, s, C(2)H_2), 6.89 – 7.07 (3H, m, C(2'',6'')*H* and C(3')*H*), 7.16 – 7.28 (1H, m, C(5')*H*), 7.30 – 7.41 (2H, m, C(4')*H* and C(6')*H*), 8.17 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 35.6 (*C*(2)H_2), 117.2 (*C*(2'',6'')H), 120.7 (Ar*C*H), 125.9 (Ar*C*H), 126.0 (*C*(3'',5'')H), 126.2 (*C*(1')), 129.7 (Ar*C*H), 132.3 (Ar*C*H), 142.9 (*C*(4'')), 153.1 (*C*(2')), 162.9 (*C*(1'')), 177.2 (*C*(1)=O); **HRMS** (NSI^-) $C_{14}H_{10}NO_5$ $[M-H]^-$ found 272.0564, requires 272.0564. (LNB ref: CM095, CM098, CM101, CM113)

4'''-Nitrophenyl 2-(2'-(4''-nitrophenoxy)phenyl)acetate (**496**)

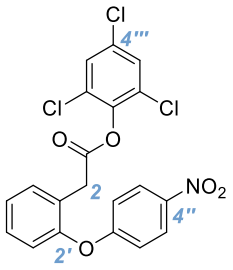


496

Following general procedure A, using 2-(2-(4-nitrophenoxy)phenyl)acetic acid **495** (1.24 g, 4.55 mmol, 1.0 equiv), EDCI·HCl (1.13 g, 5.90 mmol, 1.3 equiv), *p*-nitrophenol (0.70 g, 5.00 mmol, 1.1 equiv) and CH_2Cl_2 (8 mL, 0.6 M) for 20 h gave, after purification by column chromatography (0 to 5% Et_2O in CH_2Cl_2, R_f 0.79 at 10% Et_2O in CH_2Cl_2), the title compound (0.99 g, 73%) as a white solid. **mp** 76–78 °C; **ν_{max}** (film, cm^{-1}) 3109, 3086, 1749 (C=O), 1510, 1485, 1340, 1253, 1139, 1099, 866; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.93 (2H, s, C(2)H_2), 7.01 – 7.08 (3H, m, C(2'',6'')*H* and C(3')*H*), 7.15

(2H, d, *J* 9.2, C(2''',6''')*H*), 7.29 (1H, td, *J* 7.5, 1.1, C(5')*H*), 7.40 (1H, td, *J* 7.9, 1.7, C(4')*H*), 7.47 (1H, dd, *J* 7.6, 1.5, C(6')*H*), 8.17 – 8.25 (4H, m, C(3'',5'')*H* and C(3''',5''')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 36.0 (*C*(2)H_2), 117.3 (*C*(2'',6'')H), 120.7 (Ar*C*H), 122.3 (*C*(2''',6''')H), 125.3 (*C*(3'',5'')H), 125.6 (*C*(1')), 126.0 (Ar*C*H), 126.2 (*C*(3''',5''')H), 130.0 (Ar*C*H), 132.2 (Ar*C*H), 143.1 (*C*(4'')), 145.5 (*C*(4''')), 153.3 (*C*(2')), 155.3 (*C*(1''')), 162.7 (*C*(1'')), 168.6 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{20}H_{15}N_2O_7$ $[M+H]^+$ found 395.0877, requires 395.0868 (+2.3 ppm). (LNB ref: CM096, CM100, CM103, CM117)

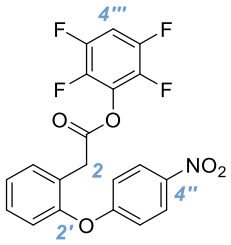
2''',4''',6'''-Trichlorophenyl 2-(2'-(4''-nitrophenoxy)phenyl)acetate (**500**)



500

Following general procedure A, using 2-(2-(4-nitrophenoxy)phenyl)acetic acid **495** (0.55 g, 2.0 mmol, 1.0 equiv), EDCI·HCl (0.50 g, 2.60 mmol, 1.3 equiv), 2,4,6-trichlorophenol (0.59 g, 3.00 mmol, 1.5 equiv) and CH_2Cl_2 (3.2 mL, 0.6 M) for 16 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.65), the title compound (0.55 g, 61%) as a white solid. **mp** 80–82 °C; **ν_{max}** (film, cm^{-1}) 3084, 1778 (C=O), 1519, 1344, 1238; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.01 (2H, s, C(2)H_2), 7.03 (1H, d, *J* 8.3, C(3')*H*), 7.05 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.27 (1H, td, *J* 7.5, 0.9, C(5')*H*), 7.32 (2H, s, C(3''',5''')*H*), 7.38 (1H, td, *J* 8.0, 1.6, C(4')*H*), 7.49 (1H, dd, *J* 7.6, 1.4, C(6')*H*), 8.19 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 35.0 (*C*(2)H_2), 117.5 (*C*(2'',6'')H), 120.4 (Ar*C*H), 125.2 (Ar*C*), 125.7 (Ar*C*H), 126.1 (*C*(3'',5'')H), 128.7 (*C*(2''',6''')H), 129.5 (Ar*C*), 129.9 (Ar*C*H), 132.3 (Ar*C*), 132.4 (Ar*C*H), 142.8 (Ar*C*), 143.1 (Ar*C*), 153.5 (Ar*C*), 162.8 (*C*(1'')), 167.3 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{20}H_{13}Cl_3NO_5$ $[M+H]^+$ found 451.9864, requires 451.9854 (+2.2 ppm). (LNB ref: CM138)

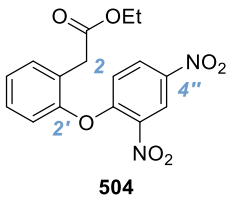
2''',3''',5''',6'''-Tetrafluorophenyl 2-(2'-(4''-nitrophenoxy)phenyl)acetate (**501**)



501

Following general procedure A, using 2-(2-(4-nitrophenoxy)phenyl)acetic acid **495** (273 mg, 1.0 mmol, 1.0 equiv), EDCI·HCl (249 mg, 1.3 mmol, 1.3 equiv), 2,3,5,6-tetrafluorophenol (249 mg, 1.5 mmol, 1.5 equiv) and CH_2Cl_2 (1.6 mL, 0.6 M) for 14 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.72), the title compound (360 mg, 85%) as a white solid. **mp** 90–91 °C; ν_{max} (film, cm^{-1}) 3080, 1789 (C=O), 1521, 1485, 1387, 1234; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.00 (2H, s, C(2)H_2), 6.98 (1H, tt, *J* 9.9, 7.1, C(4''')*H*), 7.03 – 7.04 (1H, m, C(3')*H*), 7.06 (2H, d, *J* 9.3, C(2'',6'')*H*), 7.28 (1H, td, C(5')*H*), 7.39 (1H, td, C(4')*H*), 7.47 (1H, dd, *J* 7.6, 1.6, C(6')*H*), 8.21 (2H, d, *J* 9.2, C(3'',5'')*H*); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F:-153.1– -152.9 (m), -138.9– -138.6 (m); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 35.0 (*C*(2)H_2), 103.5 (t, $^2J_{CF}$ 22.8, *C*(4''')H), 117.4 (*C*(2'',6'')H), 120.4 (ArCH), 125.0 (*C*(1')), 125.9 (ArCH), 126.2 (*C*(3'',5'')H), 129.3 – 129.9 (m, *C*(1''')), 130.1 (ArCH), 132.2 (ArCH), 139.4 – 141.9 (m, ArCF), 143.2 (*C*(4'')), 144.9 – 147.3 (m, ArCF), 153.4 (*C*(2')), 162.6 (*C*(1'')), 167.0 (*C*(1)O); **HRMS** (ASAP$^+$) $C_{20}H_{12}F_4NO_5$ $[M+H]^+$ found 422.0652, requires 422.0646 (+1.4 ppm). (LNB ref: CM139)

Ethyl 2-(2'-(2'',4''-dinitrophenoxy)phenyl)acetate (**504**)

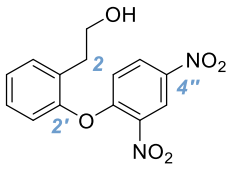


504

Following general procedure J, using ethyl 2-(2-hydroxyphenyl)acetate **497** (1.26 g, 0.55 mmol, 1.0 equiv), potassium carbonate (1.45 g, 10.5 mmol, 1.5 equiv), 1-fluoro-2,4-dinitrobenzene (1.53 g, 8.25 mmol, 1.2 equiv) and DMF (18 mL, 0.4 M) at room temperature for 14 h gave, after purification by flash column chromatography (CH_2Cl_2, R_f 0.42) to give the title compound (1.83 g, 75%) as an orange oil. ν_{max} (film,

cm^{-1}) 3109, 1730 (C=O), 1605, 1526, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.15 (3H, t, *J* 7.1, C*H*$_3$), 3.67 (2H, s, C(2)*H*$_2$), 4.02 (2H, q, *J* 7.1, OC*H*$_2$), 7.05 (1H, dd, *J* 8.0, 1.1, C(3')*H*), 7.09 (1H, d, *J* 9.3, C(6'')*H*), 7.31 (1H, td, *J* 7.5, 1.3, C(5')*H*), 7.36 – 7.45 (3 H, m, C(6')*H* and C(4')*H*), 8.30 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.84 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 14.2 (*C*H$_3$), 35.8 (*C*(2)H$_2$), 61.3 (OCH$_2$), 118.6 (ArCH), 120.7 (ArCH), 122.1 (ArCH), 127.0 (ArCH), 127.3 (*C*(1')), 128.8 (ArCH), 129.6 (ArCH), 132.7 (ArCH), 139.4 (*C*(2'')), 141.5 (*C*(4'')), 152.0 (*C*(2')), 155.9 (*C*(1'')), 170.7 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{16}H_{15}N_2O_7$ [M+H]$^+$ found 347.0879, requires 347.0874 (+1.4 ppm). (LNB ref: CM140, CM147, CM173)

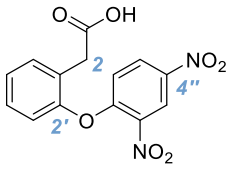
2-(2'-(2'',4''-Dinitrophenoxy)phenyl)ethan-1-ol (**507**)



507

Following general procedure L, using ethyl 2-(2-(2,4-dinitrophenoxy)phenyl)acetate **504** (1.39 g, 4.02 mmol, 1.0 equiv), DIBAL-H (1 M in hexane, 8.0 mL, 8.04 mmol, 2.0 equiv) and THF (67 mL, 0.06 M) at 0 °C for 4 h gave, after purification by flash column chromatography (10-60% EtOAc in petrol; R_f 0.19 at 40% EtOAc in petrol) the title compound (0.93 g, 76%) as an orange solid. **mp** 55–56 °C; **ν_{max}** (film, cm^{-1}) 3315 (br, O-H), 3078, 2954, 1602, 1537, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.71 (1H, s, O*H*) 2.83 (2H, t, *J* 6.5, C(2)*H*$_2$), 3.84 (2H, t, *J* 6.5, C(1)*H*$_2$O), 6.97 (1H, d, *J* 9.3, C(6'')*H*), 7.04 (1H, dd, *J* 7.8, 1.4, C(3')*H*), 7.25 – 7.39 (2H, m, C(4')*H* and C(5')*H*), 7.43 (1H, dd, *J* 7.3, 1.9, C(6')*H*), 8.29 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.84 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 33.5 (*C*(2)H$_2$), 62.4 (*C*(1)H$_2$OH), 117.7 (ArCH), 120.9 (ArCH), 122.3 (ArCH), 127.1 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 131.3 (*C*(1')), 132.4 (ArCH), 139.1 (*C*(2'')), 141.4 (*C*(4'')), 151.7 (*C*(2')), 156.1 (*C*(1'')); **HRMS** (EI$^+$) $C_{14}H_{12}N_2O_6$ [M]$^+$ found 304.0692, requires 304.0690 (+0.6 ppm). (LNB ref: CM175, CM177)

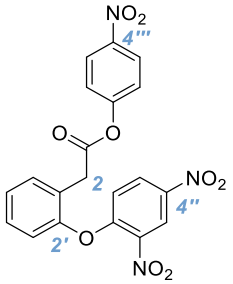
2-(2'-(2'',4''-Dinitrophenoxy)phenyl)acetic acid (**505**)



505

Following general procedure M, using 2-(2-(2,4-dinitrophenoxy)phenyl)ethan-1-ol **507** (0.75 g, 2.5 mmol, 1.0 equiv), periodic acid (1.14 g, 5.0 mmol, 2.0 equiv), PCC (10.8 mg, 0.05 mmol, 0.02 equiv) and MeCN (20 mL, 0.125 M) at room temperature for 3 h gave, after work-up the title compound (0.63 g, 84%) as a peach solid. **mp** 150-151 °C; **ν_{max}** (film, cm^{-1}) 3086, 2901, 1695 (C=O), 1602, 1526, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.69 (2H, s, C(2)H_2), 7.02 – 7.09 (2H, m, 2 ArC*H*), 7.27 – 7.36 (1H, m, ArC*H*), 7.36 – 7.45 (2H, m, 2 ArC*H*), 8.28 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.82 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 35.5 (*C*(2)H_2), 118.5 (Ar*C*H), 120.6 (Ar*C*H), 122.2 (Ar*C*H), 126.3 (*C*(1')), 127.0 (Ar*C*H), 128.8 (Ar*C*H), 129.9 (Ar*C*H), 132.8 (Ar*C*H), 139.5 (*C*(2'')), 141.7 (*C*(4'')), 152.1 (*C*(2')), 155.6 (*C*(1'')), 176.4 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{14}H_{10}N_2O_7$ $[M]^+$ found 318.0489, requires 318.0483 (+1.9 ppm). (CM178, CM180)

4'''-Nitrophenyl 2-(2'-(2'',4''-dinitrophenoxy)phenyl)acetate (**508**)

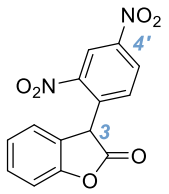


508

Following general procedure A, 2-(2-(2,4-dinitrophenoxy)phenyl)acetic acid **505** (500 mg, 1.57 mmol, 1.0 equiv), EDCI·HCl (391 mg, 2.04 mmol, 1.3 equiv), *p*-nitrophenol (328 mg, 2.36 mmol, 1.5 equiv) and CH_2Cl_2 (7.8 mL, 0.2 M) for 13 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.39), the title compound (586 mg, 85%) as an off-white solid. **mp** 109–111 °C; **ν_{max}** (film, cm^{-1}) 3111, 2900, 2353, 1749 (C=O), 1609, 1525, 1508, 1342; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.99 (2H, s, C(2)H_2), 7.10 (1H, dd, *J* 8.1, 1.0 C(3')*H*), 7.14 (1H, d, *J* 9.3, C(6')*H*), 7.21 (2H, d, *J* 9.2, C(2'',6'')*H*), 7.37 (1H, td, *J* 7.5, 1.2, C(5')*H*), 7.45 (1H, td, *J* 7.8, 1.8, C(4')*H*), 7.51 (1H, dd, *J* 7.6, 1.6,

C(6')*H*), 8.23 (2H, d, *J* 9.2, C(3'',5'')*H*), 8.31 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.83 (1H, d, *J* 2.7, C(3'')*H*); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ_C: 36.0 (*C*(2)H_2), 118.5 (ArCH), 120.5 (ArCH), 122.1 (ArCH), 122.4 (*C*(2''',6''')H), 125.4 (*C*(3''',5''')H), 125.7 (*C*(1')), 127.1 (ArCH), 129.0 (ArCH), 130.2 (ArCH), 132.8 (ArCH), 139.7 (*C*(2'')), 141.9 (*C*(4'')), 145.6 (*C*(4''')), 152.2 (*C*(2')), 155.2 (*C*(1'') or *C*(1''')), 155.3 (*C*(1'') or *C*(1''')), 168.4 (*C*(1)=O); **HRMS** (EI^+) $C_{20}H_{13}N_3O_9$ $[M]^+$ found 439.0646, requires 439.0646. (LNB ref: CM179, CM184, CM225)

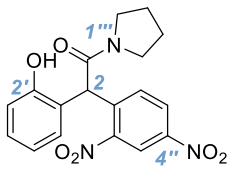
3-(2',4'-Dinitrophenyl)benzofuran-2(3H)-one (**506**)



506

4-Nitrophenyl 2-(2-(2,4-dinitrophenoxy)phenyl)acetate **508** (52 mg, 0.12 mmol, 1.0 equiv) and HyperBTM (7.4 mg, 0.024 mmol, 20 mol%) were dissolved in CH_2Cl_2 (1 mL, 0.12 M). *i*-Pr_2NEt (31 μL, 0.18 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (10 mL)and washed with 1 M HCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2, R_f 0.4) to give the title compound (31 mg, 86%) as a purple solid. ν_{max} (film, cm^{-1}) 3101, 1798 (C=O), 1530, 1344; **^1H NMR** (400 MHz, $CDCl_3$) δ_H: 5.80 (1H, s, C(3)*H*), 7.14 (1H, d, *J* 7.4, C(7)*H*), 7.20 (1H, t, *J* 7.5, C(5)*H*), 7.22 – 7.26 (1H, m, C(4)*H*), 7.44 (1H, t, *J* 7.8, C(6)*H*), 7.58 (1H, d, *J* 8.5, C(6')*H*), 8.47 (1H, dd, *J* 8.5, 2.3, C(5')*H*), 8.97 (1H, d, *J* 2.3, C(3')*H*); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ_C: 47.5 (*C*(3)H), 111.6 (ArCH), 121.6 (ArCH), 124.6 (2 ArCH), 125.2 (ArCH), 128.1 (ArCH), 130.6 (ArCH), 133.4 (*C*(3a)), 136.5 (*C*(1')), 148.0 (*C*(4')), 148.9 (*C*(2')), 154.2 (*C*(7a)), 172.3 (*C*(2)=O); **HRMS** could not be obtained for this compound and was obtained after derivatisation to the corresponding amide **509**. (LNB ref: CM143, CM181, CM186, CM224, CM234)

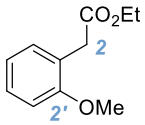
2-(2'',4''-Dinitrophenyl)-2-(2'-hydroxyphenyl)-1-(pyrrolidin-1'''-yl)ethan-1-one (**509**)



509

4-Nitrophenyl 2-(2-(2,4-dinitrophenoxy)phenyl)acetate **508** (87 mg, 0.20 mmol, 1.0 equiv) and HyperBTM (12.3 mg, 0.04 mmol, 20 mol%) were dissolved in CH_2Cl_2 (1 mL, 0.20 M). *i*-Pr_2NEt (52 μL, 0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure before the addition of pyrrolidine (25 μL, 0.3 mmol, 1.5 equiv) and toluene (2 mL, 0.1 M), and the reaction was heated at 110 °C for 14 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with 1 M HCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20 to 70 % EtOAc in petrol; R_f 0.24 at 50% EtOAc in petrol) to give the title compound (47 mg, 63%) as an off-white solid. **mp** 170-171 °C (decomp). **ν_{max}** (film, cm^{-1}) 3113, 2877, 1620 (C=O), 1597, 1451, 1340; **^{1}H NMR** (400 MHz, MeOD) δ_H: 1.74 – 2.07 (4H, m, C(3''')*H*$_2$ and C(4''')*H*$_2$), 3.04 – 3.17 (1H, m, N(1''')C*H*^{A}H^B), 3.37 – 3.50 (1H, m, N(1''')C*H*^{A}H^B), 3.50 – 3.62 (1H, m, N(1''')CH^A*H*^{B}), 3.62 – 3.75 (1H, m, N(1''')CH^A*H*^{B}), 6.10 (1H, s, C(2)*H*), 6.87 (1H, dd, *J* 8.1, 1.0, C(3')*H*), 6.94 (1H, td, *J* 7.5, 1.1, C(5')*H*), 7.18 (1H, dd, *J* 7.7, 1.6, C(6')*H*), 7.22 – 7.33 (2H, m, C(4')*H* and C(6'')*H*), 8.35 (1H, dd, *J* 8.7, 2.4, C(5'')*H*), 8.83 (1H, d, *J* 2.4, C(3'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, MeOD) δ_C: 25.3 (*C*(3)H$_2$ or *C*(4)H$_2$), 26.9 (*C*(3)H$_2$ or *C*(4)H$_2$), 47.3, 47.7, 48.1, 116.6 (ArCH), 120.7 (ArCH), 121.3 (ArCH), 123.1 (*C*(1')), 127.7 (ArCH), 130.0 (ArCH), 131.0 (ArCH), 134.4 (ArCH), 142.9 (*C*(1'')), 148.1 (*C*(4'')), 150.7 (*C*(2'')), 156.7 (*C*(2')), 171.1 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{18}H_{18}N_3O_6$ $[M+H]^+$ found 372.1194, requires 372.1190 (+1.1 ppm). (LNB ref: CM236, CM259)

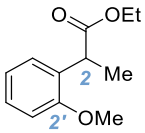
Ethyl 2-(2'-methoxyphenyl)acetate (**511**)



511

Following general procedure I, using 2-(2-methoxyphenyl)acetic acid (9.97 g, 60 mmol, 1.0 equiv), thionyl chloride (10.9 mL, 17 g, 150 mmol, 2.5 equiv), EtOH (60 mL, 1 M) for 20 h gave, after purification by flash column chromatography (30 to 50% EtOAc in petrol, R_f 0.44 at 30% EtOAc in petrol) the title compound (10.57 g, 91%) as a colourless oil with spectroscopic data in accordance with the literature.[285] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.25 (3H, t, *J* 7.1, CH_3), 3.62 (2H, s, C(2)H_2), 3.82 (3H, s, OCH_3), 4.15 (2H, q, *J* 7.2, OCH_2), 6.85 – 6.89 (1H, m, C(3')*H*, 6.87 – 6.96 (1H, m C(5')*H*), 7.18 (1H, dd, *J* 7.4, 1.8, C(6')*H*), 7.26 (1H, td, *J* 7.7, 1.8, C(4')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.4 (*C*H_3), 36.2 (*C*(2)H_2), 55.5 (O*C*H_3), 60.7 (O*C*H_2), 110.6 (Ar*C*H), 120.6 (Ar*C*H), 123.3 (*C*(1')), 128.6 (Ar*C*H), 131.0 (Ar*C*H), 157.6 (*C*(2')), 172.0 (*C*(1)=O). (LNB ref: CM185, CM195, CM200)

Ethyl 2-(2'-methoxyphenyl)propanoate (**512**)

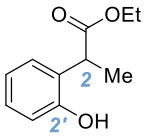


512

Ethyl 2-(2-methoxyphenyl)acetate **511** (6.22 g, 32 mmol, 1.0 equiv) was dissolved in THF (139 mL, 0.23 M) and the reaction mixture was cooled to 0 °C. LiHMDS (1 M in PhMe, 33.6 mL, 33.6 mmol, 1.05 equiv) was added and the reaction was stirred at 0 °C for 30 mins. The reaction mixture was cooled to −78 °C and methyl iodide (3.0 mL, 48 mmol, 1.5 equiv) was added and the reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 40 % EtOAc in petrol; R_f 0.60 at 20% EtOAc in petrol) to give the title compound (5.52 g, 83%) as a colourless oil. ν_{max} (film, cm^{-1}) 2980, 1730 (C=O), 1492, 1242; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.20 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.45 (3H, d, *J* 7.2, C(3)H_3), 3.82 (3H, s,

OC*H*$_3$), 4.02 (1H, q, *J* 7.2, C(2)*H*), 4.14 (2H, q, *J* 7.1, OC*H*$_2$), 6.87 (1H, d, *J* 8.1, C(3')*H*), 6.94 (1H, td, *J* 7.5, 1.1, C(5')*H*), 7.18 – 7.28 (2H, m, C(4')*H* and C(6')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.3 (*C*H$_3$), 17.5 (*C*H$_3$), 39.5 (*C*(2)H), 55.5 (OCH$_3$), 60.6 (OCH$_2$), 110.7 (ArCH), 120.8 (ArCH), 128.0 (ArCH), 128.1 (ArCH), 129.8 (*C*(1')), 156.8 (*C*(2')), 175.3 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{12}H_{17}O_3$ $[M+H]^+$ found 209.1170, requires 209.1172 (−1.0 ppm). (LNB ref: CM187, CM189, CM198, CM229)

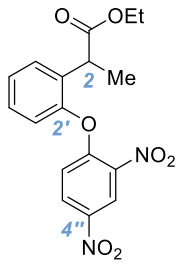
Ethyl 2-(2'-hydroxyphenyl)propanoate (**513**)



513

Ethyl 2-(2-methoxyphenyl)propanoate **512** (5.19 g, 24.9 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (240, 0.1 M) and the reaction mixture was cooled to −78 °C. Boron tribromide (1 M in CH_2Cl_2, 37.4 mL, 33.4 mmol, 1.5 equiv) was added and the reaction was stirred at −78 °C for 30 mins and then 0 °C for 2 h. The reaction mixture was diluted with EtOAc and washed successively with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 to 30 % EtOAc in petrol; R_f 0.31 at 30% EtOAc in petrol) to give the title compound (2.84 g, 59%) as a colourless oil. ν_{max} (film, cm^{-1}) 3392 (br, O-H), 2980, 2937, 1701 (C=O), 1455, 1194; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.27 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.57 (3H, d, *J* 7.3, C(3)*H*$_3$), 3.85 (1H, q, *J* 7.3, C(2)*H*), 4.19 (1H, q, *J* 7.1, OC*H*^{A}H^B), 4.21 (1H, q, *J* 7.1, OCH^A*H*^{B}), 6.88 (1H, td, *J* 7.5, 1.3, C(5')*H*), 6.92 (1H, dd, *J* 8.1, 1.2, C(3')*H*), 7.10 (1H, dd, *J* 7.6, 1.7, C(6')*H*), 7.15 – 7.21 (1H, m, C(4')*H*), 7.76 (1H, s, O*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.1 (*C*H$_3$), 16.6 (*C*H$_3$), 43.2 (*C*(2)H), 62.0 (OCH$_2$), 118.2 (ArCH), 120.9 (ArCH), 125.8 (*C*(1')), 129.0 (ArCH), 129.2 (ArCH), 155.0 (*C*(2')), 177.3 (*C*(1)=O); **HRMS** (NSI$^+$) $C_{11}H_{15}O_3$ $[M+H]^+$ found 195.1013, requires 195.1016 (−1.5 ppm). (LNB ref: CM188, CM191, CM192, CM201, CM239)

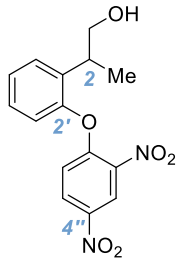
Ethyl 2-(2'-(2'',4''-dinitrophenoxy)phenyl)propanoate (**514**)



514

Following general procedure J, using ethyl 2-(2-hydroxyphenyl)propanoate **513** (2.74 g, 14.2 mmol, 1.0 equiv), potassium carbonate (2.93 g, 21.2 mmol, 1.5 equiv), 1-fluoro-2,4-dinitrobenzene (3.10 g, 16.7 mmol, 1.2 equiv) and DMF (35 mL, 0.5 at room temperature for 14 h gave, after purification by flash column chromatography (CH_2Cl_2, R_f 0.35) to give the title compound (4.75 g, 93%) as an orange oil. ν_{max} (film, cm^{-1}) 3101, 2982, 1728 (C=O), 1525, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H:1.11 (3H, t, *J* 7.1, OCH_2CH_3), 1.50 (3H, d, *J* 7.2, C(3)H_3), 3.88 – 4.10 (3H, m, C(2)*H* and OCH_2), 7.02 (1H, d, *J* 9.2, C(6'')*H*), 7.03 (1H, dd, *J* 7.7, 1.7, C(3')*H*) 7.29 – 7.42 (2H, m, C(4')*H* and C(5')*H*), 7.48 (1H, dd, *J* 7.1, 2.3, C(6')*H*), 8.30 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.86 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.2 (CH_3), 17.6 (CH_3), 39.4 (*C*(2)H), 61.2 (OCH_2), 118.3 (ArCH), 120.8 (ArCH), 122.2 (ArCH), 127.3 (ArCH), 128.8 (ArCH), 129.2 (ArCH), 129.8 (ArCH), 133.5 (*C*(1')), 139.4 (*C*(2'')), 141.5 (*C*(4'')), 151.0 (*C*(2')), 156.0 (*C*(1'')), 173.7 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{17}H_{17}N_2O_7$ $[M+H]^+$ found 361.1031, requires 361.1030 (+0.3 ppm). (LNB ref: CM190, CM203, CM240)

2-(2'-(2'',4''-Dinitrophenoxy)phenyl)propan-1-ol (**515**)

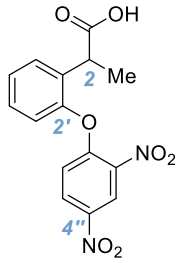


515

Following general procedure L, using ethyl 2-(2-(2,4-dinitrophenoxy)phenyl)propanoate **514** (4.61 g, 12.8 mmol, 1.0 equiv), DIBAL-H (1 M in hexane, 25.6 mL, 25.6 mmol, 2.0 equiv) and THF (213 mL, 0.06 M) at 0 °C for 4 h gave, after purification by flash column chromatography (10-100% EtOAc in petrol;

R_f 0.25 at 40% EtOAc in petrol) the title compound (2.62 g, 64%) as an orange oil. **ν_{max}** (film, cm^{-1}) 3366 (Br, O-H), 3109, 2934, 1602, 1521, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.26 (3H, d, *J* 7.0, C(3)H_3), 1.43 (1H, t, *J* 5.9, O*H*), 3.20 (1H, app q, *J* 6.9, C(2)*H*), 3.70 – 3.79 (2H, m, C(1)H_2), 6.99 (1H, d, *J* 9.3, C(6'')*H*), 7.01 – 7.05 (1H, m, ArC*H*), 7.29 – 7.40 (2H, m, ArC*H*), 7.43 – 7.50 (1H, m, ArC*H*), 8.30 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.86 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 17.0 (*C*(3)H_3), 35.7 (*C*(2)H), 67.6 (*C*(1)H_2), 117.8 (ArCH), 121.0 (ArCH), 122.3 (ArCH), 127.4 (ArCH), 128.5 (ArCH), 129.0 (ArCH), 129.1 (ArCH), 136.4 (*C*(1')), 139.2 (*C*(2'')), 141.3 (*C*(4'')), 151.4 (*C*(2')), 156.4 (*C*(1'')); **HRMS** (ASAP$^+$) $C_{15}H_{18}N_3O_6$ $[M+NH_4]^+$ found 336.1196, requires 336.1190 (+1.8 ppm). (LNB ref: CM204, CM242)

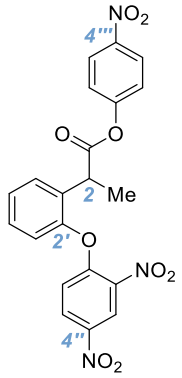
2-(2'-(2'',4''-Dinitrophenoxy)phenyl)propanoic acid (**516**)



516

Following general procedure M, using 2-(2-(2,4-dinitrophenoxy)phenyl)propan-1-ol **515** (2.55 g, 8.01 mmol, 1.0 equiv), periodic acid (3.65 g, 16.0 mmol, 2.0 equiv), PCC (34.5 mg, 0.16 mmol, 0.02 equiv) and MeCN (64 mL, 0.125 M) at room temperature for 3 h gave, after work-up the title compound (2.2 g, 83%) as an orange solid. **mp** 116–118 °C, **ν_{max}** (film, cm^{-1}) 2987, 1687 (C=O), 1541, 1520, 1340; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.50 (3H, d, *J* 7.2, C(3)H_3), 3.96 (1H, q, *J* 7.2, C(2)*H*), 6.99 – 7.06 (2H, m, C(3')*H* and C(6'')*H*), 7.31 – 7.41 (2H, m, C(4')*H* and C(5')*H*), 7.46 (1H, dd, *J* 7.4, 2.0, C(6')*H*), 8.28 (1H, dd, *J* 9.3, 2.8, C(5'')*H*), 8.84 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 17.2 (*C*(3)H_3), 39.5 (*C*(2)H), 118.4 (ArCH), 120.7 (ArCH), 122.3 (ArCH), 127.2 (ArCH), 128.9 (ArCH), 129.5 (ArCH), 130.0 (ArCH), 132.7 (*C*(1')), 139.4 (*C*(2'')), 141.6 (*C*(4'')), 151.1 (*C*(2')), 155.8 (*C*(1'')), 179.5 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{15}H_{16}N_3O_7$ $[M+NH_4]^+$ found 350.0985, requires 350.0983 (+0.6 ppm). (LNB ref: CM209, CM244)

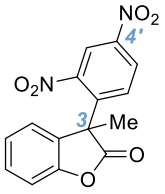
4'''-Nitrophenyl 2-(2'-(2'',4''-dinitrophenoxy)phenyl)propanoate (**517**)



517

Following general procedure A, using 2-(2-(2,4-dinitrophenoxy)phenyl)propanoic acid **516** (1.99 g, 6.0 mmol, 1.0 equiv), EDCI·HCl (1.50 g, 7.8 mmol, 1.3 equiv), 4-nitrophenol (1.25 g, 9.0 mmol, 1.5 equiv) and CH_2Cl_2 (30 mL, 0.2 M) for 20 h gave, after purification by column chromatography (CH_2Cl_2, R_f 0.57), the title compound (1.27 g, 46%) as a white crystalline solid. **mp** 116–118 °C; ν_{max} (film, cm^{-1}) 3082, 1749 (C=O), 1521, 1344, 1143; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.65 (3H, d, *J* 7.2, C(3)*H*$_3$), 4.28 (1H, q, *J* 7.2, C(2)*H*), 7.08 (1H, d, *J* 9.3, C(6'')*H*), 7.08 (1H, dd, *J* 7.8, 1.4, C(3')*H*), 7.15 (2H, d, *J* 9.1, C(2''',6''')*H*), 7.40 (1H, td, *J* 7.5, 1.5, C(5')*H*), 7.44 (1H, td, *J* 7.7, 1.9, C(4')*H*), 7.55 (1H, dd, *J* 7.5, 1.9, C(6')*H*), 8.22 (2H, d, *J* 9.1, (C(3''',5''')*H*), 8.29 (1H, dd, *J* 9.3, 2.7, C(5'')*H*), 8.86 (1H, d, *J* 2.7, C(3'')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 17.4 (*C*(3)H_3), 39.7 (*C*(2)H), 118.4 (Ar*C*H), 120.7 (Ar*C*H), 122.3 (*C*(2''',6''')H and 1 Ar*C*H), 125.3 (*C*(3''',5''')H), 127.4 (Ar*C*H), 128.9 (Ar*C*H), 129.7 (Ar*C*H), 129.8 (Ar*C*H), 132.0 (*C*(1')), 139.7 (*C*(2'')), 141.9 (C(4'')), 145.5 (*C*(4''')), 151.3 (*C*(2')), 155.4 (*C*(1'') or *C*(1''')), 155.5 (*C*(1'') or *C*(1''')), 171.3 (*C*(1)=O); **HRMS** (ASAP$^+$) $C_{21}H_{19}N_4O_9$ $[M+NH_4]^+$ found 471.1155, requires 471.1147 (+1.7 ppm). (LNB ref: CM211, CM245)

3-(2',4'-Dinitrophenyl)-3-methylbenzofuran-2(3H)-one (**518**)



518

Following general procedure H, using 4-nitrophenyl 2-(2-(2,4-dinitrophenoxy)phenyl)propanoate **517** (68 mg, 0.15 mmol, 1.0 equiv), *i*-Pr_2NEt (39

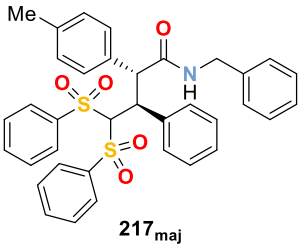
μL, 0.15 mmol, 1.5 equiv) and DMF (1 mL, 0.15 M) at 80 °C for 15 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (10 mL) and washed successively with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (50 to 100% CH_2Cl_2 in petrol; Rf 0.32 at 100% CH_2Cl_2 in petrol) to give the title compound as a yellow solid (47 mg, quant.). **mp** 139–141 °C; ν_{max} (film, cm^{-1}) 3086, 1800 (C=O), 1525, 1354; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.00 (3H, s, C*H*$_3$), 6.83 (1H, dd, *J* 7.5, 0.9, C(7)*H*), 7.09 (1H, td, *J* 7.6, 0.9, C(5)*H*), 7.23 (1H, d, *J* 8.0, C(4)*H*), 7.38 (1H, td, *J* 8.0, 1.3, C(6)*H*), 8.17 (1H, d, *J* 8.8, C(6')*H*), 8.60 (1H, dd, *J* 8.7, 2.5, C(5')*H*), 8.70 (1H, d, *J* 2.4, C(3')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 27.5 (*C*H$_3$), 50.1 (*C*(3)), 111.5 (Ar*C*H), 121.2 (Ar*C*H), 121.9 (Ar*C*H), 124.9 (Ar*C*H), 127.3 (Ar*C*H), 130.3 (Ar*C*H), 130.7 (*C*(3a)), 131.9 (Ar*C*H), 138.8 (*C*(1')), 147.8 (*C*(4')), 149.1 (*C*(2')), 153.6 (*C*(7a)), 175.6 (*C*(2)=O); **HRMS** (ASAP$^+$) $C_{15}H_{11}N_2O_6$ $[M+H]^+$ found 315.0616, requires 315.0612 (+1.3 ppm). (LNB ref: CM221, CM246)

7.8. X-Ray Structures

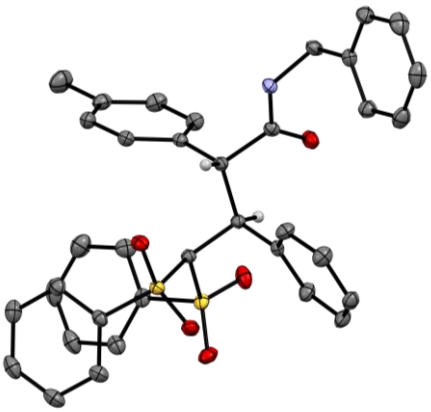
217$_{maj}$

All measurements were made on a Rigaku XtaLAB P200 diffractometer using graphite monochromated Cu-Kα radiation

217$_{maj}$ (2*R*,3*S*)	
CCDC	1939040
empirical formula	$C_{36}H_{33}NO_5S_2$
formula weight	623.78
crystal description	colourless, prism
space group	$P2_12_12_1$ (#19)
***a* [Å]**	10.42000(5)
***b* [Å]**	14.50400(6)
***c* [Å]**	20.50210(10)
vol [Å]^3	3098.52(2)
Z	4
reflns collected	35895
Ind. reflns (R_{int})	6287 (0.0155)
R_1 [l > 2σ(l)]	0.0227
wR_2 (all data)	0.0624
Flack parameter	0.000(2)



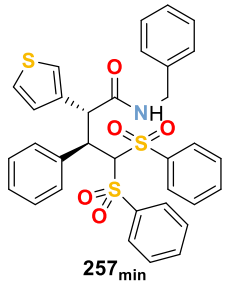
217$_{maj}$



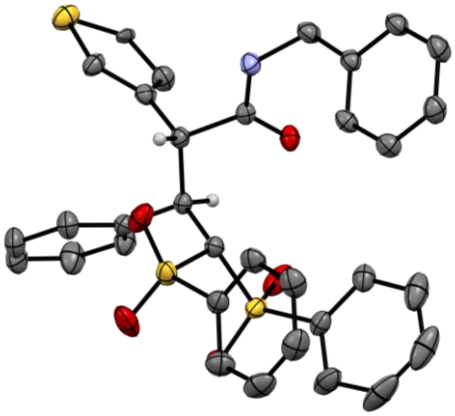
257$_{min}$

All measurements were made on a Rigaku XtaLAB P200 diffractometer using multi-layer mirror monochromated Cu-Kα radiation.

257$_{min}$ (2*R*,3*R*)	
CCDC	1939041
empirical formula	$C_{33}H_{29}NO_5S_3$
formula weight	615.78
crystal description	colourless, prism
space group	$P2_12_12_1$ (#19)
***a* [Å]**	7.88843(7)
***b* [Å]**	13.11430(11)
***c* [Å]**	28.6324(3)
vol [Å]^3	2962.06(5)
Z	4
reflns collected	34576
Ind. reflns (R_{int})	6061 (0.0238)
R_1 [l > 2σ(l)]	0.0363
wR_2 (all data)	0.1015
Flack parameter	0.002(4)



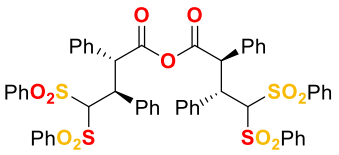
257$_{min}$



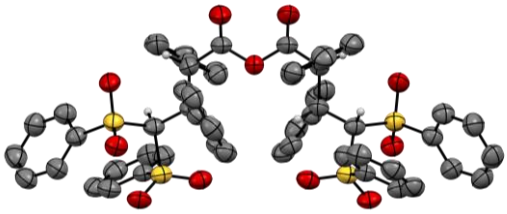
316

All measurements were made on a Rigaku XtaLAB P200 diffractometer using multi-layer mirror monochromated Cu-Kα radiation.

316 (2*R*,3*S*)	
empirical formula	$C_{56}H_{46}O_{11}S_4$
formula weight	1023.21
crystal description	colourless, prism
space group	$C222_1$ (#20)
***a* [Å]**	12.9929(7)
***b* [Å]**	13.3123(8)
***c* [Å]**	28.9067(15)
vol [Å]^3	4999.9(5)
Z	4
reflns collected	26081
Ind. reflns (R_{int})	5101 (0.1066)
R_1 [l > 2σ(l)]	0.0723
wR_2 (all data)	0.2370
Flack parameter	-0.03(2)

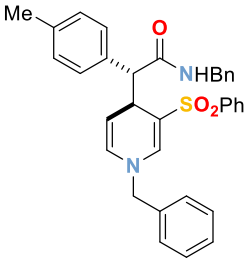


316

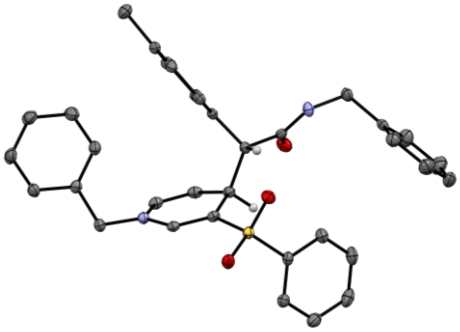


395

395 (±)	
empirical formula	$C_{35}H_{34}Cl_2N_2O_3S$
formula weight	633.63
crystal description	colourless, prism
space group	C2/c (#15)
***a* [Å]**	27.4341(8)
***b* [Å]**	14.0679(4)
***c* [Å]**	16.1319(5)
vol [Å]^3	6191.0(3)
Z	8
reflns collected	35889
Ind. reflns (R_{int})	6726 (0.0627)
R_1 [l > 2σ(l)]	0.0372
wR_2 (all data)	0.1065



395



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