APPLICATIONS OF ISOTHIOUREAS IN SURFACE CHEMISTRY:
MODIFICATION OF SELF-ASSEMBLED MONOLAYERS AND IMMOBILISATION ON POLYMER SUPPORTS

Ross Chisholm

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

2017

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Applications of Isothioureas in Surface Chemistry:
Modification of Self-Assembled Monolayers and Immobilisation on Polymer Supports

Ross Chisholm

2016

This thesis is submitted in partial fulfilment for the degree of PhD at the University of St Andrews
Always look on the bright side of life.

Monty Python
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I, Ross Chisholm, hereby certify that this thesis, which is approximately 58,000 words in length, has been written by me, and that it is the record of work carried out by me, or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for a higher degree.

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Date……………………signature of candidate………………..

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Acknowledgements

I would like to start by thanking Professor Andrew Smith for giving me the opportunity to work within his highly talented research group, and for seeing the potential in me at an early stage, hopefully he benefitted from me as much as I have from him over the last 4 years. I would also like to thank Dr Georg Hähner whose expert knowledge of surface chemistry helped me pick up some of the trickier concepts, and who has helped drive the project and PhD over the years. Thanks must go to Dr John Parkin who was in this with me from the start contributed greatly to my understanding of surface science. Thanks go to the other members of the Hähner group, Dr Richard Bailey and David Jones who were able to lend a hand towards the end.

As I have found out over the last 4 years, a PhD is not just about science but about the people you meet and share experiences with along the way, making my time in St Andrews some of the best years of my life.

Firstly, I would like to thank Angeliki who has helped me immensely over the last 2 years with her support and encouragement and reminded me that life isn’t just about chemistry. Next, I will thank the other members of “The Ranch” lab bay; Tom West for being a good friend and housemate over the past years, his questionable chat and chemistry knowledge making him a tolerable lab mate! Don Diego Javier Barrios Antunez who’s extremely loose….chat kept the bay entertaining during my time there (breakfast of champions!); Danger K for being, well, the most German man I think I’ve ever met, except when it comes to safety. Next thanks go to the office bay; Claire Young for sharing the same level of enthusiasm for a good mug of scald, “there’s always time for tea”; Dr Dan Stark for being the first of our cohort to get through the pearly gates and showing us how it’s done; Stéphanie Spoehrle for putting up with my antics in the office and in general! Notable mentions go to Ryan “Coug’s” Kerr for his emphatic love of HP; Sam Smith for his love of all things sporty (Sky Sports watch out!) and his computer monitor turned 95 °; Dr James Taylor for his constant and sometimes infectious love for chemistry, all ready (and willing) to proof read regardless of how full his plate might be and his keenness for a chat/chop and Rifa for taking on my project after I leave. Previous group members such as Ed “The Boss” Richmond who willingness to show me the ropes when I started have contributed to the chemist I am today; Dr Eoin Gould whom I had the good fortune to spend 6 months in the same fume hood with and the rest of the ADS group who have contribute to my learning experiences during my time here.

Praise must go to the great post-docs we’ve had in the ADS in my time; Dr David Daniels, who was never afraid to voice his opinion and to Dr Mark Greenhalgh and Dr Aileen Frost for helping out with proof reading this thesis. Outside the lab there are many people who deserve thanks for hepsling me through the difficult times, most notably my parents Glenda and Martin who have
helped me immensely both emotionally (and financially!) and my grandparents Veronica and Tommy (1941-2013), all of whom I would like to dedicate this PhD thesis to.

I’d like to also thank all the technical services that have contributed to this work; Dr Tomas Lebl and Mrs Melanja Smith at the NMR service, University of St Andrews, Dr Steve Francis at the St Andrews XPS facility; EPSRC UK National Mass Spectrometry Facility at Swansea University and the National EPSRC XPS Users Service, Newcastle University.
Abstract

The research outlined in this thesis describes the development of organocatalytic methodology for the modification of self-assembled monolayers on silicon dioxide surfaces and its extension towards an asymmetric protocol and immobilisation of isothiourea organocatalysts to polystyrene supports.

Chapter 1 aims to describe the fundamental aspects of self-assembled monolayers and their place within the wider area of surface chemistry. A recent overview of catalytic surface functionalisation is discussed as well as the historical context of this project, with respect to research within the Smith group, is also presented. A statement of the initial aims and objectives of the research is presented.

Chapter 2 describes the proof-of-concept study undertaken to develop methodology towards the functionalisation of silicon oxide surfaces using an isothiourea-catalysed organocatalytic Michael addition-lactonisation process. Subsequent characterisation of the resulting surfaces and a reaction scope is also carried out in this system.

Chapter 3 describes an extension of the methodology carried out in the previous chapter to allow for an asymmetric protocol. The sense of enantioenduction of the resulting surfaces was then examined using chemical force microscopy using a novel AFM probe with the results show that chiral discrimination can be achieved using this methodology. Control experiments were also undertaken by depositing enantiopure starting materials on a surface and measuring the adhesion forces confirming the presence of a chiral surface.

Chapter 4 describes the immobilisation ($R$)-BTM and ($2R,3S$)-HyperBTM analogues onto polystyrene supports and their evaluation in several different reaction classes previously investigated within the Smith group. Results show that the polymer-supported catalyst ($2R,3S$)-HyperBTM can be recycled up to 8 times without any major loss in yield or selectivity.

Chapter 5 offers a brief summary of the work undertaken in this PhD and some of the conclusions that can be drawn from it as well as an insight into the potential future developments of this research and areas where it could possibly expand and develop.
The work described in this thesis has formed the basis of the following peer reviewed publications:

1) “Isothiourea-Mediated Organocatalytic Michael Addition-Lactonization on a Surface: Modification of SAMs on Silicon Oxide Substrates”
Ross Chisholm, John D. Parkin, Andrew D. Smith and Georg Hähner.

2) “Synthesis and chiral discrimination of enantioenriched C(6)-trifluoromethyldihydropyranones by chemical force microscopy”
John D. Parkin, Ross Chisholm, Andrew D. Smith and Georg Hähner.
*Manuscript in preparation, 2016.*
Abbreviations

Ac Acetyl
APCI Atmospheric pressure chemical ionisation
app. Apparent
aq. Aqueous
Ar Aromatic
AFM Atomic force microscopy
atm Atmosphere
ATR Attenuated total reflectance
BEMP 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINOL 1,1’-Bi-2-naphthol
Bn Benzyl
Boc N-tert-Butyloxycarbonyl
br Broad
BTM Benzotetramisole
Bu Butyl
Bz Benzoyl
c Concentration
C Celsius
CA Contact angle
CFM Chemical force microscopy
CI Chemical ionisation
Cy Cyclohexyl
cm Centimeter
d Doublet
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT Density functional theory
DHPB 3,4-Dihydro-2H-pyrimido[2,1-b]benzothiazole
DMAP 4-Dimethylaminopyridine
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<tr>
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<th>Full Form</th>
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<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diasteroisomeric ratio</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalent molar quantity</td>
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<tr>
<td>ESI</td>
<td>Electrospray ionisation</td>
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<td>Et</td>
<td>Ethyl</td>
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<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
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<tr>
<td>g</td>
<td>Gram(s)</td>
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<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
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<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
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<td>HRMS</td>
<td>High resolution mass spectrometry</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>iPrOH</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>i</td>
<td>Iso</td>
</tr>
<tr>
<td>ITU</td>
<td>Isothiourea</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium di-iso-propylamide</td>
</tr>
<tr>
<td>m</td>
<td>Molar (i.e. mol dm$^{-3}$)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
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<tr>
<td>m</td>
<td>Multiplet</td>
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<td>m</td>
<td>Meta</td>
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<td>Me</td>
<td>Methyl</td>
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<td>Mesityl</td>
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<td>MHz</td>
<td>Megahertz</td>
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<td>mg</td>
<td>Milligram(s)</td>
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<tr>
<td>mL</td>
<td>Millilitre(s)</td>
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<td>--------------</td>
<td>--------------------------------</td>
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<tr>
<td>mol</td>
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<tr>
<td>mp</td>
<td>Melting point</td>
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<tr>
<td>M.S.</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave-assisted reaction</td>
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<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Np</td>
<td>Naphthyl</td>
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<td>Nucleophile</td>
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<td>o</td>
<td>ortho</td>
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<td>p</td>
<td>para</td>
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<tr>
<td>PG</td>
<td>Protecting group</td>
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<tr>
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<td>Phenyl</td>
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<tr>
<td>PMP</td>
<td>para-Methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>PS</td>
<td>Polymer-supported</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>quant.</td>
<td>Quantitative</td>
</tr>
<tr>
<td>quint</td>
<td>Quintuplet</td>
</tr>
<tr>
<td>RMS</td>
<td>root mean squared</td>
</tr>
<tr>
<td>S</td>
<td>selectivity factor</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>rt</td>
<td>Ambient (room) temperature</td>
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<tr>
<td>s</td>
<td>Singlet</td>
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<tr>
<td>sat.</td>
<td>Saturated</td>
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<td>t</td>
<td>Triplet/time</td>
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<td>T</td>
<td>Temperature</td>
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<tr>
<td>TBD</td>
<td>1,5,7-Triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
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<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>XPS</td>
<td>X-Ray photoelectron spectroscopy</td>
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Chapter 1: Introduction

1.1 Molecular self-assembly

For billions of years Nature has used molecular self-assembly to construct a dazzling array of well-defined supramolecular structures, such as proteins and bio-macromolecules, from smaller and more available building blocks.\(^1\) By studying the intricate chemical strategies and cooperative molecular processes by which supramolecular architectures are assembled in Nature, we can begin to exploit self-assembly processes for the synthesis of entirely new materials.\(^1\) The term self-assembly encompasses a diverse range of processes ‘where a disordered system of components spontaneously form an organised structure or pattern as a consequence of local interactions, importantly, without external direction’ (Figure 1).\(^2\) The concept of self-assembly is being used in an increasingly large number of disciplines with a different emphasis in each one.

Self-assembly has several beneficial attributes such as cost-effectiveness, versatility, and a facile nature owing to the fact that the process occurs towards the systems’ thermodynamic minima. Self-assembly is also one of the few practical strategies for making ensembles from nanostructures.\(^3\) There are two main types of self-assembly: static and dynamic. Static self-assembly is the most well studied to date and includes processes such as the assembly of ionic and molecular crystals,\(^4\) liquid crystals,\(^5\) as well as self-assembled monolayers.\(^6\) Dynamic self-assembly includes more complicated processes such as the formation of bacterial colonies,\(^7\) swarms,\(^8\) and weather patterns.\(^4\) To build a molecular scale device, a purpose many self-assembled systems are originally designed for, requires a means of modifying a surface with molecular level control. The main route to achieving this level of control is the use of self-assembled monolayers.\(^9\)

![Figure 1: Modular and convergent example of self-assembly. Figure modified from reference 4.](image-url)
1.2 **Self-assembled monolayers on Si/SiO$_2$**

While there exists a myriad of sub-divisions within the realm of molecular self-assembly, the focus of this thesis is on the modification of silicon oxide surfaces using self-assembled monolayers (SAMs) and their subsequent functionalisation using Lewis base organocatalysis. “Self-assembled monolayers are ordered molecular assemblies formed by the adsorption of an active surfactant on a solid surface” (Figure 2).[10]

![Figure 2: Schematic representation of the deposition and sequent modification of self-assembled monolayers. Figure modified from reference 111.](image)

SAMs were first reported by Zisman and co-workers in a 1946 publication titled “Oleophobic Monolayers I. Films Adsorbed From Solution In Non-Polar Liquids”.[11] The authors discovered that upon immersion of a suitable surface (Pt) into a solution of eicosyl alcohol (C$_{20}$H$_{41}$OH), an oleophobic monolayer formed that was thought to be monomolecular in nature. Subsequent analysis of the resulting SAMs gave strong support for this hypothesis. Surprisingly though, barring a few sporadic reports, [12-15] the field lay dormant for over three decades and it wasn’t until 1980 when Sagiv reported the use of octadecyltrichlorosilanes (OTS) as amphipathic precursors for the formation of a well-ordered SAM on glass from dilute solutions (Figure 3).[16] This report inspired a new wave of academic interest in the field of self-assembled monolayers on a variety of solid surfaces.[10, 17-18]
Figure 3: Use of OTS on glass to fabricate a SAM reported by Sagiv.

1.2.1 Deposition mechanism of alkylsilanes on SiO$_2$

While many, if not all, suitable oxide surfaces can facilitate the formation of an alkylsilane based SAM to some degree, certain surfaces are better than others.\textsuperscript{[19]} The properties of these films, that is; thickness, orientation, chemical composition and order of the alkyl chains, has been studied in detail with a general trend in terms of effectiveness evident (Figure 4).\textsuperscript{[16, 20-24]} Some of the advantages of using alkylsilanes on Si/SiO$_2$ to form SAMs are their physical,\textsuperscript{[25-27]} thermal \textsuperscript{[28-29]} and chemical stability\textsuperscript{[10, 18]} over their alkanethiol on Au counterparts.

![Chemical structure](image1)

**Figure 4:** Effectiveness of silane deposition on a variety of oxide surfaces.

The most common protocol for the preparation of alkylsilane based SAMs is the immersion of a hydrophilic Si/SiO$_2$ surface into a dilute (0.25-2.5 mM) solution of the desired silane for a suitable time (~16 h) at room temperature. Removal and subsequent cleaning usually affords a densely packed SAM. Commonly, the oxide surface in question is activated prior to self-assembly in order to expose the maximum amount of hydroxyl groups.\textsuperscript{[30]} Several methods have been developed to achieve this but usually strong acids and/or oxygen plasma are used.\textsuperscript{[31-32]} This cleaning procedure renders the surface extremely hydrophilic, which makes it prone to the formation of a thin water layer. There is a general consensus that trace amounts of water on the oxide surface is needed to form a well-packed monolayer. In the original report by Sagiv\textsuperscript{[16]} he recognised that water adsorbed onto a surface was necessary to hydrolyse the chlorosilane, and assumed that the hydrolysed silanes underwent condensation reactions with the surface hydroxyl groups as well as adjacent OTS molecules to form a polymerised chain where each OTS molecule is individually anchored to the surface. However, this view was adjusted when Finklea and co-workers showed that a well-packed monolayer of OTS could be formed on an Au surface - a surface devoid of any
The authors concluded that self-assembly must occur on the adsorbed water layer on the Au surface and that the silane groups are incorporated into a 2D cross-linked network of Si-O-Si bonds. In the case of alkylsilanes on Si/SiO$_2$ the overall deposition picture is similar but with some modifications. It is proposed that only 10-20% of the alkylsilanes need to form a covalent bond to the surface, which suggests that SAM formation is driven primarily by interactions between hydrocarbon chains and Si-O linkages between adjacent silanols (Figure 5). X-ray reflectivity experiments by Silberzan and co-workers$^{[34]}$ also indicated that not all of the molecules are covalently linked to the surface but rather exist in a cross-linked network similar to that proposed by Finklea et al.$^{[33]}$ This also explains the observation that alkylsilane SAMs on Si/SiO$_2$ are mechanically and chemically more robust than the alkylsilane SAMs on Au counterpart.

The ease of preparation of SAMs on Si/SiO$_2$ is a major advantage towards their use in nanoscale device fabrication. However, despite their ease of preparation it is exceedingly difficult to reproduce a well-defined SAM as their formation is strongly dependant on a range of parameters including solution age,$^{[35]}$ solvent,$^{[36]}$ water content,$^{[35, 37]}$ deposition time,$^{[38]}$ and temperature.$^{[39, 40]}$ One of the major issues with the preparation of alkylsilanes with a headgroup consisting of trichlorosilane (R-SiCl$_3$), trimethoxysilane (R-Si(OMe)$_3$) or triethoxysilane (R-Si(OEt)$_3$) is adventitious formation of polysiloxanes that can physisorb onto the SiO$_2$ surface.$^{[9, 34]}$ However, it is very difficult to distinguish physically adsorbed silanes from chemically adsorbed ones, which in turn impacts on the performance of the SAM in subsequent applications. An ill-defined

Figure 5: Self-assembly process of alkylsilanes on Si/SiO$_2$ surfaces. $^\dagger$

$^\dagger$ 2D Si-O-Si network has been greatly simplified (2D vs 3D) in Figure 5 for clarity purposes.
SAMs can present a major concern when the monolayer is to be used as the base layer for truly molecular devices.\textsuperscript{[41]}

1.2.2 Applications of SAMs on Si/SiO\textsubscript{2}

Alkylsilane-based SAMs have varying applications in the field of microelectromechanical systems (MEMS) and their smaller equivalents nanoelectromechanical systems (NEMS). MEMS and NEMS are often made from silicon because of its desirable mechanical properties.\textsuperscript{[42]} The field of MEMS has grown rapidly over the last few years due to the expanded market for micromachined mechanical transducers.\textsuperscript{[43]} Specific applications of MEMS and NEMS include the fabrication of DNA chips and protein microarrays\textsuperscript{[44,45]} as well as microelectrical devices\textsuperscript{[46]} and electrochemical sensors.\textsuperscript{[47]}

Yoshioka et al. demonstrated one of the first examples of immobilisation of a monoclonal antibody to a silicon surface (Figure 6).\textsuperscript{[48]} The aim was to immobilise monoclonal antibody 7 on a surface of a glass tube as a model to confirm the stability of ultra-thin SAMs by enzyme immunoassay. The authors deposited an initial amine terminated SAM 4 from 3-aminotriethoxysilane (APTES), which was modified with glutaraldehyde 5 to generate aldehyde terminated SAM 6. Reductive amination of amine functionalised normal mouse monoclonal Ab 7 afforded surface 8. The amount of antibody immobilised on the surface was measured using an enzyme immunoassay by reaction with anti-mouse IgG and p-nitrophenylphosphate in alkaline phosphatase buffer. The amount of p-nitrophenol was monitored by fluorescence to quantify the amount of antibody immobilised.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{reaction_scheme.png}};
\end{tikzpicture}
\end{center}

\textbf{Figure 6: Immobilisation of anti-mouse immunoglobulin G on a glass tube.}
1.3 **Self-assembled monolayers on Au**

Thiolates on Au surfaces are the most studied within the scientific literature,[18] as there are several advantages to using them over other solid surfaces. Au is easy to obtain and is straightforward to prepare as a thin film on a suitable surface. Au is a reasonably inert metal and does not form oxides at ambient temperatures as it does not react with atmospheric O₂. Au can also bind thiols with high affinity and readily forms Au-S bonds on a surface,[49] which is a highly desirable property as they readily displace adventitious materials from the surface during the deposition process. A detailed structure of a thiolate based SAM on Au showing the various impurities and structural defects possible is shown in Figure 7.

![Figure 7: Schematic illustration of some of the intrinsic and extrinsic features of SAMs on Au surfaces. Figure taken from ref 18.](image)

Not long after the seminal work by Sagiv using alkylsilanes on Si/SiO₂, Allara *et al.* published the first report of forming a thiol based SAM on a Au surface.[49] The authors deposited a series of disulfides on Au⁰ surfaces and measured the resulting film thickness, contact angle and IR spectra, all of which indicated a densely packed SAM was being formed on the Au surface (Figure 8).

![Figure 8: Deposition of series of disulfides by Allara *et al.*[49]](image)

### 1.3.1 Deposition mechanism

The chemistry involved for the absorption of thiols on Au is, in principle, the most straightforward but in many ways remains the most perplexing. As Au does not form stable oxides in ambient
conditions, the formation of SAMs from thiols is not complicated by chemistries that may be required to reduce or displace surface oxides. Surprisingly, the nature of the gold-thiol bond is still a subject of controversy even though many characterisation techniques have been used to study it. While the exact details still remain elusive, a qualitative picture may be presented for certain classes. The formation of a thiolate requires the activation of the S-H bond of the thiol or the S-S bond of a disulfide. The reaction may be considered as a formal oxidative addition of the S-H bond to the Au surface followed by reductive elimination of the hydrogen. The thiol-gold bond is sometimes described as a surface bound thiolate with a bond energy of 170 kJ mol\(^{-1}\) due to the polar nature of the bond, and is regarded as a pseudo-covalent bond (Equation 1) with van der Waals forces between neighbouring molecules stabilising the structure.

\[
\text{Equation 1: Reaction of an alkanethiol with a Au}^0 \text{ surface to form a Au-S bond.}
\]

The initial stage of thiolate chemisorption on Au involves the formation of ‘lying down’ phases where alkanethiol molecules are parallel to the surface (Figure 9). When the surface coverage increases, a transition from parallel to ‘standing-up’ configuration takes place and the resulting monolayer formed has the alkyl chains in the all \textit{trans}-conformation, that is, tilted 20-30° from the normal to the Au surface.

Despite their ease of preparation and widespread use, alkanethiol based SAMs often face stability issues. Their poor long term stability is due to oxidation of the Au-S bond to either sulfinates (-SO\(_2\)) or sulfonates (-SO\(_3\)) with the rate of oxidation varying significantly with chain length. Alkanethiol based SAMs also suffer from low thermal stability as the desorption of thiols from the Au surface occurs at ~60 °C, which means that any modification of thiolate SAMs on Au must be performed below this temperature to keep the SAM intact.
1.3.2 **Applications of SAMs on Au**

Despite the aforementioned disadvantages, alkanethiol based SAMs are still the most popular system for forming molecular assemblies where a molecular level control is desired. These type of SAMs are suited towards a wide variety of applications including electron transfer processes,[60-61] protein resistant surfaces,[62-63] immobilisation of DNA,[64-65] carbohydrates arrays for use in glycomics,[66-67] and antibody immobilisation[68-69]

Ozoemena and co-workers have reported the use of thiol based SAMs on Au as an electrochemical sensor for the recognition of anti-mycolic acid antibody, which is present in tuberculosis positive human serum co-infected with human immunodeficiency virus (HIV).[70] The authors were able to attach a SAM of steric acid *via* an amide coupling reaction and subsequently integrate a mycolic acid (MA) antibody 14 into the Au electrode (Figure 10). This electrode was then able to discriminate between TB-positive and TB-negative serum. The results show that the Au electrode 15 could detect HIV*-TB* serum diluted as high as 1:2000, indicating that this particular immunosensor has a high degree of sensitivity. The authors also conduct cyclic voltammetry scans and show no detectable deviations even after 20 repetitive scans indicating electrochemical stability.

![Figure 10: Fabrication of a mycolic acid antibody onto a Au surface via a SAM.](image)

Leigh and co-workers have fabricated a photo-responsive Au surface based on a switchable fluorinated molecular shuttle.[71] The authors deposited a pre-synthesised rotaxane onto a carboxylic acid terminated Au surface and tested the effects of a photo-induced wetting/dewetting protocol (Figure 11). A drop of diiodomethane was placed on the rotaxane surface and irradiated with a perpendicular beam of 240-400 nm light focused on one side of the drop. After
irradiation for 900 s the droplet had elongated 0.8 mm and the contact angle decreased from 35 ±2° to 13 ±2°. Amazingly, transport of the entire droplet occurred at a mean speed of ~1 µm s⁻¹ signifying that discrete changes in surface polarity can translate to the macroscopic level.

![Image](image.png)

**Figure 11:** A photo-responsive surface based on switchable molecular shuttles. Reprinted with permission from reference 73. Copyright 2016 Nature Publishing Group.

### 1.4 Modification of other oxide surfaces

Gademann and co-workers have developed a molecular surface modification platform based on nitrocatechol derivatives that allows functionalisation of TiO₂ and efficient release of a nanoparticle bound cargo by photoinduction using UV light at 366 nm.[72] The authors designed a nitrocatechol derivative which was anchored to a TiO₂ nanoparticle (Figure 12) and used HPLC analysis to measure the increase in concentration of fluorophore 18 upon photocleavage of 16. The features of this protocol are the ease of functionalisation of TiO₂ particles, the stability of the resulting particle and rapid release of the bound cargo (ca. 50% in 46 min).
Figure 12: Photocleavage of nitrocatechol 16 under UV light at 366 nm.

Talham and co-workers have developed a Mn\textsuperscript{III} porphyrin catalyst 21 supported on zirconium phosphonate films and evaluated its catalytic efficiency in the epoxidation of cyclooctene.\textsuperscript{[73]} The authors impressively deposited a series of organic monolayers using a combination of Langmuir-Blodgett and SAM methodologies to afford a Zr\textsuperscript{4+} surface. A pre-synthesised Mn\textsuperscript{III} porphyrin complex was then anchored to the surface via phosphonate moieties where each Zr\textsuperscript{4+} site is bound to a single octadecylphosphonic acid moiety. The macrocycle plane is believed to be oriented almost parallel to the surface. The surface bound porphyrin was evaluated in the epoxidation of cyclooctene 19 as well as that of its homogeneous equivalent. The results showed that thin films of the Mn\textsuperscript{III} porphyrin 21 were more effective, in terms of TON, than the homogeneous reaction. This is in part due to the deactivation of the homogeneous system after a certain time due to the formation of dimers in solution. While the authors cite that monolayers on flat surfaces have limited utility as practical catalysts due to the difficulty in achieving large surface areas, these types of systems can be useful tools in the study of heterogeneous reactions.

Figure 13: Epoxidation of cyclooctene using supported Mn\textsuperscript{III} porphyrin catalyst 21. OTS = octadecyltrichlorosilane. ODPA = octadecylphosphonic acid.

1.5 Analytical techniques

With surface science many spectroscopic and analytical techniques can be employed to investigate various properties of surfaces and nanostructures. During the course of this work four main techniques were employed to assess the success of the self-assembly process as well as the subsequent reactions performed on the surface. These include X-ray photoelectron spectroscopy (XPS), atomic force microscopy (AFM), ellipsometry and static water contact angle (CA) and are discussed in detail in the following section.
1.5.1 **Atomic force microscopy**

Atomic force microscopy (AFM) is a type of scanning probe microscopy and can demonstrate resolutions on the nanometre scale. The sensing part of an AFM consists of a microcantilever that is fixed at one end, connected to a support chip which is held in place by the AFM system while the other end of the cantilever has a sharp tip attached. When the tip is brought into proximity with the sample surface, intermolecular forces, such as van der Waals, between the tip and sample lead to a deflection of the cantilever.\cite{74-75} This movement is detected by a laser which is reflected off the back of the cantilever and relays back information to the detector (Figure 14). If the tip is scanned over the surface and the response of cantilever movement is monitored then a topographic image of the surface can be generated.\cite{78}

![Figure 14: Main components of an AFM setup.](image)

There are several different operational modes in AFM; static, and dynamic mode. In static mode the feedback system of the instrument keeps a set force between the tip and surface by monitoring the microcantilevers static bending and moving.\cite{77} Essentially the tip is dragged across the surface and the resulting image is a contour of constant force. In tapping mode the tip oscillates up and down, contacting the surface then retracting.\cite{78} In tapping mode there is often no hard contact between the tip and surface, which makes damage to the tip and/or surface much less likely. AFM can provide a topographic image of the surface and helps the user ascertain the roughness and cleanliness level of the surface under inspection.

1.5.2 **X-Ray photoelectron spectroscopy (XPS)**

XPS is one of the most important spectroscopic methods used for analysing surfaces.\cite{79-80} XPS is based on the photoelectric effect, where the binding energy of a core-level electron is overcome by the energy of an X-ray photon and the core level electron is ejected from the surface.\cite{81} The kinetic energies ($E_K$) of the ejected electrons are measured by an electron spectrometer. Since the total energy is conserved, $E_K = h\nu - E_B$, where $h\nu$ is the energy of the photons and $E_B$ is the binding
energy. The binding energy of each photoelectron is characteristic of the orbital from which the photoelectron came and the binding energy depends on the final state configuration after photoemission. The final state is characterised by full relaxation of all atomic orbitals towards the hole in the core level (Figure 15).

![Diagram of photoelectron emission process.](image)

**Figure 15: Photoelectron emission process.**

The study of ejected photoelectrons can provide a wealth of information about the composition of a surface. Identification of the surface can be obtained through survey scans that scan over the entire range of binding energies (measured in eV) that are relevant to the organic components and the surface. Each element has a characteristic set of peaks in the spectrum, with peak positions influenced by oxidation state of the element and its chemical environment.

1.5.3 **Contact angle**

The static water contact angle of a solid surface can be used to establish its hydrophilicity or hydrophobicity. It is a basic technique that measures the resulting angle of a drop of deionised water on a surface that can indicate changes in the terminal functional groups of a monolayer. Depending on the roughness and interactions on a surface, the contact angle can be lower than 90°, which is considered hydrophilic, or greater than 90°, which is considered hydrophobic (Figure 16).

![Diagram of contact angle.](image)

**Figure 16: Degrees of hydrophilicity and hydrophobicity on a solid surface.**
1.5.4 Ellipsometry

Ellipsometry is an optical spectroscopic technique that is used to determine the thickness of thin films on solid surfaces. The film thickness can be calculated by measuring changes of an elliptically polarised light beam resulting from an interaction with the sample (Figure 17). A beam of monochromatic light, which is polarised in a known state, is released upon a sample and the state of the polarized light is examined.\[83\] Ellipsometry measures the change in phase shift and amplitude component of the light that is reflected or transmitted by the sample and from this a monolayer thickness, relative to the known oxide layer (in the case of Si/SiO\(_2\)), can be calculated.\[84\]

![Figure 17: Schematic representation of a typical ellipsometry experiment.](image)

1.6 Catalytic surface functionalisation

Most of the methods reported for the functionalisation of oxide surfaces are based on stoichiometric reactions between the surface and alkoxy- or allylsilanes and are usually carried out at high temperatures and sometimes harsh conditions.\[85-86\] Therefore, the development of catalytic methods that offer facile and mild conditions for the functionalisation of oxide surfaces, which also circumvent the use of moisture sensitive silane reagents commonly employed in the deposition process, are highly desirable.

Jun and co-workers reported a one-step grafting procedure for the preparation of azide, chloride, cyano and aldehyde terminated silica surface at room temperature using a catalytic amount of Sc(OTf)\(_3\) to promote the reaction.\[87\] The authors synthesised a range of silanes and through the grafting procedure, derivatives of 24 were attached to a silica surface in a one-pot process (Figure 18). The grafting process is thought to proceed through a carbocation intermediate 29 and following attack of silanol 28 on organosilane 29 to release isobutene, a Si-O bond is formed to the surface forming 30. Subsequent repetition of this reaction sequence, confirmed by disappearance of \(^{13}\)C resonances associated with the methallyl group in the CP-MAS \(^{13}\)C NMR spectrum, afforded 25 with both methallylsilyl groups covalently bonded to the surface.
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Figure 18: Grafting of organomethylallylsilane to a silica surface in the presence of catalytic Sc(OTf)$_3$ proposed to proceed via carbocation 29.

Another report from the research group of Jun has shown that hydroxyl-terminated Si/SiO$_2$ surfaces (glass) can be functionalised with vinylsilanes in the presence of catalytic [Ir(COE)$_2$Cl]$_2$ 33 to afford various alkyl terminated surfaces. The authors deposited a series silanes on hydroxyl-terminated glass surfaces in the presence of [Ir(COE)$_2$Cl]$_2$ 33 and N,N-dimethylacetamide HCl 34, which successfully promoted the grafting of silanes to the surface as confirmed by contact angle (CA) analysis (Figure 19).

Figure 19: Grafting of vinylsilanes onto hydroxyl terminated silicon surfaces promoted by catalytic [Ir(COE)$_2$Cl]$_2$. COE = cyclooctene.

Nakanishi and Shimada have shown the functionalisation of silica can proceed in the presence of catalytic B(C$_6$F$_5$)$_3$ 38 through an organocatalytic Si-H activation of hydrosilanes. The reaction is thought to proceed initially by complexation of hydrosilane 37 with B(C$_6$F$_5$)$_3$, catalyst 38 to form 40. This highly reactive intermediate then reacts with surface silanol 36 to form complex 41. One of the possible reasons for such a fast reaction between silane 40 and surface silanol 36 is the acidity of the surface silanol (pK$_a$ = 4.9-8.5), which makes the silanol oxygen prone to electrophilic attack by the silicon in complex 40. Finally borane hydride 41b deprotonates the
acidic proton in 41a, forming H₂ and regenerating the B(C₆F₅)₃ catalyst 38. This procedure was tolerant of a variety of functional groups including halogens, azides, amines, esters, carboxylic acids and ketones, some of which are readily reduced in the presence of hydrosilanes in homogeneous reactions.\(^{[91-93]}\)

\[ \text{Me} \quad \text{O} \quad \text{Si-O-Si-R} \quad \text{Me} \quad \text{B(C₆F₅)₃} \quad 38 \quad (1 \text{ mol%}) \quad \text{Me} \quad \text{O} \quad \text{Si-O-Si-R} \quad \text{Me} \quad \text{H₂} \]

\[ \text{Me} \quad \text{O} \quad \text{Si-O-Si-R} \quad \text{Me} \quad \text{B(C₆F₅)₃} \quad 38 \quad \text{Me} \quad \text{O} \quad \text{Si-O-Si-R} \quad \text{Me} \quad \text{R} = \text{alkyl, aryl, hetero} \]

\[ \text{18 examples} \quad 0.52-1.75 \text{ mmol/g loading} \]

Figure 20: Functionalisation of silica in the presence of catalytic B(C₆F₅)₃ 38 through an organocatalytic Si-H activation of hydrosilanes and plausible mechanism.

While the grafting of various functionalities directly onto an oxide surface is a desirable property, the post-deposition functionalisation of monolayers can also be useful as the molecular control SAMs provide is tuneable and a variety of known procedures are available for this process. This type of surface modification has not yet been fully acknowledged because of low yields and the fact that little is known about the rules that govern organic reactions on surfaces.\(^{[59, 94]}\) Despite this potential disadvantage, several transition metal-catalysed reactions have been developed for the functionalisation of SAMs on silicon, gold and germanium surfaces. Several research groups have reported the use of catalytic Pd in various cross-coupling reactions on SAMs.\(^{[95-98]}\) For example, Nguyen and Bedzyk sought to establish whether sequential Pd-catalysed Sonogashira cross coupling reactions would occur on acetylene terminated SAMs to afford conjugated organic surfaces.\(^{[96]}\) The authors synthesised an aryl iodide terminated SAM 42 on Si and performed a Sonogashira coupling on the surface using a microwave assisted procedure (Figure 21). The authors achieved high conversion in short reaction times with no noticeable over coupling of bromoacetylene 44 to give the diacetylated product.
Lewis and co-workers have utilised the well-known Pd-catalysed Heck reaction to couple olefins to a mixed monolayer surface.\textsuperscript{[98]} A silicon surface comprised of a thiophenyl and methyl mixed monolayer was subjected to catalytic Pd(PPh\textsubscript{4}) followed by immersion in a solution of the appropriate terminal olefin to afford the Heck coupled product (Figure 22). The reaction proceeded cleanly, as no residual surface bound Pd was detected by XPS. Electrochemical studies also showed that the surface bound thiophene linker did not shift the electrochemical potential or impede electron transfer from the Si surface to the bound redox moieties when tested with Co, Cu and Zn.

Choi and co-workers have used an in-plane enyne metathesis strategy and subsequent Diels-Alder reaction sequence to afford tetracyano, maleic anhydride and maleimide groups on the surface of Au based SAMs.\textsuperscript{[59]} Based on previous work,\textsuperscript{[99]} they postulated that an in-plane dimerization reaction may take place in the presence of Ru metathesis catalyst 48. The authors synthesised a mixed surface consisting of a terminal alkyne and alkenes and subjected it to olefin cross-metathesis conditions using catalyst 48 (Figure 23). FTIR, XPS and time-of-flight secondary-ion mass spectrometry (TOF-SIMS) confirmed the presence of enyne metathesis products, which
were then subjected to a Diels-Alder reaction with tetracyanoethylene 50, maleic anhydride and malemide which afforded the corresponding surfaces.

Other transition metals have also been used in surface modification reactions on SAMs. Locklin and co-workers have reported the formation of electroactive polymer brushes on a surface via a surface-initiated Kumada-type polycondensation reaction. The authors used an \textit{in situ} formed Ni(COD)(PPh\(_3\))\(_2\) complex to initiate the polymerisation reaction. The Ni\(^{\text{II}}\) inserts into the C-Br bond of the thiophene to form Ni\(^{\text{II}}\) complex 54 on the surface. Following the addition of Grignard 55 and intramolecular transfer of the Ni\(^{\text{II}}\) species into the C-I bond of the thiophene, Ni\(^{\text{II}}\)I surface 56 is formed. Addition of another equivalent and repetition of the previous steps, using dilute HCl as a termination agent, affords a conjugated polymer brush on the surface with a measured thickness of 42 nm.

1.7 Previous work within the Smith group
The Smith group have previously investigated the generation and uses of ammonium enolates formed from carboxylic acid derivatives and Lewis basic isothiourea (ITU) organocatalysts. For
example, ammonium enolates generated from arylacetic acids and achiral isothioureas undergo Michael addition-lactonisation reactions with trifluoromethylenones, affording racemic dihydropyranones (DHPs) in solution with moderate to high diastereoselectivity (Figure 25).

![Figure 25: Generation of racemic DHPs with high diastereoselectivity in solution using DHPB.](image)

Furthermore, chiral isothioureas such as HyperBTM-(2S,3R) 61 catalyse the enantioselective Michael addition-lactonisation of trifluoromethylenones in solution, yielding anti-DHPs with high diastereo- and enantiocontrol (Figure 26).

![Figure 26: Generation of enantiopure DHPs in solution using HyperBTM.](image)

The proposed mechanism of the Michael addition-lactonisation proceeds via initial formation of a mixed anhydride 62 formed in situ from pivaloyl chloride and the appropriate phenylacetic acid. Subsequent N-acylation with HyperBTM-(2S,3R) 61 generates the corresponding acyl isothiouronium 63, with deprotonation generating the (Z)-ammonium enolate 64. This undergoes a stereoselective Michael addition with the trifluormethylenone 59, followed by intramolecular cyclisation, to generate DHP 66 (Figure 27).
Figure 27: Proposed catalytic cycle for the enantioselective Michael-lactonisation process.

Detailed DFT calculations were used to investigate the minimum energy transition state(s) involved in the conjugate addition step of the reaction (Figure 28). The structure of 69 highlights the preference for the intermediate isothiouronium enolate 64 to adopt a half-chair type confirmation with the phenyl component pseudo-axial. The enantioselectivity of the process arises from the stereodirecting groups on the isothiourea that block the Si face of the enolate favouring addition onto the Re face, while the diastereoselectivity comes from enolate geometry ((E) vs (Z)). The 1,5-planar geometry associated with O=S interactions allows for the orbital containing the non-bonding lone pair of electrons on the donor atom to overlap more effectively with the σ* orbital of C-S bond (n_o to σ*C-S). Tantillo and Romo have shown that n_o to σ*C-S interactions can govern the selectivity of Diels-Alder cycloadditions by restricting rotation about the C-N bond of the acylammonium salt intermediate (64 in this case) giving high endo selectivity in the products. Birman and Houk have also used computational studies to model the origin of enantioselectivity in benzotetramisole-catalysed dynamic kinetic resolution of azalactones. The authors postulate that the oxygen atom of the acyl carbonyl is nearly coplanar with the thiazolium moiety and points towards the sulfur atom, basing their arguments on non-bonding S-O interactions.
Figure 28: Possible pre-transition state assembly for conjugate addition step

Such $n_\sigma$ to $\sigma^*_{C-S}$ interactions have been reported by others in reaction processes utilising isothioureas$^{[106-107]}$ and is well-precedented in the literature.$^{[108]}$ Stahl and co-workers have shown, through a comprehensive study of small molecule crystals, that carbonyl groups display a strong preference for 1,5-\(\text{O-S}\) interactions.$^{[109]}$ An example of a non-covalent \(\text{O-S}\) interaction was elegantly shown by Nagao and co-workers where the authors show, through analysis of X-ray crystal structures and \textit{ab initio} calculations, that (acylamino)thiadiazoline derivatives exhibit an \(\text{O-S}\) attractive force.$^{[110]}$ This attractive force holds the thiadiazoline in a rigid \emph{cis} conformation (70b) and reduces the bond distance to 2.65 Å, which is significantly shorter than the sum of the Van der Waals radii (3.32 Å) (Figure 29).

Figure 29: $n_\sigma$ to $\sigma^*_{C-S}$ interactions in thiadiazoles.

In the context of isothioureas, Birman and co-workers have proposed that the 1,5-\(\text{O-S}\) interaction present in acylated isothioureas may provide enhanced activity compared with their amidine derivatives due to a conformational lock being present (Figure 30 (a)).$^{[107]}$ This view was corroborated by Romo and co-workers who postulated the reason for high selectivity in their nucleophile-catalysed aldol lactonisation (NCAL) process using (S)-HBTM 73 was due to a conformation lock in the pre-transition state assembly between the sulfur atom of the \(N\)-acylated catalyst and the oxygen atom on the carbonyl group (Figure 30 (b)).
The challenges associated with transferring a well studied homogeneous reaction to the heterogenous state are many. How the enantioselection process will proceed is a large unknown. How will the reaction proceed mechanistically? Indeed chiral molecules on surfaces have been shown to form complex two-dimensional structures with specific enantiomeric characteristics, different from what might be expected when considering the single molecule itself. As surfaces can lower the symmetry of the adsorbates, chiral molecules can display more complex behaviours on surfaces than in the gas/liquid phase and prochiral molecules can become chiral upon adsorption, also displaying specific enantiomeric characteristics. How this intrinsic feature of surfaces may play a role in the development of new enantioselective processes on surfaces is unknown. The concept of homo and heterochirality may come into play where particular domains of the monolayer on a surface posseses different chirality, possibly influencing the reaction pathway and potentially increasing or decreasing the resulting enantioselectivity. As homochirality is proposed to have originated from specific enantioselective processes occurring on chiral surfaces this may potentially play a major role in the selectivity of the reaction. One of the main challenges associated with the analysis of chiral surfaces is the measurement and quantification of the resulting selectivity. These difficulties arise from the limitations of the current state-of-the-art methodologies, not allowing for quantification of the reaction selectivity on the surface. These limitations must be overcome in order to obtain a clearer picture of what is occurring during the reaction process.

The generality and scope of this Michael addition-lactonisation procedure led us to believe that it would be a suitable candidate for optimisation on a surface functionalised with SAMs. Moreover, the potential for the generation of enantioenriched surfaces from an achiral starting material on a
surface via enantioselective organocatalysis offers a direct route towards highly functionalised SAMs with what is hoped to be high levels of selectivity.

### 1.8 Previous work within the Hähner group

Previous studies within the Hähner group has shown that a series of vinyl terminated SAMs can be deposited on SiO$_2$ using vapour phase methodology.$^{[3][11]}$ Vapour phase deposition can be conducted by vapourising a volatile silane in the presence of freshly cleaned SiO$_2$ surfaces and in a sealed reaction vessel (Figure 12 (a)). This demonstrated that a suitable silane precursor could be utilised in a vapour deposition process to afford virtually identical results to that of the solution based analogue.

*Figure 12: (a) Experimental set-up for vapour phase deposition, (b) vinyl silanes used in the deposition process.*

While this report was a proof of concept study and no subsequent reaction was performed on the surface, follow up reports show that vinyl-terminated SAMs can be exploited in a gas phase in a C-C bond forming reaction with bis(trifluoromethyl)carbenes (Figure 31).$^{[114]}$ In this study the vinyl terminated SAMs were treated with hexfluoroacetone azine (HFAA) 78 in the gas phase with the resulting films being consistent with the presence of a bis(trifluoromethyl) cyclopropane group on the surface after nitrogen extrusion.
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Figure 31: Postulated mechanism for Bis(trifluoromethyl) cyclopropane formation on a surface.

Further work in the area, has also shown that a range of dihalocarbenes can be added across vinyl terminated SAMs (Figure 32).\textsuperscript{[113]} The reactive species (dihalocarbenes) were generated from CHCl\textsubscript{3}, CHBr\textsubscript{3} and TMS-CF\textsubscript{3} (Ruppert-Prakash reagent) and were reacted with vinyl terminated SAMs to afford the subsequent dihalocarbene surfaces. XPS analysis showed that after reaction with the carbene species the overall surface coverage was around 30%.

Figure 32: Previous work showing synthesis of dihalocarbene terminated SAMs.

1.9 Project aims & objectives

Organocatalysis has become one of the main methods for selective carbon-carbon bond formation over the last decade and can provide products with high levels of stereocontrol. At the beginning of this PhD there was no example of using organocatalysis to immobilise a reactive species onto a surface. We therefore sought to modify pre-existing SAMs using isothiourea organocatalysis in the late-stage formation of functionalised trifluoromethylidihydropyranones on a Si/SiO\textsubscript{2} surface (Figure 33 (a)). Initial work focused on a proof of concept study where racemic DHPs were generated using the achiral isothiourea catalyst DHPB 60. The ultimate aim for this work was the \textit{in situ} generation of enantiomerically enriched surfaces using the chiral isothiourea HyperBTM-(2R,3S) 61 (Figure 33 (b)). A second aim was to develop a procedure for the immobilisation of reactive isothiourea organocatalysts onto a solid support and evaluate their use as heterogeneous Lewis base catalysts in a range of processes.
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Figure 33: (a) Synthesis of racemic DHP using isothiourea organocatalysis (b) Chiral discrimination of enatioenriched surfaces using chemical force microscopy (c) immobilisation of isothiourea catalyst on a polystyrene support.

1.1 References and Notes

Chapter 1: Introduction


Chapter 2: Isothiourea-catalysed Michael addition-lactonisation on a surface

Introduction

This chapter describes the post-deposition functionalisation of alkylsilane based self-assembled monolayers, deposited on Si/SiO$_2$, using organocatalytic methodology previously developed within the Smith group.$^{[101]}$ The achiral isothiourea catalyst, 3,4-dihydro-2H-pyrimido[2,1-$b$]benzothiazole (DHPB $^{60}$), promotes the intermolecular Michael addition-lactonisation using a trifluoromethylenone terminated SAM and a variety of arylacetic acids affording C(6)-trifluoromethylidihydropyranones (DHP) tethered to a surface (Figure 34). X-ray photoelectron spectroscopy, atomic force microscopy, contact angle and ellipsometry analysis were conducted to confirm the presence of the substituted dihydropyranone (DHP) on the surface.

![Figure 34: Michael addition-lactonisation of trifluoromethylenones using DHPB as a catalyst.](image)

2.1 Aims

As previous work has shown that isothioureas can catalyse the intermolecular Michael addition-lactonisation of arylacetic acids and trifluoromethylenones, we envisaged that this methodology could be applicable to the late stage functionalisation of SAMs in situ on Si/SiO$_2$ surfaces. Commercially available arylacetic acids containing marker atoms which are clearly visible in the XPS spectrum of a surface would give a good indication of the conversion obtained in the reaction. In solution, this system is robust, and tolerant of a variety of functional groups in either the arylacetic acid portion or the trifluoromethylenone component of the reaction ranging from para-substituted electron withdrawing and electron-donating groups to heteroaromatic and alkyl groups. We hoped that our investigations into this system would provide a proof of concept
regarding Michael addition-lactonisation on a Si/SiO₂ surface for generating racemic DHPs with high selectivity. We also hoped that using DHPB 60 in the synthesis of racemic DHPs would serve as a model system for optimisation of a similar enantioselective process using a chiral isothiourea catalyst. The enantioinduction obtained from the asymmetric process can be probed on the surface using chemical force microscopy, which will be discussed in detail in Chapter 3.

2.2 Initial strategy – formation of vinyl-terminated SAMs

Previous work in the Hähner group has shown that vinyl-terminated SAMs can be easily prepared from the appropriate alkyl chain length trichlorosilane and subsequently functionalised using a variety of organic reactions.[31][115] Based on this work the initial strategy was to synthesise several vinyl-terminated trichlorosilanes and deposit them on an Si/SiO₂ surface. Following this, oxidation to the aldehyde using an ozonolysis approach would be pursued with the aim of attaching a suitable Michael acceptor to the surface via a modified Horner-Wadsworth-Emmons reaction (Figure 35).

![Figure 35: Retrosynthetic route towards trifluoromethylenone terminated surface 83.](image)

2.2.1 Synthesis of starting materials for SAM formation

In order to obtain vinyl-terminated monolayers the requisite alkylsilane precursors needed to be synthesised. Self-assembling molecules, with different alkyl chain lengths and reactive head groups i.e. SiCl₃, Si(OMe)₃ and Si(OEt)₃, can affect the overall SAM quality by altering the self-assembly process.[10] Wöll and co-workers[116] have shown that the optimum molecular chain length is eighteen carbons to form a well ordered, homogeneous SAM. Moreover, short alkyl chain silanes with three[116] or eight[117] carbons form disordered films, whereas longer chain silanes ca. thirty[116] carbons also form less ordered monolayers. Based on these parameters we decided that the synthesis of two alkyltrichlorosilane derivatives, C₁₁ and C₁₅ would be prepared and deposited to decide on the most appropriate chain length for further modification. The target molecules were vinyl-terminated trichlorosilanes with alkyl chain lengths of eleven (trichloro(undec-10-en-1-yl)silane) 86, and fifteen (trichloro(tridec-14-en-1-yl)silane 76.
For the synthesis of 86 commercially available undec-10-en-1-ol 87 was transformed to the corresponding bromide under Appel conditions to afford 11-bromoundec-1-ene 88 in 82% yield after chromatographic purification. Following on from bromide 88 the corresponding trichlorosilane was synthesised using a Grignard reaction, and purification by Kugelrohr distillation afforded 86 in low yield 26% but high purity (Figure 36).

**Figure 36: Synthesis of trichloro(undec-10-en-1-yl)silane 86.**

For the synthesis of 76 a procedure outlined by Hähner and co-workers was used. Starting from commercially available ω-pentadecalactone 89 an acid catalysed ring opening was used to afford the corresponding methyl ester 90 in 90% yield, which was used in the next step without further purification. Alcohol 90 was then subjected to PPh₃ and N-bromo succinimide in DMF at 55 °C for 0.5 h, which afforded the desired bromide in 77% yield (Figure 37).

**Figure 37: Synthetic route towards bromide 91.**

Bromide 91 was then treated with a 1 M solution of KO'Bu which gave the corresponding alkene 92, with slightly lower yield than previous steps. Subsequent reduction of tert-butyl ester 92 using LiAlH₄ afforded desired alcohol 93 in a 71% yield after purification (Figure 38).

**Figure 38: Synthetic route towards alkyl alcohol 93.**

With alkenyl alcohol in hand, the desired trichlorosilane was synthesised in a further two steps. Alcohol 93 was treated with PPh₃ and N-bromo succinimide in DMF at 55 °C for 0.5 h, which afforded the desired bromide in 80% yield. Upon treatment of alkyl bromide 94 with Mg, the corresponding Grignard was formed which was treated with an excess of SiCl₄ to form trichlorosilane 76 in low yield (Figure 39).
2.3 Deposition of vinyl-terminated SAMs

2.3.1 Cleaning procedure

It is established in the literature that in order for a well-ordered, smooth, homogeneous monolayer to be deposited on Si/SiO$_2$ in solution or vapour phase there needs to be a clean hydroxy terminated surface devoid of any external contaminants.

There are two main methods, wet and dry, used to achieve this kind of hydrophilic surface. As wet methods are the focus of this chapter, only these are discussed. Liquid phase (wet) cleaning procedures usually employ hot acidic and alkali solutions, however the immersion time, order of reagents and temperature may vary.[116] The silicon wafers are first immersed in a mixture of H$_2$SO$_4$ and H$_2$O$_2$ known as ‘Piranha solution’ which removes any organic contaminant on the surface. The next step uses a mixture of H$_2$O$_2$, NH$_4$OH and H$_2$O, also known as SC-1 which removes inorganic contaminants such as heavy metal complexes that includes Au, Cu, Ag, Cd, Zn and Cr.[117] In the last step, a mixture of H$_2$O, H$_2$O$_2$ and HCl, also known as SC-2, removes residual trace metals such as Au and metal hydroxides such as Mg(OH)$_2$, Fe(OH)$_3$ and Al(OH)$_3$. This cleaning process should, in theory, generate a thin hydrophilic oxide layer.

A procedure outlined by Hähner and co-workers was used as a starting point for the cleaning procedure.[115] This procedure did not give consistent results as contaminants such as nitrogen and chlorine were noted in the N 1s and Cl 2p regions of the XPS spectra and attributed to NH$_4$OH and HCl respectively. As such several modifications were made to the original procedure which are outlined below:

1. The SiO$_2$ wafer was immersed in Piranha solution (conc. H$_2$SO$_4$/30% H$_2$O$_2$ – 2:1) at 70°C for 15 mins.
2. The wafer was then removed and transferred directly into a solution of NH$_4$OH, deionised (DI) water and 30% H$_2$O$_2$ (1:5:1) at 70°C for 15 mins
3. The wafer was removed again and transferred straight into a solution of conc. HCl, DI water and 30% H$_2$O$_2$ (1:6:1) at 70°C for 15 mins.
4. After cleaning the wafer was washed with copious amounts of DI water and placed in an oven at 130 °C for 30 mins to remove all but a single layer of water on the surface.
5. Once dried, the wafer was immersed in a 1mM solution of silane precursor in toluene for 16 h.

6. After deposition the wafers were removed from solution and sonicated in vials of toluene, CH$_2$Cl$_2$ and DI water respectively for 5 mins. Finally they were dried under a stream of Ar.

AFM images of the SiO$_2$ surface after the cleaning procedure were obtained to assess the success of the cleaning procedure (Figure 40). The AFM image showed a clean surface devoid of any artefacts and the high resolution scans of the N 1s and Cl 2p region shows no sign of contaminants.

![AFM image of clean Si/SiO$_2$ surface](image)

Figure 40: AFM image of 5 µm x 5 µm area of clean Si/SiO$_2$.

XPS spectra of clean Si/SiO$_2$ surfaces after oven drying were also obtained and characterised showing the presence of several different chemical environments for silicon and oxygen as expected (Figure 41). A large asymmetric peak appears in the Si 2p spectrum which is attributed to the combination of the Si 2p$_{1/2}$ (98.7 eV) and Si 2p$_{3/2}$ (98.1 eV) components in the elemental bulk silicon of the substrate. A peak with a binding energy of 102.0 eV also appears in the spectrum and is assigned to the Si 2p of the silicon in the silicon oxide layer. XPS survey scans also showed no sign of any unwanted contaminants and as such the surface was deemed sufficiently clean.
Figure 41: High resolution XPS scans of Si 2p region of clean Si/SiO₂.

2.3.2 Deposition of SAMs in solution

Solution phase deposition is by far the most common method of preparing SAMs on a small scale. Although it is relatively simple to produce SAMs of good quality, it can be difficult to reproduce the results as SAM formation is very dependent on reaction parameters such as solvent, solution age, solvent concentration, deposition time and temperature. Rozlosnik and co-workers have shown that using a wide range of concentrations (25 µM to 2.5 mM) of octadecltrichlorosilane (OTS) facilitates the formation of a full-coverage self-assembled monolayer on hydrophilic silicon oxide. Other studies have shown that using toluene as a deposition solvent can produce SAMs of full coverage and of reproducible quality. This was used as a starting point for monolayer deposition in solution.

SAMs were prepared from trichlorosilane self-assembling molecules 76 and 86. Freshly cleaned SiO₂ wafers (as per the cleaning procedure outlined in 2.3.1) were placed in a glass vial and 5 mL of a 1 mM solution of the appropriate silane was added to the vial (Figure 42). The silicon wafers were left immersed in the solution for 16 h at room temperature. It should also be noted that solutions of surfactants had to be freshly prepared in order to avoid possible contaminants such as water. Water contamination can result in silane polymerisation which in turn results in a non-homogeneous film on the surface.
Chapter 2: Isothiourea-catalysed Michael addition-lactonisation on a surface

2.4 Vinyl-terminated SAMs

As previously stated, the initial strategy focused on the deposition of two alkylsilane based SAMs with a vinyl group as a functional handle and assessed their viability as precursors for further surface chemistry. Vinyl-terminated monolayers have shown promise as model systems for study of the interactions of atmospheric oxidants with boundary layer surfaces. In the present study two different SAMs were deposited on Si/SiO₂ surfaces from the solution phase and assessed. The self-assembling molecules both contain the same vinyl terminal group and -SiCl₃ reactive head group but varied in alkyl chain length (Figure 43).

![Deposition of vinyl terminated SAMs from precursor molecules 76 and 86.](image)

2.4.1 X-Ray Photoelectron Spectroscopy

The XPS spectra of each of the vinyl terminated SAMs in this study showed the presence of Si (2s 151.6 eV, 2p 99.6 eV), C (1s 284.6 eV) and O (1s 532.7 eV) as expected. A typical survey scan of vinyl terminated SAM 96 is shown in Figure 44. There were no unexpected elements detected from XPS scans of the surface such as unreacted silane (no Cl signal was detected). The data obtained for C 1s, Si 2s and Si 2p was consistent with monolayer films in the literature.
Figure 44: XPS survey scan of vinyl terminated SAM 96.

High resolution scans of each element were taken to reveal their elemental composition. An example single region scan of the C 1s of SAMs 97 is shown in Figure 45. As photoelectrons are lost during the photoemission process a positive charge builds up on the sample, known as sample charging. As this happens, the kinetic energy of the emitted photoelectrons decrease in energy resulting in a shift to a higher binding energy. All analysed samples were shifted and corrected for sample charging. The main C 1s aliphatic peak in SAM 97 appears at a binding energy of 284.6 eV. On the majority of samples a shoulder peak was fitted at a higher binding energy (286.4 eV) to the main C 1s peak. Based on the polarity of the double bond it is possible that this is the more electropositive carbon in the olefin moiety which shifts its overall binding energy higher in the XPS spectrum. It is difficult to definitively detect the different chemical states of carbon in alkene moieties using XPS and as such the shoulder peak could not be conclusively assigned.\textsuperscript{[128]}

\textsuperscript{130}
Figure 45: XPS C 1s high resolution scan of vinyl terminated SAM 97.

2.4.2 Contact Angle
The vinyl terminated SAMs 96 and 97 gave similar water contact angle values within several degrees of each other which is expected given the identical surface termination. Experimental and literature values are shown in Table 1. Reported values were measured directly after placing drops of water onto modified silicon samples. These results are consistent with values reported for similar films.\textsuperscript{[131]}

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Liquid deposition</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{11}-vinyl 96</td>
<td>97±1.5</td>
<td>96±1.4</td>
</tr>
<tr>
<td>C\textsubscript{15}-vinyl 97</td>
<td>101±1</td>
<td>101±1,0\textsuperscript{[115,132]}</td>
</tr>
</tbody>
</table>

Table 1: Comparison of experimental and literature values

2.4.3 Atomic Force Microscopy
Atomic Force Microscopy was used to determine the quality of the deposited SAMs as well as the overall topography of the surface. AFM is also useful for determining whether any aggregations from the self-assembly process are present on the surface. A typical AFM image of a vinyl terminated SAM 97 is shown in Figure 46. The AFM image shows a relatively smooth surface with a root mean squared (RMS) value of ~96 pm averaged over a 1 \mu m \times 1 \mu m area for the solution phase deposited SAM of 97. In this case the RMS value gives an estimate of how homogeneous the resulting surface is after SAM deposition. The majority of vinyl terminated
surfaces imaged gave smooth surfaces with RMS roughness values in the range of 48-250 pm which agrees with the literature. For comparison, a clean Si/SiO₂ surface has an RMS of ~50 pm. These results, coupled with results from the other surface analysis techniques, suggest the presence of a dense, well-ordered and homogeneous SAM on the surface.

![Figure 46: AFM image of 1 µm × 1 µm area of C₁₅-vinyl SAM 97.](image)

### 2.4.4 Reactivity of vinyl terminated SAM

Pd-mediated cross-coupling reactions are a valuable method for the construction of C-C bonds. In particular the Mizoroki-Heck reaction\[133\] is a useful method for the construction of substituted alkenes and has widespread use in organic synthesis\[134\] as well as on solid supports.\[135\] Mizoroki-Heck reactions have been reported on a variety of functionalised silicon surfaces\[98,136-137\] and as such seemed a suitable candidate to test the reactivity of the vinyl group on the surface. Vinyl terminated SAM 97 was subjected to Heck conditions using \( p \)-bromophenylacetic acid 98 as a coupling partner (Figure 47). Reaction at 125 °C for 2 h gave the corresponding phenylacetic acid on the surface as confirmed by XPS and contact angle.

![Figure 47: Mizoroki-Heck reaction of aryl bromide with vinyl terminated SAM 97.](image)
High resolution scans of the C 1s region of the XPS spectrum show the appearance of a peak at 288.6 eV and this is attributed to the C in the C=O of the newly attached phenylacetic acid component (Figure 48).

Figure 48: High resolution XPS scans of C 1s region of phenylacetic acid terminated SAM 99.

The contact angle of the sample was also measured, with a significant decrease, from 97 to 55 °, attributed to the change in hydrophilicity of the monolayer. This, coupled with XPS results, suggested successful attachment of the phenylacetic acid unit thus confirming the reactivity of the vinyl group in the monolayer.

2.5 Modification of vinyl-terminated SAMs using ozonolysis

The aldehyde functional group is one of particular importance as it can partake in a variety of reactions based on its electrophilic character. It is also important as the aldehyde carbonyl serves as an anchoring site for amines, and has shown to be useful in microarray technology and chemical biology.[138] Following a procedure outlined by Sukenik and co-workers,[136] the appropriate vinyl terminated SAM was subjected to a solution phase ozonolysis reaction which afforded the subsequent aldehyde terminated SAM in quantitative conversion after quenching with dimethyl sulfide (Figure 49). Complete monolayer cleavage from the surface and possible over oxidation to the carboxylic acid and/or anhydride may occur,[139-140] neither of these being observed in our case based on comparative contact angle and XPS analysis of the resulting SAMs with the literature.

The ozonolysis was almost instantaneous, indicated by a significant colour change from colourless to blue, which is indicative of the CH$_2$Cl$_2$ solution being saturated with unreacted...
ozone. This colour change indicated complete consumption of any alkene present. Simple quenching of the reaction with excess dimethyl sulfide afforded aldehyde terminated SAMs in quantitative conversion as measured by XPS, contact angle and ellipsometry. AFM was also performed to assess the resulting surfaces for possible contaminants from the reaction.

Figure 49: Heterogeneous ozonolysis reaction on vinyl terminated SAMs 76 and 86.

2.5.1 Contact angle and ellipsometry
In this particular transformation, the water contact angle can be extremely useful as it operates on the basis of hydrophobic and hydrophilic interactions on the surface. Therefore, transformation from a hydrophobic vinyl terminated SAM to a hydrophilic SAM, based on hydrogen bonding interactions, can be easily ascertained. Vinyl terminated SAMs 96 and 97 were subjected to ozonolysis in solution with the results presented in Table 2. The initial contact angles of the vinyl terminated SAMs 96 and 97 are similar so it could be assumed that upon treatment with ozone the subsequent contact angle would also be similar. The contact angle obtained from aldehyde terminated SAM 96 is in good agreement with the literature and gave a solid basis for further exploration into SAMs consisting of longer alkyl chains.

However, upon treatment of vinyl terminated SAM 97 with ozone in CH₂Cl₂ the resulting contact angles did not correspond in the same fashion as 96. This could possibly be explained by the molecular packing density in the monolayer. At the terminal end of a SAM, there needs to be conformational mobility available to interact with an incoming molecule. In the case of the vinyl terminated SAM 96 the contact angle, ellipsometry and XPS would suggest a highly ordered and densely packed monolayer which in turn could possibly restrict the interaction of the terminal alkene with the ozone. The results may suggest that the ozone could not get sufficient access to react with the alkene, causing the subsequent contact angle to be higher than expected.
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Water Contact Angle (°) and ellipsometry

<table>
<thead>
<tr>
<th>SAM precursor</th>
<th>CA vinyl (*) SAM(^{a,b})</th>
<th>CA aldehyde (*) SAM(^{a,b})</th>
<th>Film thickness (Å) vinyl SAM</th>
<th>Film thickness (Å) aldehyde SAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>98 ±1.0</td>
<td>60 ±1.5</td>
<td>15.3</td>
<td>13.7</td>
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<tr>
<td>97</td>
<td>97 ±1.1</td>
<td>81 ±1.9</td>
<td>19.2</td>
<td>17.1</td>
</tr>
</tbody>
</table>

Table 2: Comparison of contact angle and ellipsometry values for vinyl and aldehyde terminated SAMs. \(^{a}\)Average taken over a minimum of five samples. \(^{b}\)Standard deviation between different samples.

2.5.2 X-Ray Photoelectron Spectroscopy

High resolution scans of the C 1s region of the resulting aldehyde terminated SAMs 96\(^{a}\) and 97\(^{a}\) were obtained and a typical spectrum is shown below in Figure 50. The main C 1s aliphatic peak appears at a binding energy of 284.6 eV which is shifted to account for sample charging as before. There is clear evidence of a peak at 288.3 eV which is attributed to the C=O π bond and conclusive evidence of an aldehyde moiety. This specific set of binding energies is consistent with other aldehyde terminated SAMs on Si/SiO\(_2\) in the literature.\(^{144-145}\) It is also worth noting that there was no evidence of any other possible contaminants, such as sulfur, present in the XPS spectra.

![XPS C 1s high resolution scan of aldehyde terminated SAM 96a.](image)

2.5.3 Aldehyde reactivity

A common method for the detection of aldehydes is by reaction with dinitrophenylhydrazine (DNPH) to form the corresponding hydrazone which is usually accompanied by a characteristic colour change in solution. This methodology was used to gain an insight into the reactivity of the newly generated aldehyde (Figure 51). Although a significant colour change was not detected in
the reaction mixture, subsequent analysis by XPS, ellipsometry and contact angle suggested the presence of the hydrazine moiety on the surface.

Figure 51: Reaction of aldehyde terminated surface with DNPH.

High resolution scans of the C 1s region of the resulting hydrazone terminated SAM 101 were obtained (Figure 52). A peak at 288.3 eV appears in the C 1s spectrum which can be assigned to the newly formed C=N bond in the hydrazone moiety. A shoulder peak also appears next to the main C 1s aliphatic peak in the spectrum which can be attributed to either advantageous atmospheric carbon contaminants or possibly the aromatic region in the hydrazone moiety or a combination of both.\textsuperscript{[132]} A peak at 400.2 eV appears in the N 1s spectrum which can be attributed to the amine in the monolayer, while a peak with a binding energy of 406.1 eV also appears and is assigned to the more electronegative nitro group.\textsuperscript{[132]} This confirms that that the aldehyde on the surface is reactive, at least towards nucleophilic amines.

Figure 52: High resolution scans of the C 1s region of hydrazone terminated SAM 101.
2.5.4 Attempted synthesis of Michael acceptor on the surface

Having shown that ozonolysis can afford aldehyde terminated SAMs via oxidation of the corresponding vinyl-terminated monolayer, initial attempts sought to use aldehyde surface 96a to afford a suitable CF₃ enone terminated surface. Previous work within the Smith group has shown that the use of imidoyl chloride 102, in a modified Horner-Wadsworth-Emmons reaction,[146-147] can afford a series of CF₃ enone Michael acceptors for use in a Michael addition-lactonisation procedure (Figure 53).

![Figure 53: Synthesis of a series of CF₃ enones using a modified HWE reaction.](image)

Following a procedure from Uneyama[148] reaction of trifluoroacetic acid with aniline in the presence of PPh₃ and NEt₃ using CCl₄ as solvent afforded N-phenyltrifluoroacetimodoyl chloride 102 in 62% overall yield (Figure 54). Imidoyl chloride 102 was used as starting material in the synthesis of the required CF₃ enone on the surface.

![Figure 54: Synthesis of N-phenyltrifluoroacetimodoyl chloride 102.](image)

With starting materials in hand, synthesis of the desired CF₃ Michael acceptor was attempted using a modified HWE reaction. Diethyl methylphosphonate 103 was reacted aldehyde surface 96a in the presence of imidoyl chloride 102 and nBuLi but disappointingly gave no observable conversion to enone surface 104 as judged by XPS, contact angle and ellipsometry analysis. As this route gave no conversion to the desired surface it was no longer pursued and a different approach towards the fabrication of the enone surface was adopted.
2.6 Click Chemistry

Click chemistry can be used to build upon a molecular framework that is already in place and structured molecular layers can be constructed from a bottom up approach. The advantage of using click chemistry to functionalise a surface is that large bulkier groups can be introduced on the surface that would be otherwise difficult using classical organic chemistry methods.

One of the first examples of using click chemistry on SAMs was carried out by Choi et al.\cite{149} where the authors used alkyne-terminated SAM for the formation of 1,2,3-triazoles on the surface while varying the azide used (Figure 56). The success of the reaction was determined by analysis using XPS, FTIR, ellipsometry and contact angle.

Coster et al. have also deposited alkyne terminated SAMs but on a Si-H terminated surface.\cite{150} The authors proceeded to attach pre-synthesised polypeptide to the surface using a CuAAC reaction (Figure 57).
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Figure 57: Attachment of polypeptide 107 to an alkyne terminated SAM on Si.

Mi et al. has shown the utility of azide-terminated SAMs, readily derived from the corresponding bromine-terminated SAMs, in click chemistry to attach a zwitterionic polymer 111 to a surface (Figure 58 (a)).\cite{Mi} Using a similar approach Hacker and co-workers\cite{Hacker} have shown that click chemistry can be used to attach redox active diruthenium complex 113 to a Si/SiO$_2$ or Au based azide SAM (Figure 58 (b)).

Our strategy for the construction of a suitable enone terminated surface consisted of using an initial bromine terminated SAM which can be easily transformed into an azide terminated surface using NaN$_3$. From the resulting azide surface, a click reaction can be performed using catalytic CuSO$_4$ in the presence of (+)-sodium ascorbate with a suitable enone tethered alkyne (Figure 59). This route would allow for the fabrication of an enone terminated surface in three steps which could then be optimised for the organocatalytic Michael-addition lactonisation process.
Figure 59: Retrosynthetic analysis of CF₃ Michael acceptor on the surface.

2.7 Optimisation of bromine terminated monolayer deposition

2.7.1 Deposition of 11-bromoundecyltrichlorosilane in solution

Commercially available 11-bromoundecyltrichlorosilane 115 was chosen as a potential starting material for the deposition of the bromine-terminated monolayer 116. Initial studies focused on deposition conditions for the formation of a well-ordered homogeneous SAM. Reports have shown that an ideal Br-terminated SAM should have a contact angle of 83° ± 1°[153] and a film thickness of 1.9 nm.[153] Several different deposition conditions were tested including deposition solution concentration and solvent. Initial studies focused on toluene as a deposition solvent in a 1 mM concentration which provided the most consistent ellipsometry and contact angle values over the largest sample range (entry 1 Table 3). Several of the results using bicyclohexane as a deposition solvent gave reasonable contact angles but displayed thickness values that were considered either too high (entries 3, 5), or were one-off results that could not be reproduced under the same experimental conditions (entry 4). Other deposition solvents such as hexane (entry 6), heptane:CHCl₃ (entry 7) and hexadecane (entry 8) gave unacceptable contact angles and were deemed unsuccessful. Overall entry 1 (Table 1) gave the most reproducible and consistent results for solution-phase deposition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deposition solvent</th>
<th>Concentration (mM)</th>
<th>Contact Angle (std. dev.)</th>
<th>Ellipsometry (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>1</td>
<td>83.2 (±0.9)</td>
<td>1.90</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>2</td>
<td>87.2 (±1.2)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Table 3: Optimisation of deposition of 11-bromoundecyltrichlorosilane in solution. *If the contact angle was not deemed sufficient no ellipsometry measurement was obtained. **Deposition time was 4 h and temperature was 6 °C. Standard deviation of contact angle is between at least two samples or more of similar quality.

Survey scans of the Br terminated surface were obtained and a typical spectrum is shown below (Figure 60). In addition to the expected Si and O signals the XPS spectrum showed three additional peaks consistent with the presence of bromine SAM. A peak at a binding energy of 71 eV was assigned to Br 3d[^153], and a peak at a binding energy of 190 eV which is attributed to the Br 3p signal[^155] A more intense peak, relative to the Br signals, is shifted to 284.6 eV which is to account for sample charging and this is assigned to the C 1s signal. Overall this data suggests the presence of a bromine-terminated SAM.[^154, 156]

![XPS survey scan of Br terminated surface](image)

**Figure 60: XPS survey scan of Br terminated surface 115.**

### 2.7.2 Deposition of 11-bromoundecyltrichlorosilane from the vapour phase

While solution-phase deposition offered a route towards the desired bromine terminated SAM 115, vapour phase deposition could provide a viable alternative. Vapour phase deposition has the potential to eliminate some of the common problems associated with solution-phase deposition...
such as the inability to wet all parts of a microstructure due to the presence of microscopic air bubbles from the air-water interface.\textsuperscript{157-158} Higher quality SAMs can also be obtained from the vapour phase as aggregated organosilanes, which may be deposited in the solution phase, do not vapourise and therefore are not deposited on the surface.\textsuperscript{159}

Commercially available 11-bromoundecyltrichlorosilane 115 was chosen as a suitable starting material for vapour-phase deposition as it had already shown promising results in the analogous solution phase deposition procedure. The deposition procedure was performed using a reduced pressure set-up and carried out in a sealed reaction vessel (Figure 61).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure61.png}
\caption{Reaction vessel for vapour phase deposition, (b) experimental set-up for vapour phase deposition}
\end{figure}

Following a procedure outlined by Hähner\textsuperscript{115} a freshly cleaned SiO\textsubscript{2} wafer was placed in the reaction vessel shown in Figure 61(a) and subjected to varying reaction parameters including solvent concentration, deposition time and temperature (Table 4).\textsuperscript{1} Several of the resulting contact angles were promising (entries 4-6, 9,11) but interrogation by AFM revealed a variety of unusual features present on the surface depending on the reaction conditions. Entry 4 (Table 4) gave a contact angle within range (\textit{ca.} 82.7°) but upon examination with AFM a series of small depositions roughly 5 nm in height were detected (Figure 62(a)). This is indicative of an inhomogeneous SAM and which could not be used in subsequent reactions. Entry 9 (Table 4) also gave a contact angle within the usual range and was examined using AFM. The AFM image showed a particularly large membrane type structure on the surface over a large area (Figure

\textsuperscript{1} Several samples prepared by project student Baptiste Fasseau.
62(b)). This was attributed to polymerisation of the silane precursor and as such was could not be used for subsequent functionalisation.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (mM)</th>
<th>Temperature (°C)</th>
<th>Deposition time (h)</th>
<th>Contact Angle (Std. dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>60</td>
<td>24</td>
<td>89.6(±2.4)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>60</td>
<td>36</td>
<td>84.3(±0.7)</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>60</td>
<td>48</td>
<td>84.5(±0.9)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>60</td>
<td>72</td>
<td>82.7(±1.3)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>70</td>
<td>72</td>
<td>83.0(±1.0)</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>80</td>
<td>72</td>
<td>82.0(±1.0)</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>85</td>
<td>72</td>
<td>85.3(±0.8)</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>60</td>
<td>96</td>
<td>89.1(±1.3)</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>70</td>
<td>96</td>
<td>82.0(±1.0)</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>80</td>
<td>96</td>
<td>79.0(±1.0)</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>60</td>
<td>120</td>
<td>83.0(±1.0)</td>
</tr>
</tbody>
</table>

Table 4: Summary of vapour phase deposition of 11-bromoundecyltrichlorosilane. Standard deviation of contact angle is between at least two samples or more of similar quality.

![AFM Images](image)

Figure 62(a): 5×5 μm² AFM image of small features of unknown origin on the surface, (b) 40×40 μm² AFM image of membrane type structure on the surface.

Although both solution phase and vapour phase methodologies gave suitable bromine terminated SAMs that could be used in subsequent modification, the solution phase methodology was carried forward as it produced more reliable and reproducible films.
2.8 Conversion of bromine to azide surface

With optimised conditions in hand (entry 1, Table 3) Br terminated monolayer 116 was subjected to a saturated solution of NaN$_3$ in DMF for 24 h which afforded azide terminated surface 112, usually in >80% conversion (Figure 63).

![Conversion of Br-terminated SAM to azide terminated monolayer.](image)

Pleasingly this protocol was reproducible and conversions of >80% were routinely obtained. Ellipsometry measurements gave a thickness value of 1.7 ±0.2 nm and a roughness of 0.1 ±0.02 nm which suggests the presence of a smooth homogenous surface after reaction with NaN$_3$. High resolution scans of the N 1s region of the azide terminated SAM 112 were obtained and a typical spectrum is shown in Figure 64. Two major components at a lower binding energy and a single component at higher binding energy are evident in the high resolution scans and can be attributed to the electron-rich and electron-poor nitrogen atoms respectively.$^{[160]}$ The first of three components relating to the azide moiety appears at a binding energy of 399.5 eV and is attributed to N3. There is also another peak close in binding energy that appears at 400.1 eV and is attributed to N1. Based on the resonance forms of the azide functionality shown in Figure 64, both N1 and N3 are chemically very similar and as a result have a closely related binding energy. The peak at a higher binding energy of 403.4 eV can be attributed to the electron-poor nitrogen (N2) in the azide moiety. All of the peaks associated with the azide are consistent with azide terminated monolayers in the literature.$^{[167-168]}$
A peak at 398.1 eV is also present in the XPS spectrum which cannot be attributed to the azide moiety. Unger and Schalley have shown that during the irradiation process of azide terminated monolayers on Au, a new peak at 399.0 eV appears in the XPS spectrum. The authors recorded multiple XPS spectra of azide terminated monolayers over a period of 142 min and detailed XPS data showed that significant decomposition of the azide occurs. Given that the azide samples in this study are typically irradiated by X-rays for a minimum of 30-40 mins during XPS analysis it is reasonable to assume that these surfaces are experiencing the same degradation as those in the Unger and Schalley report. The authors suggest a potential mechanism for degradation, whereby decomposition of azide and subsequent \( \text{N}_2 \) extrusion gives a nitrene on the surface. This reactive intermediate undergoes a subsequent [1,2]-hydride shift which affords an imine on the surface (Figure 65). Analysis by XPS and NEXAFS spectroscopy shows a peak at a binding energy 399.0 eV which is consistent with the presence of an imine moiety.

![Figure 64: High resolution scan of N 1s region of azide terminated SAM 112.](image)

![Figure 65: Possible mechanistic pathway for the degradation of azide terminated surface 112.](image)

### 2.9 Synthesis of starting materials

#### 2.9.1 Synthesis of DHPB 60

Following a procedure outlined by Smith, DHPB 60 was obtained via a two-step procedure. Reaction of 2-chlorobenzothiazole 117 with 3-aminopropan-1-ol 118 and \( i\text{Pr}_{2}\text{NEt} \) in \( o-\)
dichlorobenzene gave the corresponding amino alcohol 119 in excellent yield. Subsequent treatment of alcohol 119 with methanesulfonyl chloride and Et₃N in CH₂Cl₂ afforded DHPB 60 in 70% yield after recrystallisation from toluene (Figure 66).

![Diagram](image)

**Figure 66: Synthesis of isothiourea DHPB 60.**

### 2.9.2 Synthesis of alkyl trifluoromethyl enone

Initial attempts focused on the preparation of alkyl trifluoromethylenone 124. Starting with commercially available 4-pentyn-1-ol 120, this was subjected to nBuLi and TMS-Cl to afford the corresponding TMS protected alkyne 121 in 61% yield. Reaction under Swern conditions gave the corresponding aldehyde 122 in 44% yield (Figure 67).

![Diagram](image)

**Figure 67: Synthesis of alkynyl aldehyde 121.**

Aldehyde 122 was then subjected to an aldol reaction using trifluoroacetone 123 and piperidine as a base but disappointingly this gave no trace of product and returned only starting material. Aldehyde 122 was also subjected to a modified Horner-Wadsworth-Emmons reaction[146-147] using acetoimidoyl chloride 102 and diethylmethylphosphonate 103 but again this returned only starting material with no sign of any of the desired enone (Figure 68). As none of the conditions were successful when tested on this substrate, this route was not pursued further and an alternative β-aryl Michael acceptor was synthesised.

![Diagram](image)

**Figure 68: Attempted synthesis of α,β-unsaturated enone 124.**
2.9.3 Synthesis of aryl trifluoromethylene

Commercially available 4-bromobenzaldehyde was subjected to Sonogashira cross coupling conditions with trimethylsilylacetylene to afford 125 in 75% yield. The TMS-protected alkyne 125 was treated with imidoyl chloride 102 in the presence of phosphonate 103 and nBuLi which afforded (E)-enone 126 in 29% yield. Finally, treatment of TMS alkyne 126 with K$_2$CO$_3$ in MeOH afforded alkyne 127 in 32% yield as a precursor for the click reaction (Figure 69).

![Figure 69: Synthesis of aryl CF$_3$ enone 127.](image)

2.10 Generation of trifluoromethylene 128 on the surface

With azide terminated surface in hand, alkyne 127 was attached to the surface via a CuAAC reaction using catalytic CuSO$_4$·5H$_2$O and (+)-sodium ascorbate (Figure 70).

![Figure 70: CuAAC using enone 127 and azide terminated monolayer 112.](image)
A clear change in the contact angle, thickness, and surface roughness accompanied this step. The contact angle decreased from 79.1±1.0 to 72.6±2.5 nm after addition of the enone moiety. Ellipsometry measurements gave a thickness of 2.64 nm which is consistent with the addition of the enone moiety. The roughness was calculated to be 0.16 ±0.04 nm which suggested the presence of a smooth homogenous surface after the click reaction. High resolution XPS spectra of the N 1s region were obtained that included characteristic peaks suggesting the presence of a 1,2,3-triazole (Figure 71). Often peaks from the nitrogen atoms in the residual unreacted azide groups were also observed with a reproducible conversion from azide to enone in the region 89%. It is evident from the peak fitting that there are three different chemical environments present in the N 1s region that can be attributed to the triazole. Two peaks close in binding energy, 399.4 and 400.1 eV, can be assigned to N2/N3 respectively.\textsuperscript{[165-166]} The last peak present appears at a binding energy of 401.4 eV and is attributed to the slightly more electropositive N1.\textsuperscript{[167-168]}

![Figure 71: High resolution XPS scans of the N 1s region in 128.](image)

High resolution XPS scans from the C 1s region further supported the claim that enone 127 had been successfully clicked onto the surface (Figure 72 (a)). Apart from the main C 1s aliphatic peak there are three peaks that appear in the C 1s spectrum. The first is at a binding energy of 286.1 eV, and can be attributed to the near neighbours of the nitrogen atoms and the aromatic regions.\textsuperscript{[169]} Peaks at 292.5 eV and 288.3 eV were assigned to the C1 and C2 respectively. Both these peaks suggest the presence of a CF\textsubscript{3} containing carbonyl functionality on the surface. AFM also showed a clean smooth homogeneous surface that also further suggested a successful click reaction as no unexpected features or tip modifications were detected in the majority of samples tested (Figure 72 (b)).
2.10.1 Summary of enone generation

Clean Si/SiO$_2$ surfaces, bromine, azide and enone terminated SAMs were all tested using contact angle, ellipsometry, XPS and AFM. The cleaned Si/SiO$_2$ surface gave between 5-20° contact angle value which is expected given the hydroxyl termination on the surface.$^{170}$ After deposition of the Br-terminated SAM, there was an increase in the contact angle to 82.9 ±0.8 consistent with the formation of a well ordered SAM. The thickness was also well within range for the expected presence of a Br-terminated SAM. Upon reaction with NaN$_3$ the thickness decreased slightly to 1.76 nm (entry 3, Table 5). This observation can be attributed to the decrease in bond lengths of C-Br vs N-N≡N (1.966 and 1.216 Å respectively) and also that bromine has a larger atomic radius compared to azides.$^{171}$ After the click reaction with enone 127 the thickness increases to 2.76 nm (Entry 4, Table 5) which is within range given the introduction of a number of carbon units. The contact angle also decreases which is slightly surprising as SAMs with fluorine as the terminal group tend to display higher contact angles, attributed to the hydrophobic fluorine atoms.$^{172}$ Coupled with data from the N 1s region it can be inferred that the click reaction was successful and enone 127 was covalently attached to the surface (Table 5).
2.11 Model study in solution

As none of the methods of characterisation (XPS, ellipsometry, contact angle or AFM) allow the diastereoselectivity of the organocatalytic process on the surface to be evaluated a solution based approach was evaluated. To show that productive ITU catalysis works with a triazole functionality present and to estimate the level of diastereomeric control that may be expected in this process, a model system was devised whereby a system analogous to that assumed on the Si/SiO$_2$ surface was subjected to the same reaction conditions in solution. A solution analogue of the surface tethered trifluoromethylenone was designed to undergo an analogous Michael addition-lactonisation. Commercially available 1-bromooctane 129 was treated with NaN$_3$ at 100 °C in DMF to afford the corresponding azide 130 in 90% yield. Reaction with enone 127 in the presence of catalytic CuSO$_4$:5H$_2$O gave the corresponding 1,2,3-triazole in a moderate 47% yield (Figure 73)

![Figure 73: Synthesis of triazole 131 using click methodology.](image)

Reaction of 4-bromophenylacetic acid 98 with pivaloyl chloride, iPr$_2$NEt and enone 127 in the presence of catalytic DHPB 60 (5 mol%) gave ring-opened product 132 in 70% yield. The diastereoselectivity of the solution phase Michael addition-lactonisation reaction, after ring opening with MeOH, was measured by $^1$H NMR spectroscopy, with a dr of 80:20 (anti:syn) obtained from the crude reaction mixture (Figure 74 (a)). The diastereoselectivity remained the same after purification of the crude reaction mixture by column chromatography. This diastereoselectivity is in line with what was obtained in the previous work with a variety of
substituted phenylacetic acid components. This level of relative stereocontrol, combined with the $^{1}H-^{1}H$ coupling constants of $^{3}J=10.9$ and 3.8 Hz for the major diastereoisomers, corresponding to the C(3)H and C(5)H resonances respectively, is consistent with the expected “anti”-stereocontrol observed in previous solution based studies (133 Figure 73 (b)). This result suggests that DHPB 60 catalyses the reaction of phenylacetic acid 98 with enone 127.

Figure 74: (a) Synthesis of ring-opened DHP (±)-132 (b) Analogous DHP 133 with corresponding $^{1}H$ NMR spectroscopic resonances. aDetermined by $^{1}H$ NMR spectroscopy of the purified reaction mixture.

2.12 Michael addition-lactonisation on a surface

2.12.1 Initial results

With the starting material for catalysis, enone 128, in hand, a Michael addition-lactonisation protocol was developed to allow for surface functionalisation. Pleasingly, reaction of 3-thiophenylacetic acid 134 with pivaloyl chloride, iPr$_2$NEt and enone 128 in the presence of catalytic DHPB 60 (5 mol%) gave DHP terminated surface 135 (Figure 78).
The formation of thiophene-substituted DHP 135 was confirmed by the appearance of a peak corresponding to the sulfur atom in the thiophene moiety (Figure 76(b)). A peak with a binding energy of 286.2 eV was detected in the C 1s spectrum and this was attributed to the near neighbours of the aromatic substituents in the monolayer. The peak at 288.1 eV was assigned as C2 in the DHP ring. The peak at 289.6 eV is assigned as C1 and differs slightly in binding energy to the carbonyl peak in enone 128 and this can be taken as indication that the lactonisation process was successful. Ellipsometry measurements gave a thickness of 3.87 ± 0.24 nm (entry 1, Table 6) which is consistent with the expected monolayer thickness. The expected monolayer thickness was determined using the equation proposed by Whitesides et al., where L is the length of a methyl-terminated monolayer containing n methylene units (Equation 2). \[ L = 1.26n + 4.78 \]

Equation 2: Equation used to calculate the theoretical thickness of a SAM.

AFM gave a roughness of 0.247 ± 0.04 nm (entry 1, Table 6) which is in the expected region given the number of reaction steps performed on the surface. AFM also showed a clean surface over a 5×5 µm² area in thiophene-substituted DHP 135 (Figure 76(c)).
Chapter 2: Isothiourea-catalysed Michael addition-lactonisation on a surface

As not all of the enone terminations were converted to DHPs, there remained some residual signals in the C 1s spectrum associated with the starting enone. This was used to calculate the conversion from enone to DHP by comparison of the relative peaks areas in the XPS spectra (Figure 77).

The conversion for the reaction of enone 128 to 3-thiophenyl DHP surface 135 was calculated to be ~54% according to Equation 2. Furthermore, no unidentified sulfur or nitrogen was detected in the XPS spectra, consistent with the catalyst 60 being successfully removed from the surface by the post-deposition cleaning procedure. To further probe the catalytic necessity of the isothiourea for surface functionalisation, a control reaction was performed where a CF₃ enone sample 128 was subjected to the same Michael addition-lactonisation conditions with the omission of the catalyst DHPB 60. Formation of a DHP was not observed and the surface had properties equivalent to that of other trifluoromethylene surfaces.
Equation 2: Equation used to calculate conversion from enone 128 to DHP terminated surfaces.

2.13 Scope of the phenylacetic acid component
The generality of the Michael addition-lactonisation process was investigated through variation of the arylacetic acid component. The arylacetic acids were chosen specifically as they contained marker atoms that would give characteristic peaks in the XPS spectra and made it possible to obtain a conversion for the catalysis. Using the standard conditions the reaction readily tolerates heteroaryl (3-thiophenyl) as well as 4-aryl substitution, including electron-donating (4-NMe₂) and electron-withdrawing (4-CF₃) substituents giving moderate to good conversions in the reactions on the surface.

Formation of the DHP species was confirmed by XPS in all cases based on the appearance of a peak at 289.6 eV in the C 1s XPS spectra, corresponding to the carbonyl species (Cl₁, Figure 77).
isothiourea-catalysed Michael addition-lactonisation on a surface

along with the appearance of the marker atoms in the XPS spectra. Formation of DHP terminated samples was generally accompanied by a small drop in contact angle compared to that of the enone samples. The Michael addition-lactonisation step increased the thickness of the organic layer by around 0.5–1.3 nm in comparison to the enone samples to a total value of around 3.1–3.9 nm. The roughness of the DHP samples was greater that for the corresponding enone sample, as a result of the additional reaction step which is expected. 4-Fluorine 136 4-bromine 137, 4-dimethylamino 138 and 4-trifluoromethyl 139 terminated samples were all analysed in an analogous fashion, using the marker atoms for an estimate of conversion (Table 6). The conversions from the reaction of enone terminated surface 128 with the appropriate arylacetic acids to afford DHP terminated surfaces 135-139 were not as high yielding as their solution-phase analogues. For example, in the solution-phase reaction of 3-thiophenylacetic acid to afford (±)-135 occurred with full conversion and a 75% yield, lower than the conversion on the surface, possibly due to lower reactivity. (Table 6). The relative conversions of enone 128 to DHP terminated surfaces are within approximately 10% of each other (with the exception of 138). This reactivity may indicate that regardless of phenylacetic acid, consumption of the starting material can only proceed to a certain conversion. A possible steric based explanation for the lack of reactivity, compared to the homogeneous system, could be that the surface bound DHPs formed in the reaction begin to form domains or islands and this does not allow access for the incoming nucleophile to react with the remaining enone functionalities. However, at the present time there is no evidence for this claim and further experiments are needed in order to confirm this hypothesis.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sample</th>
<th>CA (°)(^a)</th>
<th>Thickness (nm)(^{ab})</th>
<th>Roughness (nm) (^a)</th>
<th>Conv. (%) (^a)</th>
<th>Conv./Yield (%) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-thiophene 135</td>
<td>69.8 ±2.4</td>
<td>3.87 ±0.24</td>
<td>0.247 ±0.04</td>
<td>~54</td>
<td>100/75</td>
</tr>
<tr>
<td>2</td>
<td>4-FC(_6)H(_4) 136</td>
<td>71.3 ±1.1</td>
<td>3.60 ±0.12</td>
<td>0.178 ±0.05</td>
<td>~41</td>
<td>100/81</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC(_6)H(_4) 137</td>
<td>68.6 ±1.0</td>
<td>3.10 ±0.28</td>
<td>0.162 ±0.02</td>
<td>~51</td>
<td>100/72</td>
</tr>
<tr>
<td>4</td>
<td>4-NMe(_2)C(_6)H(_4) 138</td>
<td>70.0 ±2.2</td>
<td>3.89 ±0.15</td>
<td>0.155 ±0.06</td>
<td>~70</td>
<td>100/80</td>
</tr>
<tr>
<td>5</td>
<td>4-CF(_3)C(_6)H(_4) 139</td>
<td>72.8 ±1.5</td>
<td>3.76 ±0.24</td>
<td>0.16 ±0.05</td>
<td>~42</td>
<td>100/60</td>
</tr>
</tbody>
</table>
2.14 Conclusions and Future Work

In this work a small library of dihydropyranones have been synthesised on a surface through an isothiourea-mediated Michael addition-lactonisation procedure using a range of arylacetic acids. The conversions were in the range of 40-70% and as such this methodology offers an effective route to build a variety of complex surfaces containing this functionality. As this was a proof of concept study only a small range of arylacetic acids were tested but the consistency of this methodology suggests that a wide range of phenylacetic acid derivatives could be applied providing a flexible methodology for surface functionalisation.

It has also been shown in solution that these types of dihydropyranone motifs are prone to ring opening by a range of nucleophiles [174] which opens up the possibility for covalent attachment of an external nucleophile, such as a protein or amino acid. Such strategies may have applications in biosensor technologies. Several of the resulting dihydropyranones also contain useful functional handles that may allow for further modification, such as transition metal mediated cross-coupling and $S_N$Ar reactions.

2.15 References and Notes

Chapter 2: Isothiourea-catalysed Michael addition-lactonisation on a surface


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Chapter 3: Synthesis and chiral discrimination of enantioenriched C(6)-trifluoromethylidihydropyranones by chemical force microscopy

Introduction

Having demonstrated the use of an achiral isothiourea organocatalyst for the generation of racemic C(6)-trifluoromethylidihydropyranone-terminated surfaces (Chapter 2), this chapter describes the use of a either enantiomer of a chiral isothiourea catalyst, HyperBTM 61, to give either enantiomer of the dihydropyranone (DHP) on a surface (Figure 79). The enantioinduction imparted on the surface was analysed using chemical force microscopy, including the development of a novel chiral AFM probe, which gave a clear level of enantiodiscrimination between different enantiomers of DHPs attached to the surface.

Figure 79: Michael addition-lactonisation of enones using either HyperBTM-(2S,3R) 61 or HyperBTM-(2R,3S) 61.

The generation of chiral surfaces is an area of great interest and they are finding uses in fields such as chiral selectors,[175] selective crystallisation[176] and enantioselective heterogeneous catalysis.[177-178] Surfaces can be considered chiral if they are based on chiral crystals or on templates with chiral molecules.[179] For example, chiral selectors are used to separate the two enantiomers of a racemate, with the most widespread use of chiral selectors being in high performance liquid chromatography (HPLC).[180] Chiral resolution on chiral stationary phases (CSPs) is realised through the formation of non-covalent diastereomeric complexes between the chiral selector and the enantiomers in a racemic mixture resulting in discrimination between the two enantiomers.[175] These transient diastereomeric interactions result in a difference in binding affinity with the chiral selector and hence a difference in retention time ($t_R$). Chiral surfaces have also found use in the study of biomaterials, as certain cell types are known to attach themselves
differentially to surfaces based on the chirality of the surface, demonstrating sensitivity at the angstrom scale.\textsuperscript{179,181}

### 3.1 Aims

The aim of this project was to investigate whether a chiral isothiourea catalyst could be used to induce asymmetry onto a surface through a catalytic enantioselective transformation. As enantiominduction on a surface is difficult to quantify and detect using classical organic chemistry methods (HPLC, optical polarimetry etc.) chiral force microscopy was used to obtain a quantitative picture of the enantioenrichment on the surface. We hoped that the design of a novel chiral AFM tip and its subsequent use in chiral force microscopy would provide a clear discrimination between different enantiomerically-enriched surfaces, to confirm that asymmetry can be induced using enantioselective catalysis on a surface.

### 3.2 Measuring molecular chirality at surfaces

Classically, there are two main approaches to induce chirality at surfaces: the deposition of enantipure molecules directly onto a surface or via careful cutting of the crystal to expose chiral kinked and stepped surfaces.\textsuperscript{182} It was envisaged that the modification of a surface with a prochiral termination using enantioselective means could be used as a third novel method to create a chiral environment on a surface. To the best of our knowledge, to date there has been no example in the literature of using catalytic enantioselective methodology on a SAM to generate enantioenriched surfaces. Consequentially, measuring the enantioinduction imparted on the surface, as a result of enantioselective catalysis has not been demonstrated. Many different techniques have been developed to measure the level of chirality on a surface.\textsuperscript{183} The following section offers a review of different approaches to measuring chirality at surfaces.

#### 3.2.1 Second harmonic generation circular dichroism (SHG-CD)

Circular dichroism (CD) detects the slight differences in optical absorption between left and right circularly polarised light interacting with enantiomers in solution.\textsuperscript{184} The theory behind this type of spectroscopy centres on the rotational strength which results from a weak interaction between the electric and magnetic dipole transition moments within a given molecule.\textsuperscript{185} However, CD cannot be used to detect chirality in ultrathin films of small molecules as the response is too weak.\textsuperscript{186} SHG-CD is an effect that depends on the handedness of the chromophore, thereby revealing chirality and can be used to detect chirality at surfaces of ultrathin films.\textsuperscript{185} McGilp and co-workers have shown that SHG-CD can be used to detect the chiral nature of thin films of (R)- and (S)-1,1'-binaphthlene-2,2'-dioI.\textsuperscript{186} A small difference in chirality can been seen in this system demonstrating the potential for the use of SHG-CD in the detection and quantification of chirality of ultrathin organic films.
3.2.2 **Enantioselective crystallisation**

As early as 1858 Pasteur discovered that the crystals of (±)-sodium ammonium tartrate, isolated from the overheated deposition of fermented grape juice, consisted of two different kinds of enantiomorphic shapes (Figure 80).[187] He could manually sort these crystals into each type of shape using a pair of tweezers, and found that each type of crystal rotated polarised light in opposite directions. This experiment, and those that followed spawned the field of resolution and selective crystallisation.

![Figure 80: Ammonium sodium tartaric acid enantiomers separated by Pasteur in 1858.](image)

The basic assumption of enantioselective crystallisation on surfaces follows that of classical resolution, where the chiral surface will serve as a selective chiral nucleus, lowering the energy needed for crystal formation of one of the enantiomers.[188] This particular enantiomer will then crystallise in excess on the surface and can easily be separated from the mixture. Mastai and Dressler have shown that both enantiomers of (±)-glutamic acid can be selectively crystallised using surfaces of L- and D-cysteine.[176] The authors selectively crystallised D-glutamic acid in 31% ee from (±)-glutamic acid on an L-cysteine surface (Figure 81) while also selectively crystallising L-glutamic acid on a D-cysteine surface in 27% ee. This demonstrated the potential of chiral surfaces for the resolution of racemates, albeit in low to moderate ee.

![Figure 81: Selective crystallisation of D-glutamic acid from (±)-glutamic acid on L-cysteine surface 142.](image)
Mastai et al. reported the first example of a chiral nanosized metal oxide surface based on chiral SAMs coated with a metal oxide. The authors deposited a known enantiomer of cysteine on an Au coated glass surface and subsequently grew a TiO$_2$ film on the cysteine SAM using atomic layer deposition (ALD) and [Ti{N(CH$_3$)$_2$}]$_4$ as a promoter (Figure 82). TiO$_2$ was used as a protective nanolayer for SAM while also preserving the chirality of the surface. SHG-CD was used to assess the chiral nature of the surface and the results showed a significant difference in the polarisation of light by each of the different enantiomers indicating a chiral surface. An enantioselective crystallisation experiment was also employed to assess the chirality of the surface. The surface was immersed vertically in a super saturated solution of (±)-threonine and macro sized crystals formed on the surface where they were carefully removed and tested for ee. The results showed a modest ee of 38%, for L-enantiomer, was obtained from (±)-threonine on an L-cysteine derived surface which further suggested that the surfaces were indeed chiral.

**Figure 82**: Deposition of enantiopure cysteine onto an Au followed by ALD of TiO$_2$.

### 3.2.3 Chemical force microscopy

Chemical force microscopy (CFM) has proven a useful tool in the detection of different functional groups on surfaces since its introduction by Lieber and co-workers in the mid 1990’s. CFM works by measuring the adhesive and friction forces between molecularly modified AFM probe tips and organic SAMs with a suitable terminal functional group. It builds on the classical area of force microscopy where information about adhesion and friction may be obtained but it cannot directly probe the specific chemical groups on the sample. CFM can overcome this obstacle by the introduction of chemically modified probes which makes them sensitive to specific molecular interactions (Figure 83).
Figure 83: Illustrative example of specific molecular interactions in CFM (hydrogen bonding between a primary amide and carboxylic acid).

Since the introduction of CFM it has been applied to various studies including the binding of biotin and streptavadin,[193-194] binding between DNA base pairs[195] and most importantly, with reference to this work, been used as a method for the discrimination of chiral surfaces.[196]

Abell and co-workers were the first to demonstrate a proof of principle study on the chiral discrimination of enantiopure Au surfaces using CFM.[196] A novel chiral precursor 147 was synthesised based on Pirkle’s resin[197], used originally in chiral HPLC, and deposited on an Au coated micro cantilever (Figure 84(a)). This chiral AFM tip was then tested against a series of Au surfaces functionalised with enantiopure mandelic acids (Figure 84(b)). The authors showed that discrimination (measured in nN) can be obtained in the cases of the (S)-functionalised tip 147 vs both (R)-148 and (S)-148 ether surfaces (1.1 ±0.1 and 0.4 ±0.1 nN respectively) and the same tip vs both (R)-149 and (S)-149 aromatic surfaces (0.9 ±0.2 and 0.5 ±0.1 nN respectively). Similar discrimination was observed in the case of (R)-functionalised tip 147 vs both (R)-148 and (S)-148 ether surfaces (0.5 ±0.1 and 1.2 ±0.1 nN respectively) and the same tip vs both (R)-149 and (S)-149 aromatic surfaces (0.6 ±0.1 and 1.1 ±0.2 nN respectively). Experiments with (R)-150 and (S)-150 surfaces (ester) were inconclusive and gave no discrimination using any of the enantiopure or racemic tips. This study showed that CFM was sufficiently sensitive to permit discrimination between enantiomers of simple chiral molecules. The authors also hypothesise that the chiral discrimination observed must arise from the differing non-covalent complexes formed between the probe tip and the surface but do not give any stereochemical model to support this theory.

Another report from the research group of Abell showed that chiral discrimination can also be achieved using either enantiomer of Pirkle’s resin (Figure 84(a)), deposited on a probe tip, when tested against a series of hydrophobic coated Au surfaces derived from enantiopure amino
The study showed that chiral discrimination could be demonstrated in all cases when measuring the adhesion forces between the (R)- or (S)-tip and the surfaces 151 to 154 (Table 7). A greater adhesion force was measured for the chiral amines 151 and 152 (Entries 1-8, Table 7) and it was theorised that the amines on the surface were protonated under experimental conditions, resulting in adhesion with the probe tip due to the presence of a net positive charge. Surfaces 153 and 154 showed less of an adhesion force overall but still gave a large enough difference in adhesion to suggest discrimination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tip enantiomer</th>
<th>Surface</th>
<th>Adhesion (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-147</td>
<td>(R)-151</td>
<td>0.2 ±0.1</td>
</tr>
<tr>
<td>2</td>
<td>(R)-147</td>
<td>(S)-151</td>
<td>0.7 ±0.1</td>
</tr>
<tr>
<td>3</td>
<td>(S)-147</td>
<td>(R)-152</td>
<td>0.5 ±0.1</td>
</tr>
<tr>
<td>4</td>
<td>(S)-147</td>
<td>(S)-152</td>
<td>0.2 ±0.1</td>
</tr>
<tr>
<td>5</td>
<td>(R)-147</td>
<td>(R)-153</td>
<td>0.9 ±0.1</td>
</tr>
<tr>
<td>6</td>
<td>(R)-147</td>
<td>(S)-153</td>
<td>1.2 ±0.1</td>
</tr>
<tr>
<td>7</td>
<td>(S)-147</td>
<td>(R)-154</td>
<td>0.4 ±0.1</td>
</tr>
<tr>
<td>8</td>
<td>(S)-147</td>
<td>(S)-154</td>
<td>0.2 ±0.1</td>
</tr>
</tbody>
</table>

Table 7: Adhesion forces for phenyalnine and serine derived surfaces tested against both (R)- and (S)-147.

Takahara and co-workers have also shown that chiral discrimination can be achieved by depositing simple enantiopure molecules on a probe tip and on a surface. The authors used 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) 155 and N-(3,5-dinitrobenzoyl)phenylglycine (DNPB) 156 as the enantiomeric pairs, which were immobilised to a Si-based probe tip and a Si/SiO₂ surface respectively using an aminosilane anchor (Figure 85). The authors examined all four possible combinations i.e. (R)-TFAE 155 vs. (R)-DNPB 156, (R)-TFAE 155 vs. (S)-DNPB156, (S)-TFAE 155 vs. (R)-DNPB 156, (S)-TFAE 155 vs. (S)-DNPB 156 and showed that chiral discrimination events were occurring between the probe tip and the surface. The authors also hypothesised that the interactions that lead to chiral discrimination must be coming from weak non-covalent interactions such as hydrogen bonding and charge transfer between the two acids. The study showed that chiral discrimination could be demonstrated in all cases when measuring the adhesion forces between the (R)- or (S)-tip and the surfaces 151 to 154 (Table 7). A greater adhesion force was measured for the chiral amines 151 and 152 (Entries 1-8, Table 7) and it was theorised that the amines on the surface were protonated under experimental conditions, resulting in adhesion with the probe tip due to the presence of a net positive charge. Surfaces 153 and 154 showed less of an adhesion force overall but still gave a large enough difference in adhesion to suggest discrimination.

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<th>Tip enantiomer</th>
<th>Surface</th>
<th>Adhesion (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-147</td>
<td>(R)-151</td>
<td>0.2 ±0.1</td>
</tr>
<tr>
<td>2</td>
<td>(R)-147</td>
<td>(S)-151</td>
<td>0.7 ±0.1</td>
</tr>
<tr>
<td>3</td>
<td>(S)-147</td>
<td>(R)-152</td>
<td>0.5 ±0.1</td>
</tr>
<tr>
<td>4</td>
<td>(S)-147</td>
<td>(S)-152</td>
<td>0.2 ±0.1</td>
</tr>
<tr>
<td>5</td>
<td>(R)-147</td>
<td>(R)-153</td>
<td>0.9 ±0.1</td>
</tr>
<tr>
<td>6</td>
<td>(R)-147</td>
<td>(S)-153</td>
<td>1.2 ±0.1</td>
</tr>
<tr>
<td>7</td>
<td>(S)-147</td>
<td>(R)-154</td>
<td>0.4 ±0.1</td>
</tr>
<tr>
<td>8</td>
<td>(S)-147</td>
<td>(S)-154</td>
<td>0.2 ±0.1</td>
</tr>
</tbody>
</table>

Table 7: Adhesion forces for phenyalnine and serine derived surfaces tested against both (R)- and (S)-147.

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entities and elude to these types of systems being used for the rational design of novel silica based chiral columns.

Figure 85 (a): Deposition of enantiopure TFAE 155 onto a silicon based cantilever, (b) Deposition of enantiopure DNPB 156 onto a Si/SiO\textsubscript{2} surface.

Hodacova et al. have demonstrated that CFM can be performed using enantiopure trianglamines deposited onto both a silicon surface and a Si\textsubscript{3}N\textsubscript{4} based AFM tip\textsuperscript{[199]} The authors grafted enantiopure triangleamine 158 to a surface through reaction with an isocyanate moiety 157 to give a urea 159\textsubscript{a} and subsequently measured the adhesion forces between the surface and a probe tip 159\textsubscript{b} (Figure 86). The results showed that chemical force discrimination could be achieved in this system with the adhesion force values showing a matched and mismatched effect between the probe and the surface. Weaker interactions occurred between the enantiomers of the trianglamines than with trianglamines of the same configuration.

Figure 86: Direct attachment of trianglamine 158 to the surface via an isocyanate functionality.
Kimura et al. have shown that chiral discrimination can also be achieved using an AFM tip bearing optically active crown ethers and a Au surface coated with cysteine derivatives. The authors deposited a perchlorate cysteine derivative of known enantiomeric purity on the Au surface. The adhesions forces were measured for the surface vs the probe tip and the results show that the chiral recognition ability of the crown ether modified tip, (R,R,R,R)-161, was opposite to that of its enantiomer (S,S,S)-161 on the tip (Table 8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tip enantiomer</th>
<th>Surface</th>
<th>Adhesion (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R,R,R)-161</td>
<td>(R)-160</td>
<td>0.22 ±0.08</td>
</tr>
<tr>
<td>2</td>
<td>(R,R,R,R)-161</td>
<td>(S)-160</td>
<td>0.26 ±0.08</td>
</tr>
<tr>
<td>3</td>
<td>(S,S,S,S)-161</td>
<td>(R)-160</td>
<td>0.25 ±0.08</td>
</tr>
<tr>
<td>4</td>
<td>(S,S,S,S)-161</td>
<td>(S)-160</td>
<td>0.21 ±0.08</td>
</tr>
</tbody>
</table>

Table 8: Summary of the adhesion forces obtained when testing both enantiomers of crown ether functionalised AFM tip against both enantiomers of cysteine derivatives (R)-160 and (S)-160 on the surface.

3.2.4 Enantiospecific wetting

Ducker and co-workers recently introduced a new technique known as enantiospecific wetting where either enantiomer of a chiral liquid can be placed onto a chiral surface and the resulting contact angles are measured. In one experiment the authors placed a drop of (S)-leucinol 162 onto a silicon surface functionalised with (R)-leucinol 162 and measured the resulting contact angle. The results showed a clear difference in contact angle (Table 9) suggesting chiral discrimination. The same was also shown for the opposite case where (S)-leucinol 162 was deposited on a surface and both enantiomers of leucinol were tested. The measurements were also carried out in hexadecane as this provided a clearer visual result with respect to the contact angles and also indicated that contact angles are dependent on environment.
Table 9: Contact angles of leucinol droplets on a leucinol modified surface measured in a hexadecane medium. Taken from reference 201.

Shundo and Tanaka have shown enantioselective wetting of a chiral polymer on quartz and silicon surfaces that involves conformational reorganisation at the surface and a subsequent change in the contact angle. The (R)- and (S)-enantiomers of polymer 163 (Figure 87(a)) were deposited on a surface and the contact angles probed using (R)- and (S)-1,2-propanediol 164 (Figure 87(b)). The results showed that a contact angle of 63 ° was obtained for (S)-164 being placed on an (S)-163 film, whilst a contact angle of 41 ° was obtained when (R)-164 was placed on the same film. Importantly this trend was also observed for the opposite case where (R)- and (S)-164 were placed on an (R)-163 film. The authors attribute this inherent difference in contact angle to the reorganisation of the chiral polymer when it comes into contact with the chiral liquid ((R)- or (S)-164) which is induced by the hydrogen bonding between the carbonyl in the polymer and the hydroxyl group in the chiral liquid.

Figure 87: (a) Chiral polymer deposited on the surface, (b) chiral aliphatic diols used to probe the chiral surfaces.
3.3 **Synthesis of dihydropyranones using HyperBTM 61 on a surface**

3.3.1 **Re-optimisation of bromine terminated SAM deposition**

As the deposition of 11-bromoundecyltrichlorosilane 115 on the Si/SiO$_2$ did not give consistent results, a new approach was targeted using 11-bromoundecyltrimethoxysilane 165. The advantage of using alkoxysilanes over chlorosilanes is the increased stability of the Si-O vs Si-Cl bond (799 vs 406 kJ mol$^{-1}$)$^{[203]}$ during monolayer preparation, although because of this inherent stability they do not form SAMs as readily as halosilanes.$^{[204-205]}$ Following a procedure from Braun,$^{[206]}$ 11-bromoundecyltrimethoxysilane 165 was used, along with NEt$_3$ as an additive, for the formation of a bromine-terminated SAM (Table 10).

During the optimisation process several solvents were tested in the formation of a bromine terminated SAM. As NEt$_3$ is known to aid the self-assembly process it was used as an additive in some cases.$^{[206]}$ Although several entries show a reasonable contact angle (ca. 83°), ellipsometry gave a low (entries 1, 2 and 4) or unreliable value (entries 6 and 7). When using bicyclohexyl or hexadecane as the deposition solvent (Entries 3 and 5) the ellipsometry value was close to the optimum reported in the literature (ca.1.9 nm) but unfortunately these were isolated results and disappointingly could not be reproduced. As toluene gave the most consistent results, with respect to ellipsometry and contact angle, over the largest sample range (Entry 1), this was taken forward as the optimum conditions for deposition for all of the samples discussed in the following sections. A potential reason for the low thickness value could be due to the lack of complete monolayer formation in the self-assembly process. Alkoxysilanes are not as reactive as the corresponding chlorosilanes and as such may not allow for the complete hydrolysis of the Si-OMe groups.$^{[207-208]}$

![Chemical structure of 165 and 116](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deposition solvent</th>
<th>Concentration (mM)</th>
<th>Additive (mmol)</th>
<th>Contact Angle (°)</th>
<th>Ellipsometry (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>10</td>
<td>NEt$_3$ (15)</td>
<td>83.7</td>
<td>0.85</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>10</td>
<td>-</td>
<td>81.5</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>Bicyclohexane</td>
<td>10</td>
<td>NEt$_3$ (15)</td>
<td>82.2</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>Hexadecane</td>
<td>1</td>
<td>-</td>
<td>81.3</td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>Hexadecane</td>
<td>5</td>
<td>-</td>
<td>83.7</td>
<td>1.30</td>
</tr>
<tr>
<td>6</td>
<td>Hexadecane</td>
<td>10</td>
<td>-</td>
<td>84.5</td>
<td>n/a$^a$</td>
</tr>
</tbody>
</table>

$^a$n/a: Not applicable
Table 10: Optimisation of deposition of 11-bromoundecyltrimethoxysilane in solution. *If the contact angle was not deemed sufficient, no ellipsometry measurement was obtained. Ellipsometry data could not be fitted reasonably.

<table>
<thead>
<tr>
<th>Hexadecane</th>
<th>NEt₃ (15)</th>
<th>84.0</th>
<th>n/a</th>
</tr>
</thead>
</table>

All subsequent reactions to afford the CF₃ trifluoromethylenone surface 128 remained unchanged from the original procedure as they gave reproducible results. These surfaces displayed similar characteristics to that of surfaces derived from 11-bromoundecyltrichlorosilane 115. AFM showed a clean surfaces devoid of any external contaminants for all cases considered which suggested a smooth homogeneous SAM. Ellipsometry gave an increase in thickness from 0.9-1.7 nm for the reaction of 112 with 127. The resulting contact angle for 128 was 76° ±1.2. Furthermore, XPS showed the expected elemental composition for surface 128 (C, N, O, Si and F) as well as routine conversions of 85% for the click reaction (Figure 88).

Figure 88: Generation of CF₃ Michael acceptor from bromine terminated SAM.

Having demonstrated the capability of achiral isothiourea to successfully promote the catalytic Michael addition-lactonisation of trifluoromethylenones with arylacetic acids, attention was focused on the synthesis of enantioenriched C(6)-trifluoromethylidihydropyranones. In an attempt to generate enriched (3R,4R) and (3S,4S) surfaces, a simple modification of the protocol developed in chapter 2, using either enantiomer of the chiral isothiourea catalyst HyperBTM 61, was applied (Figure 89). The resulting characteristics of the surfaces were similar to that of the surfaces obtained from reaction with DHPB 60. AFM showed a smooth surface in most of the surfaces examined, giving an RMS roughness of 0.14 nm which is in line with previous results. XPS showed the expected elemental composition (Si, O, N, C and F) with an increase in fluorine content as expected upon successful Michael addition-lactonisation, while the value obtained from ellipsometry was lower, 2.0 nm, given the lower value from the initial bromine-terminated SAM while the contact angle dropped slightly to 73° ±1.5.
3.4 Synthesis of chiral precursor for AFM probe

In donor-acceptor type chiral stationary phases in HPLC, \( \pi - \pi \) stacking interactions between electron poor and electron rich aromatic groups play a significant part in discriminating chiral compounds, in addition to hydrogen bonding, and steric interactions.\(^{[209]}\) It was envisaged that a chiral probe could be devised based on the stationary phase of a Chiracel™ OD-H column (Figure 90) and used to probe a surface comprised of enantioenriched DHPs. As these type of CSPs, based on Pirkle’s resin,\(^{[210]}\) are known to possess capabilities for enantiomeric separation within the realm of chiral HPLC, we hoped this property would translate across to our system and manifest as a strong adhesion force when attached to an AFM probe tip and tested against a surface comprised of DHPs synthesised using the chiral isothiourea catalyst 61.

As thiols are known to form well-ordered monolayers on Au surfaces (discussed detail in Section 1.3), initial attempts focused on synthesising a thiol based chiral phenylglycine precursor 166 for use as an AFM probe, based on the CSP reported by Pirkle.\(^{[210]}\) Conceptually this chiral precursor could be accessed \textit{via} a series of amino acid coupling reactions starting with commercially available (S)-phenylglycine 169 and amine 168 which could potentially be accessed from a variety of routes (Figure 91).
Chapter 3: Chiral discrimination by chemical force microscopy

Figure 91: Retrosynthetic analysis of chiral AFM tip precursor 166.

Commercially available 3,5-dimethyl benzoic acid 171 was reacted with thionyl chloride at reflux which afforded the corresponding acid chloride 170 in 85% yield. Commercially available (S)-phenylglycine 169 was then reacted with acid chloride 170 in the presence of NaOH to give (S)-172 in a good 82% yield (Figure 92).

Figure 92: Synthesis of phenylglycine derivative 172.

Next, the coupling partner was synthesised in two steps using a Gabriel amine synthesis starting from 11-bromoundecene 174 and potassium phthalimide 173. Alkyl phthalimide 175 was obtained in a 75% yield and then subsequently reduced to the corresponding amine using hydrazine monohydrate in refluxing EtOH in 75% yield (Figure 93).
Figure 93: Gabriel amine synthesis of alkyl amine 168.

Following the synthesis of both coupling partners, carboxylic acid 172 and amine 168 were subjected to N-ethyl-N’-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) to afford amide 176 in 66% yield. With amide 176 in hand, the thiol group needed to anchor the molecule to the Au surface was ready to be installed. Treatment with thioacetic acid in the presence of catalytic benzoyl peroxide and irradiation under UV light afforded the desired thioacetate 177 in a low 10% yield but afforded enough material to proceed with the synthetic route (Figure 94).

![Chemical structures](image)

**(S)-172 (1.5 equiv.)**

H₂N

EDCI (1 equiv.)

EDCI (1.8 equiv.)

HOBt (1.8 equiv.)

NMM (2.5 equiv.)

CH₂Cl₂, rt, 16 h

66% yield

**(S)-176**

Ph

Ac

Ac

Ac

CCl₄, UV light,

16 h, 10% yield

**(S)-177**

Deprotection of thioacetate (S)-177 was attempted using a variety of nucleophiles to cleave the acetate group in several different solvent systems, but disappointingly the thiol could not be obtained, and in most cases only starting material was recovered. Reaction of (S)-177 with the nucleophilic acylation catalyst DMAP in MeOH gave only 60% recovered starting material after work up with no trace of product (entry 1, Table 11). Next, treatment with hydride reducing agents LiBH₄ (entry 2, Table 11) and LiAlH₄ (entry 3, Table 11) gave 28% recovered starting material and decomposition products respectively. Attempted deprotection with conc. HCl in MeOH at reflux gave back mostly starting material (entry 4, Table 11) while hydrolysis using LiOH (entry 5, Table 11) and NaOH (entry 6, Table 11) disappointingly gave no trace of desired product. Cleavage of thioacetate 177 was attempted using MeMgBr in THF but gave only decomposition products (entry 7, Table 11) and finally treatment with N₂H₄·H₂O gave only starting material after work up (entry 8, Table 11).
Table 11: Reaction conditions tested for the deacylation of 177. SM = starting material. Decomp = decomposition.

As none of the reaction conditions produced the desired product, a modification of the initial strategy was envisaged where a reactive hydrazide moiety would be used, in combination with phenylglycine derivate 172. This synthesis involved a change in polarity from the original strategy and also relied on leaving the thiol unprotected (Figure 95).

Figure 95: Retrosynthetic analysis of benzamide 179 utilising hydrazide 180 and acid 181.
Treatment of acid 172 with catalytic H$_2$SO$_4$ in the presence of MeOH afforded the corresponding methyl ester 182 in 79% yield. Reaction with hydrazine monohydrate in refluxing EtOH at reflux gave the desired hydrazine 180 in reasonable yield (Figure 96).

![Figure 96: Synthesis of hydrazine 180 from phenylglycine derivative 182.](image)

Commercially available 11-bromoundecanoic acid 183 was heated with thiourea at reflux in H$_2$O which afforded the corresponding thiol 181 in an excellent 90% yield (Figure 97). This gave both coupling partners in relatively good yields over all reaction steps.

![Figure 97: Synthesis of 11-mercaptoundecanoc acid 181 using thiourea.](image)

Pleasingly, using conditions described previously for the coupling of 168 with 172, pure amide 179 was synthesised after recrystallisation from EtOH (Figure 98). This synthetic protocol was reliable and was used for the synthesis of the (R)-179 and (±)-179, starting from (R)- and (±)-phenylglycine.

![Figure 98: Synthesis of precursor 179 for AFM probe using an amide coupling reaction.](image)

### 3.5 Synthesis of alkyne substituted DHPs

To assess the potential viability of the CFM methodology, both enantiomers of 4-fluoro DHP derivative 182 were synthesised in solution and attached to a surface. Reaction of 4-fluorophenylacetic acid 182 with enone 127 in the presence of (2R,3S)-HyperBTM 61 or
Chapter 3: Chiral discrimination by chemical force microscopy

HyperBTM-(2S,3R)-61 gave (3S,4S)-183 and (3R,4R)-183 enantiomers of DHP, in 87% and 90% ee respectively (Figure 99).

Figure 99: Synthesis of enantioenriched DHPs using both enantiomers of HyperBTM. \(^{a}\)Isolated yield of major diastereoisomer of 183 (>95:5 dr). \(^{b}\)Determined by \(^1\)H NMR spectroscopy analysis of the crude reaction mixture. \(^{c}\)Determined by chiral HPLC analysis.

With enantioenriched products (3S,4S)-183 and (3R,4R)-183 in hand, both were attached to separate azide terminated surfaces 112 using the standard conditions for click chemistry affording enantioenriched DHP terminated surfaces (3S,4S)-184 and (3R,4R)-184 (Figure 100).
Figure 100: Attachment of enantioenriched DHP derivatives onto azide terminated surfaces using click methodology.

3.6 Model system for chiral force microscopy

To assess whether this methodology was suitable for analysis of our system, a model system consisting of Au surfaces and Au coated AFM probe tips functionalised with both L- and D-cysteine was devised and subjected to chiral force microscopy (Figure 101). In this model study D-cysteine and L-cysteine were deposited onto separate Au coated Si surfaces (Figure 101(a)) and also onto separate Au coated AFM probe tips (Figure 101(b)) and assessed using chiral force microscopy. Cysteines deposited onto Au surfaces gave static water contact angles of 33.8 ±1.1 ° (L-cysteine) and 29.2 ±1.7 ° (D-cysteine) which are within the range for SAMs of cysteine reported in the literature.[212-213]

![Figure 101](image)

Figure 101 (a): Both enantiomers of cysteine deposited on an Au surface, (b) both enantiomers of cysteine deposited on an Au coated AFM tip.

The results of measurements between both combinations of surface and probe tip of the adhesion force are shown in Table 12.† The adhesion histogram shows the distribution of adhesion or pull-off forces (measured in nN) for an L-cysteine coated AFM tip L-185 tested against both L-cysteine L-142 and D-cysteine D-142 deposited on Au-coated surfaces. The model system shows a clear difference in adhesion values arising from the different interactions of the L-cysteine tip L-185 with both L-cysteine L-142 (0.9 ±0.3 nN, Entry 2, Table 12) and D-cysteine D-142 (2.4 ±1.0 nN, Entry 1, Table 12) terminated surfaces. A second set of measurements were taken between the L-cysteine tip L-185 and D-cysteine surface D-142 in order to eliminate the possibility of

† All AFM measurement and analysis performed by PDRA Dr John Parkin.
experimental error as AFM cantilevers are prone to blunting and can be easily damaged during operational conditions, which results in larger adhesion values as the tip-surface contact area is larger.\cite{214,215} Although the adhesion value was slightly higher (1.3 nN vs 0.9 nN) suggesting some possible tip blunting, the value obtained (1.3 nN) was still significantly lower than that using the D-cysteine surface (2.4 nN) validating the chiral discrimination. The peaks for the adhesion histograms were fit using a normal distribution using the ‘hisfit’ MATLAB function.†

![Figure 102: Adhesion histogram of L-cysteine coated AFM tip tested against separate samples of both L- and D-cysteine on Au. All measurements were taken using the same D-cysteine coated AFM tip. Measurements are snap out of contact. At least four areas tested per sample.](image)

To further assess the reliability of the model system, an Au-coated AFM tip was functionalised with D-cysteine and tested against both L-cysteine L-142 and D-cysteine D-142 deposited on Au coated surfaces (Figure 103). Pleasingly, when D-cysteine tip D-185 was tested against a D-cysteine surface D-142 a reasonable discrimination value was obtained (0.8 ±0.6 nN, Entry 4, Table 12) which is similar to L-cysteine tip L-185 vs L-cysteine surface L-142 (0.9 ±0.3 nN). When D-cysteine tip D-185 was tested against an L-cysteine surface L-142 a value of 2.0 ±0.7 nN (Entry 5, Table 12) was obtained which is lower, but similar to, that of L-cysteine tip L-185 vs D-cysteine D-142 surface (2.4 ±1.0 nN). Both results show a similar trend indicating similar chiral discrimination in each case with opposite enantiomers giving the largest interaction. These results
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show that chemical force microscopy is sufficiently sensitive to allow for discrimination between enantiomers of simple chiral molecules.

![Adhesion histogram of D-cysteine coated AFM tip tested against separate samples of both L- and D-cysteine on Au. All measurements were taken using the same D-cysteine coated AFM tip. Measurements are snap out of contact. At least four areas tested per sample.](image)

Table 12: Summary of adhesion forces from L-cysteine derived AFM tips tested against L- and D-cysteine surfaces.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Probe tip</th>
<th>Surface</th>
<th>Mean (nN)</th>
<th>Std. dev. (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-cysteine L-185</td>
<td>D-cysteine D-142</td>
<td>2.4</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>L-cysteine L-185</td>
<td>L-cysteine L-142</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>L-cysteine L-185</td>
<td>L-cysteine L-142 (2)</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>D-cysteine D-185</td>
<td>D-cysteine D-142</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>D-cysteine D-185</td>
<td>L-cysteine L-142</td>
<td>2.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

3.7 Cysteine coated AFM tips vs ‘clicked’ enantioenriched DHPs

With a reliable model system and both enantiomers of DHP 183 in hand, attention was focused on the chiral discrimination of enantioenriched surfaces (3S,4S)-184 and (3R,4R)-184 using the developed CFM methodology with L/D-cysteine as probe tips. When L-cysteine functionalised tip L-185 was tested against a (3S,4S)-184 surface (87% ee) an adhesion value of 1.9 ±0.1 nN (entry 2, Table 13) was obtained. When L-cysteine functionalised tip L-185 was tested against a (3R,4R)-184 surface (90% ee) an adhesion value of 1.5 ±0.1 nN (entry 1, Table 13) was obtained.
When a d-cysteine functionalised tip d-185 was tested against a surface comprised of (3S,4S)-184 DHPs (90% ee) an adhesion value of 1.3 ±0.2 nN (entry 3, Table 13) was obtained. Finally, a d-cysteine functionalised tip d-185 was tested against a surface comprised of (3R,4R)-184 DHPs (87% ee) an adhesion value of 1.9 ±0.2 nN (entry 4, Table 13) was obtained. From the measurements obtained (Figure 104 and Figure 105) it can be said that there is a clear chiral discrimination event occurring on the surfaces in question. It is a clear that when the enantiomer of the AFM probe tip is changed, the magnitude of values is reversed, indicating that a chiral discrimination event is occurring specific to the enantiomeric/diastereomeric pairing.
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3.8 Chiral benzamide tips vs ‘clicked’ enantioenriched DHPs

As shown in Section 3.4, two enantiomerically pure thiol based benzamides, and a racemic version, were synthesised to evaluate their capacity as chiral probes in chemical force microscopy. The (R)- and (S)-enantiomers, as well as the racemic functionalised tips were tested against enantioenriched surfaces (3R,4R)-184 and (3S,4S)-184 (Figure 106).

Figure 106: \((R)/(S)-179\) modified AFM tips evaluated against DHPs terminated surfaces prepared from enantiomerically enriched starting materials.

When (S)-benzamide tip 179 was tested against a surface comprised of (3S,4S)-184 DHPs (90% ee) an adhesion value of 5.7 ±1.0 nN (entry 6, Table 13) was obtained. When (S)-benzamide tip
179 was tested against a surface comprised of (3R,4R)-184 DHPs (87% ee) an adhesion value of 3.5 ±0.3 nN (entry 5, Table 13) was obtained which shows a clear difference in adhesion values for this system.

When (R)-benzamide tip 179 was tested against a surface comprised of (3S,4S)-184 DHPs (90% ee) an adhesion value of 4.6 ±0.4 nN (entry 7, Table 13) was obtained. When (S)-benzamide tip 179 was tested against a surface comprised of (3R,4R)-184 DHPs (87% ee) an adhesion value of 7.0 ±0.8 nN (entry 8, Table 13). This result agrees with the trend observed in the previous system, that is when the enantiomer of the AFM probe tip is changed, the magnitude of values is reversed, indicating a diasterospecific event occurring.
Figure 108: Adhesion histogram of (R)-benzamide coated AFM tips tested against separate samples of both (3R,4R)-184 and (3S,4S)-184 clicked DHP surfaces respectively. All measurements were taken using the same L-cysteine coated AFM tip. Measurements are snap out of contact.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Probe tip</th>
<th>Surface</th>
<th>Mean ± Std. dev. (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-cysteine L-185</td>
<td>(3R,4R)-184</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>L-cysteine L-185</td>
<td>(3S,4S)-184</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>D-cysteine d-185</td>
<td>(3S,4S)-184</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>4</td>
<td>D-cysteine d-185</td>
<td>(3R,4R)-184</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>5</td>
<td>(S)-benzamide 179</td>
<td>(3R,4R)-184</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>6</td>
<td>(S)-benzamide 179</td>
<td>(3S,4S)-184</td>
<td>5.7 ± 1.0</td>
</tr>
<tr>
<td>7</td>
<td>(R)-benzamide 179</td>
<td>(3S,4S)-184</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>8</td>
<td>(R)-benzamide 179</td>
<td>(3R,4R)-184</td>
<td>7.0 ± 0.8</td>
</tr>
</tbody>
</table>

Table 13: Summary of adhesions forces from L- and d-cysteine and (S)/(R)-benzamide derived AFM tips tested against (3R,4R)-184 and (3S,4S)-184 surfaces.

3.9 **Cysteine coated AFM tips vs DHPs prepared using HyperBTM 61**

Having demonstrated a proof of principle with respect to the cysteine model study and pre-synthesised enantioenriched DHPs attached to the surface, attention was then focused on chiral discrimination of DHP surfaces functionalised using enantioselective catalysis. For a direct comparison with the model system, L-cysteine was deposited onto an AFM tip and evaluated in CFM against two modified SAM surfaces prepared using the previously described Michael addition-lactonisation methodology using either enantiomer of isothiourea HyperBTM 61 as the catalyst (Figure 109).
Initial results showed some discrimination between the L-cysteine tip L-185 and the 186 and 187 surfaces (Figure 110). Adhesion values obtained for the L-cysteine tip L-185 tested against the 186 surface gave a value of 2.8 ±0.7 nN (Entry 1, Table 14) while adhesion values obtained for the L-cysteine tip L-185 tested against 187 surface gave a value of 3.8 ±0.8 nN (Entry 2, Table 14). This shows a reasonable difference in adhesion values for this specific case but also noteworthy was the presence of significant overlap in adhesion values. This may suggest possible tip blunting during AFM measurements or homogeneity of the SAMs may be an issue.
Figure 110: Adhesion histogram of $L$-cysteine coated AFM tips tested against separate samples of both 186 and 187 surfaces respectively. All measurement were taken using the same $L$-cysteine coated AFM tip. Measurements are snap out of contact. At least four areas tested per sample.

When $D$-cysteine functionised AFM tip $D$-185 was tested against both 186 and 187 surfaces a small difference in adhesion force was detected (Figure 111). Adhesion values obtained for the $D$-cysteine tip $D$-185 tested against surface 186 gave an adhesion value of $2.3 \pm 0.3$ nN (Entry 4, Table 14) while adhesion values obtained for the $D$-cysteine tip $D$-185 tested against surface 187 gave a value of $1.8 \pm 0.3$ nN (Entry 3, Table 14). These results show an overall decrease in adhesion values for this system when compared to the $L$-185 tested against the same surfaces (Figure 110). Moreover the adhesion values obtained for the $D$-cysteine tip $D$-185 seem to be the ‘opposite’ to that of the $L$-cysteine tip $L$-185. The $D$-cysteine tip $D$-185 has a higher affinity for the 186 surface whereas the $L$-cysteine tip $L$-185 has a higher affinity for the 187 surface.

Figure 111; Adhesion histogram of $D$-cysteine coated AFM tips tested against separate samples of both 186 and 187 surfaces respectively. All measurement were taken using the same $D$-cysteine coated AFM tip. Measurements are snap out of contact.
Table 14: Summary of adhesions forces from l-cysteine derived AFM tips tested against surfaces 186 and 187.

3.10 Chiral benzamide tip vs DHPs prepared using HyperBTM 61

CFM measurements showed discrimination in all cases. The previously developed chiral AFM tip 179 was tested against surfaces 186, 187 and 188 obtained from the in situ Michael addition-lactonisation procedure using HyperBTM 61 (Figure 112).

Figure 112: (R)/(S) and (±)-179 modified AFM tips evaluated against DHPs terminated surfaces prepared from a Michael addition-lactonisation procedure using both enantiomers and (±)-HyperBTM 61.

The (S)-benzamide tip 179 vs surface 186 gave an adhesion value of 4.7 ±2.1 nN (Entry 1 Table 15) while the same probe tip tested against a 187 surface gave an adhesion value 9.6 ±3.0 nN (Entry 2 Table 15). When (S)-benzamide 179 was tested against surface 188 an adhesion value of 11.3 ±4.5 nN was obtained (Entry 3 Table 15). In theory, when (S)-benzamide 179 is tested against surface 188 an adhesion value halfway between those obtained for 186 and 187 surfaces should be obtained. However this discrimination was not observed, which may suggested that the 188
surface may have particular domains consisting of either enantiomer and not an equal mixture of both distributed on the surface as expected.[216-217]

![Figure 113: Adhesion histogram of (S)-benzamide coated AFM tip tested against separate samples of 186, 187 and 188 DHP terminated surfaces respectively. All measurement were taken using the same (S)-benzamide coated AFM tip. Adhesion force before snap out of contact. At least four areas tested per sample.](image)

When (R)-benzamide 179 was tested against surfaces 186 and 187 a notably larger set of adhesion values were obtained than in the previous measurements (Table 14). The (R)-benzamide 179 vs 186 gave an adhesion value of 4.8 ± 4.2 nN (Entry 4 Table 15). The same probe tip tested against a 187 surface gave a mean adhesion value 28.5 ± 9.6 nN (Entry 5 Table 15) which greatly differs from that of the corresponding (S)-benzamide 179 tested against the same surface (Entry 2 Table 15). Finally, when the surface 188 was tested against (R)-benzamide 179, a mean adhesion value of 28.9 ± 9.6 nN (Entry 6, Table 15) which is the same as that obtained for the 187 surface. The higher adhesion values may be a result of a greater interaction between tip and surface which may be expected given the magnitude of values observed when (S)-benzamide 179 was tested. These results suggest that chiral discrimination is not as clear with this combination of probe tip and surface and are not consistent with what has been observed in the previous measurements using L- and D-cysteine as probe tips. In previous measurements the magnitude of the interactions are reversed upon the use of a different enantiomer of AFM probe tip, suggesting different chiral interactions events are happening. It is not obviously clear why this is the case and due to time constraints, this particular set of measurements could not be repeated. A possible reason for the lack of chiral discrimination of these surfaces may be due to the homogeneity of the SAM.
Lattanzi and co-workers have shown using DFT calculations that the introduction of large bulky groups to the terminal end of a SAM ((6-(2-triptycenylcarboxy)hexylphosphonic acid in this case) can interfere with homogeneity and result in irregular and rough surfaces.\textsuperscript{1218} The preparation of these surfaces most likely play a crucial role in the overall quality and final distribution of molecules on the surface. Conversely, as the distribution and molecular packing on the (\textit{R})-179 tip is unknown and cannot be verified it may potentially be that the AFM tip used added to anomalous results. Repeat experiments are needed in order to validate these measurements and as such these results may not be relied upon to draw any conclusions at the present time.

To complete the measurements and obtain a clearer picture of the discrimination occurring on the surfaces, a racemic variant of the probe tip was constructed by depositing (\textpm)-179 on an Au coated AFM tip. When (\textpm)-benzamide 179 was tested against surfaces 186 and 187 no discrimination was observed (Figure 115) Adhesion values obtained were similar and with error of each other (Entries 7 and 8 Table 15). Similarly when the (\textpm)-179 tip was tested against the surface 188 an adhesion value between the two, 3.5 ± 1.5 nN, was obtained (entry 9, Table 15). Overall this was the expected result from the measurement of surfaces 186, 187 and 188 using the (\textpm)-179 tip and no discrimination was observed in any of the cases.

![Figure 114: Adhesion histogram of (\textit{R})-benzamide coated AFM tips tested against separate samples of 186, 187 and 188 DHP terminated surfaces respectively. All measurement were taken using the same (\textit{R})-benzamide coated AFM tip. Measurements are snap out of contact. At least four areas tested per sample.](image-url)
Figure 115: Adhesion histogram of (±)-benzamide coated AFM tips tested against separate samples of 186, 187 and 188 DHP terminated surfaces respectively. All measurements were taken using the same (R)-benzamide coated AFM tip. Measurements are snap out of contact. At least four areas tested per sample.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Probe tip</th>
<th>Surface</th>
<th>Mean (nN)</th>
<th>Std. dev. (nN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-benzamide 179</td>
<td>186</td>
<td>4.7</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>(S)-benzamide 179</td>
<td>187</td>
<td>9.6</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>(S)-benzamide 179</td>
<td>188</td>
<td>11.3</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>(R)-benzamide 179</td>
<td>186</td>
<td>4.8</td>
<td>4.2</td>
</tr>
<tr>
<td>5</td>
<td>(R)-benzamide 179</td>
<td>187</td>
<td>28.5</td>
<td>9.6</td>
</tr>
<tr>
<td>6</td>
<td>(R)-benzamide 179</td>
<td>188</td>
<td>28.9</td>
<td>9.6</td>
</tr>
<tr>
<td>7</td>
<td>(±)-benzamide 179</td>
<td>186</td>
<td>4.0</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>(±)-benzamide 179</td>
<td>187</td>
<td>3.0</td>
<td>1.2</td>
</tr>
<tr>
<td>9</td>
<td>(±)-benzamide 179</td>
<td>188</td>
<td>3.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 15: Summary of adhesive forces from (R)-179, (S)-179 and racemic 179 derived AFM tips tested against surfaces 186, 187 and 188.

As it is not particularly informative to directly compare adhesion values obtained using different AFM tips, ratios of the adhesion force obtained with one particular enantiomer of the AFM tip tested against the same surface termination was calculated e.g. L-cysteine tip 185 tested against 186 and (3R, 4R)-184, importantly keeping the AFM tip constant. A ratio of 1.0:2.3 for the measurement an L-cysteine tip 185 vs (3R,4R)-184 and 186 was obtained which corresponded to
double the magnitude of adhesion force (entry 1, Table 16). A possible reason for the increase in magnitude may be due to the roughness and/or homogeneity of the surfaces. A ratio of 1.0:1.1 for an L-cysteine tip \(185\) vs (3S,4S)-184 and 187 surface was obtained indicating surfaces of similar molecular packing (entry 2, Table 16). Similar trends are observed when the same D-cysteine tip \(185\) was used to probe the (3S,4S)-184, (3R,4R)-184, 186 and 187 surfaces. A ratio of 1.0:1.2 for the same D-cysteine tip \(185\) vs (3R,4R)-184 and 187 surfaces again indicating consistent films on the surfaces (entry 3, Table 16). When D-cysteine tip \(185\) was tested against (3S,4S)-184 and 187 surfaces a ratio of 1.3:1.0 was obtained (entry 4, Table 16). When (S)-benzamide tip 179 was tested against surfaces 186 and 187 similar ratios were obtained to that of the previous measurements. A ratio of 1.0:1.3 was obtained for an (S)-benzamide tip 179 vs (3R,4R)-184 surface and 187 (entry 5, Table 16) and a ratio of 1.7:1.0 for a (3S,4S)-184 and 187 surface indicating consistent films on both surfaces. As the results from the (R)-benzamide tip 179 in the \textit{in situ} Michael addition lactonisation protocol were inconclusive they will not be compared in further detail but are presented below for completeness (entries 7-8, Table 16). It should be mentioned however, that the results obtained from the (R)-benzamide tip 179 tested against the ‘clicked’ surfaces followed the same trend as previously observed, that is the magnitude of the adhesion values were reversed, and as such may be a true reflection of the discrimination events on the surface. Based on these results we can suggest that the molecular packing of the DHPs is similar on some of the surfaces concerned regardless of fabrication method.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Probe tip</th>
<th>Surfaces</th>
<th>‘Clicked’ mean (nN)</th>
<th>\textit{In situ} mean (nN)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-cysteine (185)</td>
<td>(3R,4R)-184/186</td>
<td>1.5 ± 0.1</td>
<td>2.8 ± 0.7</td>
<td>1.0:2.3</td>
</tr>
<tr>
<td>2</td>
<td>L-cysteine (185)</td>
<td>(3S,4S)-184/187</td>
<td>1.9 ± 0.1</td>
<td>3.8 ± 0.8</td>
<td>1.0:1.1</td>
</tr>
<tr>
<td>3</td>
<td>D-cysteine (185)</td>
<td>(3S,4S)-184/187</td>
<td>1.3 ± 0.2</td>
<td>1.8 ± 0.4</td>
<td>1.0:1.2</td>
</tr>
<tr>
<td>4</td>
<td>D-cysteine (185)</td>
<td>(3R,4R)-184/186</td>
<td>1.9 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>1.3:1.0</td>
</tr>
<tr>
<td>5</td>
<td>(S)-benzamide 179</td>
<td>(3R,4R)-184/186</td>
<td>3.5 ± 0.3</td>
<td>4.7 ± 2.1</td>
<td>1.0:1.3</td>
</tr>
<tr>
<td>6</td>
<td>(S)-benzamide 179</td>
<td>(3S,4S)-184/187</td>
<td>5.7 ± 1.0</td>
<td>9.6 ± 3.0</td>
<td>1.7:1.0</td>
</tr>
<tr>
<td>7</td>
<td>(R)-benzamide 179</td>
<td>(3S,4S)-184/187</td>
<td>4.6 ± 0.4</td>
<td>28.5 ± 9.6</td>
<td>1.0:6.2</td>
</tr>
<tr>
<td>8</td>
<td>(R)-benzamide 179</td>
<td>(3R,4R)-184/186</td>
<td>7.0 ± 0.8</td>
<td>4.8 ± 4.2</td>
<td>1.5:1.0</td>
</tr>
</tbody>
</table>

\textit{Table 16: Summary of adhesions forces from L- and D-cysteine and (S)/(R)-benzamide derived AFM tips tested against (3R,4R)-184 and (3S,4S)-184 surfaces.}
3.11 Enantiospecific wetting on enantioenriched DHPs

An enantiospecific wetting experiment was undertaken using the synthesised assumed enantioenriched surfaces to evaluate a possible chiral interaction with a chiral probe liquid.† Following a procedure from Ducker,[201] the chiral surface was tested using a leucinol by placing ~3 µL drop on the appropriate surface synthesised from the in situ Michael addition-lactonisation procedure (Figure 116). Initially the contact angle was measured using (S)-leucinol 190 as a chiral liquid. This gave a small difference in contact angle on the surface when tested against all assumed enantioenriched surfaces (186-189) (Table 17). In the Ducker report hexadecane was used as a surrounding medium for the measurements to allow a more measureable contact angle. Unfortunately this was not the case in these set of experiments and only a slight difference in angle was measured between all surfaces. Practically it is difficult to measure contact angles below 15-20° as they do not give a large contact angle (θ) with the surface and tend to have large experimental error. However, a small difference is noticed and this may tentatively be attributed to the chiral interactions taking place on the surface between the assumed enantioenriched DHPs and the leucinol.

![Figure 116: Experimental set-up for contact angle measurement using enantiospecific wetting methodology.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surface</th>
<th>Leucinol</th>
<th>Surrounding medium</th>
<th>Contact Angle (°)ᵃᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186</td>
<td>(S)-leucinol 190</td>
<td>Atmosphere</td>
<td>11.5 ±1.0</td>
</tr>
<tr>
<td>2</td>
<td>186</td>
<td>(S)-leucinol 190</td>
<td>Hexadecane</td>
<td>16.6 ±2</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>(S)-leucinol 190</td>
<td>Hexadecane</td>
<td>19.9 ±1.2</td>
</tr>
<tr>
<td>4</td>
<td>188</td>
<td>(S)-leucinol 190</td>
<td>Hexadecane</td>
<td>11 ±0.8</td>
</tr>
</tbody>
</table>

Table 17: Contact angles of enantiospecific wetting experiments of (S)-leucinol tested against all the combinations of chiral surfaces.ᵃAverage of two samples of the same termination.ᵇAverage of at least two measurements on the same sample.

† Enantiospecific wetting experiment performed by Dr John D. Parkin.
3.12 Conclusion and future outlook

In this work enantioenriched surfaces were synthesised using a Michael addition-lactonisation the chiral isothiourea catalyst HyperBTM in both (2S,3R) and (2R,3S) 61 enantiomeric forms. A model system was developed that gave reliable and reproducible results when used in chemical force microscopy measuring chiral discrimination. A novel chiral AFM probe tip was also developed and tested in our system against the enantioenriched surfaces giving a reasonable level of discrimination.

Both enantiomers of the enantioenriched DHP 184 were also synthesised and attached to the surface using click chemistry. The results from this show that regardless of fabrication method, both types of surfaces give similar adhesion values, within error of each other, suggesting that similar chiral discrimination events are happening on the surfaces as well as comparable molecular packing of the surfaces.

Additional experiments measuring contact angles using a chiral, enantiopure liquid were also undertaken to ascertain the possible differing diastereomeric interactions occurring between the liquid and solid interface. These results did not show a huge difference in the resulting contact angles, and this was attributed to practical issues with the measurements, although some information may be tentatively taken from this.

The limitations of the current methodology include the inability of the chiral force measurements to allow for quantification of the levels of enantioselectivity imparted on the surface. Non-linear effects in ee generation\(^{[219]}\) (on the surface) may come into play but this is difficult to measure using classical methods. A possible remedy to this would be to prepare a series of surfaces using enantioenriched catalysts of varying ee’s, that is, with the idea of creating a series of surfaces with DHPs present in increasing levels of ee and testing using the aforementioned methodology. This may provide insight into the sensitivity of the CFM methodology developed in this work.

Future work in this area could include the derivatisation of these surfaces to attach desired functional groups in a selective manner and possibly even be used as chiral selectors in enantioselective reactions.

3.13 References and Notes

Chapter 3: Chiral discrimination by chemical force microscopy

Chapter 4: Synthesis and immobilisation of isothiourea catalysts onto polystyrene supports

**Introduction**

This chapter describes the immobilisation of reactive isothiourea-based organocatalysts onto Merrifield-type polystyrene supports (Figure 117). At the onset of this study there was no examples of a solid support isothiourea-based organocatalyst in the literature. In this study, two polymer-supported (PS) isothioureas synthesised (PS-(R)-BTM 191 and PS-(2R,3S)-HyperBTM 61) have been evaluated in heterogeneous Michael addition-lactonisation reactions, kinetic resolutions of secondary aryl-alkyl alcohols, kinetic resolutions of heteroaromatic tertiary alcohols and stereoselective annulations of α,β-unsaturated acyl ammonium intermediates with 1,3-dicarboxyls. These separate protocols all provide excellent selectivity, comparable with the corresponding homogeneous system, with good yields in most cases. A recyclability study of PS-(2R,3S)-HyperBTM 61 as a catalyst for the kinetic resolution of tertiary alcohols was also undertaken and this showed that the catalyst can be recycled up to 8 times with only a small loss in selectivity.

**Figure 117: Polymer-supported isothioureas synthesised and used in this work.**

4.1 **Aims**

The aim of this chapter was to immobilise reactive isothiourea-based organocatalysts onto a polystyrene support and perform studies to test the robustness and recyclability of the resulting catalytic resins. Secondly, we wanted to assess the applicability of these catalysts to a wide range of enantioselective processes that are known to be mediated by (2R,3S)-HyperBTM 61 and PS-(R)-BTM 191. Comparison of the efficiency and selectivity with the homogeneous counterparts was also an initial aim of this work.

4.2 **Polymer-supported synthesis**

Since the introduction of insoluble polymer-supports by R. Bruce Merrifield in 1963\[220\] there has been a huge uptake in their use as a solid-support for reagent and catalyst immobilisation.\[221\]
Originally these polymer-supports were to be used for solid-phase peptide synthesis, but their generality and applications in chemical synthesis quickly caught on and is now widespread. Insoluble polymer-supports offer the advantage of being easily removed from reaction mixtures by filtration, rinsing and drying allowing them to be readily reusable. This is a desirable property for any system where the aim is to minimise waste products and abide by the principles of green chemistry. After initial research by Merrifield using several different polymeric materials, the chloromethyl and divinylbenzene (DVB) crosslinked PS were introduced, commonly known at Merrifield resin 192 (Figure 118).

![Merrifield resin 192](image)

Figure 118: Polymer-support (PS) introduced by R. B. Merrifield in 1963.

Favourable properties of Merrifield resin 192 included swelling in non-polar organic solvents although this proved restrictive when synthesising long peptide sequences. As a result several improvements were made to make the resin more compatible with a wider range of reagents/catalysts. The most notable was the introduction of a tetrahydrofuran-derived cross-linker to enhance swelling characteristics by Toy and Janda, known as JandaJel™ (193), which is now commercially available (Figure 119).

![JandaJel™ 193](image)

Figure 119: JandaJel™ containing a THF derived cross-linker introduced by Toy and Janda.

Polymer swelling is a major characteristic of polystyrene derived resins which can play an important role in the reactivity. Swelling of a gel-like resin is considered a prerequisite for facilitating reactions to occur within the solid support. Early research in the area focused on enhancing the swelling properties by introducing polymeric regions that are more compatible with polar solvents, thus increasing the scope of reactions that can performed using polymer-supports. The introduction of polyethylene glycol (PEG) units into the polymer-support gave the
desired swelling properties and a series of resins was developed from this methodology.\cite{228} TantaGel™ 194 and later ArgoGel™ 195 received the most significant commercial success and both are prepared by grafting the PEG chains through polymerisation and not installing prefabricated PEG linkers (Figure 120).

\[ \text{Figure 120: Typical examples of the PEG-PS family of resins.} \]

4.3 Polymer-supported tertiary Lewis base organocatalysts

The section offers a brief history of the development of immobilised tertiary amine Lewis basic organocatalysts, with particular emphasis on chiral derivatives and their use in stereoselective synthesis. An overview of recent noteworthy developments within the area is also given.

4.3.1 Polymer-supported Cinchona alkaloids

The first example of a polymer-supported Lewis basic organocatalyst for use in enantioselective synthesis was reported by Nakamura and co-workers in 1974.\cite{229} Following from the original work by Pracejus, who used phenylmethylketene 196 in the synthesis of \((\text{−})\)-\(\alpha\)-phenyl methylpropionate,\cite{230} the authors immobilised a Cinchona derived catalyst onto a polymer-support using AIBN as initiator in a co-polymerisation procedure. PS-(1S,2R,4S,5R)-197 was examined in the enantioselective addition of methanol to phenylmethylketene 196 affording ester 198, in 35% ee (Figure 121). Unfortunately the recyclability of this system was not tested. Although the ee’s are mediocre by today’s standards, this example served as a starting point for organocatalyst immobilisation.
Figure 121: Seminal work by Nakamura and co-workers using PS Cinchona derivative 197 for enantioselective addition to ketenes.

Although this particular catalyst class went through several incremental improvements,[231-234] it was not until a report from d’Angelo and co-workers in 1999 that showed that PS Cinchona alkaloids could compete with their non-supported counterparts.[235] As such, PS-(1S,2R,4S,5S)-201 was an efficient catalyst for the enantioselective Michael addition of 199 to methyl vinyl ketone (MVK) 200, forming (R)-202 in an 85% yield and 87% ee (Figure 122). This was the highest ee value for this reaction obtained by using either a non-supported or polymer-support catalyst.

Figure 122: PS quinine derivative 201 catalysed Michael addition

Lectka and co-workers have shown that PS-Cinchona alkaloids catalyse the formation of β-lactams in a [2+2] cycloaddition between ketenes and N-tosyl imines.[236] In this report the authors packed solid phase reagents into sequentially linked columns and eluted the reagents through using gravity. Reaction of acid chloride 203 with PS-BEMP generates the corresponding ketene 204 in situ, which in the presence of imine 205 and PS-206 undergoes a [2+2] cycloaddition to afford a range of β-lactams in moderate yields, good dr and excellent ee’s (Figure 123). Interestingly, the catalyst took between five and 10 runs to ‘equilibrate’ and afford consistent
results, after which the system could be recycled up to 60 times without erosion of yield or selectivity.

![Figure 123: Lectka's synthesis of β-lactams using PS Cinchona 206 on sequentially linked columns](image)

### 4.3.2 Polymer-supported amidines

Nagai and Endo have reported the use of a polymer-supported amide in the catalytic synthesis of a range of 1H-quinazoline-2,4-diones from 2-aminobenzonitriles.[237] The authors synthesised the polymer support using a radical polymerisation procedure. The polymer-supported catalyst 209 was able to fix CO\(_2\) from the atmosphere and subsequently react with 2-aminobenzonitriles 208 to afford the products in low to excellent yield (Figure 124). The authors report that PS-209 could be recycled at least twice without loss in activity.

![Figure 124: Use of PS amidine 209 in CO\(_2\) fixation and synthesis of 1H-Quinazline-2,4-diones.](image)

A more recent example of using amidines in polymer-supported synthesis was reported by Khalafi-Nezhad and co-workers who used PS-PEG-DBU 215 as an organocatalytic base in the multi-component one-pot synthesis of a range of 8-substituted pyro[2,3-d]-pyramidine-6-carbonitriles in water (Figure 125).[238] The reaction of barbituric acid 211, malonitrile 212, benzaldehyde 213 and adeonside 214 in the presence of PS-215 affords the corresponding
substituted pyrimidines in high yields. PS-215 can be recycled up to 12 times without any loss of selectivity.

Figure 125: One-pot multicomponent synthesis of pyro[2,3-d]-pyrimidine-6-carbonitriles using PS-215.

### 4.3.3 Polymer-supported guanidines

Matsukawa and co-workers have shown that a PS-TBD organocatalyst can be used in the regioselective ring-opening of racemic aziridines with silylated nucleophiles, giving good yields and generally excellent regioselectivity (Figure 126). The authors also comment that the PS-TBD 219 used gave better regioselectivity than a previously reported PS-TBD catalyst in the ring-opening of epoxides under similar conditions.

Ishikawa and co-workers have shown the use of PS guanidine ‘superbases’ in the enantioselective Michael reaction of glycine imine 221 with methyl vinyl ketone 199 to afford the corresponding Michael product 223 in good yield and good ee (85% ee). Reaction of PS-(R,R)-222 with imine 221 is thought to generate the corresponding enolate, which undergoes a stereoselective Michael addition with MVK 199 to give (S)-223 with good stereocontrol. The authors recycled PS-(R,R)-222 three times with only a slight loss in yield and negligible loss of stereoinduction. A stereochemical model was not proposed for the polymer-support system, however the same authors have proposed one for the analogous homogeneous system. In this case, the guanidine derivative blocks the Si face of the enolate allowing addition from the Re face (Figure 127).
As the same sense of enantioselectivity in both non-supported and PS-\((R,R)\)-222 is similar (91\% vs 85\% ee) the same sterochemical rationale may potentially be assumed.

![Figure 127: Enantioselective Michael addition of glycine imine 221 to MVK using PS-222.](image)

### 4.3.4 Polymer-supported DMAP derivatives

Since the first report of a polymer-supported DMAP derivative\[^{244}\] there have been many reports of their use in a variety of useful transformations.\[^{245-249}\] It was not until 2003 that a chiral analogue of DMAP was immobilised onto a polymer-support and evaluated in the kinetic resolution of secondary alcohols (Figure 128).\[^{248}\] Kinetic resolution of racemic alcohol 224 using PS-\((S)\)-225 and isobutyric anhydride allowed the unreacted alcohol 224 to be isolated in 93\% ee at 67\% conversion. This corresponds to a low selectivity factor \(s = k_{\text{fast}}/k_{\text{slow}}\), suggesting that the enantiodiscrimination between the enantiomers of 224 is low. No significant effects were found regarding changes in catalyst loading or nature of the support. Recycling of PS-\((S)\)-225 showed a decrease in efficiency after four runs as selectivity dropped significantly.
4.3.5 Polymer-supported isothioureas

During the course of this thesis, Pericás and co-workers published a report using a polymer-supported derivative of the isothiourea \((R)-\text{benzotetramisole (BTM)}\) \(229\). PS-(R)-229 can efficiently catalyse the enantioselective formation of a series of DHP derivatives as well as several saccharin-derived products in a Michael addition-lactonisation protocol (Figure 129). PS-(R)-229 can also be recycled at least 6 times without any loss of selectivity. The diastereoselectivity obtained from these processes are reportedly generally higher than those of the original homogeneous system, originally reported by the Smith group.\(^{[101]}\) This is attributed to the introduction of the substituent at C3 on PS-(R)-BTM that possibly destabilises the transition state that leads to the formation of the minor diastereoisomer.
4.4 Synthesis of starting materials for PS-(S)-benzotetramisole analogue

The CuAAC reaction is a versatile method for the regioselective construction of 1,2,3-triazoles. Several reports have shown that the CuAAC reaction can be used to attach alkynes to azide terminated polymer supports.[250-254] We envisaged that the synthesis of an alkyne BTM-234 analogue would give a species that could react with a polymer-supported azide, affording the desired immobilised isothiourea organocatalysts (Figure 130).

![Retrosynthetic analysis of polymer-supported (S)-BTM 232.](image)

We envisaged the synthesis of a 2-aminobenzothiazole core 235 via an oxidative ring closing reaction using the appropriate thiourea 236 (Figure 131).

![Retrosynthetic analysis of (S)-234 using the Hugerschoff reaction](image)

4.4.1 Benzothiazole synthesis from thioureas

Initial attempts focused on the synthesis of the benzothiazole core from the corresponding thiourea with the pre-installation of an alkyne moiety, which would circumvent the need for any late stage installation of this functionality. The most important strategy for the synthesis of benzothiazoles is the condensation of ortho-amino-phenol, thiophenol or aniline with a carboxylic acid, aldehyde, acyl chloride or acid anhydride (Figure 132).[255]
Figure 132: Various ortho-condensation reactions for the synthesis of 2-benzothiazoles.

Another important reaction for the synthesis 2-benzothiazoles is the oxidative ring closure of arylamine-thioamides affording 2-aminobenzothiazoles, known as the Hugershoff reaction.\(^{[256-257]}\)

In the original report, Hugershoff used 1-phenylthiourea 243 and elemental bromine in the presence of acetic acid, which cyclised to give the corresponding 2-aminobenzothiazole 244 (Figure 133(a)).

![Figure 133 (a): Original conditions reported by Hugershoff for the formation of 2-aminobenzothiazoles, (b) Proposed mechanism of the Hugershoff reaction.](image)

Synthesis of thiourea 236 began with commercially available 4-iodoaniline 246. TMS-acetylene was reacted with 246 under Sonogashira conditions to afford the corresponding alkynyl aniline 247 in excellent yield. Treating 247 with 1,1-thiocarbonyldiimidazole 248 in CHCl\(_3\) gave the isothiocyanate 249 in excellent 92% yield (Figure 134).
As aryl thioureas can be generated from addition of a primary or secondary amine to the appropriate isothiocyanate, a variety of amino alcohols were used for the synthesis of several substituted thioureas. In this protocol, the appropriate amino alcohol was reacted with isothiocyanate neat for 10 mins then toluene was added and the reaction stirred for 20 mins. This procedure gave thioureas in moderate to excellent yields (Figure 135).

With a variety of substituted thioureas in hand, the oxidative cyclisation into 2-aminobenzothiazoles was evaluated. Initial attempts focused on the use of Br\(_2\) in AcOH with LiBr as an additive using AcOH as a solvent, but this gave no observable conversion in any of the cases (entries 1-3, Table 18). Switching the solvent to CH\(_2\)Cl\(_2\) and using Br\(_2\) also gave no conversion (entries 4-6, Table 18). Catalytic Pd(OAc)\(_2\) was next trialled with 1,10-phenanthroline as an additive but again no conversion was observed (entry 7, Table 18). Patel and co-workers have reported the use of catalytic Cu(OTf)\(_2\) in the formation of intramolecular C-S bonds.\(^{[258]}\) Therefore catalytic Cu(OTf)\(_2\) (10 mol\% ) was used under an O\(_2\) atmosphere, but again none of the desired cyclised product was observed (entries 8-11, Table 18). Use of Cu(OTf)\(_2\) with (S)-252 gave none of the desired benzothiazole, however gave several isolable products were obtained after column chromatography (entry 11, Table 18). Using \(^1\)H and \(^13\)C NMR spectroscopic analysis alongside high-resolution mass spectrometry, the isolated products were identified as oxazolidine 254 and thiazolidine 255, respectively\(^2\) (Figure 136). Heinelt et al. have also reported similar findings in the synthesis of aza-heterocycles where O- vs S-cyclisation of substituted thioureas occurs in

\(^2\) Assigned with the assistance of Dr James Taylor.
differing ratios depending on the substitution of the nitrogen atoms.\textsuperscript{(259)} As this methodology gave no conversion to the desired aminobenzothiazole a new strategy was developed involving the use of commercially available benzothiazole derivatives.

**Table 18:** Conditions tested for the oxidative cyclisation of thioureas to 2-aminobenzothiazoles. Conversion determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture. PMB = para-methoxybenzyl. TBS = tert-butyldimethylsilyl. Phen = phenanthroline. * Several products isolated after column chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R(^1)</th>
<th>Reagents (equiv.)</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>SM recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Br(_2) (1.0)</td>
<td>LiBr</td>
<td>AcOH</td>
<td>rt</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>H</td>
<td>Br(_2) (1.0)</td>
<td>LiBr</td>
<td>AcOH</td>
<td>rt</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>PMB</td>
<td>TBS</td>
<td>Br(_2) (1.0)</td>
<td>LiBr</td>
<td>AcOH</td>
<td>rt</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>Br(_2) (1.0)</td>
<td>n/a</td>
<td>CH(_2)Cl(_2)</td>
<td>reflux</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>PMB</td>
<td>H</td>
<td>Br(_2) (1.0)</td>
<td>n/a</td>
<td>CH(_2)Cl(_2)</td>
<td>reflux</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>PMB</td>
<td>TBS</td>
<td>Br(_2) (1.0)</td>
<td>n/a</td>
<td>CH(_2)Cl(_2)</td>
<td>reflux</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>PMB</td>
<td>H</td>
<td>Pd(OAc)(_2)/K(_2)CO(_3)</td>
<td>1,10-phen</td>
<td>DMF</td>
<td>85 °C</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>H</td>
<td>Cu(OTf)(_2) (10 mol%)</td>
<td>O(_2)</td>
<td>PhMe</td>
<td>reflux</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>TBS</td>
<td>Cu(OTf)(_2) (10 mol%)</td>
<td>O(_2)</td>
<td>PhMe</td>
<td>reflux</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>PMB</td>
<td>TBS</td>
<td>Cu(OTf)(_2) (10 mol%)</td>
<td>O(_2)</td>
<td>PhMe</td>
<td>reflux</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>PMB</td>
<td>H</td>
<td>Cu(OTf)(_2) (10 mol%)</td>
<td>O(_2)</td>
<td>PhMe</td>
<td>reflux</td>
<td>0*</td>
</tr>
</tbody>
</table>

**Figure 136:** Structures of major and minor products obtained from reaction in Table 18.

### 4.4.2 Sonogashira cross-coupling methodology

As a scalable and chromatography free method for the synthesis of \((R), (S),\) and \((\pm)\)-BTM \textsuperscript{191} has been reported within the Smith group,\textsuperscript{(164)} it was decided that this methodology would next be used towards the synthesis of PS-(S)-BTM. In the original BTM \textsuperscript{191} synthesis
benzochlorothiazole 256 was reacted with a slight excess of phenylglycinol 257 at reflux, which gave the corresponding amino alcohol 258 in good yields (74-79%). Subsequent mesylation of 258 using MsCl and cyclisation gave BTM 191 over two steps in good yields (73-84%).

Figure 137: Scalable and chromatography free synthesis for the synthesis of (±)-BTM 191.

Initial attempts for the synthesis of an alkyne substituted PS-(S)-BTM 234 analogue focused on the installation of a protected acetylene to the benzothiazole core via a palladium catalysed cross-coupling reaction. Commercially available 6-bromo-2-benzothiazolinone 259 was subjected to Sonogashira conditions\(^{[260]}\) using either NEt\(_3\) or K\(_2\)CO\(_3\) as base and TMS-acetylene as a coupling partner, but unfortunately neither conditions afforded the desired product (Figure 138).

Figure 138: Unsuccessful synthesis of alkylnyl benzothiazolinone.

It was thought that the nitrogen atom in the benzothiazolinone ring may be coordinating to the catalyst and hampering reactivity. Benzothiazolinone 259 was therefore Boc-protected using Boc-anhydride and DMAP, which afforded Boc-protected amide 260 in 76% yield. This was subjected to the Sonogashira conditions, but as before no conversion into the product was observed and only starting material was returned (Figure 139).
Next, lithium-halogen exchange using tBuLi was attempted on bromobenzothiazole 259. Following a procedure from DeOrazia,261 259 was reacted with tBuLi and MeMgBr at −78 °C to generate the lithiated heterocycle. Quenching with DMF afforded the desired benzaldehyde 262 in 76% yield. This was reacted with the Ohira-Bestmann reagent 263 to try and obtain terminal acetylene in one pot, unfortunately, no 264 was obtained and only starting material was recovered. Aldehyde 262 was then reacted under Corey-Fuchs conditions262 to synthesise vinyl dibromide 265, which upon treatment with nBuLi should form terminal alkyne 264. Unfortunately, no 265 was obtained and only starting material was recovered. (Figure 140).

As BTM 191 itself is known to be compatible with Pd-catalysts in cooperative dual-catalytic systems,263-265 direct attachment of a protected acetylene to a bromo-(S)-BTM analogue 268, using Pd-catalysed cross-coupling was investigated. Bromo-(S)-BTM analogue 268 was synthesised in three steps from commercially available 6-bromo-2-benzothiazolinone 259. Chlorination using POCl3 as solvent and catalytic DMF afforded the corresponding chlorobenzothiazole 266 in 82% yield. Reaction of chlorobenzothiazole 266 with (S)-phenylglycinol 257 and iPr2NEt in o-dichlorobenzene gave the amino alcohol 267 in good yield after recrystallisation from PhMe. Subsequent treatment of alcohol 267 with methanesulfonyl chloride and Et3N in CH2Cl2 afforded (S)-268 in good yield (Figure 141).
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Figure 141: Synthesis of (S)-268.

Disappointingly, reaction of (S)-268 with TMS-acetylene under Sonogashira conditions did not give any of desired alkyne (S)-BTM 269 and returned only starting material. As such, this route was no longer pursued and a different strategy utilising Suzuki-Miyaura methodology was adopted.

Figure 142: Attempted synthesis of alkyne tethered (S)-BTM.

4.4.3 Suzuki-Miyaura cross-coupling methodology

Next, an alternative strategy to introduce an alkyne onto BTM 191 was trialled using the Suzuki-Miyaura reaction. Nolan and co-workers have shown that N-heterocyclic carbenes (NHCs) are good ligands for the Suzuki-Miyaura cross-coupling of aryl chlorides with aryl boronic acids at low catalyst loadings using a commercially available, air-stable [Pd(IPr)(cin)Cl] 272 pre-catalyst (Figure 144). The reaction can tolerate a wide variety of functional groups, most importantly para-acetylene substituted aromatics. Initial attempts focused on the synthesis of a suitable boronic acid coupling partner for reaction with (S)-268 in the presence of a Pd catalyst. A triisopropylsilyl (TIPS) protecting group was chosen as TMS is typically not stable under the Suzuki-Miyaura reaction conditions.
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Synthesis of boronic acid 277 began with Sonogashira coupling of commercially available 1-bromo-4-iodobenzene 274 with TIPS-protected acetylene 275 to give 276 in 68% yield. Treatment with nBuLi generated the corresponding lithium anion, which was quenched *in situ* with B(OiPr)$_3$ to give the isopropyl borate ester. Hydrolysis with 1 M HCl gave boronic acid 277 in a reasonable 43% yield (Figure 144).

With the desired boronic acid 277 in hand, Suzuki-Miyaura coupling was attempted with (S)-268. Disappointingly however, treatment of (S)-268 and 277 in the presence of [Pd(IPr)(cin)Cl] 272 gave no observed product and returned only (S)-268 along with degradation products (Figure 145).
Hiyama\textsuperscript{[268]} and Hilt\textsuperscript{[269]} have both reported the use of alkenyl halides for use in Suzuki-Miyaura cross-coupling reactions using aromatic boronic esters as coupling partners. Therefore, attempts were made to synthesise a boronic ester analogue of (S)-268 and TMS protected alkynyl iodide 282. Iodo TMS alkyne 282 was synthesised in one step from commercially available TMS-acetylene 281. Reaction with \(n\)BuLi at \(-78^\circ\)C and subsequent quenching with I\(_2\) afforded iodo-acetylene 282 in 82\% yield (Figure 146). Synthesis of the boronic ester of (S)-268 was attempted using both \(n\) and \(t\)BuLi with a B(\(\text{O}i\text{Pr}\))\(_3\) quench, but unfortunately this returned only degradation products after work up (Figure 147).

\[
\begin{align*}
\text{H-TMS} & \quad \begin{array}{c}
\text{nBuLi (1 equiv.)} \\
\text{I\(_2\) (1 equiv.)}
\end{array} \\
\text{281 (1 equiv.)} & \quad \begin{array}{c}
\text{I-TMS}
\end{array}
\end{align*}
\]

\(-78^\circ\)C-rt, 16 h, 82\% yield

Figure 146: Synthesis of iodoalkyne 282.

\[
\begin{align*}
\text{Br} & \quad \begin{array}{c}
\text{nBuLi or tBuLi (2 equiv.)} \\
\text{B(\(\text{O}i\text{Pr}\))\(_3\) (6 equiv.)}
\end{array} \\
\text{(S)-268} & \quad \begin{array}{c}
\text{(\(\text{PrO}\))\(_2\)B}
\end{array}
\end{align*}
\]

\(-78^\circ\)C-rt, 16 h, Degradation products

Figure 147: Attempted synthesis of boronic ester 283 using \(t\)BuLi.

4.4.4 Synthesis of PS-(R)-BTM using benzothiazole derivatives

As all attempts to introduce an alkyne directly onto BTM were unsuccessful, attention was turned to their incorporation via an oxygen linker. To this end, 2-amino-6-methoxybenzothiazole 286 was chosen as a viable starting point for the attempted synthesis of the (R)-284.

\[
\begin{align*}
\text{Ph} & \quad \begin{array}{c}
\text{MeO}
\end{array} \\
\text{(R)-284} & \quad \begin{array}{c}
\text{MeO}
\end{array}
\end{align*}
\]

Cheap, commercially available

Initial attempts focused on the conversion of aniline 286 into aryl fluoride 289, which may be capable of participating in an S\(_\text{N}\)Ar reaction. Both the Sandmeyer\textsuperscript{[270]} and Balz-Schiemann\textsuperscript{[271]} reactions are known to afford aromatic halides \textit{via} isolated or \textit{in situ} formed diazonium
intermediates. This strategy was utilised to gain access to fluorobenzothiazole 289. Commercially available 2-amino-6-methoxybenzothiazole 286 was tested under several reaction conditions using a variety of fluorine and nitrite sources (Table 19). Following a procedure outlined by Fukuhara,[272] a one-pot synthesis of fluorobenzothiazole 289 was attempted using HF pyridine, however this protocol gave a mixture of products in the $^1$H and $^{19}$F NMR spectra (Table 19, Entry 1). A two-step procedure was next evaluated to try to isolate a stable tetrafluoroborate diazonium salt which, under thermal decomposition, are known to form aryl fluorides (Balz-Scheimann reaction). Several attempts to isolate the desired salt were unsuccessful (Table 19, entries 2-4) due to solubility issues. However, using tBuONO as a nitrite source allowed for the successful isolation of intermediate tetrafluoroborate salt 288 in 71% yield (Table 19, Entry 5).

![Diagram of synthesis process](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fluoride source</th>
<th>Nitrite source</th>
<th>Solvent</th>
<th>Temperature ($^\circ$C)</th>
<th>Diazonium 288 isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>HF pyridine</td>
<td>NaNO$_2$</td>
<td>neat</td>
<td>−30-rt then 50</td>
<td>No</td>
</tr>
<tr>
<td>2$^b$</td>
<td>HBF$_4$ (8 M)</td>
<td>NaNO$_2$</td>
<td>HCl/H$_2$O</td>
<td>−5-rt</td>
<td>No</td>
</tr>
<tr>
<td>3$^b$</td>
<td>HBF$_4$ (8 M)</td>
<td>NaNO$_2$</td>
<td>THF/H$_2$O</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>4$^b$</td>
<td>HBF$_4$ (8 M)</td>
<td>NaNO$_2$</td>
<td>H$_2$O</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>5$^b$</td>
<td>BF$_3$OEt$_2$</td>
<td>tBuONO</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>Yes (71)</td>
</tr>
</tbody>
</table>

Table 19: Conditions tested for the Sandmeyer and Balz-Scheimann reactions. $^a$Conversion determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture after work up. $^b$Conversion determined by $^{19}$F and $^{11}$B NMR spectroscopic analysis of the reaction mixture after work up.

Subsequent thermal decomposition was evaluated on diazonium salt 288. Heating in ortho-dichlorobenzene at 135 °C gave small amounts of desired product 289, but in low overall yield and as a mixture that included traces of starting material. Heating neat with a temperature increase of 80-130 °C showed no trace of product in the $^1$H or $^{19}$F NMR spectra.
Figure 149: Attempted synthesis of fluorobenzothiazole 289.

As the conditions listed in Table 19 afforded only trace amounts of the product in low purity, synthesis of the analogous, but possibly less reactive, 2-chloro-6-methoxybenzo[d]thiazole 290 was attempted. 2-Amino-6-methoxybenzothiazole 286 was reacted with tert-butyl nitrite in the presence of CuCl₂ and pleasingly this gave 2-chloro-6-methoxybenzo[d]thiazole 290 in 71% yield (Figure 150). This reaction can also be performed on a multi-gram scale with reproducible yields and purity.

![Figure 150: Synthesis of chlorobenzothiazole 290 using the Sandmeyer reaction.](image)

With starting material in hand, 2-chloro-6-methoxybenzo[d]thiazole 290 was reacted with (R)-phenylglycinol 257 in the presence of iPr₂NEt to afford amino alcohol 285 in a moderate 49% yield. Mesylation of alcohol (R)-285 and heating gave the cyclised (R)-291 BTM product in excellent yield (Figure 151).

![Figure 151: Synthesis of (R)-291 from the corresponding 2-chlorobenzothiazole.](image)

With BTM derivative (R)-291 in hand, a demethylation protocol was attempted using excess BBr₃. Pleasingly this gave the desired demethylated product (R)-292 in good yield, isolated as the HBr salt (Figure 152).

![Figure 152: Synthesis of phenol BTM derivative (R)-292.](image)

BTM derivative (R)-292 was then subjected to a variety of conditions to attach the desired alkyne via an O-alkylation reaction. Propargyl bromide was used as the electrophile and a base screen...
was conducted to obtain the optimum conditions. Initial attempts focused on milder bases such as K$_2$CO$_3$ which is known to facilitate O-alkylations.$^{[251-253]}$ However, reaction of (R)-292 with propargyl bromide in the presence of K$_2$CO$_3$ in DMF gave no conversion (Table 20, entry 1). Increasing the amount of base, switching the solvent to acetone and using KI as an additive also gave no conversion (Table 20, entry 2). Increasing the equivalents of base used in DMF resulted in a small amount of conversion (15%) into the desired product 292 but this was not satisfactory. To obtain full deprotonation of the phenol, NaH was used in DMF but this gave a complex crude reaction mixture with no trace of product. Pleasingly, stirring in NaOH (2.2 equiv.) for 3 h prior to adding propargyl bromide gave a promising 60% conversion (Table 20, entry 5). Increasing the amount of base to four equivalents gave 80% conversion, allowed 292 to be isolated and a 41% yield (Table 20, entry 7) but five equivalents of NaOH resulted in decomposition products. Using Cs$_2$CO$_3$ as the base gave full conversion on a 0.1 mmol scale (Table 20, entry 9) but attempts to repeat this on a preparative scale were unsuccessful. The electrophile was then changed to the more reactive propargyl tosylate but this proved unsuccessful most likely due to solubility issues (Table 20, entry 10). Finally, the use of KOtBu (2.6 equiv.) in a mixture of THF/DMSO at low temperature led to complete conversion, allowing 292 to be isolated in a good 68% yield after chromatography (Table 20, entry 11).

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>R (equiv.)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)$^1$ (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ (2.2)</td>
<td>DMF</td>
<td>Br (1.1)</td>
<td>0-rt</td>
<td>0</td>
</tr>
<tr>
<td>2$^a$</td>
<td>K$_2$CO$_3$ (5)</td>
<td>Acetone</td>
<td>Br (5.0)</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$ (6)</td>
<td>DMF</td>
<td>Br (1.1)</td>
<td>rt</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>NaH (6)</td>
<td>DMF</td>
<td>Br (1.1)</td>
<td>0-rt</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NaOH (2.2)</td>
<td>DMSO</td>
<td>Br (1.05)</td>
<td>rt</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>NaOH (3)</td>
<td>DMSO</td>
<td>Br (1.5)</td>
<td>rt</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>NaOH (4)</td>
<td>DMSO</td>
<td>Br (1.1)</td>
<td>rt</td>
<td>80 (41)</td>
</tr>
<tr>
<td>8</td>
<td>NaOH (5)</td>
<td>DMSO</td>
<td>Br (1.1)</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cs$_2$CO$_3$ (3)</td>
<td>DMF</td>
<td>Br (1.5)</td>
<td>rt</td>
<td>c</td>
</tr>
<tr>
<td>10$^b$</td>
<td>KOH (3)</td>
<td>DMF/MeCN</td>
<td>OTs (1.3)</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>KOtBu (2.6)</td>
<td>THF/DMSO</td>
<td>Br</td>
<td>0-rt</td>
<td>100 (68)</td>
</tr>
</tbody>
</table>
Table 20: Reaction optimisation for O-alkylation of HBr salt ($R$)-292. Determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture. $^a$ KI (5 equiv.) was added to the reaction. $^b$ 18-crown-6 (5 mol%) was used as an additive. $^c$ Only gave full conversion on small scale (0.1 mmol).

4.5 Synthesis of polymer-supported isothioureas

4.5.1 Attachment of propargyl BTM 292 to polymer support

Following a procedure outlined by Pericàs,$^{[252]}$ (azidomethyl)polystyrene 293 was synthesised in one step from commercially available (chloromethyl)polystyrene (Merrifield resin) (100-200 mesh). Merrifield resin 191 ($f = 1.23$ mmol/g) was treated with excess NaN$_3$ in DMSO resulting in the desired (azidomethyl)polystyrene 293 (Figure 153). Elemental analysis showed that the resulting functionalisation ($f$) was 1.20 mmol/g and a stretch in the IR spectrum at 2094 cm$^{-1}$ was indicative of an azide being present (Figure 154). The level of functionalisation ($f$) (mmol/g) was calculated based on nitrogen elemental analysis ($\% \text{ N}$) using the formula proposed by Pericàs (Equation 3).$^{[273]}$ This method of functionalisation calculation assumes 100% consumption of the starting azide (which is the case with 293) based on the disappearance of the azide band in the IR spectrum. An alternative method for the calculation of functionalisation of PS-organocatalysts would be to subtract the expected contribution for the azide nitrogen atoms from the $\% \text{ N}$ measured for the new organocatalyst resin using elemental analysis. This would give the increase in nitrogen content as a result of introducing the triazole appended functionalities and give an estimation of the $\%$ conversion of azides to the desired products.

$$f = \% \text{ N} \times 1000 \times \text{(number of N atoms in functional unit)}^{-1} \times (14.001)^{-1} \times 100^{-1}$$

Equation 3: Formula used to calculate catalyst loading on polystyrene resins

![Merrifield resin 191 to (azidomethyl)polystyrene 293](image)

Figure 153: Conversion of Merrifield resin 191 to (azidomethyl)polystyrene 293.
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4.5.2 Attachment of propargyl HyperBTM 306 to polymer support

Using identical methodology developed for the synthesis of PS-(R)-BTM 191, a propargyl derivative of (2R,3S)-HyperBTM was synthesised and attached to the same azidomethyl PS-293. Following the procedure outlined by Smith,\cite{Smith2014} benzaldehyde 294 was reacted with tert-butyl carbamate 295 and sodium benzene sulfonate in the presence of formic acid to afford the carbamate 296 in excellent yield. Carbamate 296 was treated with K₂CO₃ in a CH₂Cl₂/H₂O
mixture to give the corresponding imine in good yield. Imine 297 was used immediately in an (R)-proline catalysed Mannich reaction with isovaleraldehyde 298 affording the syn-diastereoisomer of Boc-amino aldehyde (1R,2R)-299 in excellent diastereo and enantiocontrol (>95.5:5 dr, >99% ee). The absolute and relative configuration was assigned by comparison with the specific rotation and 1H NMR spectroscopy in the literature.\(^{[10]}\) Subsequent reduction of Boc-amino aldehyde (1R,2R)-299 using NaBH₄ gave Boc-amino alcohol (1R,2R)-300 in good yield. Finally, removal of the Boc-protecting group using HCl in dioxane afforded HCl salt (1R,2R)-301 in 87% yield (Figure 156).

![Image](image-url)  
**Figure 156: Synthesis of enantiopure amino alcohol (1R,2R)-301.** *Isolated yield of major diastereoisomer of 298 (>95:5 dr). *\(^{a}\)*Determined by 1H NMR spectroscopy analysis of the crude reaction mixture. *\(^{b}\)*Determined by chiral HPLC analysis.

A stereochemical model explaining the diastereo- and enantioselectivity of the proline-catalysed Mannich reaction has been proposed by Córdova et al. (Figure 157).\(^{[274]}\) The model shows the enamine, formed upon reaction of (R)-proline with isovaleraldehyde 298, reacting with the Și face of the N-Boc imine 297 that is stabilised by hydrogen bonding with the catalyst. This arrangement directs the facial selectivity of the enamine. The N-Boc orients itself away from the pyrrolidine ring to minimise the energy of the pre-TS assembly, which results in a highly diastereoselectivity reaction.
Figure 157: Pre-transition state assembly for the (R)-proline catalysed Mannich reaction.

Amino alcohol (1R,2R)-301 was then subjected to the same reaction sequence as propargyl derivative (R)-BTM 284 (Section 4.4.4). Reaction with 2-chloro-6-methoxybenzo[d]thiazole 290 gave amino alcohol (1R,2R)-302 which was isolated and used without further purification. Treatment with methane sulfonyl chloride in the presence of iPr2NEt at 40 °C afforded cyclised (2R,3S)-303 in good yield. Demethylation of the methoxy group was achieved by treatment with BBr3 to give the HBr salt (2R,3S)-304 in excellent yield. Using previously optimised conditions (Entry 11, Table 20), (2R,3S)-304 was successfully alkylated to give the desired propargyl derivative (2R,3S)-306 in good yield (Figure 158).

Figure 158: Synthesis of propargyl derivative (2R,3S)-306.

Propargyl derivative (2R,3S)-306 was attached to the polymer-support using the same click methodology as before. In the presence of catalytic CuI and excess iPr2NEt, (2R,3S)-306 was attached to azide PS-293 and the progress of the reaction was conveniently monitored by disappearance of the azide band in the IR spectrum. A final loading of 0.97 mmol/g was calculated by nitrogen elemental analysis (Figure 159).
4.6 Initial investigation into heterogeneous Michael addition-lactonisation

With both PS-(R)-BTM 191 and PS-(2R,3S)-HyperBTM 60 in hand, their use in a Michael addition-lactonisation model reaction using phenylacetic acid 307 and trifluoromethylenone 308 could be investigated. Reaction conditions for the heterogeneous Michael addition-lactonisation were chosen based on the corresponding homogeneous Michael addition-lactonisation reaction developed within the Smith group. Using pivaloyl chloride as an activating agent and iPr2NEt as a base, PS-(R)-BTM 191 gave anti-dihydropyranone 309 with reasonable diastereoselectivity (81:19 dr) 2 h at 0 °C (entry 1 Table 22). Switching to PS-HyperBTM-(2R,3S) 61 gave anti-dihydropyranone 309 with reasonable diastereoselectivity (82:18 dr) after 2 h at 0 °C (Table 21, entry 1). Decreasing the temperature over an extended reaction period (2 h) gave full consumption of the starting material and a crude dr of 81:19 with the major diastereoisomers formed in an excellent 97% ee (Table 21, entry 2). Encouraged by this result, the reaction temperature was further decreased in order to improve the dr. Performing the reaction at −78 °C for 2 and 4 h did not give full consumption of the starting material however the isolated DHP 309 did have excellent ee’s in both cases (Table 21, entries 3,4). Extending the reaction time to 6 h at −78 °C gave full consumption of the starting material (entry 5, Table 21) affording DHP 309 in 64% yield with high diastereo- and enantioselectivity. The catalyst loading was then decreased to 15 mol%, which gave an increase in yield and crude dr (88:12) while still maintaining a high level of enantioselectivity (98% ee). Attempts to lower the catalyst loading further were unsuccessful as 10 mol% of PS-HyperBTM-(2R,3S) 61 gave only a 40% conversion of the enone and a decreased crude dr (80:20). While both PS-(R)-BTM 191 and PS-HyperBTM-(2R,3S) 61 gave good results, only PS-(2R,3S)-(HyperBTM)-61 was taken forward as the supported catalyst to evaluate in a recyclability study and several different reaction classes.
Table 21: Optimisation studies for heterogeneous Michael addition-lactonisation protocol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isothiourea (mol%)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PS-191 (20)</td>
<td>0</td>
<td>2</td>
<td>100</td>
<td>56</td>
<td>81:19</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>PS-61 (20)</td>
<td>0</td>
<td>2</td>
<td>100</td>
<td>72</td>
<td>82:18</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>PS-61 (20)</td>
<td>-78</td>
<td>2</td>
<td>57</td>
<td>28</td>
<td>81:19</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>PS-61 (20)</td>
<td>-78</td>
<td>4</td>
<td>70</td>
<td>35</td>
<td>85:15</td>
<td>99</td>
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<td>PS-61 (20)</td>
<td>-78</td>
<td>6</td>
<td>100</td>
<td>64</td>
<td>88:12</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>PS-61 (15)</td>
<td>-78</td>
<td>6</td>
<td>100</td>
<td>66</td>
<td>89:11</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>PS-61 (10)</td>
<td>-78</td>
<td>6</td>
<td>40</td>
<td>-d</td>
<td>80:20</td>
<td>-d</td>
</tr>
</tbody>
</table>

Table 21: Optimisation studies for heterogeneous Michael addition-lactonisation protocol.

- Determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture.
- Isolated yield of major diastereoisomer (>95:5 dr).
- Determined by chiral HPLC analysis of major diastereoisomer.
- Product not isolated from crude reaction mixture.

4.7 Kinetic resolution of secondary alcohols

Previous work within the Smith group has shown that HyperBTM 61 catalyses the acylative kinetic resolution (KR) of a range of secondary alcohols using propionic anhydrides, giving high levels of enantiodiscrimination between the two enantiomers of substrate (Figure 160). \(^{[275]}\) The efficiency of a KR is characterised by the selectivity factor (s), which is defined as the ratio of the rate constants for the fast and slow reacting enantiomers of substrate. In practice the s-factor can be calculated using equations developed by Kagan (Equation 4),\(^{[276]}\) which relate s to the reaction conversion (c) and the enantiomeric excess of the recovered alcohol (ee\(_{alc}\)). To be synthetically useful, the selectivity factor of a KR needs to be greater than S = 10.\(^{[277-278]}\)

Figure 160: Kinetic resolution of secondary alcohols via enantioselective acylation.

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

\[
ee = \frac{[R] - [S]}{[R] + [S]}
\]

\[
ee_{alc} = \frac{ee_{SM}}{ee_{p} + ee_{SM}}
\]

Equation 4: Derivation of selectivity factor, enantiomeric excess and conversion.
To evaluate the KR of secondary alcohols using PS-(2R,3S)-HyperBTM \(61\), 1-(naphthalen-2-yl)ethan-1-ol \(313\) was chosen as a model substrate. Alcohol \(313\) was synthesised in one step from 2-naphthaldehyde \(312\) by reaction with methylmagnesium bromide to give \(313\) in 86% yield.

![Figure 161: Synthesis of model substrate 1-(naphthalene-2-yl)prop-2-en-1-ol 313.](image)

Under homogeneous conditions using HyperBTM \(61\), alcohol \(313\) is resolved with \(s = 65\). Reacting alcohol \((\pm)-313\) with propionic anhydride (0.6 equiv.) in the presence of 5 mol% PS-(2R,3S)-HyperBTM \(61\) and \(iPr_2NEt\) (0.6 equiv.) at 0 °C gave 56% conversion to ester \((R)-314\) after 24 h. This allowed \((S)-313\) to be recovered in >99% ee and \((R)-314\) to be isolated in 78% ee, giving a calculated selectivity of \(S = 95\) (Figure 162). The absolute configuration of the products were confirmed by specific rotation calculation and comparison with the literature in each case.

![Figure 162: Acylative KR of secondary alcohols using PS-(2R,3S)-HyperBTM 61.](image)

The high levels of selectivity observed is consistent with a preference for the \((R)\)-enantiomer of the racemate to undergo esterification, which results in the isolation of the unreacted enantioenriched \((S)\)-alcohol. This high selectivity can be rationalised by the stereochemical model proposed in Figure 163. The conformation of the key \(N\)-acyl ammonium is thought to be locked by a favourable \(n_o\) to \(\sigma^*_{C-S}\) interaction between the carbonyl and the isothiourea sulfur atom (discussed in chapter 1). The pseudoaxial phenyl substituent on the catalyst blocks the \(Re\) face of the \(N\)-propionyl group. The enantiodiscrimination is proposed to be achieved through favourable interactions of the fast reacting enantiomer with \(N\)-acyl ammonium \(315\). For example, there may be a favourable \(\pi\)-cation interaction between the aryl substituent on the alcohol and the catalyst, while \(\pi\)-\(\pi\) interactions between the extended napthy ring and the benzenoid ring of the catalyst may provide additional stabilisation (Figure 163). While this stereochemical rationale was originally proposed for the homogeneous system, a similar sense of selectivity is observed in this
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case therefore it can be postulated that a similar mechanism of enantioenduction occurs. Pleasingly, this represents the first highly selective KR of secondary alcohols catalysed by a polymer-support isothiourea. Previous studies by Pericas and co-workers has shown that their version of PS-(R)-BTM 229 was unable to selectively catalye this type of resolution (secondary benzylic alcohols), giving an s factor of 3.\[249\]

![Figure 163: Proposed pre-transition state assembly accounting for the enantioselectivity of the kinetic resolution.](image)

### 4.8 Kinetic resolution of tertiary alcohols

Work within the Smith group has shown that HyperBTM 61 can catalyse the efficient acylative kinetic resolution of tertiary heterocyclic alcohols under mild conditions using cheap and commercially available starting materials (Figure 164). Therefore, PS-(2R,3S)-HyperBTM 61 was also trialled in this process.

![Figure 164: Acylative kinetic resolution of heterocyclic tertiary alcohols by HyperBTM 61.](image)

Benzylphenyl indolinone 319 was used as the model substrate and was synthesised in a one-step procedure by addition of phenylmagnesium bromide to benzylindoline dione 318 affording 319 in 89% yield (Figure 165).\[^1\]

\[^1\]Synthesised and characterised by PDRA Dr Mark Greenhalgh.
Figure 165: Synthesis of benzylphenyl indolinone 319 used in the kinetic resolution protocol.

Reaction conditions for the heterogeneous kinetic resolution of tertiary alcohols were chosen based on the already optimised corresponding homogeneous kinetic resolution within the Smith group. Using isobutyric anhydride and iPr₂NEt as a base in CHCl₃ at 0 °C, PS-(2R,3S)-HyperBTM 61 (5 mol%) gave a $s = 145$ at 46% conversion after 24 h reaction time. The selectivity is higher and comparable to that obtained with the homogeneous system ($s = 131$) and this represents the first example of a KR of tertiary alcohols using a polymer-supported catalyst.

Figure 166: Kinetic resolution of tertiary heteroarmatic alcohols using PS-(2R,3S) HyperBTM-61.

In collaboration with Professor Paul Ha-Yeon Cheong at Oregon State University, a computational study for the stereochemical rationale was conducted for the homogeneous system.† The pre-transition state assembly for the fast reacting enantiomer of alcohol (S) of the ester was calculated to be 3.5 kcal/mol lower in energy than slow reacting enantiomer, which is in line with experimental observations. The pre-transition state assembly in Figure 167 shows the preference for the acylated intermediate to adopt a half-chair type conformation. Non-classical hydrogen bonding between the pseudo-equatorial hydrogen on the acylated catalyst and the carboxylate aids in the organisation of the pre-transition state assembly which further favours the conformation shown in Figure 167.

† Computational studies performed on (2S,3R)-HyperBTM 61.
4.9 Recyclability studies

Once high catalytic activity and versatility of PS-(2R,3S)-HyperBTM 61 in the KR of tertiary alcohols had been established, the robustness of the polymer-supported catalyst was tested. To this end, a recyclability study was performed on the KR of tertiary alcohols using optimised conditions (entry 8, Table 21). The experiments were carried out by fresh addition of reagents to PS-(2R,3S)-HyperBTM 61 and after 24 h at 0 °C the catalytic resin was filtered off from the reaction mixture and washed with EtOAc, before reuse. Pleasingly PS-(2R,3S)-HyperBTM 61 can be recycled up to 8 times without significant loss in selectivity. Throughout the recyclability study the er of the enantioenriched ester stayed high (entries 1-8, Table 22) while the er of the alcohol diminishes slightly as the conversion decreases. A noticeable result was run 6 (Table 22) where the conversion dropped significantly (23%). This results seems anomalous given the subsequent experiments (runs 7,8 Table 22) gave conversions similar to that obtained in previous runs (1-5, Table 22). Given the time constraints of this project there was no time to repeat the recyclability study.

<table>
<thead>
<tr>
<th>Run</th>
<th>Conversion (%)a</th>
<th>Alc. erb (%) yieldf</th>
<th>Est. erb (%) yieldf</th>
<th>Sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>91.5:8.5 (46)</td>
<td>98:2 (38)</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>95:5 (36)</td>
<td>98:2 (34)</td>
<td>237</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>85.5:14.5 (43)</td>
<td>98:2 (37)</td>
<td>141</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>81:19 (42)</td>
<td>98:2 (33)</td>
<td>92</td>
</tr>
</tbody>
</table>
4.10 Catalytic enantioselective annulation of α,β-unsaturated acyl ammonium precursors

Previous work in the Smith group has shown that (2S,3R)-HyperBTM 61 can catalyse the enantioselective annulation of α,β-unsaturated acyl ammonium intermediates with 1,3-dicarboxyls, azaaryl ketones or β-ketoesters affording functionalised esters (upon ring-opening), dihydropyranones or dihydropyridones in good yield and selectivities (Figure 168).279

The acyl ammonium intermediates can be generated from readily available α,β-unsaturated anhydrides. Based on this work, it was expected that PS-HyperBTM (2R,3S) 61 could act as a catalyst for the reaction of α,β-unsaturated acyl ammonium intermediates with 1,3-dicarboxyls giving a functionalised ester as the product. The desired homoanhydride can be generated from the appropriate α,β-unsaturated carboxylic acid by reaction with EDCI in CH₂Cl₂ at rt giving 329 in 65% yield (Figure 169).

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<td>40</td>
<td>82:18 (42)</td>
<td>98.5:1.5 (35)</td>
<td>126</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>62:38 (45)</td>
<td>89:10 (17)</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>80:20 (42)</td>
<td>98:2 (34)</td>
<td>102</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>85:15 (43)</td>
<td>98:2 (38)</td>
<td>106</td>
</tr>
</tbody>
</table>

Table 22: Recyclability of PS-(2R,3S)-HyperBTM 61 in the kinetic resolution of tertiary alcohols. a Determined by 1H NMR spectroscopy of the crude reaction mixture and chiral HPLC analysis. b Determined by chiral HPLC analysis. c Isolated yield after column chromatography. d Calculated using equations developed by Kagan (reference 280).

Figure 168: Enantioselective annulation of α,β-unsaturated acyl ammonium precursors.

Figure 169: Synthesis of homoanhydride used as α,β-unsaturated acyl ammonium precursor.
opening \textit{in situ} with MeOH. Pleasingly this protocol afforded the desired ring-opened functionalised ester 331 in 94% ee and 75% yield, which is comparable with the homogeneous system (96% ee) (Figure 170).

\begin{center}
\includegraphics[width=\textwidth]{figure170.png}
\end{center}

\textbf{Figure 170:} Use of PS-HyperBtm (2S,3R)-61 in the asymmetric annihilation of \(\alpha,\beta\)-unsaturated acyl ammonium precursors.

The catalytic cycle involve initial N-acylation of (2R,3S)-HyperBtm 61 with homoanhydride 329 generating the corresponding \(\alpha,\beta\)-unsaturated acyl ammonium intermediate 334. The \textit{s-cis} conformation of ammonium 334 is favoured with the carbonyl oxygen atom adopting a \textit{syn} conformation with respect to the thiourea sulfur atom based on a non-bonding O-S interaction (\(n_o\) to \(\sigma^*_{C-S}\)) discussed previously. In the Michael addition pathway (Figure 171) addition of diketone enolate 330 to the \textit{Re} face of ammonium 334 gives intermediate 335 with subsequent proton transfer followed by lactonisation generating dihydropyranone 336 or ester 331 by addition of MeOH. This work represents the first example of the use of a polymer-supported catalyst in the annihilation of \(\alpha,\beta\)-unsaturated acyl ammonium intermediates.

\begin{center}
\includegraphics[width=\textwidth]{figure171.png}
\end{center}

\textbf{Figure 171:} Proposed mechanisms of asymmetric dihydropyranone formation \textit{via} Michael addition-lactonisation.
4.11 Conclusions and future outlook

Two isothiourea-based organocatalysts, PS-(2R,3S)-HyperBTM 61 and (R)-BTM 191, were synthesised and attached to a polymer-support. PS-(2R,3S)-HyperBTM 61 was taken and evaluated in a variety of different reaction classes previously developed within the Smith group. PS-(2R,3S)-HyperBTM 61 shows promise in several model studies including a Michael addition-lactonisation procedure giving consistently high ee values (>97% ee) over an optimisation study.

Furthermore PS-(2R,3S)-HyperBTM 61 was evaluated in a model study for the KR of secondary alcohols, where its performance was comparable with the homogeneous counterpart affording both enantioenriched alcohol 313 (>99% ee) and ester 314 (78% ee) with an $S$ factor of 95 at 56% conversion. Following on, PS-(2R,3S)-HyperBTM 61 also able catalyses the KR of heteroaromatic tertiary alcohols, a reaction which has not yet been performed in the literature using a polymer-supported catalyst. The resulting alcohol and ester were both highly enantioenriched with the process affording an excellent $S$ factor of 172 at 46% conversion. These two examples show that PS-(2R,3S)-HyperBTM 61 can compete with the homogeneous system in terms of selectivity, yield and overall efficiency. PS-(2R,3S)-HyperBTM 61 can also be recycled up to 8 times without a major loss in conversion or selectivity. Further recyclability studies are need to fully validate the potential for PS-(2R,3S)-HyperBTM 61 to act as a catalyst in the KR of tertiary alcohols.

Finally PS-(2R,3S)-HyperBTM 61 was evaluated in a catalytic enantioselective annulation of $\alpha,\beta$-unsaturated acyl ammonium precursors with 1,3-dicarbonyls. Results from the model study shown very similar levels of enantioselectivity (96% vs 94% ee) comparable with the homogeneous system. Again this work represents the first example of the use of a polymer-supported catalyst in the annulation of $\alpha,\beta$-unsaturated acyl ammonium intermediates.

Future work in this area would be examination of the scope of all of the reaction classes discussed to assess the generality of the processes. More work is needed to examine the possible recyclability of the PS-(2R,3S)-HyperBTM 61 in the aforementioned catalytic processes. While PS-(2R,3S)-HyperBTM 61 was chosen as the optimal catalyst for these specific classes of reaction, (S)-BTM 191 is an efficient organocatalysts in the [2,3]-rearrangement of quaternary ammonium ylides$^{[280]}$ and as such PS-(R)-BTM may be applied to this methodology as a recyclable catalyst.

4.12 References and Notes

Chapter 4: Synthesis and immobilisation of isothiourea catalysts onto polystyrene supports


Chapter 4: Synthesis and immobilisation of isothiourea catalysts onto polystyrene supports


[264] Personal communication with PhD colleague Stephanie Spoehrle.


This thesis has described investigations into applications of isothioureas in surface chemistry. State-of-the-art methodology has been developed for the chiral discrimination of enantioenriched surfaces as well as the synthesis of novel polystyrene-supported recyclable organocatalysts.

Firstly, the DHBP catalysed synthesis of a small library of racemic dihydropyranones on a SAM has been achieved through a Michael addition-lactonisation procedure using a range of arylacetic acids (Figure 172). The conversions in this process range from 40-70% and as such this methodology offers an effective route to build a variety of complex surfaces containing these functionalities. The consistency of this methodology suggests that a wide range of phenylacetic derivatives could be applied providing a flexible methodology for facile surface functionalisation.

Figure 172: Michael addition-lactonisation of trifluoromethylenones on a surface using DHPB.

Following the initial report on the synthesis of racemic dihydropyranones on a surface, attention was focused towards the development of an asymmetric protocol. Both enantiomers of
HyperBTM 61 were used to synthesis surfaces that consisted of an enantiomeric excess of one particular enantiomer ((3R,4R), (3S,4S)) of DHP (Figure 173) A novel chiral AFM probe tip 179 was also developed and tested in the system against the enantioenriched surfaces giving a reasonable level of discrimination in the majority of cases. Both enantiomers of the enantioenriched DHP were also synthesised in solution then attached to the surface using click chemistry methodology. The results from this show that regardless of fabrication method, both types of surfaces give similar adhesion values, within error of each other, suggesting that similar chiral discrimination events are happening on the surfaces as well as comparable molecular packing of the surfaces. While the current methodology does not allow for the quantification of the level of enantioinduction imparted on the surfaces there is some evidence that the same sense of enantioinduction is occurring, that is, the same enantiomer is being formed in the solution phase homogeneous system as the heterogeneous, however contradictory results demand further investigation. Evidence for this hypothesis comes from the results obtained in the experiments conducted using the pre-synthesis enantioenriched DHPs. They show very similar results to those obtained in the heterogeneous system, suggesting similar molecular packing and possibly implying a significant enantiomeric excess. Further experiments using surfaces and probe tips of varying ee to test possible non-linear effects are needed to confirm this theory. Subsequent endeavours within the area of surface functionalisation of the discussed SAMs will aim to attach desired functional groups in a selective manner and possibly use as model systems for chiral selectors in enantioselective reactions.

![Figure 173: Chiral AFM probe evaluated in the chemical force microscopy of enantioenriched dihydorpyranones.](image)
Two novel polymer-supported isothiourea organocatalysts were synthesised and evaluated in several different reaction classes previously developed within the Smith group. The supported catalyst PS-(2R,3S)-HyperBTM 61 showed promise in an optimisation study for a Michael addition-lactonisation process giving consistently high ee values (≥97% ee) (Figure 174). Furthermore, PS-(2R,3S)-HyperBTM 61 was evaluated in the KR of both secondary aryl and tertiary heteroaromatic alcohols giving high selectivity in both cases (up to S of 171). PS-(2R,3S)-HyperBTM 61 was also shown to be recyclable in the KR of tertiary heteroaromatic alcohols over at least 8 runs with no major loss in selectivity. Finally, PS-(2R,3S)-HyperBTM 61 was shown to be an effective catalyst in the enantioselective annulation of α,β-unsaturated acyl ammonium precursors with 1,3-dicarbonyls. Results show very similar levels of enatioselectivity (96% vs 94%) to those previously reported. This work represents the first example of KR of tertiary heteroaromatic alcohols and also annulation of α,β-unsaturated acyl ammonium intermediates using a polymer-supported catalyst. While PS-(2R,3S)-HyperBTM 61 was shown to work in a variety of processes using model substrates (Figure 174), more work is need to evaluate recyclability of the catalyst in different reaction processes as well as optimisation studies to lower catalyst loadings to assess the true robustness of this particular isothiourea catalyst.

While PS-(2R,3S)-HyperBTM 61 was chosen as the optimal catalyst for these specific classes of reaction, PS-(R)-BTM 191 was also synthesised and is known to catalyse a series of reaction classes. For example, PS-(R)-BTM 191 is an efficient organocatalysts in the [2,3]-rearrangement of quaternary ammonium ylides[284] and as such PS-(R)-BTM may be applied to this methodology as a recyclable catalyst however due to time constraints this could not be fully evaluated.
Figure 174: Summary of processes catalysed by PS-(2R,3S)-HyperBTM 61.

Recyclable up to at least 8 runs

\[(\text{S})-319\] 91.5:8.5 er 46% yield

\[(\text{R})-320\] 98.5:1.5 er 47% yield

61 (5 mol%) 
\((i\text{Pr})_2\text{CO})_2\text{O} (0.6 \text{ equiv.})
\((i\text{Pr})_2\text{NET} (0.7 \text{ equiv.})
\text{CHCl}_3 (0.17 \text{ m}, 0^\circ \text{C}, 24 \text{ h})

\[\text{329}\]

61 (5 mol%) 
\((i\text{Pr})_2\text{NET} (1.1 \text{ equiv.})
\text{CH}_2\text{Cl}_2, 0^\circ \text{C}-\text{rt}, 5 \text{ h}
\text{then MeOH, 16 h}

\[\text{330}\] 75% yield 94% ee

61 (5 mol%) 
\((i\text{Pr})_2\text{NET} (0.6 \text{ equiv.})
\((\text{Et})\text{CO})_2\text{O} (0.6 \text{ equiv.})
\text{CHCl}_3, 0^\circ \text{C}, 24 \text{ h}
56% conversion

S = 95

66% yield 95:5 dr 98%ee

61 (5 mol%) 
\((i\text{Pr})_2\text{NET} (2.5 \text{ equiv.})
\text{CH}_2\text{Cl}_2, -78^\circ \text{C}, 6 \text{ h}

\[\text{308}\]  

\[\text{309}\]  

\[\text{(S)}-313\]  
>99% ee 45% yield

\[\text{(R)}-314\]  
78% ee 41% yield
Chapter 6 Experimental

6.1 General Information

Reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum. For moisture sensitive reactions, solvents (THF, CHCl₃, toluene, and Et₂O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Pet. ether is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and CO₂(s)/acetone baths respectively. Reflux conditions were obtained using an oil bath or DrySyn® equipped with a contact thermometer. In vacuo refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica). Plates were visualised under UV light (254 nm) or by staining with either phosphomolybdic acid or KMnO₄ followed by heating. Flash column chromatography was performed on Kieselgel 60 silica or Biotage® IsoleraTM 4, using Biotage® Snap Ultra or Biotage® KP Sil columns (CV = column volume) under the solvent system stated.

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

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatography SIL-20AHT autosampler, CMB-20A communications bus module, SPDM20A diode array detector and a CTO-20A column oven that allows the temperature to be set from 25-40 °C. Separation was achieved using a Chiralcel OJ-H or Chiralpak AD-H column.

GC analyses were obtained on a Shimadzu GC-2025 consisting of an AOC-20i auto injector, SPL1 injection port, column oven and flame ionisation detector (FID). Helium (He) was used as the carrier gas in split injection mode at constant linear velocity. An Agilent DB-5 analytical column was used for analyses (30 m, 0.25 mm ID, 0.5 μm film thickness).
Infrared spectra ($\nu_{\text{max}}$) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer using either thin film or solid using Pike MIRacle ATR accessory. Analysis was carried out using Shimadzu IRsolution v1.50 and only characteristic peaks are reported.

$^1\text{H}$, $^{13}\text{C}$,$^\text{1}$H, $^{19}\text{F}$,$^\text{1}$H, $^{11}\text{B}$ and $^{29}\text{Si}$ NMR spectra were acquired on either a Bruker Avance 300 {δ$\text{H}$ (300 MHz), δ$\text{C}$ (75 MHz), δ$\text{F}$ (282 MHz), δ$\text{Si}$ (60 MHz)}, a Bruker Avance II 400 {δ$\text{H}$ (400 MHz), δ$\text{C}$ (100 MHz), δ$\text{F}$ (376 MHz), δ$\text{B}$ (128 MHz), δ$\text{Si}$ (60 MHz)}, Bruker Ultrashield 500 {δ$\text{H}$ (500 MHz), δ$\text{C}$ (126 MHz), δ$\text{F}$ (471 MHz), δ$\text{Si}$ (79 MHz)} or a Bruker AVIII-HD 700 {δ$\text{H}$ (700 MHz), δ$\text{C}$ (175 MHz)} spectrometer at ambient temperature (unless otherwise stated) in the deuterated solvent stated. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants, $J$, are quoted in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; dd, doublet of doublets; ddt, doublet of doublets of triplets; dtt, doublet of triplets of triplets; dq, doublet of quartets; td, triplet of doublets; ttd, triplet of triplets of doublets; tt, triplet of triplets; m, multiplet; and br, broad.

Mass spectrometry (HRMS)
Mass spectrometric (m/z) data was acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility (quoted [M+H]) or from the EPSRC National Mass Spectrometry Service Centre, Swansea (quoted [M+H]$^+$).

Elemental analysis was carried out by the analytical services at London Metropolitan University and obtained for the determination of carbon, hydrogen and nitrogen analysis (%CHN). All values are quoted in mass percentage (%).

X-ray photoelectron spectroscopy analysis was performed either at the University of Newcastle (NEXUS at nanoLAB) or at the University of St Andrews. St Andrews X-ray photoelectron spectroscopy spectra were obtained on a Scienta ESCA 300 instrument; all spectra were obtained using monochromated Al Ka radiation at 1486.6 eV. Survey scans were obtained using a pass energy of 300eV and the detailed scans at 150 eV, giving a resolution of approximately 0.8 eV on the detailed scans. All spectra were collected at normal emission, the operating pressure of the instrument is below 5x10$^{-9}$ mbar. The XPS spectra were corrected for charging by referencing the aliphatic C 1s peak of hydrocarbons to 284.6 eV. Elemental compositions of the various surfaces were determined from the area under individual elemental peaks using sensitivity factors provided with the software as well as taking the transmission
function of the analyser into account. CasaXPS (Casa Software Ltd., UK) was used for the analysis. The spectra were fitted using Gaussian/Lorentzian peak shapes with a ratio of 70%/30%. A Shirley background was subtracted for the quantitative analysis.

**Water contact angles (DI water)** were measured with a G10 goniometer microscope (KRÜSS GmbH, Hamburg, Germany) under ambient conditions at room temperature. Droplets of ~3 µL were dispensed from a microburette. All reported values are the average of three measurements taken from different places of the surface.

**Ellipsometry analysis** was measured with an M-2000Di™ spectroscopic ellipsometer (J. A. Woollam Co., Inc., USA). Thickness values were extracted from fits to the data taken from 45 to 70° in steps of 5° over wavelengths from 200 to 1000 nm. The sample surface was modelled as a Si substrate with an oxide layer and a Cauchy layer. The thickness of the silicon oxide after the oxidative cleaning treatment was 16 ± 1 Å (average of three samples). The thickness of the monolayer films was calculated with a refractive index of 1.45. The error based on the observed variation of the thickness of the organic films prepared under identical conditions was ~2 Å.

**Atomic Force Microscopy (AFM) images** were obtained using Bruker Dimension Icon AFM system. AFM images were collected in the PeakForce Tapping™ mode using V-shaped cantilevers of nominal spring constant 0.58 N/m (Veeco SNL-A) with a peak force set point of around 1-4 nN and scan rate of 1 Hz. The RMS roughness of the surfaces was characterized from 1 × 1 µm² images of 512 × 512 pixels after appropriate image levelling. Quoted roughness values were calculated from an average of at least two samples and three images of each sample.

**AFM force curve collection.** A Bruker Dimension Icon AFM system was used to collect force curves between the thiol SAM coated AFM tip (Au coated Veeco SNL-B or SNL-D) and a modified surface in Millipore filtered deionized water. Force curves were collected at a ramp rate of ~1 Hz with 0.5 s of surface dwell time, with a ramp size of 200-500 nm, and with the maximum deflection minimized on a cantilever by cantilever basis to be as small as possible (typically ~0.5-8.0 nm). For each tip – sample system 25 force curves were collected in 5 × 5 grids in each of four different 500 × 500 nm² areas resulting in 100 force curves per surface. The same tip was used to interrogate multiple samples sequentially without alteration of optical readout positioning. Repeat measurements of samples were executed to check for tip changes. The modified tips were not used for imaging to preserve the thiol coating.
Section 6.2 contains the synthetic and experimental procedures for bulk reagents and catalysts that were used on multiple occasions throughout this work. Section 6.3 describes all other compounds in the order in which they appear in the text.

6.2 Synthesis of Bulk reagents and Catalysts

1-Hydroxy-1-oxo-1λ5-benzo[d][1,2]iodaioxol-3(1H)-one (IBX) 337

Following a procedure outlined by Santagostino et al.\textsuperscript{[281]} iodobenzoic acid (75.0 g, 0.30 mol, 1 equiv.) was added to a solution of Oxone (241.7 g, 0.39 mol, 1.3 equiv.) in deionised H\textsubscript{2}O (975 mL, 0.31 M) in a 2 L round bottomed flask. The reaction mixture was heated at 70 °C for 3 h then cooled to 0 °C in an ice bath and stirred for 1.5 h. The mixture was filtered through a sintered funnel and rinsed with H\textsubscript{2}O (3 × 100 mL) and acetone (3 × 100 mL) and dried for 16 h at rt to afford a colourless solid (67.8 g, 81% yield) mp 230 °C (dec.) \{lit.\textsuperscript{[281]}233 °C dec.\}; \textsuperscript{1}H NMR (500 MHz, d\textsubscript{6}-DMSO) δ\textsubscript{H}: 7.84 (1H, t, J 7.3, Ar\textsubscript{C}(4)\textsubscript{H}), 7.98-8.02 (2H, m, Ar\textsubscript{C}(5,6)\textsubscript{H}), 8.14 (1H, d, J 7.0, Ar\textsubscript{C}(7)\textsubscript{H}). All data in accordance with the literature.\textsuperscript{[281]}

3-oxo-1λ5-benzo[d][1,2]iodaioxole-1,1,1(3H)-triyl triacetate (Dess-Martin Periodinane) 338

Following a procedure outlined by Ireland\textsuperscript{[282]} IBX 337 (68.7 g, 0.245 mol, 1 equiv.), acetic anhydride (300 mL) and AcOH (150 mL) were added to a 3-neck round bottomed flask under Ar. The mixture was heated to 85 °C (internal temperature) over 30 mins. The mixture was kept at 85 °C for 20 mins until all solids were dissolved affording a clear yellow solution. The solution was cooled to rt slowly over 24 h. The resulting reaction mixture was filtered under vacuum under a blanket of Ar. The filtered solid was washed with anhydrous Et\textsubscript{2}O (200 mL) to afford the pure product as a colourless solid (52.1 g, 50% yield), mp 123-126 °C. \{lit.\textsuperscript{[283]}133-134 °C dec.\}; \textsuperscript{1}H NMR (500 MHz, d\textsubscript{6}-DMSO) δ\textsubscript{H}: 1.91 (6H, s, 2 × CH\textsubscript{3}), 2.20 (3H, s, CH\textsubscript{3}), 7.93 (1H, td, J 7.4,1.0, Ar\textsubscript{C}(4)\textsubscript{H}), 8.10 (2H, m, Ar\textsubscript{C}(5,6)\textsubscript{H}), 8.37 (1H, dd, J 8.3,1.0, Ar\textsubscript{C}(7)\textsubscript{H}). All data in accordance with the literature.\textsuperscript{[283]}
3-(Benzo[d]thiazol-2-ylamino)propan-1-ol 118

To a round bottomed flask containing 3-amino-1-propanol 117 (4.93 mL, 64.5 mmol, 1.05 equiv.), 2-chlorobenzothiazole 116 (8 mL, 61.5 mmol, 1 equiv.) and o-dichlorobenzene (30 mL, 2 M) was added iPr2NEt (26.5 mL, 153 mmol, 2.5 equiv.) with stirring. The resulting yellow solution was stirred vigorously and heated at reflux (195 °C DrySyn® temperature) until completion as judged by GC conversion (>95%, ca. 24 h). The resulting mixture was cooled to rt, H2O (100 mL) was added and the aqueous phase was extracted with CH2Cl2 (3 × 100 mL). The organic layers were combined, washed with brine, dried (MgSO4) and concentrated in vacuo to afford the crude product which was recrystallised from toluene to afford the pure product as a colourless solid (11.93 g, 93% yield); mp 119-121 °C. [Lit.107] 123-123.5 °C; GC [Agilent DB-5, 40 cm/s (He), inj. temp 250 °C, FID temp 325 °C; temp profile: initial 120 °C (2 min), then ramp to 320 °C (20 °C/min, hold 5 min), total run = 17 min]: tR iPr2NEt, 1.84 min; o-dichlorobenzene, 3.15 min; 3-amino-1-propanol 118, 5.62 min; 2-chlorobenzothiazole 117, 5.74 min; 10.30 min; 1H NMR (500 MHz, CD3OD) δH: 1.85 (1H, q, J 6.6, C(2)CH2), 3.49 (1H, t, J 6.9, C(3)CH2), 3.64 (1H, t, J 6.2, C(1)CH2), 7.01 (1H, td, J 7.6, 1.2, ArC(5)H), 7.21 (1H, ddd, J 8.2, 7.6, 1.2, ArC(6)H), 7.37 (1H, J 7.6, ArC(4)H), 7.52 (1H, J 7.6, ArC(7)H). All data in accordance with the literature.107

3,4-Dihydro-2H-pyrimido[2,1-b]benzothiazole (DHPB) 60

To a round bottomed flask was containing anhydrous CH2Cl2 (250 mL, 0.2 M) was added alcohol 118 (11.93 g, 57.3 mmol, 1 equiv.) with stirring under Ar. Et3N (30.7 mL, 229.2 mmol, 4 equiv.) was added via syringe and the suspension was cooled to 0 °C. After 10 mins, methanesulfonyl chloride (5.76 mL, 74.5 mmol, 1.3 equiv.) was added dropwise, during which time the suspension dissolved to give a pale yellow solution. The ice/water bath was removed and the reaction was stirred for 30 mins. Once complete consumption of alcohol 118 was observed, as judged by TLC, iPrOH (11 mL) was added and the reaction was heated at reflux (50 °C DrySyn® temperature) for 16 h. The reaction was quenched with aq. 1 M NaOH (150 mL) and stirred for 30 mins. The aqueous phase was extracted with CH2Cl2 (3 × 100 mL). The organic layers were combined,
washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Et₂O (50 mL) was added to the crude solid and the mixture was heated at reflux with stirring for 30 mins. An equal volume of pet. ether (50 mL) was added and the mixture was cooled to rt then filtered. The filter cake was washed with pet. ether (3 × 50 mL) and dried to afford the pure product as a pale yellow solid (7.56 g, 70% yield); mp 120-122 °C; {Lit. [107] 122-123 °C}; ¹H NMR (400 MHz, CDCl₃) δH: 1.96 (2H, q, J 6.0, C(3)CH₂), 3.51 (2H, t, J 6.0, CH₂), 3.71 (2H, t, J 6.3, CH₂), 6.67 (1H, dd, J 8.1, 0.8, ArH), 6.92, (1H, td, J 7.7, 1.1, ArH), 7.12 (1H, td, J 7.7, 1.1, ArH), 7.20-7.22 (1H, m, ArH). All data in accordance with the literature. [107]

4-Methylbenzenesulfonyl azide 339

To a round bottomed flask containing acetone (85 mL) and H₂O (85 mL) was added p-toluenesulfonyl chloride (5.72 g, 30 mmol, 1 equiv.) and sodium azide (1.95 g, 30 mmol, 1 equiv.) at 0 °C with stirring. The mixture was stirred at 0 °C for 2 h and then warmed to rt. The solvent was concentrated in vacuo. The aqueous layer was extracted with EtOAc (3 × 30 mL), washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the pure product as a colourless oil (3.96 g, 67% yield); ¹H NMR (500 MHz, CDCl₃) δH: 2.51 (3H, s, ArCH₃), 7.42 (2H, app. dd, J 7.9, ArC(3,5)H), 7.85 (2H, app. dt, J 8.4, ArC(2,6)H); vₘₐₓ (thin film, cm⁻¹) 2130 (N₃). All data in accordance with the literature. [284]

Dimethyl (1-diazo-2-oxopropyl)phosphonate (Ohira-Bestmann reagent) 340

To round bottomed flask containing anhydrous toluene (45 mL) and THF (15 mL) was added NaH (0.86 g, 21.5 mmol, 1.1 equiv, 60% in mineral oil) at 0 °C with stirring. A solution of dimethyl acetylmethylphosphonate (3.15 mL, 19.6 mmol, 1 equiv.) in toluene (15 mL) was added and a white precipitate formed. The reaction was stirred for 1 h at rt and tosylazide 339 (3.2 g, 20.8 mmol, 1.05 equiv.) was added in toluene (7.5 mL) resulting in an orange solution that was stirred for 16 h. The reaction mixture was diluted with pet. ether, filtered through celite and washed with Et₂O (100 mL). The resulting solution was concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (1:1 hexane:EtOAc) afforded the pure product as a colourless oil (2.29 g, 61% yield); ¹H NMR (500 MHz, CDCl₃) δH: 2.23 (3H, s, CH₃), 3.81 (6H,
d, $^3J_{HH} 12.0, 2 \times \text{OCH}_3$; $\nu_{\text{max}}$ (thin film, cm$^{-1}$) 2135 (N$_3$). All data in accordance with the literature.$^{[285]}$

2-Chloro-6-methoxybenzo[d]thiazole 290

To a round bottomed flask was added CuCl$_2$ (13.56 g, 100.1 mmol, 1.2 equiv.) and dried for 1 h under vacuum at 110 °C. Anhydrous MeCN (500 mL) was added to the flask with stirring under Ar. To the reaction mixture was added tert-butyl nitrite (15 mL, 126.1 mmol, 1.5 equiv.) with stirring followed by dropwise addition of 6-methoxybenzo[d]thiazole-2-amine 287 (15.15 g, 84.1 mmol, 1 equiv.) in MeCN (50 mL). The reaction mixture was stirred at 65 °C for 3 h and allowed to cool to rt. 4 M HCl (200 mL) was added and the aqueous phase was extracted with Et$_2$O (3 × 100 mL). The organic layers were combined, washed with brine, dried (MgSO$_4$) and concentrated in vacuo to afford the crude product as a dark brown solid. Flash chromatography on silica gel (hexane: EtOAc 0→10%) afforded the pure product as a colourless solid (11.74 g, 71% yield); $\text{mp}$ 51-52 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H: 3.87 (3H, s, OC$_3$H$_3$), 7.07 (1H, dd, $J$ 9.0, 2.6, ArC(5)H), 7.23 (1H, d, $J$ 2.6, ArC(7)H), 7.82 (1H, d, $J$ 9.0, ArC(4)H). All data in accordance with the literature.$^{[286]}$

(E)-2,2,2-Trifluoro-N-phenylacetimidoyl chloride 102

Following a procedure outlined by Uneyama.$^{[148]}$ to a round bottomed flask containing freshly distilled CCl$_4$ (90 mL, 1 M) was added TFA 103 (6.8 mL, 88 mmol, 1 equiv.), Et$_3$N (14.6 mL, 106 mmol, 1.2 equiv.) and triphenylphosphine (69.0 g, 264 mmol, 3 equiv.) with stirring. The reaction mixture was stirred at rt for 10 mins then aniline 104 (9.66 mL, 106 mmol, 1.2 equiv.) was added and the mixture was heated at reflux for 3 h and allowed to cool to rt. The mixture was concentrated in vacuo and hexane (300 mL) was added and the crude residue was stirred for 1 h and filtered to afford the crude product. Purification by Kugelrohr distillation afforded the pure product as a pale yellow oil (11.3 g, 62%); $\text{bp}$ 120-122 °C (5 mbar); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H: 7.08-7.12 (2H, m, ArC(2,6)H), 7.23 (1H, d, $J$ 2.6, ArC(7)H), 7.82 (1H, d, $J$ 9.0, ArC(4)H). All data in accordance with the literature.$^{[148]}$
6.3 Experimental for Chapter 2

**General Procedure A: Formation of trichlorosilanes from alkyl bromides**

To a flame dried round bottomed flask containing magnesium turnings (1 equiv.) in anhydrous Et₂O (15 mL) was added a crystal of iodine at rt. The reaction was stirred until the brown colour disappeared. The appropriate bromide (1 equiv.) in anhydrous Et₂O (15 mL) was added dropwise with gentle heating until initiation occurred. The reaction mixture was stirred for 30 mins at rt. Silicon tetrachloride (1.2 equiv.) in anhydrous Et₂O (15 mL) was added via syringe over 1 h and the subsequent mixture stirred at rt for 16h. Upon completion anhydrous hexane was added via cannula to the 2 necked flask and the product was filtered under nitrogen using a fritted filter to remove any inorganic material. The solution was concentrated under reduced pressure to afford an oil that was purified by Kugelrohr distillation to afford the pure product as a colourless oil.

**General procedure B: Preparation of vinyl terminated surfaces on SiO₂**

Freshly cleaned silicon wafers were placed in a vial containing a freshly prepared 1 mM solution of the appropriate trichlorosilane in toluene for 16 h. The wafer was removed and rinsed with toluene and sequentially sonicated in toluene, CH₂Cl₂, and CHCl₃ for 5 min each. The vinyl terminated wafers were dried under a stream of Ar.

**General procedure C: Ozonolysis of vinyl terminated surfaces on SiO₂**

To a 250 mL round bottomed flask containing CH₂Cl₂ (200 mL) was added the appropriate vinyl terminated wafer at −78 °C. The mixture was subjected to ozonolysis until the reaction mixture turned blue (ca. 1 min) and the solution was quenched with dimethylsulfide (~2 mL) at −78 ° C. The mixture was allowed to warm to rt and the wafer was removed from the solution, sonicated in CH₂Cl₂, toluene and H₂O for 5 mins each then dried in a stream of Ar.

**General procedure D: Michael addition lactonisation on a surface using DHPB 60**

To a round-bottomed flask containing a stirrer bar and a solution of acid (1 equiv.) in CH₂Cl₂ (3 mL) was added iPr₂NEt (1.5 equiv) and pivaloyl chloride (1.5 equiv.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 20 min. DHPB 60 (5 mol %), the Michael acceptor terminated surface and iPr₂NEt (2.5 equiv) were added. The reaction was stirred at rt for 24 h. Upon completion, the DHP terminated surface was removed and rinsed with CH₂Cl₂ and sonicated in CH₂Cl₂ and CHCl₃ for 5 mins each. DHP terminated surfaces were dried under a stream of Ar.
Trichloro(undec-10-en-1-yl)silane 86

Following general procedure A, magnesium turnings (1.67 g, 68.7 mmol, 1 equiv), 11-bromo-undecene (5.00 mL, 22.9 mmol, 1 equiv), silicon tetrachloride (8.30 mL, 80.0 mmol, 1.1 equiv) were reacted to afford the crude product. Purification by Kugelrohr distillation (105 °C, 1 mbar) afforded the pure product as a colourless oil (1.64 g, 26% yield); \textit{v}_{\text{max}} (thin film, cm$^{-1}$) 2924 (C-H), 1641 (C=C), 1193 (Si-C); $^1$H NMR (400 MHz, C$_6$D$_6$) \(\delta_H\): 0.98 (2H, m, C$_2$H$_2$SiCl$_3$), 1.07-1.26 (8H, bs, 4 \(\times\) C$_2$H$_2$), 1.30-1.35 (4H, m, 2 \(\times\) C$_2$H$_2$), 2.00 (2H, app. q, \(J = 7.1\), C$_2$H$_2$), 4.98 (1H, dd, \(J = 10.1, 1.9\), =C$_2$H$_2$), 5.03 (1H, app. dq, \(J = 17.1, 1.9\), =C$_2$H$_2$); $^{13}$C\{$^1$H\} NMR (75 MHz, C$_6$D$_6$) \(\delta_C\): 22.5 (C$_2$H$_2$), 24.3 (C$_2$H$_2$), 29.3 (C$_2$H$_2$), 29.4 (C$_2$H$_2$), 29.5 (C$_2$H$_2$), 29.7 (C$_2$H$_2$), 29.8 (C$_2$H$_2$), 32.0 (C$_2$H$_2$), 34.3 (C$_2$H$_2$), 114.6 (=C$_2$H$_2$), 139.1 (CH); $^{29}$Si NMR (79 MHz, C$_6$D$_6$) \(\delta_{Si}\): 13.1 (SiCl$_3$); HRMS (APCI) C$_{11}$H$_{21}$SiCl$_3$ [M+H]$^+$, found 286.7251, requires 286.0673 (+3.8 ppm).

Methyl 15-hydroxypentadecanoate 90

To a round bottomed flask containing methanol (81 mL) was added concentrated H$_2$SO$_4$ (9 mL) and \(\omega\)-pentadecalactone 89 (10.0 g, 41 mmol, 1 equiv) with stirring. The solution was stirred at reflux for 3 h and cooled to rt. Brine (100 mL) was added to the reaction mixture and the aqueous layer was extracted with Et$_2$O (3 \(\times\) 30 mL). The organic layers were combined, washed with brine, dried (MgSO$_4$) and concentrated \textit{in vacuo} to afford the pure product as a colourless solid (10.1g, 90% yield); mp 50-51.5 °C. [Lit.$^{[287]}$ 47-48 °C]; $^1$H NMR (300 MHz, CDCl$_3$) \(\delta_H\): 1.23-1.36 (20H, bs, 10 \(\times\) CH$_2$), 1.51-1.63 (4H, m, 2 \(\times\) CH$_2$), 2.30 (2H, t, \(J = 8.2\), C(O)CH$_2$), 3.63 (2H, t, \(J = 6.7\), CH$_2$OH), 3.65 (3H, s, OCH$_3$). All data in accordance with the literature.$^{[287]}$

Methyl 15-bromopentadecanoate 91

Following a procedure outlined by Katzenellenbogen$^{[287]}$ to a round bottomed flask containing DMF (30 mL) was added triphenylphosphine (2.53g, 9.66 mmol, 1.1 equiv) and alcohol 90 (2.39 g, 8.8 mmol, 1 equiv) with stirring under Ar. N-Bromosuccinimide (1.71g, 9.66 mmol, 1.1 equiv) was added in portions until fully dissolved. The reaction mixture was heated at 55 °C for 30 mins and allowed to cool to rt. Methanol (15 mL), followed by aq. HCl (1 M, 60 mL) was added to the
solution. The aqueous layer was extracted with Et₂O (3 × 20 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (20:1 Hexane:EtOAc) afforded the pure product as a colourless solid (2.27 g, 77% yield); mp 37-38.5 °C {Lit.[287] 38-39 °C}; ¹H NMR (400 MHz, CDCl₃) δH: 1.22-1.35 (18H, bs, 9 × CH₂), 1.41 (2H, m, CH₂), 1.61 (2H, m, CH₂), 1.85 (2H, m, CH₂), 2.30 (2H, t, J 7.6, C(O)CH₂), 3.40 (2H, t, J 6.9, CH₂Br), 3.66 (3H, s, CH₃). All data in accordance with the literature.[287]

**tert-Butyl pentadec-14-enoate 92**

Following a procedure outlined by Katzenellenbogen,[287] to a round bottomed flask containing bromide 91 (4.43 g, 13.2 mmol) was added to a solution of potassium tert-butoxide (2.96 g, 26.4 mmol, 2 equiv.) in THF (20 mL) under Ar. The mixture was stirred at room temperature for 1 h and quenched with aq. HCl (1 M, 20 mL) and the aqueous layer extracted with Et₂O (3 × 10 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (98:2 pet. ether:Et₂O) afforded the pure product as a colourless oil (1.6 g, 41% yield); ¹H NMR (400 MHz, CDCl₃) δH: 1.18-1.26 (14H, bs, 7 × CH₂), 1.32 (2H, m, CH₂), 1.38 (9H, s, C(CH₃)₃), 1.52 (2H, m, CH₂), 1.82 (2H, m, CH₂), 1.97 (2H, m, CH₂CH₂), 2.16 (2H, t, J 8.0, CH₂ C(O)CH₂), 4.86 (1H, app. dq, J 10.1, 1.8, =CH), 4.93 (1H, app. dq, J 17.0, 1.8, =CH₄H'B), 5.75 (1H, dd, J 17.0, 10.1, 6.6, =CH). All data in accordance with the literature.[287]

**Pentadec-14-en-1-ol 93**

To a round bottomed flask containing anhydrous THF (5 mL) was added alkene 92 (490mg, 1.65 mmol, 1 equiv) and LiAlH₄ (1.81 mL, 4.5 mmol, 2.5 m in hexanes, 2.7 equiv.) was added at 0 °C with stirring. The reaction mixture was stirred for 1 h and quenched with a saturated solution of potassium sodium tartrate (10 mL). The mixture was filtered through celite, washed with CH₂Cl₂ (3 × 20 mL) and the filtrate concentrated in vacuo to yield the crude product as an off white solid. Flash chromatography on silica gel (CH₂Cl₂) afforded the pure alcohol as a colourless solid (289 mg, 77% yield); mp 38-39°C {Lit.[288] 38-39°C}; ¹H NMR (400 MHz, CDCl₃) δH: 1.23-1.38 (20H, bs, 10 × CH₂), 1.56 (2H, t, J 6.7, CH₂), 2.04 (2H, m, CH₂), 3.64 (2H, t, J 6.6 Hz, CH₂OH), 4.92 (1H, app. ddt, J 10.2, 2.3, =CH₄H'B), 4.99 (1H, app. d, J 17.0, =CH₄H'B) 5.81 (1H, ddt, J 17.0, 10.2, 6.7, =CH). All data in accordance with the literature.[288]
15-Bromopentadec-1-ene 94

Following a procedure outlined by Katzenellenbogen,[287] to a round bottomed flask containing DMF (15 mL) was added triphenylphosphine (577 mg, 2.20 mmol, 1.1 equiv.) and alcohol 93 (2.39 g, 8.8 mmol, 1 equiv.) with stirring under Ar. N-bromosuccinimide (392 mg, 2.20 mmol, 1.1 equiv.) was added in portions until fully dissolved. The reaction mixture was heated at 55 °C for 30 mins and allowed to cooled to rt. Methanol (10 mL), followed by aq. HCl (1 M, 20 mL) was added to the solution. The aqueous layer was extracted with Et2O (3 × 20 mL). The organic layers were combined, washed with brine, dried (MgSO4) and concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (20:1 hexane:EtOAc) afforded the pure product as a brown oil (461 mg, 80% yield); 1H NMR (400 MHz, CDCl3) δH: 1.19–1.33 (16H, bs, 8 × CH2), 1.34–1.46 (4H, m, 2 × CH2), 2.03 (2H, m, CH2CH2Br), 3.39 (2H, t, J 6.9, CH2Br), 4.98 (1H, app. d, J 17.0), 5.81 (1H, ddt, J 17.0, 10.2, 6.7, =CH). All data in accordance with the literature.[289]

Trichloro(pentadec-14-en-1-yl)silane 76

Following general procedure A, magnesium turnings (190 mg, 7.92 mmol, 1 equiv.), 15-bromopentadec-1-ene 94 (2.30 g, 7.92 mmol, 1 equiv.), silicon tetrachloride (1 mL, 8.71 mmol, 1.1 equiv.) were reacted to afford the crude product. Purification by Kugelrohr distillation afforded the pure product as a colourless oil (560 mg, 20% yield); bp 115 °C, 1 mbar; {Lit.[114] 145-150 °C, 4 mbar} 1H NMR (400 MHz, C6D6) δH: 0.98 (2H, m, CH2SiCl3), 1.11-1.30 (18H, bs, 9 × CH2), 1.32-1.36 (4H, m, 2 × CH2), 2.02 (2H, app. q, J 7.1, CH2), 4.98 (1H, app. dd, J 10.1, 1.9, =CH3H8), 5.01 (1H, app. dq, J 17.1, 1.9, =CH3H8) 5.78 (1H, ddt, J 17.1, 10.1, 6.7, =CH); All data in accordance with the literature.[114]

C11-vinyl-terminated SAM on SiO2 96

Freshly cleaned silicon wafers (as per the cleaning procedure outlined in chapter 2) were placed in a vial containing a 5 mL of freshly prepared 1mM solution of trichloro(undec-10-en-1-yl)silane 86 (5.70 mg, 0.02 mmol, in 20 mL toluene) for 16 h. Once deposition was complete the wafer
was removed and rinsed with toluene and subsequently sonicated in toluene, CH$_2$Cl$_2$ and CHCl$_3$ for 5 mins each. The vinyl terminated wafers were dried under a stream of Ar.

**C$_{15}$-vinyl-terminated SAM on SiO$_2$ 97**

![Chemical structure](image)

Freshly cleaned silicon wafers (as per the cleaning procedure outlined in chapter 2) were placed in a vial containing a 5 mL of freshly prepared 1mM solution of trichloro(pentadec-14-en-1-yl)silane 76 (6.90 mg, 0.02 mmol, in 20 mL toluene) for 16 h. Once deposition was complete the wafer was removed and rinsed with toluene and subsequently sonicated in toluene, CH$_2$Cl$_2$ and CHCl$_3$ for 5 mins each. The vinyl terminated wafers were dried under a stream of Ar.

**Phenylacetic acid terminated surface 99**

![Chemical structure](image)

To a round bottomed flask containing DMF (2 mL) was added Pd(OAc)$_2$ (16 mg, 0.069 mmol, 10 mol%), P(o-tol)$_3$ (21 mg, 0.069 mmol, 10 mol%), p-bromophenylacetic acid 98 (150 mg, 0.69 mmol, 1 equiv.) and Et$_3$N (0.49 mL, 3.48 mmol, 5 equiv.) with stirring. C$_{11}$-vinyl terminated surface 96 was immersed in the reaction mixture and heated at 125 °C for 2 h then cooled to rt. The wafer was removed and rinsed with Et$_2$O (20 mL) and further sonicated in Et$_2$O for 5 mins then rinsed with EtOH (20 mL) and dried under a stream of argon to afford the phenylacetic acid terminated surface.

**C$_{10}$-aldehyde terminated surface on SiO$_2$ 96a**

![Chemical structure](image)

Following general procedure C, C$_{11}$-vinyl terminated SAM 96 was reacted with ozone at −78 °C to afford aldehyde terminated surface 96a after rinsing and sonication.
C\textsubscript{14}-aldehyde terminated surface on SiO\textsubscript{2} 97a

Following general procedure C, C\textsubscript{15}-vinyl terminated SAM 97 was reacted with ozone at \(-78\) °C to afford aldehyde terminated surface 97a after rinsing and sonication.

(3,4-Dinitrophenyl)hydrazine 100

To a round bottomed flask containing EtOH (100 mL) was added 2,4-dinitrochlorobenzene (5.0 g, 24.6 mmol, 1 equiv) with stirring. Hydrazine monohydrate (12 mL, 256 mmol, 10 equiv.) in EtOH (50 mL) was added dropwise over 30 mins. The reaction mixture was heated at reflux for 3 h, cooled to rt and brine was added to the mixture. The resulting solid was filtered to afford the pure product as a bright orange solid (4.09 g, 84% yield); mp 205 dec. °C {Lit.\textsuperscript{[290]} 202-203 °C}; \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD) δ\textsubscript{H}: 7.83 (1H, d, \(J = 9.7\), ArC(5)H), 8.27 (1H, dd, \(J = 9.7, 2.6\), ArC(6)H), 8.99 (1H, d, \(J = 2.6\), ArC(2)H). All data in accordance with the literature.\textsuperscript{[290]}

Dinitrophenylhydrazine (DNPH) terminated surface 101

To a round bottomed flask containing DMSO (20 mL) was added 3,4-dinitrophenylhydrazine 100 (50 mg, 0.254 mmol) and aldehyde terminated wafer 96a. The reaction was stirred for 72 h and the wafer was removed and rinsed with EtOH (20 mL) and dried under a stream of Ar.

Bromine terminated SAM on Si/SiO\textsubscript{2} 115 (solution deposition)

Freshly cleaned silicon wafers (as per the cleaning procedure outlined in chapter 2) were placed in a vial containing a 5 mL of freshly prepared 1 mM solution of 11-bromoundecyltrichlorosilane
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114 (5.80 µL, 0.0198 mmol, in 20 mL toluene) for 16 h. Once deposition was complete the wafer was removed and rinsed with toluene and subsequently sonicated in toluene, CH₂Cl₂ and CHCl₃ for 5 mins each. The bromine terminated wafers were dried under a stream of Ar.

**Bromine terminated SAM on Si/SiO₂ 114 (vapour deposition)**

A freshly cleaned silicon wafer (as per the cleaning procedure outlined in chapter 2) was placed in the centre of a 100 mL Schott Duran bottle with a sidearm modification (for vacuum use). Next, 11-bromoundecyltrichlorosilane 114 (50 µL, 172 mmol) was added to a standard grade HPLC vial and placed inside the 100 mL Schott Duran bottle. The lid was placed on the bottle and the internal atmosphere was removed under reduced pressure. The bottle was clamped and placed in a preheated oil bath at 60°C, paying careful attention to ensure the external level of the oil bath was above the top of the HPLC vial. Once deposition was complete (ca. 36 h) the wafer was removed and rinsed with toluene and subsequently sonicated in toluene, CH₂Cl₂ and CHCl₃ for 5 mins each. The bromine terminated wafers were dried under a stream of Ar.

**Azide terminated surface 112**

Bromine terminated SAM 114 was immersed in a saturated solution of sodium azide in DMF (10 mL) and the reaction was stirred for 24 h. Upon completion the azide terminated wafer was removed and rinsed with DMF. The wafer was sonicated in EtOH and H₂O for 5 mins each, and dried under a stream of Ar.

**5-(Trimethylsilyl)pent-4-yn-1-ol 121**

To a round bottomed flask containing anhydrous THF (45 mL, 0.5 M) at −78 °C was added pent-4-yn-1-ol 120 (2 mL, 26.3 mmol, 1 equiv.) and nBuLi (21.0 mL, 52.6 mmol, 2.5 M in hexanes, 2 equiv.) and the resulting solution was stirred at −78°C for 30 mins under Ar. Trimethylchlorosilane (8 mL, 63.1 mmol, 2.4 equiv.) was added to the yellow solution and the
reaction was stirred for a further 30 mins at −78 °C then allowed to warm to rt over 30 mins. The reaction was quenched with aq. 2 M HCl (40 mL) and the aqueous phase was extracted with Et₂O (3 × 50 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product as a light yellow oil. Purification by Kugelrohr distillation afforded the pure product as a colourless oil (2.50 g, 61% yield); **bp** 100-104 °C (2 mbar) {Lit.[291] 118-120 °C (29 Torr)}; **¹H NMR** (400 MHz, CDCl₃) δH: 0.13 (9H, s, Si(CH₃)₃), 1.71–1.79 (2H, m, CH₂), 2.33 (2H, t, J 6.9, CH₂), 3.73 (2H, t, J 6.1, C(1)H₂). All data in accordance with the literature{Lit.[292]}

5-(Trimethylsilyl)pent-4-ynal 122

To a round bottomed flask containing anhydrous CH₂Cl₂ (40 mL, 0.4 M) at −78 °C was added oxalyl chloride (1.62 mL, 18.8 mmol, 1.2 equiv.) with stirring under Ar. Dimethylsulfoxide (2.44 mL, 31.4 mmol, 2 equiv.) in anhydrous CH₂Cl₂ (10 mL) was added dropwise to the solution over 10 mins and allowed to stir for 20 mins. Alcohol 121 (2.45 g, 15.7 mmol, 1 equiv.) in anhydrous CH₂Cl₂ (20 mL) was added to the reaction mixture and the resulting solution was stirred at −78 °C for 1 h. Et₃N (8.41 mL, 62.7 mmol, 4 equiv.) was added dropwise to the solution at −78 °C and the reaction was stirred for 30 mins then warmed to rt and stirred for a further 30 mins at this temperature. The reaction was quenched with aq. 1 M HCl (30 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 × 40 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the pure product which was purified by Kugelrohr distillation to afford the pure product as a colourless oil (1.06 g, 44% yield); **bp** 170-172 °C (atm pressure) {Lit.[293] 125 °C (35 Torr)}; **¹H NMR** (300 MHz, CDCl₃) δH: 0.13 (9H, s, Si(CH₃)₃), 2.53 (1H, app. d, J 7.7, 6.7, C(3)H₂), 2.67 (2H, app. ddt, J 7.7, 6.7, 1.3, C(2)H₂), 9.78 (1H, t, J 1.3, CHO). All data in accordance with the literature{Lit.[293]}

4-((Trimethylsilyl)ethyl)benzaldehyde 125

To a round bottomed flask containing THF (135 mL, 0.2 M degassed with Ar) was added copper (I) iodide (52 mg, 0.27 mmol, 1 mol%), triethylamine (18.10 mL, 13.5 mmol, 5 equiv.) and Pd(PPh₃)₄Cl₂ (190 mg, 0.27 mmol, 1 mol%) with stirring. 4-Bromobenzaldehyde (5.00 g, 27 mmol, 1 equiv.) was added with stirring followed by dropwise addition of trimethylsilylacetylene (3.82 mL, 27 mmol, 1 equiv.). The reaction mixture was stirred for 16 h at rt then concentration
in vacuo, water (50 mL) was added to the crude reaction mixture and the aqueous phase was extracted with Et₂O (3 × 50 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (9:1 pet ether:Et₂O) afforded the pure product as a tan solid (4.09 g, 75%); **mp** 60-62 °C [Lit.[294] 65-66 °C]; **¹H NMR** (400 MHz, CDCl₃) δH: 0.27 (9H, s, Si(CH₃)₃), 7.59 (2H, d, J 8.5, ArH), 7.82 (2H, d, J 8.5, ArH), 10.0 (1H, s, CHO). All data in accordance with the literature.[294]

**(E)-1,1,1-Trifluoro-4-(4ꞌ-((trimethylsilyl)ethyl)phenyl)but-3-en-2-one 126**

Following a procedure outlined by Smith[101]; to a round bottomed flask containing anhydrous THF (25 mL, 0.2 M) was added diisopropylamine (1.35 mL, 9.66 mmol, 2 equiv.) and nBuLi (4.60 mL, 9.66 mmol, 1.92 M in hexanes, 2 equiv.) at −78 °C and the solution was allowed to stir for 20 minutes. Diethyl methylphosphonate (0.71 mL, 4.83 mmol, 1 equiv.) was added at −78 °C followed by a further 30 minutes of stirring. (Z)-2,2,2-trifluoro-N-phenylacetimidoyl chloride 102 (1.00 g, 4.83 mmol, 1 equiv.) was then added slowly followed by stirring at −78 °C for 1 h. A solution of aldehyde 125 (0.976 g, 4.83 mmol, 1 equiv.) in anhydrous THF (10 mL) was added dropwise at −78 °C. The reaction mixture was then warmed over 2 h and stirred at rt for 16 h. Aq. 2 M HCl (12 mL, 4 equiv.) was added and the reaction mixture was stirred for a further 4 h before being extracted with Et₂O (3 × 50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (50 mL), brine (50 mL), dried (MgSO₄) and concentrated in vacuo to give the crude reaction mixture. Flash chromatography on silica gel (9:1 Pet:Et₂O) afforded the pure product as a colourless solid (675 mg, 47%); **mp** 40-42 °C; νmax (thin film, cm⁻¹) 2158 (C≡C), 1608 (C=O), 1595 (C=C); **¹H NMR** (400 MHz, CDCl₃) δH: 0.27 (9H, s, Si(CH₃)₃), 7.00 (1H, d, J 16.0, C(3)H), 7.52 (2H, d, J 8.3, ArC(3,5)H), 7.58 (2H, d, J 8.1, ArC(2,6)H), 7.92 (1H, d, J 16.0, C(4)H); **¹³C{¹H} NMR** (100 MHz, CDCl₃) δC: −0.04 (Si(CH₃)₃), 98.6 (C≡C-Si(CH₃)), 104.2 (C≡C-Si(CH₃)), 117.2 (C(3)), 117.6 (q, ²J 290, CF₃), 127.3 (ArC(1)), 129.1 (ArC(2,6)H), 132.7 (ArC(3,5)H), 133.2 (C(4)H), 149.1 (ArC(4)), 179.9 (q, ²J 35.3, C=O); **¹⁹F {¹H} NMR** (376 MHz, CDCl₃) δF: −78.1 (CF₃); **HRMS** (ESI⁺) C₁₅H₁₅OF₃Si [M]⁺, found 296.0848, requires 296.0839 (−1.4 ppm).
(E)-4-(4'-Ethynlyphenyl)-1,1,1-trifluorobut-3-en-2-one 127

To a round bottomed flask containing MeOH (20 mL) was added 126 (675 mg, 2.28 mmol, 1 equiv.). K$_2$CO$_3$ (724 mg, 5.24 mmol, 2.3 equiv.) was added and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated in vacuo, H$_2$O (20 mL) was added and the crude product was extracted using EtOAc (3 × 30 mL). The combined organic extracts were washed sequentially with sat. aq. NaHCO$_3$ (30 mL) and brine (30 mL), dried (MgSO$_4$), and concentrated in vacuo to afford the crude reaction mixture. Flash chromatography on silica gel (9:1 pet. ether:Et$_2$O) afforded the pure product as a colourless solid (228 mg, 45%); mp 50-52 °C; $\nu_{\text{max}}$ (thin film, cm$^{-1}$) 3253 (≡C−H), 2104 (C≡C), 1681 (C=O), 1620 (C=C); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.27 (1H, s, C≡CH), 7.01 (1H, d, $J$ 16.0, C(3)H), 7.56 (2H, d, $J$ 8.4, ArC(3,5)H), 7.60 (2H, d, $J$ 8.4, ArC(2,6)H), 7.93 (1H, d, $J$ 16.0, C(4)H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$: 80.7 (C=CH), 82.9 (C=CH), 117.5 (q, $J$ 290, CF$_3$), 126.2 (ArC(1)), 129.2 (ArC(2,6)H), 130.0 (ArC(3,5)H), 133.6 (ArC(4)), 148.9 (C(4)), 180.2 (q, $J$ 35.8, C=O); $^{19}$F{$^1$H} NMR (376 MHz, CDCl$_3$) $\delta$: −78.1 (CF$_3$); HRMS (CI$^+$) C$_{12}$H$_8$OF$_3$ [M+H]$^+$ found 225.0527, requires 225.0522 (+0.0 ppm).

CF$_3$ enone terminated surface 128

To a solution of enone 127 (7 mg, 0.03 mmol, 1 equiv.) in EtOH (8 mL) was added 1 mL of a 25 mL solution of CuSO$_4$.5H$_2$O (7.5 mg, 0.03 mmol, 1 equiv.) and 1 mL of a 25 mL solution of sodium ascorbate (8.9 mg, 0.045 mmol, 1.5 equiv.) with stirring. The azide terminated wafer 112 was immersed in the reaction mixture for 24 h. Upon completion the enone terminated wafer was removed and rinsed with EtOH. The wafer was sonicated in EtOH and H$_2$O for 5 mins each, and dried under a stream of Ar.

1-azidooctane 130
To a round bottomed flask containing DMF (20 mL) was added 1-bromo-octane 129 (2.00 mL, 11.5 mmol, 1 equiv.) and sodium azide (900 mg, 13.5 mmol, 1.2 equiv.) with stirring at 100 °C for 2 h. The reaction was quenched using sat. aq. NaNO₂ (30 mL) and diluted with H₂O (10 mL). The aqueous phase was extracted with hexane (3 × 20 mL) and organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the pure product as a colourless oil (1.60 g, 90% yield); ¹H NMR (400 MHz, CDCl₃) δH: 0.88 (3H, t, J 6.9, CH₃), 1.23-1.31 (8H, m, 4 × CH₂), 1.32-1.38 (2H, m, CH₂), 1.96 (2H, app. quintet, J 6.5, N₃CH₂C₂H₂), 3.24 (2H, t, J 7.0, N₃CH₂). All data in accordance with the literature[295].

\[ \text{1H, 1,1,1-Trifluoro-4-(4'-(1-octyl-1H-1,2,3-triazol-4-yl)phenyl)but-3-en-2-one 131} \]

To a round bottomed flask containing EtOH (8 mL) was added enone 127 (50 mg, 0.23 mmol, 1 equiv.) and azide 130 (76 mg, 0.46 mmol, 2 equiv.) with stirring. CuSO₄.5H₂O (6 mg, 0.023 mmol, 10 mol%) in 1 mL H₂O and sodium ascorbate (7.5 mg, 15 mol%) in 1 mL H₂O were then added and the reaction was stirred overnight at rt then concentrated in vacuo. CH₂Cl₂ (10 mL) and water (10 mL) were added and the crude product extracted using CH₂Cl₂ (3 × 10 mL). The organic layers were combined, washed with brine, dried (MgSO₄), and concentrated in vacuo to give the crude reaction mixture which was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, CH₂Cl₂:EtOAc (97:3 5CV, 97:3 to 90:10 10CV, 90:10 5CV)] to afford the pure product as a colourless solid (74 mg, 47% yield); mp 60-62 °C; v_max (thin film, cm⁻¹): 2924 (C-H), 1712 (C=O), 1602 (C=C); ¹H NMR (500 MHz, CDCl₃) δH: 0.88 (3H, t, J 6.6, CH₃), 1.23-1.30 (6H, m, 3 × CH₂), 1.33-1.39 (4H, m, 2 × CH₂), 1.96 (2H, quintet, J 7.2, ArNCH₂C₂H₂), 4.42 (2H, t, J 7.2, ArNCH₂), 7.04 (1H, d, J 16.0, C(3)H), 7.71 (2H, d, J 8.3, (ArC(2,6)H), 7.83 (1H, s, N(1)CH), 7.93 (2H, d, J 8.3, (ArC(3,5)H), 7.98 (1H, d, J 16.0, C(4)H); ¹³C{¹H} NMR (100 MHz) δC: 14.2 (CH₃), 22.8 (CH₂), 26.6 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 30.5 (ArN(1)CH₂(CH₂), 30.9 (CH₂), 50.8 (ArN(1)CH₂), 116.5 (C(3)H), 117.7 (q, J 289, CF₃) 120.3 (N(1)CH), 126.3 (ArC(3,5)H), 130.1 (ArC(2,6)H), 132.9 (ArC(1)), 134.7 (ArC(4)), 146.7 (N(3)C=C), 149.6 (C(4)), 179.9 (q, J 34.8, C=O); ¹⁹F {¹H} NMR (470 MHz) δF: -78.6 (CF₃); HRMS (ESI⁺) C₂₀H₂₅F₃N₃O [M+H]⁺, found 380.1940, requires 380.1944 (−1.1 ppm).
Methyl (2R,3R)-2-(4-bromophenyl)-6,6,6-trifluoro-3-(4′-(1-octyl-1H-1,2,3-triazol-4-yl)phenyl)-5-oxohexanoate (anti 132) and methyl (2S,3R)-2-(4-bromophenyl)-6,6,6-trifluoro-3-(4′-(1-octyl-1H-1,2,3-triazol-4-yl)phenyl)-5-oxohexanoate (syn 132)

To a round bottomed flask containing CH₂Cl₂ (5 mL) was added 4-bromophenylacetic acid 98 (45 mg, 0.21 mmol, 1 equiv.), iPr₂NEt (55 µL, 0.32 mmol, 1.5 equiv.) and pivaloyl chloride (39 µL, 0.32 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 20 mins. DHPB (3 mg, 0.0143 mmol, 5 mol%), enone 127 (74 mg, 0.21 mmol, 1 equiv.) and iPr₂NEt (91 µL, 0.53 mmol, 2.5 equiv.) were then added and the resulting mixture was stirred at rt for 1 h. MeOH (5 mL) was added and stirring was continued for a further 16 h. The reaction was quenched by addition of aq. 1 M HCl (5 mL), poured into water and extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and concentrated in vacuo to give an 80:20 mixture (anti:syn) of 132. The crude mixture was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, CH₂Cl₂ : EtOAc (97 : 3 5CV, 97 : 3 to 90 : 10 10CV, 90 : 10 5CV)] to afford an 80:20 mixture of anti and syn diastereoisomers as a colourless solid (89 mg, 70% yield); mp 110-117 °C; νmax (thin film, cm⁻¹) 2972 (C-H), 1757 (C=O), 1728 (C=O);

Data for major diastereomer anti 132: [H NMR (500 MHz) δH: 0.86 (3H, m, CH₃), 1.23-1.30 (6H, m, 3 × CH₂), 1.33-1.39 (4H, m, 2 × CH₂), 1.96 (2H, m, ArN(1)CH₂CH₂), 3.14 (1H, dd, J 18.4, 3.8, C(4)H), 3.32 (1H, dd, J 18.4, 9.8, C(4)H), 3.70 (3H, s, CO₂CH₃), 3.85 (1H, d, J 10.9, C(2)H), 3.95 (1H, app. td, J 10.3, 3.8, C(3)H), 4.36 (2H, t, J 7.2, ArN(1)CH₂), 7.00 (2H, d, J 8.4, (C(3)ArC(2,6)H)), 7.05 (2H, d, J 8.4, (C(3)ArC(3,5)H)), 7.28 (2H, d, J 8.5, (C(2)ArC(2,6)H)), 7.61 (2H, d, J 8.5, (C(2)ArC(3,5)H)), 7.65 (1H, s, N(1)CH); 13C[1H] NMR (126 MHz) δC: 14.2 (CH₃), 22.7 (CH₂), 26.6 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 30.5 (ArN(1)CH₂CH₂), 31.9 (CH₂), 41.2 (C(4)H₂), 43.2 (C(3)), 50.6 (ArN(1)CH₂), 52.7 (OCH₃), 56.4 (C(2)), 118.6 (q, J 288, CF₃), 119.5 (N(3)C=C), 121.9 (N(1)CH), 126.0 (C(2)ArC(3,5)), 128.6 (C(3)ArC(3,5)), 130.2 (C(3)ArC(2,6)), 131.8 (C(2)ArC(2,6)), 132.5 (C(3)ArC(1)), 135.2 (C(2)ArC(1)), 139.0 (C(2)ArC(4)), 147.3 (C(3)ArC(4)), 172.8 (C(1)), 188.9 (q, J 35.1, C(5)); 19F [1H] NMR (470 MHz) δF: −79.5 (CF₃).

Data for minor diastereomer syn 132: [H NMR (500 MHz) (selected) δH: 2.71 (1H, dd, J 18.3, 3.5, C(4)H), 2.99 (1H, dd, J 18.3, 10.3, C(4)H), 3.41 (3H, s, CO₂CH₃), 3.89 (1H, d, J 11.4, C(2)H),...
4.00 (1H, app. td, J 10.5, 3.5, C(3)H), 7.33 (2H, m, C(3)ArC(2',6')H), 7.34 (2H, m, C(2)ArC(2,6)H), 7.72 (1H, s, N(1)CH), 7.78 (2H, m, C(2)ArC(3,5)H); $^{13}$C{¹H} NMR (126 MHz) δc: 40.3 (C(4)H$_2$), 43.0 (C(3)H), 52.3 (OCH$_3$), 56.7 (C(2)H), 119.6 (N(1)C=C), 126.2 (C(2)ArC(3,5)H), 129.9 (C(3)ArC(3',5')H), 130.3 (C(3)ArC(2',6')), 134.9 (C(2)ArC(1), 171.9 (C(1)); $^{19}$F {¹H} NMR (470 MHz) δF: −79.7 (CF$_3$); HRMS (ESI$^+$) C$_{29}$H$_{34}$F$_3$N$_3$O [M+H]$^+$, found 608.1714, requires 608.1730 (−2.67 ppm).

(±)-3-thiophene dihydropyranone terminated surface 135

Following General Procedure D, 3-thiophenylacetic acid 134 (28 mg, 0.2 mmol), iPr$_2$NEt (51 μL, 0.30 mmol), pivaloyl chloride (36.0 μL, 0.29 mmol) in CH$_2$Cl$_2$ (3 mL), DHPB 60 (3.0 mg, 0.001 mmol, 5 mol%), enone terminated wafer 128 and iPr$_2$NEt (85 μL, 0.5 mmol) were stirred for 24 h at rt affording lactone terminated surface 135.

(±)-4-FC$_6$H$_4$ dihydropyranone terminated surface 136

Following General Procedure D, 4-fluorophenylacetic acid (30 mg, 0.2 mmol), iPr$_2$NEt (51 μL, 0.30 mmol), pivaloyl chloride (33.0 μL, 0.27 mmol) in CH$_2$Cl$_2$ (3 mL), DHPB 60 (3.0 mg, 0.001 mmol, 5 mol%), enone terminated wafer 128 and iPr$_2$NEt (85 μL, 0.5 mmol) were stirred for 24 h at rt affording lactone terminated surface 136.
(±)-4-BrC₆H₄ dihydropyranone terminated surface 137

Following General Procedure D, 4-bromophenylacetic acid 98 (28 mg, 0.2 mmol), iPr₂NEt (51 μL, 0.30 mmol), pivaloyl chloride (36.0 μL, 0.29 mmol) in CH₂Cl₂ (3 mL), DHPB 60 (3.0 mg, 0.001 mmol, 5 mol%), enone terminated wafer 128 and iPr₂NEt (85 μL, 0.5 mmol) were stirred for 24 h at rt affording lactone terminated surface 137.

(±)-4-NMe₂C₆H₄ dihydropyranone terminated surface 138

Following General Procedure D, 4-(dimethylamino)phenylacetic acid (35 mg, 0.196 mmol), iPr₂NEt (51 μL, 0.30 mmol), pivaloyl chloride (36.0 μL, 0.29 mmol) in CH₂Cl₂ (3 mL), DHPB 60 (3.0 mg, 0.001 mmol, 5 mol%), enone terminated wafer 128 and iPr₂NEt (85 μL, 0.5 mmol) were stirred for 24 h at rt affording lactone terminated surface 138.

(±)-4-CF₃C₆H₄ dihydropyranone terminated surface 139

Following General Procedure D, 4-(Trifluoromethyl)phenylacetic acid (40 mg, 0.196 mmol), iPr₂NEt (51 μL, 0.30 mmol), pivaloyl chloride (36.0 μL, 0.29 mmol) in CH₂Cl₂ (3 mL), DHPB 60 (3.0 mg, 0.001 mmol, 5 mol%), enone terminated wafer 128 and iPr₂NEt (85 μL, 0.5 mmol) were stirred for 24 h at rt affording lactone terminated surface 139.
6.4 Experimental for Chapter 3

General Procedure E: Generation of carboxylic acids from phenylglycines

To a round bottomed flask containing aq. 2 M NaOH (50 mL) at 0 °C was added the appropriate amino-2-phenylacetic acid (1 equiv.) with stirring. Acid chloride 170 (1.1 equiv.) was added dropwise over 10 mins. The solution was allowed to warm to rt and stir for 2 h. The reaction mixture was acidified with 2 M HCl (50 mL) and adjusted to between pH 3-4. The mixture was filtered and washed with ice cold water (3 × 50 mL) to afford the pure product as a colourless solid.

General Procedure F: Generation of methyl esters from carboxylic acids

To a round bottomed flask containing MeOH (15 mL) was added the appropriate phenylacetic acid (1 equiv.) with stirring. H₂SO₄ (2 mL) was added and the reaction was stirred at reflux for 16 h. The reaction was cooled to rt and concentrated in vacuo then dissolved in CH₂Cl₂ and washed with sat. aq. NaHCO₃ and brine to afford the crude product. Recrystallisation from EtOH/H₂O afforded the pure ester.

General Procedure G: Generation of hydrazines from methyl esters

To a round bottomed flask containing MeOH (0.4 M) the appropriate methyl ester (1 equiv.) was added hydrazine monohydrate (20 equiv.) and the reaction as stirred at reflux for 16 h. The reaction was cooled to rt and concentrated in vacuo to afford the crude hydrazine which was recrystallised from EtOH to afford the pure product.

General Procedure H: Amino acid coupling of hydrazines with carboxylic acids

To a round bottomed flask containing DMF:CH₂Cl₂ (10:10 mL) was added the appropriate acid (1.5 equiv.), EDCI (1.8 equiv.), HOBt (1.8 equiv.) and the resulting yellow solution was stirred at rt for 30 mins. To the reaction mixture was added hydrazide (1 equiv.) and N-methyl morpholine (2.5 equiv.) and the solution was stirred for 16 h. The resulting mixture was quenched with H₂O (30 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL), washed with NaHCO₃ (30 mL), citric acid (30 mL) and H₂O (30 mL) and the combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to afford the crude product. Recrystallisation from EtOH afforded the pure product as a colourless solid.

General Procedure I: Deposition of cysteine on Au coated SiO₂ and Au coated AFM tips

The tip side of an AFM cantilever was coated with ~5 nm of Ti as an adhesion promotor followed by ~50 nm of Au using a thermal evaporator which afforded Au coated AFM tips. The Au coated AFM tip or wafer was rinsed with EtOH and immersed in a 2 mM solution of the appropriate
cysteine in H$_2$O. After 24 h the AFM tip or wafer was removed from the solution and rinsed with H$_2$O, EtOH and dried under a stream of Ar to afford the appropriate cysteine terminated surface.

**General Procedure J: Deposition of chiral benzamide on Au coated SiO$_2$ and Au coated AFM tips**

The Au coated AFM tip or wafer was rinsed with EtOH and immersed in a 0.5 mM solution of the appropriate benzamide in EtOH. After 24 h the AFM tip or wafer was removed from the solution and rinsed with H$_2$O, EtOH and dried under a stream of Ar to afford the appropriate benzamide terminated surface.

**General procedure K: Michael addition lactonisation using HyperBTM 61**

To a round-bottomed flask containing a stirrer bar and a solution of acid (1 equiv.) in CH$_2$Cl$_2$ (3 mL) was added iPr$_2$NEt (1.5 equiv) and pivaloyl chloride (1.5 equiv.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 20 min. The solution was cooled to −78 °C and the appropriate enantiomer of HyperBTM 61 (5 mol %) was added. A pre-cooled (−78 °C) solution of enone 127 in CH$_2$Cl$_2$ (2 mL) added followed by iPr$_2$NEt (2.5 equiv). The reaction was stirred at −78 °C for 16 h and quenched with aq. 1 M HCl. The aqueous phase was extracted using CH$_2$Cl$_2$ (2 × 10 mL) and the combined organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (pet. ether: Et$_2$O) to afford the pure product.

**Bromine terminated SAM on Si/SiO$_2$ using 11-bromoundecyltrimethoxysilane (solution deposition) 115**

![Bromine terminated SAM](image)

Freshly cleaned silicon wafers (as per the cleaning procedure outlined in chapter 2) were placed in an oven at 130 °C for 30 mins prior to being immersed in a freshly prepared solution of 11-bromoundecyltrimethoxysilane 165 (64 µL, 10 mmol, 1 equiv.) and NEt$_3$ (42 µL, 15 mmol, 1.5 equiv.) in toluene (20 mL) for 24 h. Once deposition was complete the wafer was removed and rinsed with copious amounts of toluene, EtOH and H$_2$O and dried under a stream of Ar.

**3,5-Dimethylbenzoyl chloride 170**
To a round bottomed flask containing thionyl chloride (20.0 mL, 266.0 mmol, 8 equiv.) was added 3,5-dimethylbenzoic acid 171 (5.0 g, 33.3 mmol, 1 equiv.) with stirring and the mixture was heated at reflux for 16 h. Excess thionyl chloride was removed by azeotrope with toluene (2 × 10 mL) under reduced pressure. The crude product was purified by Kugelrohr distillation to afford the pure product as a colourless oil (4.75 g, 85% yield); bp 140 °C, (5 mbar) {Lit.\[296\] bp 85-86 °C, (1.2 mbar)}; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\_H: 2.37 (6H, s, 2 \times \text{ArC}_H^3), 7.31 (1H, s, \text{ArC}(4)H), 7.73 (2H, s, \text{ArC}(2,6)H)\}. All data in accordance with the literature.\[296\]

(±)-2-[(3,5-Dimethylphenyl)formamido]-2-phenylacetic acid 172

Following general procedure E, (±)-2-amino-2-phenylacetic acid 169 (3.0 g, 19.9 mmol, 1 equiv.), acid chloride 170 (3.66 g, 21.8 mmol, 1.1 equiv.) afforded the pure product as a colourless solid after recrystallisation (2.16 g, 83% yield); mp 176-179 °C; \(v_{\text{max}}\) (thin film, cm\(^{-1}\)) 3307 (N-H), 2912 (C-H), 1705 (N-C=O), 1635 (C=O); \(^1\)H NMR (400 MHz, d\(_6\)-DMSO) \(\delta\_H: 2.31 (6H, s, 2 \times \text{ArC}_H^3), 5.58 (1H, d, \text{J}=7.5, \text{C}(2)H), 7.16 (1H, s, \text{ArC}(4)H), 7.29-7.36 (1H, m, PhC(4)H), 7.38 (2H, s, 2 \times \text{ArC}(2,6)H), 7.49 (2H, d, \text{J}=7.3, \text{PhC}(2,6)H), 7.53 (2H, s, \text{ArC}(2,6)H), 8.91 (1H, d, \text{J}=7.5, \text{NH}), 12.8 (1H, bs, COOH); \(^{13}\)C\{\(^1\)H\} NMR (100 MHz, d\(_6\)-DMSO) \(\delta\_C: 20.8 (2 \times \text{ArC}_H^3), 56.8 (\text{C}(2)H), 125.4 (\text{ArC}(2,6)H), 127.9 (\text{PhC}(2,6)H), 128.1 (\text{PhC}(4)H), 128.4 (\text{PhC}(3,5)H), 132.7 (\text{ArC}(4)H), 133.7(\text{ArC}(3,5)), 137.2 (\text{PhC}(1)), 137.3 (\text{ArC}(1)), 166.4 (\text{NC}=\text{O}), 171.9 (\text{C}=\text{O}); \text{HRMS (NSI)} \text{ C}_{17}\text{H}_{17}\text{NO}_3 [\text{M−H}]^−, \text{found 282.1136, requires 282.1136 (+0.0 ppm).}

(2S)-2-[(3,5-dimethylphenyl)formamido]-2-phenylacetic acid 172

Following general procedure E, (S)-2-amino-2-phenylacetic acid 169 (1.40 g, 9.22 mmol, 1 equiv.), acid chloride 170 (1.7 g, 10.14 mmol, 1.1 equiv.) afforded the pure product as a colourless solid after recrystallisation (2.11 g, 81% yield) \([\alpha]_{D}^{20} = −74.9 (c 1.0 \text{ MeOH}), \text{mp} 170-172 °C\}; All spectroscopic data were identical to those of (±)-172.

(2R)-2-[(3,5-dimethylphenyl)formamido]-2-phenylacetic acid 172
Following general procedure E, (R)-2-amino-2-phenylacetic acid 169 (1.40 g, 9.22 mmol, 1 equiv.) and acid chloride 170 (1.7 g, 10.14 mmol, 1.1 equiv.) afforded the pure product as a colourless solid after recrystallisation (2.23 g, 82% yield); \([\alpha]_D^{20} = +65.6 (c 1.0\,\text{MeOH}),\) mp 176-178 °C; All spectroscopic data were identical to those of (±)-172.

2-(undec-10-en-1-yl)isoindoline-1,3-dione 175

To a round bottomed flask containing 11-bromo-1-undecene 174 (10.9 g, 47 mmol, 1 equiv.) in DMF (100 mL) was added potassium phthalimide 173 (8.70 g, 47 mmol, 1 equiv.) under Ar. The reaction mixture was stirred for 16 h, poured into a 1:1 mix of H$_2$O:brine and extracted with Et$_2$O (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated \textit{in vacuo} to afford the pure product as a colourless solid (8.09 g, 75 % yield); mp 37-40 °C {Lit.$^{[297]}$ 42-45 °C}; $^1$H NMR (400 MHz, CDCl$_3$) 1.26-1.36 (12H, bs, 6 × CH$_2$), 1.66 (2H, m, CH$_2$), 2.02 (2H, tdd, J 6.6, 5.4, 1.4, CH$_2$), 3.67 (2H, t, J 7.6, NCH$_2$), 4.93 (1H, dq, J 10.2, 1.2, =CH$_A$H$_B$), 4.98 (1H, dq, J 17.0, 1.8, =CH$_A$H$_B$), 5.81 (1H, ddt, J 17.0, 10.2, 6.7, =CH), 7.70 (2H, dd, J 5.5, 3.0, ArH), 7.84 (2H, dd, J 5.5, 3.0, ArH). All data in accordance with the literature.$^{[298]}$

Undec-10-en-1-amine 168

To a round bottomed flask containing EtOH (30 mL) was added phthalimide 175 (2.42 g, 6.44 mmol, 1 equiv.) with stirring. Hydrazine monohydrate (0.345 mL, 7.1 mmol, 1.1 equiv.) was added and the suspension was heated at reflux for 16 h. The reaction was cooled to rt, quenched with 2 M HCl (30 mL) and the aqueous layer washed with Et$_2$O (3 × 30 mL). The organic layers were discarded and the aqueous layer was basified to pH 8 with aq. 2 M NaOH. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated \textit{in vacuo} to afford the crude product as a colourless oil which was used without further purification or if desired purified using flash chromatography on silica gel (89:10:1 CHCl$_3$:MeOH:NH$_4$OH) (801 mg, 75% yield); $^1$H NMR (400 MHz, CDCl$_3$) 1.25-1.33 (12H, bs, 6 × CH$_2$), 1.36 (2H, m, CH$_2$), 1.44 (4H, m, 2 × CH$_2$), 2.03 (2H, m, CH$_2$), 2.67
(R)-3,5-Dimethyl-N-(2-oxo-1-phenyl-2-(undec-10-en-1-ylamino)ethyl)benzamidine 176

To a round bottomed flask containing CH$_2$Cl$_2$ (40 mL) was added EDCI (2.28 g, 11.9 mmol, 1.8 equiv.), HOBt (1.61 g, 11.9 mmol, 1.8 equiv.) and acid (S)-172 (2.81 g, 9.93 mmol, 1.5 equiv.) and the resulting mixture was stirred for 30 mins. Amine 168 (1.12 g, 6.62 mmol, 1 equiv.), was added to the bright yellow reaction mixture as a solution in CH$_2$Cl$_2$ (10 mL). N-Methyl morpholine (1.82 mL, 16.5 mmol, 2.5 equiv.) was added and the reaction was stirred for 16 h. The reaction was quenched with H$_2$O (40 mL), and the aqueous phase was extracted with EtOAc (3 × 50 mL) and washing of the organic phase with sat. aq. NaHCO$_3$ (40 mL), citric acid (40 mL, 10 %) and brine afforded the crude product. Flash chromatography on silica gel (8:2 Hex:EtOAc) afforded the pure product as an off white solid (3.27 g, 66% yield); [$\alpha$]$_D^{20}$ = −1.1 (c 1.0 MeOH), mp 108-111 °C; $\nu$$_{max}$ (thin film, cm$^{-1}$) 3282 (N-H), 2922 (C-H), 2852 (C-H), 1629 (NC=O), 1539 (C=O); $^1$H NMR (400 MHz, CDCl$_3$) 1.21-1.29 (10H, bs, 5 × C$_2$H$_2$), 1.37 (2H, m, C$_2$H$_2$), 1.44 (2H, m, C$_2$H$_2$), 2.02 (2H, ddt, $J$ 8.1, 6.7, 1.4, C$_2$H$_2$), 2.34 (6H, s, 2 × ArC$_3$H$_3$), 3.23 (2H, tdd, $J$ 7.1, 5.8, 1.2, NCH$_2$), 4.93 (1H, dd, $J$ 10.2, 2.3, CH$_3$H$^B$), 4.99 (1H, dq, $J$ 17.0, 1.8, CH$_3$H$^B$), 5.67 (1H, d, J 6.6, CH), 5.80 (1H, ddt, $J$ 17.0, 10.1, 6.7, =CH), 6.09 (1H, t, $J$ 5.8, NH), 7.13 (1H, s, ArC(4)H), 7.28-7.36 (2H, m, PhC(2,6)H), 7.43-7.38 (3H, m, Ph(3,5)H and PhC(4)H), 7.63 (1H, d, J 6.6, ArH); $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) 21.4 (ArCH$_3$), 26.8 (CH$_2$), 29.0 (CH$_2$), 29.2 (CH$_2$), 29.3 (CH$_2$), 29.4 (CH$_2$), 29.5 (CH$_2$), 29.6 (CH$_2$), 33.94 (CH$_2$), 40.1 (NCH$_2$), 57.5 (CH), 114.2 (=CHH), 125.05 (ArC(3,5)H), 127.4 (PhC(2,6)H), 128.4 (ArC(4)H), 129.1 (PhC(3,5)H), 133.5 (ArC(4)H), 133.8 (PhC(1)H), 138.3 (ArC(2,6)H), 138.6 (PhC(1)), 139.3 (=CH), 167.1 (C=O), 170.1 (C=O); HRMS (NSI$^+$) C$_{28}$H$_{39}$N$_2$O$_2$ [M+H]$^+$, found 435.3006, requires 435.2993 (+3.0 ppm).

(R)-S-(11-(2-(3,5-Dimethylbenzamido)-2-phenylacetamido)undecyl) ethanethioate 177

To a round bottomed flask containing carbon tetrachloride (30 mL) was added alkene 176 (1.2 g, 2.76 mmol, 1 equiv.) with stirring under Ar. Benzyol peroxide, Luperox$^\circledR$ A75 (80 mg, 0.276
mmol, 10 mol%) and thioacetic acid (1.0 mL, 13.8 mmol, 5 equiv.) were added and irradiated at 365 nm in a photochemical reactor (made in house) for 16 h under Ar. The reaction was quenched with cyclohexene (1 mL) and the solvent removed in vacuo to afford the crude product. The residue was dissolved in CH$_2$Cl$_2$ andaq. 1 M NaOH was used to adjust to pH 7. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 30 mL) and the combined organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated in vacuo to afford the crude product. The crude residue was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min$^{-1}$, hexane : EtOAc (95 : 5 2CV, 95 : 5 to 70 : 30 10 CV, 60 : 40 3 CV)] to give the title compound as a colorless solid (370 mg, 10% yield); [α]$_D^{20}$ = +0.4 (c 1.0 CHCl$_3$); mp 88-91 °C; $\nu_{\text{max}}$ (thin film, cm$^{-1}$) 3323 (N-H), 2914 (C-H), 2848 (C-H), 1687 (NC=O), 1629 (C=O); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$: 1.20-1.30 (12H, bs, 6C-H$_2$), 1.34 (2H, m, C-H$_2$), 1.43 (2H, m, C-H$_2$), 2.32 (3H, s, C=OCH$_3$), 2.34 (6H, s, ArC-H$_3$), 2.86 (2H, t, J 7.4, SCH$_2$), 3.25 (2H, td, J 7.1, 5.9, NCH$_2$), 5.57 (1H, d, J 6.8, C-H), 5.71 (1H, t, J 5.9, NH), 7.12 (1H, s, ArC(4)H), 7.31 (1H, dd, Ph(4)H), 7.34 (2H, t, Ph(3,5)H), 7.43 (2H, s, Ar(2,6)H), 7.46 (2H, d, J 6.3, Ph(2,6)H), 7.36 (1H, d, J 6.8, N(1)H); $^{13}$C{$^1$H} NMR (126 MHz) δ$_C$: 21.4 (2× ArC-H$_3$), 26.8 (CH$_2$), 28.9 (C-H$_2$), 29.1 (2× CH$_2$), 29.2 (SCH$_2$), 29.3 (2× CH$_2$), 29.4 (2× CH$_2$), 29.5 (NCH$_2$CH$_2$), 29.6 (CH$_2$), 30.8 (C=OCH$_3$), 40.1 (NCH$_2$), 57.5 (C(2)H), 125.1 (ArC(2,6)H), 127.5 (PhC(2,6)H), 128.4 (PhC(4)H), 129.1 (PhC(3,5)H), 133.5 (ArC(4)H), 133.9 (ArC(1)), 138.4 (ArC(2,6)H), 138.6 (PhC(1)), 167.1 (O=CN(1)H), 170.1 (O=CN(2)H), 196.3 (SC=O); HRMS (NSI$^+$) C$_{30}$H$_{43}$N$_2$O$_3$ [M+H]$^+$, found 511.2989, requires 511.2916 (+1.4 ppm).

(±)-Methyl 2-(3,5-dimethylbenzamido)-2-phenylacetate 182

![Diagram](image)

Following general procedure F, (±)-2-(3,5-dimethylphenyl)formamido]-2-phenylacetic acid 172 (500 mg, 1.76 mmol, 1 equiv.) in MeOH and H$_2$SO$_4$ afforded pure methyl ester as a colourless solid after recrystallisation (346 mg, 62% yield), mp 128-129 °C; $\nu_{\text{max}}$ (thin film, cm$^{-1}$) 3454 (C-H), 1743 (C=O), 1635 (C=O), 1602 (N-C=O), 1525 (N-C=O); $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$: 2.35 (6H, s, 2ArCH$_3$), 3.78 (1H, s, OCH$_3$), 5.78 (1H, d, J 7.1, C(2)H), 7.09 (1H, d, J 7.1, NH), 7.14 (1H, s, ArC(4)H), 7.32-7.40 (3H, m, PhC(3,5)H and PhC(4)H), 7.42 (2H, s, ArC(2,6)H), 7.45 (2H, d, J 7.3, PhC(2,6)H); $^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$) δ$_C$: 21.4 (2× ArCH$_3$), 53.1 (OCH$_3$), 58.9 (C(2)H), 125.0 (ArC(2,6)H), 127.5 (PhC(2,6)H), 128.7 (PhC(4)H), 129.2 (PhC(3,5)H), 133.6 (ArC(4)H), 133.7 (ArC(3,5)), 136.8 (PhC(1)), 138.5 (ArC(1)), 167.0
(NC=O), 171.7 (C=O); HRMS (NSI\(^+\)) \(C_{18}H_{20}O_3N\) [M+H]\(^+\), found 298.1438, requires 298.1455 (+2.5 ppm).

**Methyl (R)-2-(3,5-dimethylbenzamido)-2-phenylacetate 182**

Following general procedure F, (2R)-2-[(3,5-dimethylphenyl)formamido]-2-phenylacetic acid 172 (500 mg, 1.76 mmol, 1 equiv.) in MeOH and \(H_2SO_4\) afforded pure methyl ester as a colourless solid after recrystallisation (221 mg, 42 % yield); \([\alpha]^{20}_D = +72.0\ (c\ 1.0\ MeOH), mp\ 148-150 \degree C. All spectroscopic data were identical to those of (±)-182.

**Methyl (S)-2-(3,5-dimethylbenzamido)-2-phenylacetate 182**

Following general procedure F, (2S)-2-[(3,5-dimethylphenyl)formamido]-2-phenylacetic acid 172 (450 mg, 1.51 mmol, 1 equiv.) in MeOH and \(H_2SO_4\) afforded pure methyl ester as a colourless solid after recrystallisation (310 mg, 55% yield); \([\alpha]^{20}_D = -65.3\ (c\ 1.0\ MeOH), mp\ 150-152 \degree C. All spectroscopic data were identical to those of (±)-182.

(±)-N-(2-hydrazinyl-2-oxo-1-phenylethyl)-3,5-dimethylbenzamide 180

Following general procedure G, (±)-methyl-2-(3,5-dimethylbenzamido)-2-phenylacetate 182 (243 mg, 0.817 mmol, 1 equiv.) and \(N_2H_4\cdot H_2O\) (0.8 mL, 16.3 mmol, 20 equiv.) in MeOH afforded pure hydrazine as a colourless solid after recrystallisation (134 mg, 55% yield); mp 186-188 \degree C; \(v_{max}\) (thin film, cm\(^{-1}\)) 3340 (N-H), 1635 (C=O), 1600 (C=O), 1510 (N-C=O); \(^1\text{H NMR}\) (700 MHz, \(d_6\)-DMSO) \(\delta_H\): 2.31 (6H, s, 2 × C\(_2\)H\(_3\)), 4.31 (2H, d, J 3.7, NH\(_2\)), 5.66 (1H, d, J 8.1, C(1)H), 7.16 (1H, s, ArC(4)H), 7.28 (1H, t, J 7.3, ArC(2)H), 7.34 (1H, t, J 7.5, ArC(6)H), 7.48-7.55 (3H, m, PhC(2,6)H) and PhC(4)H), 8.67 (1H, d, J 8.1, NH), 9.50 (1H, t, J 3.7, NH\(_2\)), \(\delta_C\) (13C\(^{13}\)H) NMR (126 MHz, \(d_6\)-DMSO) \(\delta_C\): 20.8 (2 × ArCH\(_3\)), 55.4 (CH), 125.4 (ArC(2,6)H), 127.4 (PhC(2,6)H), 127.5 (PhC(4)H), 128.2 (PhC(3,5)H), 132.6 (ArC(4)H), 133.8 (ArC(3,5)), 137.2 (PhC(1)), 138.7
(ArC(1)), 166.2 (NC=O), 169.2 (NH$_2$NHC=O); **HRMS (NSI)** C$_{17}$H$_9$O$_2$N$_3$ [M+H]$^+$, found 298.1552, requires 298.1550 (+0.7 ppm).

**(R)-N-(2-Hydrazone-2-oxo-1-phenylethyl)-3,5-dimethylbenzamide 180**

![Chemical structure](image)

Following general procedure G, methyl (R)-2-(3,5-dimethylbenzamido)-2-phenylacetate 182 (221 mg, 0.743 mmol, 1 equiv.) and N$_2$H$_4$·H$_2$O (0.72 mL, 14.9 mmol, 20 equiv.) in MeOH afforded pure hydrazine as a colourless solid after recrystallisation (117 mg, 53% yield); $\left[\alpha\right]^{20}_D = +9.0$ (c 1.0 MeOH), mp 196-198 °C; **Chiral HPLC analysis**: Chiralcel AD-H (10% iPrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm) $t_R$ (1R): 16.0 min, >99% ee. All spectroscopic data were identical to those of (±)-180.

**(S)-N-(2-Hydrazone-2-oxo-1-phenylethyl)-3,5-dimethylbenzamide 180**

![Chemical structure](image)

Following general procedure C, methyl (S)-2-(3,5-dimethylbenzamido)-2-phenylacetate 182 (273 mg, 0.92 mmol, 1 equiv.) and N$_2$H$_4$·H$_2$O (0.9 mL, 18.3 mmol, 20 equiv.) in MeOH afforded pure hydrazine as a colourless solid after recrystallisation (104 mg, 39% yield) $\left[\alpha\right]^{20}_D = -8.8$ (c 0.5 MeOH), mp 198-200 °C; **Chiral HPLC analysis**: Chiralcel AD-H (10% iPrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm) $t_R$ (1S): 26.7 min, >99% ee. All spectroscopic data were identical to those of (±)-180.

11-Mercaptoundecanoic acid 181

![Chemical structure](image)

To a round bottomed flask containing H$_2$O (25 mL) was added 11-bromoundecanoic acid 183 (4.0 g, 15.1 mmol, 1 equiv.) and thiourea (1.51 g, 19.8 mmol, 1.3 equiv.). The mixture was stirred at reflux for 3 h, aq. 2 M NaOH (16 mL, 2 equiv.) was added and the reaction stirred at reflux for one additional hour. The reaction was cooled in an ice bath and aq. 1 M HCl was added until the solution reached pH 2. The aqueous phase was extracted using Et$_2$O (2 × 30 mL) and the combined
organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to
afford the pure product as a colourless solid (3.1 g, 94% yield); mp 40-42 °C {Lit.[299] 43.5-45
°C}; 'H NMR (400 MHz, d₆-DMSO) δH: 1.24 (10H, bs, 5 × CH₂), 1.28–1.37 (4H, m, 2 × CH₂),
1.44–1.57 (2H, m, CH₂), 2.16-2.20 (3H, m, SCH₂ and SH), 2.45 (2H, q, J 7.3, C=OCH₂), 11.97
(1H, s, COOH). All data in accordance with the literature.[299]

(±)-N-(2-(2-(11-mercaptoundecanoyl)hydrazinyl)-2-oxo-1-phenylethyl)-3,5-
dimethylbenzamide 179

Following general procedure H, acid 181 (77 mg, 0.35 mmol, 1.5 equiv.), EDCI (81 mg, 0.42
mmol, 1.8 equiv.), HOBt (57 mg, 0.42 mmol, 1.8 equiv.), (±)-hydrazide 180 (70 mg, 0.24 mmol,
1 equiv.) and N-methyl morpholine (65 µL, 0.59 mmol, 2.5 equiv.) afforded the pure product as
a colourless solid after recrystallisation (15 mg, 13% yield); νmax (thin film, cm⁻¹); 3203 (N
-H), 2922 (C-H), 1640 (C=O), 1600 (C=O); mp 172-174 °C; 'H NMR (400 MHz, d₆-DMSO) δH:
1.24 (12H, bs, 6 × CH₂), 1.32–1.36 (2H, m, SCH₂CH₂), 1.50-1.57 (4H, m, 2 × CH₂), 1.59 (2H, app. q, J
7.0, SCH₂), 2.09 (2H, t, J 7.0, C=OCH₂), 2.31 (6H, s, 2 × ArCH₃), 2.68 (1H, t, J 7.2, SH), 5.81
(1H, d, J 8.6, CH), 7.16 (1H, s, ArC(4)H), 7.31 (1H, d, J 7.0, PhC(4)H), 7.35 (2H, t, J 7.0,
PhC(2,6)H), 7.54 (2H, s, ArC(2,6)H), 7.57 (2H, d, J 7.4, PhC(3,5)H), 8.75 (1H, d, J 8.6, N(1)H),
9.82 (1H, d, J 1.4, N(3)H), 10.30 (1H, d, J 1.4, N(2)H); ¹³C{¹H} NMR (125 MHz, d₆-DMSO) δH:
20.7 (2 × ArCH₃), 25.0 (2CH₂), 28.2 (CH₂), 28.4 (SCH₂CH₂), 28.5 (CH₂), 28.6 (CH₂), 28.7 (CH₂),
28.8 (CH₂), 28.9 (CH₂), 33.1 (C=OCH₂), 55.1 (CH), 125.4 (ArC(2,6)H), 127.6 (PhC(3,5)H and
PhC(4)H), 128.2 (PhC(2,6)H), 132.7 (ArC(4)H), 133.7 (ArC(3,5)), 137.3 (ArC(1)), 138.2
(PhC(1)), 166.7 (N(1)C=O), 169.2 (N(2)C=O), 171.5 (N(3)C=O); HRMS (ESI⁻) C₂₈H₃₉N₃O₃S
[M–H]⁻; found 497.2645, requires 497.2631 (+2.8 ppm).

(S)-N-(2-(2-(11-Mercaptoundecanoyl)hydrazinyl)-2-oxo-1-phenylethyl)-3,5-
dimethylbenzamide 179
Following general procedure \( \text{H} \), acid 181 (115 mg, 0.53 mmol, 1.5 equiv.), EDCI (120 mg, 0.63 mmol, 1.8 equiv.), HOBt (85 mg, 0.63 mmol, 1.8 equiv.), (S)-hydrazide 180 (104 mg, 0.43 mmol, 1 equiv.) and \( N \)-methyl morpholine (96 mL, 1.93 mmol, 2.5 equiv.) afforded the pure product as a colourless solid after recrystallisation (29 mg, 17% yield); \([\alpha]_D^{20} = -5.3 \) (c 0.25 MeOH), mp 173-175 °C; All spectroscopic data were identical to those of (±)-179

\((R)-N-(2-(2-(11\text{-Mercaptoundecanoyl})\text{hydrazinyl})-2\text{-oxo-1-phenylethyl})\text{-3,5-dimethylbenzamide} \) 179

Following general procedure \( \text{H} \), acid 181 (130 mg, 0.59 mmol, 1.5 equiv.), EDCI (136 mg, 0.70 mmol, 1.8 equiv.), HOBt (95 mg, 0.70 mmol, 1.8 equiv.), (R)-hydrazide 180 (117 mg, 0.39 mmol, 1 equiv.) and \( N \)-methyl morpholine (0.11 mL, 98 mmol, 2.5 equiv.) in DMF:CH\(_2\)Cl\(_2\) (10:10 mL) afforded the pure product as a colourless solid after recrystallisation (35 mg, 18% yield); \([\alpha]_D^{20} = +5.8 \) (c 0.25 MeOH), mp 172-176 °C; All spectroscopic data were identical to those of (±)-179.

**Generation of (R), (S) and (±)-cysteine terminated surfaces 184**

Following general procedure \( \text{I} \), the Au coated AFM tip or wafer was rinsed with EtOH (10 mL) and immersed in a 2 mM solution (2.5 mg, 2 mmol) of the appropriate cysteine H\(_2\)O (10 mL). After 24 h the AFM tip or wafer was removed from the solution and rinsed with H\(_2\)O (10 mL), EtOH (10 mL) and dried under a stream of Ar to afford the appropriate cysteine terminated surface.

**Generation of (R), (S) and (±)-benzamide terminated surfaces 186**
Following general procedure J, the Au coated AFM tip or wafer was rinsed with EtOH (10 mL) and immersed in a 0.5 mM solution (2.5 mg, 0.5 mmol) of the appropriate benzamide ((R), (S) or (±)) in EtOH (10 mL). After 24 h the AFM tip or wafer was removed from the solution and rinsed with H₂O (10 mL), EtOH (10 mL) and dried under a stream of Ar to afford the appropriate benzamide terminated surface.

(±)-4-(4-ethynylphenyl)-3-(4-fluorophenyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 183

Following general procedure K 4-fluorophenylacetic acid 182 (138 mg, 0.892 mmol, 1 equiv.), pivaloyl chloride (165 µL, 1.34 mmol, 1.5 equiv.) and iPr₂NEt (232 µL, 1.34 mmol, 1.5 equiv.) were stirred at 0 °C followed by addition of (±)-HyperBTM-61 (14 mg, 0.045 mmol, 5 mol%) and enone 127 (200 mg, 0.982 mmol, 1 equiv.) and iPr₂NEt (386 µL, 2.23 mmol, 2.5 equiv.) at −78 °C gave crude (±)-188 (85:15 dr). The crude mixture was purified by Biotage® Isolera™ [SNAP Ultra 10 g, 75 mL min⁻¹, pet. ether :Et₂O (100 : 0 3 CV, 100 : 0 to 90 : 0 10 CV] afforded (±)-188 as a colourless oil (155 mg, 48% yield, >95:5 dr); \( \nu_{\text{max}} \) (thin film, cm⁻¹) 3311 (C-H), 1786 (C=O), 1726 (C=C); \(^1\)H NMR (500 MHz, CDCl₃) δH: 3.09 (1H, s, C≡H), 3.87 (1H, d, \( J = 10.7 \), C(3)H), 3.99 (1H, dd, \( J = 10.7, 2.8 \), C(4)H), 6.11 (1H, d, \( J = 2.8 \), C(5)H), 6.94 (2H, d, \( J = 8.2 \), ArC(3,5)H), 6.98 (4H, m, ArC(2,6)H and ArC(2',6')H), 7.39 (2H, d, \( J = 8.2 \), ArC(3,5)H), \(^{13}\)C\(^{1}H\) NMR (126 MHz, CDCl₃) δC: 44.9 (C(4)H), 52.1 (C(5)H), 78.3 (C≡C), 82.8 (C=C), 110.7 (d, \( J_{C,F} = 3.1 \), C(5)H), 116.1 (d, \( J_{C,F} = 21.8 \), C(3)ArC(3,5)H), 119.5 (q, \( J_{C,F} = 273.0 \), CF₃), 122.2 (C(4)ArC(4)), 127.6 (C(3)ArC(3,5)H), 130.3 (C(4)ArC(2,6)H), 133.0 (C(3)ArC(2,6)H), 139.3 (C(4)ArC(1)), 141.3 (q, \( J_{C,F} = 38.3 \), C(6)), 162.5 (d, \( J_{C,F} = 247.8 \), C(3)ArC(4)), 165.6 (C=O); \(^{19}\)F \(^{1}H\) NMR (470 MHz, CDCl₃) δF: −72.2 (CF₃), −113.3 (ArCF); HRMS (ESI) C₂₀H₁₁O₂F₄ [M-H]⁻ found 359.0703, requires 359.0701 (+0.6 ppm).
(3R,4R)-4-(4-Ethynylphenyl)-3-(4-fluorophenyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 183

Following general procedure K, 4-fluorophenylacetic acid 182 (138 mg, 0.892 mmol, 1 equiv.), pivaloyl chloride (165 µL, 1.34 mmol, 1.5 equiv.) and iPr₂NEt (232 µL, 1.34 mmol, 1.5 equiv.) were stirred at 0 °C followed by addition of (2S,3R)-HyperBTM 61 (14 mg, 0.045 mmol, 5 mol%) and enone 127 (200 mg, 0.982 mmol, 1 equiv.) and iPr₂NEt (386 µL, 2.23 mmol, 2.5 equiv.) at −78 °C affording crude (3R,4R)-188 (85:15 dr). The crude mixture was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 75 mL min⁻¹, pet. ether : Et₂O (100 : 0 to 90 : 0 10 CV] afforded 183 as a colourless oil (155 mg, 48% yield, >95:5 dr); [α]²⁰_D = −105.3 (c 1.0 CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (10% iPrOH:hexane, flow rate 1 mL min⁻¹, 211 nm) tₗ (3S,4S): 19.6 min, (3R,4R): 11.8 min, 87% ee. All spectroscopic data were identical to those of (±)-188.

(3S,4S)-4-(4-Ethynylphenyl)-3-(4-fluorophenyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 183

Following general procedure K, 4-fluorophenylacetic acid (138 mg, 0.892 mmol, 1 equiv.), pivaloyl chloride (165 µL, 1.34 mmol, 1.5 equiv.) and iPr₂NEt (232 µL, 1.34 mmol, 1.5 equiv.) were stirred at 0 °C followed by addition of HyperBTM (2R,3S)-61 (14 mg, 0.045 mmol, 5 mol%) and enone 127 (200 mg, 0.982 mmol, 1 equiv.) and iPr₂NEt (386 µL, 2.23 mmol, 2.5 equiv.) at −78 °C affording crude (3S,4S)-183 (90:10 dr). The crude mixture was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 75 mL min⁻¹, Pet. ether : Et₂O (100 : 0 to 90 : 0 10 CV] afforded 183 as a colourless oil (133 mg, 42% yield, >95:5 dr); [α]²⁰_D = +71.6 (c 1.0 CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (10% iPrOH:hexane, flow rate 1 mL min⁻¹, 211 nm) tₗ (3S,4S): 19.6 min, (3R,4R): 11.8 min, 90% ee. All spectroscopic data were identical to those of (±)-183.
Generation of (3R,4R)-terminated surface from DHP (3R,4R)-183

To a solution of (3R,4R)-188 (10 mg, 0.027 mmol, 1 equiv.) in EtOH (8 mL) was added 1 mL of a 25 mL solution of CuSO₄·5H₂O (7.5 mg, 0.03 mmol, 1 equiv.) and 1 mL of a 25 mL solution of sodium ascorbate (8.9 mg, 0.045 mmol, 1.5 equiv.) with stirring. The azide terminated wafer 112 was immersed in the reaction mixture for 24 h. Upon completion the enone terminated wafer was removed and rinsed with EtOH. The wafer was sonicated in EtOH and H₂O for 5 mins each, and dried under a stream of Ar.

Generation of (3S,4S)-terminated surface from DHP (3S,4S)-183

To a solution of (3S,4S)-188 (10 mg, 0.027 mmol, 1 equiv.) in EtOH (8 mL) was added 1 mL of a 25 mL solution of CuSO₄·5H₂O (7.5 mg, 0.03 mmol, 1 equiv.) and 1 mL of a 25 mL solution of sodium ascorbate (8.9 mg, 0.045 mmol, 1.5 equiv.) with stirring. The azide terminated wafer 112 was immersed in the reaction mixture for 24 h. Upon completion the enone terminated wafer was removed and rinsed with EtOH. The wafer was sonicated in EtOH and H₂O for 5 mins each, and dried under a stream of Ar.

6.5 Experimental for Chapter 4

General procedure L: Generation of thioureas from isothiocyanates

Isothiocyanate (1 equiv.) and the appropriate amino alcohol (1.1 equiv.) were added (neat) to a round bottomed flask and stirred for 10 mins. Toluene (5 mL) was added and the resulting solution was stirred for 20 mins. The reaction mixture was washed with H₂O (5 mL), 0.1 M HCl (5 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were combined, dried (MgSO₄) and concentrated in vacuo to afford the pure product. If necessary the products were purified using flash chromatography.
**General procedure M:** Kinetic resolution of secondary and tertiary alcohols using PS-(2R,3S)-HyperBtm.

To a round bottomed flask containing CHCl₃ (0.17 M) was added the appropriate alcohol with stirring at 0 °C. The appropriate anhydride and tPr₂NEt were subsequently added followed by the addition of PS-(2R,3S)-HyperBtm (5 mol%) and the reaction was allowed to stir (200 rpm) at 0 °C for 24 h. Upon completion the reaction mixture was filtered using a sintered funnel and the filtrate was washed with aq. 1M HCl, sat. aq. NaHCO₃ and brine. The organic layer was dried (MgSO₄) and concentrated in vacuo to afford the crude products which were purified using flash chromatography to afford the enantioenriched alcohol and ester.

**tert-Butyl 6-bromo-2-oxobenzo[d]thiazole-3(2H)-carboxylate 260**

To a round bottomed flask containing anhydrous CH₂Cl₂ (10 mL) was added 6-bromo-2-benzothiazolinone 259 (500 mg, 2.2 mmol, 1 equiv.) under Ar with stirring. Boc₂O (524 mg, 2.4 mmol, 1.1 equiv.), DMAP (44 mg, 0.36 mmol, 15 mol%) and NEt₃ (0.321 mL, 2.4 mmol, 1.1 equiv.) were added and the reaction mixture was stirred for 16 h and then quenched with sat. aq. NH₄Cl (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the pure product as a light purple solid (546 mg, 76% yield); mp 211-213 °C; v_ismax (thin film, cm⁻¹) 2980 (C-H), 1675 (C=O), 1645 (N=C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 1.64 (9H, s, C(CH₃)₃), 7.41 (dd, J 8.9, 2.1, C(5)H), 7.48 (d, J 2.1, C(7)H), 7.77 (d, J 8.9, C(4)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 27.6 (C(CH₃)₃), 29.1 (C(CH₃)₃), 114.1 (C(7)H), 125.1 (C(4)H), 126.3 (C(3a)), 129.4 (C(5)H), 136.3 (C(7a)), 147.7 (C(6)), 170.2 (C=O), 171.4 (BocC=O); HRMS (Cl)⁺ C_{12}H_{13}BrNO₃S [M+H]⁺, found 329.9786, requires 329.9800 (−4.2 ppm).

**2-oxo-2,3-Dihydrobenzo[d]thiazole-6-carbaldehyde 262**

Following a procedure outlined by DeOrazio[300], to a three-necked round bottomed flask containing anhydrous THF (50 mL) was added 6-bromo-2-benzothiazolinone 259 (1.0 g, 4.37
mmol, 1 equiv.) at −78 °C with stirring under Ar. MeMgBr (1.92 mL, 4.8 mmol, 2.5 M, 1.1 equiv.) was added and the mixture was stirred at −78 °C for 45 mins. The reaction mixture was diluted with anhydrous THF (100 mL) while the internal temperature was kept below −50 °C. Once the solution was at −78 °C t-BuLi (4.60 mL, 8.74 mmol, 1.9 M in pentane, 2 equiv.) was added dropwise and stirred for 15 mins. DMF (2.1 mL, 26.2 mmol, 6 equiv.) was added to the yellow reaction mixture and the solution was warmed to rt. The reaction was stirred for 2 h, quenched with H₂O (100 mL) and the aqueous phase was extracted with EtOAc (3 × 70 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product.

Flash chromatography on silica gel (9:1 CH₂Cl₂:MeOH) afforded the pure product as an off white solid (595 mg, 76% yield); mp 229–231 °C {lit.[300] 227–228 °C};

¹H NMR (400 MHz, d₆-DMSO) δH: 7.28 (1H, d, J 8.2, C(4)H), 7.83 (1H, dd, J 8.2, 1.7, C(5)H), 8.16 (1H, d, J 1.7, C(7)H), 9.89 (1H, s, CHO), 12.38 (1H, bs, NH). All data in accordance with the literature.[300]

6-Bromo-2-chlorobenzo[d]thiazole 266

To a round bottomed flask containing DMF (1.21 mL, 15.7 mmol, 1.2 equiv.) was added phosphoryl chloride (12.2 mL, 131 mmol, 10 equiv.) and the mixture was stirred for 15 mins. 6-bromo-2-benzothiazolinone 259 was added and the reaction mixture was heated to 100 °C for 16 h. Upon cooling to rt the reaction mixture was slowly poured into a saturated solution of K₂CO₃ (75 g) in water (200 mL). The resulting mixture was stirred for 1 h at rt, filtered and washed with water to afford the pure product as a brown solid (3.00 g, 93%); mp 80–83 °C; ¹H NMR (400 MHz, CDCl₃) δH: 7.59 (1H, dd, J 8.7, 2.0, ArC(5)H), 7.80 (1H, dd, J 8.7, ArC(4)H), 7.92 (1H, d, J 1.9, ArC(7)H). All data in accordance with the literature.[301]

(S)-2-((6-Bromobenzo[d]thiazol-2-yl)amino)-2-phenylethanol 267

Following the procedure outline by Smith[164], to a round bottomed containing o-dichlorobenzene (2.1 mL, 2.0 M) was added (S)-phenylglycinol 257 (583 mg, 4.25 mmol, 1.05 equiv.), iPr₂NEt (2.9 mL, 28.3 mmol, 2.5 equiv.), 6-bromo-2-chlorobenzothiazole 266 (1.0 g, 4.05 mmol, 1 equiv.) and the resulting pale yellow suspension was heated at reflux (195 °C DrySyn° temperature) for
24 h. After 24 h the orange mixture was allowed to cool to rt. The solvent was removed in vacuo and the resulting crude mixture purified using flash chromatography on silica gel (95:5 CH2Cl2/iPrOH) to afford the crude product which was recrystallised from toluene to afford the pure product as a colourless solid (1.0 g, 71% yield); \( \alpha \) [D]20 = −72.0 (c 0.5 MeOH), mp 157-160 °C (thin film, cm−1); 3224 (C-H), 1541 (C=N), 1060 (CH2OH); 1H NMR (400 MHz, d6-DMSO) δ ppm: 3.67 (2H, m, C(1)H2), 4.99 (1H, app. q, J 6.8, C(2)H), 5.05 (1H, t, J 5.5, CH), 7.22-7.27 (2H, m, Ph(2,6)H), 7.30 (1H, d, J 2.1, ArC(7)H), 7.33 (2H, d, J 7.5, PhC(3,5)H), 7.35 (d, J 8.2, C(4)H), 7.37-7.42 (1H, m, PhC(4)H), 7.89 (1H, dd, J 8.2, 2.1, ArC(5)H), 8.69 (1H, d, J 7.9, N-H); 13C[1H] NMR (126 MHz, d6-DMSO) δ ppm: 60.4 (C(1)H2), 64.9 (C(2)H), 112.2 (ArC(5)H), 119.4 (ArC(7)H), 123.3 (ArC(7a)), 126.9 (PhC(2,6)H), 127.1 (PhC(4)H), 128.2 (PhC(3,5)H), 128.4 (ArC(4)), 132.6 (ArC(3a)), 140.7 (PhC(1)), 151.6 (ArC(6)), 166.5 (C=N); HRMS C15H14N2BrOS+ [M+H]+, found 330.9894, requires 330.9899 (−1.5 ppm).

(S)-7-Bromo-2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole 268

Following the procedure outlined by Smith et al. [164] to a round bottomed flask containing CH2Cl2 (20 mL) was added amino alcohol 267 (500 mg, 1.43 mmol, 1 equiv.), Et3N (0.77 mL, 5.72 mmol, 4 equiv.) and the reaction mixture was stirred at 0 °C. After 10 mins methanesulfonyl chloride (144 µL, 1.87 mmol, 1.3 equiv.) was added with stirring. The ice/water bath was removed and the reaction stirred for 15 mins. The reaction was checked by TLC (CH2Cl2 / Et2O 1:1, UV254 / KMnO4, Rr (S)-267 ~0.3, and a further portion of MsCl (0.1 equiv.) added if (S)-267 remains. Once complete consumption of (S)-267 was observed, iPrOH (0.5 mL) was added and the reaction was heated to reflux for 16 h. The reaction was quenched with aq. 1 M NaOH (20 mL) and the biphasic mixture stirred vigorously for 30 mins. The aqueous layer was extracted with CH2Cl2 (3 x 20 mL) and the combined organic washed with brine (50 mL), dried (MgSO4) and concentrated in vacuo to afford the crude product which was purified by flash chromatography (8:2 hex: EtOAc) to afford the pure product as a white crystalline solid (274 mg, 58% yield); \( \alpha \) [D]20 = +67.5 (c 1.0 CHCl3); mp 122-126 °C; νmax (thin film) 2912 (C-H), 1687 (C=N); 1H NMR (400 MHz, CDCl3) δ ppm: 3.70 (1H, dd, J 8.9, 8.1, C(1)H3H0), 4.26 (1H, dd, J 10.2, 8.9, C(1)H3H0), 5.68 (1H, dd, J 10.2, 8.1, C(2)H), 6.53 (1H, d, 8.3, ArC(5)H), 7.28-7.31 (2H, m, ArC(6)H and ArC(8)H), 7.35-7.38 (4H, m, PhH), 7.42 (1H, d, J 1.9, PhC(4)H); 13C[1H] NMR (126 MHz, CDCl3) δ ppm: 52.9 (C(3)H), 75.9 (C(3)H), 109.9 (ArC(5)H), 113. 6 (ArC(8)H), 126.07 (ArC(6)H), 126.8 (PhC(2,6)H), 128.1 (ArC(8a)), 129.2 (PhC(3,5)H), 129.6 (PhC(4)H), 129.9 (ArC(4a)), 136.5

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(ArC(3)), 142.9 (PhC(1)), 158.4 (ArC(7)), 166.3 (C=N) HRMS C_{15}H_{12}N_{2}BrS^+ [M+H]^+, found 330.9891, requires 330.9899 (−2.4 ppm).

((4-Bromophenyl)ethyl)triisopropylsilane 276

To a round bottomed flask containing 1-bromo-4-iodobenzene 274 (5.0 g, 17.6 mmol, 1 equiv.) in bench grade THF (90 mL, 0.2 M) (degassed for 10 mins) was added Pd(PPh$_3$)$_2$Cl$_2$ (246 mg, 0.352 mmol, 2 mol%) and NEt$_3$ (13 mL, 88 mmol, 5 equiv.) with stirring at rt. CuI (67 mg, 0.352 mmol, 2 mol%) was added to the reaction mixture followed by the dropwise addition of ethynyltriisopropylsilane 275 (4.15 mL, 19.4 mmol, 1.05 equiv.). The reaction was stirred at rt for 16 h followed and subsequently quenched with aq. 0.1 M HCl (100 mL). The aqueous layer was extracted with Et$_2$O (3 × 50 mL) and the combined organic washed with brine, dried (MgSO$_4$) and concentrated in vacuo to afford the crude product which was purified by flash chromatography (95:5 hex: tOAc) to afford the pure product as a brown oil (3.82 g, 68% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ$_H$: 1.13 (21H, s, Si((CH$_2$)$_3$)), 7.33 (2H, d, J 8.6, ArC(3,5)H), 7.43 (2H, d, J 8.7, ArC(2,6)H). All data in accordance with the literature.$^{[302]}

(4-((Triisopropylsilyl)ethyl)phenyl)boronic acid 277

To a round bottomed flask containing bromide 276 (3.81 g, 11.3 mmol, 1 equiv.) in anhydrous THF (60 mL, 0.2 M) at −78 °C was added $n$-BuLi (5.63 mL, 12.4 mmol, 2.2 M in hexanes, 1.1 equiv.) with stirring under Ar. The reaction mixture was stirred for 30 mins at −78 °C then triisopropylborate (2.9 mL, 12.4 mmol, 1.1 equiv.) was added. The reaction was allowed to warm to rt over 16 h then 1 M HCl (35 mL, 3 equiv.) was subsequently added and the reaction was stirred for 2 h. The aqueous layer was extracted with Et$_2$O (3 × 50 mL) and the combined organic layers washed with brine, dried (MgSO$_4$) and concentrated in vacuo to afford the crude product which was purified by flash chromatography (1:1 hex:Et$_2$O) to afford the pure product as a colourless solid (1.36 g, 43% yield); mp 196-198 °C; $^1$H NMR δ$_H$ (400 MHz, CDCl$_3$) 1.16 (21H, s, Si((CH$_2$)$_3$)), 7.59 (2H, d, J 8.3, ArC(3,5)H), 7.43 (2H, d, J 8.3, ArC(2,6)H). All data in accordance with the literature.$^{[302]}

Iodoethynyltrimethylsilane 282
To a round bottomed flask containing trimethylsilyl acetylene 281 (1.0 mL, 14.3 mmol, 1 equiv.) in anhydrous THF (25 mL, 0.5 M) at −78 °C was added nBuLi (6.6 mL, 14.3 mmol, 2.17 M in hexanes, 1 equiv.) with stirring under Ar. The reaction mixture was stirred for 15 mins at −78 °C then iodine (3.6 g, 14.3 mmol, 1 equiv.) was added. The reaction flask was covered in aluminium foil and allowed to warm to rt over 16 h.† The reaction mixture was diluted with CH₂Cl₂ (20 mL), and washed with Na₂S₂O₃ (30 mL) and H₂O (30 mL). The organic phase was washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product which was purified by distillation to afford the pure product as a colourless oil (2.62 g, 82% yield); bp 70-72 °C, (20 mbar) {Lit.303 bp 61-63 °C, 26 mbar}; ¹H NMR (400 MHz, CDCl₃) δH: 0.18 (Si(C(H₃))₃). All data in accordance with the literature.304

4-((Trimethylsilyl)ethynyl)aniline 247

To a round bottomed flask containing THF (115 mL, 0.2 M) was added iodoaniline 246 (5.0 g, 22.8 mmol, 1 equiv.), NEt₃ (15.3 mL, 114 mmol, 5 equiv.), Pd(PPh₃)₂Cl₂ (160 mg, 0.23 mmol, 1 mol %), CuI (88 mg, 0.46 mmol, 2 mol%) was added with stirring and the solution was degassed for 10 mins. Trimethylsilylacetylene (3.55 mL, 25 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred for 16 h.†† The reaction was quenched with 0.1 M HCl and the aqueous phase was extracted with Et₂O (3 × 50 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product which was purified by flash chromatography (9:1 pet ether:Et₂O) to afford the pure product as a brown solid (3.27 g, 76% yield); mp 72-74 °C {Lit.305 93-95 °C}; ¹H NMR (400 MHz, CDCl₃) δH: 0.22 (9H, s, SiC(CH₃)₃), 3.79 (2H, bs, NH₂), 6.57 (2H, d, J 8.5, ArC(2,6)H), 7.27 (2H, d, J 8.5, ArC(3,5)H). All data in accordance with the literature.305

((4-Isothiocyanatophenyl)ethynyl)trimethylsilane 249

† Work up was performed in the dark inside the fume hood.

†† If the reaction conversion was not satisfactory then the crude material was subjected to the same reaction conditions again.
To a solution of 1,1'-thiocarbonyldiimidazole 248 (1.90 g, 10.6 mmol, 1 equiv.) in CHCl₃ (50 mL, 0.2 M) was added amine 247 (2.0 g, 10.6 mmol, 1 equiv.) in one portion and the resulting solution was stirred for 16 h. The mixture was concentrated in vacuo and re-dissolved in CH₂Cl₂ and washed with H₂O (30 mL) and brine (30 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Flash chromatography on silica gel (9:1 pet ether:Et₂O) afforded the pure product as an orange oil (2.25 g, 92% yield); ν_max (thin film, cm⁻¹) 2156 (C≡C), 2021 (N=C=S), 1498 (C=C); ¹H NMR (500 MHz, CDCl₃) δ_H: 0.25 (9H, s, Si(CH₃)₃), 7.14 (2H, d, J 8.8, ArC(3,5)H), 7.43 (2H, d, J 8.8, ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 0.0 (Si(CH₃)₃), 96.7 (C≡C-Si(CH₃)₃), 103.9 (C≡C-Si(CH₃)₃), 122.3 (ArC(4)), 125.8 (ArC(3,5)H), 131.2 (ArC(1)), 133.2 (ArC(2,6)H), 138.8 (NCS); HRMS (CI⁺) C₇H₄BrNOS [M+H]+, found 232.2290, requires 232.2281 (+3.9 ppm).

(R,Z)-2-((4-Methoxybenzylidene)amino)-2-phenylethan-1-ol 341

To a round bottomed flask containing anhydrous CH₂Cl₂ (40 mL) and MgSO₄ (5 g) was added (R)-phenylglycinol 257 (2.5 g, 17.86 mmol, 1 equiv.) with stirring under Ar. 4-Methoxybenzaldehyde (2.67 g, 19.7 mmol, 1.1 equiv.) was added and the reaction was stirred for 16 h at rt. The reaction mixture was filtered and washed with CH₂Cl₂ (30 mL), and the filtrate was dried (MgSO₄) and concentrated in vacuo to afford the crude product which was recrystallised from EtOH to afford the pure product as a colourless solid (3.27 g, 72%); [α]D²⁰ = +97.6 (c 1.0 CHCl₃) [Lit.⁴¹⁰ [α]D²⁰ = +110.7 (c 1.0 CHCl₃)]; mp 78-80 °C, [Lit.⁴¹⁰ 62 °C.]; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.85 (3H, s, OC₃H₃), 3.87–4.00 (2H, m, OCH₂)，4.46 (1H, dd, J 8.3, 4.5, C(2)H)，6.93 (2H, d, J 8.7, ArC(3,5)H)，7.27 (1H, d, J 6.9, PhC(4)H)，7.35 (2H, ddd, J 8.1, 7.1, 0.8, PhC(3,5)H)，7.43 (2H, d, J 7.6, PhC(2,6)H)，7.74 (2H, d, J 8.7, ArC(2,6)H)，8.33 (1H, s, N=CH); All data in accordance with the literature.⁴¹⁰

(R)-2-((4-Methoxybenzyl)amino)-2-phenylethan-1-ol 342
To a round bottomed flask containing CH$_2$Cl$_2$:EtOH (5:5 mL) at 0 °C was added imine 341 (500 mg, 1.96 mmol, 1 equiv.) with stirring. NaBH$_4$ (119 mg, 3.13 mmol, 1.6 equiv.) was added portionwise and the solution was warmed to rt and stirred for 16 h. The reaction mixture was poured into ice water and conc. HCl was added until the pH was ~1. The biphasic mixture was then basified with aq. 5 M NaOH (30 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layers were combined, washed with brine, dried (MgSO$_4$) and concentrated in vacuo to afford the pure product as a pale yellow oil (346 mg, 69% yield); \([\alpha]_D^{20} = -149.2 (c 0.5 \text{ CHCl}_3), v_{\text{max}} (\text{thin film, cm}^{-1}) 3307 (\text{N-H}), 2954 (\text{C-H}), 1508 (\text{C=C}); ^1\text{H NMR} \delta_{\text{H}} (700 \text{ MHz, CDCl}_3) \delta_{\text{H}}: 3.51–3.58 (2\text{H, m, NC}_A\text{H} \text{and OC}_B\text{H}), 3.67–3.72 (2\text{H, m, NC}_A\text{H} \text{and OC}_B\text{H}), 3.79–3.93 (4\text{H, m, C(2)H} \text{and OC}_3\text{H}), 6.86 (2\text{H, d, J 8.0, ArC(3,5)H}), 7.20 (2\text{H, d, J 8.6, ArC(2,6)H}), 7.32 (3\text{H, m, PhC(3,5)H} \text{and PhC(4)H}), 7.38 (2\text{H, d, J 7.1, PhC(2,6)H}); ^13\text{C}\{^1\text{H}\} \text{NMR} \delta_{\text{C}} (176 \text{ MHz, CDCl}_3) \delta_{\text{C}}: 50.7 (\text{OCH}_2), 55.4 (\text{OCH}_3), 63.7 (\text{C(2)H}), 66.8 (\text{C(3,5)H}), 113.9 (\text{ArC(3,5)H}), 127.4 (\text{PhC(3,5)H}), 127.8 (\text{PhC(4)H}), 128.8 (\text{PhC(2,6)H}), 129.5 (\text{ArC(2,6)H}), 132.2 (\text{ArC(1)}), 140.6 (\text{PhC(1)}), 158.8 (\text{ArC(4)}); \text{HRMS} (\text{ESI}^+) \text{C}_{16}\text{H}_{20}\text{NO}_2 [\text{M+H}]^+ \text{, found 258.1484, requires 258.1489 (}\sim 1.9 \text{ ppm).}

(R)-2-((tert-Butyldimethylsilyl)oxy)-N-(4-methoxybenzyl)-1-phenylethan-1-amine 343

To a round bottomed flask containing CH$_2$Cl$_2$ (95 mL, 0.2 M) at 0 °C was added alcohol 342 (4.95 g, 19.3 mmol, 1 equiv.) with stirring under Ar. Imidazole (1.44 g, 21.1 mmol, 1.1 equiv.) and DMAP (1 crystal) were added followed by portionwise addition of tert-butyldimethylsilyl chloride (3.18 g, 21.1 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 1 h and quenched with sat. aq. NaHCO$_3$ (50 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layers were combined, washed with brine, dried (MgSO$_4$) and concentrated in vacuo to afford the pure product as a colourless oil (4.63 g, 65% yield); \([\alpha]_D^{20} = +56.6 (c 1.0 \text{ CHCl}_3), v_{\text{max}} (\text{thin film, cm}^{-1}) 2953 (\text{N-H}), 2854 (\text{C-H}), 1462 (\text{C=C}); ^1\text{H NMR} (700 \text{ MHz, CDCl}_3) \delta_{\text{H}}: 0.04 (6\text{H, s, 2SiCH}_3), 0.88–0.95 (9\text{H, s, SiC(CH}_3)_3), 3.51 (1\text{H, m, OCH}_A), 3.60 (1\text{H, m, NCH}_A), 3.65–3.75 (2\text{H, m, NCH}_B \text{and OCH}_B), 3.80–3.86 (4\text{H, m, C(2)H} \text{and OCH}_3), 6.88 (2\text{H, d, J 8.4, ArC(3,5)H}), 7.19–7.24 (2\text{H, m, ArC(2,6)H}), 7.31 (1\text{H, m, PhC(4)H}), 7.34–7.40 (2\text{H, m, PhC(3,5)H}), 7.43 (2\text{H, d, J 6.8, PhC(2,6)H}); ^13\text{C}\{^1\text{H}\} \text{NMR} (175 \text{ MHz}) \delta_{\text{C}}: -5.29 (2 \times \text{SiCH}_3)
18.4 (SiC(CH$_3$)$_3$), 26.0 (SiC(CH$_3$)$_3$), 50.8 (OCH$_2$), 55.4 (OCH$_3$), 64.1 (C(2)H), 68.5 (NCH$_2$), 113.9 (ArC(3,5)H), 127.5 (PhC(3,5)H), 128.0 (PhC(4)H), 128.5 (PhC(2,6)H), 129.3 (ArC(2,6)H), 133.0 (ArC(1)), 140.9 (PhC(1)), 158.6 (ArC(4)); HRMS (ESI$^+$) C$_{22}$H$_{34}$NO$_2$Si [M+H]$^+$, found 372.2353, requires 372.2361 (−1.3 ppm).

(R)-1-(2-Hydroxy-1-phenylethyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)thiourea 251

Following general procedure L, isothiocyanate 249 (530 mg, 2.3 mmol, 1 equiv.), (R)-phenylglycinol 257 (346 mg, 2.52 mmol, 1.1 equiv.) were reacted to afford the crude product. Flash chromatography on silica gel (hex:CH$_2$Cl$_2$, 100:0→80:20) afforded the pure product as a crunchy orange solid (715 mg, 85% yield); $[\alpha]^2_D = +133.4$ (c 1.0 CHCl$_3$), mp 59-62 $^\circ$C; $\nu_{max}$ (thin film, cm$^{-1}$) 3252 (C-H), 2154 (C≡C), 1506 (C=NH), 1246 (C=S); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H: 0.25 (9H, s, SiC(CH$_3$)$_3$), 3.85–4.07 (2H, m, C(2)H$_2$), 5.68 (1H, bs, OH), 7.01 (1H, d, J 7.8, C(1)H), 7.18 (2H, d, J 8.6, ArC(2,6)H), 7.24 (2H, d, J 8.5, PhC(2,6)H), 7.30 (1H, d, J 7.0, PhC(4)H), 7.35 (2H, d, J 7.7, PhC(3,5)H), 7.48 (2H, d, J 8.8, ArC(3,5)H); $^{13}$C{$^1$H} NMR (126 MHz, CDCl$_3$) $\delta$C: 0.04 (Si(CH$_3$)$_3$), 60.3 (C(1)H), 66.2 (C(2)H), 95.7 (C≡C-Si(CH$_3$)$_3$), 104.0 (C≡C-Si(CH$_3$)$_3$), 124.1 (ArC(2,6)H), 126.8 (PhC(2,6)H), 128.2 (PhC(4)H), 129.1 (PhC(3,5)H), 133.7 (ArC(4)), 136.4 (ArC(1)), 138.1 (PhC(1)), 180.4 (C=S); HRMS (ESI$^+$) C$_{20}$H$_{24}$N$_2$NaOSSi [M+Na]$^+$, found 391.1266, requires 391.1271 (−1.3 ppm).

(R)-1-(2-hydroxy-1-phenylethyl)-1-(4-methoxybenzyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)thiourea 252

Following general procedure L, isothiocyanate 249 (2.95 g, 12.7 mmol, 1 equiv.) and amino alcohol 342 (3.27 g, 13.9 mmol, 1.1 equiv.) were reacted to afford the pure product as a dark orange solid (5.77 g, 94% yield); $[\alpha]^2_D = +63.2$ (c 1.0 CHCl$_3$); mp 76-79 $^\circ$C; $\nu_{max}$ (thin film, cm$^{-1}$) 2963 (C-H), 2154 (C≡C), 1508 (C=N-H), 1244 (C=S); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H: 0.25 (9H, s, Si(CH$_3$)$_3$), 3.77 (2H, m, C(2)H$_2$), 3.82 (3H, s, OCH$_3$), 4.24 (1H, dd, J 11.3, 9.5, NCH$_2$), 4.55 (1H, dd, J 11.3, 9.5, NCH$_2$).
4.35 (1H, dd, J 11.3, 4.3, NCH₃), 4.52 (1H, m, C(1)H), 4.81 (1H, bs, OH), 6.88 (2H, d, J 8.6, C(1)ArC(3,5)H), 7.11 (2H, d, J 8.5, C(1)ArC(2,6)H), 7.26 (3H, m, ArC(2,6)H and PhC(4)H), 7.33–7.43 (6H, m, 4PhH and ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: δ 0.1 (Si(CH₃)₃), 52.2 (OCH₃), 55.5 (OCH₃), 63.5 (C(2)H), 64.3 (NCH₃), 94.2 (SiC=C), 104.9 (SiC=C), 114.3 (C(1)ArC(3,5)H), 114.7 (ArC(4)), 124.3 (ArC(2,6)H), 125.8 (ArC(1)), 128.0 (PhC(3,5)H), 128.2 (PhC(4)H), 129.1 (PhC(2,6)H), 132.3 (C(1)ArC(2,6)H), 136.4 (C(1)ArC(1)), 139.7 (PhC(1)), 159.5 (C(1)ArC(4)), 183.9 (C=S); HRMS (ESI)⁺ C₂₅H₂₉N₂O₂SSi[M+H]⁺, found 489.2013, requires 489.2027 (−0.9 ppm).

(R)-1-(2-Hydroxy-1-phenylethyl)-1-(4-methoxybenzyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)thiourea 253

Following general procedure L, isothiocyanate 249 (887 mg, 3.8 mmol, 1 equiv.) and amine 343 (1.41 g, 3.8 mmol, 1.1 equiv.) were reacted and purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, Hexane : Et₂O (95 : 5 5 CV, 95 : 5 to 75 : 25 10 CV, 75 : 25 3 CV)] to afford the pure product as a dark orange solid (540 mg, 24% yield); [α]₂⁰D = +89.2 (c 1.0 CHCl₃); mp 58-60 °C; νmax (thin film, cm⁻¹) 2953 (C-H), 2154 (C≡N), 1508 (C=C), 1246 (C=S); ¹H NMR (500 MHz, CDCl₃) δ: 0.05 (3H, s, SiCH₃), 0.08 (3H, s, SiCH₃), 0.22 (9H, s, Si(CH₃)₃), 0.85 (9H, s, Si(CH₃)₃), 3.80 (1H, s, OCH₃), 4.17 (1H, dd, J 10.9, 3.7, C(2) H₄H₃), 4.23 (1H, dd, J 10.9, 6.3, C(2) H₄H₃), 4.36 (1H, m, NCH₃), 4.45 (1H, m, NCH₃), 4.71 (1H, m, C(1)H), 6.85 (2H, d, J 8.7, C(1)ArC(3,5)H), 7.09 (2H, d, J 8.5, ArC(3,5)H), 7.27-7.30 (2H, m, C(1)ArC(2,6)H), ¹³C{¹H} NMR (126 MHz) −5.4 (SiCH₃) δ: 0.1 (2 × Si(CH₃)₃), 18.5 (Si(CH₃)₃), 26.0 (Si(CH₃)₃), 51.4 (OCH₃), 55.4 (OCH₃), 63.5 (C(2)H), 64.3 (NCH₃), 93.9 (SiC=C), 105.1 (SiC=C), 114.3 (ArC(3,5)H), 119.8 (ArC(4')), 122.5 (ArC(3,5)H), 124.4 (ArC(2,6)H), 125.8 (ArC(1')), 127.8 (PhC(3,5)H), 128.2 (PhC(4)H), 128.9 (PhC(2,6)H), 129.5 (ArC(2,6)H), 136.9 (ArC(1)), 140.1 (PhC(1)), 159.3 (ArC(4)); 183.8 (C=S); HRMS (ESI)⁺ C₁₃H₁₂N₂O₂SSi₂ [M+H]⁺, found 603.2891, requires 603.2897 (−0.9 ppm).
(R,Z)-3-(4-Methoxybenzyl)-4-phenyl-N-(4-(((trimethylsilyl)ethynyl)phenyl)oxazolidin-2-imine 254 and (R,Z)-3-(4-Methoxybenzyl)-4-phenyl-N-(4-(((trimethylsilyl)ethynyl)phenyl)thiazolidin-2-imine 255

A solution of thiourea 252 (1.0 g, 2.05 mmol, 1 equiv.) in PhMe (20 mL) was purged with O₂ (1 balloon) and Cu(OTf)₂ (74 mg, 0.205 mmol, 10 mol%) was added with stirring. The reaction mixture was heated to reflux for 12 h under an O₂ atmosphere (1 atm) then H₂O (20 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product. Flash chromatography (7:3 Hexane: Et₂O) afforded the pure products as a colourless oils:

**Data for 254**: (418 mg, 45% yield); νmax (thin film) 2954 (C-H), 2150 (C=C), 1660 (C≡N); ¹H NMR (500 MHz, CDCl₃) δH: 0.26 (9H, s, Si(CH₃)₃), 3.67 (1H, d, J 14.7, NCH²H²B), 3.81 (3H, s, OCH₃), 4.11 (1H, dd, J 8.2, 7.2, C(4)H), 4.49 (1H, dd, J 8.3, 7.1, C(5)H¹H²B), 4.55 (1H, t, J 8.3, C(5)H²H²B), 5.07 (1H, d, J 14.7, NCH²H²B), 6.84 (2H, d, J 8.6, ArC(3,5)H), 7.13 (2H, d, J 8.5, PhC(3,5)H), 7.16 (2H, d, J 8.6, ArC(2,6)H), 7.28 (1H, d, J 6.9, PhC(4)H) 7.40 (5H, m, PhC(2,6)H) and ArC(2′,6′)H; ¹³C¹H NMR (126 MHz, CDCl₃) δC: 0.18 (Si(CH₃)₃), 45.6 (NCH₂), 55.3 (OCH₃), 59.5 (C(5)H₂), 72.5 (C(4)H) 92.3 (SiC=C), 106.2 (SiC=C), 113.8 (ArC(3,5)H), 116.2 (ArC(4′)), 123.6 (ArC(3,5)H), 127.4 (PhC(4)H), 128.1 (ArC(1)), 128.90 (ArC(3′,5′)H), 129.23 (PhC(2,6)H), 130.3 (ArC(2,6)H), 132.5 (ArC(2′,6′)H), 137.5 (PhC(1)), 148.2 (ArC(1′)), 153.4 (C≡N), 159.1 (ArC(4)); HRMS (ESI⁺) C₂₈H₃₉N₂O₂Si [M+H]⁺, found 545.2139, requires 455.2077 (+1.4 ppm).

**Data for 255**: (212 mg, 22% yield); νmax (thin film, cm⁻¹) 2955 (C-H), 2150 (C=C), 1581 (C≡N); ¹H NMR (500 MHz, CDCl₃) δH: 0.25 (9H, s, Si(CH₃)₃), 3.03 (1H, dd, J 11.0, 7.0, C(5)H²H²B), 3.40 (1H, dd, J 11.0, 7.4, C(5)H¹H²B), 3.67 (1H, d, J 14.7, NCH²H²B), 4.61 (1H, t, J 7.1, C(4)H), 5.35 (1H, d, J 14.7, NCH²H²B), 6.83 (2H, d, J 8.6, ArC(3,5)H), 6.99 (2H, d, J 8.4, ArC(2′,6′)H), 7.11 (2H, d, J 8.5, ArC(2′,6′)H), 7.29 (2H, d, J 6.8, PhC(2,6)H), 7.38 (1H, d, J 6.9, PhC(4)H), 7.41 (2H, d, J 7.1, PhC(3,5)H), 7.44 (2H, d, J 8.4, ArC(3′,5′)H); ¹³C¹H NMR (126 MHz, CDCl₃) δC: 0.11 (Si(CH₃)₃), 35.2 (C(5)H₂), 47.4 (NCH₂), 64.2 (C(4)H), 92.9 (SiC=C), 105.8...
(Si≡C), 113.8 (ArC(3,5)H), 117.3 (ArC(4)), 122.1 (ArC(2’,6’)H), 127.2 (PhC(2,6)H), 128.6 (PhC(4)H), 128.7 129.0 (ArC(1)), 130.0 (ArC(2,6)H), 132.9 (PhC(3,5)H), 139.2 (ArC(1’)), 152.3 (ArC(1’)), 158.9 (ArC(4)), 159.5 (C=N); HRMS (ESI+) C_{28}H_{30}N_{2}OSSi [M+H]^+, found 471.1913, requires 471.1898 (+3.2 ppm).

(R)-2-((6-Methoxybenzo[d]thiazol-2-yl)amino)-2-phenylethan-1-ol 285

Following a procedure outline by Smith[164] to a round bottomed containing o-dichlorobenzene (5 mL, 2.0 M) was added (R)-phenylglycinol 257 (1.51 g, 11 mmol, 1.05 equiv), iPr$_2$NEt (4.35 mL, 25 mmol, 2.5 equiv.), 2-chloro-6-methoxybenzothiazole 290 (2.0 g, 10 mmol, 1 equiv.) and the resulting pale yellow suspension was heated at reflux (195 °C DrySyn$^\circledR$) until completion as judged by GC conversion (>95%, ca. 48 h). The orange mixture was allowed to cool to rt. H$_2$O (15 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic layers were combined, washed with brine, dried (MgSO$_4$) and concentrated in vacuo. The resulting residue was triturated with hexane to afford the crude product as an off-white solid that was recrystallised from toluene to give the pure product as fluffy colourless crystals (1.43 g, 48% yield), $[\alpha]_D^{20} = -36.5$ (c 1.0 CHCl$_3$); mp 130-133 °C; $v_{\text{max}}$ (thin film, cm$^{-1}$) 1604 (C=C), 1548 (C=N); GC [Agilent DB-5, 40 cm/s (He), inj. temp 250 °C, FID temp 325 °C; temp profile: initial 120 °C (2 min), then ramp to 320 °C (20 °C/min, hold 5 min), total run = 17 min]: $t_R$ iPr$_2$NEt, 1.87 min; o-dichlorobenzene, 3.20 min; (R)-phenylglycinol 257, 5.30 min; 2-chloro-6-methoxybenzothiazole 290, 7.65 min; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.80 (3H, s, OC$_3$H$_3$), 3.98 (2H, m, C(1)H$_2$), 4.88 (1H, dd, J 6.3, 4.0, C(2)H), 5.98 (1H, bs, NH), 6.88 (1H, dd, J 8.8, 2.6, C(5)ArH), 7.07 (1H, d, J 2.6, C(7)ArH), 7.32 (1H, m, PhC(4)H), 7.39 (4H, m, PhC(2,6)H and PhC(3,5)H), 7.43 (1H, d, J 8.8, C(4)ArH); $^{13}$C[$^1$H] NMR (125 MHz, CDCl$_3$) $\delta$: C: 56.0 (OCH$_3$), 62.1 (C(1)H$_2$), 67.5 (C(2)H), 105.4 (ArC(5)H), 113.6 (ArC), 119.6 (ArC), 127.0 (2 × PhCH), 128.4 (PhCH), 129.1 (2 × PhCH), 131.7 (PhC), 138.9 (ArC(a7)), 145.7 (ArC(3a)), 155.5 (ArC(6)), 165.8 ArC=N), HRMS (ESI+) C$_{16}$H$_{17}$N$_2$O$_2$S [M+H]$^+$, found 301.1005, requires 301.1011 (−1.9 ppm).

Following a procedure outlined by Smith et al.,\textsuperscript{[164]} to a round bottomed flask containing anhydrous \( \text{CH}_2\text{Cl}_2 \) (20 mL) was added 285 (500 mg, 1.66 mmol, 1 equiv.), \( \text{Et}_3\text{N} \) (0.9 mL, 6.64 mmol, 4 equiv.) and the reaction mixture was stirred at 0 °C. After 10 mins methanesulfonyl chloride (167 μL, 2.17 mmol, 1.3 equiv.) was added with stirring. The ice/water bath was removed and the reaction stirred for 15 mins. Once complete consumption of \((R)-285\) was observed, \( \text{iPrOH} \) (0.3 mL) was added and the reaction was heated at reflux for 16 h. The reaction was quenched with 1 M \( \text{NaOH} \) (20 mL) and the biphasic mixture stirred vigorously for 30 mins. The aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 20 mL) and the combined organic washed with brine (50 mL), dried (\( \text{MgSO}_4 \)) and concentrated \textit{in vacuo} to afford the crude product which was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min\textsuperscript{-1}, \( \text{CH}_2\text{Cl}_2 : \text{EtOAc} \) (95 : 5 5 CV, 95 : 5 to 80 : 20 10 CV, 80 : 20 3 CV)] to afford the pure product as a colourless solid (374 mg, 80% yield); \([\alpha]_D^{20} = +58.2 \text{ (c 0.5 CHCl}_3\text{)}; \text{ mp 106-108 °C; } \nu_{\text{max}} \text{ (thin film) 1597 (C=C), 1573 (C=N); } ^1\text{H NMR} \) (500 MHz, \( \text{CDCl}_3\)) \( \delta_{\text{H}} \): 3.67 (1H, t, \( J 8.6, \text{C(3)H}^\text{A} \)), 4.25 (1H, dd, \( J 10.1, 8.6, \text{C(3)H}^\text{B} \)), 6.54 (1H, dd, \( J 10.1, 8.6, \text{C(2)H} \)), 6.59 (1H, d, \( J 8.5, \text{C(5)H} \)), 6.74 (1H, dd, \( J 8.6, 2.5, \text{C(6)ArH} \)), 6.93 (1H, d, \( J 2.6, \text{C(8)ArH} \)), 7.29 (1H, m, PhH), 7.38 (4H, m, PhH); \(^{13}\text{C}[^1\text{H}] \text{ NMR} \) (125 MHz, \( \text{CDCl}_3\)) \( \delta_{\text{C}} \): 53.2 (OCH\(_3\)), 56.1 (C(1)H), 75.4 (C(2)H), 108.9 (ArC(5)H), 109.8 (ArC(6)H), 112.3 (ArC(8)H), 126.7 (2 × PhCH), 127.7 (PhCH), 128.6 (PhC(2)), 128.9 (PhCH), 131.5 (ArC), 143.0 (ArC(3a)), 155.2 (ArC(6)), 167.4 (ArC=N); HRMS (ESI\textsuperscript{+}) \( \text{C}_{16}\text{H}_{18}\text{N}_2\text{OS [M+H]}^+ \), found 283.0900, requires 283.0905 (−1.7 ppm).

\textbf{\((R)-7\text{-hydroxy-2-phenyl-2,3-dihydrobenzo[\(d\)]imidazo[2,1-\text{i}]thiazol-1-ium bromide 292\)}}

![Chemical structure](image)

To a solution of \((R)-291\) (900 mg, 3.19 mmol, 1 equiv.) in \( \text{CH}_2\text{Cl}_2 \) (10 mL) at 0 °C was added BBr\(_3\) (32 mL, 32 mmol, 1 M in \( \text{CH}_2\text{Cl}_2 \), 10 equiv.) dropwise. The solution was stirred at 0°C for 2 h then warmed to rt and stirred for 16 h. The reaction was carefully quenched with MeOH (10 mL) at and warmed to rt. \( \text{CH}_2\text{Cl}_2 \) (10 mL) was added and the aqueous phase was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 20 mL). The organic layers were combined, dried (\( \text{MgSO}_4 \)) and concentrated \textit{in vacuo} to afford the pure product as a colourless solid (932 mg, 84 % yield); \([\alpha]_D^{20} = +93.6 \text{ (c 1.0 MeOH)}; \text{ mp 182-185 °C; } \nu_{\text{max}} \text{ (thin film, cm}^{-1}) \) 3026 (C-H), 1558 (C=N), 1550 (N=C); \(^1\text{H NMR} \) (500 MHz, d\(_6\)-DMSO) 4.34 (1H, dd, \( J 10.7, 8.4, \text{C(1)H}^\text{A} \)), 4.92 (1H, app. t, \( J 10.7, \text{C(1)H}^\text{B} \)), 5.91 (1H, dd, \( J 10.7, 8.4, \text{C(2)H} \)), 6.98 (1H, dd, \( J 8.7, 2.4, \text{ArC(6)H} \)), 7.34 (1H, d, \( J 8.7, \text{ArC(5)H} \)), 7.43 (1H, d, \( J 7.7, \text{PhC(4)H} \)), 7.46 (2H, d, \( J 8.2, \text{PhC(3,5)H} \)), 7.50 (1H, s, \( \text{ArC(8)H} \)), 7.54 (2H, d, \( J 7.7, \text{PhC(2,6)H} \)), 10.09 (1H, s, NH), 11.1 (1H, s, OH); \(^{13}\text{C}[^1\text{H}] \text{ NMR} \) (125 MHz, d\(_6\)-DMSO)
53.7 (C(1)H₂), 66.5 (C(2)H), 111.0 (ArC(8)H), 113.4 (ArC(5)H), 115.7 (ArC(6)H), 127.1 (PhC(2,6)H), 127.3 (ArC(8a)), 128.7 (ArC(4a)), 128.9 (PhC(4)H), 129.0 (PhC(3,5)H), 138.8 (PhC(1)), 155.0 (ArC(7)), 168.7 (C=N); HRMS (ESI⁺) C₁₅H₁₃N₂O₂ [M+H]⁺, found 269.0736, requires 269.0743 (−2.6 ppm).

(R)-2-phenyl-7-(prop-2-yn-1-yloxy)-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole 284

To a solution of salt 292 (52 mg, 0.15 mmol, 1 equiv.) in THF/DMSO (1:1 mL) was added KOrBu (44 mg, 0.39 mmol, 2.6 equiv.) and the reaction mixture was stirred at 0 °C for 2 h. Propargyl bromide (25 µL, 0.23 mmol, 80% in toluene, 1.5 equiv.) was then added and the reaction mixture was allowed to warm to rt (ca. 2 h) and quenched with brine (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated in vacuo to afford the crude product was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, CH₂Cl₂:EtOAc (95 : 5 5CV, 95 : 5 to 60 : 40 10 CV, 60 : 40 5 CV)] to afford the pure product as a colourless semi-solid (32 mg, 70% yield); [α]D²⁰ = +26.4 (c 1.0 CHCl₃); vmax (thin film, cm⁻¹) 1591 (C=C), 1575 (C=N); ¹H NMR (500 MHz, CDCl₃) δH: 2.53 (1H, t, J 2.4, C≡H), 3.68 (1H, app. t, J 8.5, C(1)H), 4.25 (1H, dd, J 10.2, 8.7, C(1)H), 4.66 (2H, d, J 2.4, OCH₂), 5.64 (1H, dd, J 10.2, 8.2, C(2)H), 6.60 (1H, d, J 8.5, ArC(5)H), 6.83 (1H, dd, J 8.5, 2.5, ArC(6)H), 7.02 (1H, d, J 2.5, ArC(8)H), 7.29 (1H, m, PhH), 7.37 (4H, m, PhC(2,6)H and PhC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) 53.1 (C(1)H₂), 57.0 (OCH₂), 75.5 (C(2)H), 75.9 (C≡CH), 78.5 (C≡CH), 108.8 (ArC(5)H), 111.4 (ArC(6)H), 113.8 (ArC(8)H), 126.6 (2 × PhCH), 127.7 (PhC(4)H), 128.5 (PhC), 128.9 (2 × PhCH), 132.3 (ArC(8a)), 143.0 (ArC(4a)), 152.9 (ArC(7)), 167.2 (C=N); HRMS (ESI⁺) C₁₅H₁₃N₂O₂ [M+H]⁺, found 307.0895, requires 307.0900 (−1.6 ppm).

(Azidomethyl)polystyrene 293

Following a procedure outlined by Pericàs et al.(253) to a round bottomed flask containing NaN₃ (780 mg, 51 mmol) was added (chloromethyl)polystyrene resin 191 (3.0 g, f = 1.23 mmol/g) in
DMSO (30 mL). The mixture was heated at 60 °C (without stirring) for 16 h and then cooled to rt. The suspension was filtered and washed sequentially with H₂O (500 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The resulting solid was dried in vacuo for 24 h at 40 °C.

ν_max (thin film, cm⁻¹) 2094 (N₃)

Elemental analysis (%) C 85.61, H 6.75, N 5.48

f = 1.20 mmol/g

(R)-2-Phenyl-7-(prop-2-yn-1-yloxy)-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole on polymer support 191:

To a round bottomed flask containing (azidomethyl)polystyrene (156 mg, 0.188 mmol, f = 1.20 mmol/g, 1 equiv.) suspended in THF:DMF 1:1 (6 mL) was added alkyne 284 (75 mg, 0.207 mmol, 1.1 equiv.), iPr₂NEt (94 µL, 0.724 mmol, 3.5 equiv.) and CuI (18 mg, 0.094 mmol, 5 mol%) with slow stirring. The reaction mixture was stirred until disappearance of the azide band (~2094 cm⁻¹) was confirmed by IR (ca. 21 h). The suspension was filtered and washed sequentially with THF (130 mL), H₂O (130 mL), H₂O-MeOH (1:1, 130 mL), MeOH (130 mL), MeOH-THF (1:1, 130 mL), THF (130 mL) and CH₂Cl₂ (130 mL) and the resin was dried in vacuo at 40 °C for 24 h to afford a dark brown resin (188 mg);

Elemental analysis (%) C 71.53, H 5.25, N 6.49

f = 0.927 mmol/g

tert-Butyl (phenyl(phenylsulfonyl)methyl)carbamate 295

Following a literature procedure[101] to a round bottomed flask was added benzaldehyde 294 (20 mL, 164 mmol, 1.5 equiv.) in 2:1:0.7 H₂O/MeOH/HCO₂H (4 mL/mmol) with stirring. Sodium benzenesulfinate (35.7 g, 220 mmol, 2 equiv.) and tert-butyl carbamate (12.83 g, 110 mmol, 1
equiv.) were added and the reaction was stirred at rt for 72 h. The resulting solids were collected by filtration and triturated with H₂O for 1 h followed by a second trituration with hexane:Et₂O (4:1) for 1 h. The resulting solids were collected by filtration and washed with hexane:Et₂O (4:1) (200 mL) which afforded the pure product as a colourless solid (32.83 g, 86%); mp 162-164 °C {Lit. [101] 164-165 °C}; ¹H NMR δH (500 MHz, d₆-DMSO) 1.17 (9H, s, C(CH₃)₃), 5.94 (1H, d, J 10.6, CH), 7.37-7.44 (3H, m, ArC(3,5)H and ArC(4)H), 7.55-7.80 (5H, 5×PhC₆H), 7.81-7.93 (2H, m, SO₂ArC(2,6)H), (2H, t, J 7.8, PhC(2)H), 7.71 (1H, d, J 7.6, C(4)H), 8.74 (1H, d, J 10.6, NH). All data in accordance with the literature. [101]

**tert-Butyl (E)-benzylidenecarbamate 297**

Following a modified literature procedure, [101] to a stirred slurry of tert-butyl (phenyl(phenylsulfonyl)methyl)carbamate 295 (10.0 g, 28.8 mmol, 1 equiv.) in bench grade CH₂Cl₂ (120 mL) was added a solution of K₂CO₃ (39.8 g, 288 mmol, 10 equiv.) in water (200 mL) and the reaction mixture was stirred at rt for 2 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3×100 mL). The combined organic fractions were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to give the title compound as a colourless oil (5.55 g, 94% yield); ¹H NMR (500 MHz, d₆-DMSO) δH: 1.50 (9H, s, C(CH₃)₃), 7.09 (2H, d, J 8.8, ArC(2,6)H), 7.90-7.95 (3H, m, ArC(2,6)H and ArC(4)H), 8.79 (1H, s, NC=H). All data in accordance with the literature. [101]

**tert-Butyl ((1R,2R)-2-formyl-3-methyl-1-phenylbutyl)carbamate 299**

Following a literature procedure, [101] to a stirred solution of tert-butyl (E)-benzylidenecarbamate 297 (5.0 g, 24.3 mmol, 1 equiv.) in dry HPLC grade CH₃CN (100 mL) was added freshly distilled isovaleraldehyde 298 (5.35 mL, 48.7 mmol, 2 equiv.) at 0 °C. (R)-Proline (140 mg, 1.22 mmol, 20 mol%) was added and the reaction mixture was stirred for 16 h at 0 °C before warming to rt. Water (100 mL), Et₂O (80 mL) and brine (20 mL) were added and the organic layer separated. The aqueous layer was extracted with Et₂O (3×100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to afford the crude product. The crude product was triturated with hexane (200 mL) and filtered to give the title compound (1R,2R)-299 as a colourless solid (10.5 g, 77% yield, >95:5 dr isolated); [α]D²⁰ = +60.4 (c 1.0
CHCl₃) {Lit.¹⁰¹} [α]D²⁰ = −66.7 (c 1.0 CHCl₃) ent >99% ee; mp 139-140 °C {Lit.¹⁰¹} 141-142 °C; Chiral HPLC analysis: Chiralcel OD-H (98:2 hexane:iPrOH, flow rate 1 mL/min⁻¹, 210 nm, 30 °C) t_R(1S,2S): 11.4 min, t_R(1R,2R): 12.3 min, >99% ee; ¹H NMR (400 MHz, CDCl₃) δ_H: 1.02 (1H, d, J 6.9, CH₃), 1.12 (3H, d, J 6.9, CH₃), 1.40 (9H, s, C(CH₃)₃), 2.04-2.12 (1H, m, C(3)H), 2.46 (1H, td, J 7.1, 4.2, C(2)H), 5.10 (2H, bs, C(1)H and NH), 7.14-7.38 (5H, m, PhH), 9.48 (1H, d, J 4.2, CHO). All data in accordance with the literature.¹⁰¹

**tert-Butyl ((1R,2R)-2-(hydroxymethyl)-3-methyl-1-phenylbutyl)carbamate 300**

Following a literature procedure,¹⁰¹ to a slurry of tert-butyl ((1R,2R)-2-formyl-3-methyl-1-phenylbutyl)carbamate 299 (10.0 g, 31.1 mmol, 1 equiv.) in bench grade MeOH (200 mL) at 0 °C was added NaBH₄ (1.76 g, 46.7 mmol, 1.5 equiv.) portion wise over 10 minutes and the reaction mixture was left to stir at rt for 1 h. Sat. aq. NaHCO₃ (30 mL) was added drop wise over 10 minutes forming a white precipitate. The methanol was removed under reduced pressure after which water (50 mL) and CH₂Cl₂ (250 mL) were added. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were combined and washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to give the title compound as a colourless solid (8.35 g, 83% yield, >95:5 dr isolated); [α]D²⁰ = +22.4 (c 1.0 CHCl₃) {Lit.¹⁰¹} [α]D²⁰ = −26.7 (c 1.0 CHCl₃) ent >99% ee }; mp 90-91 °C {Lit.¹⁰¹}92-94 °C; ¹H NMR (400 MHz, CDCl₃) δ_H: 0.85 (3H, d, J 6.9, CH₃), 1.00 (1H, d, J 6.9, CH₃), 1.42 (9H, s, C(CH₃)₃), 1.73 (1H, m, iPrCH), 1.87 (1H, m, C(2)H), 2.09 (1H, m, OH), 3.49 (1H, ddd, J 11.4, 8.8, 4.4, C(3)H²H³), 3.67 (1H, m, C(3)H²H³), 5.03 (1H, m, C(1)H), 5.49 (1H, d, J 9.3, NH), 7.23-7.36 (5H, m, PhH). All data in accordance with the literature ¹⁰¹

**(1R,2R)-2-(Hydroxymethyl)-3-methyl-1-phenylbutan-1-aminium chloride 301**

Following a literature procedure,¹⁰¹ to a slurry of tert-butyl ((1R,2R)-2-(hydroxymethyl)-3-methyl-1-phenylbutyl)carbamate 299 (2.37 g, 8.1 mmol, 1 equiv.) in bench grade 1,4-dioxane (20 mL) at rt was added 4 M HCl in 1,4-dioxane (11.0 mL, 41 mmol, 5 equiv.) drop wise over 30 minutes and the reaction mixture was left to stir at rt for 4 h before being concentrated under
reduced pressure. The resulting solid was triturated with Et₂O (500 mL) and filtered to give the
title compound as a white solid (1.67 g, 90% yield, >95:5 dr); \[\alpha_D^{20} = -17.4 (c 1.0 \text{ MeOH})\];
{Lit.\[101\]} \[\alpha_D^{20} = +25.0 (c 1.0 \text{ MeOH}) \text{ en}t >99\%\text{ee} \}; \text{ mp 138-140 °C } \{\text{Lit.\[101\]} 142-144 °C\}; \text{ }^{1}H \text{ NMR (500 MHz, CDCl}_3\} \delta_H: 0.84 (3H, d, \text{ J 6.8, C(3)H}), 1.14 (1H, d, \text{ J 6.8, C(3)H}), 1.54 (1H, dq, \text{ J 13.7, 6.8, iPrCH}), 2.02 (1H, ddt, \text{ J 9.2, 7.2, 4.4, C(2)H}), 3.48 (1H, dd, \text{ J 10.7, 9.2, C(1)H}_A\text{H}_B), 3.75 (1H, ddd, \text{ J 10.7, 4.6, 0.9, C(1)H}_A\text{H}_B), 4.57 (1H, d, \text{ J 4.3, C(3)H}), 7.47-7.51 (3H, m, C(3,5)H \text{ and C(4)H}), 7.51-7.55 (2H, m, C(2,6)H). All data in accordance with the literature.\[101\]}


Following a procedure outline by Smith \[101\] to a round bottomed flask containing was added
(1R,2R)-301 (4.81 g, 21.0 mmol, 1.05 equiv.), o-dichlorobenzene (7.5 mL, 2.0 M), iPr₂NEt (10.45
mL, 60.0 mmol, 4 equiv.) was added 2-chloro-6-methoxybenzo[d]thiazole 290 (4.0 g, 20 mmol,
1 equiv.) and the resulting pale yellow suspension was heated at reflux (195 °C DrySyn\® temperature)
until completion as judged by GC conversion (>95%, ca. 48 h). The resulting mixture was cooled to rt, H₂O (15 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated \textit{in vacuo} to afford the crude product which was triturated with hexane to afford a
brown solid which was used in the next step without further purification (5.43 g, 76% yield); GC
[Agilent DB-5, 40 cm/s (He), inj. temp 250 °C, FID temp 325 °C; temp profile: initial 120 °C (2
min), then ramp to 320 °C (20 °C/min, hold 5 min), total run = 17 min]; \text{t}_R \text{ iPr}_2\text{NEt, 1.87 min; o-
dichlorobenzene, 3.20 min; (1R, 2R)-301, 7.56 min; 2-chloro-6-methoxybenzo[d]thiazole 290,
7.65 min; }^{1}H \text{ NMR for 302 (500 MHz, CDCl}_3\} \delta_H: 0.81 (3H, d, \text{ J 6.8, C(3)H}), 1.09 (3H, d, \text{ J 6.8,
C(3)H}), 1.69 (1H, m, iPrCH), 2.10 (1H, app. ddt, \text{ J 10.2, 6.3, 4.2, C(2)H}), 3.66 (1H, dd, \text{ J 11.0, 9.8,
C(1)H}_A\text{H}_B), 3.78 (3H, s, OCH₃), 3.85 (1H, dd, \text{ J 11.0, 4.0, C(1)H}_A\text{H}_B), 4.94 (1H, d, \text{ J 4.3,
C(2)H}), 6.84 (1H, d, \text{ J 8.8, 2.6, ArC(4)H}), 7.08 (1H, d, \text{ J 2.6, ArC(7)H}), 7.25 (1H, d, \text{ J 7.2, ArC(4)H},
7.31-7.35 (3H, m, PhC(3,5)H and PhC(4)H), 7.46 (2H, d, \text{ J 7.9, PhC(2,6)H});
To a slurry of crude (1R, 2R)-amino alcohol 302 (5.43 g, 15.2 mmol, 1 equiv.) in anhydrous CH₂Cl₂ (80 mL, 0.2 m) was added Et₃N (8.47 mL, 60.8 mmol, 4 equiv.) and the reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (1.53 mL, 19.8 mmol, 1.3 equiv.) was added and the reaction mixture was stirred at rt for 30 mins. The reaction mixture was quenched with MeOH (10 mL) add water and the reaction was heated at reflux for 16 h. The reaction was quenched with aq. 1 M NaOH (20 mL) and the biphase mixture stirred vigorously for 30 mins. The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo to afford the crude product which was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, CH₂Cl₂ :EtOAc (95 : 5 CV, 95 : 5 to 60 : 40 10 CV, 60 : 40 5 CV)] to afford an off white solid (566 mg, 95% yield, >95:5 dr); [α]₂⁰ D = −249.1 (c 1.0 CHCl₃), mp 139-141 °C; vmax (thin film, cm⁻¹) 1614 (C=N), 1487 (C=C); ¹H NMR (500 MHz, CDCl₃) δH: 0.84 (1H, d, J 6.7, CH₃), 1.13 (1H, d, J 6.5, CH₃), 1.30 (1H, m, iPrCH), 1.95 (1H, ddt, J 11.4, 9.4, 4.4, C(3)H), 3.33 (1H, app. t, J 11.4, 11.4 C(4)H₃H), 3.83 (1H, s, OCH₃), 3.86 (1H, m, C(4)H₃H), 4.91 (1H, dd, J 4.4, 1.8, C(2)H), 6.72 (1H, d, J 8.6, ArC(6)H), 6.79 (1H, dd, J 8.7, 2.5 ArC(7)H), 6.95 (1H, d, J 2.5, ArC(9)H), 7.20 (2H, d, J 6.6, PhC(3,5)H), 7.25 (1H, m, PhC(4)H), 7.30 (2H, t, J 7.0 PhC(2,6)H); ¹³C[¹H] NMR (125 MHz, CDCl₃) δC: 20.2 (CH₃), 22.2 (CH₃), 27.1 (iPrCH), 41.0 (C(3)H), 42.1 (C(4)H₂), 56.1 (OCH₃), 61.1 (C(2)H), 108.1 (ArC(6)H), 108.3 (ArC(9)H), 111.8 (ArC(7)H), 124.3 (ArC(5a)), 127.3 (PhC(4)H), 128.2 (PhC(3,5)H), 128.5 (PhC(2,6)H), 134.9 ((ArC(9a)), 140.7 (PhC(1))), 155.5 (ArC(8)), 158.8 (C=N); HRMS (ESI⁺) C₁₂H₂₃N₂OS [M+H]⁺, found 339.1516, requires 339.1526 (−2.8 ppm).


To a solution of (2S,3R)-303 (500 mg, 1.48 mmol, 1 equiv.) in CH₂Cl₂ (10 mL) at 0 °C was added BBr₃ (15 mL, 8.86 mmol, 1 m in CH₂Cl₂, 10 equiv.) dropwise. The solution was stirred at 0°C for 2 h then warmed to rt and stirred for 16 h. The reaction was carefully quenched with MeOH (10 mL) at rt and warmed to rt. CH₂Cl₂ (10 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the pure product as a colourless solid (566 mg, 95% yield, >95:5 dr); [α]₂⁰ D =
−174.7 (c 1.0 MeOH), \textbf{mp} 194–196 °C; ν\text{max} (thin film, \text{cm}⁻¹) 3140 (O-H), 2920 (C-H), 1597 (C=N), 1450 (C=C); \textbf{¹H NMR} (500 MHz, \text{d}_{6}-\text{DMSO}) δH: 0.79 (3H, d, J 6.7, CH₃), 1.07 (3H, d, J 6.5, CH₃), 1.21 (1H, app. td, J 13.2, 6.0, 3.2), 2.32 (1H, ddt, J 11.6, 9.4, 4.8, C(3)H), 3.68 (1H, dd, J 13.3, 11.6, C(4)H²H⁸), 4.40 (1H, m, C(4)H⁴H⁸), 5.17 (1H, d, J 4.8, C(2)H), 6.99 (1H, dd, J 8.8, 2.4, C(7)H), 7.30 (2H, d, J 7.4, PhC(2,6)H), 7.36–7.43 (3H, m, PhC(3,5)H and PhC(4)H), 7.46 (1H, d, J 2.4, ArC(9)H), 7.64 (1H, d, J 8.9, ArC(6)H), 9.98 (1H, s, OH), 11.14 (1H, s, NH); \textbf{¹C[¹H] NMR} (125 MHz, \text{d}_{6}-\text{DMSO}) δC: 19.2 (CH₃), 21.5 (CH₃), 26.3 (iPrCH), 39.8 (C(3)H), 42.1 (C(4)H₂), 55.4 (C(2)H), 109.7 (ArC(9)H), 114.0 (ArC(6)H), 115.2 (ArC(7)H), 123.4 (ArC(5a)), 127.8 (PhC(2,6)H), 128.4 (PhC(4)H), 128.9 (PhC(3,5)H), 131.2 ((ArC(9a)), 137.6 (PhC(1)), 155.4 (ArC(8)), 162.3 (C=N); \textbf{HRMS} (ESI⁺) C₁₉H₂₀N₂O [M+H]⁺ found 324.1361, requires 324.1296 (−2.5 ppm).


To a solution of salt 305 (1.00 g, 2.47 mmol, 1 equiv.) in \text{THF}/\text{DMSO} (1:1, 10mL) was added KOtBu (722 mg, 6.43 mmol, 2.6 equiv.) and the reaction mixture was stirred at 0 °C for 2 h. Propargyl bromide (413 µL, 3.71 mmol, 80% in toluene, 1.5 equiv.) was then added and the reaction mixture was allowed to warm to rt (ca. 2 h) and quenched with brine (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, dried (MgSO₄) and concentrated \textit{in vacuo} to afford the crude product was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min⁻¹, CH₃Cl₂:EtOAc (95 : 5 5CV, 95 : 5 to 60 : 40 10 CV, 60 : 40 5 CV)] to afford the pure product as a colourless fluffy solid (495 mg, 68% yield, >95:5 dr); [α]₂⁰_D = −201.4 (c 1.0 CHCl₃), \textbf{mp} 60-63 °C; ν\text{max} (thin film, \text{cm}⁻¹) 2956 (C-H), 1616 (C=N), 1487 (C=C); \textbf{¹H NMR} (500 MHz, CDCl₃) δH: 0.84 (1H, d, J 6.7, CH₃), 1.13 (1H, d, J 6.5, CH₃), 1.28–1.32 (1H, m, iPrCH), 1.94 (1H, ddt, J 11.4, 9.4, 4.8, C(3)H) 2.54 (1H, t, J 2.4, C=H), 3.33 (1H, t, J 11.5, C(4)H²H⁸), 3.83 (1H, dd, J 11.5, 5.3, 1.8, C(4)H⁴H⁸), 4.68 (1H, d, J 2.4, CH₂O), 4.90 (1H, dd, J 4.5, 1.7, C(2)H), 6.72 (1H, d, J 8.7, ArC(6)H), 6.87 (2H, dd, J 8.7, 2.5, ArC(7)H), 7.04 (1H, d, J 2.5, ArC(9)H), 7.20 (2H, d, J 7.2, PhC(3,5)H), 7.23–7.25 (1H, m, PhC(4)H), 7.30 (2H, d, J 6.8, PhC(2,6)H); \textbf{¹C[¹H] NMR} (126 MHz, CDCl₃) δC: 20.2 (CH₃), 22.1 (CH₃), 27.1 (iPrCH), 41.0 (C(3)H), 42.5 (C(4)H₂), 57.0 (CH₂O), 61.1 (C(2)H), 75.9 (C=CH), 78.6 (C=CH), 108.0 (ArC(9)H), 110.0 (ArC(6)H), 113.2 (ArC(7)H), 124.4 (ArC(5)), 127.4 (PhC(4)H), 191
128.1 (PhC(2,6)H), 128.5 (PhC(3,5)H), 135.8 ((ArC(9a)), 140.6 (PhC(1)), 153.3 (ArC(8)), 158.7 (C=N); HRMS (ESI⁺) C₂₂H₂₃N₂O⁺ [M+H]⁺ found 363.1517, requires 363.1526 (−2.4 ppm).


![Chemical structure](image)

To a round bottomed flask containing azidomethyl polystyrene 293 (1.04 g, 1.25 mmol, \( f = 1.20 \) mmol/g, 1 equiv.) suspended in THF:DMF 1:1 (14 mL) was added alkyne 306 (495 mg, 1.37 mmol, 1.1 equiv.), \( \text{iPr}_2\text{NEt} \) (762 µL, 0.546 mmol, 3.5 equiv.) and CuI (12 mg, 0.625 mmol, 5 mol%) with slow stirring (100 rpm). The reaction mixture was stirred until disappearance of the azide band (~2094 cm⁻¹) was confirmed by IR (ca. 17 h). The suspension was filtered and washed sequentially with THF (1:1, 130 mL), \( \text{H}_2\text{O} \) (130 mL), \( \text{H}_2\text{O}-\text{MeOH} \) (1:1, 130 mL), \( \text{MeOH} \) (130 mL), \( \text{MeOH-THF} \) (1:1, 130 mL), \( \text{THF} \) (130 mL) and \( \text{CH}_2\text{Cl}_2 \) (130 mL) and the resin was dried \textit{in vacuo} at 40 °C for 24 h to afford a brown resin (1.22 g) with a loading of \( f = 0.972 \) mmol/g.

Elemental analysis (%) C 78.66, H 6.20, N 6.81

\( f = 0.972 \) mmol/g

\( (E)-1,1,1\)-Trifluoro-4-phenylbut-3-en-2-one 308

Following a procedure outlined by Smith[101] to a round bottomed flask containing anhydrous THF (25 mL, 0.2 M) was added \( \text{iPr}_2\text{NEt} \) (3.32 mL, 24.0 mmol, 2 equiv.) and \( \text{nBuLi} \) (13.7 mL, 24.0 mmol, 1.75 M in hexanes, 2 equiv.) at −78 °C and the solution was allowed to stir for 20 minutes. Diethyl methylphosphonate (1.75 mL, 12.0 mmol, 1 equiv.) was added at −78 °C followed by a further 30 minutes of stirring. \( (Z)-2,2,2\)-Trifluoro-\( N\)-phenylacetimidoyl chloride 102 (2.50 g, 12.0 mmol, 1 equiv.) was then added slowly followed by stirring at −78 °C for 1 h. A solution of benzaldehyde (1.28 mL, 12.0 mmol, 1 equiv.) in anhydrous THF (10 mL) was added dropwise at −78 °C. The reaction mixture was then warmed over 2 h and stirred at rt for 16 h. Aq. 2 M HCl (24 mL, 4 equiv.) was added and the reaction mixture was stirred for a further 4 h before
being extracted with Et₂O (3 × 50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (50 mL), brine (50 mL), dried (MgSO₄) and concentrated in vacuo to give the crude reaction mixture. Flash chromatography on silica gel (9:1 Pet:Et₂O) afforded the pure product as a yellow oil (950 mg, 40% yield); \( ^1H \) NMR (700 MHz, CDCl₃) \( \delta_H \): 7.02 (1H, d, \( J = 16.0 \), C(3)H), 7.43 (2H, t, \( J = 7.3 \), ArC(2,6)H), 7.50 (1H, d, \( J = 8.1 \), ArC(4)H), 7.61–7.66 (2H, t, \( J = 7.3 \), ArC(3,5)H), 7.97 (1H, d, \( J = 16.0 \), C(3)H). All data in accordance with the literature.\(^{[101]}\)

\((3R,4R)-3,4\)-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one 309

![Diagram](309)

To a Schlenk flask containing CH₂Cl₂ (2 mL) was added phenylacetic acid 307 (27 mg, 0.2 mmol, 1 equiv.), pivaloyl chloride (37 µL, 0.3 mmol, 1.5 equiv.) and iPr₂NEt (52 µL, 0.3 mmol, 1.5 equiv.) and the resulting solution was allowed to stirred for 5 mins at rt. The solution was then cooled to −78 °C and PS-(2R,3S)-HyperBTM 61 (31 mg, 0.03 mmol, \( f = 0.972 \text{ mmol/g}, 15 \text{ mol%} \)) was added with slow stirring (200 rpm) followed by enone 308 (40 mg, 0.2 mmol, 1 equiv.) and iPr₂NEt (35 µL, 0.2 mmol, 1 equiv.). The reaction mixture was stirred (200 rpm) at −78 °C for 16 h and allowed to warm to rt. The reaction was filtered using a sintered funnel to remove the polymer-supported catalyst. The filtrate was washed with aq. 1 M HCl (5 mL) and brine (10 mL). The organic layers were combined, dried (MgSO₄) and concentrated in vacuo to afford the crude product (89:11 dr) which was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 75 mL min⁻¹, pet. ether:Et₂O (100 : 0 5CV, 100 : 5 to : 90 : 10 CV, 90 : 10 5 CV)] to afford the pure product as a colourless solid with spectroscopic data in accordance with the literature.\(^{[101]}\) (42 mg, 66% yield, 95:5 dr); \([\alpha]^{20}_D = +171.6 \text{ (c 0.5 CH₂Cl₂)} \{/\text{Lit.}^{[101]} -227.2 \text{ (c 0.25 CH₂Cl₂)} \text{ en}}, >99\text{%ee}\}; \text{mp 42-44 °C} \{/\text{Lit.}^{[101]} 90-92 °C\}; \text{Chiral HPLC: Chiralcel OD-H (98:2 hexane,flow rate 1 mL/min, 210 nm, 30 °C) \( t_k(3S,4S) = 8.7 \text{ min, } t_k(3R,4R) = 9.4 \text{ min, 98% ee} \); \( ^1H \) NMR (500 MHz, CDCl₃) \( \delta_H \): 4.00 (1H, d, \( J = 8.9 \), C(3)H), 4.05 (1H, m, C(4)H), 4.17 (1H, d, \( J = 3.8 \), C(5)H), 7.03-7.08 (2H, m, 2 × PhCH), 7.09-7.15 (2H, m, 2 × PhCH), 7.31 (6H, m, 6 × PhCH). \( ^{19}F \) \( ^1H \) NMR (376 MHz, CDCl₃) \( \delta_F \): −72.2 (CF₃).

1-(naphthalen-2-yl)prop-2-en-1-ol 313

![Diagram](313)
To a round bottomed flask containing anhydrous THF (40 mL, 0.3 M) was added 2-naphthaldehyd 312 (2.0 g, 12.8 mmol, 1 equiv.) followed by MeMgBr (4.3 mL, 12.8 mmol, 3.0 M in THF, 1 equiv.) at −78 °C with stirring under Ar. The solution was stirred at −78 °C for 16 h and allowed to warm to rt. The reaction was quenched with NH4Cl (15 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine, dried (MgSO4) and concentrated in vacuo to afford the pure product as a off-white solid (1.89 g, 86 % yield); mp 60–63 °C {Lit[307] 56–58 °C}; 1H NMR (400 MHz, CDCl3) δH: 5.08 (1H, q, J 6.5, C(1)H), 7.49 (3H, 3 × ArH), 7.80 – 7.88 (4H, m, ArH). All data in accordance with the literature.[307]

1-(naphthalen-2-yl)ethyl propionate 314

To a round bottomed flask containing CH2Cl2 (2 mL) was added alcohol 313 (71 mg, 0.39 mmol, 1 equiv.), isobutyric anhydride (63 µL, 0.39 mmol, 1 equiv.), DMAP (1 crystal, ~10 mol%) and iPr2NEt (68 µL, 0.39 mmol, 1 equiv.). The reaction was stirred at rt for 16 h and diluted with CH2Cl2 (10 mL). The organic phase was washed with aq. 1 M HCl (5 mL), NaHCO3 (5 mL) and brine. The organic layer was dried (MgSO4) and concentrated in vacuo to afford the pure product as a colourless oil (85 mg, 86% yield); mp 60-63 °C {Lit[275] 60-63 °C}; 1H NMR (400 MHz, CDCl3) δH: 1.16 (3H, t, J 7.6, C2H5CH3), 1.61 (3H, d, J 6.6, C3H5), 2.39 (2H, app. qd, J 7.6, 1.8, C2H2CH3), 6.08 (1H, q, J 6.6, C(1)H), 7.44 – 7.52 (3H, m, ArH), 7.78 – 7.88 (4H, m, ArH). All data in accordance with the literature.[275]

(R)-1-(naphthalen-2-yl)prop-2-en-1-ol 313 and (S)-1-(naphthalen-2-yl)ethyl propionate 314

Following general procedure M, (±)-1-(naphthalen-2-yl)ethan-1-ol 313 (50 mg, 0.291 mmol, 1 equiv.), propionic anhydride (19 µL, 0.145 mmol, 0.6 equiv.), PS-(2R,3S)-HyperBTM 61 (15 mg, 0.014 mmol, f = 0.972 mmol/g, 5 mol%) and iPr2NEt (30 µL, 0.174 mmol, 0.5eqiv.) were reacted in CHCl3 (2 mL) at 0 °C for 24 h to give the crude products, which were purified by Biotage®
Isolera 4 chromatography (eluent: 0%→30% EtOAc in pet.ether) to give (S)-1-(naphthalen-2-yl)ethyl propionate 314 (47 mg, 48% yield) and (R)-1-(naphthalen-2-yl)ethan-1-ol 313 (46 mg, 41%).

(R)-1-(naphthalen-2-yl)ethan-1-ol 313: \([\alpha]_D^{20} = +35.6 \ (c \ 0.5 \ \text{CHCl}_3) \) \cite{275} \(-53.0 \ (c \ 0.4 \ \text{CHCl}_3) \) \text{ent} >99%ee; **Chiral HPLC analysis**: Chiralpak OJ-H (95:5 hexane:iPrOH, flow rate 1 mL min\(^{-1}\), 254 nm, 30 °C) \(t_R\) (S): 14.9 min, \(t_R\) (R): 19.2 min, >99% ee

(S)-1-(naphthalen-2-yl)ethyl propionate 314: \([\alpha]_D^{20} = -80.6 \ (c \ 0.5 \ \text{CHCl}_3) \) \cite{275} +71.2 \ (c 0.6 CHCl\(_3\)), 67% ee; **Chiral HPLC analysis**: Chiralpak AD-H (90:10 hexane:iPrOH, flow rate 0.5 mL min\(^{-1}\), 254 nm, 30 °C) \(t_R\) (R): 21.4 min, \(t_R\) (S): 24.1 min, 79% ee.

\(S\) factor = 95

1-Benzy1-3-hydroxy-3-phenylindolin-2-one 319

To a round bottomed flask containing anhydrous THF (140 mL, 0.1 M) at −78 °C was added 1-benzyindoline-2,3-dione 318 (3.33 g, 14 mmol) with stirring. Phenylmagnesium bromide (3.0 M, 5.6 mL, 16.8 mmol) was added and the reaction mixture was stirred for 30 at −78 °C then warmed to rt over 30 mins. The reaction was quenched with sat. aq. NH\(_4\)Cl (50 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine, dried (MgSO\(_4\)) and concentrated in vacuo to afford the crude product that was purified by Biotage® Isolera 4 chromatography (eluent: 0%→30% EtOAc in hexanes) to give a yellow solid. The product was further purified by recrystallisation by dissolving in a minimal amount of CH\(_2\)Cl\(_2\) (~30 mL), layering with hexane (~150 mL), and cooling at −10 °C overnight to give 1-benzyl-3-hydroxy-3-phenylindolin-2-one as a colourless solid (3.94 g, 89% yield); **mp** 140-142 °C \cite{275} **mp** 139-141 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_H\): 3.39 (1H, br, s, OH), 4.84 (1H, d, \(J\) 15.7, CH\(_3\)H\(_2\)Ph), 5.05 (1H, d, \(J\) 15.7, CH\(_3\)H\(_2\)Ph), 6.79 (1H, app. d, \(J\) 7.9, C(7)H), 7.05 (1H, app. td, \(J\) 7.6, 1.0, C(5)H), 7.23 (1H, td, \(J\) 7.8, 1.3, C(6)H), 7.27-7.38 (9H, m, ArH), 7.39-7.44 (2H, m, ArH). All data in accordance with the literature \cite{275}.

1-benzy1-2-oxo-3-phenylindolin-3-yl isobutyrate 320
To a Schenk flask containing CHCl₃ (2 mL) was added alcohol 319 (50 mg, 0.158 mmol, 1 equiv.), isobutyric anhydride (29 μL, 0.174 mmol, 1.1 equiv.), iPr₂NEt (29 μL, 0.158 mmol, 1 equiv.) and DMAP (10 mol%, 1 crystal) at rt with stirring. The reaction was stirred at rt for 16 h and diluted with EtOAc (10 mL). The organic phase was washed with 1M HCl (5 mL), sat. aq. NaHCO₃ (5 mL) and brine. The organic layer was dried (MgSO₄) and concentrated in vacuo to afford the pure product as a colourless oil (51 mg, 83% yield); νmax (thin film, cm⁻¹) 2974 (C-H), 1728(C=O), 1614 (C=C); ¹H NMR (400 MHz, CDCl₃) δH: 1.23 (3H, d, J 7.0, CH(CH₃)₃(CH₂)₃), 1.27 (3H, d, J 7.0, CH(CH₃)₃(CH₂)₃), 2.74 (1H, sept, J 7.0, iPrCH), 4.86 (1H, d, J 15.9, CH₃Ph), 5.01 (1H, d, J 15.9, CH₃H), 6.72 (1H, d, J 7.8, C(7)H), 7.05 (1H, app td, J 7.5, 1.0, C(5)H), 7.18-7.39 (12H, m, C(3)ArH and CH₂ArH and ArC(4,6)H); ¹³C NMR (101 MHz, CDCl₃) δC: 18.8 (CH₃), 19.0 (CH₃), 34.0 (CH(CH₃)₃), 44.4 (NCH₂Ph), 81.1 (C(3)), 109.9 (ArC(7)H), 123.2 (ArC(5)H), 123.9 (ArC(4)H), 126.4 (C(3)PhC(2,6)H), 127.3 (CH₂PhC(2,6)H), 127.7 (CH₂PhC(4)H), 128.6 (3(3)a), 128.8 (CH₂PhC(3,5)H), 128.9 (C(3)PhC(3,5)H), 129.0 (C(3)PhC(4)H), 130.1 (ArC(6)H), 135.8 (CH₂PhC(1)), 137.0 (C(3)PhC(1)), 143.8 (C(7)a), 174.3 (C(2)=O), 175.2 (CO₂R); HRMS (NSI⁺) calculated for C₂₅H₂₇N₂O₅⁺ ([M+NH₄]⁺) requires 403.2016; found 403.2012 (−1.0 ppm).

(R)-1-benzyl-2-oxo-3-phenylindolin-3-yl isobutyrate 320 and (S)-1-benzyl-3-hydroxy-3-phenylindolin-2-one 319

Following general procedure M, 1-benzyl-3-hydroxy-3-phenylindolin-2-one 319 (100 mg, 0.317 mmol, 1 equiv.), isobutyric anhydride (37 μL, 0.22 mmol, 0.7 equiv.), PS-(2S,3R)-HyperBTM 61 (16.4 mg, 0.016 mmol, f = 0.972 mmol/g, 5 mol%) and iPr₂NEt (33 μL, 0.19 mmol, 0.6 equiv.) were reacted in CHCl₃ (2 mL, 0.17 M) at 0 °C for 24 h to give the crude products, which were purified by Biotage® Isolera 4 chromatography (eluent: 0%−30% EtOAc in pet.ether) to give (R)-1-benzyl-2-oxo-3-phenylindolin-3-yl isobutyrate 320 (47 mg, 46% yield) and (S)-1-benzyl-3-hydroxy-3-phenylindolin-2-one 319 (46 mg, 38%);
(R)-1-Benzyl-2-oxo-3-phenylindolin-3-yl isobutyrate 320: 
\[ \alpha_{D}^{20} = -83.6 \text{ (c 1.0, CHCl}_3) \];

**Chiral HPLC analysis:** Chiralpak AD-H (90:10 hexane:iPrOH, flow rate 1.25 mL min\(^{-1}\), 211 nm, 40 °C) \( t_R \) (S): 12.7 min, \( t_R \) (R): 25.7 min, 98.5:1.5 (S:R) er;

(S)-1-Benzyl-3-hydroxy-3-phenylindolin-2-one 319:
\[ \alpha_{D}^{20} = -39.4 \text{ (c 1.0, CHCl}_3) \text{ (Lit.}\[275]\ -35.4 \text{ (c 1.0, CHCl}_3) \text{ 98% ee); Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane: iPrOH, flow rate 1.25 mL min}^{-1}, 211 \text{ nm, 40 °C) } t_R \text{ (S): 21.4 min, } t_R \text{ (R): 27.1 min, 91.5:8.5 (R:S) er.}

\( S \) factor = 145.

**trans-Cinnamic anhydride 329**

To a round bottomed flask containing CH\(_2\)Cl\(_2\) (6 mL) was added *trans*-cinnamic acid 328 (741 mg, 5 mmol, 1 equiv.) and EDCI (959 mg, 5 mmol, 1 equiv.) with stirring. The reaction was stirred at rt for 2 h and diluted with CH\(_2\)Cl\(_2\). NaHCO\(_3\) (40 mL) was added and the aqueous phase was extracted. The organic layers were combined, washed with brine, dried (MgSO\(_4\)) and concentrated in vacuo to afford the pure product as a colourless solid (450 mg, 65% yield); mp 116-119 °C {Lit.}\[279\] 118-120 °C; \(^1\)H NMR \( \delta \text{H} \text{(400 MHz, CDCl}_3) \) 6.53 (1H, d, \( J = 15.9 \), ArCH=C\( \text{H} \)), 7.36–7.47 (6H, m, Ar\( \text{CH} \)), 7.55–7.60 (4H, m, Ar\( \text{CH} \)), 7.86 (1H, d, \( J = 15.9 \), Ar\( \text{CH}=\text{C} \)). All data in accordance with the literature.\[279\]

(3R)-methyl 4-benzoyl-5-oxo-3,5-diphenylpentanoate 331

To a Schlenk flask containing anhydrous CH\(_2\)Cl\(_2\) (250 \( \mu \text{L, 0.75 m} \) was added PS-(2R,3S)-HyperBTM 61 (19 mg, 0.018 mmol, \( f = 0.972 \text{ mmol/g, 5 mol%) under argon with stirring (200 rpm). Anhydride 329 (100 mg, 0.36 mmol, 2 equiv.), 1,3-diphenylpropane-1,3-dione 330 (40 mg, 0.18 mmol, 1 equiv.) and iPr\(_2\)NEt (78 \( \mu \text{L, 0.45 mmol, 1 equiv.} \) were added to the reaction mixture. The reaction was stirred at 0 °C and allowed to warm to rt over 5 h then MeOH (2 mL) was added and the reaction was stirred for a further 16 h at rt. The reaction mixture was filtered to remove the polymer supported catalyst and the catalyst was washed with CH\(_2\)Cl\(_2\) (10 mL). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (CH\(_2\)Cl\(_2\)→2% EtOAc; CH\(_2\)Cl\(_2\)) to afford the pure product as a colourless solid (52 mg, 75%
yield); \([\alpha]_D^{20} = -17.2 \text{ (c 0.5, CHCl}_3\) \{Lit.\} +9.6 \text{ (c 0.25, CHCl}_3\) ent 96% ee\}; mp 100-101 °C \{Lit.\} 104-107 °C; Chiral HPLC analysis Chiralpak AD-H (80:20 hexane/iPrOH, flow rate 1 mL min\(^{-1}\), 211 nm, 30 °C) \(t_R\) (S) 11.3 min, \(t_R\) (R) 16.1 min, 94 % ee; \(^1\)H NMR \(\delta_H\) (500 MHz, CDCl\(_3\)) 2.76–2.94 (2H, m, C(2)\(H\)), 3.49 (3H, s, OCH\(_3\)), 4.40 (1H, app. dd, J 9.5, 4.7, C(3)\(H\)), 5.84 (1H, d, J 9.5, C(4)\(H\)), 7.06–7.10 (1H, m, Ar\(H\)), 7.15 (2H, dd, J 8.4, 6.9, 2Ar\(H\)), 7.24-7.34 (4H, m, 4 \times Ar\(H\)), 7.39–7.47 (3H, m, 3 \times Ar\(H\)), 7.54 (1H, t, J 7.4, Ar\(H\)), 7.75 (2H, d, J 7.2, 2 \times Ar\(H\)), 7.98 (2H, d, J 6.8, 2 \times Ar\(H\)). All data in accordance with the literature. 

6.6 References and Notes