Studies in Synthesis and Organocatalysis: (i) The Design and Synthesis of Novel Electron Deficient Dienes and their Application in the First Enamine Activated Organocatalytic 1,6-Conjugate Addition. (ii) The Development of a New Organocatalytic Methodology through the Combination of DNA-Based Catalysis and Organocatalysis.

A thesis submitted by

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Dr. John C. Stephens

October 2012

Declaration

This is to certify that the material presented within this thesis has not been submitted previously for a Degree to this or any other University. All material presented, except where acknowledged and cited, is the original work of the author.

John Joseph Patrick Murphy

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National University of Ireland, Maynooth October 2012.

Dedication

“Those who dare to fail miserably can achieve greatly”
– John F. Kennedy

To my Family and Supervisor,

Acknowledgements

Firstly I would like to thank my supervisor Dr. John Stephens for giving me this opportunity and putting up with my incessant hammering on his door, Dr. Frances Heaney for all her advice over the years and Prof. Alex Alexakis for his invitation to Geneva and all the advice and encouragement you offered me. Secondly I would like to thank my late-night proof readers Niall, Connor and Ursula, for doing a great job at short notice. Thirdly I have to mention my parents for all the support and constant questioning about if my thesis was written yet, well here it is. I cannot thank you guys enough, especially for the financial aid towards the end, and not going crazy that yet another son is not getting a 'real job'.

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A few memories will stick out for me in no particular order; Rob spraining his ankle at the Christmas party; Lorna 'falling' into the Christmas tree, nearly setting Niamh on fire with LithAl (although I remember it differently), having a butyllithium fire while explaining to a student how dangerous it is, Niamh making that tiger noise during a group meeting, the time when Nico showered our hood in white powder, Rob pouring liquid oxygen into the solvent waste, Ruth and her planet-fridge, and Roisin being 'hung-over like a donkey'.

A final acknowledgment to the my housemates over the years, Joey, Rob and Connor and of course to the producers of the Stargate franchise for making working every weekend for a year bearable.

Good-luck to all of you in the future.

John M.

Abstract

A novel approach to substrate design led to the development of charge de-localized extended Michael acceptors. Using this methodology a family of both alkyl and aryl bis-phenylsulfonyl butadienes were synthesised and characterised. The first enamine activated organocatalytic 1,6-conjugate addition was performed on the sulfonyl acceptors, using aldehydic enamines, giving excellent yields and selectivities (up to 98% yield, uniformly 99% *ee*). The mechanism of this reaction was explored in detail. The products of these additions were fully characterised and were subsequently used as substrates for the conjugate addition of methyllithium (52% yield, 12 : 1 d.r.) and an organocatalysed inverse electron demand Diels-Alder reaction (DA_{INV}) (76% yield, 3.1 : 1 : 1.5 d.r.). Combining the 1,6-addition and DA_{INV} methodology let to the development of an enamine/iminium ion organocatalytic cascade reaction which delivered a product with 5 contiguous stereocenters (75% yield, 3.1 : 1 : 1.5 d.r.). We attempted to apply our 1,6-conjuagate addition methodology to the synthesis of Sildenafil analogues. Several steps of this challenging synthesis were completed. The step involving the oxidation of a homo-allylic alcohol remains to be solved. Interestingly a DMSO-based oxidation generated a sulfur ylide in high yield (90%), a possible explanation is provided.

A second class of butadienes, bis-cyano butadienes, that are suitable substrates for 1,6-conjugate additions, were prepared and characterised. Addition of aldehydic enamines to these acceptors also yielded a regioselective 1,6-adduct in high yield and selectivity (up to 75% yield, up to 99% *ee*). An experimental investigation was performed into the synthesis of suitable trienes for 1,8-conugate additions. A 1,3-bis-phenylsulfonyl hexatriene was synthesised and characterised which did not undergo a selective 1,8-conjugate addition with aldehydic enamines. Upon heating, this triene was found to undergo an electrocyclisation reaction to give a biphenyl with a near zero twist angle. Synthesis of α,γ,ε-tris activated triene led to the isolation of a bis-phenylsulfonyl-cyano-arene and not the desired triene.

A final experimental study was undertaken exploring the use of DNA and a suitable intercalating organocatalyst in asymmetric transformations. The design, synthesis and characterization of a novel achiral DNA-intercalating imidazolidinone was realized in high yield (40% yield over 4 steps). Several synthetic routes to the intercalating imidazolidinone were explored. The catalyst was found to still retain the ability to generate a reactive iminium ion and participate in a Diels-Alder reaction without DNA, albeit in reduced potency (24% yield). Future work will entail the application of the intercalating catalyst with salmon testes DNA.

Abbreviations

3D	Three dimensional
Ac	Acetyl
ACN	Acetonitrile
Addn	Addition
AIBN	Azobisisobutyronitrile
Ala	Alanine
Ar	Aryl
Asp	Aspartic acid
BA	Benzoic acid
BINOL	1,1'-Bi-2,2'-naphthol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bu	Butyl
BuLi	Butyllithium
Cat	Catalytic
CDI	Carbonyldiimidazole
cGMP	Cyclic guanosine monophosphate
c-Hexyl	Cyclohexyl
COSY	Correlated Spectroscopy
*c*DNA	Complementary strand deoxyribonucleic acid
CuTC	Copper(I) Thiophenecarboxylate
d.r.	Diastereomeric ratio
DA	Diels-Alder reaction
DA_{INV}	Inverse electron demand Diels-Alder reaction
DAST	Diethylaminosulfur trifluoride
DBE	Dibromoethane
DBM	Dibromomethane
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	Methylene Chloride
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density Functional Theory
DIBAL-H	Di-*iso*-butyl aluminium hydride
DIPEA	Diethyl-*iso*-propylamine (Hünig's Base)
DMAP	4-Dimethylaminopyridine

DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPPB	1,4-Bis(diphenylphosphino)butane
E	Electrophile
EDG	Electron-donating group
ee	Enantiomeric excess
emim	Ethyl methyl imidazolium
En	Enamine catalysis
ESI-MS	Electron-spray ionization mass spectroscopy
Et	Ethyl
EtOH	Ethanol
EWG	Electron-withdrawing group
FGI	Functional Group interconversion
Fmoc	9-Fluorenylmethyloxycarbonyl
GC	Gas chromatography
Gly	Glycine
H-bonding	Hydrogen bonding
HOBt	1-hydroxy-benzotriazole
HOMO	Highest Occupied Molecular Orbital
HPLC	High performance liquid chromatography
H-shift	Hydrogen shift
HSQC	Heteronuclear Single-Quantum Coherence
HWE	Horner-Wadsworth-Emmons reaction
IBX	2-Iodoxybenzoic acid
*i*Pr	*iso*-Propyl
*i*PrOH	*iso*-Propanol
IR	Infra-red spectrum
LAH	Lithium Aluminium Hydride
Leu	Leucine
LG	Leaving Group
LUMO	Lowest Occupied Molecular Orbital
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol

Mes	Mesityl
MOPS	3-(*N*-morpholino)propanesulfonic acid
MP	Melting point
Ms	Mesyl
MTBE	Methyl *tert*-butyl ether
n/a	Not applicable
NBA	4-nitrobenzoic acid
*n*Bu	*n*-butyl
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic Carbene
NMO	*N*-methylmorpholine oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
*n*Pr	*n*-propyl
Nu	Nucleophile
OTf	Triflate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PG	Protecting group
Ph	Phenyl
Pip	piperidine
PMP	*para*-methoxy-phenyl
Pr	Propyl
Pro	Proline
PTC	Phase-Transfer Catalysis
PTLC	Preparative thin layer chromatography
p-TSA	*para*-toluenesulfonic acid monohydrate
Pyr	Pyridine
R	Non-defined
R_f	Retention factor
RSM	Returned starting material
R_T	Retention time
RT	Room-temperature
SET	Single Electron Transfer
SOMO	Singly Occupied Molecular Orbital
st-DNA	DNA from Salmon testes
TADDOL	α,α,α´,α´-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride

TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
*t*Bu	*tert*-Butyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMS	Trimethyl silyl
TPAP	Tetrapropylammonium perruthenate
TS	Transition state
Val	Valine
Z	Carbobenzyloxy

Contents

Chapter 1

1.1 Introduction to organocatalysis

In 1815, Jean-Baptiste Biot discovered that some chemical compounds are optically active.[1] Since that time the scientific community has been establishing the importance of chirality in the natural and chemical world. Nowhere is the importance of chirality more apparent than in biological systems. The bio-chemical reactions within these systems more often than not contain chiral molecules that interact with one another in a stereospecific manner. An example of such stereospecificity is during the biosynthesis of proteins where only L-amino acids are incorporated into the macromolecule.[2] These chiral biomolecules, proteins, are common targets for medicinal chemistry and when treated with a racemic mixture of molecules different biological responses can result that depend on which enantiomer the protein interacted with. This effect can have interesting results, for example the response of the olfactory receptors in one's nose, to the two different enantiomers of carvone, causes one to recognise a different aroma for each enantiomer.[3] The importance of chirality in potential medicines is highlighted by the tragic thalidomide incident where there was an unexpected teratogenous response to one of the enantiomers of the medicine. With the continuing search for, design and use of new chiral pharmaceuticals, the control of enantiopurity continues to be of paramount importance.[4]

Enzymes are an important class of chiral proteins. Enzymes are the catalysts of the biological world and their ability to control stereochemistry in chemical/biochemical transformations is unparalleled in the synthetic world.[5] Not only do enzymes conduct these transformations at incredible reaction rates, they are also substrate specific and are able to recognise and respond to molecules other than their specific substrate preventing unwanted chemistry from occurring. While this is an impressive characteristic, the field of asymmetric synthesis, due to its relative infancy, places the efficiency of the transformation as the primary objective.[6] The industrial manufacturing of chiral molecules does not require substrate specificity to the same level that it is required in the cell, rather the efficient turn-over and activity of the catalyst are principal. In order to achieve improved turn-over and catalyst activity, one can look to enzymes for inspiration. In order to mimic the activity of enzymes one must first understand the catalytic mechanisms of enzymes.

Pauling stated in the 1940's that the catalytic activity of enzymes is related to their stabilisation of the reaction transition state. The modern belief is much more complex and involves a plethora of different methodologies such as enhanced substrate binding, which causes destabilisation of the ground state without affecting the transition state, traditional stabilisation of the transition state

(Pauling effect) and conversely transition state destabilisation (anti-Pauling effect).[7] The development of small molecule catalysts, that can mimic enzymes, can also progress along these lines either by a) destabilisation of the reactants by either raising the HOMO or lowering LUMO to increase the rate of reaction, or b) influence either an increase or decrease in the stability of the transition state of the reaction. Furthermore, the chiral nature of the various amino-acid residues comprising the enzyme gives rise to the stereochemical outcome of the reaction. This implies the obvious; that the design of any stereodirecting synthetic catalyst must include a chiral component much in the way an enzyme does.

Substrate-enzyme interactions can be broken down into two groups; firstly reflexive binding to the substrates through hydrogen-bonding and hydrophobic interactions (non-covalent interactions) and secondly through reversible substrate-enzyme bond formation (covalent interactions).[6] It is no surprise then that the evolution of synthetic catalysts has also been derived along these same two basic mechanisms, namely non-covalent catalysis and covalent catalysis.

While there has been much reported advancement in the field of enzyme mimics, through supramolecular chemistry and transition metal-based catalysts, this thesis will focus on the development and progress of organocatalysis and in particular enamine organocatalysis.

1.2 History of organocatalysis

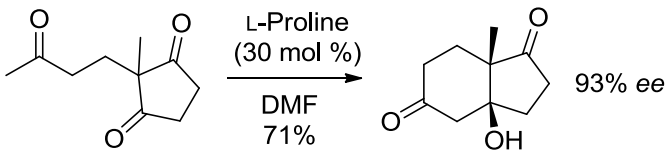
Asymmetric organocatalysis has been postulated, among a variety of alternate postulates, to be the source of homo-chirality of life on earth. According to the work of Pizzarello, L-isovaline found on a meteorite was able to generate sugars in a slight enantiomeric excess from a self-aldol reaction of glycolaldehyde.[8] The more potent organocatalysts such as L-proline, may have been delivered to earth by interstellar clouds.[9] This production of enantioenriched pre-biotic compounds through asymmetric organocatalysis could possibly have led to the observed homo-chirality in biological systems on earth. It would be almost poetic, if it were through the chiral systems that evolved from these building blocks that intelligent life capable of understanding the concept of organocatalysis was achieved.

Pasteur is credited with discovering the first asymmetric reaction when he noticed that *Penicillium glauca* resolved a racemic solution of ammonium tartrate in a decarboxylative kinetic resolution.[10] Breding continued this work using non-enzymatic conditions. Breding demonstrated that the enantioenrichment of the products from the thermal decarboxylation of camphorcarboxylic acid could be achieved when the reaction was performed in either D or L Limonene. Furthermore, he established the basic kinetic equations for this kinetic resolution in the presence of chiral alkaloids such as nicotine and quinine. Breding continued his landmark work by performing the first small

molecule asymmetric C-C bond forming reaction in the synthesis of mandelonitrile, again in the presence of chiral alkaloids.[11] While the enantioselectivity of these reactions remained below 10%, and the difficulty in measuring enantiomeric excess was hindered by the problems in purification of the stereoisomers, these reports laid the foundation for asymmetric synthesis.

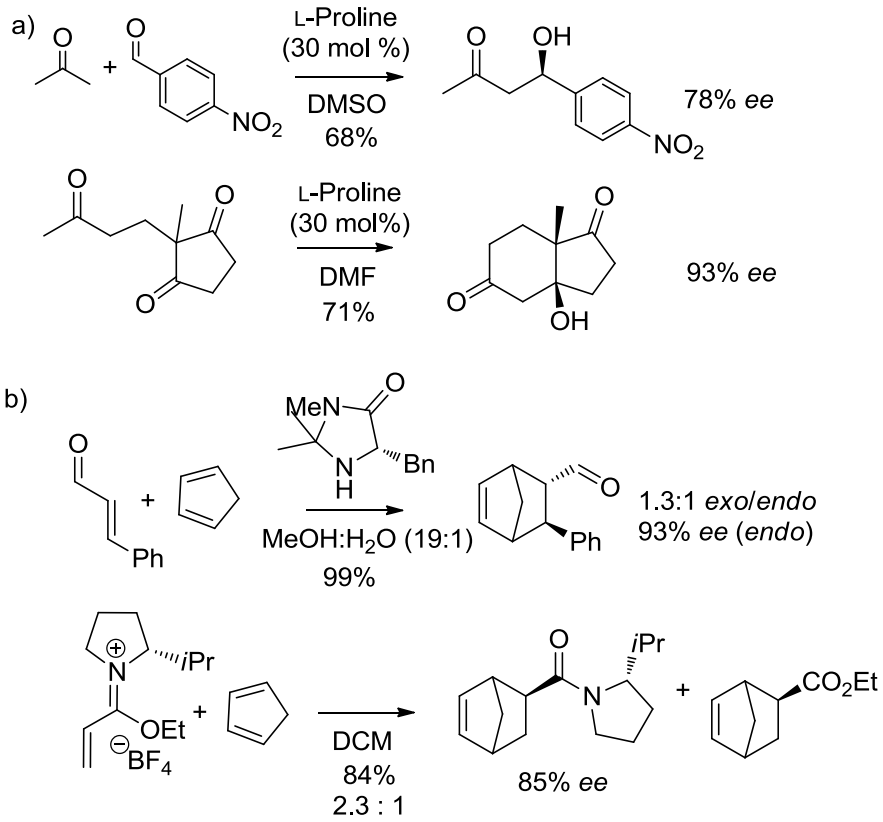
The development of organic catalysis continued with the further use of nitrogen containing alkaloids and amino acids. The importance of enamines, generated from amino acids, was realised by the mediation of the Knoevenagel condensation of malonates and malonic acid with aldehydes, albeit in a racemic fashion.[12] It was not until the reinvestigation of Bredings work by Prelog, and the addition of methanol to phenyl methyl ketene by Pracejus, that asymmetric organic catalysis was able to deliver synthetically useful levels of enantioselectivity.[13]

While there was steady progress after the ground breaking work by Pracejus the next major breakthrough could be considered to be the Hajos-Parrish reaction developed in the 1970's. The two workers at Hoffman-La-Roche reported using a catalytic quantity of proline to affect an asymmetric intra-molecular aldol reaction in a ring-closure Robinson annulation with high enantiomeric excess (**Scheme 1**).[14]



Scheme 1: Hajos-Parrish reaction

While there is still some debate over the mechanism of the reaction the involvement of covalent catalysis, *via* an enamine generated from proline, is beyond doubt. The continuing research in covalent catalysis during the 1970's and 80's resulted an the increase in the number of publications describing organic catalysts and their use in asymmetric reactions and resolutions.[11] In 2000 the publications of both Barbas[15] and MacMillan[16], representing enamine and iminium ion covalent catalysis respectively began what can be described as the golden era of organic catalysts and it was during this time that MacMillan coined the phrase organocatalysis. Barbas' work described an intermolecular aldol condensation using L-proline as the catalyst and compares favourably to the original aldol reaction reported by Hajos and Parrish (**Scheme 2**).[14, 17] MacMillan's paper reports an iminium ion mediated Diels-Alder cycloaddition and one may postulate that the inspiration for MacMillan's work may lie in the alkoxy iminium ion mediated Diels-Alder cycloaddition of Jung (**Scheme 2**).[17-18]



Scheme 2: a) Comparison of the work of Barbas-List[15] and the Hajos-Parrish[14] reaction, b) Comparison of work done by MacMillan[16] and the alkoxyiminium ion of Jung[18]

Similarly, the concept of non-covalent organocatalysis was developing steadily over the same period. Inspired by the aforementioned work of Breding using chiral alkaloids, Bergson and Långström applied (2-hydroxymethyl)-quinuclidine as a catalyst to perform the first Michael addition of β-keto esters to acrolein.[19] The versatility of cinchona alkaloids as a chiral platform for both Lewis-base and nucleophilic catalysis was expounded by Wynberg who showcased a variety of additions of nucleophiles to carbonyl substrates in both a 1,2- and 1,4- fashion. The importance of the C-9 hydroxy group as a Lewis acid was also established in his findings.[11, 20] In 2005, in a paper that would later become a landmark publication, Takemoto reported the use of a thiourea–amine catalyst in the addition of malonates to nitroolefins.[21] Takemoto's catalyst was bifunctional in nature with both Lewis acid (thiourea) and basic (amine) functionalities. In 2005 Soós[22] and Connon[23] concurrently reported replacement of the C-9 hydroxy group of the cinchona alkaloids with the improved Lewis acid functionality offered by thiourea and urea respectively. The success and simplicity of the Soós/Connon catalyst led to a vast expansion in the number of catalysts and catalytic reactions reported using the bifunctional organocatalytic systems.

1.3.1 Covalent catalysis

The majority of reported organocatalytic reactions can be described as occurring *via* covalent catalysis.[11] The principle behind covalent catalysis is that the substrate and catalyst form an adduct covalently through a Lewis-acid-base pairing. The resultant adduct is more reactive either through an increase in nucleophilicity or electrophilicity compared to the original substrate. This results in an increase in reactivity and conversion to products. The Lewis-base, *e.g.* amine catalyst, should not be consumed or altered during the course of the reaction. While sometimes these catalysts can be referred to as nucleophilic (*e.g*. enamine) or electrophilic (*e.g.* iminium ion) catalysts, they can also be described as Lewis-base catalysts due to the catalytic effect they elicit as a Lewis-acid-base adduct between the catalyst and the substrate.[24] While amine-based reactions are the most typical type of transformation, *via* either an enamine or an iminium ion intermediary, there are also a number of different methodologies, some of which will be presented in brief below.

1.3.1.1 Enamine catalysis

The generation of enamines from the condensation of secondary amines with carbonyl compounds has become a powerful tool in modern synthetic chemistry. Enamines are 'softer' and more reactive nucleophiles than their enolic counterparts due to the distorted coefficients of the HOMO frontier orbitals. The enamine can tautomerize to the iminium ion which can be hydrolysed in a facile manner to regenerate the catalyst and the corresponding carbonyl group, thereby creating a catalytic cycle. The ability to construct a secondary amine catalyst with a chiral framework, that places the enamine in a chiral environment, can allow the generation of asymmetric transformations. The design, synthetic versatility, catalytic cycle and stereoselectivity of amine catalysts used in enamine catalysis will be discussed in more detail later in this chapter (**See Section 1.4**).

1.3.1.2 Iminium ion catalysis

The reactivity of α,β-unsaturated carbonyl compounds has made them one of the most useful substrates in organic chemistry. Being electrophilic at both the carbonyl carbon and the 4-position allows for an interesting array of transformations. The reactivity of these substrates can be increased through the use of Lewis-acidic conditions. Co-ordination of a Lewis-acid to the carbonyl

group withdraws electron density and increases the respective electrophilicities of the carbonyl carbon the and 4- position (**Fig. 1**).[25]

The principle of iminium ion catalysis is to replicate the effect of Lewis-acid catalysis using an amine salt, which condenses with the carbonyl compound to form an iminium ion. This iminium ion replicates the π-electronics usually associated with Lewis-acid catalysis and results in a lowering of the LUMO of the entire π-system and hence promotes reactivity (**Fig. 1**).[16]

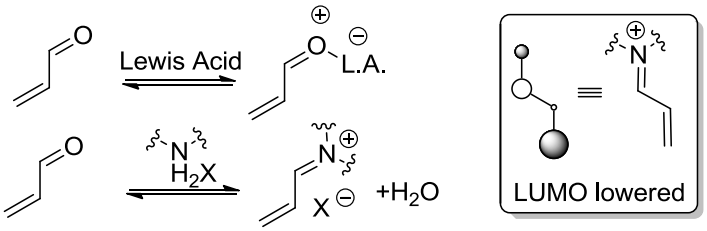
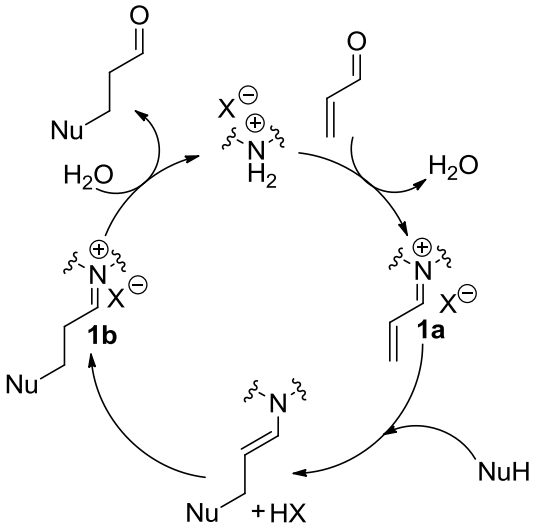


Figure 1: LUMO lowering effects of both iminium ion catalysis and Lewis-acid catalysis[26]

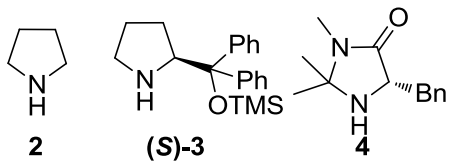
The major advantage that iminium ion catalysis has over Lewis-acid catalysis is its inherent ability to tolerate moisture and air. This allows the development of more robust and environmentally friendly catalytic methodologies, particularly when compared to air/moisture sensitive transition metal catalysis.

The general catalytic cycle for any iminium ion based reaction follows the same basic steps (**Scheme 3**). Firstly, the reversible generation of the iminium ion **1a** from condensation of the chiral amine with the carbonyl compound**.** This is followed by the reversible interaction of a nucleophile or diene with the lowered LUMO of the iminium ion **1a**. This results in the formation of the adduct enamine which tautomerises to the iminium ion **1b**. The iminium ion **1b** is subsequently hydrolysed to eliminate the product and regenerate the catalyst.[26]



Scheme 3: General iminium ion catalytic cycle.[26]
Note: All arrows are in equilibria

It has been found that the use of either acids or water enhances the rate of reaction of iminium ion based catalysts. Mayr and co-workers, using DFT calculations, found that the transition state for the formation of the hemi-aminal during iminium ion generation had much lower energy when water was employed. Mayer describes the water acting as a 'proton shuttle' between the salt of the amine catalyst and the carbonyl oxygen. It is also suggested in this paper that the rate-determining step in iminium ion catalysis is the iminium ion formation.[27] In the same report, Mayr established that the electrophilicity of iminium ions was directly linked to the amine catalyst, and showed that catalysts with electron withdrawing substituents had increasingly greater electrophilicity associated with their respective iminium ions. For example, the iminium ion generated from simple pyrrolidine **2** was found to be 20 times less electrophilic than the iminium ion generated from the silylated Jørgensen-Hayashi catalyst **3**, while the iminium ion generated from MacMillans imidazolidinone **4** was found to be the most electrophilic (**Fig. 2**).[27]

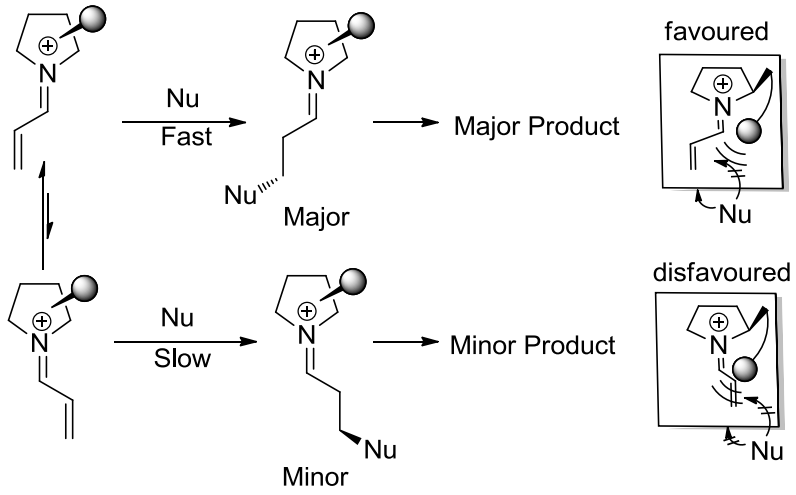


2 **(*S*)-3** **4**

Figure 2: Iminium ion catalysts

The stereodirecting power in iminium ion catalysis, as with enamine catalysis, results from the catalyst controlling the approach of the substrate through either electronic effects or through steric shielding. Whether the *E*- or *Z*- iminium ion is formed can also be considered to be important, as each iminium ion isomer may form opposite enantiomers when they react with a nucleophile. The presence of steric bulk on the catalyst framework will usually favour one isomer over the other,

most usually the *E*- isomer. It has been suggested that even if the *Z*-isomer is present, the steric repulsion generated in the transition state when a nucleophile attacks will render it disfavoured resulting in a slower reaction for the *Z*-isomer. The result of this is that the *Z*-isomer could isomerise to the more stable *E*-isomer, which is consumed at a faster rate in the reaction, giving rise to the desired product (**Scheme 4**).[26]



Scheme 4: Kinetic resolution of *E/Z*-iminium ions gives enantioselectivity[26]

Since MacMillan's seminal report in 2000,[16] describing the imidazolidinone **4** (**Scheme 2** and **Fig. 2**) catalysed Diels-Alder reaction, the use of organocatalysts to generate chiral iminium ions for asymmetric transformations has increased rapidly. This has led to a wealth of catalysts and reactions exploiting this methodology to generate valuable chiral products.

1.3.1.3 SOMO catalysis

The basic principle of SOMO catalysis involves using a stoichiometric single electron oxidant to interrupt the rapid 2 π-electron redox cycle between the iminium ion and enamine tautomers. The transient radical generated from this represents a 3 π-electron system with a singly occupied molecular orbital (**Fig. 3**).

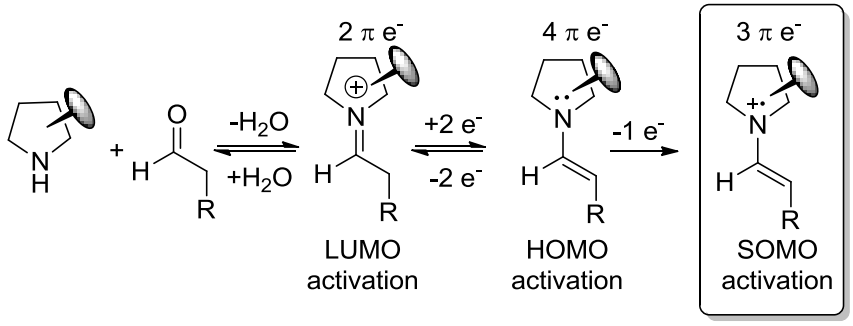
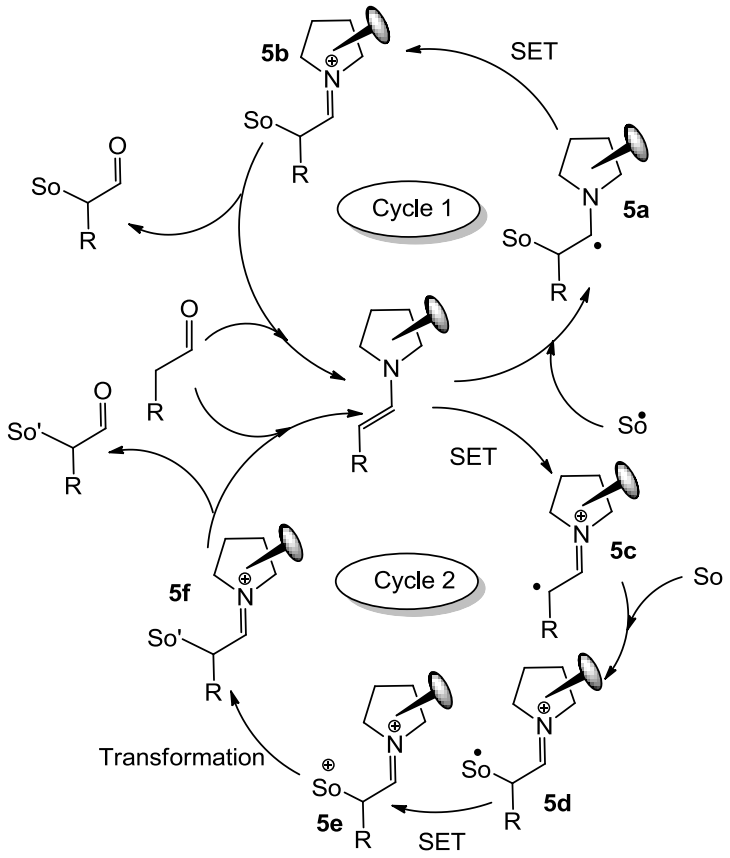


Figure 3: Generation of SOMO activated radical cation

This cationic radical species allows the nucleophilic α-carbon of an enamine to become electrophilic in an inversion of polarity known as umpolung. This electrophilic site can then undergo direct nucleophilic α-functionalization. The reaction was first reported, independently, by both MacMillan[28] and Sibi,[29] although Sibi's mechanism was later revised not to be through SOMO activation but rather enamine attack on an electrophilic TEMPO-Iron complex.[30]

The catalytic cycle is thought to proceed through two possible routes (**Scheme 5**). In cycle 1, the enamine acts as the SOMOphile by reacting with the highly electrophilic radical, $So^{\bullet}$, forming an α-amino radical **5a**. This radical is then oxidized by SET generating the iminium ion **5b**, which can be hydrolysed to release the product and regenerate the catalyst (**Scheme 5**). In cycle 2, the enamine is oxidized *via* SET first, generating the radical cation **5c**, which then reacts with the SOMOphile, So, giving the radical cation **5d**. This radical cation ion **5d** is subsequently oxidized, again *via* SET, to cation **5e**. At this point the SOMOphile undergoes a transformation (e.g. proton loss, nucleophilic addition, cycloaddition… etc.) that results in the generation of the iminium ion **5f**, which is subsequently hydrolysed to produce the regenerated catalyst and the product (**Scheme 5**).[26]



Scheme 5: Two possible SOMO activation catalytic cycles[26]

Note So' refers to transformed So and So = SOMOphile

Cycle 1 refers only to species in which the SOMOphile is preferentially oxidized over the enamine, whereas cycle 2 is a more general case in that the enamine is usually the reagent with the lowest ionisation potential.[31]

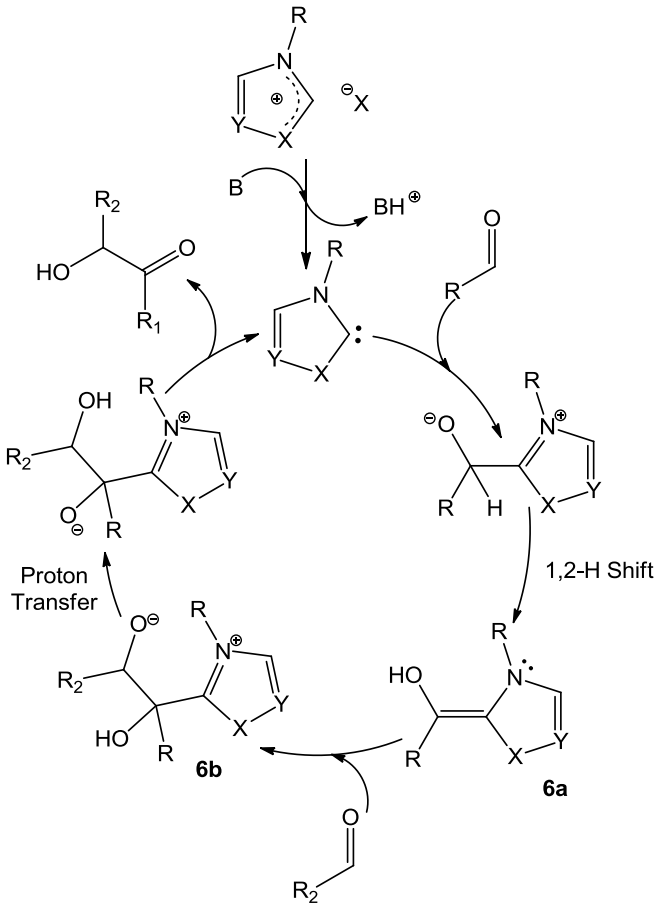
The stereodirecting ability of SOMO catalysis is derived from the ability of the catalyst framework to effectively block one face of the cation radical, either through an electronic interaction with the SOMOphile or through steric shielding. The relative geometry of the cation radical itself is also determined by the chiral framework. The radical cation will favour the isomer (*E/Z*) that is *anti*- to a bulky substituent so as to avoid steric repulsion, as calculated by Houk.[32]

SOMO catalysis has been used to perform enantioselective α-allylation[28], α-arylation[28], α-nitroalkylation[31] and other such reactions that use π-electron rich nucleophiles. The advantages of SOMO catalysis is that it can provide enantioselective access to α-functional groups that could not be achieved using other catalytic methodologies e.g. enamine activation.

1.3.1.4 *N*-Heterocyclic carbenes as organocatalysts

SOMO catalysis is not alone in its role of providing access to organocatalytic umpolung transformations. In fact *N*-heterocyclic carbenes (NHC) are responsible for the majority of umpolung organocatalysed transformations, most often as acyl anion equivalents.[33] While NHCs are not restricted to umpolung modes of action, it is in this regard that they are most useful.

While there has been a good deal of debate over carbene reactivity, Breslow' s 1958 description of the mechanism is the most generally accepted version.[34] **Scheme 6** depicts a typical catalytic cycle for the benzoin condensation using an NHC. NHCs are generated *in situ* from deprotonation of an azolium salt by a Brønsted-base. The nucleophilic carbene attacks an aldehyde, which undergoes a 1,2-H shift to form the Breslow-intermediate **6a.** This intermediate is a nucleophilic enolamine which can attack an electrophile, in this case a carbonyl compound. The resultant product **6b** then undergoes proton exchange. This allows the cationic azolium moiety to be eliminated under basic conditions to regenerate the catalyst and release the product, in this case the benzoin condensation product (**Scheme 6**).



Scheme 6: Catalytic cycle of an NHC catalysed benzoin condensation
Note: All arrows are in equilibria

If the NHC has chiral substituents then the transformation can be performed asymmetrically. The (*E*/*Z*) geometry of the enolamine (Breslow intermediate) usually favours the larger group to be *anti*- so as to avoid the large stereodirecting group. From here, either side of the enolamine can be shielded efficiently by either steric bulk or electronic interactions. The substrate itself can sometimes engage in directing which face the electrophile approaches.[35] An example of a chiral NHC **7a** and corresponding chiral Breslow-intermediate **7b** developed by Glorius[36] is depicted in **Figure 4**.

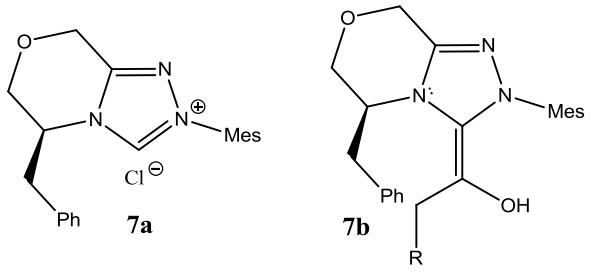
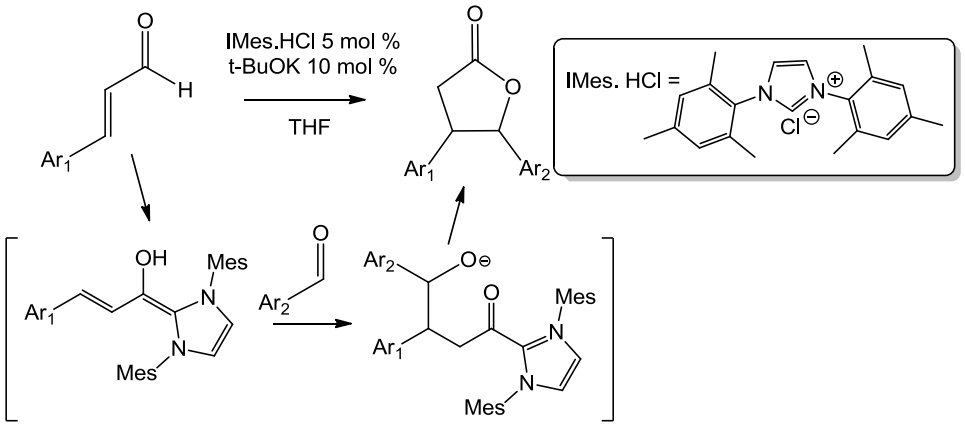


Figure 4: Left to right; a chiral NHC; the corresponding chiral Breslow-intermediate[36]

Mes = mesityl

While NHC structure varies dramatically depending on reaction type, to-date there is no generally applicable NHC catalyst, it is generally accepted that the triazolium salt-derived NHCs are superior for most asymmetric organocatalytic purposes.[33]

An interesting use of NHCs in organocatalysis was introduced by both Bode[37] and Glorius[38] in 2004. Using α,β-unsaturated aldehydes they were able generate a homoenolate which could add to an aldehyde. The resulting 'activated carboxylic acid' was then attacked by the alcoholate to release the catalyst and generate the cyclized lactone (**Scheme 7**).



Scheme 7: Homoenolate generation using NHC catalysis[38]

The use of NHC organocatalysis to invert the polarity of electrophilic functional groups has led to many innovative and stereoselective reports. Despite the instability and water sensitivity that is

inherent with carbenes, they offer the reactivity that is unavailable through other means and have the potential to include a chiral framework for the induction of stereoselectivity.

1.3.2 Non-covalent catalysis

There are a large number of reports utilising weak-interactions, and non-covalent catalysis, to asymmetrically accelerate chemical transformations. Similar to covalent catalysis the substrate must be activated, by interaction with the catalyst, through either an increase in nucleophilicity or electrophilicity. The catalyst must also not be consumed or altered during the course of the transformation.

The substrate activating weak interactions can include neutral host-guest complexation, or acid-base association.[11] While neutral host-guest complexation is related to larger macro-molecules, which resemble small enzymes in terms of functions and in *modus operandi*, the acid-base association interaction is more relevant to this thesis. The association of these acids and bases follow two principal means, firstly through implicit hydrogen bonding (Lewis acid) and secondly through deprotonation followed by cation/anion association (ion-pair). Both of these types of interactions have been widely reported and developed, this thesis will provide only a brief overview of these topics.

1.3.2.1 Hydrogen bonding catalysis

Hydrogen-bonding (H-bonding) catalysis functions in much the same vein as classical Lewis acid catalysis. This entails interaction with the electrophile causing a lowering in the energy of the LUMO as a result of the decrease in electron-density. In this respect the proton is acting as a Lewis acid through H-bonding (**Figure 5**).

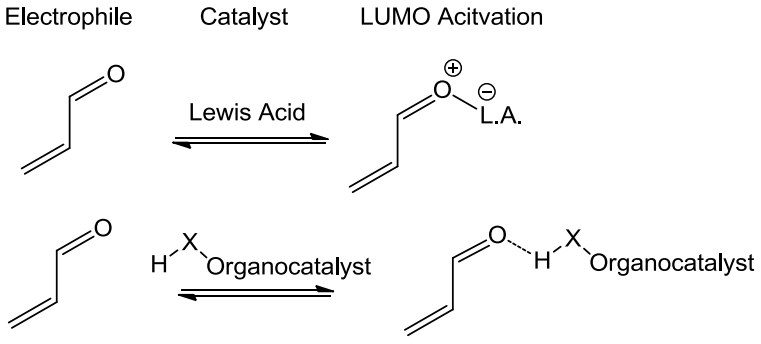
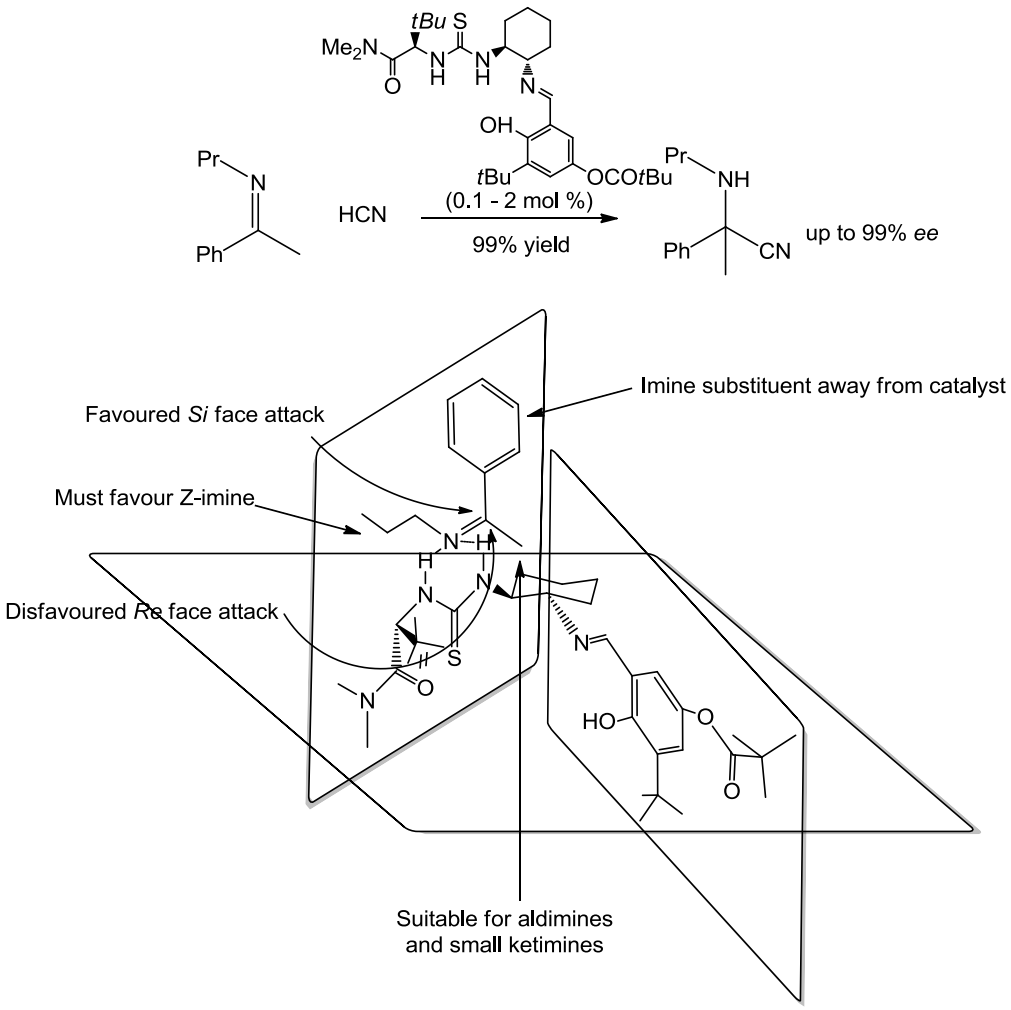


Figure 5: Substrate activation through H-bonding

By using chiral architecture on the Lewis acid we can create a chiral environment around the activated substrate. Efficient small molecule asymmetric H-bonding additives were first deployed by Jacobsen in 1998 to perform an asymmetric Strecker reaction.[39] Using this as a model reaction we can explain the rationale behind many hydrogen bonding catalysts. In **Scheme 8** we can see a 3D representation of the catalyst structure, calculated using molecular modelling,[40] of one of the H-bonding catalysts used by Jacobsen. The imine substrate is 'bound' to the thiourea moiety, which serves to hold the molecule in place and to activate its LUMO, as mentioned above. The imine is bound as the *Z*-isomer, which is important as imines can rapidly interconvert between geometrical isomers and preference for one isomer over the other is essential for facial selectivity. The binding of two protons to the substrate is also important as the product of the reaction is calculated to be bound to a single proton. This makes product-catalyst interactions higher in energy and less favoured and allows the release of the catalyst and hence catalyst turnover. The spatially restricted environment created by the catalyst structure allows the *Z*-imine to bind in a particular manner. The imine substituent, phenyl in this case, must be facing away from the catalyst superstructure. The same can be said for the *N*-substituent. The bulk generated from the peptide end of the catalyst prevents the nucleophile from approaching the *Re* face of the imine. As a result the nucleophile must attack from the *Si* face, over the diaminocyclohexyl ring. These factors give rise to the high level of enantioselectivity observed in the Strecker reaction.[40]



Scheme 8: Model for H-bonding based catalysis from asymmetric Strecker reaction[40]

The activation of electrophiles is of course not limited to urea and thiourea derivatives. The alcohol moieties of TADDOL and BINOL and other chiral alcohols have also been used to promote various reactions such as the Diels-Alder reaction[41] and Mukaiyama-Aldol processes.[42] Usage of organic H-bond donors as catalytic Lewis acids has grown rapidly since 1998 and it's facile approach to both activation and asymmetric induction makes it both very practical and a pragmatic tool for organic chemists.

1.3.2.2 Bifunctional catalysis

While H-bonding catalysis can be considered mono-functional, the employment of catalysts with two synergistic modes of activation is called bifunctional catalysis. The bifunctionality of such catalysts involves, for example, the concerted actions of both H-bonding catalysis to activate the electrophile and general-base catalysis to activate the nucleophile. Both the acidic and basic sites

are linked *via* a chiral scaffold, this allows not only a chiral environment for the electrophile but also for control of the nucleophiles approach (**Fig. 6**). This system of dual activation often leads to higher yields, selectivities and quicker reaction times.

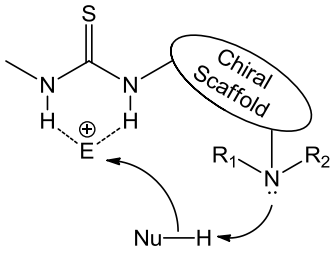
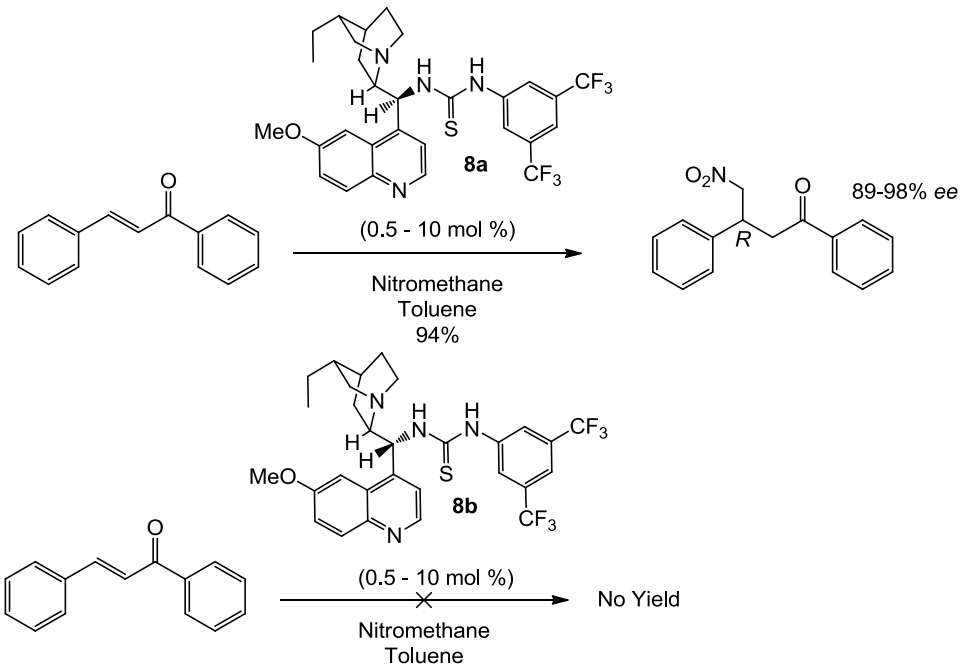


Figure 6: Schematic of a chiral bifunctional catalyst

Cinchona alkaloids can be considered to be natural bifunctional catalysts as they contain both a chiral hydrogen bonding alcohol at the C-9 position and a chiral basic tertiary nitrogen in a quinuclidine ring system. The first synthetic bifunctional organocatalyst was reported by Takemoto in 2003.[21] Expanding on the observed synergistic effect, there has been a wealth of different catalytic systems developed using this methodology. One of the more dominant architectures constructed uses the natural bifunctionality of cinchona alkaloids and replaces the hydroxy group with a more potent urea or thiourea moiety. This catalyst (Soós-Connon catalyst) was reported independently by 4 groups in 2005.[22-23, 43] Using this scaffold many high yielding enantioselective methodologies have been developed. Examining the stereochemistry of the catalyst structure allows a better understanding as to how the catalyst may function.

The Soós-Connon **8a** catalyst depicted in **Scheme 9** can catalyse the Michael addition of nitromethane to chalcones in excellent yields and near perfect selectivity, while the natural configuration pseudo-enantiomer **8b** is unable to produce any detectable yield. The reason for this is the misalignment of the basic nitrogen in relation to the activated electrophilic site on the chalcone. This rigid specificity for substrate geometry is what gives bifunctional catalysts their stereodirecting power.[22]



Scheme 9: Rate-acceleration comparison of pseudo-enantiomers[22]

Bifunctional organocatalysis has been adapted to many different transformations and as with pure hydrogen bonding catalysts high yields and selectivities have been obtained with relatively low catalyst loadings.

1.3.2.3 Ion-pair catalysis and phase-transfer catalysis

An ion-pair is an entity composed of both a cationic and anionic species in close proximity, with their association only due to Coulombic attraction. For clarity, in definition over traditional Brønsted base catalysis, both partners must interact during the reaction mechanism either through activation of the substrates or by chirality transfer.[44] The design of many ion-pair catalysts is outlined in **Figure 7**.

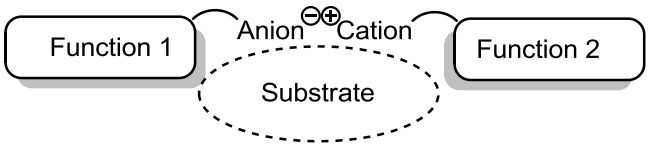
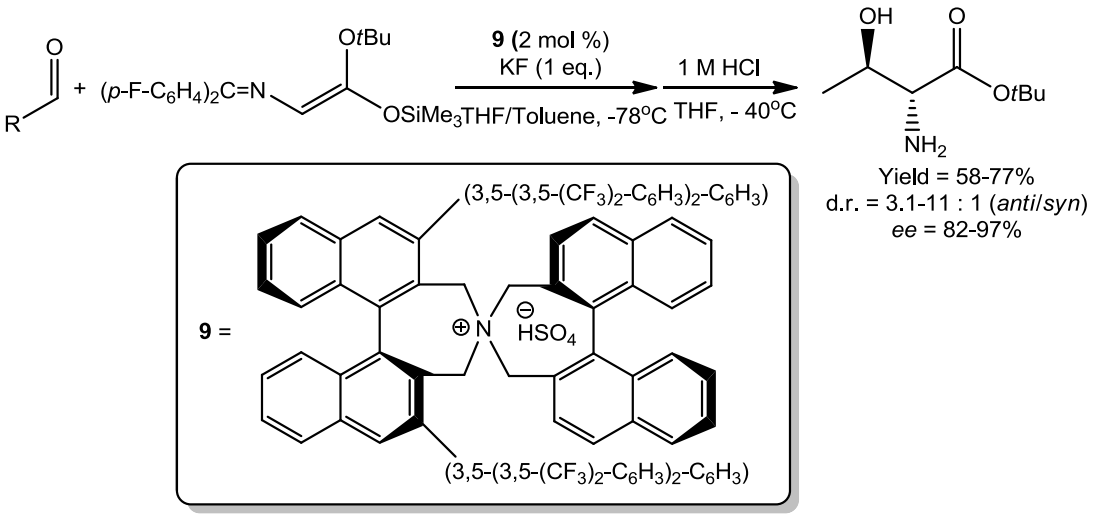


Figure 7: Ion-pair catalysis

A classic example of ion-pair catalysis is the employment of chiral quaternary ammonium fluoride salts. The reactive ion-pair is generated *in situ* using a catalytic quantity of a chiral salt and stoichiometric potassium fluoride. Maruoka was the first to report a highly selective version of these catalytic systems in 2004.[45] In this paper the chiral ammonium fluoride salt from **9** is used to

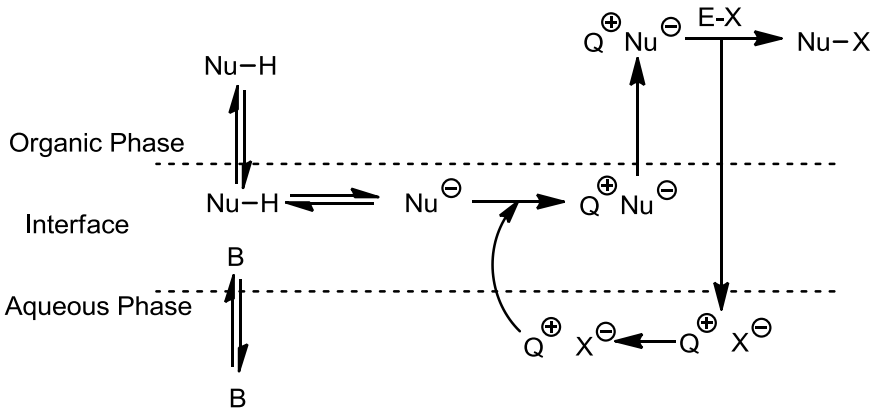
promote the fluoride ion catalysed Mukaiyama-Aldol reaction in high yield and excellent selectivity (**Scheme 10**).



Scheme 10: Ion-pair catalysed Mukaiyama-Aldol reaction.[45]

The vast number of different anion/cation combinations allows for a near limitless variety of catalyst constructs. This allows ion-paired catalysis to offer a viable alternative to either new or existing organocatalysts.

In phase-transfer catalysis (PTC) the reacting substrates are separated by heterogeneous phases and the catalyst induces reaction by transferring one reactant to the opposing phase. In a general scheme the anionic nucleophile, dissolved in the aqueous phase, is separated from the electrophile in the organic phase. An aqueous-soluble Brønsted base must be employed to initially deprotonate the nucleophile and generate anionic character. The cationic phase transfer catalyst (PTC) forms an association with the deprotonated nucleophile. This causes increased solubility in the organic phase due to the decrease in ionic character of the ion-pair. This effectively delivers the active nucleophile to the electrophile thus promoting the reaction. The resultant reaction restores the cationic character of the PTC which returns to the aqueous phase closing the catalytic cycle (**Scheme 11**).

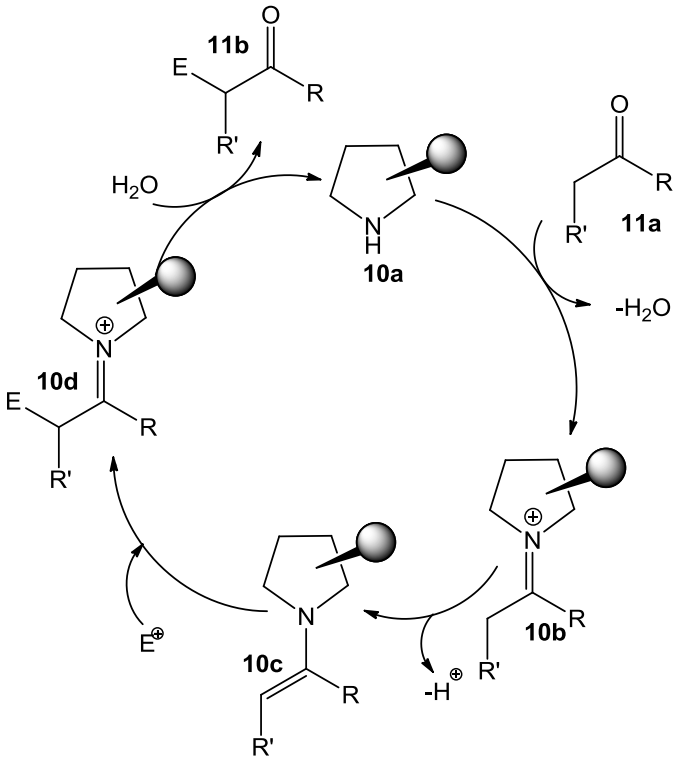


Scheme 11: Schematic of PTC. Note Q = PTC, B = Brønsted Base.

Of course PTC is not limited to organic/aqueous liquid –liquid biphasic mixtures. In many cases a homogenous organic mixture can be used with an inorganic polar base. In this case, the interface exists between the solid and the organic liquid. PTC has the inherent 'green-chemistry' appeal due to its tolerance of water and high catalytic turnovers.

1.4 Enamine catalysis

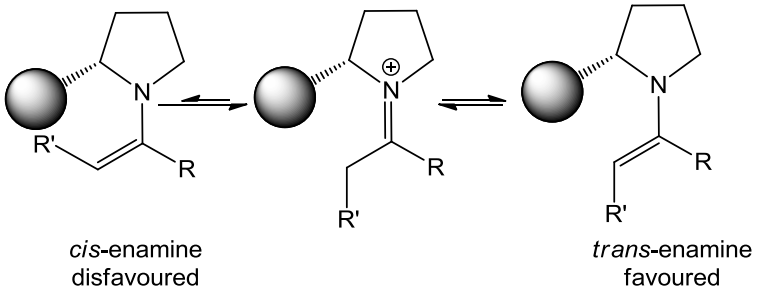
The basis of enamine catalysis is the catalytic generation of an enamine from the reversible condensation of a carbonyl containing compound **11a** with an amine **10a** (**Scheme 12**). Generation of the enamine **10c** is promoted by the substantial increase in acidity of the α-hydrogen of the iminium ion **10b** compared to the starting carbonyl compound **11a**. The enamine **10c** should be able to undergo nucleophilic addition to various electrophiles **E** and the resulting iminium ion **10d** is then hydrolysed by the *in situ* generated water to give the α-substituted carbonyl product **11b** (**Scheme 12**).[46]



Scheme 12: Catalytic cycle of an enamine[26]
Note: All arrows are in equilibria

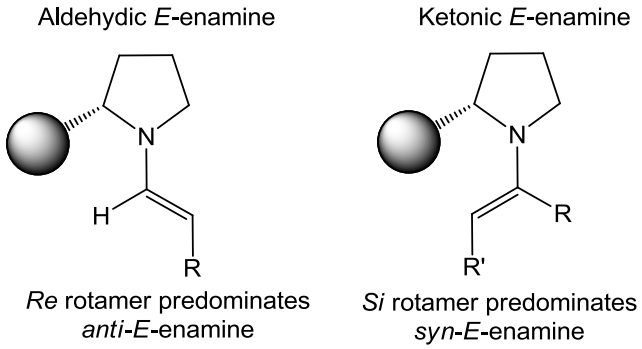
The formation of the enamine causes the HOMO of the carbonyl compound to be raised. This is due to the generation of an amine substituted electron rich olefin. The electron rich π-system is then able to participate in nucleophilic addition reactions.[47]

The steric environment of the catalyst determines the enamine *E*/*Z* ratio through a thermodynamic equilibrium.[48] The interaction of the α-substituent of the enamine with the catalyst structure raises the energy of the conformation, usually making the *cis*-enamine disfavoured (**Scheme 13**).



Scheme 13: Thermodynamic equilibrium of enamine geometry

If the catalyst also presents a chiral environment, then there will be a preference for one of the enamine rotamers which contributes to the facial selectivity in subsequent reactions with an electrophile. A second contributing factor to the facial selectivity is the size of the substituents on the enamine. If the carbonyl compound is an aldehyde then the least sterically hindering substituent is the aldehydic hydrogen. This leads to the predominance of the more stable *Re* rotamer or *anti*-enamine (**Scheme 14**). If the carbonyl compound is a ketone then the least sterically hindering moiety is the planar alkene, this shifts the equilibrium to the *Si* rotamer or *syn*-enamine (**Scheme 14**), excluding exogenous interactions.[48]

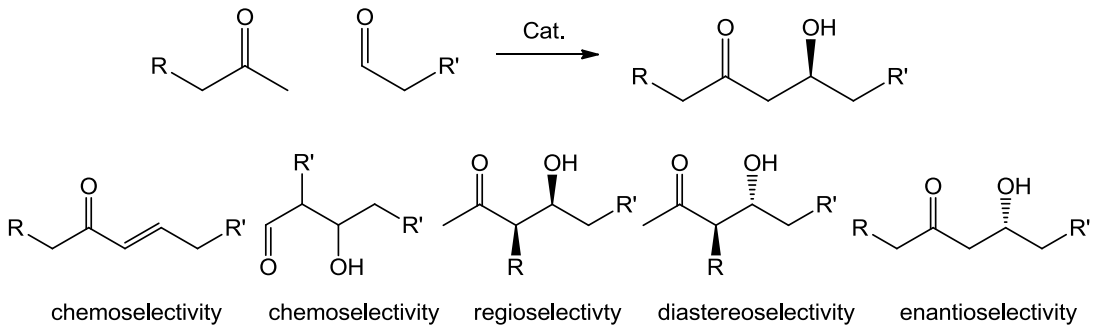


Scheme 14: Substrate promoted enamine rotamer preference
Note *Re Si* assignment through C of rotameric C-N bond

The last twelve years, since the work of Barbas and List,[15] have seen huge developments in enamine catalysis, both in terms of substrate expansion and the synthesis of novel catalysts. Herein is but a selection of the transformations and catalyst structures reported in the literature.

1.4.1 Aldol reaction

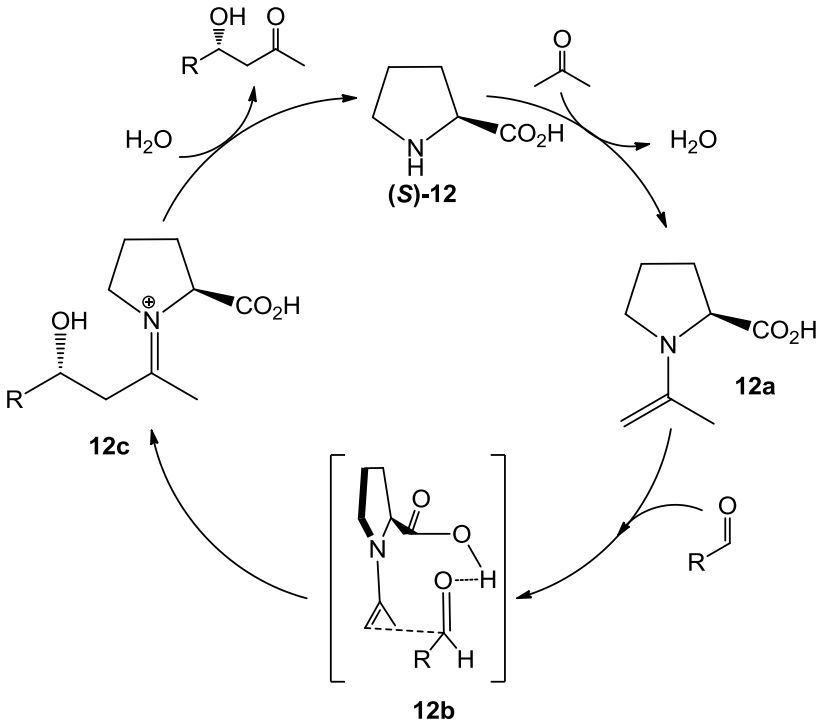
The aldol reaction, discovered by Wurtz in 1872,[49] has become one of the most studied reactions in chemistry. It is both a powerful transformation and a challenging one. The challenges encountered are of a chemo-, regio-, diastereo-, and enantioselective nature (**Scheme 15**).[50]



Scheme 15: Challenges associated with the aldol reaction[50]

As previously mentioned, (**See Section 1.2**), the Barbas-List report in 2000 used L-proline in catalytic amounts to effect the aldol reaction of acetone, and later cyclic ketones, to aryl aldehydes and branched aliphatic aldehydes in high enantiomeric excess and yield.[15] The reaction was however less successful when the aldehyde was unbranched at the α-carbon, resulting in appreciable amounts of self-condensation. The difficulty in controlling certain aldol additions is exemplified in a later publication by List, which describes a proline catalysed aldol addition where the authors could not prevent the product iminium ion from undergoing a competing Mannich type reaction.[51]

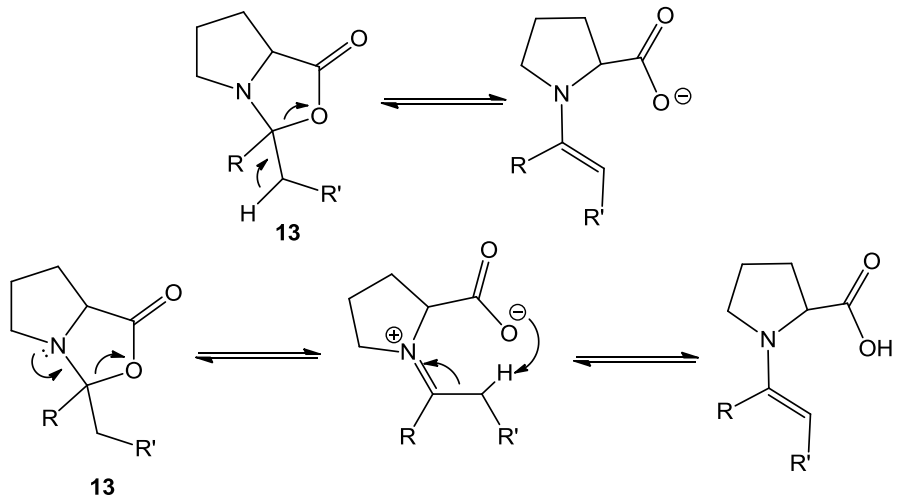
The reaction mechanism of proline-catalysed asymmetric aldol reaction has been intensely studied and debated. Although there are several mechanistic proposals, the most widely accepted are the reports by Arno[52] and by Houk (**Scheme 16**).[53]



Scheme 16: Proline catalysed asymmetric aldol-reaction[26]
Note: All arrows are in equilibria

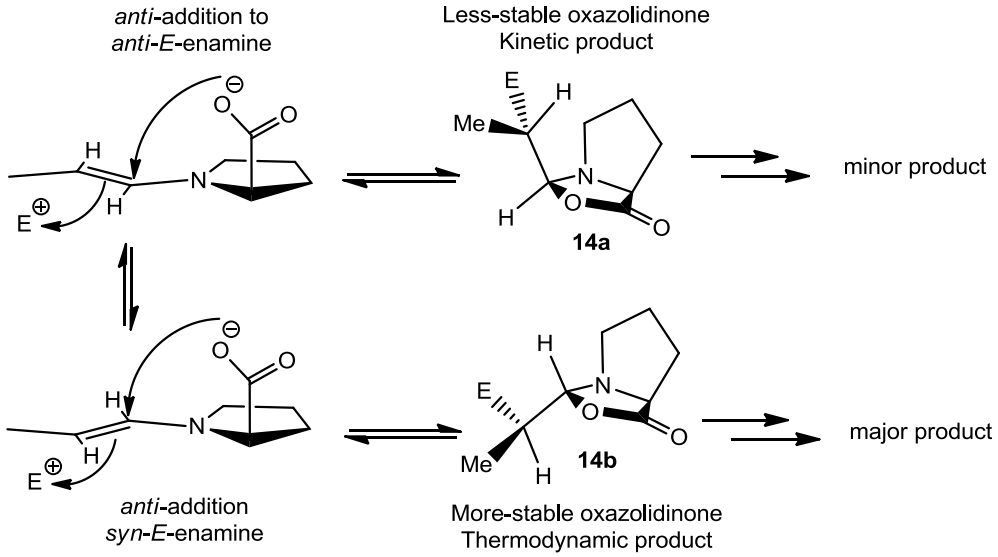
The formation of the enamine **12a**, resulting from the condensation of L-proline **(*S*)-12** with acetone, has been considered the rate-limiting step in the proline catalysed aldol reaction, but recent evidence suggests that the addition of the enamine **12a** to the aldehyde **12b** has a similar if not higher energy barrier.[54]

It must also be mentioned that the presence of detectable amounts of oxazolidinone **13** (**Scheme 17**) has been associated with proline catalysed aldol reaction. The formation of this oxazolidinone has been cited as a 'catalytic-sink', which can usually be avoided by using large quantities of the aldol donor in the reaction.[50] However, Seebach and Eschenmoser proposed that the oxazolidinone **13** is a key player in the mechanistic cycle. In their version of the mechanism the formation of the oxazolidinone **13** allows for regioselective enamine formation *via* an E2 elimination or through a two-step iminium on formation and intramolecular proton exchange (**Scheme 17**).[55]



Scheme 17: Enamine formation as proposed by Seebach and Eschenmoser[55]

Furthermore the group postulated that the attack of the electrophile was in concert with oxazolidinone formation. The stereoselectivity of the reaction was then considered to be a result of which *E*-enamine rotamer (*syn*/*anti*) gave the thermodynamically more stable oxazolidinone. Interestingly the DFT calculations showed that the electronically favoured addition led to the least stable (kinetic product) oxazolidinone **14a**, while the electronically disfavoured addition led to the more stable (thermodynamic product) oxazolidinone **14b** (**Scheme 18**). As the observed product stereochemistry matched the more stable oxazolidinone **14b** the authors assumed the reaction must be under thermodynamic control and thus operates in a reversible fashion.[55]



Scheme 18: *anti*-Addition of carboxylate to enamine and electrophilic attack leads to thermodynamically controlled oxazolidinone formation and observed stereochemistry[55]

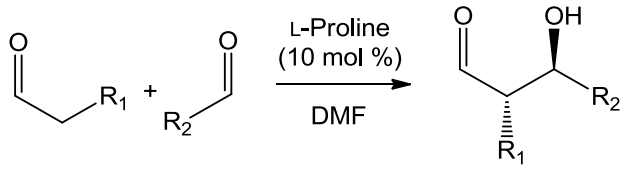
While the paper is extensive and has many interesting arguments it can only be applied to catalysts with a carboxylic acid moiety capable of forming an oxazolidinone. The model is also difficult to apply when high levels of diastereoselectivity are observed, when using pro-chiral electrophiles, as

only facial selectivity at the enamine α-carbon is accounted for and any electronic interactions of the electrophile with the carboxylate are reduced.

The use of proline as a catalyst in the aldol reaction has continued to develop with new reaction conditions generating some impressive results. In 2007, Hayashi reported using solvent free conditions and was able to achieve high yields, diastereoselectivity and enantioselectivity in the cross-aldol reaction between aldehydes. Using a slight excess of water, or neat conditions, cyclohexanone could be added to a selection of substituted benzaldehydes generating the aldol adduct with up to 14 : 1 *anti*- diastereoselectivity and 98% ee.[56] The use of the ionic liquid ([emim][OTf]) over DMSO allowed the achievement of even higher diastereoselectivities, with a 20 : 1 *anti* : *syn* ratio for the addition of cyclohexanone to *p*-CF_3-benzaldehyde.[57]

It is also worth noting that proline has been employed to catalyze the addition of other, more challenging, aldol donors such as α-substituted ketones; hydroxyacetone,[58] protected hydroxyacetone[59] and trifluoromethyl ketones.[60]

The use of aldehydes as aldol donors has also been extensively explored. Jørgensen reported the coupling of aldehydes to non-enolisable α-ketoesters in excellent yield (up to 98%), high *ee* (up to 90%), although with a limited substrate scope, using 50 mol% of proline.[61] MacMillan and Northrup presented an impressive methodology describing the slow addition of the aldehydic donor to a solution of L-proline and the acceptor at 4 °C.[62] This approach was applicable to both α-branched and α-unbranched aldehydes although, at reduced selectivities for the latter (**Table 1**).



R_1	R_2	Yield%	d.r. (*anti/syn*)	ee%
Me	Et	80	4 : 1	99
Me	*c*-Hexyl	87	14 : 1	99
Me	Ph	81	3 : 1	99
Bn	*i*Pr	75	19 : 1	91

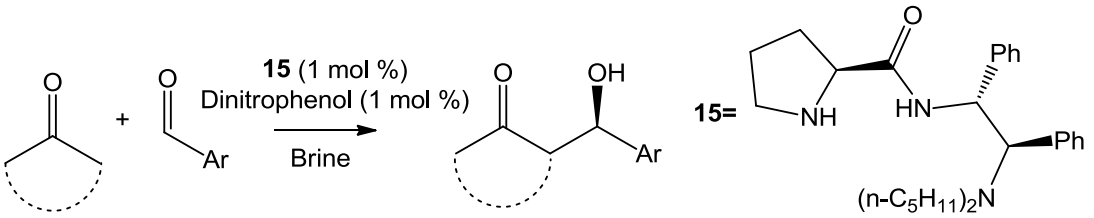
Table 1: Selected results of cross-aldol reaction reported by MacMillan[62]

While L-proline is inexpensive and has a wide reaction scope, the interest in modification and development of new catalysts highlighted some of the problems associated with proline. These problems include long reaction times (typically approx. two days), poor selectivity when using α-unbranched aldehydes, need for large excess of ketones and high catalyst loadings. While some of these issues are related to the poor solubility of the zwitterionic L-proline in the reaction media,

others are not so easily overcome. A selection of catalysts that have been developed to overcome some of prolines limitations in the aldol reaction will now be discussed.

In 2005, Wennemers showed that the tripeptide **H-L-Pro-D-Ala-D-Asp-NH_2** could be used to efficiently promote the aldol reaction of acetone with aldehydes in as little time as 4 hours at 1 mol% catalyst loading. The opposite enantiomer to that from L-proline was generated in up to 98% yield and 90% *ee*.[63] The authors suggest this improved catalytic power is a result of the conformation of the tripeptide. The amine of the proline residue is in close proximity to the carboxylic acid of the aspartic acid residue, which may allow for more efficient proton donation.

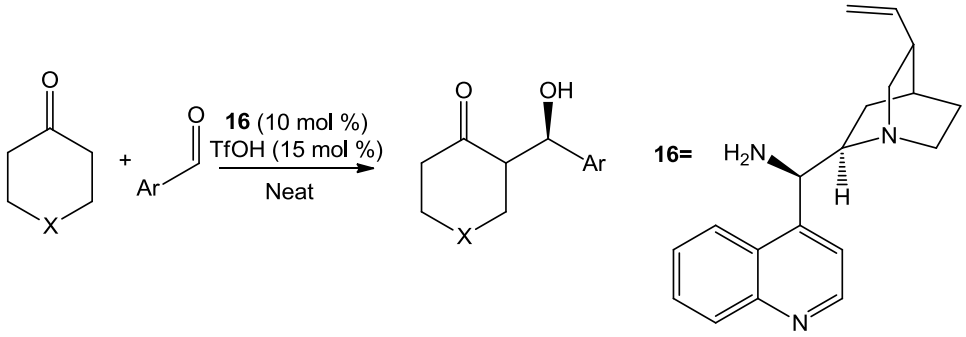
The use of Brønsted-acids as co-catalysts has improved not only the reaction times of the aldol reaction but has also generally increased enantioselectivity. The reported explanation as to how they promote the aldol reaction is through disruption of the enamine/free-catalyst equilibria favouring the enamine, and secondly to help orientate the substrate on approach to the enamine.[64] A good example of the co-operative partnership between Brønsted-acids and Lewis-bases can be found in the proline derived stilbene **15** developed by Da.[65] Using 1 mol% catalyst, Da and co-workers were able to achieve high yields and excellent selectivity using both acetone and cyclohexanone as the aldol donor (**Table 2**).



Ketone	Ar	Time (h)	Yield(%)	d.r. (*syn/anti*)	*ee(%)*
Acetone	4-NO_2-C_6H_4	20	96	-	94
Acetone	3-NO_2-C_6H_4	12	97	-	91
Acetone	4-Br- C_6H_4	120	64	-	90
Cyclohexanone	4-NO_2-C_6H_4	22	84	79 : 21	93
Cyclohexanone	4-Br- C_6H_4	60	73	85 : 15	93
Cyclopentanone	4-NO_2-C_6H_4	11	97	63 : 37	77

Table 2: Selected results of cross-aldol reaction reported by Da[65]

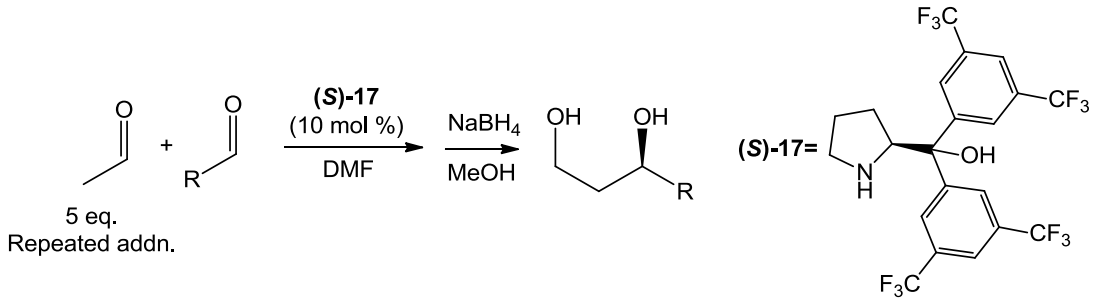
The design of catalysts for the asymmetric aldol reaction has not remained limited to proline derivatives and many other chiral frameworks have been employed. Most interesting is the use of the cinchona alkaloid derivate **16** by Liu in 2007.[66] Although the reaction is rather poor when using acetone, cyclic ketones are coupled to aldehydes in excellent yields and impressive selectivities (**Table 3**). The use of a sub-stoichiometric quantity of triflic acid and neat cyclohexanone at room temperature resulted in a relatively quick nine hour reaction.



Ar	X	Yield%	d.r. (*syn/anti*)	ee%
4-NO_2- C_6H_4	CH_2	99	9.2 : 1	99
4-NO_2- C_6H_4	O	92	5.4 : 1	91
Ph	CH_2	31	1 : 1	86
Fural	CH_2	39	1 : 2.5	94 (*anti*)

Table 3: Selected results of cross-aldol reaction reported by Liu[66]

In 2005, Hayashi and Jørgensen introduced diarylprolinols to organocatalysis. The effectiveness of these systems was demonstrated by Hayashi when he was able to "tame" acetaldehyde in an asymmetric cross-aldol reaction.[67] Acetaldehyde has previously been reported by Barbas to undergo trimerization in 13% yield when L-proline was employed as a catalyst.[68] In Hayashi's methodology the fluorinated diarylprolinol **(*S*)-17**, in 10 mol%, could perform the addition of acetaldehyde to a variety of aryl aldehydes in high yields and excellent stereoselectivities, albeit with long reaction times and repeated addition of 5 equivalents of acetaldehyde (**Table 4**).



R	T (^{o}C)	Time (hr)	Yield%	ee%
Ph	23	120	53	99
4-NO_2- C_6H_4	23	24	85	96
4-CF_3- C_6H_4	4	72	74	99
4-Pyridinyl	23	43	83	99
$CH(OMe)_2$	4	72	92	80

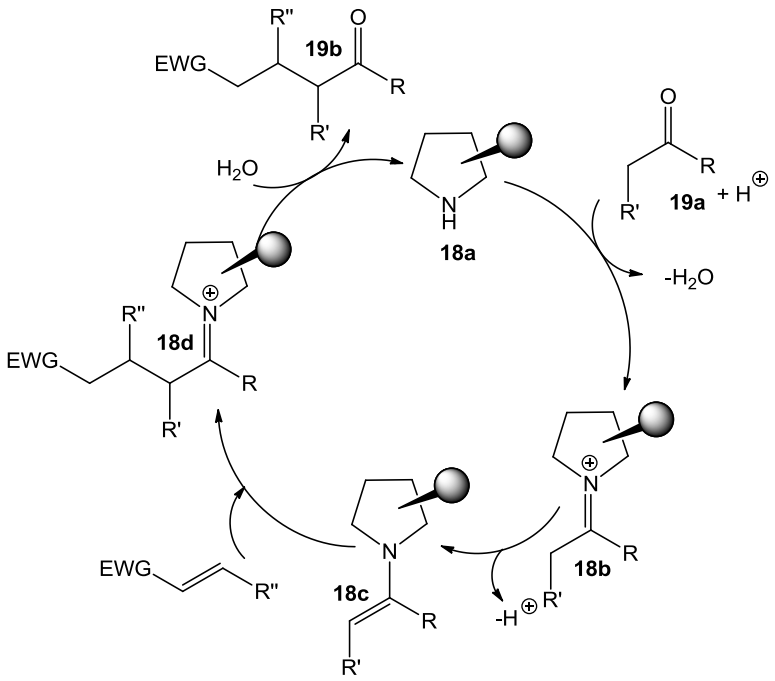
Table 4: Selected results of cross-aldol reactions of acetaldehyde reported by Hayashi[67]

While the cross-aldol and other aldol reactions are readily catalysed *via* enamine organocatalysis, the application of chiral enamines is not limited to this type of transformation.

1.4.2 Michael type addition

The Michael addition is one of the mildest C-C bond forming reactions in chemistry. Since its discovery by Arthur Michael in 1887,[69] the Michael addition or 1,4-conjugate addition has dramatically increased in scope with thousands of papers describing the catalysed and uncatalysed addition of many different nucleophiles to a selection of electron-deficient π-systems.[70]

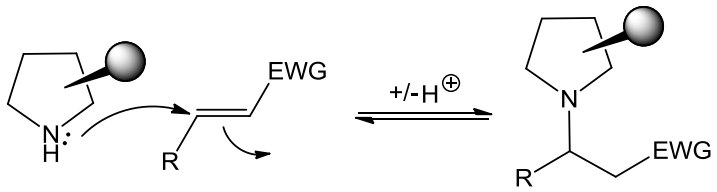
Chiral amines can also catalyze the addition of ketones and aldehydes to Michael acceptors through the formation of enamines (**Scheme 19**).



Scheme 19: Enamine catalysis of a Michael addition[26]
Note: All arrows are in equilibria

As explained previously, the chiral amine **18a** condenses reversibly with the carbonyl compound **19a**. The tautomerisation, *via* deprotonation, to the enamine form **18c** is caused by the dramatic increase in acidity of α-hydrogen of the iminium ion **18c**. The enamine is a carbanion equivalent which can then react with the electron deficient olefin **19a** to create a new C-C bond. The resultant iminium ion **18d** is hydrolysed generating the desired product **19b** and the chiral amine **18a** re-enters the cycle.[48]

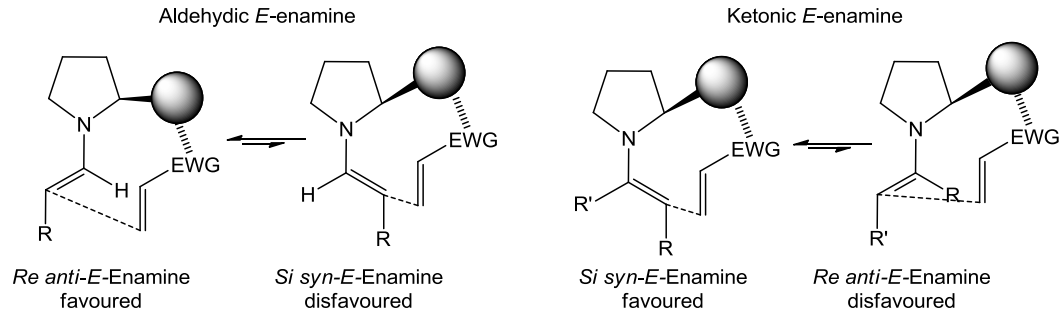
A potential problem with this form of catalysis relates to the chiral amine itself undergoing an aza-Michael addition to the electrophilic substrate thus 'trapping' the catalyst. The ability of the catalyst to reverse this in a retro-aza-Michael reaction is paramount to the success of the desired conjugate addition (**Scheme 20**).



Scheme 20: Substrate 'trapping' of the catalyst[48]

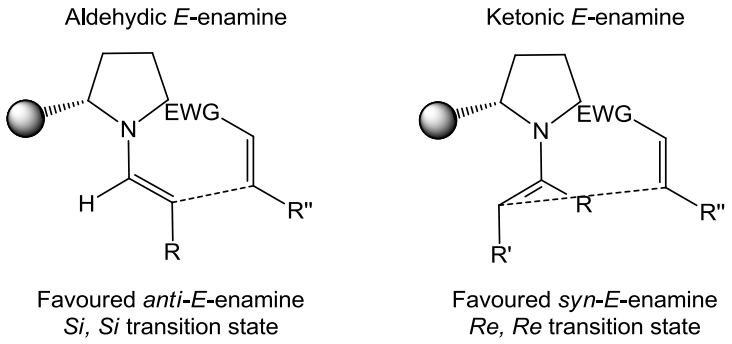
While the chemoselectivity of enamines is innate, as enamines are 'soft-nucleophiles',[71] the enantioselectivity is dependent on the chiral framework of the catalyst. The *E*-enamine reacts as a carbanion equivalent, and as discussed previously the preference of the *Si* or *Re* rotamer (*syn*/*anti* rotamer) of the enamine is determined by the pro-nucleophile (aldehyde or ketone). The selective

approach of the electrophile to one face of the enamine determines the final geometry of the product. The most common model used to explain this is the acyclic synclinal transition model proposed by Seebach which can progress through two different pathways; electronic or steric (**Scheme 21, 22**).[72] The first pathway, applicable to enamines from both ketones and aldehydes, involves the electronic interactions of the chiral directing group (most-usually through H-bonding) with the Michael acceptor. As a result the Michael-acceptor would approach from the same face as the chiral substituent (**Scheme 21**). It has also been suggested that the stabilizing H-bonding interactions between the stereodirecting group and the Michael acceptor in the transition state could counter the steric repulsion holding the *E*-enamine in its favoured *Re* (aldehyde) or *Si* (ketone) enamine rotamer. This would allow the equilibrium to shift to the alternate rotamer of the enamine (*Re/Si* interconversion) which can further complicate matters (**Scheme 21**).[48]



Scheme 21: Electronic interactions between stereodirecting group and Michael acceptor[48]
Note *Re* and *Si* face assignments through α-carbon

The other pathway, again applicable to the enamine derived from both ketones and aldehydes, is one where the steric nature of the stereodirecting group directs the facial selectivity of the Michael acceptor (**Scheme 22**). Rather than inducing an electronic interaction, the steric bulk of the chiral framework may force the Michael acceptor to approach from the opposite face to the stereodirecting group. In this case, an enamine derived from an aldehyde would be expected to proceed through the less sterically hindered *Si, Si* transition state, *via* the favoured *anti*-enamine (**Scheme 22**). Similarly the ketone enamine would react through a *Re, Re* transition state *via* the *syn*-enamine (**Scheme 22**).[48]

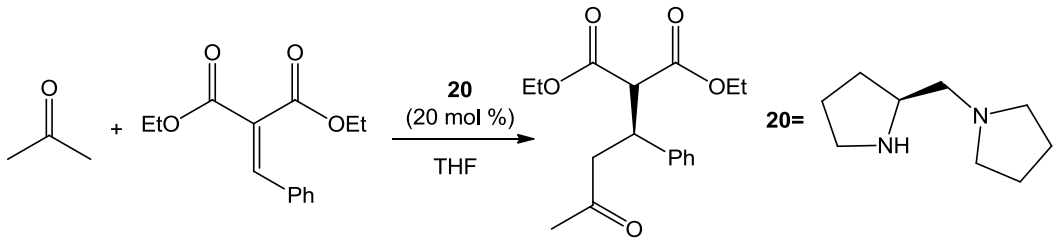


Scheme 22: Steric interaction between stereodirecting group and Michael acceptor
Note that structures have been inverted to show electrophile approach from the front, and *Re* and *Si* face assignments through α-carbon

The development of the asymmetric Michael addition has included many different Michael acceptors, Michael donors and catalysts. This thesis will provide a small selection of some of the more important transformations.

The first reported organocatalysed asymmetric inter-molecular Michael addition was by List in 2001.[73] List demonstrated the viability of enamine catalysis to activate nucleophiles for conjugate addition. List used L-proline derived enamines of acetone and cyclohexanone to add to both alkyl and aryl substituted nitroolefins. Although the yields were excellent and the diastereoselectivity was high, the enantiomeric excess did not exceed 23%. Enders was able to improve this result shortly afterward. By switching the solvent from DMSO to methanol, Enders was able to double the enantioselectivity. This would suggest that DMSO was interrupting the carboxylic acids electronic interaction with the nitro group of the Michael acceptor and highlights the importance of solvent in asymmetric reactions.[74]

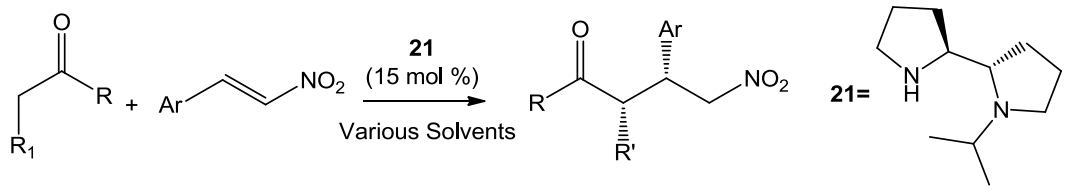
Barbas and co-workers widened the scope of acceptors to include alkylidene malonates.[75] Using the diamino catalyst **20** the group was able to achieve much higher levels of stereoselectivity than possible with proline (**Table 5**). This illustrates prolines dependence on more highly activated substrates.



Catalyst	Yield%	ee%
L-Proline	Not Reported	Racemic
20	47	59

Table 5: Selected results from Barbas showing unsuitability of L-proline[75]

This sort of diamine framework, featuring a secondary amine and a tertiary amine, has found use in an array of different catalysts. One example is the *iso*-propyl bis-pyrrolidine **21** reported by Alexakis in 2002[76] and then again in 2004.[77] Using catalyst **21**, they were able to add both aldehydes and ketones to nitro olefins in good yield and excellent selectivity (**Table 6**).

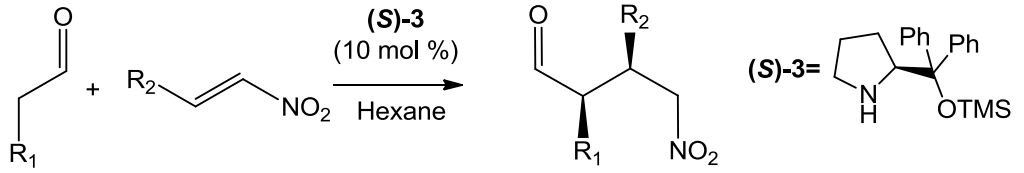


R	R_1	Ar	Additive	Yield(%)	d.r. (*syn*/*anti*)	*ee*(%)
CH_3	OMe	Ph	-	75	83 : 17	69
CH_3	OH	Ph	-	79	17 : 83	98
Cyclohexanone		Ph	HCl (15 mol %)	74	94 : 6	81
H	Me	Ph	-	71	94 : 6	93
H	Me	4-OMe-C_6H_4	-	64	94 : 6	93
H	Me	2-Thienyl	-	66	94 : 6	93

Table 6: Selected results of Michael addition of both ketones and aldehydes to nitro olefins as reported by Alexakis[77]

Interestingly the α-hydroxy ketone gave a high preference for the *anti*-diastereomer. The authors attribute this to efficient binding of the tertiary amine as a Lewis-base to the hydroxy group, *via* a H-bond, leading to stabilisation of the *Z*-enamine in the transition state.

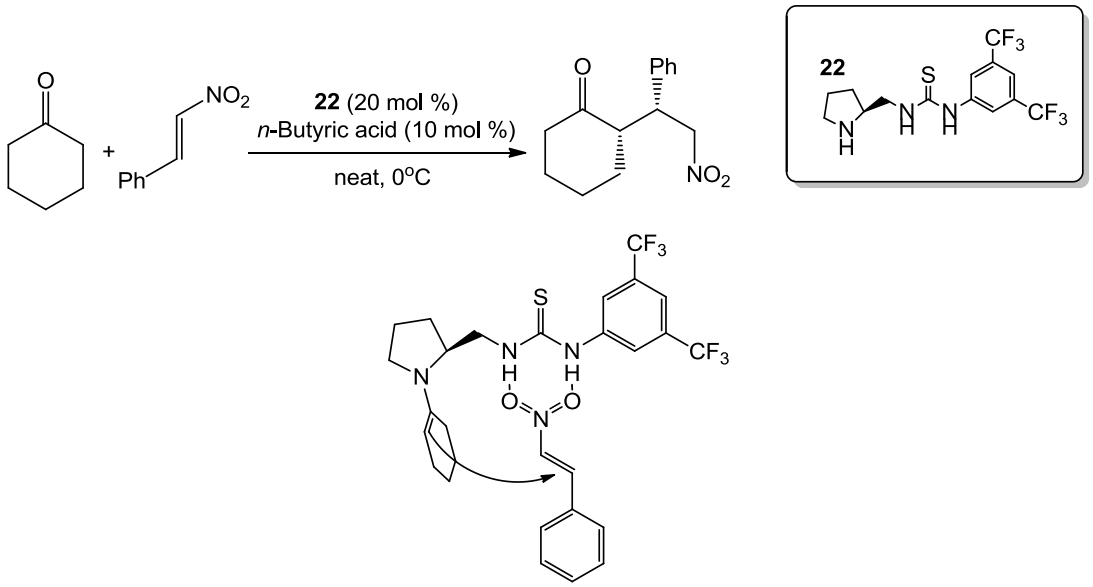
The arrival of diarylprolinols in 2005 has set the bar for enamine catalysed asymmetric Michael additions. While ineffectual for ketones, the silyl ether diphenylprolinol **3** has proven that it is the general catalyst of choice for the Michael addition of aldehydes.[78] The first example of its introduction into the field of Michael additions was by Hayashi.[79] This report gave perfect enantioselectivity, very high diastereoselectivity and quick reaction times despite a rather large catalyst loading (10-20%) (**Table 7**). The only drop in enantioselectivity was observed for the severely hindered *iso*-butyraldehyde.



R_1	R_2	Time (h)	Yield(%)	d.r. (*syn*/*anti*)	*ee*(%)
Me	Ph	5	85	94 : 6	99
Me	Fural	5	81	94 : 6	99
Me	*n*Bu	25	52	84 : 16	99
*n*Pr	Ph	48	74	95 : 5	99
iso-butyraldehyde	Ph	96	85	-	68

Table 7: Selected results for the Michael addition of aldehydes to nitro olefins suing diarylprolinol catalysis[79]

An interesting application of Lewis-acid catalysis has been employed by Tang and co-workers in developing their thiourea substituted pyrrolidine **22**. The thiourea moiety interacts with the nitro group through H-bonding, much like the carboxylate in L-proline, bringing the Michael acceptor to the *Re* face of the ketonic enamine (**Scheme 23**). This approach leads to very high levels of diastereoselectivity (up to 99 : 1 *syn*/*anti*) and enantioselectivity (up to 98%) as thiourea is a more potent H-bond donor than a carboxylate.[80]



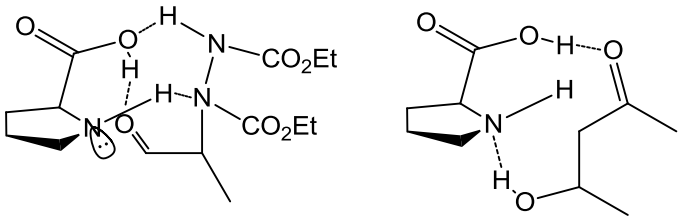
Scheme 23: Application of thiourea moiety in enamine catalysis[80]

The Michael addition is not only limited to nitroolefins and alkylidene malonates as acceptors. There have also been reports of asymmetric additions to non-enolisable chalcones,[81] vinyl sulfones[82] and vinyl phosphonates.[83]

1.4.3 Heteroatom substitution at the α-carbon

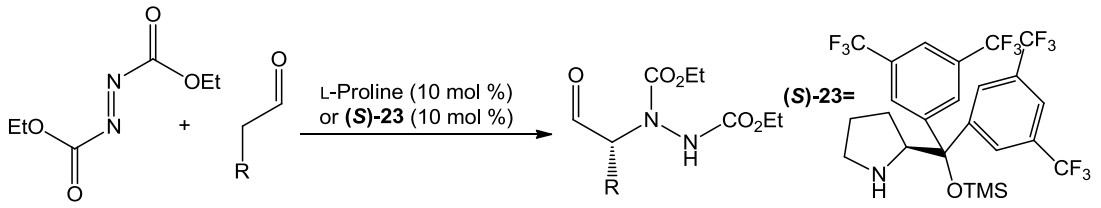
The nucleophilicity that is generated at the α-carbon in an enamine, as previously discussed, can be used to attack electrophilic compounds. Substrate depending, this can result in a direct substitution of the α-carbon with a heteroatom.

The first examples of these substitution reactions were reported by List[84] and Jørgensen[85] who employed L-proline to achieve the direct α-amination of unbranched aldehydes by attack on azodicarboxylates. Both papers suggest similar transition states, the carboxylic acid interacts with the nitrogen of the azodicarboxylate and directs it towards the *R*e face of the *anti*-enamine (the *anti*-enamine rotamer is favoured by aldehydes). The yields are very high (up to 99%) and the enantioselectivity is excellent (up to 97%). The proline can be used in low loading without having a large effect on the selectivity but a 10 mol% catalyst loading is preferred to bring the reaction time to 120 minutes (2 mol% reaction goes to completion in 300 minutes). An interesting point about this reaction is the auto-inductive effect of the product on the catalyst. This was noticed also in the α-aminoxylation of aldehydes using L-proline.[86] The product acts a H-bond acceptor, which upon H-bonding with the catalyst N-H causes the lone pair of the catalyst's nitrogen to be exposed (**Scheme 24**). This is not observed in the aldol reaction due to the aldol product H-bonding to the catalysts nitrogen atom (**Scheme 24**).[26]



Scheme 24: Auto-inductive effect of product on catalyst present in α-aminoxylation and α-amination but not in an aldol reaction[26]

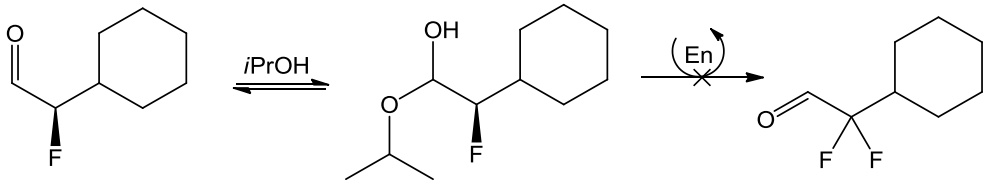
Jørgensen applied his fluorinated silyl-protected diarylprolinol **23** methodology to the α-amination of aldehydes and achieved similar yields to proline, although a slight general improvement in enantioselectivity was observed (**Table 8**). The most obvious difference was the inversion of configuration. This can be attributed to the stereodirecting group operating by steric repulsion causing the electrophile to approach the reverse *Si* face of the *anti*-enamine.[87]



Catalyst	R	Time (mins)	Yield(%)	*ee*(%)
L-Proline	*i*Pr	120	83	93
(*S*)-23	*i*Pr	15	88	-97
L-Proline	Allyl	120	92	93
(*S*)-23	Allyl	15	81	-92

Table 8: Selected results comparing α-amination of aldehydes with L-proline and **(*S*)-23**[87]

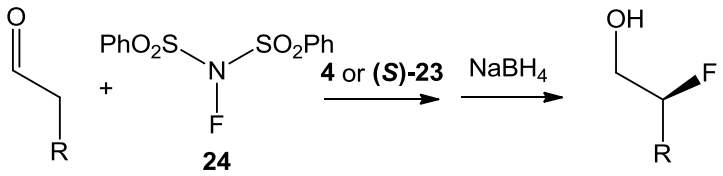
The enantioselective formation of C-F bonds has also been achieved using enamine catalysis. MacMillan reported this in 2005 using the dichloroacetate salt of his imidazolidinone **4** and NFSI **24** as a source of electrophilic fluorine.[88] The transformation was very efficient and gave yields of 54-96%, with enantioselectivities up to 99%, for both aliphatic and aromatic α-substituted aldehydes. It was found that using *iso*-propanol as a co-solvent increased both yield and enantioselectivity of the reaction. This effect has been attributed to the facile addition of the alcohol to the highly electrophilic α-fluoro-aldehyde forming a hemi acetal which protects the product from both further halogenation to the α,α-difluoro-aldehyde and racemisation of the product by increasing the pK_a of the α-hydrogen of the product (**Scheme 25**).[89]



Scheme 25: Illustration of selectivity in α-fluorination of aldehydes with imidazolidinone **4**

Remarkably, MacMillan was able to reduce his catalyst loading from 20 mol% to 2.5 mol% without affecting the enantioselectivity, although the reaction length went from 30 minutes to 12 hours.

Jørgensen again demonstrated the superiority of the diarylprolinol methodology employing the fluorinated silyl-protected catalyst **23** in the same C-F bond forming reaction.[87] The careful choice of MTBE as solvent prevented the NFSI **24** from de-protecting the silyl group and allowed the reaction to proceed in catalytic quantities as low as 1 mol% - 0.2 mol%. Shorter reaction times were achieved with comparable enantioselectivity (**Table 9**).



Catalyst	Loading (mol %)	R	Time (h)	Yield(%)	*ee*(%)
4	20	*c*-Hexyl	12	96	99
(*S*)-23	1	*c*-Hexyl	2-6	69	-96
4	20	Bn	12	71	96
(*S*)-23	1	Bn	2-6	n.d.	-93
4	20	1-Adamantyl	12	82	98
(*S*)-23	1	1-Adamantyl	2-6	64	-91

Table 9: Selected results comparing α-fluorination of aldehydes using catalysts **4** and **(*S*)-23**[87]

The α-substitution of aldehydes with other halogens has also been reported. MacMillan, using a similar approach to the α-fluorination methodology mentioned above, achieved α-chlorination in an equally impressive transformation with high yields and enantioselectivities.[90] The substrate scope of this reaction was extended shortly afterward by Jørgensen and co-workers to include ketones. This time Jørgensen used 4,5-diphenylimidazolidine as the catalyst.[91] Asymmetric bromination of ketones was first reported by Jørgensen in 2005 when he used the same catalytic system as in his α-chlorination.[92] The bromination of aldehydes was again best performed using the diarylprolinol catalyst series. This methodology could also be extended to α-iodination.[87]

One of the more spectacular reactions that can be achieved using enamine catalysis is the α-sulfenylation of aldehydes. Using a triazole based source of electrophilic sulfur the fluorinated silyl protected diarylprolinol **23** was able to achieve sulfenylation in high levels of enantioselectivity (95-98%), after *in situ* reduction of the aldehyde to prevent racemisation of the highly acidic α-hydrogen. The reaction time had to be controlled in order to prevent α,α-sulfenylation and also racemisation of the desired product but the isolated yields ranged from 60-94% with a range of both sterically bulky and small aldehydes.[87]

Descending further down group 16 of the periodic table, α-selenylation was first reported organocatalytically by Wang for both ketones and aldehydes. Wang employed prolinamide as the catalyst giving rise to racemic products.[93] Melchiorre further developed this reaction by employing the fluorinated silyl diarylprolinol **17** with 4-nitro-benzoic acid as a co-catalyst. The enantioselectivities were extremely high (95-99%) using this catalytic system and yields ranging from 81-99% were achieved for a host of different aldehydes.[94]

1.4.4 Mannich Reaction

The Mannich reaction is mechanistically similar to both the aldol reaction and Michael addition as it requires the attack of a nucleophile on an electron deficient sp^2 carbon. The electrophile in this case however is a Schiff base and reduces after attack to the Mannich base.[95] Enamines have been employed as the nucleophile in many organocatalytic Mannich reactions. The source of selectivity in the Mannich reaction is quite similar to the Aldol reaction as both electrophiles have a Lewis-basic atom, which can engage in H-bonding, allowing for similar catalytic systems and models to be employed.

List was the first to report the L-proline catalysed asymmetric Mannich reaction in 2000.[96] In this report he employed 4-anisidine to generate the Schiff base *in situ* from an aldehyde. The proline and ketone were then added afterwards in a 3-component reaction. List achieved excellent yields, although they dropped dramatically when aromatic or bulky α-branched groups were added to the Schiff base. The enantiomeric excess was excellent (70-96%) with all substrates. The use of asymmetric ketones also caused a drop in yield due to the lack of regioselectivity, while enantioselectivity remained very high. What is most interesting is the inversion of configuration and preference for the *syn* diastereoisomer observed for the Mannich product compared to the aldol product. The author suggested a chair-like intermediate with the *Z*-imine. However, Houk and Bahmanyar used DFT calculations to examine the transition states and suggested that the origin of the reversed selectivity can be explained as follows. The imine nitrogen requires full protonation from the carboxylic acid to become reactive and the carboxylate, in this case, is more Brønsted acidic in the *anti*-enamine rotamer due to the orientation of the imine lone pair (**Fig. 8**). If the imine approaches the *syn*-enamine the developing iminium ion is distorted from planarity in order to accommodate the proton transfer rendering the transition state high energy and thus disfavoured (**Fig. 8**).[97]

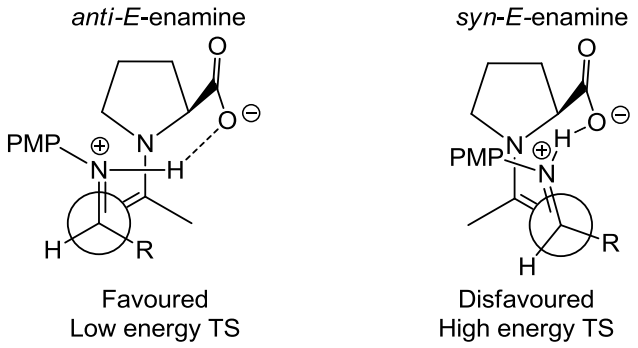


Figure 8: Protonation of imine in transition state by enamine rotamers[97]

The imine is more stable as the *E*-isomer and so approaches in this conformation. The bulk of the PMP group is repulsed by both the carboxylate and pyrrolidine ring forcing the substituent into the pseudo-axial position giving *Si* face selectivity (**Fig. 9**).[98]

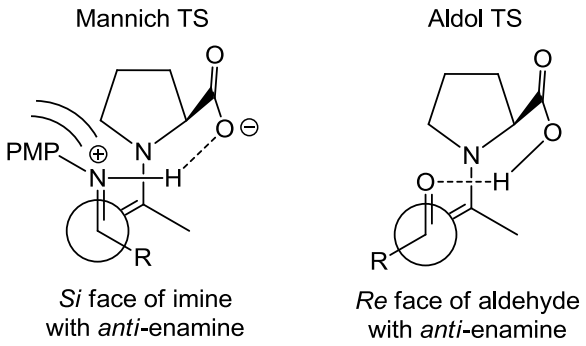
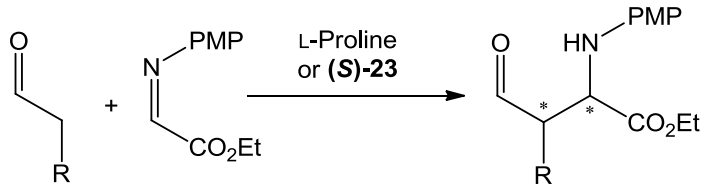


Figure 9: *Si* face selectivity in Mannich reaction compared to aldol reaction[26]

Barbas and co-workers independently conducted their own research and found that L-proline again was an excellent catalyst for the Mannich reaction of ketones with *N*-PMP-α-imino ethyl glyoxylate. They also observed *syn* selectivity and inversion of configuration compared to aldol products.[99] Further experimentation allowed the group to reduce the L-proline loading to 5 mol% and use only two equivalents of the ketones without affecting the enantioselectivity. A change of solvent allowed Barbas and co-workers to employ aldehydes as the pro-nucleophile in perfect enantioselectivity (99%) and with moderate diastereoselectivity, which improved as the bulk of the α-chain increased.[100] Barbas' comprehensive report on the Mannich reaction a year later rediscovered the three component reaction style employed by List and employed aldehydes as both pro-nucleophiles and precursors for the imine. Barbas also noted that the d.r. decreased after aqueous work-up and chromatography suggesting epimerisation.

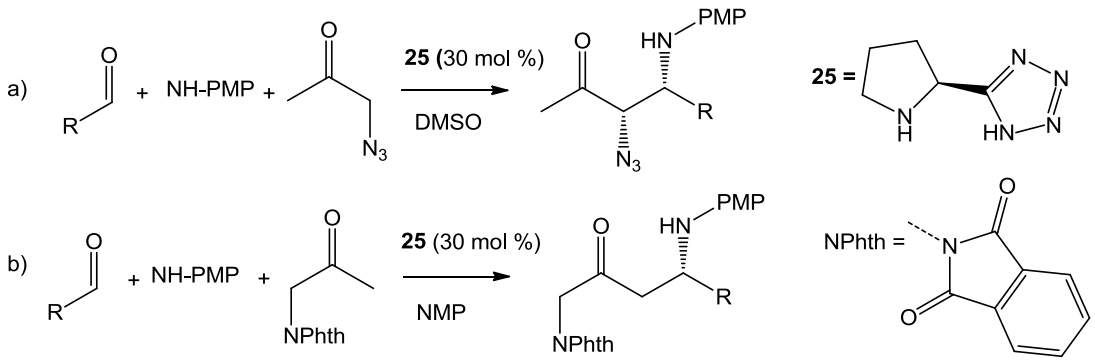
The use of diarylprolinol **23** by Jørgensen in 2004 also gave very high enantioselectivities and as expected, due to the steric stereodirecting nature of the catalyst (**See Section 1.4**), furnished the *anti*-isomer in good selectivity (**Table 10**).[87]



Catalyst	Loading (mol %)	R	Time (h)	Yield(%)	d.r. (*syn*/*anti*)	*ee*(%)
L-proline	5	Me	2-24	72	3 : 1	99
(*S*)-23	10	Me	16	76	14 : 86	98
L-proline	5	*i*Pr	2-24	81	19 : 1	93
(*S*)-23	10	*i*Pr	16	79	8 : 92	98
L-proline	5	CH_2Allyl	2-24	71	19 : 1	99
(*S*)-23	10	Allyl	16	63	10 : 90	98

Table 10: Selected results comparing Mannich reaction of aldehydes with Proline and **(*S*)-23**[87, 99]

In 2006, Barbas and co-workers used the tetrazole proline analogue **25** to add protected α-amines to *in situ* prepared imines. The Mannich reaction allows access to a family of chiral diamines.[101] What was very interesting about this work was that the regioselectivity of the reaction was protecting group dependant, which meant that both chiral 1,2- and 1,4- diamines could be obtained after de-protection. When the group initially performed the reaction using L-proline they found that despite high yields and enantioselectivities the diastereoselectivity was poor, even when the Brønsted acidic *i*PrOH was used as a co-solvent. This led them to the tetrazole **25**, which is known to be more Brønsted acidic than proline and had been previously used in organocatalytic aldol reactions.[102] Using α-azido ketones they attained perfect regioselectivity for the substituted α- position as well as high yields, excellent *syn* selectivity and exceptional enantioselectivity (**Table 11**). When the group switched to phthalimide as a protecting group the reaction occurred at the unsubstituted α-carbon with equally good results (**Table 11**).



Reaction	R	Time (h)	Yield(%)	d.r. (*syn*/*anti*)	*ee*(%)
a	CO_2Et	0.5	96	91 : 9	99
a	OBn	0.5	83	80 : 20	85
b	CO_2Et	40	83	-	90
b	4-NO_2-C_6H_4	84	68	-	97
b	4-CN-C_6H_4	60	56	-	95

Table 11: **:** Selected results of Mannich reaction of different α-amino protected ketones[101]

Barbas concluded that the regioselectivity must arise from the steric effect of the phthalimide. The azido ketone forms an enamine with the more substituted α-carbon, which is more easily deprotonated as the azido group makes the α-H more acidic. This enamine adopts *anti*-rotamer and forms an electronic interaction between the acidic tetrazole hydrogen and the imine lone pair. From here the approach is the standard model for Mannich reactions (**Fig. 10**).

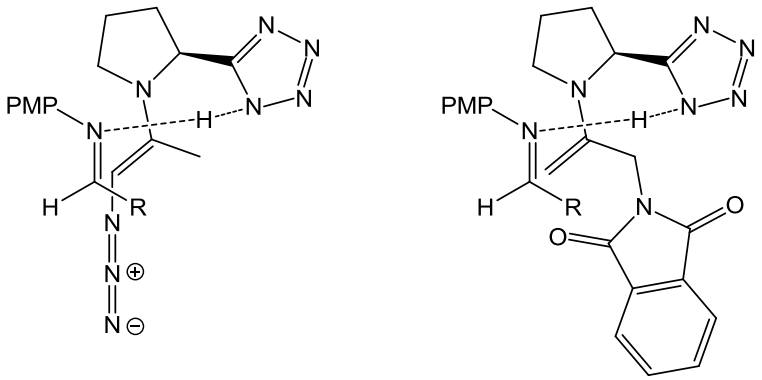


Figure 10: Transition states for Mannich reaction of different α-amino protected ketones[101]

The enamine from the phthalimidyl ketone reacts through the least substituted α-carbon as the competing enamine suffers from steric hindrance and is unable to react. This explains the rather long reactions times observed with the phthalimide group, as the less substituted alkene is the less stable.

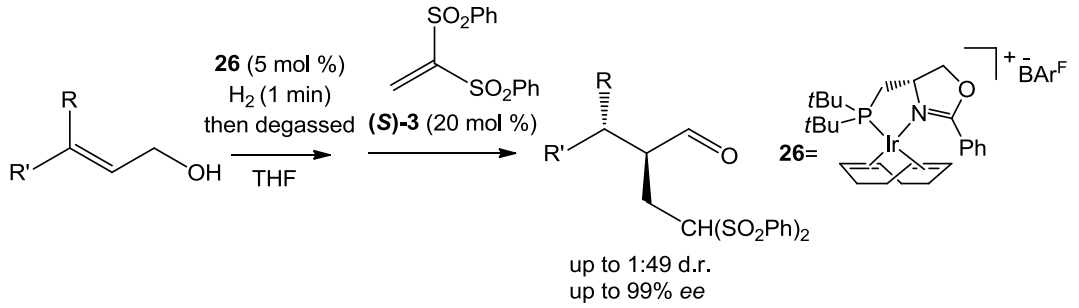
An interesting point about the mechanism of enamine promoted Mannich reactions is that when using unactivated aldimines the nitrogen has to be fully protonated by the Brønsted acid part of the

catalyst in order to become reactive. If there is no acidic moiety on the catalyst structure then an additional acid must be included to promote the reaction. Ketimines do not require complete protonation to initiate the reaction so can be performed without the use of added acid.[26]

1.4.5 Enamine organocatalysis with transition metal catalysis

We have just examined the exceptional ability of enamines in making stereoselective bonds at the α-carbon. Combining this ability with transition metal catalysts allows for *in situ* generation of the carbonyl and enamine activation. While this remains a rather unexplored region there have been a few excellent examples of such work.

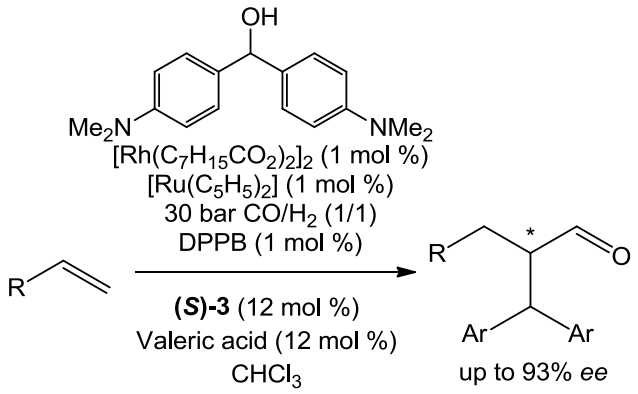
Mazet and co-workers published an elegant report in 2011 using iridium catalysed isomerisation of allyl alcohols, combined with enamine catalysis, to generate α,β-chiral aldehydes in excellent yields and enantioselectivities. Though the diastereoselectivities were very much substrate dependant (**Scheme 26**).[103]



up to 1:49 d.r.
up to 99% *ee*

Scheme 26: Sequential iridium isomerisation/enamine Michael addition to produce α,β-chiral aldehydes[103]

In another nice example, Christmann used a tandem rhodium/ruthenium catalysed hydroformylation and enamine catalysed α-alkylation. After a lot of optimisation the group established good yields and enantioselectivities (**Scheme 27**).[104]



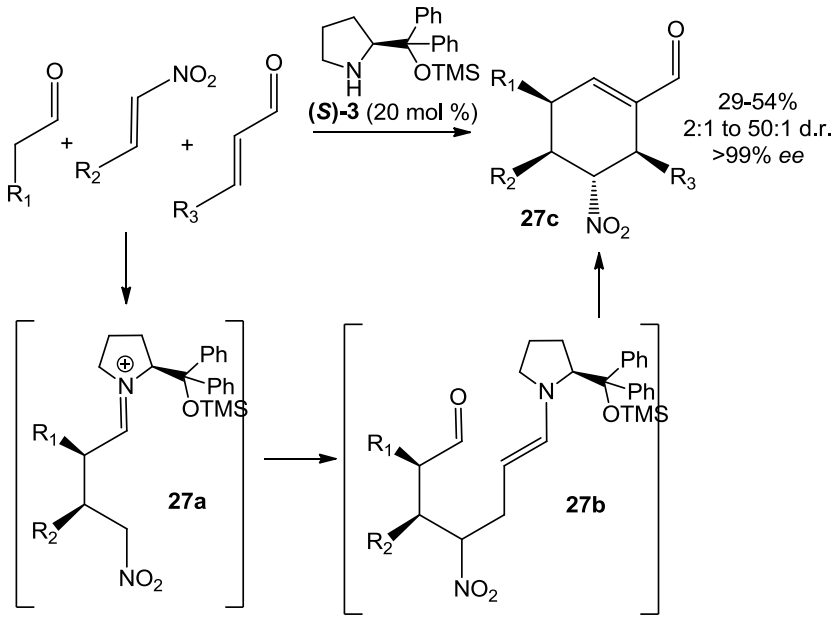
Scheme 27: Tandem hydroformylation and enamine alkylation[104]

The deployment of organic enamine catalysts in conjunction with transition-metal catalyst is only in its infancy. Initial results are very promising and do not report much of the predicted disruption of either catalytic cycle. While it is important to consider the role each catalyst has to play in the transformation it can also be possible for the product of the initial reaction to be stereodirecting in the secondary step. This kind of effect is known as 'substrate-control' and must be accounted for in any multiple step transformation.

1.4.6 Enamines in domino reactions

One of the most interesting aspects of chiral secondary amine catalysts is that they offer the possibility of forming both the nucleophilic enamine and the electrophilic iminium ion. This allows for the further transformations to occur and create larger amounts of structural complexity if the correct substrates are chosen. These types of systems are known are 'domino reactions' or 'cascade reactions'.

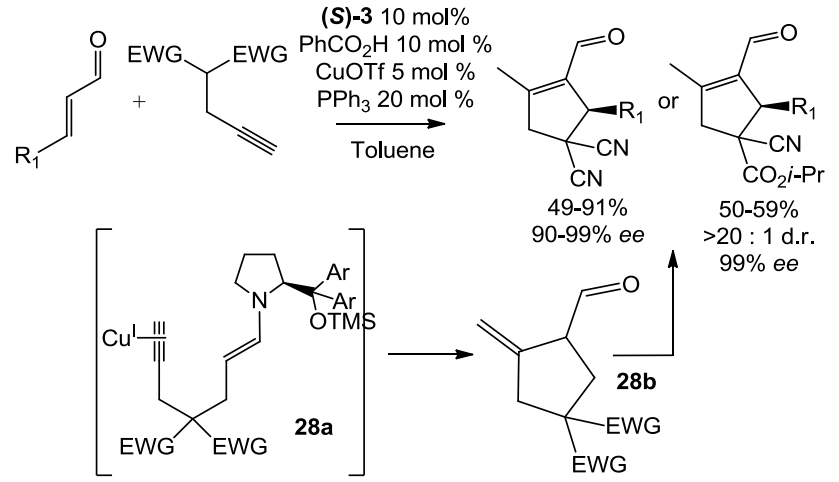
Enders developed a very interesting triple cascade in 2006 utilising the potency of both the enamine and iminium ion derived diarylphenylprolinol catalyst **3**.[105] The cascade proceeds through an enamine/iminium ion/enamine process creating a tetrasubstituted cyclohexene carbaldehyde with 4 stereocenters (**Scheme 28**). The reaction begins with a standard enamine formation with an unsaturated aldehyde, which undergoes conjugate addition to a nitro-olefin. The resulting reduced nitro-alkane **27a** then adds again, in a conjugate fashion, to the iminium ion generated from an α,β-unsaturated aldehyde to give the enamine **27b**. The ring closure is furnished through an enamine attack on the electrophilic carbonyl to give the product **27c** (**Scheme 28**).



Scheme 28: Triple-cascade reaction enamine/iminium/enamine[105]

The success of this approach hinges of the selection of substrates, as both the nitro-olefin and α,β-unsaturated aldehyde are Michael acceptors. The nitro-olefin is much more electrophilic than the α,β-unsaturated aldehyde however and out-competes the side reaction when performed at 0 °C.

In 2010 Jørgensen used a similar approach but incorporated inorganic Lewis acids, in an iminium ion/enamine-Lewis-acid cascade, generating cyclopentene carbaldehydes (**Scheme 29**).[106] The initial step involves an iminium ion promoted Michael addition of the alkyne to the α,β-unsaturated aldehyde. The resultant enamine **28a** then undergoes a 5-*exo-dig* cyclisation to the Lewis acid activated alkyne. The saturated cyclic-aldehyde **28b** then isomerises to give the product cyclopentene (**Scheme 29**).



Scheme 29: Double-cascade reaction iminium/enamine-Lewis-acid[106]

In depth investigation of the reaction showed that when the cyano acetate alkynes were used the reaction product was isolated as a single diastereomer. When the reaction was stopped before cyclisation the intermediate was a 1 : 1 mixture of diastereomers. Only one of the diastereomers can undergo cyclisation while the intermediate can revert to starting material *via* a retro-Michael reaction. In this way the diastereomers are resolved giving a single product.[78]

The ability for rapid construction of complexity in high yields and excellent stereocontrol promotes the practicality of domino reactions beyond mere chemical curiosities. The combination of different organocatalysts with different activation routes or the use of a pluripotent catalytic system represents impressive demonstrations of the progress in organocatalysis to date.

1.5 General conclusion

The rapid development of so many organocatalytic systems and methodologies is evidence for the potency and accuracy that can be achieved using small molecule organic catalysts. Although the development of organocatalysis was gradual, the culmination of nearly 100 years of research led to the break-through works of Hajos and Parrish and then later MacMillan and Barbas. In the 12 years since MacMillan coined the term organocatalysis the field has grown in scope to rival the traditional asymmetric transformations of metal catalysis and enzyme catalysis. The mild conditions usually involved in the transformations have made organocatalysis an obvious choice for natural product synthesis and medicinal chemistry.

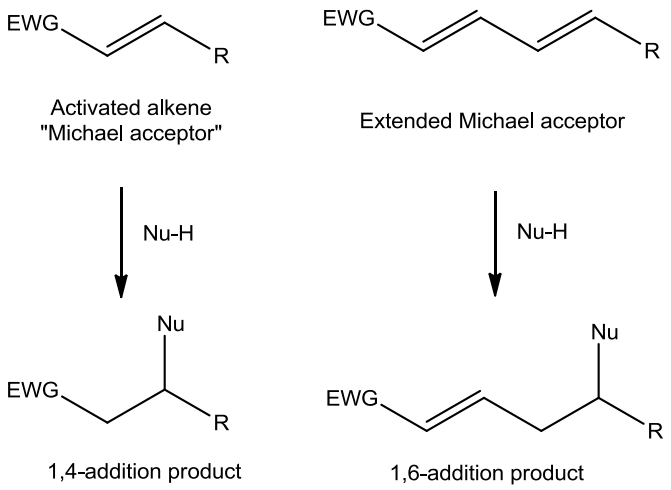
A large amount of literature is devoted to the study of organocatalytic 1,4-conjugate additions to electron deficient π-systems. We hoped to expand the versatility of organocatalytic methodology to include 1,6-conjugate additions to electron deficient dienes. This type of regioselectivity is currently dominated by organometallic reagents and upon our entering the field there had been only a single report of an organocatalysed 1,6-conjugate addition which was under phase-transfer conditions. This thesis represents four years of research into this interesting and challenging chemistry.

Furthermore, we also began development of an organocatalytic system that could be integrated with the emerging area of DNA-based catalysis. Using DNA's natural chirality as a scaffold, we hoped to be able to employ organocatalytic methodology to effect asymmetric transformations. This thesis will cover the beginnings of our research into this exciting and novel field.

Chapter 2

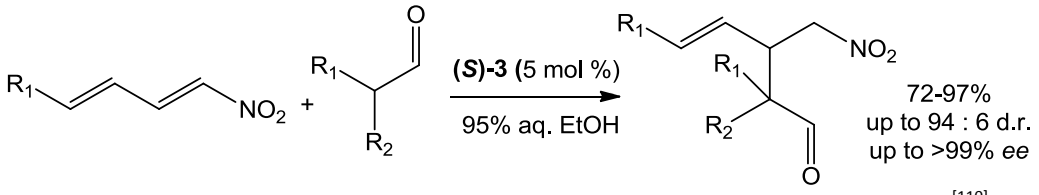
2.1 Introduction

Since 2000 there has been an explosion of reports describing the asymmetric organocatalytic conjugate addition to activated dienes.[107] Several different approaches have been employed including covalent, non-covalent and bifunctional catalysis.[48, 70] In contrast, the vinylogous asymmetric conjugate addition (**Scheme 30**) to extended Michael acceptors has proven much more challenging organocatalytically. There are few reports describing the organocatalysed 1,6-conjugate addition,[108] this is in contrast to the several articles detailing the organometallic and metal-catalysed equivalent.[109].



Scheme 30: 1,4- vs. 1,6- addition

The main impediment in achieving a regioselective 1,6-conjugate addition is the obvious competition with the 4-position. This effect is clearly demonstrated by a number of publications which report 1,4-conjugate additions to extended Michael acceptors with no evidence of the vinylogous 1,6-product being formed (**Scheme 31**).[110]

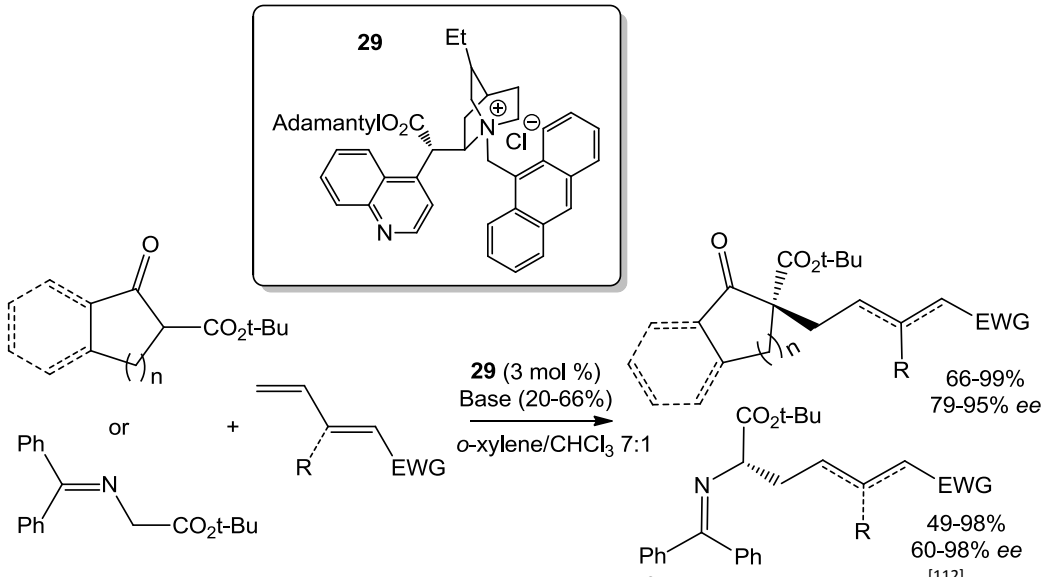


Scheme 31: 1,4-conjugate addition to nitro-dienes with no evidence of 1,6-addition[110]

The most logical explanation of this can be attributed to poor charge-delocalisation through the conjugated π-π system, this is at odds with the principle theory of vinylogy[111] which imparts that

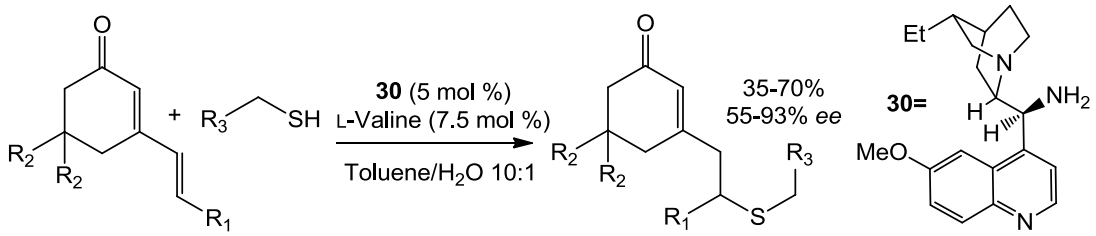
the reactivity should be equally shared through the π systems. Therefore, one would expect to see a mixture of regioisomeric products.

Jørgensen and co-workers have reported a 1,6-conjugate addition, under PTC conditions, of β-ketoesters using inorganic Brønsted bases.[112] The group were able to rapidly develop conditions that gave them exclusive regioselectivity and excellent enantioselectivity (**Scheme 32**). The use of benzophenone imines as pro-nucleophiles also yielded the 1,6-adduct in good yields and excellent stereoselectivities (**Scheme 32**). They however required an unsubstituted 6-position on the acceptor to prevent regioselectivity issues, substantially limiting the substrate scope. In addition the use of non-cyclic ketones as pro-nucleophiles gave racemic products.



Scheme 32: PTC conditions employed by Jørgensen for 1,6-conjugate addition[112]

More recently we reported an organocatalytic 1,6-conjugate addition using enamine activation of aldehydes.[108a] This work makes up part of this thesis and will be discussed later. Subsequently, Melchiorre and co-workers described the enantioselective addition of alkyl thiols, *via* iminium ion activation, to cyclic dienones (**Scheme 33**).[108b] The iminium ion was generated using the 9-amino cinchona derivative **30**, and surprisingly the stereodirecting power of the catalyst could successfully control selectivity at the remote σ-position. The enantioselectivity and yield could be further ameliorated with the addition of a chiral amino acid co-factor. The group went on to perform a double thio-alkylation at the 6- and 4- position using extra equivalents of the mercaptan.



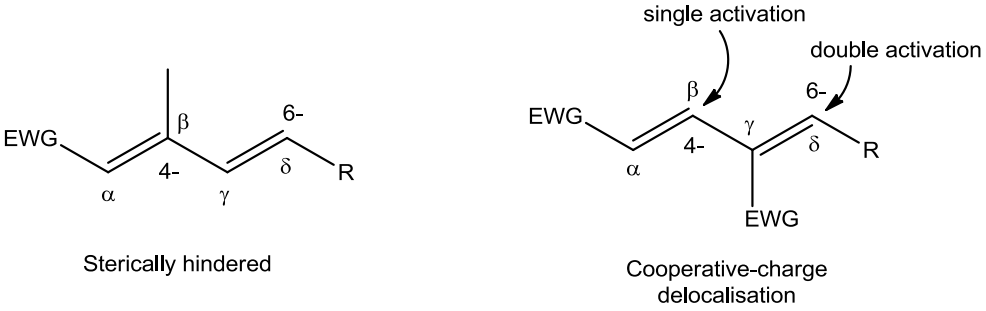
Scheme 33: 1,6-thioalkylation presented by Melchiorre[108b]

When we began our work in this field there were no entirely metal free organocatalytically promoted examples of 1,6-conjugate additions to extended Michael acceptors in the literature. Jørgensen's 2007 paper was the sole example of a non-metal catalysed 1,6-conjugate addition. We hoped to pioneer organocatalysed 1,6-additions by exploiting the reactivity of enamines, generated from pyrrolidines, on intelligently designed Michael acceptors.

2.2 Results and Discussion

2.2.1 Dienes for vinylogous Michael-additions

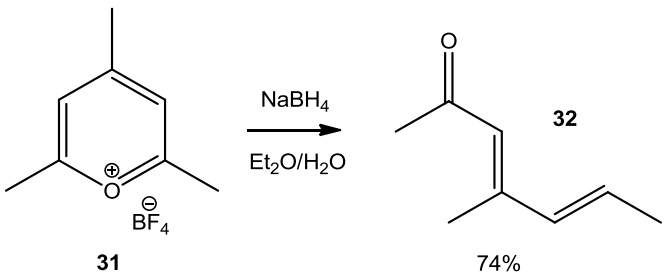
In order to circumvent the experimentally evident greater reactivity of the 4- position we identified two strategies for the design of dienes which would preferentially favour the vinylogous addition (**Fig. 11**). Firstly the steric hindrance at the 4- position was to be increased in order to discourage nucleophilic attack; and secondly the electronic properties of the diene would be altered so as to directly influence the charge delocalisation, favouring attack at the 6-position (**Scheme 34**).



Scheme 34: Proposed modifications to Michael acceptors

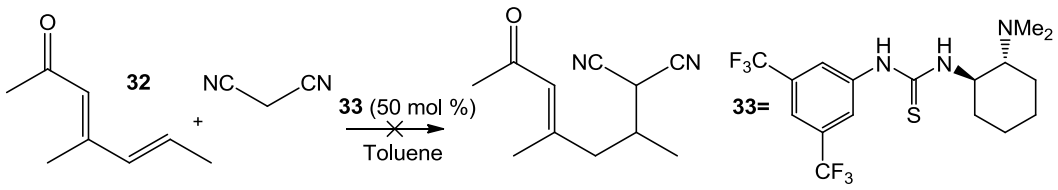
2.2.1.1 Synthesis and reactivity of sterically hindered dienes

The first sterically hindered diene was synthesised in one step by reduction of the commercially available 2,4,6-trimethylpyrylium salt **31** to give (3*E*,5*E*)-4-methylhepta-3,5-dien-2-one **32** in good yield (**Scheme 35**).[113]



Scheme 35: Synthesis of sterically hindered diene **32**

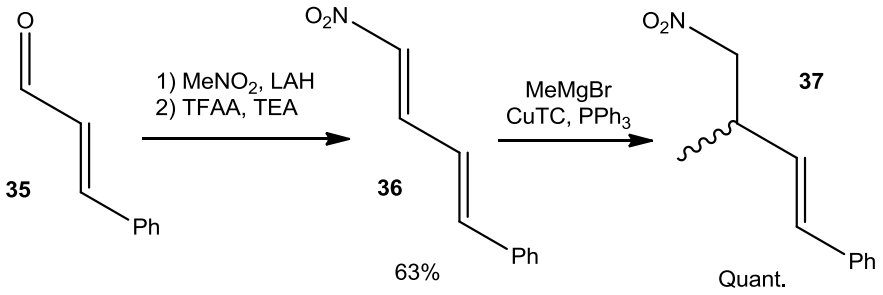
A ketone was chosen as the electron withdrawing group as it would firstly give a strong mesomeric effect, which we hoped would be propagated down the π systems; and secondly 1,4-conjugate additions had previously been reported on dienones using cinchona alkaloids as bifunctional catalysts.[114] Trial reactions using the substrate **32**, employing malononitrile as the pro-nucleophile and Takemoto' s catalyst **33**, gave polymeric mixtures of the diene and returned malononitrile (**Scheme 36**).



Scheme 36: Attempted addition to β-hindered diene

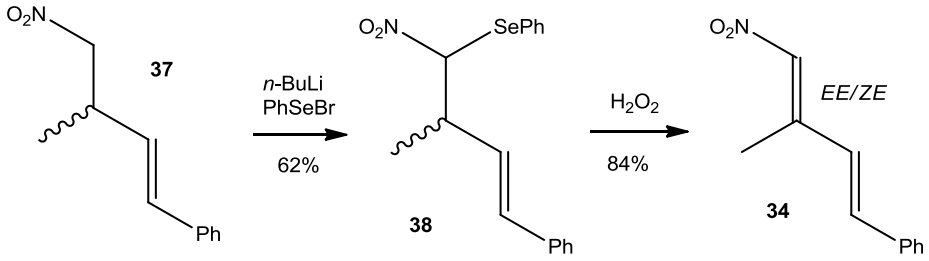
In fact the substrate **32** itself polymerised on standing in a freezer over the course of a week, as had been reported by Balaban.[113] The polymerisation of the dienone may be caused by self-aldol condensation with the reactive enol of **32**. This could be catalysed by the presence of Takemoto' s catalyst **33**. Possibly the use of a non-enolisable ketone, such as phenyl ketone, would prevent the unwanted side-reactions and allow the reaction to proceed. However, with these results we decided to choose another electron withdrawing group which would not polymerise and would offer enhanced reactivity over the ketone or the proposed phenyl-ketone.

The second of the hindered dienes to be synthesised was the nitrodiene **34**. Our collaborators had previously been experimenting with organocatalytic 1,4-conjugate additions to nitrodienes and had reported high yields and enantioselectivities using these substrates as mentioned previously.[110a, 115]



Scheme 37: Synthesis of nitroalkane **37**

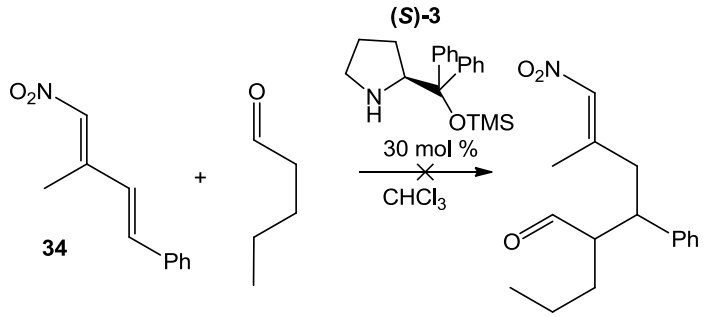
The synthesis of nitroalkane **37** proceeded without incident (**Scheme 37**), using a methodology developed by our collaborators.[109c] Firstly, a Henry reaction between nitromethane and trans-cinnamaldehyde **35** and a subsequent dehydration generated the nitrodiene **36** in good yield. This was then subjected to a copper mediated Grignard addition generating the nitroalkane **37** racemically.



Scheme 38: Completion of hindered nitrodiene **34**

The nitroalkane **37** was then deprotonated using butyl lithium and treated with phenyl selenium bromide to yield the phenyl selenide **38** in good yield (62%). A simple oxidation was then performed by treating the selenide with hydrogen peroxide, releasing phenylselenium oxide and oxidising the alkane to the alkene **34** in high yield (84%) (**Scheme 38**).[116]

In a trial reaction the hindered nitrodiene **34** was treated with 30 mol % Jørgenson's catalyst **(*S*)-3** and 5 equivalents of *n*-valeraldehyde at room temperature (**Scheme 39**). After one week there had been no detectable addition of the aldehyde to the nitrodiene.



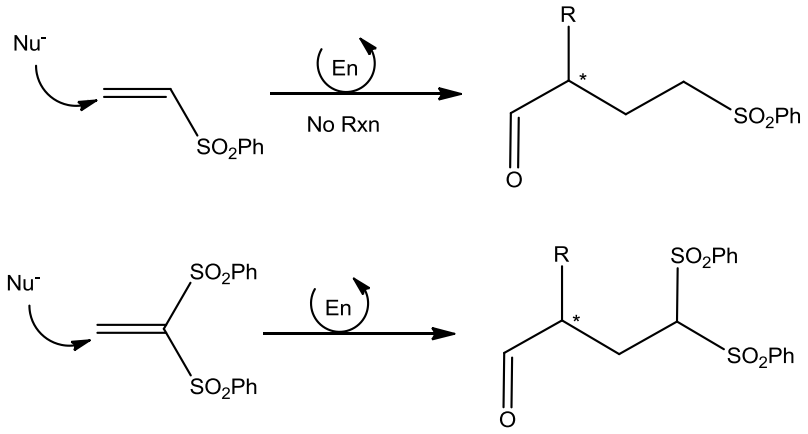
Scheme 39: Attempted addition to β-hindered diene

With no immediate results the theory of hindering the β-carbon as a means for controlling the regiochemistry was abandoned. We focused our attention on controlling the electronic properties of the conjugated π systems so as to favour a 1,6-conjugate addition.

2.2.1.2 Synthesis and reactivity of electronically rearranged dienes

The lack of reactivity at the 6- position contrasted the principle of vinylogy and led us to theorise that in order to generate a 1,6-conjugate addition we needed to increase the electrophilicity at the 6- position relative to the 4- position. To this end we focused on the vinyl sulfone moiety, which has been demonstrated to have great synthetic flexibility[117] and is known for its electron withdrawing capabilities.[118] It is also known in the literature that a vinyl sulfone with a single sulfone activating

the π-system is not sufficiently electrophilic to promote enamine addition, forming the conjugate adduct intermolecularly (**Scheme 40**).[119] When a second electron withdrawing sulfone moiety is introduced the addition proceeds in high yield with excellent enantioselectivity (**Scheme 40**).[120]



Scheme 40: Intermolecular enamine catalysis requires two activating sulfones

With this knowledge we envisioned creating a sulfonyl diene with a strategically placed second sulfone group at the γ-carbon to promote reactivity at the δ-carbon over the β-carbon. The use of such bis-phenylsulfonyl butadienes have been reported by Masuyama[121] for achiral enamine promoted Michael additions and by Padwa[122] for use in inverse-electron demand Diels-alder reactions using an enamine dienophile. The sulfone in the α position would not sufficiently activate the β-carbon atom toward enamine addition but would be expected to sufficiently activate the δ-carbon atom thanks to the cooperative effect of the second sulfonyl group, thus promoting the single 1,6-addition (**Fig. 12**).

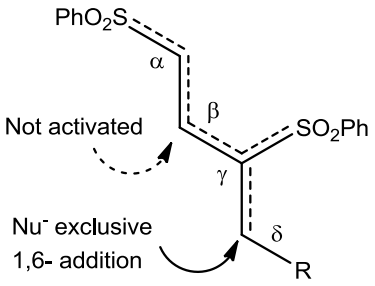
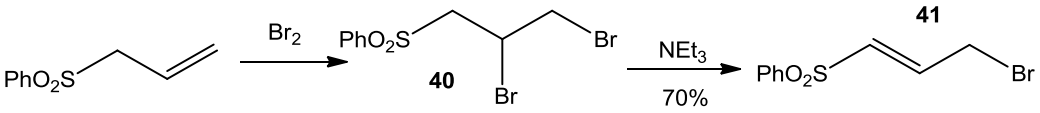


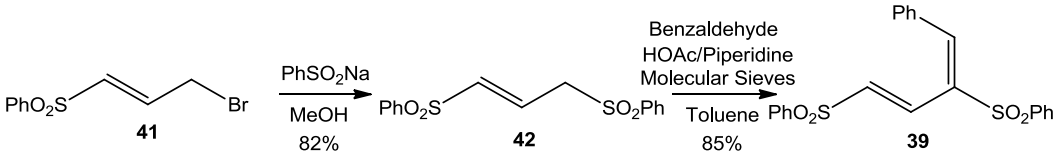
Figure 12: Rational design of substrate to give only 1,6-conjugate adduct.

The bis-phenylsulfonyl diene **39** was synthesised following a literature procedure.[123] We began by the bromination of the commerically available allyl phenylsulfone with elemental bromine followed by selective elimination of the secondary halide using triethylamine to generate 3-bromo-1-phenylsulfonyl-propene **41** as a single isomer (**Scheme 41**).[124]



Scheme 41: Synthesis of bromo-1-phenylsulfonyl-propene **41**

The crude material is then reacted with the sodium salt of benzenesulfinic acid in a simple S_N2 reaction to generate 1,3-bis-phenylsulfonyl-propene **42** which can be crystallised as the single *E*-isomer in an excellent 82% yield.[122b] The final step is a Knoevenagel condensation with benzaldehyde, which was modified from the literature[122b] by replacing the Dean-Stark apparatus with molecular sieves and using toluene instead of benzene. Comparable yields were obtained and the structure of the *EE*-isomer of the electron-deficient diene **39** was confirmed by X-ray crystallography (**Fig. 13**).



Scheme 42: Completion of bis-phenylsulfonyl diene **39**

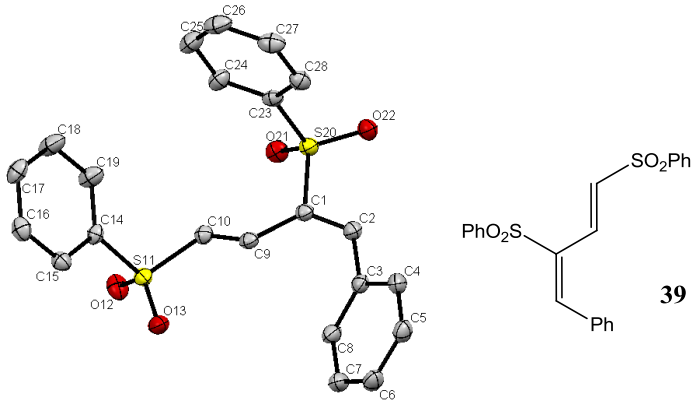
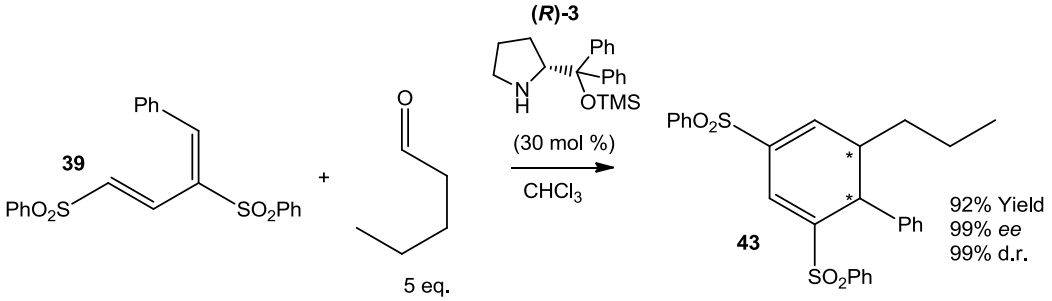


Figure 13: Crystal structure of 1,3-bis-phenylsulfonyl-4-phenyl-butadiene **39**

2.2.1.3 Trial reaction

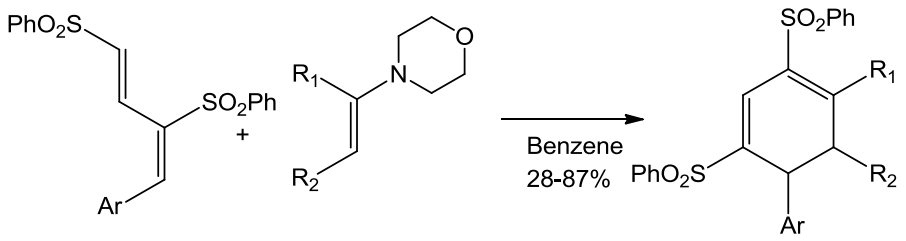
With the substrate **39** in hand a trial addition was performed using five molar equivalents of *n*-valeraldehyde with 30 mol % of the Jørgensen-Hayashi catalyst **(*R*)-3** in chloroform. The diarylprolinol **(*R*)-3** was chosen as it is known to be a general catalyst for enamine generation with aldehydes.[78] After 24 hours the consumption of the diene was complete and a simple trituration with methanol to remove the catalyst and excess aldehyde yielded the cyclic diene **43** in 92% yield, 99% enantiomeric excess and with no evidence of another diastereomer (**Scheme 43**).



Scheme 43: Trial reaction with *n*-valeraldehyde

Reaction was performed on a 0.2 mmol scale in 0.5 mL $CHCl_3$ for 24 hours

The product of this reaction was not unexpected and a similar achiral morpholine promoted reaction by Masuyama also gave a cyclic product (**Scheme 44**).[121]

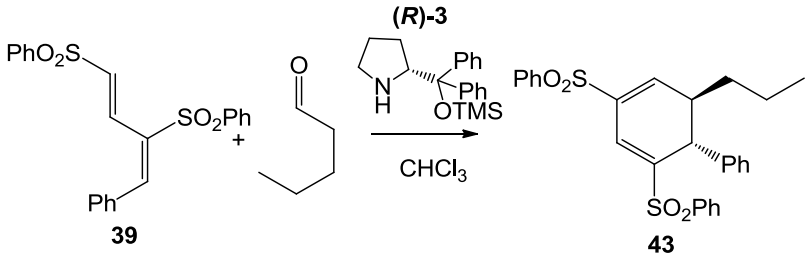


Scheme 44: Michael addition followed by cyclisation reported by Masuyama[121]

2.2.1.4 Optimisation of reaction conditions

With our initial results we next proceeded to investigate optimum conditions for the reaction. The use of chloroform as a solvent was considered to be appropriate, as the solubility of the diene was much less in other media and as it had proven to be a good choice in our preliminary efforts in terms of yield and enantioselectivity.

We next focused on the loading of the catalyst and the number of equivalents of the aldehyde used as summarised in **Table 12**. In conclusion, the number of equivalents of aldehyde had little effect on the yield and selectivity (**Entries 1-2**). We theorised that lowering levels of catalyst decreased the amount of available enamine in the reaction mixture, prolonging the length of the transformation (**Entries 3-4**). Due to the commercial availability of the catalyst **3** we believed that the rather high 30 mol % loading was an appropriate trade-off for the shorter reaction times. The use of 20-30 mol % of catalyst **3** is also quite common and has been reported in the literature.[78]



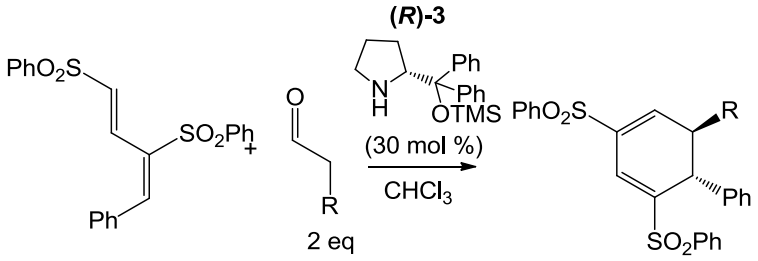
Entry	Aldehyde (molar equivalents)	Catalyst (mol %)	Yield (%)[a]	Time (h)	d.r. [b] (*syn*/*anti*)	*ee*[c] (%)
1	3	30	95	24	1:99	99
2	2	30	98	24	1:99	99
3	2	20	98	48	1:99	99
4	2	10	93	120	1:99	99

Reactions were performed on a 0.2 mmol scale, in 0.5 mL of $CHCl_3$ at RT, [a] isolated yield, [b] measured by ^1H NMR spectroscopy, [c] measured for *anti*- by chiral HPLC

Table 12: Optimisation of reaction conditions

2.2.1.5 Additions using various aldehydic pro-nucleophiles

The potential of this methodology, if universal, interested us greatly. To this end we employed a family of other aldehydes as pro-nucleophiles for our 1,6-conjugate addition chemistry. The results of these experiments can be seen in **Table 13**.



Entry	Cat.	Time (hr)	R	Yield(%)[a]	d.r.[b] (*syn*/*anti*)	*ee*[c] (%)
1	**(*R*)-3**	24	Et	91 (**44**)	1:99	99
2	**(*R*)-3**	24	*n*Pr	98 (**43**)	1:99	99
3	**(*S*)-3**	24	*n*Pr	98 (**43b**)	1:99	-99[d]
4	**(*R*)-3**	24	Allyl	92(**45**)	1:99	99
5	**(*R*)-3**	40	*i*Pr	95 (**46**)	1:99	99
6	**(*R*)-3**	144	(*S*)-citronellal	89[e] (**47**)	1:99	-
7	**(*R*)-3**	24	Ph	96 (**48**)	1:99	99

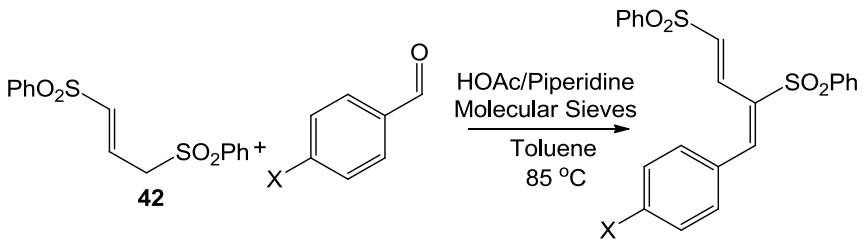
Reactions were performed on a 0.2 mmol scale, in 0.5 mL of $CHCl_3$ at RT, [a] isolated yield, [b] measured by ^{1}H NMR spectrscopy, [c] measured for *anti*- by chiral HPLC, [d] (*S*,*S*)-enantiomer obtained, [e] single diastereomer by ^{1}H NMR

Table 13: Scope of aldehydes as pro-nucleophiles for 1,6-conjugate addition

All the aldehydes employed in this study gave solely the 1,6-product and no evidence of any 1,4-product was obtained. The unbranched alkyl aldehydes reacted quickly to give the products **43, 44** and **45** in excellent yield with perfect stereoselectivity (**Entries 1-4**). The branched isopropyl valeraldehyde and chiral citronellal took longer to complete but maintained the excellent yields and stereospecificity (**Entries 5-6**). This long reaction time is not surprising considering the enhanced steric hindrance these substrates provide. The methodology also gave excellent results with phenyl acetaldehyde as the pro-nucleophile, generating the enantiomerically pure bis-phenyl diene **48** in high yield in only 24 hours.

2.2.1.6 Additions using various unsaturated 1,3-phenylsulfonyl butadienes

With the knowledge that the methodology allowed for a variety of pro-nucleophiles, be they branched, unbranched or unsaturated, we next began to alter the electronic properties of the dienes. The series of dienes as tabulated in **Table 14** were synthesised from the same precursor, propene **42,** and various commercial *para*-substituted benzaldehydes *via* a Knoevenagel condensation.

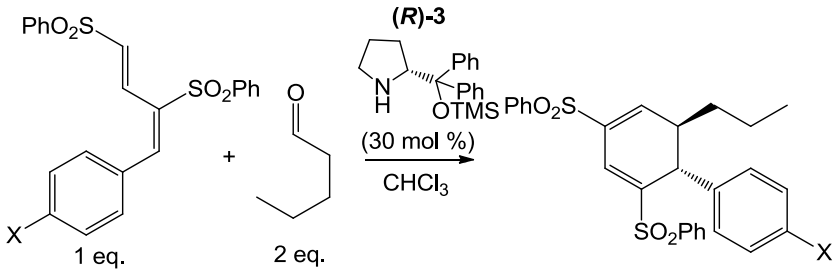


Entry	X	Time (hr)	Yield[a] (%)	Geometry[b]
1	H	0.5	85 (**39**)	*EE*
2	F	2	63 (**49**)	*EE*
3	Cl	2	65 (**50**)	*EE*
4	Br	2	83 (**51**)	*EE*
5	OMe	0.5	82 (**52**)	*EE*
6	NO_2	4	81 (**53**)	*EE*

Reactions were performed on a 1 mmol scale, in 20 mL of toluene, with 100 µL of catalysts and 1 g of molecular sieves, [a] isolated yield, [b] measured by ^{1}H NMR spectroscopy

Table 14: Synthesis of family of aromatic dienes by Knoevenagel condensation

With a library of aromatic dienes now synthesised we were able to probe the electronic effects the aromatic ring had on the electrophilicity of the 6- position and the resulting 1,6-conjugate addition (**Table 15**).



Entry	Time (hr)	X	Yield[a] (%)	d.r.[b] (*syn*/*anti*)	*ee*[c] (%)
1	24	OMe	75 (**54**)	1:99	99
2	24	H	98 (**43**)	1:99	99
3	24	F	81 (**55**)	1:99	99
4	20	Cl	81 (**56**)	1:99	99
5	20	Br	70 (**57**)	1:99	99
6	4	NO_2	75 (**58**)	1:99	99

Reactions were performed on a 0.2 mmol scale, in 0.5 mL of $CHCl_3$ at RT, [a] isolated yield, [b] measured by ^{1}H NMR spectroscopy, [c] measured for *anti*- by chiral HPLC

Table 15: Scope of varying phenylsulfonyl dienes

Interestingly a wide variety of dienes with different electronic properties could be employed without any impact on the regioselectivity of the reaction or to the control of stereoselectivity. Conversion was greater than 99% by ^{1}H NMR spectroscopy in all cases. The diminished isolated yields are a result of lost material during trituration process. The increase in the electron density on the aromatic ring by the electron-donating *para*-methoxy group did not retard reactivity and required only 24 hours for complete consumption of the diene (**Entry 1**). Conversely the gradual reduction of electron-density in the ring by introduction of electron withdrawing groups resulted in a decrease in the reaction time (**Entries 3-5**), dramatically so in the case of the *para*-nitro group (**Entry 6**). These results correspond with our assumption and ^{1}H NMR spectroscopic experiments (**See Section 2.2.1.7**) that the rate-determining step in the reaction is the C-C bond formation from the 1,6-conjugate Michael addition and not the cyclisation reaction. We hypothesise that the electron withdrawing properties of the aryl ring provide stabilisation of the carbanion, formed after the initial addition of the enamine, and prevents a reversible reaction (**See Section 2.2.1.7**).

In an effort to further vary the functionality of the substrates the dienes **59** and **60** were synthesised from furfural and 9-anthraldehyde respectively (**Fig. 14**). Using the same methodology these dienes were synthesised in a 78% yield for the furan derivative and a 98% yield for the anthracenyl.

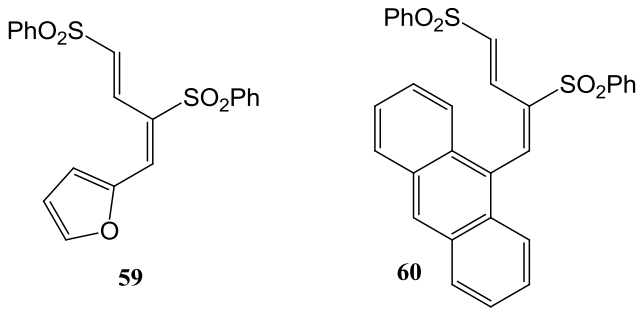


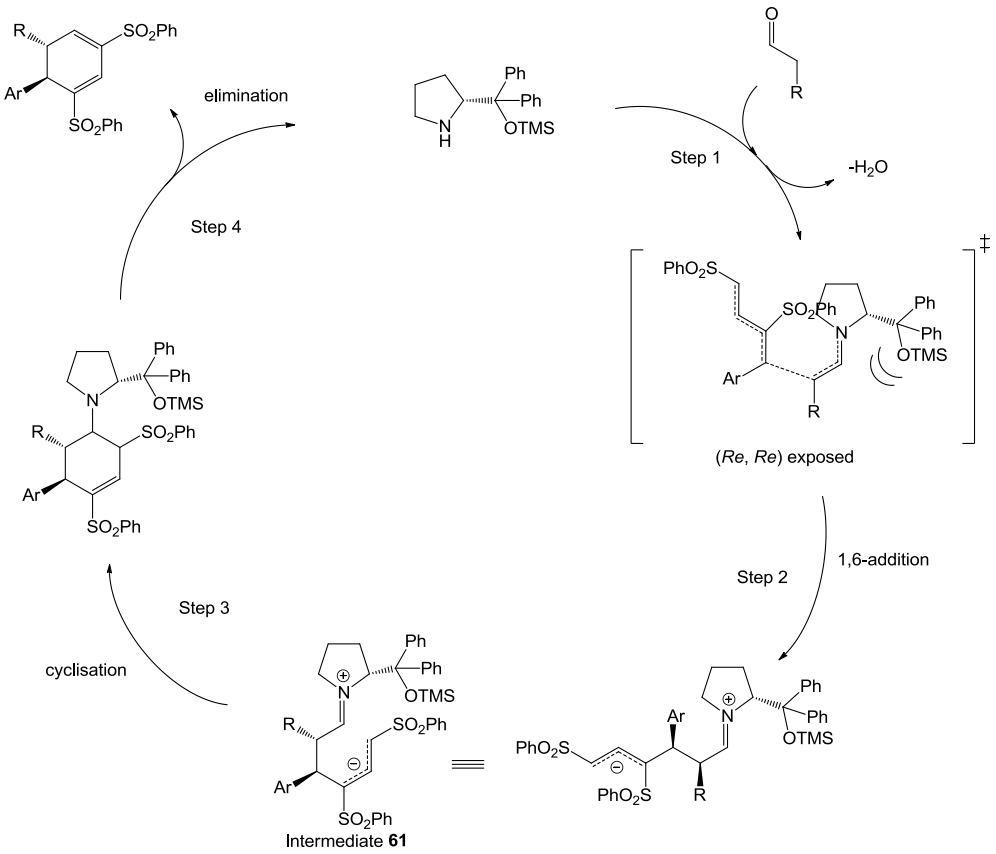
Figure 14: Varying aromatic functionalities

Furan was chosen as it is a desirable component that can either be oxidised or reduced easily to various different functional groups.[125] An anthracene was chosen as it is very large and would prove a challenging substrate. The anthracenyl diene did not undergo any detectable addition of the enamine, generated from *n*-valeraldehyde, after 1 week. This is unsurprising as the Charton value for anthracene is 1.18[126] while phenyl is 0.57,[127] implying that the anthracene moiety has over twice the steric character of the simple phenyl group. The furyl diene however had been completely consumed after 24 hours, but contained an inseparable mixture of numerous products. The number of products and rapid reaction time may likely be a result of different Diels-Alder reactions between the starting material and the products giving a number of diastereomers of different products. The use of furan as a dienophile in an inverse electron demand Diels-Alder cycloaddition with electron deficient alkenes has been previously reported.[128]

2.2.1.7 Proposed mechanisms

The product of the reaction could be explained through two different mechanisms. Firstly the conjectured 1,6-addition and cyclisation reaction followed by an elimination. Secondly a Diels-Alder inverse electron demand cycloaddition reaction. We proposed to study each pathway in detail in order to deduce which pathway was more evident.

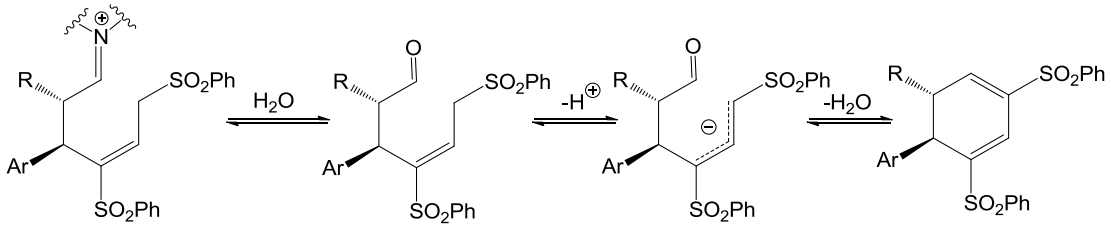
2.2.1.7.1 1,6-addition and cyclisation reaction



Scheme 45: Proposed catalytic cycle

The catalyst initially forms the chiral enamine, step 1, which then undergoes conjugate addition to the δ-carbon, step 2. A subsequent intramolecular cyclisation reaction then occurs between the iminium ion generated from the catalyst and the α-carbon, step 3. The last step releases the final product and regenerates the catalyst, step 4. We speculate that this elimination of the catalyst proceeds through a general acid-catalyzed mechanism similar to both a retro-aza-Michael addition and to the piperidine catalysed Knoevenagel condensation.[129] In an alternative catalytic cycle the iminium ion is first hydrolysed, eliminating the catalyst prior to the cyclisation reaction. The

subsequent deprotonation of the acyclic intermediate by the catalyst allows for an intra-molecular condensation (**Scheme 46**). This alternate catalytic cycle cannot presently be ruled out.

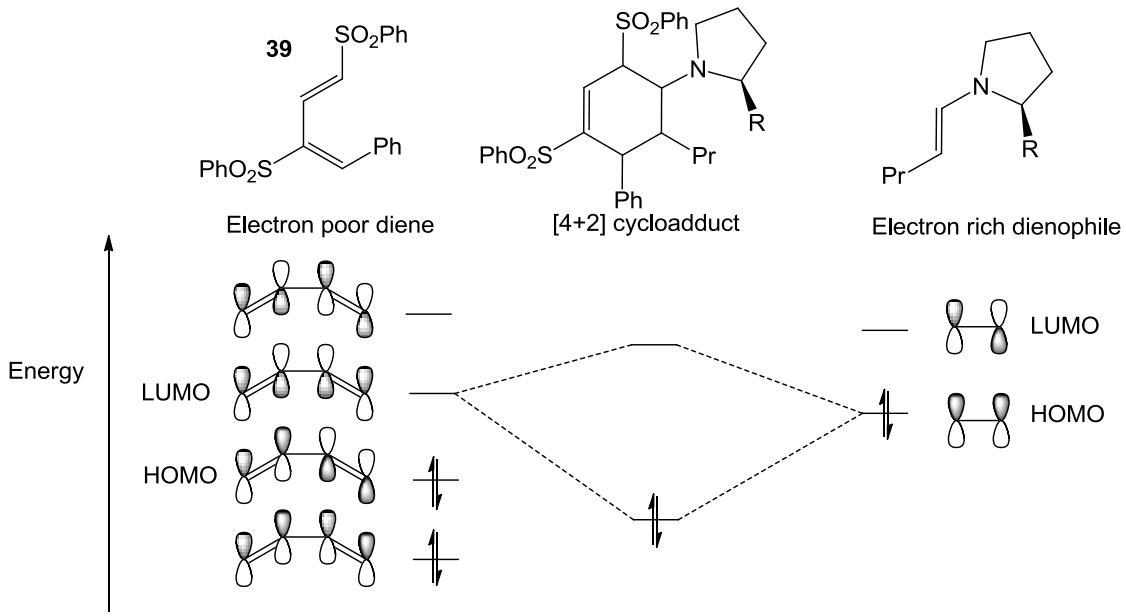


Scheme 46: Alternative reaction mechanism

The two electron withdrawing sulfone moieties allows for two possible carbonaceous sites of charge accumulation on intermediate **61**, namely the α-carbon and the γ-carbon. Two products, a 4-membered or a 6-membered ring, could be formed by the attack of the negatively charged α-carbon or γ-carbon on either the iminium ion or aldehydic carbonyl, depending on the catalytic pathway. The 6-membered ring is formed exclusively. Baldwin's rules predict that both the 6-*exo*-*trig* and 4-*exo*-*trig* cyclisations are favoured,[130] however the stability of the six-membered ring over a four-membered ring would allow the product from the 6-*exo*-*trig* cyclisation to dominate in a reversible system.

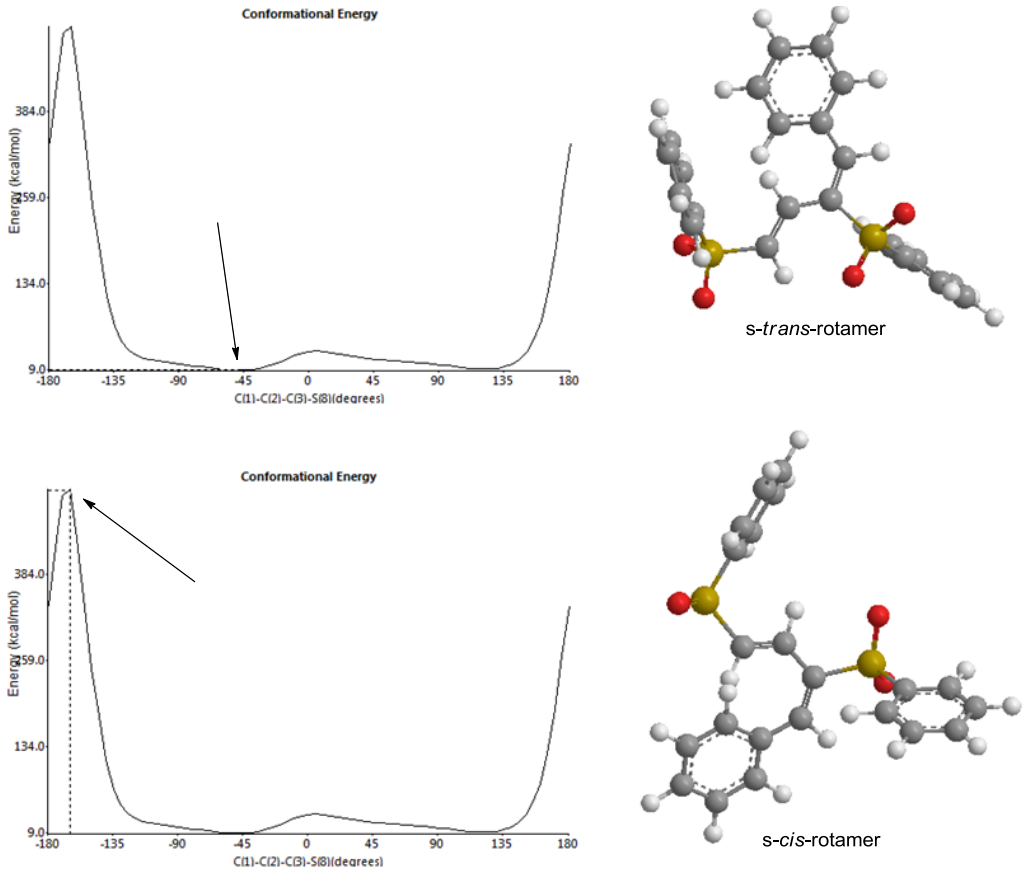
2.2.1.7.2 Inverse electron demand Diels-Alder cycloaddition

A 1,6-conjugate addition and subsequent 6-*exo*-*trig* cyclisation seemed to be the most likely mechanism for the formation of cyclic diene **43**. We also considered that the reaction may proceed through an inverse electron demand Diels-Alder (DA_{INV}) reaction. In this case the electron deficient diene **39**, possessing a lower energy LUMO, could interact with the electron-rich enamine, which has a high energy HOMO, causing a [4+2] cycloaddition to occur (**Scheme 47**).



Scheme 47: Possible DA_{INV} reaction between the diene **39** and enamine from valeraldehyde

There are several reasons why we do not prefer this mechanism. Firstly, we have to examine the geometry of the diene **39** which has two ground states we are interested in, the s-*cis*- and the s-*trans*- diene. Using low level MM2 calculations we determined roughly the conformational energies of both rotamers.[131] The s-*cis*- rotamer, which is the active conformation for the DA_{INV}, shows quite high conformational energy compared to the s-*trans*- rotamer which is the lowest energy conformation (**Scheme 48**). The increase in energy is due to the steric repulsion of the alkenyl substituents, a repulsion which is not evident in the *trans*- rotamer. One would therefore expect the s-*trans*- rotamer to dominate in solution but one cannot 100% rule out the possibility of a reaction taking place *via* the small amount of the s-*cis*- rotamer.



Scheme 48: MM2 calculated conformational energies for *cis*- and *trans*- diene **39**[131]

In addition, the cyclic diene **43** is itself an electron deficient diene that is locked in the *cis*-conformation. As such, one might expect the cyclic diene product to undergo a DA_{INV} cycloaddition with the excess enamine activated valeraldehyde in the reaction mixture. No DA_{INV} product is observed. Chen and co-workers reported the use of enamine activated saturated aldehydes (using the Jørgensen-Hayashi catalyst **3**) in the DA_{INV} cycloaddition with aza-butadienes.[22] Our lack of DA_{INV} reactivity supports our hypothesis that the bis-phenylsulfonyl dienes are not suitable substrates for the DA_{INV} with enamine activated saturated aldehydes. Accordingly we believe that the cyclic diene product **43** is much more likely to be formed *via* a 1,6-conjugate addition.

2.2.1.8 Enantioselectivity of the reaction

In forming the product only a single enantiomer was generated out of the possible two diastereomers. In order to determine how the chiral enamine imparted this enantioselectivity we grew a crystal of the product to ascertain its absolute stereochemistry, this was determined to be (*R,R*) by the Cahn-Ingold-Prelog rules (**Fig. 15**).[132]

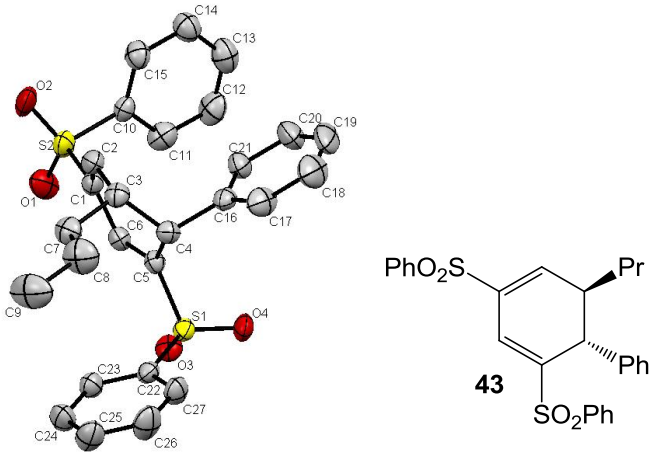


Figure 15: Crystal structure of product diene **43**

Applying the acyclic synclinal transition-state model proposed by Seebach (**Fig. 16**), we are able to describe the enantioselectivity of the C-C bond forming step.[34] As mentioned previously the enamine generated from aldehydes favours the *anti*-enamine due to steric repulsion (**See Section 1.4**) and hence is the only rotamer considered.[48] The steric bulk of the enamine, created from the aldehyde and the silylated prolinol, blocks the *Si* face of the electrophile completely and allows only the *Re* face of the enamine to approach the *Re* face of the electrophile in a gauche or synclinal fashion. This gives rise to the enantioselectivity of (*R,R*) in the product **43**.

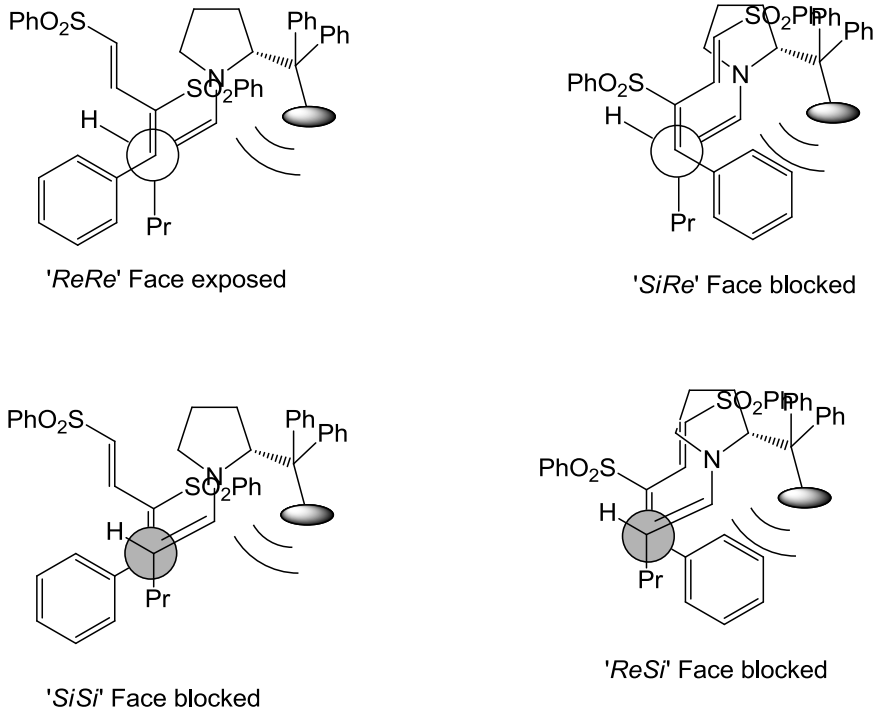


Figure 16: Newman Projection of C-C bond formation

To confirm this hypothesis we performed the reaction using the opposite (*S*)-enantiomer of the catalyst **3** and grew a crystal of the product **43b,** which showed the opposite stereochemistry (**Fig. 17**).

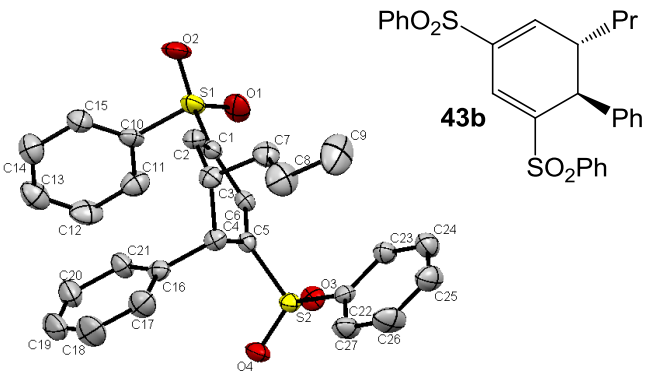


Figure 17: Opposite enantiomer of diene **43b**

Using the same logic as above, the *Si* face of the electrophile attacks the *Si* face of the enamine to give the (*S,S*)-enantiomer of the product **43b**. Previous literature reports have used a similar model to describe enantioselectivities displayed in the 1,4-conjugate addition of aldehydes to vinyl sulfones.[120a, 133]

We next considered the stereochemical outcome if we modelled a DA_{INV} reaction using the enamine generated from **(*R*)-3** as the dienophile and the *cis*-conformation of diene **39** (**Fig. 18**)**.**

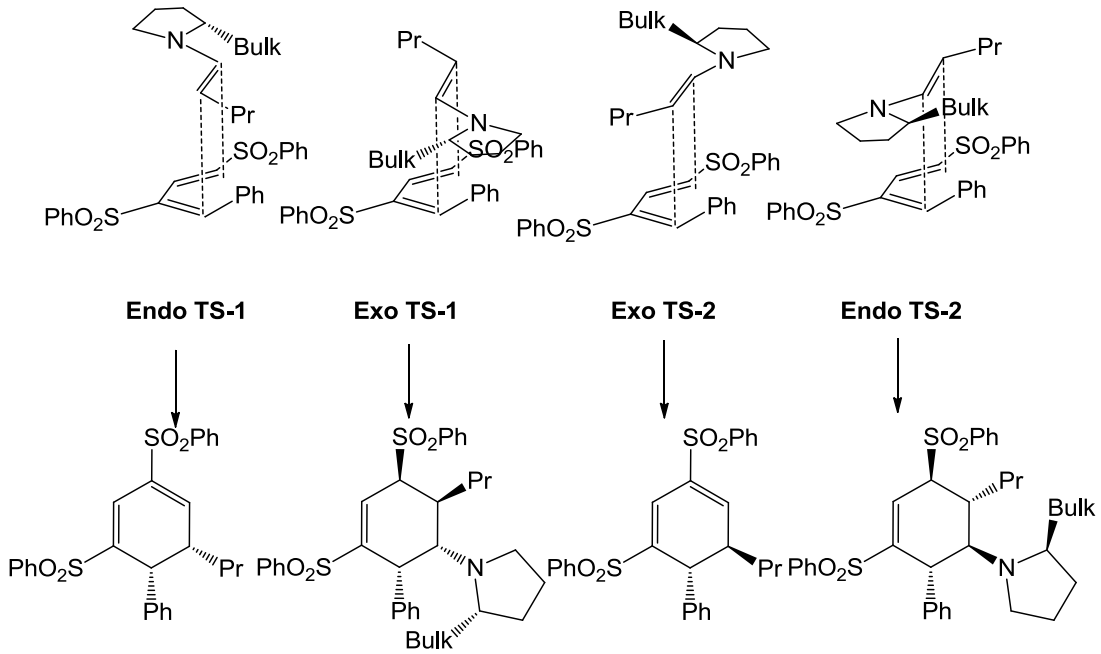
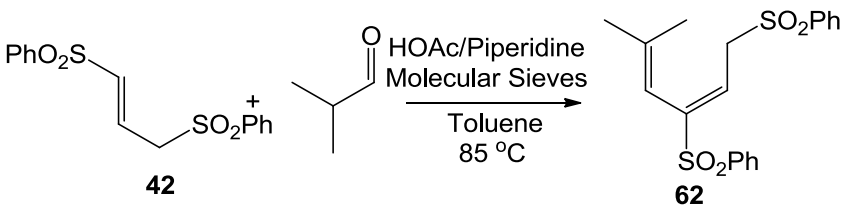


Figure 18: Stereochemical predictions of DA_{INV}

The projected transition states show that the *endo*- transition state 1 (**Endo TS-1**) gives the incorrect geometry, and that *endo*- transition state 2 (**Endo TS-2**) gives the incorrect product. The *exo*- transition state 1 (**Exo TS-1**) again gives the incorrect product, and the *exo*- transition state 2 (**Exo TS-2**) gives the correct geometry but suffers from steric hindrance of the enamine. It is generally known that the endo transition state is favoured in Diels-Alder reaction (The Endo Rule) but more specifically, in the reported DA_{INV} cycloadditions using pyrrolidine based catalysts with saturated aldehydes, the *endo*- transition state is used to explain the stereochemical outcome.[134] In our case the *endo*- transition states deliver the incorrect geometry and the incorrect product (**Endo TS-1, Endo TS-2** respectively), which is further confirmation that the reaction does not proceed through a DA_{INV}.

2.2.1.9 Attempted additions to alkyl 1,3-bis-phenylsulfonyl butadienes

Having established a high yielding and highly selective addition to aromatic dienes we next decided to try to extend the substrate scope to alkyl dienes. The synthesis of these compounds was initially unsuccessful as the reaction conditions used to generate the aromatic dienes did not give the desired product and instead compound **62** was formed (**Scheme 49**).



Scheme 49: Attempted Knoevenagel of bis-phenylsulfonyl propene **42** with isobutyraldehyde

The structure of compound **62** was confirmed by X-Ray crystallography (**Fig. 19**).

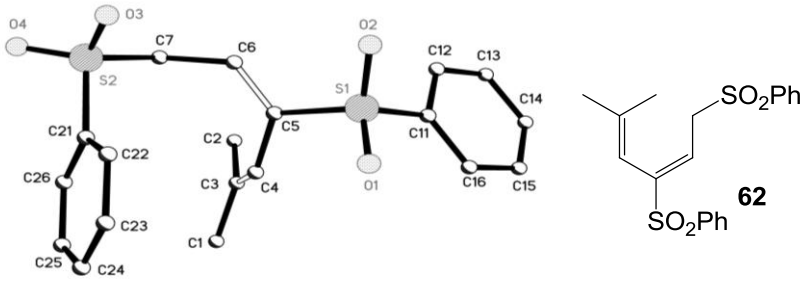
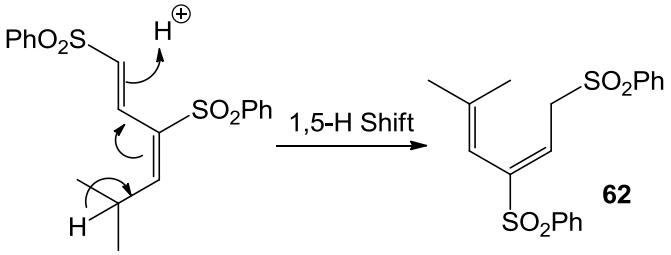


Figure 19: Crystal structure of compound **62**

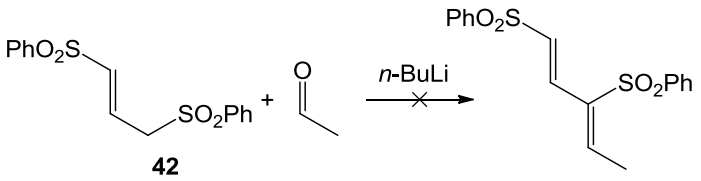
We proposed that this product was a result of a 1,5-hydrogen shift of the acidic proton from the ε-carbon to the α-carbon on the desired bis-phenylsulfonyl diene (**Scheme 50**). A similar hydrogen shift involving vinylic phenylsulfones has been reported by Padwa.[135] An attempt was made to isomerise the compound **62** using a variety of basic conditions but failed to produce the desired compound and returned compound **62** after prolonged reaction times.



Scheme 50: Proposed mechanism for formation of compound **62**

We next tried to repeat the work of Masuyama who had reportedly made the alkyl diene **62**, again using piperidinium acetate, but employing refluxing pentane as a solvent.[121] In our hands, only returned starting material was obtained as the bis-phenylsulfonyl-propene **42** was completely insoluble in the pentane solution. We rationalised that the 1,5-hydrogen shift may be promoted by heat and that reaction at lower temperature might yield the desired product. Unfortunately, when this was tried using either toluene or benzene, the result was a mix of returned starting material and the 1,5-shift product **62** (after 72 hours of stirring at either room temperature or 45 °C).

We next tried to synthesise the alkyl diene from acetaldehyde. Again the reaction failed under a variety of conditions, giving foul-smelling black polymers almost instantaneously upon addition of acetic acid. The polymerisation of acetaldehyde to poly-acetaldehyde using acetic acid has been reported.[136] We concluded that acidic conditions could promote the polymerisation of acetaldehyde and strictly basic conditions would be preferable. We came upon a strategy of using organolithium bases, which had been employed by Padwa to make some of his bis-phenylsulfonyl dienes.[135] Using *n*-butyllithium, at cold temperatures, we tried an array of conditions and stoichiometry's in an attempt to isolate the methyl diene (**Table 16**). Unfortunately, these experiments either returned starting material or polymerisation occurred in all cases.



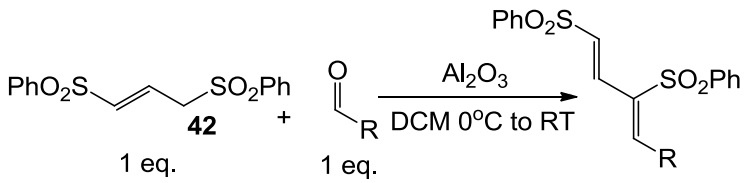
42

Entry	Sulfone Eq.	Aldehyde Eq.	*n*-BuLi Eq.	Solvent	Temp. (^{o}C)	Yield[a] (%)
1	1	1	1	DME	-78	R.S.M.
2	1	2	2	DME	-78	R.S.M.
3	1	10	5	DME	-60	R.S.M.
4	1	10	2	THF	-78	Polymer
5	1	1.1	1.1	THF	-78	Polymer

Reactions were performed on a 0.5 mmol scale under an atmosphere of argon, [a] determined by ^{1}H NMR spectroscopy

Table 16: Attempted synthesis of methyl diene using organolithium

It became clear that a low temperature, less basic, variation of the Knoevenagel condensation was required. Literature searches indicated that activated aluminium oxide had been used to generate alkenes from alkyl aldehydes at room temperature using diethyl glutaconate as the nucleophile.[137] The same methodology was applied to the Knoevenagel condensation of isobutyraldehyde and 1,3-bis-phenylsulfone propene **42**. When performed at room temperature there was a 50:50 mixture of the desired diene and the isomerised hydrogen shift product was obtained. The reaction was repeated and this time activated alumina was stirred in an ice-bath before the aldehyde was added. This resulted in a complete conversion to the desired product in 4 hours. We then extended the reaction to different alkyl aldehydes (**Table 17**).



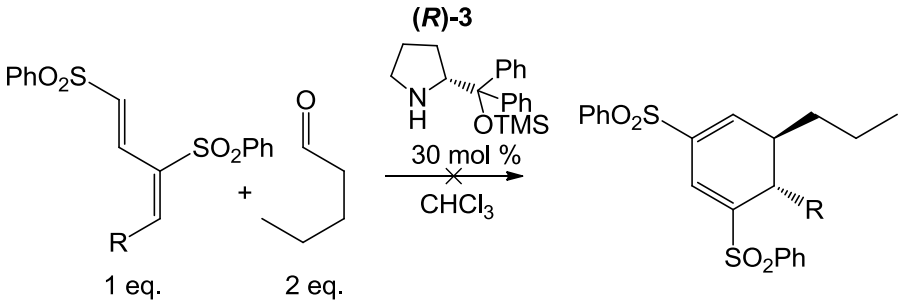
Entry	Time (h)	R	Yield[a] (%)
1	4	*i*Pr	81 (**63**)
2	2	CH_2*i*Pr	88 Isomerised (**64**)
3	1.5	*n*Bu	83 Isomerised (**65**)
4	Overnight	Cyclohexyl	80 (**66**)
5	1	Me	Polymer[b]
6	1 week	*t*Bu	R.S.M.[b]

Reactions were performed on a 1 mmol scale with 30 equivalents of aluminium oxide in 5 mL of DCM, [a] isolated yield, [b] determined by ^{1}H NMR spectroscopy

Table 17: Synthesis of a family of alkyl dienes

The use of non α-branched aldehydes led to isomerisation of the product in the reaction (**Entry 2-3**). We attribute this to the increased acidity of the ε-H due to the decreased substitution of the alkyl carbon leading to a drop in electron-density at this position. The cyclohexane carboxaldehyde derivative **66** required longer reaction times most likely due to the increased steric bulk of the cyclohexyl group which has a Charton value of 0.97 (**Entry 4**).[127] When the even more sterically hindered pivalaldehyde was tested there was no reaction after 1 week. A *t*-butyl group has a Charton value of 1.34 and hence this result was not unexpected (**Entry 6**).[127] Interestingly when the methodology was applied to acetaldehyde again polymerisation was observed, even when the reaction was conducted at -40 ^{o}C. A literature search provided the answer in that the aluminium oxide, although amphoteric in nature, is acidic enough to initiate polymerisation of acetaldehyde to both polyacetaldehyde and paraldehyde.[138]

The alkyl dienes (**63, 66**) were then subjected to the optimised conditions that had been developed for the 1,6-conjugate addition to aromatic dienes. The results are summarized in **Table 18**.



Entry	R	Time (days)	Yield[a]	Charton Value for R Group[127]
1	*i*Pr	7	R.S.M.	0.76
2	Cyclohexyl	7	R.S.M.	0.97

Reactions were performed on a 0.2 mmol scale, in 0.5 mL of $CHCl_3$ at RT, [a] determined by ^{1}H NMR spectroscopy

Table 18: Attempted 1,6-conjugate addition to alkyl dienes

Unfortunately, the alkyl dienes proved to be completely unreactive. We initially suspected that the catalyst may isomerise the diene to the 1,5-H shift product and prevent reaction. Following both reactions by ^{1}H NMR spectroscopy we observed no isomerisation after 65 hours under either the reaction conditions or with just catalyst. We can assume, therefore, that lack of reactivity is most likely due to a combination of electronic and steric effects.

The alkyl substitution on the δ-carbon will donate electron density through the C-C σ-bond by induction; in contrast a phenyl substituted δ-carbon will withdraw electron-density through the π system. The electron-density at the electrophilic site is vital in lowering the LUMO of the unsaturated system to the point where the HOMO of the enamine can interact with it.[139]

The Charton values indicated that every one of the alkyl dienes synthesised was much more sterically hindered than the phenyl diene. The alkyl diene derived from acetaldehyde is the closest match, sterically, to the phenyl diene with Charton values of 0.58 and 0.57 respectively but would most likely isomerise.[127]

With the lack of reactivity we observed in the alkyl dienes we next tried to synthesis the unhindered terminal diene **67** (**Fig. 20**) as a final attempt to develop a 1,6-conjugate addition to a non-aromatic diene.

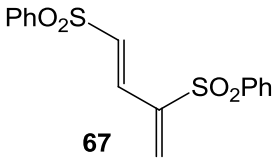
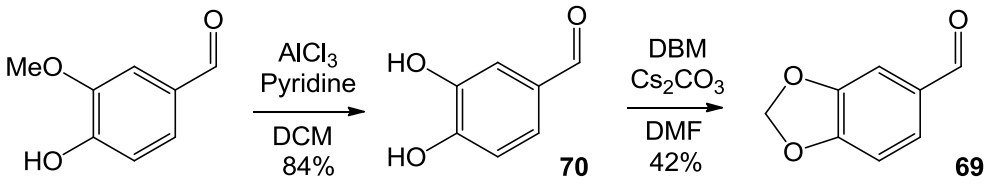


Figure 20: Terminal diene **67**

The synthesis of diene **67** has been reported by Padwa.[135] We initially employed the same procedure with *n*-butyllithium in DME, and later using THF, at -78 ^{o}C bubbling gaseous formaldehyde generated by heating paraformaldehyde under a stream of N_2. We were unable to reproduce Padwa's result which we ascribe to our inability to prevent formaldehyde from re-forming paraformaldehyde before the desired condensation could take place. A similar unsuccessful result was obtained when using aluminium oxide.

2.2.1.10 Ketones as pro-nucleophiles for 1,6-conjugate additions to dienic sulfones

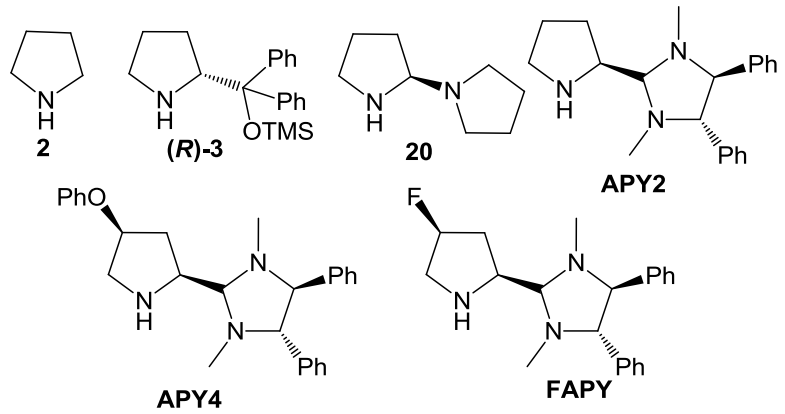
In order to further expand the scope of our 1,6-conjugate additions we investigated the use of ketones as pro-nucleophiles. Masuyama had performed the Michael addition and cyclisation of cyclohexanone to a bis-phenylsulfone derived from piperonal using a stoichiometric amount of morpholine and catalytic quantities of toluenesulfonic acid.[121] We initially employed the bis-phenylsulfonyl butadiene **39** as the Michael acceptor in these reactions and received a complicated mixture of products, so we decided to replicate the methodology of Masuyama as closely as possible. In order to mimic these conditions the diene 1,3-bis-phenylsulfonyl-4-(1,3-benzodioxole)-butadiene **68** had to be synthesised.



Scheme 51: Synthesis of piperonal **69** from vanillin

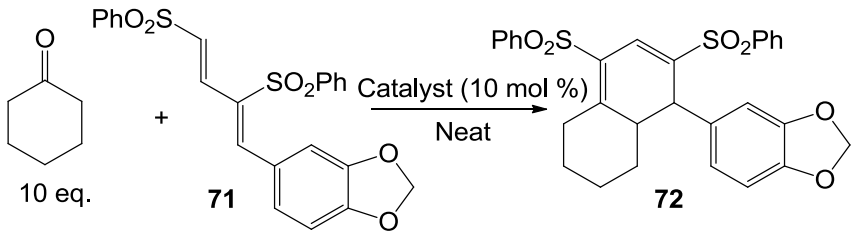
Piperonal **69** is no longer commerically available and was produced readily from the de-methylation of vanillin to generate protocatechualdehyde **70**,[140] from which the benzodioxole ring was closed using dibromomethane under basic conditions (**Scheme 51**).[141] The diene **71** was then completed using the conditions previously developed for the synthesis of the aromatic dienes in high yield (90%).

The trial reaction was conducted using neat conditions with 10 equivalents of cyclohexanone and 30 mol % of the catalyst. An array of catalysts, including achiral pyrrolidine, known for their ability to catalyse the conjugate addition of cyclic ketones to vinyl sulfones were used in a catalyst screen (**Scheme 52**).[142] The original catalyst phenyl prolinol **3,** was also used although it is known to be an ineffective catalyst for the enamine activation of ketones.[78] Catalysts **2** and **20** were bought commerically while the aminal catalysts **APY2, APY4** and **FAPY** were gifted by our collaborators who had recently reported their use in the addition of cyclic ketones to 1,2-disulfones and nitrodienes respectively.[143]



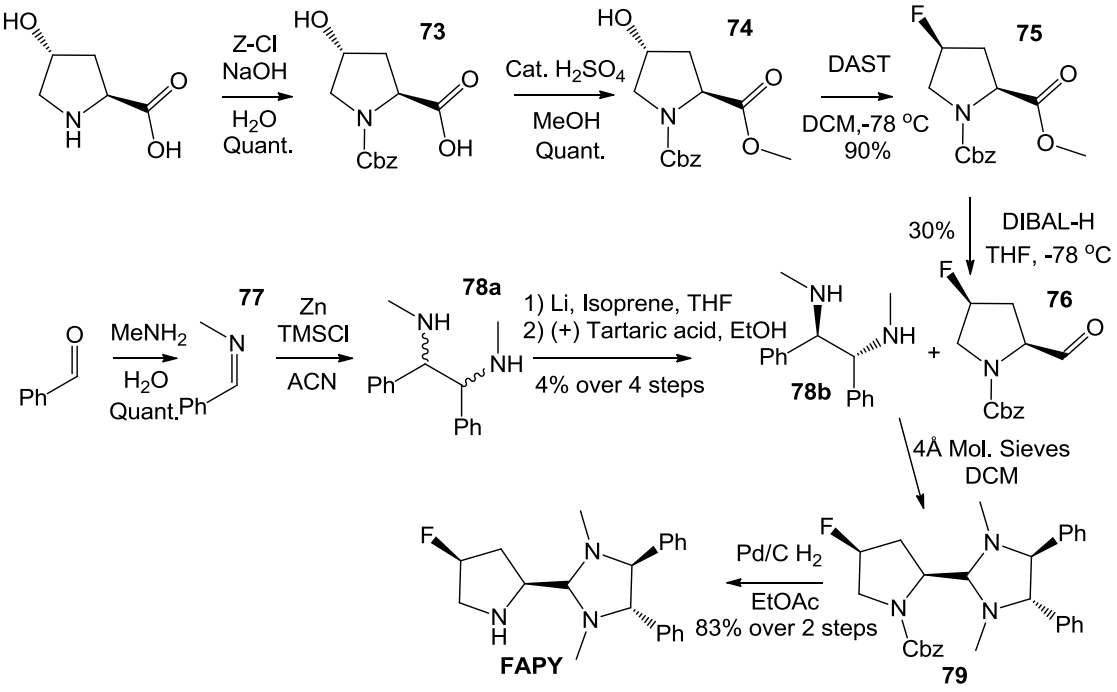
Scheme 52: Catalysts screened in the addition of ketones

We were pleased to find that all the catalysts employed in this study gave 100% conversion of the starting material after 24 hours, with the exception of the silyl-prolinol **(*R*)-3** which unsurprisingly gave returned starting material**.** Unfortunately the reactions employing a chiral catalyst gave a mixture of different products that proved very difficult to identify and purify. Pyrrolidine appeared to react much faster and give a cleaner sample of the desired product **72** albeit racemic (**Scheme 53**).



Scheme 53: 1,6-conjugate addition of ketonic enamines to 1,3-bis-phenylsulfonyl dienes

We chose the fluorinated catalyst **FAPY** to proceed with as it gave the cleanest reaction products. The synthesis of **FAPY** is outlined in **Scheme 54**.



Scheme 54: The synthesis of **FAPY**

The convergent synthesis began with a slight modification from the procedure given by our collaborators. The Cbz-protected hydroxyproline **73** derived from commercial hydroxyproline was esterified to **74** under acid catalysis, which we found to be superior over the acid chloride approach reported in terms of both time and work-up.[143b] The ester **74** was then treated with DAST to insert the fluorine *via* an S_N2 reaction causing the classical Walden inversion of stereochemistry. Reduction of the fluoro-ester **75** with a solution of DIBAL-H at low temperature gave the aldehyde at an acceptable yield (30%). Chromatographic removal of the over reduced alcohol would have resulted in dramatic loss of yield, so the mixture was carried through as a mixture of both aldehyde **76** and the alcohol in a 62.6% mass pure (by ^{1}H NMR spectroscopy) sample. A similar procedure was employed in the literature synthesis.[143b] The chiral amine was synthesised using the detailed paper from Alexakis.[144] *N*-methyl benzylimine **77** was prepared by treating benzaldehyde with an aqueous solution of methylamine. The imine was dimerized and reduced using SET zinc mediated pinacol-coupling with trimethylsilyl chloride to give a mixture of the *RR*, *SS* and meso isomers of the diamine **78a**. The meso isomers were isomerised by treating the mixture with lithium and isoprene at room temperature. The resulting mixture of *RR* and *SS* enantiomers was resolved using L-tartaric acid to give pure ***(R,R)*-78b** after hydrolysis of the tartrate with sodium hydroxide, in a disappointing 4% yield following recrystallisation from pentane. After repeated attempts trying different sources of zinc and re-purifying the *N*-methyl benzylimine, the yield could not be improved. However the reaction could be performed on a large scale and gram quantities could be obtained. The diamine **78b** and aldehyde **76** were then stirred overnight to yield the Cbz-protected aminal **79**. The catalyst

FAPY was completed after hydrogenolysis of the protecting group with palladium on charcoal in 83% yield after chromatography.

Using the cyclohexyl-enamine generated from **FAPY** and the piperonal diene **71** we were unable to develop conditions that gave an improvement in the selectivity of the reaction. Multiple attempts to purify the material were also unsuccessful. Our collaborators in Geneva, Prof. Alexakis and Dr. Chellat, were able to solve the structures of the side products, using a more powerful NMR spectrometer, allowing us to determine the following results (**Fig. 21, 22**).

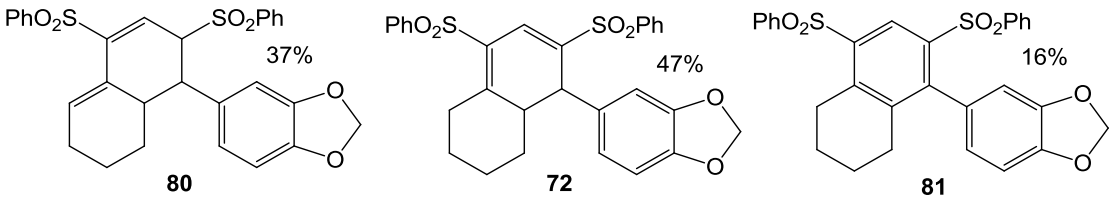


Figure 21: Products of **FAPY** catalysed addition of cyclohexanone to piperonal diene **71**
Note yield is based on crude ^{1}H NMR spectroscopy after 5 hours reaction

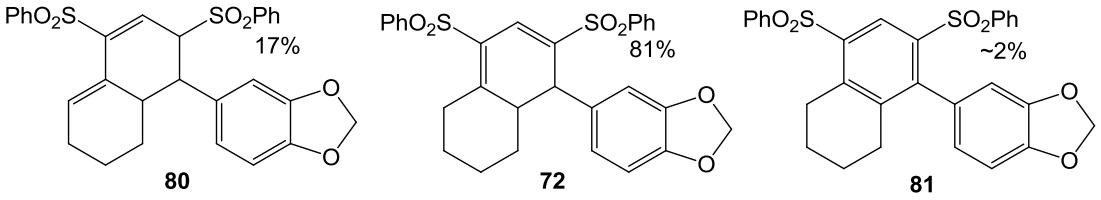
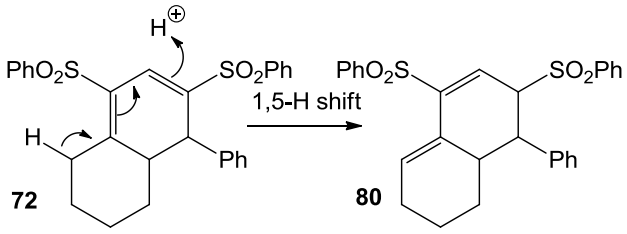


Figure 22: Products of pyrrolidine **2** catalysed addition of cyclohexanone to piperonal diene **71**
Note yield is based on crude ^{1}H NMR spectroscopy after 15 minutes reaction

Compound **81** was mostly likely formed as a result of simple base promoted aromatisation.[121] The more complicated unsaturated product **80** is the result of 1,5-hydrogen shift (**Scheme 55**). Shifts of this type are not uncommon in dienic-sulfones and were observed earlier, in a similar alkyl substrate (**See Section 2.2.1.9, Scheme 50**).



Scheme 55: Possible generation of unsaturated product **80** by H-shift.

Although we could generate the desired cyclic diene **72** and its isomer **80** *via* a 1,6-conjugate addition, we could not get any of the chiral catalysts to mimic the more selective results of

pyrrolidine **2** and purification of any of the products was too difficult to warrant continued investigation.

2.2.1.11 Synthesis of a conformationally restricted *trans*- diene

Although we had accumulated theoretical evidence that suggested the cyclic diene **43** was being formed by a 1,6-conjugate addition and cyclisation rather than a DA_{INV} cycloaddition we were interested in obtaining experimental evidence. To this end a conformationally restricted s-*trans*-diene **82**, which could not undergo a DA_{INV} cycloaddition, was proposed (**Figure 23**).

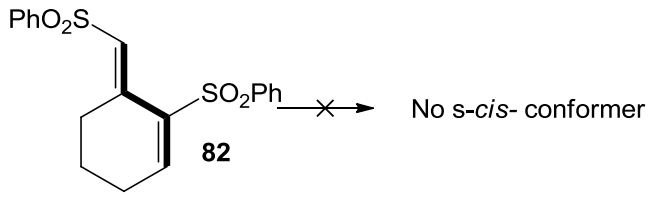
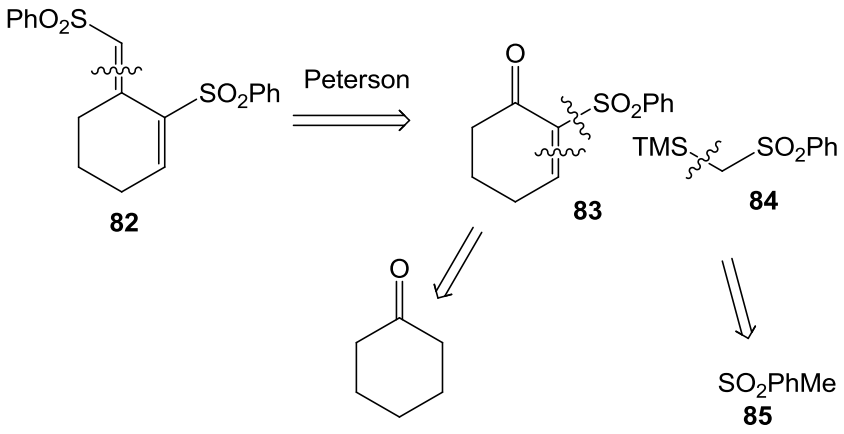


Figure 23: Conformationally restricted s-*trans*- diene **82**

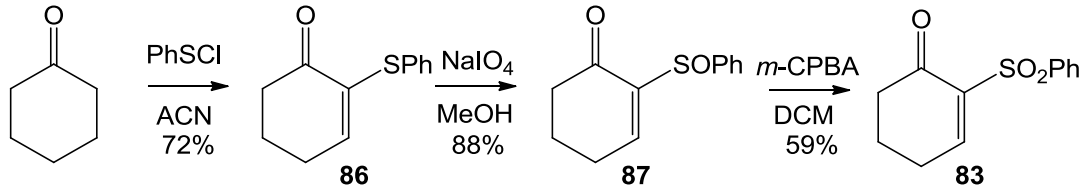
The initial retrosynthesis of this compound is presented in **Scheme 56**.



Scheme 56: Retrosynthetic pathway using a Peterson olefination

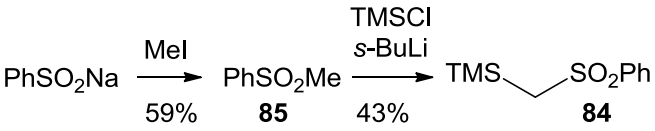
We hoped that by using a Peterson olefination we could generate the *trans*- diene **82** in a relatively short number of steps. To do this we would have to synthesise both the trimethylsilyl methylphenylsulfone **84** and the α-phenylsulfonated cyclohexanone **83.**

The substituted cyclohexanone was synthesised using a literature procedure.[145] Careful step-wise oxidation was carried out to avoid oxidising the alkene and the desired sulfone **83** was isolated in good yield (**Scheme 57**).



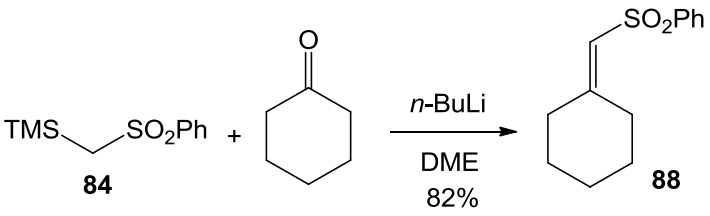
Scheme 57: Synthesis of α-phenylsulfone cyclohexanone **83**

Beginning with the sodium salt of benzenesulfinic acid, standard methylation conditions were used to deliver methylphenylsulfone in good yield after recrystallisation. The TMS group was added using an organolithium base, as suggested by the literature,[146] to yield the Peterson pro-nucleophile **84** in a modest yield (**Scheme 58**).



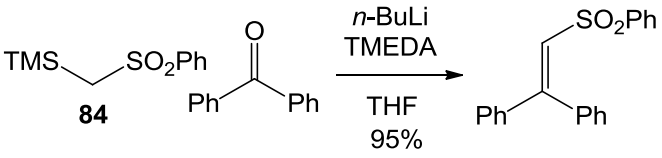
Scheme 58: Synthesis of trimethylsilyl methylphenylsulfone **84**

The first reaction conditions we tried for the Peterson olefination were those reported by Ley *et al.* for the generation of olefin **88** from cyclohexanone (**Scheme 59**).[147] These conditions proved unsuccessful giving an inseparable mixture of products.



Scheme 59: Peterson olefination reported by Ley *et al.*[147]

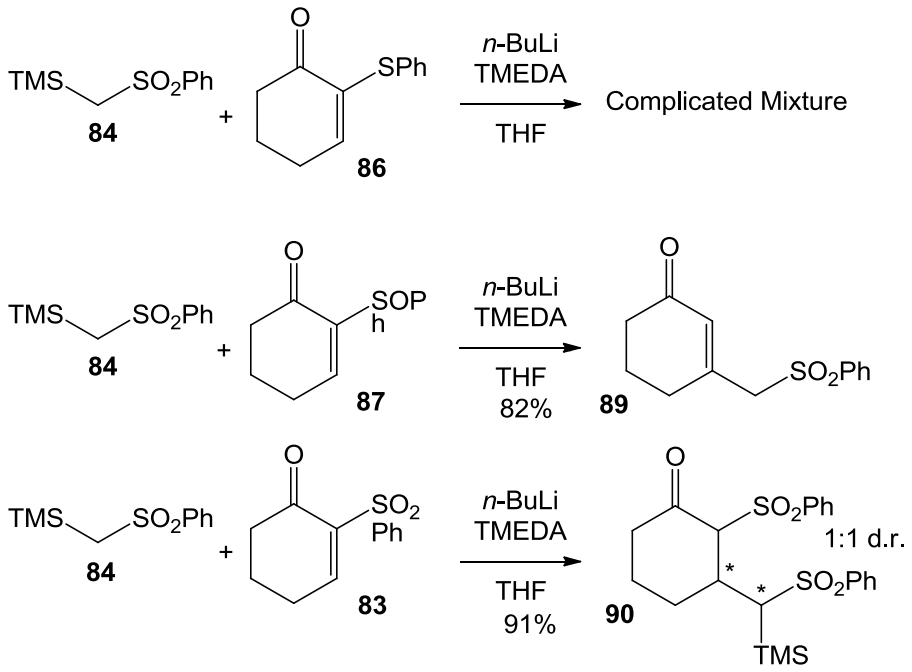
We then employed the reaction conditions reported by Eisch and co-workers for the Peterson olefination of trimethylsilyl methylphenylsulfone and benzophenone (**Scheme 60**).[148]



Scheme 60: Peterson olefination reported by Eisch *et al.*[148]

The experiments were conducted in tetrahydrofuran at -78 ^{o}C with one equivalent of the trimethylsilyl methylphenyl sulfone **84**, 1.05 equivalents of TMEDA, 1.05 equivalents of *n*-

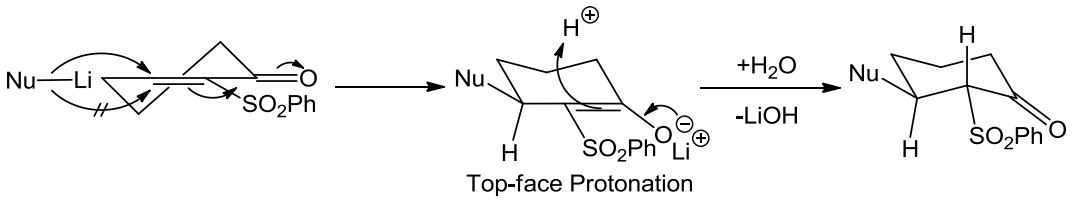
butyllithium and one equivalent of the electrophile (**Scheme 61**). Upon addition of the electrophile the mixtures were allowed to come to room temperature and quenched with ammonium chloride.



Scheme 61: Trial reactions using 3 electrophiles **86**, **87** and **83**

Reactions were performed on a 1 mmol scale in 5 mL of THF under an atmosphere of argon at -78 °C

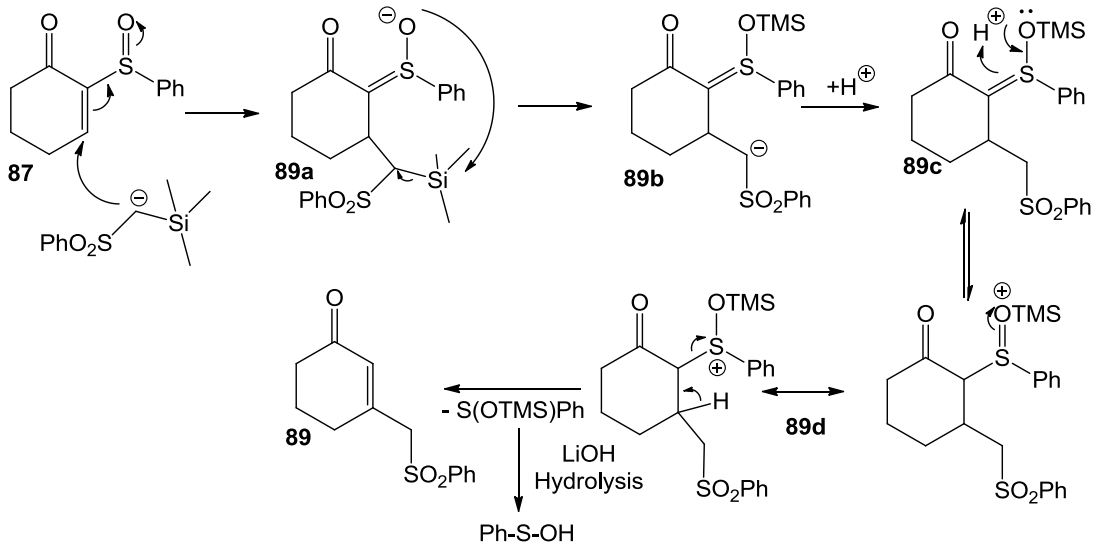
When the cyclohexenone **86** was used the starting material was consumed completely giving a complex and inseparable mixture. ^{13}C NMR showed several carbonyl peaks, indicating that conjugate addition may have occurred. Cyclohexenone **87** underwent a conjugate addition, followed by a Brook type rearrangement/sulfoxide elimination, with both the TMS and the sulfoxide being eliminated giving the product **89** (**Scheme 63**). Finally, using cyclohexenone **83**, the reaction went *via* a high yielding conjugate addition. This time there was no elimination of the sulfur group or the TMS moiety. The product was a mixture of an equal amount of two diastereomers of **90**; most likely stereocontrol was achieved during attack of the cyclohexene ring which would have occurred on the least hindered face and during the saturation of the α-carbon where the protonation would occur on the top face to allow the cyclohexanone ring to be in the pseudo-chair conformation following the nucleophilic conjugate addition (**Scheme 62**).[149]



Scheme 62: Stereoselective conjugate addition and protonation of α-carbon

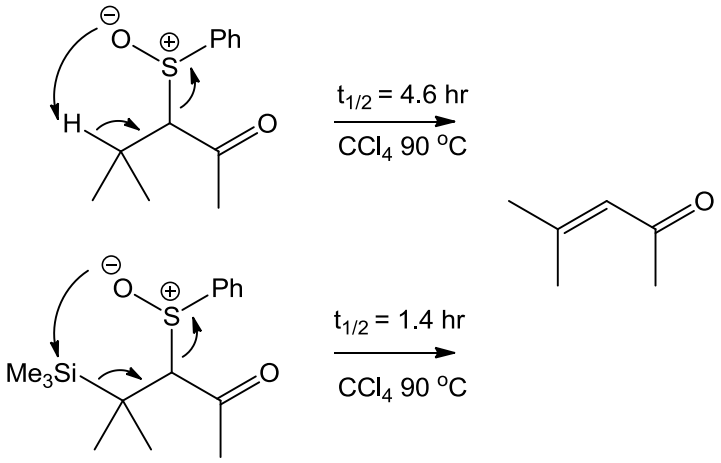
We were aware, before starting the synthesis, of the competition between the carbonyl carbon and the β-carbon for nucleophilic addition. We had theorised that a sufficiently hard nucleophile should deliver us to the correct direct addition site, hence the use of a lithium TMEDA complex as a nucleophile. We imagined that the sulfide would contain a majority of the desired Peterson olefination product, the sulfoxide would contain a mixture of both the conjugate adduct and the Peterson product, and the sulfone would be mainly conjugate adduct, in line with their respective electron-withdrawing properties. However in all cases it seemed that a conjugate addition was favoured.

The most interesting result from the experiments was the unusual Brook-type rearrangement/sulfoxide elimination, which occurred after the conjugation addition to the α-phenylsulfinyl cyclohexenone **87**. We proposed a mechanism for the reaction as depicted in **Scheme 63**.



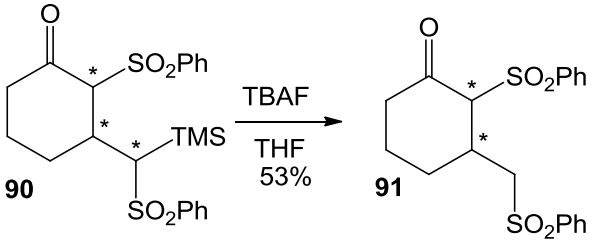
Scheme 63: Proposed mechanism for the formation of cyclohexenone **89**

The organolithium reagent attacks at the β-carbon to give **89a**. The sulfinate anion then attacks the silyl group similar to a Brook rearrangement to give **89b**.[150] The anion is stabilized on the carbon bound directly to the phenyl sulfone and is protonated to give the intermediate **89c**. Protonation to **89d** followed by an elimination step gives the cyclohexenone **89**. The eliminated trimethylsilyl phenylsulfanol is most likely hydrolysed to phenylsulfenic acid which is known to degrade to volatiles.[151] This type of sulfoxide elimination is well established. Sulfoxides are known to eliminate under thermal conditions, when α- to a carbonyl group, *via* a reverse-cycloaddition.[152] Fleming has also reported that the thermal cyclo-elimination is faster when the β-proton is replaced with a trimethyl silyl group, which could explain why the elimination occurred for us at either room-temperature or at 40 ^{o}C while in a water bath during the work-up procedure (**Scheme 64**).[153]



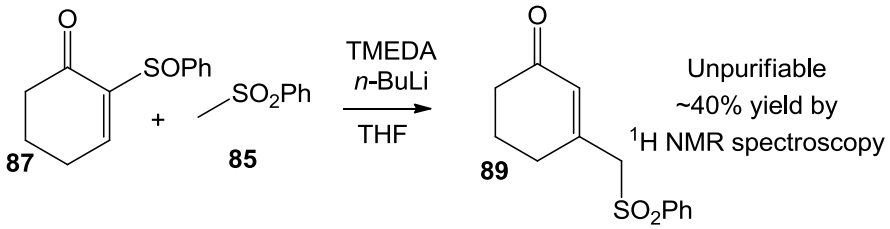
Scheme 64: Increase in rate of reaction reported by Fleming[153]

In order to probe the feasibility of our mechanism we first tested if the removal of the TMS group could be achieved for the related cyclohexanone **90**. This was achieved using TBAF, and gave good conversion; however isolation proved difficult, as indicated by the moderate yields (**Scheme 65**).



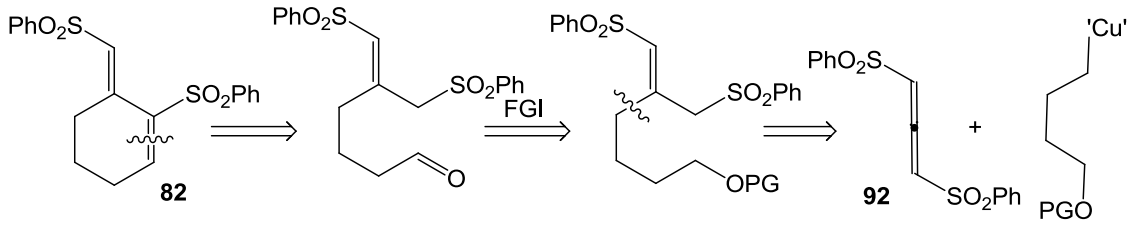
Scheme 65: Removal of the TMS group using TBAF

We then explored whether the TMS group played a role in the elimination of the sulfoxide group. We hypothesised that without the TMS group the elimination of the sulfoxide group may not occur or may occur in a reduced yield. To test this hypothesis we carried out the addition of methylphenylsulfone **85** to cyclohexenone **87**, under the same reaction conditions (**Scheme 66**). The conjugate addition and subsequent sulfoxide elimination did occur but in a lower yield of **89** with many unidentifiable side products. The elimination product could not be fully purified but was identified by ^{1}H NMR as the major product in less than 40% yield. The lower yield may indicate that the TMS does play a role in promoting the sulfoxide elimination as proposed in our mechanism (**Scheme 63**).



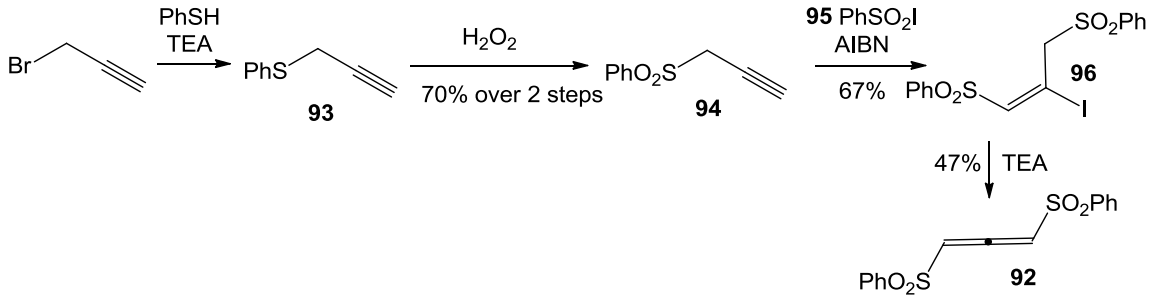
Scheme 66: Conjugate addition of methylphenyl sulfone

While we had observed some interesting chemistry, we did not synthesise the conformational restricted *trans*- diene **82** and a new retrosynthesis was needed (**Scheme 67**).



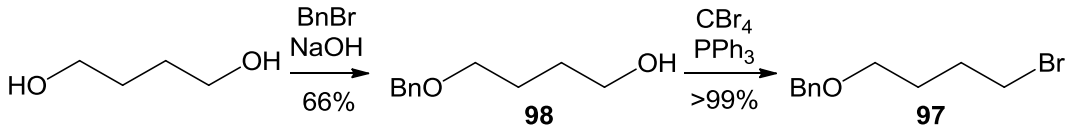
Scheme 67: Second retrosynthesis of conformationally restricted *trans*- diene **82**
Note PG = protecting group

Our second approach would focus on the step by step construction of the cyclohexene ring system. We planned to use a Knoevenagel condensation to form the cyclohexene ring. To do this we needed an aldehyde functionality, which we planned to derive *via* the oxidation of an alkyl alcohol. We hoped that by using an oxidation method that involved basic conditions we could perform the oxidation and Knoevenagel condensation in one step. The sulfonyl alcohol would be generated by organocuprate conjugate addition to the allene **92**. The allene could be synthesised in 4 steps from propargyl bromide (**Scheme 68**).



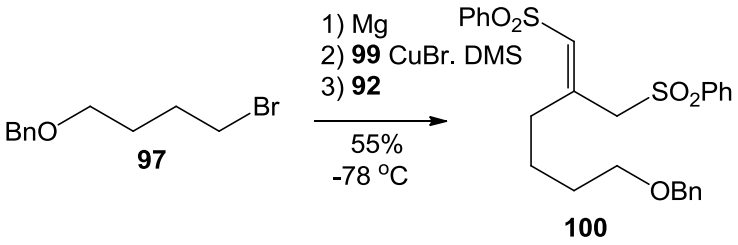
Scheme 68: Synthesis of allene **92**

A simple S_N2 attack by thiophenol on propargyl bromide[154] followed by oxidation gave the propargyl phenylsulfone **94** in good yield over 2 steps, comparable to the literature.[155] The allene **92** was completed, according to the work of Bull, by free-radical addition of phenylsulfonyl iodide **95** to the alkyne **94** to give *Z*-alkene **96** and subsequent dehydroiodination at low temperature to give **92** in good yield.[156] In order to generate the required organocuprate we first had to synthesise the alkyl bromide **97** (**Scheme 69**).



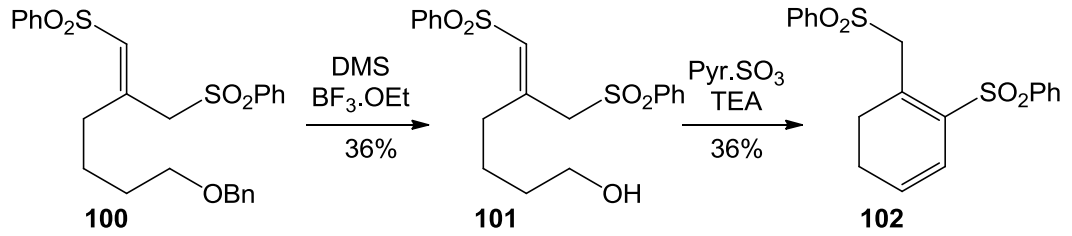
Scheme 69: Synthesis of alkyl halide **97**

Protection of 1,4-butane diol was accomplished in good yield using benzyl bromide. The alcohol **98** was then subjected to classical Appel conditions to give the alkyl bromide **97** quantitatively.[157] The organocuprate was generated by treating the Grignard, derived from the alkyl bromide **98,** with copper(I) bromide dimethylsulfide complex **99**. The resultant organocuprate was added to the allene **92** at low temperature to yield the desired conjugate adduct **100** in good yield as a mix of *E/Z* isomers (**Scheme 70**).



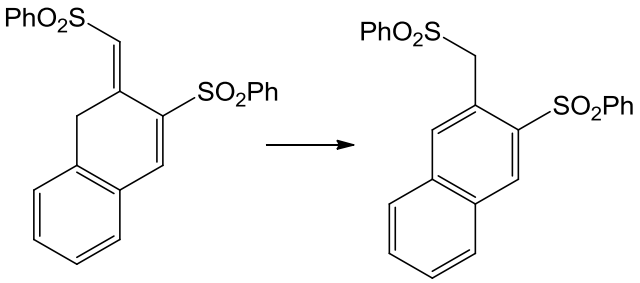
Scheme 70: Addition of organocuprate to allene **92**

The benzyl ether was next removed under Lewis-acidic conditions and the ring closure was completed by performing a standard Parikh-Doering oxidation with an extra equivalent of base to complete the Knoevenagel condensation in one pot (**Scheme 71**). Extensive chromatography gave the 1,5-shifted isomer **102** in low yield.



Scheme 71: Ring closure of cyclohexenone ring leading to isomer **102**

The result was disappointing but not surprising. We had seen with the alkyl dienes that α-unbranched dienes undergo isomerisation even at low temperature and mild conditions. The construction of an α-branched conformationally restricted *trans*- diene was designed, however due to time constraints was not completed. Synthesising an aromatic version of the conformationally restricted s-*trans*- diene was also considered but we believe that this compound would just aromatise (**Scheme 72**).



Scheme 72: Predicted aromatisation of phenyl substituted aromatic diene

Although we have not definitively proved that a 1,6-conjugate addition, and not a DA_{INV} cycloaddition is occurring we believe that overall our results point to a 1,6-conjugate addition mechanism (**See Section 2.2.1.7**).

2.2.1.12 Applications for the 1,6-conjugate addition

The 1,6-conjugate addition of aldehydes to bis-phenylsulfonyl dienes generates a product whose structure contains an electron deficient diene. We anticipated that this diene would (1) act as a substrate for further conjugate additions and (2) due to the fact that it is locked in the *cis*-conformation, undergo an inverse-electron demand Diels-Alder reaction (DA_{INV}) with the correct dienophile (**Fig. 24**).

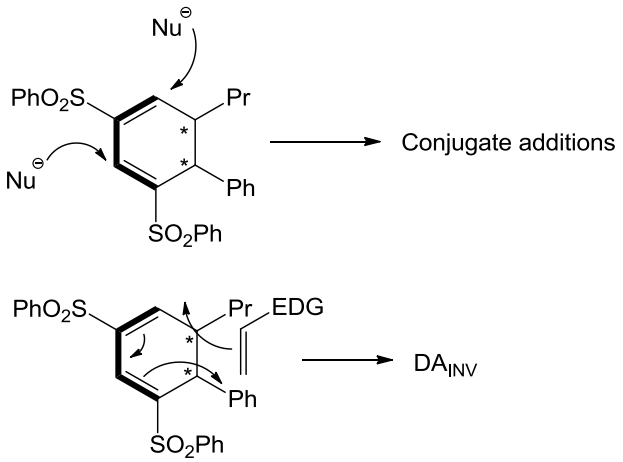


Figure 24: Possible transformations of cyclic diene **43**

2.2.1.12.1 Methylation of cyclic diene 43 with methyllithium

When we were first studying the reaction mechanism for the initial 1,6-conjugate addition we were expecting to observe species resulting from multiple conjugate additions. The product itself contains two electrophilic carbons which are activated by ring strain and the aldehydic pro-nucleophile was used in excess. We attributed the lack of multiple additions to the following, a) the diene is unactivated at the β-carbon, b) the steric hindrance at the δ-carbon, created by the propyl group, inhibits nucleophilic attack and c) the disruption of conjugation and thus charge de-localization, caused by the loss of planarity in the π-π system, reduces electrophilicity (**Figure 25**). Indeed the only reported C-C bond forming addition to cyclohexenyl phenyl sulfones involved using organolithium reagents.[158] With this knowledge we decided to employ a hard nucleophile, methyllithium, which would also be small enough to overcome any steric hindrance.

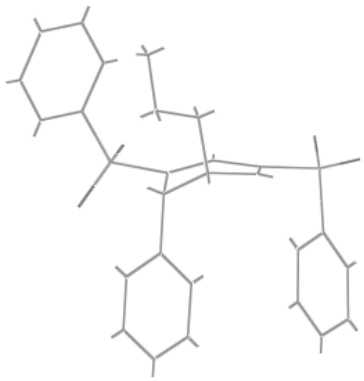
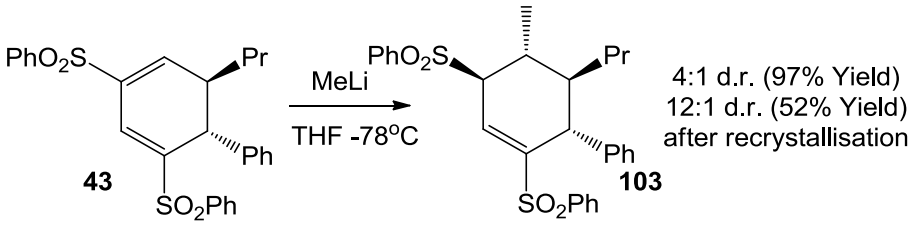


Figure 25: Wire frame model of cyclic diene **43** showing loss of planarity in the π-π system

The addition was performed at -78 ^{o}C in tetrahydrofuran with 1.2 equivalents of methyllithium and after 20 minutes there was complete conversion of the starting material. The methylated product **103** could be isolated by triturating with ice-cold methanol to give a mixture of diastereoisomers (4:1, d.r.). The diastereomeric ratio could be improved to 12:1 after crystallisation from an equi-voluminous mixture of methanol and chloroform and a subsequent recrystallisation from DCM (**Scheme 73**).



Scheme 73: Methylation using MeLi

It was not surprising that the methylation occurred at the 6- position in preference to the 4- position as the initial design of the 1,3-bis-phenylsulfonyl-butadiene acceptors was to promote addition at the 6- position over the 4- by charge delocalisation as previously discussed. A NOE experiment was used to determine the stereochemistry of the newly created stereocenters (**Figure 26**).

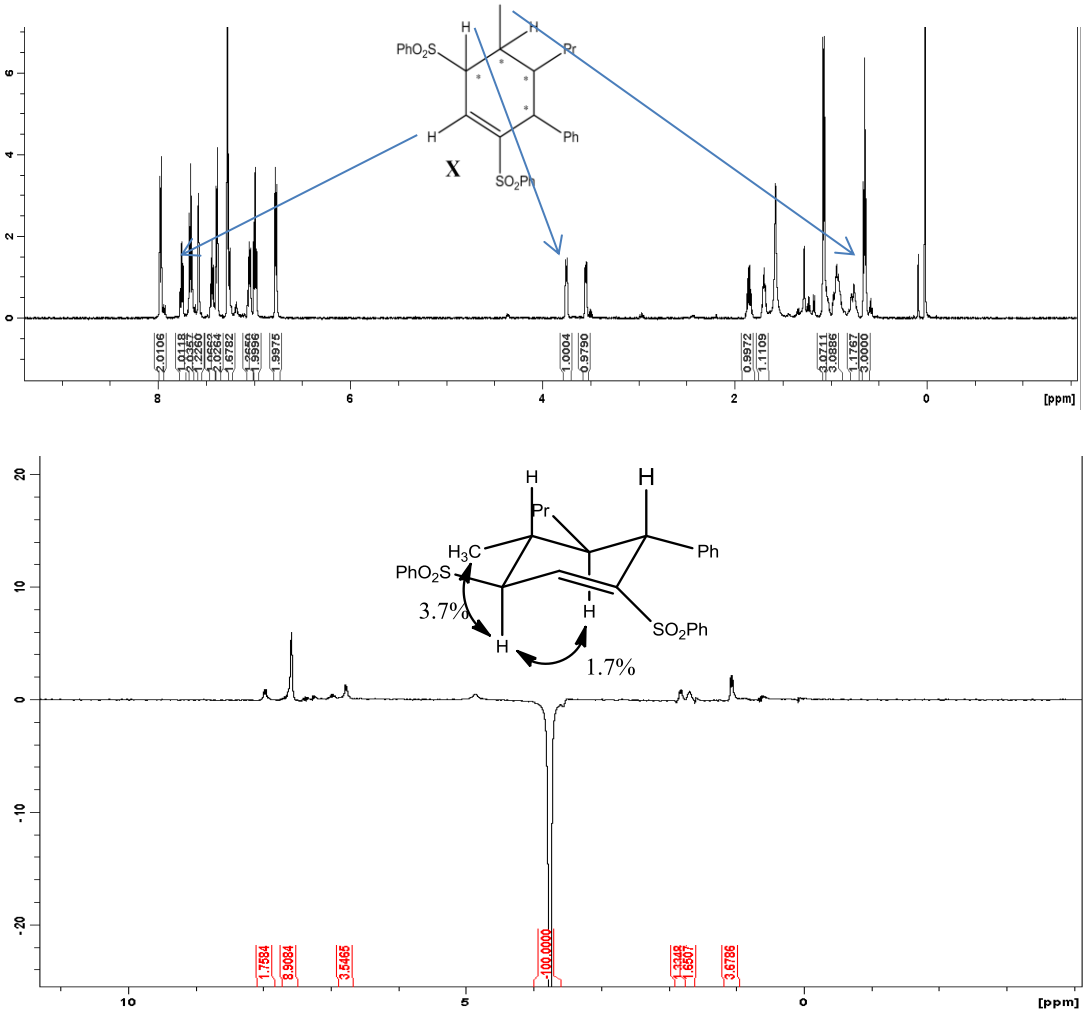


Figure 26: a) ^{1}H NMR of methylated product **103**, b) NOE irradiating at 3.72 ppm

The NOE spectrum in **Figure 26** confirmed what we had suspected, that the organolithium reagent had approached the δ-carbon at the least hindered face *Re* as pictured in **Figure 27**.

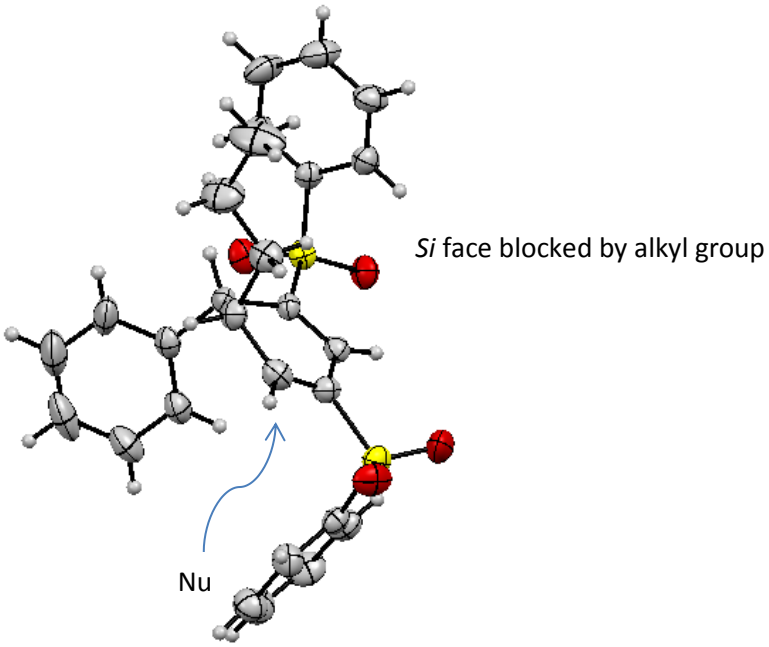
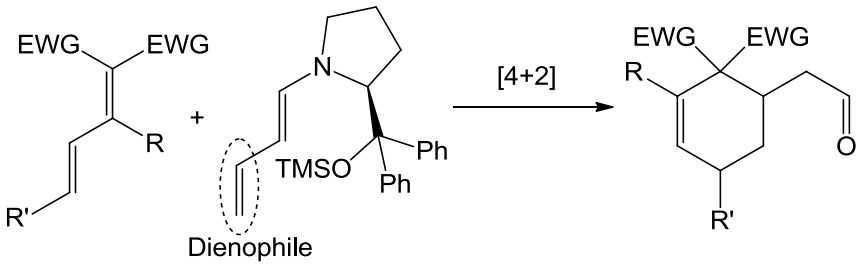


Figure 27: Depiction of nucleophile approach to diene **43**

In just two steps, the organocatalysed 1,6-conjugate addition followed by addition of methyllithium generated four contiguous stereocenters in good yield (51% over 2 steps) and good selectivity (12:1 d.r.). This demonstrates that our 1,6-conjugate addition methodology can deliver useful building blocks which can then be converted to more complex chiral molecules.

2.2.1.12.2 Inverse electron demand Diels-Alder reaction

In 2010 Chen published a paper reporting an inverse electron demand Diels-Alder (DA_{INV}) reaction using an *in situ* generated electron rich dienophile and an electron poor diene (**Scheme 74**).[134b]



Scheme 74: Chen's DA_{INV} using a chiral enamine generated from crotonaldehyde[134b]

We postulated that the product from our 1,6-conjugate addition, compound **43**, would act as a substrate for a DA_{INV}. Compound **43** has several characteristics that favour this proposal (1) like Chen's diene, compound **43** is an electron poor diene, (2) compound **43** is locked in the reactive *cis*

conformation (**Figure 28**), (3) compound **43** is a cyclic diene and hence subject to inherent ring strain. This ring strain would be relieved upon reaction with a suitable dienophile through a tetrahedral transition state. Recently Tang *et al.* used DFT calculations to predict the rate constants of DA reactions and found that cyclic dienes were much more efficient substrates their acyclic equivalents.[159] Extending this to the DA_{INV} and our cyclic diene **43** would suggest that our substrate should be more reactive.

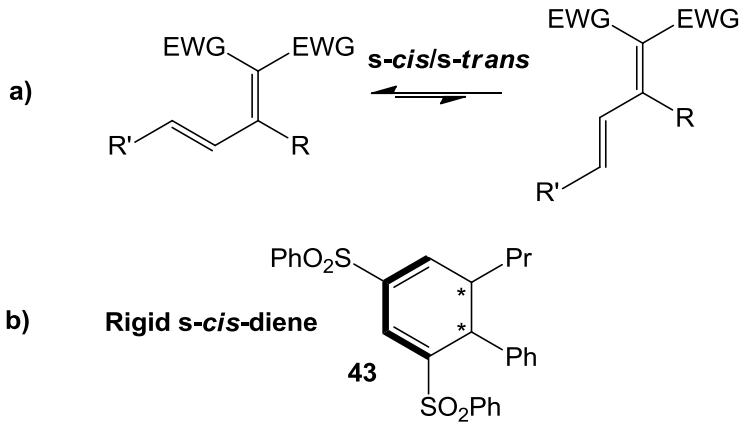
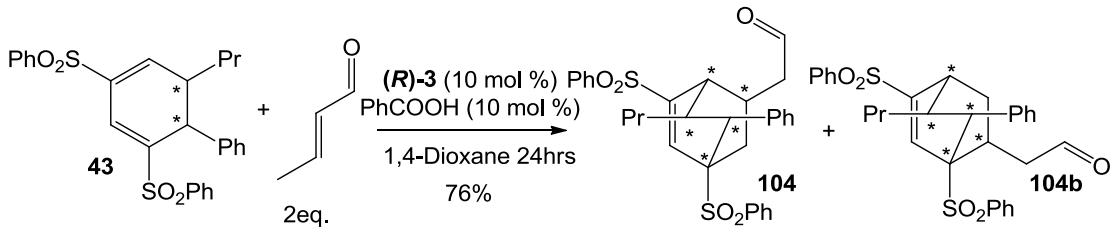


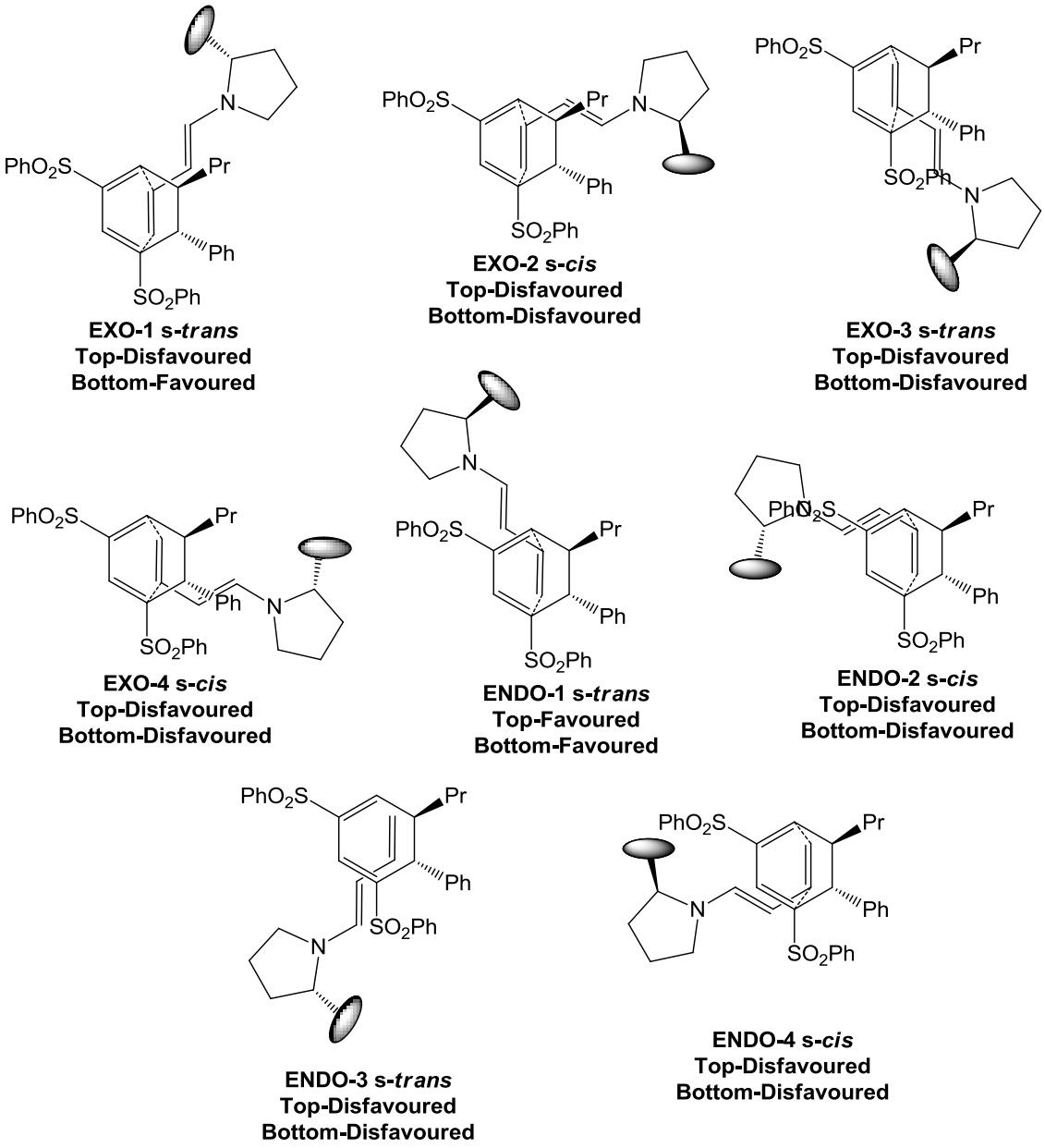
Figure 28: a) Chen's motif,[134b] b) product of 1,6-addition **43**

Using Chen's methodology we performed the DA_{INV} using our cyclic diene **43** as depicted in **Scheme 75**.



Scheme 75: DA_{INV} of cyclic diene **43** with the enamine of crotonaldehyde

We were delighted to find that the tricycle **104** was produced in a 76% yield that appeared to consists of 3 isomers in a ratio of 3.1 : 1 : 1.5 by ^{1}H NMR spectroscopy. The isomers of **104** were inseparable using flash chromatography and were separated and characterised using HPLC-MS. The origin of the 3 isomers was explored by looking at possible transition states (**Scheme 76**). In order to fully understand the origin of the products one would need to undertake a full computational study.



Scheme 76: Possible transition states for DA_{INV}
Note: Top and Bottom refer to the facial approach of the dienophile to the diene

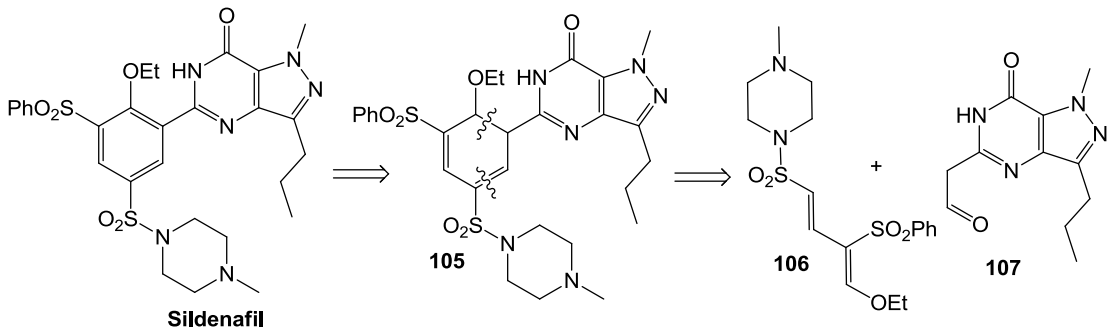
We began by discarding the transition states where the steric bulk of the catalyst faced toward the ring (**EXO-2-Bottom**, **EXO-4-Top**, **ENDO-2-Top**, **ENDO-4-Bottom**), as they would be disfavoured. This left 12 possible isomers that could have been formed. Examining the transition states further we decided that the phenyl group pointing toward the dienophile would cause a steric repulsion. This would make **EXO-3-Bottom** and **EXO-4-Bottom** higher energy transformations (furthermore the steric repulsion of the perpendicular phenyl ring may completely disfavour **EXO-4-Bottom**). Similar interactions with the propyl group would disfavour the **EXO-1-Top** and **EXO-2-Top** transition states. Interactions with the bulky phenyl sulfones would disfavour **EXO-3-Top**, **ENDO-2-Bottom**, **ENDO-3-Top**, **ENDO-3-Bottom** and **ENDO-4-Top** also. This would leave the 2 major isomers (**EXO-1-Bottom** and **ENDO1-Top**) and 1 minor isomer (**ENDO-1-Bottom**, with catalyst bulk toward diene), possibly

corresponding to three isomers detected by HPLC-MS and ^{1}H NMR spectroscopy. We were also able to perform the reaction in one-pot from the bis-phenylsulfonyl diene **39** in a comparable yield and similar isomeric ratios (75% yield).

While we were unable to develop this interesting reaction further at the time we have clearly begun the early stages of a powerful organocatalytic cascade methodology which could be used to generate enantioenriched bicycles in one-pot.

2.2.1.12.3 Synthesis of Sildenafil analogues

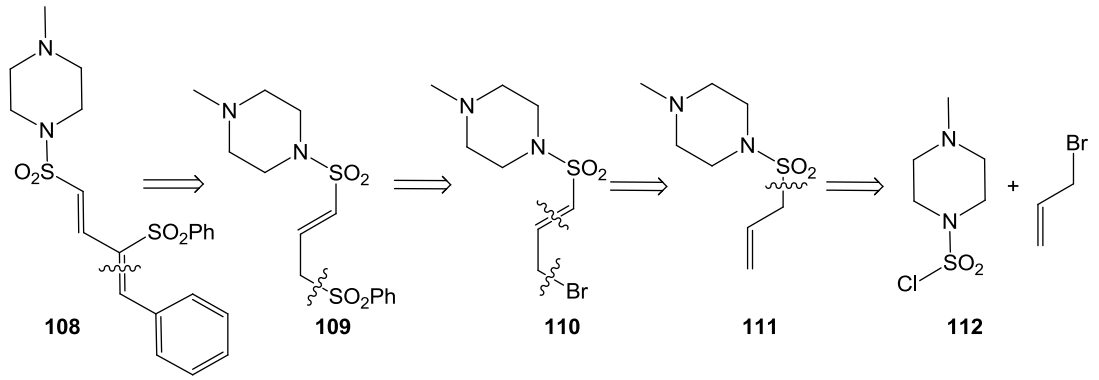
Having demonstrated the synthetic versatility of the 1,6-conjugate addition products, we now wanted to apply the methodology itself to making biologically active compounds. Although a wide variety of bioactive small-molecule compounds contain sulfonyl[160] and sulfonamide moieties[161], we chose Sildenafil (**Scheme 77**) as our target due to the fact that we could exploit our 1,6-methodology in its synthesis and that the chemistry of its synthetic precursors had been well explored.[162] Sildenafil is an inhibitor of PDE5 (cGMP-specific phosphodiesterase type 5), an enzyme which degrades cGMP (cyclic guanosine monophosphate) causing increased levels of cGMP. These increased levels of cGMP result in vasodilation and cause erection of the penis.[163]



Scheme 77: Sildenafil retrosynthesis

We reasoned that the aromatic ring could be formed by the base induced elimination of phenylsulfinic acid and subsequent aromatisation. The elimination of phenylsulfinic acid and subsequent aromatisation of 1,3-bis-phenylsulfonyl cyclic dienes by refluxing in toluene has been previously reported by Masuyama.[121] Although the aromatisation of the ring would result in a loss of chirality, its immediate precursor **105** is chiral, and a library of chiral derivatives of Sildenafil could prove valuable to medicinal chemists.

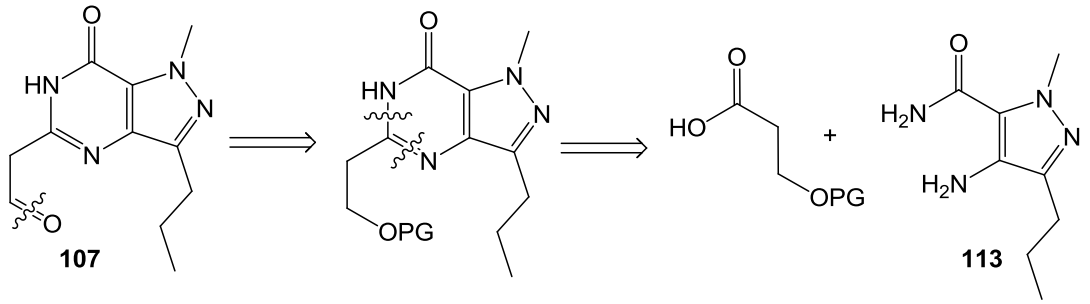
The disconnection of compound **105,** formed by a 1,6-conjugate addition and cyclisation, brought us to the structures of the dienic Michael acceptor **106** and the aldehyde **107**. Although the aldehydic pro-nucleophile **107** looked quite bulky on paper, the relative planarity of the fused pyrimidone and pyrazole ring system gave us confidence that the enamine would be comparable in reactivity to that of phenyl acetaldehyde. Previously we had successfully added phenylacetaldehyde to a bis-sulfone (**See Section 2.2.1.5)**. The diene **106** on the other hand looked less promising. Although the sulfonamide group has comparable electron-withdrawing properties to that of the phenyl sulfone (as indicated by its Hammett constant of σ_p=0.65 for R=$SO_2N(Me)_2$ versus σ_p=0.68 for R=SO_2Ph)[164] we were concerned with the ethoxy group attached to the δ-carbon. We felt this ethoxy group could deactivate the 6- position electronically by donation of electron-density through the C-O bond. We anticipated that replacement of the ethoxy group with something less electron donating may be required. A review of the literature suggested that the ethoxyphenyl group in Sildenafil fitted into a hydrophobic pocket in the active site of PDE5 (Phosphodiesterase 5) created by the amino acid residues Phe 786, Ala 783, Leu 804 and Val 782.[165] This suggested that we could perhaps replace the ethoxy group with another hydrophobic group, one which would not decrease the reactivity of the δ-carbon, and maintain bio-activity. Having previously used a δ-phenyl moiety in our additions to bis-sulfonyl dienes, it seemed rational that replacing the ethoxy group with a phenyl group would be a sensible starting point and we continued our retrosynthesis with this in mind (**Scheme 78**).



Scheme 78: Completed retrosynthesis of diene **108**

As with our previous diene syntheses, the styrene unit could be installed with a Knoevenagel condensation, leaving us with the sulfonamide **109**. We postulated that this in turn could be obtained using the previously described methodology of S_N2 attack by the sodium salt of benzenesulfinic acid on the vinyl-halide **110.** The halide in turn could be derived from the bromination of allyl-sulfonamide **111** and subsequent elimination of HBr. S_N2 attack of the zinc sulfinate anion, generated from sulfonyl chloride **112** and zinc dust, on allyl bromide would allow access to the desired allyl sulfonamide **111**.[166] Sulfonyl chloride **112** has been reported in the literature.[167]

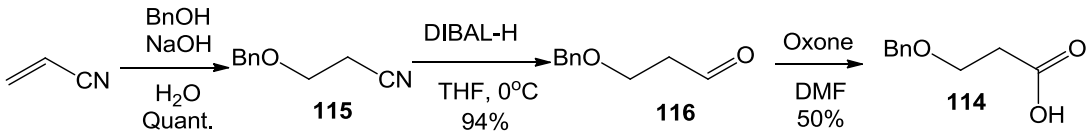
The retrosynthesis of aldehyde **107** is shown in **Scheme 79**. Aldehyde **107** retained much of the functionality found in Sildenafil and so could be synthesised from commercially available advanced intermediates.



Scheme 79: Retrosynthesis of aldehyde **107**

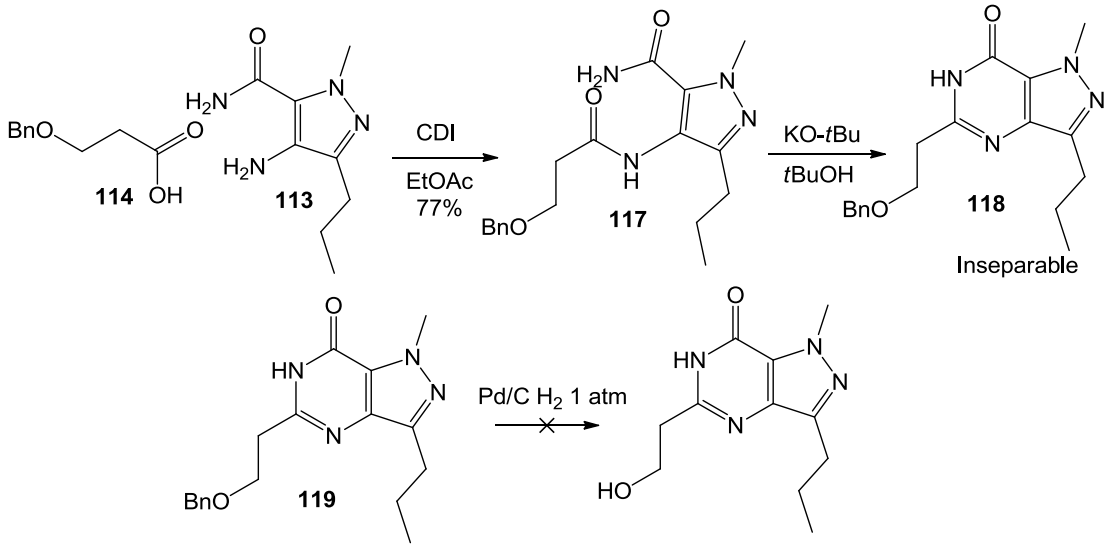
We envisaged that the aldehyde functionality in the pro-nucleophile **107** could be generated oxidatively from the protected alcohol. The protected alcohol could be furnished from the amide coupling of protected 3-hydroxy propanoic acid with the advanced intermediate **113**, which is commercially available, followed by the base promoted cyclisation and subsequent dehydration could deliver the pyrimidone ring system.

Initially a benzyl ether protecting group was chosen and the protected alcohol **114** was easily synthesised by the addition of benzyl alcohol to acrylonitrile,[168] reduction of the nitrile with DIBAL-H at low temperature[169] and subsequent Oxone mediated oxidation to the desired carboxylic acid **114** (**Scheme 80**).



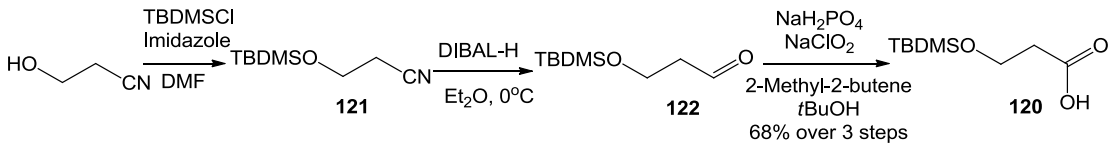
Scheme 80: Synthesis of benzyl ether protected 3-hydroxypropanoic acid.

Carboxylic acid **114** was successfully coupled to the aminopyrazole **113** using the same conditions as described in the synthesis of Sildenafil.[162] Attempts to cyclize the resultant amide **117** generated crude material that appeared to contain the desired product (by ^{1}H NMR spectroscopy) **118** but could not be purified by chromatography. When the crude material was subjected to hydrogenation conditions the benzyl ether could not be removed (**Scheme 81**). As a result an alternative strategy was developed replacing the benzyl ether with a silyl protecting group (**Scheme 82**).



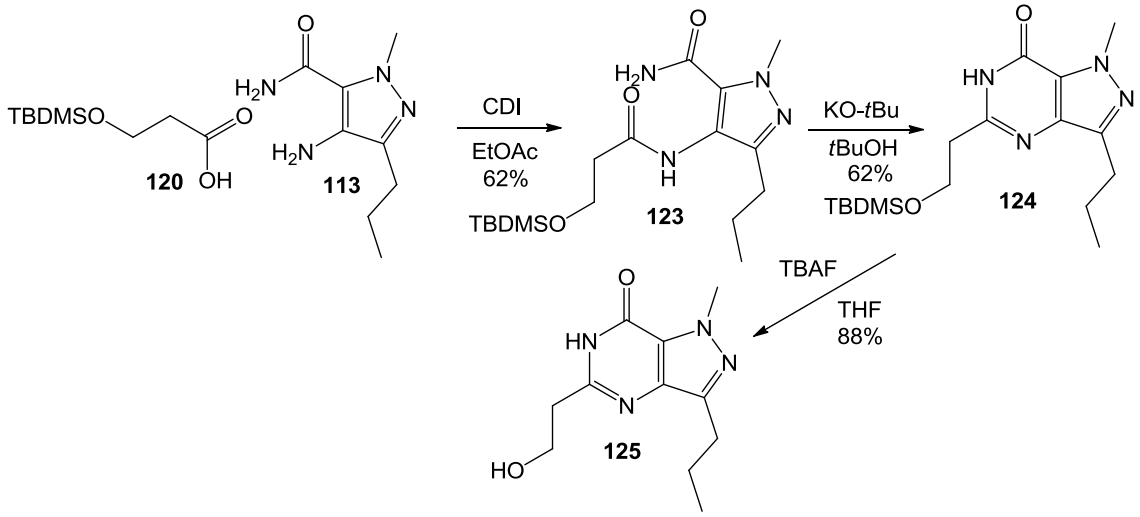
Scheme 81: Attempted synthesis using a benzyl ether protecting group

The hydroxy group on 3-hydroxy propionitrile was protected with *tert*-butyl dimethylsilyl ether using stoichiometric imidazole and TBDMSCl.[170] Interestingly the yield was low unless freshly recrystallised imidazole was used, which is possibly due to the commercial sample having absorbed water over time. This water can react with the *in situ* generated *N*-dimethyl-*tert*-butylsilylimidazole resulting in a loss of yield.[171] The crude nitrile was reduced, again using DIBAL-H, to give the aldehyde which was oxidized using classic Pinnick conditions to give carboxylic acid **120** in good yield (**Scheme 82**).[172]



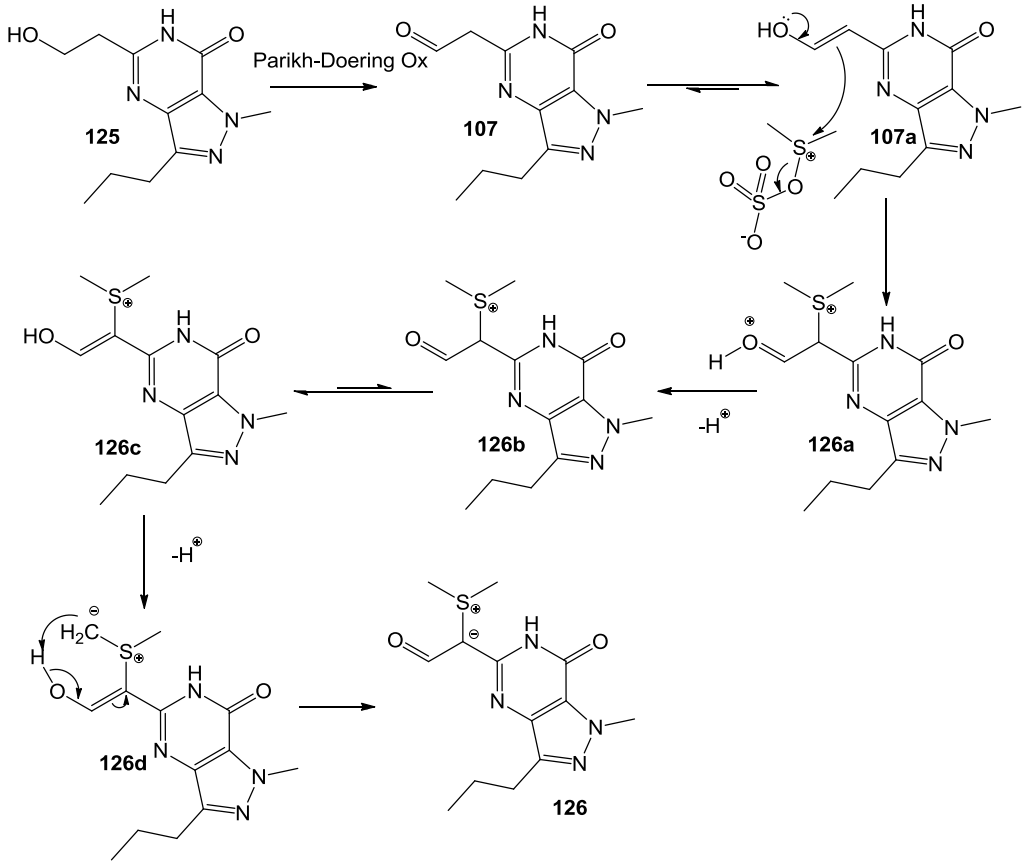
Scheme 82: Synthesis of silyl ether protected 3-hydroxypropanoic acid

The coupling of aminopyrazole **113** and carboxylic acid **120** using CDI again delivered the amide **123** in good yield (**Scheme 83**). This time the cyclisation went smoothly and the newly formed bicycle **124** could be isolated relatively simply using flash chromatography. De-protection of the silyl ether using TBAF generated the alcohol **125** in excellent yield (**Scheme 83**).



Scheme 83: Completed synthesis of alcohol **125**

With gram quantities of alcohol **125** to hand we embarked on its oxidation to the desired aldehyde **107**. Initially we employed the Parikh-Doering methodology, using 5 equivalents of triethylamine and 4 equivalents of pyridine sulfur-trioxide complex. After 2 hours the reaction was quenched and purified with flash chromatography to yield a white solid. Analysis of the NMR data generated by this white solid indicated that it was not the desired aldehyde **107**. Instead the sulfur ylide **126** was proposed as the product and a possible reaction mechanism is shown in **Scheme 84**. Although there is no precedence for such a reaction in the literature we postulate that the homoallylic aldehyde **107** is formed *via* the normal oxidation protocol. The aldehyde **107** immediately tautomerises to the enol form **107b,** which it is stabilized by conjugation. The enol then attacks the intermediate formed from DMSO and sulfur trioxide to give compound **126a**. Compound **126a** is subsequently deprotonated by triethyl amine to give the aldehyde **126b** which again favours the enol tautomer **126c**. Deprotonation of one of the methyl groups followed by proton transfer leads to the final product, a sulfur ylide **126**.



Scheme 84: Proposed mechanism for the formation of sulfur ylide **121**

The product ylide was isolated in a 90% yield and its structure confirmed using both multidimensional NMR and high resolution mass spectrometry. The ^{1}H NMR has some notable features that indicate the structure of ylide **126** (**Figure 29**). The rather sharp peak at 13 ppm is due to the proton bonded to the unsaturated nitrogen of the pyrimidone ring. With regard to aprotic solvents, protons in similar environments usually have a much lower chemical shift and are broad due to the fast T_1 relaxation of the ^{14}N nucleus, proton exchange and a degree of coupling (I = 1 for ^{14}N). In this case proton must be engaged in hydrogen bonding with the amido carbonyl, possibly in an intermolecular dimeric fashion, resulting in both a decrease in the rate of exchange of the amido proton (peak sharpening) and a further deshielding of the signal by removal of electron density. The aldehydic proton has a shift of 8.76 ppm, this is again unusual for protons bound directly to carbonyl carbons which more often have shifts of 9.5-10.0 ppm. This lower shift could be rationalised by the increased electron density on the carbonyl carbon resulting from electron donation from the carbanion of the ylide, causing an increased level of shielding on the aldehydic proton. A literature example of an α-dimethylsulfenyl aldehyde prepared by Ito *et al.* shows a similarly shielded chemical shift for the aldehydic proton (singlet at 8.35 ppm).[173] The methyl protons are equivalent and appear as a singlet at 3.28 ppm. Such a high chemical shift for an unsaturated alkyl proton is direct evidence for the presence of the ylide. The sulfenyl cation withdraws electron density through the σ-bond with the sp^3 carbon causing the deshielding of the adjacent protons.

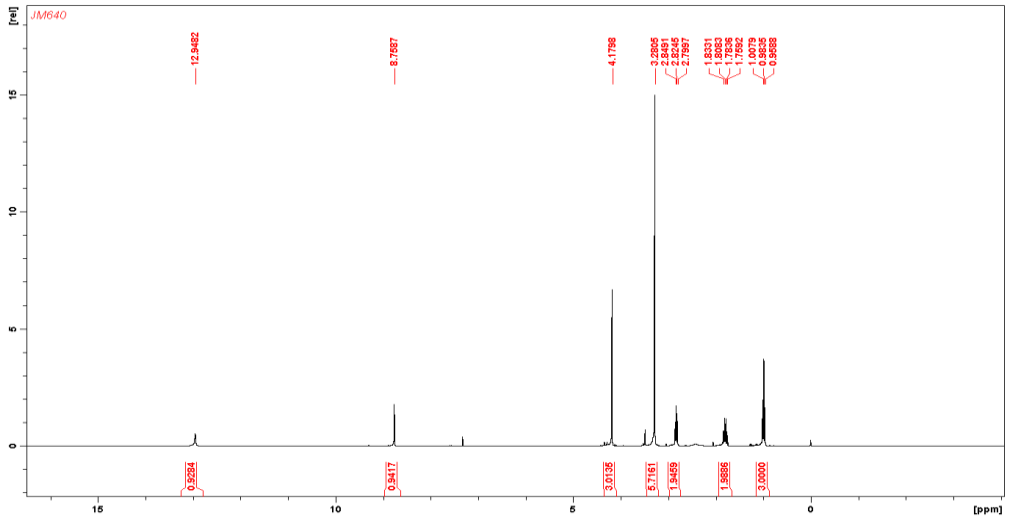


Figure 29: ^{1}H NMR of the sulfur ylide **126**

Furthermore, the ^{13}C NMR spectrum also contains interesting shifts that led us to propose the ylide **126** as the structure (**Figure 30**). The ylide methyl carbon signal overlaps with the methylene carbon on the alkyl chain of the pyrazole and can only be observed through DEPT experiments. The shift is 27.8 ppm which again corresponds to a similar compound prepared by Ito *et al* (30.5 ppm).[173] The aldehydic carbonyl carbon again is lower than usual with a shift of 178.1 ppm compared to the more usual shifts of around 200 ppm. The most interesting peak is the carbanion which appears as a negative peak in the DEPT-Q, **Figure 30**, indicating it is not bonding with any protons and has a very high shift for a sp^3 hybridized carbon, 78.1 ppm. This is again due to the large electron density associated with a carbanion causing deshielding of the nucleus.

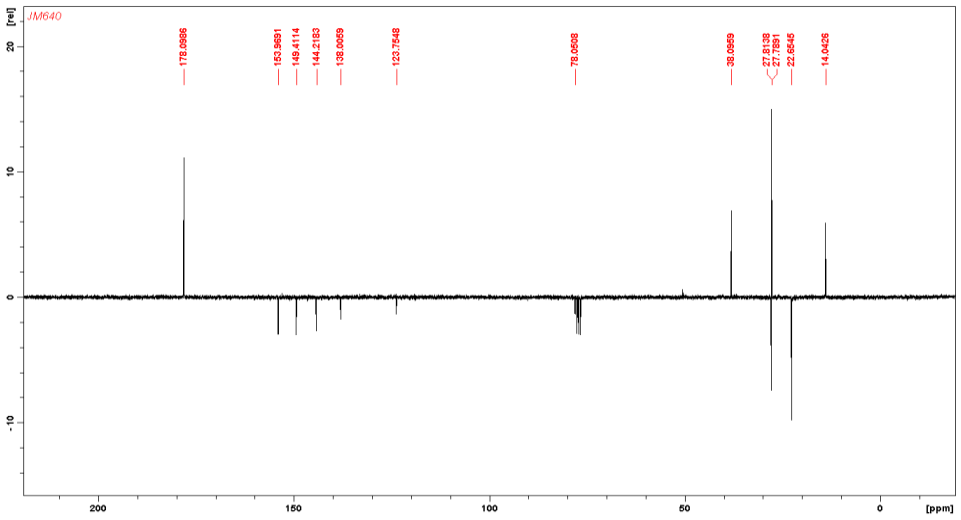


Figure 30: ^{13}CPD DEPT-Q NMR of sulfur ylide **126**

The failure of the Parikh-Doering oxidation prompted us to try alternative methods. A selection of oxidising reagents and conditions were screened in an attempt to generate aldehyde **107**. The results of these efforts are summarized in **Table 19**.

Entry	Reagent, Solvent	Time (h)	Result[a]
1	NMO/TPAP (2.5 eq. / 5 mol %), DCM	4	R.S.M.
2	PDC (2 eq.), DCM	48	R.S.M.
3	PCC (4 eq.), DCM	48	R.S.M.
4	IBX (2 eq.), DMSO	24	R.S.M.
5	IBX (3 eq.), DMSO	72	R.S.M.
6	DMP (1.1 eq.), Wet THF	3	R.S.M.
7	NMO/TPAP (2.5 eq./15 mol %), MeCN	72	R.S.M.
8	$Pyr.SO_3/NEt_3$ (1.1 eq./2.1 eq.), DCM/DMSO	3	R.S.M.

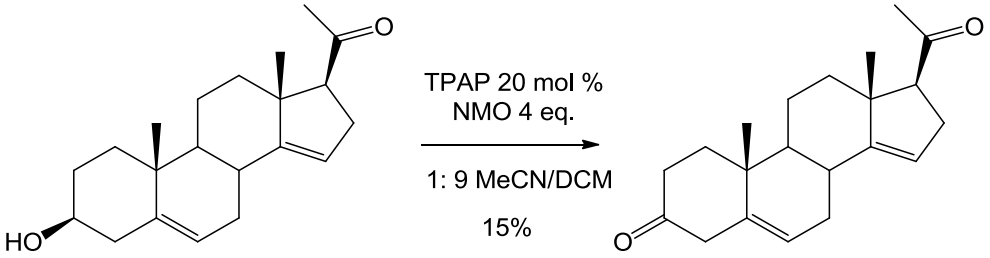
Reactions were performed on a 0.5 mmol scale, [a] determined by ^1H NMR spectroscopy

Table 19: Attempted oxidation of alcohol **125**

The oxidation of alcohol **125** was exhaustively explored. Initially it was thought that the insolubility of the alcohol in chlorinated solvents may have been responsible for the lack of reactivity (**Entries 1-3**). As a result a selection of oxidative conditions that are compatible with non-chlorinated solvents were explored. The relatively unpopular IBX oxidation was performed in DMSO (**Entry 4-5**). The oxidation was presumably unsuccessful because IBX is incredibly insoluble, even in DMSO, and is useful only when the compound can be rapidly oxidised. The more common, but expensive, Dess-Martin periodinane (DMP) was also unsuccessful. It should be noted that the DMP oxidation is usually performed in DCM however its use in wet tetrahydrofuran has been reported[174] and that the rate accelerating effect of water in DMP oxidations is also well known.[175] We returned to the Ley oxidation conditions, this time using acetonitrile as a solvent (**Entry 7**). Again only returned starting material was observed. The use of acetonitrile in the Ley oxidation is known to give improved catalyst turnover when compared with DCM.[176] Sharpless suggests that the use of acetonitrile prevents competing complexation to the active ruthenium species that can retard the reaction and can either be used with DCM or as the lone solvent.[177] In a final effort the Parikh-Doering oxidation was again repeated using reduced quantities of reagents in an attempt to prevent any side reactions. Unfortunately only returned starting material was recovered. This was of no great surprise as the Parikh-Doering oxidation is known to require several equivalents of both reagents.[178]

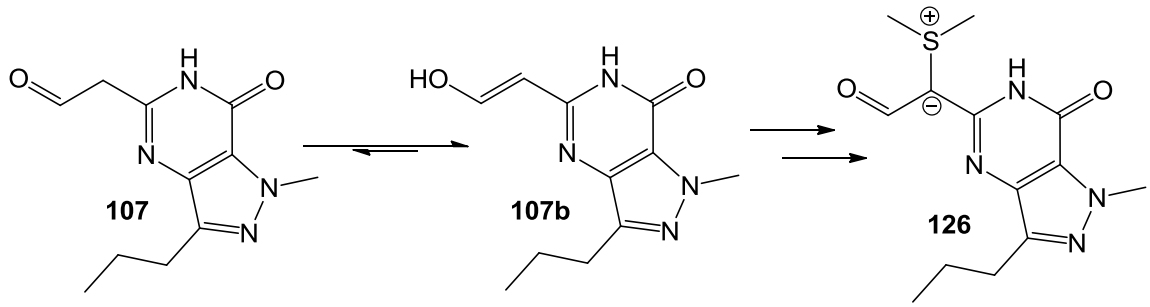
In an effort to understand why these oxidations did not succeed a literature review was performed. The oxidation of homoallylic alcohols is known to be problematic. For example, the oxidation of heptadiene-4-ols was attempted by Mistryukov and co-workers with modest results despite a screen of a large variety of both known and novel reagents and conditions.[179] Some of the problems associated with homoallylic alcohol oxidation may arise from the tautomerism of the product aldehyde to its enol form and subsequent reactions leading to complex mixtures. The Ley oxidation has also been reported to be slow and inefficient when homoallylic alcohols are the substrates.

Acosta *et al.* experienced dramatically reduced yields upon encountering a substrate containing a homoallylic alcohol during the oxidation of various cholesterols using the Ley conditions (**Scheme 85**).[180]



Scheme 85: Attempted oxidation of homoallylic alcohol by Acosta *et al.* [180]

In summary the oxidation failed for two main reasons, firstly the compound was insoluble in the reaction medium and the transformation could not be effected. Secondly, if the aldehyde **107** can be formed it immediately tautomerises to the enol form **107b**, due to increased stabilisation through π-π conjugation, and this enol form renders the α-carbon nucleophilic causing side reactions (**Scheme 86**).



Scheme 86: Keto-enol tautomerism of aldehyde **107**

This troublesome oxidation step could be avoided if an acetal were used instead of the protected alcohol, however the acidic hydrolysis of this acetal may cause opening of the pyrimidone ring. Even if the aldehyde was exposed from the acetal, the problem of enol tautomerism would remain**.** It may be possible to affect the 1,6-conjugate addition of the enol to our diene using a lithium enolate, but the point of the synthesis was to utilise our organocatalytic methodology. For this reason the synthesis of Sildenafil analogues was halted.

2.3 Conclusion

In conclusion we have developed an unprecedented enamine 1,6-conjugate addition by exploiting the properties of charge delocalisation in 1,3-bis-phenylsulfonyl butadienes. This unique reactivity was achieved through a rational design process of the substrate leading to the formation of highly valuable dienes containing two versatile vinyl sulfone moieties. The use of the highly successful Jørgensen-Hayashi diarylprolinol catalyst provided exceptional levels of stereoselectivity (typically 99% *ee* and 99:1 d.r.) and allowed the use of a variety of aldehydes in the methodology. This methodology represents the first reported organocatalytic enamine promoted 1,6-conjugate conjugate addition and remains the only example in the literature to date.

We have proposed a mechanism that follows a 1,6-conjugate addition of the chiral enamine to the diene followed by a 6-exo-trig cyclisation and dehydration to give a bis-phenylsulfonyl cyclic diene. Using literature model systems we have provided compelling evidence that suggest the reaction mechanism proceeds through a conjugate addition rather than *via* a Diels-Alder inverse electron demand reaction.

New methodology was developed to allow the synthesis of ε-branched alkyl bis-phenylsulfonyl dienes, which exploits the amphoteric nature of aluminium oxide in low temperature Knoevenagel condensations. Unbranched aldehydes were found to isomerise completely *via* a 1,5-hydrogen shift. 1,6-Conjugate addition to the alkyl dienes using the developed methodology was unsuccessful due to both steric and electronic factors.

Using the conformationally restricted catalyst **FAPY**, we and our collaborators successfully observed the 1,6-conjugate addition of cyclohexanone to dienic sulfones. The resulting product was found to both isomerise *via* a 1,5-hydrogen shift and aromatise under the reaction conditions. The use of achiral pyrrolidine gave better results however in a racemic fashion. Future work would include using less active electron withdrawing groups, such as phosphonate esters, to prevent the products from undergoing side-reactions while still retaining the reactivity of the 6- position. The enamine promoted organocatalytic 1,6-addition of ketones is still unreported in the literature.

In order to develop a conformationally restricted diene to provide experimental evidence of a 1,6-conjugate addition over a Diels-Alder inverse electron demand reaction, a Peterson olefination of a series of α-substituted cyclohexenones was attempted. In all cases the 1,4-conjugate adduct was observed rather than the expected direct adduct. An interesting Brook-type rearrangement followed by sulfoxide elimination was also observed and a mechanism was proposed. In an alternative strategy the restricted diene was synthesised through a copper mediated Grignard addition to an allene. During the final oxidation/Knoevenagel condensation the product was found to isomerise in the reaction conditions *via* a 1,5-hydrogen shift.

To further develop our organocatalytic methodology we showcased the usefulness of our product cyclic diene by performing a methylation reaction using organolithium reagents. The result was a highly selective reaction producing 4 contiguous stereocenters (12:1 d.r.) which was confirmed by NOE experiments. A cascade reaction was also developed producing a fused bi-cycle *via* a Diels-Alder inverse electron demand reaction. While the product could not be isolated by chromatography the selectivity was measured by NMR and the product confirmed by high resolution mass spectrometry. The represents the first example of an organocatalytic cascade reaction involving either a 1,6-conjugate addition or DA_{INV} reaction.

The development of a synthetic route to chiral Sildenafil analogues *via* organocatalytic 1,6-conjugate addition was attempted. The synthesis failed on the final oxidation step under multiple conditions. The classic Parikh-Doering oxidation conditions gave a high yielding side-product, identified by NMR, as sulfur ylide in an unprecedented reaction. A mechanism for this transformation was proposed. Future work includes re-designing the synthesis to involve a saturated dihydropyrimidone ring which would prevent the homo-allylic aldehyde from tautomerizing to the enol form.

2.4 Experimental

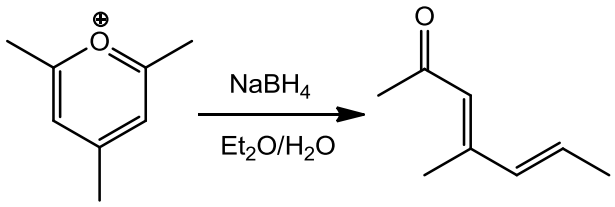
2.4.1 General Experimental

Solvents were purified by distillation from commerically available sources. Anhydrous THF, diethyl ether and DME were distilled under an atmosphere of argon over the ketyl radical. Anhydrous toluene and benzene was distilled under a nitrogen atmosphere over sodium wire. Anhydrous DCM and DMSO was distilled under nitrogen over CaH_2. Anhydrous methanol was distilled under nitrogen over activated magnesium turnings. Chemicals were purchased from Sigma-Aldrich, Acros-Organics, TCI and Alfa-Aesar. Yields refer to isolated compounds unless otherwise indicated. Thin Layer Chromatography was performed on Merck 0.25 mm silica gel plates (60F-254) using either UV lamp as a visualizing agent or appropriate stain. Evaporation under reduced pressure was always effected with the bath temperature kept below 40 °C. Flash column chromatography was performed according to the method of Still *et al.* with Merck Silica Gel 60, using adjusted mixtures of ethyl acetate in petroleum ether unless otherwise stated.[181] Dry-Column Vacuum Chromatography (DCVC) was performed according to the method of Pedersen *et al.* using a 4 cm fritted Hirsch funnel with Merck Silica Gel 15-40 µm and vacuum applied by a diaphragm pump under stated conditions.[182]

All ^{1}H, ^{13}C, DEPT, COSY, HSQC and HMBC nuclear magnetic resonance spectra were recorded in $CDCl_3$, on either a Bruker Avance spectrometer operating at 300 MHz for the ^{1}H nucleus, 75 MHz for the ^{13}C nucleus, 212 MHz for the ^{19}F nucleus and 128 MHz for the ^{31}P nucleus or a Bruker Avance III spectrometer operating at 500 MHz for the ^{1}H nucleus and 125 MHz for the ^{13}C nucleus. All shifts are reported in ppm as downfield from TMS as standard. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quintet, hextet, m (multiplet), br s (broad singlet), dd (doublet of doublets), td (triplet of doublets). Proton and carbon signals were assigned with the aid of 2D NMR experiments (COSY, HSQC or HCCOSW) and DEPT experiments. HCCOSW is a HSQC type of experiment. Coupling constants *J* are reported in Hz. Electrospray (ESI) mass spectra were collected on an Agilent Technologies 6410 Time of Flight LC/MS. Compounds for LC/MS analysis were dissolved in ethanol with the aid of ultrasound and heating. The interpretation of mass spectra was made with the help of the program “Agilent Masshunter Workstation Software”. Enantiomeric excesses were determined by chiral HPLC measurement using a Perkin Elmer chromatography system connected to a Chiral Pak IA or IB 0.46 x 25 cm column with a cartridge loaded Chiral Pak 0.4 x 1 cm guard column as the stationary phase and mobile phase prepared as indicated, de-gassed by ultrasound with a flow of 1 mL/min unless stated otherwise. Samples were dissolved in $CHCl_3$ with aid of ultrasound and heat and injected in 10µl amounts with retention time (R_T) measured in minutes. Optical rotations were obtained using a AA-100 polarimeter. $[\alpha]^{25}_{D}$ values are given in 10^{-1}

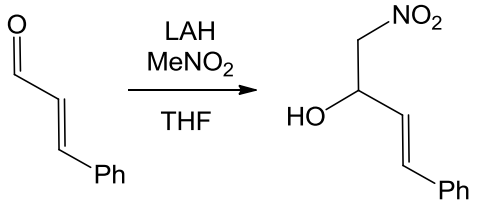
cm^2g^{-1}. Infra-red spectra were obtained in the region 4000–400 cm^{-1} using a Perkin Elmer 2000 FTIR spectrometer.

2.4.2 Experimental



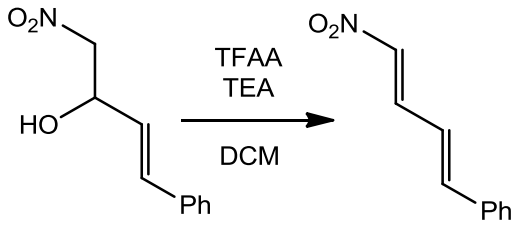
31 **32**

(1*E*/*Z*,3*E*)-4-methylhepta-3,5-dien-2-one 32: To a vigorously stirred mixture of distilled water (2 mL) and diethyl ether (1 mL), at 0 °C, was added commercial 2,4,6-trimethyl pyrylium tetrafluoroborate (210 mg, 1 mmol, 1 eq.). To this was added, cautiously, sodium borohydride (38 mg, 1 mmol, 1 eq.). The resulting solution was stirred at 0 °C for 1 hour at which point the aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined ethereal solutions were dried over Na_2SO_4. Concentration *in vacuo* yielded a colourless oil which was purified by vacuum distillation (57-60 °C @ 10 mbar), 92 mg (74%). Single isomer by ^{1}H NMR spectroscopy. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (d, 1 H, *J* = 15.7 Hz, C*H*CH), 6.12-6.30 (m, 1 H, C*H*CH_3), 5.95 (s, 1 H, C*H*), 2.16 (s, 3 H, CH_3CO), 1.95 (s, 3 H, CCH_3), 1.86 (d, 3 H, *J* = 6.8 Hz, CHCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.5 (*C*O), 149.2 (*C*), 135.1 (*C*HCH_3), 129.6 (*C*HCH), 123.4 (*C*H), 31.8 (CO*C*H_3), 20.9 (C*C*H_3), 18.8 (CH*C*H_3). **ESI-MS** $C_8H_{12}O$ Calc. ($M+H^+$) = 125.0961 found ($M+H^+$) 125.0958 (-2.38 ppm).



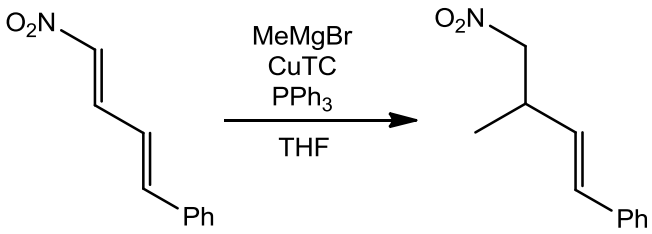
35 **36a**

(*E*)-1-Nitro-4-phenylbut-3-en-2-ol 36a:[109c] Lithium aluminium hydride (15 mg, 0.4 mmol, 0.1 eq.) was slurried in anhydrous THF (20 mL) at 0 °C under a positive pressure of nitrogen. To this was added nitromethane (1.07 mL, 20 mmol, 5 eq.). The reaction was stirred at 0 °C for a further 30 minutes before *trans*-cinnamaldehyde (0.5 mL, 4 mmol, 1 eq.) was added in a single portion. The mixture was stirred for 12 hours at 0 °C at which point 1 M HCl (10 mL) was added followed by distilled water (10 mL). The reaction was extracted with methylene chloride (3 x 30 mL) and the organic extracts combined and dried over Na_2SO_4. Concentration *in vacuo* yielded an orange oil which was used without further purification, 788 mg (102%).



36a **36**

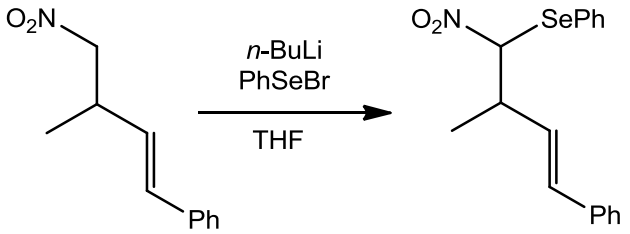
(1*E*,3*E*)-4-phenyl-1-nitrobuta-1,3-diene 36:[109c] The crude nitroaldol product **36a** (4 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (20 mL). The solution was brought to -40 °C and trifluoroacetic anhydride (0.59 mL, 4.2 mmol, 1.05 eq.) was added followed by triethylamine (1.17 mL, 8.4 mmol, 2.1 eq.). The reaction was allowed to come to room temperature over which time the solution's colour turned to a brilliant yellow. The reaction was then diluted with methylene chloride (20 mL) and washed with saturated NH_4Cl (50 mL), water (50 mL) and saturated brine solution (50 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to give a bright yellow oil. The oil was dissolved in minimal hot methanol and stored at -20 °C for 2 days. The resultant bright yellow crystals were separated by filtration, 441 mg (63% over 2 steps from *trans*-cinnamaldehyde). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.67-7.83 (m, 1 H, β*H*), 7.47-7.59 (m, 2 H, Ar*H*), 7.34-7.47 (m, 3 H, Ar*H*), 7.23 (d, 1 H, *J* = 15.5 Hz, δ*H*), 7.11 (d, 1 H, *J* = 15.5 Hz, α*H*), 6.84 (dd, 1 H, *J* = 11.5 Hz, *J* = 15.5 Hz, γ*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 146.1 (β-*C*H), 139.3 (δ-*C*H), 138.6 (α-*C*H), 135.2 (*C*), 130.4 (Ar*C*), 129.1 (Ar*C*), 127.8 (Ar*C*), 120.7 (γ-*C*H). **M.P.** 38-40 °C (Lit. 39-40 °C).[183] Matches known data.[183]



36 **37**

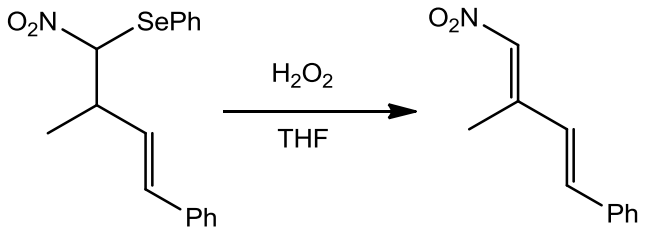
(3*E*)-2-Methyl-4-phenyl-1-nitrobut-3-ene 37:[109c] An oven-dried Schlenk tube purged with nitrogen was charged with copper(I)-thiophene-2-carboxylate (22 mg, 0.115 mmol, 5 mol%) and triphenyl phosphine (32 mg, 0.121 mmol, 5.25 mol%). The mixture was suspended in anhydrous THF (14 mL) and stirred at room temperature for 30 minutes. The reaction was then brought to -10 °C in temperature and methylmagnesium bromide (1.82 mL, 1.4 M in hexanes, 2.53 mmol, 1.1 eq.) was added dropwise. The reaction was stirred for a further 30 minutes at -10 °C at which point the nitrodiene **36** (400 mg, 2.3 mmol, 1 eq.), dissolved in anhydrous THF (3 mL) was added over the course of an hour. The reaction was stirred for 5 hours at -10 °C and subsequently quenched with 1 M tartaric acid (2 mL). The mixture was stirred at room temperature for 30 minutes and then

extracted with diethyl ether (3 x 30 mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a pale-yellow oil which was essentially pure, 440 mg (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25-7.45 (m, 5 H, Ar*H*), 6.54 (d, 1 H, *J* = 15.9 Hz, CHC*H*Ph), 6.09 (dd, 1 H, *J* = 7.9 Hz, *J* = 15.9 Hz, C*H*CHPh), 4.32-4.48 (m, 2 H, CH_2), 3.24 (septet, 1 H, C*H*CH_3), 1.25 (d, 3 H, *J* = 6.8 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.7(Ar*C*), 131.8 (Ar*C*H), 129.2 (Ar*C*H), 128.7 (*C*HPh), 127.9 (Ar*C*H), 126.5 (*C*HCH), 80.9 (*C*H_2), 36.5 (*C*H), 17.5 (CH_3). Matches known data.[109c]



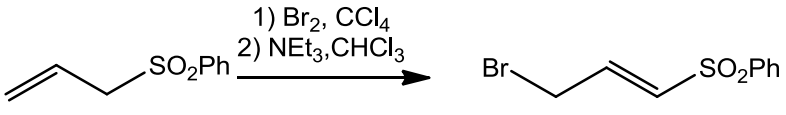
37 **38**

(3*E*)-2-Methyl-4-phenyl-1-phenylselenyl-1-nitrobut-3-ene 38:[116] An oven-dried Schlenk tube purged with nitrogen was charged with the nitroalkane (126 mg, 0.66 mmol, 1 eq.) and anhydrous THF (2 mL). The mixture was stirred until homogenous and brought to 0 ^oC. To this was added *n*-butyllithium (0.27 mL, 2.5 M in hexanes, 0.73 mmol, 1.1 eq.) and the reaction was stirred at 0 ^oC for 15 minutes. Phenylselenium bromide (311 mg, 1.32 mmol, 2 eq.) dissolved in anhydrous THF (1.5 mL) was added in a rapid stream. The colour of the solution changed from orange to brown. The reaction was stirred for 40 minutes at 0 ^oC and quenched with distilled water (10 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) and passed through a pad of Celite. The solvent was removed *in vacuo* and the residue was purified with flash chromatography eluting with 95% *n*-hexane in ethyl acetate. R_F (95% *n*-hexane in ethyl acetate) 0.74. Yellow solid, 141 mg (62%). (1 : 0.68 Mixture of diastereomers A and B) **^{1}H NMR** (300 MHz, $CDCl_3$) δ A; 7.36-7.55 (m, 2 H, Ar*H*), 6.97-7.30 (m, 8 H, Ar*H*), 6.32 (d, 1 H, *J* = 15.8 Hz, C*H*Ph), 5.91 (dd, 1 H, *J* = 8.7 Hz, *J* = 15.8 Hz, C*H*CHPh), 5.31 (d, 1 H, *J* = 8.3 Hz, C*H*SePh), 2.88 (apparent hextet, 1 H, *J* = 6.9 Hz, C*H*CH_3), 1.16 (d, 3 H, *J* = 6.8 Hz, CH_3). B; 7.36-7.55 (m, 2 H, Ar*H*), 6.97-7.30 (m, 8 H, Ar*H*), 6.32 (d, 1 H, *J* = 15.8 Hz, C*H*Ph), 5.91 (dd, 1 H, *J* = 8.7 Hz, *J* = 15.8 Hz, C*H*CHPh), 5.34 (d, 1 H, *J* = 8.3 Hz, C*H*SePh), 3.01 (apparent hextet, 1 H, *J* = 6.9 Hz, C*H*CH_3), 1.07 (d, 3 H, *J* = 6.8 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ A; 136.2 (Ar*C*), 135.5 (Ar*C*H), 133.0 (Ph*C*H), 129.6 (Ar*C*H), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.5 (*C*HCHPh), 126.6 (Se*C*Ar), 126.4 (overlapping Ar*C*H + Ar*C*H), 91.3 (*C*HNO_2), 40.9 (*C*HCH_3), 17.9 (*C*H_3). B; 136.4 (Ar*C*), 135.7 (Ar*C*H), 132.8 (Ph*C*H), 129.5 (Ar*C*H), 128.6 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (*C*HCHPh), 126.6 (Se*C*Ar), 126.4 (overlapping Ar*C*H + Ar*C*H), 90.8 (*C*HNO_2), 40.9 (*C*HCH_3), 18.1 (*C*H_3). **ESI-MS** $C_{17}H_{17}NO_2Se$ Calc. ($M+Na^+$) = 370.0317 found ($M+Na^+$) 370.0319 (-0.10 ppm).



38 **34**

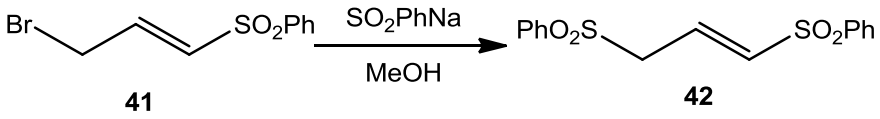
(1*E/Z*,3*E*)-2-Methyl-4-phenyl-1-nitrobuta-1,3-diene 34:[116] The nitroselenide **38** (141 mg, 0.41 mmol, 1 eq.) was dissolved in THF (2 mL). To this was added hydrogen peroxide solution (0.4 mL, 30% w/v solution, 3.53 mmol, 8.6 eq.) and the mixture was vigorously stirred for 1 hour. The reaction was then diluted with distilled water (10 mL) and extracted with methylene chloride (3 x 30 mL). The organic layers were passed through a pad of Celite and concentrated *in vacuo* to a brown residue. The residue was purified using PTLC eluting with gradient systems of 100% petroleum ether -> 8% ethyl acetate in petroleum ether, increasing in 1% increments. $\boldsymbol{R_F}$ (95% *n*-hexane in ethyl acetate) 0.61. Bright yellow solid, 65 mg (84%). (1 : 0.73 mixture of geometrical isomers A and B) **^{1}H NMR** (300 MHz, $CDCl_3$) δ A; 8.26 (d, 1 H, *J* = 16.2 Hz, δ*H*), 7.44-7.65 (m, 2 H, Ar*H*), 7.29-7.44 (m, 3 H, Ar*H*), 7.12 (d, 1 H, *J* = 16.2 Hz, C*H*CH), 6.96 (s, C*H*NO_2), 2.11 (d, 3 H, *J* = 1.0 Hz, CH_3). B; 7.44-7.65 (m, 2 H, Ar*H*), 7.29-7.44 (m, 3 H, Ar*H*), 7.19 (s, 1 H, C*H*NO_2), 7.15 (d, 1 H, *J* = 15.8 Hz, δ*H*), 6.71 (d, 1 H, *J* = 15.8 Hz, 2.45 (d, 3 H, *J* = 1.1 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ A; 144.1 (*C*), 140.5 (*C*HCH), 135.7 (Ar*C*), 134.4 (*C*HNO_2), 130.0 (Ar*C*H), 129.0 (Ar*C*H), 128.0 (Ar*C*H), 122.5 (δ*C*), 18.2 (*C*H_3). B; 146.7 (*C*), 138.9 (δ*C*), 138.0 (*C*HNO_2), 135.5 (Ar*C*), 129.8 (Ar*C*H), 129.0 (Ar*C*H), 126.6 (*C*HCH), 127.5 (Ar*C*H), 13.6 (*C*H_3). **ESI-MS** $C_{11}H_{11}NO_2$ Calc. (M+Na$^+$) = 212.0682 found (M+Na$^+$) = 212.0675 (-3.43 ppm).



41

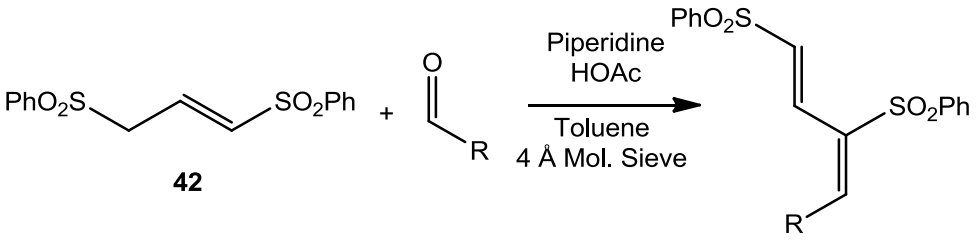
(*E*)-3-Bromo-1-phenylsulfonylprop-1-ene 41:[124] Allyl phenylsulfone (9.11 g, 50 mmol, 1 eq.) was dissolved in carbon tetrachloride (200 mL) and stirred at room temperature. Elemental bromine (3.02 mL, 55 mmol, 1.1 eq.) was added and the reaction was stirred for 4 hours at room temperature. The solvent and excess bromine were removed *in vacuo* and the residue was suspended in cold diethyl ether (50 mL). The intermediate dibromide was isolated quantitatively as a white solid after vacuum filtration. This solid was dissolved in chloroform (200 mL) and triethylamine (5.31 mL, 52.5 mmol, 1 eq.) was added in one portion. The reaction was stirred for 5 minutes at room temperature and washed sequentially with 1 M HCl (100 mL) and diluted with distilled water (100 mL). The organic layer was removed and washed with brine (100 mL), dried over Na_2SO_4 and concentrated in *in vacuo* to give a colourless oil that solidifies on standing. The residue was

crystallised from ether/*n*-hexane to give colourless needles, 9.14 g (70%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82-8.04 (m, 2 H, Ar*H*), 7.49-7.64 (m, 3 H, Ar*H*), 7.03 (dt, 1 H, *J* = 6.8 Hz, *J* = 14.8 Hz, CH_2CH), 6.60 (dt, 1 H, *J* = 1.3 Hz, *J* = 14.8 Hz, $CHSO_2Ph$), 4.03 (dd, 2 H, *J* = 1.3 Hz *J* = 6.8 Hz, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.7 (Ar*C*), 139.5 ($CHCH_2$), 133.9 (Ar*C*H), 133.8 ($CHSO_2Ph$), 129.5 (Ar*C*H), 127.8 (Ar*C*H), 27.5 (CH_2). **M.P.** 50-52 °C (Lit. 50-51 °C).[124] Matches known data.[124]



41 **42**

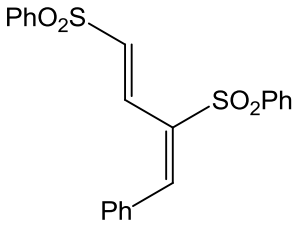
(1*E*)-1,3-Bis-phenylsulfonylprop-1-ene 42:[122b] Bromo-phenylsulfonyl propene **41** (2.61 g, 10 mmol, 1 eq.) was dissolved in methanol (30 mL). To this was added benzenesulfinic acid sodium salt (3.78 g, 23 mmol, 2.3 eq.) and the mixture was refluxed for 30 minutes. The solvent was removed *in vacuo* and the residue partitioned between distilled water (50 mL) and methylene chloride (50 mL). The organic layer was separated and washed with brine solution, dried over Na_2SO_4 and concentrated in *in vacuo* to give a colourless oil that solidifies on standing. The residue was crystallised from ether/*n*-hexane to give colourless needles, 2.64 g (82%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72-7.86 (m, 4 H), 7.52-7.72 (m, 4 H), 7.39-7.52 (m, 2 H), 6.80 (dt, 1 H, *J* = 7.7 Hz, *J* = 15.2 Hz, C*H*CH), 6.37 (dt, 1 H, *J* = 1.1 Hz, *J* = 15.2 Hz, CHC*H*), 3.95 (dd, 2 H, *J* = 7.7 Hz *J* = 1.1 Hz, CH_2). **^{13}C NMR** (75MHz, $CDCl_3$) δ 139.3 (Ar*C*), 138.5 ($CHCH_2$), 137.6 (Ar*C*), 134.4 (Ar*C*H), 134.0 (Ar*C*H), 131.5 (*C*HCH), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 128.3 (Ar*C*H), 127.9 (Ar*C*H), 57.7 (CH_2). **M.P.** 110-112 °C (Lit. 101-102 °C).[121] Matches known data.[184]



42

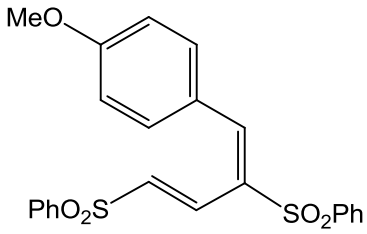
General Procedure for the synthesis of aryl 1,3-bis-phenylsulfonyldienes: Bis-sulfone **42** (323 mg, 1 mmol, 1 eq.), toluene (20 mL), aryl aldehyde (1.1 mmol, 1.1 eq.), 4 Å molecular sieves (2 g), piperidine (50 µL) and HOAc (50 µL) were refluxed for an appropriate amount of time as indicated by TLC. Saturated ammonium chloride (20 mL) was added and the mixture was extracted three times with methylene chloride (30 mL). The organic layer was then washed with saturated sodium bicarbonate (100 mL) and water (100 mL) and concentrated under reduced pressure to yield the crude diene. The resulting residue was then dissolved in a minimal amount of hot isopropyl alcohol and stored at -20 °C for 2 hours. The precipitate was then collected and recrystallised using a

minimal amount of methylene chloride and an equivalent amount of hexane. The crystals were grown by slow evaporation, at room temperature, until crystallisation occurred, yielding the pure diene.



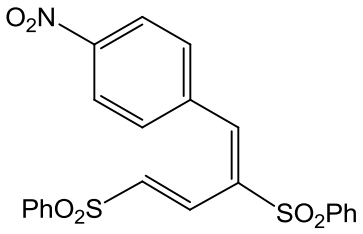
39

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene 39: From benzaldehyde according to general procedure. Yield after recrystallisation, white needles 349 mg (85%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.20 (s, 1 H, δ*H*), 7.78-7.7.64 (m, 5 H), 7.56-7.26 (m, 12 H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 145.3 (δ*C*), 139.9, 139.0, 135.2, 134.1, 133.7, 133.7, 132.3, 131.6, 131.0, 130.9, 129.5, 129.2, 129.2, 127.85, 127.7. **ESI-MS** $C_{22}H_{18}O_4S_2$ Calc. ($M+H^+$) = 411.0719 found ($M+H^+$) = 411.0717 (-0.53 ppm). **M.P.** 156-160 ^{o}C. Matches known data.[122b]



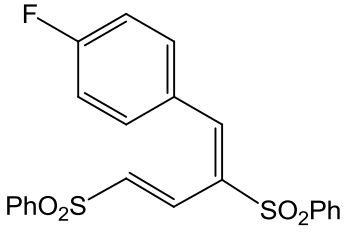
52

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-(4-methoxy)phenyl-buta-1,3-diene 52: From 4-methoxybenzaldehyde according to general procedure. Yield after recrystallisation, pale-yellow solid 361 mg (82%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.13 (s, 1 H, δ*H*), 7.77-7.74 (m, 2 H), 7.69-7.63 (m, 3 H), 7.55-7.48 (m, 3 H), 7.43-7.29 (m, 6 H), 7.02-6.97 (m, 2 H), 3.88 (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 162.6, 145.1 (δ*C*), 140.2, 139.5, 134.2, 133.6, 133.4, 133.2, 131.5, 131.2, 129.5, 129.1, 127.7, 127.7, 125.0, 114.8, 55.6. **M.P.** 150-152 ^{o}C. **ESI-MS** $C_{23}H_{20}O_5S_2$ Calc. ($M+H^+$) = 441.0825 found ($M+H^+$) = 441.0835 (2.23 ppm).



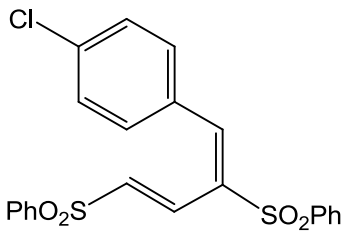
53

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-(4-nitro)phenyl-buta-1,3-diene 53: From 4-nitrobenzaldehyde according to general procedure. Yield after recrystallisation, off-white solid 369 mg (81%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.32-8.27 (m, 2 H), 8.17 (s, 1 H, δ*H*), 7.74-7.68 (m, 5 H), 7.61-7.55 (m, 5 H), 7.42-7.36 (m, 2 H), 7.3 (br s, 1 H), 7.25 (d, *J* = 1.0 Hz, 1 H). **^{13}C NMR** (75 MHz, $CDCl_3$) C= 148.8 (δ*C*), 141.3, 139.3, 138.3, 138.2, 138.1, 137.3, 134.1, 134.1, 131.3, 129.6, 129.6, 129.4, 128.1, 127.8, 124.2. **M.P.** Decomposition. **ESI-MS** $C_{22}H_{17}NO_6S_2$ Calc. ($M+H^+$) = 456.0570 found ($M+H^+$) = 456.0589 (4.17 ppm).



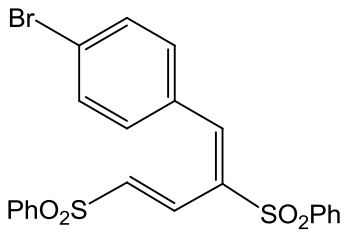
49

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-(4-fluoro)phenyl-buta-1,3-diene 49: From 4-fluorobenzaldehyde according to general procedure. Yield after recrystallisation, pale-orange solid 270 mg (63%). **^{1}H NMR** (300 MHz, $(C_4D_8)O$) *δ* 8.15 (s, 1 H, δ*H*), 7.75-7.64 (m, 5 H), 7.57-7.49 (m, 5 H), 7.36-7.21 (m, 6 H). **^{13}C NMR** (75 MHz, $(C_4D_8)O$) *δ* 164.3 (d, *J* = 250 Hz, *i*-F), 143.1 (δ*C*), 140.6, 139.7, 136.0, 134.7, 133.3 (d, *J* = 15 Hz, *m*-F), 133.3, 130.7, 129.3, 129.2 (d, *J* = 3Hz, *p*-F), 129.0, 127.8, 127.6, 116.2 (d, *J* = 23 Hz, *o*-F). **M.P.** 136-138^{o}C. **ESI-MS** $C_{22}H_{17}FO_4S_2$ Calc. ($M+H^+$) = 429.0625 found ($M+H^+$) = 429.0634 (2.13 ppm).



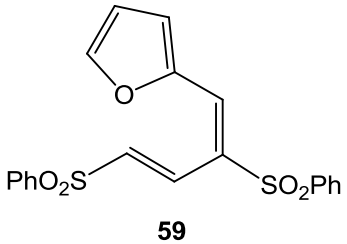
50

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-(4-chloro)phenyl-buta-1,3-diene 50: From 4-chlorobenzaldehyde according to general procedure**.** Yield after recrystallisation, off-white solid 289 mg (65%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.12 (s, 1 H, δ*H*), 7.77-7.74 (m, 2 H), 7.70-7.65 (m, 3 H), 7.57-7.51 (m, 3 H), 7.47-7.43 (m, 2 H), 7.38-7.33 (m, 4 H), 7.30-7.29 (m, 2 H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 143.5 (δ*C*), 139.7, 138.8, 138.0, 135.8, 134.7, 133.8, 133.8, 132.0, 130.7, 130.5, 129.6, 129.5, 129.3, 127.9, 127.8. **M.P.** 134-136 ^{o}C **ESI-MS** $C_{22}H_{17}ClO_4S_2$ Calc. ($M+H^+$) = 445.0330 found ($M+H^+$) = 445.0352 (4.94 ppm).



51

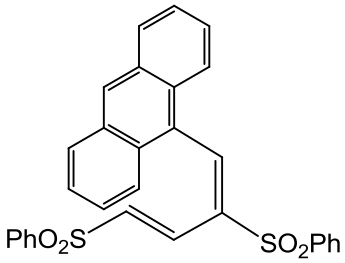
(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-(4-bromo)phenyl-buta-1,3-diene 51: From 4-bromobenzaldehyde according to general procedure. Yield after recrystallisation, pale-yellow solid 405 mg (83%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.10 (s, 1 H, δ*H*), 7.77-7.74 (m, 2 H), 7.71-7.65 (m, 3 H), 7.62-7.51 (m, 5 H), 7.38-7.33 (m, 2 H), 7.30-7.23 (m, 4 H). **^{13}C NMR** (75MHz, $CDCl_3$) *δ* 143.5 (δ*C*), 139.7, 138.8, 135.8, 134.8, 133.8, 133.8, 132.5, 132.1, 131.1, 130.5, 129.5, 129.3, 127.9, 127.8, 126.4. **M.P.** 156-158 ^{o}C. **ESI-MS** $C_{22}H_{17}BrO_4S_2$ Calc. ($M+H^+$) = 488.9824 found ($M+H^+$) = 488.9816 (-1.71 ppm).



59

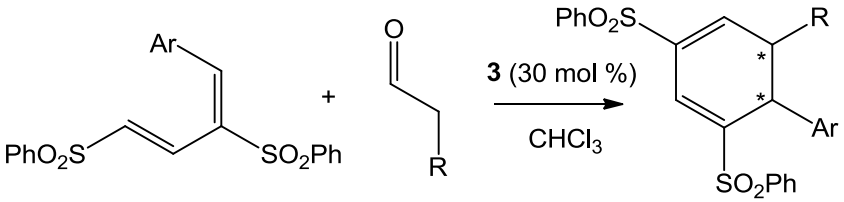
(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-furyl-buta-1,3-diene 59: From 2-furfural according to general procedure. Yield after recrystallisation, pale-yellow solid 312 mg (78%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ*

8.03 (d, 1 H, *J* = 15.6 Hz), 7.78-7.85 (m, 3 H), 7.69-7.77 (m, 3 H), 7.60-7.68 (m, 1 H), 7.48-7.51 (m, 3 H), 7.35-7.44 (m, 2 H), 7.25 (d, 1 H, *J* = 15.6 Hz), 6.98 (d, 1 H, *J* = 3.4 Hz), 6.58-6.65 (m, 1 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.2, 148.5, 140.2, 139.6, 133.6, 133.5, 133.4, 131.1, 129.9, 129.5, 129.4, 129.2, 127.8, 127.6, 122.5, 113.4. **M.P.** 136-138 ^{o}C. **ESI-MS** $C_{20}H_{16}O_5S_2$ Calc. ($M+H^+$) = 401.0512 found ($M+H^+$) = 401.0512 (1.64 ppm).

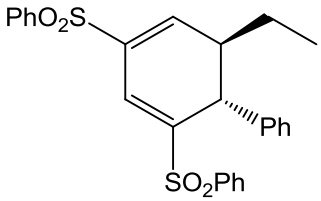


60

(1*E*,3*E*)-1,3-Bis(phenylsulfonyl)-4-anthracenyl-buta-1,3-diene 60: From 9-anthracene aldehyde according to general procedure. Yield after recrystallisation, dark-orange solid 501 mg (98%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.51 (s, 1 H), 7.97-8.07 (m, 4 H), 7.69-7.75 (m, 2 H), 7.40-7.68 (m, 8 H), 7.34-7.40 (m, 4 H), 7.11 (d, 1 H, *J* = 15.7 Hz), 6.63 (d, 1 H, *J* = 15.7 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.9, 139.6, 139.3, 139.1, 134.8, 134.1, 133.5, 131.0, 130.9, 130.3, 129.6, 129.3, 129.3, 129.2, 128.0, 127.8, 127.5, 125.7, 124.7, 124.4. **M.P.** 170-174 ^{o}C. **ESI-MS** $C_{30}H_{22}O_4S_2$ Calc. ($M+H^+$) = 511.1032 found ($M+H^+$) = 511.1039 (1.36 ppm).

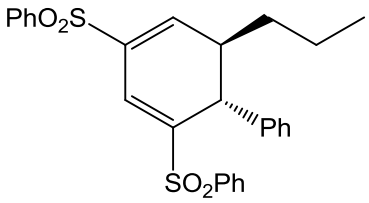


General procedure for 1,6-conjugate addition: A sample vial of catalyst (0.06 mmol, 0.3 eq), dissolved in chloroform (0.5 mL), was treated with diene (0.2 mmol, 1 eq.) followed by direct addition of the aldehyde (0.4 mmol, 2 eq.). The reaction mixture was then stirred at room temperature until the reaction was complete as indicated by TLC. The reaction mixture was concentrated under reduced pressure and triturated with ice cold methanol (2 x 3 mL) to yield the solid product.



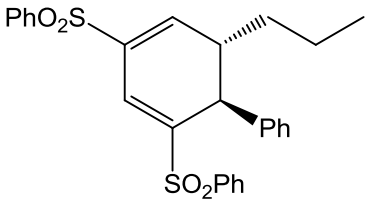
44

(1*R*,2*R*)-2-Ethyl-4,6-bis(phenylsulfonyl)-1,2-dihydro-1,1'-biphenyl 44: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and *n*-butyraldehyde according to general procedure. Yield after 24 hours, white solid 85 mg (91%). Absolute stereochemistry assigned from **43**. No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 34.7 (*R,R*) 32.8 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2 H), 7.74-7.68 (m, 1 H), 7.63-7.53 (m, 5 H), 7.44-7.38 (m, 1 H), 7.30-7.25 (m, 2 H), 7.06-6.97 (m, 2 H), 6.90-6.85 (m, 2 H), 6.50 (d, 2 H, *J* = 7.0 Hz), 3.75 (br s, 1 H, C*H*Ph), 2.57 (q, 1 H, *J* = 6.5 Hz, C*H*(Et)), 1.54-1.40 (m, 1 H), 1.29-1.15 (m, 1 H), 0.91-0.74 (m, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.0, 142.0, 139.3, 138.5, 137.8, 137.6, 133.9, 133.5, 129.6, 128.9, 128.6, 128.3, 128.0, 127.2, 126.5, 126.1, 46.5, 41.4, 25.7, 10.8. **M.P.** 160-165 ^{o}C. **ESI-MS** $C_{26}H_{24}O_4S_2$ Calc. ($M+H^+$) = 465.1189 found ($M+H^+$) = 465.1203 (3.00 ppm). **$[\alpha]_{589}^{21}$** -105.5^o (c = 0.2).



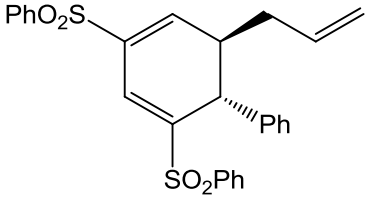
43

(1*R*,2*R*)-4,6-Bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 43: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and *n*-valeraldehyde according to general procedure. Yield after 24 hours, white solid 94 mg (98%). The crystals used for x-ray crystallography were grown in 50:50 methylene chloride, methanol. Absolute stereochemistry assigned from crystal structure. No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 26.4 (*R,R*) 30.4 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2 H), 7.73-7.68 (m, 1 H), 7.63-7.54 (m, 5 H), 7.44-7.40 (m, 1 H), 7.04-6.98 (m, 2 H), 6.90-6.85 (m, 2 H), 7.06-6.97 (m, 2 H), 6.50 (d, 2 H, *J* = 7.0 Hz), 3.72 (br s, 1 H, C*H*Ph), 2.66 (q, 1 H, *J* = 6.5 Hz, C*H*(Pr)), 1.41-1.09 (m, 4H), 0.80 (t, 3 H, *J* = 7.0 Hz) . **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2, 141.8, 139.3, 138.5, 137.7, 137.5, 133.9, 133.5, 129.6, 128.9, 128.6, 128.3, 128.0, 127.2, 126.5, 126.2, 44.6, 41.6, 34.4, 19.3, 13.7. **M.P.** 158-160 ^{o}C. **ESI-MS** $C_{27}H_{26}O_4S_2$ Calc. ($M+H^+$) = 479.1345 found ($M+H^+$) = 479.1364 (3.86 ppm). **$[\alpha]_{589}^{21}$** -152.6^o (c = 0.2).



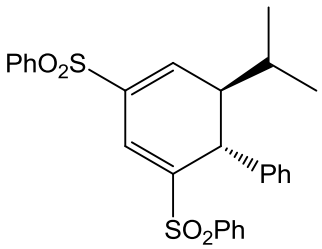
43b

(1*S*,2*S*)-4,6-Bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 43b: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and *n*-valeraldehyde according to general procedure using *S* enantiomer of catalyst. Yield after 24 hours, white solid 93 mg (98%). The crystals used for x-ray crystallography were grown in 50:50 methylene chloride, methanol. Absolute stereochemistry assigned from crystal structure. No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 32.0 (*S,S*) 25.9 (*R,R*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2 H), 7.73-7.68 (m, 1 H), 7.63-7.54 (m, 5 H), 7.44-7.40 (m, 1 H), 7.04-6.98 (m, 2 H), 6.90-6.85 (m, 2 H), 7.06-6.97 (m, 2 H), 6.50 (d, 2 H, *J* = 7 Hz), 3.72 (br s, 1 H, C*H*Ph), 2.66 (q, 1 H, *J* = 6.5 Hz, C*H*(Pr)), 1.41-1.09 (m, 4H), 0.80 (t, 3 H *J* = 7 Hz) . **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.3, 141.9, 139.3, 138.5, 137.7, 137.5, 133.9, 133.5, 129.6, 128.9, 128.6, 128.3, 128.0, 127.2, 126.5, 126.2, 44.6, 41.6, 34.4, 19.3, 13.7. **M.P.** 158-160 ^{o}C. **ESI-MS** $C_{27}H_{26}O_4S_2$ Calc. ($M+H^+$) = 479.1345 found ($M+H^+$) = 479.1356 (2.21 ppm). **$[\alpha]_{589}^{21}$** +148.5^o (c = 0.2).



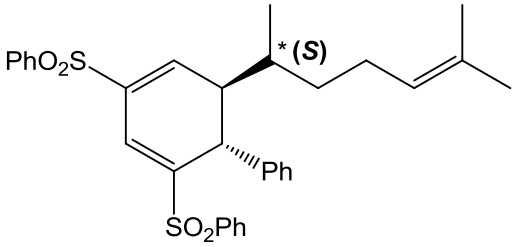
45

(1*R*,2*R*)-2-Allyl-4,6-bis(phenylsulfonyl)-1,2-dihydro-1,1'-biphenyl 45: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and 4-pentenal according to general procedure. Yield after 24 hours, white solid 88 mg (92%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 32.3 (*R,R*) 35.4 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2 H), 7.75-7.69 (m, 1 H), 7.64-7.56 (m, 5 H), 7.44-7.38 (m, 1 H), 7.30-7.24 (m, 2 H), 7.04-6.98 (m, 2 H), 6.91-6.86 (m, 2 H), 6.50 (d, 2 H, *J* = 7 Hz), 5.67-5.53 (m, 1 H), 5.08 (d, 1 H, *J* = 10.5 Hz), 4.84-4.78 (m, 1 H), 3.81 (br s, 1 H, C*H*Ph), 2.76-2.68 (m, 1 H, C*H*(allyl)), 2.24-2.15 (m, 1 H), 1.95-1.85 (m, 1 H) . **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.4, 141.9, 139.2, 138.5, 137.8, 137.7, 134.0, 133.5, 132.8, 129.6, 128.9, 128.7, 128.4, 128.1, 127.2, 126.5, 126.2, 119.5, 44.5, 40.7, 36.1. **M.P.** 137-138 ^{o}C. **ESI-MS** $C_{27}H_{24}O_4S_2$ Calc. ($M+H^+$) = 477.1189 found ($M+H^+$) = 477.1208 (4.00 ppm). **$[\alpha]_{589}^{21}$** -169.1^o (c = 0.2).



46

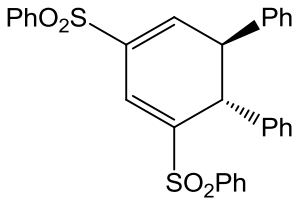
(1*R*,2*R*)-2-Isopropyl-4,6-bis(phenylsulfonyl)-1,2-dihydro-1,1'-biphenyl 46: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and isovaleraldehyde according to general procedure. Yield after 40 hours, white solid 98 mg (91%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 23.9 (*R,R*) 31.8 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2 H), 7.74-7.68 (m, 1 H), 7.64-7.51 (m, 5 H), 7.41-7.36 (m, 1 H), 7.27-7.22 (m, 2 H), 7.05-6.95 (m, 2 H), 6.89-6.84 (m, 2 H), 6.50 (d, 2 H, *J* = 7.0 Hz), 3.88 (br s, 1 H, C*H*Ph), 2.45-2.40 (m, 1 H, C*H*(^{i}Pr)), 1.74-1.58 (m, 1 H), 0.90 (d, 3 H, *J* = 6.8 Hz), 0.80 (d, 3 H, *J* = 6.8 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.5, 141.2, 138.3, 137.6, 137.6, 137.0, 132.9, 132.4, 128.6, 127.8, 127.6, 127.3, 127.0, 126.0, 125.3, 125.3, 50.8, 38.6, 31.5, 18.6, 18.5. **M.P.** 168-170 ^{o}C. **ESI-MS** $C_{27}H_{26}O_4S_2$ Calc. ($M+H^+$) = 479.1345 found ($M+H^+$) = 479.1336 (-2.03 ppm). **$[\alpha]_{589}^{21}$** -165.6^o (c = 0.2).



47

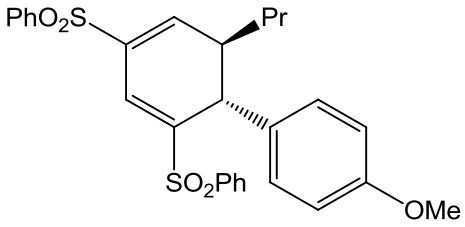
(1*R*,2*R*)-2-((*S*)-6-Methylhept-5-en-2-yl)-4,6-bis(phenylsulfonyl)-1,2-dihydro-1,1'-biphenyl 47: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and (*S*)-citronellal according to general procedure. Yield after 144 hours, yellow oil 97 mg (89%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR. **^{1}H NMR** (300M Hz, $CDCl_3$) δ 7.91-7.94 (m, 2 H), 7.68-7.73 (m, 1 H), 7.50-7.63 (m, 5 H), 7.35-7.40 (m, 1 H), 7.20-7.27 (m, 2 H), 6.95-7.02 (m, 2 H), 6.84-6.89 (m, 2 H), 6.51 (d, 2 H, *J* = 7.5 Hz), 4.96-5.00 (m, 1 H, C*H*C(CH_3)$_2$), 3.88 (br s, 1 H, C*H*Ph), 2.55-2.59 (m, 1 H, C*H*CH(CH_3)), 1.79-1.94 (m, 2 H, CH_2CH_2CHC(CH_3)$_2$), 1.68 (s, 3 H, CHC(CH_3)$_2$), 1.55 (s, 3 H, CHC(CH_3)$_2$), 1.38-1.47 (m, 1 H, CHC*H*(CH_3)), 1.22-1.36 (m, 2 H, CHCH(CH_3)CH_2), 0.72 (d, 3 H, *J* = 6.9 Hz, CH(CH_3)). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.7, 142.3, 139.4, 139.2, 138.7, 138.0, 134.0, 133.4, 132.1, 129.6, 128.8, 128.7, 128.3, 128.0, 127.1, 126.4, 123.6, 50.3, 38.7, 36.9, 33.4, 25.7, 25.3, 17.7, 15.6. **ESI-MS**

$C_{32}H_{33}O_4S_2$ Calc. ($M+NH_4^+$) = 564.2237 found ($M+NH_4^+$) = 564.2245 (1.42 ppm). **$[\alpha]_{589}^{21}$** -161.566° (c = 0.2).



48

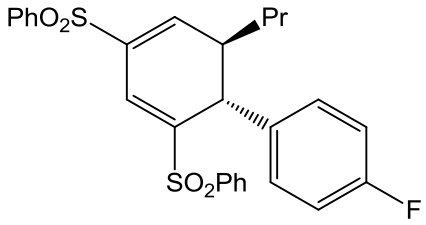
(1'*R*,2'*R*)-3',5'-Bis(phenylsulfonyl)-1',2'-dihydro-1,1':2',1''-terphenyl 48: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-phenyl-buta-1,3-diene **39** and phenylacetaldehyde according to general procedure. Yield after 24 hours, white solid 98 mg (96%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 51.9 (*R,R*) 59.1 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.95-7.93 (m, 2 H), 7.76-7.71 (m, 1 H), 7.65-7.60 (m, 3 H), 7.44-7.41 (m, 2 H), 7.36-7.31 (m, 1 H), 7.26-7.06 (m, 7 H), 7.00-6.90 (m, 4 H), 6.70 (d, 2 H, *J* = 7.0 Hz), 3.95 (br s, 1 H, C(SO_2Ph)C*H*(Ph)), 3.87 (d, 1 H, *J* = 6.3 Hz, CHC*H*(Ph)). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 141.7, 139.5, 139.2, 138.6, 138.5, 138.3, 138.0, 134.1, 133.3, 129.7, 129.2, 128.9, 128.8, 128.1, 128.0, 127.6, 126.9, 126.7 126.6, 50.1, 45.6. **M.P.** Decomposition. **ESI-MS** $C_{30}H_{24}O_4S_2$ Calc. ($M+H^+$) = 495.1083 found ($M+H^+$) = 495.1087 (0.72 ppm). **$[\alpha]_{589}^{21}$** -405.2° (c = 0.2).



54

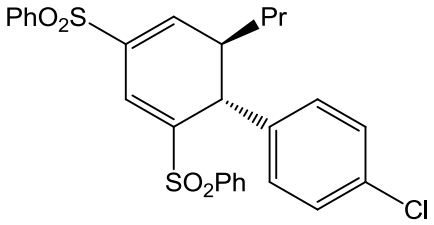
(1*R*,2*R*)-4'-Methoxy-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 54: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-(4-methoxy)phenyl-buta-1,3-diene **52** and *n*-valeraldehyde according to general procedure. Yield after 24 hours, white solid 76 mg (75%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 43.1 (*R,R*) 46.5 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.91-7.88 (m, 2 H), 7.73-7.68 (m, 1 H), 7.63-7.59 (m, 4 H), 7.50-7.42 (m, 2 H), 7.33-7.27 (m, 2 H), 7.04 (d, 1 H, *J* = 6.6 Hz), 6.42 (m, 4 H), 3.67 (s, 3 H), 3.66 (br s, 1 H, C*H*Ph), 2.64 (q, 1 H, *J* = 6.6 Hz, C*H*(Pr)), 1.40-1.06 (m, 4 H), 0.79 (t, 3 H, *J* = 6.9 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.6, 143.3, 142.3, 139.3, 138.7, 137.4, 133.9, 133.4, 129.8, 129.6, 128.9, 128.3, 128.0, 127.6, 125.9, 114.0, 55.2, 44.7, 40.9, 34.4, 19.3, 13.7. **M.P.**

Decomposition. **ESI-MS** $C_{28}H_{28}O_5S_2$ Calc. ($2M+H^+$) = 1017.2829 found ($2M+H^+$) = 1017.2791 (-3.74 ppm). $[\alpha]_{589}^{21}$ -129.5° (c = 0.2).



55

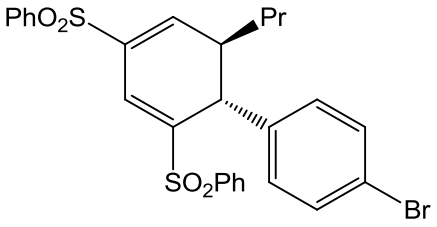
(1*R*,2*R*)-4'-Fluoro-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 55: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-(4-fluoro)phenyl-buta-1,3-diene **49** and *n*-valeraldehyde according to general procedure. Yield after 24 hours, white solid 80 mg (81%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiomeric excess was determined by **HPLC R_T** (IA) 29.1 (*R,R*) 33.9 (*S,S*) eluted from 10% IPA in heptane**.** **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2 H), 7.75-7.69 (m, 1 H), 7.65-7.60 (m, 4 H), 7.53 (d, 1 H, *J* = 1.4 Hz), 7.50-7.44 (m, 1 H), 7.35-7.27 (m, 2 H), 7.05-7.02 (m, 1 H), 6.60-6.43 (m, 4 H), 3.70 (br s, 1 H, C*H*(Ph)), 2.63 (q, 1 H, *J* = 6.4 Hz, C*H*(Pr)), 1.65-1.07 (m, 4 H), 0.79 (t, 3 H, *J* = 6.9 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.7 (d, *J* = 250 Hz, *i*-F), 143.1, 141.9, 139.3, 138.5, 137.6, 133.8 (d, *J* = 31 Hz, *m*-F), 133.5, 129.7, 129.0, 128.3, 128.1 (d, *J* = 8 Hz, *p*-F), 128.0, 126.2, 115.5 (d, 21 Hz, *o*-F), 44.6, 40.8, 34.3, 19.3, 13.7. **M.P.** Decomposition. **ESI-MS** $C_{27}H_{25}FO_4S_2$ Calc. ($M+H^+$) = 497.1521 found ($M+H^+$) = 497.1270 (3.83 ppm). $[\alpha]_{589}^{21}$ -157.1° (c = 0.2).



56

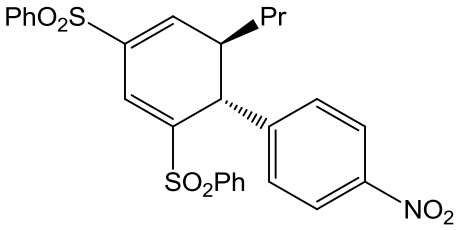
(1*R*,2*R*)-4'-Chloro-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 56: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-(4-chloro)phenyl-buta-1,3-diene **50** and *n*-valeraldehyde according to general procedure. Yield after 20 hours, white solid 83 mg (81%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiomeric excess was determined by **HPLC R_T** (IA) 30.6 (*R,R*) 33.0 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2 H), 7.76-7.71 (m, 1 H), 7.65-7.59 (m, 4 H), 7.53 (d, 1 H, *J* = 1.4 Hz), 7.52-7.46 (m, 1 H), 7.36-7.31 (m, 2 H), 7.04-7.02 (m, 1 H), 6.87-6.82 (m, 2 H), 6.46-6.41 (m, 2 H), 3.67 (br s, 1 H, C*H*Ph), 2.66-2.59 (m, 1 H, C*H*(Pr)), 1.41-1.05 (m, 4 H), 0.79 (t, 3 H, *J* = 6.9 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.9, 140.6, 138.2,

137.3, 136.6, 135.3, 133.0, 132.6, 132.0, 128.7, 128.0, 127.7, 127.3, 127.0, 126.9, 125.3, 43.4, 40.0, 33.3, 18.3, 12.7. **M.P.** Decomposition. **ESI-MS** $C_{27}H_{25}ClO_4S_2$ Calc. ($M+H^+$) = 513.0956 found ($M+H^+$) = 519.0980 (4.68 ppm). $\mathbf{[\alpha]_{589}^{21}}$ -102.0° (c = 0.2).



57

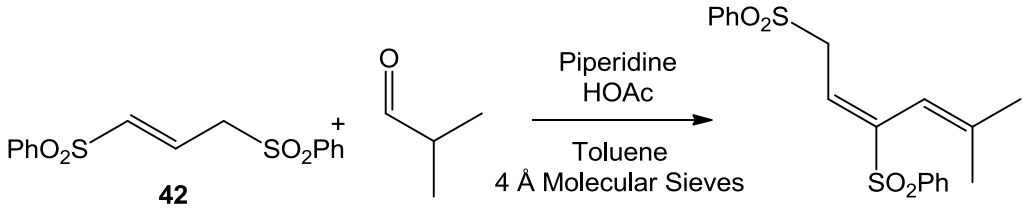
(1*R*,2*R*)-4'-Bromo-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 57: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-(4-bromo)phenyl-buta-1,3-diene **51** and *n*-valeraldehyde according to general procedure. Yield after 20 hours, white solid 78 mg (70%). Absolute stereochemistry assigned from **43**. No diastereoisomers detected by NMR, enantiomeric excess was determined by **HPLC R_T** (IA) 27.0 (*R,R*) 27.7 (*S,S*) eluted from 30% IPA in heptane (flow 0.75 mL/min). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2 H), 7.77-7.71 (m, 1 H), 7.65-7.59 (m, 4 H), 7.53-7.47 (m, 2 H), 7.36-7.31 (m, 2 H), 7.04-6.98 (m, 3 H), 6.38 (d, 2 H, *J* = 8.4 Hz), 3.65 (br s, 1 H, C*H*Ph), 2.62 (q, 1 H, *J* = 6.5 Hz, C*H*(Pr)), 1.41-1.08 (m, 4 H), 0.79 (t, 3 H, *J* = 6.9 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.9, 140.6, 138.2, 137.3, 136.6, 135.9, 133.0, 132.6, 130.7, 128.7, 128.1, 127.3, 127.3, 127.0, 125.4, 120.1, 43.4, 40.0, 33.3, 18.3, 12.7. **M.P.** Decomposition. **ESI-MS** $C_{27}H_{25}BrO_4S_2$ Calc. ($M+Na^+$) = 581.0252 found ($M+Na^+$) = 581.0279 (4.73). $\mathbf{[\alpha]_{589}^{21}}$ -117.5° (c = 0.2).



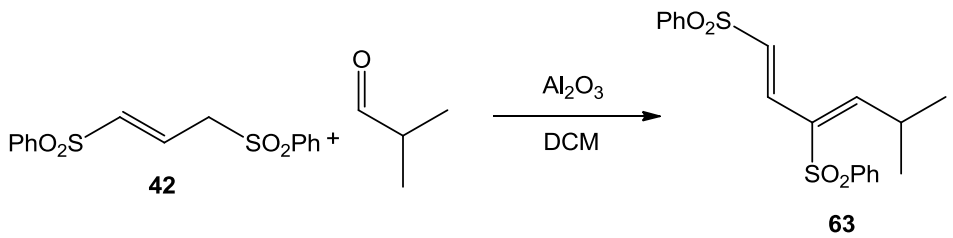
58

(1*R*,2*R*)-4'-Nitro-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 58: From (1*E*,3*E*)-1,3-bis(phenylsulfonyl)-4-(4-nitro)phenyl-buta-1,3-diene **53** and *n*-valeraldehyde according to general procedure. Yield after 4 hours, white solid 79 mg (92%). Absolute stereochemistry assigned from **43.** No diastereoisomers detected by NMR, enantiopurity determined by **HPLC R_T** (IA) 17.4 (*R,R*) 31.2 (*S,S*) eluted from 10% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2 H), 7.80-7.74 (m, 3 H), 7.68-7.60 (m, 5 H), 7.52-7.47 (m, 1 H), 7.39-7.34 (m, 2 H), 7.03 (d, 1 H, *J* = 6.2 Hz), 6.69 (d, 2 H, *J* = 8.7 Hz), 3.78 (br s, 1 H, C*H*Ph), 2.64 (q, 1 H, *J* = 6.5 Hz, C*H*(Pr)), 1.42-1.32 (m, 1 H), 1.27-1.06 (m, 3 H),

0.79 (t, 3 H, *J* = 6.8 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.0, 144.3, 141.4, 139.8, 138.1, 137.0, 137.0, 133.3, 132.9, 128.8, 128.2, 127.3, 127.0, 126.5, 125.9, 122.8, 43.2, 40.3, 33.2, 18.3, 12.6. **M.P.** Decomposition. **ESI-MS** $C_{27}H_{25}NO_6S_2$ Calc. ($M+H^+$) = 524.1196 found ($M+H^+$) = 524.1204 (1.44 ppm). **$[\alpha]_{589}^{21}$** -100.5° (c = 0.2).

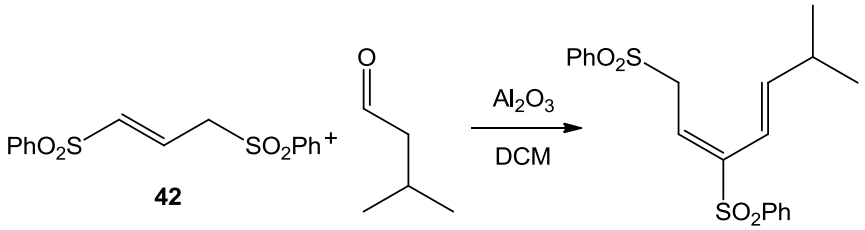


(*E*)-(5-Methylhexa-2,4-diene-1,3-diyldisulfonyl)dibenzene 62: Bis-sulfone **42** (323 mg, 1 mmol, 1 eq.), toluene (20 mL), *iso*-butyraldehyde (107 µL, 1.1 mmol, 1.1 eq.), 4 Å molecular sieves (2 g), piperidine (50 µL) and HOAc (50 µL) were refluxed for two hours. Saturated ammonium chloride (20 mL) was added and the mixture was extracted with methylene chloride (3 x 20 mL). The organic layer was then washed with saturated sodium bicarbonate (100 mL) and water (100 mL) and concentrated under reduced pressure to yield the crude diene. The resulting residue was then dissolved in a minimal amount of hot isopropanol and cooled to 0 °C until a precipitate had formed. The precipitate was then collected and recrystallised using a minimal amount of methylene chloride and an equivalent amount of hexane. Colourless needles 343 mg (91%). Samples for X-ray analysis were grown by dissolving the crystals in minimal methylene chloride and adding an equivalent amount of *n*-hexane, slow evaporation of the solution yielded translucent blocks. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.97 (m, 10 H, Ar*H*), 6.87 (t, 1 H, *J* = 7.5 Hz, CH_2CH), 4.95 (s, 1 H, CC*H*C), 3.82 (d, 2 H, *J* = 7.6 Hz, CH_2), 1.64 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.3 (CSO_2Ph), 146.1 ($C(CH_3)_2$), 138.2 (Ar*C*), 137.9 (Ar*C*), 134.2 (Ar*C*H), 133.6 (Ar*C*H), 129.4 (Ar*C*H), 129.0 (Ar*C*H), 128.6 (Ar*C*H), 128.4 (Ar*C*H), 126.6 (CH_2CH), 112.2 (CCHC), 56.1 (CH_2), 25.2 (CH_3), 18.9 (CH_3). **M.P.** 82-83 °C. **ESI-MS** $C_{19}H_{20}O_4S_2$ Calc. ($M+H^+$) = 377.0876 found ($M+H^+$) = 377.0881 (1.46 ppm).

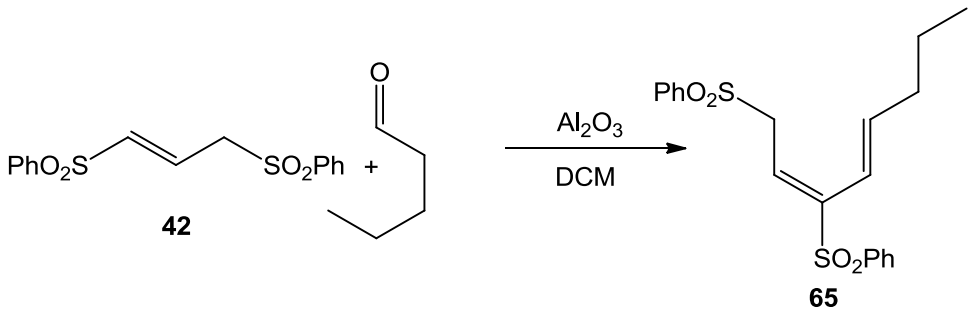


(1*E*,3*E*)-1,3-Bis-phenylsulfonyl -5-methylhexa-1,3-diene 63: Activated aluminium oxide (3.06 g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an

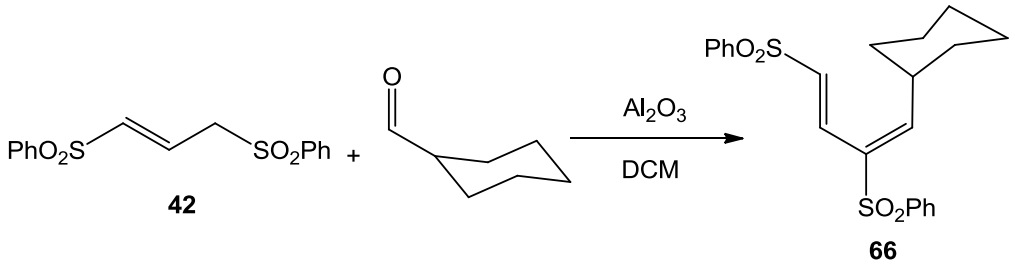
ice bath for 10 minutes at which point bis-phenylsulfonyl propene **42** (323 mg, 1 mmol, 1 eq.) was added followed by *iso*butyraldehyde (107 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred for 4 hours at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room temperature water bath. Methanol (10 mL) was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 ^{o}C for 2 hours and the precipitate was filtered and washed with ice-cold methanol (5 mL) to yield a colourless solid, 305 mg (81%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74-7.81 (m, 2 H), 7.61-7.70 (m, 3 H), 7.48-7.59 (m, 3 H), 7.36-7.45 (m, 2H), 7.30 (d, 1 H, *J* = 15.5 Hz, CHC*H*), 7.20 (d, 1 H, *J* = 10.5 Hz, δ*H*), 7.08 (d, 1 H, *J* = 15.5 Hz, C*H*CH), 2.77-2.96 (m, 1 H, C*H*$(CH_3)_2$), 1.14 (d, 6 H, *J* = 6.6 Hz, C*H*$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.2, 139.7, 139.2, 134.3, 133.7, 133.6, 129.5, 129.4, 129.4, 129.3, 129.1, 127.7, 127.6, 28.6 (*C*H$(CH_3)_2$), 21.8 (*C*H$_3$). **M.P.** 120-124 ^{o}C (Lit. 121-122 ^{o}C).[135] Matches known data.[135]



(2*E*,4*E*)-6-Methylhepta-2,4-diene-1,3-diyldisulfonyl)dibenzene 64: Activated aluminium oxide (3.06 g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an ice bath for 10 minutes at which point bis-phenylsulfonyl propene **42** (323 mg, 1 mmol, 1 eq.) was added followed by *iso*-valeraldehyde (118 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred for 2 hours at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room temperature water bath. Methanol (10 mL was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 ^{o}C for 2 hours and the precipitate was filtered and washed with ice-cold methanol (5 mL) to yield a colourless needles, 343 mg (88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71-7.88 (m, 4 H), 7.59-7.69 (m, 2 H), 7.45-7.57 (m, 4 H), 6.81 (t, 1 H, *J* = 8.1 Hz CH_2CH), 5.41-5.51 (m, 2 H, overlapping C*H*C*H*), 4.00 (d, 2 H, *J* = 8.1 Hz, C*H*$_2$), 2.07-2.27 (m, 1 H, C*H*$(CH_3)_2$), 0.81 (d, 6 H, *J* = 6.8 Hz, C*H*$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.3 (*C*HCH), 147.8 (*C*SO_2Ph), 138.7, 138.1, 134.2, 133.6, 129.5, 129.0, 128.4, 128.3, 125.1 (CH_2*CH*), 114.1 (CH*C*H), 56.0 (*C*H$_2$), 31.8 , *C*H$(CH_3)_2$), 21.5 (*C*H$_3$). **M.P.** 108-110 ^{o}C. **ESI-MS** $C_{20}H_{22}O_4S_2$ Calc. (M+Na^+) = 413.0852 found (M+Na^+) = 413.0868 (3.85 ppm).

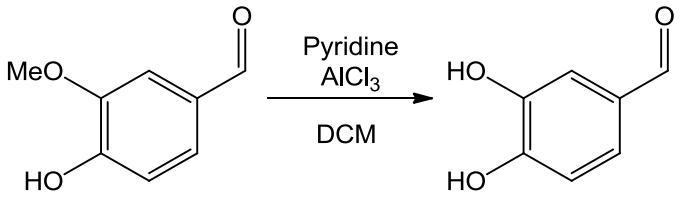


(2E,4E)-Octa-2,4-diene-1,3-diyldisulfonyl)dibenzene 65: Activated aluminium oxide (3.06 g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an ice bath for 10 minutes at which point bis-phenylsulfonyl propene **42** (323 mg, 1 mmol, 1 eq.) was added followed by *n*-valeraldehyde (118 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred for 1.5 hours at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room temperature water bath. Methanol (10 mL) was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 ^{o}C for 2 hours and the precipitate was filtered and washed with ice-cold methanol (5 mL) to yield a colourless solid, 324 mg (83%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.97 (m, 10 H, Ar*H*), 6.80 (t, 1 H, *J* = 8.1 Hz, CC*H*CH_2), 5.41-5.67 (m, 2 H, overlapping C*H*C*H*), 4.03 (d, 2 H, *J* = 8.1 Hz, C*H*$_2$$SO_2$Ph), 1.73-2.06 (m, 2 H, CHC*H*$_2$$CH_2$), 1.06-1.36 (m, 2 H, CH_2C*H*$_2$$CH_3$), 0.73 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.5 (*C*), 143.7 (C*C*HCH), 138.7 (Ar*C*), 138.1 (Ar*C*), 134.3 (Ar*C*H), 133.6 (Ar*C*H), 129.4 (Ar*C*H), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 125.2 (C*C*HCH_2), 116.9 (CH*C*H), 56.0 (*C*H_2SO_2Ph), 35.2 (CH*C*$H_2$$CH_2$), 21.6 ($CH_2$*C*$H_2$$CH_3$), 13.5 (*C*$H_3$). **M.P.** 82-84 ^{o}C. **ESI-MS** $C_{20}H_{22}O_4S_2$ Calc. (M+H^{+}) = 391.1032 found (M+H^{+}) = 391.1046 (3.59 ppm).



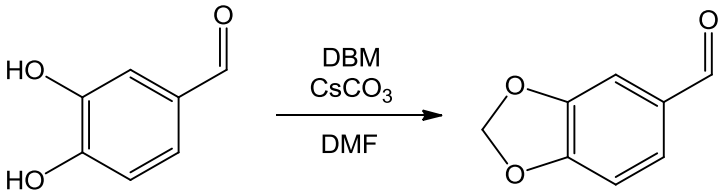
(1*E*,3*E*)-1,3-Bis-phenylsulfonyl -5-methylhexa-1,3-diene 66: Activated aluminium oxide (3.06g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an ice bath for 10 minutes at which point bis-phenylsulfonyl propene **42** (323 mg, 1 mmol, 1 eq.) was added followed by cyclohexane carboxaldehyde (133 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred overnight at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room

temperature water bath. Methanol (10 mL) was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 °C for 2 hours and the precipitate was filtered and washed with ice-cold methanol (5 mL) to yield a colourless solid, 333 mg (80%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.71-7.80 (m, 2 H), 7.59-7.70 (m, 3 H), 7.46-7.58 (m, 3 H), 7.26-7.42 (m, 3 H), 7.22 (d, 1 H, *J* = 10.4 Hz, δ*H*), 7.09 (d, 1 H, *J* = 15.5 Hz, SO_2PhC*H*), 2.42-2.65 (m, 1 H, C*H*(CH_2)$_2$), 1.58-1.85 (m, 5 H, *c*-hexyl *H*), 1.18-1.42 (m, 5 H, *c*-hexyl *H*). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 156.0 (δ*C*), 139.7 (SO_2Ph*C*H), 139.2, 134.0, 133.7, 133.7, 133.5, 129.4, 129.2, 127.6, 127.5, 38.1 (*C*H(CH_2)$_2$), 31.6 (*c*-hexyl *C*), 25.3 (*c*-hexyl *C*), 24.9 (*c*-hexyl *C*). **M.P.** 132-136 °C. **ESI-MS** $C_{22}H_{24}O_4S_2$ Calc. (2M+Na^+) = 855.2124 found (2M+Na^+) = 855.2151 (3.15 ppm).



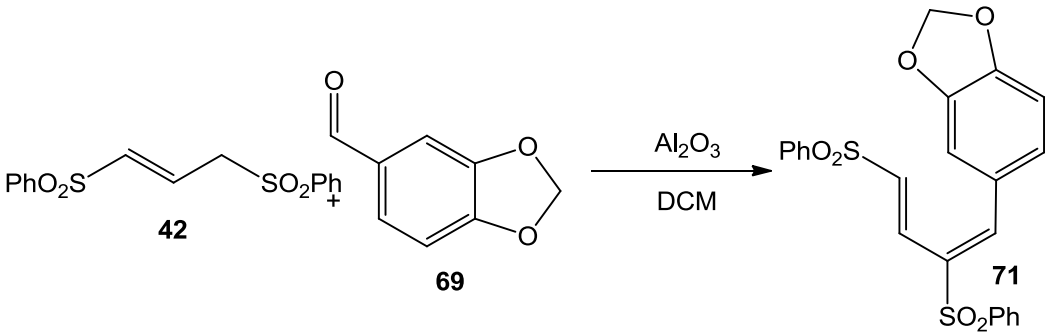
70

Protocatechualdehyde 70:[140] To a 3-neck flask fitted with a thermometer, condenser with gas bubbler and a septum, purged with argon, was added vanillin (5 g, 32.86 mmol, 1 eq.) and anhydrous aluminium trichloride (4.85 g, 36.15 mmol, 1.1 eq.). The solids were suspended in anhydrous methylene chloride (50 mL) and placed in a water bath. Pyridine (11.66 mL, 144.58 mmol, 4.4 eq.) was added cautiously not letting the internal temperature rise above 30 °C. The pyridine complex turns the solution bright yellow which starts to brown as the solution was heated at 45 °C for 24 hours. The reaction was allowed to cool and a yellow precipitate forms. A solution of 10% (v/v) HCl was added dropwise until the precipitate was completely dissolved. The methylene chloride layer was removed and discarded; the aqueous phase was extracted with diethyl ether (2 x 100 mL). The combined ethereal extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give a yellow powder which is essentially pure, 3.80 g (84%). **^{1}H NMR** (300 MHz, DMSO) *δ* 9.60-10.10 (br m, 2 H, O*H*), 9.74 (s, 1 H, C*H*O), 7.25-7.35 (m, 2 H, overlapping 2-,6-*H*) 6.96 (d, 1 H, *J* = 7.9 Hz, 5-*H*). **^{13}C NMR** (75 MHz, DMSO) *δ* 191.0 (*C*O), 152.1 (4-*C*OH), 145.8 (3-*C*OH), 128.8 (*C*), 124.5 (6-*C*H), 115.5 (2-*C*H), 114.3 (5-*C*H). **M.P.** 152-153 °C (Lit. 153 °C).[185] Matches known data.[186]



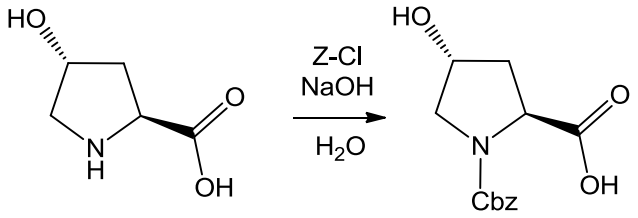
70 **69**

Piperonal 69:[141] To a solution of protocatechualdehyde **70** (3.70 g, 26.8 mmol, 1 eq.) in dimethylformamide (40 mL) was added caesium carbonate (13.10 g, 40.2 mmol, 1.5 eq.) and dibromomethane (2.87 mL, 40.2 mmol, 1.5 eq.). The reaction was brought to reflux for 1.5 hours during which time the mixture turned from red to brown and a white precipitate formed. The reaction was allowed to cool and the solvent was removed *in vacuo* leaving an off-white residue. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL), the organic layer was removed and washed with a saturated brine solution (100 mL). The organic layer was then concentrated to a brown oil which was then passed through a pad of silica with a mixture of ethyl acetate (100 mL) and *n*-hexane (100 mL). The solvent was removed *in vacuo* to give a yellow oil which was crystallised from a 70% aqueous ethanol solution to give pale yellow needles, 1.54 g (42%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.81 (s, 1 H, C*H*O), 7.41 (d, 1 H, *J* = 8.0 Hz, 6-*H*), 7.32 (s, 1 H, 2-*H*), 6.93 (d, 1 H, *J* = 8.0 Hz, 5-*H*), 6.07 (s, 2 H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.2 (*C*O), 153.1 (4-*C*), 148.7 (3-*C*), 131.9 (*C*), 128.6 (6-*C*H), 108.3 (2-*C*H), 106.9 (5-*C*H), 102.1 (CH_2). **M.P.** 38-39 °C (Lit. 37-39 °C).[187] Matches known data.[141]



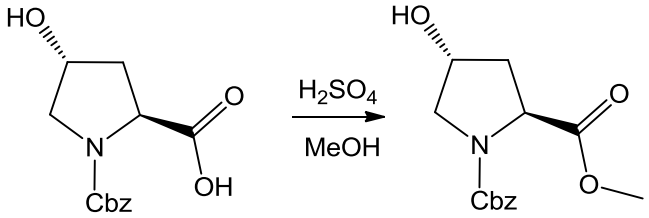
(1*E*,3*E*)-1,3-Bis-phenylsulfonyl -5-[phenyl-3,4-dioxole]-1,3-diene 71: Activated aluminium oxide (3.06 g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an ice bath for 10 minutes at which point bis-phenylsulfonyl propene **42** (323 mg, 1 mmol, 1 eq.) was added followed by piperonal **69** (165 mg, 1.1 mmol, 1.1 eq.). The reaction was stirred overnight at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room temperature water bath. Methanol (10 mL) was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 °C for 2 hours and the precipitate was

filtered and washed with ice-cold methanol (5 mL) to yield a yellow solid, 491 mg (90%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 8.07 (s, 1 H, δ*H*), 7.26-7.87 (m, 12 H), 6.83-7.05 (m, 3 H, benzodioxole Ar*H*), 6.07 (s, 2 H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 150.9 (δ*C*), 148.6, 144.9, 140.0, 139.2, 134.6, 133.7, 133.5, 131.8, 129.5, 127.7, 127.6, 127.3, 126.4 (benzodioxole Ar*C*H), 110.2 (benzodioxole Ar*C*H), 109.1 (benzodioxole Ar*C*H), 102.1(*C*H_2). **IR** (KBr disc) 3066 (alkene), 2919 (aromatic), 1608 (alkene), 1490 (sulfone), 1448 (sulfone), 1307, 1268 (ether), 1154 (sulfone), 1033 (sulfone), 917 (alkene), 817 (aromatic), 717 (aromatic), 548 (ether) cm^{-1}. **M.P.** 151-152 ^{o}C. **ESI-MS** Calc. $C_{23}H_{18}O_6S_2$ (M+Na^+) = 477.0437 found (M+Na^+) = 477.0447 (2.04 ppm).



73

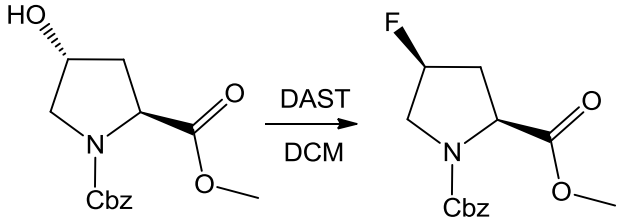
(2*S*,4*R*)-1-((Benzyloxy)carbonyl)-4-hydroxyproline 73: A solution of 4-hydroxyproline (10.0 g, 76.3 mmol, 1 eq.) in distilled water (67 mL) was brought to 4 ^{o}C. Sodium hydroxide (6.1 g, 152.5 mmol, 2 eq.) was added in one portion and stirred until dissolution. When the reaction temperature returned to 4 ^{o}C, Z-Cl (11.0 mL, 76.3 mmol, 1 eq.) was added over 1 minute and the reaction was left to come to room temperature overnight. The reaction was acidified to pH = 2 with 10% (v/v) HCl solution causing a white precipitate. The precipitate was extracted with ethyl acetate (3 x 200 mL) and the combined organics were dried over $MgSO_4$. The solvent was removed *in vacuo* to give a clear oil, 20.15 g (>99%). This oil was used without further purification.



73 **74**

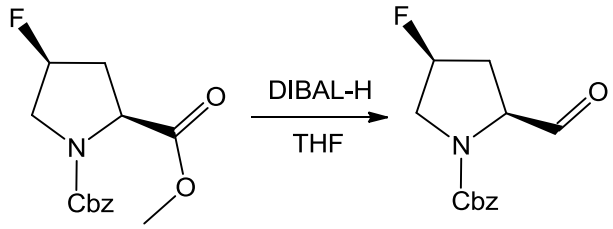
(2*S*,4*R*)-1-((Benzyloxy)carbonyl)-4-hydroxyproline methyl ester 74: Crude *N*-Cbz-4-hydroxyproline **73** (20.15 g, 76.26 mmol, 1 eq.) was dissolved in methanol (120 mL). The reaction was placed in an ice-bath and concentrated sulphuric acid (0.40 mL, 7.63 mmol, 10 mol %) was added. The reaction was then refluxed for 3 hours under a positive pressure of nitrogen. The reaction was then allowed to cool and saturated sodium hydrogen carbonate (100 mL) was added. The reaction was then

extracted with methylene chloride (3 x 200 mL) and the combined organics were dried with Na_2SO_4. The solvent was removed *in vacuo* to give a light brown oil, 21.12 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21-7.41 (m, 5 H, Ar*H*), 4.92-5.26 (m, 2 H, O*C*H_2 rotamers), 4.38-4.56 (m, 2 H, *C*H_2N rotamers), 3.46-3.82 (m, 5 H, overlapping *C*H_3 + *CH*OH + *CH*COOMe rotamers), 2.82-3.04 (two br s, 1 H, *J* = 29.3 Hz, O*H* rotamers), 1.98-2.38 (m, 2 H, CHCH_2CH). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (*C*OOMe rotamer A), 173.3 (*C*OOMe rotamer B), 155.2 (N*C*OO rotamer B), 154.8 (N*C*OO rotamer A), 136.3 (Ar*C* rotamer B), 136.1 (Ar*C* rotamer A), 128.5 (Ar*C*H rotamer B), 128.4 (Ar*C*H rotamer A), 128.1 (overlapping Ar*C*H + Ar*C*H rotamers), 127.8 (Ar*C*H rotamer B), 127.8 (Ar*C*H rotamer A), 69.7 (*C*HOH rotamer B), 68.9 (*C*HOH rotamer A), 67.3 (*C*H_2Ph rotamer A), 67.3 (*C*H_2Ph rotamer B), 58.0 (*C*HCOOMe rotamer B), 57.8 (*C*HCOOMe rotamer A), 55.1 (*C*H_2N rotamer A), 54.6 (*C*H_2N rotamer B), 52.4 (*C*H_3 rotamer B), 52.2 (*C*H_3 rotamer A), 39.0 (CH*C*H_2CH rotamer A), 38.2 (CH*C*H_2CH rotamer B). Matches known data.[188]



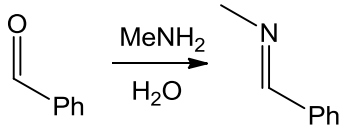
74 **75**

(2*S*,4*S*)-1-((Benzyloxy)carbonyl)-4-fluoro-proline methyl ester 75:[143b] To a solution of *N*-Cbz-4-hydroxyproline methyl ester **74** (7.61 g, 27.23 mmol, 1 eq.) in anhydrous methylene chloride (45 mL) at -78 ^oC under an atmosphere of nitrogen was added fresh diethylaminosulfur trifluoride (7.78 mL, 55.00 mmol, 2 eq.) in one portion. The solution was stirred at -78 ^oC for 7 hours and then allowed to come to room temperature where stirring was continued for 14 hours. The reaction was quenched with the addition of water (25 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organics were dried over $MgSO_4$. Concentration *in* vacuo yielded an orange oil which was purified by flash chromatography eluting with 90% methylene chloride ethyl acetate**.** R_F (80% methylene chloride in ethyl acetate) 0.42. Viscous yellow oil, 6.82 g (90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22-7.43 (m, 5 H, Ar*H*), 5.01-5.37 (m, 3 H, overlapping O*C*H_2 + *CH*F), 4.57 (dd, 1 H, *J* = 22.2 Hz, *J* = 9.5 Hz, *C*H_2N), 3.58-3.96 (m, 5 H, overlapping *C*H_2N + *C*H_3 + *CH*COOMe), 2.20-2.61 (m, 2 H, CHCH_2CH). **^{19}F NMR** (212 MHz, $CDCl_3$) δ -172.9 (m). Matches known data.[143b]



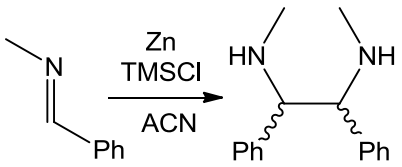
75 **76**

(2*S*,4*S*)-Benzyl 4-fluoro-2-formylpyrrolidine-1-carboxylate 76: To a 3-neck flask fitted with a low temperature thermometer, glass-tapped swan-neck and septum purged with argon was added *N*-Cbz-fluoroproline methyl ester **75** (6.82 g, 24.3 mmol, 1 eq.) dissolved in anhydrous THF (135 mL). The solution was brought to -70 ^{o}C at which point DIBAL-H (61.0 mL, 1 M in hexane, 60.8 mmol, 2.5 eq.) was added dropwise over 30 minutes. The reaction was then stirred for an additional 6 hours at -70 ^{o}C and quenched with the addition of MeOH (30 mL) followed rapidly with 1 M HCl (80 mL) and the mixture was stirred vigorously at room temperature to break up the aluminium salts. The mixture was then extracted with methylene chloride (3 x 50 mL) and the combined organics were dried over $MgSO_4$. Concentration *in vacuo* gave a foul-smelling residue which was passed through a pad of silica eluting with 70% *n*-hexane in ethyl acetate (200 mL). A total of 2.88 g of a foul-smelling yellow gum was obtained of which, by ^{1}H NMR, 62.6% is product aldehyde and ~36% is over reduced alcohol and starting material which was inseparable. Used as 62.6% mass pure sample (contains 1.83 g of aldehyde, a yield of 30% from starting material).



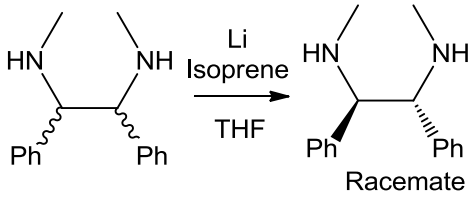
77

***N*-Methyl benzimine 77:**[144] To a solution of aqueous methylamine (100 mL, 40% w/v) was added benzaldehyde (25.47 mL, 0.25 mol, 1 eq.). The flask was securely sealed and the mixture was stirred at RT for 15 hours. The emulsion was then extracted with diethyl ether (3 x 100 mL) and dried with anhydrous K_2CO_3. Concentration *in vacuo* yielded an orange oil which was purified by distillation through a 10 cm Vigreux column at reduced pressure (aspirator) to give a clear liquid, 29.65 g (>99%), which was used immediately in the next step.



77 **78a**

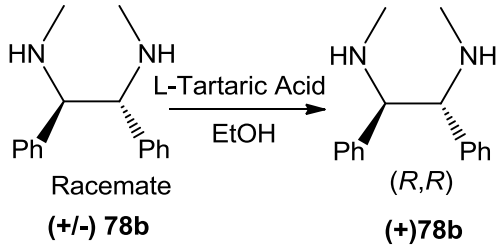
***N,N*-Dimethyl-1,2-diphenylethane-1,2-diamine 78a:** To a 3-neck flask fitted with a glass-tapped swan-neck, a condenser with a gas-bubbler**,** a septum, and purged with nitrogen was added zinc dust (13.1 g, 0.2 mol, 1 eq.). The zinc was suspended in anhydrous acetonitrile (50 mL) and activated by refluxing for 1 min after the addition of 1,2-dibromoethane (1.5 mL, 17.4 mmol, 0.09 eq.). The reaction was allowed to cool and to this trimethylsilyl chloride (1 mL, 7.9 mmol, 0.04 eq.) was added causing the evolution of gas. The suspension was stirred for 45 minutes at RT at which point anhydrous acetonitrile (100 mL) was added followed by methyl benzimine (27.4 mL, 0.2 mol, 1 eq.) in one portion. The septum was replaced with a pressure equalizing dropping funnel and the swan-neck was replaced with an alcohol thermometer under a positive pressure of nitrogen. Trimethylsilyl chloride (38 mL, 0.3 mol, 1.5 eq.) was added cautiously through the dropping funnel using a water-bath to prevent the internal temperature from rising above 30 ^{o}C. The reaction was stirred for a further two hours at room-temperature and was placed in an ice-bath. The reaction was hydrolysed with the cautious addition of a mixture of concentrated ammonium hydroxide (60 mL) and saturated ammonium chloride solution (140 mL). The suspension was then passed through glass-wool and the zinc washed with diethyl ether (200 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (200 mL) and methylene chloride (2 x 200 mL). The combined organics were dried with K_2CO_3 and concentrated *in vacuo* to a yellow-orange semi-solid, 17.81 g. This is used without purification in the next step. ^{1}H NMR analysis shows a ratio of products; Meso isomer (s, 2 H @ 3.62 ppm; s, 6 H @ 2.09 ppm) : DL isomers (s, 2 H @ 3.53 ppm; s, 6 H @ 2.25 ppm) : *N*-methyl benzylamine (s, 2 H @ 3.75 ppm; s, 3 H @ 2.45 ppm), (0.8 : 1 : 0.32). Matches known data.[144]



78a **78b**

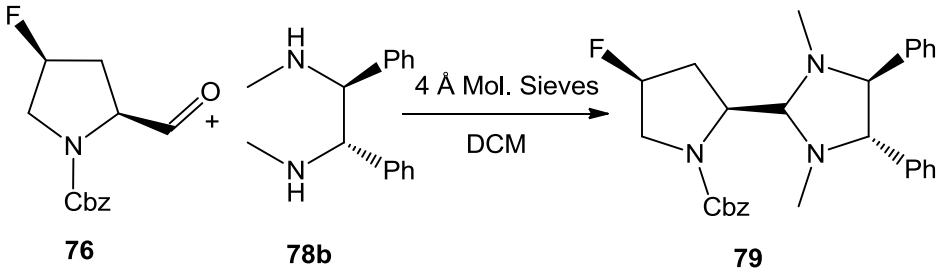
Isomerisation of meso-*N,N*-dimethyl-1,2-diphenylethane-1,2-diamine (+/-)78b:[144] A 3-neck flask fitted with a condenser, thermometer and septum containing the crude diamine **78a** was evacuated with stirring over-night. The vessel was then flushed with argon and anhydrous THF (200 mL) was added with stirring until the solution was homogenous. Lithium wire (1.8 g, 0.26 mol, 3.5 eq.) was added in small pieces over a stream of argon. The septum was then replaced with a dropping funnel

filled with isoprene (15 mL, 0.15 mol, 2 eq.) and the reaction was placed in a water-bath. The isoprene was added drop-wise preventing the internal temperature from rising above 40 °C. The reaction was monitored by ^{1}H NMR and isomerisation was complete after 45 minutes (0.5 mL aliquot withdrawn from reaction and mixed with 0.5 mL of ethyl acetate and 0.5 mL of saturated ammonium chloride solution. The mixture is shaken in a vial and the organic phase concentrated *in vacuo* for NMR analysis). The reaction is then cooled in an ice-bath and the excess lithium was removed by filtration through glass wool. The filtrate is placed in an ice-bath and hydrolysed with the careful addition of 2.5 M HCl (200 mL). The aqueous phase was separated, washed with diethyl ether (2 x 200 mL) and then treated with 35% NaOH (w/v, 50 mL) causing a white precipitate. The suspension was extracted with diethyl ether (2 x 200 mL) and dried with K_2CO_3. The ethereal extract was then concentrated *in vacuo* to give a brown oil, 18.83 g (73% DL amine by ^{1}H NMR). The oil was then dissolved in absolute ethanol (570 mL) and DL-tartaric acid (11.76 g, 0.0783 mol, 1.37 eq.) was added and the suspension was refluxed until dissolution. The solution was allowed to cool and the precipitate was collected by suction filtration. The retentate was rinsed with ethanol (40 mL) and added to a mixture of 35% NaOH (w/v, 60 mL), distilled water (200 mL) and diethyl ether (200 mL). The mixture was stirred vigorously until clarity was observed in both layers. The organic phase was removed and the aqueous phase extracted with diethyl ether (200 mL). The combined organics were dried with K_2CO_3 and concentrated *in vacuo* into a clear oil, 10.31 g (21% over 2 steps). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98-7.17 (m, 10 H, Ar*H*), 3.52 (s, 2 H, C*H*), 2.24 (s, 6 H, CH_3), 1.95 (br s, 2 H, N*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0 (Ar*C*), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 126.9 (Ar*C*H), 71.2 (NH*C*H_3), 34.6 (*C*H). Matches known data.[144]



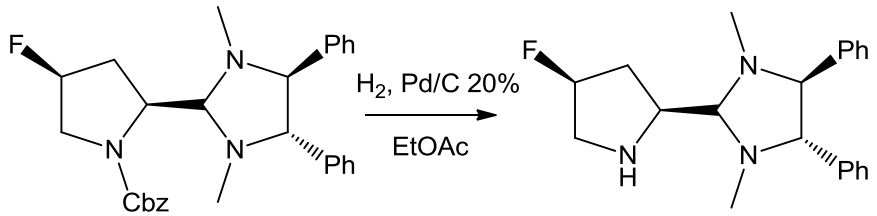
(*R*,*R*)-*N*,*N*-Dimethyl-1,2-diphenylethane-1,2-diamine 78b:[144] The pure DL-diamine **(+/-) 78b** (10.31 g, 42.89 mmol, 1 eq.) was dissolved in absolute ethanol (300 mL). L-Tartaric acid (6.44 g, 42.89 mmol, 1 eq.) was added and the reaction was refluxed until dissolution. The solution was left for two days at room temperature and the precipitate was collected by filtration. The filtrate was discarded as the (*S*,*S*)-enantiomer in the filtrate was not needed. The retentate was rinsed with ethanol (2 x 40 mL) and added to a mixture of 35% NaOH (w/v, 30 mL), distilled water (100 mL) and diethyl ether (100 mL). The mixture was stirred vigorously until clarity was observed in both layers. The organic phase was removed and the aqueous phase extracted with diethyl ether (100 mL). The combined organics were dried with K_2CO_3 and concentrated *in vacuo* into a clear oil which solidified on standing. The

solid was crystallised from pentane to give white flakes, 2.21 g (21%). **^{1}H NMR** (300MHz, $CDCl_3$) δ 6.98-7.17 (m, 10 H, Ar*H*), 3.52 (s, 2 H, C*H*), 2.24 (s, 6 H, CH_3), 1.95 (br s, 2 H, N*H*). **^{13}C NMR** (75MHz, $CDCl_3$) δ 141.0 (Ar*C*), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 126.9 (Ar*C*H), 71.2 (NH*C*H_3), 34.6 (*C*H). **$[\alpha]_{589}^{21}$** +21.2° (c = 1.0). **Melting-point** 50-52 °C (Lit. 50-51 °C). Matches known data.[144]



76 **78b** **79**

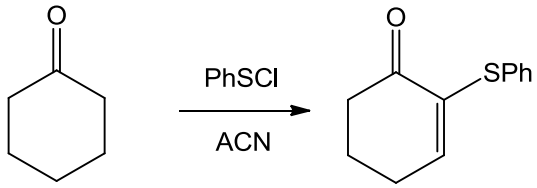
***N*-Cbz-FAPY 79:**[143b] To a solution of the *N*-Cbz fluoroprolinal **76** (2.88 g (63.6% mass pure, 1.83 g aldehyde), 7.29 mmol, 1 eq.) in anhydrous methylene chloride (30 mL) was added (*R*,*R*)-*N*,*N*-dimethyl-1,2-diphenylethane-1,2-diamine **78b** (2.10 g, 8.75 mmol, 1.2 eq.) and 4 Å molecular sieves (3 g). The reaction was stirred under a positive pressure of argon for 48 hours. The solution was passed through a pad of silica eluting with a mixture of ethyl acetate (100 mL) in *n*-hexane (100 mL) and concentrated *in vacuo* to give a yellow gum, which was used without purification.



79 **FAPY**

FAPY:[143b] The crude protected FAPY **79** (7.29 mmol, 1 eq.) was dissolved in ethyl acetate (30 mL) and 500 mg of palladium on activated charcoal (20% w/w) was added. The reaction was stirred under an atmosphere of hydrogen for 48 hours, and then washed through Celite with ethyl acetate (100 mL). The solvent was removed *in vacuo* and the residue purified by flash chromatography eluting with 90% methylene chloride ethyl acetate, then 80% ethyl acetate in 20% methanol with 2.5% ammonium hydroxide. R_F (80% ethyl acetate in 20% methanol with 2.5% ammonium hydroxide) 0.68. Green gum, 2.05 g (83%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08-7.34 (m, 10 H, Ar*H*), 5.15-5.45 (m, 1 H, C*H*F), 4.20 (d, 1 H, *J* = 4.5 Hz, C*H*(N)(N)), 3.68 (s, 2 H, PhC*H*C*H*Ph), 3.28-3.46 (m, 2 H, overlapping NHCH_2CHF + NHC*H*)), 2.82 (ddd, 1 H, *J* = 4.0 Hz, *J* = 13.3 Hz, *J* = 35.4 Hz, NHCH_2CHF), 2.56 (s, 3 H, CH_3), 2.14-2.48 (m, 6 H, overlapping CH_3 + CHFCH_2CH + N*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.9 (Ar*C*), 138.7 (Ar*C*), 128.6 (Ar*C*H), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 127.8 (Ar*C*H), 127.5

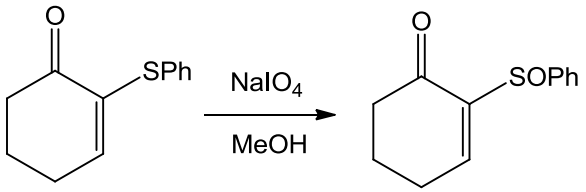
(Ar*C*H), 127.3 (Ar*C*H), 95.6 (d, 173.6 Hz, *C*HF), 85.5 (*C*H(N)(N)), 78.7 (*C*HPh), 75.1 (*C*HPh), 62.6 (NH*C*H), 54.2 (d, *J* = 23.6 Hz, NH*C*H_2), 43.3 (N*C*H_3), 36.0 (d, *J* = 21.1 Hz, CHF*C*H_2), 34.3 (N*C*H_3). **^{19}F NMR** (212 MHz, $CDCl_3$) δ -169.2 (m). **$[\alpha]_{589}^{21}$** +3.9^{o} (c = 0.8). Matches known data.[143b]



86

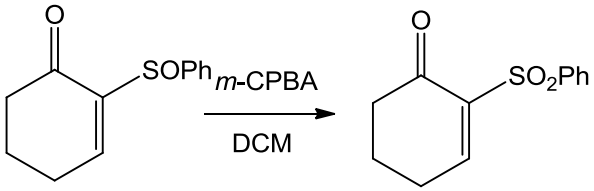
2-(Phenylthio)cyclohex-2-enone 86:[145, 189] A solution of phenylsulfenyl chloride was prepared as follows; under an atmosphere of argon *N*-chlorosuccinimide (4.50 g, 33.66 mmol, 1.02 eq.) was dissolved in anhydrous methylene chloride (33 mL). A small portion of thiophenol was then added causing an immediate exotherm and turning the solution orange. An ice-bath was then applied to the reaction and the remaining thiophenol (3.38 mL, 33 mmol, 3.3 eq.) was added slowly. The reaction was then allowed to come to room temperature and stirred for 1 hour giving a quantitative 1 M solution of phenylsulfenyl chloride.[190]

To a solution of cyclohexanone (1.04 mL, 10 mmol, 1 eq.) in anhydrous acetonitrile (15 mL) under an argon atmosphere was added a fresh solution of phenylsulfenyl chloride (33 mL, 1 M in methylene chloride, 33 mmol, 3.3 eq.). The reaction turned green and was stirred at room temperature for 24 hours. The reaction mixture was then filtered through a glass frit under a positive pressure of argon, and the solvent was removed *in vacuo* to leave a yellow residue. Hot methanol (10 mL) was added to the residue and then subsequently removed *in vacuo*, this process was repeated twice more to remove any residual thiophenol. The residue was purified with flash chromatography eluting with 100% petroleum ether -> 50% petroleum ether in ethyl acetate. $\boldsymbol{R_F}$ (70% petroleum ether in 30% ethyl acetate) 0.52. White solid, 1.47 g (72%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14-7.36 (m, 5 H, Ar*H*), 6.40 (t, 1 H, *J* = 4.5 Hz, C*H*), 2.38-2.50 (m, 2 H, COCH_2), 2.21-2.31 (m, 2 H, CHCH_2), 1.89-1.96 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.2 (*C*O), 145.5 (Ar*C*), 137.1 (*C*SPh), 133.6 (*C*HAr), 131.9 (*C*H), 129.4 (*C*HAr), 128.2 (*C*HAr), 38.6 (*C*OCH_2), 27.1 (CH*C*H_2), 22.7 ($CH_2CH_2CH_2$). **M.P.** 55-58 ^{o}C (Lit. 54-55 ^{o}C).[191] Matches known data.[145]



86 **87**

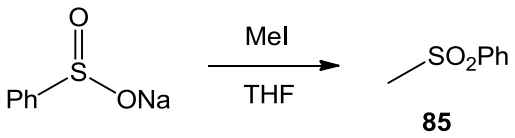
2-(Phenylsulfinyl)cyclohex-2-enone 87:[145] To a suspension of the phenylsulfenyl cyclohexanone **86** (1.30g, 6.4 mmol, 1 eq.) in a mixture of methanol (6 mL) and water (6 mL) was added sodium periodate (2.73 g, 12.8 mmol, 2 eq.). The reaction was stirred at room temperature overnight and then precipitate removed by suction filtration. The filtrate was concentrated *in vacuo* to give a yellow residue which was purified by flash chromatography eluting with 100% diethyl ether. R_F (100% diethyl ether) 0.50. Off-white solid, 1.24 g (88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64-7.82 (m, 3 H), 7.32-7.49 (m, 3 H), 2.22-2.73 (m, 4 H, overlapping COCH_2 and CHCH_2), 1.79-2.11 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.5 (*C*O), 149.6 (Ar*C*), 143.8 (*C*SOPh), 143.8 (*C*H), 131.1 (Ar*C*H), 128.9 (Ar*C*H), 125.2 (Ar*C*H), 38.2 ($COCH_2$), 26.1 ($CHCH_2$), 22.0 ($CH_2CH_2CH_2$). **M.P.** 55-56 ^{o}C (Lit. 56-57 ^{o}C).[192] Matches known data.[145]



87 **83**

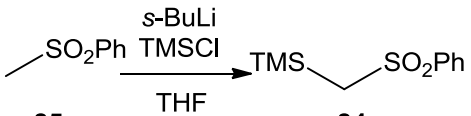
2-(Phenylsulfonyl)cyclohex-2-enone 83:[145] To a solution of phenylsulfinyl cyclohexenone **87** (456 mg, 2.05 mmol, 1 eq.) in methylene chloride (12 mL) was added *meta*-chloroperoxybenzoic acid (224 mg, 1.3 mmol, 0.63 eq.). The solution was stirred overnight at room temperature. Another portion of *meta*-chloroperoxybenzoic acid (65 mg, 0.38 mmol, 0.18 eq.) was added and the solution was stirred for a further 8 hours at room temperature. Another portion of *meta*-chloroperoxybenzoic acid (65 mg, 0.38 mmol, 0.18 eq.) was added and the solution was stirred overnight at room temperature. A final portion of *meta*-chloroperoxybenzoic acid (65 mg, 0.38 mmol, 0.18 eq.) was added and the solution was stirred for a further 2 hours at which point the reaction was complete by TLC and saturated sodium hydrogen carbonate solution (20 mL) was added. The organic layer was removed and the aqueous layer was extracted with methylene chloride (2 x 30 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow residue which was purified by flash chromatography eluting with 100% petroleum ether -> 60% petroleum ether in ethyl acetate. R_F (60% petroleum ether in ethyl acetate) 0.38. Colourless solid, 287 mg (59%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.23 (t, 1 H, *J* = 4.1 Hz, C*H*), 7.94-8.07 (m, 2 H, Ar*H*), 7.43-7.64 (m, 3 H, Ar*H*),

2.59-2.73 (m, 2 H, COCH_2), 2.36-2.47 (m, 2 H, CHCH_2), 1.93-2.08 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.6 (*C*O), 158.9 (Ar*C*), 140.4 (*C*SO_2Ph), 139.9 (*C*H), 133.5 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 38.6 (CO*C*H_2), 26.5 (CH*C*H_2), 21.7 ($CH_2CH_2CH_2$). **M.P.** 110-112 °C (Lit. 110-112 °C).[145] Matches known data.[145]



85

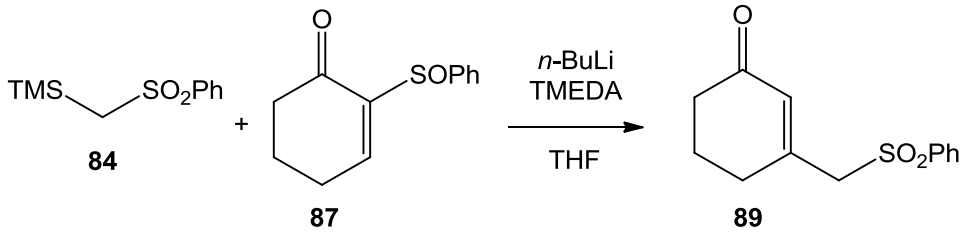
Methylphenylsulfone 85: A suspension of phenylsulfinic acid sodium salt (1.64 g, 10 mmol, 1 eq.) in THF (20 mL) was treated with methyl iodide (1.25 mL, 20 mmol, 2 eq.) and then refluxed for 16 hours. The reaction turns yellow upon heating and is subsequently transferred to a separatory funnel with ethyl acetate (50 mL). The organic phase is washed with half-saturated sodium thiosulfate solution (50 mL) and then with a saturated brine solution (50 mL). The organic layer is dried over Na_2SO_4 and is concentrated *in vacuo* to an off-white solid which was dissolved in hot methanol and allowed to crystallize over-night in a freezer to give colourless micro-needles, 924 mg (59%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91-8.05 (m, 2 H, Ar*H*), 7.52-7.76 (m, 3 H, Ar*H*), 3.07 (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.5 (Ar*C*), 140.6 (Ar*C*H), 133.7 (Ar*C*H), 129.4 (Ar*C*H), 127.3 (Ar*C*H), 44.5 (*C*H_3). **M.P.** 85-86 °C (Lit. 84-86 °C).[193] Matches known data.[194]



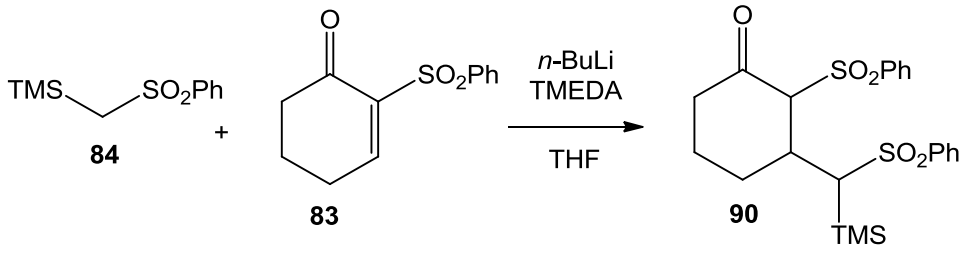
85 **84**

Trimethyl((phenylsulfonyl)methyl)silane 84:[146] In an oven-dried Schlenk-tube purged with nitrogen was added methylphenylsulfone **85** (300 mg, 1.92 mmol, 1 eq.). Anhydrous THF (20 mL) was added and the solution was stirred until dissolution. The solution was then brought to -78 °C and *sec*-butyllithium (1.51 mL, 1.4 M in cyclohexane, 2.11 mmol, 1.1 eq.) was added dropwise. The reaction was stirred at -78 °C for 30 minutes at which point trimethylsilyl chloride (256 µL, 2.02 mmol, 1.05 eq.) was added in one portion. Stirring was continued for 2 hours at -78 °C and then brought to -20 °C over the course of 3 hours. The reaction was then quenched with the addition of saturated ammonium chloride solution (20 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined ethereal layers were washed with saturated brine solution and dried over Na_2SO_4. The reaction was then concentrated *in vacuo* to give a yellow oil which was purified by flash chromatography eluting with 100% petroleum ether -> 70% petroleum ether in ethyl acetate. R_F (70% petroleum ether in ethyl acetate) 0.52. Colourless oil, 187

mg (43%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79-7.86 (m, 2 H, Ar*H*), 7.34-7.54 (m, 3 H, Ar*H*), 2.72 (s, 2 H, CH_2), 0.20 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5 (Ar*C*), 131.7 (Ar*C*H), 127.9 (Ar*C*H), 125.4 (Ar*C*H), 47.2 (*C*H_2), -1.9 (*C*H_3). Matches known data.[148]

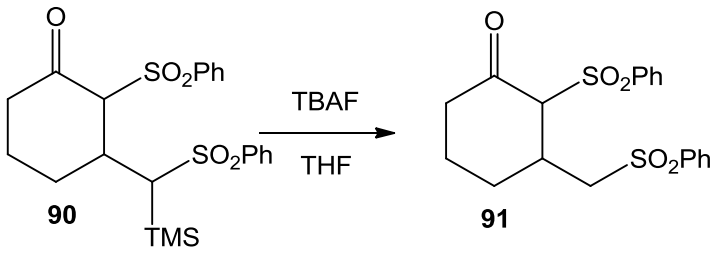


3-((Phenylsulfonyl)methyl)cyclohex-2-enone 89:[148] In an oven-dried Schlenk-tube purged with argon was added trimethylsilyl methylphenylsulfone **84** (228 mg, 1 mmol, 1 eq.) dissolved in anhydrous THF (5 mL) and tetramethylethylenediamine (150 µL, 1 mmol, 1 eq.). The reaction was cooled to -78 ^{o}C and *n*-butyllithium (420 µL, 2.5 M in hexanes, 1.05 mmol, 1.05 eq.) was added. The reaction was stirred at -78 ^{o}C for thirty minutes at which point phenylsulfinyl cyclohexenone **87** (220 mg, 1 mmol, 1 eq.) in anhydrous THF (3 mL) was added in one portion. The reaction was stirred at -78 ^{o}C for 10 minutes to ensure homogeneity and was then allowed to come to room temperature. The reaction was quenched after 30 minutes with saturated ammonium chloride (10 mL) and extracted with methylene chloride (3 x 30 mL) to give an off-white solid which was triturated with cold methanol to give a colourless solid, 205 mg (82%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74-7.84 (m, 2 H, Ar*H*), 7.43-7.66 (m, 3 H, Ar*H*), 5.55 (s, 1 H, C*H*), 3.88 (s, 2 H, C$H_2$$SO_2$Ph), 2.34-2.50 (m, 2 H, COCH_2), 2.15-2.33 (m, 2 H, CCH_2), 1.81-1.99 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5 (Ar*C*), 131.7 (Ar*C*H), 127.9 (Ar*C*H), 125.4 (Ar*C*H), 47.2 (*C*H_2), -1.9 (*C*H_3). ^{13}C NMR (75MHz, $CDCl_3$) δ 198.5 (*C*O), 151.0 (Ar*C*), 137.9 (*C*), 134.4 (Ar*C*H), 132.5 (*C*H), 129.5 (Ar*C*H), 128.3 (Ar*C*H), 64.4 (*C*H_2), 37.0 (CO*C*H_2), 29.7 (*C*CH_2), 22.5 (CH_2C$H_2$$CH_2$). **ESI-MS** $C_{13}H_{14}O_3S$ Calc. (M+Na^+) = 273.05559 found (M+ Na^+) = 273.0554 (-0.7 ppm). Matches known data.[195]



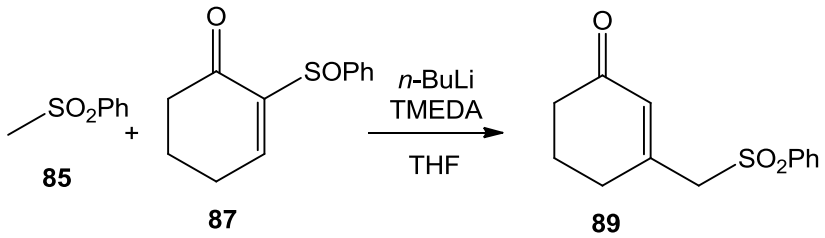
2-(Phenylsulfonyl)-3-((phenylsulfonyl)(trimethylsilyl)methyl)cyclohexanone 90:[148] In an oven-dried Schlenk-tube purged with argon was added trimethylsilyl methylphenylsulfone **84** (228 mg, 1 mmol, 1 eq.) dissolved in anhydrous THF (5 mL) and tetramethylethylenediamine (150 µL, 1 mmol, 1

eq.). The reaction was cooled to -78 °C and *n*-butyllithium (420 µL, 2.5 M in hexanes, 1.05 mmol, 1.05 eq.) was added. The reaction was stirred at -78 °C for thirty minutes at which point phenylsulfonyl cyclohexenone **83** (236 mg, 1 mmol, 1 eq.) in anhydrous THF (3 mL) was added in one portion. The reaction was stirred at -78 °C for 10 minutes to ensure homogeneity and was then allowed to come to room temperature. The reaction was quenched after 30 minutes with saturated ammonium chloride (10 mL) and extracted with methylene chloride (3 x 30 mL) to give a brown oil which was which was purified with flash chromatography eluting with 100% petroleum ether -> 50% petroleum ether in ethyl acetate. $\boldsymbol{R_F}$ (50% petroleum ether in ethyl acetate) 0.81. Colourless oil, 412 mg (91%). (1 : 1 mixture of diastereomers A and B, assigned by ^{1}H-^{1}H COSY) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-8.07 (m, 4H, Ar*H* overlapping A and B), 7.43-7.71 (m, 16 H, Ar*H* overlapping A and B), 4.34-4.46 (m, 1 H, COC*H*SO_2Ph A), 3.89-4.00 (m, 1 H, CHC*H*SO_2Ph A), 3.67-3.81 (m, 2 H, overlapping COC*H*SO_2Ph B + CHC*H*SO_2Ph B), 3.30-3.47 (m, 1 H, CH_2C*H* A), 3.06-3.22 (m, 1 H, CH_2C*H* A), 2.77-2.97 (m, 1 H, CH_2CH B), 2.59-2.76 (m, 1 H CH_2CO A), 2.42-2.59 (m, 1 H CH_2CO A), 2.16-2.42 (m, 4 H, overlapping CH_2CH A + CH_2CO B), 1.62-2.03 (m, 4 H, overlapping CH_2C$H_2$$CH_2$ A and B), 1.43-1.61 (m, 1 H, CH_2CH B), 0.46 (s, 9 H, CH_3 A), 0.29 (s, 9 H, CH_3 B). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.4 (*C*O), 201.3 (*C*O), 142.9 (Ar*C*), 139.9 (Ar*C*), 137.8 (Ar*C*), 137.1 (Ar*C*), 134.1(Ar*C*H), 133.9 (Ar*C*H), 133.4 (Ar*C*H), 133.3 (Ar*C*H), 129.3 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 127.2 (Ar*C*H), 75.9 (CO*C*HSO_2Ph B), 74.4 (CO*C*HSO_2Ph A), 59.8 (CH*C*HSO_2Ph B), 59.7 (CH*C*HSO_2Ph A), 38.0 (CO*C*H_2 B), 37.9 (CO*C*H_2 A), 36.6 (CH_2*C*H B), 36.5 (CH_2*C*H A), 26.8 (*C*H_2CH B), 26.4 (*C*H_2CH A), 21.3 (CH_2*C*$H_2$$CH_2$ B), 21.3 (CH_2*C*$H_2$$CH_2$ B), 1.3 (*C*H_3 A), -0.4 (*C*H_3 B). **ESI-MS** $C_{22}H_{28}O_5S_2Si$ Calc. ($M+H^+$) = 465.1220 found ($M+H^+$) = 465.1218 (-0.53 ppm).



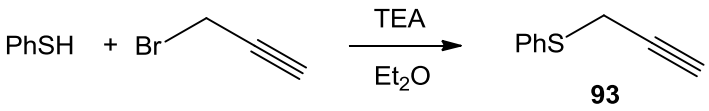
2-(Phenylsulfonyl)-3-((phenylsulfonyl)methyl)cyclohexanone 91: To a solution of 2-(phenylsulfonyl)-3-((phenylsulfonyl)(trimethylsilyl)methyl)cyclohexanone **90** (400 mg, 0.86 mmol, 1 eq.) in THF (5 mL) in an ice-acetone slush bath was added dropwise tetrabutylammonium fluoride (1.3 mL, 1 M in THF, 1.3 mmol, 1.5 eq.). The reaction was stirred at room temperature for 8 hours at room temperature at which point saturated ammonium chloride solution (10 mL) was added at the mixture was transferred to a separatory funnel with ethyl acetate (30 mL), the organic layer was removed and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil which was purified using flash chromatography eluting with 100% petroleum ether -> 50% petroleum ether in ethyl

acetate. R_F (60% petroleum ether in ethyl acetate) 0.58. Off-white solid, 208 mg (53%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72-7.99 (m, 4 H, Ar*H*), 7.44-7.72 (m, 6 H, Ar*H*), 4.09-4.31 (m, 1 H, C*H*SO_2Ph), 3.30-3.49 (m, 1 H, CH_2CHCH_2), 2.87-3.23 (m, 3 H, overlapping CH_2SO_2Ph + CH_2CO), 2.31-2.67 (m, 2 H, overlapping CH_2CH + CH_2CO), 1.87-2.09 (m, 1 H, $CH_2CH_2CH_2$), 1.51-1.81 (m, 2 H, overlapping CH_2CH + $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.2 (*C*O), 138.5 (Ar*C*), 137.7 (Ar*C*), 134.4 (Ar*C*H), 134.2 (Ar*C*H), 129.6 (Ar*C*H), 129.4 (Ar*C*H), 128.6 (Ar*C*H), 128.1 (Ar*C*H), 75.1 (*C*HSO_2Ph), 57.9 (*C*H_2SO_2Ph), 40.4 (*C*H_2CO), 32.1 (CH_2CHCH_2), 26.6 (*C*H_2CH), 21.4 ($CH_2CH_2CH_2$). **ESI-MS** $C_{19}H_{20}O_5S_2$ Calc. ($M+H^+$) = 393.0825 found ($M+H^+$) = 393.0817.



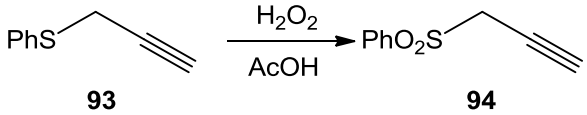
85 87 89

3-((Phenylsulfonyl)methyl)cyclohex-2-enone:[148] In an oven-dried Schlenk-tube purged with argon was added methylphenylsulfone (156 mg, 1 mmol, 1 eq.) dissolved in anhydrous THF (5 mL) and tetramethylethylenediamine (150 µL, 1 mmol, 1 eq.). The reaction was cooled to -78 ^oC and *n*-butyllithium (420 µL, 2.5 M in hexanes, 1.05 mmol, 1.05 eq.) was added. The reaction was stirred at -78 ^oC for thirty minutes at which point phenylsulfinyl cyclohexenone **87** (220 mg, 1 mmol, 1 eq.) in anhydrous THF (3 mL) was added in one portion. The reaction was stirred at -78 ^oC for 10 minutes to ensure homogeneity and was then allowed to come to room temperature. The reaction was quenched after 30 minutes with saturated ammonium chloride (10 mL) and extracted with methylene chloride (3 x 30 mL) to give an oily residue which was purified by flash chromatography eluting with petroleum ether 100% -> 70% petroleum ether in ethyl acetate. R_F (70% petroleum ether in ethyl acetate) 0.60, brown-white solid 128 mg (impure, around 40% yield by crude ^{1}H NMR). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74-7.84 (m, 2 H, Ar*H*), 7.43-7.66 (m, 3 H, Ar*H*), 5.55 (s, 1 H, C*H*), 3.88 (s, 2 H, CH_2SO_2Ph), 2.34-2.50 (m, 2 H, COCH_2), 2.15-2.33 (m, 2 H, CCH_2), 1.81-1.99 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.5 (Ar*C*), 131.7 (Ar*C*H), 127.9 (Ar*C*H), 125.4 (Ar*C*H), 47.2 (CH_2), -1.9 (CH_3). ^{13}C NMR (75MHz, $CDCl_3$) δ 198.5 (*C*O), 151.0 (Ar*C*), 137.9 (*C*), 134.4 (Ar*C*H), 132.5 (*C*H), 129.5 (Ar*C*H), 128.3 (Ar*C*H), 64.4 (CH_2), 37.0 (COCH_2), 29.7 (CCH_2), 22.5 ($CH_2CH_2CH_2$). Matches known data and previous compound.[195]



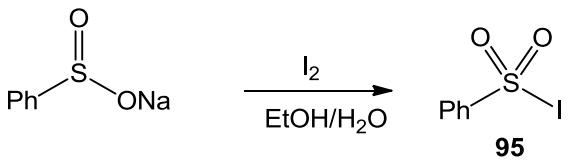
93

Phenyl propargyl sulfide 93:[154] A solution of propargyl bromide (7.44 mL, 80% in toluene, 50 mmol, 1 eq.), triethylamine (13.95 mL, 100 mmol, 2 eq.) in distilled diethyl ether (150 mL) was brought to 0 ^{o}C in temperature. Thiophenol (5.12 mL, 50 mmol, 1 eq.) was added dropwise. The solution was allowed to come to room temperature and stirred for 1.5 hours. The precipitate was separated by filtration and washed with an additional 50 mL of diethyl ether. The combined filtrates were washed with water (100 mL) and dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil which was used without further purification, 7.40 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48-7.57 (m, 2 H, Ar*H*), 7.21-7.44 (m, 3 H, Ar*H*), 3.65 (d, 2 H, J=2.5 Hz, CH_2), 2.30 (t, 1 H, J=2.5 Hz, CC*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.1 (Ar*C*), 130.1 (Ar*C*H), 129.1 (Ar*C*H), 127.0 (Ar*C*H), 79.4 (*C*), 71.4 (*C*H), 23.0 (*C*H_2). Matches known data.[196]



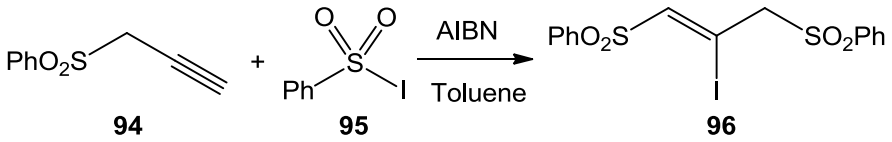
93 **94**

Phenyl propargyl sulfone 94:[155] To a solution of crude phenyl propargyl sulfide **93** (7.40 g, 50 mmol, 1 eq.) and glacial acetic acid (50 mL) was added hydrogen peroxide solution (22.7 mL, 30% w/v solution in water, 200 mmol, 4 eq.). The mixture was heated to 100 ^{o}C for 2 hours, and directly poured into ice-water (200 mL). Solid sodium sulfite (10 g) was added to the suspension which was stirred for an additional 0.5 hours and filtered. The retentate was washed with water (100 mL) and dissolved in methylene chloride (100 mL) and dried over Na_2SO_4 and concentrated *in vacuo* to yield a white solid which was crystallised from chloroform and pentane to give white needles, 6.28 g (70% over 2 steps). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95-8.03 (m, 2 H, Ar*H*), 7.65-7.75 (m, 1 H, Ar*H*), 7.54-7.64 (m, 2 H, Ar*H*), 3.99 (d, 2 H, *J* = 2.7 Hz, CH_2), 2.41 (t, 1 H, *J* = 2.7 Hz, C*H*). **M.P.** 77-78 ^{o}C (Lit. 92-93 ^{o}C).[197] **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.5 (Ar*C*), 134.4 (Ar*C*H), 129.2 (Ar*C*H), 128.8 (Ar*C*H), 76.4 (*C*), 71.7 (*C*H), 48.3 (*C*H_2). Matches known data.[198]



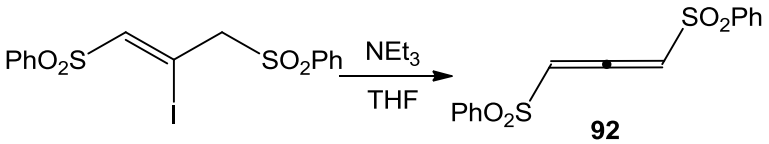
95

Phenylsulfonyl iodide 95:[199] Iodine (8.5 g, 33.5 mmol, 0.67 eq.) was dissolved with heating in absolute ethanol (100 mL). The iodine solution was then added dropwise over the course of an hour to a solution of phenylsulfinic acid sodium salt (8.21 g, 50 mmol, 1 eq.) in distilled water (750 mL). The precipitate was collected by filtration and dissolved in a minimal amount of carbon tetrachloride and dried over Na_2SO_4. The solution was then stored at -20 °C overnight to afford intense orange needles which were collected by filtration and dried under high vacuum with exclusion of light for immediate use, 5.44 g (41%). Unstable and not characterised. Matches physical description.[200]



94 **95** **96**

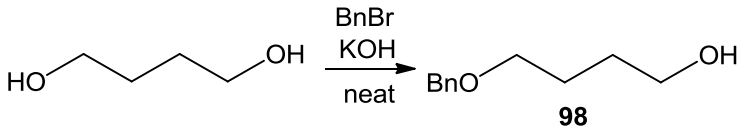
2-Iodo-1,3-bis-phenylsulfonyl-prop-2-ene 96:[156] Phenyl propargyl sulfone **94** (3.51 g, 19.46 mmol, 1 eq.) was dissolved in toluene (15 mL) and a catalytic amount of azobisisobutyronitrile (10 mg, <1% mol) was added. The reaction mixture was brought to 90 °C where a solution of freshly filtered phenyl sulfonyl iodide **95** (5.22 g, 19.46 mmol, 1 eq.) in toluene (10 mL) was added dropwise over an hour. The reaction was then allowed to return to room temperature and was stirred overnight. The solids were collected and washed with a 40% w/v solution of sodium thiosulfate pentahydrate (50 mL) and ice-cold water (50 mL). The resulting red-brown solid was dried under high vacuum and recrystallised from chloroform and pentane to give colourless crystals which brown over time, 5.87 g (67%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99-8.01 (m, 2 H, Ar*H*), 7.89-7.98 (m, 2 H, Ar*H*), 7.51-7.78 (m, 6 H, Ar*H*), 7.21 (s, 1 H, C*H*), 5.22 (s, 2 H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.8 (*C*H), 139.1 (Ar *C*), 138.9 (Ar *C*), 135.5 (Ar *C*H), 135.4 (Ar *C*H), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 98.9 (*C*I), 63.0(*C*H_2). **M.P.** 108-110 °C (Lit. 118-120 °C).[156] Matches known data.[156]



96 **92**

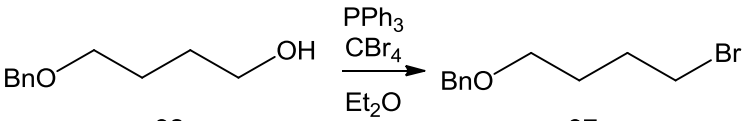
1,3-Bis-phenylsulfonylallene 92:[156] A solution of 2-iodo-1,3-bis-phenylsulfonyl-prop-2-ene **96** (4.48 g, 10 mmol, 1 eq.) in anhydrous tetrahydrofuran (17 mL) was brought to -78 °C under a positive pressure of nitrogen. To this was added dropwise triethylamine (1.46 mL, 10.5 mmol, 1.05 eq.) in anhydrous tetrahydrofuran (6 mL). The reaction was stirred at -78 °C for 30 mins and was quenched with cold 1 M HCl (17 mL). The mixture was allowed to come to room temperature and extracted with ethyl acetate (4 x 30 mL). The organic phases were combined and dried over Na_2SO_4 and

concentrated to a brown oil which was purified by flash chromatography eluting with 100% petroleum ether -> 60% petroleum ether in ethyl acetate. R_F (30% ethyl acetate in petroleum ether) 0.45. Crystallised from carbon tetrachloride to give colourless needles, 1.49 g (47%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89-8.13 (m, 4 H, Ar*H*), 7.52-7.79 (m, 6 H, Ar*H*), 6.75 (s, 2 H, C*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.5 (Allene *C*), 139.9 (Ar *C*), 134.5 (Ar *C*H), 129.6 (Ar *C*H), 128.1 (Ar *C*H), 108.0 (*C*H). **M.P.** 107-108 °C (Lit. 105-106 °C).[156] Matches known data.[156]



98

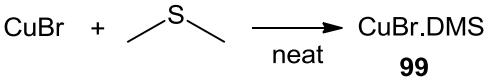
4-(Benzyloxy)butan-1-ol 98:[201] Powdered KOH (8.42g, 150 mmol, 5 eq.) and benzyl bromide (3.57 mL, 30 mmol, 1 eq.) were added sequentially in four equal portions to neat 1,4-butanediol (13.3 mL, 150 mmol, 5 eq.) over the course of an hour. The reaction was then stirred for a further 3 hours at room temperature. Water (20 mL) was then added and the mixture was extracted with diethyl ether (4 x 35 mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated to a yellow liquid which was purified by flash chromatography eluting with 50% ethyl acetate in petroleum ether to give a colourless oil, 4.81 g (66%). R_F (50% ethyl acetate in petroleum ether) 0.52. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19-7.38 (m, 5 H, Ar*H*), 4.48 (s, 2 H, PhCH_2), 3.56 (t, 2 H, J=5.8 Hz, CH_2OH), 3.48 (t, 2 H, J=5.9 Hz, CH_2OBn), 3.06 (br s, 1 H, O*H*), 1.54-1.73 (m, 4 H, CH_2CH_2 overlapping). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.6 (Ar *C*), 128.4 (Ar *C*H), 127.7 (Ar *C*H), 127.7 (Ar *C*H), 73.0 (*C*H_2Ph), 70.4 (*C*H_2OBn), 62.4 (*C*H_2OH), 29.9 (*C*H_2), 26.5 (*C*H_2). Matches known data.[201]



98 **97**

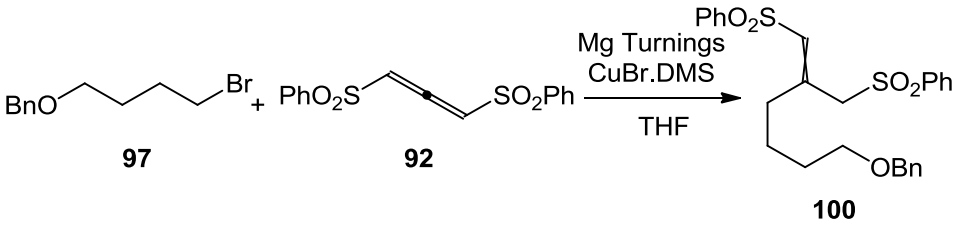
4-(Benzyloxy)-1-bromobutane:[157] Under an atmosphere of N_2, triphenylphosphine (10.38 g, 39.58 mmol, 2 eq.) was dissolved in anhydrous diethyl ether (40 mL) and stirred at -15 °C for 10 minutes. Solid carbon tetrabromide (13.13 g, 39.58 mmol, 2 eq.) was added and stirring was continued for 30 minutes at -15 °C. A solution of 4-(benzyloxy)butan-1-ol **98** (4.811 g, 19.79 mmol, 1 eq.) in anhydrous diethyl ether (40 mL) was added slowly to the reaction. The reaction was then refluxed under a positive pressure of N_2 for 2 hours and stirred at room temperature overnight. To this was added petroleum ether (50 mL) and the resulting suspension was concentrated *in vacuo* to an amorphous residue. The residue was suspended in petroleum ether (100 mL) and filtered, the filtrate was concentrated *in vacuo* and suspended in petroleum ether where the filtration, concentration and

suspension steps were repeated until the triphenylphosphine oxide was removed. The yellow oil obtained was purified by flash chromatography eluting with 2% diethyl ether in petroleum ether to give a colourless oil, 4.81 g (>99%). R_F (2% diethyl ether in petroleum ether) 0.18. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30-7.50 (m, 5 H, Ar*H*), 4.56 (s, 2 H, PhC*H*$_2$), 3.56 (t, 2 H, J=6.2 Hz, C*H*$_2$Br), 3.49 (t, 2 H, J=6.7 Hz, C*H*$_2$OBn), 1.97-2.12 (m, 2 H, C*H*$_2$CH$_2$Br), 1.75-1.88 (m, 2 H, C*H*$_2$CH$_2$OBn). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.6 (Ar *C*), 128.5 (Ar *C*H), 127.7(Ar *C*H, Ar *C*H overlapping), 73.0 (*C*H$_2$Ph), 69.3 (*C*H$_2$OBn), 33.8 (*C*H$_2$Br), 29.8 (*C*H$_2$), 28.4 (*C*H$_2$). Matches known data.[157]



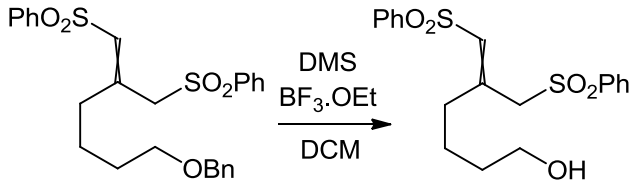
Copper(I)bromide dimethylsulfide complex 99:[202] An oven-dried Schlenk-tube purged with N_2 was charged with freshly ground copper(I)bromide (7.17 g, 50 mmol, 1 eq.). To this was added dimethylsulfide (9 mL, 122 mmol, 2.44 eq.) which had been stored overnight with molecular sieves (3 Å). The resulting red mixture was stirred vigorously for 10 minutes and the solution was transferred to a dry flask under a nitrogen atmosphere with a syringe. An additional portion of dimethylsulfide (5.36 mL, 73 mmol, 1.47 eq.) was then added to the residue remaining in the Schlenk-tube and was stirred for 10 minutes and the solutions were combined. To this was added *n*-hexane (37 mL) and the precipitate was collected by filtration and dried under N_2 until a colourless solid was obtained (1 hour), 9.10 g (89%). This was stored under Ar and crystallised freshly when needed. **M.P.** 130-133 ^{o}C (Lit. 132 ^{o}C). Matches known data.[202]

Crystallisation procedure for CuBr.DMS 99: In an oven-dried flask containing the crude copper complex (9 g) purged with N_2 was added was added dimethylsulfide (30 mL) which had been stored overnight with molecular sieves (4 Å). The solution was stirred until homogenous and *n*-pentane (15 mL) was added. The solution was then placed in an ice-bath until crystallisation was complete. The colourless crystals were separated by filtration and dried under N_2 and used immediately.



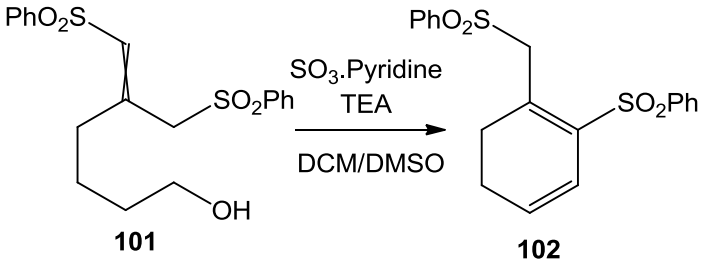
***(1E/Z)*-(2-(4-(Benzyloxy)butyl)prop-1-ene-1,3-bis-phenylsulfone 100:** In an oven-dried flask with an Ar atmosphere freshly ground magnesium turnings (267 mg, 11 mmol, 2.2 eq.) were suspended in anhydrous tetrahydrofuran (12 mL). To this was added dibromoethane (70 µL, 1 mmol, 0.2 eq.) and

the reaction was stirred for 1 hour at room temperature. The solvent was removed using a syringe and the turnings were washed with a further 10 mL of anhydrous tetrahydrofuran. The now activated magnesium turnings were suspended in anhydrous tetrahydrofuran (25 mL). Under a positive pressure of Ar a small portion of 4-(benzyloxy)-1-bromobutane **97** and a single flake of iodine was added and the reaction was gently heated until the colour of the iodine had disappeared. The reaction flask was then placed in an ice-bath and the remaining 4-(benzyloxy)-1-bromobutane **97** (1.91 mL, 10 mmol, 2 eq.) was added slowly. The reaction was stirred until the majority of the magnesium had dissolved where upon an additional portion of magnesium turnings (122 mg, 5 mmol, 1 eq.) was added and the reaction stirred for 1 hour at room temperature to complete the Grignard synthesis. An oven-dried Schlenk-tube purged with Ar was charged with freshly crystallised CuBr.DMS **99** (2.06 g, 10 mmol, 2 eq.). The complex was suspended in anhydrous tetrahydrofuran (40 mL) and brought to -78 ^{o}C. To this was added the Grignard reagent *via* a cannula under a positive pressure of Ar. An orange/red solution was obtained which was stirred at -78 ^{o}C for 20 minutes completing the synthesis of the organocuprate. In an oven-dried flask purged with Ar, 1,3-bis-phenylsulfonylallene **92** (1.6 g, 5 mmol, 1 eq.) was dissolved in anhydrous tetrahydrofuran (25 mL) and brought to -78 ^{o}C. To this was added the organocuprate via a cannula over the course of 1 hour. The reaction was stirred at -78 ^{o}C for 45 minutes and quenched with 30 mL of a 50:50 solution of NH_4Cl (20% w/v) and ammonium hydroxide. The reaction was stirred at room temperature until the phases were completely separated and the aqueous layer had turned dark blue. The aqueous layer was washed with ethyl acetate (3 x 25 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to yield a brown oil which was purified using flash chromatography eluting with 30% ethyl acetate in petroleum ether to give a colourless gum, 1.34 g (55%). $\boldsymbol{R_F}$ (30% ethyl acetate in petroleum ether) 0.59. Ratio of isomers 0.9 : 1 (*Z* : *E*) *E*- isomer assigned by NOE between signal @ 6.03 and 3.79 ppm (4.7% enhancement), *Z*-isomer differentiated by ^{1}H-^{1}H COSY . **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96-8.06 (m, 2 H, Ar*H*), 7.87-7.95 (m, 2 H, Ar*H*), 7.75-7.84 (m, 2 H, Ar*H*), 7.45-7.75 (m, 12 H, Ar*H*), 7.21-7.42 (m, 12 H, Ar*H*), 6.24 (s, 1 H, C*H* *Z*-isomer), 6.03 (s, 1 H, C*H* *E*-isomer), 4.75 (s, 2 H, C$H_2$$SO_2$Ph *Z*-isomer), 4.48 (s, 2 H, CH_2Ph *E*-isomer), 4.46 (s, 2 H, CH_2Ph *Z*-isomer), 3.79 (s, 2 H, C$H_2$$SO_2$Ph *E*-isomer), 3.41-3.49 (m, 4H, CH_2OBn), 2.63 (t, 2 H, J=7.9 Hz, CH_2 vinyl *E*-isomer), 2.53 (t, 2 H, J=6.3 Hz, CH_2 vinyl *Z*-isomer), 1.42-1.77 (m, 8 H, CH_2CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.6 (*C*), 144.6 (*C*), 141.2 (Ar *C*), 140.6 (Ar *C*), 139.3 (Ar *C*), 138.5 (Ar *C*), 138.4 (Ar *C*), 137.4 (Ar *C*), 134.2 (Ar *C*H), 134.1(Ar *C*H), 134.1 (*C*H *E*-isomer), 133.7 (Ar *C*H), 131.0 (*C*H *Z*-isomer), 129.4 (Ar *C*H), 129.3 (Ar *C*H), 129.3 (Ar *C*H), 128.4 (Ar *C*H), 128.4 (Ar *C*H), 127.7 (Ar *C*H), 127.7 (Ar *C*H), 127.6 (Ar *C*H), 127.6 (Ar *C*H), 127.4 (Ar *C*H), 73.0 (*C*H_2Ph), 69.6 (*C*H_2OBn), 69.5 (*C*H_2OBn), 62.2 (*C*$H_2$$SO_2$Ph *E*-isomer), 55.7 (*C*$H_2$$SO_2$Ph *Z*-isomer), 37.8 (*C*H_2 vinyl *Z*-isomer), 30.8 (*C*H_2 vinyl *E*-isomer), 29.4 (*C*H_2), 28.9 (*C*H_2), 24.8 (*C*H_2), 24.0 (*C*H_2). **ESI-MS** $C_{26}H_{28}O_5S_2$ Calc. ($M+H^+$) = 485.1451 found ($M+H^+$) = 485.1451 (0.00 ppm).



100 **101**

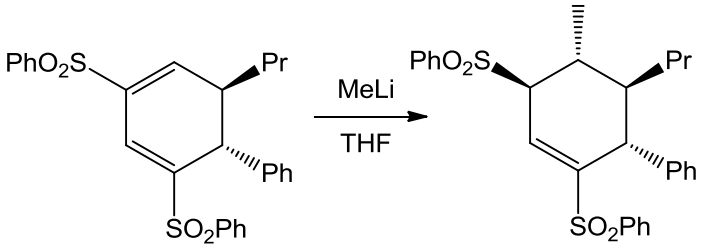
6-(Phenylsulfonyl)-5-((phenylsulfonyl)methyl)hex-5-en-1-ol 101: A mixture of the *E*/*Z* isomers of (2-(4-(benzyloxy)butyl)prop-1-ene-1,3-bis-phenylsulfone **100** (1.217 g, 2.51 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (50 mL) under a positive pressure of N_2. To this was added dimethylsulfide (5.53 mL, 75.3 mmol, 30 eq.) and boron trifluoride diethyl etherate (3.41 mL, 27.6 mmol, 11 eq.) and the reaction was stirred at 35 ^{o}C for 2 hours. The reaction was then transferred to a separatory funnel and quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with methylene chloride (4 x 25 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil which was purified using flash chromatography eluting with 75% ethyl acetate in petroleum ether to yield a cloudy oil, 357 mg (36%). $\boldsymbol{R_F}$ (75% ethyl acetate in petroleum ether) 0.34. Ratio of isomers 1 : 0.8 (*Z* : *E*) *E/Z* isomers assigned with reference to **100**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94-8.06 (m, 2 H, Ar*H*), 7.84-7.93 (m, 2 H, Ar*H*), 7.73-7.80 (m, 2H Ar*H*), 7.49-7.68 (m, 12 H, Ar*H*), 7.26-7.39 (m, 2 H, Ar *H*), 6.31 (s, 1 H, C*H* *Z*-isomer), 6.07 (s, 1 H, C*H* *E*-isomer), 4.78 (s, 2 H, C$H_2$$SO_2$Ph *Z*-isomer), 3.90 (s, 2 H, CH_2Ph *E*-isomer), 3.50-3.60 (m, 4 H, CH_2OH), 2.79 (br s, 2 H, O*H*), 2.61 (t, 2 H, J=7.3 Hz, CH_2 vinyl *E*-isomer), 2.49 (t, 2 H, J=6.2 Hz, vinyl *Z*-isomer), 1.50 (br s, 8 H, CH_2CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.0 (*C*), 144.7 (*C*), 140.9 (Ar *C*), 140.5 (Ar *C*), 139.2 (Ar *C*), 137.2 (Ar *C*), 134.2 (Ar *C*H), 134.0 (Ar *C*H), 133.8 (*C*H *E*-isomer), 130.9 (*C*H *Z*-isomer), 129.5 (Ar *C*H), 129.4 (Ar *C*H), 129.3 (Ar *C*H), 129.3 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 127.9 (Ar *C*H), 127.5 (Ar *C*H), 127.2 (Ar *C*H), 61.9 (*C*$H_2$$SO_2$Ph *E*-isomer), 61.6 (*C*H_2OH), 61.5 (*C*H_2OH), 55.7 (*C*$H_2$$SO_2$Ph *Z*-isomer), 37.6 (*C*H_2 vinyl *Z*-isomer), 32.0 (*C*H_2), 31.6 (*C*H_2), 30.6 (*C*H_2 vinyl *E*-isomer), 24.2 (*C*H_2), 23.4 (*C*H_2). **ESI-MS** $C_{19}H_{22}O_5S_2$ Calc. ($M+H^+$) = 395.0981 found ($M+H^+$) = 395.099 (2.14 ppm).



101 **102**

(((2-(Phenylsulfonyl)cyclohexa-1,3-dien-1-yl)methyl)sulfonyl)benzene 102: To an-oven dried 3 neck flask fitted with a tapped glass swan-neck, and two septa was added a mixture of *E*- and *Z*- isomers of 6-(phenylsulfonyl)-5-((phenylsulfonyl)methyl)hex-5-en-1-ol **100** (357 mg, 0.905 mmol, 1 eq.). The flask was then purged with argon and anhydrous methylene chloride (3 mL) was added followed by

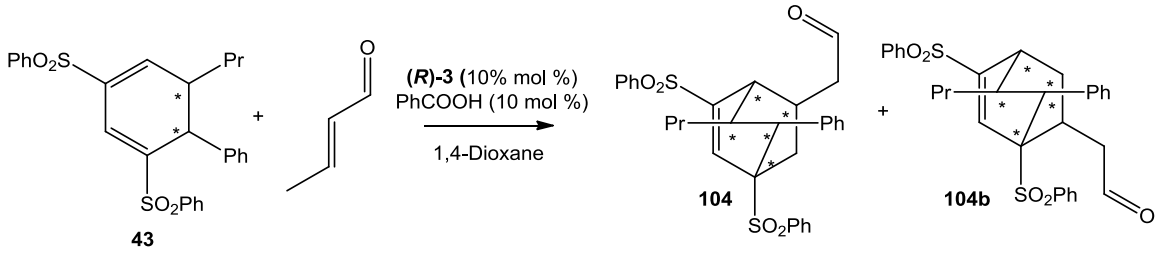
anhydrous dimethylsulfoxide (1.5 mL). The reaction was then placed in an ice-bath and triethylamine (631 µL, 4.525 mmol, 5 eq.) was added followed by solid sulfur trioxide pyridine complex (576 mg, 3.620 mmol, 4 eq.). The mixture was allowed to come to room temperature and then stirred for 2 hours. The reaction was quenched with water (10 mL) and transferred to a separatory funnel where it was extracted with ethyl acetate (4 x 20 mL). The organics were dried over Na_2SO_4 and concentrated *in vacuo* to a brown oil which was purified by column chromatography eluting with 30% diethyl ether in pentane -> 50% diethyl ether in pentane to give a white solid, 123 mg (36%). $\boldsymbol{R_F}$ (50% diethyl ether in pentane) 0.45. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97-8.06 (m, 2 H, Ar*H*), 7.86-7.94 (m, 2 H, Ar*H*), 7.64-7.73 (m, 1 H, Ar*H*), 7.55-7.63 (m, 3 H, Ar*H*), 7.46-7.55 (m, 2 H, Ar*H*), 5.94-6.06 (m, 2 H, overlapping C*H* + C*H*), 4.90 (s, 2 H, C$H_2$$SO_2$Ph), 2.64 (t, 2 H, J=9.0 Hz, CH_2C), 2.12-2.27 (m, 2 H, $CH_2CH_2CH_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.0 (CH_2C), 139.4 (Ar *C*), 137.8 (Ar *C*), 134.1 (Ar *C*H), 133.9 (*C*SO_2Ph), 133.6 (Ar *C*H), 131.0 (C*C*H), 129.3 (Ar *C*H), 239.2 (Ar *C*H), 128.4 (Ar *C*H), 127.8 (Ar *C*H), 121.3 (CH_2CH), 58.7 (C*C*H_2), 29.9 (CH*C*H_2), 22.0 ($CH_2CH_2CH_2$). **M.P.** 83-85 ^{o}C. **ESI-MS** $C_{19}H_{18}O_4S_2$ Calc. ($M+H^+$) = 375.0719 found ($M+H^+$) = 375.0716 (-0.8).



43 **103**

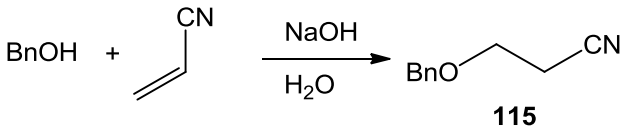
(1*R*,2*R*,3*R*,4*S*)-3-Methyl-4,6-bis(phenylsulfonyl)-2-propyl-1,2,3,4-tetrahydro-1,1'-biphenyl 103: In a dried Schlenk tube (1*R*,2*R*)-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl **43** (96 mg, 0.2 mmol, 1 eq.) was dissolved in anhydrous THF (2 mL). This was stirred in a dry-ice and isopropanol slush bath at -78 ^{o}C. Methyllithium (138 µL, 0.24 mmol, 1.2 eq. 1.6 M in diethyl ether) was added dropwise over 5 minutes. The reaction was stirred for a further 20 minutes in the slush bath at which point the reaction was quenched with sat. NH_4Cl (5 mL). The reaction was extracted with methylene chloride (3 x 20 mL). The organic layer was concentrated under reduced pressure to yield a clear oil. The oil was then triturated with ice-cold methanol twice to yield the product as a white solid, (mixture of diastereoisomers 4 : 1) 96 mg (97%). The white solid was then dissolved in a minimum amount of hot chloroform and an equal amount of methanol was added. Crystals were grown from the chloroform/methanol solution by slow evaporation. These crystals were then recrystallised from methylene chloride to yield 51 mg (52%) of 103 as white needles (mixture of diastereoisomers 12 : 1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d,2 H, *J* = 7.5 Hz, Ar*H*), 7.73-7.76 (m, 1 H, Ar*H*), 7.64-7.67 (m, 2 H, Ar*H*), 7.57 (br s, 1 H, C*H*C(SO_2Ph)), 7.42-7.45 (m, 1 H, Ar*H*), 7.38 (d, 2 H *J* = 7.5 Hz, Ar*H*), 7.24-7.27 (m, 2 H, Ar*H*), 7.03-7.06 (m, 1 H, Ar*H*), 6.96-7.00 (m, 2H, Ar*H*), 6.77 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 3.75 (m,

1 H, C*H*SO_2Ph), 3.54 (m, 1 H, C*H*Ph), 1.85 (m, 1 H, C*H*CH3), 1.69 (m, 1 H, C*H*CH_2), 1.07 (d, 3 H, J = 6.9 Hz, CHC*H*$_3$), 0.93 (m, 3 H, overlapping C*H*$_2$C*H*$_2$), 0.76 (m, 1 H, CH_2C*H*$_2$$CH_3$), 0.64 (t, 3 H, *J* = 7.0 Hz, CH_2C*H*$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.8, 139.6 , 138.6, 136.2, 134.4, 133.1, 132.8 (*C*HC(SO_2Ph)), 129.4, 128.7, 128.5, 128.2, 127.8, 127.0, 69.4 (*C*HSO_2Ph), 48.1 (*C*HCH_2), 44.3 (*C*HPh), 32.8 (*C*HCH_2), 31.9 (*C*HCH_3), 20.2 (CH*C*H$_3$), 18.0 (*C*H$_2$$CH_3$), 14.1 ($CH_2$C*H*$_3$). **ESI-MS** $C_{28}H_{30}O_4S_2$ Calc. (M+Na^+) = 517.1478 found (M+Na^+) = 517.1490 (2.32). **[α]$_{589}$**^{21} -18.5^o (c = 0.2).



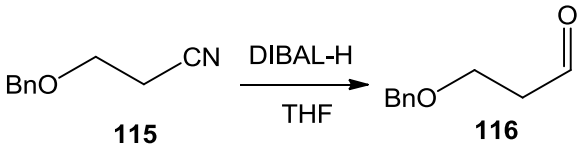
Cascade reaction 104 + 104b: One-pot procedure as follows; A sample vial of **(*R*)-3** (20 mg, 0.06 mmol, 0.3 eq) dissolved in chloroform (0.5 mL) was treated with 1,3-bis-phenylsulfonyl-4-phenyl-butadiene **39** (82 mg, 0.2 mmol, 1 eq.) followed by direct addition of *n*-valeraldehyde (42 µL, 0.4 mmol, 2 eq.). The reaction was left to stir at room temperature for 24 hours. The reaction was then diluted with an addition of chloroform (1.5 mL). The cycloaddition step was begun with the sequential addition of benzoic acid (7 mg, 0.06 mmol, 0.3 eq.) and crotonaldehyde (33 µL, 0.4 mmol, 2 eq.). The reaction was stirred for a further 24 hours at which point all volatiles were removed *in vacuo*. The residue was purified by flash chromatography eluting with 100% petroleum ether -> 60% petroleum ether in ethyl acetate. R_F (60% petroleum ether in 40% ethyl acetate) 0.72. Colourless semi-solid, 83 mg (75%).

Step-wise procedure as follows;[134b] A sample vial of **(*R*)-3** (6.5 mg, 0.02 mmol, 0.1 eq.) dissolved in 1,4-dioxane (1 mL) was treated with (1*R*,2*R*)-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl **43** (96 mg, 0.2 mmol, 1 eq.) and benzoic acid (2.4 mg, 0.02 mmol, 0.1 eq.) followed by direct addition of crotonaldehyde (33 µL, 0.4 mmol, 2 eq.). The reaction was stirred for 24 hours at which point all volatiles were removed *in vacuo*. The residue was purified by flash chromatography eluting with 100% petroleum ether -> 60% petroleum ether in ethyl acetate. R_F (60% petroleum ether in ethyl acetate) 0.72. Colourless semi-solid, 84 mg (76%). Mixture of products 3.11 : 1 : 1.50 by **^{1}H NMR** (500 MHz, $CDCl_3$). NMR complicated by multiple products, ratios taken from obvious C*H*O @ 9.78 (s, 1 H), 9.67 (s, 0.33 H), 9.63 (s, 0.48 H), ratios compared with obvious C*H*$_3$ @ 0.67 (t, 3 H, *J* = 4.3 Hz), 0.59 (t, 0.91 H, 4.3 Hz), 0.53 (t, 1.37 H, *J* = 4.3 Hz). **ESI-MS** $C_{31}H_{29}O_5S_2$ Product 1: Calc. (M+H^+) = 549.1764 found (M+H^+) = 549.1764 (1.44 ppm), Product 2: Calc. (M+H^+) = 549.1764 found (M+H^+) = 549.1768 (0.74 ppm), Product 3: Calc. (M+H^+) = 549.1764 found (M+H^+) = 549.1768 (0.71 ppm).



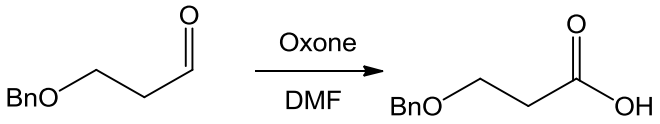
115

3-(Benzyloxy)propionitrile 115:[168] Caution, acrylonitrile is extremely toxic! Neat acrylonitrile (3.6 mL, 55 mmol, 1.1 eq.) was dropped onto a stirred solution of benzyl alcohol (5.18 mL, 50 mmol, 1 eq.) in 40% (w/v) sodium hydroxide (5 mL). The reaction was stirred overnight and was then neutralized with 1 M HCl (10 mL). The reaction was transferred to separatory funnel with methylene chloride (20 mL). The phases were separated and the aqueous phase was washed with methylene chloride (2 x 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to a colourless oil which was essentially pure, 8.04 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24-7.45 (m, 5 H, Ar*H*), 4.46-4.57 (s, 2 H, PhCH_2O), 3.49-3.64 (m, 2 H, OCH_2CH$_2$), 2.43-2.59 (m, 2 H, CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.6 (Ar*C*), 128.6 (Ar*C*H), 128.0 (Ar*C*H), 127.8 (Ar*C*H), 118.4 (*C*N), 73.0 (Ph*C*H$_2$), 64.7 (O*C*H$_2$CH$_2$), 18.8 (CH$_2$*C*H$_2$). Matches known data.[168]



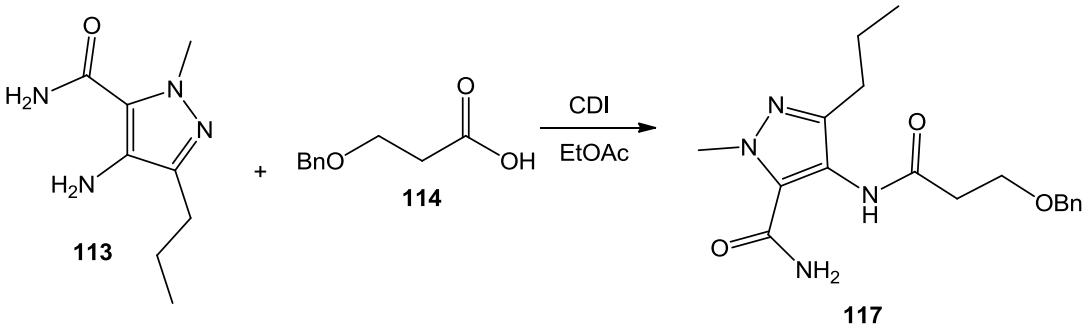
115 **116**

3-(Benzyloxy)propanal 116: A solution of 3-(benzyloxy)propionitrile **115** (3.21 g, 20 mmol) in anhydrous THF (40 mL) under an atmosphere of nitrogen was brought to 0 ^{o}C. To this was added cautiously DIBAL-H (18.67 ml, 1.5 M in Toluene, 28 mmol, 1.4 eq.) and the solution was stirred for 1.5 hours at 0 ^{o}C at which point is was allowed to return to room temperature and stirring was continued for 0.5 hours. The solution was again brought to 0 ^{o}C and diluted with diethyl ether (30 mL). Distilled water (1.12 mL) was added slowly to destroy the residual hydride and was followed immediately with the addition of 15% (w/v) sodium hydroxide (1.12 mL) and a further portion of water (2.8 mL). The mixture was stirred vigorously for 15 minutes at room temperature. Anhydrous $MgSO_4$ (2-5 g) was then added and stirring was continued for another 15 minutes to dehydrate the solution. The suspension was passed through a pad of Celite and the filter cake was washed with diethyl ether (100 mL). The filtrate was reduced *in vacuo* to give a colourless oil which was essentially pure, 3.07 g (94%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.73 (t, 1 H, *J* = 1.9 Hz, C*H*O), 7.25-7.45(m, 5 H, Ar*H*), 4.53 (s, 2 H, PhCH_2), 3.76-3.85 (td, 2 H, *J* = 6.1 Hz, *J* = 1.9 Hz, OCH_2CH$_2$), 2.62-2.72 (m, 2 H, CH$_2$CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.1 (*C*HO), 138.0 (Ar*C*), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 73.2 (Ph*C*H$_2$), 63.9 (O*C*H$_2$CH$_2$), 43.8 (CH$_2$*C*H$_2$). Matches known data.[203]



116 **114**

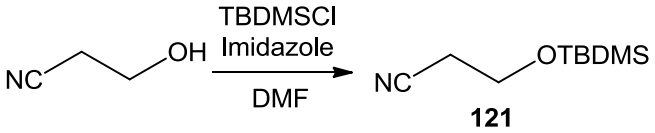
3-(Benzyloxy)propionic acid 114: A solution of 3-(benzyloxy)propanal **116** (1 g, 6.1 mmol) and Oxone monopersulfate (928 mg, 6.1 mmol, 1 eq.) in dimethyl formamide (472 µL, 6.1 mmol, 1 eq.) was stirred at room temperature for 2 hours. Distilled water (20 mL) was added and the solution was extracted with methylene chloride (3 x 40 mL). The combined organics were dried over Na_2SO_4 and the solvent removed *in vacuo* to give the crude acid. The acid was purified by the addition of 10% (w/v) sodium hydroxide (25 mL) to the residue and washing the aqueous solution with methylene chloride (2 x 50 mL). The aqueous solution is then carefully acidified (pH = 4) with concentrated HCl and when cool, extracted with diethyl ether (1 x 100 mL). The ethereal layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give the purified acid as a colourless oil, 550 mg (50%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (br s, 1 H, COO*H*), 7.22-7.44 (m, 5 H, Ar*H*), 4.58 (s, 2 H, PhCH_2), 3.79 (t, 2 H, *J* = 6.3 Hz), 2.69 (t, 2 H, *J* = 6.3 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.3 (*C*OOH), 137.8 (Ar*C*), 128.5 (Ar*C*H), 127.8 (overlapping Ar*C*H + Ar*C*H), 73.1 (Ph*C*H_2), 65.3 (O*C*H_2CH_2), 34.9 (CH_2*C*H_2). Matches known data.[204]



113 **114** **117**

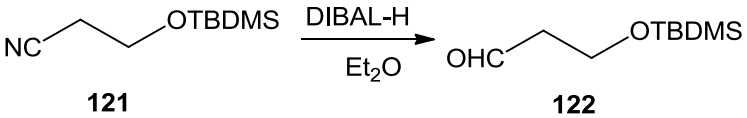
4-(3-(Benzyloxy)propanamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide 117:[162] To a 50 mL 3-neck round-bottomed flask fitted with a tapped glass swan-neck, condenser with a glass stopper and a septum was added 3-(benzyloxy)propionic acid (423 mg, 2.35 mmol, 1 eq.). The flask was then purged with nitrogen and anhydrous EtOAc (10 mL) was added followed by stirring until the solution was homogeneous. The stopper was then replaced with a nitrogen bubbler and over a stream of nitrogen carbonyl diimidazole (160 mg, 2.47 mmol, 1.05 eq.), was added in one portion. The suspension was heated to 55 ^{o}C in temperature for 30 minutes causing complete dissolution. The reaction was then refluxed under a positive pressure of nitrogen for 2 hours and allowed to cool to room temperature. Over a stream of nitrogen was added 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **113** (428 mg, 5 mmol, 1 eq.). The brown solution was left to stir at room temperature for 3 days. The solution was then concentrated *in vacuo* to an off-white solid which was purified by

flash chromatography eluting with 0% pet. ether -> 100% ethyl acetate. R_F (80% ethyl acetate in pet. ether) 0.38. White powder, 623 mg (77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (s, 1 H, NH_2), 7.22-7.44 (m, 6 H, overlapping NH_2 + ArH), 5.67 (br s, 1 H, NHCO), 4.56 (s, 2 H, PhCH_2), 3.99 (s, 3 H, NCH_3), 3.83 (t, 2 H, J = 5.6 Hz, OCH_2), 2.67 (t, 2 H, J = 5.6 Hz, CH_2NHCO), 2.40 (t, 2 H, J = 7.4 Hz, CCH_2), 1.56 (apparent hextet, 2 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 0.87 (t, 3 H, J = 7.3 Hz, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.1 (NH*C*O), 161.4 (NH_2CO), 147.2 (CCH_2), 137.0 (Ph*C*), 132.4 ($CCONH_2$), 128.7 (Ph*C*H), 128.3 (Ph*C*H), 128.0 (Ph*C*H), 115.3 (CONH*C*), 73.7 (Ph*C*H_2), 66.2 (O*C*H_2), 39.3 (N*C*H_3), 37.1 (CH_2NHCO), 27.5 (CCH_2), 22.1 ($CH_2CH_2CH_3$), 13.9 (CH_2CH_3). **IR** (liquid, DCM) 3466 (prim. amide), 3303 (sec. amide), 3054 (methyl), 2932 (methylene), 2884 (aromatic), 1679 (amide), 1601 (amide), 1543 (methyl), 1470 (methylene), 1421 (methylene), 1090 (amide), 838 (aromatic), 782 (aromatic) cm^{-1}. **M.P.** 128-130 ^{o}C. **ESI-MS** $C_{18}H_{26}N_4O_3$ Calc. ($M+H^+$) = 345.1921 found ($M+H^+$) = 345.1926 (1.44 ppm).



121

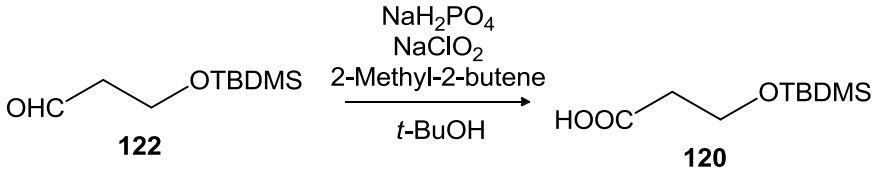
3-((*tert*-Butyldimethylsilyl)oxy)propiononitrile 121:[170] Anhydrous DMF (30 mL) was added to hydroxypropionitrile (1.37 mL,20 mmol, 1 eq.) under a nitrogen atmosphere. The resulting solution was stirred until homogeneous. *tert*-Butyl dimethylsilylchloride (4.52 g, 30 mmol, 1.5 eq.) was added in one portion under a stream of nitrogen and stirred until dissolution had occurred. Crystalline imidazole (2.72 g, 40 mmol, 2 eq.) was then added to the reaction mixture which was subsequently stirred overnight at room temperature. The reaction was diluted with water (60 mL) and extracted with diethyl ether (4 x 50 mL). The combined ethereal layers were washed with saturated brine solution and dried over Na_2SO_4. Concentration *in vacuo* yielded a free flowing yellow oil which was used without further purification, crude yield 5.21 g, 141% (residual TBDMSCl).



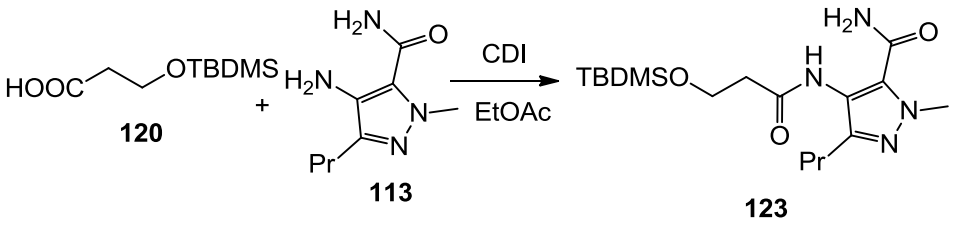
121 **122**

3-((*tert*-Butyldimethylsilyl)oxy)propanal 122:[170] Crude 3-((*tert*-butyldimethylsilyl)oxy)propiononitrile **122** (20 mmol) was transferred to a 3-neck, 250 mL round-bottomed flask, fitted with a tapped glass swan-neck, thermometer and septum. The flask was purged with nitrogen and anhydrous diethyl ether (100 mL) was added. The mixture was stirred until homogeneous and the temperature was subsequently reduced to 0 ^{o}C. DIBAL-H (20 mL, 1.5 M in toluene, 30 mmol, 1.5 eq.) was added dropwise to the solution. The reaction temperature was not

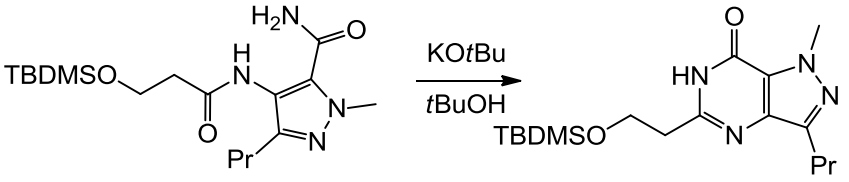
allowed rise above 2 °C during the addition of DIBAL-H. When the addition was finished the reaction was stirred for a further 30 mins at 0 °C and gradually allowed to warm to room temperature over the course of two hours. The solution was left to stir overnight at room temperature and then cooled to 0 °C. MeOH (4 mL) was added cautiously followed by 1 M HCl (30 mL). The reaction was then allowed to come to room temperature and 1 M HCl (40 mL) added. The solution was allowed to stir until two layers formed. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined ethereal solutions were dried over Na_2SO_4. Concentration *in vacuo* yielded a free flowing red oil which was used without further purification, 4.88 g, 140% (residual TBDMSCl).



3-((*tert*-Butyldimethylsilyl)oxy)propanoic acid 120:[172] Crude 3-((*tert*-butyldimethylsilyl)oxy)propanal **122** (20 mmol) was stirred with *tert*-butanol (85 mL) and 2-methyl-2-butene (10 mL, 94.40 mmol, 4.72eq.) until dissolution. To this was added *via* a pressure-equalising dropping funnel, a solution of sodium chlorite (3.62 g, technical grade 80% w/w, 40 mmol, 2 eq.) and sodium hydrogen phosphate monobasic (12 g, 100 mmol, 5 eq.) in 100 mL of distilled water. The rate of dropping was adjusted to prevent significant exotherm, and once completed the reaction was stirred for an additional hour at room temperature during which time the red solution became bright yellow. A saturated brine solution (200 mL) was then added to the reaction mixture which was then allowed to settle into a biphasic system. The aqueous layer was extracted with methylene chloride (3 x 100 mL). The combined organic layers were washed with a brine solution and dried over Na_2SO_4. Concentration *in vacuo* gave a yellow free-flowing oil. The crude mixture was purified with flash chromatography using a gradient of 0%->5% diethyl ether in petroleum ether until elution of the residual TBDMSCl, followed by 5%->50% diethyl ether in petroleum ether to elute the product which was visualized using $KMnO_4$ solution. $\boldsymbol{R_F}$ (30% diethyl ether in petroleum ether) 0.62. Clear-colourless, free flowing oil, 2.78g (68% over 3-steps from 3-hydroxypropionitrile). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.69 (br s, 1 H, COO*H*), 3.82 (t, 2 H, *J*=9 Hz, OCH_2), 2.48 (t, 2 H, *J*=9 Hz, CH_2COOH), 0.79 (s, 9H, C(CH_3)$_3$), -0.03 (s, 6H, Si(CH_3)$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.0 (*C*OOH), 57.8 (SiO*C*H$_2$), 36.8 (*C*H$_2$COOH), 24.8 (SiC(*C*H$_3$)$_3$), 17.2 (Si*C*(CH$_3$)$_3$), -6.5(Si(*C*H$_3$)$_2$). Matches known data.[172]

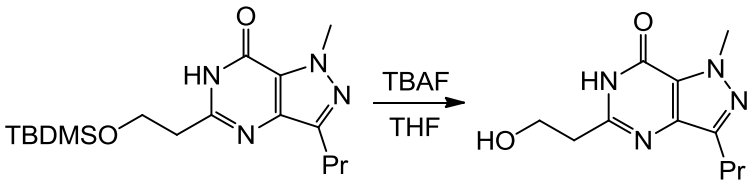


4-(3-((*tert*-Butyldimethylsilyl)oxy)propanamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide 123:[162] To a 50 mL 3-neck round-bottomed flask fitted with a tapped glass swan-neck, condenser with a glass stopper and a septum was added 3-((*tert*-butyldimethylsilyl)oxy)propanoic acid **120** (1.022 g, 5 mmol, 1 eq.). The flask was then purged with nitrogen and anhydrous EtOAc (20 mL) was added followed by stirring until the solution was homogeneous. The stopper was then replaced with a nitrogen bubbler and over a stream of nitrogen, carbonyl diimidazole (851 mg, 5.25 mmol, 1.05 eq.), was added in one portion. The suspension was heated to 55 ^{o}C in temperature for 30 minutes causing complete dissolution. The reaction was then refluxed under a positive pressure of nitrogen for 2 hours and allowed to cool to room temperature. Over a stream of nitrogen, was added 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **113** (911 mg, 5 mmol, 1 eq.). The brown solution was left to stir at room temperature for 3 days. The solution was then concentrated *in vacuo* to an off-white solid which was purified by flash chromatography eluting with 0% petroleum ether -> 100% ethyl acetate. $\boldsymbol{R_F}$ (80% ethyl acetate in petroleum ether) 0.41. White powder, 1.143 g (62%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 (s, 1 H, CON*H*), 7.48 (br s, 1 H, CON*H*H), 6.22 (s, 1 H, CONH*H*), 4.02-3.91 (m, 5 H, overlapping NCH_3 + OCH_2), 2.58 (t, 2 H, J=6 Hz, CH_2CONH), 2.44 (t, 2 H, J=6 Hz, CCH_2), 1.59 (q, 2 H, J= 7.5 Hz, $CH_2CH_2CH_3$), 0.95-0.80 (m, 12 H, overlapping $CH_2CH_2CH_3$ + $C(CH_3)_3$), 0.88 (s, 6H, $Si(CH_3)_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (*C*ONH), 161.8 (*C*ONH_2), 147.1 (*C*CH_2), 132.9 (*C*$CONH_2$), 115.1 (CONH*C*), 59.5 ($SiOCH_2$), 39.3 (*C*H_2CONH), 39.2 (NCH_3), 27.5 (CCH_2), 25.9 ($SiC(CH_3)_3$), 22.2 ($CH_2CH_2CH_3$), 18.3 ($SiC(CH_3)_3$), 13.9 (CH_2CH_3), -5.4 ($Si(CH_3)_2$). **IR** (liquid, DCM) 3447 (prim. amide), 3304(sec. amide), 2883 (methyl), 2858 (methylene), 2685 (aromatic), 2411 (aromatic), 1679 (prim. amide), 1600 (sec. amide), 1548, 1470 (methylene), 1421 (methyl), 1089 (silyl ether), 1059, 896 (methylene), 811 (silyl ether), 430 (aromatic) cm^{-1}. **M.P.** 176-178 ^{o}C. **ESI-MS** $C_{17}H_{32}N_4O_3Si$ Calc. ($M+H^+$) = 368.2244 found ($M+H^+$) = 368.2242 (-0.44 ppm).



123 **124**

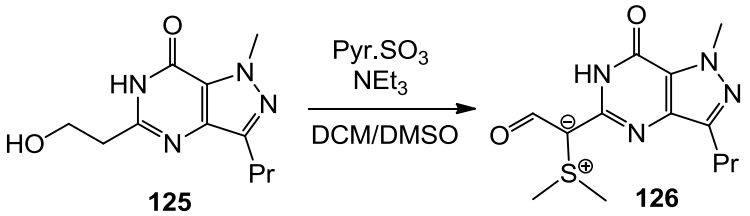
5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one 124:[162] To a 50 mL 3-neck round-bottomed flask fitted with a tapped glass swan-neck, condenser with a stopper and a septum purged with nitrogen was added 4-(3-((*tert*-butyldimethylsilyl)oxy) propanamido)-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **123** (737mg, 2 mmol, 1 eq.). Anhydrous *tert*-butanol (2 mL) was then added *via* syringe and the suspension was stirred until dissolution. The stopper was replaced with a nitrogen bubbler and over a stream of nitrogen potassium *tert*-butolate (247 mg, 2.2 mmol, 1.1 eq.), was added. The reaction was then refluxed under a positive pressure of nitrogen for 8 hours and was allowed to cool to room temperature. The reaction was quenched with the addition of 5 mL of distilled water. The resulting solution was then completely dissolved in methanol and absorbed onto Celite *in vacuo* and purified directly with flash chromatography 0% ethyl acetate -> 50% petroleum ether in ethyl acetate. R_F (50% ethyl acetate in pet. ether) 0.45. White powder, 437 mg (62%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.13 (s, 1 H, CON*H*), 4.14 (s, 3 H, NCH_3), 3.96 (t, 2 H, J=5.8 Hz, SiOCH_2), 2.85 (t, 2 H, J=5.8 Hz, SiOCH$_2$CH_2), 2.75 (t, 2 H, J=7.4 Hz, CCH_2CH$_2$CH$_3$), 1.70 (q, 2 H, J=7.5 Hz, CCH$_2$CH_2CH$_3$), 0.89 (t, 3 H, J=7.4 Hz, CCH$_2$CH$_2$CH_3), 0.79 (s, 9 H, C(CH_3)$_3$), -0.04 (s, 6 H, Si(CH_3)$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.1 (*C*ONH), 152.3 (*C*(N)(NH)), 145.7 (*C*CH$_2$), 138.5 (CO*C*(N)(C)), 124.5 ((N)*C*(C)), 60.9 (SiO*C*H$_2$), 38.1 (N*C*H$_3$), 37.8 (SiOCH$_2$*C*H$_2$), 27.6 (*C*H$_2$CH$_2$CH$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 22.3 (CH$_2$*C*H$_2$CH$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 13.9 (CH$_2$*C*H$_3$), -5.6 (Si(*C*H$_3$)$_2$). **ESI-MS** $C_{17}H_{30}N_4O_2Si$ Calc. (M+H$^+$) = 351.2211 found (M+H$^+$) = 351.2223 (3.45 ppm).



124 **125**

5-(2-Hydroxyethyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one 125: To a nitrogen flushed flask was added 5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one **124** (437 mg, 1.25 mmol, 1 eq.). This was dissolved in 6 mL of anhydrous tetrahydrofuran. The solution was stirred for 10 minutes in an acetone/ice slush bath before tetrabutylammonium fluoride (1.88 mL, 1 M in THF, 1.875 mmol, 1.5 eq.) was added dropwise over 5 minutes. The reaction was left to stir for 1 hour at room temperature and was then concentrated *in*

vacuo to a colourless oil. The oily residue was dissolved in ethyl acetate (20 mL) and washed sequentially with 100 mL portions of saturated sodium bicarbonate solution and saturated brine solution. The organic phase was then dried over Na_2SO_4. Concentration *in vacuo* yielded a white powder which was purified by flash chromatography 100% ethyl acetate. $\boldsymbol{R_F}$ (100% ethyl acetate) 0.41. White powder, 191 mg (81%). **^{1}H NMR** (300 MHz, DMSO) δ 12.00 (s, 1 H, CON*H*), 4.12 (s, 3 H, NCH_3), 3.83 (t, 2 H, *J* = 6.5 Hz, HOCH_2), 2.78 (t, 2 H, *J* = 6.3 Hz, HOCH$_2$CH_2), 2.71 (t, 2 H, *J* = 7.4 Hz, CCH_2CH$_2$CH$_3$), 1.72 (apparent hextet, 2 H, *J* = 7.4 Hz, CCH$_2$CH_2CH$_3$), 0.93 (t, 3 H, *J* = 7.3 Hz, CCH$_2$CH$_2$CH_3). **^{13}C NMR** (75 MHz, DMSO) δ 154.2 (*C*ONH), 152.7 (*C*(N)(NH)), 144.0 (*C*CH$_2$), 137.8 (CO*C*(N)(C)), 124.2 ((N)*C*(C)), 58.9 (HO*C*H$_2$), 37.6 (N*C*H$_3$), 37.5 (HOCH$_2$*C*H$_2$), 27.1 (*C*H$_2$CH$_2$CH$_3$), 21.6 (CH$_2$*C*H$_2$CH$_3$), 13.7 (CH$_2$*C*H$_3$). **M.P.** 76-77 ^{o}C. **ESI-MS** $C_{11}H_{16}N_4O_2$ Calc. (M+H$^+$) = 238.1373 found (M+H$^+$) = 238.1366 (-3.14ppm).



2-(1-Methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-2-dimethylsulfanylide-acetaldehyde 126: To an oven-dried 2-neck flask purged with argon was added the alcohol **125** (140 mg, 0.6 mmol, 1eq.) followed by anhydrous methylene chloride (2 mL) and anhydrous dimethylsulfoxide (1 mL). The solution was stirred and heated gently until dissolution occurred. The reaction was placed in an ice-water bath and triethylamine (418 µL, 3 mmol, 5 eq.) was added in one portion and stirred until homogenous. Sulfur trioxide pyridine complex (382 mg, 2.4 mmol, 4 eq.) was added causing the reaction to become a bright yellow colour. The reaction was allowed to come to room-temperature and stirred for 3 hours during which time the reaction colour faded to light brown. Distilled water (10 mL) was then added and the reaction was extracted with ethyl acetate (20 mL). The aqueous layer was extracted further with ethyl acetate (4 x 10 mL) and the combined organics were dried over Na_2SO_4. The solvent was removed *in vacuo* and the residual DMSO was removed under high vacuum. The pale yellow residue was purified using flash chromatography eluting with 100% chloroform -> 95% chloroform in 5% methanol. $\boldsymbol{R_F}$ (95% chloroform in 5% methanol) 0.75. The collected product was dissolved in methylene chloride (10 mL) and ethyl acetate (10 mL), petroleum ether was added until precipitation began and was then stored overnight at -20 ^{o}C. The precipitate was collect by vacuum filtration to yield a highly static white solid, 159 mg (90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 12.93 (br s, 1 H, N*H*CO), 8.77 (s, 1 H, C*H*O), 4.19 (s, 3 H, NCH_3), 3.26 (s, 6 H, S$^-$(CH_3)$_2$), 2.82 (t, 2 H, *J* = 7.4 Hz, CCH_2), 1.80 (apparent hextet, 2 H, *J* = 7.4 Hz, CH$_2$CH_2CH$_3$), 0.98 (t, 3 H, *J* = 7.4 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.1 (*C*HO), 154.0 (*C*ONH), 149.4

(*C*(N)(NH)), 144.2 (*C*CH_2), 138.0 (CO*C*(N)(C)), 123.8 ((N)*C*(C)), 87.1 (C^+) , 37.1 (N*C*H_3), 27.8 (*C*$H_2CH_2CH_3$), 27.8 ($S^-(CH_3)_2$), 22.6 ($CH_2CH_2CH_3$), 14.0 (CH_2CH_3). **ESI-MS** $C_{13}H_{18}N_4O_2Si$ Calc. (M)* = 294.115 found (M)* = 294.1137 (-4.68 ppm).

Chapter 3

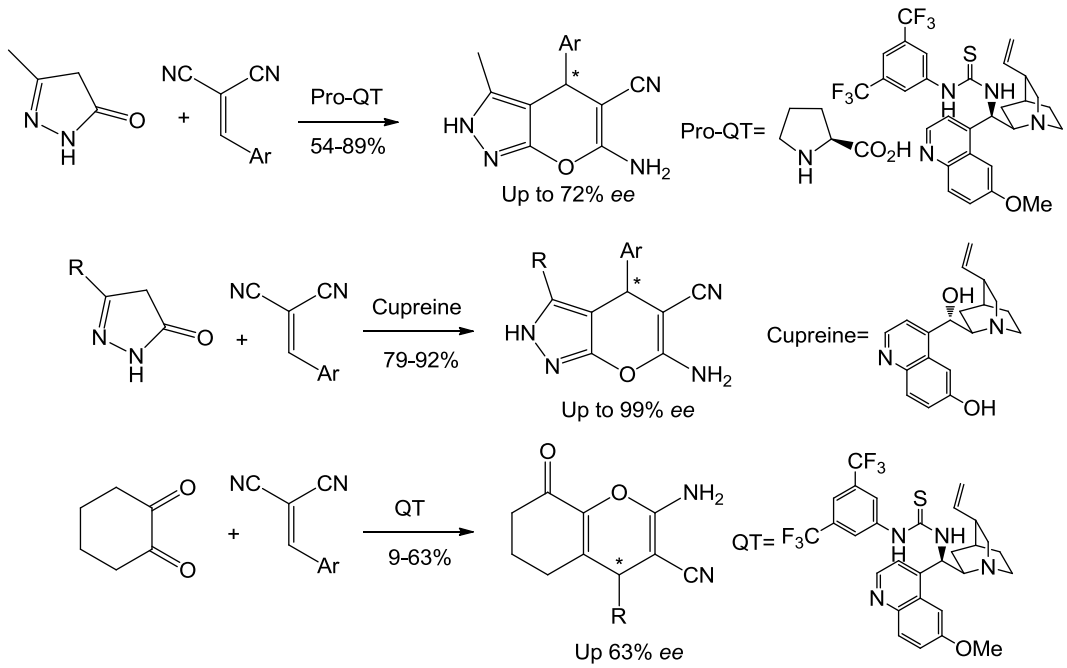
3.1 Introduction

Having developed a highly selective organocatalytic asymmetric 1,6-conjugate addition to sulfonyl dienes we wanted to further develop the concept in two directions. The first being to change the electron-withdrawing groups to nitriles and the second to further extend the charge de-localization in an attempt to develop 1,8-conjugate addition methodology.

3.1.1 Nitriles as electron withdrawing groups in organocatalytic reactions

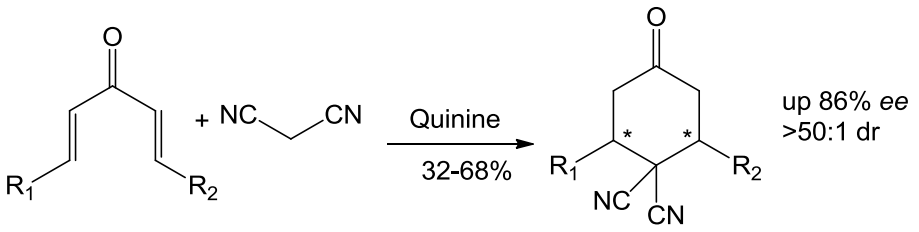
The relative versatility of nitriles in chemical synthesis has made them a desirable functionality to incorporate into chiral frameworks. Nitriles can be hydrolysed under either acid or basic conditions to generate a primary amide or a carboxylic acid.[205] They can also be reduced under hydrogenation conditions to an amine, which can be isolated or itself hydrolysed in the Stephen aldehyde synthesis.[206] The carbon molecule in a nitrile group is also inherently electrophilic allowing for nucleophilic attack of a variety of nucleophiles.[207] The nitrile can also undergo a carbocyanation reaction with an alkyne, mediated by an organometallic catalyst,[208] or can be simply eliminated as the cyanide ion such as occurs in the benzoin condensation.

The asymmetric organocatalytic Michael addition to unsaturated nitriles has been rather under exploited. To the best of our knowledge the organocatalysed addition of aldehydes to unsaturated nitriles has not been reported. Similarly the addition of ketones has been limited to a single report by Kang *et al.* who employed the enamine generated from α-substituted cyclic ketones in an addition to acrylonitrile catalysed by a thiourea functionalized Corey diamine.[209] There is comparably more literature regarding organocatalytic additions to the dual activated benzylidenemalononitrile. Recently Tao published the NHC catalysed tandem Michael addition and cyclisation of benzoin to arylidenemalononitriles with good results (up to 94:6 d.r., yields up to 88%).[210] There are three reports which employ partial protonation thiourea-based organocatalysts, of which two utilise pyrazolin-5-ones as the Michael donor (**Scheme 87**).[211] Elnagdi *et al.* recently added an enamine ester generated from L-proline and ethyl propiolate to benzylidenemalononitrile, although the group did not report an enantiomeric excess.[212]



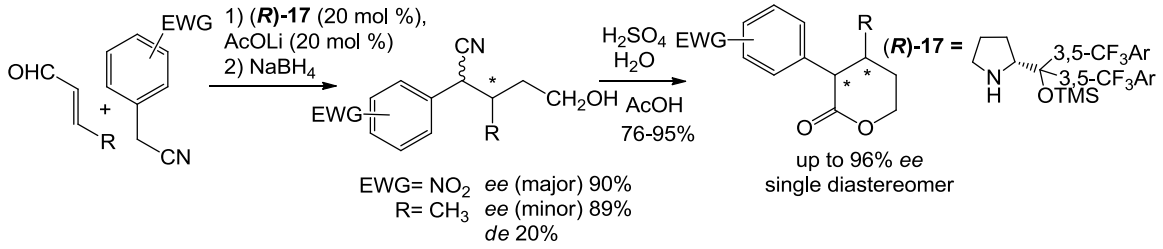
Scheme 87: Reported additions to benzylidenemalononitrile[211]

Nitriles have been more commonly used as α-substituents on pro-nucleophiles in Michael additions.[213] The suitability of nitriles for this purpose stems from two characteristics, firstly their extremely high polar-inductive effect which will stabilize an α-carbanion and secondly the rather small steric hindrance associated with the nitrile functionality (A value = 0.2 kcal/mol).[214] This is epitomised in the much reported addition of malononitrile, a bis-nitrile substituted methylene, to various Michael acceptors using non-covalent catalysis.[215] A particularly illustrative report of the Michael-donor ability of malononitrile was published by Lattanzi and co-workers and shows double addition of the malononitrile to 1,5-pentadienones in good yields and *ee* (**Scheme 88**).[216]



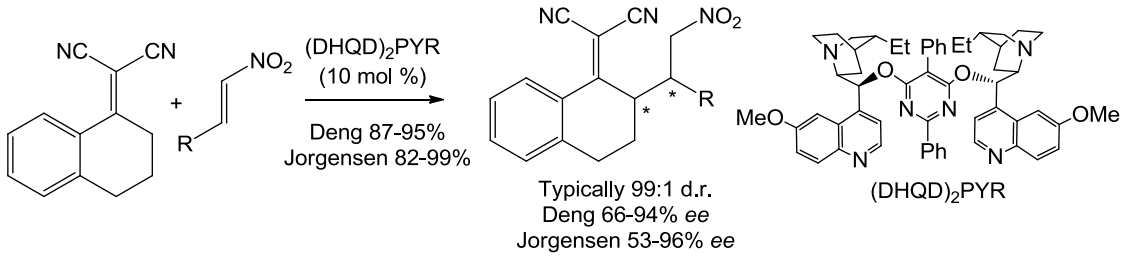
Scheme 88: Double Michael addition of malononitrile[216]

Ruano and co-workers also exploited the use of the nitrile group on pro-nucleophiles in their report on the addition of electron deficient aryl-acetonitriles to iminium ion activated enals.[217] Though the addition proceeded in high enantioselectivity, the diastereoselectivity was less impressive. Conversion of the addition product to a lactone, under acidic conditions, proceeded with epimerization to the most stable diastereomer (**Scheme 89**).



Scheme 89: Functional group transformation led to epimerisation of one of the diastereomers[217]

The mesomeric effect that nitriles have on conjugated pro-nucleophiles has also been exploited. Deng and Jorgensen simultaneously reported the first direct vinylogous Michael addition of vinyl malononitriles to α,β-unsaturated nitro compounds using dihydroquinidine based catalysts (**Scheme 90**).[218] Deng later expanded this work to include the diarylprolinol catalysed addition of vinyl malononitriles to enal Michael acceptors.[219]



Scheme 90: Direct vinylogous Michael addition to α,β-unsaturated nitro compounds[218]

3.1.2 Extended Michael acceptors and 1,8-conjugate addition

In the previous chapter we discussed addition to extended Michael acceptors. Our research led us to develop a method of regioselectively preforming 1,6-conjugate addition reactions using a strategy we described as cooperative charge de-localization.[108a] The vinylogous version of this reaction is known as the 1,8-conjugate addition (**Fig. 31**).

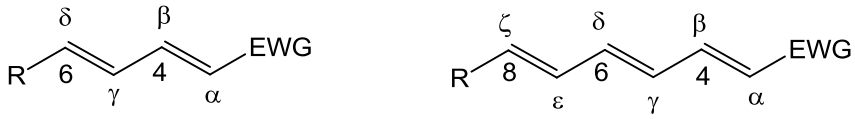
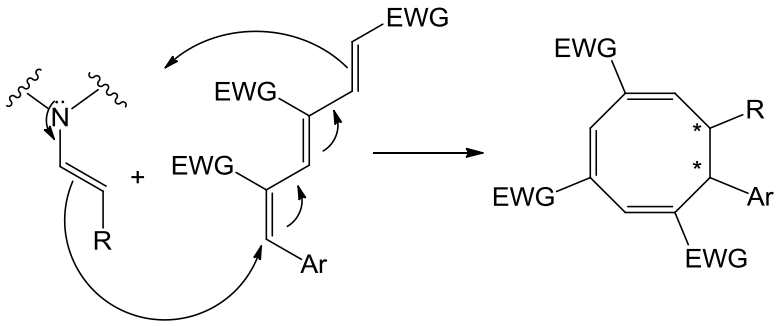


Figure 31: Extended Michael acceptors

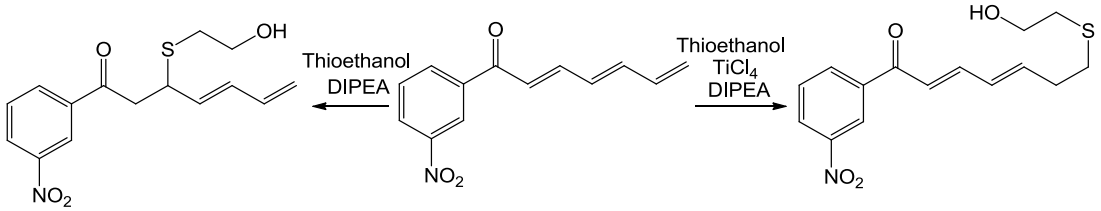
Using strategically placed electron-withdrawing groups along the π-systems we would hope to emulate our previous work in selectively activating the 8-position over the 6- and 4- positions. With this enhanced activation of the 8-position, we would hope to be able to regioselectively add nucleophilic enamines that were generated from aldehydic pro-nucleophiles (**Scheme 91**).



Scheme 91: Proposed 1,8-conjugate addition to tris- activated trienes

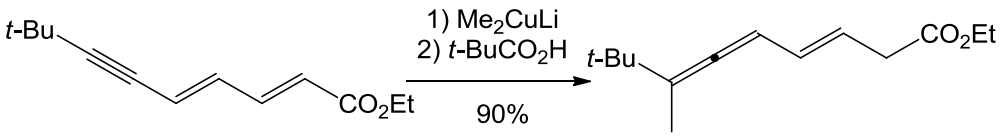
This 1,8-conjugate addition of an enamine and expected 8-*exo-trig* cyclisation would give access to valuable functionalized chiral cyclooctatrienes.

Although there has been no report of an organocatalytic 1,8-conjugate addition to date, the metal-catalysed 1,8-conjugate addition has been reported for a variety of substrates. Lawton has reported the $TiCl_4$ promoted 1,8-conjugate addition of mercaptoethanol to trienones catalysed with DIPEA.[220] Without the titanium additive the reaction is regioselective for the 4- position (**Scheme 92**).



Scheme 92: Regioselectivity of addition determined by $TiCl_4$ additive[220]

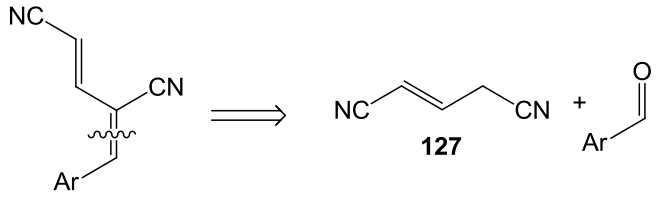
Other examples of 1,8-conjugate addition can be found using organocuprates and extended π-systems. As early as 1963 Andersen reported that the use of catalytic copper salts gave a regioselective 1,8-conjugate addition of *sec*-butyl Grignard to dienoates.[221] A similar report by Krause and co-workers demonstrated that the organocuprates derived from organolithium compounds also undergo conjugate addition to extended acceptors.[222] In this case the dienynoate was treated with Me_2CuLi resulting in a regioselective 1,8-conjugate addition (**Scheme 93**). The group extended the π-system further and observed that the addition always took place at the alkyne. The apparent selectivity of these reagents is attributed to the formation of an initial cuprate π-complex with the alkene adjacent to the acceptor group, this complex is translated through the conjugated system *via* an allenic σ-copper(III) intermediate which produces the addition product by reductive elimination of RCu.[223]



Scheme 93: 1,8-Conjugate addition an organocuprate to a dienynoate[223]

3.2 Synthesis of 1,3-bis-cyano-4-phenyl-butadiene

The target family of bis-cyano butadienes, **Scheme 94**, are very similar in structure to the bis-phenylsulfonyl dienes synthesised earlier (**See Section 2.2.1.2**). They would contain an unsaturated nitrile conjugated to another unsaturated nitrile substituted with an aromatic group. This family of compounds would be known as the bis-cyano dienes (**Scheme 94**).

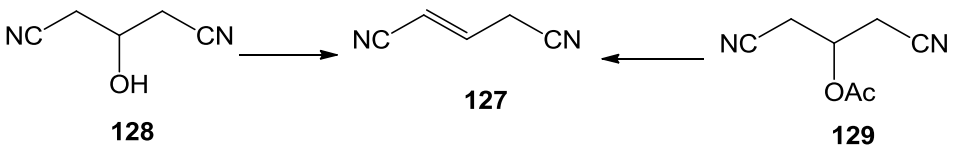


Scheme 94: Retrosynthesis of bis-cyano aryl-butadienes

Similarly to the synthesis of the bis-sulfonyl dienes our proposed synthetic route to the bis-cyano dienes would employ a Knoevenagel condensation of 1,3-bis-cyano-prop-2-ene **127** with aryl aldehydes as the final step.

3.2.1 Synthesis of 1,3-bis-cyano-prop-2-ene by dehydration of 3-hydroxyglutarononitrile

The bis-cyano propene **127** has been reported in the literature and was synthesised from both the pyrolysis of 3-acetoxyglutarononitrile and the dehydration of 3-hydroxylutarononitrile (**Scheme 95**).[224]

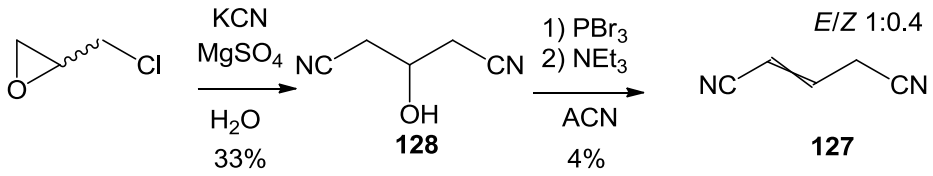


Scheme 95: Reported synthesis of 1,3-bis-cyano-prop-2-ene **127**

The pyrolysis of 3-acetoxy glutaronitrile **129** required the use of a pyrolytic apparatus and furnace,[225] while the dehydration of 3-hydroglutarononitrile **128** was reportedly dangerous on a large scale.[224] For this reason we chose to perform an elimination reaction to generate the olefin.

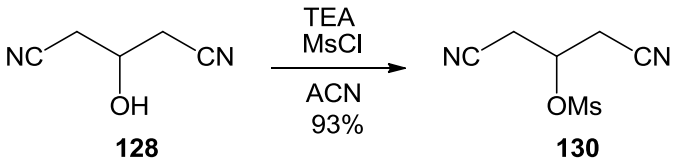
The synthesis of 3-hydroxyglutarononitrile **128** was performed in 33% yield from the detailed procedure of Panella.[226] We achieved a much lower yield than the literature due to the difficulty in

extracting the 3-hydroxyglutarononitrile, which is appreciably soluble in water. In Pandella's methodology a liquid-liquid extractor was used, which was unavailable to us. We instead used a simple biphasic extraction which proved much less efficient. Phosphorus tribromide was used to substitute the alcohol for a bromide. Subsequent elimination of HBr, at low temperature, gave the bis-cyano propene **127** (**Scheme 96**). This elimination reaction was high yielding, 71%, when performed on a one mmol scale but was much less successful on a 50 mmol scale, 4%.



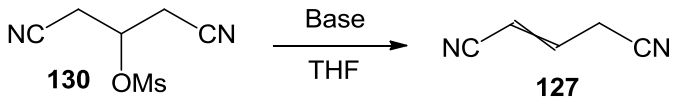
Scheme 96: Generation of 1,3-bis-cyano-prop-2-ene **127** by elimination reaction

In order to screen optimal conditions for the elimination reaction we wanted to isolate the intermediate with an intact leaving group. To this end 3-mesyloxy glutaronitrile **130** was synthesised in high yield, at low temperature, using one equivalent triethylamine (**Scheme 97**). The mesylate **130** was stable at room temperature and could be produced in large quantities.



Scheme 97: Mesylation of 3-hydroxyglutarononitrile **128**

We next experimented with a variety of conditions for the elimination step (**Table 20**).



Entry	Base	Time (h)	Temperature	Yield of **127** [a]	*E*/*Z* Ratio[b]
1	NEt_3	1	0 °C	64%	1 : 0.4
2	NEt_3	1	-20 °C	67%	1 : 0.4
3	NEt_3	1	-40 °C	73%	1 : 0.5
4	NEt_3	1	RT	50%	1 : 0.4
5	NaOAc	48	RT	R.S.M.	-
6	NaOAc	16	40 °C	60%	1 : 0.3

Reactions were performed on a 1 mmol scale using 1.1 equivalent of base to 1 equivalent of mesylate in 5 mL of tetrahydrofuran at specified temperature and period of time, [a] isolated yield, [b] determined by ^{1}H NMR spectroscopy

Table 20: Conditions for mesylate elimination

We found that lowering the temperature gave the best yields albeit with reduced preference for the *E*-isomer (**Entries 1-4**). Using the weak base sodium acetate, at 40 °C, gave better selectivity in a slightly reduced yield (**Entry 6**). However when we scaled the reaction up to 20 mmol from 1 mmol, the yields dropped to a meagre 13% with triethylamine and 30% with sodium acetate.

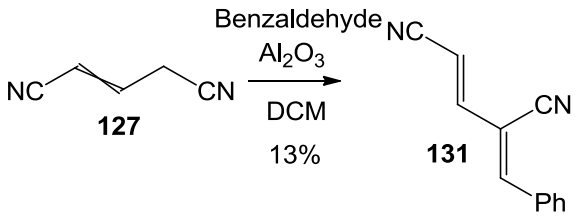
During the larger sale reactions the mixture blackened quickly upon addition of the base forming an amorphous tar suggesting that the product **127** was polymerising. It was found that the bis-cyano propene **127** turned black and hardened on prolonged exposure to temperatures over 4 °C.

The geometry of the product **127** was identified through ^{1}H NMR spectroscopy of the distinct doublet of triplets apparent for both alkene protons at 6.62 ppm and 5.80 ppm for the *E*-isomer with a large *J* value of 16.3 Hz, and at 6.49 ppm and 5.86 ppm for the *Z*-isomer with a smaller *J* value of 10.8 Hz.

We combined the small quantities of the bis-cyano propene **127** we had synthesised and attempted the Knoevenagel condensation using the previously developed aluminium oxide methodology (**See Section 2.2.1.9**).

This resulted in a disappointing 13% yield of the bis-cyano diene **131**, which could be isolated as a single isomer. The majority of the material was a mixture of products that co-eluted during chromatographic purification, and whose structure could not be elucidated. The geometry of the 1,2-alkene in bis-cyano diene **131** was evident through ^{1}H NMR analysis of the doublets apparent at

7.14 ppm and 5.91 ppm indicating a *trans*- relationship through the large *J* value of 16 Hz. The 3,4-alkene could not be immediately assigned as only a singlet for the σ-H was observed at 7.32 ppm. A later synthesis (**See Section 3.2.5**) from starting material with known geometry allowed confirmation of the *EZ* geometry. The presence of two nitrile groups was confirmed by ^{13}C NMR spectroscopy by the observed chemical shifts at 116.9 ppm and 114.6 ppm and an IR band at 2218 cm^{-1}.

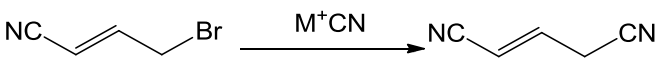


Scheme 98: Synthesis of 1,3-bis-cyano-4-phenyl-butadiene

Although the bis-cyano diene **131** had been synthesised we were keen to change our approach. Firstly, the large scale yields of the bis-cyano propene **127** were low and as such prevented access to sufficient quantities of starting material for the Knoevenagel condensation. Secondly, the use of two stoichiometric equivalents of potassium cyanide in the preliminary synthesis of 3-hydroxyglutarononitrile was unappealing due to the fatally toxic nature of metal cyanides and the inefficiency of product extraction resulting in a low yield (33%). We hoped to either lower or remove the quantity of potassium cyanide employed in the synthesis.

3.2.2 Attempted synthesis of 1,3-bis-cyano-prop-2-ene by the Kolbe nitrile methodology

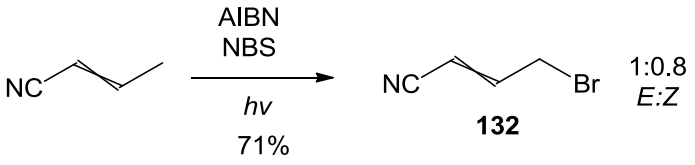
The Kolbe nitrile synthesis is an S_N2 type reaction for the preparation of alkyl nitriles from the corresponding alkyl halide and metal cyanide. We had employed a similar methodology in the synthesis of the bis-phenylsulfonyl propene **39** (**See Section 2.2.1.2**). The drawback to this kind of reaction is that the ambident nucleophilic nature of the cyanide ion can lead to the isonitrile side product.[227]



Scheme 99: Proposed Kolbe nitrile synthesis

In order to complete the Kolbe nitrile synthesis we would first have to synthesise the alkyl halide **132**. The literature suggested a similar strategy to that we used with the phenylsulfones. This entailed bromination of the starting allyl cyanide followed by elimination of the secondary bromide

to give the *E*-isomer selectively.[228] Our collaborators at the University of Geneva had previously attempted this synthetic route. They had found it very unsatisfactory: requiring a difficult purification process and giving poor selectivity. We instead opted to use radical bromination of crotononitrile in a slight modification of the procedure of Padwa (**Scheme 100**).[229]



Scheme 100: Synthesis of alkyl halide **132**

With the alkyl halide **132** synthesised we tried a number of different of conditions and sources of cyanide to promote the nitrile addition, as summarised in **Table 21**. Unfortunately all of these reactions resulted in the formation of a black polymer.

Entry	Metal Cyanide	Cyanide Equivalents	Conditions	Result
1	NaCN	1	DMSO	Polymer
2	KCN	1	DMSO	Polymer
3	Cu(I)CN	1	DMSO	Polymer
4	Cu(I)CN	2	Neat 60 ^{o}C	Polymer
5	KCN	1	H_2O/DCM, TBAI (10 mol %)	Polymer
6	KCN	1	Acetone, 1 eq. NaI	Polymer
7	KCN	1	EtOH, 1 eq. NaI	Polymer
8	KCN	1	H_2O, 2 eq. $MgSO_4$	Polymer

Reactions were performed on a 1 mmol scale with 5 mL of solvent mixture at room temperature with the exception of entry 4

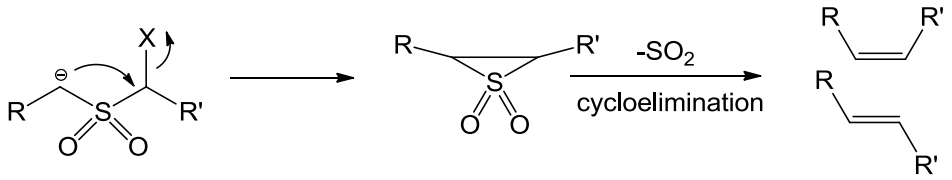
Table 21: Attempted Kolbe nitrile synthesis of bis-cyano propene

The formation of the polymer was exothermic and almost instantaneous in all cases. Initially we employed the classical conditions using three common sources of the cyanide ion at room temperature, with stirring in DMSO (**Entries 1-3**).[227] The resultant polymerisation forced us to return to the literature. Takashina *et al.* had reported in 1962 the cyanation of a vinyl bromide using copper(I) cyanide as the cyanide source.[230] In our hands this methodology again caused immediate polymerisation (**Entry 4**). The reaction was attempted using phase transfer catalysis and a biphasic system, but again the result was an almost instantaneous black polymer (**Entry 5**). In order to

promote the desired S_N2 reaction over the competing conjugate addition we performed an *in situ* Finkelstein reaction. The result was again polymerisation (**Entries 6-7**). We postulated that controlling the basicity of the reaction might help control the polymerisation. To this end we employed magnesium sulphate heptahydrate to buffer the reaction to approximate pH = 9.5.[231] It is important to note that acidic conditions were avoided for fear of generating hydrogen cyanide. The resulting buffered solution again caused polymerisation upon addition of the metal cyanide (**Entry 8**). With the consistent polymerisation in the reaction we decided to investigate alternative synthetic routes.

3.2.3 Attempted synthesis of 1,3-bis-cyano-prop-2-ene by Ramberg-Bäcklund reaction

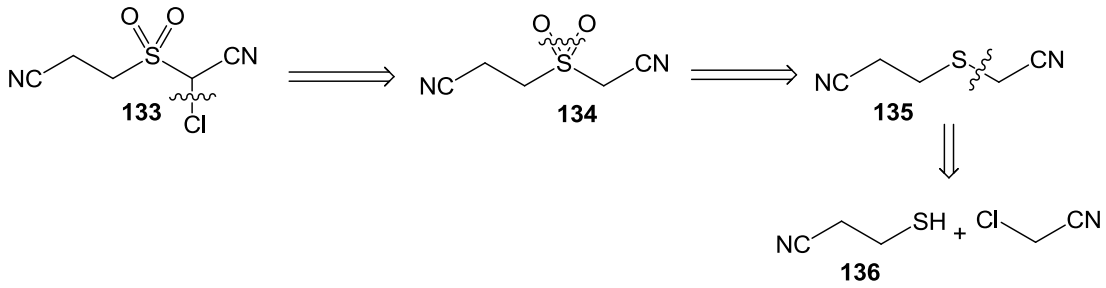
Due to the toxicity of metal cyanides we were eager to develop a cyanide-free synthetic route to the bis-cyano propene **127**. A review of the literature led us to the Ramberg-Bäcklund reaction. The classical reaction involves the generation of an olefin by extrusion of sulfur dioxide from an α-halosulfone under basic conditions (**Scheme 101**).[95]



Scheme 101: Classical Ramberg-Bäcklund reaction

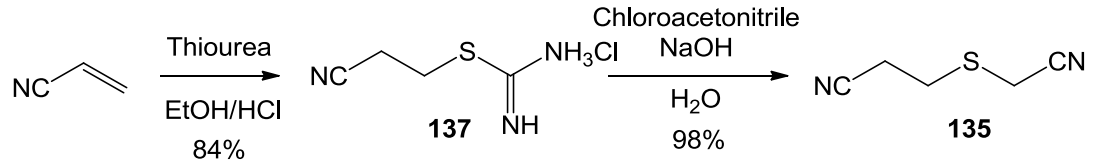
In order to use this methodology to generate the bis-cyano propene **127** (R=CN, R'=CH_2CN), we would first have to synthesise the corresponding α-halosulfone **133**. To this end we proposed the retrosynthesis outlined in **Scheme 102**.

We reasoned that radical chlorination of the sulfone **134**, after oxidation of the corresponding sulfide **135**, would be the most convenient route to the halosulfone **133**. The sulfide itself would be accessible by a simple S_N2 reaction with β-mercaptopropionitrile **136** and commercial chloroacetonitrile.



Scheme 102: Retrosynthesis of α-halosulfone **133**

When we first began the synthesis we used the methodology of Miller[232] to synthesise β-mercaptopropionitrile **136** from acrylonitrile and sodium hydrosulfite. This method gave an impure product at moderate yields (<50%). The β-mercaptopropionitrile **136** itself was found to have an extremely unpleasant penetrating odour. This made the purification difficult and unappealing and rendered all glassware unusable (even after treatment with peroxide solution). We instead opted to use the thiouronium salt **137** to 'mask' the mercaptan. We could then generate the mercaptan *in situ* and avoid exposure to the substance. The addition of thiourea to acrylonitrile was performed in high yield according to the literature.[233] With the thiouronium salt **137** available we undertook a series of experiments to find the appropriate conditions that would allow the hydrolysis of the urea and the sequential nucleophilic addition of the mercaptan. It was found that simple treatment with 2 equivalents of NaOH for 2 minutes at 60 ^{o}C, followed by addition of 1 equivalent chloroacetonitrile and immediate extraction after 5 minutes, gave near quantitative yields of the sulfide **135** (**Scheme 103**). The use of additional equivalents of chloroacetonitrile, or organic solvent, led to side-products and drastically reduced yields, even when employing mild bases such a K_2CO_3. The ^{1}H NMR of the thioether **135** shows a singlet at 3.41 pm and two triplets at 2.98 ppm and 2.74 ppm as expected. The ^{13}C NMR shows two quaternary shifts for the nitriles, 118.1 ppm, 116.5 ppm and the IR spectrum contains a nitrile band at 2245 cm^{-1}.



Scheme 103: Synthesis of sulfide **135**

We next focused on the oxidation of sulfide **135**. This step proved to be more troublesome than anticipated and a host of common oxidising reagents were tested before a suitable system was found (**Table 22**).

Entry	Oxidising Agent	Time (h)	Conditions	Result
1	*m*-CPBA	48	DCM, RT	Complex Mixture
2	Oxone	96	MeOH, RT	R.S.M.
3	Oxone	96	EtOH, RT	R.S.M.
4	Oxone	96	ACN/H_2O, $NaHCO_3$, RT	R.S.M.
5	Peroxy acetic acid	72	Acetic acid, 85 ^oC	Complex Mixture
6	Peroxy acetic acid	72	Acetic acid, Cat. H_2SO_4, 40^o C	65%

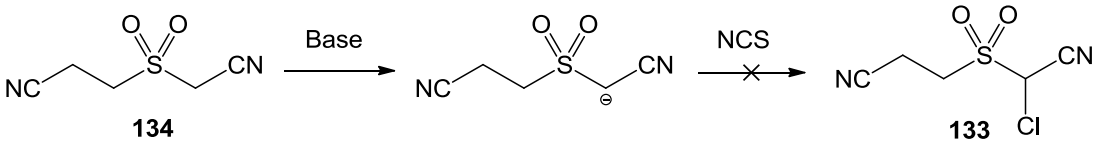
Reactions were performed on a 1 mmol scale with 5 mL of solvent under the specified conditions and time.

Table 22: Oxidation of sulfide **135**

The initial oxidation attempt using *m*-chloroperoxybenzoic acid gave an inseparable mixture of compounds, which by IR spectroscopy (signal at 1100 cm^{-1} for sulfoxide S-O and 1300 cm^{-1} for sulfone S=O) indicated the presence of a sulfoxide and a sulfone (**Entry 1**). The common alternative method of treatment with Oxone returned starting material in all cases (**Entries 2-3**), even when a mixed solvent system was employed to improve solubility (**Entry 4**). Heating the mixture with peroxy acetic acid again gave in a complex mixture which seemed to contain both the sulfoxide and the sulfone functionality (**Entry 5**). When a catalytic amount of sulphuric acid was employed, in conjunction with peroxy acetic acid, the oxidation to the desired sulfone **134** was achieved after 3 days at 40 ^oC (**Entry 6**). The difficulty in oxidising the sulfide **135** can most likely be attributed to the cyano group. The presence of an α-cyano group has been reported to greatly retard the oxidation of sulfides, and the use of catalytic sulphuric acid is known to improve reaction times.[234] Interestingly the sulfone was extremely insoluble, even in DMSO, and had to be dissolved in a mixed system of TFA and $CDCl_3$ in order to be characterised by ^1H NMR. The singlet for the methylene protons shifted to 4.44 ppm showing increased deshielding from the sulfone moiety over the sulfide. Similarly the triplets from the ethylene unit showed increased deshielding, 3.80 ppm and 3.17 ppm.

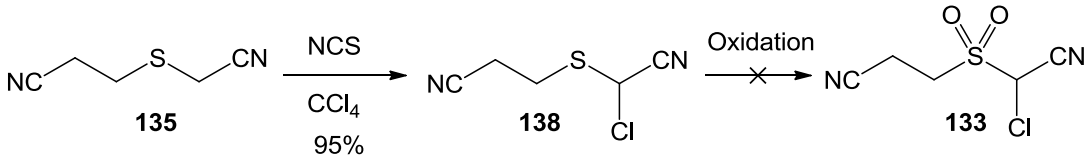
With the sulfone **134** in hand we attempted the α-chlorination using standard Wohl-Ziegler conditions, *N*-chlorosuccinimide in carbon tetrachloride with catalytic AIBN. The result was returned starting material. We decided that perhaps a specific-base catalysed approach would be more suitable as the resulting carbanion would be stabilized by both the sulfone and the nitrile (**Scheme 104**). We experimented with three different bases; NaOH, NaH and *n*-BuLi. However in all cases the result was a polymeric mixture of compounds. We assumed that the α-chloro cyano sulfone **133** was being formed, but that upon quenching the reaction with water the resulting alkali hydroxides were causing a premature Ramberg-Bäcklund reaction to the desired bis-cyano propene **127**, which under

basic conditions, was polymerizing. As it is known that the α-chlorination of sulfones can be troublesome,[235] we decided that a better approach might be to chlorinate the sulfide first and then oxidise it afterward in acidic conditions (**Scheme 105**).



Scheme 104: Attempted specific-base catalysed α-chlorination of sulfone **134**

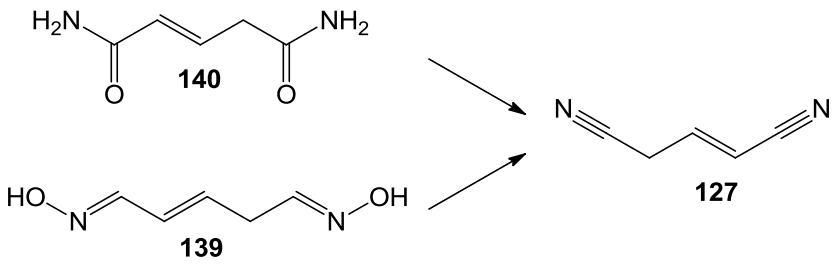
We were able to synthesise the α-chlorosulfide **138** in high yield after separation from the bis-chlorinated product. The subsequent oxidation could not be achieved using the sulphuric acid catalysed conditions developed previously (**Table 22**, **Entry 6**). Even after 2 weeks there was no evidence of the desired sulfone **133**. As mentioned previously the α-cyano group is known to retard oxidation, we concluded that the addition of another electron withdrawing group compounded this problem. Furthermore a literature search showed that Zajc and co-workers had encountered similar problems during their synthesis of an α-fluoro cyano sulfone. They reported both a lack of reactivity of a fluorinated sulfide with an oxidant, and difficulty in the fluorination of an cyano sulfone.[236] At this point we decided to explore another route to the bis-cyano propene **127**.



Scheme 105: Attempted oxidation of α-chlorosulfide **138**

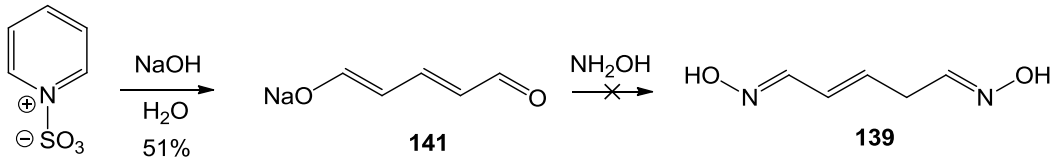
3.2.4 Synthesis of 1,3-bis-cyano-prop-2-ene by acid dehydration

We had experienced the rapid polymerisation of the bis-cyano propene **127** under basic conditions and were keen to develop a route that would employ acidic conditions in the final step. The use of acidic dehydration conditions would hopefully avoid polymerisation. Distillation of the product *in situ* would also prevent any water present in the system from hydrolysing the nitrile. Amides and aldoximes are known to dehydrate to nitriles.[237] With this in mind we considered compounds **139** and **140** and their possible dehydration to give the bis-cyano propene **127** (**Scheme 106**).



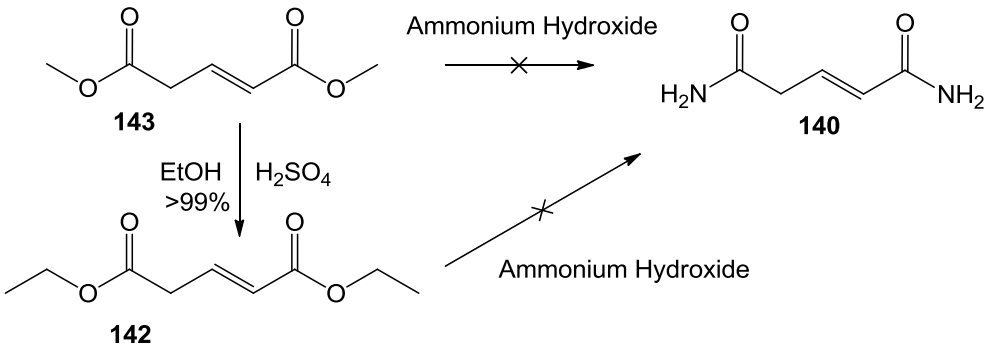
Scheme 106: Dehydration of compounds **139** and **140** to give bis-cyano propene **127**

We initially began with the synthesis of the bis-oxime **139**, which had been reported by Baumgarten in 1933, from glutaconaldehyde sodium salt **141**.[238] Glutaconaldehyde sodium salt **141** was prepared from the hydrolysis of sulfur trioxide pyridine complex in good yield (**Scheme 107**).[239] However, we were unable to convert the aldehyde functionalities to oximes using the procedure of Baumgarten. Instead a dark red mixture was obtained. The ^{1}H NMR of this red mixture showed the disappearance of the alkene protons and the aldehydic proton. This suggested that the hydroxyl amine had possibly undergone a conjugate addition as well as oxime formation.



Scheme 107: Attempted synthesis of bis-oxime **139**

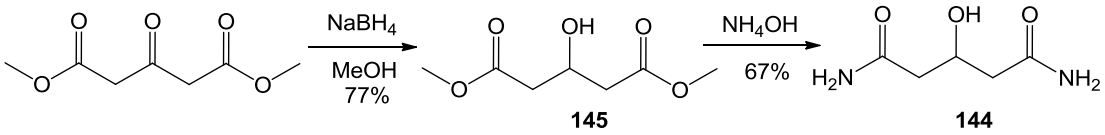
A variety of conditions were tried such as the use of low temperature and mixtures of both the free amine and hydrochloride salt forms of hydroxylamine. In all cases the reaction generated complex mixtures. We then decided to divert our attention to the bis-amide **140**. The literature had a reported synthesis of the bis-amide **140**, by Cappuyns in 1945, using diethyl glutaconate **142**.[240] We tried repeating this reaction using commercial dimethyl glutaconate **143** and aminolysis with ammonia (**Scheme 107**). Again a red mixture was obtained, which by ^{1}H NMR showed that no alkene protons remained in the sample. When the methyl ester **143** was transformed to an ethyl ester **142** we again observed a red mixture and the loss of the alkene protons in the ^{1}H NMR after the aminolysis with ammonia (**Scheme 108**).



Scheme 108: Attempted aminolysis of methyl and ethyl glutaconate

Again this was assumed to be the result of conjugate addition of ammonia to the molecule. We surmised that if the alkene were replaced with an alcohol we could prevent the conjugate addition and dehydrate it in tandem with the amides. To this end we synthesised hydroxy-bis-amide **144** (**Scheme 109**).

β-Hydroxy dimethyl glutaconate **145** was generated from dimethyl acetonedicarboxylate according to a literature procedure with slight modification.[241] The hydroxy-glutaconate **145** was treated with ammonium hydroxide to give β-hydroxy glutaconamide **144** in good yield. With large quantities of the amide **144** available we attempted the triple dehydration reaction under different reaction conditions. We found that the use of phosphorus pentoxide under high vacuum gave a reasonable 33% yield on a 3.5 mmol scale. However, as we scaled up the reaction a large amount of heat was generated during the dehydration and a white solid was deposited around the flask. The ^{1}H NMR of the compound matches the reported spectrum of 2,6-hydroxypyridine (broad singlet at 9.00 ppm, a triplet at 7.34 ppm and a doublet at 5.71 ppm).[242] Panella reported the same side-product during the dehydration of 3-hydroxyglutaronitrile **128**.[224] Again, we were able to generate the bis-cyano propene **127** but only in small uneconomical amounts.



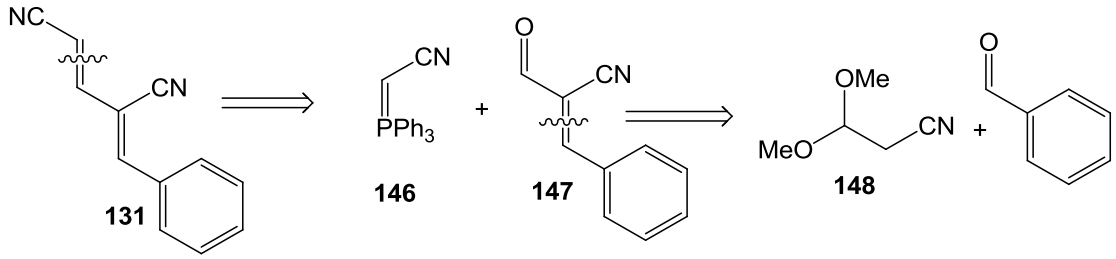
Scheme 109: Synthesis of hydroxy-bis-amide **144**

3.2.5 Synthesis of 1,3-bis-cyano-prop-2-ene by HWE olefination

The difficulty in acquiring large quantities of the bis-cyano propene **127**, in addition to its unstable nature, prompted us to find an alternative synthetic route to the bis-cyano diene **131**. To do this we

redesigned the retrosynthesis of the bis-cyano diene **131**, changing the disconnection to the primary 1,2- olefin as shown in **Scheme 110**.

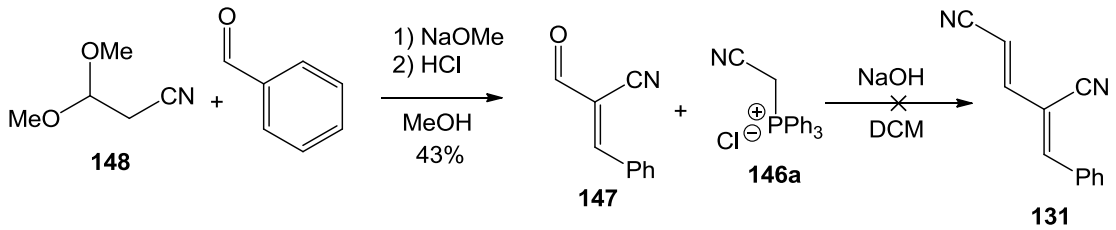
This disconnection led us to a Wittig reaction between the stabilized ylide **146** and α-cyano cinnamaldehyde **147.** The α-cyano cinnamaldehyde **147** could in turn be generated from a Knoevenagel condensation with the acetal of α-cyano acetaldehyde.



Scheme 110: Revised retrosynthesis of diene **131**

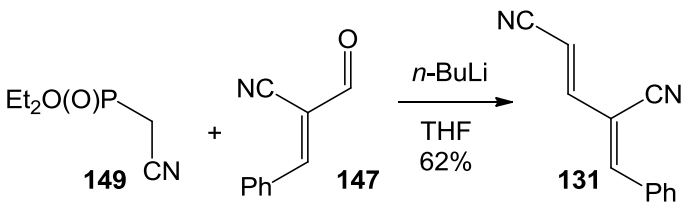
We began the synthesis with the Knoevenagel condensation of the commercial acetal **148** and benzaldehyde.[243] The crude mixed isomer (3:2 *E*/*Z*) could be de-protected and the *E*-isomer of α-cyano cinnamaldehyde **147** isolated by crystallisation in good yield (43%) (**Scheme 111**).

The phosphonium salt **146a** was readily prepared in the usual manner from triphenylphosphine and chloroacetonitrile.[244] When we performed the Wittig reaction, generating the ylide **146** *in situ* with NaOH, we observed immediate consumption of the starting material and complex mixture of products. When the ylide **146** was pre-formed we again observed a complex mixture of products and immediate consumption of the starting material. We assumed that the ylide **146** was undergoing 1,4-conjugate addition to the α,β-unsaturated aldehyde **147**, which is activated by the mesomeric effects of both the aldehyde and the nitrile. We also performed the reaction at -78 ^{o}C to encourage the direct addition of the ylide **146**. After 24 hours there was little to no consumption of the starting material.



Scheme 111: Attempted Wittig reaction to synthesise diene **131**

We decided to turn to the Horner-Wadsworth-Emmons (HWE) reaction to generate the diene **131** because the lithiated cyanomethyl phosphonate **149** would be more nucleophilic than the corresponding ylide **146**, which would favour direct addition to the aldehyde. The use of a hard base such as butyllithium would generate a hard lithiated nucleophile from the phosphonate which should again favour direct addition (**Scheme 112**).

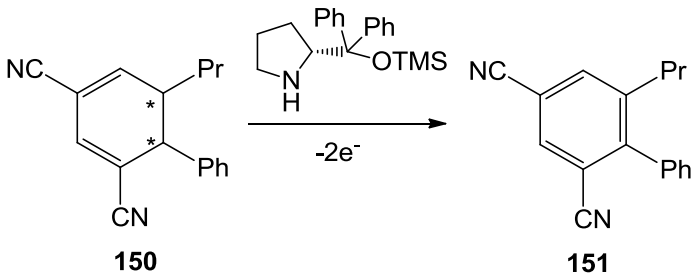


Scheme 112: HWE olefination to create diene **131**

Using the commercially available phosphonate **149**, we were able to isolate the diene **131** in good yield and as a single isomer, presumably *EZ*, as the starting α-cyanocinnamaldehyde was in the *E* configuration and HWE reactions are known to favour the *E*-isomer.[245] The geometry of the 1,2-alkene was confirmed by NMR (J = 15.7 Hz). After experimenting with a variety of conditions it was found that addition of the aldehyde to organolithium reagent at low temperature gave the best yields of diene **131** and allowed us to recover unused starting material. With gram quantities of the diene **131** available we began a series of experiments to obtain optimum conditions for the organocatalytic 1,6-conjugate addition of aldehydes to 1,3-bis-cyano butadienes.

3.2.6 Study of the aromatisation of the addition product

When we first performed the addition of *n*-valeraldehyde to the bis-cyano diene **131** we found the presence of the desired cyclic diene **150** along with considerable amounts of a side product which we established to be the arene **151**. We reasoned that this product was resulting from the base promoted oxidation with molecular oxygen of the 1,6-adduct (**Scheme 113**), as we had observed during the addition of ketonic enamines to bis-phenylsulfonyl diene **71** (**See Section 2.2.1.10**).

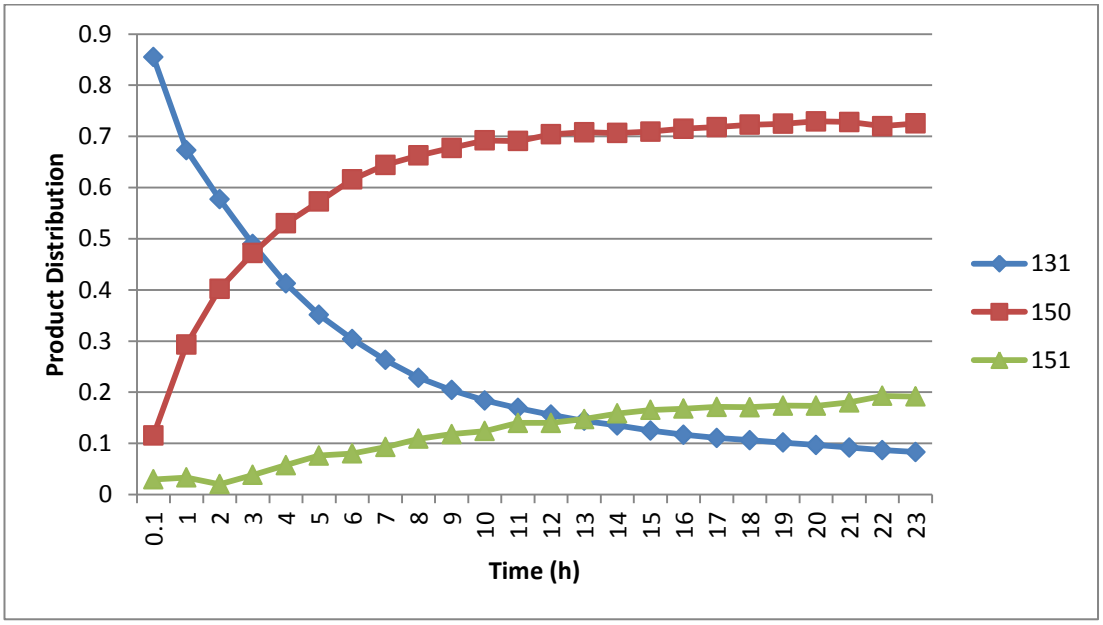


Scheme 113: Base-promoted oxidation of cyclic bis-cyano diene **150**

While the cyclic diene, substituted with phenylsulfonyl groups, required treatment with DBU to aromatise, the cyclic bis-cyano diene **150** could be susceptible to oxidative aromatisation at much milder conditions due to the increased electron withdrawing properties of the nitrile. Based on the reported acidities of similar compounds we can estimate the pK_a values of the relevant protons of the bis-cyano cyclic diene **150** and the cyclic bis-phenylsulfonyl diene **43** to be around 11 and 21

respectively,[246] while the pK_a of the conjugate acid of pyrrolidine has been recently calculated to be 19.56 in acetonitrile.[247] This would support our supposition that the catalyst can promote basic oxidative aromatisation with molecular oxygen of the cyclic bis-cyano diene **150** but not the cyclic bis-phenyl sulfonyl diene **43**.

In order to explore the aromatisation of the product in the reaction we monitored the product distribution by ^{1}H NMR spectroscopy hourly over 24 hours (**Plot 1**).

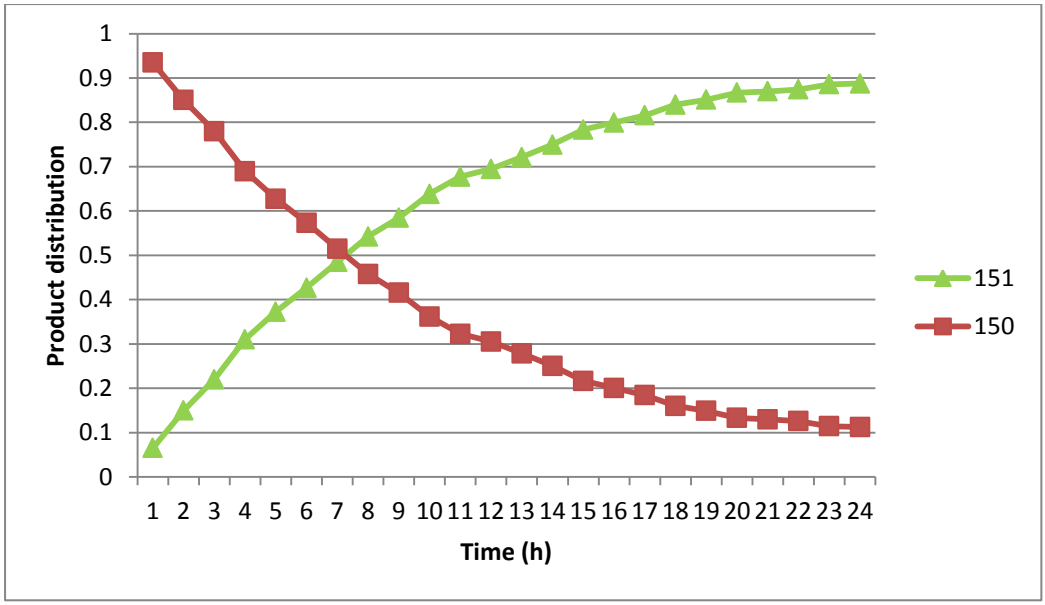


Reaction was run with diene **131** 0.1 mmol, **(*R*)-3** (20 mol %), 4-nitrobenzoic acid **(**20 mol %) and *n*-valeraldehyde 0.4 mmol in 0.5 mL $CDCl_3$

Plot 1: Product distribution over 24 hours as monitored by ^{1}H NMR spectroscopy

The near linear increase of the aromatised product could indicate that the reaction is extremely slow and is in the initial stages of a higher order reaction and could account for the reduced yields we were observing. When the desired product **151** was purified and isolated there was no observed aromatisation over a 7 day storage period.

We next studied the rate of aromatisation when only the desired product **150** and the catalyst **(*R*)-3** (20 mol %) were present in the system over a 24 hour period by ^{1}H NMR (**Plot 2**).



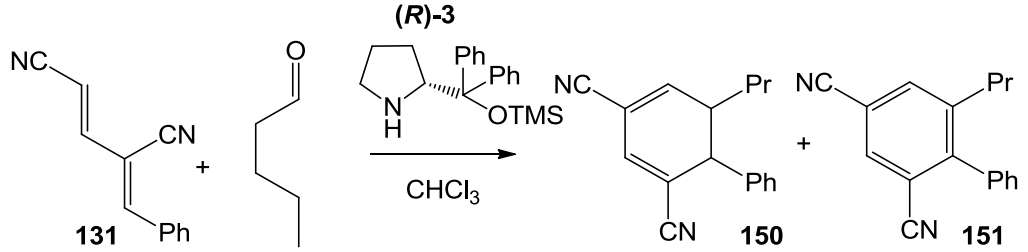
Reaction was run with product **150** 0.1 mmol, **(*R*)-3** (20 mol %) in 0.5 mL of $CDCl_3$

Plot 2: Aromatisation over 24 hours as monitored by ^1H NMR

The experiment demonstrates that catalyst **3** is indeed causing the aromatisation of the product diene **150** into arene **151**, even in catalytic quantities. The rate of the conversion of the diene **151** remains constant through the early stages of the reaction and only slows when there is less than 35% of the diene remaining. Heating the reaction to reflux for four hours completed the aromatisation and the arene **151** was isolated by flash chromatography for characterization.

Despite the rather discouraging development that our preferred catalyst **3** was causing loss of the product we decided to continue with the development of the methodology. Importantly the catalyst **3** was not being deactivated by the aromatisation (90% aromatisation using **(*R*)-3** 20 mol%). We were aware that the concentration of the product diene did not overly affect the rate of aromatisation due to the slow rate of reaction, which would benefit us if the reaction time could be shortened and the catalyst loading dropped. Secondly we had noticed that the rate of aromatisation seemed dependant on temperature. With this knowledge we proceeded to optimize the reaction.

3.2.7 Optimisation of 1,6-conjugate addition reaction conditions



Entry	Cat. (mol %)	Molarity (M)	Aldehyde (eq.)	Time (h)	Additive	**150** : **151**	Conversion (%)
1	30	0.4	2	24	-	1 : 0.26	96
2	20	0.4	2	48	-	1 : 0.21	91
3	20	0.4	2	48	AcOH	1 : 0.35	100
4	20	0.4	4	48	-	1 : 0.20	100
5	10	0.4	4	48	-	1 : 0.21	89
6	20	0.4	6	48	-	1 : 0.21	100
7	20	0.2	4	48	-	1 : 0.19	88
8	20	0.2	4	48	B.A. (0.2 eq.)	1 : 0.19	100
9	20	0.2	4	48	N.B.A. (0.2 eq.)	1 : 0.18	98
10	20	0.2	4	24	N.B.A. (1 eq.)	1 : 0.17	95
11	20	0.2	4	24	N.B.A. (0.2 eq.)	1 : 0.18	95
12	20	0.2	4	24	B.A. (1 eq.)	1 : 0.24	85
13	20	0.2	4	48	B.A. (1 eq.)	1 : 0.24	88
14	20	0.2	4	48[a]	B.A. (0.2 eq.)	1 : 0.17	100
15	20	0.2	4	48[a]	N.B.A. (0.2 eq.)	1 : 0.10	98
16	20	0.2	4	24[b]	N.B.A. (0.2 eq.)	1 : 0.08	68
17	20	0.2	4	24[a]	N.B.A. (0.2 eq.)	1 : 0.10	92
18	20	0.2	4	24[a]	T.F.A. (0.2 eq.)	1 : 0.24	68

Reactions were performed on a 0.1 mmol scale. Conversion and product distribution by ^{1}H NMR, B.A. = benzoic acid, N.B.A. = 4-nitrobenzoic acid, T.F.A. = trifluoroacetic acid, [a] reaction was conducted at 4 ^{o}C, [b] reaction was conducted at 0 ^{o}C

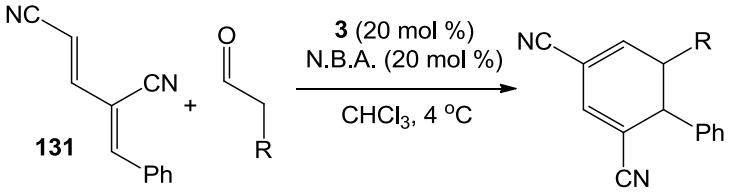
Table 23: Optimisation of reaction conditions

We had initially employed identical conditions to that which we had used in the 1,6-additon to bis-phenylsulfonyl butadienes (**See Section 2.2.1.4**) and observed a quite substantial product distribution (**Entry 1**). The reduction of catalyst loading caused a slight drop in the level of

aromatisation but required a longer reaction time (**Entry 2**). Increasing the molar equivalents of aldehyde employed allowed a slight improvement in the yield and was found to be optimal at 4 equivalents (**Entries 4-6**). Increasing the dilution of the reaction caused a drop in conversion but gave a slight reduction in the product distribution (**Entry 7**). Experimentation with acidic additives generally showed an increase in rate of reaction but with similar levels of product distribution. 4-Nitrobenzoic acid was found to be the additive of choice as it gave slightly lower levels of aromatisation, albeit with partially reduced conversion (**Entries 3 and 8-13**). The use of reduced temperatures gave the best results (**Entries 14-18**) suggesting that aromatisation of the product may be under thermodynamic control. Of note is that the rate of reaction was significantly lowered when the reaction was performed at 0 ^{o}C, affording only 68% conversion compared to 4 ^{o}C which gave 92% (**Entries 16 and 17 respectively**).

3.2.8 Scope of 1,6-conjugate addition reaction

With our optimised conditions we proceeded to expand the substrate scope of the 1,6-conjugate addition of aldehydes to 1,3-bis-cyano-butadienes.



Entry	Cat.	Time (h)	R	Yield (%)[a]	d.r. (*syn*/*anti*)[b]	*ee* (%)[c]
1	**(*R*)-3**	24	*n*Pr	72 (**150**)	1:99	99
2	**(*R*)-3**	68	*i*Pr	66 (**152**)	1:99	99
3	**(*R*)-3**	30	allyl	75 (**153**)	1:99	99
4	**(*R*)-3**	30	Ph	66 (**154**)	1:99	69
5	**(*S*)-3**	30	Ph	3[d] (**154**)	n/a	n/a
6	**(*S*)-3**	38	Ph	75[e] (**154**)	1:99	-96

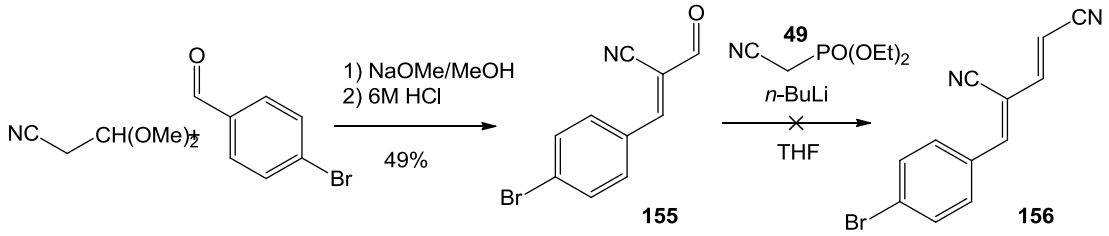
Reactions were performed on a 0.2 mmol scale, with 4 molar equivalents of aldehyde at 0.2 M concentration. N.B.A. = 4-nitrobenzoic acid. [a] isolated yield, [b] measured by ^{1}H NMR spectroscopy, [c] determined by HPLC on a chiral stationary phase for presumed *anti* products, [d] 8 equivalents of aldehyde employed, [e] no acid co-catalyst employed

Table 24: Scope of aldehydes for 1,6-conjugate addition

We found that the aldehyde addition proceeded much in the same manner as with the phenyl sulfonyl dienes (**See Section 2.2.1.5**). The addition was both diastereoselective and enantioselective. The yields in general were lower than we had observed with the sulfones most likely due to the loss

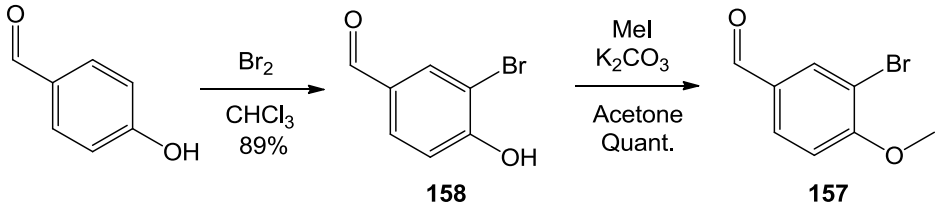
of product from aromatisation and subsequent chromatography, however in all cases the conversion of starting material was over 90%. The yield of product **154**, when phenylacetaldehyde was used as the Michael donor, was only 66% and gave 69% ee when an acidic co-catalyst was employed (**Entry 4**). Increasing the number of aldehyde equivalents gave almost none of the desired cyclic diene (**Entry 5**). The product of the self-aldol condensation was obtained in large quantities in both reactions. Not only does this side reaction consume the aldehyde but produces water as a by-product which can interfere with the catalytic system prematurely hydrolyzing the iminium ion resulting in decreased yields and selectivities. When we removed the acid co-catalyst in order minimize the acid-catalysed aldol-condensation the result was a return to the excellent enantioselectivities we were expecting without much drop in yield or increase in aromatisation (**Entry 6**).

In order to determine the absolute stereochemistry of the products we were interested in obtaining a product cyclic diene which contained an electron-dense heavy atom. Initially we synthesised the 4-bromo derivative of α-cyano cinnamaldehyde **155** (**Scheme 114**). However, we found the HWE reaction with lithiated diethyl cyanomethylphosphonate **149** to be particularly poor yielding (<5%) (**Scheme 114**). This lack of reactivity could be attributed to the decreased electron-density in the aromatic system, due to the electronegative bromine atom causing the activation of the 4-position over the 2-position.



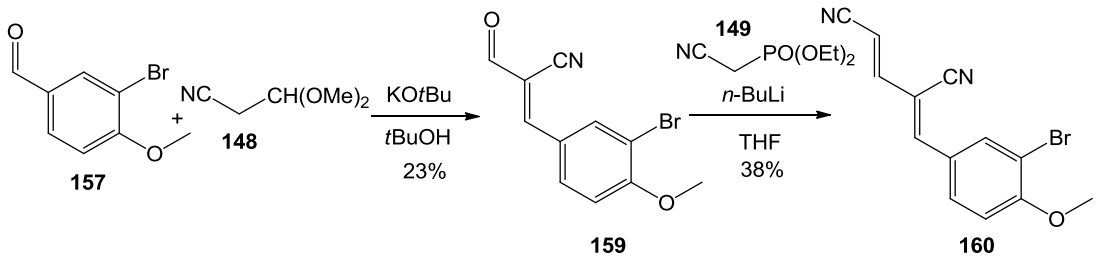
Scheme 114: Attempted synthesis of 4-bromo bis-cyano-diene **156**

In order to over-come this problem of reactivity we chose to employ an electron-donating methoxy-group in the 4-position while maintaining a bromine in the 3-position, where it would have little activating ability. To this end 3-bromo-anisaldhyde **157** was synthesised from 4-hydroxy benzaldehyde (**Scheme 115**).



Scheme 115: Synthesis of 3-bromo-anisaldehyde **157**

When benzaldehyde **157** was employed in the Knoevenagel condensation with the cyanoacetaldehyde acetal **148**, using sodium methoxide as a base, the result was a very poor yield of the desired cinnamaldehyde **159** and the isolation of a large amount of the benzoic acid. The benzoic acid most likely originated from the reaction of the methoxide anion with the aldehyde forming the methyl ester which was then hydrolysed in the acidic conditions to give the benzoic acid. In order to circumvent this we employed the non-nucleophilic bulky butoxide anion and, in anhydrous conditions, the reaction proceeded with rather poor conversion due to the reduced reactivity of the aldehyde (**Scheme 116**). We continued without Optimisation and successfully isolated the diene **160** after the HWE reaction with the phosphonate **149** (**Scheme 116**).

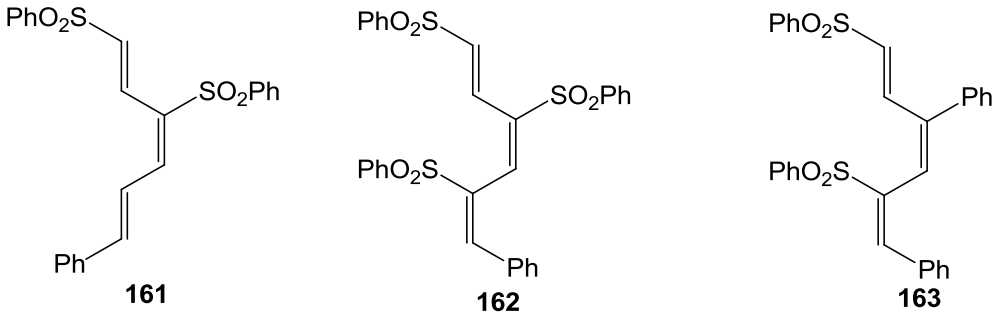


Scheme 116: Synthesis of 3-bromo-4-methoxy diene **160**

Unfortunately we were not able to detect any addition of *n*-valeraldehyde to the diene **160** under the optimised conditions after 24 hours. While we had observed the addition of aldehydes to the 4-methoxy substituted bis-phenylsulfonyl diene **52** at room temperature in high yield (**See Section 2.2.1.6**), it would appear that at 4 ^{o}C the addition is severely retarded even with a slightly more reactive bis-cyano substrate. Research into other substituted bis-cyano dienes is on-going in our laboratories.

3.3 Design and synthesis of cooperative charge delocalised trienes for 1,8-conjugate addition

To develop a trienic substrate that would favour a 1,8-conjugate addition we employed a similar approach as that used for the dienic substrates. Using what we had learned we designed three possible trienes that we felt would be suited for 1,8-conjugate addition (**Scheme 117**).

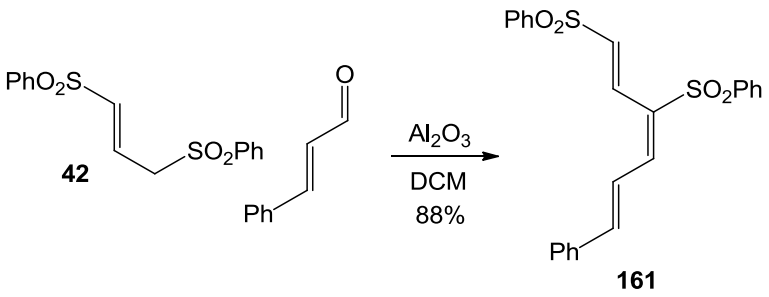


Scheme 117: Design of 3 different trienes that could favour 1,8-conjugate addition

The first design **161** was based on a simple extension of the π-system. We anticipated that without an additional electron withdrawing group at the ε-carbon we may not get the selective activation of the 8-position and a mixture of 1,6- and 1,8- additions may occur. The second triene **162** would be triply activated by electron withdrawing groups. Again, we may get competition between the 6- and the 8- position but in this case one may expect attack at the 8-position to be more favoured due to its extreme electron deficiency. Finally the third triene **163**, we hoped, could be expected to give only the 1,8-adduct. Presumably only the 8-position would be activated by the cooperative charge delocalisation from the electron withdrawing groups positioned at the α- and ε- carbons. This cooperative charge delocalisation was observed in our 1,6-addition to the bis-phenyl sulfonyl diene (**See Section 2.2.1.2**).

3.3.1 Synthesis of α-,γ- bis-activated diene

The synthesis of diene **161** was completed in one step from the bis-phenysulfonyl propene **42** and *trans*-cinnamaldehyde in good yield using the previously developed aluminium oxide methodology (**Scheme 118**).



Scheme 118: Synthesis of triene **161**

The ^{1}H NMR spectrum of the triene **161** contained only aromatic signals and the geometry of the alkenes could not be assigned. In order to confirm all *trans*- geometry an X-ray crystal structure was obtained (**Fig. 32**).

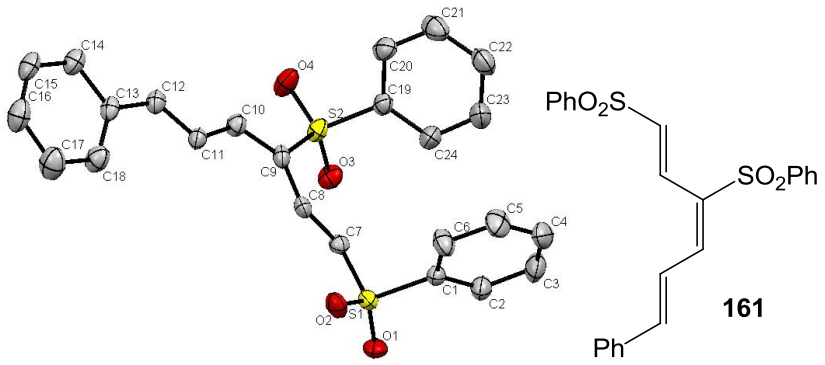


Figure 32: Crystal structure of triene **161**

Interestingly when the compound was crystallised using high vacuum gradient sublimation[248] a different structure was obtained (**Fig. 33**).

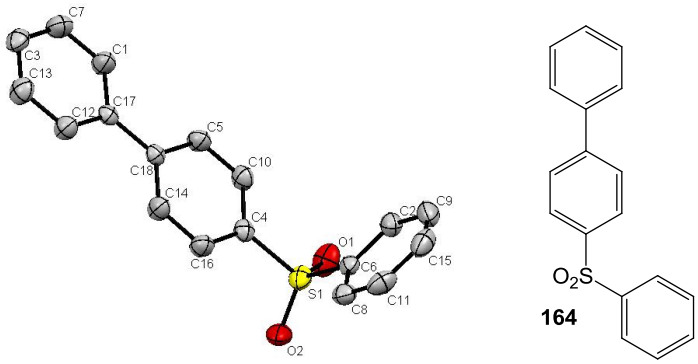
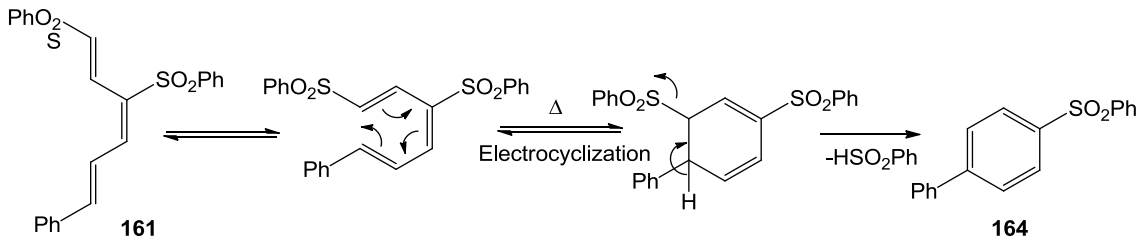


Figure 33: Crystal structure of the biphenyl **164** crystallised from vacuum sublimation

This biphenyl compound **164** was mostly likely a result of a thermal electrocyclic reaction. As depicted in **Scheme 119**, the triene in the *cis-,cis-* conformation is able to undergo an electrocyclic cyclisation and eliminate phenyl sulfinic acid to give the biphenyl **164**.



Scheme 119: Thermal electrocyclic reaction and elimination of phenylsulfinic acid

Analysis of the frontier molecular orbitals involved in this transformation allowed us to assign a disrotatory overlap of the HOMO orbitals as depicted in **Figure 34**. This is supported by application of Woodward-Hoffman rules for pericyclic reactions[249] which dictate that since there is no (4r) component, the single (4q+2) component must interact suprafacially for this reaction to be symmetry allowed, indicating a disrotatory overlap of the p-orbitals. This would predict the intermediate cyclic diene to be the *syn* diastereomer (**Fig. 34**). This cyclic diene however was not isolated and we were unable to confirm whether this reaction is indeed a Woodward-Hoffman 'symmetry allowed' transformation.

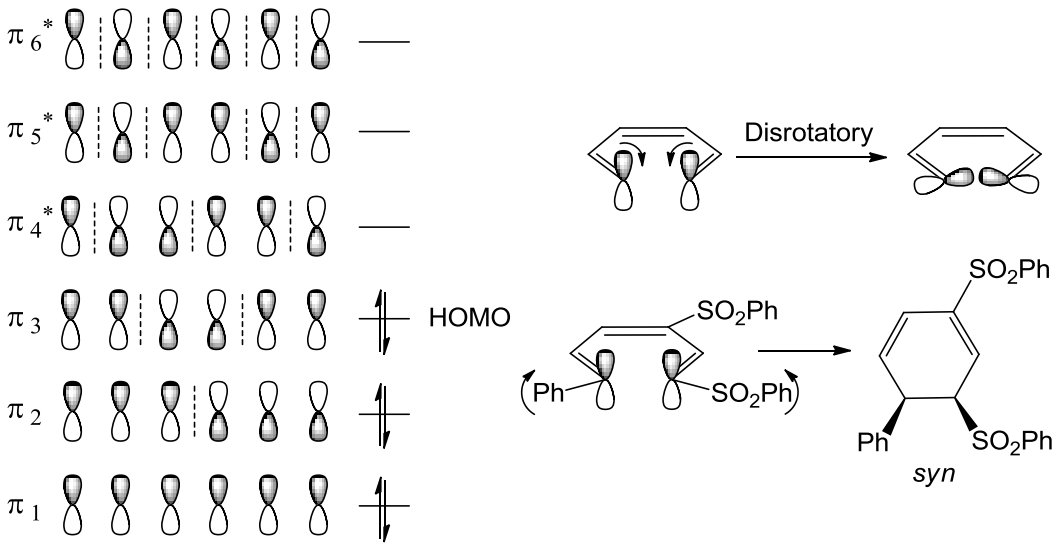


Figure 34: FMO diagram for $\pi 6_s$ thermal electrocyclisation

What is very unusual about the sulfonyl biphenyl **164** is the near zero twist angle (*φ*) between the two adjacent aromatic rings which give the biphenyl structure planarity. In the crystal-state, unsubstituted biphenyl also appears to be planar. However, according to Delugeard and co-workers this is a statistically centred arrangement caused by the rotation of the rings in a double minimum conformational potential.[250] This means that even in the crystal state the rings are not planar as they appear (it is well known that in the gas-phase that biphenyl has a twist-angle of around 45°).[251] This can be evidenced by the intermolecular distances between the biphenyl systems corresponding to their Van-der-Waals radii and not being influenced by any π-π interactions.[250] In the sulfonyl biphenyl **164** derived from the triene **161** there is a huge amount of π-π interaction in the lattice (**Fig. 35**). This involvement of both the aromatic rings in π-π stacking is believed to give flattening energy to the conformation. The phenyl sulfone functionality itself is involved with edge-to-face interactions (**Fig. 35**).

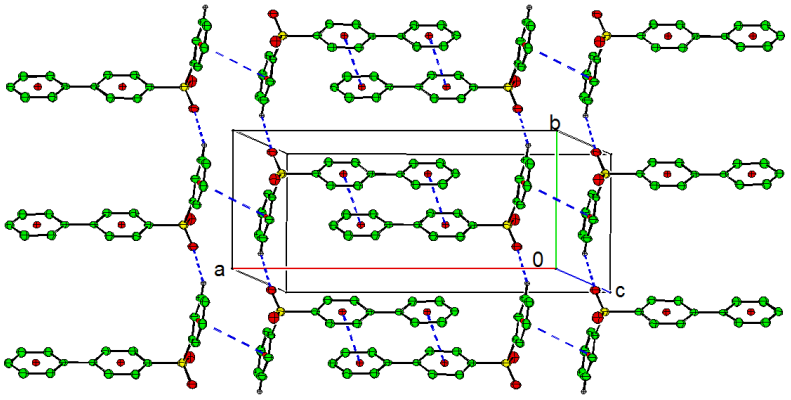
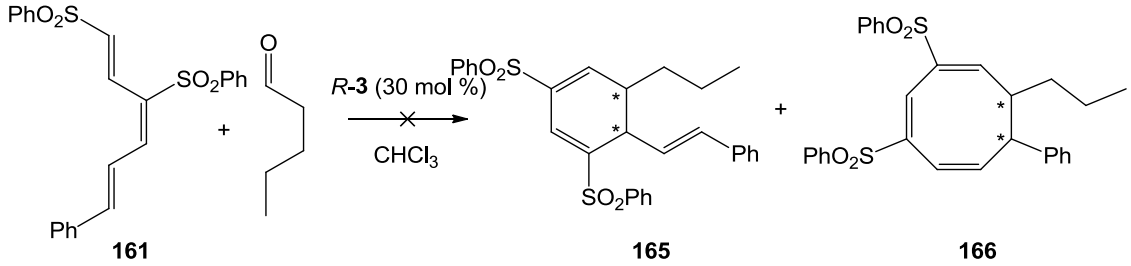


Figure 35: Crystal Lattice for biphenyl **164**

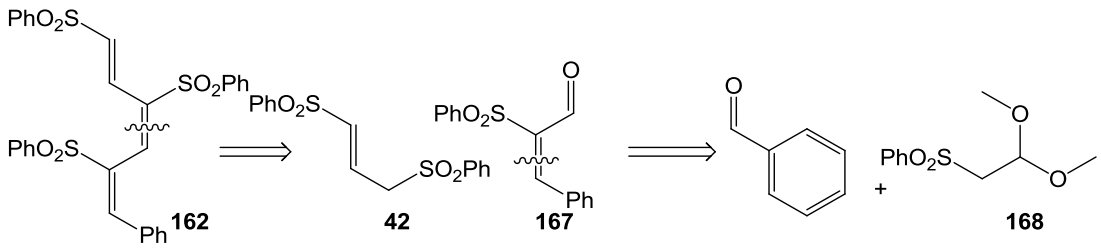
When the triene **161** was tested in a conjugate addition reaction the result was a complex mixture of products which we were unable to separate (**Scheme 120**).



Scheme 120: Attempted addition to triene **161**

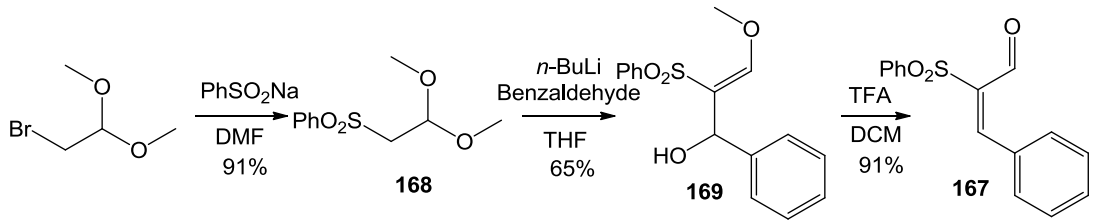
3.3.2 Attempted synthesis of α-,γ-,ε- tris-activated triene

The retrosynthesis of the triene **162** is shown in (**Scheme 121**). Again, a Knoevenagel condensation was proposed for the last step in the synthesis. We therefore would first need to synthesise α-phenylsulfonyl cinnamaldehyde **167**.



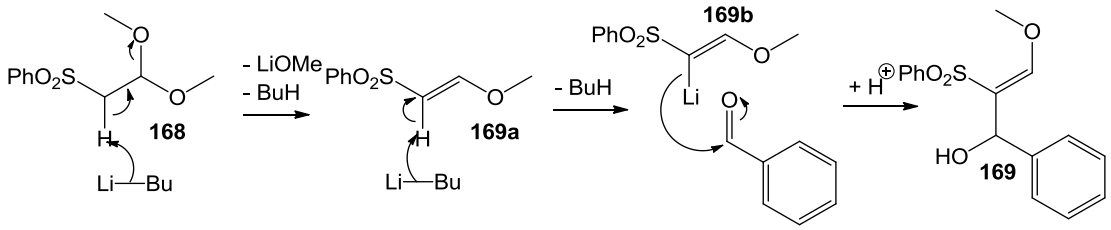
Scheme 121: Retrosynthesis of triene **162**

The α-phenylsulfonyl cinnamaldehyde **167** was prepared from the acetal **168** in three steps (**Scheme 122**). Simple nucleophilic addition of benzenesulfinic acid sodium salt to bromo-acetaldehyde dimethyl acetal yielded the acetal **168** was achieved in high yield. The phenylsulfonyl dimethyl acetaldehyde **168** was deprotonated with butyllithium at low temperature and treated with benzaldehyde to yield the alcohol **169**. Finally the alcohol **169**, although an unexpected product, could be converted to α-phenylsulfonyl cinnamaldehyde in high yield (91%) by exposure to acidic conditions.



Scheme 122: Synthesis of α-phenylsulfonyl cinnamaldehyde **167**

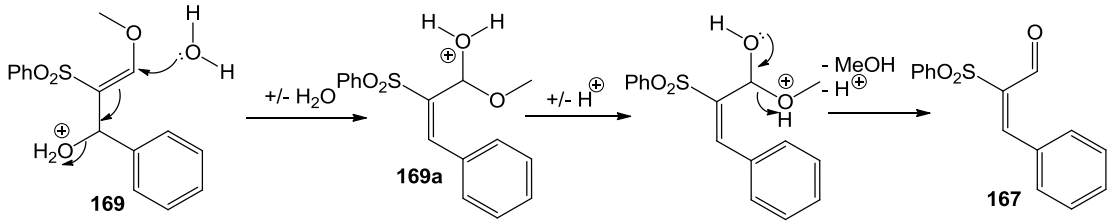
A proposed mechanism for the formation of alcohol **169** is given in **Scheme 123**. A review of the literature found two reports that shed light on our result.[252] They suggested that the initial equivalent of butyllithium caused the elimination of one of the methoxy groups to generate alkene **169a** (**Scheme 123**)**.** The second portion caused selective lithiation of the α-carbon. The lithiated intermediate **169b** can then react with the electrophilic benzaldehyde to give alcohol **169** (**Scheme 123**).



Scheme 123: Mechanism for the formation of alcohol **169**

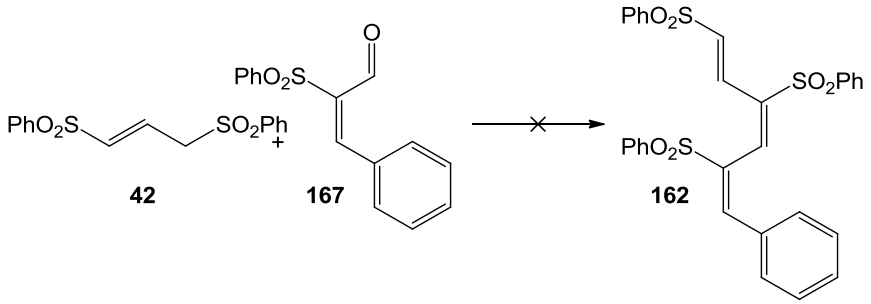
Fortunately, alcohol **169** could be converted to the desired α-phenylsulfonyl cinnamaldehyde **167** under acidic conditions. A proposed mechanism for this transformation is shown in **Scheme 124**.

Nucleophilic attack of a water molecule on the vinyl sulfone **169** with the elimination of water, followed by the normal loss of methanol yielded the aldehyde **167.**



Scheme 124: Generation of aldehyde **167** in acidic conditions

With the synthesis of α-phenylsulfonyl cinnamaldehyde **167** complete we then attempted the final Knoevenagel condensation with bis-phenylsulfonyl propene **42** (**Scheme 125**).



Scheme 125: Attempted Knoevenagel to synthesise triene **162**

A variety of reaction conditions were employed but in all cases only returned starting material was observed (**Table 25**).

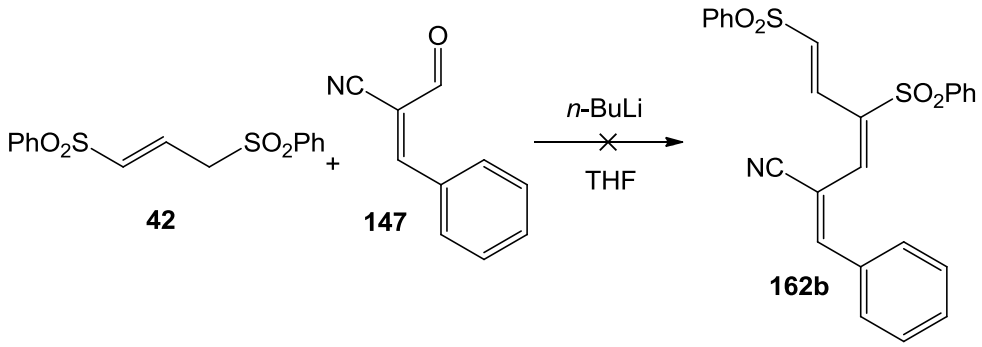
Entry	Equivalents (E^+/Nu^-)	Conditions	Time (h)	Result[a]
1	1/1	*n*-BuLi (1.1 eq.), THF, -78 °C	2	R.S.M.
2	2/1	*n*-BuLi (2.1 eq.), THF, -78 °C	2	R.S.M.
3	1/1	Al_2O_3(30 eq.), DCM, 0 °C	24	R.S.M.
4	1/1	Al_2O_3(30 eq.), DCM, RT	24	R.S.M.
5	1/1	Al_2O_3(30 eq.), Toluene, 111 °C	24	R.S.M.

Reactions were performed on a 1 mmol scale using 5 mL of solvent using the specified conditions, [a] determined by ^{1}H NMR spectroscopy

Table 25: Conditions attempted for the Knoevenagel condensation for the generation of triene **162**

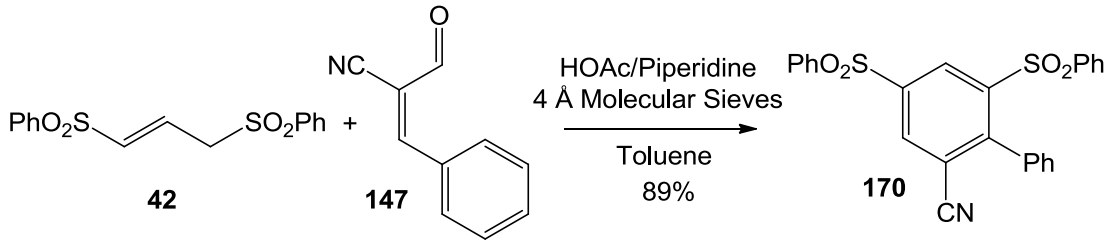
We found that at low temperatures the α-lithiated intermediate from propene **42** was unable to add in a direct fashion or in a conjugate manner (**Entries 1-2**). The lack of direct addition could be accounted for by the bulk of the α-phenylsulfonyl group blocking the electrophilic site, indeed, to the best of our knowledge, there are no reported 1,2-additions to α-phenylsulfonyl aldehydes in the literature. Similarly, we could not find a publication reporting conjugate-additions to α-phenylsulfonyl unsaturated aldehydes. Conjugate-additions have been reported to α-phenylsulfonyl unsaturated esters and ketones using trimethyl aluminium reagents[253] and organocuprates.[254] These reported additions required temperatures above -78 ^{o}C, which may explain why we did not observe conjugate addition at -78 ^{o}C when using butyllithium (**Entries 1-2**). When aluminium oxide was used we again observed returned starting material (**Entries 3-5**). The bulk of the sulfonyl group may have again prevented direct addition from occurring, while aluminium oxide may just not be a suitable catalyst for promoting conjugate addition. We were finding similar results when applying this Knoevenagel condensation chemistry to the synthesis of the α-,ε- bis-activated triene **163** (**See Section 3.3.3**).

The lack of reactivity with the phenyl sulfonyl cinnamaldehyde prompted us to return to the α-cyano cinnamaldehyde **147**. This promised to give us access to the triene **162b** (**Scheme 126**) using the same organolithium chemistry we had developed previously during the HWE olefination in synthesis of the bis-cyano butadiene **131** (**See Section 3.2.5**).



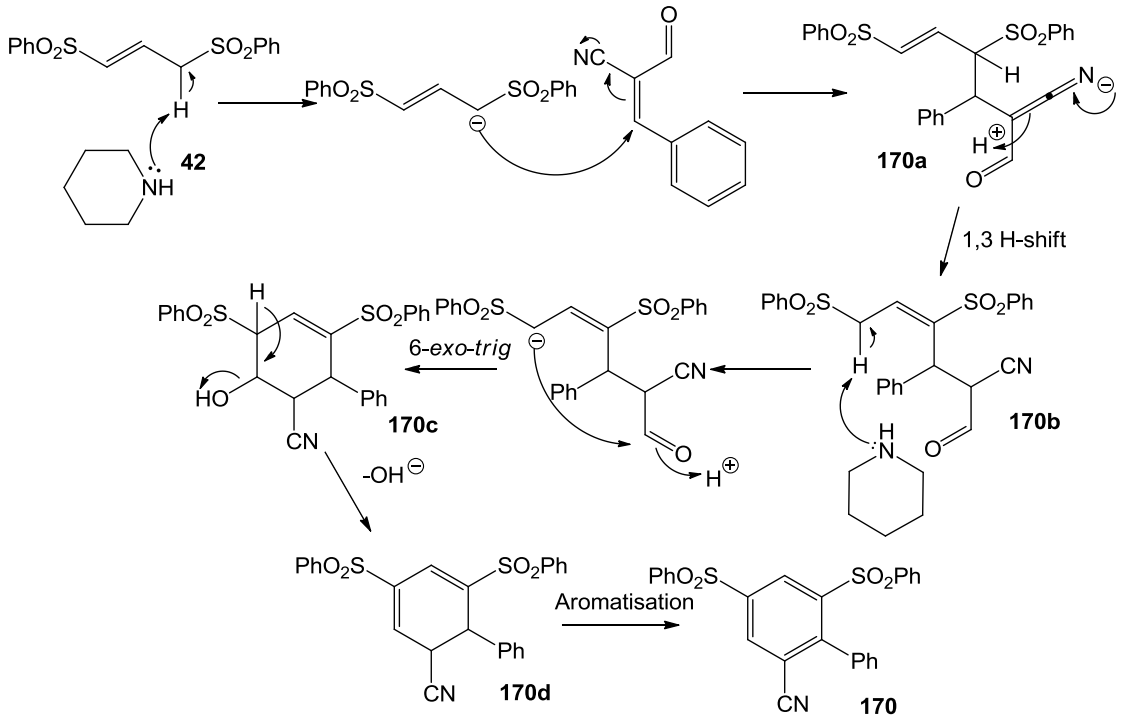
Scheme 126: Attempted organolithium direct addition to α-cyanocinnamaldehyde

Unfortunately butyllithium, at low temperature this time, afforded a complex mixture of products which could not be deciphered. We next applied the aluminium oxide protocol and observed very little conversion after 48 hours at room temperature. When the traditional Knoevenagel conditions were applied we were able to isolate a white solid in good yield. This product was characterised as the arene **170** after considerable NMR spectroscopic analysis (**Scheme 127**).



Scheme 127: Generation of arene **170**

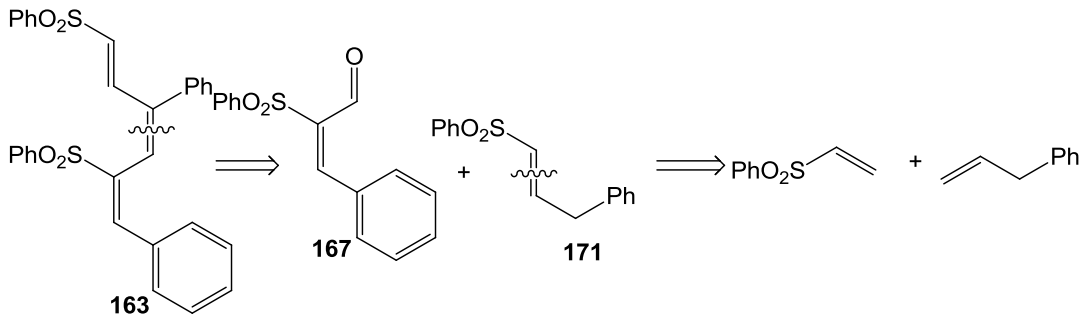
A possible formation of the arene **170** is depicted in **Scheme 128**. The transformation begins with a conjugate addition of propene **42** to the cinnamaldehyde **147**. The resulting carbanion is stabilized by the mesomeric effects of the nitrile, promoting the reduction of the alkene over a retro-Michael. The resultant Michael adduct **170a** isomerises to **170b** under basic conditions in a 1,3-H shift to the more stabilized secondary carbanion. The isomerised adduct then undergoes intramolecular cyclisation in a favoured 6-*exo-trig* fashion[130] to give the cycloalkene **170c**. A subsequent dehydration gives the cyclo diene **170d** which then undergoes base promoted aromatisation to give the arene **170**.



Scheme 128: Formation of arene **170** by conjugate addition and cyclisation

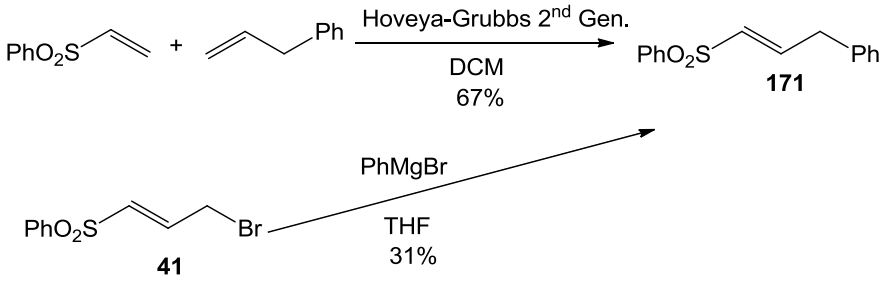
3.3.3 Attempted synthesis of an α-,ε- bis-activated triene

The synthesis of the α-,ε- bis-activated triene **163** was conducted concurrently with the synthesis of the tris-activated triene **162**, which we had hoped to achieve using a Knoevenagel condensation with the α-phenylsulfonyl aldehyde **167**. We applied the same approach in the retrosynthesis of the α,ε-bis activated triene **163** (**Scheme 129**). A similar disconnection led us to the previously synthesised α-phenylsulfonyl cinnamaldehyde **167** and the phenylsulfonyl propene **171**. The literature suggested that the phenylsulfonyl propene **171** could be synthesised using a cross-metathesis reaction.[255]



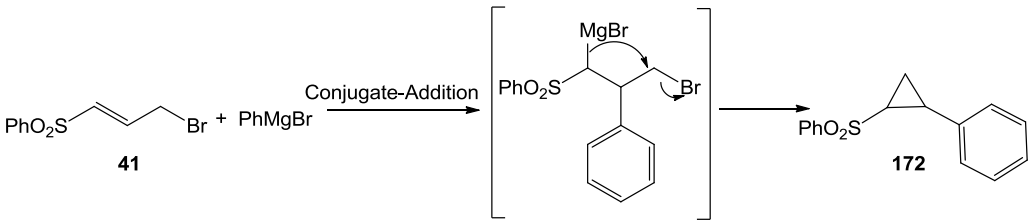
Scheme 129: Retrosynthesis of α,ε-bis activated triene **163**

We initially generated phenylsulfonyl propene **171** using the Hoveyda-Grubbs second generation catalyst to effect a cross-metathesis between vinyl-phenylsulfone and allyl benzene (**Scheme 129**). Despite good yield the relative cost of this reagent forced us to explore a more economical route for large scale production. The addition of phenyl Grignard to 3-bromo-1-phenylsulfonyl-prop-2-ene **41** proceeded in good yield with only trace amounts of unknown by-products. These by-products, presumably, could be the result of competing S_N2' and conjugate addition reactions. When the reaction was scaled up these side-reactions became more pronounced and the yield dropped to 31% (**Scheme 130**).



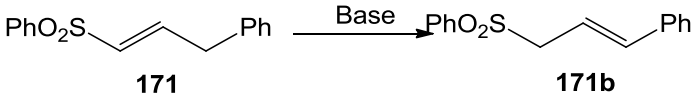
Scheme 130: Synthetic routes to propene **171**

The addition of phenyl Grignard at 0 °C to bromo-propene **41** is reported to give a 40% yield of the cyclopropanone **172.**[123] This competing side reaction is the result of a conjugate-addition and subsequent nucleophilic displacement of the bromide anion (**Scheme 131**).



Scheme 131: Result of conjugate-addition to bromo-propene **41**[123]

With the phenylsulfonyl propene **171** available we attempted the Knoevenagel condensation with benzaldehyde using similar conditions as that which we employed with the bis-phenylsulfonyl propene **42** (**See Section 3.3.2**). The use of butyllithium at low temperatures gave the isomerised product **171b** only. Vinyl sulfones are known to isomerise to allyl sulfones under basic conditions (**Scheme 132**).[256]



Scheme 132: Base promoted isomerisation of phenylsulfonyl propene **171**

When aluminium oxide was employed as a base we did not observe any reaction or isomerisation. The lack of reactivity of the α,β-unsaturated aldehyde **167** can be attribute to the factors discussed previously (**See Section 3.3.2**). The isomerisation of the propene most likely did not occur as the vinylic proton was not acidic enough for deprotonation by the aluminium oxide. The pK_a of the bis-sulfone **42** is approximately 12 while the mono-sulfone **171** is approximately 23.[246, 257]

3.4 Conclusion

In conclusion, our initial efforts to synthesise a 1,3-bis-cyano-diene *via* a Knoevenagel condensation were extremely low yielding. We attempted the synthesis of 1,3-bis-cyano-prop-2-ene through four routes. Firstly, the dehydration of 3-hydroxy-glutacononitrile gave low yields and mixed isomers of the product. We next tried to employ the Kolbe nitrile synthesis which resulted in polymeric mixtures. The synthesis of 3-((chloro(cyano)methyl)sulfonyl)propanenitrile for the purposes of performing a Ramberg-Bäcklund failed as we were unable to oxidize the sulfide derivate or chlorinate the sulfide derivative. Finally, the triple acid-dehydration of 3-hydroxy-glutaconamide resulted in low yields of the desired bis-cyano propene.

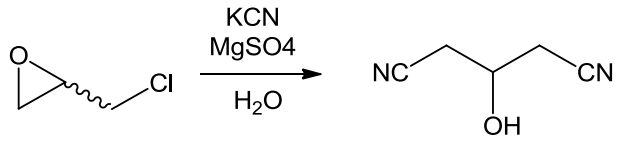
Our repeated efforts lead us to the knowledge that the instability of 1,3-bis-cyano-prop-2-ene under basic conditions made the Knoevenagel condensation an unattractive route. We instead were able to isolate the bis-cyano diene, after employing a Horner-Wadsworth-Emmons reaction, in substantial yield and with isomeric purity.

We then employed the bis-cyano diene in a 1,6-conjugate addition with several aldehydes achieving excellent yields and selectivities. We examined the base promoted aromatisation of the product of the 1,6-conjugate addition by the catalyst and optimised the methodology to maximize the desired product yield. This work represents our continuing efforts to build on the substrate scope for 1,6-conjugate additions promoted by charge de-localization. The promising results detailed in this thesis suggest that nitriles are suitable electron-withdrawing moieties for this purpose and expansion of substrate scope is underway. This is work that is complementary with our own group's research into bis-phosphonate ester butadienes and our collaborator's investigations into diester butadienes.

We next attempted to synthesise a family of trienes that may allow for the development of 1,8-conjugate addition methodology. There are currently no reported examples of organocatalysed 1,8-conjugate addition. Our initial triene gave a mixture of inseparable products under the standard reaction conditions. The triene was found to undergo an electro-cyclisation reaction under thermal conditions to give a biphenyl compound with an unusual crystal structure with a near zero twist angle. This planar biphenyl structure is unique in the literature. Attempted syntheses of alternative trienes failed due to the lack of reactivity of α-phenylsulfonyl cinnamaldehyde, and the conjugate addition of the starting material to α-cyano cinnamaldehyde. Future work includes Synthesising a charge de-localized triene using our developed Horner Wadsworth Emmons methodology.

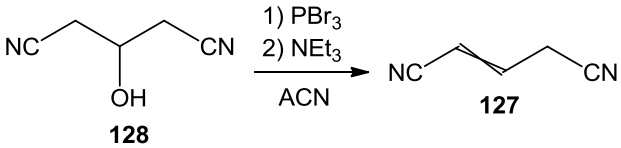
3.5 Experimental

For general experimental detail see section 2.4.1



128

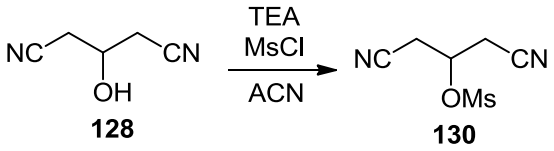
3-Hydroxyglutaronitrile 128:[226] This reaction was performed in triplicate to avoid using large quantities of KCN which is fatally toxic. To a 3-necked 100 mL round-bottomed flask fitted with a dropping funnel, condenser and thermometer was added Epsom salt (24 g, 97.2 mmol, 1.8 eq.) and water (35 mL). The solution was stirred until dissolution and placed in a bath of trichloroethylene. Dry-ice was added to the bath until the reaction temperature had decreased to 5 ^{o}C. Potassium cyanide (7.04 g, 108 mmol, 2 eq.) was added in one portion and the reaction temperature was maintained at 8 ^{o}C for a period of 45 minutes. (±) Epichlorohydrin (4.23 mL, 54 mmol, 1 eq.) was added dropwise over 30 minutes, strictly controlling the reaction temperature between 8-12 ^{o}C. The reaction was then cautiously allowed to warm to room temperature and stirred for 24 hours during which time the reaction mixture turned orange in colour. The mixture was then extracted with ethyl acetate (6 x 200 mL). The combined organics were washed with a saturated brine solution (100 mL) and dried overnight with Na_2SO_4. The 3 organic phases from the individual experiments were combined and concentrated to a dark brown oil. The oil was transferred to a Claisen flask fitted with a pipette sparger, thermometer and 5 cm Vigreux condenser and set up for vacuum distillation. Forerun of mainly 4-hydroxycrotononitrile (90 ^{o}C at 0.2 mbar), product condenses as a yellow free-flowing liquid, 5.83g (33%, **boiling point** 140 ^{o}C at 0.2 mbar). **^{1}H NMR** (300 MHz, D_2O) δ 4.76 (br d, 1 H, J=13.8 Hz, O*H*), 4.42-4.56 (m, 1 H, C*H*OH) 2.84-3.01 (m, 4 H, CH_2CN). **^{13}C NMR** (75 MHz, D_2O) δ 118.5 (*C*N), 63.0 (*C*H), 24.9 (*C*H_2). Matches known data.[258]



128 **127**

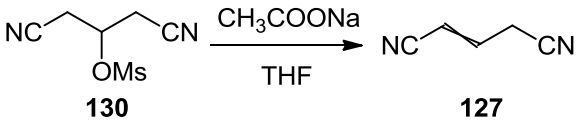
Glutacononitile 127: Phosphorus tribromide (11.1 mL, 117 mmol, 2 eq.) was added to a solution of 3-hydroxyglutaronitrile **128** (6.44 g, 58.5 mmol, 1 eq.) dissolved in acetonitrile (300 mL) which was subsequently refluxed at 85 ^{o}C for 1 hour. The precipitate was removed by filtration and the filtrate was placed in an ice-bath. To this was added triethylamine (33 mL, 234 mmol, 4 eq.) cautiously. The reaction was then poured onto a saturated solution of NH_4Cl (200 mL), and extracted with

methylene chloride (2 x 400 mL), the combined organics were dried over Na_2SO_4 and concentrated to give an orange oil and transferred to a Claisen flask fitted with a pipette sparger, thermometer and 5 cm Vigreux condenser and set up for vacuum distillation. Product condenses as a colourless free-flowing liquid which darkened on standing, 216 mg (4%, **boiling point** 60-65 °C at 0.2 mbar). Mixture of isomers (*E*/*Z* = 1/0.4). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* *E*-isomer; 6.62 (dt, 1 H, *J* = 16.3 Hz, *J* = 5.2 Hz, C*H*CH_2), 5.80 (dt, 1 H, *J* = 16.3 Hz, *J* = 2.0 Hz, CNC*H*), 3.37 (dd, 2 H, *J* = 5.2 Hz, 2.0 Hz C*H*$_2$). *Z*-isomer; 6.49 (dt, 1 H, *J* = 10.8 Hz, *J* = 7.1 Hz, C*H*CH_2), 5.86 (dt, 1 H, *J* = 10.8 Hz, *J* = 1.6 Hz, CNC*H*), 3.51 (dd, 2 H, *J* = 7.1 Hz, *J* = 1.6 Hz C*H*$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* *E*-isomer; 142.0 (*C*HCH_2), 115.8 (CH_2*C*N) 114.8 (*C*NCH), 104.5 (CN*C*H), 21.1 (CH_2). *Z*-isomer; 141.0 (*C*HCH_2), 115.8 (CH_2*C*N), 114.8 (*C*NCH), 105.3 (CN*C*H), 19.7 (CH_2). **ESI-MS** Calc. ($M+H^+$) = 93.0447 found ($M+H^+$) = 93.0447 (-0.61 ppm). Matches known data.[259]



128 **130**

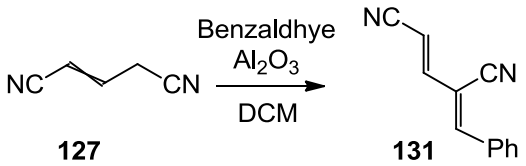
3-Mesyloxy-glutaronitrile 130: A solution of 3-hydroxyglutarononitrile **128** (2 mL, 20.89 mmol, 1 eq.) dissolved in anhydrous acetonitrile (100 mL) was brought to -40 °C at which point triethylamine (3.06 mL, 21.93 mmol, 1.05 eq.) was added dropwise. Stirring was continued for 2 hours at -40 °C and then allowed to come to room temperature overnight. The solvent was removed *in vacuo* and the green residue was dissolved in ethyl acetate and washed with distilled water (50 mL) and a saturated brine solution (50 mL). The organic layer was then dried with Na_2SO_4 and concentrated *in vacuo* to give a green oil. This oil was dissolved in a mixture of chloroform (10 mL) and ethyl acetate (10 mL) and stored at -20 °C overnight to afford thick colourless needles which were separated by suction filtration, 3.66 g (93%). **^{1}H NMR** (300 MHz, DMSO) *δ* 5.16-5.29 (m, 1 H, C*H*), 3.35 (s, 3 H, C*H*$_3$), 3.03-3.24 (m, 4 H, C*H*$_2$). **^{13}C NMR** (75 MHz, DMSO) *δ* 116.3 (*C*N), 71.4 (*C*H_3), 38.0 (*C*H), 23.0 (CH_2). **IR** (KBr disc) 3036 (methyl), 2973 (methyl), 2942 (methylene), 2259 (nitrile), 1431 (sulfonate), 1346 (methyl), 1176 (sulfonate), 1020, 959, 917, 854, 800, 733 (methylene), 531. **M.P.** 62-64 °C. **ESI-MS** $C_6H_8N_2O_3S$ Calc. ($M+H^+$) = 189.0328 found ($M+H^+$) = 189.0321 (-3.84 ppm).



130 **127**

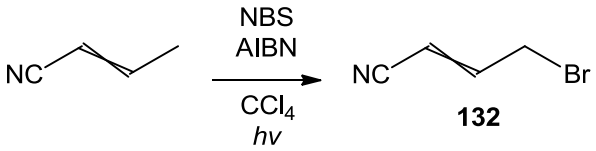
Glutacononitile 127: To a solution of 3-mesyloxy-glutaronitrile (941 mg, 5 mmol, 1 eq.) in THF (20 mL) was added anhydrous sodium acetate (441 mg, 5 mmol, 1 eq.). The reaction was heated to 40 °C

for 16 hours and the solvent was removed *in vacuo* to give an oily residue. The residue was partitioned between diethyl ether (20 mL) and distilled water (20 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined ethereal layers were passed through a pad of silica and then concentrated to a colourless liquid which darkened on standing, 276 mg (60%). Mixture of isomers (*E*/*Z* = 1/0.3). **^{1}H NMR** (300 MHz, $CDCl_3$) δ *E*-isomer; 6.62 (dt, 1 H, *J* = 16.3 Hz, *J* = 5.2 Hz, C*H*CH_2), 5.80 (dt, 1 H, *J* = 16.3 Hz, *J* = 2.0 Hz, CNC*H*), 3.37 (dd, 2 H, *J* = 5.16 Hz, 2.0 Hz CH_2). *Z*-isomer; 6.49 (dt, 1 H, *J* = 10.8 Hz, *J* = 7.1 Hz, C*H*CH_2), 5.86 (dt, 1 H, *J* = 10.8 Hz, *J* = 1.6 Hz, CNC*H*), 3.51 (dd, 2 H, *J* = 7.1 Hz, *J* = 1.6 Hz CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ *E*-isomer; 142.0 (*C*HCH_2), 115.8 (CH_2*C*N) 114.8 (*C*NCH), 104.5 (CN*C*H), 21.1 (CH_2). *Z*-isomer; 141.0 (*C*HCH_2), 115.8 (CH_2*C*N), 114.8 (*C*NCH), 105.3 (CN*C*H), 19.7 (CH_2). Matches known data and previous compound.[259]

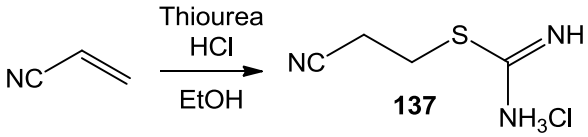


127 **131**

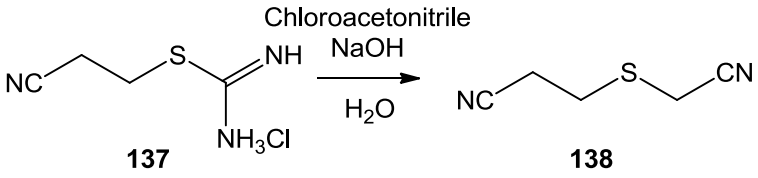
(1*E*,3*Z*)-1,3-Bis-cyano-4-phenyl-buta-1,3-diene 131: A suspension of activated aluminium oxide (28.39 g, 278.42 mmol, 33 eq.) in methylene chloride (50 mL) was stirred at 0 ^{o}C for 10 minutes. To this was added benzaldehyde (946 µL, 9.28 mmol, 1.1 eq.) and (*E*/*Z*) glutacononitrile **127** (777 mg, 8.437 mmol, 1 eq.). The reaction was stirred at room temperature for 30 minutes during which time the reaction darkened quickly. The suspension was passed through a pad of Celite which was washed with methylene chloride (200 mL). The solvent was removed *in vacuo* to yield a red/brown semi-solid which was purified by flash chromatography eluting with 100% petroleum ether -> 90% petroleum ether in diethyl ether. $\boldsymbol{R_f}$ (90% petroleum ether in diethyl ether) 0.53. Colourless-solid, 198 mg (13%). Single isomer, *EZ* identified by comparison with sample of **131** from HWE olefination. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83-7.98 (m, 2 H, Ar*H*), 7.42-7.61 (m, 3 H, Ar*H*), 7.32 (s, 1 H, δ*H*), 7.14 (d, 1 H, *J* = 15.7 Hz, CHC*H*), 5.91 (d, 1 H, *J* = 16 Hz, CNC*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.8 (δ*C*H), 147.0 (βCH), 132.7 (Ar*C*), 132.2 (Ar*C*H), 130.3 (Ar*C*H), 129.4 (Ar*C*H), 116.9 (*C*N), 114.6 (*C*N), 107.9 (*C*CN), 100.4 (CN*C*H). **M.P.** 110-112 ^{o}C (Lit. 101-103 ^{o}C).[225] Matches known data.[225]



(*E*/*Z*) 4-Bromocrotononitrile 132:[229] Freshly ground *N*-bromosuccinimide (14.24 g, 0.08 mol, 1 eq.) was suspended in distilled carbon tetrachloride (200 mL), to this was added a catalytic amount of azobisisobutyronitrile (10 mg, < 1% mol) and a commercial mixture of *cis*- and *trans*- isomers of crotononitrile (6.51 mL, 0.08 mol, 1 eq.). The reaction was refluxed at 80 ^{o}C and exposed to a 700 W tungsten lamp overnight. The reaction mixture was allowed to cool and the solids removed by filtration through Celite. The Celite was washed with an additional 20 mL of carbon tetrachloride and the combined filtrates were concentrated to an orange free-flowing liquid which was essentially pure (8.34 g, 0.057 mol, 71%). Analytically pure material was obtained by vacuum distillation (**boiling point** 90-95 ^{o}C at 0.4 mbar) giving a pale yellow free-flowing liquid. (**d** = 1.6786 @ 26 ^{o}C). Ratio of isomers 0.8 : 1 (*Z* : *E*). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* *E*-isomer; 6.74-6.88 (m, 1 H, C*H*CH_2), 5.65 (dt, 1 H, J=16.0 Hz, J=1.4 Hz, CNC*H*), 4.02 (dd, 2 H, J=7.1 Hz, J=1.4 Hz, CH_2). *Z*-isomer; 6.21-6.74 (m, 1 H, C*H*CH_2), 5.46 (dt, 1 H, J=10.7 Hz, J=0.7 Hz, CNC*H*), 4.16 (dd, J=8.1 Hz, J=0.7 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* *E*-isomer; 148.3 (*C*HCH_2), 116.2 (*C*N), 103.5 (CN*C*H), 28.8 (*C*H_2). *Z*-isomer; 147.6 (*C*HCH_2), 114.4 (*C*N), 102.3 (CN*C*H), 26.3 (*C*H_2). Matches known data.[260]

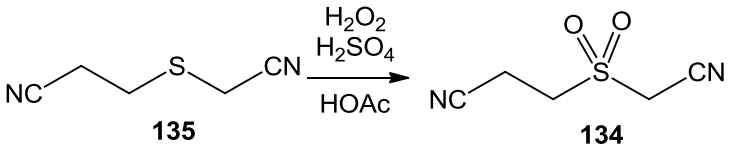


S-(β-Cyanoethyl)isothiuronium chloride 137:[233] Caution, acrylonitrile is extremely toxic! Thiourea (3.81 g, 50 mmol, 1 eq.) was dissolved in concentrated hydrochloric acid (7 mL) with the aid of heating. The excess reagent was then removed *in vacuo* and distilled water (20 mL) was added and the residue re-dissolved. The solution was again concentrated *in vacuo* to give a white solid that was free of excess acid. This solid was dissolved in hot absolute ethanol (17 mL) and acrylonitrile (4.91 mL, 75 mmol, 1.5 eq.) was added in one portion to the solution. The reaction was refluxed for 2 hours and allowed to cool. The precipitate was collected by vacuum filtration and washed with cold absolute ethanol (10 mL). Colourless crystals, 6.99 g (84%). **^{1}H NMR** (300 MHz, D_2O) *δ* 3.57 (t, 2 H, *J* = 6.7 Hz, CH_2S), 3.12 (t, 2 H, *J* = 6.7 Hz, CNCH_2). **^{13}C NMR** (75 MHz, D_2O) *δ* 172.3 (S*C*), 121.5 (*C*N), 28.9 (CN*C*H_2), 20.7 (*C*H_2S). **M.P.** 156-160 ^{o}C (Lit. 163-165 ^{o}C).[233] **ESI-MS** $C_4H_8ClN_3S$ Calc. ($M+Na^+$) = 120.0532 found ($M+Na^+$) = 120.0535 (2.61 ppm).



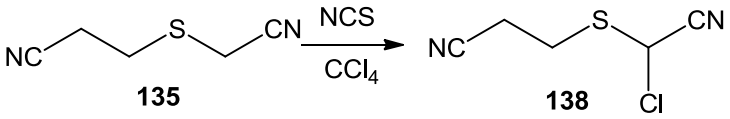
137 **138**

3-((Cyanomethyl)thio)propanenitrile 138: A solution of sodium hydroxide (80 mg, 2 mmol, 2 eq.) in distilled water (6 mL) was heated to 60 °C. To this was added the thiouronium salt **137** (166 mg, 1 mmol, 1 eq.) which was stirred for 2 minutes at 60 °C at which point chloroacetonitrile (63 µL, 1 mmol, 1 eq.) was added in one portion and stirring was continued at 60 °C for 5 minutes. The aqueous solution was then extracted with methylene chloride (3 x 20 mL) and the organic extracts were dried over Na_2SO_4. Removal of the solvent *in vacuo* yielded a clear oil, 124 mg (98%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.41 (s, 2 H, SCH_2CN), 2.98 (t, 2 H, J = 6.9 Hz, CH_2S), 2.74 (t, 2 H, J = 6.9 Hz, CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 118.1 (*C*N), 116.5 (*C*N), 27.9 (S*C*H_2CN), 18.4 (*C*H_2CN), 17.2 (*C*H_2S). **IR** (neat) 3646, 2974 (sulfide), 2934 (methylene), 2247 (nitrile), 1721, 1626, 1421 (methylene), 1399, 1328, 1292, 1210, 1066, 967, 923, 906, 435 cm^{-1}. **ESI-MS** $C_5H_6N_2S$ Calc. (M+H$^+$) = 127.0324 found (M+H$^+$) = 127.0329 (3.34 ppm).

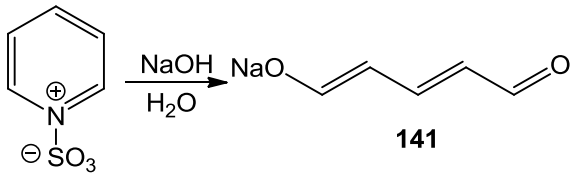


135 **134**

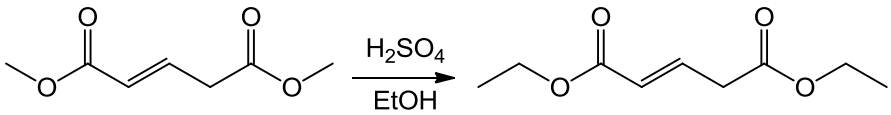
3-((Cyanomethyl)sulfonyl)propanenitrile 134:[234] A solution of the thioether **135** (1 g, 8 mmol, 1 eq.) in acetic acid (1.6 mL) was brought to 0 °C in an ice-water bath. To this was added, over 5 minutes, a solution of hydrogen peroxide (2.18 mL, 30% v/v, 19.2 mmol, 2.4 eq.), concentrated sulphuric acid (136 µL, 2.55 mmol, 0.32 eq.) in acetic acid (2.4 mL). The exotherm ceased after 30 minutes and the reaction was subsequently heated to 40 °C for 72 hours. The reaction was diluted with chloroform (30 mL) and the solid removed by filtration. The retentate was washed with cold acetone (20 mL) and dried in a vacuum oven. White solid, 823 mg (65%). TFA was used to solubilize sample for NMR analysis and was added dropwise until dissolution had occurred. **^{1}H NMR** (300 MHz, $CDCl_3$ + TFA) δ 4.44 (s, 2 H, SO_2CH_2CN), 3.80 (t, 2 H, J = 7.0 Hz), 3.17 (t, 2 H, J = 7.0 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$ + TFA) δ 109.3 (overlapping *C*N + *C*N), 48.4 (*C*H_2SO_2), 43.0 (CN*C*H_2SO_2), 10.9 (*C*H_2CN). **IR** (KBr disc) 2973 (alkane), 2938 (alkane), 2266 (nitrile), 1237 (sulfone), 1061 (sulfone), 779 (alkane), 625 (sulfone) cm^{-1}. **M.P.** 66-67 °C. **ESI-MS** $C_5H_6N_2O_2S$ Calc. (M+H$^+$) = 181.0042 found (M+H$^+$) = 184.0043 (0.55 ppm).



3-((Chloro(cyano)methyl)thio)propanenitrile: A solution of thioether **135** (1.26 g, 10 mmol, 1 eq.) and *N*-chlorosuccinimide (1.34 g, 10 mmol, 1 eq.) in distilled carbon tetrachloride (10 mL) was stirred for 12 hours at room temperature. The resultant suspension was filtered and the filtrate was concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography 100% petroleum ether -> 80% petroleum ether in diethyl ether. $\boldsymbol{R_F}$ (80% petroleum ether in diethyl ether) 0.18, bis-chlorinated side-product has an R_F of 0.22. Yellow oil, 1.53 g (95%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.75 (s, 1 H, C*H*CN), 3.27 (td, 2 H, *J* = 7.0 Hz, *J* = 2.4 Hz, CH_2S), 2.92 (t, 2 H, *J* = 7 .0 Hz, CH_2CN). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 117.7 (*C*N), 114.2 (*C*N), 45.5 (*C*HCl), 27.2 (*C*H_2CN), 18.2 (S*C*H_2). **IR** (Neat) 3468 , 3349, 3194, 2953 (methylene), 2252 (nitrile), 1751, 1695, 1420 (methylene), 1329, 1292, 1209, 949, 905, 744 (methylene), 676 (alkyl halide) cm^{-1}. **ESI-MS** $C_5H_5ClN_2S$ Calc. ($M+H^+$) = 182.9754 found ($M+H^+$) = 182.9763 (4.92 ppm).

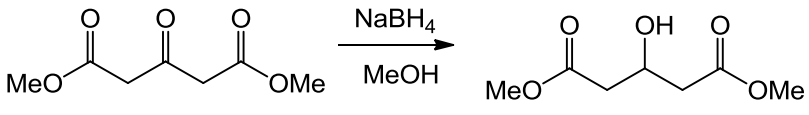


Glutaconaldehyde sodium salt 141:[239] To a 2-necked flask fitted with a mechanical stirrer and a glass stopper was added sodium hydroxide (14.67 g, 366.75 mmol, 3.67 eq.) and distilled water (56 mL). The reaction was stirred until dissolution and then cooled to -20 ^{o}C. Commercial sulfur trioxide pyridine complex (15.92 g, 100 mmol, 1 eq.) that had been previously chilled to -20 ^{o}C was added in one portion to the reaction. The yellow mixture was stirred for a further 20 minutes at -20 ^{o}C before being allowed to come to room temperature over 30 minutes. The dark-orange suspension was then heated for 1 hour at 60 ^{o}C and then stored at -5 ^{o}C until crystallisation was complete. The green/brown precipitate was collected by vacuum filtration and packed into a tight cake before being washed with acetone (3 x 100 mL). The crystals were dissolved in methanol (200 mL) and brought to reflux at which point activated charcoal (3.5 g) was added. The solution was refluxed for a further 15 minutes at which point it was rapidly filtered and the filtrate was reduced *in vacuo* to a third of its volume and stored at -20 ^{o}C overnight. The orange crystals were separated by vacuum filtration and dried under high vacuum. Orange needles, 6.13 g (51%). **^{1}H NMR** (300 MHz, DMSO) 8.61 (d, 2 H, *J* = 9.2 Hz, OC*H* + C*H*O), 7.09 (t, 1 H, *J* = 13.0 Hz, CHC*H*CH), 5.01-5.29 (m, 2 H, OCHC*H* + C*H*CHO). **^{13}C NMR** (75 MHz, DMSO) δ 185.0 (O*C*H + *C*HO), 160.6 (CH*C*HCH), 107.0 (OCH*C*H + *C*HCHO). **M.P.** >300 ^{o}C (Lit. >350 ^{o}C).[239] Matches known data.[239]



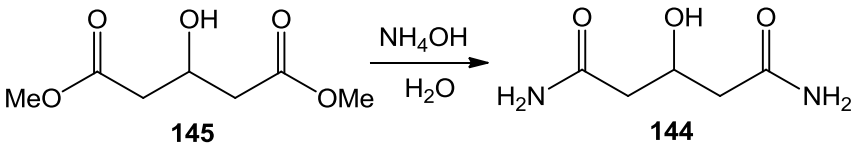
142

Diethyl glutaconate 142: A solution of commercial dimethyl glutaconate (10 mL, 71.07 mmol, 1 eq.) in absolute ethanol (200 mL) was treated with concentrated sulphuric acid (1 mL) and refluxed for 3 hours. The solvent was then removed *in vacuo* and the residue partitioned between methylene chloride (100 mL) and a saturated sodium hydrogen carbonate solution (100 mL) the organic layer was separated and the aqueous layer was extracted further with methylene chloride (2 x 100 mL). The combined extracts were dried over Na_2SO_4 and reduced *in vacuo* to give a colourless oil, 13.18 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) 6.71-7.0 (m, 1 H, C*H*CH_2), 5.76 (d, 1 H, *J* = 15.7 Hz, C*H*CH), 3.90-4.11 (m, 4 H, C*H*$_2$$CH_3$), 3.00-3.15 (m, 2 H, C*H*$_2$), 1.02-1.18 (m, 6 H, C*H*$_3$). Matches commercial sample.



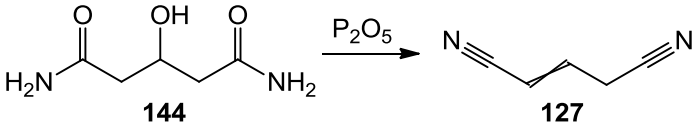
142

β-Hydroxy dimethylglutaconate 142:[241] To a solution of freshly distilled methanol (10 mL) was added dimethyl acetonedicarboxylate (1.44 mL, 10 mmol, 1 eq.). The solution was then stirred vigorously in an ice-water bath for ten minutes. Sodium borohydride (151 mg, 4 mmol, 0.4 eq.) was added piecemeal to the cooled reaction mixture (so neither the exotherm nor generation of hydrogen caused the reaction to boil over). After the addition was complete the reaction was allowed to return to room temperature and stirred for 3 hours. The methanol was then removed *in vacuo* and the residue was dissolved in water (10 mL). The aqueous solution was extracted with diethyl ether (4 x 25 mL). The combined ethereal solution was subsequently dried with Na_2SO_4 and concentrated to a colourless liquid, 1.35 g (77%). **^{1}H NMR** (300 MHz, $CDCl_3$): 4.51 (m, 1 H, C*H*), 3.83 (s, 6 H, CH_3), 3.47 (s, 1 H, O*H*), 2.55 (d, 4 H, *J* = 6.3 Hz, C*H*$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$): 172.4, 64.8 (*C*OH), 52.0 (*C*H_2), 40.7. Matches known data.[241]



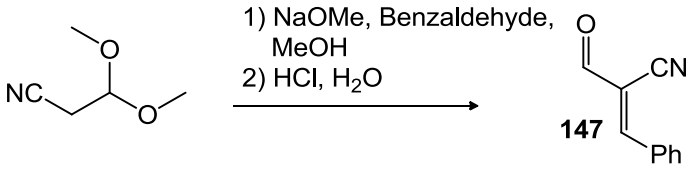
145 **144**

β-Hydroxy glutaconamide 144: To a 100 mL round-bottomed flask containing β-hydroxy dimethylglutaconate 145 (1.35 g, 7.68 mmol, 1 eq.) was added 30 mL of concentrated ammonium hydroxide. The solution was stirred overnight at room temperature. The reaction was monitored by removing aliquots of the reaction, extraction of the aliquot with diethyl ether and running a TLC of the extract in 50:50 EtOAc:Pet. ether (b.p. 40-60 ^{o}C). A $KMnO_4$ stain was used to visualize the starting material. The reaction mixture was cherry red upon completion and was then concentrated *in vacuo* to give an aqueous residue; the aqueous residue was dark green in colour. Methanol (10 mL) was added to the aqueous residue and the reaction was concentrated again. This procedure was repeated until no water remained and the residue was a dark red solid. Absolute ethanol (20 mL) was then added and the residue was dissolved by vigorous heating. The product precipitated after storing the ethanolic solution at -20 ^{o}C overnight. The product was collected by suction filtration and washed with 5 mL of chilled absolute ethanol and 10 mL of petroleum ether to yield a purple/grey powder, 0.76 g (67%). **^{1}H NMR** (300 MHz, D_2O): 4.32 (s, 1H), 2.42 (s, 4H). **^{13}C NMR** (75 MHz, D_2O): 176.3, 65.6 (*C*OH), 42.4. **IR** (KBr disc) 3410 (hydroxy), 3303 (hydroxy), 3179 (amide), 1651 (amide), 1435 (alkane), 1302, 1253 (amide), 1177 (hydroxy), 1096, 865, 778 (alkane), 620, 579 cm^{-1}. **M.P.** Decomposition. **ESI-MS** $C_5H_{10}N_2O_3$ Calc. ($M+H^+$) = 147.0764 found ($M+H^+$) = 147.0763 (-0.72 ppm).

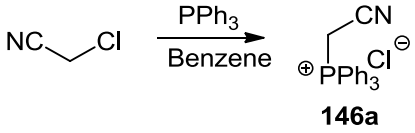


144 **127**

Glutacononitrile 127: To a 25 mL round bottom flask was added β-hydroxy bis-amide **144** (500 mg, 3.42 mmol, 1 eq.), followed by dry powdered P_2O_5 (2.5 g, 17.61 mmol, 5.15 eq.) The powders were thoroughly mixed with a spatula and distilled to an iced flask using a Buchi Kugelröhr oven whose temperature was slowly raised from 120 ^{o}C to 170 ^{o}C over 30 mins under an atmosphere of 0.2 mbar. The product was a clear, free flowing liquid, 104 mg, (33%). Mixture of isomers (*E*/*Z* = 2.5/1) **^{1}H NMR** (300 MHz, $CDCl_3$) δ *E*-isomer; 6.62 (dt, 1 H, *J* = 16.3 Hz, *J* = 5.2 Hz, C*H*CH_2), 5.80 (dt, 1 H, *J* = 16.3 Hz, *J* = 2.0 Hz, CNC*H*), 3.37 (dd, 2 H, *J* = 5.2 Hz, 2.0 Hz CH_2). *Z*-isomer; 6.49 (dt, 1 H, *J* = 10.8 Hz, *J* = 7.1 Hz, C*H*CH_2), 5.86 (dt, 1 H, *J* = 10.8 Hz, *J* = 1.6 Hz, CNC*H*), 3.51 (dd, 2 H, *J* = 7.1 Hz, *J* = 1.6 Hz CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ *E*-isomer; 142.0 (*C*HCH_2), 115.8 (CH_2*C*N) 114.8 (*C*NCH), 104.5 (CN*C*H), 21.1 (CH_2). *Z*-isomer; 141.0 (*C*HCH_2), 115.8 (CH_2*C*N), 114.8 (*C*NCH), 105.3 (CN*C*H), 19.7 (CH_2). Matches known data and previous compound.[259]

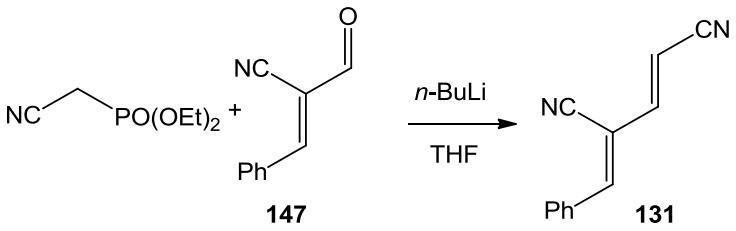


***E*-α-Cyano-cinnamaldehyde 147:**[243] Sodium metal (540 mg, 23.4 mmol, 2.34 eq.) was carefully dissolved in methanol (4 mL). A neat mixture of cyano acetaldehyde dimethyl acetal (1.15 mL, 10 mmol, 1 eq.) and benzaldehyde (1.02 mL, 10 mmol, 1 eq.) was dropped onto the methoxide over the course of an hour. The reaction was then left to stir at room temperature overnight at which point the solvent was removed *in vacuo* and the reaction was dissolved in 6 M HCl (40 mL) and stirred for 1 hour. The precipitate was collected by filtration and dissolved in diethyl ether (50 mL). Petroleum ether was added until precipitation began and was then stored overnight at -20 °C. The resultant crystals were isolated by vacuum filtration, colourless needles, 676 mg (43%). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 9.61 (s, 1 H, C*H*O), 8.06 (d, 2 H, *J* = 7.4 Hz, Ar*H*), 7.95 (s, 1 H, C*H*), 7.48-7.24 (s, 3 H, Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 187.1 (*C*HO), 159.3 (*C*H), 134.4 (Ar*C*H), 131.4 (Ar*C*H), 131.3 (Ar*C*), 129.6 (Ar*C*H), 114.2 (*C*), 112.4 (*C*N). **M.P.** 82-84 °C (Lit. 85-86 °C).[261] Matches known data for *E*-isomer.[262]

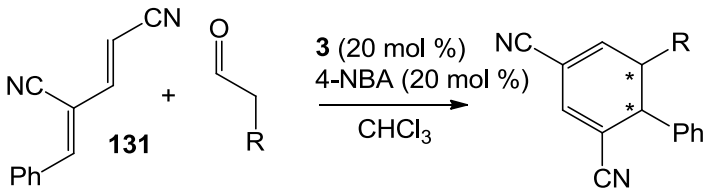


146a

(Cyanomethyl)triphenylphosphonium chloride 146a:[263] A solution of chloroacetonitrile (2.94 mL, 46.46 mmol, 2 eq.), triphenylphosphine (6 g, 22.88 mmol, 1 eq.) in benzene (25 mL) was refluxed overnight. The solution was allowed to cool and the resultant precipitate was isolated by vacuum filtration and washed with acetone (50 mL) to give a white solid, 4.33 g (56%). **^{1}H NMR** (300 MHz, D_2O) *δ* 7.73-7.94 (m, 3 H, Ar*H*), 7.48 – 7.73 (m, 12 H, Ar*H*), 4.70 (s, 2 H, *C*H_2). **^{13}C NMR** (75 MHz, D_2O) *δ* 136.4 (d, *J* = 3 Hz, Ar*C*H), 133.6 (d, *J* = 10.9 Hz, Ar*C*H), 130.6 (d, *J* = 13.4 Hz, Ar*C*H), 115.8 (Ar*C*), 114.6 (*C*N), 112.4 (d, *J* = 9.1 Hz, *C*H_2). **M.P.** Decomposition (Lit. Decomposition).[264] Matches known data.[264]

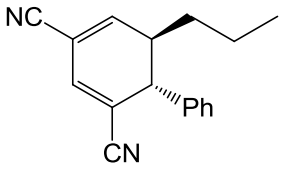


(1*E*,3*Z*)-1,3-Bis-cyano-4-phenyl-buta-1,3-diene 131: To an oven-dried Schlenk tube purged with argon was added diethyl cyanomethylphosphonate (356 µL, 2.2 mmol, 1.1 eq.) and anhydrous THF (20 mL). The solution was stirred until homogenous and then placed in an ice-acetone bath. To this was added *n*-butyllithium (880 µL, 2.2 mmol, 1.1 eq.) dropwise. When the addition was complete the reaction was stirred at room temperature for 1 hour at which point it was brought to -78 °C. To this was added a solution of α-cyano-cinnamaldehyde (314 mg, 2 mmol, 1 eq.) in anhydrous THF (2 mL) previously chilled to -78 °C. The reaction was stirred for an additional 24 hours at which point the reaction was quenched with a solution of saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts were dried over Na_2SO_4 and reduced *in vacuo* to a red oil. The oil was dissolved in minimal methylene chloride and passed through a pad of silica washing with a mixture of diethyl ether (10 mL) in petroleum ether (90 mL). The solvent was removed *in vacuo* to give a colourless solid which was crystallised from ethyl acetate : petroleum ether (1 : 2) to give colourless opaque needles, 223 mg (62%). Single isomer, presumably *EZ* from *E*-cinnamaldehyde. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.83-7.98 (m, 2 H, Ar*H*), 7.42-7.61 (m, 3 H, Ar*H*), 7.32 (s, 1 H, δ*H*), 7.14 (d, 1 H, *J* = 15.9 Hz, CHC*H*), 5.91 (d, 1 H, *J* = 15.9 Hz, CNC*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 150.8 (δ*C*H), 147.0 (*β*CH), 132.7 (Ar*C*), 132.2 (Ar*C*H), 130.3 (Ar*C*H), 129.4 (Ar*C*H), 116.9 (*C*N), 114.6 (*C*N), 107.9 (*C*CN), 100.4 (CN*C*H). **IR** (KBr disc) 3048 (alkene), 2959 (aromatic), 2218 (nitrile), 1610 (alkene), 1594 (aromatic), 1148, 1191, 965 (alkene), 753 (aromatic), 684 (aromatic) cm^{-1}. **M.P.** 110-112 °C (Lit. 101-103 °C).[225] Matches known data.[225]



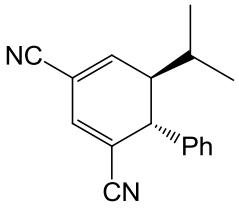
General procedure for the 1,6-addition of aldehydes to 1,3-bis-cyano-4-phenyl-buta-1,3-diene 131: To a sample vial containing **3** (13 mg, 0.04 mmol, 20 mol%), 4-nitrobenzoic acid (6.7 mg, 0.04 mmol, 20 mol%) and chloroform (1 mL) was added the aldehyde (0.8 mmol, 4 eq.) and 1,3-bis-cyano-4-phenyl-buta-1,3-diene (36 mg, 0.2 mmol, 1 eq.). The solution was stirred at 4 °C until consumption of starting material was realized by TLC. The reaction was immediately passed through a pad of silica

with 10 volumes of diethyl ether. The filtrate was directly loaded onto Celite and purified by flash chromatography.



150

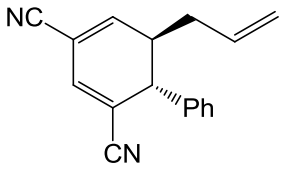
6-Propyl-1,6-dihydro-[1,1'-biphenyl]-2,4-dicarbonitrile 150: From *n*-valeraldehyde according to general procedure for 24 hours with **(*R*)-3**. Purified by flash chromatography using gradient elution 100% petroleum ether -> 90% petroleum ether in ethyl acetate. R_F (90% petroleum ether in ethyl acetate) 0.51. Colourless gum, 36 mg (72%). No diastereomer detected by NMR, relative stereochemistry applied to *anti*- products, enantiopurity determined by **HPLC R_T** (IB) 16.32(*R,R*), 17.78(*S,S*) eluted from 5% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28-7.43 (m, 3 H, Ar*H*), 7.12-7.23 (m, 2 H, Ar*H*), 6.86 (dd, 1 H, *J* = 1.1 Hz, *J* = 5.5 Hz, δ*H*), 6.76 (t, 1 H, *J* = 1.1 Hz, β*H*), 3.54 (d, 1 H, *J* = 4.7 Hz, C*H*Ph), 2.80 (apparent pentet, 1 H, *J* = 6.7 Hz, C*H*Pr), 1.37-1.70 (m, 4 H, CH_2CH_2), 0.94 (t, 3 H, *J* = 7.0 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.2 (δ*C*H), 139.0 (Ar*C*), 132.7 (β*C*H), 129.4 (Ar*C*H), 128.3 (Ar*C*H), 127.2 (Ar*C*H), 117.5, 116.4, 114.6, 109.0, 44.4 (*C*HPh), 42.0 (*C*HPr), 35.5 ($CH_2CH_2CH_3$), 19.4 ($CH_2CH_2CH_3$), 13.9 (CH_3). **IR** (neat) 2960, 2873, 2215 (nitrile), 1639, 1536, 1464, 1261, 872, 738, 700 cm^{-1}. **ESI-MS** $C_{17}H_{16}N_2$ Calc. ($M+H^+$) = 249.1386 found ($M+H^+$) = 249.1386 (-0.22 ppm). **$[\alpha]_{589}^{21}$** -332^o (c = 0.7).



152

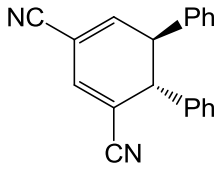
6-Isopropyl-1,6-dihydro-[1,1'-biphenyl]-2,4-dicarbonitrile 152: From *iso*-valeraldehyde according to general procedure for 68 hours with **(*R*)-3**. Purified by flash chromatography using gradient elution 100% petroleum ether -> 90% petroleum ether in ethyl acetate. R_F (90% petroleum ether in ethyl acetate) 0.49. Colourless gum, 33 mg (66%). No diastereomer detected by NMR, relative stereochemistry applied to *anti*- products, enantiopurity determined by **HPLC R_T** (IB) 16.20 (*R,R*), 18.37 (*S,S*) eluted from 5% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30-7.41 (m, 3 H, Ar*H*), 7.13-7.22 (m, 2 H, Ar*H*), 6.83 (dd, 1 H, *J* = 1.1 Hz, *J* = 5.4 Hz, δ*H*), 6.74 (t, 1 H, *J* = 1.2 Hz, β*H*), 3.61 (dd, 1 H, *J* = 1.1 Hz, *J* = 5.6 Hz, C*H*Ph), 2.69 (apparent q, 1 H, *J* = 5.4 Hz, *CHi*Pr), 1.81-1.95 (m, 1 H, C*H*$(CH_3)_2$), 1.02 (d, 3 H, *J* = 2.1 Hz, CH_3), 1.00 (d, 3 H, *J* = 2.1 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.2 (δ*C*H), 140.0

(Ar*C*), 132.5 (β*C*H), 129.4 (Ar*C*H), 128.3 (Ar*C*H), 127.2 (Ar*C*H), 117.4, 116.4, 115.2, 109.8, 48.8 (*C*H*i*Pr), 42.3 (*C*HPh), 32.6 (*C*H(CH_3)$_2$), 19.5 (*C*H_3), 18.7 (*C*H_3). **ESI-MS** $C_{17}H_{16}N_2$ Calc. ($M+H^+$) = 249.1386 found ($M+H^+$) = 249.1386 (0 ppm). **[α]$_{589}^{21}$** -241^o (c = 0.7).



153

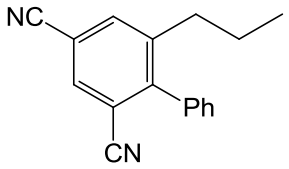
6-Allyl-1,6-dihydro-[1,1'-biphenyl]-2,4-dicarbonitrile 153: From 4-pentenal according to general procedure for 30 hours with **(*R*)-3**. Purified by flash chromatography using gradient elution 100% petroleum ether -> 90% petroleum ether in ethyl acetate. ***R*$_F$** (90% petroleum ether in ethyl acetate) 0.55. Colourless gum, 37 mg (75%). No diastereomer detected by NMR, relative stereochemistry applied to *anti*- products, enantiopurity determined by **HPLC R$_T$** (IB) 22.43 (*R*,*R*), 27.58 (*S*,*S*) eluted from 5% IPA in heptane. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.31-7.44 (m, 3 H, Ar*H*), 7.14-7.23 (m, 2 H, Ar*H*), 6.85 (dd, 1 H, *J* = 1.2 Hz, *J* = 5.3 Hz, δ*H*), 6.77 (t, 1 H, *J* = 1.3 Hz, β*H*), 5.62-5.84 (m, 1 H, CH_2CHCH_2), 5.25 (d, 1 H, *J* = 10.1 Hz, CHCH_2-*cis*), 5.18 (dd, 1 H, *J* = 1.2 Hz, *J* = 15.8 Hz, CHCH_2-*trans*), 3.65 (d, 1 H, *J* = 6.4 Hz, C*H*Ph), 2.88 (apparent pentet, 1 H, *J* = 6.7 Hz, C*H*Propene), 2.20-2.35 (m, 2 H, CH_2CHCH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 149.3 (δ*C*), 138.8 (Ar*C*), 132.9 (*C*HCH_2), 132.8 (β*C*), 129.4 (Ar*C*H), 128.4 (Ar*C*H), 127.4 (Ar*C*H), 119.9 (*C*H_2), 117.3, 116.2, 114.7, 109.4, 43.6 (*C*HPh), 41.8 (*C*HPropene), 37.1 (CH_2CHCH_2). **ESI-MS** $C_{17}H_{14}N_2$ Calc. ($M+H^+$) = 247.1230 found ($M+H^+$) = 247.1220 (-4.06 ppm). **[α]$_{589}^{21}$** -373^o (c = 0.7).



154

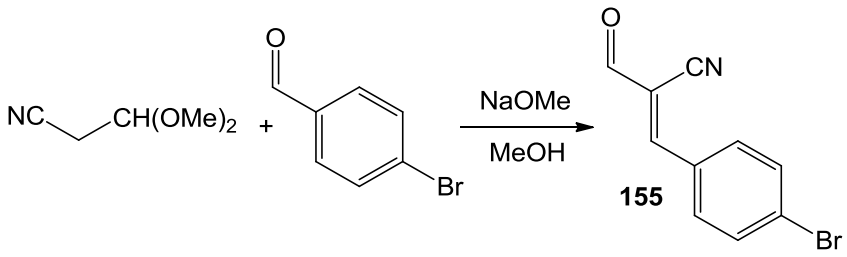
1',2'-Dihydro-[1,1':2',1''-terphenyl]-3',5'-dicarbonitrile 154: From freshly opened phenylacetaldehyde according to general procedure, without nitro-benzoic acid, for 38 hours with **(*S*)-3**. Purified by flash chromatography using gradient elution 100% petroleum ether -> 90% petroleum ether in ethyl acetate. ***R*$_F$** (90% petroleum ether in ethyl acetate) 0.39. Yellow/Green gum, 42 mg (75%). No diastereomer detected by NMR, relative stereochemistry applied to *anti*- products, enantiopurity determined by **HPLC R$_T$** (IB) 37.80 (*R*,*R*), 43.618 (*S*,*S*) eluted from 10% IPA in heptane (Flow 0.75 mL/min). **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.29-7.40 (m, 6 H, Ar*H*), 7.13-7.20 (m, 2 H, Ar*H*), 7.05-7.12 (m, 2 H, Ar*H*), 6.86-6.92 (m, 2 H, overlapping δ*H* + β*H*), 3.98 (dd, 1 H, *J* = 5.1 Hz, *J* = 7.2 Hz, CHC*H*Ph), 3.85 (dd, 1 H, *J* = 1.6 Hz, *J* = 7.2 Hz, CC*H*Ph). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 147.4 (δ*C*), 139.5

(Ar*C*), 139.3 (Ar*C*), 132.9 (β*C*), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 127.5 (Ar*C*H), 127.5 (Ar*C*H), 117.1, 116.2, 114.8, 109.5, 48.8 (CH*C*HPh), 47.8 (C*C*HPh). **ESI-MS** $C_{20}H_{14}N_2$ Calc. ($M+Na^+$) = 305.1049 found ($M+Na^+$) = 305.1039 (-3.21 ppm). **$[\alpha]_{589}^{21}$** +229° (c = 0.8).



151

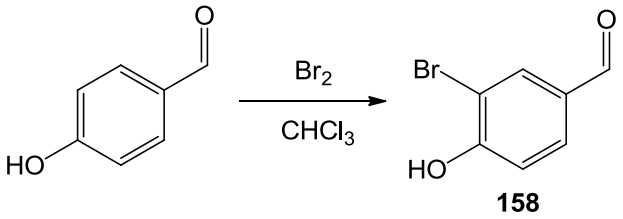
6-Propyl-[1,1'-biphenyl]-2,4-dicarbonitrile 151: Purified by flash chromatography using gradient elution 100% petroleum ether -> 90% petroleum ether in ethyl acetate. R_F (90% petroleum ether in ethyl acetate) 0.58. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, 1 H, *J* = 1.7 Hz, CNCC*H*CCN), 7.78 (d, 1 H, *J* = 1.7 Hz, CNCC*H*CCH$_2$), 7.48-7.58 (m, 3 H, Ar*H*), 7.22-7.31 (m, 2 H, Ar*H*), 2.50 (t, 2 H, *J* = 7.7 Hz, CC*H*$_2$CH$_2$), 1.42-1.52 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 0.80 (t, 3 H, *J* = 7.3 Hz, C*H*$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.6 (*C*Ph), 144.2 (Ar*C*), 136.3 (CNC*C*HCCH$_2$), 135.7 (*C*CH$_2$), 133.4 (CNCCHCCN), 129.2 (Ar*C*H), 128.9 (Ar*C*H), 128.5 (Ar*C*H), 117.0 (*C*N), 116.4 (*C*N), 115.1 (*C*CN), 112.5 (*C*CN), 34.9 (CCH$_2$), 23.8 (CH$_2$*C*H$_2$CH$_3$), 13.7 (*C*H$_3$). **ESI-MS** $C_{17}H_{14}N_2$ Calc. ($M+H^+$) = 248.1261 found ($M+H^+$) = 248.1270 (3.44 ppm).



155

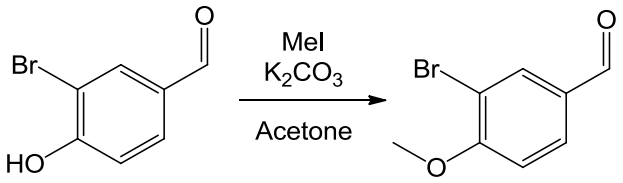
***E*-3-Bromo-4-methoxy-α-cyano-cinnamaldehyde:** To a neat solution of 5.4 M sodium methoxide in methanol (3.7 mL, 20 mmol, 2 eq.) was added dropwise a solution of cyano acetaldehyde dimethyl acetal (1.15 mL, 10 mmol, 1 eq.) and 4-bromo-benzaldehyde (1.85 g, 10 mmol, 1 eq.) in methanol 5 mL. The reaction was stirred overnight and the solvent removed *in vacuo* to give a pale-yellow residue which was stirred in 6 M HCl (50 mL) for 1 hour. The precipitate was collected by vacuum filtration and dissolved in methylene chloride (50 mL) and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a pale-yellow solid which was dissolved in minimal hot diethyl ether. Petroleum ether was added until the solution became cloudy and the mixture was stored at -20 °C overnight. The resultant crystals were collected by vacuum filtration and washed with cold diethyl ether (10 mL). Off-white needles, 1.16 g (49%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.60 (s, 1 H, C*H*O), 7.83-8.02 (m, 3 H, overlapping Ar*H* + β*H*), 7.63-7.79 (m, 2 H, Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.7 (*C*HO), 157.5 (β*C*H), 133.0 (Ar*C*H), 132.5 (Ar*C*H), 130.1 (Ar*C*), 129.6 (Ar*C*), 114.0 (*C*), 112.8 (*C*N). **IR**

(KBr disc) 2868 (aldehyde), 2221 (nitrile), 1695 (aldehyde), 1608 (alkene), 1582 (aldehyde), 1159 (aromatic), 1077 (aldehyde), 814 (alkene), 761, 602 (aromatic) cm^{-1}. **M.P.** 140-143 ^{o}C. **ESI-MS** $C_{10}H_6BrNO$ Calc. $(M+H^+)$ = 235.9706 found $(M+H^+)$ = 235.9709 (1.30 ppm).



158

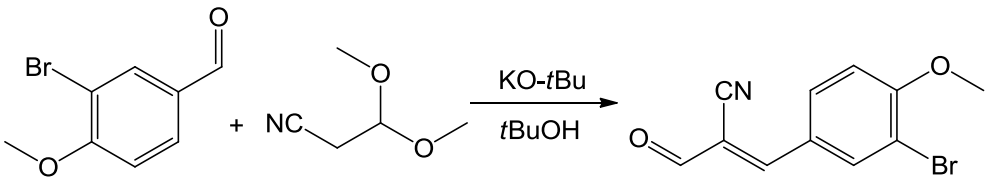
3-Bromo-4-hydroxy-benzaldehyde 158:[265] A solution of chloroform (250 mL), methanol (25 mL) and 4-hydroxy-benzaldehyde (25 g, 0.205 mol, 1 eq.) was stirred until dissolution. To this was added dropwise a solution of bromine (11.5 mL, 0.225 mol, 1.1 eq) in chloroform (50 mL). The reaction mixture turned orange during the addition and was allowed to stir at room temperature until the orange colour had faded (2.5 hours). The reaction was then washed with portions of water (200 mL) until the wash was no longer acidic. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* to a white solid. The solid was dissolved in a minimal amount of hot chloroform (~200 mL) and stored overnight at -20 ^{o}C. The crystals were collected by vacuum filtration to give colourless opaque micro-crystals, 36.62 g (89%). **^{1}H NMR** (300 MHz, DMSO) δ 11.47 (br s, 1 H, O*H*), 9.76 (s, 1 H, C*H*O), 8.01 (d, 1 H, *J* = 2.0 Hz, *o*-Ar*H*), 7.74 (dd, 1 H, *J* = 2.0 Hz, *J* = 8.4 Hz, *m*-Ar*H*), 7.10 (d, 1 H, *J* = 8.4 Hz, *o*-Ar*H*). **^{13}C NMR** (75 MHz, DMSO) δ 190.1 (*C*HO), 159.7 (*C*OH), 134.9 (Ar*C*H), 130.4 (Ar*C*H), 129.5 (*i*-Ar*C*), 116.5 (Ar*C*H), 110.0 (*C*Br). **M.P.** 125-27 ^{o}C (Lit. 123-124 ^{o}C).[266] Matches known data.[267]



158 **157**

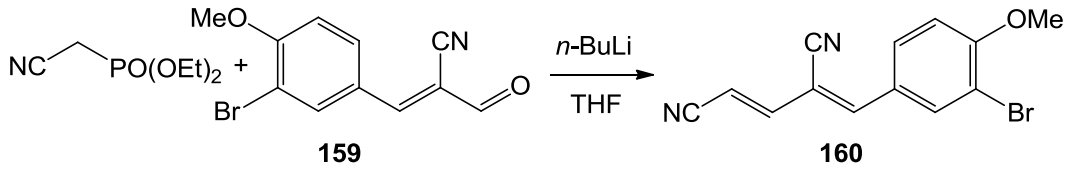
3-Bromo-*p*-anisaldehyde 157: A suspension of 3-bromo-4-hydroxy-benzaldehyde **158** (25 g, 0.124 mol, 1 eq.), anhydrous potassium carbonate (34.38g, 0.249 mmol, 2 eq.), methyl iodide (15.5 mL, 0.249 mmol, 2 eq.) and acetone (200 mL) were heated to reflux for 2 hours. When the reaction was cool the excess base was removed by vacuum filtration and the filtrate concentrated *in vacuo*. The semi-solid residue was taken into ethyl acetate (100 mL) and washed with water (3 x 100 mL) and brine solution (1 x 100 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to yield a thick yellow oil which was dissolved in diethyl ether (150 mL) and stored at -20 ^{o}C overnight. The crystals were collected by vacuum filtration to give colourless micro-crystals, 26.59g (>99%). **^{1}H**

NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1 H, C*H*O), 7.92 (d, 1 H, *J* = 1.9 Hz, *o*-Ar*H*), 7.69 (dd, 1 H, *J* = 1.9 Hz, *J* = 8.5 Hz, *m*-Ar*H*), 6.91 (d, 1 H, *J* = 8.5 Hz, *o*-Ar*H*), 3.87 (s, 3 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.5 (*C*HO), 160.5 (*C*OMe), 134.1 (Ar*C*H), 131.3 (Ar*C*H), 130.6 (*i*-Ar*C*), 112.5 (*C*Br), 111.6 (Ar*C*H), 56.6 (*C*H_3). **M.P.** 43-44 °C (Lit. 43-44 °C).[266] Matches known data.[268]



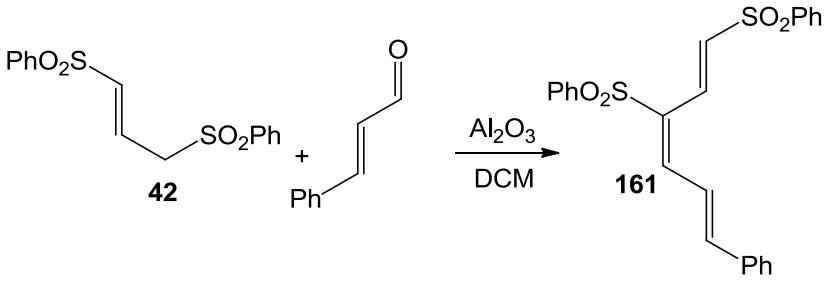
157 **159**

***E*-3-bromo-4-methoxy-α-cyano-cinnamaldehyde 159:** A solution of 3,3-dimethoxypropionitirile (1.15 mL, 10 mmol, 1 eq.), 3-bromo-*p*-anisaldehyde **158** (2.15 g, 10 mmol, 1 eq.) and anhydrous *tert*-butanol (10 mL) was heated to 50 °C with molecular sieves (3 Å) and stirred until the aldehyde had dissolved. To this was added, piecemeal over a stream of nitrogen, potassium *tert*-butoxide (2.24 g, 20 mmol, 2 eq.). The reaction was stirred for a further 20 minutes at 50 °C at which time the residue dissolved in distilled water (30 mL). The aqueous solution was extracted with ethyl acetate (3 x 50 mL) and the combined organics washed with a brine solution (100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to an orange residue. The residue was treated carefully with a 6 M HCl solution (200 mL). The resultant suspension was stirred at room temperature for 24 hours and the precipitate was collected by vacuum filtration. The solid was dissolved in methylene chloride (100 mL) and washed with a brine solution (100 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to an orange powder which was dissolved in minimal boiling ethyl acetate and precipitated with petroleum ether to give a pale-yellow solid, 624 mg (23%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.55 (s, 1 H, C*H*O), 8.19 (d, 1 H, *J* = 2.2 Hz, *o*-Ar*H*), 8.12 (dd, 1 H, *J* = 2.2 Hz, *J* = 8.7 Hz, *m*-Ar*H*), 7.77 (s, 1 H, C*H*), 7.06 (d, 1 H, *J* = 8.7 Hz, *o*-Ar*H*), 4.02 (s, 3 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.9 (*C*HO), 160.6 (*C*OMe), 156.8 (*C*H), 136.8 (Ar*C*H), 132.6 (Ar*C*H), 125.2 (*i*-Ar*C*), 114.4 (*C*), 112.9 (*C*N), 112.3 (*C*Br), 56.8 (*C*H_3). **IR** (KBr disc) 2923 (alkene), 2845 (aldehyde), 2225 (nitrile), 1693 (aldehyde), 1558 (alkene), 1493 (aldehyde), 1274, 1172 (ether), 1049 (aldehyde) cm^{-1}. **ESI-MS** Calc. ($M+H^+$) = 265.981 found **ESI-MS** $C_{11}H_8BrNO_2$ Calc. ($M+H^+$) = 265.9822 (4.17 ppm).



159 **160**

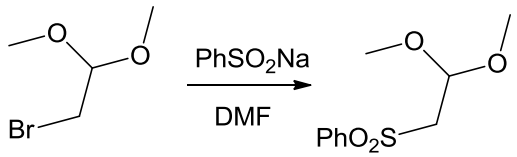
(1*E*,3Z)-1,3-Bis-cyano-4-(3-bromo-4-methoxy)phenyl-buta-1,3-diene 160: To an oven-dried Schlenk tube purged with argon was added diethyl cyanomethylphosphonate (356 µL, 2.2 mmol, 1.1 eq.) and anhydrous THF (20 mL). The solution was stirred until homogenous and then placed in an ice-acetone bath. To this was added *n*-butyllithium (880 µL, 2.2 mmol, 2.5 M in hexanes, 1.1 eq.) dropwise, when the addition was complete the reaction was stirred at room temperature for 1 hour at which point it was brought to -78 ^{o}C. The organolithium reagent was added dropwise *via* cannula to a suspension of 3-bromo-4-methoxy-α-cyano-cinnamaldehyde **160** (532 mg, 2 mmol, 1 eq.) in anhydrous THF (2 mL) previously chilled to -78 ^{o}C. Dissolution of the aldehyde occurred slowly over the course of 30 minutes stirring at -78 ^{o}C. The reaction was stirred for an additional 24 hours at -78 ^{o}C at which point the reaction was quenched with a solution of saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts were dried over Na_2SO_4 and reduced *in vacuo* to a red oil. The oil was dissolved in minimal methylene chloride and passed through a pad of silica washing with a mixture of ethyl acetate (50 mL) in petroleum ether (50 mL). The solvent was removed *in vacuo* to give a yellow solid which was precipitated from diethyl ether using petroleum ether to give a pale-yellow solid, 224 mg (38%). Single isomer, presumably *EZ* from *E*-cinnamaldehyde. **^{1}H NMR** (300 MHz, DMSO) *δ* 8.14 (d,1 H, *J* = 2.0 Hz, *o*-ArH), 7.93 (dd, 1 H, *J* = 2.0 Hz, *J* = 8.8 Hz, *m*-ArH), 7.73 (s, 1 H, δ*H*), 7.55 (d, 1 H, *J* = 16.2 Hz, β*H*), 7.32 (d, 1 H, *J* = 8.8 Hz, *o*-Ar*H*), 6.00 (d, 1 H, *J* = 16.2 Hz, CNC*H*), 3.95 (s, 3 H, C*H*$_3$). **^{13}C NMR** (75 MHz, DMSO) *δ* 158.4 (*C*OMe), 149.5 (δ*C*H), 147.6 (β*C*H), 134.3 (*o*-Ar*C*H), 131.6 (*m*-Ar*C*H), 126.3 (*i*-Ar*C*), 117.8 (*C*N), 115.0 (*C*N), 113.2 (*o*-ArCH), 111.4 (*C*Br), 105.7 (*C*CN), 99.0 (CN*C*H), 56.8 (*C*H$_3$). **IR** (KBr disc) 2945 (alkene), 2844 (aldehyde), 2216 (nitrile), 1585 (aldehyde), 1497, 1274 (methoxy), 1051 cm^{-1}. **M.P.** 175-180 ^{o}C. **ESI-MS** $C_{13}H_9BrN_2O$ Calc. (M+H^{+}) = 288.9771 found (M+H^{+}) = 288.9969 (-0.74 ppm).



42 **161**

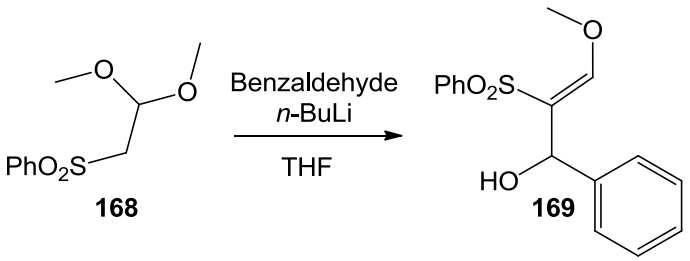
(1*E*,3*E*,5*E*)-1,3-Bis-phenylsulfonyl-6-phenyl-hexa-1,3,5-triene 161: Activated aluminium oxide (3.06 g, 30 mmol, 30 eq.) was suspended in anhydrous methylene chloride (5 mL). The mixture was stirred in an ice bath for 10 minutes at which point bis-phenylsulfonyl propene (323 mg, 1 mmol, 1 eq.) was

added followed by *trans*-cinnamaldehyde (126 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred for 24 hours at room temperature. The suspension was then filtered through a pad of Celite and washed with methylene chloride (50 mL). The solvent was removed *in vacuo* using a room temperature water bath. Methanol (10 mL) was added and the solution was sonicated until the residue was fully suspended. The solution was stored at -20 ^{o}C and the precipitate was filtered and washed with ice-cold methanol (5 mL) to yield a bright yellow solid, 383 mg (88%). Crystals for X-ray analysis were grown by slow evaporation from *iso*-propanol. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78-7.88 (m, 3 H), 7.71-7.78 (m, 2 H), 7.61-7.70 (m, 1 H), 7.50-7.61 (m, 6 H), 7.36-7.48 (m, 5 H), 7.08-7.24 (m, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.8, 145.5, 139.9 (SO_2Ar*C*), 139.7 (SO_2Ar*C*), 135.0 (Ar*C*), 133.7, 133.6, 132.9, 132.2 (*C*), 130.8, 129.4, 129.3, 129.1, 128.3, 127.7, 127.5, 120.3. **IR** (KBr disc) 3077, 3057, 3031, 1590, 1446, 1310, 1213, 1178, 1145, 1072, 976, 848, 719, 545 cm^{-1}. **M.P.** 164-168 ^{o}C. **ESI-MS** $C_{24}H_{20}O_4S_2$ Calc. ($M+H^+$) = 437.0876 found ($M+H^+$) = 437.0871 (-1.17 ppm).

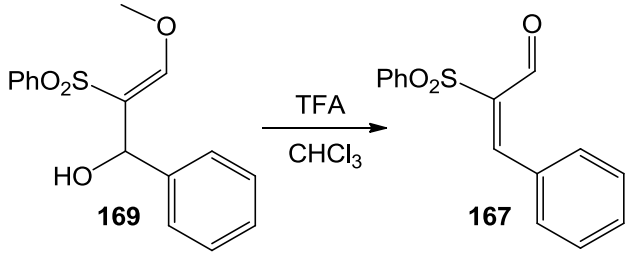


168

α-Phenylsulfonyl acetaldehyde dimethyl acetal 168:[252a] A suspension of bromoacetaldehyde dimethyl acetal (1.18 mL, 10 mmol, 1 eq.) and phenylsulfinic acid sodium salt (1.64 g, 10 mmol, 1 eq.) in dimethylformamide (20 mL) was heated to 100 ^{o}C for 18 hours. The solvent was removed *in vacuo* and the residue partitioned between methylene chloride (20 mL) and saturated ammonium chloride (20 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil which was essentially pure, 2.10 g (91%). **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.91 (d, 2 H, *J* = 7.7 Hz, Ar*H*), 7.52-7.71 (m, 3 H, Ar*H*), 4.86 (t, 1 H, *J* = 5.3 Hz, C*H*), 3.45 (d, 2 H, *J* = 5.3 Hz, CH_2), 3.23 (s, 6 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.8 (Ar*C*), 133.7 (Ar*C*H), 129.0 (Ar*C*H), 128.1 (Ar*C*H), 99.1 (CH_3), 58.7 (*C*H$_2$), 53.3 (*C*H). Matches known data.[269]

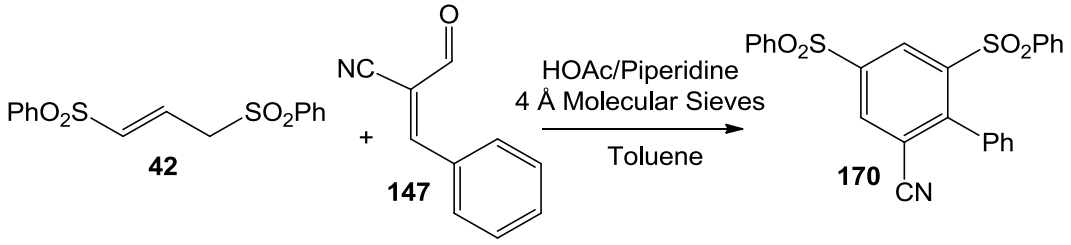


3-Methoxy-1-phenyl-2-(phenylsulfonyl)prop-2-en-1-ol 169:[252a] To an oven-dried Schlenk tube, purged with argon, was added phenylsulfonyl acetaldehyde dimethyl acetal **168** (2.10 g, 9.1 mmol, 1 eq.) and anhydrous THF (50 mL) and was stirred until homogenous. The solution was then brought to -78 °C at which point *n*-butyllithium was added (7.28 mL, 2.5 M in hexanes, 18.2 mmol, 2 eq.) and stirring was continued for 1 hour at -78 °C. Benzaldehyde (1.86 mL, 18.2 mmol, 2 eq.) was added and the reaction was stirred for 10 minutes at -78 °C before being allowed to come to room temperature. The reaction was subsequently quenched with saturated ammonium chloride solution and extracted with methylene chloride (3 x 40 mL). The combined organics were dried over Na_2SO_4 and concentrated to an off-yellow solid, which was purified by flash chromatography eluting with 100% petroleum ether -> 40% petroleum ether in ethyl acetate. R_F (60% petroleum ether in ethyl acetate) 0.43. The resulting semi-solid residue was triturated with cold diethyl ether (20 mL) and the precipitate isolated by vacuum filtration. Colourless solid, 1.80 g (65%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49-7.58 (m, 3 H, overlapping C*H*OMe + SO_2Ar*H*), 7.33-7.46 (m, 1 H, SO_2Ar*H*), 7.23-7.99 (m, 2 H, SO_2Ar*H*), 7.03-7.177 (m, 5 H, Ar*H*), 5.80 (d, 1 H, *J* = 9.4 Hz, C*H*COH), 3.94 (s, 3 H, CH_3), 3.61 (d, 1 H, *J* = 9.4 Hz, O*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.1 (*C*HOMe), 141.6 (*C*), 140.2 (SO_2Ar*C*), 132.5 (SO_2Ar*C*H), 128.7 (SO_2Ar*C*H), 127.9 (SO_2Ar*C*H), 127.1(Ar*C*H), 127.1 (Ar*C*), 125.6 (Ar*C*H), 121.7 (Ar*C*H), 67.9 (*C*H_3), 62.8 (*C*HOH). **M.P.** 135-140 °C. **ESI-MS** $C_{16}H_{16}O_4S$ Calc. ($M+Na^+$) = 327.0662 found ($M+Na^+$) = 327.0653 (-2.45 ppm).

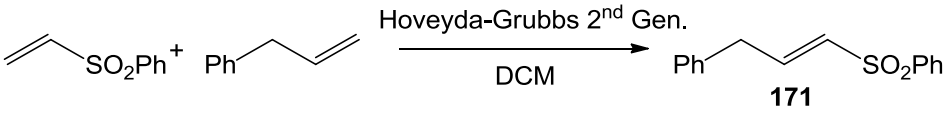


α-Phenylsulfonyl cinnamaldehyde 167:[252a] To a solution of the benzoate **169** (304 mg, 1 mmol, 1 eq.) in chloroform (2 mL) was added trifluoroacetic acid (84 µL, 1.1 mmol, 1.1 eq.). The reaction was stirred at room temperature for 3 days at which time an addition portion of trifluoroacetic acid (84 µL, 1.1 mmol, 1.1 eq.) was added and stirring was continued for 24 hours. The reaction was then cautiously quenched with a saturated $NaHCO_3$ solution and extracted with methylene chloride (3 x

30 mL). The combined organics were dried over Na_2SO_4 and reduced *in vacuo* to give an-off white solid which was passed through a plug of silica with a solution of ethyl acetate (50 mL) and petroleum ether (50 mL). The solvent was removed to give a colourless solid, 248 mg (91%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.75 (s, 1 H, C*H*O), 8.80 (s, 1 H, C*H*), 7.99-8.12 (m, 2 H, SO_2Ar*H*), 7.40-7.67 (m, 8 H, overlapping SO_2Ar*H* + Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.9 (*C*HO), 153.8 (*C*H), 139.8, 139.6, 133.8, 132.6, 131.4, 130.6, 129.2, 129.1, 128.8. **M.P.** 106-108 ^{o}C **ESI-MS** $C_{15}H_{12}O_3S$ Calc. ($M+H^+$) = 273.0580 found ($M+H^+$) = 273.0582 (0.79 ppm).

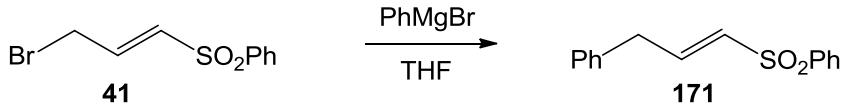


4,6-Bis-(phenylsulfonyl)-[1,1'-biphenyl]-2-carbonitrile 170: A suspension of 1,3-bis-phenylsulfonyl buta-1,3-diene **42** (162 mg, 0.5 mmol, 1 eq.), α-phenylsulfonyl cinnamaldehyde **147** (78 mg, 0.5 mmol, 1 eq.), piperidine (25 µL), acetic acid (25 µL) and 4 Å molecular sieves (1 g) in toluene (10 mL) was brought to reflux for 4 hours. The solution was allowed to cool and passed through a pad of Celite with methylene chloride (50 mL). The filtrate was then washed with saturated ammonium chloride (30 mL) and a brine solution (30 mL). The organic phase was dried over Na_2SO_4 and concentrated to a light brown oil. The oil was treated with methanol (10mL) and the product was precipitated with the aid of ultrasound. The solution was stored overnight at -20 ^{o}C and the precipitate collected by vacuum filtration and washed with cold methanol. White solid, 204 mg (89%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.16 (d, 1 H, *J* = 1.8 Hz, (SO_2Ph)CC*H*C(SO_2Ph)), 8.45 (d, 1 H, *J* = 1.8 Hz, (SO_2Ph)CC*H*C(CN)), 8.03-8.15 (m, 2 H, Ar*H*), 7.61-7.77 (m, 3 H, Ar*H*), 7.39-7.52 (m, 2 H, Ar*H*), 7.11-7.31 (m, 6 H, Ar*H*), 6.83-6.92 (m, 2 H, Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.7 (Ar*C*), 143.7 (Ar*C*), 143.2 (Ar*C*), 139.4 (Ar*C*), 138.6 (Ar*C*), 135.6 (*C*HCCN), 134.7 (Ar*C*H), 133.8 (Ar*C*H), 132.2 (Ar*C*), 131.1 (*C*HCSO$_2$Ph), 130.2 (Ar*C*H), 129.9 (Ar*C*H), 129.5 (Ar*C*H), 129.0 (Ar*C*H), 128.4 (Ar*C*H), 128.2 (Ar*C*H), 128.1 (Ar*C*H), 118.4 (Ar*C*CN), 115.0 (*C*N). **IR** (KBr disc) 3069 (aromatic), 2919 (aromatic), 2238 (nitrile), 1447 (aromatic), 1327 (sulfone), 1154 (sulfone), 1082, 829 (aromatic), 724 (aromatic), 688, 578 (sulfone) cm^{-1}. **M.P.** 148-150 ^{o}C. **ESI-MS** $C_{25}H_{17}NO_4S_2$ Calc. ($M+H^+$) = 460.0672 found ($M+H^+$) = 460.0666 (-1.27 ppm).



171

(*E*)-((3-Phenylprop-1-en-1-yl)sulfonyl)benzene 171:[255] To a 3-neck flask fitted with a glass-tapped swan-neck, septum and condenser with gas-bubbler purged with argon was added vinyl sulfone (505 mg, 3 mmol, 1 eq.), Hoveyda-Grubbs 2nd generation catalyst (47 mg, 0.075 mmol, 2.5 mol%) and anhydrous methylene chloride (10 mL). The reaction was stirred until homogenous and allyl benzene (1.01 mL, 7.5 mmol, 2.5 eq.) was added in one portion. The reaction was refluxed under a positive pressure of argon with the exclusion of light for 12 hours. When cool a saturated solution of ammonium chloride (20 mL) was added the organic layer was removed and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organics were reduced *in vacuo* to a brown oil. The oil was dissolved in hot methanol and stored overnight at -20 ^{o}C. The crystals were collected by vacuum filtration, colourless micro needles, 519 mg (67%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80-7.91 (m, 2H, SO_2Ar*H*), 7.45-7.66 (m, 3 H, SO_2Ar*H*), 7.06-7.35 (m, 6 H, overlapping CH_2C*H* +Ar*H*), 6.27 (dt, 1 H, *J* = 1.5 Hz, *J* = 15.0 Hz, C*H*SO_2Ph), 3.54 (dd, 2 H, *J* = 1.4 Hz, *J* = 6.5 Hz, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.5, 140.5, 136.3, 133.4, 131.6, 129.3, 128.9, 128.9, 127.6, 127.1, 37.6. (*C*H_2). **M.P.** 106-108 ^{o}C (Lit. 107-109 ^{o}C).[270] **ESI-MS** $C_{15}H_{14}O_2S$ Calc. ($M+H^+$) = 259.0787 found ($M+H^+$) = 259.0799 (4.60 ppm).



41 **171**

(*E*)-((3-Phenylprop-1-en-1-yl)sulfonyl)benzene 171: To an oven-dried Schlenk tube purged with argon was added bromophenyl sulfone **41** (1.31 g, 5 mmol, 1 eq.) and anhydrous THF (25 mL). The reaction was stirred until homogenous and phenylmagnesium bromide (5 mL, 1 M in THF, 5 mmol, 1 eq.) was added in a slow stream. The reaction was stirred at room temperature for 2 hours and subsequently quenched with distilled water (10 mL). The reaction was transferred to a separatory funnel using diethyl ether (30 mL) and the aqueous phase was removed. The organic phase was then washed with a saturated solution of ammonium chloride (30 mL) and concentrated brine solution (30 mL). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* to a colourless oil. The oil was purified using flash chromatography eluting with 70% hexane in ethyl acetate. $\boldsymbol{R_F}$ (70% hexane in ethyl acetate) 0.51. Colourless solid, 405 mg (31%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80-7.91 (m, 2H, SO_2ArH), 7.45-7.66 (m, 3 H, SO_2ArH), 7.06-7.35 (m, 6 H, overlapping CH_2CH +Ar*H*), 6.27 (dt, 1 H, *J* = 1.5 Hz, *J* = 15.0 Hz, $CHSO_2Ph$), 3.54 (dd, 2 H, *J* = 1.4 Hz, *J* = 6.5 Hz, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.5, 140.5, 136.3, 133.4, 131.6, 129.3, 128.9, 128.9, 127.6, 127.1, 37.6. **M.P.** 98-100 ^{o}C (Lit. 107-109 ^{o}C).[270] Matches previous sample.

Chapter 4

4.1 Introduction

The generation of stereocenters using supramolecular catalysts has been inspired by natural systems. Enzymes, nature's excellent catalysts,[271] have been emulated many times in the creation of new catalytic systems.[272] The use of enzymes themselves for asymmetric transformations is usually limited by the substrate scope[273] and their synthetic mimics, are more often than not less efficient.[272b] Combining nature's impressive reaction turnover and ability to control stereochemistry with a conveniently modifiable catalyst is the 'Holy-Grail' of catalyst development.

4.1.1 DNA

The structure of deoxyribonucleic acid (DNA), the nucleic acid which contains the genetic instructions for the functions of life, was determined more than fifty years ago and has been studied extensively.[274] DNA consists of helically arranged nucleobases which are neutrally charged and an anionic 'backbone' consisting of sugar-phosphates. The base pairs are stacked perpendicular to the axis of the helix within Van-der-Waals contact of one another. The nucleobases themselves consist of one of four polar nitrogen heterocycles, namely mono-cyclic pyrimidines (cytosine and thymine) or bi-cyclic purines (adenine and guanine). The polar nature of these heterocycles allows intermolecular hydrogen bonding to stabilize the structure known as 'Watson and Crick pairing' (**Figure 36**). The anionic backbone is formed by the 2-deoxyribose moieties bound to the nucleobases, which are then inter-linked by phosphate diesters (**Figure 36**). The anionic backbone not only orients and holds the nucleobases in place but also renders DNA highly polar at neutral pH.

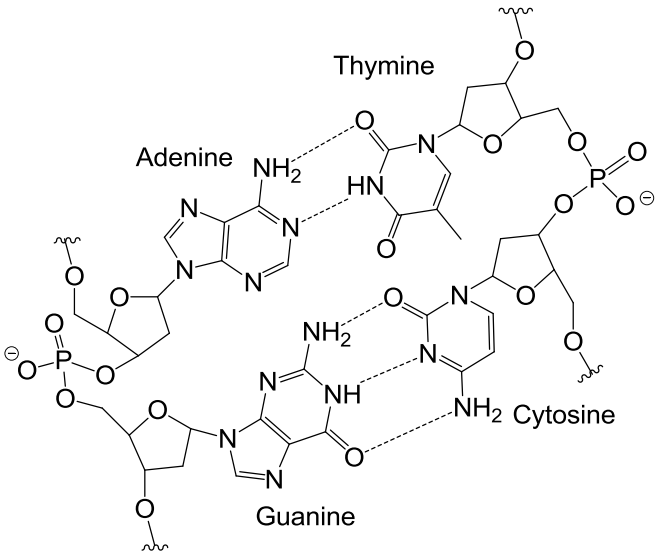


Figure 36: Arrangement of nucleobases and anionic back-bone in DNA with Watson and Crick pairing

The backbone curls in a twin helical fashion with ten nucleotides per turn leaving gaps of 22 Å and 12 Å wide, known as the major and minor groove respectively (**Fig. 37**).[275]

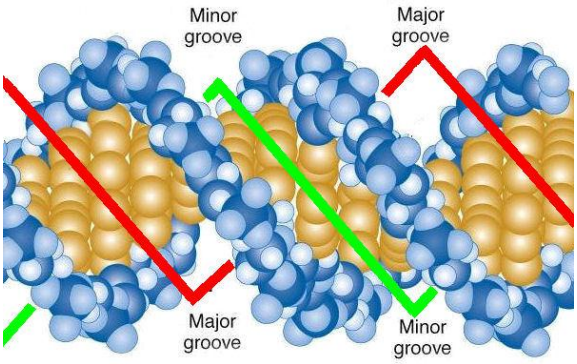


Figure 37: Major and minor groove in helical DNA
http://www.mun.ca/biology/scarr/MGA2-02-07_space_filling4.jpg

DNA can exist in a plethora of different conformations owing to the inherent flexibility of the phosphate backbone joining the polynucleotide. These structural variations can vary from minor changes, caused by slight variations in the Watson-Crick pairing, to structures that differ completely in handedness (Z-DNA, **Fig. 38**) or in base-pairing (e.g. Hoogsteen base-pairing) or even in number of strands (e.g. G-quadruplex).[275b]

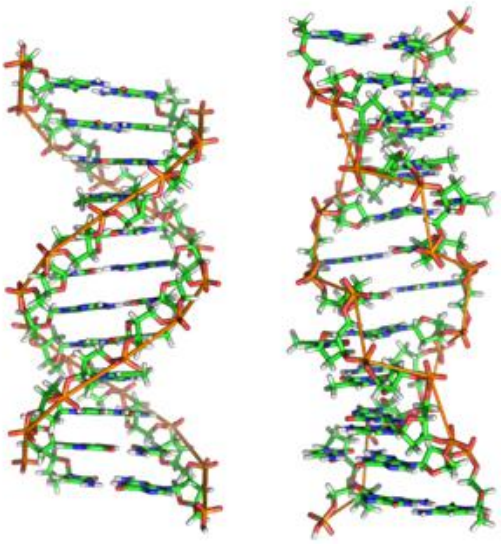


Figure 38: From left to right, B-DNA and Z-DNA
http://www.molecularstation.com/molecular-biology-images/502-dna-pictures/36-a-dna-b-dna-z-dna.html?size=big

B-DNA in its duplex form has a right hand twist and is one of the most recognisable structures in chemistry (**Fig. 38**). The family of B-DNA conformations is the most common in living cells and is the closest to the original Watson and Crick model, although Z-DNA has also been found in functioning organisms.[275b]

4.2 DNA-based catalysis

When DNA is in the duplex form the helix is rigid and inflexible, it is this rigidity that makes it so well suited in its role as genetic material.[276] Feringa and Roelfes exploited the innate chirality in the rigid right-handed helix by employing DNA as a chiral co-factor in a hybrid bio-supramolecular chemistry/metal based catalytic system (**Figure 39**).[277]

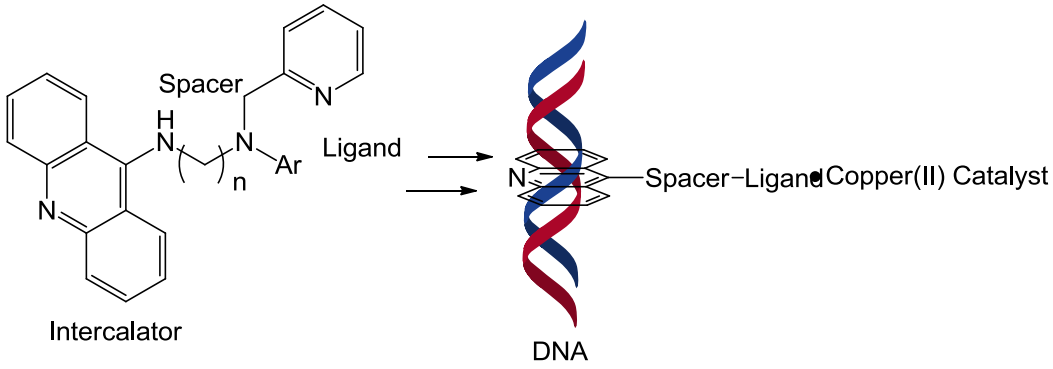
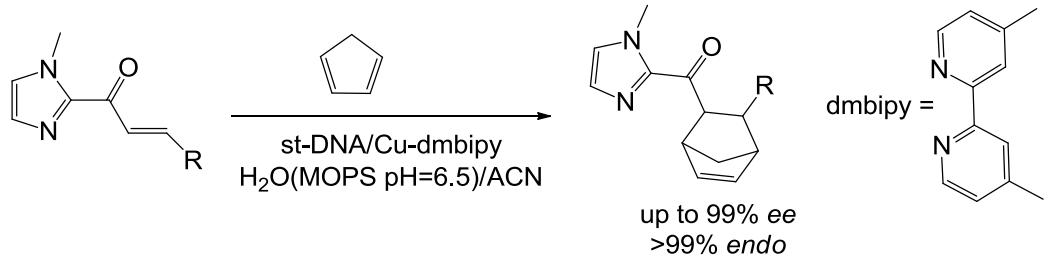


Figure 39: Formation of hybrid bio-supramolecular/transition metal asymmetric catalyst

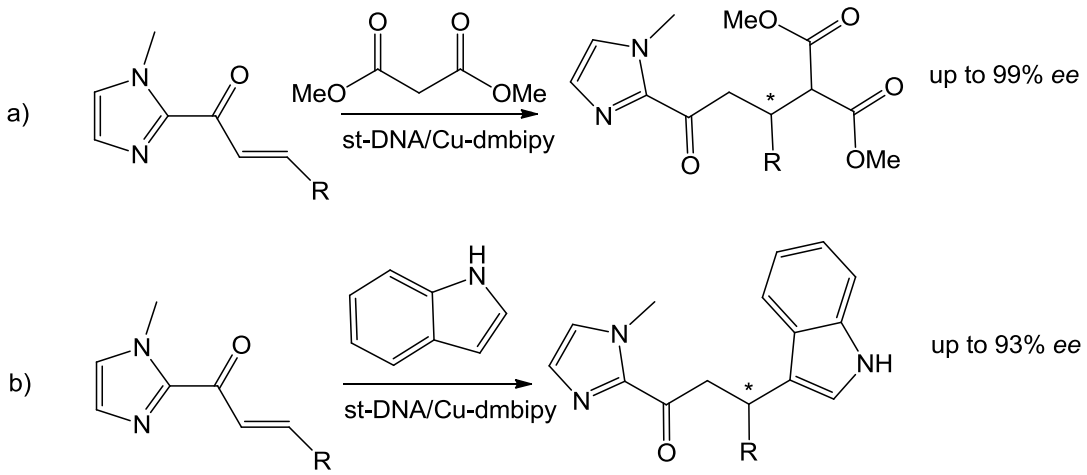
The Feringa/Roelfes catalytic system showed that DNA chirality, *via* an intercalating ligand-copper(II) complex, could effect enantioselectivity on a copper(II) catalysed Diels-Alder reaction.[278] Subsequent optimisation of this methodology generated near perfect diastereoselectivity and enantioselectivity. Removing the spacer and having both the ligand and intercalating moiety integrated, brought the catalytic centre much closer to the DNA and an improvement in selectivity (**Scheme 133**).[278a]



Scheme 133: DNA/metal based catalysis of asymmetric Diels-Alder reaction[278a]
Note st-DNA is commercial salmon testes DNA

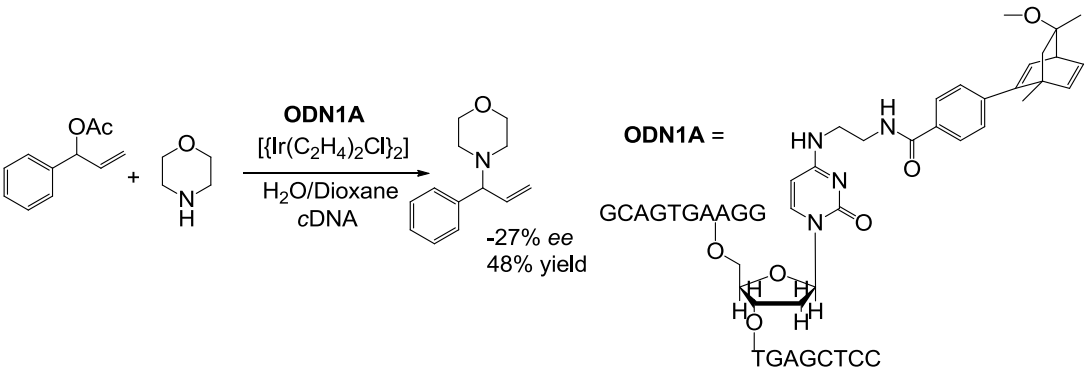
In subsequent publications the DNA was found to not only have an important effect on directing the stereochemistry of the product but was found to also have a rate-accelerating effect.[279] The rate of this enhancement and even the enantioselectivity was reported to be linked to the DNA sequence.[280] It was found that the activity of the copper(II) catalyst was influenced by where it had intercalated in the DNA sequence providing a heterogeneous array of 'micro-environments' in which catalysis could take place. Some of these micro-environments were found to give higher rate

acceleration than others. Rather fortunately, it seems that the sequences which provide environments with highest rate acceleration also give the highest levels of selectivity leading to the excellent observed *ee*'s. This work has culminated in the development of two additional asymmetric DNA-based copper(II) catalysed reactions, namely the Friedel-crafts alkylation and the Michael-addition (**Scheme 134**).[281]



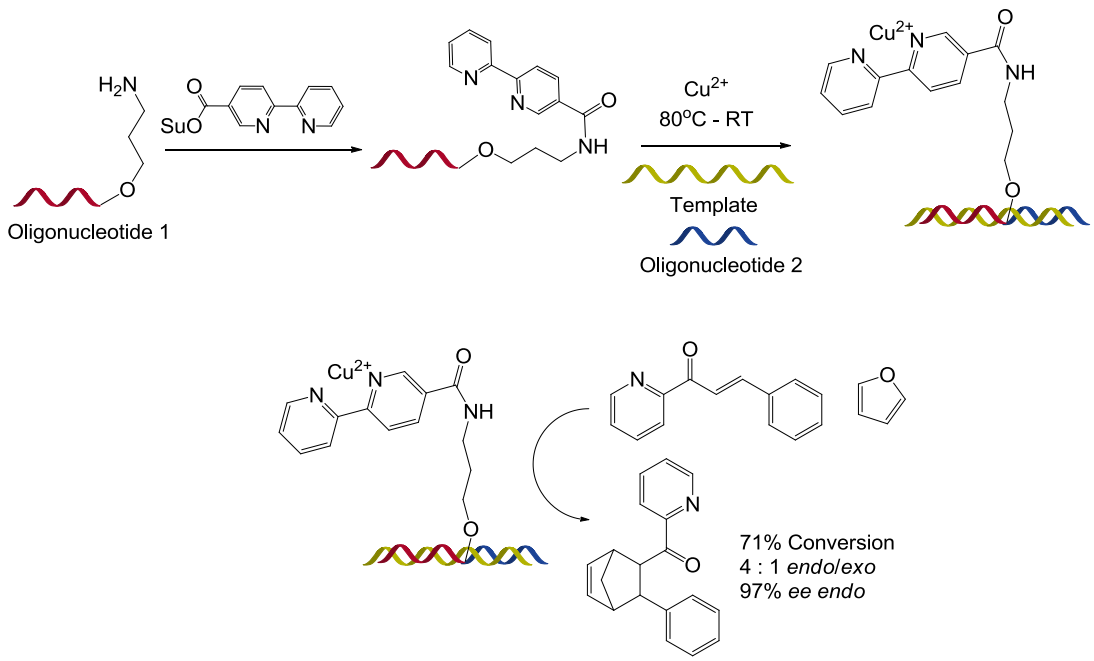
Scheme 134: a) Michael addition and b) Friedel-Crafts alkylation using st-DNA/Cu-dmbipy[281]

In a complementary report, Jäschke and co-workers described a DNA-based catalytic system composed of a 19mer strand of DNA with a covalently linked dienic ligand.[282] This DNA-ligand was employed in an iridium catalysed allylic amination with good yields but with only modest enantioselectivity (**Scheme 135**).



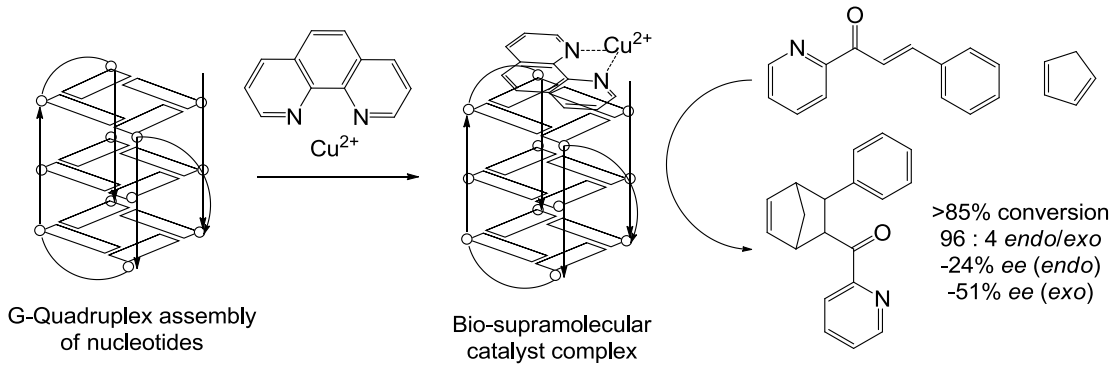
Scheme 135: DNA-based ligand for iridium catalysed allylic amination[282]
Note *c*DNA is complementary DNA strand

In an equally impressive paper, the Roelfes group also employed DNA covalently linked to a ligand (**Scheme 136**).[283] This time the DNA-ligand was used in a copper(II) catalysed Diels-Alder reaction producing conversions up to 76% and *ee*'s of up to 93%. The DNA-ligand was synthesised in an astute fashion from commercially available terminally modified single stranded DNA sequences to which a ligand could be covalently attached. Complementary strands were then added to form the duplex with the ligand located at the interface of the sequences.



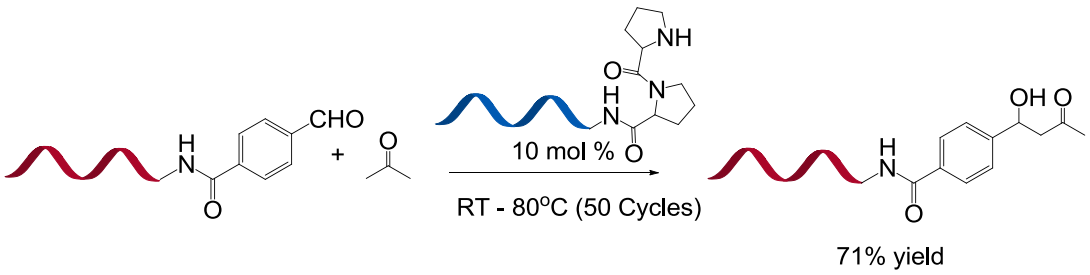
Scheme 136: Assembly of DNA-based catalyst by Roelfes[283]

In 2010, Moses and co-workers reported a novel variant of the Feringa/Roelfes catalytic system.[284] Instead of a DNA/intercalating ligand complex, the group employed a G-quadruplex/intercalating ligand complex and again applied this to the copper(II) catalysed Diels-Alder reaction (**Scheme 137**). Despite good conversion only modest *ee*'s were obtained.



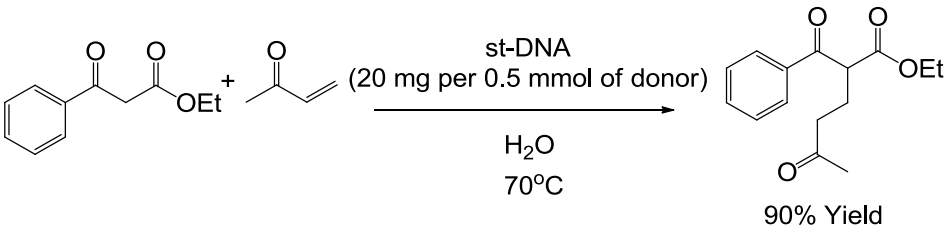
Scheme 137: G-quadruplex/intercalating ligand complex catalytic system[284]

There have been a few reported methodologies involving DNA in organocatalysis and, to the best of our knowledge, none of literature describes any enantioselectivity. In one example by Marx and co-workers, a DNA template of proline was used in sub-stoichiometric quantities to catalyze an aldol reaction.[285] Catalytic turnover was achieved by cycling the temperature to allow denaturing and re-annealing of the catalytic strand with a fresh strand of substrate (**Scheme 138**). Although there was no reported enantioselectivity, the group achieved surprisingly good conversion considering the inefficiencies in catalytic turnover.



Scheme 138: DNA template prolinamide catalyst[285]

More recently Soriente has reported that genomic salmon testes DNA on its own can catalyze the Michael addition in aqueous conditions in moderate to excellent yields (**Scheme 139**).[286] The group used fluorescence spectroscopy to observe the activating effect the DNA had on the Michael acceptors and donors. Although the authors do not specify a mode of activation one could postulate that it may arise through Brønsted-base activation by the anionic phosphodiester backbone.



Scheme139: st-DNA catalysis of aqueous Michael reaction[286]

4.3 Strategies for asymmetric DNA-based supramolecular organocatalysis

We considered three possible methodologies for asymmetric DNA-based supramolecular organocatalysis; (i) DNA templated organocatalysts, (ii) covalently linked supramolecular DNA-organocatalysts and (iii) non-covalently linked supramolecular DNA-organocatalyst complexes.

4.3.1 DNA templated organocatalysts

Using DNA templates for effecting chemical reactions has been well documented.[287] The basic concept is that the molecules to be transformed are covalently attached with a linker to two hybridizing DNA strands, most usually as either an A+B+A'B' style duplex (**Figure 40 a**) or as A+A' known as end-of-helix architecture (**Figure 40 b**). The strands are allowed to anneal through Watson-Crick pairing along a template strand or by complementary base pairs. The reaction is then promoted by the increase in effective concentration of the reactants.[288]

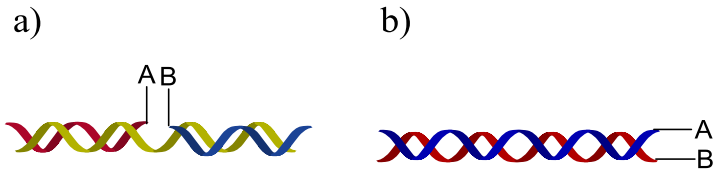
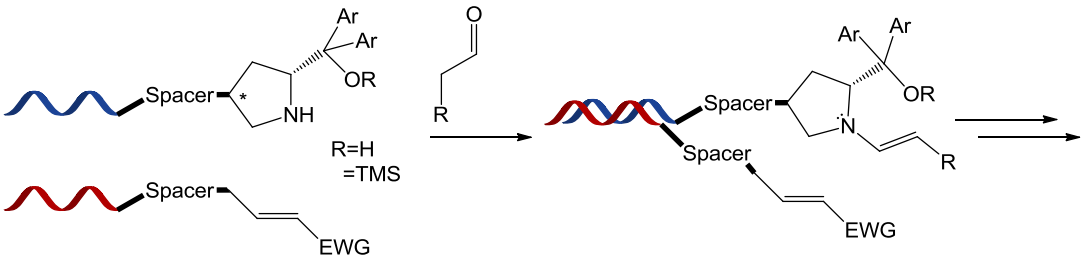


Figure 40: a) A+B+A'B' style duplex, b) A+A' (end-of-helix)

The work of Marx, discussed earlier (**See Section 4.2**), employed end-of-helix templating of a racemic prolinamide organocatalyst and the aldol acceptor.[285] The catalyst in this case would form the reactive enamine with the unbound acetone and add to the carbonyl of the aldol acceptor on the complementary DNA template. We considered expanding on Marx's work employing a chiral catalyst in place of the racemic prolinamide.

The utilization of chiral pyrrolidine, such as a tethered Hayashi-Jørgensen catalyst, would allow the generation of reactive chiral enamines and iminium ions from aldehydes. Annealing these reactive species with a complementary strand bearing the appropriate substrate could result in a chiral transformation (**Scheme 140**). These enamines have been reported in a variety of asymmetric C-C bond forming reactions (**See Section 1.4**).[78]



Scheme 140: Formation of an enamine using DNA Templates

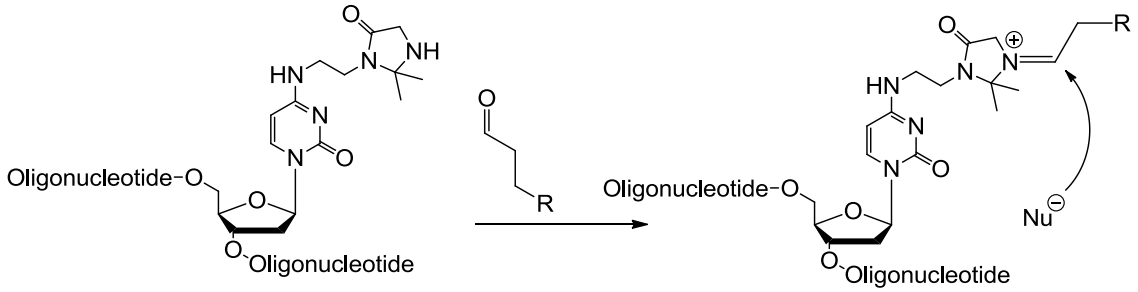
A problem with DNA templated organocatalysis is the difficulty in recycling the DNA-catalyst. As previously discussed, (**See Section 4.2**), Marx employed a technique of cycling temperature to cause denaturation of the DNA and then re-annealing. Using this technique the group achieved 71% yield in the proline catalysed aldol reaction over 50 cycles using 10 mol% of the catalyst. This process is time consuming and may be detrimental to the stereoselectivity of a reaction. The ideal method of providing this constant annealing and re-annealing cycle would be through chemical means.

A second problem lies in the choice of reaction media. As the majority of organocatalytic reactions are performed in organic solvents, which are unsuitable for Watson-Crick pairing,[289] the scope of this methodology is reduced to reactions that are reported in aqueous systems. Liu however has reported using DNA-templated substrates to effect high yielding Heck coupling, Wittig olefination and amine acylation in wet-organic systems.[290] Such aqueous systems may be applicable to organocatalytic transformations which require a small amount of water for hydrolysis of the catalyst.

4.3.2 Covalently linked supramolecular DNA-organocatalysts

We envisaged that a covalently linked supramolecular DNA-organocatalyst would consist of an achiral organocatalyst covalently linked to DNA. When the DNA-organocatalyst construct interacts with a substrate, the chiral environment, generated by the chiral DNA, should impart asymmetry on the reaction.[291]

In Jäschke's work, as previously discussed (**See Section 4.1**), the group covalently linked a ligand to the assembled duplex *via* an activated nucleoside.[282] By using this same strategy it could be possible to bind an achiral organocatalyst to the base pairs (**Scheme 141**).



Scheme 141: Achiral organocatalyst covalently linked to DNA

This strategy of employing achiral catalysts tethered to a chiral DNA scaffold could yield some interesting results, particularly if some of Tomkinson's very potent substituted hydrazines were employed (**Figure 41**).[292]

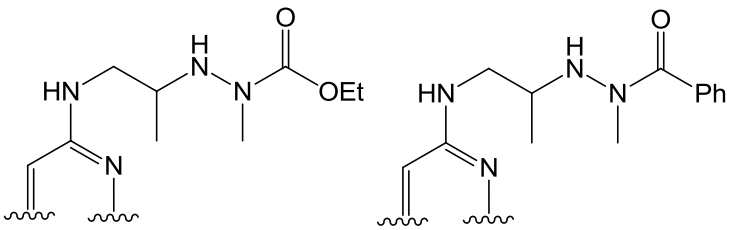


Figure 41: Tomkinson's hydrazines attached to a cytosine ring

The advantage of using a covalently linked catalyst over a non-covalently linked one is that the reaction environment remains unchanged. If the catalyst is bound to a specific nucleic acid residue, its position relative to the superstructure of the DNA should not alter. This could generate a reproducible catalytic site, which should give reproducible results and the possibility of good selectivity.

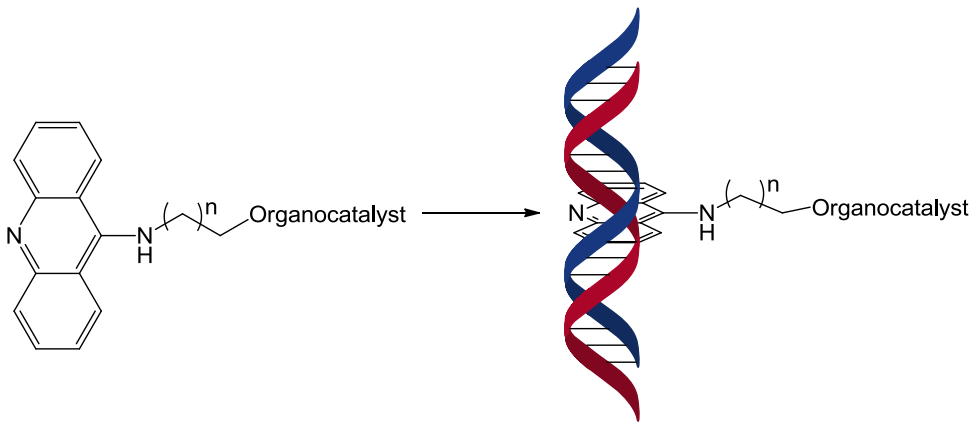
Similarly to the DNA template reaction, the main drawback to this catalysis is that it requires an aqueous environment which is not suited to the majority of organocatalysts. However the same work-around could be employed. Modifications of the DNA could be performed in water followed by lyophilising the solution and replacing the water with organic solvent and adding the necessary reactants/reagents.[290]

Typical loadings of the MacMillan imidazolidinone catalysts, and the hydrazines developed by Tomkinson, are between 5-10 mol%.[16, 292] This presents a cost implication as oligonucleotide sequences, with the modified uridine nucleotide, would have to be synthesised and then the catalyst would need to be appended. This type of methodology may be more suited to metal catalysis which requires lower catalyst loadings. For example, the metal catalytic system Jäschke modelled his DNA-catalyst on employs 1.5 mol% catalyst,[293] over 6 times less catalyst than Tomkinson's organocatalyst. Higher loadings would obviously require the synthesis and purification of considerably more oligonucleotide sequences.

4.3.3 Non-covalently linked supramolecular DNA-organocatalytic complexes

In a similar manner to covalent bound catalytic molecules, one might expect that the non-covalent interaction of an achiral catalytic moiety with DNA could be used in the transfer of chirality from the DNA superstructure to reaction substrates. This was successfully demonstrated by Feringa as previously discussed (**See Section 4.1**).[277] There are six principle modes of reversible interaction with DNA: i) interaction with the anionic sugar-phosphate backbone electrostatically, ii) interaction with the minor groove (**Fig. 37**), iii) interaction with the major groove (**Fig. 37**), iv) intercalation in the minor groove, v) intercalation in the major groove, and vi) threaded intercalation with cation ionic interaction between the major and minor groove.[294]

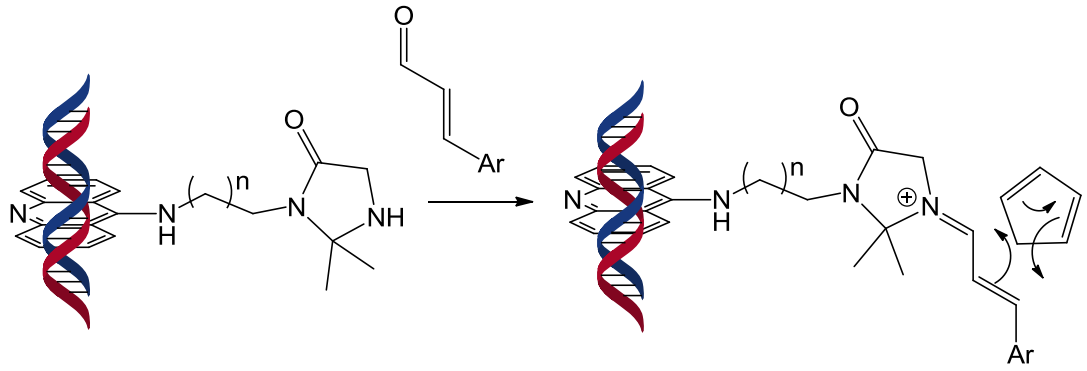
Our preferred method is non-covalent intercalation as this would avoid the electrostatic charges required by the other modes of reversible-binding. There are many DNA intercalating systems reported in the literature.[295] We considered the aminoacridine moiety as the most suitable of these organic intercalators for our purposes. The chemistry of acridine is well known.[296] It is reported to be a strong intercalator with double stranded DNA,[297] while the amino functionality on aminoacridine will allow derivatization. We envisaged using an aminoacridine intercalator tethered to an organocatalyst *via* an adjustable linker. The linker could be shortened or lengthened depending on the influence of the proximity of the helix to the organocatalyst has on the reaction yield and selectivity (**Scheme 142**).



Scheme 142: Organocatalyst tethered to an aminoacridine intercalating moiety

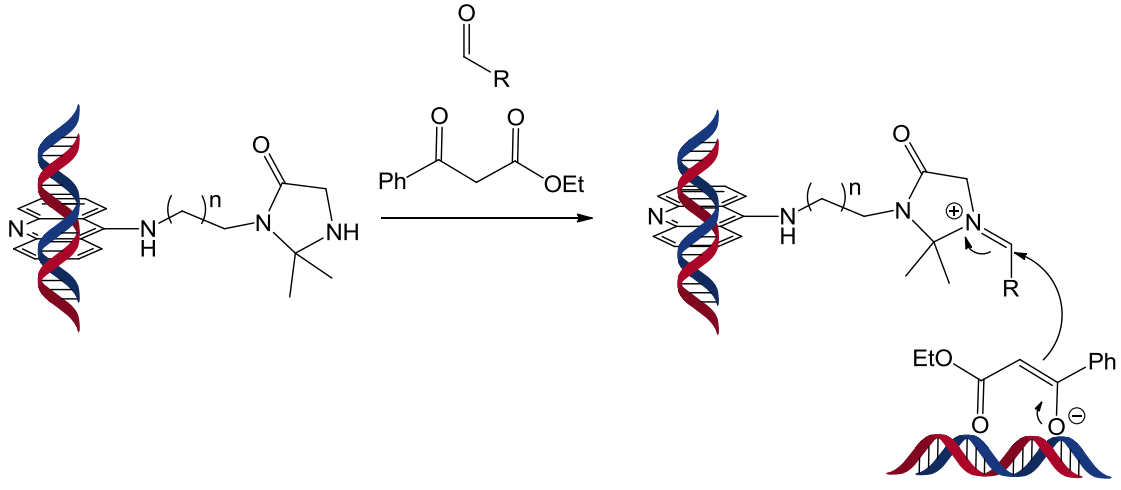
The advantages to using this sort of system would be the relative ease of the experimental conditions, as relatively cheap commercial sources of DNA could be used such as calf thymus and salmon testes.

We envisaged two applications of our non-covalent DNA-organocatalyst system. The first of these would be to use the conventional methodology of employing imidazolidinones or hydrazones to form an iminium ion of an α,β-unsaturated aldehyde or ketone. With the resultant activated species, a Diels-Alder transformation could be conducted in an asymmetric manner (**Scheme 143**).



Scheme 143: Mono-functional catalysis of non-covalently bound organocatalyst

The second application would take into account the work of Soriente who used unmodified genomic salmon testes DNA to effect Michael additions (**See Section 4.2**).[286] By utilising our organocatalyst to generate the iminium ion of an electrophile, we could use similar pro-nucleophiles to Soriente and allow the DNA itself to perform the deprotonation step. Using this approach the organocatalyst moiety would activate the electrophile in a chiral environment, generated by the DNA, and the DNA would activate the nucleophile in a bifunctional system (**Scheme 144**).



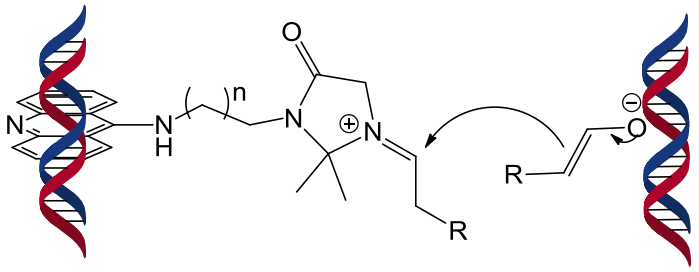
Scheme 144: Bifunctional catalysis of non-covalently bound organocatalyst

The application of our non-covalent DNA-organocatalyst could be extended beyond the Michael addition to other reactions which have been performed using genomic salmon testes DNA such as the Henry reaction[298] and aldol reaction.[299]

The relative insolubility of genomic salmon testes DNA in non-aqueous media would again be a major draw-back. The presence of excessive water would cause premature hydrolysis of the iminium

ion dramatically reducing catalytic activity. It may be possible to pre-intercalate the system in an aqueous environment and then replace the water with an organic solvent as mentioned earlier.

Another possible problem to consider is that the DNA itself could promote unwanted side reactions, for example self aldol reaction between enolisable electrophiles (**Scheme 145**). This would somewhat limit the substrate scope of the electrophile but may be overcome by carefully considering the reaction conditions employed, e.g. order of addition and stoichiometry.



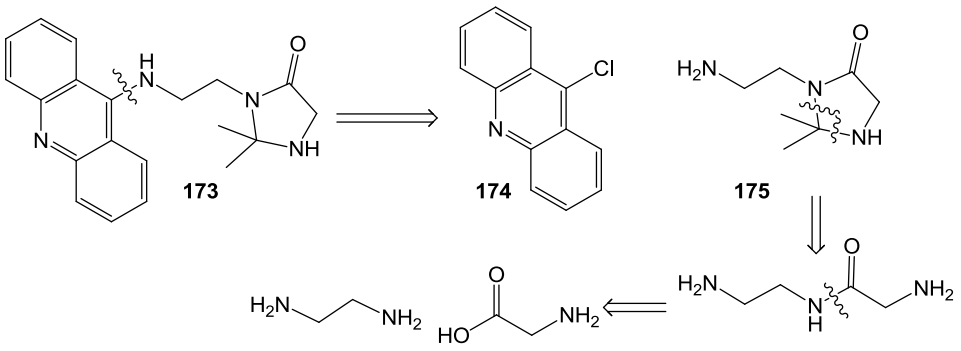
Scheme 145: Unwanted aldol reaction of enolisable aldehydes promoted by DNA

4.4 Synthesis of a DNA intercalating organocatalyst

Having considered three possible methodologies for asymmetric DNA-based organocatalysis we decided that the non-covalently linked catalytic system was the most immediately promising and we undertook the design and synthesis of a DNA intercalating organocatalyst.

4.4.1 Initial retrosynthesis and synthesis of a DNA-intercalating organocatalyst

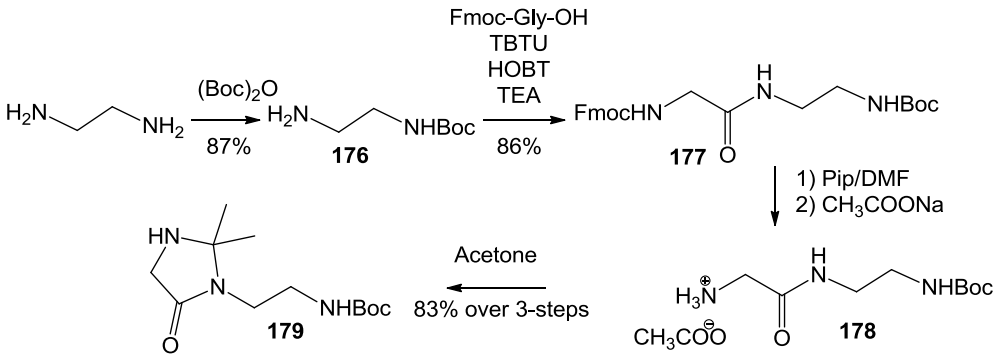
We began our design process by considering the imidazolidinone system that had been employed by MacMillan.[16] Removal of the benzyl moiety results in an achiral imidazolidinone. This achiral imidazolidinone could be synthesised from glycine, instead of phenylalanine as used by MacMillan.[16] We planned to first synthesise the linker and the catalyst and then append the acridine (**Scheme 146**).



Scheme 146: Retrosynthesis of intercalating organocatalyst **173**

The first disconnection generates chloroacridine and a linker-imidazolidinone conjugate **175.** We hoped to effect this reaction using a standard S_NAr approach. The ring closure forming the imidazolidinone **175** would employ aminal formation using acetone, methodology similar to MacMillan's.[16] The derivative amide could be derived from ethylene diamine and glycine.

We began the synthesis with the simple Boc protection of ethylenediamine[300] and its subsequent coupling to the commercial Fmoc-glycine. The coupling reaction was troublesome at first and required the screening of several solvents and coupling reagents. A combination of TBTU and HOBt in DMF was found to be the most effective, giving a good 86% yield of amide **177** after precipitation from ether. The Fmoc orthogonal-protecting group was removed under basic conditions, 20% piperidine in DMF, without problem. Macmillan's procedure for cyclisation of the imidazolidinone with acetone used a catalytic amount of *p*-toluenesulfonic acid. When these conditions were tried for our substrate **178** the acid-labile Boc group was cleaved and no cyclisation occurred. The cyclisation was next tried using the hydrochloride salt of **178**, and this resulted in returned starting material. We then used sodium acetate to neutralize the hydrochloride salt, generating acetic acid and salt. We hoped that the *in situ* generated acetic acid would catalyze the cyclisation. To our delight the imidazolidinone **179** was formed in good yield over 3-steps (83%) without chromatography.



Scheme 147: Synthesis of Imidazolidinone **179**

The structure of imidazolidinone **179** was confirmed by x-ray crystallography (**Fig. 42**). The ^{1}H NMR spectrum of this imidazolidinone **179** showed a multiplet between 3.23 and 3.33 ppm which was later confirmed as the overlapping signals from the ethylene linker by ^{1}H-^{13}C HSQC NMR. The carbonyl carbon from the imidazolidinone ring system had a shift of 174.6 ppm, typical of an amide carbonyl.

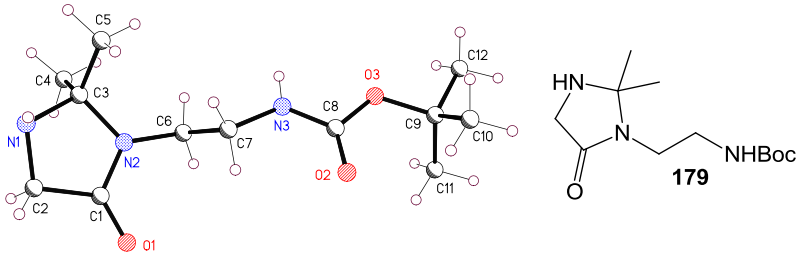
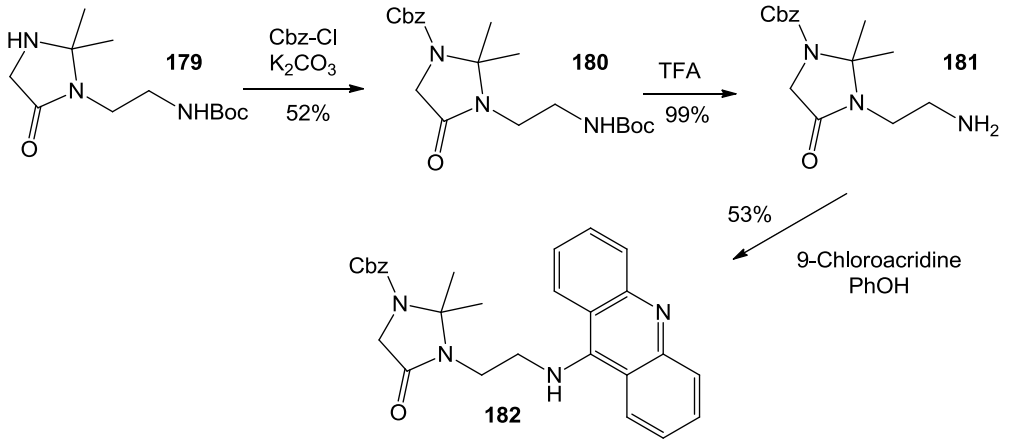


Figure 42: Crystal structure of imidazolidinone **179**

With gram quantities of protected imidazolidinone **179** in hand we continued our synthesis of the intercalating organocatalyst. The Boc group was removed efficiently, without ring opening to give the free primary amine. Initially, we had hoped that the primary amine would be more nucleophilic than the secondary amine in the imidazolidinone ring. If so, we would be able to immediately attach the imidazolidinone-linker conjugate to the acridine ring system. However, this reaction generated mixed products and separation of these products by normal phase chromatography was extremely difficult due to the polar nature of the amino acridine. We decided to return to the precursor **179** and install a Cbz protecting group on the imidazolidinone secondary nitrogen.



Scheme 148: Continued synthesis of intercalating organocatalyst **173**

We chose Cbz as it is orthogonal to Boc and is much more soluble than Fmoc protected substrates. When the Cbz protected imidazolidinone-linker construct was isolated after chromatography the NMR spectrum showed some unexpected extra signals for the CH_2 of the Cbz protecting group and of the CH_3 signal from the methyl groups on the imidazolidinone ring. We believe that these extra

signals are in fact caused by hindered rotation around the N-C (imidazolidinone-Cbz) bond. This restricted rotation would allow for different conformations of the molecule to be observed on the ^{1}H NMR timescale. Such different conformations are known as rotamers.[301] Further investigations were conducted using variable temperature NMR (**Fig. 43**).

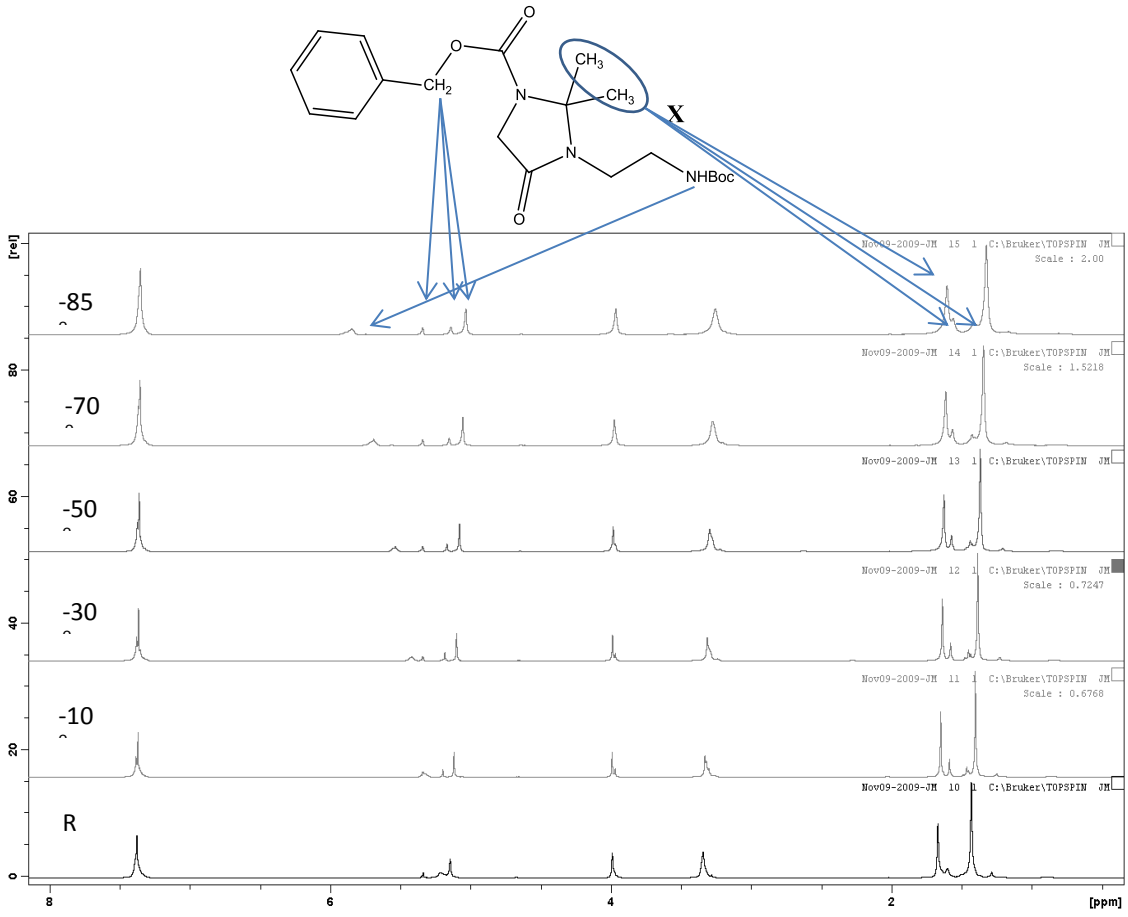


Figure 43: Low temperature ^{1}H NMR on compound **180**

We can see that as the temperature decreases and the rotation about the N-C bond slows further (-30 ^{o}C) the three different conformations of the molecule are visible. This is most apparent when focusing on the Cbz CH_2 signals. This restricted rotation is not unusual for carbamates,[302] and has been reported previously in related systems.[303]

In order to have complete confidence in the structure of **180** a crystal was grown and X-ray data was generated to give conclusive evidence (**Fig. 44**).

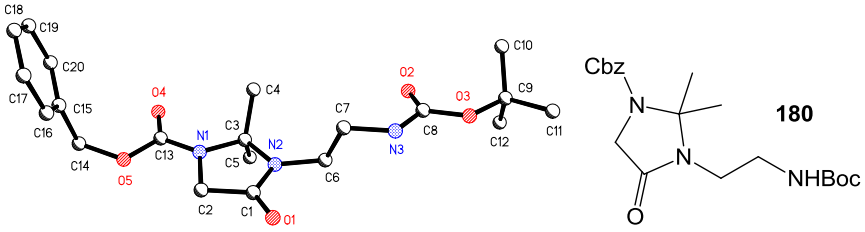


Figure 44: Crystal Structure of protected imidazolidinone **180**

With the Cbz protecting group in place the Boc group was removed using normal acidic conditions to yield the primary amine **181** (**Scheme 148**). We were now ready to append the acridine moiety. It must be mentioned at this point that the commercial source of 9-chloroacridine was initially used in these experiments and was found to be very impure. This caused great difficulty in later purification attempts. Pure 9-chloroacridine **174** could be synthesised using the method of Albert,[296] on a large scale at low cost, from fenamic acid. Using the primary amine **181** to attack the intermediate phenoxy acridine, generated from phenol and 9-chloroacridine, the desired S_NAr product **182** was isolated as a hydrochloride salt (**Scheme 148**). Purification of this compound was found to be quite difficult. After much experimentation an adaption of a method developed by Feringa for the purification of his intercalating aminoacridine ligands was found to be successful.[277] By stirring the amorphous solid from the reaction in diethyl ether over several days the phenol was extracted and the hydrochloride salt of product **182** precipitated as a yellow powder in 53% yield.

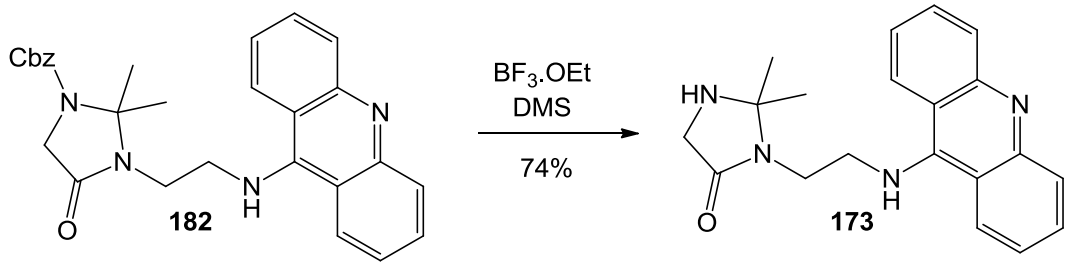
We initially tried to de-protect the Cbz group using hydrogenation conditions but with no success. We had successfully de-protected tertiary Cbz carbamates using hydrogenation conditions in the synthesis of the **FAPY** catalyst (**See Section 2.2.1.10**). We were hopeful therefore that a slight modification of the protocol might result in de-protection. To this end we experimented with different palladium catalysts and reduction conditions as depicted in **Table 26**.

Entry	Conditions	Yield[a]
1	Pd/C (10 mol %), H_2 1 atm, EtOAc	R.S.M.
2	Pd/C (20 mol %), H_2 1 atm, EtOH	R.S.M.
3	Pd/C (50 mol %), H_2 1 atm, THF	R.S.M.
4	Pd/C (100 mol %), H_2 1 atm, THF pre-saturated with H_2	R.S.M.
5	$Pd(OH)_2$/C (50 mol %), H_2 1 atm, THF pre-saturated with H_2	R.S.M.
6	HBr/HOAc	Complex Mixture
7	$Pd(OH)_2$/C (50 mol %), H_2 1 atm, 1,4-Dioxane/H_2O/0.5 M HCl	R.S.M.
8	Na/NH_3	Complex Mixture
9	BF_3.OEt/DMS, DCM	Quantitative[b]

Reactions were conducted on a 0.2 mmol scale with 3 mL of solvent at stated conditions, [a] determined by ^{1}H NMR, [b] isolated yield

Table 26: Conditions for removal of Cbz protecting group

Despite using an array conditions and quantities of palladium catalyst we were unable to get any removal of the Cbz group (**Entries 1-4**). Even when the unreduced Pearlman's catalyst was used only starting material was returned after several days (**Entry 5**).[304] A possible explanation for this is that the palladium catalyst was being poisoned by the acridine nitrogen coordinating to the metal centre. This kind of poisoning of Pd (0) catalysts has been reported for pyridine.[305] Using the more traditional de-protection procedure yielded a complicated mess of products, possibly from hydrolysis of the imidazolidinone ring (**Entry 6**). It was thought that by protonating the amino groups we could reduce the risk of catalyst poisoning, but again only starting material was returned (**Entry 7**). When classical electron transfer reduction was tried a complicated mixture of products was obtained (**Entry 8**). It is possible that an unwanted Birch reduction of the acridine aromatic system is occurring.[306] Finally, to our delight, when Lewis-acidic conditions were applied the reaction went to completion over-night (**Entry 9**). The bis-hydrochloride salt of the intercalating catalyst was isolated in 74% yield after precipitation from *iso*-propanol (**Scheme 149**).



Scheme 149: De-protection of Cbz and completion of synthesis of **173**

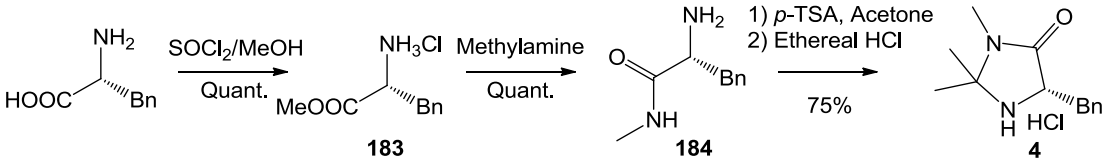
The ^{1}H NMR of the intercalating catalyst again features an overlapping ethylene multiplet between 3.44 and 3.55 ppm and two broad singlets inter-changeable with D_2O at 7.95 and 2.05 ppm representing the amino acridine and imidazolidinone NH respectively. The presence of the intercalating organocatalyst **173** was confirmed by mass spectrometry.

The synthesis of intercalating catalyst **173** was completed in 9 steps with a somewhat disappointing 20% overall yield. We felt that this synthesis was inefficient as it required excessive use of protecting groups which was detrimental to the overall yield and required a considerable amount of time to generate a small amount of product. Furthermore, we were somewhat limited in the quantities of amide **177** we could produce as the coupling reagent TBTU was rather expensive. We decided to consider another synthetic route that might avoid these conditions generating a more efficient synthetic pathway.

4.4.2 Alternative route to the DNA-intercalating organocatalyst

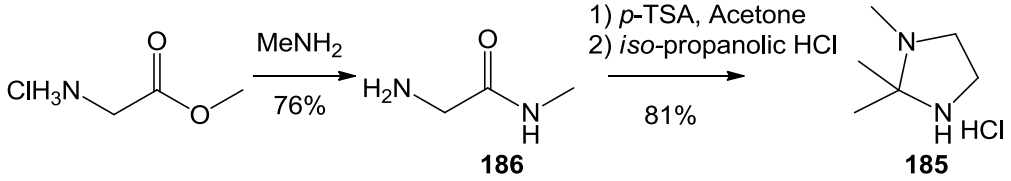
Having gained valuable experience with the previous synthesis we identified two key aspects that could make the process more efficient. Firstly, the purification of compounds after the addition of the aminoacridine moiety was near impossible using normal phase flash chromatography. Purification would more preferably be achieved by precipitation of a salt from an alcoholic solvent at the end of the synthesis. This would mean that the strategy of installing acridine systems toward the end of the synthesis, in a clean high yielding reaction, would have to be maintained/improved. Secondly, we felt that the synthesis of the amide bond between glycine and the linker would be much more efficient if it could be achieved by the aminolysis of a glycine ester.

To better understand the chemistry of the imidazolidinone formation we first replicated the procedure of MacMillan[16] to make the chiral catalyst **4** (**Scheme 150**).



Scheme 150: Synthesis of MacMillan's imidazolidinone **4**

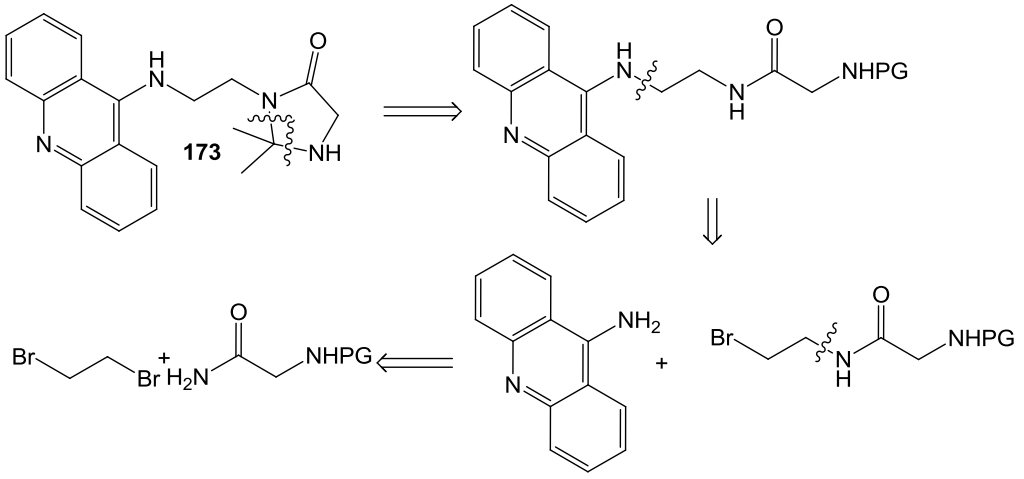
The methyl ester of phenylalanine **183** was generated quantitatively by the standard thionyl chloride esterification procedure. We then employed MacMillan's approach of over-night aminolysis of the ester with ethanolic methylamine, giving the amide **184** in a quantitative yield. The acetone ring-closure was catalysed by *p*-toluenesulfonic acid, and the product **4** could be conveniently precipitated from ether using ethereal hydrochloric acid. We then replicated the conditions using glycine instead of phenylalanine to give the achiral catalyst **185** (**Scheme 151**).



Scheme 151: Synthesis of achiral imidazolidine **185** from glycine

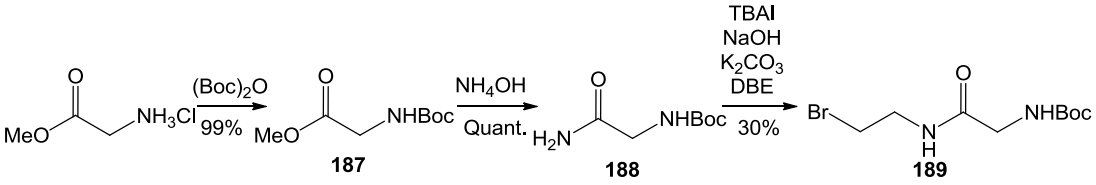
Using aminolysis conditions from Tomkinson[307] we prepared the amide **186** in good yield. Using the same conditions as with the phenylalanine derivative, we performed the ring-closure with catalytic amounts of *p*-toluenesulfonic acid. Precipitation of the hydrochloride salt from *iso*-propanol gave the imidazolidinone **185** in excellent yield.

We now wished to employ the same strategies in the synthesis of our intercatalor and began a new retrosynthesis (**Scheme 152**).



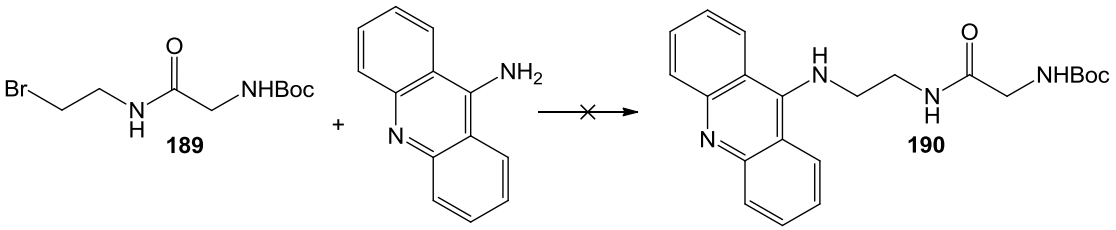
Scheme 152: Second retrosynthesis of intercalator **173**

We again proposed that the ring closure should be the final step so purification could be achieved by precipitation of the resultant hydrochloride salt. The acridine moiety would be added by the nucleophilic attack of commercial 9-aminoacridine on an alkyl-halide. This alkyl-halide would in turn be generated from another nucleophilic attack of a protected glycinamide on 1,2-dibromoethane.



Scheme 153: Synthesis of alkyl-halide **189**

Starting from glycine methylester hydrochloride, the amine was protected with Boc anhydride in excellent yield.[308] The resultant *N*-Boc glycine methylester **187** was treated with ammonium hydroxide to give *N*-Boc glycinamide **188** quantitatively.[309] Finally the alkyl halide **189** was synthesised using phase-transfer catalysis in a disappointing 30% yield after chromatography (**Scheme 153**). We next attempted to perform the S_N2 reaction with 9-aminoacridine.



Scheme 154: Attempted S_N2 reaction with aminoacridine

Unfortunately this reaction was not as straight-forward as first anticipated. Several different methodologies were employed as summarised in **Table 27**.

Entry	Conditions	Yield[a]
1	$CsCO_3$/TEA, DMF Reflux	R.S.M.
2	KOH, DMSO 150 ^oC	Complex Mixture
3	NaH/KI, DMF 60 ^oC	R.S.M.
4	KI, ACN 170 ^oC, microwaves, 20 mins	R.S.M.

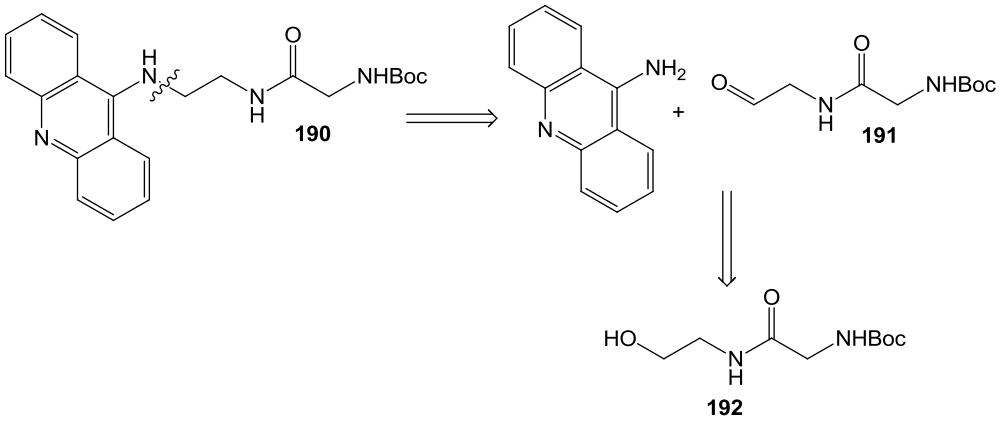
Reactions were performed on a 0.5 mmol scale under stated conditions, [a] determined by ^1H NMR spectroscopy

Table 27: Screened reaction conditions of the S_N2 reaction of **189** with aminoacridine

Following a procedure reported by Gellerman[310] we initially attempted the reaction using caesium carbonate in refluxing DMF. The result was returned starting material (**Entry 1**). This lack of reactivity could be explained by the fact that Gellerman had used an aromatic-halide which cannot undergo S_N1 or S_N2 substitution but rather S_NAr, which proceeds through a different mechanism. The next

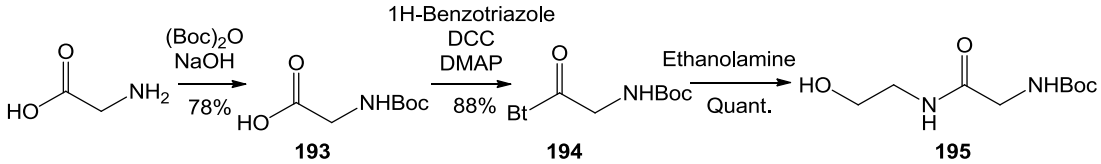
approach involved using KOH in DMSO at elevated temperatures (**Entry 2**). This procedure had been used previously to add aminoacridine to long-chain alkyl halides.[311] In our hands this gave a complex mixture of products. The most likely cause of this was the hydrolysis of the amide by potassium hydroxide. In order to prevent any side reactions we endeavoured to use a strong base and perform an *in situ* Finkelstein reaction with potassium iodide (**Entry 3**). The reaction gave back the starting material demonstrating how non-nucleophilic the aminoacridine nitrogen appears to be. In a final attempt we employed microwave conditions in an effort to promote the reaction. The result was again returned starting material (**Entry 4**). Such a microwave assisted alkylation has been reported before,[312] but only for anilines which are more nucleophilic than aminoacridine.

Having been unable to perform the desired S_N2 reaction we decided to change the synthons so that the acridine moiety could be appended in a straight forward reductive-amination (**Scheme 154**). Such a reductive-amination using aminoacridine with aromatic aldehydes and glyoxylic acid had been reported previously.[310]



Scheme 155: Retrosynthesis of compound **190** using reductive amination

To synthesise aldehyde **191** for the reductive-amination reaction we decided to use an oxidative protocol. An alternative approach using acetal hydrolysis would have involved acidic conditions which may have compromised the Boc protecting group.



Scheme 156: Synthesis of alcohol **195**

We began with the standard protection of glycine with Boc anhydride.[313] In order to install the amino alcohol we experimented with a variety of coupling conditions and also the aminolysis of the methyl ester. However, we found that by Synthesising the activated amide **194** derived from benzotriazole[314] and its subsequent treatment with excess ethanolamine gave the desired alcohol

195 in high yields. We next tried to oxidise the alcohol to the aldehyde. The summary of these attempts are compiled in **Table 27**.

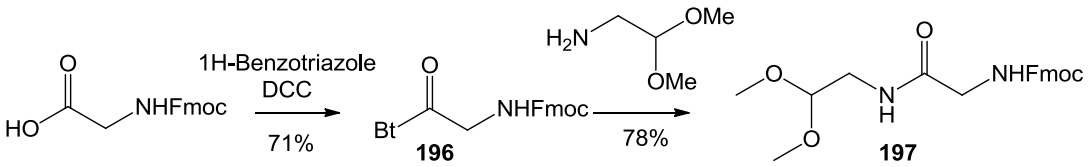
Entry	Conditions	Result[a]
1	SO_3.Py(4 eq.)/NEt_3(8 eq.)	<10%
2	SO_3.Py(4 eq.)/NEt_3(5 eq.)	No product detected
3	PCC(1.5 eq.)/NaOAc(1.5 eq.)	No product detected
4	PCC(3 eq.)	No product detected
5	PDC(2 eq.)	No product detected
6	NMO(1.5 eq.)/TPAP(5 mol%)	No product detected
7	DMP(1.05 eq.)	<10%

Reactions performed on 0.5 mmol scale with 5 mL of solvent, [a] determined by ^{1}H NMR spectroscopy

Table 27: Attempts to oxidise amino alcohol **195**

We initially tried to use the classic Parikh-Doering oxidation conditions but the crude ^{1}H NMR showed very little product (as indicated by a signal at 9.15 ppm) and a complicated mixture of other products (**Entry 1**). We lowered the equivalents of base for fear that it may be causing side reactions but this resulted in the loss of any product formation, as indicated by the crude ^{1}H NMR (**Entry 2**). We decided to switch oxidant as the DMSO based oxidations were proving fruitless. The chromium based oxidants again gave no product as did the Ley oxidation protocol (**Entries 3-6**). Unfortunately, Dess-martin periodinane gave only a small amount of detectable aldehyde (**Entry 7**). The failure of this oxidation under either acid or basic conditions must be related to the electronic properties of the alcohol. The alcohol in question is an α-amino alcohol, such alcohols are known in the literature to resist oxidation through either intra- or inter- molecular hydrogen bonding.[178]

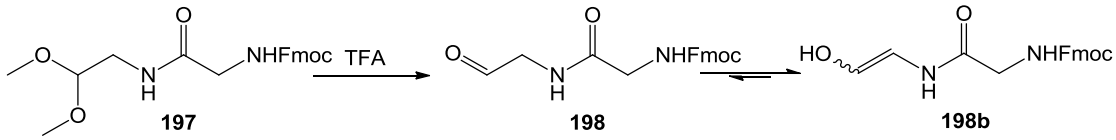
We decided that instead of using an oxidation strategy we would instead generate the aldehyde *via* the acetal. This, however, would require switching the acid labile Boc protecting-group to the base sensitive Fmoc group (**Scheme 157**).



Scheme 157: Synthesis of acetal **197**

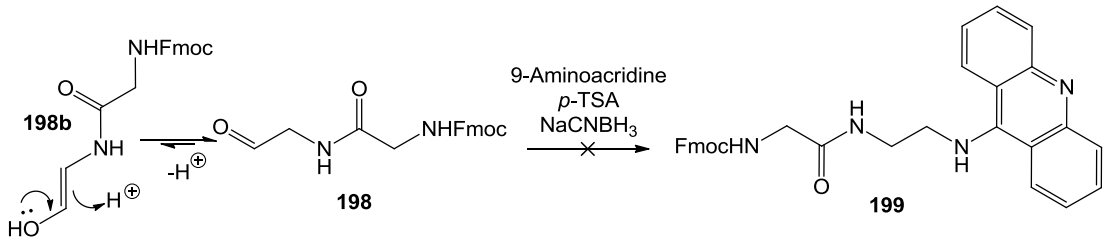
The Fmoc-protected glycine was commercially available and was converted to the activated amide **196**, derived from benzotriazole, in good yield. Reaction of **196** with aminoacetaldehyde dimethyl acetal gave the amino acetal **197** in excellent yield after chromatography. With ample quantities of the acetal available we moved onto the hydrolysis. Exposure of the amino acetal **197** to acidic

conditions did not yield the expected aldehyde **198**, but instead gave the enol tautomer **198b** (**Scheme 158**).



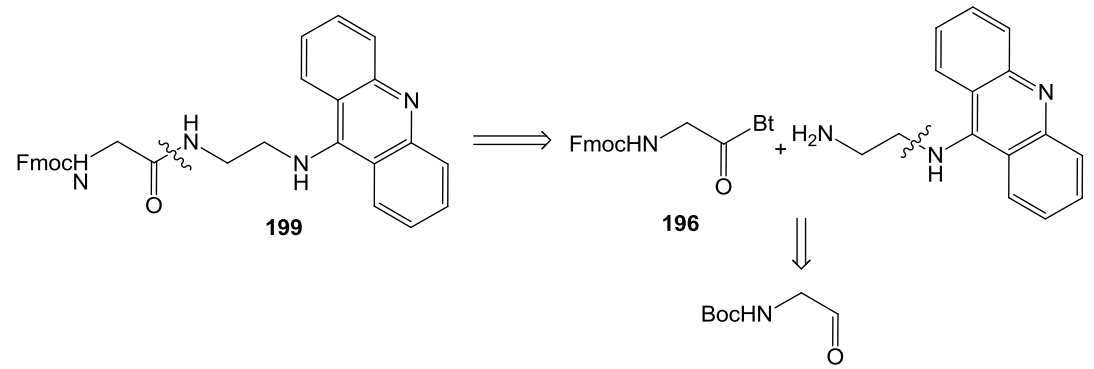
Scheme 158: Generation of the enol tautomer **198b**

Again we believe that H-bonding between the amide carbonyl and the OH group is responsible for the increased stability of the enol form. Also the double-bond "character" of the C-N bond in the amide functionality[315] may stabilize the enol tautomer through conjugation with the π-system of the enol. We never the less hoped that we could use the enol tautomer **198b** in the reductive amination as a source of the aldehyde **198**, which could be generated *in situ* through the use of acidic conditions (**Scheme 159**).



Scheme 159: Attempted reductive amination of enol tautomer **198b** using acid catalysed tautomerisation

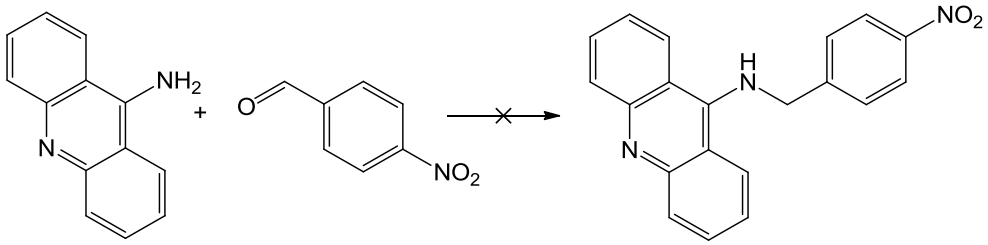
Unfortunately, the result of the reaction was the return of the enol tautomer and the cyanoborohydride salt of aminoacridine. At this point we decided to change our strategy so that we would first append acridine to the linker and then couple this to the activated amide **196** (**Scheme 160**).



Scheme 160: Revised retrosynthesis of **199**

Using the commercially available *N*-Boc aminoacetaldehyde we again attempted the reductive amination with aminoacridine. Employing the same conditions as used by Gellerman[310] we were only able to isolate the cyanoborohydride salt of aminoacridine, in high yield, but no desired

product. The borohydride salt was identified by ^{1}H NMR as indicated by the clear presence of a 4 line multiplet superimposed with a smaller 7 line multiplet representing the 3 equivalent protons being split by ^{11}B with a spin of 3/2 and 80% abundance , and ^{10}B with a spin of 3 and 20% abundance, respectively. The relative integration of this multiplet suggests a 1 : 1 ratio of the aminoacridine anion with the borohydride anion. Repetition of the experiment using sodium triacetoxyborohydride as the reducing reagent, again yielded only the triacetoxyborohydride salt of aminoacridine as identified by ^{1}H NMR. When the reaction was studied in more detail it was found that the nucleophilic attack on the aldehyde was not occurring at all, rather the amine from aminoacridine was getting protonated by the acetic acid catalyst and then exchanging ions with the reducing reagent. This was very surprising as Gellerman had used this exact methodology to generate a number of aminoacridine compounds.[310] We next decided to try to reproduce some of Gellerman's examples in order to better understand the chemistry. Trying first with 2-carboxybenzaldehyde and then with glyoxylic acid hydrate, we were unable to repeat any of the results obtained in his paper. Indeed the reactants appeared insoluble in the solvent system and only the reducing agent salt of aminoacridine could be recovered after extended reaction periods. We deduced that the amino group was not nucleophilic enough to attack the electrophile even with an acetic acid catalyst. We decided to pick the more reactive *p*-nitrobenzaldehyde and try some alternative conditions as outlined in **Table 28**.



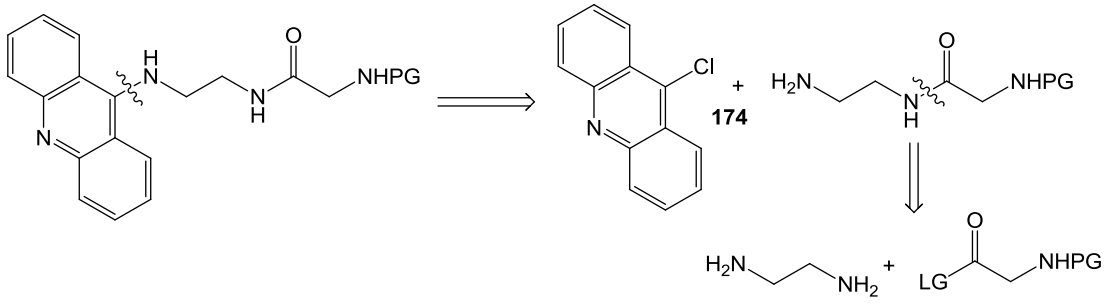
Entry	Reducing Agent	Solvent	Result[a]
1	$NaCNBH_3$	MeOH:HOAc (99:1)	Borohydride salt
2	$NaBH(OAc)_3$	MeOH:HOAc (99:1)	Borohydride salt
3	$NaCNBH_3$	DCM:TFA (99:1)	TFA salt
4	TES	MeOH:HOAc (99:1)	R.S.M.

Reactions were performed on a 1 mmol scale in 5 mL of solvent at RT, [a] determined by ^{1}H NMR

Table 28: Attempted reductive amination of aminoacridine with *p*-Nitrobenzaldehyde

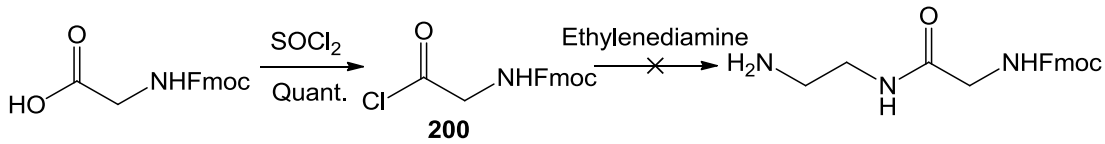
Using the more reactive aldehyde did not give the expected aminoacridine but instead gave, again, the borohydride salt of both reducing reagents (**Entries 1-2**). We next tried to use the more acidic trifluoroacetic acid as the catalyst. This time the TFA salt of aminoacridine was obtained almost immediately in high yield and exchange with the borohydride ion did not occur (**Entry 3**). In a final attempt we switched to the non-ionic triethyl silane for the reducing reagent, but this time the

result was returned starting material. It became clear that amino acridine was just not nucleophilic enough to attack the aldehyde, even when it was activated by an electron-withdrawing *p*-nitro group. It was decided at this point to return to 9-chloroacridine as the source for the acridine moiety and a new synthetic route was proposed (**Scheme 161**).



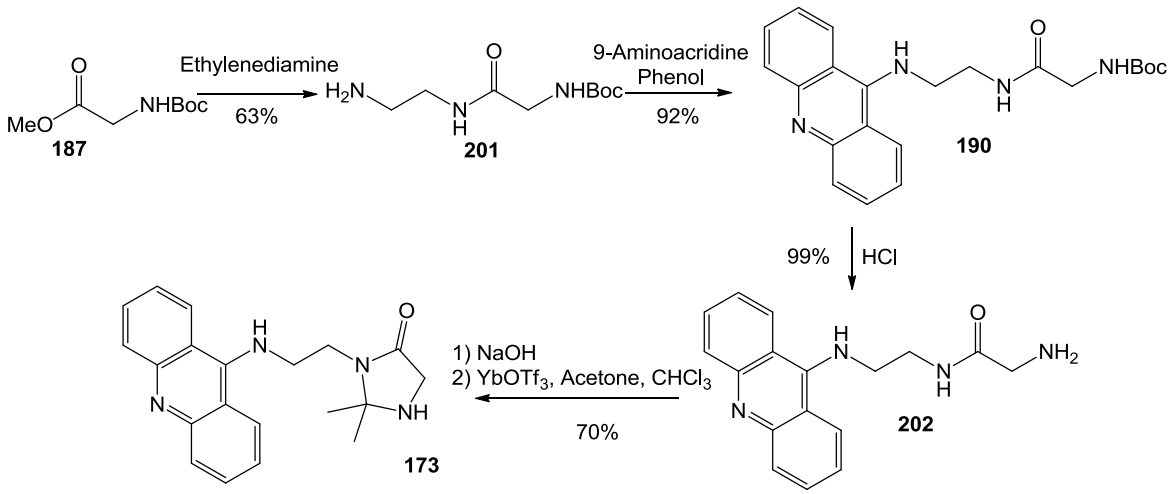
Scheme 161: Revised retrosynthesis of intercalating catalyst **173**

We hoped to bind the linker to the activated protected glycine residue and then perform a S_NAr reaction with 9-chloroacridine. Subsequent de-protection of the terminal amine followed by cyclisation would deliver the final intercalating imidazolidinone catalyst **173**.



Scheme 162: Use of Fmoc-protected glycine

We initially tried to use Fmoc as the protecting group for glycine as it is commercially available and forms a stable acid-chloride (**Scheme 162**).[316] Although the Fmoc group is labile under basic conditions we hoped that we would be able to generate the amide directly from ethylene diamine without the need to protect one of the amines. In order to avoid formation of the bis-amide we used an excess of the ethylenediamine (5 molar equivalents) and added the acid chloride **200** dropwise onto the solution. Unfortunately, the basic conditions of the reaction media caused premature de-protection of the Fmoc group forcing us to change to the orthogonal Boc group (**Scheme 163**).



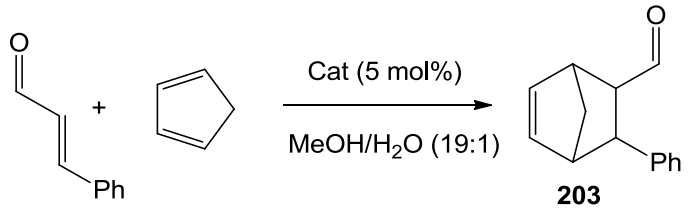
Scheme 163: Completed synthesis of intercalating catalyst **173**

Using the Boc protected methyl ester **187**, which we had prepared earlier (**Scheme 152**), we performed an aminolysis reaction using ethylenediamine. This reaction proceeded with excellent conversion but some loss occurred during workup as the product **201** is quite soluble in water. We next performed the S_NAr reaction using the primary amine **201**. An excellent 92% yield of **202** was achieved after precipitation of the hydrochloride salt from diethyl ether. Finally, with the aminoacridine **202** in hand we were able to quantitatively de-protect the Boc group. This resultant amine was isolated as the hydrochloride salt. Sodium hydroxide was then used to generate the free-amine, which resulted in the degradation of some of the material. The crude free-amine was then treated with acetone and a catalytic quantity of the Lewis acidic ytterbium triflate in refluxing chloroform.[307] The final product was purified as the free-amine using flash chromatography. The intercalating imidazolidinone catalyst **173** is a hydroscopic solid which could be isolated after precipitation from cold acetone in a 70% yield.

4.5 Attempted development of a DNA-organocatalytic reaction

With the synthesis of the DNA-intercalating imidazolidinone organocatalyst **173** completed we began exploring some possible transformations which we would be able to effect. We immediately identified the iminium ion catalysed Diels-Alder reaction as a suitable candidate as the use of imidazolidin-4-ones is well known to generate reactive dienophiles from both ketones and aldehydes.[317]

We initially decided to verify whether our intercalating imidazolidinone was capable of generating a reactive iminium ion and comparing it to both our achiral imidazolidinone **185** and MacMillan's imidazolidinone **4**.[16] To this end we performed the iminium ion catalysed cycloaddition of cinnamaldehyde and cyclopentadiene (**Table 29**).



203

Entry	Catalyst	Time (h)	Conversion(%)[a]	Yield(%)[b]	d.r. (*exo*/*endo*)[c]	*ee*(%)[d]
1	**185**	16	87	81%	1.67 : 1	0%
2	**4**	16	88	81%	1.32 : 1	94%
3	**173**	16	27	24%	1:1	0%

Reactions were carried out on a 1 mmol scale using 5 mol% of the hydrochloride salt of each catalyst, 1 eq. of *trans*-cinnamaldehyde, 1.5 eq. of cyclopentadiene in 0.5 mL of 95% methanol for 16 hours at room temperature. [a] measured by ^{1}H NMR, [b] isolated yield, [c] measured by ^{1}H NMR spectroscopy, [d] determined by chiral-GC

Table 29: Iminium-ion catalysed Diels-Alder reaction

Unsurprisingly, both the achiral catalysts returned racemic products (**Entries 1 and 3**) while MacMillan's imidazolidinone gave excellent selectivity (**Entry 2**). The achiral catalyst **185** however showed improved *exo* selectivity over MacMillan's catalyst (**Entries 1 and 2**), we believe this is a result of the reduced bulk at C-2 on the catalyst compared to MacMillan's imidazolidinone **4** which bears a benzyl group at this position. The reduced bulk may allow the reaction to proceed through its thermodynamically favoured *exo* transition state in a more facile manner. The imidazolidinone bearing the intercalator **173** gave much lower yields (**Entry 3**) and no observable selectivity. The decrease of both yield and *exo* selectivity would suggest that the bulk of the tethered aminoacridine moiety has retarded the reaction.

Having found that our intercalating catalyst **173** can form a reactive iminium we next sought to establish conditions which could tolerate both the existence of an iminium ion and solubilize DNA in its duplex form. The insolubility of DNA in its duplex conformation in methanol is known to occur at aqueous levels above 40% v/v,[318] well below the 95% v/v solution required for a stable iminium ion. Due to time restrictions further investigation into this class of organocatalysts was not completed. The research in this area is on-going and currently we are focusing toward the use of ionic liquids as a reaction medium. Ionic liquids have been used in asymmetric organocatalytic Diels-Alder reactions in several reports.[319] DNA is also known to be stable in its duplex form in particular ionic liquids.[320] It is hoped that by employing ionic liquids we will be able to generate a stable iminium ion while also maintaining the DNA superstructure to allow for intercalation of the catalyst.

Another possible method for solubilizing the DNA in organic solvents would be cation exchange with an alkyl PEG chain to form a DNA-lipid complex (**Fig. 45**).

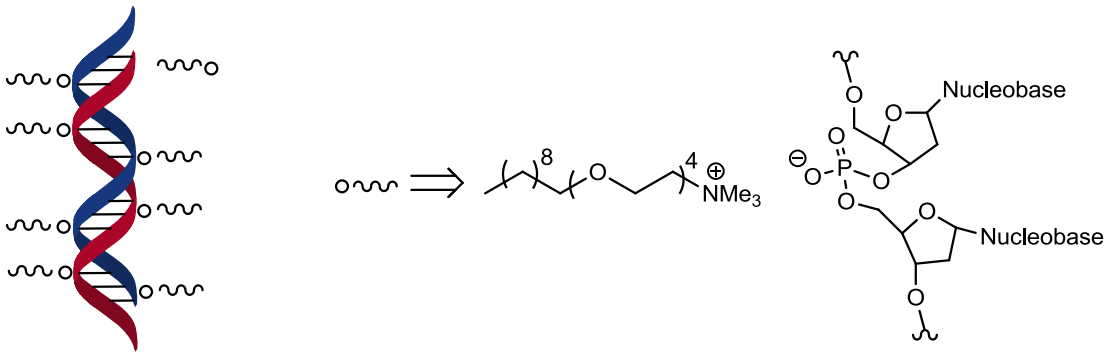


Figure 45: Organic solvent soluble DNA-lipid complex[321]

This methodology has been used by Tanaka to create organic solvent soluble DNA, which maintains its B-conformation in solution and still retains the ability to allow intercalation.[321]

4.6 Conclusion

In conclusion, we have examined three possible methods for the development of a DNA-based asymmetric organocatalytic system. In the first, DNA templates could be used to bring chiral catalysts in close proximity to appropriate substrates to effect an asymmetric transformation. In the second approach, we postulated that achiral organocatalysts could be linked covalently to the DNA superstructure by modified nucleosides. These DNA-organocatalyst conjugates could then generate reactive intermediates in a chiral environment and effect asymmetry in the reaction products. In the third approach, we examined the feasibility of creating a DNA-organocatalyst complex through non-covalent binding using intercalators. This achiral DNA-intercalating organocatalyst could also affect asymmetry on a transformation through the natural chirality of the helical DNA superstructure.

A synthetic route to the DNA intercalator was then proposed and the target synthesised in 9 steps in 20% overall yield by using a combination of protecting groups. The final Cbz de-protection step was unresponsive to hydrogenation conditions and required chemical reduction.

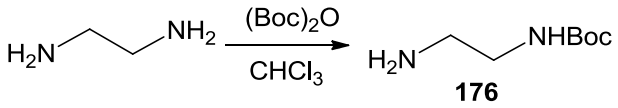
The synthetic route to the catalyst was revised to improve efficiency. Both MacMillan's imidazolidinone and an achiral imidazolidinone based on glycine were synthesised. An attempted S_N2 reaction with aminoacridine was unsuccessful requiring a further redesign of the synthetic route. Reductive amination was chosen as the key reaction step, however oxidation of an α-amino alcohol to the requisite aldehyde proved fruitless. Revision of the aldehyde generation led to acetal de-protection, which unfortunately revealed an unreactive enol. Reductive amination of aminoacridine with simple aliphatic aldehydes and aryl aldehydes led to ion exchange with the reducing reagents.

The synthetic route was again redesigned to include a S_NAr reaction with 9-chloroacridine. The catalyst was synthesised in 4 steps in 40% overall yield. This represents the first synthesis of an organocatalyst which is capable of intercalating with DNA.

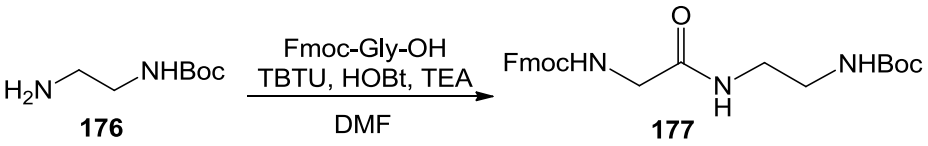
Both the achiral and intercalating catalysts were found to generate reactive iminium ions from cinnamaldehyde. Future work includes experimentation using ionic liquids as a reaction media to solubilize DNA in its B-conformation without the use of mixed aqueous systems. Also the synthesis of an organic solvent soluble DNA-lipid complex is currently underway. It is hoped this complex will allow both the intercalation of the catalyst and remain in its B-conformation in organic solvent. The application of organocatalysis into the field of DNA-based catalysis is novel in itself, and represents both a challenging and innovative topic.

4.7 Experimental

For general experimental detail see section 2.4.1



***tert*-Butyl (2-aminoethyl)carbamate 176:** Ethylenediamine (28 mL, 450 mmol, 10 eq.) was dissolved in anhydrous methylene chloride (400 mL) and stirred in an acetone/ice bath under a positive pressure of nitrogen. To this solution Boc anhydride (8.74 g, 40 mmol, 1 eq.) in methylene chloride (200 mL) was added dropwise over 4 hours *via* a pressure-equalising dropping funnel. The cloudy solution was then left to stir overnight at room temperature. The reaction was then washed with a saturated brine solution (3 x 400 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to yield a colourless oil, 5.55 g (86.7%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.00 (br s, 1 H, N*H*Boc), 3.14 (q, 2 H, *J* = 5.7 Hz, CH_2NHBoc), 2.76 (t, 2 H, *J* = 5.9 Hz, CH_2NH$_2$), 1.54 (br s, 2 H, NH_2), 1.41 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.3 (*C*O), 79.3 (*C*$(CH_3)_3$), 43.4 (*C*H_2NH$_2$), 41.9 (*C*H_2NHBoc), 28.5 (*C*$H_3)_3$. Matches known data.[300]

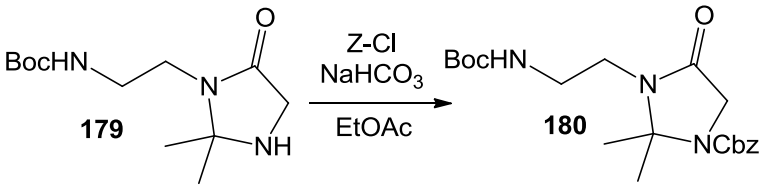


(9H-Fluoren-9-yl)methyl (2-((*tert*-butyl (ethyl)carbamate)amino)-2-oxoethyl)carbamate 177: To a nitrogen flushed flask was added Fmoc-glycine (1.49 g, 5 mmol, 1 eq.) and anhydrous dimethylformamide (25 mL) was added. The suspension was stirred until dissolution. Under a stream of nitrogen was added O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (1.77 g, 5.5 mmol, 1.1 eq.) and hydroxybenzotriazole hydrate (0.74 g, 5.5 mmol, 1.1 eq.). Anhydrous triethylamine (0.84 mL, 5.5 mmol, 1.1 eq.) was added causing the solution to yellow. The reaction was stirred at room temperature for 20 minutes. To this was added a solution of *tert*-butyl (2-aminoethyl)carbamate **176** (0.88 g, 5.5 mmol, 1.1 eq) in anhydrous dimethylformamide (5 mL). The reaction was then stirred for 5 hours at room temperature. Methylene chloride (20 mL) was then added and the solution was washed sequentially with saturated brine solution (100 mL), of 0.5 M HCl solution (100 mL), and saturated $NaHCO_3$ solution (200 mL). The organic phase was dried with solid Na_2SO_4 and concentrated *in vacuo* to yield a colourless oil. This oil was dissolved in diethyl ether (50 mL) and left overnight to afford a white precipitate, 1.88 g (86%). **^{1}H NMR** (300 MHz, DMSO) δ 7.82-7.95 (m, 3 H, overlapping *ArH* + N*H*Boc), 7.72 (d, 2 H, *J* = 6.2 Hz, *ArH*), 7.50 (t, 1 H, *J* =

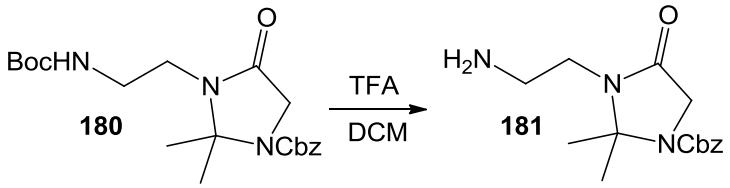
5.9 Hz, N*H*Fmoc), 7.42 (t, 2 H, *J* = 7.2 Hz, *ArH*), 7.33 (t, 2 H, *J* = 7.2 Hz), 6.80 (t, 1 H, *J* = 4.9 Hz, CON*H*), 4.17-4.34 (m, 3 H, overlapping C*H* + CHCH_2), 3.58 (d, 2 H, *J* = 6 Hz, NHCH_2CO), 3.10 (q, 2 H, *J* = 6.4 Hz, CH_2NHBoc), 2.98 (t, 2 H, *J* = 6.2 Hz, CH_2CH2NHBoc), 1.38 (s, 9 H, (CH_3)$_3$). **^{13}C NMR** (75 MHz, DMSO) *δ* 169.1 (*C*ONH), 156.4 (*C*OOCH$_2$), 155.6 (*C*OOC(CH$_3$)$_3$), 143.8 (*Ar C*), 140.7 (*Ar C*), 127.6 (*Ar CH*), 127.0 (*Ar CH*), 125.2 (*Ar CH*), 120.1 (*Ar CH*), 77.6 (*C*(CH$_3$)$_3$), 65.7 (CCH$_2$O), 46.6 (*C*CH$_2$O), 43.5 (NHCH$_2$CO), 39.6 (*C*H$_2$NHBoc), 38.7 (*C*H$_2$CH$_2$NHBoc), 28.2 ((*C*H$_3$)$_3$). **M.P.** 138-140 °C. Matches known data.[322]

177 **179**

***tert*-Butyl (2-(2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl)carbamate 179:** (9H-fluoren-9-yl)methyl (2-((*tert*-butyl (ethyl)carbamate)amino)-2-oxoethyl)carbamate **177** (1.88 g, 4.27 mmol, 1 eq.) was dissolved in a 20% v/v solution of piperidine in dimethylformamide (10 mL) and stirred for 1 hour at room temperature. The solution was concentrated *in vacuo* to yield an off white powder. The powder was suspended in water (100 mL) with the aid of an ultrasonic bath. To the suspension was added 0.5 M HCl dropwise until the solution had reached pH = 7. The solution was then washed with methylene chloride (2 x 100 mL). The aqueous layer was concentrated *in vacuo* to yield the de-protected hydrochloride salt as a white powder. To the salt was added methanol (10 mL) and sodium acetate trihydrate (581 mg, 4.27 mmol, 1 eq.) and the solution was heated with stirring at 30 °C for 30 minutes. Acetone (1.57 mL, 21.35 mmol, 5 eq.) was added to the reaction mixture which was subsequently refluxed at 80 °C for 18 hours under a positive pressure of nitrogen. The reaction was then concentrated *in vacuo* to a brown oil which was suspended in water and was neutralized by careful addition of solid $NaHCO_3$. The aqueous solution was then extracted with methylene chloride (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield an orange power, 912 mg (83%). Crystals for X-ray analysis grown from slow evaporation of an equi-voluminous solution of methylene chloride and *n*-hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 5.46 (br s, 1 H, COCH$_2$N*H*), 3.42-3.47 (m, 2 H, COCH_2), 3.23-3.33 (m, 4 H, overlapping CH_2CH_2), 2.16 (br s, 1 H, N*H*Boc) 1.43 (s, 9 H, (CH_3)$_3$), 1.39 (s, 6 H, (CH_3)$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 174.6 (*C*OCH$_2$), 156.1 (*C*OOC(CH$_3$)$_3$), 79.1 (*C*(CH$_3$)$_3$), 78.3 (*C*(CH$_3$)$_2$), 48.1 (COCH$_2$), 40.0 (*C*H$_2$NHBoc), 39.8 (*C*H$_2$CH$_2$NHBoc), 28.3 ((*C*H$_3$)$_3$), 26.2 ((*C*H$_3$)$_2$). **ESI-MS** $C_{12}H_{23}N_3O_3$ Calc. (M+H$^+$) = 258.1812 found = 258.1825 (5.00 ppm).

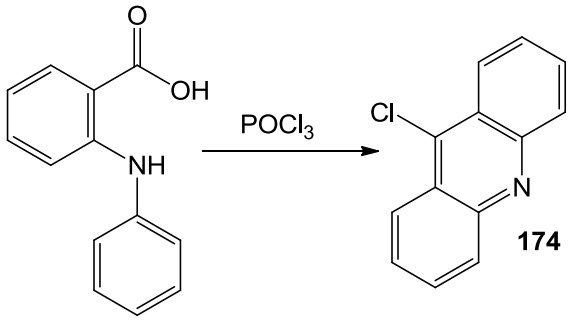


Benzyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate 180: *tert*-Butyl (2-(2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl)carbamate **179** (2.19 g, 8.5 mmol, 1 eq.) was dissolved in ethyl acetate (10 mL). To this was added benzyl chloroformate (1.46 mL, 10.2 mmol, 1.2 eq.) and 10 mL of a saturated solution of $NaHCO_3$. The biphasic mixture was stirred vigorously overnight. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield an orange oil which was purified using flash chromatography, 50% ethyl acetate in *n*-hexane, visualization with ninhydrin, to yield a white solid, 1.73 g (52%). $\boldsymbol{R_F}$ (50% ethyl acetate in *n*-hexane) 0.55. Crystals for X-ray analysis grown from slow evaporation of an equi-voluminous solution of methylene chloride and *n*-hexane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28-7.50 (m, 5 H, *ArH*), 5.03-5.49 (m, 3 H, overlapping N*H*Boc + CH_2Ph rotamers), 3.99 (s, 2 H, COCH_2), 3.23-3.46 (m, 4 H, overlapping CH_2CH_2), 1.54-1.79 (m, 6 H, (CH_3)$_2$ rotamers), 1.42 (s, 9 H, (CH_3)$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (N*C*OCH$_2$), 156.0 (N*C*OOC(CH$_3$)$_3$), 153.0 + 152.0 (rotamers, N*C*OOCH$_2$), 136.0 + 135.6 (rotamers, Ar *C*), 128.5 + 128.4 (rotamers, Ar *C*H), 128.3 + 128.2 + 128.1 + 128.1 (rotamers Ar *C*H), 127.7 (Ar *C*H), 79.4 + 79.0 (rotamers, *C*(CH$_3$)$_2$), 79.2 (*C*(CH$_3$)$_3$) 67.7 + 66.7 (rotamers, NCOO*C*H$_2$), 48.3 + 47.7 (rotamers, NCO*C*H$_2$), 39.4 (*C*H$_2$NHBoc), 39.1 (*C*H$_2$CH$_2$NHBoc), 28.3 ((C(*C*H$_3$)$_3$), 25.5 + 24.4 (rotamers, C(*C*H$_3$)$_2$). **ESI-MS** $C_{20}H_{29}N_3O_5$ (Low Res.) Calc. (M+H$^+$) = 392.22 found (M+H$^+$) = 392.23.



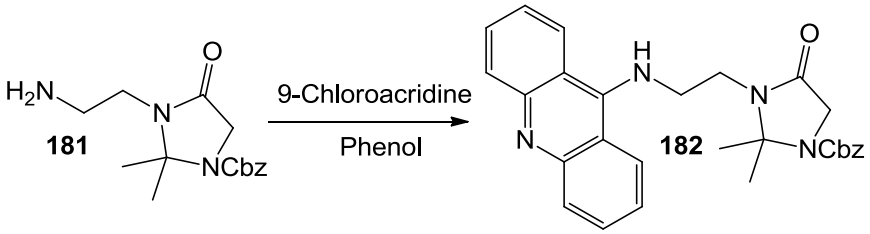
Benzyl 3-(2-aminoethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate 181: Benzyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate **180** (1.73 g, 4.42 mmol, 1 eq.) was dissolved in methylene chloride (5 mL). The solution was stirred in an acetone/ice bath for 10 minutes and trifluoroacetic acid (2 mL) was subsequently added dropwise. The reaction was allowed to come to room temperature and was stirred for 2 hours. A saturated solution of $NaHCO_3$ (10 mL) was added, and the aqueous layer was extracted with methylene chloride (2 x 25 mL), the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to yield a dark yellow oil, 1.27 g (99%) which was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 (br s, 2 H, NH_2), 7.30-7.37 (m, 5 H, *ArH*), 5.04-5.24 (m, 2 H, CH_2Ph rotamers), 5.42 (br s, 1 H, N*H*) 4.00 (s, 2

H, COCH_2), 3.61 (br s, 2 H, CH_2NH$_2$), 3.26 (br s, 2 H, CH_2CH$_2$NH$_2$), 1.50-1.75 (m, 6 H, (CH_3)$_2$ rotamers). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.4 (N*C*OCH$_2$), 152.1 (N*C*OOCH$_2$), 136.1 (Ar *C*), 128.9 + 128.7 (rotamers, Ar *C*H), 128.5 +128.4 (rotamers, Ar *C*H), 128.0 (Ar *C*H), 80.2 (*C*(CH$_3$)$_2$), 67.2 (NCOO*C*H$_2$), 48.0 (NCO*C*H$_2$), 40.3 (*C*H$_2$NH$_2$), 31.1 (*C*H$_2$CH$_2$NH$_2$), 25.4 + 24.3 (rotamers, C(*C*H$_3$)$_2$). **ESI-MS** $C_{15}H_{21}N_3O_3$ Calc. (M+H$^+$) = 292.1656 found (M+H$^+$) = 292.1660 (1.40 ppm).

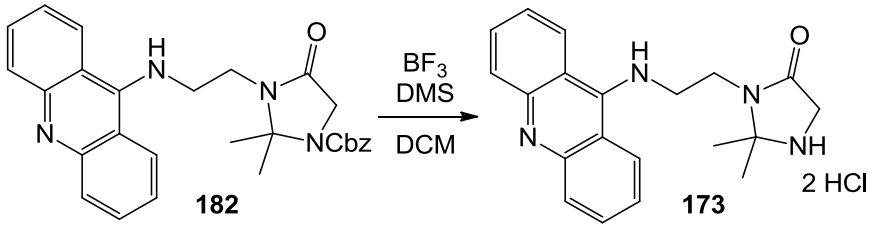


174

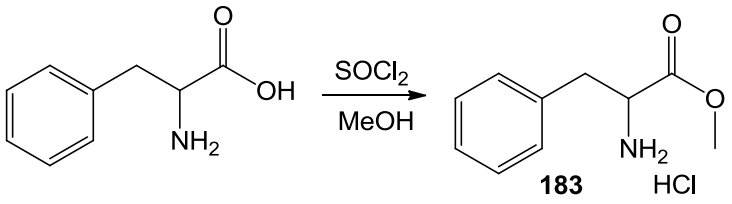
9-Chloroacridine 174:[296] 9-Chloroacridine is a strong irritant and must be handled inside the fumehood. A mixture of fenamic acid (4 g, 18.76 mmol, 1 eq.) and phosphorus oxychloride (12.24 mL, 131.32 mmol, 7 eq.) was heated to 130 °C for 2 hours. The excess phosphorus oxychloride was removed by distillation under reduced pressure to give an oily dark red residue. The residue was carefully added to a stirring solution of concentrated ammonium hydroxide (30 mL), chloroform (30 mL) and crushed ice (80 g). The mixture was stirred overnight and the organic phase was separated. The aqueous phase was then extracted with methylene chloride (2 x 100 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give a green solid. The solid was dissolved in a minimal amount of boiling absolute ethanol. To the hot ethanolic solution was added dropwise a solution of 0.05% (w/v) ammonium hydroxide until the ethanolic solution became milky. At this point activated charcoal (2 g) was added cautiously (activated charcoal can ignite the ethanol vapour) and the solution was brought to reflux for 5 minutes. The hot solution was rapidly filtered through a pad of Celite and the filtrate stored in an ice bath for 2 hours. The crystals were separated by filtration to give pale-yellow micro-needles, 2.45 g (61%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.38 (d, 2 H, *J* = 8.8 Hz, Ar*H*), 8.20 (d, 2 H, *J* = 8.8 Hz, Ar*H*), 7.73-7.82 (m, 2 H, Ar*H*), 7.55-7.64 (m, 2 H, Ar*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.8 (Ar*C*), 141.0 (Ar*C*), 130.4 (Ar*C*H), 129.7 (Ar*C*H), 126.8 (Ar*C*H), 124.5 (Ar*C*H), 124.1 (Ar*C*). **M.P.** 115-117 °C (Lit. 117-118 °C).[296] Matches known data.[323]



Benzyl 3-(2-(acridin-9-ylamino)ethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate 182: To a 250 mL 3-necked round-bottomed flask fitted with a tapped swan-neck, septum and stopper was added benzyl 3-(2-aminoethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate **181** (1.27 g, 4.37 mmol, 1 eq.). The flask was then purged with nitrogen and the stopper replaced with a bubbler. Over a stream of nitrogen was added 9-chloroacridine **174** (0.93 g, 4.37 mmol, 1 eq.) and solid phenol (4 g). The reaction was then stirred at a temperature of 100 ^{o}C under a positive pressure of nitrogen for 2 hours. The dark brown reaction mixture was allowed to cool and diethyl ether (150 mL) was added. The heterogeneous solution was stirred for one hour at room temperature and then allowed to settle. The diethyl ether was decanted and a further portion of diethyl ether (150 mL) was added and the mixture was stirred for 2 days at room temperature until the insoluble mass had become suspended in the diethyl ether as a yellow solid. The yellow solid was removed by filtration and dissolved in hot methanol, which upon cooling to -20 ^{o}C for 2 hours precipitated the hydrochloride salt. The yellow solid was then treated with a saturated solution of $NaHCO_3$ which was extracted with DCM to yield a yellow powder, 1.32 g (53%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, 2 H, *J* = 8.6 Hz, *ArH acridine*), 7.81 (d, 2 H, *J* = 6.2 Hz, *ArH acridine*), 7.46 (t, 2 H, *J* = 7.8 Hz, *ArH acridine*), 7.10-7.30 (m, 7 H, overlapping *ArH* a*cridine + ArH benzyl*), 4.96-5.10 (m, 2 H, C*H*$_2$Ph rotamers), 3.84-4.02 (m, 4 H, overlapping COC*H*$_2$ + C*H*$_2$NHacridine), 3.51 (t, 2 H, *J* = 5.9 Hz, C*H*$_2$CH$_2$NHacridine), 1.36-1.61 (m, 6 H, (C*H*$_3$)$_2$ rotamers). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (N*C*OCH$_2$), 151.8 (N*C*OOCH$_2$), 151.4 (Ar *C acridine*), 148.1 (Ar *C acridine*), 135.9 (Ar *C benzyl*), 129.9 (Ar *C*H *acridine*), 128.4 (Ar *C*H *benzyl*), 128.0 (Ar *C*H *benzyl*), 127.5 (Ar *C*H *benzyl*), 123.7 (overlapping Ar *C*H acridine + Ar *C*H acridine), 122.2 (Ar *C*H *acridine*), 116.3 (Ar *C acridine)*, 79.6 (*C*(CH$_3$)$_2$), 66.7 (NCOO*C*H$_2$), 51.3 (*C*H$_2$NHacridine), 47.8 (NCO*C*H$_2$), 40.92 , (*C*H$_2$CH$_2$NHacridine), 25.7 + 24.6 (rotamers, C(*C*H$_3$)$_2$). **ESI-MS** $C_{28}H_{28}N_4O_3$ Calc. (M+H^{+}) = 469.2234 found = 469.2257 (4.87 ppm).

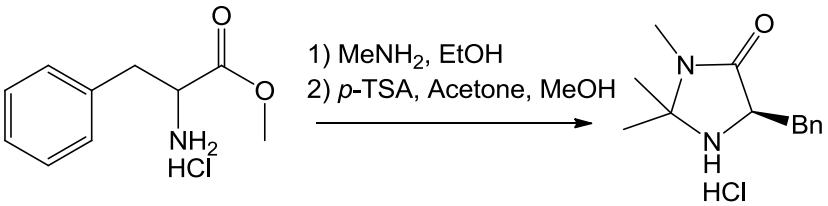


3-(2-(Acridin-9-ylamino)ethyl)-2,2-dimethylimidazolidin-4-one dihydrochloride 173: Benzyl 3-(2-(acridin-9-ylamino)ethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate **182** (145 mg, 0.31 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (6 mL) under a positive pressure of nitrogen. To this was added in one portion boron trifluoride diethyl etherate (0.38 mL, 3.1 mmol, 10 eq.) followed by dimethyl sulfide (0.62 mL, 8.37 mmol, 27 eq.). The reaction was stirred at room temperature overnight. The reaction was quenched with the addition of water (5 mL), and concentrated ammonium hydroxide (10 mL). The aqueous phase was extracted with methylene chloride (3 x 25 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to yield the free amine as a yellow solid. The free amine was dissolved in isopropanol (5 mL) and *iso*-propanolic hydrochloric acid (0.1 mL, 6 M) was added causing precipitation of the dihydrochloride salt which was collected by filtration as a yellow solid, 93 mg (74%). Characterised as free-amine: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 8.00 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 7.95 (br s, 1 H, ArN*H*), 7.54-7.65 (m, 2 H, Ar*H*), 7.24-7.35 (m, 2 H, Ar*H*), 3.95 (t, 2 H, *J* = 5.1 Hz, COCH_2), 3.44-6.55 (m, 4 H, CH_2CH_2), 2.05 (br s, 1 H, CH_2NHC), 1.29 (s, 6 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.3 (*C*O), 150.6 (Ar*C*), 148.0 (Ar*C*), 128.9 (Ar*C*H), 127.6 (Ar*C*H), 122.5 (Ar*C*H), 121.5 (Ar*C*H), 114.8 (Ar*C*), 77.7 (*C*), 51.0 (CO*C*H_2), 47.0 (ArNH*C*H_2), 40.1 (*C*H_2N), 25.1 (*C*H_3). **IR** (KBr disc) 3238 (acridine), 3056 (sec. amine), 2975 (alkane), 1685 (amide), 1559 (acridine), 1407 (alkane), 1259 (tert. amine), 1162 (sec. amine), 762 (acridine) cm^{-1}. **M.P.** 158-161 ^oC. **ESI-MS** $C_{20}H_{22}N_4O$ Calc. ($M+H^+$) =335.1866 found ($M+H^+$) = 355.1877 (3.05 ppm).



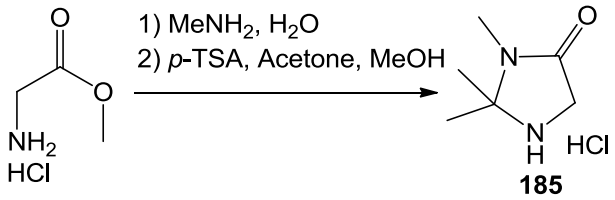
L-Phenylalanine methyl ester hydrochloride 183: A suspension of L-phenylalanine (21.47 g, 130 mmol, 1 eq.) in distilled methanol (150 mL) was stirred in an ice-acetone slush bath. To this was added thionyl chloride (18.9 mL, 260 mmol, 2 eq.) cautiously. When the added was complete the reaction was refluxed for 2 hours under a calcium chloride tube. The volatiles were then removed *in vacuo* to give a white residue which was dissolved in a minimal amount of hot absolute ethanol. When the solution was cool diethyl ether was added until precipitation began and the solution was

stored at -20 °C overnight. The resultant crystals were collected by filtration and washed with diethyl ether (100 mL), a second crop of crystals was grown from the filtrate, colourless needles, 28.01 g (>99%). **^{1}H NMR** (300 MHz, D_2O) δ 7.14-7.44 (m, 5 H, Ar*H*), 4.20-4.43 (m, 1 H, C*H*), 3.76 (s, 3 H, CH_3), 3.07-3.33 (m, 2 H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 (*C*O), 133.7 (Ar*C*), 129.4 (Ar*C*H), 129.3 (Ar*C*H), 128.1 (Ar*C*H), 54.1 (*C*H), 35.6 (*C*H_2). **M.P.** 158-159 °C (Commercial 158-162 °C). Matches commercial sample.



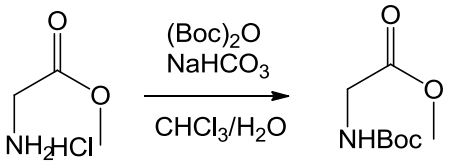
183 **4**

MacMillan imidazolidinone 4:[16] Phenylalanine methyl ester hydrochloride **183** (26.0 g, 121 mmol, 1 eq.) was added to an ethanolic solution of methylamine (60 mL, 8 M in EtOH, 480 mmol, 4 eq.). The solution was stirred at room temperature for 20 hours and then the volatiles were removed *in vacuo*. The residue was suspended in diethyl ether and concentrated *in vacuo*. This process was repeated until no methylamine was detectable. The white solid was treated with a solution of saturated sodium hydrogen carbonate (100 mL) and the aqueous phase was extracted with methylene chloride (3 x 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a colourless residue. The residue was dissolved in methanol (240 mL) and both acetone (45 mL, 605 mmol, 5 eq.) and *para*-toluene sulfonic acid mono hydrate (230 mg, 1.2 mmol, 1 mol%) was added to the solution. The reaction was then refluxed for 18 hours and concentrated *in vacuo*. The residue was dissolved in diethyl ether (100 mL) and a solution of 4 M hydrochloric acid in dioxane was added until precipitation of the product ceased. The precipitate was collected by vacuum filtration and washed with diethyl ether (50 mL). The solid was dissolved in minimal hot isopropanol and allowed to cool overnight in ice. The crystals separated by suction filtration, colourless cubes, 23.12 g (75%). **^{1}H NMR** (300 MHz, D_2O) δ 7.21-7.42 (m, 5 H, Ar*H*), 4.55 (dd, *J* = 4.7 Hz, *J* = 9.5 Hz, C*H*), 3.38 (dd, *J* = 4.7 Hz, *J* = 15 .1 Hz CH_2Ph), 3.03 (dd, *J* = 9.5 Hz, *J* = 15.1 Hz, CH_2Ph), 2.78 (s, 3 H, NCH_3), 1.57 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3). **^{13}C NMR** (75 MHz, D_2O) 167.5 (*C*O), 134.4 (Ar*C*), 129.2 (Ar*C*H), 129.0 (Ar*C*H), 127.9 (Ar*C*H), 78.5 (*C*), 58.4 (NCH_3), 33.5 (*C*H_2), 25.3 (*C*H), 23.3 (*C*H_3), 21.6 (*C*H_3). **M.P.** 158-160 °C (Commercial 157-161 °C). Matches commercial sample.



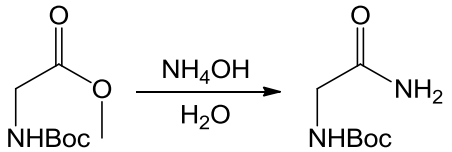
185

2,2,3-Trimethylimidazolidin-4-one hydrochloride 185:[307] Glycine methyl ester hydrochloride (20 g, 160 mmol, 1 eq.) was stirred in a concentrated aqueous solution of methylamine (37.5 mL, 480 mmol, 3 eq.) at 50 °C for 1.5 hours. The reaction was allowed to cool and sodium hydroxide (7.2 g, 180 mmol, 1.13 eq.) was added and the solution stirred until dissolution. The water was removed *in vacuo* to give a slurry which was triturated with ethyl acetate (3 x 75 mL). The ethyl acetate extracts were combined and dried over Na_2SO_4 and then concentrated to leave a colourless oil. The oil was dissolved in methanol (240 mL) and both acetone (59 mL, 800 mmol, 5 eq.) and *para*-toluene sulfonic acid mono hydrate (304 mg, 1.6 mmol, 1 mol%) was added to the solution. The reaction was then refluxed for 18 hours and concentrated *in vacuo*. The residue was dissolved in diethyl ether (100 mL) and a solution of 4 M hydrochloric acid in dioxane was added until precipitation of the product ceased. The precipitate was collected by vacuum filtration and washed with diethyl ether (50 mL). The solid was dissolved in minimal hot *iso*-propanol and allowed to cool overnight in ice. The crystals separated by suction filtration, colourless cubes, 21.34 g (75%). **^{1}H NMR** (300 MHz, D_2O) δ 4.10 (s, 2 H, CH_2), 2.90 (s, 3 H, NCH_3), 1.76 (s, 6 H, CH_3). **^{13}C NMR** (75 MHz, D_2O) δ 166.5 (*C*O), 80.2 (*C*), 44.2 (*C*H_2), 22.5 (*C*H_3). **IR** (KBr disc) 3095 (sec. amine), 2703 (alkane), 1710 (amide), 1576 (alkane), 1390 (tert. amine), 934 (sec. amine), 663 (alkane). **M.P.** 156-158 °C. **ESI-MS** $C_6H_{12}N_2O$ Calc. ($M+H^+$) = 129.1022 found ($M+H^+$) = 129.1026 (3.10 ppm).



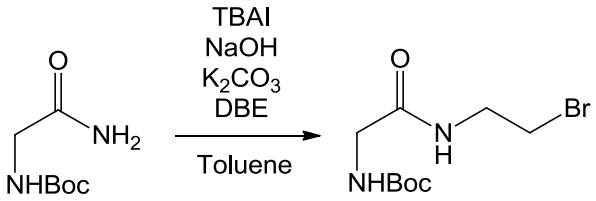
187

***N*-Boc-glycine methyl ester 187**:[308] To a suspension of glycine methyl ester hydrochloride (8.79 g, 70 mmol, 1 eq.) in chloroform (80 mL) was added Boc anhydride (15.25 g, 70 mmol, 1 eq.), sodium hydrogen carbonate (5.88 g, 70 mmol, 1 eq.), distilled water (100 mL) and sodium chloride (14 g). The reaction was stirred vigorously and refluxed for 1.5 hours. When cool the aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to a clear oil, 13.43 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.30 (br s, 1 H, N*H*Boc), 3.80 (d, 2 H, *J* = 5.7 Hz, CH_2), 3.64 (s, 3 H, OCH_3), 1.34 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (*C*OOMe), 155.8 (N*C*O), 79.7 (*C*), 52.0 (O*C*H_3), 42.1 (*C*H_2), 28.1 (*C*H_3). Matches known data.[324]



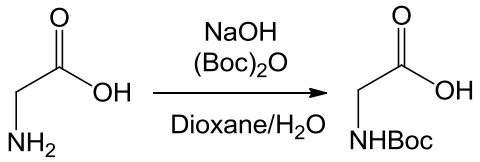
187 **188**

***N*-Boc-glycinamide 188:**[309] *N*-Boc-glycine methyl ester **187** (13.43 g, 70 mmol, 1 eq.) was stirred in concentrated ammonium hydroxide (15 mL, 272 mmol, 4 eq.) at room temperature for 24 hours, during which time the emulsion visibly entered solution. The solvent was then removed *in vacuo* and the residue taken into distilled water (100 mL). The volatiles were again removed; this process was repeated until no ammonia vapour was detectable. Colourless solid, 12.19 g (>99%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.82 (br s, 1 H, NH_2), 6.68 (br s, 1 H, NH_2) 5.90 (br s, 1 H, N*H*), 3.56-3.88 (m, 2 H, CH_2), 1.36 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.2 (*C*$CONH_2$), 156.3 (O*C*O), 79.9 (*C*), 43.6 (*C*H_2), 28.3 (CH_3). **M.P.** 80-82 ^{o}C (Lit. 85-86 ^{o}C).[325] Matches known data.[325]



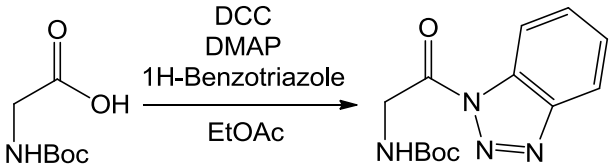
188 **189**

***tert*-Butyl (2-((2-bromoethyl)amino)-2-oxoethyl)carbamate 189:** A mixture of *N*-Boc-glycinamide **188** (8.47 g, 48.6 mmol, 1 eq.), tetra-butylammonium iodide (1.80 g, 4.86 mmol, 0.1 eq.), sodium hydroxide (7.78 g, 194.4 mmol, 4 eq.), potassium carbonate (1.34 g, 9.72 mmol, 0.2 eq.) and dibromoethane (21 mL, 243 mmol, 5 eq.) in toluene (250 mL) was refluxed for 2 hours. The reaction was transferred to a separatory funnel with ethyl acetate (50 mL) and the organic phase was washed with water (50 mL), saturated sodium thiosulfate solution (50 mL) and brine (100 mL). The organic phase was then dried over Na_2SO_4 and concentrated to an orange oil. This oil was purified using flash chromatography eluting with 80% ethyl acetate in petroleum ether, visualizing with ninhydrin solution. $\boldsymbol{R_F}$ (80% ethyl acetate in petroleum ether) 0.53. Colourless gum, 1.36 g (30%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (br s, 1 H, CON*H*), 5.58 (br s, 1 H, N*H*Boc), 3.83 (d, 2 H, *J* = 5.4 Hz, CH_2NHBoc), 3.68 (apparent quartet, 2 H, *J* = 5.9 Hz, NHC$H_2$$CH_2$), 3.47 (t, 2 H, *J* = 5.9 Hz, CH_2Br), 1.46 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 (*C*ONH), 156.2 (N*C*O), 80.3 (*C*), 44.3 (*C*H_2NHBoc), 41.1 (NH*C*$H_2$$CH_2$), 31.7 (*C*$H_2$Br), 28.3 (*C*$H_3$). **ESI-MS** $C_9H_{17}BrN_2O_3$ Calc. (M+Na^+) = 303.0315 found (M+Na^+) = 303.0315 (0.00 ppm).



193

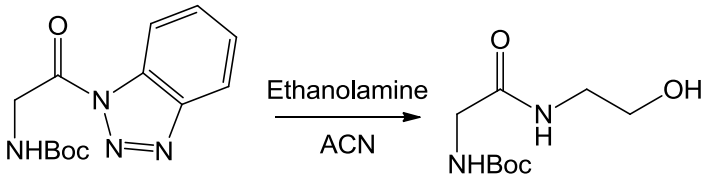
***N*-Boc-glycine 193:**[313] A solution of glycine (4 g, 53 mmol, 1 eq.) in a mixture of 1,4-dioxane/distilled water (2 : 1, 150 mL) was stirred in an acetone-ice bath. To this was added a room temperature solution of sodium hydroxide (2.12 g, 53 mmol, 1 eq.) in distilled water (50 mL) and solid Boc anhydride (12.72 g, 58 mmol, 1.1 eq.). The reaction was allowed to come to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was suspended in ethyl acetate (100 mL) and washed with 10% w/v citric acid solution (100 mL). The organic phase was washed with a concentrated brine solution, dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil. This oil was solidified by suspension in petroleum ether (100 mL) with the aid of ultrasound and collected by vacuum filtration to give a static white solid, 6.84 g (78%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.72 (s, 1 H, COO*H*), 6.64 (br s, 0.40 H, rotamer A, N*H*Boc), 5.37 (br s, 0.60 H, rotamer B, N*H*Boc), 3.76-3.97 (m, 2 H, overlapping rotamers A + B CH_2), 1.34 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.4 (rotamer B, *C*OOH), 174.0 (rotamer A, *C*OOH), 157.4 (rotamer A, N*C*O), 156.2 (rotamer B, N*C*O), 81.8 (rotamer A, *C*), 80.4 (rotamer A, *C*), 43.3 (rotamer B, *C*H_2), 42.1 (rotamer A, *C*H_2), 28.2 (rotamer B, *C*H_3), 28.1 (rotamer B, *C*H_3). **M.P.** 87-90 °C (Commercial 86-89 °C). Matches commercial sample.



193 **194**

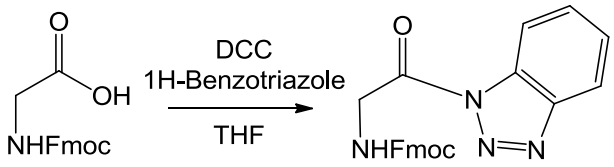
***N*-Boc-glycine-Bt 194:**[314] Boc-glycine **193** (1.47 g, 8.4 mmol, 1 eq.) was dissolved in ethyl acetate (20 mL). To this was added benzotriazole (1 g, 8.4 mmol, 1 eq.) and DMAP (10 mg, (<1 mol%). The reaction was stirred until dissolution had occurred and was placed in an acetone-ice bath. Dicyclohexylcarbodiimide (1.73 g , 8.4 mmol, 1 eq.) was added in one portion to the solution, which was subsequently allowed to come to room temperature and stirred overnight. The precipitated urea was removed by vacuum filtration and was washed with ethyl acetate (20 mL). The filtrate was concentrated *in vacuo* to give a solid residue which was dissolved in minimal methylene chloride and petroleum ether was added until precipitation began. The solution was stored at -20 °C overnight, and the resultant crystals were collected by vacuum filtration and washed with a mixture of methylene chloride (5 mL) and petroleum ether (15 mL). Colourless micro-needles, 2.04 g (88%). **^{1}H**

NMR (300 MHz, $CDCl_3$) δ 8.26 (d, 1 H, *J* = 8.2 Hz, Ar*H*), 8.12 (d, 1 H, *J* = 8.3 Hz, Ar*H*), 7.66 (t, 1 H, *J* = 7.7 Hz, Ar*H*), 7.52 (t, 1 H, *J* = 8.0 Hz, Ar*H*), 5.39 (br s, 1 H, N*H*), 5.03 (d, 2 H, *J* = 5.9 Hz, CH_2), 1.50 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9 (*C*OBt), 155.9 (*C*ONH), 145.9 (Ar*C*), 130.9 (Ar*C*), 130.7 (Ar*C*H), 126.5 (Ar*C*H), 120.3 (Ar*C*H), 114.1 (Ar*C*H), 80.5 (*C*), 44.5 (CH_2), 28.3 (CH_3). **M.P.** 135-139 °C (Lit. 140 °C).[314] Matches known data.[314]



194 **195**

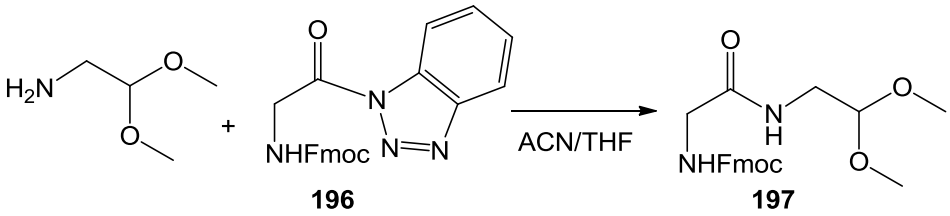
***tert*-Butyl (2-((2-hydroxyethyl)amino)-2-oxoethyl)carbamate 195:** A solution of aminoethanol (302 µL, 5 mmol, 2 eq.) in acetonitrile (5 mL) was stirred in an acetone-ice bath. To this was added dropwise a solution of Boc-Gly-Bt (687 mg, 2.5 mmol, 1 eq.) in acetonitrile (15 mL) over 30 minutes. The reaction was then allowed to come to room temperature and stirred for an additional 30 minutes. The volatiles were removed *in vacuo* and the residue was triturated with ethyl acetate (30 mL) and the filtrate was purified by flash chromatography eluting with 100% ethyl acetate, visualization with ninhydrin. R_F (100% ethyl acetate) 0.25. Pale-yellow oil, 545 mg (>99%).**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (br s, 1 H, CON*H*), 6.07 (br s, 1 H, CH_2N*H*Boc), 4.48 (br s, 1 H, O*H*), 3.64 (d, 2 H, *J* = 5.2 Hz, CH_2NHBoc), 3.51 (t, 2 H, *J* = 4.8 Hz, CH_2CH_2NH), 3.24 (d, 2 H, *J* = 4.8 Hz, $HOCH_2$), 1.29 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.9 (*C*ONH), 156.5 (*C*ONHBoc), 79.9 (*C*), 60.8 (CH_2OH), 43.9 (CH_2NHBoc), 41.9 (CH_2NH), 23.8 (CH_3). Matches known data.[326]



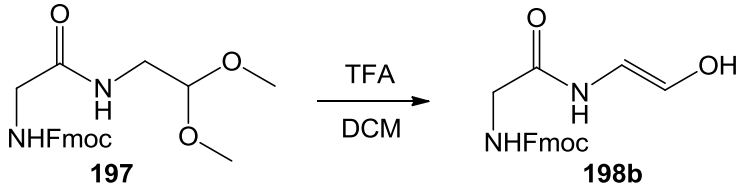
196

Fmoc-glycine-Bt 196: A solution of Fmoc-Gly-OH (2.97 g, 10 mmol, 1 eq.) and benzotriazole (1.19g, 10 mmol, 1 eq.) in THF (30 mL) was stirred in an acetone-ice bath. To this was added dicyclohexylcarbodiimide (2.06 g, 10 mmol, 1 eq.), the reaction was allowed to come to room temperature and stirred overnight. The urea precipitate was removed by filtration and washed with THF (10 mL). The filtrate was concentrated to a white solid and dissolved in minimal hot ethyl acetate, petroleum ether was added until precipitation began and the solution was stored at -20 °C overnight. The crystals were isolated by vacuum filtration and washed with a solution of

ethylacetate (5 mL) and petroleum ether (15 mL), colourless micro-needles 2.83 g (71%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09-8.30 (m, 2 H Ar*H*), 7.27-7.83 (m, 10 H, Ar*H*), 5.62 (br s, 1 H, N*H*), 5.09 (d, 2 H, *J* = 5.8 Hz, NHCH_2CO), 4.48 (d, 2 H, *J* = 6.9 Hz, CH_2O), 4.27 (t, 1 H, *J* = 6.9 Hz, C*H*). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (*C*OBt), 156.6 (*C*ONH), 146.0 (Ar *C*), 143.8 (Ar *C*), 141.3 (Ar *C*), 130.9(Ar *C*), 130.8 (Ar *C*), 127.8 (Ar*C*H), 127.1 (Ar*C*H), 126.6 (Ar*C*H), 125.1 (Ar*C*H), 120.4 (Ar*C*H), 114.1 (Ar*C*H), 67.4 (*C*H_2O), 47.1 (*C*H), 44.8 (*C*H_2CO). **M.P.** 160-164 °C (Lit. 160-162 °C).[327] Matches known data.[328]

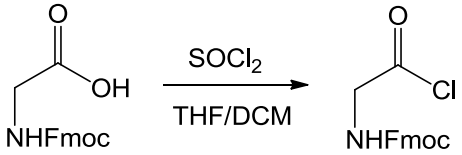


(9H-Fluoren-9-yl)methyl (2-((2,2-dimethoxyethyl)amino)-2-oxoethyl)carbamate 197: To a solution of Fmoc-Gly-Bt **196** (398 mg, 1 mmol, 1 eq.) in a mixture of THF (10 mL) and acetonitrile (10 mL) was added aminoacetaldehyde dimethyl acetal (109 µL, 1 mmol, 1 eq.). The reaction was stirred at room temperature for 5 minutes at which point the solvent was removed *in* vacuo and the residual oil was purified by dry vacuum column chromatography (DCVC) eluting with 0% ethyl acetate in petroleum ether -> 100% ethyl acetate in 25 mL fractions, visualization with ninhydrin. $\boldsymbol{R_F}$ (100% ethyl acetate) 0.36. Colourless gum, 300 mg (78%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 7.56 (d, 2 H, *J* = 7.3 Hz, Ar*H*), 7.20-7.39 (m, 4 H, Ar*H*), 6.75 (br s, 1 H, N*H*Fmoc), 6.11 (t, 1 H, *J* = 5.6 Hz, CH_2N*H*), 4.26-4.43 (m, 3 H, overlapping CH_2OCO + C*H*$(OMe)_2$), 4.16 (t, 1 H, *J* = 6.9 Hz, C*H*), 3.86 (d, 2 H, *J* = 5.4 Hz, CH_2NHFmoc), 3.38 (t, 2 H, *J* = 6.9 Hz, CH_2CH), 3.29 (s, 6 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) 169.1 (*C*ONH), 156.6 (N*C*O), 143.7 (Ar*C*), 141.3 (Ar*C*), 127.8 (Ar*C*H), 127.1 (Ar*C*H), 125.0 (Ar*C*H), 120.0 (Ar*C*H), 102.4 (*C*H$(OMe)_2$), 67.2 (*C*H_2O), 54.4 (*C*H_3), 47.1 (*C*HCH_2O), 44.5 (*C*H_2NHFmoc), 40.9 (CONH*C*H_2). **ESI-MS** $C_{21}H_{24}N_2O_5$ Calc. $(M+H^+)$ = 385.1759 found $(M+H^+)$ = 385.1758 (0.30 ppm).



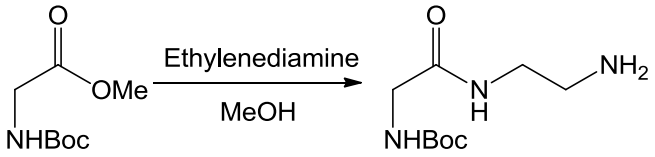
(9H-Fluoren-9-yl)methyl (2-((2-hydroxyvinyl)amino)-2-oxoethyl)carbamate 198b: A solution of the amino acetal **197** (384 mg, 1 mmol, 1 eq.) in methylene chloride (3 mL) was treated with neat trifluoroacetic acid (1 mL) and stirred for 30 minutes. The reaction was then carefully neutralized with a solution of saturated sodium hydrogen carbonate (10 mL) and extracted with methylene

chloride (3 x 30 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid which was dissolved in minimal methylene chloride and petroleum ether was added until precipitation began. The solution was stored overnight at -20 ^oC and the precipitate was collected by vacuum filtration to give a colourless solid, 291 mg (86%). Mixture of isomers (1 : 1.3) assigned by ^1H-^1H COSY. **^1H NMR** (300 MHz, $CDCl_3$) δ 8.10-8.51 (br m, 1 H, O*H* isomers), 7.77 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 7.56 (d, 2 H, *J* = 7.3 Hz, Ar*H*), 7.27-7.47 (m, 4 H, Ar*H*), 6.16-6.51 (m, 1 H, NHC*H* isomers), 5.52-5.70 (m, 1 H, C*H*OH isomers), 4.51 (d, 2 H, *J* = 6.6 Hz, CH_2OCO), 4.15-4.37 (m, 3 H, overlapping C*H* + CH_2NHFmoc). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.4 (*C*ONH major isomer), 164.8 (*C*ONH minor isomer), 153.0 (O*C*ONH minor isomer), 152.7 (O*C*ONH major isomer), 143.5 (Ar*C*), 141.3 (Ar*C*), 127.9 (Ar*C*H), 127.2 (Ar*C*H), 124.9 (Ar*C*H), 120.1 (Ar*C*H), 109.2 (NH*C*H minor isomer), 108.6 (NH*C*H major isomer), 107.9 (*C*HOH major isomer), 107.8 (*C*HOH minor isomer), 68.4 (*C*H_2OCO), 47.0 (*C*H), 46.7 (*C*H_2NHFmoc). **ESI-MS** $C_{19}H_{28}N_2O_4$ Calc. ($M+H^+$) = 339.1339 found ($M+H^+$) = 339.1351 (3.36 ppm).



200

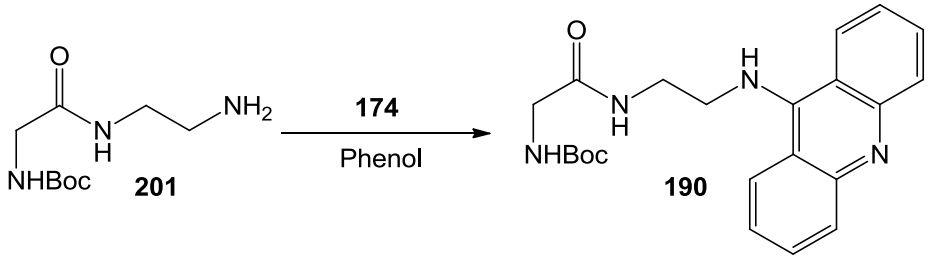
Fmoc-glycine-Cl 200:[316] To a suspension of Fmoc-Gly-OH (4 g, 13.45 mmol, 1 eq.) in anhydrous methylene chloride (16 mL) and THF (4 mL) was added thionyl chloride (8 mL, 110 mmol, 8 eq.). The reaction was refluxed for 30 minutes at which point the volatiles were removed *in vacuo* and the residue dissolved in methylene chloride (10 mL). The solvent was removed *in vacuo* and this addition removal process was repeated twice more to give a solid yellow residue. The residue was taken into methylene chloride and precipitated by addition of petroleum ether. The precipitate was collected by vacuum filtration and the retentate was washed with petroleum ether 30 mL. The solid was dried under reduced pressure. Colourless solid, 4.24 g (>99%). **M.P.** 105-110 ^oC (Lit. 108-109 ^oC).[329]



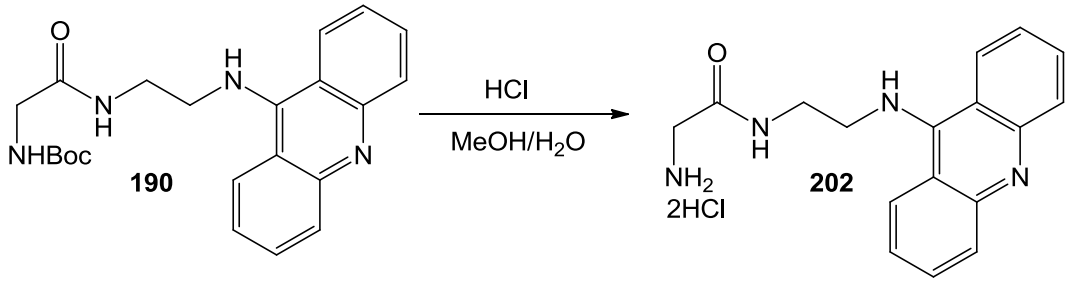
187 **201**

***tert*-Butyl (2-((2-aminoethyl)amino)-2-oxoethyl)carbamate 201:**[330] A solution of *N*-Boc-glycine methyl ester (946 mg, 5 mmol, 1 eq.) dissolved in methanol (1 mL) was stirred with neat ethylenediamine (13.4 mL, 200 mmol, 40 eq.) for 5 hours at room temperature. The excess ethylene diamine was then removed by distillation under reduced pressure to give a yellow residue which was

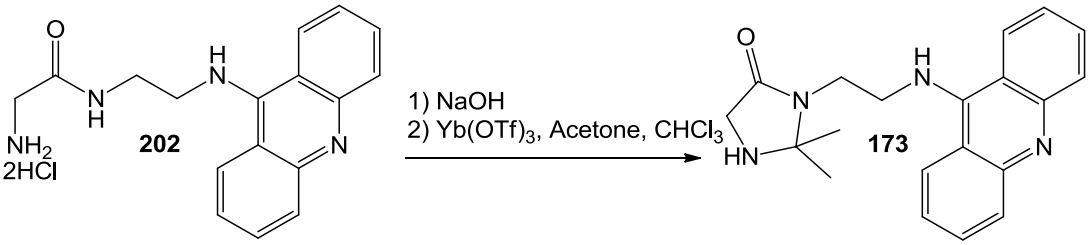
purified by flash chromatography eluting with a solution of 2% concentrated ammonium hydroxide in methanol, visualization with ninhydrin. $\boldsymbol{R_F}$ (2% conc. ammonium hydroxide in methanol) 0.44. Pale-yellow viscous oil, 687 mg (63%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 (br s, 1 H, CON*H*), 6.33 (N*H*Boc), 3.73 (br d, 2 H, *J* = 4.4 Hz, CH_2NHBoc), 3.26 (q, 2 H, *J* = 5.7 Hz, CH_2NH_2), 2.75 (t, 2 H, *J* = 5.7 Hz, NHCH_2), 1.58 (br s, 2 H, NH_2), 1.39 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.4 (*C*ONH), 156.2 (O*C*ONH), 79.6 (*C*), 53.5 (CH_2NHBoc), 42.1 (CH_2NH_2), 41.2 (NHCH_2), 28.2 (*C*H_3). Matches known data.[331]



***tert*-Butyl (2-((2-(acridin-9-ylamino)ethyl)amino)-2-oxoethyl)carbamate 190:** In a nitrogen atmosphere was mixed 9-chloroacridine **174** (395 mg, 1.85 mmol, 1 eq.), the primary amine **201** (402 mg, 1.85 mmol, 1 eq.) and crystalline phenol (2 g). The slurry was heated to 100 ^{o}C for 2 hours, and allowed to cool. To the residue was added diethyl ether (50 mL) and the reaction was suspended with the aid of ultrasound and allowed to settle. The ether was removed by decantation and a fresh portion of diethyl ether (100 mL) was added. The reaction was stirred until completely suspended in the ethereal solvent (1-2 days). The precipitate was collected by vacuum filtration and washed with diethyl ether (20 mL). The hydroscopic residue was dissolved in 0.05 M HCl (20 mL), and washed with methylene chloride (3 x 30 mL). The aqueous phase was then made basic with slow addition of 15% (w/v) sodium hydroxide solution. The precipitate was extracted with methylene chloride (4 x 20 mL), the extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a brilliant yellow foam, 672 mg (92%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 7.89 (br s, 2 H, Ar*H*), 7.62 (br s, 1 H, ArN*H*), 7.50 (t, 2 H, *J* = 7.8 Hz, Ar*H*), 7.19 (t, 2 H, *J* = 7.5 Hz, Ar*H*), 5.78 (br s, 1 H, N*H*Boc), 3.68-3.88 (m, 4 H, CH_2CH_2), 3.46-3.61 (m, 2 H, CH_2NHBoc), 1.37 (s, 9 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.8 (*C*ONH), 156.3 (O*C*ONH), 151.8 (Ar*C*NH), 130.1 (overlapping Ar*C*H +Ar*C*H), 123.5 (overlapping Ar*C*H + Ar*C*), 122.5 (overlapping Ar*C*H + Ar*C*), 80.3 (*C*), 51.7 (*C*H_2NHBoc), 44.3 (*C*H_2NHAr), 40.5 (*C*H_2NHCO), 28.3 (*C*H_3). **ESI-MS** $C_{22}H_{26}N_4O_3$ Calc. ($M+H^+$) = 395.2093 found ($M+H^+$) = 395.2078 (3.75 ppm).

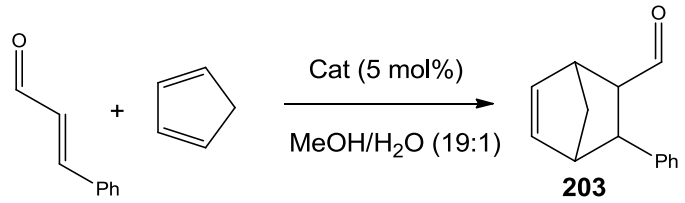


***N*-(2-(Acridin-9-ylamino)ethyl)-2-aminoacetamide dihydrochloride 202:** To a solution of Boc-Gly-ethylene-acridine **190** (1.15 g, 2.91 mmol, 1 eq.) in methanol (200 mL) was added 10% (w/w) HCl (20 mL) and the reaction was heated to 30 ^{o}C and stirred overnight. The volatiles were removed *in vacuo* to give a brilliant yellow gum, 1.05 g (>99%). ^{1}H NMR (300 MHz, D_2O) δ 7.88 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 7.70 (t, 2 H, *J* = 8.0 Hz, Ar*H*), 7.33 (t, 2 H, *J* = 8.1 Hz, Ar*H*), 7.21 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 3.90 (t, 2 H, *J* = 6.0 Hz, CH_2NHAr), 3.78 (s, 2 H, CH_2NH$_2$), 3.60 (t, 2 H, *J* = 6.1 Hz, CH_2NHCO). ^{13}C NMR (75 MHz, D_2O) δ 168.1 (*C*ONH), 156.4 (Ar*C*), 138.3 (Ar*C*), 135.2 (Ar*C*H), 124.0 (overlapping Ar*C*H + Ar*C*H), 117.9 (Ar*C*H), 111.3 (Ar*C*), 48.3 (*C*H$_2$NH$_2$), 40.3 (*C*H$_2$NHAr), 38.8 (*C*H$_2$NHCO). **ESI-MS** $C_{17}H_{18}N_4O$ Calc. (M+H$^+$) = 295.1553 found (M+H$^+$) = 295.1567 (4.70 ppm).



3-(2-(acridin-9-ylamino)ethyl)-2,2-dimethylimidazolidin-4-one 173:[307] A solution of *N*-(2-(acridin-9-ylamino)ethyl)-2-aminoacetamide dihydrochloride **202** (1.0 g, 2.72 mmol, 1 eq.) in 0.05 M HCl (20 mL) was made basic with slow addition of 15% (w/v) sodium hydroxide solution. The precipitate was extracted with methylene chloride (4 x 20 mL), the extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a brilliant yellow foam which was suspended in chloroform (25 mL). To this was added acetone (4 mL, 54.4 mmol, 20 eq.) and ytterbium triflate (42 mg, 0.068 mmol, 2.5 mol%). The suspension was refluxed for 14 hours and allowed to cool. The volatiles were removed *in vacuo* and the residue purified by flash chromatography eluting with a solution of 2% concentrated ammonium hydroxide in methanol. $\boldsymbol{R_F}$ (2% conc. ammonium hydroxide in methanol) 0.51. The orange amorphous residue was suspended in acetone (10 mL) and stored overnight at -20 ^{o}C. The precipitate was collected by vacuum filtration to give a bright yellow solid, 722 mg (77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 8.00 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 7.95 (br s, 1 H, ArN*H*), 7.54-7.65 (m, 2 H, Ar*H*), 7.24-7.35 (m, 2 H, Ar*H*), 3.95 (t, 2 H, *J* = 5.1 Hz, COCH_2), 3.44-6.55 (m, 4 H, CH_2CH_2), 2.05 (br s, 1 H, CH_2N*H*C), 1.29 (s, 6 H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.3 (*C*O), 150.6 (Ar*C*), 148.0 (Ar*C*), 128.9 (Ar*C*H), 127.6 (Ar*C*H), 122.5 (Ar*C*H), 121.5 (Ar*C*H), 114.8 (Ar*C*), 77.7 (*C*), 51.0 (CO*C*H$_2$), 47.0 (ArNH*C*H$_2$), 40.1 (*C*H$_2$N), 25.1 (*C*H$_3$). **IR** (KBr disc) 3238 (acridine), 3056 (sec. amine),

2975 (alkane), 1685 (amide), 1559 (acridine), 1407 (alkane), 1259 (tert. amine), 1162 (sec. amine), 762 (acridine) cm^{-1}. **M.P.** 158-161 °C. Matches previous compound.



203

General procedure for the iminium-ion catalysed Diels-Alder reaction: To a vial containing the hydrochloride salt of the catalyst (0.05 mmol, 5 mol%) and a 95% aqueous methanol solution (0.5 mL) was added cinnamaldehyde (63 µL, 1 mmol, 1 eq.) and the reaction was stirred for 10 minutes at room temperature. To this was added freshly cracked cyclopentadiene (126 µL, 1.5 mmol, 1.5 eq.) and the reaction was stirred at room temperature for 16 hours. The solvent was then removed *in vacuo* and a mixture trifluoroacetic acid (1 mL), water (1 mL) and methylene chloride (2 mL) was added. The mixture was then stirred at room temperature for 2 hours at which point the organic layer was extracted with diethyl ether (2 x 10 mL) and washed with a solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated to a yellow residue. The residue was then purified by flash chromatography eluting with 100% petroleum ether -> 5% diethyl ether in petroleum ether. $\boldsymbol{R_F}$ (5% diethyl ether in petroleum ether) 0.68. Colourless oil. Diastereoselectivity determined by ^{1}H NMR of C*H*O (*endo* = 9.51 ppm, *exo* = 9.83), enantiopurity determined by **GC $\mathbf{R_T}$** 10.39 (*exo*, minor), 10.62 (*exo*, major), 10.86 (*endo*, minor), 11.04 (*endo*, major), SUPLECO β-Dex (30 m x 0.25 mm x 0.25 µm) chiral stationary phase and sample was injected at 200 °C, oven temperature 160 °C ramp at 2 °C/min for 20 minutes, FID at 250 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) *exo δ* 9.83 (d, 1 H, *J* = 2.0 Hz, C*H*O), 7.02-7.27 (m, 5 H, Ar*H*), 6.25 (dd, 1 H, *J* = 3.5 Hz, *J* = 6.0 Hz, CHC*H*), 5.99 (dd, 1 H, *J* = 3.2 Hz, 5.7 Hz, C*H*CH), 3.64 (dd, 1 H, *J* = 3.6 Hz, *J* = 4.7 Hz, C*H*Ph), 3.10-3.17 (m, 2 H, overlapping C*H*CH_2 + C*H*CH_2), 2.47-2.56 (m, 1 H, C*H*CHO), 1.43-1.58 (m, 2 H, CH_2). *endo δ* 9.51 (d, 1 H, *J* = 2.2 Hz, C*H*O), 7.02-7.27 (m, 5 H, Ar*H*), 6.33 (dd, 1 H, *J* = 3.2 Hz, *J* = 5.6 Hz, CHC*H*), 6.09 (dd, 1 H, *J* = 2.8 Hz, *J* = 5.6 Hz, C*H*CH), 3.21-3.30 (m, 1 H, C*H*Ph), 2.97-3.08 (m, 2 H, overlapping C*H*CH_2 + C*H*CH_2), 2.85-2.94 (m, 1 H, C*H*CHO), 1.43-1.58 (m, 2 H, CH_2). Matches known data.[292]

Appendix

5.1 X-ray crystal structure data

5.1.1 (1*E*,3*E*)-1,3-bis-phenylsulfonyl-4-phenyl-butadiene 39

Identification code	ng_sulf
Empirical formula	C22 H18 O4 S2
Formula weight	410.48
Temperature	180(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.9489(2) Å, α = 90°
	b = 9.2891(3) Å, β = 90°
	c = 26.2614(6) Å, γ = 90°
Volume	1939.08(9) $Å^3$
Z	4
Density (calculated)	1.406 Mg/m^3
Absorption coefficient	2.712 mm^{-1}
F(000)	856
Crystal size	0.2065 x 0.1627 x 0.0656 mm^3
Theta range for data collection	3.37 to 73.37°
Index ranges	-8<=h<=9, -11<=k<=11, -32<=l<=32
Reflections collected	10973
Independent reflections	3815 [R(int) = 0.0277]
Completeness to theta = 73.37°	98.9%
Absorption correction	Analytical
Max. and min. transmission	0.842 and 0.640
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	3815 / 0 / 254
Goodness-of-fit on F^2	1.034
Final R indices [I>2σ(I)]	R1 = 0.0371, wR2 = 0.0997
R indices (all data)	R1 = 0.0384, wR2 = 0.1012
Absolute structure parameter	0.31(2)
Largest diff. peak and hole	0.507 and -0.205 e.$Å^{-3}$

Table 30: Crystal data and structure refinement for **39**

S(11)-O(13)	1.4292(18)	C(9)-H(9)	0.9500
S(11)-O(12)	1.4405(19)	C(10)-H(10)	0.9500
S(11)-C(10)	1.763(2)	C(14)-C(19)	1.373(3)
S(11)-C(14)	1.774(2)	C(14)-C(15)	1.382(3)
S(20)-O(21)	1.4363(18)	C(15)-C(16)	1.389(4)
S(20)-O(22)	1.4431(18)	C(15)-H(15)	0.9500
S(20)-C(23)	1.774(2)	C(16)-C(17)	1.382(4)
S(20)-C(1)	1.785(2)	C(16)-H(16)	0.9500
C(1)-C(2)	1.341(3)	C(17)-C(18)	1.378(4)
C(1)-C(9)	1.466(3)	C(17)-H(17)	0.9500
C(2)-C(3)	1.473(3)	C(18)-C(19)	1.393(4)
C(2)-H(2)	0.9500	C(18)-H(18)	0.9500
C(3)-C(8)	1.390(3)	C(19)-H(19)	0.9500
C(3)-C(4)	1.396(3)	C(23)-C(24)	1.374(3)
C(4)-C(5)	1.385(3)	C(23)-C(28)	1.390(3)
C(4)-H(4)	0.9500	C(24)-C(25)	1.385(4)
C(5)-C(6)	1.385(4)	C(24)-H(24)	0.9500
C(5)-H(5)	0.9500	C(25)-C(26)	1.374(4)
C(6)-C(7)	1.376(4)	C(25)-H(25)	0.9500
C(6)-H(6)	0.9500	C(26)-C(27)	1.381(4)
C(7)-C(8)	1.388(4)	C(26)-H(26)	0.9500
C(7)-H(7)	0.9500	C(27)-C(28)	1.382(4)
C(8)-H(8)	0.9500	C(27)-H(27)	0.9500
C(9)-C(10)	1.327(3)	C(28)-H(28)	0.9500

Table 31: Bond Lengths in Å for **39**

O(13)-S(11)-O(12)	118.54(12)	C(6)-C(5)-C(4)	119.9(2)
O(13)-S(11)-C(10)	109.26(11)	C(6)-C(5)-H(5)	120.0
O(12)-S(11)-C(10)	106.49(11)	C(4)-C(5)-H(5)	120.0
O(13)-S(11)-C(14)	107.84(10)	C(7)-C(6)-C(5)	120.1(2)
O(12)-S(11)-C(14)	107.39(11)	C(7)-C(6)-H(6)	120.0
C(10)-S(11)-C(14)	106.75(11)	C(5)-C(6)-H(6)	120.0
O(21)-S(20)-O(22)	118.77(10)	C(6)-C(7)-C(8)	120.3(2)
O(21)-S(20)-C(23)	108.56(11)	C(6)-C(7)-H(7)	119.8
O(22)-S(20)-C(23)	107.95(11)	C(8)-C(7)-H(7)	119.8
O(21)-S(20)-C(1)	108.76(11)	C(7)-C(8)-C(3)	120.2(2)
O(22)-S(20)-C(1)	108.42(10)	C(7)-C(8)-H(8)	119.9
C(23)-S(20)-C(1)	103.28(10)	C(3)-C(8)-H(8)	119.9
C(2)-C(1)-C(9)	125.1(2)	C(10)-C(9)-C(1)	128.4(2)
C(2)-C(1)-S(20)	116.27(18)	C(10)-C(9)-H(9)	115.8
C(9)-C(1)-S(20)	118.47(16)	C(1)-C(9)-H(9)	115.8
C(1)-C(2)-C(3)	126.5(2)	C(9)-C(10)-S(11)	119.59(17)
C(1)-C(2)-H(2)	116.7	C(9)-C(10)-H(10)	120.2
C(3)-C(2)-H(2)	116.7	S(11)-C(10)-H(10)	120.2
C(8)-C(3)-C(4)	119.0(2)	C(19)-C(14)-C(15)	122.1(2)
C(8)-C(3)-C(2)	122.8(2)	C(19)-C(14)-S(11)	120.09(17)
C(4)-C(3)-C(2)	118.3(2)	C(15)-C(14)-S(11)	117.75(17)
C(5)-C(4)-C(3)	120.4(2)	C(14)-C(15)-C(16)	118.5(2)
C(5)-C(4)-H(4)	119.8	C(14)-C(15)-H(15)	120.7
C(3)-C(4)-H(4)	119.8	C(16)-C(15)-H(15)	120.7
C(17)-C(16)-C(15)	120.1(2)	C(17)-C(18)-C(19)	119.9(2)
C(17)-C(16)-H(16)	119.9	C(17)-C(18)-H(18)	120.0
C(15)-C(16)-H(16)	119.9	C(19)-C(18)-H(18)	120.0
C(18)-C(17)-C(16)	120.5(2)	C(14)-C(19)-C(18)	118.8(2)
C(18)-C(17)-H(17)	119.7	C(14)-C(19)-H(19)	120.6
C(16)-C(17)-H(17)	119.7	C(18)-C(19)-H(19)	120.6
C(24)-C(23)-C(28)	121.8(2)	C(23)-C(24)-C(25)	119.2(3)
C(24)-C(23)-S(20)	119.61(19)	C(23)-C(24)-H(24)	120.4
C(28)-C(23)-S(20)	118.61(18)	C(25)-C(24)-H(24)	120.4
C(26)-C(25)-C(24)	119.7(3)	C(25)-C(26)-C(27)	121.0(2)

C(26)-C(25)-H(25)	120.2	C(25)-C(26)-H(26)	119.5
C(24)-C(25)-H(25)	120.2	C(27)-C(26)-H(26)	119.5
C(26)-C(27)-C(28)	120.1(3)	C(26)-C(27)-H(27)	119.9
C(27)-C(28)-C(23)	118.3(3)	C(23)-C(28)-H(28)	120.8
C(27)-C(28)-H(28)	120.8		

Table 32: Bond angles in [^{o}] for **39**

O(21)-S(20)-C(1)-C(2)	138.69(19)	C(5)-C(6)-C(7)-C(8)	-2.2(5)
O(22)-S(20)-C(1)-C(2)	8.2(2)	C(6)-C(7)-C(8)-C(3)	0.7(4)
C(23)-S(20)-C(1)-C(2)	-106.1(2)	C(4)-C(3)-C(8)-C(7)	2.5(4)
O(21)-S(20)-C(1)-C(9)	-45.5(2)	C(2)-C(3)-C(8)-C(7)	-177.0(3)
O(22)-S(20)-C(1)-C(9)	-175.96(17)	C(2)-C(1)-C(9)-C(10)	-160.9(2)
C(23)-S(20)-C(1)-C(9)	69.68(19)	S(20)-C(1)-C(9)-C(10)	23.7(3)
C(9)-C(1)-C(2)-C(3)	5.8(4)	C(1)-C(9)-C(10)-S(11)	175.85(18)
S(20)-C(1)-C(2)-C(3)	-178.7(2)	O(13)-S(11)-C(10)-C(9)	-18.6(2)
C(1)-C(2)-C(3)-C(8)	34.4(4)	O(12)-S(11)-C(10)-C(9)	-147.8(2)
C(1)-C(2)-C(3)-C(4)	-145.1(3)	C(14)-S(11)-C(10)-C(9)	97.7(2)
C(8)-C(3)-C(4)-C(5)	-4.1(4)	O(13)-S(11)-C(14)-C(19)	153.8(2)
C(2)-C(3)-C(4)-C(5)	175.4(3)	O(12)-S(11)-C(14)-C(19)	-77.4(2)
C(3)-C(4)-C(5)-C(6)	2.7(4)	C(10)-S(11)-C(14)-C(19)	36.5(2)
C(4)-C(5)-C(6)-C(7)	0.5(4)	O(13)-S(11)-C(14)-C(15)	-28.9(2)
O(12)-S(11)-C(14)-C(15)	99.89(19)	C(17)-C(18)-C(19)-C(14)	-1.7(5)
C(10)-S(11)-C(14)-C(15)	-146.23(18)	O(21)-S(20)-C(23)-C(24)	9.7(2)
C(19)-C(14)-C(15)-C(16)	0.6(4)	O(22)-S(20)-C(23)-C(24)	139.63(19)
S(11)-C(14)-C(15)-C(16)	-176.67(18)	C(1)-S(20)-C(23)-C(24)	-105.68(19)
C(14)-C(15)-C(16)-C(17)	-1.6(4)	O(21)-S(20)-C(23)-C(28)	-170.74(17)
C(15)-C(16)-C(17)-C(18)	1.0(4)	O(22)-S(20)-C(23)-C(28)	-40.8(2)
C(16)-C(17)-C(18)-C(19)	0.7(5)	C(1)-S(20)-C(23)-C(28)	73.92(19)
C(15)-C(14)-C(19)-C(18)	1.0(4)	C(28)-C(23)-C(24)-C(25)	0.1(4)
S(11)-C(14)-C(19)-C(18)	178.2(2)	S(20)-C(23)-C(24)-C(25)	179.7(2)
C(23)-C(24)-C(25)-C(26)	-0.5(4)	C(26)-C(27)-C(28)-C(23)	-0.1(4)
C(24)-C(25)-C(26)-C(27)	0.5(4)	C(24)-C(23)-C(28)-C(27)	0.1(3)
C(25)-C(26)-C(27)-C(28)	-0.3(4)	S(20)-C(23)-C(28)-C(27)	-179.45(18)

Table 33: Torsion angles in [^{o}] for **39**

5.1.2 (1*R*,2*R*)-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 43

Identification code	js_prophen2
Empirical formula	$C_{27}H_{26}O_4S_2$
Formula weight	478.60
Temperature	293(2) K
Wavelength	0.7107 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 9.5626(11)Å, α = 90°
	b = 10.4209(15)Å, β = 90°
	c = 25.687(3)Å, γ = 90°
Volume	2559.7(5) $Å^3$
Z	4
Density (calculated)	1.242 Mg/m^3
Absorption coefficient	0.238 mm^{-1}
F(000)	1008
Crystal size	0.62 x 0.45 x 0.22 mm
Theta range for data collection	2.8846 to 28.0369 º.
Index ranges	-11<=h<=10; -13<=k<=8; -28<=l<=33
Reflections collected	6354
Independent reflections	4232 [R_{int} = 0.0402]
Reflections observed (>2σ)	2867
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.71097
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4232 / 0 / 300
Goodness-of-fit on F^2	0.996
Final R indices [I>2σ(I)]	R_1 = 0.0619 wR_2 = 0.1389
R indices (all data)	R_1 = 0.0969 wR_2 = 0.1830
Absolute structure parameter	-0.29(14)

Largest diff. peak and hole	0.377 and -0.372 e.Å^{-3}

Table 34: Crystal data and structure refinement for **43**

Atom	x	y	z	U(eq)
S(1)	3643(1)	8732(1)	8160(1)	52(1)
S(2)	333(2)	6657(2)	9682(1)	65(1)
O(4)	3112(4)	9122(4)	7659(1)	68(1)
O(2)	-405(5)	7059(5)	10146(1)	83(1)
O(3)	4277(4)	7482(4)	8208(1)	65(1)
O(1)	1492(5)	5782(4)	9719(2)	89(1)
C(1)	943(5)	8042(6)	9358(2)	55(1)
C(2)	362(6)	9199(6)	9447(2)	63(2)
C(3)	869(6)	10390(6)	9173(2)	59(1)
C(4)	1381(5)	10065(5)	8611(2)	52(1)
C(5)	2260(5)	8854(5)	8612(2)	48(1)
C(6)	2048(5)	7897(5)	8960(2)	51(1)
C(7)	2022(7)	11004(6)	9513(2)	72(2)
C(8)	2439(10)	12353(8)	9364(3)	114(3)
C(9)	3596(9)	12907(9)	9710(3)	143(4)
C(10)	-903(6)	6047(5)	9240(2)	53(1)
C(11)	-503(7)	5302(6)	8811(2)	76(2)
C(12)	-1502(9)	4965(7)	8443(3)	89(2)
C(13)	-2864(9)	5353(7)	8497(3)	91(2)
C(14)	-3294(7)	6053(7)	8927(3)	83(2)
C(15)	-2293(6)	6421(7)	9288(2)	72(2)
C(16)	175(5)	9990(6)	8210(2)	57(1)
C(17)	-113(7)	11038(7)	7907(3)	89(2)
C(18)	-1213(9)	11020(11)	7550(3)	116(3)
C(19)	-2016(8)	9954(12)	7494(3)	114(3)
C(20)	-1739(7)	8869(9)	7786(3)	93(2)
C(21)	-650(6)	8902(7)	8147(2)	70(2)
C(22)	4827(5)	9925(5)	8382(2)	52(1)
C(23)	5574(6)	9691(6)	8837(2)	63(2)

C(24)	6486(7)	10628(7)	9019(2)	78(2)
C(25)	6628(8)	11761(8)	8759(3)	90(2)
C(26)	5878(8)	11971(8)	8304(3)	95(2)
C(27)	4965(6)	11062(6)	8118(2)	70(2)

Table 35: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **43**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

S(1)-O(3)	1.442(4)	S(1)-O(4)	1.444(3)
S(1)-C(5)	1.764(5)	S(1)-C(22)	1.776(5)
S(2)-O(1)	1.438(5)	S(2)-O(2)	1.448(4)
S(2)-C(10)	1.757(5	S(2)-C(1)	1.764(6)
C(1)-C(2)	1.347(8)	C(1)-C(6)	1.478(7)
C(2)-C(3)	1.506(8)	C(3)-C(7)	1.546(8)
C(3)-C(4)	1.561(7)	C(4)-C(5)	1.516(7)
C(4)-C(16)	1.548(7	C(5)-C(6)	1.355(7)
C(7)-C(8)	1.511(10)	C(8)-C(9)	1.533(10)
C(10)-C(15)	1.391(8)	C(10)-C(11)	1.402(8)
C(11)-C(12)	1.389(9)	C(12)-C(13)	1.372(10)
C(13)-C(14)	1.385(10	C(14)-C(15)	1.388(8)
C(16)-C(17)	1.369(8)	C(16)-C(21)	1.392(8)
C(17)-C(18)	1.396(10)	C(18)-C(19)	1.359(12)
C(19)-C(20)	1.381(12	C(20)-C(21)	1.394(8)
C(22)-C(27)	1.371(8)	C(22)-C(23)	1.391(7)
C(23)-C(24)	1.390(8)	C(24)-C(25)	1.363(9)
C(25)-C(26)	1.389(9)	C(26)-C(27)	1.374(9)

Table 36: Bond Lengths in Å for **43**

O(3)-S(1)-O(4)	118.5(2)	O(3)-S(1)-C(5)	109.0(2)
O(4)-S(1)-C(5)	107.7(2)	O(3)-S(1)-C(22)	109.7(2)
O(4)-S(1)-C(22)	108.2(2)	C(5)-S(1)-C(22)	102.5(2)
O(1)-S(2)-O(2)	120.3(3)	O(1)-S(2)-C(10)	109.4(3)
O(2)-S(2)-C(10)	108.0(3)	O(1)-S(2)-C(1)	107.1(3)

O(2)-S(2)-C(1)	108.2(3)	C(10)-S(2)-C(1)	102.3(2)
C(2)-C(1)-C(6)	120.2(5)	C(2)-C(1)-S(2)	121.1(4)
C(6)-C(1)-S(2)	118.6(4)	C(1)-C(2)-C(3)	121.8(5)
C(2)-C(3)-C(7)	107.8(5)	C(2)-C(3)-C(4)	110.7(5)
C(7)-C(3)-C(4)	112.9(5)	C(5)-C(4)-C(16)	111.9(4)
C(5)-C(4)-C(3)	110.7(4)	C(16)-C(4)-C(3)	113.1(4)
C(6)-C(5)-C(4)	122.0(4)	C(6)-C(5)-S(1)	119.5(4)
C(4)-C(5)-S(1)	118.4(4)	C(5)-C(6)-C(1)	119.2(5)
C(8)-C(7)-C(3)	115.5(6)	C(7)-C(8)-C(9)	113.2(8)
C(15)-C(10)-C(11)	119.1(5)	C(15)-C(10)-S(2)	118.9(4)
C(11)-C(10)-S(2)	121.7(5)	C(12)-C(11)-C(10)	119.2(6)
C(13)-C(12)-C(11)	120.6(6)	C(12)-C(13)-C(14)	121.3(7)
C(13)-C(14)-C(15)	118.3(7)	C(14)-C(15)-C(10)	121.5(6)
C(17)-C(16)-C(21)	118.0(6)	C(17)-C(16)-C(4)	119.2(6)
C(21)-C(16)-C(4)	122.7(5)	C(16)-C(17)-C(18)	121.0(8)
C(19)-C(18)-C(17)	120.4(8)	C(18)-C(19)-C(20)	120.2(7)
C(19)-C(20)-C(21)	119.0(8)	C(16)-C(21)-C(20)	121.4(6)
C(27)-C(22)-C(23)	121.1(5)	C(27)-C(22)-S(1)	120.6(4)
C(23)-C(22)-S(1)	118.3(4)	C(24)-C(23)-C(22)	118.8(6)
C(25)-C(24)-C(23)	120.4(6)	C(24)-C(25)-C(26)	119.8(7)
C(27)-C(26)-C(25)	120.8(6)	C(22)-C(27)-C(26)	119.0(6)

Table 37: Bond angles in [^{o}] for **43**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	54(1)	59(1)	44(1)	-2(1)	1(1)	6(1)
S(2)	71(1)	76(1)	48(1)	16(1)	-6(1)	-10(1)
O(4)	77(2)	90(3)	37(2)	-5(2)	-5(2)	8(2)
O(2)	103(3)	110(4)	37(2)	3(2)	3(2)	-31(3)
O(3)	70(2)	57(2)	69(2)	-8(2)	2(2)	17(2)
O(1)	79(3)	88(3)	99(3)	42(3)	-11(3)	2(3)
C(1)	58(3)	60(4)	45(3)	2(3)	-2(2)	-8(3)
C(2)	56(3)	82(4)	50(3)	-6(3)	1(2)	1(3)
C(3)	62(3)	55(4)	59(3)	-4(3)	2(2)	9(3)

C(4)	49(3)	45(3)	60(3)	10(3)	2(2)	3(3)
C(5)	49(3)	47(3)	47(2)	0(3)	-6(2)	5(3)
C(6)	50(3)	53(3)	52(3)	0(3)	-8(2)	0(3)
C(7)	76(4)	69(4)	72(4)	-20(4)	3(3)	3(4)
C(8)	124(6)	86(6)	131(7)	-27(5)	-3(6)	-20(6)
C(9)	122(6)	135(8)	170(8)	-86(7)	15(7)	-43(7)
C(10)	67(3)	48(3)	44(3)	2(3)	3(2)	-3(3)
C(11)	86(4)	62(4)	79(4)	-3(3)	12(4)	-2(4)
C(12)	117(6)	77(5)	72(4)	-26(4)	4(4)	-14(5)
C(13)	107(6)	76(5)	89(5)	3(4)	-25(4)	-8(5)
C(14)	81(4)	86(5)	82(4)	-8(4)	-10(4)	-5(4)
C(15)	80(4)	71(4)	64(3)	-10(3)	-5(3)	4(4)
C(16)	53(3)	68(4)	51(3)	4(3)	6(2)	14(3)
C(17)	84(4)	89(5)	95(4)	40(4)	6(4)	30(4)
C(18)	102(6)	141(9)	107(6)	48(6)	-9(5)	45(6)
C(19)	80(5)	185(10)	77(5)	11(6)	-20(4)	51(7)
C(20)	67(4)	128(7)	86(4)	-4(5)	-22(3)	6(5)
C(21)	63(3)	84(4)	61(3)	6(4)	-10(3)	9(4)
C(22)	53(3)	58(3)	45(2)	1(3)	8(2)	1(3)
C(23)	65(3)	67(4)	57(3)	10(3)	-2(3)	-4(3)
C(24)	72(4)	92(5)	70(4)	2(4)	-11(3)	-23(4)
C(25)	103(5)	91(5)	75(4)	0(4)	4(4)	-42(5)
C(26)	129(6)	84(5)	73(4)	21(4)	2(4)	-39(5)
C(27)	82(4)	73(4)	56(3)	17(3)	-2(3)	-13(4)

Table 38: Anisotropic displacement parameters ($Å^2$ x 10^3) for **43**

Note the anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	x	y	z	U(eq)
H(2)	-371	9264	9683	81
H(3)	87	10995	9147	76
H(4)	1994	10768	8502	67
H(6)	2593	7158	8949	67
H(7A)	1703	11012	9872	94

H(7B)	2846	10463	9498	94
H(8A)	1624	12904	9385	148
H(8B)	2757	12354	9005	148
H(9A)	3325	12836	10069	200
H(9B)	3741	13794	9625	200
H(9C)	4447	12438	9654	200
H(11)	420	5036	8773	99
H(12)	-1244	4471	8157	116
H(13)	-3512	5143	8241	118
H(14)	-4229	6272	8971	108
H(15)	-2557	6929	9570	93
H(17)	433	11773	7939	116
H(18)	-1397	11743	7349	151
H(19)	-2754	9953	7258	148
H(20)	-2271	8130	7742	122
H(21)	-472	8180	8349	90
H(23)	5466	8922	9016	82
H(24)	7002	10480	9320	102
H(25)	7226	12392	8886	116
H(26)	5995	12737	8123	124
H(27)	4448	11216	7818	92

Table 39: Hydrogen coordinates (x 10^4) and isotropic displacement parameters for **43** ($Å^2$ x 10^3) .

5.1.3 (1*S*,2*S*)-4,6-bis(phenylsulfonyl)-2-propyl-1,2-dihydro-1,1'-biphenyl 43b

Identification code	js_prophen
Empirical formula	$C_{27}H_{26}O_4S_2$
Formula weight	478.60
Temperature	293(2) K
Wavelength	0.7107 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.4906(3)Å, α = 90°

	b = 10.3452(4)Å, β = 90°
	c = 25.4418(7)Å, γ = 90°
Volume	2497.92(13) $Å^3$
Z	4
Density (calculated)	1.273 Mg/m^3
Absorption coefficient	0.244 mm^{-1}
F(000)	1008
Crystal size	0.50 x 0.42 x 0.15 mm
Theta range for data collection	3.0147 to 29.1326 º.
Index ranges	-12<=h<=7; -14<=k<=6; -32<=l<=32
Reflections collected	11532
Independent reflections	4568 [R_{int} = 0.0169]
Reflections observed (>2σ)	3598
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90815
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4568 / 0 / 299
Goodness-of-fit on F^2	0.941
Final R indices [I>2σ(I)]	R_1 = 0.0320 wR_2 = 0.0709
R indices (all data)	R_1 = 0.0450 wR_2 = 0.0737
Absolute structure parameter	0.07(5)
Largest diff. peak and hole	0.175 and -0.189 e.$Å^{-3}$

Table 40: Crystal data and structure refinement for **43b**

Atom	x	y	z	U(eq)
S(2)	1358(1)	1267(1)	1839(1)	44(1)
S(1)	4667(1)	3344(1)	318(1)	56(1)
O(4)	1884(2)	864(2)	2341(1)	60(1)
O(2)	5403(2)	2941(2)	-148(1)	74(1)
O(3)	726(2)	2517(1)	1791(1)	57(1)
O(1)	3510(2)	4223(2)	281(1)	78(1)

C(1)	4063(2)	1949(2)	646(1)	43(1)
C(2)	4639(2)	813(2)	552(1)	51(1)
C(3)	4126(2)	-377(2)	826(1)	50(1)
C(4)	3626(2)	-62(2)	1390(1)	44(1)
C(5)	2742(2)	1144(2)	1381(1)	38(1)
C(6)	2958(2)	2092(2)	1040(1)	41(1)
C(7)	2967(2)	-999(2)	484(1)	63(1)
C(8)	2558(4)	-2352(3)	636(1)	96(1)
C(9)	1414(4)	-2903(3)	285(1)	128(1)
C(10)	5912(2)	3954(2)	764(1)	49(1)
C(11)	5498(3)	4698(2)	1190(1)	68(1)
C(12)	6494(4)	5037(3)	1563(1)	81(1)
C(13)	7856(4)	4657(3)	1504(1)	78(1)
C(14)	8268(3)	3952(3)	1074(1)	75(1)
C(15)	7291(2)	3592(3)	708(1)	62(1)
C(16)	4812(2)	13(2)	1787(1)	48(1)
C(17)	5113(3)	-1047(3)	2092(1)	79(1)
C(18)	6194(3)	-1042(4)	2444(1)	107(1)
C(19)	7002(3)	30(4)	2510(1)	101(1)
C(20)	6735(3)	1107(3)	2211(1)	81(1)
C(21)	5637(2)	1092(3)	1849(1)	63(1)
C(22)	172(2)	82(2)	1615(1)	44(1)
C(23)	-580(2)	303(2)	1164(1)	54(1)
C(24)	-1485(3)	-619(3)	979(1)	68(1)
C(25)	-1626(3)	-1762(3)	1242(1)	77(1)
C(26)	-874(3)	-1985(3)	1693(1)	84(1)
C(27)	37(2)	-1063(2)	1883(1)	64(1)

Table 41: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **43b**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

S(2)-O(3)	1.4306(14)	S(2)-O(4)	1.4325(14)
S(2)-C(22)	1.758(2)	S(2)-C(5)	1.7611(19)

S(1)-O(1)	1.4290(18)	S(1)-O(2)	1.4367(17)
S(1)-C(10)	1.755(2	S(1)-C(1)	1.763(2)
C(1)-C(2)	1.318(3)	C(1)-C(6)	1.458(3)
C(2)-C(3)	1.497(3)	C(3)-C(7)	1.543(3)
C(3)-C(4)	1.547(3)	C(4)-C(5)	1.504(3)
C(4)-C(16)	1.513(3	C(5)-C(6)	1.326(3)
C(7)-C(8)	1.503(3)	C(8)-C(9)	1.518(4)
C(10)-C(15)	1.369(3)	C(10)-C(11)	1.386(3)
C(11)-C(12)	1.386(4)	C(12)-C(13)	1.360(4)
C(13)-C(14)	1.372(4)	C(14)-C(15)	1.366(3)
C(16)-C(21)	1.373(3)	C(16)-C(17)	1.374(3)
C(17)-C(18)	1.362(4)	C(18)-C(19)	1.359(5)
C(19)-C(20)	1.374(4)	C(20)-C(21)	1.391(3)
C(22)-C(23)	1.372(3)	C(22)-C(27)	1.372(3)
C(23)-C(24)	1.366(3)	C(24)-C(25)	1.365(4)
C(25)-C(26)	1.372(4)	C(26)-C(27)	1.374(3)

Table 42: Bond Lengths in Å for **43b**

O(3)-S(2)-O(4)	119.02(9)	O(3)-S(2)-C(22)	109.51(9)
O(4)-S(2)-C(22)	108.01(9)	O(3)-S(2)-C(5)	108.71(10)
O(4)-S(2)-C(5)	108.01(9)	C(22)-S(2)-C(5)	102.27(9)
O(1)-S(1)-O(2)	120.24(11)	O(1)-S(1)-C(10)	109.34(11)
O(2)-S(1)-C(10)	108.08(10)	O(1)-S(1)-C(1)	107.59(10)
O(2)-S(1)-C(1)	108.10(10)	C(10)-S(1)-C(1)	101.96(9)
C(2)-C(1)-C(6)	120.90(18)	C(2)-C(1)-S(1)	120.61(15)
C(6)-C(1)-S(1)	118.43(15)	C(1)-C(2)-C(3)	120.93(19)
C(2)-C(3)-C(7)	108.15(18)	C(2)-C(3)-C(4)	111.07(17)
C(7)-C(3)-C(4)	113.12(18)	C(5)-C(4)-C(16)	112.49(16)
C(5)-C(4)-C(3)	109.35(16)	C(16)-C(4)-C(3)	113.70(17)
C(6)-C(5)-C(4)	122.51(17)	C(6)-C(5)-S(2)	119.73(15)
C(4)-C(5)-S(2)	117.75(14)	C(5)-C(6)-C(1)	119.10(18)
C(8)-C(7)-C(3)	115.3(2)	C(7)-C(8)-C(9)	112.5(3)
C(15)-C(10)-C(11)	120.3(2)	C(15)-C(10)-S(1)	118.55(18)

C(11)-C(10)-S(1)	120.92(19)	C(12)-C(11)-C(10)	118.9(2)
C(13)-C(12)-C(11)	119.9(2)	C(12)-C(13)-C(14)	120.9(3)
C(15)-C(14)-C(13)	119.7(3)	C(14)-C(15)-C(10)	120.2(2)
C(21)-C(16)-C(17)	117.8(2)	C(21)-C(16)-C(4)	122.84(18)
C(17)-C(16)-C(4)	119.4(2)	C(18)-C(17)-C(16)	121.7(3)
C(19)-C(18)-C(17)	120.7(3)	C(18)-C(19)-C(20)	119.3(3)
C(19)-C(20)-C(21)	119.8(3)	C(16)-C(21)-C(20)	120.8(2)
C(23)-C(22)-C(27)	120.7(2)	C(23)-C(22)-S(2)	119.23(16)
C(27)-C(22)-S(2)	120.08(17)	C(24)-C(23)-C(22)	119.9(2)
C(25)-C(24)-C(23)	119.9(2)	C(24)-C(25)-C(26)	120.3(3)
C(25)-C(26)-C(27)	120.3(2)	C(22)-C(27)-C(26)	119.0(2)

Table 43: Bond angles in [^{o}] for **43b**

5.1.4 (*E*)-(5-methylhexa-2,4-diene-1,3-diyldisulfonyl)dibenzene 62

Identification code	jm156r
Empirical formula	C19 H20 O4 S2
Formula weight	376.47
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.4107(10) Å, α = 105.392(2)°
	b = 9.0677(11) Å, β = 94.860(2)°
	c = 12.7953(15) Å, γ = 96.775(2)^{o}
Volume	927.38(19) Å^{3}
Z	2
Density (calculated)	1.348 Mg/m^{3}
Absorption coefficient	0.307 mm^{-1}
F(000)	396
Crystal size	0.30 x 0.12 x 0.11 mm^{3}
Crystal description	colourless block
Theta range for data collection	2.35 to 26.00°.
Index ranges	-10<=h<=10, -11<=k<=11, -15<=l<=15
Reflections collected	7518

Independent reflections	3610 [R(int) = 0.0360]
Completeness to theta = 26.00°	99.2%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9670 and 0.9135
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3610 / 0 / 228
Goodness-of-fit on F^2	1.024
Final R indices [I>2σ(I)]	R1 = 0.0485, wR2 = 0.1191
R indices (all data)	R1 = 0.0752, wR2 = 0.1348
Largest diff. peak and hole	0.742 and -0.539 e.$Å^{-3}$

Table 44: Crystal data and structure refinement for **62**

Atom	x	y	z	U(eq)
C(1)	644(5)	-1238(4)	6732(3)	56(1)
C(2)	495(4)	644(4)	8578(3)	44(1)
C(3)	1177(3)	353(4)	7508(3)	34(1)
C(4)	2197(3)	1374(3)	7223(2)	29(1)
C(5)	2920(3)	2927(3)	7894(2)	23(1)
S(1)	2791(1)	4451(1)	7265(1)	24(1)
O(1)	3172(2)	3906(2)	6163(2)	33(1)
O(2)	3736(2)	5848(2)	7969(2)	30(1)
C(6)	3778(3)	3341(3)	8885(2)	27(1)
C(7)	4266(3)	2270(3)	9518(2)	25(1)
S(2)	6300(1)	1928(1)	9340(1)	24(1)
O(3)	7275(2)	3381(2)	9432(2)	31(1)
O(4)	6753(2)	1019(2)	10056(2)	29(1)
C(11)	749(3)	4735(3)	7201(2)	25(1)
C(12)	158(4)	5462(4)	8156(3)	34(1)
C(13)	-1424(4)	5764(4)	8095(3)	46(1)
C(14)	-2377(4)	5359(4)	7101(3)	49(1)
C(15)	-1770(4)	4639(4)	6155(3)	47(1)
C(16)	-197(4)	4304(4)	6196(3)	34(1)
C(21)	6149(3)	771(3)	7973(2)	24(1)
C(22)	6869(4)	1383(4)	7215(2)	34(1)
C(23)	6768(4)	438(4)	6153(3)	44(1)

C(24)	5982(4)	-1053(4)	5865(3)	41(1)
C(25)	5261(4)	-1642(4)	6626(2)	32(1)
C(26)	5337(3)	-740(3)	7696(2)	29(1)

Table 45: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **62**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

C(1)-C(3)	1.510(5)	S(1)-O(1)	1.442(2)
C(2)-C(3)	1.499(4)	S(1)-O(2)	1.443(2)
C(3)-C(4)	1.331(4)	S(1)-C(11)	1.765(3)
C(4)-C(5)	1.469(4)	C(6)-C(7)	1.491(4)
C(5)-C(6)	1.341(4)	C(7)-S(2)	1.797(3)
C(5)-S(1)	1.784(3)	S(2)-O(3)	1.438(2)
S(2)-O(4)	1.442(2)	C(12)-C(13)	1.389(4)
S(2)-C(21)	1.770(3)	C(13)-C(14)	1.381(5)
C(11)-C(16)	1.387(4)	C(14)-C(15)	1.384(5)
C(11)-C(12)	1.389(4)	C(15)-C(16)	1.392(4)
C(21)-C(22)	1.387(4)	C(23)-C(24)	1.372(5)
C(21)-C(26)	1.396(4)	C(24)-C(25)	1.379(5)
C(22)-C(23)	1.390(4)	C(25)-C(26)	1.389(4)

Table 46: Bond Lengths in Å for **62**

C(4)-C(3)-C(2)	124.8(3)	O(4)-S(2)-C(7)	107.48(12)
C(4)-C(3)-C(1)	119.9(3)	C(21)-S(2)-C(7)	103.80(13)
C(2)-C(3)-C(1)	115.3(3)	C(16)-C(11)-C(12)	121.7(3)
C(3)-C(4)-C(5)	127.3(3)	C(16)-C(11)-S(1)	119.5(2)
C(6)-C(5)-C(4)	128.8(3)	C(12)-C(11)-S(1)	118.7(2)
C(6)-C(5)-S(1)	115.2(2)	C(13)-C(12)-C(11)	118.7(3)
C(4)-C(5)-S(1)	115.85(19)	C(14)-C(13)-C(12)	120.3(3)
O(1)-S(1)-O(2)	118.12(13)	C(13)-C(14)-C(15)	120.3(3)
O(1)-S(1)-C(11)	108.04(12)	C(14)-C(15)-C(16)	120.4(3)
O(2)-S(1)-C(11)	107.79(12)	C(11)-C(16)-C(15)	118.5(3)
O(1)-S(1)-C(5)	107.62(12)	C(22)-C(21)-C(26)	122.0(3)

O(2)-S(1)-C(5)	108.79(12)	C(22)-C(21)-S(2)	118.9(2)
C(11)-S(1)-C(5)	105.84(13)	C(26)-C(21)-S(2)	119.0(2)
C(5)-C(6)-C(7)	126.0(3)	C(21)-C(22)-C(23)	117.8(3)
C(6)-C(7)-S(2)	110.25(19)	C(24)-C(23)-C(22)	121.1(3)
O(3)-S(2)-O(4)	119.02(12)	C(23)-C(24)-C(25)	120.4(3)
O(3)-S(2)-C(21)	108.45(13)	C(24)-C(25)-C(26)	120.4(3)
O(4)-S(2)-C(21)	108.57(13)	C(25)-C(26)-C(21)	118.2(3)
O(3)-S(2)-C(7)	108.47(13)		

Table 47: Bond angles in [^{o}] for **62**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	48(2)	38(2)	73(3)	11(2)	-9(2)	-7(2)
C(2)	20(2)	62(2)	59(2)	34(2)	4(1)	5(2)
C(3)	23(2)	36(2)	44(2)	16(2)	-3(1)	5(1)
C(4)	29(2)	29(2)	26(2)	6(1)	-1(1)	6(1)
C(5)	17(1)	29(2)	24(1)	6(1)	4(1)	7(1)
S(1)	20(1)	29(1)	23(1)	7(1)	3(1)	6(1)
O(1)	36(1)	41(1)	25(1)	10(1)	10(1)	12(1)
O(2)	24(1)	28(1)	37(1)	8(1)	-2(1)	2(1)
C(6)	24(1)	28(2)	26(1)	4(1)	2(1)	8(1)
C(7)	23(1)	29(2)	24(1)	7(1)	2(1)	5(1)
S(2)	21(1)	30(1)	22(1)	7(1)	0(1)	5(1)
O(3)	32(1)	32(1)	27(1)	7(1)	0(1)	1(1)
O(4)	26(1)	37(1)	27(1)	12(1)	-1(1)	8(1)
C(11)	22(1)	27(2)	28(2)	10(1)	1(1)	5(1)
C(12)	27(2)	41(2)	35(2)	9(1)	8(1)	10(1)
C(13)	31(2)	48(2)	65(2)	19(2)	20(2)	14(2)
C(14)	20(2)	55(2)	86(3)	42(2)	6(2)	8(2)
C(15)	29(2)	57(2)	61(2)	35(2)	-13(2)	-3(2)
C(16)	29(2)	41(2)	33(2)	15(1)	-3(1)	1(1)
C(21)	21(1)	29(2)	22(1)	6(1)	2(1)	7(1)
C(22)	37(2)	37(2)	29(2)	10(1)	3(1)	4(1)

C(23)	54(2)	48(2)	31(2)	12(2)	13(2)	6(2)
C(24)	49(2)	43(2)	25(2)	-1(1)	7(1)	13(2)
C(25)	32(2)	29(2)	33(2)	5(1)	-1(1)	6(1)
C(26)	26(2)	34(2)	29(2)	12(1)	4(1)	9(1)

Table 48: Anisotropic displacement parameters ($Å^2$ x 10^3) for **62**

Note the anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	x	y	z	U(eq)
H(1A)	1188	-1337	6075	84
H(1B)	-526	-1389	6529	84
H(1C)	922	-2022	7088	84
H(2A)	1019	88	9037	66
H(2B)	-668	280	8447	66
H(2C)	688	1755	8948	66
H(4)	2489	1064	6504	34
H(6)	4106	4416	9214	32
H(7A)	3527	1278	9267	30
H(7B)	4187	2727	10303	30
H(12)	822	5748	8837	41
H(13)	-1852	6251	8741	55
H(14)	-3455	5576	7065	59
H(15)	-2432	4371	5474	57
H(16)	219	3792	5552	41
H(22)	7414	2415	7415	41
H(23)	7250	831	5618	52
H(24)	5936	-1683	5136	49
H(25)	4708	-2671	6416	39
H(26)	4849	-1140	8226	34

Table 49: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **62**

C(2)-C(3)-C(4)-C(5)	3.5(5)	C(16)-C(11)-C(12)-C(13)	-0.1(5)
C(1)-C(3)-C(4)-C(5)	-175.8(3)	S(1)-C(11)-C(12)-C(13)	176.4(2)

C(3)-C(4)-C(5)-C(6)	55.0(4)	C(11)-C(12)-C(13)-C(14)	-0.6(5)
C(3)-C(4)-C(5)-S(1)	-130.9(3)	C(12)-C(13)-C(14)-C(15)	0.5(5)
C(6)-C(5)-S(1)-O(1)	131.6(2)	C(13)-C(14)-C(15)-C(16)	0.5(5)
C(4)-C(5)-S(1)-O(1)	-43.4(2)	C(12)-C(11)-C(16)-C(15)	1.0(5)
C(6)-C(5)-S(1)-O(2)	2.5(2)	S(1)-C(11)-C(16)-C(15)	-175.5(2)
C(4)-C(5)-S(1)-O(2)	-172.43(19)	C(14)-C(15)-C(16)-C(11)	-1.2(5)
C(6)-C(5)-S(1)-C(11)	-113.1(2)	O(3)-S(2)-C(21)-C(22)	-2.6(3)
C(4)-C(5)-S(1)-C(11)	72.0(2)	O(4)-S(2)-C(21)-C(22)	-133.3(2)
C(4)-C(5)-C(6)-C(7)	3.2(5)	C(7)-S(2)-C(21)-C(22)	112.6(2)
S(1)-C(5)-C(6)-C(7)	-171.0(2)	O(3)-S(2)-C(21)-C(26)	176.1(2)
C(5)-C(6)-C(7)-S(2)	97.7(3)	O(4)-S(2)-C(21)-C(26)	45.5(2)
C(6)-C(7)-S(2)-O(3)	44.3(2)	C(7)-S(2)-C(21)-C(26)	-68.7(2)
C(6)-C(7)-S(2)-O(4)	174.23(18)	C(26)-C(21)-C(22)-C(23)	-0.3(4)
C(6)-C(7)-S(2)-C(21)	-70.9(2)	S(2)-C(21)-C(22)-C(23)	178.4(2)
O(1)-S(1)-C(11)-C(16)	5.4(3)	C(21)-C(22)-C(23)-C(24)	-0.1(5)
O(2)-S(1)-C(11)-C(16)	134.1(2)	C(22)-C(23)-C(24)-C(25)	0.6(5)
C(5)-S(1)-C(11)-C(16)	-109.6(3)	C(23)-C(24)-C(25)-C(26)	-0.8(5)
O(1)-S(1)-C(11)-C(12)	-171.1(2)	C(24)-C(25)-C(26)-C(21)	0.4(4)
O(2)-S(1)-C(11)-C(12)	-42.5(3)	C(22)-C(21)-C(26)-C(25)	0.1(4)
C(5)-S(1)-C(11)-C(12)	73.8(3)	S(2)-C(21)-C(26)-C(25)	-178.6(2)

Table 50: Torsion angles in [^{o}] for **62**

5.1.5 ((1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-triene-1,3-diyldisulfonyl)dibenzene 161

Identification code	js_ph3_02
Empirical formula	$C_{24}\ H_{20}\ O_4\ S_2$
Formula weight	436.52
Temperature	299.1 K
Wavelength	0.7107 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 5.9436(3)Å, α = 90º

	b = 14.0768(8)Å, β = 100.537(5)º
	c = 13.0684(8)Å, γ = 90º
Volume	1074.95(11) $Å^3$
Z	2
Density (calculated)	1.349 Mg/m^3
Absorption coefficient	0.276 mm^{-1}
F(000)	456
Crystal size	0.60 x 0.10 x 0.10 mm
Theta range for data collection	3.1647 to 29.0854 º.
Index ranges	-7<=h<=6; -7<=k<=18; -17<=l<=12
Reflections collected	5206
Independent reflections	2704 [R_{int} = 0.0344]
Reflections observed (>2σ)	2287
Data Completeness	0.999
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.88884
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2704 / 1 / 271
Goodness-of-fit on F^2	1.070
Final R indices [I>2σ(I)]	R_1 = 0.0539 wR_2 = 0.1265
R indices (all data)	R_1 = 0.0666 wR_2 = 0.1406
Absolute structure parameter	-0.02(12)
Largest diff. peak and hole	0.473 and -0.223 $e.Å^{-3}$

Table 51: Crystal data and structure refinement for **161**

Atom	x	y	z	U(eq)
S(1)	-3022(2)	7800(1)	6061(1)	45(1)
S(2)	1747(2)	8008(1)	9514(1)	49(1)
O(3)	-641(5)	7965(3)	9588(2)	55(1)
O(1)	-5390(5)	7662(3)	6116(3)	57(1)
O(4)	3429(6)	7792(3)	10423(3)	67(1)
O(2)	-1990(6)	7248(3)	5349(3)	58(1)
C(1)	-2706(8)	9003(4)	5778(4)	41(1)

C(2)	-4244(9)	9660(5)	6011(5)	59(2)
C(3)	-3940(11)	10620(5)	5786(6)	76(2)
C(4)	-2116(11)	10889(5)	5323(6)	74(2)
C(5)	-617(11)	10231(5)	5105(6)	76(2)
C(6)	-868(9)	9279(4)	5331(5)	65(2)
C(7)	-1405(7)	7677(4)	7322(3)	40(1)
C(8)	652(7)	7300(3)	7510(4)	40(1)
C(9)	2222(7)	7261(4)	8500(4)	43(1)
C(10)	4154(8)	6713(4)	8692(4)	46(1)
C(11)	4857(7)	6010(4)	8055(4)	41(1)
C(12)	6847(8)	5551(4)	8364(4)	47(1)
C(13)	7807(8)	4768(4)	7873(4)	44(1)
C(14)	10038(9)	4464(5)	8298(4)	56(2)
C(15)	11012(10)	3712(5)	7873(5)	62(2)
C(16)	9837(11)	3261(6)	7055(5)	76(2)
C(17)	7628(12)	3524(6)	6598(5)	83(2)
C(18)	6665(9)	4275(5)	7013(4)	65(2)
C(19)	2327(8)	9169(4)	9097(4)	46(1)
C(20)	4566(9)	9494(4)	9299(5)	62(2)
C(21)	5014(11)	10397(5)	9002(6)	78(2)
C(22)	3277(12)	10968(5)	8498(6)	75(2)
C(23)	1092(13)	10628(5)	8311(6)	86(2)
C(24)	596(10)	9730(5)	8589(5)	68(2)

Table 52: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **161**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

S(1)-O(2)	1.432(4)	S(1)-O(1)	1.436(3)
S(1)-C(1)	1.751(5)	S(1)-C(7)	1.758(4)
S(2)-O(4)	1.437(3)	S(2)-O(3)	1.442(3)
S(2)-C(9)	1.755(5)	S(2)-C(19)	1.776(6)
C(1)-C(2)	1.374(7)	C(1)-C(6)	1.386(7)
C(2)-C(3)	1.401(9)	C(3)-C(4)	1.387(9)
C(4)-C(5)	1.351(10	C(5)-C(6)	1.386(9)

C(7)-C(8)	1.314(6)	C(8)-C(9)	1.451(6)
C(9)-C(10)	1.368(6)	C(10)-C(11)	1.406(7)
C(11)-C(12)	1.343(6)	C(12)-C(13)	1.445(7)
C(13)-C(18)	1.388(7)	C(13)-C(14)	1.407(7)
C(14)-C(15)	1.371(8)	C(15)-C(16)	1.327(9)
C(16)-C(17)	1.389(8)	C(17)-C(18)	1.361(9)
C(19)-C(24)	1.369(7)	C(19)-C(20)	1.387(7)
C(20)-C(21)	1.369(10)	C(21)-C(22)	1.377(10)
C(22)-C(23)	1.364(9)	C(23)-C(24)	1.362(9)

Table 53: Bond Lengths in Å for **161**

O(2)-S(1)-O(1)	119.9(2)	O(2)-S(1)-C(1)	108.2(3)
O(1)-S(1)-C(1)	106.6(2)	O(2)-S(1)-C(7)	109.3(2)
O(1)-S(1)-C(7)	108.2(2)	C(1)-S(1)-C(7)	103.4(2)
O(4)-S(2)-O(3)	118.7(2)	O(4)-S(2)-C(9)	108.3(2)
O(3)-S(2)-C(9)	108.8(2)	O(4)-S(2)-C(19)	107.7(3)
O(3)-S(2)-C(19)	107.9(2)	C(9)-S(2)-C(19)	104.6(2)
C(2)-C(1)-C(6)	120.8(5)	C(2)-C(1)-S(1)	120.2(4)
C(6)-C(1)-S(1)	118.9(4)	C(1)-C(2)-C(3)	119.1(6)
C(4)-C(3)-C(2)	119.7(6)	C(5)-C(4)-C(3)	120.2(6)
C(4)-C(5)-C(6)	121.1(6)	C(1)-C(6)-C(5)	119.0(6)
C(8)-C(7)-S(1)	123.0(4)	C(7)-C(8)-C(9)	127.3(4)
C(10)-C(9)-C(8)	124.5(5)	C(10)-C(9)-S(2)	116.4(4)
C(8)-C(9)-S(2)	119.0(3)	C(9)-C(10)-C(11)	128.2(5)
C(12)-C(11)-C(10)	120.1(5)	C(11)-C(12)-C(13)	129.1(5)
C(18)-C(13)-C(14)	117.0(5)	C(18)-C(13)-C(12)	124.5(5)
C(14)-C(13)-C(12)	118.5(5)	C(15)-C(14)-C(13)	120.8(6)
C(16)-C(15)-C(14)	119.8(6)	C(15)-C(16)-C(17)	122.3(6)
C(18)-C(17)-C(16)	118.0(7)	C(17)-C(18)-C(13)	122.1(5)
C(24)-C(19)-C(20)	120.8(6)	C(24)-C(19)-S(2)	120.6(4)
C(20)-C(19)-S(2)	118.6(4)	C(21)-C(20)-C(19)	118.8(5)
C(20)-C(21)-C(22)	120.7(6)	C(23)-C(22)-C(21)	119.1(7)
C(24)-C(23)-C(22)	121.6(6)	C(23)-C(24)-C(19)	119.0(6)

Table 54: Bond angles in [^{o}] for **161**

Atom	U^{11}	$U2^{2}$	U33	U^{23}	U^{13}	U^{12}
S(1)	41(1)	35(1)	57(1)	-2(1)	7(1)	-4(1)
S(2)	46(1)	51(1)	48(1)	1(1)	9(1)	14(1)
O(3)	47(2)	64(3)	57(2)	-4(2)	19(1)	9(2)
O(1)	36(2)	57(3)	76(2)	5(2)	4(1)	-10(2)
O(4)	70(2)	80(3)	47(2)	1(2)	1(2)	29(2)
O(2)	74(2)	41(2)	60(2)	-14(2)	13(2)	0(2)
C(1)	39(3)	37(3)	45(3)	6(2)	4(2)	1(2)
C(2)	52(3)	47(4)	78(4)	11(3)	9(3)	4(3)
C(3)	78(4)	53(4)	94(5)	11(4)	12(4)	24(3)
C(4)	77(4)	49(4)	90(5)	25(4)	-2(4)	-7(3)
C(5)	68(4)	62(4)	103(5)	24(4)	27(4)	-11(4)
C(6)	63(4)	44(4)	95(5)	5(3)	31(3)	-5(3)
C(7)	35(2)	38(3)	48(2)	-2(2)	10(2)	-2(2)
C(8)	47(3)	26(2)	47(3)	-1(2)	11(2)	-1(2)
C(9)	46(2)	29(3)	56(3)	5(2)	17(2)	6(2)
C(10)	46(3)	44(3)	49(3)	-1(3)	9(2)	8(2)
C(11)	41(2)	36(3)	47(3)	7(2)	8(2)	5(2)
C(12)	49(3)	40(3)	53(3)	8(3)	14(2)	6(2)
C(13)	42(3)	42(3)	53(3)	10(3)	22(2)	9(2)
C(14)	51(3)	60(4)	58(3)	9(3)	13(2)	14(3)
C(15)	53(3)	67(4)	70(4)	15(4)	18(3)	25(3)
C(16)	88(4)	69(5)	76(4)	8(4)	25(3)	29(4)
C(17)	105(5)	75(5)	70(4)	-8(4)	17(4)	23(4)
C(18)	63(3)	68(5)	63(4)	-7(3)	9(3)	18(3)
C(19)	46(3)	43(3)	49(3)	-9(3)	5(2)	11(2)
C(20)	47(3)	60(4)	75(4)	-17(4)	3(3)	12(3)
C(21)	61(4)	62(5)	112(6)	-27(4)	22(4)	-4(3)
C(22)	93(5)	46(4)	84(5)	-11(4)	12(4)	-9(4)
C(23)	86(5)	43(4)	115(6)	2(4)	-20(4)	5(4)
C(24)	57(3)	51(4)	86(4)	4(4)	-12(3)	7(3)

Table 55: Anisotropic displacement parameters ($Å^2$ x 10^3) for **161**

Note the anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	x	y	z	U(eq)
H(2)	-5471	9471	6314	77
H(3)	-4957	11075	5946	98
H(4)	-1924	11524	5163	97
H(5)	604	10421	4798	99
H(6)	182	8833	5184	85
H(7)	-2035	7888	7883	52
H(8)	1159	7027	6945	52
H(10)	5125	6819	9325	60
H(11)	3944	5863	7418	54
H(12)	7730	5767	8982	61
H(14)	10862	4777	8873	73
H(15)	12490	3519	8158	81
H(16)	10516	2750	6777	99
H(17)	6832	3197	6027	108
H(18)	5194	4464	6710	84
H(20)	5744	9107	9631	80
H(21)	6505	10627	9142	101
H(22)	3590	11578	8288	97
H(23)	-88	11019	7986	112
H(24)	-896	9502	8436	88

Table 56: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **161**

5.1.6 4-(Phenylsulfonyl)-1,1'-biphenyl 164

Identification code	phsulf_11
Empirical formula	C_{18} H_{14} O_2 S
Formula weight	294.35
Temperature	297.0 K
Wavelength	0.7107 Å
Crystal system	Monoclinic

Space group	$P2_1/c$
Unit cell dimensions	a = 16.5020(12)Å, α = 90°
	b = 7.8520(5)Å, β = 101.480(8)º
	c = 11.3748(9)Å, γ = 90°
Volume	1444.39(18) $Å^3$
Z	4
Density (calculated)	1.354 Mg/m^3
Absorption coefficient	0.225 mm^{-1}
F(000)	616
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	2.8780 to 28.9560 º
Index ranges	-15<=h<=8; -10<=k<=8; -22<=l<=22
Reflections collected	6662
Independent reflections	2650 [R_{int} = 0.0331]
Reflections observed (>2σ)	1648
Data Completeness	0.999
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.88718
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2650 / 0 / 190
Goodness-of-fit on F^2	1.066
Final R indices [I>2σ(I)]	R_1 = 0.0519 wR_2 = 0.1115
R indices (all data)	R_1 = 0.0970 wR_2 = 0.1506
Largest diff. peak and hole	0.251 and -0.353 e.$Å^{-3}$

Table 57: Crystal data and structure refinement for **164**

Atom	x	y	z	U(eq)
S(1)	1796(1)	3433(1)	1702(1)	55(1)
O(2)	1437(2)	1804(3)	1335(2)	77(1)
O(1)	1781(2)	4055(3)	2889(2)	77(1)
C(1)	5966(2)	4237(4)	1851(3)	65(1)
C(2)	1316(2)	6651(4)	1017(3)	56(1)
C(3)	7018(2)	3261(4)	849(3)	59(1)
C(4)	2835(2)	3397(3)	1524(3)	44(1)
C(5)	4224(2)	4363(4)	2102(3)	54(1)
C(6)	1332(2)	4974(4)	662(3)	44(1)

C(7)	6779(2)	4192(4)	1740(3)	74(1)
C(8)	1017(2)	4513(4)	-511(3)	56(1)
C(9)	974(2)	7864(4)	188(4)	72(1)
C(10)	3418(2)	4374(4)	2252(3)	55(1)
C(11)	681(2)	5737(5)	-1328(3)	70(1)
C(12)	5613(2)	2430(4)	187(3)	57(1)
C(13)	6429(2)	2392(4)	75(3)	65(1)
C(14)	3872(2)	2422(4)	500(3)	57(1)
C(15)	662(2)	7394(5)	-977(4)	74(1)
C(16)	3065(2)	2414(4)	637(3)	58(1)
C(17)	5356(2)	3354(3)	1079(2)	40(1)
C(18)	4482(2)	3379(3)	1229(2)	38(1)

Table 58: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of

164

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

S(1)-O(2)	1.436(2)	S(1)-O(1)	1.441(2)
S(1)-C(6)	1.758(3)	S(1)-C(4)	1.767(3)
C(1)-C(7)	1.372(4)	C(1)-C(17)	1.384(4)
C(2)-C(6)	1.379(4)	C(2)-C(9)	1.379(5)
C(3)-C(13)	1.358(4)	C(3)-C(7)	1.370(4)
C(4)-C(10)	1.372(4)	C(4)-C(16)	1.382(4)
C(5)-C(10)	1.375(4)	C(5)-C(18)	1.390(4)
C(6)-C(8)	1.381(4)	C(8)-C(11)	1.375(4)
C(9)-C(15)	1.373(5)	C(11)-C(15)	1.364(5)
C(12)-C(13)	1.377(4)	C(12)-C(17)	1.382(4)
C(14)-C(16)	1.372(4)	C(14)-C(18)	1.391(4)
C(17)-C(18)	1.484(4)		

Table 59: Bond Lengths in Å for **164**

O(2)-S(1)-O(1)	119.50(15)	O(2)-S(1)-C(6)	108.56(15)
O(1)-S(1)-C(6)	108.13(14)	O(2)-S(1)-C(4)	107.79(14)
O(1)-S(1)-C(4)	108.11(15)	C(6)-S(1)-C(4)	103.63(12)
C(7)-C(1)-C(17)	122.0(3)	C(6)-C(2)-C(9)	119.2(3)
C(13)-C(3)-C(7)	118.2(3)	C(10)-C(4)-C(16)	119.4(3)
C(10)-C(4)-S(1)	120.1(2)	C(16)-C(4)-S(1)	120.4(2)
C(10)-C(5)-C(18)	122.3(3)	C(2)-C(6)-C(8)	120.5(3)
C(2)-C(6)-S(1)	119.4(3)	C(8)-C(6)-S(1)	120.0(2)
C(3)-C(7)-C(1)	120.8(3)	C(11)-C(8)-C(6)	119.6(3)
C(15)-C(9)-C(2)	119.9(3)	C(4)-C(10)-C(5)	120.1(3)
C(15)-C(11)-C(8)	119.9(4)	C(13)-C(12)-C(17)	121.9(3)
C(3)-C(13)-C(12)	121.0(3)	C(16)-C(14)-C(18)	122.6(3)
C(11)-C(15)-C(9)	120.9(4)	C(14)-C(16)-C(4)	119.6(3)
C(12)-C(17)-C(1)	115.9(3)	C(12)-C(17)-C(18)	122.6(3)
C(1)-C(17)-C(18)	121.4(3)	C(5)-C(18)-C(14)	116.0(3)
C(5)-C(18)-C(17)	122.1(3)	C(14)-C(18)-C(17)	121.9(2)

Table 60: Bond angles in [^{o}] for **164**

Atom	U11	U22	U33	U23	U13	U12
S(1)	52(1)	57(1)	62(1)	13(1)	22(1)	3(1)
O(2)	60(2)	51(1)	123(2)	16(1)	27(2)	-9(1)

O(1)	75(2)	110(2)	52(2)	15(1)	30(1)	14(1)
C(1)	51(2)	70(2)	74(2)	-28(2)	11(2)	-5(2)
C(2)	56(2)	52(2)	64(2)	-5(2)	20(2)	3(2)
C(3)	46(2)	62(2)	71(2)	12(2)	20(2)	-1(2)
C(4)	49(2)	41(2)	44(2)	8(1)	12(1)	5(1)
C(5)	52(2)	58(2)	52(2)	-16(2)	8(2)	-6(2)
C(6)	36(2)	45(2)	54(2)	3(1)	16(1)	0(1)
C(7)	54(2)	76(2)	90(3)	-18(2)	7(2)	-13(2)
C(8)	49(2)	58(2)	62(2)	-3(2)	13(2)	-10(2)
C(9)	69(3)	47(2)	105(3)	3(2)	31(2)	8(2)
C(10)	58(2)	58(2)	50(2)	-13(2)	14(2)	4(2)
C(11)	48(2)	93(3)	63(2)	10(2)	-1(2)	-10(2)
C(12)	52(2)	70(2)	51(2)	-14(2)	12(2)	-3(2)
C(13)	59(2)	80(2)	60(2)	-10(2)	22(2)	3(2)
C(14)	52(2)	67(2)	53(2)	-21(2)	13(2)	-1(2)
C(15)	49(2)	81(3)	92(3)	31(2)	18(2)	12(2)
C(16)	49(2)	63(2)	63(2)	-18(2)	9(2)	-7(2)
C(17)	47(2)	34(2)	38(2)	6(1)	6(1)	1(1)
C(18)	44(2)	35(1)	34(2)	4(1)	4(1)	4(1)

Table 61: Anisotropic displacement parameters ($Å^2$ x 10^3) for **164**

Note the anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$$

Atom	x	y	z	U(eq)
H(1)	5821	4880	2464	84
H(2)	1533	6960	1806	73
H(3)	7569	3225	776	76
H(5)	4610	5037	2602	70
H(7)	7172	4801	2276	96
H(8)	1032	3381	-747	73
H(9)	956	8998	418	93
H(10)	3268	5044	2848	71
H(11)	466	5434	-2120	91
H(12)	5225	1816	-353	75
H(13)	6579	1762	-540	85
H(14)	4017	1760	-104	74
H(15)	435	8218	-1533	96

H(16)	2674	1750	136	76

Table 62: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **164**

5.1.7 *tert*-Butyl (2-(2,2-dimethyl-5-oxoimidazolidin-1-yl)ethyl)carbamate 179

Identification code	jm70
Empirical formula	C12 H23 N3 O3
Formula weight	257.33
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 18.347(3) Å, α = 90°
	b = 13.491(3) Å, β = 96.974(3)°
	c = 11.649(2) Å, γ = 90°
Volume	2862.1(9) $Å^3$
Z	8
Density (calculated)	1.194 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	1120
Crystal size	0.25 x 0.16 x 0.08 mm^3
Crystal description	colourless block
Theta range for data collection	1.88 to 26.34°.
Index ranges	-22<=h<=22, -16<=k<=16, -14<=l<=14
Reflections collected	12320
Independent reflections	2926 [R(int) = 0.0626]
Completeness to theta = 26.34°	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9931 and 0.9788

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2926 / 0 / 169
Goodness-of-fit on F^2	1.013
Final R indices [I>2σ(I)]	R1 = 0.0469, wR2 = 0.0979
R indices (all data)	R1 = 0.0866, wR2 = 0.1138
Largest diff. peak and hole	0.212 and -0.174 e.$Å^{-3}$

Table 63: Crystal data and structure refinement for **179**

Atom	x	y	z	U(eq)
(1)	4128(1)	5962(1)	1491(1)	35(1)
C(1)	3955(1)	6443(1)	2319(2)	27(1)
C(2)	3754(1)	7528(1)	2335(2)	35(1)
N(1)	3461(1)	7691(1)	3435(1)	32(1)
C(3)	3760(1)	6887(1)	4209(2)	29(1)
C(4)	4472(1)	7216(2)	4912(2)	43(1)
C(5)	3209(1)	6545(2)	4989(2)	38(1)
N(2)	3915(1)	6092(1)	3386(1)	25(1)
C(6)	4123(1)	5086(1)	3738(2)	28(1)
C(7)	3472(1)	4378(1)	3525(2)	31(1)
N(3)	3643(1)	3449(1)	4125(1)	32(1)
C(8)	3466(1)	2568(1)	3650(2)	27(1)
O(2)	3189(1)	2436(1)	2660(1)	37(1)
O(3)	3641(1)	1844(1)	4436(1)	29(1)
C(9)	3607(1)	794(1)	4095(2)	29(1)
C(10)	2832(1)	497(2)	3624(2)	47(1)
C(11)	4149(1)	606(2)	3241(2)	48(1)
C(12)	3837(1)	266(2)	5228(2)	43(1)

Table 64: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **179**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

O(1)-C(1)	1.236(2)	C(6)-C(7)	1.525(3)

C(1)-N(2)	1.339(2)	C(7)-N(3)	1.451(2)
C(1)-C(2)	1.510(3)	N(3)-C(8)	1.334(2)
C(2)-N(1)	1.464(3)	C(8)-O(2)	1.216(2)
N(1)-C(3)	1.473(2)	C(8)-O(3)	1.351(2)
C(3)-N(2)	1.489(2)	O(3)-C(9)	1.470(2)
C(3)-C(5)	1.511(3)	C(9)-C(11)	1.512(3)
C(3)-C(4)	1.522(3)	C(9)-C(10)	1.514(3)
N(2)-C(6)	1.455(2)	C(9)-C(12)	1.514(3)

Table 65: Bond Lengths in Å for **179**

O(1)-C(1)-N(2)	125.91(18)	N(2)-C(6)-C(7)	111.45(15)
O(1)-C(1)-C(2)	127.22(17)	N(3)-C(7)-C(6)	110.13(15)
N(2)-C(1)-C(2)	106.87(16)	C(8)-N(3)-C(7)	122.84(16)
N(1)-C(2)-C(1)	105.80(15)	O(2)-C(8)-N(3)	125.23(17)
C(2)-N(1)-C(3)	106.08(15)	O(2)-C(8)-O(3)	125.04(17)
N(1)-C(3)-N(2)	102.81(14)	N(3)-C(8)-O(3)	109.73(15)
N(1)-C(3)-C(5)	111.53(16)	C(8)-O(3)-C(9)	121.02(14)
N(2)-C(3)-C(5)	111.26(16)	O(3)-C(9)-C(11)	109.27(16)
N(1)-C(3)-C(4)	110.20(17)	O(3)-C(9)-C(10)	111.10(16)
N(2)-C(3)-C(4)	109.69(16)	C(11)-C(9)-C(10)	112.44(17)
C(5)-C(3)-C(4)	111.05(16)	O(3)-C(9)-C(12)	102.72(14)
C(1)-N(2)-C(6)	123.33(15)	C(11)-C(9)-C(12)	110.94(17)
C(1)-N(2)-C(3)	112.28(15)	C(10)-C(9)-C(12)	109.96(17)
C(6)-N(2)-C(3)	123.62(14)		

Table 66: Bond angles in [^{o}] for **179**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	43(1)	38(1)	25(1)	0(1)	7(1)	4(1)
C(1)	25(1)	31(1)	25(1)	1(1)	3(1)	-1(1)
C(2)	43(1)	28(1)	35(1)	6(1)	7(1)	0(1)
N(1)	37(1)	28(1)	32(1)	0(1)	5(1)	4(1)
C(3)	31(1)	28(1)	28(1)	-3(1)	2(1)	4(1)
C(4)	41(1)	44(1)	41(1)	-10(1)	-6(1)	5(1)

C(5)	44(1)	40(1)	32(1)	1(1)	12(1)	7(1)
N(2)	27(1)	24(1)	23(1)	1(1)	4(1)	2(1)
C(6)	32(1)	26(1)	28(1)	4(1)	6(1)	5(1)
C(7)	36(1)	26(1)	30(1)	5(1)	-3(1)	2(1)
N(3)	45(1)	25(1)	23(1)	2(1)	-6(1)	1(1)
C(8)	27(1)	29(1)	24(1)	4(1)	1(1)	-1(1)
O(2)	48(1)	35(1)	26(1)	4(1)	-9(1)	-6(1)
O(3)	42(1)	22(1)	23(1)	3(1)	-2(1)	1(1)
C(9)	35(1)	21(1)	29(1)	-2(1)	-1(1)	-1(1)
C(10)	43(1)	36(1)	58(2)	10(1)	-8(1)	-12(1)
C(11)	53(2)	45(1)	45(1)	-8(1)	9(1)	8(1)
C(12)	60(2)	26(1)	39(1)	4(1)	-6(1)	3(1)

Table 67: Anisotropic displacement parameters ($Å^2$ x 10^3) for **179**

Note the anisotropic displacement factor exponent takes the form:

$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	x	y	z	U(eq)
H(2A)	4191	7948	2286	43
H(2B)	3379	7690	1677	43
H(1)	2983(13)	7611(16)	3311(19)	48
H(4A)	4665	6676	5423	64
H(4B)	4378	7797	5377	64
H(4C)	4832	7387	4388	64
H(5A)	3424	6012	5492	57
H(5B)	2767	6300	4517	57
H(5C)	3078	7102	5464	57
H(6A)	4313	5082	4570	34
H(6B)	4520	4856	3300	34
H(7A)	3035	4682	3804	37
H(7B)	3358	4253	2685	37
H(3)	3806(12)	3491(16)	4835(19)	48
H(10A)	2502	628	4208	70
H(10B)	2820	-211	3435	70

H(10C)	2672	881	2925	70
H(11A)	4642	804	3585	71
H(11B)	4009	993	2537	71
H(11C)	4150	-101	3048	71
H(12A)	3476	394	5764	64
H(12B)	4319	510	5564	64
H(12C)	3865	-449	5088	64

Table 68: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **179**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(2)#1	0.88(2)	2.32(2)	3.157(2)	160(2)
N(3)-H(3)...O(1)#2	0.85(2)	2.08(2)	2.902(2)	163(2)

Table 69: Hydrogen bonds for **179** [Å and °]

Note Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,y+1/2,-z+1/2 #2 x,-y+1,z+1/2

5.1.8 Benzyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethyl-4-oxoimidazolidine-1-carboxylate 180

Identification code	jm124
Empirical formula	C20 H29 N3 O5
Formula weight	391.46
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.6472(11) Å, α = 90°
	b = 9.2581(9) Å, β = 103.884(2)°
	c = 22.017(3) Å, γ = 90°
Volume	2106.9(4) Å^3

Z	4
Density (calculated)	1.234 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	840
Crystal size	0.42 x 0.20 x 0.05 mm^3
Crystal description	colourless cut
Theta range for data collection	1.91 to 26.48°.
Index ranges	-13<=h<=13, -11<=k<=11, -27<=l<=27
Reflections collected	18338
Independent reflections	4348 [R(int) = 0.0368]
Completeness to theta = 26.48°	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9956 and 0.9635
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4348 / 0 / 256
Goodness-of-fit on F^2	1.032
Final R indices [I>2σ(I)]	R1 = 0.0365, wR2 = 0.0849
R indices (all data)	R1 = 0.0526, wR2 = 0.0928
Largest diff. peak and hole	0.201 and -0.170 $e.Å^{-3}$

Table 70: Crystal data and structure refinement for **180**

Atom	x	y	z	U(eq)
O(1)	712(1)	5745(1)	2251(1)	33(1)
C(1)	460(1)	6927(1)	2001(1)	25(1)
C(2)	1105(1)	8329(1)	2234(1)	26(1)
N(1)	602(1)	9307(1)	1716(1)	24(1)
C(3)	-527(1)	8706(1)	1255(1)	24(1)
C(4)	-370(1)	8812(2)	588(1)	32(1)
C(5)	-1784(1)	9411(2)	1316(1)	30(1)
N(2)	-443(1)	7194(1)	1471(1)	25(1)
C(6)	-1230(1)	6021(1)	1138(1)	28(1)

C(7)	-463(1)	5111(1)	775(1)	32(1)
N(3)	-1100(1)	3761(1)	560(1)	34(1)
C(8)	-2113(1)	3710(1)	62(1)	28(1)
O(2)	-2613(1)	4762(1)	-227(1)	38(1)
O(3)	-2477(1)	2323(1)	-63(1)	32(1)
C(9)	-3595(1)	1961(2)	-577(1)	35(1)
C(10)	-3368(2)	2450(2)	-1200(1)	44(1)
C(11)	-3611(2)	331(2)	-545(1)	54(1)
C(12)	-4812(2)	2615(2)	-449(1)	56(1)
C(13)	952(1)	10708(1)	1727(1)	28(1)
O(4)	501(1)	11608(1)	1334(1)	39(1)
O(5)	1910(1)	10967(1)	2242(1)	33(1)
C(14)	2520(1)	12375(2)	2281(1)	37(1)
C(15)	3678(1)	12352(1)	2002(1)	31(1)
C(16)	4730(1)	11474(2)	2259(1)	36(1)
C(17)	5823(1)	11497(2)	2024(1)	43(1)
C(18)	5872(2)	12402(2)	1530(1)	47(1)
C(19)	4822(2)	13258(2)	1266(1)	48(1)
C(20)	3729(2)	13226(2)	1500(1)	39(1)

Table 71: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) of **180**

Note U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

O(1)-C(1)	1.2251(15)	O(1)-C(1)	1.2251(15)
C(1)-N(2)	1.3448(16)	C(1)-N(2)	1.3448(16)
C(1)-C(2)	1.5006(18)	C(1)-C(2)	1.5006(18)
C(2)-N(1)	1.4551(16)	C(2)-N(1)	1.4551(16)
N(1)-C(13)	1.3477(17)	N(1)-C(13)	1.3477(17)
N(1)-C(3)	1.4827(16)	N(1)-C(3)	1.4827(16)
C(3)-N(2)	1.4745(16)	C(3)-N(2)	1.4745(16)
C(3)-C(4)	1.5209(18)	C(3)-C(4)	1.5209(18)
C(3)-C(5)	1.5235(18)	C(3)-C(5)	1.5235(18)
N(2)-C(6)	1.4576(16)	N(2)-C(6)	1.4576(16)

C(6)-C(7)	1.5264(19)	C(6)-C(7)	1.5264(19)
C(7)-N(3)	1.4465(17)	C(7)-N(3)	1.4465(17)
N(3)-C(8)	1.3411(17)	N(3)-C(8)	1.3411(17)
C(8)-O(2)	1.2146(16)	C(8)-O(2)	1.2146(16)
C(8)-O(3)	1.3502(16)		

Table 72: Bond Lengths in Å for **180**

O(1)-C(1)-N(2)	125.95(12)	O(1)-C(1)-N(2)	125.95(12)
O(1)-C(1)-C(2)	125.90(12)	O(1)-C(1)-C(2)	125.90(12)
N(2)-C(1)-C(2)	108.15(11)	N(2)-C(1)-C(2)	108.15(11)
N(1)-C(2)-C(1)	102.56(10)	N(1)-C(2)-C(1)	102.56(10)
C(13)-N(1)-C(2)	122.45(11)	C(13)-N(1)-C(2)	122.45(11)
C(13)-N(1)-C(3)	123.25(10)	C(13)-N(1)-C(3)	123.25(10)
C(2)-N(1)-C(3)	112.88(10)	C(2)-N(1)-C(3)	112.88(10)
N(2)-C(3)-N(1)	99.17(9)	N(2)-C(3)-N(1)	99.17(9)
N(2)-C(3)-C(4)	111.17(11)	N(2)-C(3)-C(4)	111.17(11)
N(1)-C(3)-C(4)	112.18(11)	N(1)-C(3)-C(4)	112.18(11)
N(2)-C(3)-C(5)	111.41(10)	N(2)-C(3)-C(5)	111.41(10)
N(1)-C(3)-C(5)	111.34(10)	N(1)-C(3)-C(5)	111.34(10)
C(4)-C(3)-C(5)	111.07(11)	C(4)-C(3)-C(5)	111.07(11)
C(1)-N(2)-C(6)	120.33(11)	C(1)-N(2)-C(6)	120.33(11)
C(1)-N(2)-C(3)	115.44(10)	C(1)-N(2)-C(3)	115.44(10)
C(6)-N(2)-C(3)	124.19(10)	C(6)-N(2)-C(3)	124.19(10)
N(2)-C(6)-C(7)	111.07(11)	N(2)-C(6)-C(7)	111.07(11)
N(3)-C(7)-C(6)	112.35(11)	N(3)-C(7)-C(6)	112.35(11)
C(8)-N(3)-C(7)	121.31(12)	C(8)-N(3)-C(7)	121.31(12)
O(2)-C(8)-N(3)	124.43(13)	O(2)-C(8)-N(3)	124.43(13)
C(18)-C(19)-C(20)	120.03(16)	C(19)-C(20)-C(15)	120.61(15)

Table 73: Bond angles in [^{o}] for **180**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
(1)	39(1)	26(1)	32(1)	8(1)	4(1)	2(1)

C(1)	27(1)	26(1)	23(1)	1(1)	7(1)	2(1)
C(2)	30(1)	26(1)	22(1)	2(1)	2(1)	1(1)
N(1)	25(1)	22(1)	24(1)	1(1)	2(1)	0(1)
C(3)	26(1)	22(1)	23(1)	1(1)	3(1)	-1(1)
C(4)	37(1)	33(1)	25(1)	3(1)	7(1)	-1(1)
C(5)	27(1)	30(1)	33(1)	1(1)	5(1)	1(1)
N(2)	27(1)	22(1)	24(1)	1(1)	3(1)	-1(1)
C(6)	28(1)	25(1)	30(1)	-2(1)	3(1)	-4(1)
C(7)	30(1)	28(1)	36(1)	-8(1)	3(1)	-3(1)
N(3)	37(1)	22(1)	35(1)	-4(1)	-5(1)	1(1)
C(8)	31(1)	25(1)	28(1)	-2(1)	6(1)	-3(1)
O(2)	40(1)	28(1)	40(1)	4(1)	-4(1)	-1(1)
O(3)	38(1)	25(1)	28(1)	-1(1)	-2(1)	-7(1)
C(9)	34(1)	35(1)	30(1)	-4(1)	-1(1)	-10(1)
C(10)	52(1)	48(1)	30(1)	0(1)	1(1)	-1(1)
C(11)	69(1)	36(1)	45(1)	-4(1)	-8(1)	-20(1)
C(12)	35(1)	65(1)	67(1)	-11(1)	12(1)	-14(1)
C(13)	25(1)	24(1)	35(1)	-1(1)	7(1)	0(1)
O(4)	38(1)	25(1)	49(1)	9(1)	1(1)	0(1)
O(5)	28(1)	28(1)	39(1)	-4(1)	2(1)	-6(1)
C(14)	33(1)	27(1)	50(1)	-11(1)	9(1)	-6(1)
C(15)	29(1)	23(1)	37(1)	-8(1)	1(1)	-6(1)
C(16)	34(1)	35(1)	33(1)	-4(1)	-1(1)	0(1)
C(17)	28(1)	46(1)	49(1)	-15(1)	-1(1)	2(1)
C(18)	41(1)	45(1)	58(1)	-18(1)	20(1)	-13(1)
C(19)	62(1)	33(1)	51(1)	-2(1)	20(1)	-8(1)
C(20)	41(1)	28(1)	45(1)	-2(1)	5(1)	-1(1)

Table 74: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **180**

Note the anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$$

Atom	x	y	z	U(eq)
H(2A)	863	8652	2620	32
H(2B)	2059	8247	2319	32
H(4A)	-423	9827	457	48
H(4B)	-1059	8261	308	48
H(4C)	473	8417	568	48
H(5A)	-1807	10415	1172	46
H(5B)	-1832	9391	1755	46
H(5C)	-2520	8882	1060	46
H(6A)	-2002	6427	844	34
H(6B)	-1530	5400	1441	34
H(7A)	-342	5669	410	39
H(7B)	403	4905	1046	39
H(3)	-765(16)	2953(19)	747(8)	51
H(10A)	-2575	2004	-1263	67
H(10B)	-3281	3503	-1200	67
H(10C)	-4104	2157	-1538	67
H(11A)	-2812	-54	-629	81
H(11B)	-4356	-40	-859	81
H(11C)	-3677	29	-127	81
H(12A)	-4767	3670	-473	83
H(12B)	-4885	2331	-30	83
H(12C)	-5568	2265	-761	83
H(14A)	2793	12675	2725	44
H(14B)	1887	13092	2056	44
H(16)	4697	10853	2598	43
H(17)	6539	10894	2202	51
H(18)	6628	12434	1372	56
H(19)	4850	13870	923	57
H(20)	3005	13810	1314	47

Table 75: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **180**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3)...O(4)#1	0.887(17)	2.049(18)	2.8962(15)	159.4(16)

Table 76: Hydrogen bonds for **180** [Å and °]

Note Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,y+1/2,-z+1/2 #2 x,-y+1,z+1/2

5.2 Selected Spectra

5.2.1 (1*E*/*Z*, 3*E*)-2-Methyl-4-phenyl-1-nitro-buta-1,3-diene 34

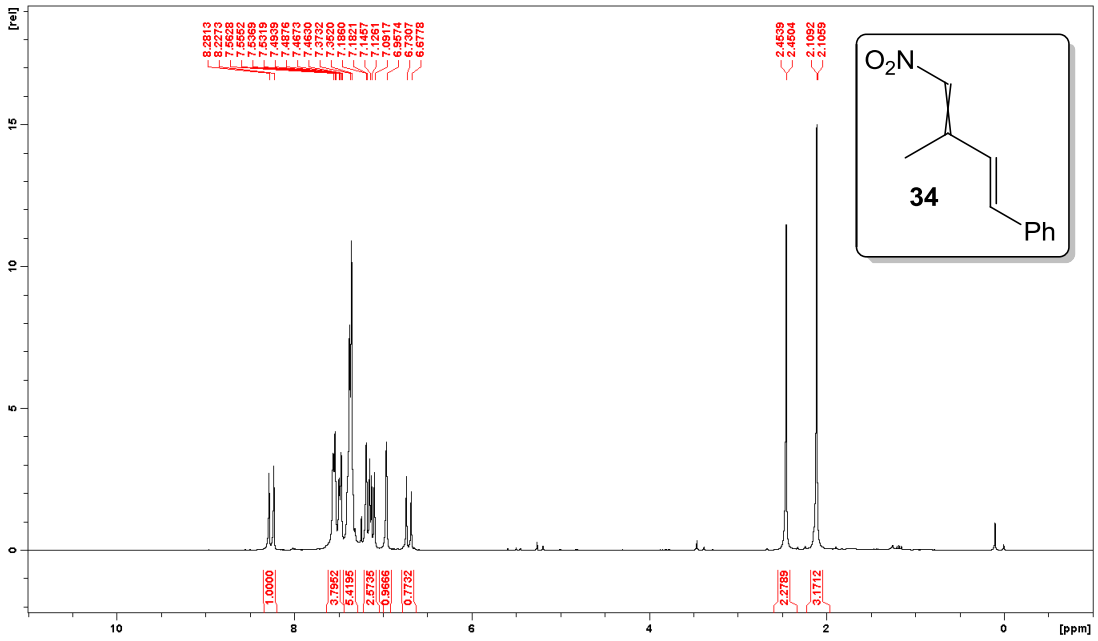


Figure 47: ^{1}H NMR of **34**

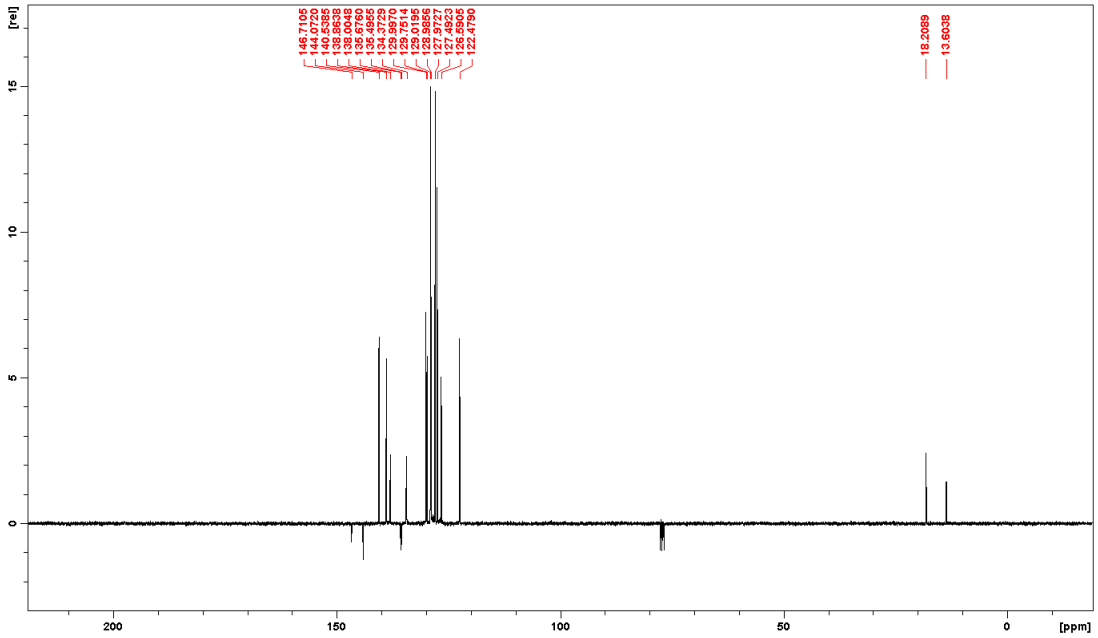


Figure 48: ^{13}CPD DEPT-Q of **34**

5.2.2 (1*E*,3*E*)-4-Phenyl-1,3-bis(phenylsulfonyl)-buta-1,3-diene 39

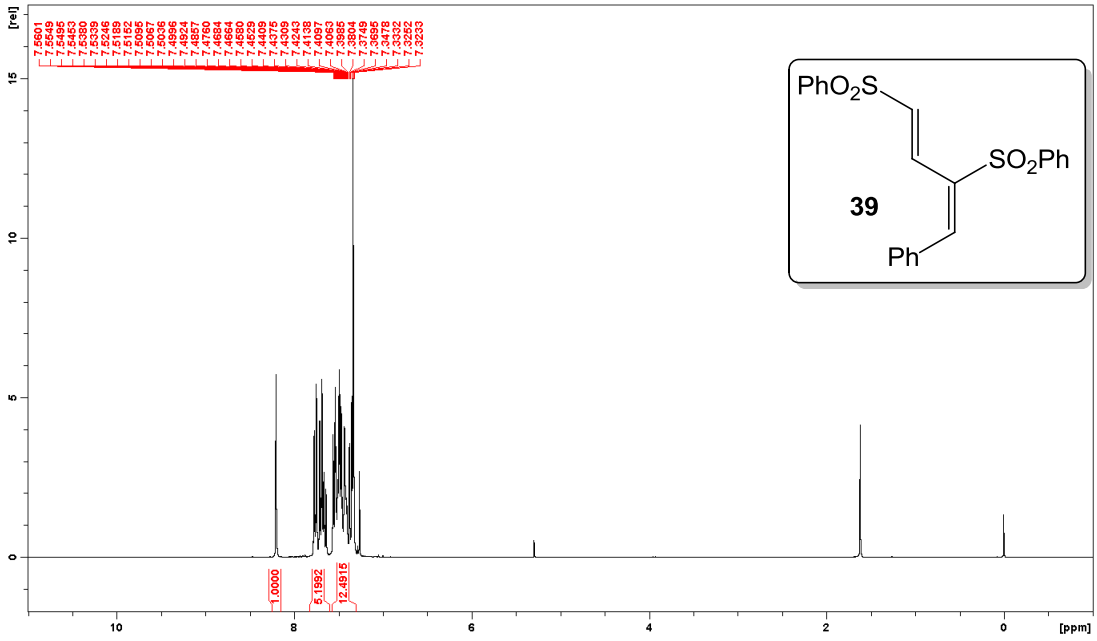


Figure 49: ^{1}H NMR of **39**

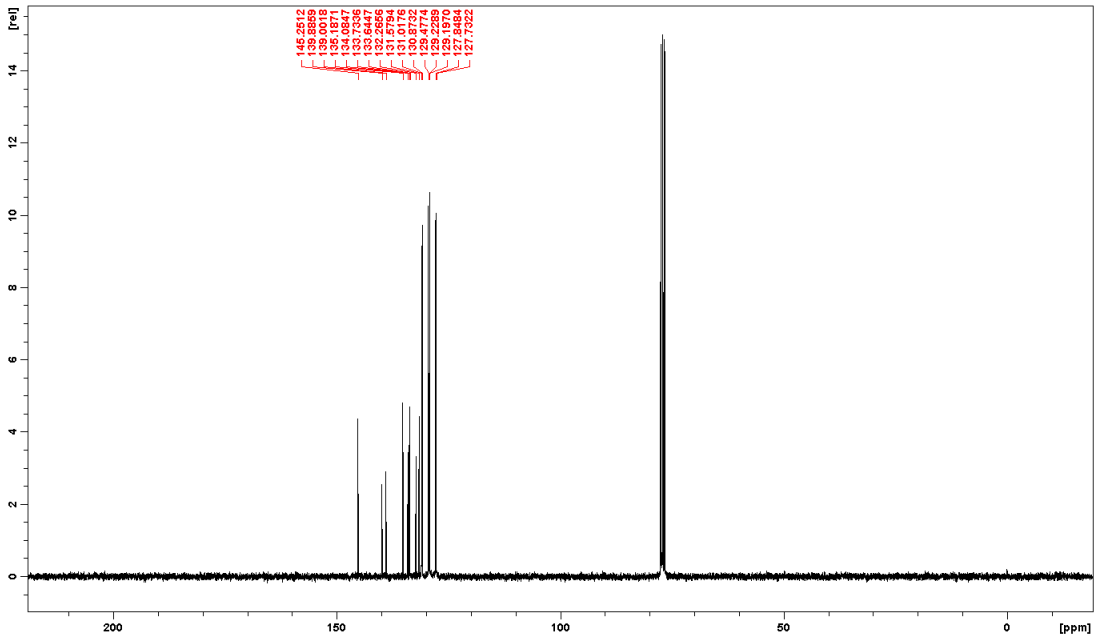


Figure 50: ^{13}CPD NMR of **39**

5.2.3 (1*R*,2*R*)-2-*iso*Propyl-4,6-bis(phenylsulfonyl)-1,2-dihydro-1,1'-biphenyl 46

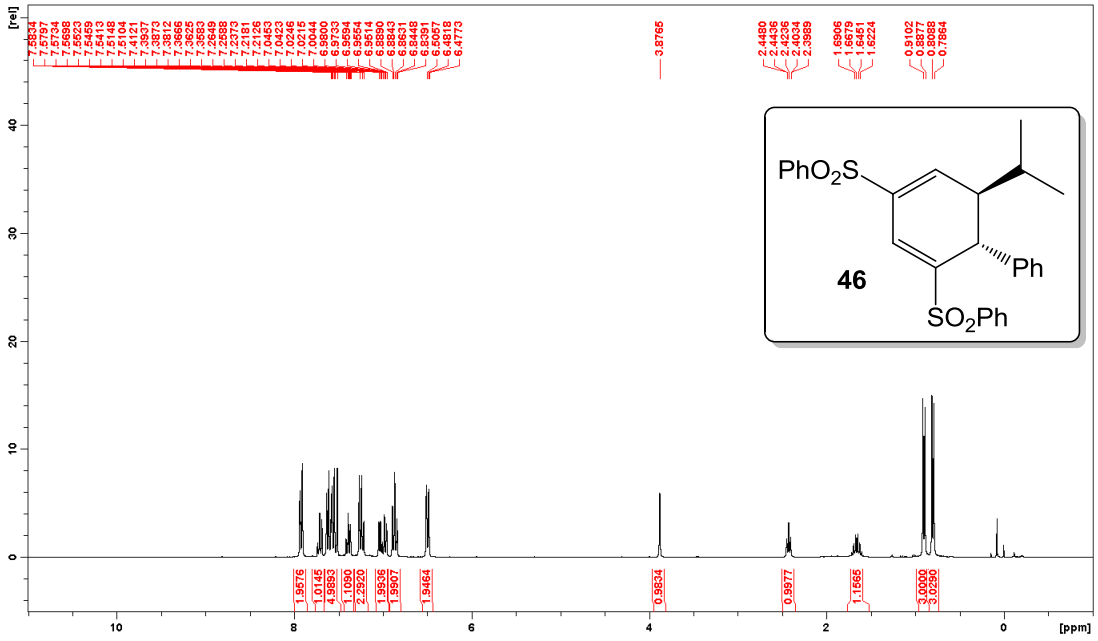


Figure 51: ^{1}H NMR of **46**

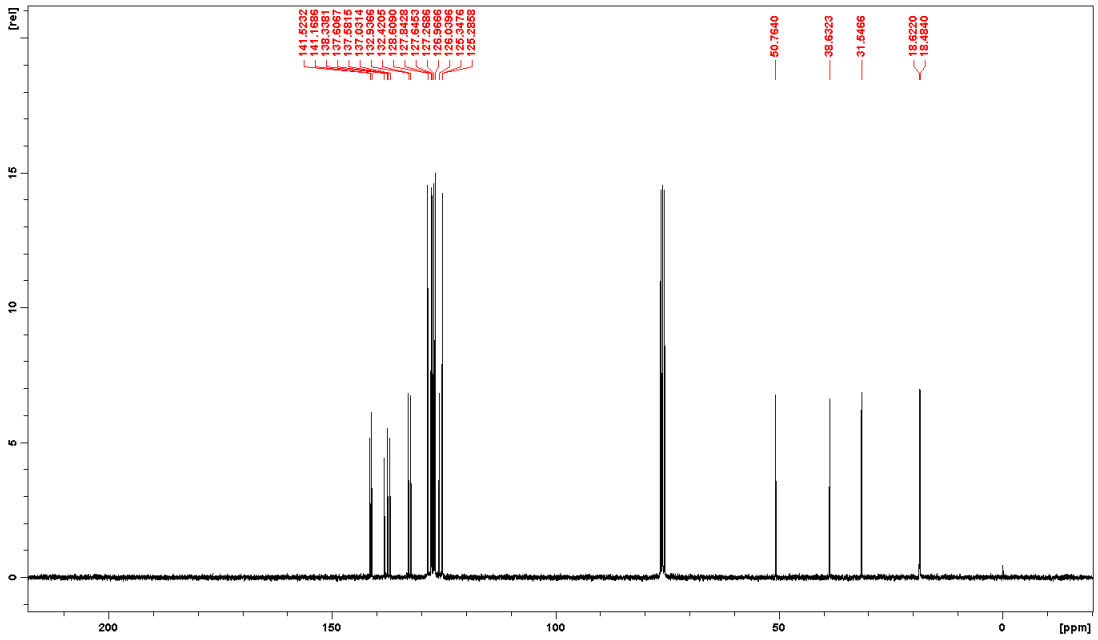


Figure 52: ^{13}CPD NMR of **46**

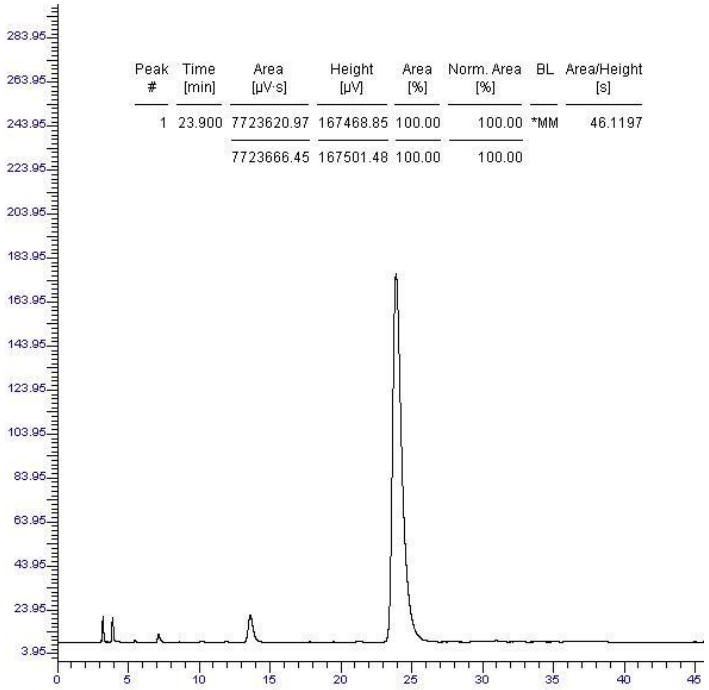


Figure 53: HPLC Trace of enantiopure **46**

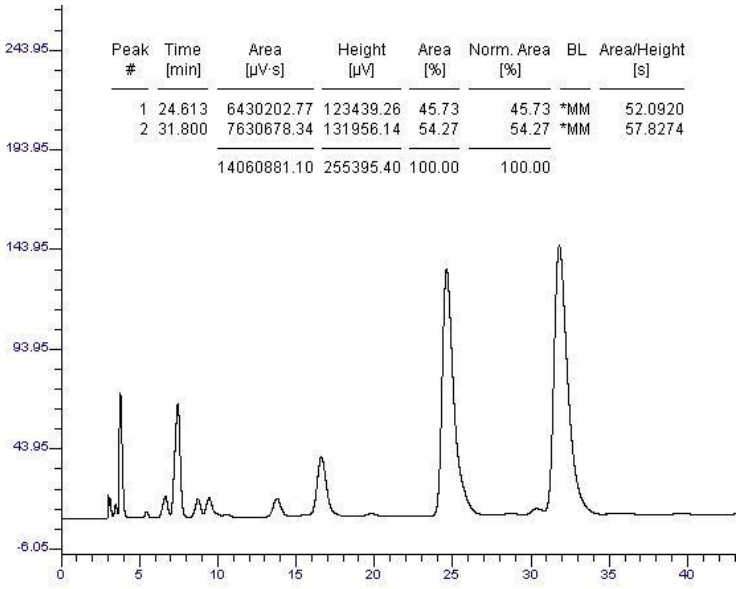


Figure 54: HPLC Trace of racemic **46**

5.2.4 Cascade reaction products 104 + 104b

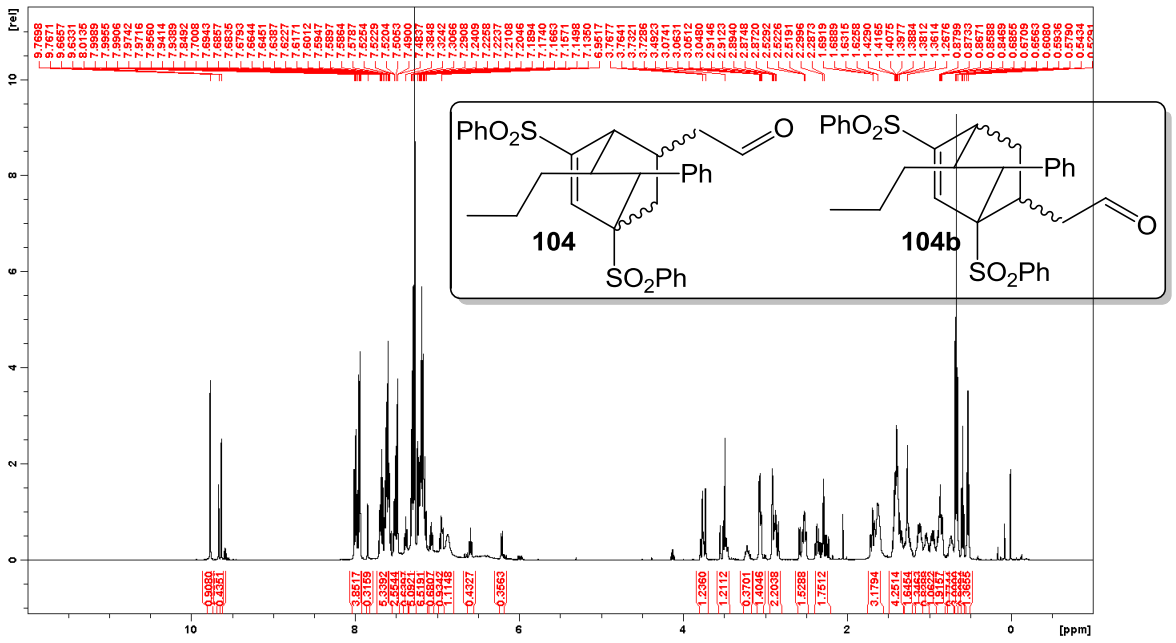


Figure 55: ^{1}H NMR of cascade reaction products **104 + 104b**

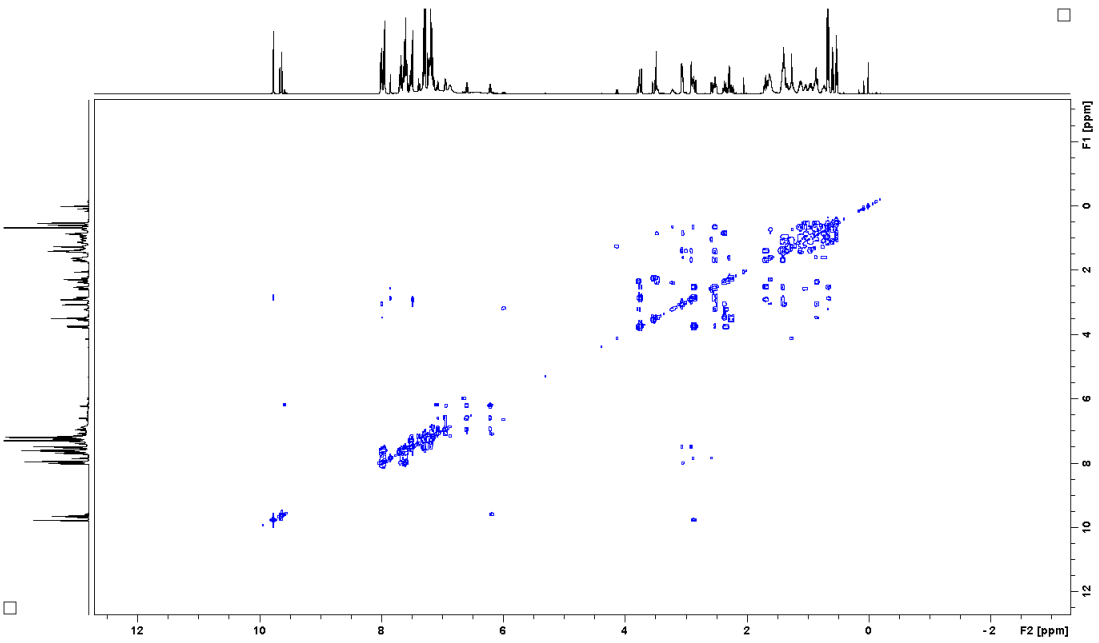


Figure 56: ^{1}H-^{1}H COSY NMR of cascade reaction products **104 + 104b**

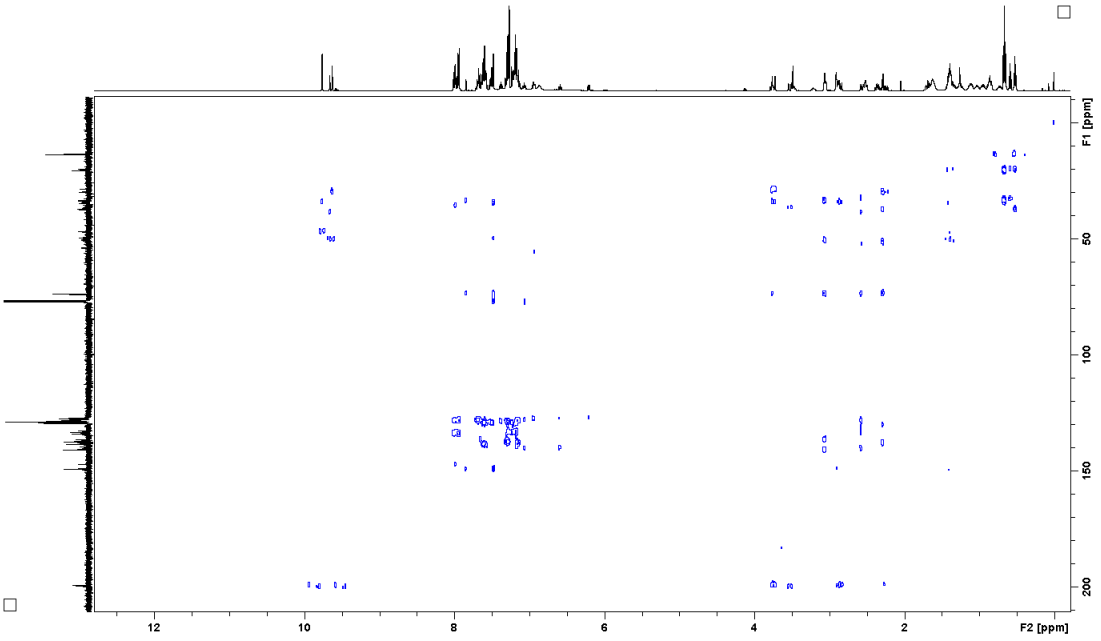


Figure 57: 1H-13C HMBC NMR of cascade reaction products **104 + 104 b**

5.2.5 (1E,3Z)-4-Phenyl-1,3-bis-cyano-buta-1,3-diene 131

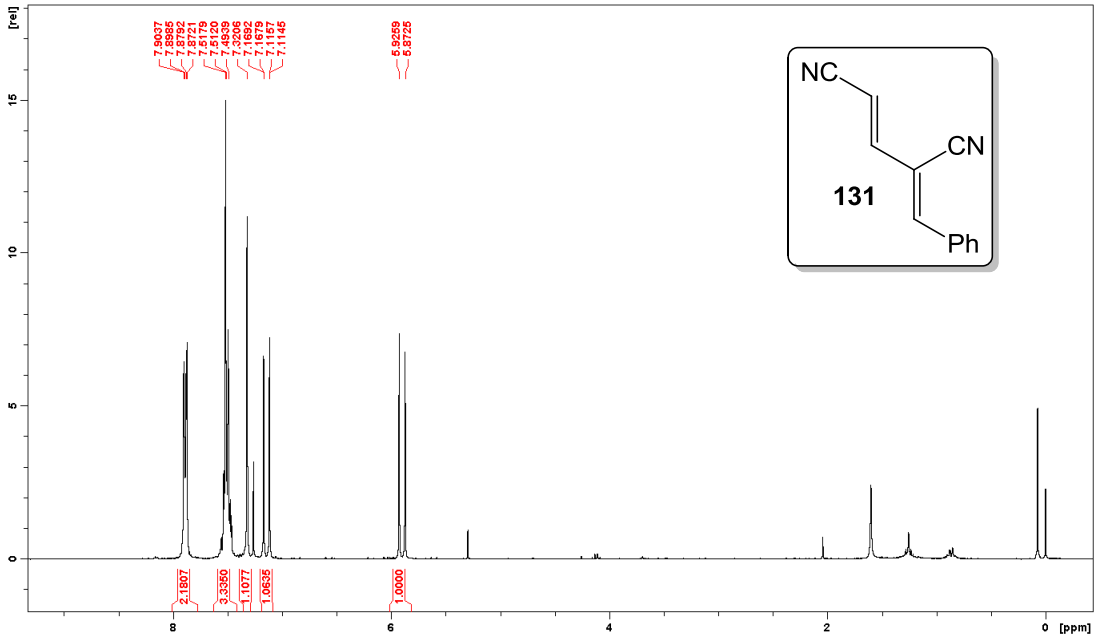


Figure 58: ^{1}H NMR of **131**

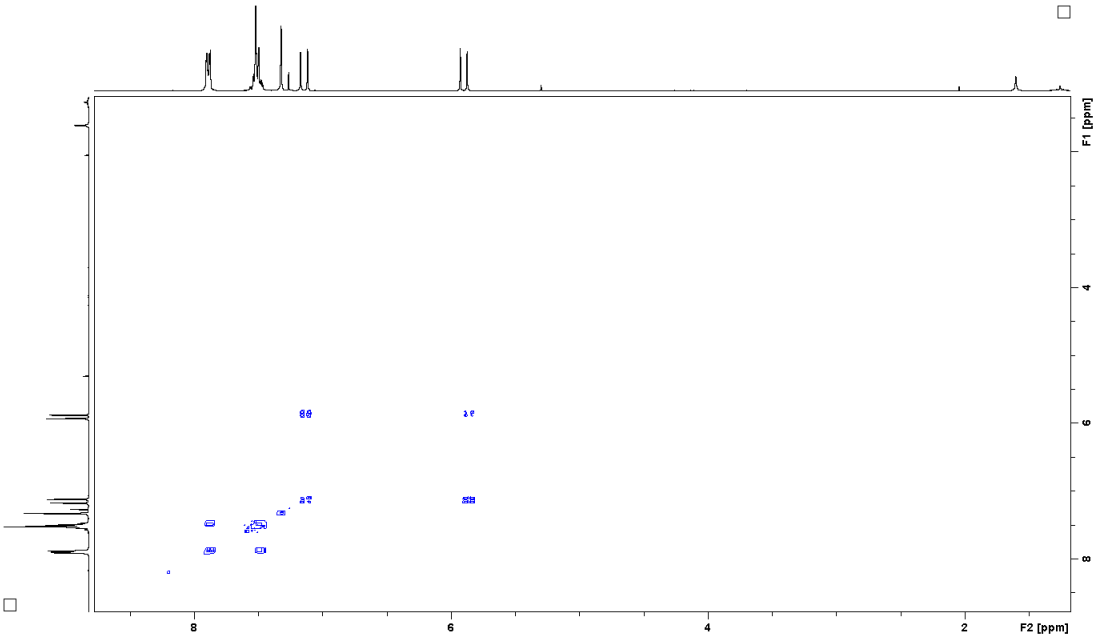


Figure 59: ^{1}H-^{1}H COSY NMR of **131**

5.2.6 6-Propyl-1,6-dihydro-[1,1'-biphenyl]-2,4-dicarbonitrile 150

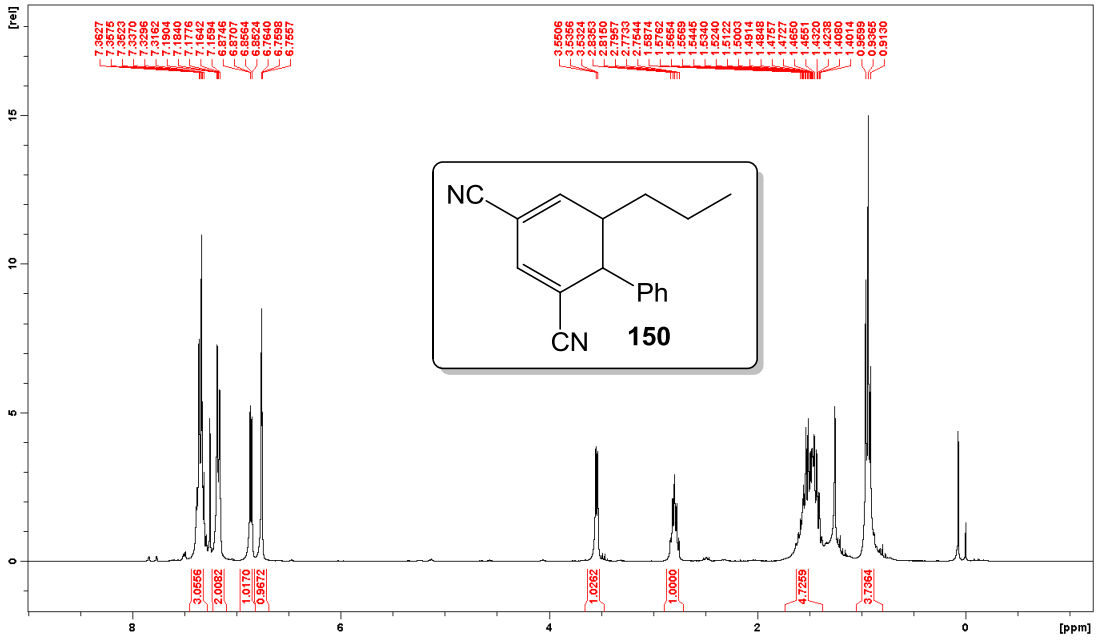


Figure 60: ^{1}H NMR of **150**

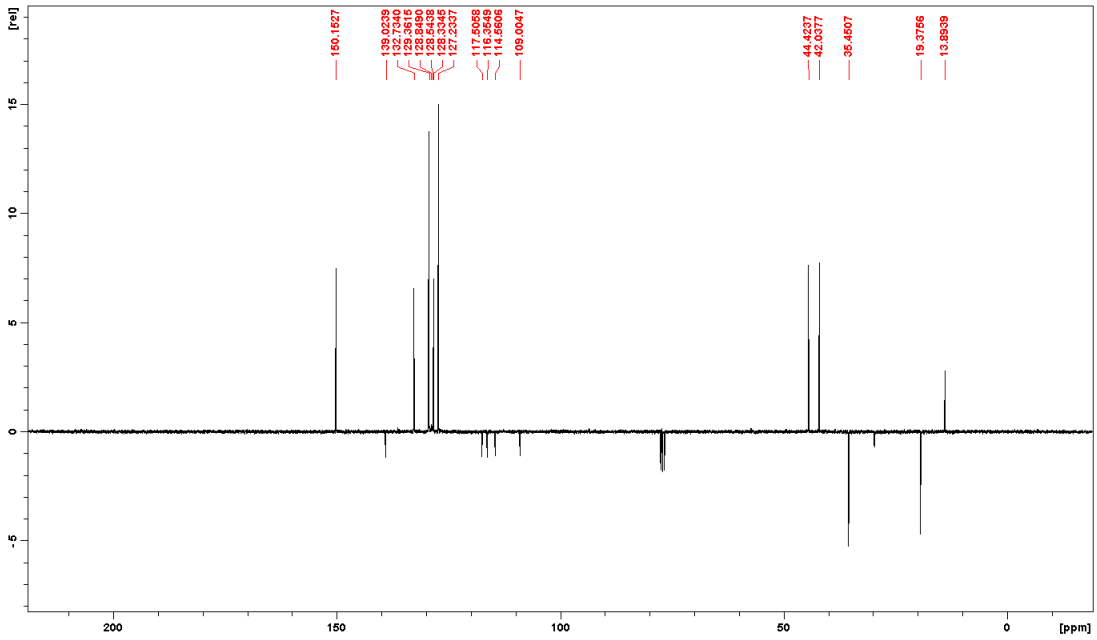


Figure 61: ^{13}CPD DEPT-Q NMR of **150**

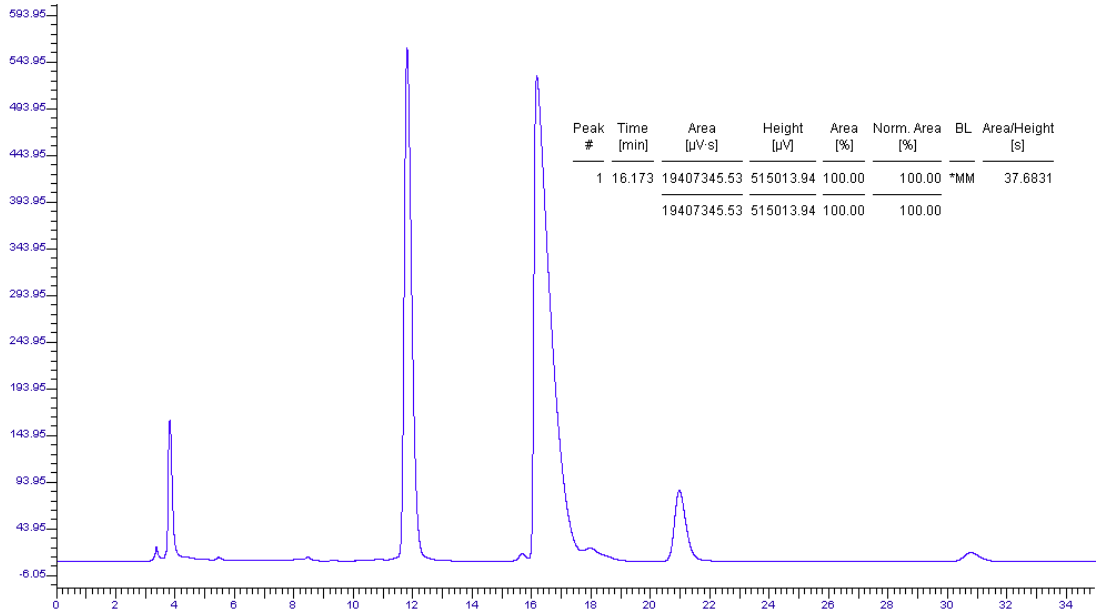


Figure 62: HPLC trace of enantiopure **150**

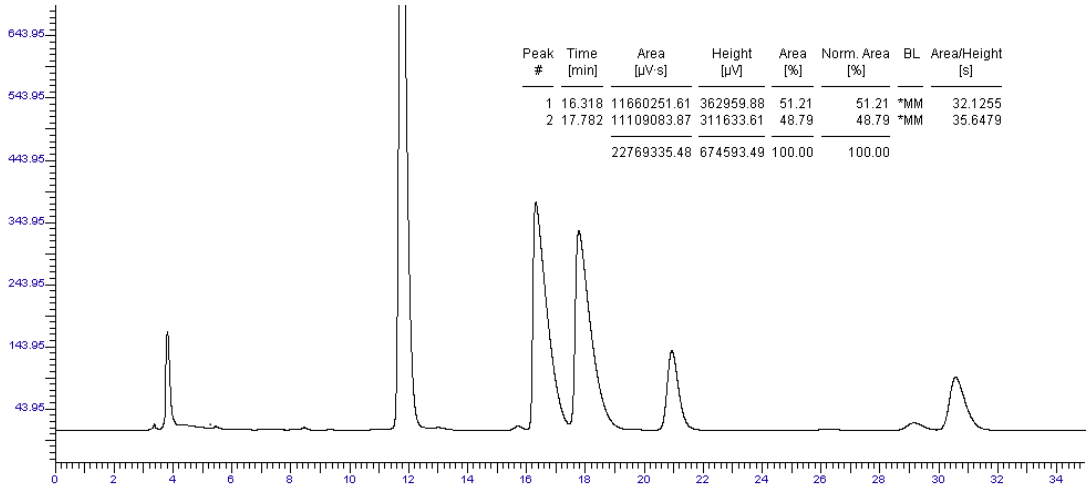


Figure 63: HPLC trace of racemic **150**

5.2.7 N-(2-(Acridin-9-ylamino)ethyl)-2-aminoacetamide 202

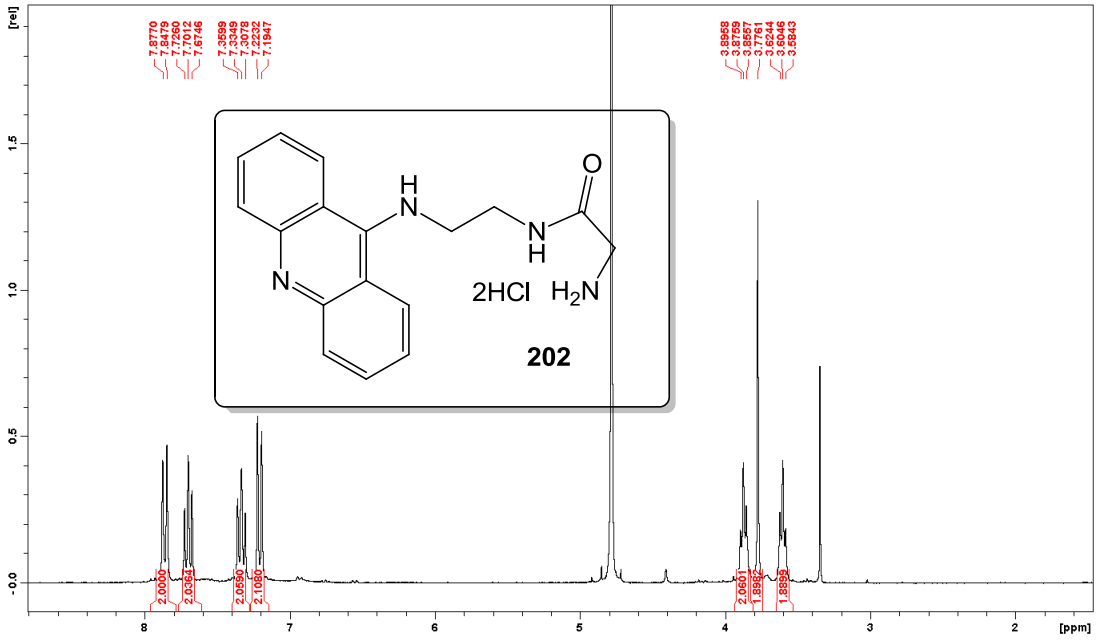


Figure 64: ^{1}H NMR of **202**

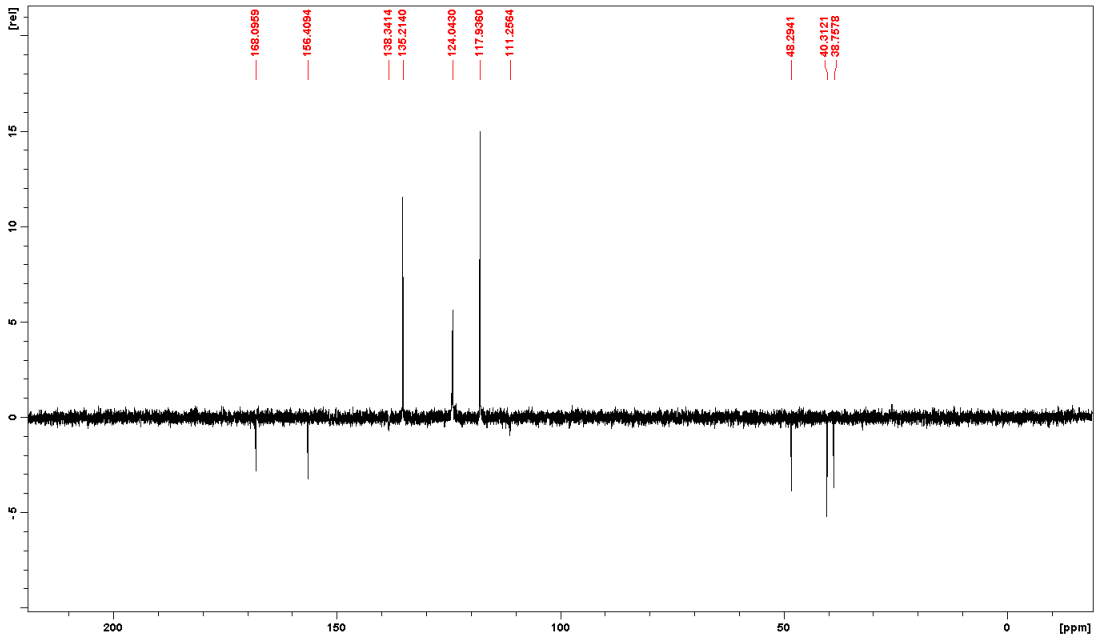


Figure 65: ^{13}CPD DEPT-Q NMR of **202**

5.2.7 3-(2-(Acridin-9-ylamino)ethyl)-2,2-dimethylimidazolidin-4-one 173

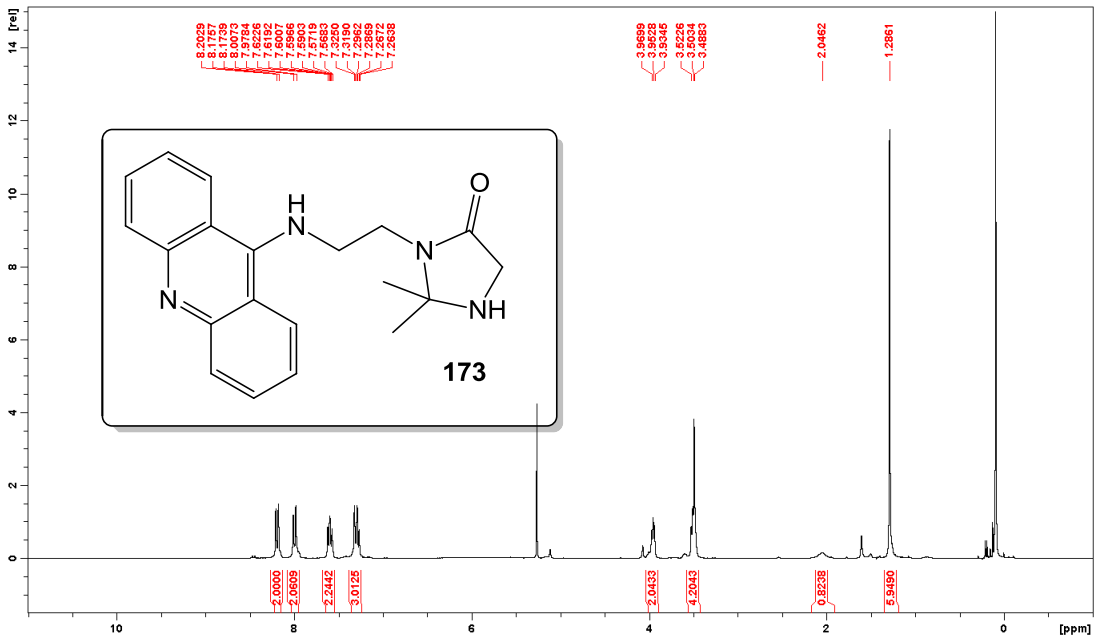


Figure 66: ^{1}H NMR of **173**

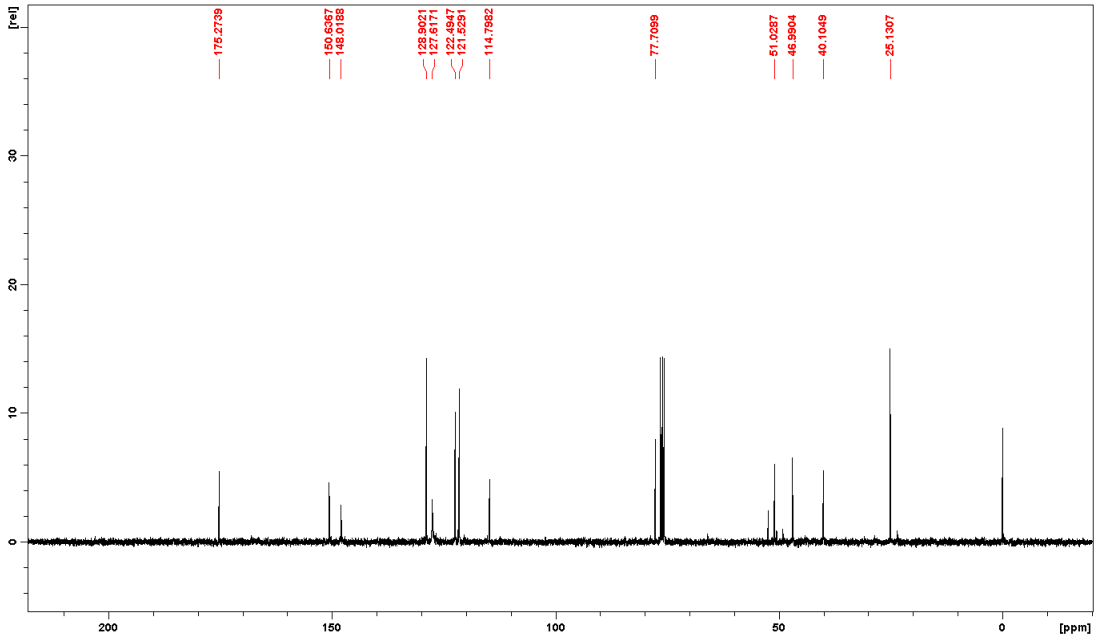


Figure 67: ^{13}CPD NMR of **173**

5.3 Author Publications

VIP Asymmetric Catalysis

DOI: 10.1002/anie.201100804

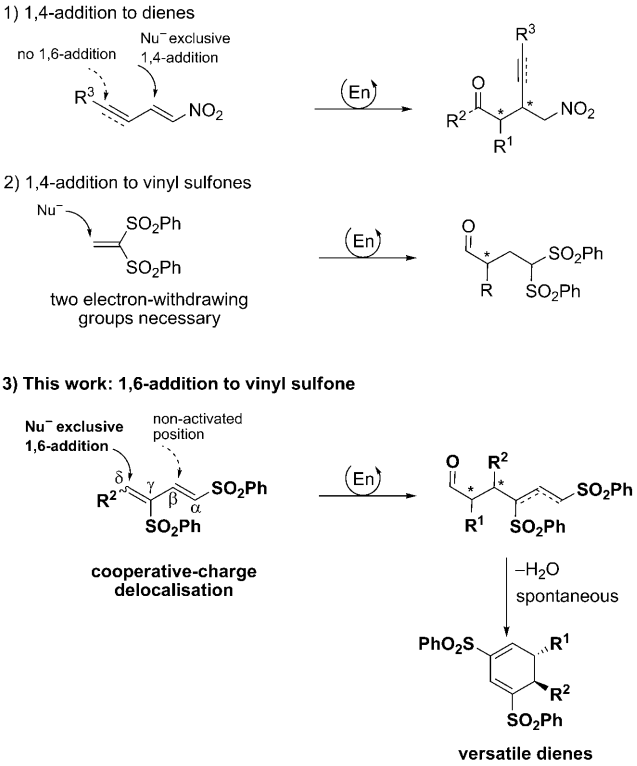
Asymmetric Organocatalytic 1,6-Conjugate Addition of Aldehydes to Dienic Sulfones**

John J. Murphy, Adrien Quintard, Patrick McArdle, Alexandre Alexakis, and John C. Stephens**

Building enantiopure complex molecules simply, in a minimum number of operations, and in an environmentally friendly approach is one of the greatest challenges for synthetic chemistry, and particularly, for chemical industry.[1] Taking into account the requirements for the industrial application of an laboratory-scale reaction (functional group/H_2O tolerance, simple procedures, no extreme temperatures), enamine catalysis has recently appeared as a method of choice to fulfil this ideal goal of reaction efficiency.[2,3]

In this field, the asymmetric conjugate addition to activated alkenes has been extensively studied, as evidenced by the large number of publications on the subject.[4] In contrast, the analogous asymmetric 1,6-addition to extended conjugated systems remains underdeveloped.[5,6] Several groups reported the 1,4-addition to activated dienes in enamine catalysis without any traces of vinylogous 1,6-addition.[7] This higher reactivity of the β position compared to the δ position seems to be a general trend difficult to overcome (Scheme 1). It probably arises from the poor propagation of the electronic effect through the conjugated system. This problem of charge delocalization is in contrast to the principle of vinylogy where the reactivity is in theory extended through the π–π system.[8] In our continuing efforts toward the development of new approaches for the stereoselective construction of enantiopure synthetically useful buildings blocks, we thought about expanding the scope of enamine Michael reactions to 1,6-addition.

We hypothesized that a suitably designed Michael acceptor would be able to promote exclusively the 1,6-addition. To this purpose, we have focused our attention on unsaturated sulfones. The sulfonyl group is known for its electron-withdrawing ability together with high synthetic versatility.[9] It has been shown that a vinyl sulfone with a single activating sulfone group was not sufficiently reactive to promote intermolecular enamine attack and generate a 1,4-conjugate addition. Instead a second sulfone was required to generate the Michael-type addition.[10] As a result, 1,3-bis-(sulfonyl) butadiene (Scheme 1), should be able to promote exclusively the 1,6-addition by the insertion of an appropriately placed second electron-withdrawing group.[11] This butadiene should serve as an exciting application of the exceptional potential of charge delocalization in vinylogous reactions. The sulfone in the α position would not sufficiently activate the β-carbon atom toward enamine addition but would be expected to sufficiently delocalize the charge of the δ-carbon atom thanks to the cooperative effect of the second sulfonyl group, thus promoting the single 1,6-addition (Scheme 1). Herein, we present our results on this unprecedented asymmetric 1,6-addition that leads, in operationally simple conditions, to exceptional levels of diastereo- and enantioselectivities for the formation of highly attractive chiral dienes.



Scheme 1. Proposal for the organocatalytic vinylogous 1,6-addition reaction. En = enamine catalysis.

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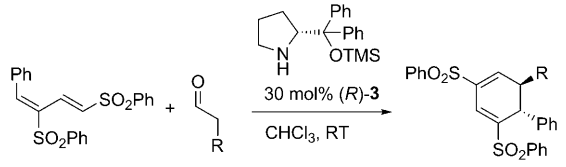
We began our study by synthesizing 1,3-bis(sulfonyl) butadiene substrates **1** by a high-yielding, four-step reaction sequence.[12] To evaluate the feasibility of the asymmetric 1,6-addition, we subjected the sulfonyl diene **1** to the addition of butanal **2a** using 30 mol% of the organocatalyst (*R*)-diphenylprolinol silyl ether **3**. Chloroform was chosen as it easily solubilized the 1,3-bis(sulfonyl) butadiene. As we expected from our proposal (Scheme 1), only the 1,6-addition product was obtained in an excellent yield of 91% using only 2 equivalents of aldehyde (Table 1, entry 1). The observed

Table 1: Scope of aldehydes for the 1,6-addition.



1 **2a–f** (2 equiv) **4a–f**

Entry	Cat.	*t* [h]	R	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* [%][c]
1	(*R*)-**3**	24	Et	91 (**4a**)	1:99	99
2	(*R*)-**3**	24	*n*Pr	98 (**4b**)	1:99	99
3	(*S*)-**3**	24	*n*Pr	98 (**4b**)	1:99	(−) 99[d]
4	(*R*)-**3**	24	allyl	92 (**4c**)	1:99	99
5	(*R*)-**3**	40	*i*Pr	95 (**4d**)	1:99	99
6	(*R*)-**3**	144	(*S*)-citronellal	89[e] (**4e**)	1:99	–
7	(*R*)-**3**	24	Ph	96 (**4f**)	1:99	99

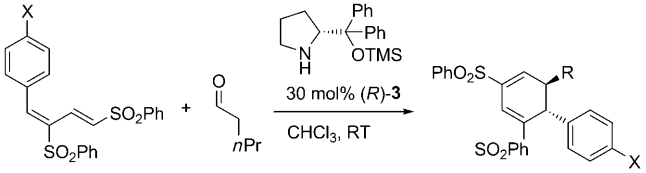
[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy and HPLC analysis. [c] Determined by HPLC on a chiral stationary phase for the *anti* products. [d] Opposite *S*,*S* enantiomer of the product formed. [e] Isolated as a single diastereoisomer as determined by ^{1}H NMR spectroscopy. TMS = trimethylsilyl.

high reactivity and regioselectivity is in total agreement with our preliminary hypothesis of charge delocalization. The intermediate linear product was not observed and spontaneously cyclized to form the conjugated diene **4**. It must be pointed out here that the cyclized product could be isolated from the crude reaction mixture by a very simple procedure. After evaporation of the solvent, the solid was only triturated with ice-cold methanol to directly obtain the pure compound. More remarkably, an exceptional diastereo- and enantiocontrol was observed in this reaction to furnish the 1,6-adduct in an astonishingly high 99% *ee* and 99:1 d.r. while performing the reaction at room temperature. Decreasing the catalyst loading to 10 mol% led to the same excellent stereoselectivities (99% *ee*, 99:1 d.r.) but as expected, a prolonged reaction time was needed to obtain 100% conversion (120 h vs. 24 h, result not shown).

We explored the scope and limitations of this reaction by testing 1,3-bis(phenylsulfonyl)butadiene **1a** with a variety of different sterically demanding aldehydes **2a–f** (Table 1). Gratifyingly, all reactions gave the 1,6-addition product exclusively with no trace of the 1,4-adduct. Furthermore, the products were all isolated as virtually pure stereoisomers. The unbranched aldehydes **2a–c** underwent a fast 1,6-addition in excellent yields, diastereoselectivities, and enantioselectivities (Table 1, entries 1–3). Perhaps most notable, branched aldehydes isovaleraldehyde **2d** and citronellal **2e** reacted efficiently even though longer reaction times where required to reach completion (40 h and 144 h respectively; Table 1, entries 5 and 6). This lower reactivity is consistent with the higher steric hindrance of the substrates. Again we were happy to see that the expected compounds were still formed with perfect stereocontrol even though they required a longer reaction time (compound **4d** and **4e** were isolated as single stereoisomers). Furthermore, this protocol could also be applied for unsaturated phenylacetaldehyde **2f**, that underwent a high-yielding reaction with excellent diastereoselectivity and enantioselectivity (Table 1, entry 7). This attractive synthon should lead to an enantiomerically pure C_2 symmetric diene by sulfone removal.

To fully explore this remarkable transformation, we then continued to investigate the scope of the reaction by testing the 1,6-conjugate addition of valeraldehyde **2b** to a family of 1,3-bis(phenylsulfonyl)butadienes **1a–e** in the presence of 30 mol% of organocatalyst in chloroform (Table 2). A variety

Table 2: Scope of the bis(arylsulfonyl) butadienes.



1a–e **2b** (2 equiv) **4b, 5b–e**

Entry	*t* [h]	X	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* [%][c]
1	24	OMe	75 (**5b**)	1:99	99
2	24	H	98 (**4b**)	1:99	99
3	24	F	81 (**5c**)	1:99	99
4	20	Cl	81 (**5d**)	1:99	99
5	20	Br	70 (**5e**)	1:99	99
6	4	NO_2	75 (**5f**)	1:99	99

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy and HPLC analysis. [c] Determined by HPLC on a chiral stationary phase for the *anti* products.

of different aryl substituents with a range of electronic properties could be used without affecting the overall selectivity of the reaction. All reactions gave greater than 99% conversion by ^{1}H NMR spectroscopy. The yields of the isolated 1,6-addition products were slightly lower in all cases (71 to 81% yield vs. 98% for the phenyl). This outcome probably arises from an increase in the solubility of the final compounds and results in product loss during workup. When the electron-withdrawing properties of the substituents were increased from F, Cl, to Br the reactions were slightly accelerated. The lower electron density of the acceptor **5f** containing a nitro substituent resulted in an impressive increase in reactivity (4 h vs. 24 h to obtain a full conversion; Table 2, entry 6 vs. entry 2). This result is in agreement with a Michael 1,6-addition mechanism and should indicate that the C–C bond formation and not the cyclization is the rate-determining step. This finding is consistent with the fact that no traces of the noncyclized product could be observed when monitoring the reaction by ^{1}H NMR spectroscopy.

In addition, the absolute and relative configuration of both the *R*,*R* adduct and *S*,*S* adduct of **4b** could be determined by X-ray crystallography (Figure 1 and the Supporting Information).[13]

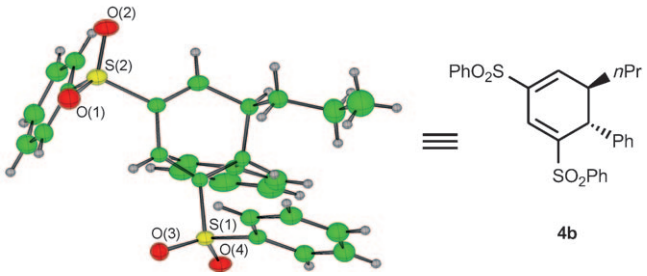
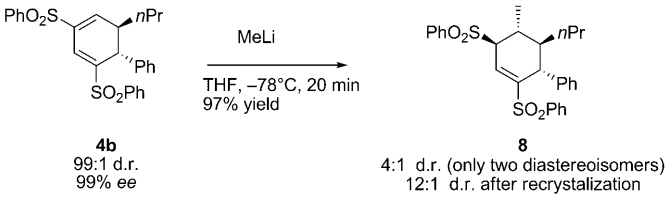


Figure 1. ORTEP drawing of (*R*,*R*)-**4b** with ellipsoids at 20% probability.

Despite the high synthetic potential of the disclosed reaction, it is also highly interesting in terms of mechanism. Although further experimentation is needed to have a complete understanding of the reaction mechanism, a plausible stepwise mechanism can be proposed (Scheme 2). The absolute configuration of the products is consistent with previous results obtained in 1,4-addition to other Michael acceptors catalyzed by catalyst **3**.[14] The acyclic synclinal transition-state model, as described by Seebach and Goliński, could be applied to the 1,6-conjugate addition of aldehydes to 1,3-bis(sulfonyl) butadienes and explains the observed high levels of stereoselectivities.[15] Steric repulsion away from the bulky groups of the pyrrolidine ring promotes the selective attack of the *Re* face of the *E-trans* enamine and the *Re* face of the Michael acceptor forming **6**. Previous studies have described a similar model for the 1,4-addition of aldehydes to vinyl sulfones,[10a,b] nitroolefins,[16] and vinyl phosphonates.[17] Even though this classical model can rationalize the observed stereoselectivity, several aspects still need to be addressed. The question on whether the catalyst is involved in the cyclization and in promoting the elimination is still not clear. This is more plausible given the fact that no linear product is observed, which implies that the cyclization/elimination steps are fast with the catalyst still involved. Despite the preliminary evidence for a 1,6-addition, a possible [4+2] cycloaddition cannot be ruled out and further investigations should shed light on these interesting problems.[11,18]

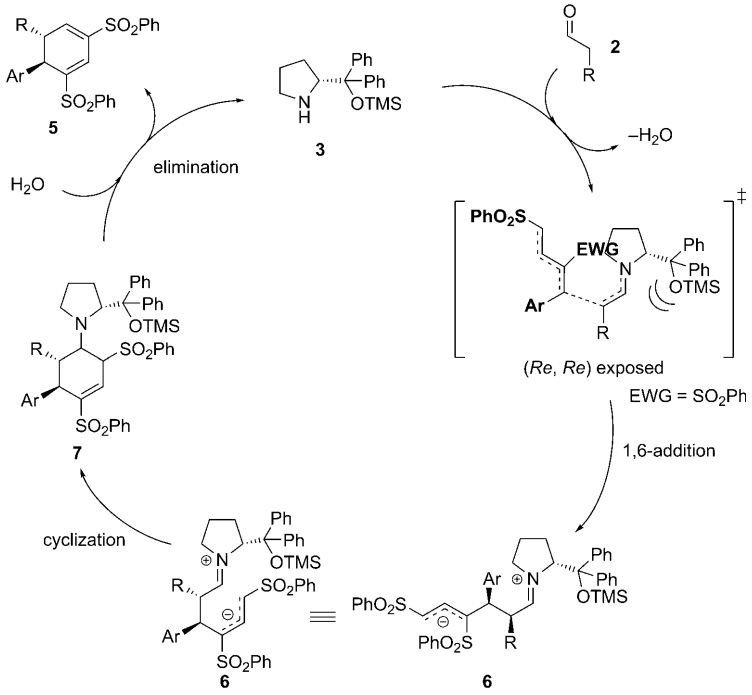
The products obtained through the 1,6-conjugate addition/condensation reaction are highly interesting building blocks. To illustrate the synthetic utility of this method the adduct **4a** was converted into **8** in excellent 97% yield through another conjugate addition of methyllithium (Scheme 3).



Scheme 3. Addition of MeLi to **4b** for the creation of four contiguous stereogenic centers. THF = tetrahydrofuran.

Perfect regioselectivity and good levels of diasteroselectivities (4:1 d.r.) were obtained for the subsequent creation of two new stereogenic centers in this final molecule containing four contiguous stereocenters. After a simple recrystallization, compound **8** was isolated as a 12:1 mixture of two diasterosiomers in 99% *ee* among the 16 possible stereosiomers. The addition *anti* to the propyl group on the adjacent carbon atom was confirmed using NOE studies and ^{1}H, ^{13}C, DEPT, and HSQC spectra. This result highlights the great potential of the obtained dienes for further transformations by indicating the most electrophilic position in **4b**.

In conclusion we have developed an unprecedented enamine 1,6-addition by exploiting the properties of charge delocalization in 1,3-bis(sulfonyl) butadienes. By appropriately designing a Michael acceptor, unique reactivities were obtained for the formation of highly valuable dienes containing two versatile vinyl sulfones. This remarkable reaction should find its applications in total synthesis thanks to its operational simplicity and to the exceptional levels of stereoselectivities of the final products (typically 99% *ee* and 99:1 d.r.). We are convinced that this activation principle by charge delocalization through the addition of a second electron-withdrawing group should serve as a keystone for the development of new powerful 1,6-



Scheme 2. Proposed mechanism and transition state. EWG = electron-withdrawing group.

addition reactions. Full mechanistic studies as well as further investigations employing ketones and additional 1,6-acceptors are currently being pursued in our laboratories and will be published in due course.

Experimental Section

Typical procedure for the organocatalytic 1,6-addition reaction: Diene (0.2 mmol, 1 equiv) was added to a sample vial containing (*R*)-diphenylprolinol silyl ether (19,5 mg, 0.06 mmol, 0.3 equiv) dissolved in chloroform (0.5 mL), followed by direct addition of the aldehyde (0.4 mmol, 2 equiv). The reaction mixture was then stirred at RT until the reaction was complete (as evident by TLC). The reaction mixture was concentrated under reduced pressure and triturated with ice-cold methanol (2 × 3 mL) to yield the solid pure product.

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