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Studies on the acyloin reaction: development of novel *N*-heterocyclic carbene catalysts

Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

Sarah O'Toole

Under the supervision of

Prof. Stephen Connon

Declaration

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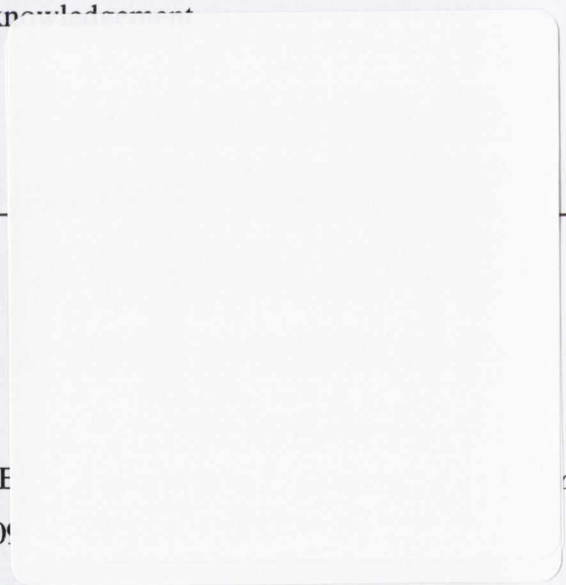

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S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2010.
(DOI 10.1021/jo101791w.)

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Acknowledgements

First and foremost I would like to thank my family. To Mam and Dad, my sincerest thanks to you both for your unwavering support, advice and encouragement and for always believing in me. (Thanks also Dad for all the proof-reading you did!) To Ruth, John, Brenda and Jimmy, thank you for all your support and for helping me along the way. It was always appreciated; even at times when you didn't think so.

I would like to thank my supervisor, Prof. Stephen Connon, for granting me the opportunity to pursue this research under his guidance. Thank you for your support, help and positivity when dealing with unexpected results.

I would like to thank all the members of the Connon labs (both past and present). Thank you for making my time in Trinity College so enjoyable, for the great friends that I have made and making the longest of days seem so short. I would also like to thank the Southern group - Mike and both past and present members. Thanks to Con for help with proof-reading, and in particular to Jen, for doing above and beyond your fair share of proof-reading. I really appreciate all the help, and for being a great friend throughout.

Thanks to all the staff of the Chemistry department for their help along the way. The biggest thanks will have to go to Dr. John O' Brien and Dr. Manuel Ruether for their assistance in running NMR's and bumping many a last-minute sample to the top of the queue! Thanks to all the staff in the Cocker lab and the Phys.Chem lab for the use of the equipment, to Fred Cowzer for the donation of stray compounds, to Martin Feeney for mass specs and to Tom McCabe for x-ray crystallography. For all things administrative thanks to Maria, Tess, Teresa, Gill and Helen.

I would like to thank Róisín, Karen, Siobháin, Fíona and the girls of Avondale Avenue for being great friends throughout and for the (sometimes unwelcomed) distractions from the work.

I would like to give a special thanks to Dan, for your loving support and encouragement and for always being able to turn a frown into a smile. Thank you for putting up with the highs and lows - I don't know how you do it! Lastly, I would like to thank my sister, Jennifer, who has been there for me throughout the Phd and since the beginning. Thank you for always having faith in me, for all your help and reassurance and for always being the pragmatic one! Thank you for your unyielding love and support. I am eternally grateful to you both and words cannot express my gratitude to you for all the help you have given me.

Abstract

The benzoin condensation reaction involves the catalytic dimerisation of two aldehydes to yield acyloins (α-hydroxy ketones), which are highly useful building blocks for the synthesis of heterocycles, natural products, agrochemicals and pharmaceutical drugs. In the 1940s thiazolium salts, in the presence of base, were found to act as catalysts for the benzoin condensation. In an effort to impart stereoselectivity to this reaction various chiral heteroazolium (thiazolium and triazolium) salt precatalysts have been developed over the past few decades, with the first asymmetric benzoin condensation reaction emerging in 1966.

Most heteroazolium salt precatalysts developed to date use a large chiral substituent to induce enantioselectivity in the benzoin reaction. The area of bifunctional catalysis has been relatively unexplored, whereby covalent catalysis occurs within a chiral pocket that benefits from simultaneous formation of the active intermediate (the Breslow intermediate) and hydrogen-bond mediated activation of the acceptor component. With this in mind, we developed a new class of chiral bifunctional triazolium salt organocatalysts which incorporated a hydrogen-bond donating substituent to activate the acceptor substrate (second aldehyde molecule) and control its interaction with the Breslow intermediate within a chiral environment. These materials catalysed enantioselective benzoin condensations and the maximum product enantiomeric excess obtained was 62%. It was unambiguously demonstrated for the first time that the donation of hydrogen bonds by the catalyst is a key control element governing the stereochemical outcome of this bimolecular reaction. Although the bifunctional precatalysts were not of sufficient activity and selectivity to be of use on a process scale, the confirmation that hydrogen bond donation can be exploited to bring about augmented stereocontrol in the asymmetric benzoin condensation reaction offers an alternative to strategies based on the construction of the highly rigid fused systems, which dominate current thinking in this field.

While significant advances in the catalysis of the asymmetric benzoin condensation reaction have been made, we were struck by the absence of a selective carbene-mediated catalytic process capable of promoting the intermolecular reaction between two different

aldehydes in a chemoselective and enantioselective fashion. We subsequently designed series of second generation bifunctional triazolium salt precatalysts which promoted highly chemo- and enantioselective intermolecular crossed acyloin condensation reactions. A key discovery was the use of *o*-substituted aromatic aldehydes that when used in conjunction with aliphatic partners enabled highly chemoselective product control. The methodology was determined to be of very broad scope, providing a swift and easy route to a range of unsymmetrically substituted α-hydroxy ketones.

Abbreviations

BAL	Benzaldehyde lyase
BINAM	2,2'-diamino-1,1'-binaphthalene
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-binaphthyl-2,2'-diol
BFD	Benzoylformate decarboxylase
Boc	*tert*-Butyloxycarbonyl
^{t}BuOK	Potassium *tert*-butoxide
^{t}BuOH	*tert*-Butanol
Cat.	Catalyst
CBS	Corey-Bakshi-Shibata
CBZ	Carboxybenzyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DPPA	Diphenylphosphoryl azide
DVB	Divinylbenzene
ee	Enantiomeric excess
Equiv.	Equivalent
ESR	Electron spin resonance
HIV-PR	Human immunodeficiency virus protease
HPLC	High Performance Liquid Chromatography
HPP	2-hydroxy-1-phenylpropanone
IUPAC	International Union of Pure and Applied Chemistry
KcdA	Keto acid decarboxylase
KHMDS	Potassium hexamethyldisilazane or *bis*(trimethylsilyl)amide
KR	Kinetic resolution

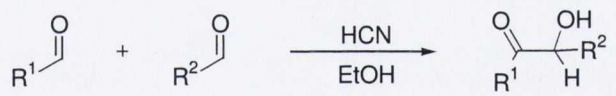
m	*Meta*
MeCN	Acetonitrile
MenD	MenoquinoneD
Mes	Mesityl (2,4,6-trimethyl)-phenyl
MS	Molecular Sieves
NBS	*N*-bromosuccinimide
n.d.	Not determined
NDDP	*Bis*-neodecanoate diaminoyclohexane platinum
NHC	*N*-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
o	*Ortho*
p	*Para*
PAC	Phenyl-acetyl-carbinol
PDC	Pyruvate decarboxylase
PEG	Polyethylene glycol
PEMP	Pentamethylpiperidine
PS	Polystyrene
PTC	Phase Transfer Catalysis
RLS	Rate limiting step
ROMP	Ring Opening Polymerisation
rt	Room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
ThDP	Thiamine diphosphate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCN	Trimethylsilyl cyanide
TTEGDA	Tetraethyleneglycol diacrylate
vic	Vicinal

1.1 The benzoin condensation

1.1.1 Historical perspective

The archetypal benzoin condensation is an organic reaction involving the catalytic dimerisation of two aldehyde molecules to form an α-hydroxy ketone (**3**, Scheme 1.1), alternatively known as an acyloin. The benzoin condensation is recognised as one of the oldest carbon-carbon bond forming reactions in organic chemistry,[1] with the earliest reported investigations dating as far back as 1832 to the experiments of Justus von Liebig and Friedrich Wöhler, using 'bitter almond oil' and potassium hydroxide to promote the reaction.[2] Interestingly, the benzoin condensation is accredited to be the first named reaction in synthetic chemistry. The benzoin condensation is an example of *Umpolung* chemistry, whereby during the course of the reaction, a reversal of the normal polarity or reactivity of a reactant is achieved. In the case of the benzoin condensation an acyl anion equivalent is generated from an aldehyde molecule, which in turn adds to a second aldehyde molecule.

Scheme 1.1 The benzoin condensation; dimerisation of two aldehyde molecules



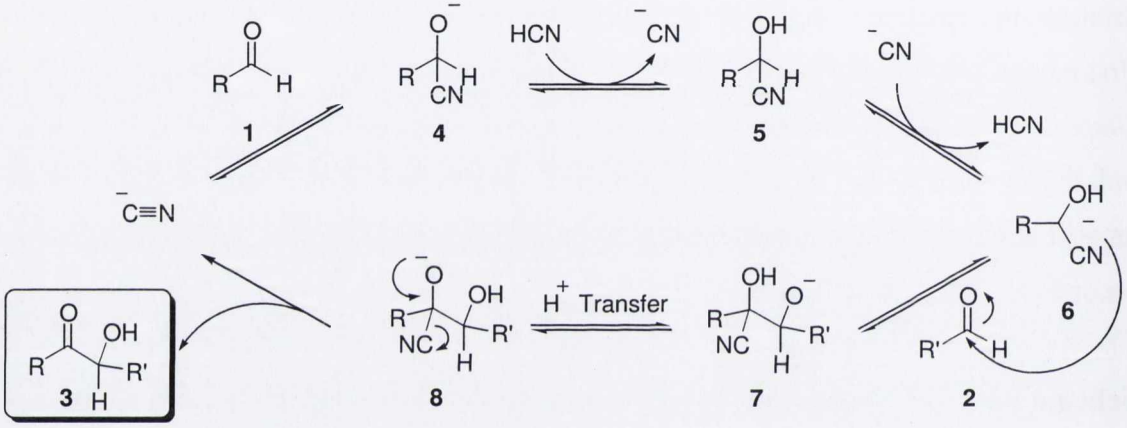
1 **2** **3**

1.1.2 Mechanism of the cyanide-catalysed benzoin condensation

Although the benzoin condensation reaction is 178 years old, a systematic examination of the catalytic nature of the reaction did not emerge for several years after the initial discovery of the process. Seminal work on the catalysis of the benzoin condensation was published by Zinin, a student of Liebig.[3,4] However, it was not until 1903 that A. Lapworth proposed a plausible mechanism for the cyanide-catalysed benzoin condensation.[5] From his investigations, he deduced that cyanohydrin-formation was involved in the cyanide-catalysed process. Lapworth postulated that the benzoin condensation was initiated *via* nucleophilic attack of a cyanide anion at the carbonyl carbon of an aldehyde, forming intermediate **4** (Scheme 1.2). Protonation of the

oxyanion furnishes a cyanohydrin **5**, which upon deprotonation at the carbon centre provided **6**, an acyl anion equivalent, which is a nitrile-stabilised carbanion. This is the key component in the reaction; it is an active aldehyde or *Umpolung* species, whereby a previously electrophilic carbonyl centre has been rendered nucleophilic. Anion **6** adds nucleophilically to a second aldehyde **2**, producing a tetrahedral intermediate. Proton transfer followed by collapse of the oxyanion **8** produces the α-hydroxy ketone **3** and regenerates the cyanide anion which re-enters into the catalytic cycle.

Scheme 1.2 Lapworth's mechanism of the cyanide-catalysed benzoin condensation



1.1.3 Thiamine: Vitamin B_1

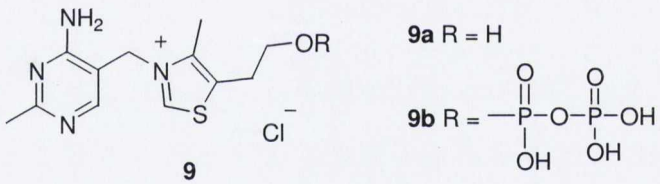
In 1911 C. Funk isolated a substance expressing antineuritic properties from rice bran which he named 'vitamine' due to the presence of an amino group within the substance.[6] It should be noted that Funk is accredited to be the founder of the concept of vitamins or 'vital amines'. Isolation and crystallisation of the active agent within this substance was achieved in 1926.[7] However, its structure was not determined until 1934,[8] by a US chemist, Williams, who shortly after reported the first synthesis of thiamine, the 'sulphur-containing vitamin' in 1936.[9]

Thiamine, or thiamin, is a water soluble vitamin of the B complex, vitamin B_1 (**9a**, Figure 1.1). Thiamine consists of a thiazole ring linked *via* a methylene bridge to a pyrimidine ring. It is synthesised in bacteria, fungi and plants. Humans however, do not produce thiamine and therefore must cover their requirement for this chemical from their

diet. Thiamine is also referred to as "aneurin" (anti-neuritic vitamin).[10] This terminology arose from a disease called Beriberi (vitamin B_1 deficiency) that affects the peripheral nervous system and cardiovascular system. The disease can be fatal if not cured by thiamine administration.[11]

Thiamine, in the form of thiamine diphosphate (ThDP **9b**), is the coenzyme for a number of important biochemical reactions, including the decarboxylation of pyruvic acid to acetaldehyde, the conversion of pyruvic acid to acetoin, the transketolase reaction and also the oxidative decarboxylation of pyruvic acid to 'active acetate'.[12] These reactions are connected in that they proceed *via* an acyl anion equivalent or 'active aldehyde', which adds to an electrophilic centre, such as another aldehyde. In nature, thiamine, being a natural thiazolium salt, utilises a catalytic variant of *Umpolung* reactivity in biochemical processes for nucleophilic acylations.[13]

Figure 1.1 Thiamine and thiamine diphosphate (ThDP)

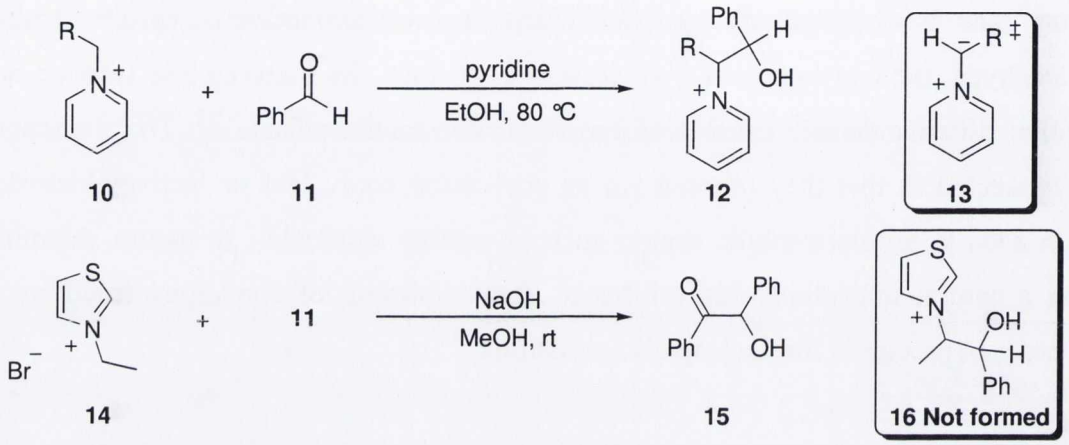


1.1.3.1 Thiamine as a catalyst in the benzoin condensation

Stemming from both the knowledge that ThDP was involved in biochemical reactions that proceeded through *Umpolung* intermediates and the new-found availability of synthetic thiamine, scientists embarked on an investigation of the use of thiamine and other such thiazolium salts in the benzoin condensation. Extensive work by Kröhnke and his colleagues had demonstrated that certain pyridinium compounds (**10**, Scheme 1.3) would react readily with aldehydes in the presence of base *via* the formation of an ylide **13**, forming hydroxy compounds such as **12**.[14] In 1943, Ugai and co-workers observed that thiazolium salts, in the presence of a weak base, could act as catalysts in the benzoin condensation.[15] He viewed this as being reminiscent of the formation of acetoin in the enzymatic decarboxylation of pyruvate. Ugai had expected, based on the outcome of Kröhnke's findings that thiazolium salts would also react with aldehydes.

Unexpectedly, he discovered that heating an alcoholic solution of thiazolium salt **14** with benzaldehyde (**11**), in the presence of one molar equivalent of base, produced not the anticipated compound **16**, but instead benzoin (**15**), an α-hydroxy ketone.

Scheme 1.3 Pyridinium salt and thiazolium salt condensation of aldehydes



Elaboration of Ugai's seminal results followed shortly after, with Mizuhara demonstrating furoin formation from furfural in the presence of thiazolium salts (including thiamine) and a base.[16] Due to the focused attention on the thiazolium ring of ThDP it became well established that vitamin B_1, thiamine, and other thiazolium salts, could convert aldehydes into acyloins in both biological systems[17,18] and in protein-free model systems.[19]

In 1953 Mizuhara revealed that the catalytic activity of thiamine was based on the thiazolium ring incorporated within the molecule.[20] He performed ^{14}C isotope labelling studies using acetaldehyde-1,2-^{14}C and pyruvic acid to verify his supposition.

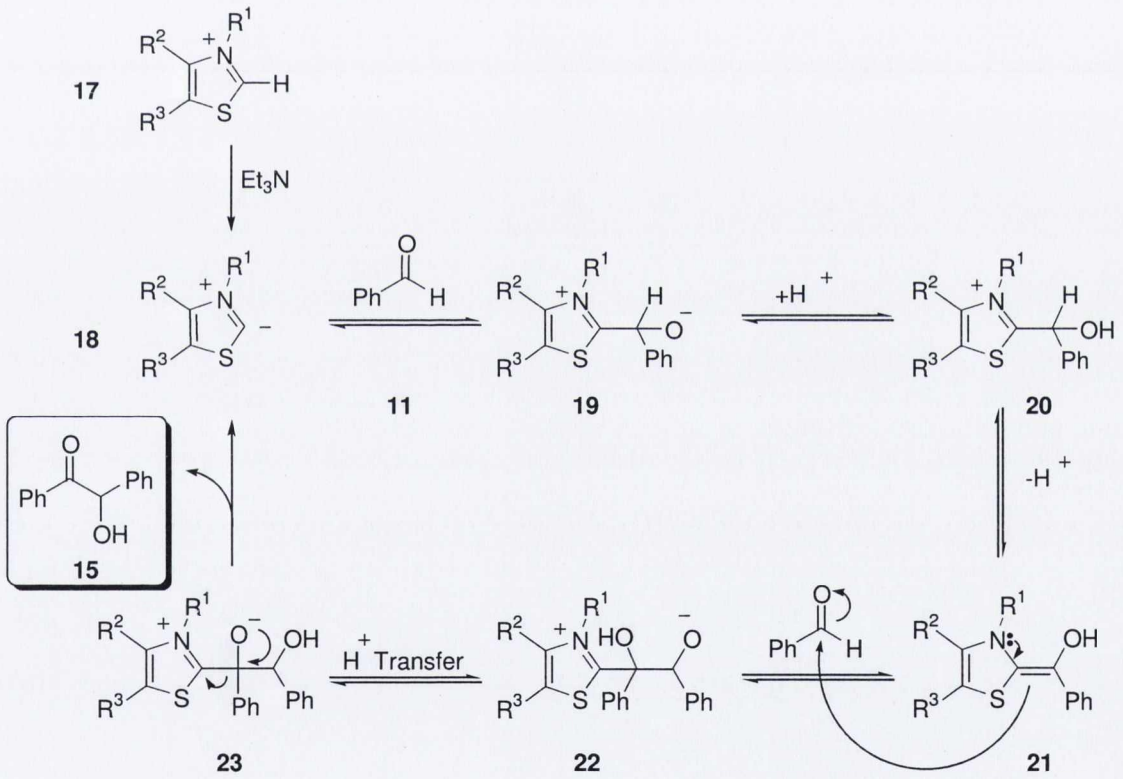
1.1.3.2 Mechanism of the thiazolium salt-catalysed benzoin condensation

There have been many suggestions and hypotheses as to the mechanism of the thiazolium salt-catalysed benzoin condensation. The earliest reported proposal was that of Langenbeck,[21] who suggested that in the decarboxylation of pyruvic acid to acetaldehyde, the amino group of thiamine condensed with pyruvic acid to form a Schiff base. Karrer postulated that the initial step in the same reaction entailed opening of the

thiazole ring to form a thioacetal of pyruvate.[22,23] Of note is an erroneous proposal put forward by R. Breslow in 1956, implicating the *N*-methylene group (joining the pyrimidine and thiazolium rings) as the catalytic moiety of thiamine.[24] This was however quickly disputed and proved to be incorrect.[25]

In 1958, Breslow published a seminal report on the mechanism of the thiazolium salt-catalysed benzoin condensation.[26] He determined that deprotonation of the acidic C-2 proton of the thiazolium ring initiated the reaction process. The mechanism is detailed *vide infra* (Scheme 1.4) using benzaldehyde (**11**) as the substrate aldehyde.

Scheme 1.4 Mechanism of thiazolium salt-catalysed benzoin condensation



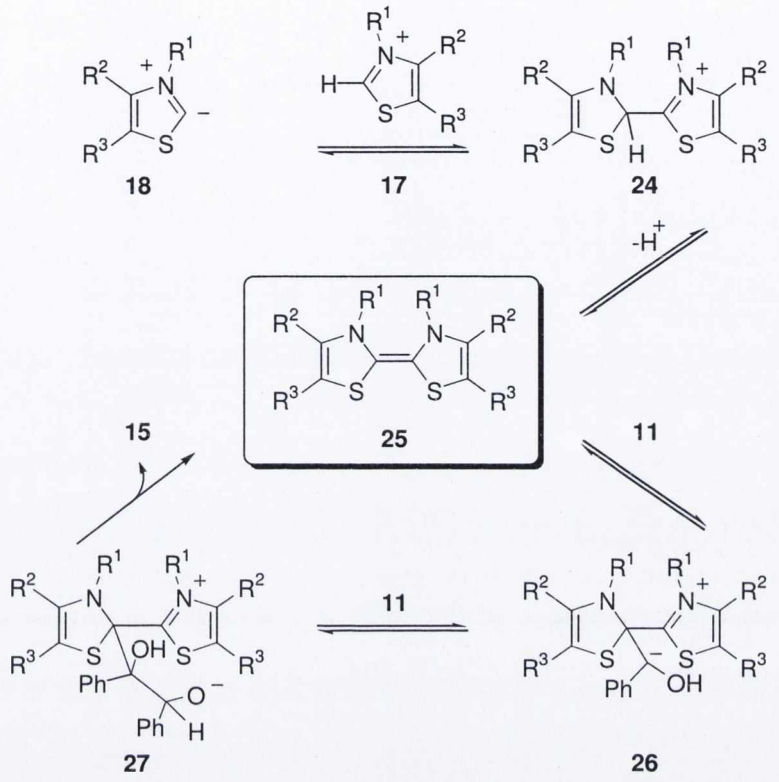
Breslow proposed that deprotonation of the acidic C-2 proton of thiazolium salt **17** *in situ*, using a mild base such a triethylamine, generates ylide **18**, a highly reactive carbene species which is the active catalyst in the benzoin condensation reaction. The carbene ylide performs a nucleophilic attack on benzaldehyde (**11**), forming oxyanion **19**. Proton transfer followed by deprotonation leads to the formation of a resonance-stabilised hydroxyl-enamine **21**. **21** Is an acyl anion equivalent; it is the *Umpolung* species and is

known as the 'Breslow intermediate'. The originally electrophilic carbonyl centre of benzaldehyde has now been converted to a nucleophilic carbon centre. **21** Adds to a second equivalent of benzaldehyde forming oxyanion **22**. Proton transfer and consequent dissociation of intermediate **23** produces benzoin (**15**) and regenerates the catalytic carbene **18** which can re-enter the catalytic cycle. It should be emphasised for clarity that the thiazolium salt acts as a precatalyst, whereas the *in situ*-generated carbene is in fact the true catalyst in the benzoin condensation.

1.1.3.3 Alternative mechanistic proposals

Following Breslow's 1958 landmark publication on the thiazolium salt-catalysed mechanism of the benzoin condensation, several alternative mechanisms were proposed.[27,28] Both groups of Lemal *et al.*[29] and Castells and co-workers[30,31,32] proposed that the benzoin condensation involved the formation of carbene dimers, *bis*(thiazolin-2-ylidene)s, (**25**, Scheme 1.5), that act as *in-situ* generated catalysts for the benzoin condensation. It had been previously determined that thiazolium salts when treated with a strong base in a non-aqueous solvent could form dimers such as **25**.[33] It was also demonstrated that such dimers could act as catalysts in the benzoin condensation.[27] However, conflicting theories were put forward on whether the formation of dimers increased or decreased the rate of benzoin production and also whether or not they contributed to a higher yield of product.[30,34] Lemal differed from Castells in that he proposed that oxyanion **26** (Scheme 1.5) fragmented to produce ylide **18** and the Breslow intermediate **21** (Scheme 1.4, *vide supra*). Enamine **21** would then continue in the reaction process as per Breslow's proposed mechanism in Scheme 1.4. Castells however suggested that no fragmentation took place and the reaction detailed in Scheme 1.5 ensued. Spectroscopic and kinetic investigations have since ruled out this dimer theory.[35,36,37] Breslow's proposal has become widely recognised as the accepted and archetypal mechanism for this reaction.

Scheme 1.5 Proposed mechanism of carbene dimer-catalysed benzoin condensation



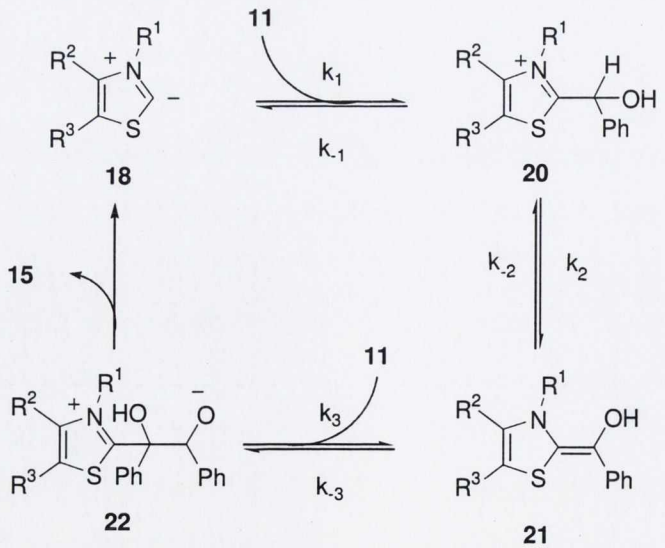
1.1.4 Kinetic studies of the benzoin condensation

The mechanism of the benzoin condensation proposed by Breslow in 1958 (Scheme 1.4, *vide supra*) - the now generally accepted mechanism for the benzoin condensation - is analogous to the reaction mechanism put forward by Lapworth in 1903 for the cyanide-catalysed benzoin condensation (Scheme 1.2). The cyanide-catalysed benzoin condensation has been studied in great detail and rate constant data for all the kinetically significant steps have been available since 1971.[38] However, this was not the case for the thiazolium salt-catalysed benzoin condensation reaction for quite some time. Much ambiguity and diversity was to be found in reports relating to the kinetics of the thiazolium salt-promoted reaction. Breslow, in his refutation of Castell's dimer theory, experimentally proved the reaction to be of first-order kinetics in relation to the thiazolium salt.[35] He stated that this could only be true if the rate-limiting step (RLS) in the reaction process was the reaction of the Breslow enamine intermediate **21** with the second aldehyde equivalent (Scheme 1.4, step **21** - **22**). His results ruled out Castell's dimer theory, as such a mechanism would exhibit second-order kinetics of the

thiazolium salt. Breslow's theory was also later verified by Challa and Pandit.[39] Subsequently, López-Calahorra (originally of Castell's group) published two reports, detailing the reaction to be of second-order kinetics with respect to both the thiazolium salt and benzaldehyde.[40,41] Breslow promptly re-examined the data presented by López-Calahorra and demonstrated that the benzoin condensation is clearly first-order with respect to the thiazolium ion.[36]

In 2001 a more thorough investigation of the kinetic parameters of the thiazolium salt-catalysed benzoin condensation was reported by White and Leeper.[42] Initial-rate studies at low catalyst concentration and variable concentrations of benzaldehyde clarified that the benzoin reaction displays approximately first-order dependence in benzaldehyde. At stoichiometric catalyst loadings, the rate constants were calculated by monitoring reaction component concentrations using ^{1}H NMR spectroscopic techniques. Using combinations of deuteriomethanol (CD_3OD) with benzaldehyde and deuterated benzaldehyde (PhCDO) with methanol Leeper determined three reaction steps within the process to each be partially rate-determining. As outlined in Scheme 1.6, these steps include attack of ylide **18** on the first molecule of benzaldehyde (k_1/k_{-1}), deprotonation of hydroxybenzyl thiazolium **20** to form enolamine **21** (k_2/k_{-2}), and attack of **21** on the second equivalent of benzaldehyde with subsequent benzoin formation (k_3/k_{-3}).

Scheme 1.6 Leeper's kinetic model of the benzoin condensation reaction



Interconversion between the thiazolium salt and ylide **18** is very rapid under these conditions and was not considered as a separate step in the scheme. Immediately after initiation of the reaction a new set of ^{1}H NMR signals was noted, which corresponded to those reported for hydroxybenzyl thiazolium salt **20**.[43] No evidence of formation of enamine **21** was observed, implying that this compound is highly reactive and is consumed very quickly once formed. Similarly, no signals were attributable to the benzoin adduct **22**, thus the kinetic model was simplified by considering the formation of benzoin (**15**) from **21** as a single step. Leeper estimated that none of the three steps outlined above are fully rate-determining and that they are all partially involved in rate-determination. He could not accurately describe the resulting kinetics as first or second-order but concluded that the reaction rate is closer to first-order than second-order within the benzaldehyde concentration range of 0.1-1.7 M.

1.2 Carbenes and *N*-heterocyclic carbenes: a brief introduction

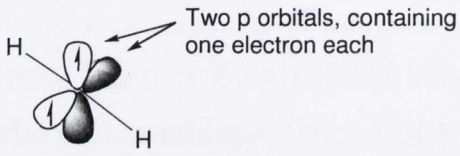
1.2.1 General overview of carbenes

A carbene can be described as a neutral organic molecule containing a divalent carbon atom with six electrons in its valence shell.[44] The prototypical carbene is $:CH_2$, also called methylene; it contains two electrons in each C-H bond and two nonbonding electrons. Attempts to prepare this parent carbene, *via* the dehydration of methanol, date as far back as 1835.[45] Another example of a much studied carbene is $:CCl_2$ or dichlorocarbene, which can be generated *in situ* from chloroform and a strong base. Carbenes were once considered to be chemical curiosities, but through the early work of Curtius,[46] Buchner[47] and Staudinger[48] carbenes have evolved over the last one hundred years to become recognised as important reactive intermediates.[49] Introduced into organic chemistry (revealing a synthetic use of dichlorocarbene) by Doering in 1954,[50] and by Fischer into organometallic chemistry in 1965,[51] carbenes are now involved in many reactions of high synthetic utility.

1.2.2 Singlet vs. triplet carbenes

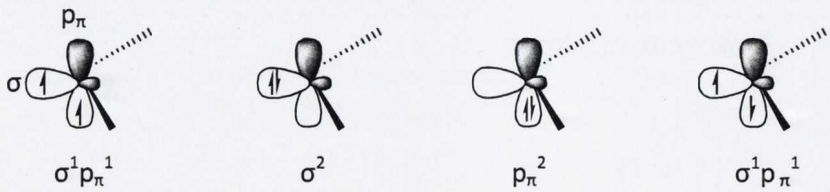
If we consider the archetypal carbene, $:CH_2$, the divalent carbon atom can be either linear or bent, each geometry being describable by a certain degree of orbital hybridisation. A completely linear geometry would indicate a sp-hybridised carbene that would contain two degenerate p orbitals as portrayed in Figure 1.2. The two nonbonding electrons of the carbene would remain unpaired, each singly occupying the two degenerate p orbitals as a result of electron-electron repulsion. However, the linear type of carbene is an extreme case and few carbenes are in fact linear.[52]

Figure 1.2 Depiction of orbitals of a linear carbene



Most carbenes are bent, with bond angles of between 100-150° indicating a possible sp^2-type hybridisation and resulting trigonal conformation.[52] This is because bending of the molecule breaks the degeneracy associated with a linear conformation and the carbene carbon adopts a sp^2-type hybridisation. A sp^2-hybridised carbene would contain three sp^2 orbitals and one p orbital. Upon bending, one of the two degenerate p orbitals (of the linear diagram, Figure 1.2) would become stabilised due to adopting partial s character, thereby becoming one of the three sp^2 orbitals, hence it is classed as the σ orbital. In this situation the p orbital is more commonly known as the p_π orbital. Most carbenes have a non-linear formation and contain two frontier orbitals that are called σ and p_π (as depicted in Figure 1.3).[53]

Figure 1.3 Electronic configuration of triplet and singlet carbenes



Given that a carbene carbon atom has access to six 'valence' electrons, there are two different means by which the nonbonding electrons can be distributed throughout the orbitals. Either the two nonbonding electrons can be unpaired or they can be paired. These two possibilities of electronic arrangement explain the two classes of carbenes that are observed - triplet and singlet carbenes.[53]

A triplet carbene is one in which the two non-bonding electrons are unpaired, each singly occupying the σ and p_π orbitals, and accordingly possess parallel spins (Figure 1.3). The triplet carbene has an associated $\sigma^1 p_\pi^1$ configuration and tends to have bond angles of 130-150°.[54,55] As a result of having unpaired electrons with parallel spins (paramagnetic) they can be detected by electron spin resonance spectroscopy (ESR).[52] In contrast, singlet carbenes contain all paired electrons and are thus undetectable by ESR. The two nonbonding electrons can either occupy the σ orbital (σ^2 configuration, Figure 1.3) or the p_π orbital (p_π^2 configuration). Lastly an excited singlet state with $\sigma^1 p_\pi^1$ configuration can be envisaged. The excited singlet state differs from the triplet state in that the two unpaired electrons have opposite spins. Singlet carbenes have smaller bond angles than triplet carbenes (100-110°) due to steric repulsion caused by the pair of electrons in the σ frontier orbital.[54]

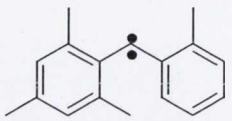
The ground-state spin multiplicity is a fundamental feature of carbenes that dictates their reactivity.[56] Triplet carbenes contain two singly occupied orbitals and are generally regarded as diradicals. Conversely, singlet carbenes feature one filled and one vacant orbital and thus possess an ambiphilic (or 1,1-dipolar) character.

It should also be noted that the electronic and steric properties of substituents attached to the carbene carbon atom can influence its electronic state. This effect was recognised in 1971 by Harrison.[57] Harrison established that σ-electron-withdrawing substituents generally favour singlet carbene formation over triplet carbene formation, due to inductive stabilisation of the σ nonbonding orbital by increasing its s character and leaving the p_π orbital relatively unchanged. In contrast, σ-electron-donating substituents induce favourable formation of the triplet state carbene. Mesomeric effects similarly play a substantial role in electronic state stabilisation. Pauling experimentally proved that preservation of the electroneutrality of a carbene centre leads to stabilisation of singlet carbenes.[58] Achievement of such neutrality can be obtained *via* three methods -

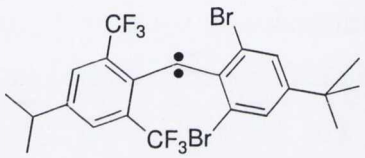
(i) two π-donor σ-attractor substituents, resulting in a 'push, push' resonance and 'pull, pull' inductive substitution pattern; (ii) two π-attractor σ-donor substituents, resulting in a 'pull, pull' resonance and 'push, push' inductive effect, and (iii) a π-donor and a π-acceptor substituent, giving a 'push, pull' mesomeric substitution pattern. It was also demonstrated that use of large bulky substituents support triplet formation, due to broadening of the carbene bond angle.[59,60] A selection of typical triplet carbenes are exhibited in Figure 1.4 below, notably containing bulky aromatic substituents.

Figure 1.4 Examples of triplet carbene structures

28 R = C_6H_5
29 R = 2,4,6-$(CH_3)_3$-C_6H_2
30 R = 2,4,6-Cl_3-C_6H_2
31 R = 2,4,6-Br_3-C_6H_2



32



33

1.2.3 Types of carbenes

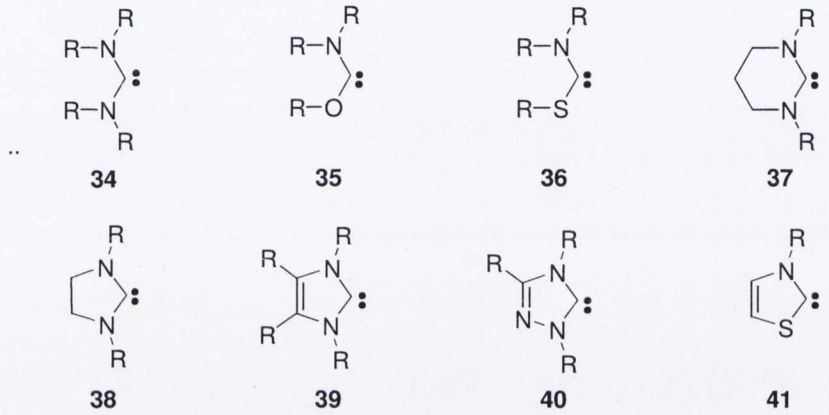
Since it is possible to create substituted carbenes with a diverse range of functional groups, it is unsurprising that many different types of carbenes have been synthesised and developed over the last century. In particular, the last 20 years have witnessed impressive developments towards the preparation of triplet diarylcarbenes and the isolation of heteroatom-substituted singlet carbenes. The pioneering work of Wanzlick *et al.*,[61] Bernard *et al.*,[53] and Arduengo *et al.*[49] have contributed to a prolific area of carbene chemistry.

1.2.3.1 *N*-heterocyclic carbenes - structure and classification

In the early 1960s Wanzlick recognised that the stability of carbenes could be dramatically enhanced by the presence of amino substituents appended to the carbene centre.[62,63,64] This revelation gave rise to a group of carbenes called aminocarbenes which, over time, have evolved to include a family of carbenes known as *N*-heterocyclic carbenes (NHCs). Figure 1.5 illustrates some of the various types of acyclic aminocarbenes (**34** - **36**) and NHCs (**37** - **41**) that have been synthesised to date. These

encompass the aminocarbenes - acyclic diaminocarbenes **34**,[65,66] aminooxycarbenes **35**[67] and aminothiocarbenes **36**[67] and NHCs - cyclic tetrahydropyrimid-2-ylidenes **37**,[68] imidazolidin-2-ylidenes **38**,[69,70] imidazol-2-ylidenes **39**,[71,72,73,74] 1,2,4-triazol-5-ylidenes **40**[75] and 1,3-thiazol-2-ylidenes **41**.[76] (Note: system **41** has been briefly introduced in Section 1.1.3.2, as the active catalyst in the thiazolium-salt catalysed benzoin condensation.)

Figure 1.5 Family of aminocarbenes and *N*-heterocyclic carbenes

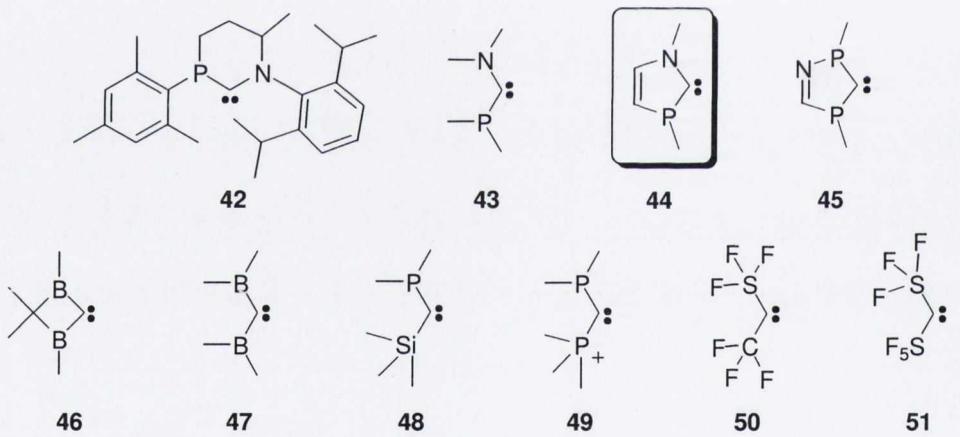


All of the members of the two groups, aminocarbenes and NHCs, (**34** - **41**) were confirmed to generally adopt the singlet carbene state and were also determined to be exceptionally stable.[70] This stability was attributed to the inductive and resonance-based properties of the π-donor σ-acceptor substituents, at least one of which on each compound is an amino group. The amino group in particular provides excellent π-donor ability, with concomitant inductive withdrawal, thereby causing a stabilising effect on the carbene centre. In the case of NHCs (**39** - **41**) an additional stabilising effect is present. This is the inherent aromaticity that certain NHCs possess. The aromaticity of NHCs was previously the subject of controversy, and has only recently gained credence.[77,78,79] Conforming to Hückel's rule of aromaticity $(4n + 2)$ π-electrons, NHCs **39** - **41** contain six π-electrons (two from each of the two heteroatoms appended to the carbene centre and the remaining two from the unsaturated C=C double bond). NHCs are also cyclic and planar, and are therefore considered to be aromatic molecules. Dihydro-analogues **37** and **38**, lacking an unsaturated C=C bond, are not considered to possess aromatic properties.

1.2.3.2 Other types of carbenes

Very recently Bertrand *et al.* reported the synthesis of a stable *P,N*-heterocyclic carbene (**42,** Figure 1.6).[80] However, extensive efforts could not bring about the isolation of pure cyclic (amino)(phosphine)carbene product. Many other carbenes containing different substituents have also been synthesised. Some of these include acyclic (amino)(phosphine)carbenes **43**,[81,82] cyclic diphosphinocarbenes **45**,[83] diborylcarbenes, **46** and **47**,[84,85] phosphinosilylcarbenes **48**,[86] phosphinophosphoniocarbenes **49**,[87,88] sulphenyl-trifluoromethylcarbenes **50**[89] and sulphenylpentafluorothiocarbenes **51** (Figure 1.6).[90] Interestingly, cyclic carbenes of type **44** have, to date, eluded the synthetic skills of investigators.[80] Although a plethora of carbenes have been synthesised to date, the predominant focus of this report shall be NHCs of the type **38** - **41**, Figure 1.5.

Figure 1.6 Other types of N, P, B, Si and S-based carbenes



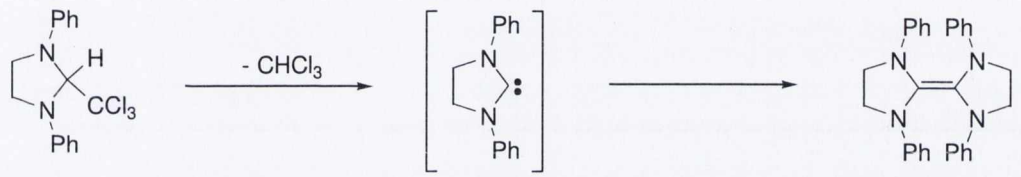
1.2.4 Stable carbenes: introduction

1.2.4.1 Stable carbenes: historical perspective

The quest for stable isolable carbenes is a prolonged saga, the origin of which has been traced back to the first half of the 18th century.[45] A persistent carbene is one which is stable, exhibiting a life-span, in solution and in a pure isolated form.[91] In recognition of the outstanding work of both Wanzlick and Arduengo in the field of isolation of persistent carbenes, stable carbenes are also termed 'Wanzlick' or 'Arduengo' type

carbenes.[53] In 1962, Wanzlick postulated that an electron-rich imidazoline nucleus should be capable of stabilising a carbene centre, and he attempted to prepare the 1,3-diphenylimidazolidin-2-ylidene (**53**) *via* thermal elimination of chloroform from **52** (Scheme 1.7).[61c] Unfortunately dimeric electron-rich alkene **54** was the only isolated product. Within his research group, Wanzlick referred to these dimers as "das doppelte Lottchen", suggesting a mischievous duality between two carbenes and their dimeric form.[92] "Das doppelte Lottchen" meaning 'The double Lottie' refers to a novel about two mischievous twins Lisa and Lottie.

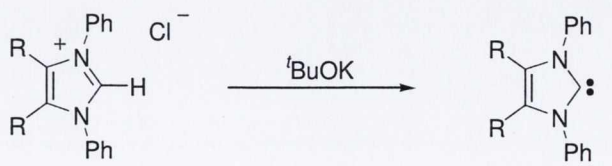
Scheme 1.7 Wanzlick's attempt at imidazolidin-2-ylidene isolation



52 **53** **54**

Much of Wanzlick's research was devoted to the isolation of stable carbenes, in particular those centred on a saturated imidazoline ring.[61] Nevertheless, there are some reports of attempts by Wanzlick to isolate unsaturated imidazole analogues. In 1970 Wanzlick and Schönherr demonstrated the use of potassium *tert*-butoxide (*t*-BuOK) as a base to deprotonate imidazolium salts **55** and generate carbenes **56** (Scheme 1.8).[93,94] The dimeric olefins of type **54** were not detected and they managed to trap monomeric carbenes **56**, although once again isolation of a crystalline material could not be achieved.

Scheme 1.8 Formation of imidazole carbenes, trapped, not isolated



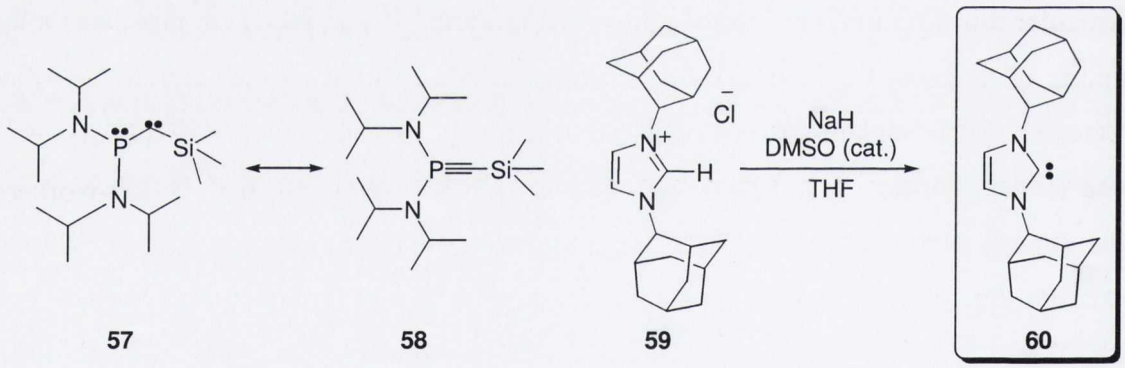
55a R = H
55b R = Ph

56a R = H
56b R = Ph

1.2.4.2 Isolatable carbenes: NHCs

It was an ambition of Wanzlick to isolate a stable carbene compound, unfortunately exhaustive efforts failed to provide an isolated stable crystalline carbene. Although Wanzlick and his research team did, in effect, have NHC carbenes in their hands at that time; it was progress in laboratory methods that was finally decisive in the successful isolation of carbenes. Bertrand *et al.* and Arduengo *et al.* almost concurrently achieved the isolation of stable carbene compounds, **57** and **60** (Scheme 1.9). In 1988, G. Bertrand and co-workers isolated a red oil, which was determined to be the phosphinocarbene **57**.[86,95] However, **57** was deemed to react rather like a phosphaacetylene **58** more so than a carbene and there was doubt as to whether this was in fact a pure isolated carbene.[87,96,97] In 1991, almost two decades after the attempts of Wanzlick, A. J. Arduengo III reported the isolation of the first crystalline stable carbene, **60**.[98]

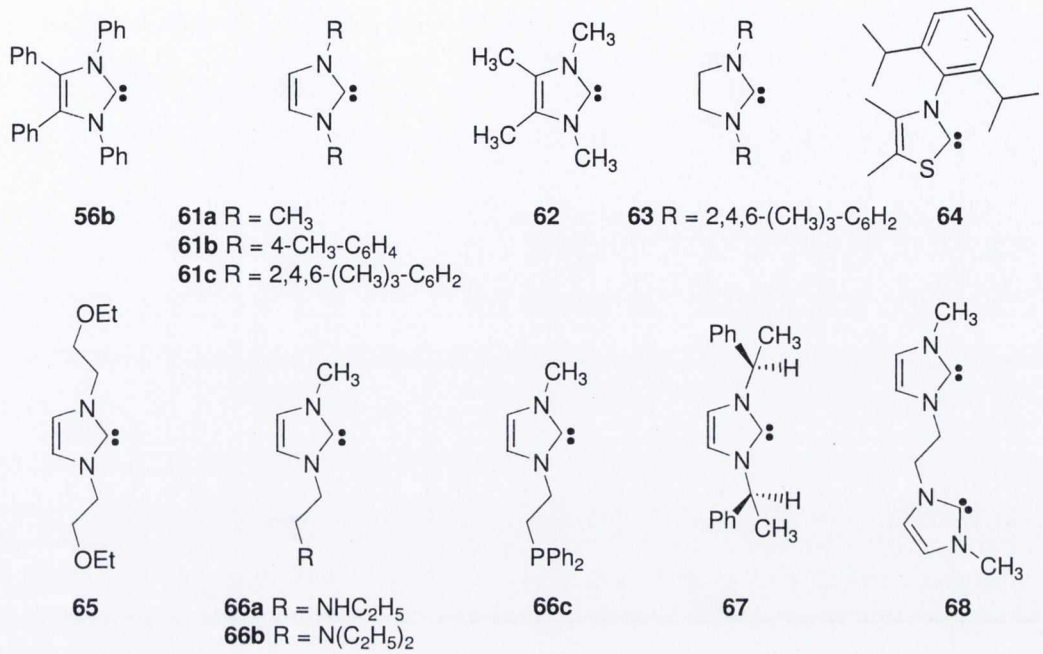
Scheme 1.9 Arduengo and Bertrand's isolation of first stable carbenes **57** and **60**



57 **58** **59** **60**

Using Wanzlick's principle of the deprotonation of an imidazolium salt, Arduengo managed to generate the bulky adamantyl-substituted imidazole carbene **60**. Replacing potassium *tert*-butoxide with NaH and using a catalytic amount of dimethyl sulphoxide (DMSO) **60** was isolated in near quantitative yield. The colourless crystals are thermally stable and melt without decomposition at 240-241 °C. The crystal structure of carbene **60** reveals features characteristic of a singlet carbene and also contains a bond angle of 102.2°. Consequently, Arduengo was accredited with the much sought after isolation of the first stable carbene compound.

Figure 1.7 Various examples of isolated carbenes

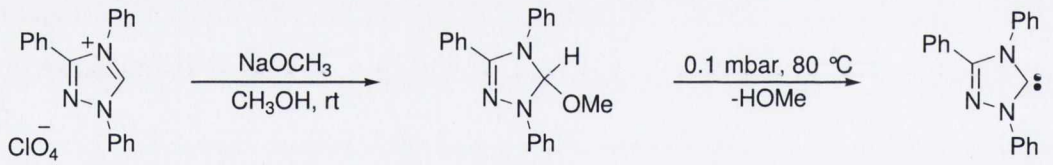


Arduengo proceeded to isolate carbenes **61b,c** (Figure 1.7) in 1992, that are quite similar in structure to carbenes **56**, that Wanzlick had yearned to isolate years before.[72] Both aryl carbenes, **61b,c**, were obtained as crystalline materials, melting without decomposition at 150 °C. Arduengo noted that when carbene **61c** was turned on edge the aryl substituent offered a steric effect in the plane of the carbene centre that was similar to that of a simple methyl group. Subsequently, Arduengo and co-workers prepared methyl-substituted imidazole-carbenes **61a** and **62**.[72] The acquisition of these two variants illustrated that small substituents appended to the carbon centre are also feasable. Carbene **61a** is a moderately stable oil at room temperature, whereas the tetramethyl derivative **62** is a stable crystalline material at room temperature. Nonetheless, carbene **62** must be stored under nitrogen as it is pyrophoric in moist air. Using steric effects to their advantage Arduengo *et al.* continued to further their isolation of novel carbenes, with imidazolin-2-ylidene **63**[69] and thiazol-2-ylidene **64**[76] yielding to their efforts. Interestingly, in 1998 Arduengo attempted the attenuation of **56b** (Figure 1.7 and Scheme 1.8), a carbene that had persistently eluded Wanzlick and with great satisfaction he successfully isolated **56b**.[71d]

Additionally, Herrmann and co-workers demonstrated that deprotonation of an imidazolium salt when using liquid ammonia as the solvent (giving a homogenous phase) occurs much faster (compared to Arduengo's use of NaH). Accordingly, oxygen, nitrogen and phosphorus *N*-functionalised carbenes **65** and **66**, chiral carbene **67** and *bis*-imidazol-2-ylidene **68** have been prepared following this procedure.[71a,b]

The birth of carbene chemistry, as initial chemical curiosities and theoretical species, has transformed into a thoroughly-investigated and highly developed area of research, resulting in the isolation of many stable carbene compounds,[99,100,101] only some of which have been discussed above. As an indication of the progress in this area, Enders reported the isolation of a stable triazole-based carbene **71** in 1995 (Scheme 1.10).[75] Addition of sodium methoxide to triazolium salt **69** generated the stable adduct **70**. Thermal α-elimination of methanol from **70** was achieved, either by heating in toluene or at 80 °C under vacuum, to yield carbene **71**. It is stable up to 150 °C and a crystal structure verified the bond angle to be 100°, which is characteristic of a singlet carbene.[54] **71** Was also the first carbene to become commercially available.

Scheme 1.10 Ender's commercially available triazol-2-ylidene **71**



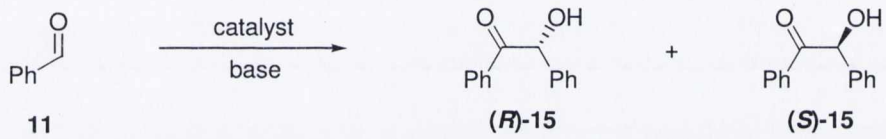
69 **70** 70% **71**

Although immense progress has been achieved in the preparation of stable singlet carbenes, this is not the case for triplet carbenes. It is interesting that the crystallographic characterisation of a triplet carbene has yet to be achieved and the synthesis of such that would be stable in room temperature solution remains an exciting challenge. The most stable triplet carbene synthesised to date has a half-life of 19 minutes at 300 K in solution.[102]

1.3 The asymmetric benzoin condensation

The benzoin condensation reaction is of much interest as a convenient method of carbon-carbon bond formation, which affords an atom-economic approach to α-hydroxy ketones. If one examines the structure of benzoin (**15**, Scheme 1.11), it is apparent that in the condensation process, when forming the α-hydroxyketone product **15**, a stereogenic centre is established. Thus, an asymmetric variant of the benzoin condensation can be envisaged with the possibility of selective formation of either the (*R*)- or (*S*)-enantiomer (Scheme 1.11).

Scheme 1.11 Asymmetric benzoin condensation



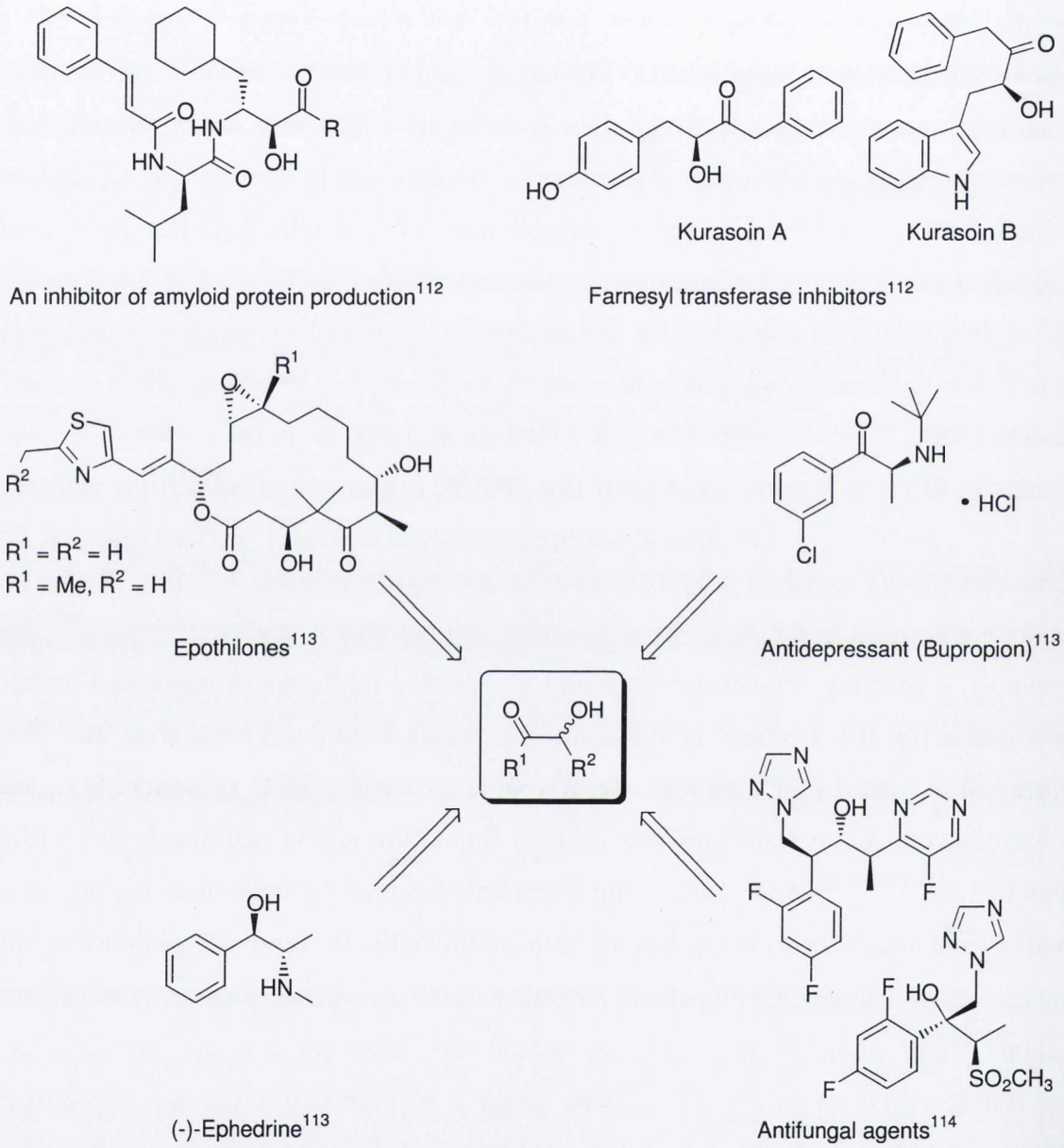
11 **(*R*)-15** **(*S*)-15**

Enantiomerically enriched α-hydroxy ketones are highly valuable building blocks for many applications in the fine chemistry sector and the pharmaceutical industry.[103] For example, α-hydroxy ketones can be found in selective inhibitors of amyloid-β-protein production (for the treatment of Alzheimer's disease), in farnesyl transferase inhibitors Kurasoin A and B, in antitumor agents, such as epotholones, Olivomycin A and Chromomycin A_3, in antidepressants such as Bupropion and in antifungal agents (See Figure 1.8).[104,105,106] Apart from being important structural subunits in many biological active compounds, α-hydroxy ketones can additionally be used as synthons in the formation of many other important structures, such as amino alcohols, benzyls and diols.[107,108]

Thus, if a chiral catalyst is introduced into the reaction, an enantioselective benzoin condensation reaction can be achieved. Scientists have embarked on designing and developing precatalysts containing a bulky chiral scaffold, with the intention of inducing enantioselective benzoin formation. This section acknowledges the seminal asymmetric benzoin condensation reaction using a chiral thiazolium salt precatalyst. It describes the suite of chiral catalysts that have been developed to date in this field, and

achievements made in terms of both reaction scope and asymmetric induction.

Figure 1.8 Examples of compounds bearing an α-hydroxy ketone moiety in their structure

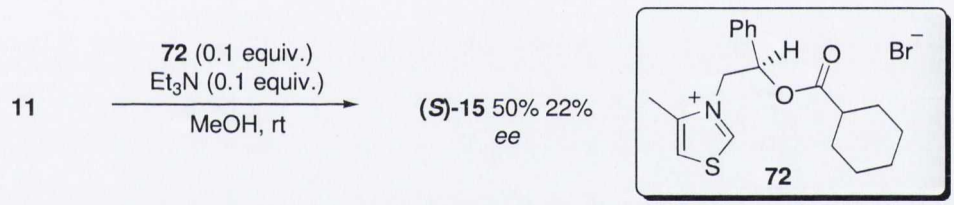


1.3.1 Chiral thiazolium ion precatalysts

1.3.1.1 Seminal studies on the asymmetric thiazolium salt-catalysed benzoin condensation

Although the benzoin condensation reaction was known to be promoted by thiazolium salts since Ugai's disclosure in 1943, it was more than 20 years later before an asymmetric variant of the reaction emerged. In 1966, Sheehan presented the first asymmetric thiazolium-salt-promoted benzoin condensation (Scheme 1.12).[109] Using chiral thiazolium precatalyst **72** (10 mol%), in conjunction with 10 mol% of triethylamine and using methanol as solvent, he returned a yield of 50% of benzoin (**15**) with an optical purity of 22%.

Scheme 1.12 The first asymmetric benzoin condensation (Sheehan)

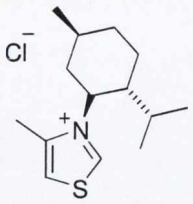


1.3.1.2 Simple thiazolium ion-derived catalysts for the asymmetric benzoin condensation

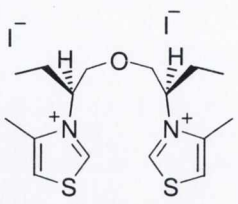
Sheehan remained the principal pioneer in this domain of organocatalysis for quite some time, releasing a second generation of thiazolium salt precatalysts in 1974.[110] Thiazolium salt **73** (Figure 1.9), containing a bulky 1-naphthyl group close to the site of deprotonation, promoted the asymmetric benzoin condensation resulting in an enhanced enantiomeric excess (52%) but with concurrent diminuation of the product yield (6%). Rawal later demonstrated that modification of Sheehan's protocol resulted in an increase in yield (52%) with comparable enantiodiscrimination (48%).[111]

Figure 1.9 Simple chiral thiazolium salts used in the benzoin condensation

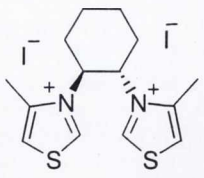
73
Sheehan (1974)
51% *ee*



74
Tagaki (1980)
35% *ee*



75
López-Calahorra (1993)
87% *ee*



76
López-Calahorra (1993)
27% *ee*

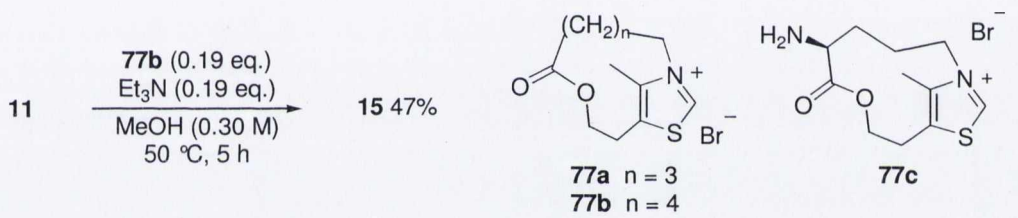
Over the next 20 years very little progress was made towards the development of efficient asymmetric catalysis of the benzoin condensation, generally speaking significant levels of enantiomeric excess were accompanied by poor yields and *vice versa*. In 1980, Tagaki and co-workers developed menthyl-derived thiazolium salts, such as **74**, that catalysed the benzoin condensation in a micellar two-phase reaction medium generating product enantiomeric excesses of up to 35% with 20% yield of benzoin product.[112] Zhao *et al.* applied Sheehan's catalysts to Tagaki's two-phase system and obtained moderate enantiomeric excess of 47-57% and yields of 20-30%.[113] Martí and López-Calahorra designed innovative bridged *bis*-thiazolium salts, **75** and **76**, that unfortunately faired rather poorly in the benzoin condensation.[114] Although precatalyst **75** (at 10 mol% loading) promoted a benzoin reaction to 87% optical purity, the yield of benzoin was only 4%. *Bis*-thiazolium salt **76** catalysed a benzoin reaction of 27% *ee* and 12% yield. It should also be noted that Benaglia reported a C_2-symmetric *bis*-(*N*-benzyl-thiazolium) salt-promoted benzoin condensation (not shown).[115] The precatalyst promoted the formation of benzoin in 40% yield and 15% *ee*.

1.3.1.3 Use of bridged monomeric thiazolium salt precatalysts

In 1995, Leeper reported the synthesis of novel bridged monomeric thiazolium salts **77**, Scheme 1.13.[116] These achiral precatalysts contained a short lactone-derived bridge between the N-3 and C-5 positions of the thiazole ring. Leeper noted in the synthesis of both **77a** and **77b** that the linker bridge was too short to allow the heterocyclic ring to rotate freely through it, and that if no rotation through the link was possible then the precatalyst itself was axially chiral. He postulated that if a chiral precursor was used to

synthesise the precatalyst (containing a pre-existing asymmetric centre), upon prohibited rotation through the bridge two diastereoisomeric forms of the catalyst should be present, which could perhaps be separated. He applied this concept to the synthesis of chiral *l*-lysine-derived salt **77c**. Disappointingly, the two diastereomeric forms were verifiably present upon analysis by ^{1}H NMR spectroscopy but were present in too low a yield to be isolated (0.6 and 1.3%). Leeper applied achiral precatalysts **77a** and **77b** to the benzoin condensation as per Scheme 1.13. Surprisingly, **77a** did not return any benzoin product. It was deemed that the linker bridge was exceedingly short and as a result introduced considerable strain into the system, which prevented the catalyst from engaging in the reaction process. The achiral precatalyst **77b** promoted the benzoin condensation in 47% yield.

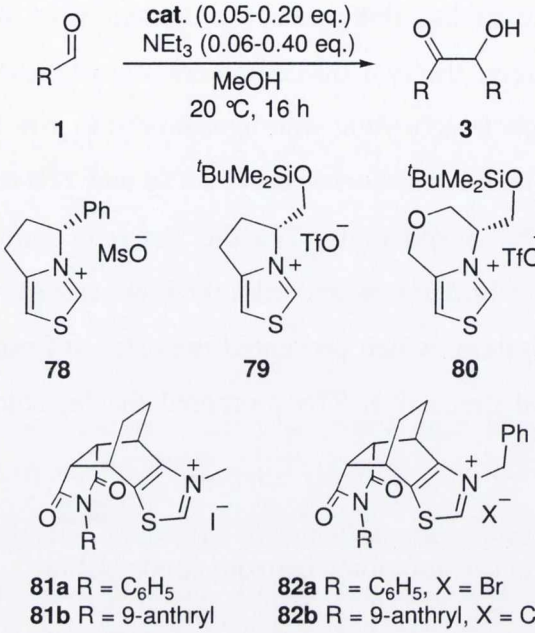
Scheme 1.13 Leeper's ester-bridged thiazolium salt-promoted benzoin condensation



1.3.1.4 Bicyclic and polycyclic thiazolium salt precatalysts

Leeper decided to adopt a different approach in the quest for an enantiopure benzoin condensation reaction. He developed a suite of cyclic thiazolium salts shown in Scheme 1.14, which incorporated five and six-membered fused ring systems onto the thiazole ring (**78** - **80**).[117] Precatalysts **78** - **80** were applied in the benzoin condensation reaction and generated modest yields (20-50%) and levels of enantiomeric excess (11-21%). In this 1997 publication, Leeper also reported the first asymmetric acyloin condensation involving an aliphatic aldehyde, butryaldehyde, as the substrate. While significant yields were afforded (75-86%), these were accompanied with meagre enantioselectivities (14-33% *ee*).

Scheme 1.14 Chiral cyclic thiazolium salts utilised in the benzoin condensation



entry	cat.	R	yield (%)	*ee* (%)	Abs. Conf.
1	**78**	C_6H_5	20	11	*R*
2	**79**	C_6H_5	50	21	*R*
3	**80**	C_6H_5	34	20	*R*
4	**81a**	C_6H_5	88[a]	1	*S*
5	**81b**	C_6H_5	46[a]	7	*S*
6	**82a**	C_6H_5	100[a]	26	*S*
7	**82b**	C_6H_5	91[a]	16	*S*
8	**78**	C_4H_9	86[b]	18	*R*
9	**79**	C_4H_9	77[b]	14	*R*
10	**80**	C_4H_9	75[b]	33	*R*

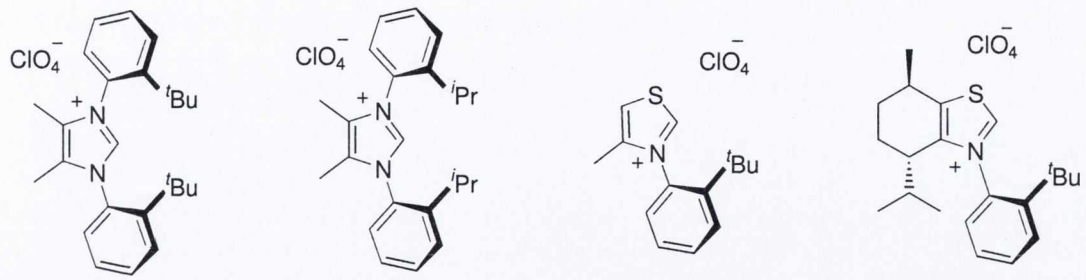
[a]Reaction performed without solvent. [b]Ethanol used as solvent at 80 °C for 3 h.

In a succeeding paper Leeper synthesised polycyclic precatalysts **81** and **82** using a Diels Alder procedure.[118] Although impressive yields were achieved using these precatalysts, they provided poor product optical purities (1-26% *ee*). It should be noted that **82a**, containing a phenyl substituted-maleimide moiety, presented both the highest yield (quantitative) and enantioselectivity (26%, entry 6). It is interesting that salts **81b** and, in particular, **82b** did not induce high levels of enantiodiscrimination considering they both contain bulky anthryl appendages. It was deemed that these groups resided too far away from the catalytic centre to induce significant enantioselectivity.

1.3.1.5 Axially chiral azolium salt precatalysts

Going beyond the customary focus of central chirality, Bach *et al.* recently demonstrated that axially chiral *N*-aryl thiazolium salts could be applied in the benzoin condensation reaction.[119] Adapting the concept applied by Leeper in Section 1.3.1.3 (*vide supra*),[116] Bach considered that placing a large bulky aromatic substituent on the nitrogen atom of the thiazole ring would cause the rotational barrier of the N-C_{aryl} bond to become too great for rotation to occur. Consequently, a stereogenic axis would form resulting in atropisomers, *i.e.*, axially chiral catalysts.

Figure 1.10 Axially chiral thiazolium salts developed by Bach



83 **84** **85** 75 - 98% **86** 85%, 40% *ee*

Using *ortho*-substituted anilines Bach attempted the synthesis of imidazolium and thiazolium salts **83** - **86**, Figure 1.10. For precatalyst **83,** the *ortho*-substituted *tert*-butyl-aniline proved to be too hindered and bulky a substrate to be tolerated in the reaction process and several different approaches to produce precatalyst **83** failed. The *iso*-propyl-substituted analogue could be converted into the corresponding imidazolium salt **84** *via* a multi-step reaction sequence. Although two diastereoisomers were formed (and isolated) in the reaction sequence, the final synthetic step, irrespective of which diastereoisomer was chosen, predominantly resulted in prevalence of the *meso*-product **84**. Bach surmised that the *in situ*-generated carbene, did not have a sufficiently restricted rotational barrier about the N-C_{aryl} bond, and this was responsible for the epimerisation. He reasoned that the preference to orientate to the *meso*-diastereoisomer was due to attractive van der Waals interactions of the lipophilic substituents.

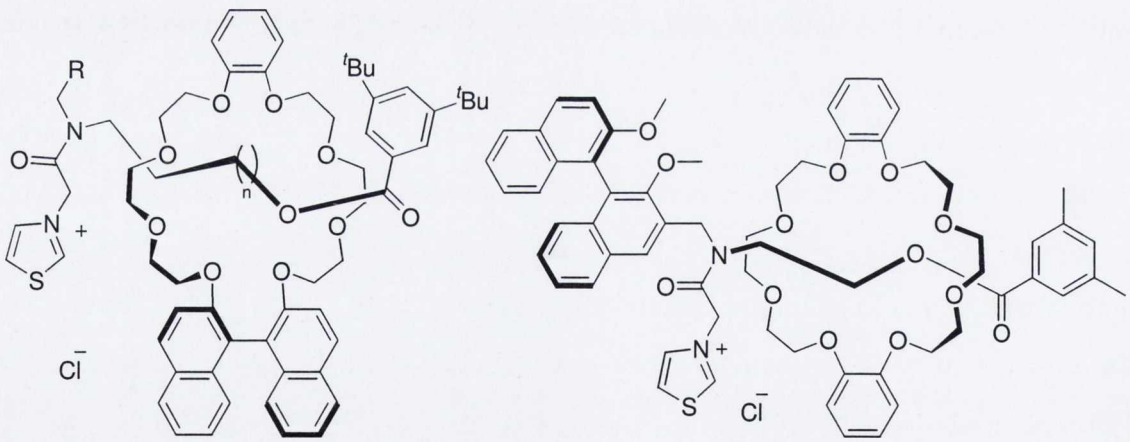
Bach next tackled the synthesis of thiazolium salt **85** using a different approach - he readily created the racemic variant of **85** and performed ion exchange of the perchlorate counterion to a chiral counterion. However, all attempts of fractional crystallisation with a chiral counterion failed and enantiopure precatalyst **85** was not isolated. Fortunately, the synthesis of α-bromomenthone-derived salt **86** proceeded smoothly to give clean conversion to diastereomerically pure product, with no evidence of epimerisation. Precatalysts **85** and **86** were employed in the benzoin condensation. Although **85** was not optically pure and accordingly racemic benzoin was produced, a yield of 75% was obtained. If the reaction was performed for 19 h under identical conditions the yield increased to 98%. Precatalyst **86** promoted the asymmetric benzoin condensation with isolation of 85% of benzoin product with optical purity of 40% of the (*R*)-enantiomer.

Despite using stereochemically pure precatalyst **86** in the reaction, recovery of the catalyst was always as a mixture of the two atropisomers in an approximate ratio of 75:25. Bach again deemed the partial racemisation (and low enantioselectivity) of the catalyst to be due to insufficient hindrance of rotation about the C-N bond.

1.3.1.6 Chiral rotaxane-based thiazolium precatalysts

A rotaxane can be described as a mechanically-interlocked molecular architecture, composed of one or more macrocycles encircling one or more linear components which are terminated by bulky stoppers at their ends.[120] Rotaxanes are kinetically trapped dumbbell shaped compounds consisting of a 'wheel' that surrounds an 'axle'. In 2004, Takata reported the use of chiral rotaxanes in the benzoin condensation (**87** and **88**, Figure 1.11).[121] Employing a crown ether as the wheel component and an amide-based chain, with an appended thiazolium salt moiety, as the axle, Takata constructed precatalysts **87** and **88**. It should be noted that rotaxane **87** contains a chiral crown ether wheel to induce enantioselectivity, whereas the chiral element of variant **88** lies in the (*R*)-binaphthyl group attached to the axle terminal.

Figure 1.11 Chiral rotaxanes containing a thiazolium salt tether

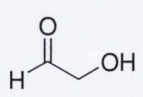

R
N
O
N
+
S
Cl⁻
n
tBu
tBu
O
O
O

formed in 90% yield but poor optical purity, 21%. Reducing the catalyst loading simultaneously decreased product return but marginally enhanced the enantioselectivity - using 1 mol% catalyst and identical reaction conditions 14% of benzoin was afforded and with 32% *ee*. Variation of the temperature did not result in significant progress towards enantiopurity. Overall, the rather complicated and intricate rotaxane scaffolds faired modestly in the benzoin condensation, generating yields of 7-90% and optical purities of 3-32%.

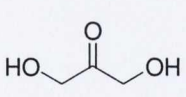
1.3.2 From thiazolium salts to triazolium salts as promoters of the asymmetric benzoin condensation

It is evident that as a result of Ugai's disclosure of the capabilities of thiazolium salts as *Umpolung*-facilitating agents, they rapidly became well established as promoters of the asymmetric benzoin condensation.[15] For the most part, the reports of thiazolium salt-mediated benzoin condensation reactions used only benzaldehyde as the aldehyde component. In 1980, Castells and López-Calahorra introduced formaldehyde as a substrate in the acyloin condensation, which was promoted by a selection of achiral thiazolium salts.[122] This was, to the best of their knowledge, the first reported example of a benzoin condensation employing formaldehyde. Instead of producing 'formoin', otherwise known as glycolaldehyde (**89**, Figure 1.12), a complex mixture of aldoses and ketoses, including dihydroxyacetone (**90**), was obtained, with no formation of the desired product **89**.

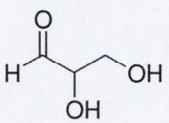
Figure 1.12 Possible products arising from benzoin condensation of formaldehyde



89
glycolaldehyde
'formoin'



90
dihydroxyacetone



91
glyceraldehyde

Consequently, Enders completed an extensive study of the formaldehyde-related benzoin condensation using thiazolium, imidazolium and triazolium salts as precatalysts.[123] The results of Enders' investigation in relation to thiazolium salt catalysis were consistent

with those of Castells. Dihydroxyacetone (**90**) was the major product in all cases with the formation of low levels of higher carbohydrates and trace amounts (< 0.2%) of **89**. Imidazolium salts did not fare as well as thiazolium salts, producing negligible glycolaldehyde and modest yields of **90** and other higher carbohydrates. Triazolium salts, on the other hand, were found to be far more active than both preceding precatalyst types, generating higher product yields at reduced temperatures and catalyst loadings. The major product in these reactions was glycolaldehyde with some glyceraldehyde (**91**) and higher carbohydrate return, and almost no dihydroxyacetone product.

Considering that the triazolium salt is structurally related to the thiazolium salt, and in view of the progress made in the use of thiazolium salts as promoters of the benzoin condensation, it is therefore surprising to us that an asymmetric triazolium salt-assisted benzoin condensation was not reported until 1996, 40 years after the first chiral thiazolium salt-promoted reaction emerged.

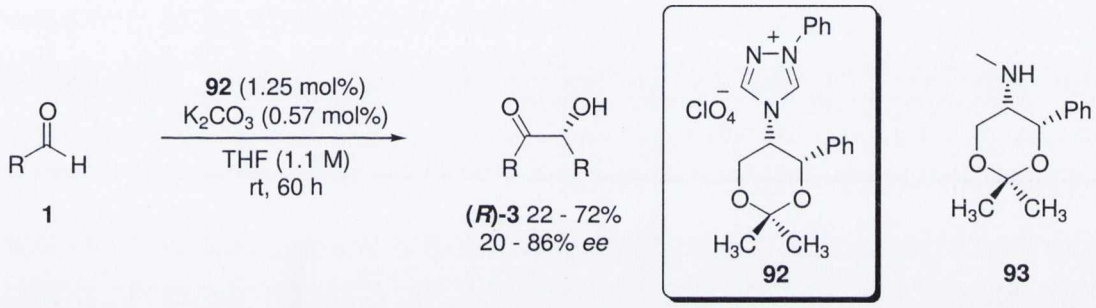
1.3.2.1 Chiral triazolium salts as precatalysts in the asymmetric benzoin condensation - seminal studies

Encouraged by the promising results of triazolium salts in the dimerisation of formaldehyde, Enders reported the synthesis of a novel chiral 1,2,4-triazolium perchlorate salt **92** (Scheme 1.15), which he used in the first asymmetric triazolium salt-assisted benzoin condensation reaction.[124] The chiral ketal-based scaffold of the catalyst was readily prepared over two steps in quantitative yield from a commercially available dioxane starting material, and subsequent annulation involving phenyl hydrazine provided precatalyst **92**. It is interesting that Enders had previously employed this chiral dioxane-based frame in the form of **93** (whereby the triazolium ring was replaced by a secondary amine functionality) as a chiral auxiliary in the asymmetric Michael addition of lithiated chiral amino-cyanides to α,β-unsaturated esters.[125] He generated varying yields and excellent enantiopurities of 90-96% of oxoesters *via* this nucleophilic acylation procedure.

Enders employed triazolium ion **92** in the benzoin condensation as per the conditions outlined in Scheme 1.15. Using a considerably reduced precatalyst loading (1.25 mol%) and K_2CO_3 as base, he achieved a return of 66% benzoin product with an optical purity

of 75%, the highest level of enantiopure benzoin reported *via* NHC organocatalysis. For the first time, the scope of the benzoin condensation was truly extended - using a broader range of aromatic aldehydes, including *meta*- and *para*-substituted electron-rich and electron-deficient substrates, Enders afforded acyloins (**3**) in yields of 22-72% and enantiomeric excesses of up to 86% in favour of the (*R*)-enantiomer. Notably, acyloins procured from electron-rich aldehydes attained the highest enantiomeric excesses (82-86%), but with concomitant reduction of chemical yields (22-48%).

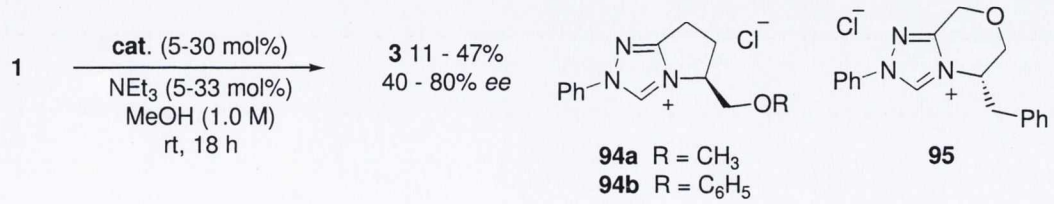
Scheme 1.15 First example of chiral triazolium salt-promoted benzoin condensation



1.3.2.2 Chiral fused-ring triazolium salt systems

Shortly after Enders' seminal study on the triazolium salt-promoted asymmetric benzoin condensation, Leeper became the second pioneer to contribute to this budding field of catalysis. Leeper introduced a bicyclic skeleton into the carbene triazolium framework creating precatalysts that were analogous to his previous thiazolium derivatives (**78-80**, Scheme 1.14).[126] Using the same reaction conditions as those previously employed,[117] he investigated the dimerisation of a selection of aromatic aldehydes using precatalysts **94** and **95**, as per Scheme 1.16.

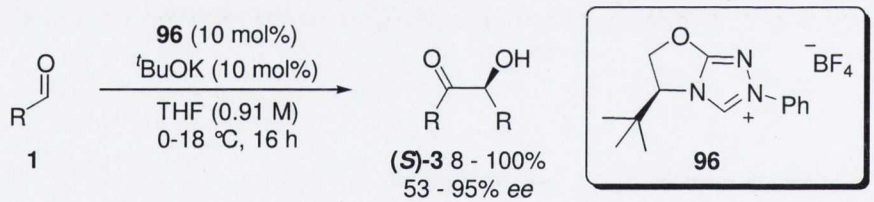
Scheme 1.16 Leeper's bicyclic triazolium precatalysts **94** and **95**



Despite the excellent results achieved by Enders using precatalyst **92**, Leeper's concept of a locked cyclic stereogenic centre embedded into a triazolium framework did not furnish such rewards. Product yields ranged between 11-47% and optical purities between 40-80%. Gratifyingly, using six-membered fused-ring system **95**, Leeper generated a yield of 45% of benzoin with an enantiopurity of 80%. This result, albeit with a lower yield than reported by Enders (66%), provided the most enantiopure benzoin that had been synthesised to date *via* triazolium salt catalysis. Precatalyst **95** proved to be the superior of the three depicted in Scheme 1.16, generating the highest enantiomeric excesses in each case and on average the highest yields.

Inspired by these successful results, Enders *et al.* used a modification of Leeper's bicyclic procedure to create triazolium salt **96**, derived from (*S*)-*tert*-leucine, which was subsequently applied in the benzoin condensation.[127] (*S*)-benzoin was obtained in 83% yield and with product enantiomeric excess of 90%. This result again raised the bar in terms of asymmetric induction, achieving the highest level of enantiopure benzoin at that time. Enders also attempted the condensation of different substituted aromatic aldehydes, which led to the corresponding α-hydroxy ketones **3**, in moderate to good yields and with excellent enantiomeric excesses of up to 95% (Table 1.1).

Table 1.1 Triazolium salt-promoted benzoin condensation using precatalyst **96**



entry	R	temp. (°C)	yield	*ee*[a] (%)	entry	R	temp. (°C)	yield	*ee*[a] (%)
1	C_6H_5	18	83	90	9	3-Cl-C_6H_4	0	85	86
2	4-F-C_6H_4	18	81	83	10	4-CH_3-C_6H_4	18	16	93
3	4-F-C_6H_4	0	61	91	11	3-CH_3-C_6H_4	18	70	86
4	4-Cl-C_6H_4	18	80	64	12	3-CH_3-C_6H_4	0	36	91
5	4-Cl-C_6H_4	0	44	89	13	4-CH_3O-C_6H_4	18	8	95
6	4-Br-C_6H_4	18	82	53	14	2-furyl	0	100	64
7	4-Br-C_6H_4	0	59	91	15	2-furyl	-78	41	88
8	3-Cl-C_6H_4	18	92	62	16	2-naphthyl	18	69	80

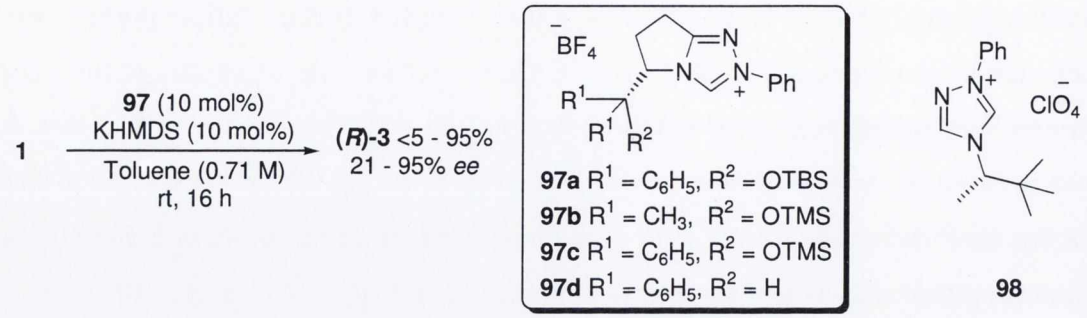
[a]Determined by HPLC (Daicel AD2 and Daicel OD3).

Applying 10.0 mol% of both precatalyst **96** and *t*-BuOK to the reaction, a yield of 83% of benzoin with 90% enantiopurity was obtained (entry 1). It should also be noted that when the precatalyst (and base) loadings were decreased, higher optical purities were obtained, albeit at a cost of product yield. When electron-poor aldehydes (being more activated than electron rich variants) were employed at 0 °C, it was observed that the stereocontrol was enhanced, but with reduced product yields (entries 2-9). Thus, reducing the temperature to 0 °C had a favourable effect on asymmetric induction, but again, concurrently decreased the product return. As previously observed, electron-rich aldehydes enabled higher asymmetric inductions than electron-deficient variants in the presence of **96**, but were accompanied by significantly reduced acyloin yields (16% and 8% yields for entries 10 and 13). Interestingly, the highly reactive furfuraldehyde formed furoin in quantitative yield in a reaction time of 45 minutes, but with only moderate enantiomeric excess (64% *ee*, entry 14). Decreasing the temperature to -78 °C increased the product enantiopurity to 88% (entry 15). **96** Remained the most effective and applicable precatalyst in terms of aldehyde scope and asymmetric induction in the benzoin condensation for quite some time. Enders postulated that the high asymmetric inductions were contributable to the rigid conformation of the bicyclic structure, coupled with the shielding effect caused by the bulky and sterically demanding *tert*-butyl group.

1.3.2.3 Further advancements in the asymmetric benzoin condensation using pyroglutamic acid-derived triazolium salts

Recently, Enders presented a new type of organocatalytic triazolium salt for the enantioselective benzoin condensation.[128] He derived a selection of bulky silyloxy-substituted precatalysts **97a-d**, Scheme 1.17, using commercially available and inexpensive (*S*)-pyroglutamic acid as the starting material. Enders' insight into developing these salts stemmed from a report by Ye, whereby bicyclic triazolium salts **97a** and **97c**, bearing an aryl-alkylsiloxy substituent, were applied in the Staudinger reaction.[129] Initial catalyst screening of the precatalysts indicated **97c** to be the more superior of the salt selection, generating a benzoin yield of 66% with 95% enantiomeric excess. Precatalyst **97d**, containing a proton in place of a bulky silyloxy group, promoted the benzoin condensation to an impressive 90% yield, but with almost no asymmetric selectivity (5%). This clearly indicates that the bulky silyloxy group is responsible for the induced enantiodiscrimination of the acyloin product.

Scheme 1.17 (*S*)-pyroglutamic acid-derived precatalysts developed by Enders



The reaction scope of the benzoin condensation was examined using different aldehydes. As per the emerging trend from previous benzoin condensation studies, it was found that electron-rich aldehydes were less active in the reaction process, affording lower yields (<5% for *p*-anisaldehyde and 8% for *p*-tolualdehyde) but were accompanied by significantly high asymmetric inductions. Electron-deficient aldehydes were converted into acyloin product in modest yields but with concomitant reduction of enantiopurity. The performance of heteroaromatic aldehydes (furfuraldehyde and thiophene-2-carbaldehyde) was probed and it was found that although they gave the highest return of acyloin product, they performed the poorest in terms of optical purity.

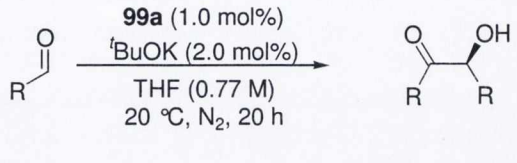
Scheme 1.17 also depicts precatalyst **98** that was synthesised by Enders *et al.*[130] It was attempted to apply this monocyclic salt in the acyloin condensation reaction involving aliphatic aldehydes. Unfortunately product yields and enantiomeric excesses were only moderate and varied widely.

1.3.2.4 *Bis*-triazolium salt precatalysts

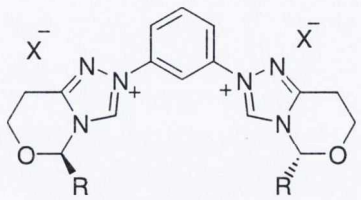
In 2008, the concept of dual-carbene catalysis in the form of *bis*-triazolium salts was introduced by J. You *et al.* You developed several chiral *bis*-bicyclic triazolium salts annulated by aliphatic cyclic skeletons, **99a-d**, which he employed in the asymmetric benzoin condensation, achieving exceptional results (see Table 1.2).[131] Optimisation of reaction conditions indicated *t*-BuOK as the superior base and THF as the most suitable reaction medium. Triazolium salt **99a**, containing a chloride counterion, was the most successful precatalyst at promoting the dimerisation process and the scope of the

reaction was evaluated using **99a**. Computational studies revealed the two triazolylidene rings (when deprotonated) and the adjoining phenyl ring were perfectly coplanar, providing an attractive chiral environment for catalysis to occur.

Table 1.2 *Bis*-triazolium salts **99a-d** developed by You *et al.*



1 **(*S*)-3** 41 - 98%, 83 - 95% *ee*



99a R = CH_2Ph, X = Cl
99b R = CH_2Ph, X = PF_6
99c R = ^iPr, X = Cl
99d R = ^iPr, X = PF_6

entry	cat.[a] (mol%)	R	yield (%)	*ee*[c] (%)	entry	cat.[a] (mol%)	R	yield (%)	*ee*[b] (%)
1	1	C_6H_5	95	95	6	1	4-CH_3O-C_6H_4	41	95
2[c]	2	C_6H_5	98	83	7[c]	2	4-CH_3O-C_6H_4	65	91
3	1	4-CH_3-C_6H_4	62	95	8	1	3-CH_3O-C_6H_4	70	93
4[c]	2	4-CH_3-C_6H_4	83	90	9	1	2-CH_3O-C_6H_4	50	85
5	1	3-CH_3-C_6H_4	82	91	10	1	2-naphthyl	80	92

[a]Reaction conditions used 1:2 precatalyst:base unless otherwise stated. [b]Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H). [c]Reaction used 2.0 mol% of precatalyst **99a** and 4.0 mol% of base.

Remarkably, it was found that only 1.0 mol% of catalyst loading was required to afford a yield of 95% of benzoin and almost complete product stereocontrol (95% *ee*, entry 1). This result became the highest return of both yield and optical purity of benzoin formed *via* triazolium salt-catalysis, surpassing Ender's previous achievement (see entry 1, Table 1.1, 83% yield, 90% *ee*). You noticed that increasing the precatalyst and base loadings caused partial erosion of optical purity (entry 2), which he attributed to the presence of excess basic components (both base and carbene catalyst) within the reaction that caused racemisation of acyloin product. Interestingly, when investigating the reaction scope You focused the majority of his experimentation upon electron-rich aldehydes, which in general tend to fare poorly in the benzoin condensation, and are thus generally avoided as substrates. The scope of the reaction process was also expanded to include the recalcitrant, hindered and deactivated *ortho*-anisaldehyde as a substrate in the benzoin condensation (entry 9). At that time, no *ortho*-substituted benzaldehydes

had been reported in the NHC-assisted asymmetric benzoin condensation, as they were considered too hindered and consequentially inactivated. You also reported the highest result of 2-naphthaldehyde dimerisation at that time; 80% yield with 92% enantioinduction (entry 10). Overall, moderate to excellent yields were obtained, with impressive achievements in asymmetric induction (83-95% *ee*). Triazolium salt **99a** was accordingly considered to be the most effective precatalyst for facilitating the condensation of a wide range of aldehydes in the asymmetric benzoin condensation.

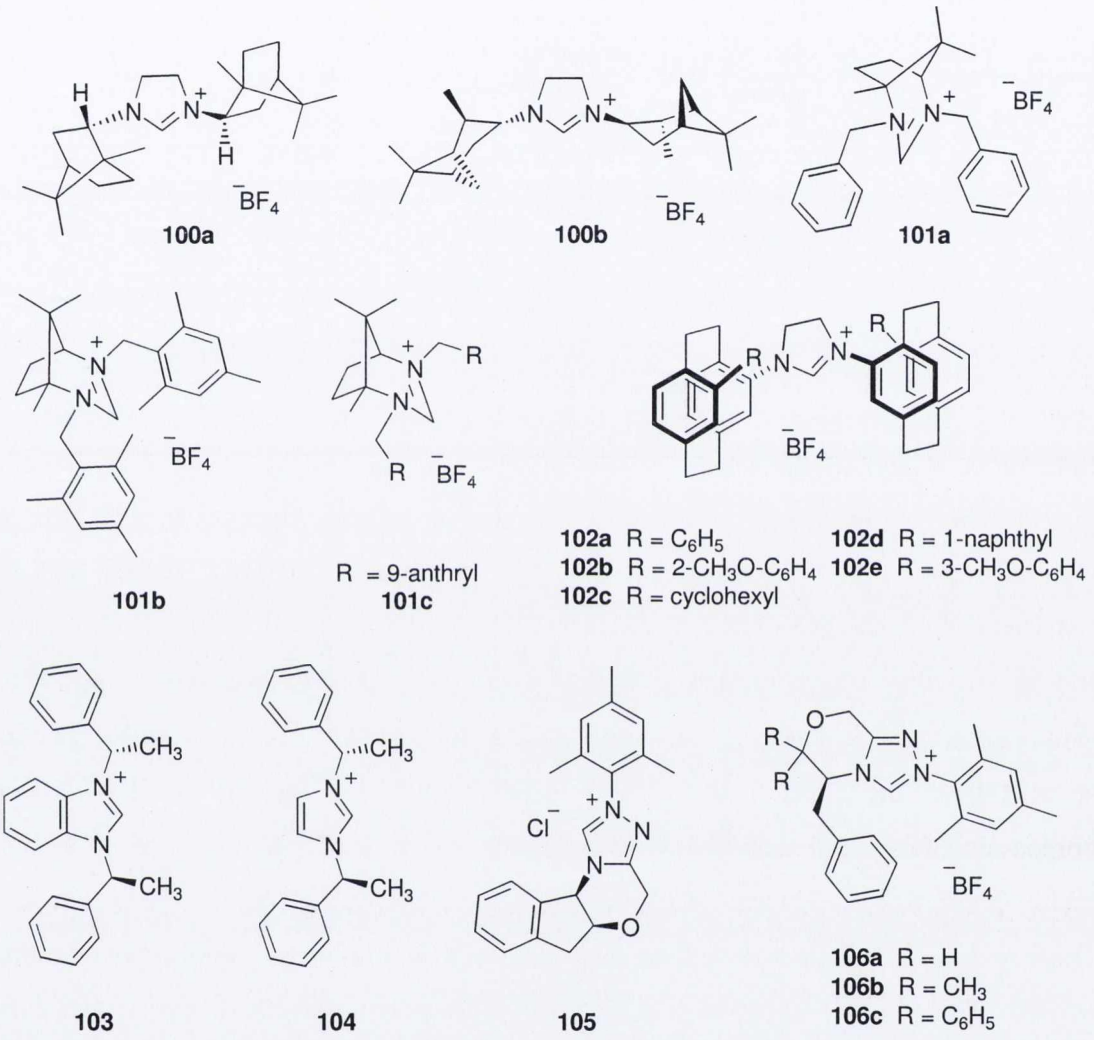
1.3.2.5 Notable chiral triazolium salt precatalyst systems not utilised in the benzoin condensation

It is evident that over the last 50 years a colourful palette of NHCs have been innovatively designed and synthesised, with the creation of intricate and complex architectures. There are however, a vast number of chiral NHC precursors, comprised of intriguing and inspiring frameworks, that although were not pertained in the benzoin condensation, are noteworthy of acknowledgement. A small selection of such carbene precursors are briefly discussed *vide infra*.

Considering that camphor is a low-cost and readily available starting material that originates from the chiral pool, it is interesting that very few examples of NHCs encompassing this chiral scaffold are known. In 2001, Hartwig reported the synthesis of camphor-derived imidazolinium salt **100a** and a similar variant **100b**, Figure 1.13, which he used as ligands in the palladium-catalysed formation of oxindoles by amide α-arylation.[132] The two ligands were created from (+)-bornylamine and (-)-isopinocampheylamine respectively, unfortunately they were rather poor at inducing a stereochemical bias. Several years later Wilhelm disclosed a new class of enantiopure imidazolinium salts whereby the N-C-N unit (carbene moiety) was embedded within the rigid C_1 symmetric chiral bicyclic system of camphor **101a-c**, Figure 1.13.[133] The innovative precatalysts contained a restricted rotation about one of the *N*-substituents due to the presence of the C-10 methyl group of the camphor skeleton, which was responsible for chirality transfer. The phenyl, mesityl and 9-anthracenyl substituted carbene precursors were applied as Lewis base precatalysts in a formal [2 + 2] reaction of ketenes and aldehydes to form β-lactones. The bulky analogue **101c** proved to be the

superior of the trio, achieving significant product yields with complementary levels of enantiopurity, across a broad substrate range.

Figure 1.13 Assortment of interesting chiral NHC precursors



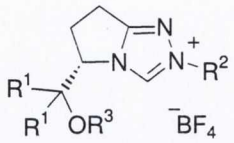
A unique family of planar chiral symmetrical imidazolinium salts (**102a-c**) derived from [2.2]paracyclophane was developed by Ma *et al.* in 2003,[134] and further extended in 2008 to include variants **102d** and **102e**.[135] The dihydroimidazolium salts **102a-e**, containing a rigid [2.2]paracyclophanyl unit and a versatile backbone structure, were revealed to be suitable ligands for rhodium- and ruthenium-catalyst promoted carbon-carbon bond formations.

Chiral imidazolium salts **103** and **104** were designed by two separate research groups and exploited as organocatalytic advocators of *Umpolung* reactions. Benzimidazolium precatalyst **103**, Figure 1.13, was determined to be an effective catalyst for generating homoenolate species from α,β-unsaturated aldehydes, thereby converting them into saturated esters.[136] Conversely, chiral NHC **104** was found to be an efficient promoter of formal [2 + 2] cycloaddition reaction of ketenes with oxoaldehydes, affording β-lactones in respectable yields, with unfortunately, almost no stereoinduction.[137]

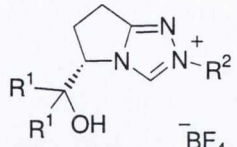
Polycyclic triazolium salts **105** and **106** were synthesised and gratifyingly revealed themselves as highly efficient promoters of a selection of organocatalytic reaction processes. Some of these include the redox esterification of formylcyclopropanes,[138] oxodiene-Diels Alder reactions,[139] desymmetrisation of 1,3-diketones producing cyclopentenes,[140] highly enantioselective intramolecular Michael Addition reactions,[141] formation of γ-lactams *via* homoenolate addition to cyclic ketimines,[142] β-protonation reactions of homoenolate equivalents,[143] and Mannich reactions utilising α-aryloxyacetaldehydes.[144] It must be noted that precatalyst structures **105** and **106** are analogous to systems developed by Rovis and his research group for use in the Stetter reaction, but contain one subtle disparity. A mesityl group governs the *N*-substituted position in both cases above, whereas the equivalent precatalysts created by Rovis *et al.* use several different aryl variants.[145] The Stetter reaction and the NHC precursors designed by Rovis are discussed in brief in Section 1.5.1.

In 2007, Ye introduced the first of a novel suite of NHC precurors, chiral *l*-pyroglutamic acid-derived triazolium salts **97a** and **97c**, which have been described briefly, *vide infra* in Section 1.3.2.3, Scheme 1.17.[129] Ye proceeded to publish many successive reports detailing highly enantioselective cycloaddition reactions that were procured using novel silyloxy-derived salts **97a** and **97c** and similar novel triazolium precatalysts **117** and **118** (all derived from *l*-pyroglutamic acid). Notably, the difference between systems **117** and **118** is the replacement of the bulky silyloxy protecting group with a hydroxyl moiety. A selected array of Ye's innovative reactions are depicted below in Scheme 1.18.

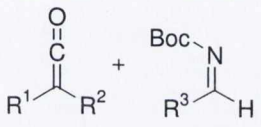
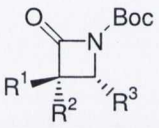
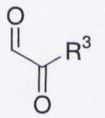
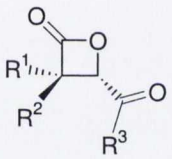
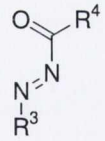
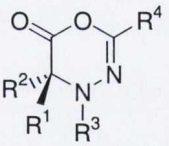
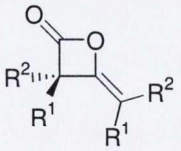
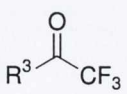
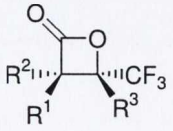
Scheme 1.18 Reactions using Ye's *l*-pyroglutamic acid-derived triazolium salts



97a $R^1 = R^2 = C_6H_5$, R^3 = TBS
97c $R^1 = R^2 = C_6H_5$, R^3 = TMS
117a R^1 = 2-naphthyl, $R^2 = C_6H_5$, R^3 = TBS
117b $R^1 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$, $R^2 = C_6H_5$, R^3 = TBS
117c $R^1 = C_6H_5$, $R^2 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$, R^3 = TMS
117d $R^1 = C_6H_5$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$, R^3 = TBS
117e $R^1 = C_6H_5$, $R^2 = 2\text{-}^i\text{Pr}\text{-}C_6H_4$, R^3 = TBS



118a $R^1 = R^2 = C_6H_5$
118b $R^1 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$, $R^2 = C_6H_5$
118c $R^1 = C_6H_5$, $R^2 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$
118d $R^1 = 3,5\text{-}(CF_3)_2\text{-}C_6H_3$, $R^2 = 4\text{-}CH_3O\text{-}C_6H_4$

Entry	Reactants		Product	Catalysts
1	 **107** **108**	**cat.** (10 mol%) Cs_2CO_3 (10 mol%) THF, rt	 **109** 53 - 99% 91 - 99% *ee*	**97a**, **97c**
2	**107** +  **110**	**cat.** (10 mol%) Cs_2CO_3 (10 mol%) THF, rt	 **111** 63 - 99% 4 - 99% *ee*	**97a**, **97c**
3	**107** +  **112**	**cat.** (10 mol%) Cs_2CO_3 (10 mol%) THF, rt	 **113** 18 - 93% 3 - 97% *ee*	**95a**, **117a**, **117c**, **118a**, **118b**, **118c**
4	**107** + **107**	**cat.** (10 mol%) Cs_2CO_3 (10 mol%) THF, rt	 **114** 26 - 99% 28 - 97% *ee*	**97a**, **97c**, **117b**, **117d**, **118a**, **118b**, **118d**
5	**107** +  **115**	**cat.** (12 mol%) Cs_2CO_3 (10 mol%) Toluene, -40 °C	 **116** 10 - 99% 73 - 99% *ee*	**97a**, **97c**, **117c**, **117d**, **117e**, **118b**, **118c**, **118d**

NHC precursors **97a** and **97c** enabled the formation of *N*-Boc-protected β-lactams (**109**) *via* Staudinger reaction of ketenes **107** and imines **108**, and were also responsible for formal cycloaddition of disubstituted ketenes with oxoaldehydes, (entries 1 and 2, Scheme 1.18).[129,137] The unprecedented [4 + 2] cycloaddition of **107** with *N*-benzoyldiazenes **112** to afford 1,3,4-oxadiazin-6-ones (**113**, entry 3),[146] and the asymmetric dimerisation of disubstituted ketenes (entry 4),[147] were both reported. Additionally, this unique collection of precatalysts delivered the highly diastereoselective and enantioselective synthesis of β-trifluoromethyl-β-lactones (**116**, entry 5) *via* cycloaddition of **107** and trifluoromethyl ketones **115**.[148] In each case, Ye's pyroglutamic acid-derived triazolium salts delivered excellent returns of the respective product, across a wide substrate scope, and with exceptional levels of enantiopurity. The work of Ye and his research team unveiled bicyclic triazolium salts **97**, **117** and **118** as remarkable NHC precursors that are capable of promoting a wide range of organocatalytic reaction processes to high yields and that concurrently exhibit excellent stereocontrol.

1.3.3 Enzyme-mediated benzoin condensation catalysis

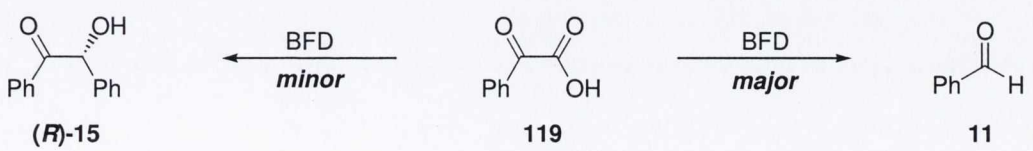
This section has focused so far solely on organocatalytic NHC-mediated dimerisation of aldehydes as a means to creating asymmetric α-hydroxy ketones. A novel organocatalytic approach to the synthesis of α-hydroxy ketones was recently disclosed by Connon *et al.*[149] Employing a reductase-mimicking thiourea organocatalyst, incorporating a covalently bound NADH analogue, efficient reduction of 1,2-diketones could be realised *via* hydride transfer. However, preliminary investigations into an asymmetric reduction were complicated by product racemisation under the reaction conditions employed. Chemical methods for the asymmetric synthesis of such acyloins, which are not based upon C-C bond formation (in contrast to the benzoin condensation), have been explored. Among them are the stereoselective oxidation of - (i) titanium enolates with dimethyldioxirane,[150] (ii) silyl enol ethers with chiral salen complexes[151] or (iii) fructose-derived dioxirane,[152,153] and the stereoselective dihydroxylation of enolates with *N*-sulphonyloxaziridines.[154,155] Other chemical protocols include ketohydroxylation of alkenes using RuO_4,[156] asymmetric mono-oxidation of 1,2-diols using *N*-bromosuccinimide (NBS) in the presence of a chiral copper catalyst,[157] and oxidative kinetic resolution of racemic acyloins *via* chiral iron or cobalt-catalysis.[158,159]

An alternative approach towards the synthesis of homochiral α-hydroxy ketones is *via* enzymatic catalysis. The enzymatic benzoin condensation reaction, furnishing α-hydroxy ketone functionality in one step, has been widely examined.[103] Other means by which acyloins can be prepared enzymatically include reduction of the corresponding α-diketone with baker's yeast,[160,161] deracemisation of racemic α-hydroxy ketones,[162] or by enzymatic kinetic resolution of a racemate of certain ketones (2-peroxo-,[163] 2-hydroxy-[164] or 2-acetoxy-ketones[165,166]). These enzyme-induced modes of generating acyloins are described briefly herein.

1.3.3.1 Asymmetric benzoin condensation using specific enzymes

Considering the importance of 2-hydroxy ketones as structural subunits and their incorporation into many biologically active compounds, and the inherent high specificity of enzyme-mediated reactions, an attractive and obvious route for the synthesis of enantiospecific acyloins was by means of an enzymatic pathway.[167,168,169] In 1999, Demir and Müller reported the seminal use of a highly enantioselective enzyme to promote the benzoin condensation reaction.[170] They employed benzoylformate decarboxylase (BFD), an enzyme that has been found in bacteria such as *Pseudomonas putida*, *Acinetobacter calcoaceticus* and *Pseudomonas aeruginosa*, to facilitate the reaction.[171,172,173] BFD is a thiamine diphosphate (ThDP)-dependent keto acid decarboxylase that is involved in the degradation of aromatic compounds. The main function of BFD is the non-oxidative decarboxylation of benzoylformate (phenyl glyoxalic acid, **119**) to yield benzaldehyde (**11**), but it also performs a side reaction of carboligation, forming (*R*)-benzoin (**15**), Scheme 1.19. The potential of BFD to catalyse C-C bond formation was first reported by Wilcocks in 1992.[174] Müller postulated that an enzymatically catalysed reaction should be a versatile stereoselective alternative to the classical benzoin condensation.

Scheme 1.19 Decarboxylation and carboligation reactions of BFD enzyme

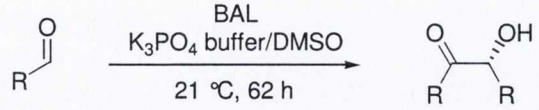


(*R*)-15 **119** **11**

Müller hypothesized that BFD, solely in the presence of benzaldehyde (with no benzoyl formate (**119**) present), could promote highly enantioselective formation of benzoin. Initial experimentation resulted in a paltry yield of 20% dimerisation, but with complete product enantiospecificity, >99% *ee*. Optimisation of reaction conditions increased the yield to 70% with no diminuation of optical purity. This was achieved using a mixture of potassium phosphate buffer (pH 7.0, containing $MgSO_4$) and 30% (*v/v*) DMSO. Note: the addition of DMSO was required to enhance the solubility of the aromatic reagent. The performance of a range of aromatic and heteroaromatic aldehydes was evaluated using BFD. Gratifyingly, BFD accepted a broad range of substrates, endowing the formation of acyloins (0-70% yield) with almost complete enantiopurity in each case (94->99% *ee*). It is notable that the conversion rate was found to be a function of the aldehyde structure, with benzaldehyde being maximal (70% yield) and *ortho*-substituted aldehydes being poorly accepted by the enzyme.

It was not long before Demir and Müller communicated the use of another ThDP-dependent enzyme, benzaldehyde lyase (BAL), for the enantioselective formation of acyloins.[175,176] BAL, isolated from *Pseudomonas fluorescens* Biovar I, was first reported by Gonzáles and Vicuña.[177] They revealed that this strain could grow on benzoin as a sole carbon and energy source due to the ability of BAL to catalyse the cleavage of the C-C acyloin linkage, thus producing benzaldehyde. The potential of BAL in the catalysis of C-C bond formation, *i.e.*, the benzoin condensation, was investigated. As per previous studies, initial experimentation returned poor yields of benzoin but with outstanding stereoinduction - >99% *ee* in favour of the (*R*)-antipode. The poor yield was attributed to the low solubility of the aromatic substrate in aqueous buffer. This hindrance was overcome by the addition of approximately 15-20% of cyclodextrin, DMSO or polyethylene glycol (PEG). Using 20% (*v/v*) DMSO in the reaction medium, conversion was effectively quantitative, with precipitation of optically pure benzoin from the reaction (96% yield, >99% *ee*, entry 1, Table 1.3). The scope of the reaction was investigated using a broad range of aromatic aldehydes and the results are depicted in Table 1.3.

Table 1.3 Highly enantioselective BAL promoted acyloin condensation



1

(*R*)-3 68 - 98%
91 - 99% *ee*

entry	R	yield (%)	*ee*[a] (%)	entry	R	yield (%)	*ee*[a] (%)
1	C_6H_5	96	>99	10	4-F-C_6H_4	89	>99
2	2-F-C_6H_4	68	96	11	4-Cl-C_6H_4	95	>99
3	2-Cl-C_6H_4	80	97	12	4-Br-C_6H_4	83	>99
4	2-Br-C_6H_4	90	>99	13	4-CH_3O-C_6H_4	95	>99
5	2-CH_3O-C_6H_4	87	>99	14	4-CH_3-C_6H_4	94	>99
6	3-F-C_6H_4	80	97	15	2,4-F_2-C_6H_3	87	>99
7	3-Cl-C_6H_4	94	>99	16	2-naphthyl	98	>99
8	3-Br-C_6H_4	94	>99	17	2-furyl	88	92
9	3-CH_3O-C_6H_4	93	>99	18	2-thienyl	73	91

[a]Determined using chiral HPLC analysis (Chiralpak AD).

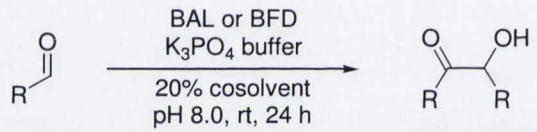
Significant yields of acyloin were obtained, with return of product ranging between 68-98% and in every case almost complete enantioinduction was achieved. It is evident that BAL is capable of coupling both electron-donating and electron-withdrawing aldehydes, including heteroaromatic variants. In contrast to BFD, *ortho*-substituted substrates are well tolerated and no bias is observed between *meta*- and *para*-substitution patterns.

In 2005, a gel stabilised two-phase reaction medium was reported that employed BAL as an activator of acyloin formation.[178] This communication differed from previous reports in that the drawback associated with previous BAL-catalysed syntheses of acyloins - the low solubility of many benzaldehyde derivatives in an aqueous medium - was overcome by utilising a biphasic system. This was accomplished by entrapping the BAL enzyme in polyvinyl alcohol and suspending it in hexane. It was determined that an enhanced productivity of acyloin formation, when compared with previous results, was achieved using this new reaction medium.[176]

The asymmetric dimerisation of aliphatic aldehydes was a relatively unexplored aspect of benzoin condensation chemistry (*via* NHC and enzyme catalysis). Aliphatic aldehydes, being susceptible to enolisation (hence aldol polymerisation), tended to give low yields and enantioselectivities, and thus had rarely been attempted in the asymmetric

benzoin condensation.[179] For the most part, reported examples of enzyme-promoted catalysis involved acetaldehyde, which was formed *via* the decarboxylation of pyruvate.[180] In 2007, the research group of Müller attempted the enzyme-endorsed asymmetric synthesis of aliphatic 2-hydroxy ketones.[181] Using both BFD and BAL enzymes the dimerisation of a range of linear and branched aliphatic aldehydes was examined. The reaction was carried out using an aqueous buffer solution that was maintained at pH 8.0 with isolated enzyme (BAL or BFD) in the presence of co-factors ThDP (**9b**, Figure 1.1) and $MgSO_4$. Note: DMSO or propan-2-ol were added in some cases (20% (*v/v*)), to assess the effect these cosolvents had on activity and selectivity. The results obtained using these cosolvents were generally lower than in their absence, and hence are not included in the results shown in Table 1.4, with the exception of entries 6 and 9.

Table 1.4 Müller's BFD and BAL-catalysed aliphatic acyloin condensation



1 **3** 0 - >90%
20 - 89% *ee*

entry	R	enzyme	yield (%)	*ee*[a] (%)	Abs. Conf.
1	CH_3	BAL	>90	40	*R*
2	CH_3	BFD	>90	34	*R*
3	CH_3CH_2	BAL	>90	60	*S*
4	CH_3CH_2	BFD	>90	63	*R*
5	$CH_3(CH_2)_2$	BAL	>90	50	*R*
6[b]	$CH_3(CH_2)_2$	BAL	>90	80	*R*
7	$CH_3(CH_2)_2$	BFD	>90	80	*R*
8	$CH_3(CH_2)_3$	BAL	>90	30	*R*
9[b]	$CH_3(CH_2)_3$	BAL	>90	60	*R*
10	$CH_3(CH_2)_3$	BFD	>90	65	*R*
11	$(CH_3)_2CH$	BAL	<1	n.d	n.d.
12	$(CH_3)_2CH$	BFD	<1	n.d	n.d.
13	$(CH_3)_3C$	BAL	<1	n.d	n.d.
14	$(CH_3)_3C$	BFD	<1	n.d	n.d.
15	$(CH_3)_2CHCH_2$	BAL	>90	89	*R*
16	$(CH_3)_2CHCH_2$	BFD	60	86	*R*
17	$(CH_3)_3CCH_2$	BAL	<1	n.d.	n.d.
18	$(CH_3)_3CCH_2$	BFD	<1	n.d.	n.d.

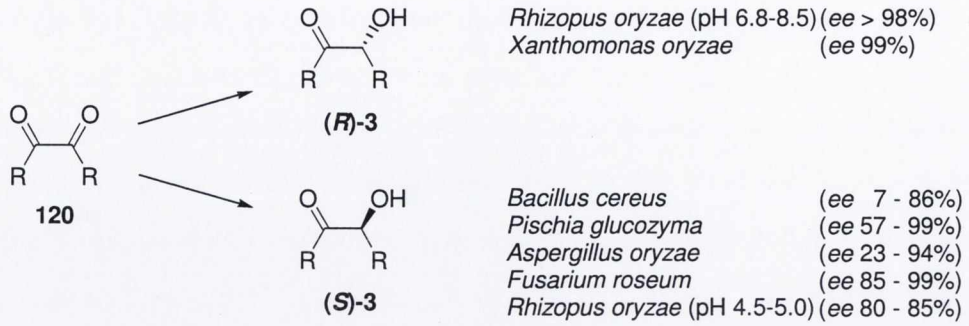
[a]Determined using chiral GC analysis (Chirasil-DEX CB or Lipodex D). [b]Using 20% (*v/v*) propan-2-ol.

The volatile substrate, acetaldehyde, was formed in high yields but with poor product enantiopurity (34 and 40% *ee*, entries 1 and 2). It is interesting that the (*R*)-enantiomer was formed preferentially in all cases, except in the BAL-catalysed dimerisation of propanal (entry 3). Of the linear aldehydes *n*-butanal was the superior, acquiring near-quantitative yields and 80% optical purity with both enzymes, albeit with the addition of propan-2-ol required in the case of BAL-catalysis (entry 6). Assessing the range of aldehydes probed within the reaction it is clear that hindered branched aldehydes were not tolerated (entries 11-14, 17 and 18).

1.3.3.2 Enzymatic stereoselective reduction of α-diketones

An alternative methodology for accomplishing enantioselective acyloin synthesis entails stereoselective bioreduction of α-diketones. It was found that using baker's yeast as a biocatalyst enabled the formation of acyloins.[160] However, this posed certain disadvantages - further reduction of the diketone to a *vic*-diol sometimes occurred, formation of both regioisomeric acyloins were frequently formed and often yields were only moderate. A considerable amount of research has pursued the selective formation of both enantiomers of different acyloins *via* reduction of the corresponding α-diketones. Microorganisms, employed as whole cell biocatalysts, have been used in the reduction of 1,2-diketones; for example, Fauve applied this concept in the formation of aliphatic acyloins using a range of different microorganisms to promote the reaction.[182] There are many recent accounts detailing the stereoselective enzymatic reduction of aromatic α-diketones or benzils (**120**).[183,184,185] As a result of extensive investigation into this practice, the reaction can now be tailored to exclusively produce one stereoisomer of a benzoin product by using a specific whole cell microorganism, as depicted in Scheme 1.20.[186,187] Although these reported methods are successful, they have so far not been sufficiently exploited for the efficient preparation of acyloins.

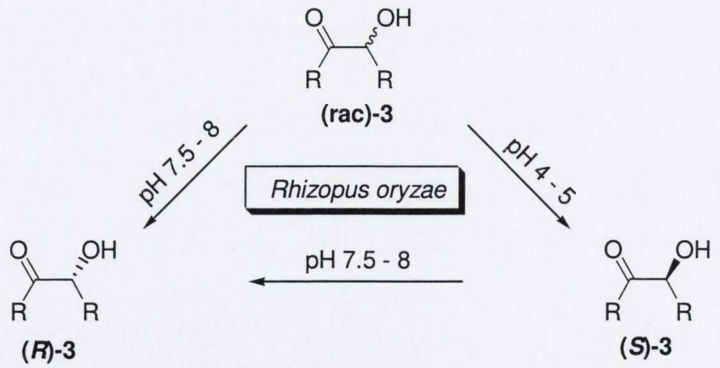
Scheme 1.20 Whole cell enzymatic stereoreduction of aromatic 1,2-diketones



1.3.3.3 Deracemisation of α-hydroxy ketones

Enzymatic deracemisation of acyloins has proved to be a promising approach to acquiring enantiopure α-hydroxy ketones.[162,188] Demir reported the ability of the mold *Rhizopus oryzae* to catalyse the chirality inversion of a racemic sample of aromatic benzoins, selectively affording either enantiomer by simple modification of the pH of the reaction medium, Scheme 1.21.[189,190] He postulated that the production of both enantiomers using different reaction conditions was due to the occurrence of different ketoreductases, displaying their optimum activity under different pH conditions.

Scheme 1.21 Enzymatic aromatic acyloin deracemisation using pH shifts

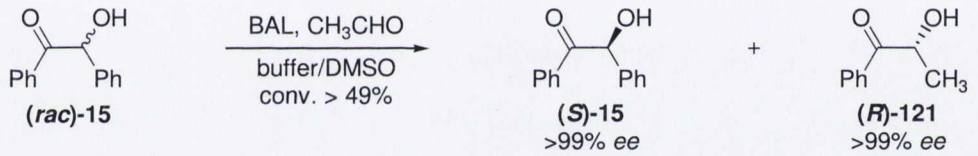


1.3.3.4 Enzymatic kinetic resolution of α-hydroxy ketones

A wide number of structurally diverse α-hydroxy ketones have been produced using enzymatic kinetic resolution procedures.[191,192] In 2001, Demir and Müller reported the enzymatic kinetic resolution of acyloins *via* a C-C bond cleavage mechanism.[175] In the

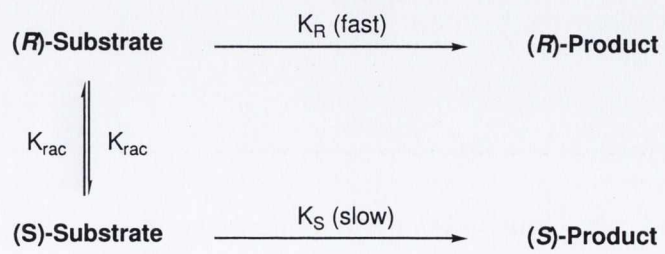
same publication the synthesis of (*R*)-benzoin from benzaldehyde, using the enzyme BAL, was described, attaining an almost quantitative yield and complete enantiopurity, (entry 1, Table 1.3). During this study it was discovered that (*S*)-benzoin was inactive towards BAL and could not be broken down by C-C- bond cleavage of the acyloin linkage. Demir and Müller also found that when (*R*)-benzoin was reacted with BAL, in the presence of acetaldehyde, quantitative formation of (*R*)-2-hydroxy-1-phenylpropanone ((*R*)-2-HPP, **121**, Scheme 1.22), in an optically pure form, occurred. The same reaction using (*S*)-benzoin failed. Using this knowledge the enzymatic kinetic resolution of a racemic sample of benzoin was achieved (Scheme 1.22). It is noteworthy that BAL, in the presence of benzaldehyde, produces the (*R*)-stereoisomer of benzoin exclusively, whereas using kinetic resolution methods, with acetaldehyde and BAL, the opposite antipode, (*S*)-benzoin, can be attained (albeit with 50% maximum yield).

Scheme 1.22 Enzymatic kinetic resolution of a racemic sample of benzoin



A disadvantage of kinetic resolution processes is that a maximum theoretical yield of only 50% can be reached. To overcome this limitation, dynamic kinetic resolutions (DKRs) have been employed, whereby an *in situ* racemisation of the remnant substrate under kinetic resolution conditions would theoretically lead to a 100% yield.[193,194] The concept of DKR of a racemate is depicted in Scheme 1.23 below.

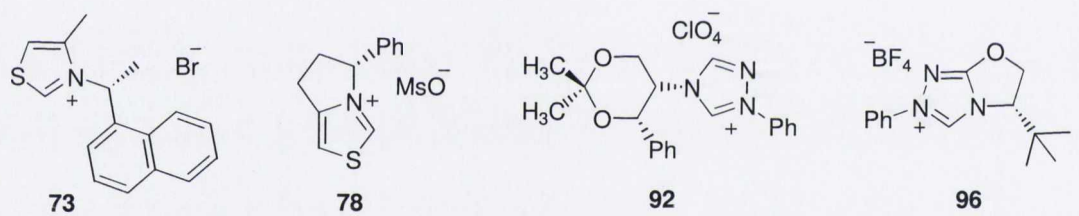
Scheme 1.23 Theoretical dynamic kinetic resolution of a racemate



1.3.4 Computational study of transition states in the benzoin condensation

Since the elucidation of the mechanism of the thiazolium salt-promoted benzoin condensation by Breslow in 1958,[26] the reaction process has been intensely examined and investigated from several standpoints. Mechanistic studies were compiled, with rate constants, deuterium exchanges and rate-limiting-steps being determined and analysed.[32-39,42] In 2004, Houk *et al.* reported the results of a computational study of the factors which influence the extent of asymmetric induction achievable by chiral thia- and triazolium catalysts in the enantioselective benzoin condensation.[195] The effect of the *E*/*Z* geometry of the Breslow intermediate and the relative energies of the transition states leading to either product antipode in the presence of a range of carbene catalysts known at the time (*i.e.*, **73**, **78**, **92** and **96,** Figure 1.14) were examined.

Figure 1.14 Chiral precatalysts examined in the benzoin condensation by Houk

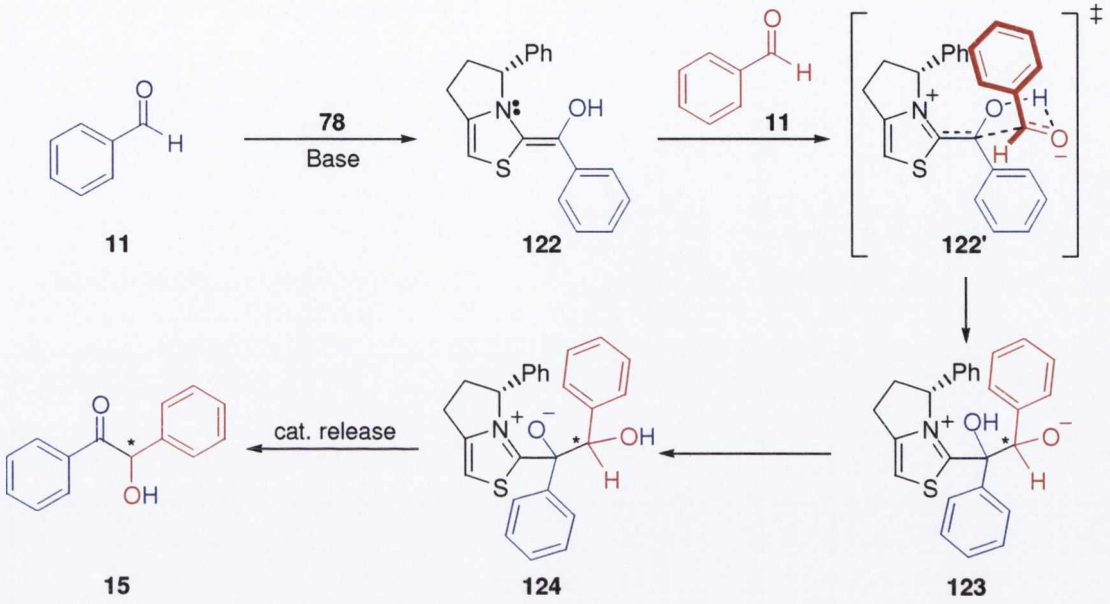


73 **78** **92** **96**

To assess the transformation of the prochiral starting material (aldehyde) to a chiral product, the reaction process was computationally assessed. Scheme 1.24 (*vide infra*) depicts the benzoin condensation mechanism using benzaldehyde as the reacting substrate and thiazolium salt **78** as the precatalyst.

Initially, precatalyst **78** in the presence of base, forms an *in situ*-generated carbene, which nucleophilically attacks a benzaldehyde molecule (highlighted in blue text) resulting in the formation of the Breslow intermediate **122**. It should be noted that Houk determined, in all cases, that the *E* conformation of the enolamine **122** predominates, being energetically more favourable than the *Z* isomer.

Scheme 1.24 Study of the origin of stereoselectivity in the benzoin condensation

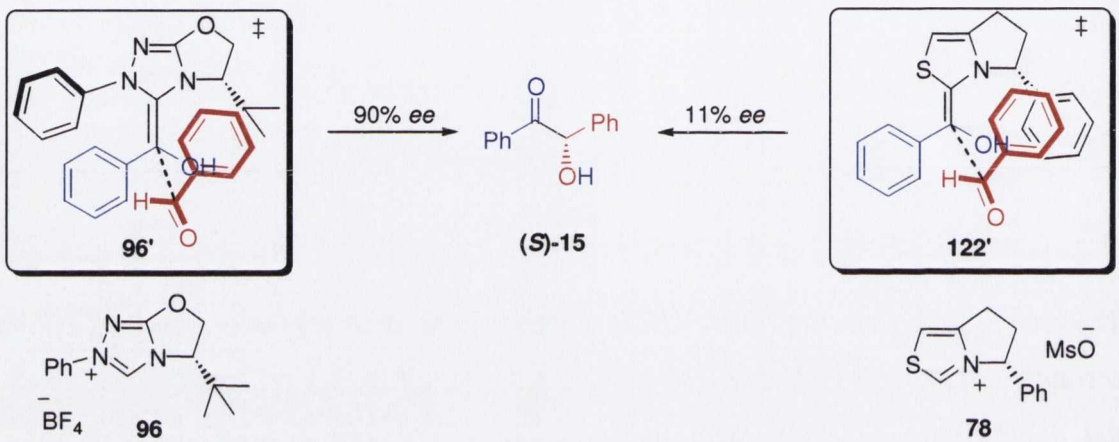


The crucial stereocentre-forming step in the reaction is attack of intermediate **122** on the second benzaldehyde molecule (indicated in red text); attack on either the *re* or *si* face of the approaching aldehyde determines the stereochemical outcome of the reaction process. The transition state (**122'**) is depicted in Scheme 1.24. It is at this point that the chiral centre of the benzoin product (**15**) is formed (on the red benzaldehyde molecule). A stabilising interaction occurs *via* an intramolecular hydrogen bond between the hydroxyl group of the Breslow intermediate and the oxygen atom of the carbonyl component of benzaldehyde. This interaction results in the formation of a 5-membered cyclic intermediate (**122'**) that was proposed to rigidify the transition state and also facilitate the subsequent intramolecular proton transfer (*i.e.*, **123** to **124**), by stabilisation of the increasing negative charge about the carbonyl oxygen atom. Proton transfer, followed by liberation of the carbene catalyst, completes the catalytic cycle. Houk focused his computational calculations on the geometry of the Breslow intermediate (enolamine) and the orientation of the approaching (red) benzaldehyde molecule, *i.e.*, from which face of the Breslow enolamine does an attack occur, and to what face of the approaching aldehyde is the addition made?

Houk noted that although there was a structural similarity between triazolium salt **96** and the thiazolium variant **78**, there was a dramatic difference observed in product yields and

enantiomeric excesses. Using precatalyst **96,** benzoin was isolated in 83% yield and with 90% optical purity, whereas **78** provided essentially racemic benzoin (11% *ee*) in 20% yield. The lack of an *N*-phenyl substituent on the thiazolium salt was deemed to be the likely cause of the poor enantioselectivity. The precatalysts alongside their calculated lowest-energy stereocentre-forming transition states (**96'** and **122'**) are shown in Scheme 1.25.

Scheme 1.25 Houk's predicted transition states for attack of Breslow intermediate



As previously stated, the *E* isomer of the enolamine was the most energetically favourable conformation in both examples. Houk's calculations also indicated that in both transition states, due to the presence of the sterically demanding *t*-Bu group (**96'**) and bulky catalyst phenyl ring (**122'**) residing below the plane of the cyclic carbene frame, attack of the Breslow intermediate occurred from its less hindered *si* face. It was also found that the most favourable orientation of the second benzaldehyde molecule resulted in attack of the enolamine to its *re* face. The decisive factor influencing the stereochemical outcome of reaction proceeding through **96'** was the orientation of the aldehyde phenyl moiety, which strives to avoid a steric clash with either the catalyst's *t*-Bu moiety or the *N*-phenyl group. Additionally, some π-aryl-iminium ion interaction was present in the most favoured *re* transition state. For transition state **122'** the most noticeable difference is the lack of a repulsive aryl-aryl steric interaction that would have been present due to an *N*-aryl substituent. A marginal disparity for alignment of the benzaldehyde molecule for attack on its *re* face exists due to a favourable but weak π-aryl-iminium ion attraction (0.7 kcal/mol). These factors are indicative of a nonselective

process, as is determined experimentally (11% *ee*). It should be noted that Houk incorporated an incorrect model of transition state **122'** in his calculations, assigning a (*S*)-configuration to the thiazolium ring *N*-benzyl stereocentre instead of the (*R*)-enantiomer, thus calculating that the opposite enantiomer, (*R*)-benzoin, would be most favourably formed.[195]

Of the four catalysts that were examined, the computational calculations allowed the authors to make predictions that were in qualitative agreement with experimental results. Houk presented a useful predictive tool for exploring and understanding the origins of stereoselectivities of large catalytic systems within the benzoin condensation. The methodology could be used as an important aid in the design of new asymmetric catalysts. His calculations revealed that the factors governing the stereoselectivity of the benzoin condensation are:

1. The *E*/*Z* geometry of the Breslow intermediate - the *E* isomer was consistently found to predominate.
2. Chiral steric bulk contained within the catalyst scaffold influences and can often determine the trajectory of the approaching aldehyde substrate.
3. The presence of a triazolium *N*-aryl substituent enables discrimination of the spatial orientation about the carbene plane. Essentially, triazolium ions of the type showed above (Figure 1.14) form Breslow intermediates in which three of the four quadrants dividing the space around the intermediate are occupied by the catalyst moieties, leaving only a single quadrant free for occupation by the benzaldehyde phenyl group. In this way, an orderly and controlled approach of the benzaldehyde electrophile is assured.
4. Favourable π-aryl-iminium ion interactions were found to stabilise the transition state.

1.4 The intramolecular benzoin condensation reaction

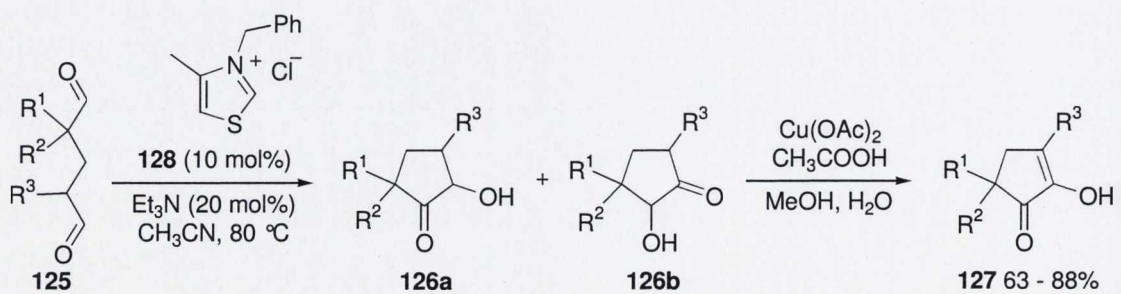
1.4.1 Historical perspective

Asymmetric organocatalysis is a rapidly and continuously evolving area of organic chemistry.[196] In the last 50 years NHCs have manifested themselves as powerful and widely applicable organocatalytic tools within this thriving and fast-moving subdiscipline.[145,197] The central core of the benzoin condensation reaction is the NHC-mediated carbon-carbon bond formation between two aldehyde molecules; this process is specifically known as the *intermolecular homobenzoin condensation.* The benzoin condensation is not limited to specifically intermolecular dimerisation and to solely aldehyde functionality. Current developments have ventured into the intramolecular condensation of both aldehydes and ketones, whereby ketones are also employed as electrophiles in the reaction process; examples of intramolecular processes include aldehyde-aldehyde,[198] and aldehyde-ketone[199] couplings.

1.4.2 Aldehyde-aldehyde intramolecular benzoin condensation

In contrast to the much studied intermolecular homobenzoin condensation, the intramolecular benzoin condensation has received far less attention and consequently has been developed for a much shorter period of time. The earliest report of an intramolecular benzoin condensation reaction (involving dimerisation of a dialdehyde) emerged in 1976; Cookson and Lane demonstrated the (achiral) cyclisation of pentanedials by NHC catalysis, Scheme 1.26.[198]

Scheme 1.26 Cookson's seminal study on the intramolecular benzoin condensation

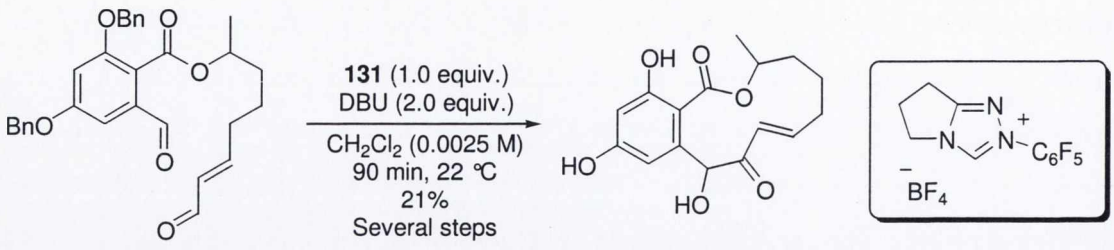


Using anhydrous glutaraldehyde (**125**, where R^1, R^2 and R^3 = H), with achiral salt **128** in the presence of triethylamine, the cyclisation of **125** was achieved in 78% yield. The 2-hydroxycyclopentanone (**126**) could be oxidised to the corresponding 2-hydroxypentenone **127**, as compounds of type **127** were attested to be used as important flavouring materials in the food industry.[200] Employing several different aliphatic dialdehydes (where R = H or CH_3) a range of cyclic ketols was synthesised, which were oxidised to their corresponding ketolenes (**127**). When the dimerisation protocol was applied to unsymmetrical dialdehydes a mixture of isomeric ketols was obtained, **126a** and **126b**, which complicated the reaction outcome.

It was several years later before another example of an intramolecular benzoin condensation appeared.[201] Gleiter utilised an intramolecular dialdehyde condensation reaction during a multi-step synthesis of cyclic vicinal tetraketones. In 2007, Miller demonstrated the macrocyclisation of a selection of aromatic-aliphatic dialdehydes, which annulated in regrettably moderate yields (16 - 47%).[202] He found that the yield was influenced by ring size, with lower yields being returned with decreasing ring size, presumably due to greater ring strain. A concerning drawback within his reaction conditions was competing aldol side reactions and non-catalytic stoichiometric employment of the bicyclic *N*-pentafluorophenyl triazolium salt **131**. Amongst the macrocycle syntheses, Miller also attempted a lengthy and rather tedious synthesis of *tran*-resorcylide **130** (Scheme 1.27). *trans*-Resorcylide is a 12-membered macrocycle that belongs to a family of naturally occurring benzoic acid-derived macrolide plant growth inhibitors[203] and the first total synthesis of both *cis*- and *trans*-resorcylide had only recently been completed.[204] Miller innovatively incorporated an intramolecular benzoin condensation step into the complicated synthesis of this highly functionalised natural product, achieving 21% yield of protected acyloin product, Scheme 1.27. After several steps requiring acylation, deprotection, deoxygenation and oxidation of the elaborate compound, *trans*-resorcylide (**130**) was isolated.

Remarkably and most surprisingly, to date, there does not appear to be an asymmetric aldehyde-aldehyde intramolecular benzoin condensation reaction reported in the literature.

Scheme 1.27 Intramolecular condensation as part of *trans*-resorcylide synthesis

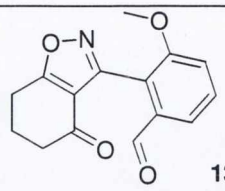
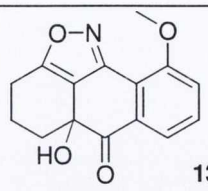
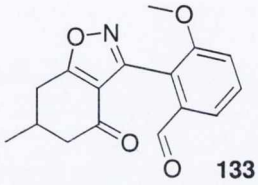
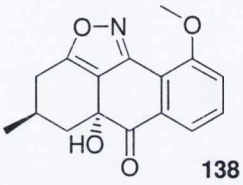
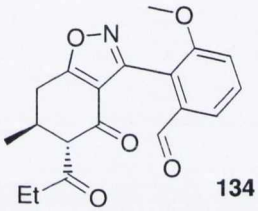
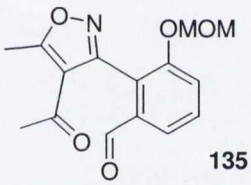
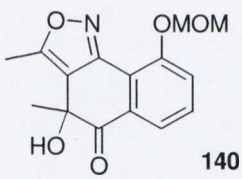
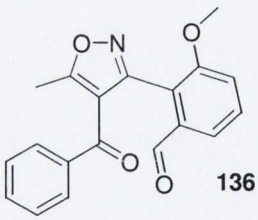
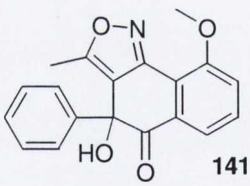


129 130 131

1.4.3 Aldehyde-ketone intramolecular benzoin condensation

The intramolecular benzoin condensation reaction involving dimerisation of an aldehyde-ketone has received far more attention than the dialdehyde version of the reaction process, and is by far the more successful of the intramolecular processes. This is as a result of the aldehyde group being generally more susceptible to nucleophilic attack by the carbene catalyst than the ketone centre, and accordingly leads to a more predictable one-product reaction outcome, if aldol side-reactions are deterred. Surprisingly, it was only in 2003 that the first keto-aldehyde intramolecular coupling attempts become known. Suzuki and Bode demonstrated an elegant yet facile synthesis of novel polycyclic preanthraquinones *via* base promoted condensation of functionalised isoxazoles.[199] This type of carbon-carbon bond coupling had not been previously reported and with optimal conditions at hand the annulations of isoxazoles (**132-136**) proceeded smoothly with excellent yields and diastereoselectivities, to give tetracyclic acyloins **137-141**, Table 1.5. Note: optimisation of the reaction process led to the reactions being performed at 0.05 M concentration in *t*-BuOH at 40 °C for 30 minutes, employing 70 mol% DBU as base and 20 mol% of an achiral thiazolium precatalyst (not shown).

Table 1.5 Suzuki's seminal achiral aldehyde-ketone intramolecular condensation

entry[a]	keto-aldehyde	product	diastereomeric ratio	yield (%)
1	 **132**	 **137**	-	95
2	 **133**	 **138**	>20:1	90
3	 **134**	**139**	>20:1	79
4	 **135**	 **140**	-	96
5	 **136**	 **141**	-	94

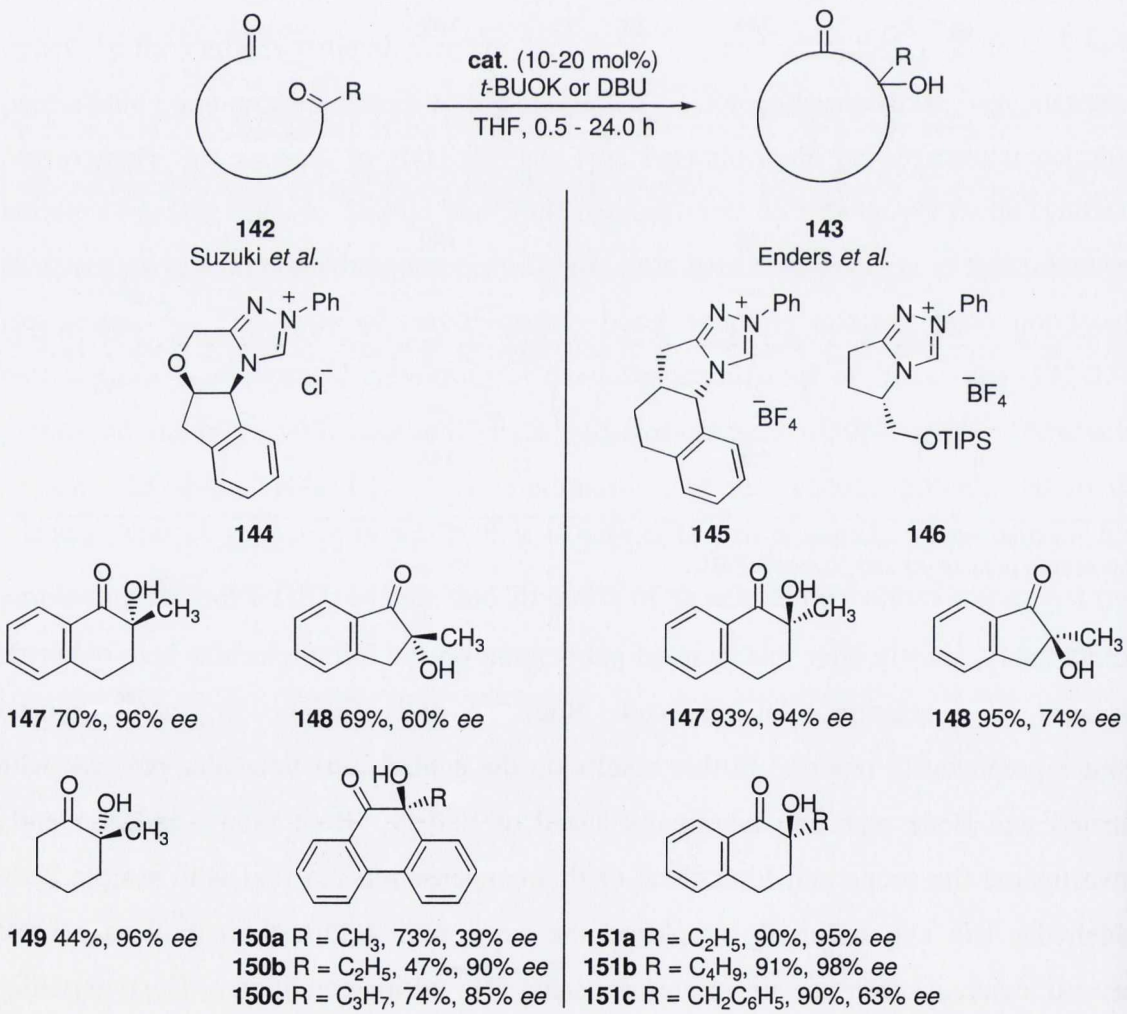
[a]All reactions were performed at 0.05 M in *t*-BuOH at 40 °C for 30 min, using 20 mol% achiral thiazolium precatalyst and 70 mol% DBU.

Remarkably, shortly after this seminal publication on the intramolecular keto-aldehyde benzoin condensation, Suzuki and Bode,[205] and Enders *et al.*[206] almost contemporaneously reported further results on the achiral intramolecular process, with Suzuki and Bode reporting marginally ahead of Enders. Both groups independently investigated the scope and limitations of this condensation reaction with simple keto-aldehydes and extraordinarily employed the same achiral thiazolium precatalyst and several identical substrates, under almost analogous reaction conditions. The two parties presented similar findings; condensations forming five and six membered ring structures

were afforded in moderate yields whereas difficulties were encountered in the cyclisation of larger ring sizes, and a trend emerged indicating that aliphatic-aromatic ketoaldehydes generally performed better than an aromatic-aliphatic ketoaldehyde.

Additionally, asymmetric intramolecular benzoin condensation reactions were synchronously reported by Suzuki and Bode[207] and Enders.[208] Remarkably similar precatalysts were chosen to facilitate the reaction process and once again, identical ketoaldehyde substrates were chosen. Scheme 1.28 displays the results of the two studies. Suzuki utilised an amino indanol-derived precatalyst **144** that had been originally designed by Rovis,[209] while Enders created novel polycyclic triazolium salts **145** and **146**.

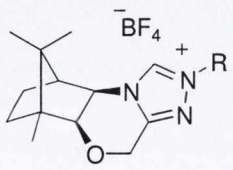
Scheme 1.28 Suzuki and Bode's asymmetric intramolecular benzoin condensations



Using precatalyst **144** and DBU as base, Suzuki and co-workers provided a suite of annulated hydroxy-compounds, with variable yields and respectable optical purities, excluding product **150a** (39% *ee*). It should be noted that biaryl ketoaldehyde-derived products **150** were formed with the opposite stereochemistry (*S*-enantiomer) to all other products; this Suzuki claimed was possibly due to a change in the geometry of the enolamine Breslow intermediate. Enders differed from Suzuki in that he employed two polycyclic precatalysts, **145** and **146**, in the synthesis of an array cyclic acyloins. Both groups reported the use of substoichiometric amounts of base, relative to the precatalyst, to suppress competing aldol side reactions. Overall, Enders' precatalysts promoted more efficient and selective reactions, though they were applied to a restricted substrate scope.

Over the last few years further progress has been made in the investigation of the intramolecular benzoin condensation. In 2006, Enders reported the asymmetric synthesis of chromanones *via* this process, in conjunction with a selection of aliphatic-aromatic ketoaldehydes.[210] S. L. You also reported the synthesis of asymmetric chromanones using novel chiral triazolium precatalysts derived from *d*-camphor (**152**, Figure 1.15), generating near-quantitative yields with excellent product enantiomeric excesses.[211] Suzuki disclosed a range of novel amino indanol-derived tetracyclic triazolium salts that were almost identical to precatalyst **144**, except that the *N*-substituent incorporated different polyfluorinated phenyl units, **153**, Figure 1.15.[212] These novel salts facilitated the successful cyclisation of a range of enolisable ketoaldehydes with excellent levels of product enantiopurity and yields.[213] The latest addition to the intramolecular acyloin formation process was the stereoselective generation of bicyclic aliphatic tertiary alcohols.[214]

Figure 1.15 Chiral salts used in the intramolecular benzoin condensation reaction



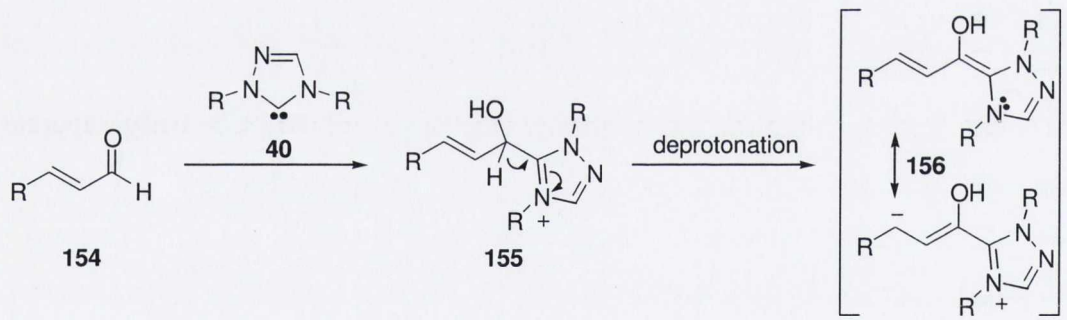
152a R = C_6H_5
152b R = 4-CH_3O-C_6H_4
152c R = 2,4,6-$(CH_3)_3$-C_6H_2
152d R = C_6F_5
152e R = 3,5-$(CF_3)_2$-C_6H_3

153a R = C_6F_5
153b R = 2,6-F_2-C_6H_3
153c R = 2-F-C_6H_4
153d R = 3,5-F_2-C_6H_3
153e R = 3,5-$(CF_3)_2$-C_6H_3

1.5 Variants of the benzoin condensation reaction

The intermolecular and intramolecular benzoin condensation reactions have been described in detail. Due to significant advancements in recent years, the scope of this reaction can now be extended beyond the use of carbonyl groups alone to include other electrophiles. Examples of such extensions include *O*- to *C*-acyl transfer involving oxyazole derivatives,[215,216,217] aldehyde oxidation (resulting in ester formation),[218] the Stetter reaction (both intramolecular and intermolecular processes involving an α,β-unsaturated aldehyde as the electrophilic counterpart),[145] aldehyde-imine coupling,[219] and most recently the intramolecular addition of an aldehyde to a nitrile component.[220] Included under the umbrella of the ever-expanding benzoin condensation reaction are addition reactions to homoenolate intermediates or equivalents. This involves formation of a catalytic *Umpolung* species or Breslow intermediate **156** from an α,β-unsaturated aldehyde **154**, which subsequently acts as the nucleophilic component within the given reaction, Scheme 1.29.

Scheme 1.29 Formation of a homoenolate equivalent species



There are a vast number of novel and synthetically important examples of homoenolate equivalent-induced reactions, whereby intriguing and extraordinary products have been obtained. Bode,[221] Scheidt[222,223] and Nair[224] are well-renowned for their efforts and innovative research in this niche area of organocatalysis. For the sake of brevity, this section shall focus on the Stetter and aldehyde-imine coupling reactions only, which rely on the formation of the standard Breslow intermediate (one that is derived from addition of the carbene catalyst to a simple aldehyde substrate, not an α,β-unsaturated aldehyde, as above).

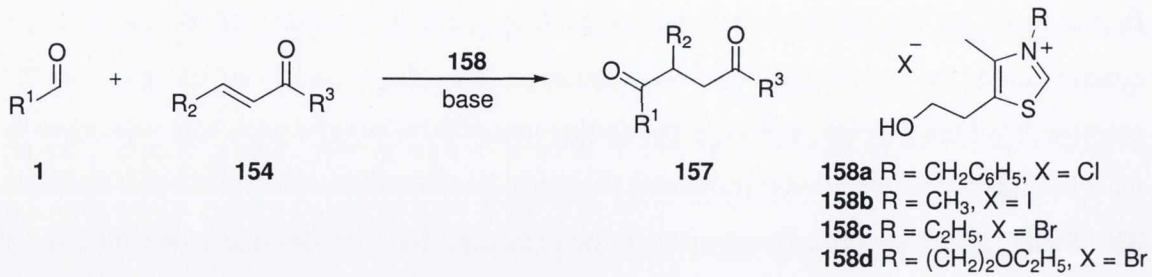
1.5.1 The Stetter Reaction - a brief overview

In the early 1970s, pioneering work by Stetter resulted in extension of the benzoin condensation to include Michael acceptors as the electrophilic counterpart of the reaction.[225] This process, entailing the conjugate addition of an acyl anion equivalent to an α,β-unsaturated carbonyl compound, has since become known as the Stetter reaction. The Stetter reaction, initially reported to be catalysed by cyanide, and subsequently by azolium salts, provides a versatile and facile method for the creation of contiguous 1,4-dicarbonyl,[226,227] 1,4-ketoester and 1,4-ketonitrile compounds.[228] The mechanism of the Stetter reaction is analogous to that of the classical benzoin condensation with formation of the Breslow intermediate from an aldehyde substrate. This nucleophilic species consequently adds to the electrophilic Michael acceptor at the 3-position, resulting in the formation of a 1,4-adduct. The Stetter reaction has attained an important status in organic chemistry due to its wide applicability in various fields of synthetic chemistry. Some of these include the synthesis of cyclopentanone derivatives,[229,230] total synthesis,[231] solid-phase organic synthesis[232] and the preparation of extended heterocyclic systems.[233,234]

1.5.1.1 The intermolecular Stetter reaction

The intermolecular Stetter reaction involves the coupling of two distinctly separate reactants, an aldehyde and a Michael acceptor, **154**, resulting in 1,4-functionalised products, **157**, Scheme 1.30. Stetter conducted considerable research on this reaction and revealed that the reaction could be catalysed by a large range of thiazolium salts, such as **158**, Scheme 1.30.[228] It was determined that thiazolium salt **158a**, containing a benzyl group, was optimal for facilitating the addition of aliphatic aldehydes, whereas **158b** and **158c** were preferable for use in reactions involving aromatic aldehydes. Heterocyclic aldehydes were compatible with all four precatalysts, while **158d** promoted the addition reaction utilising α,β-unsaturated esters. Stetter *et al.* demonstrated that a variety of aromatic and aliphatic aldehydes could participate in the intermolecular Stetter reaction. Additionally, they were able to successfully employ a range of different Michael acceptors. However, Michael acceptors that contained a β-substituent often resulted in reduced reactivity and were generally limited to chalcones.[235]

Scheme 1.30 Achiral intermolecular Stetter reaction using thiazolium salts



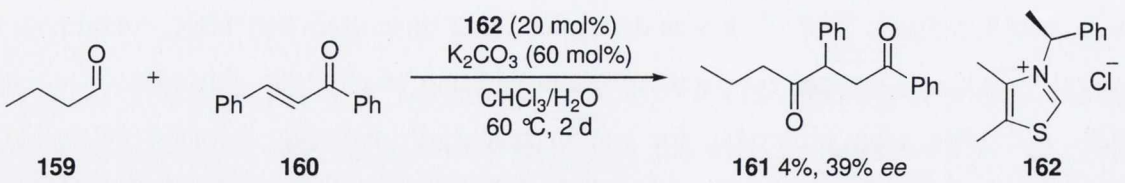
1 **154** **157**

158a R = $CH_2C_6H_5$, X = Cl
158b R = CH_3, X = I
158c R = C_2H_5, X = Br
158d R = $(CH_2)_2OC_2H_5$, X = Br

1.5.1.2 Developments in the asymmetric Stetter reaction

The involvement of a prochiral Michael acceptor can potentially result in the formation of two new contiguous stereocentres, and such 1,4-bifunctional compounds are important building blocks for the synthesis of natural products.[236] The asymmetric Stetter reaction offers a practical route to the synthesis of this class of compounds. Seminal studies on the asymmetric intermolecular variant of this reaction emerged in 1989 from Enders' research group, with two examples interestingly reported as mere footnotes in reviews.[237,238] Both studies employed thiazolium salts to promote the reaction; the more selective of the two examples is detailed in Scheme 1.31. The intermolecular dimerisation of butanal (**159**) and chalcone (**160**) was performed using a biphasic solvent system, achieving a disappointingly low yield of 1,4-diketone **161** (4%), with poor optical purity (39% *ee*).

Scheme 1.31 Seminal study on the asymmetric intermolecular Stetter reaction



159 **160** **161** 4%, 39% *ee* **162**

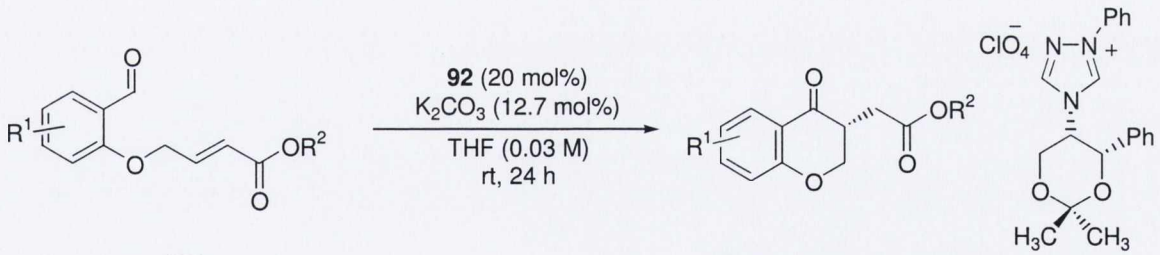
Unfortunately, the catalytic activity of chiral thiazolium salts in this intermolecular process remained generally low. Although Stetter had previously reported the use of triazolium salts as catalyst precursors in the Stetter reaction,[228] some triazol-5-ylidenes had been shown to form stable adducts with several Michael acceptors.[239] This may be a

possible reason for their poor performance and limited success in this reaction, when compared with the achievement of triazolium salts in the benzoin condensation.

1.5.1.3 The intramolecular Stetter reaction

In 1979, Trost reported the first entirely stereocontrolled total synthesis of (±)-Hirsutic acid C,[231] a tricyclic sesquiterpene known to possess antibiotic and antitumour activity.[240,241] Within the sequence of synthetic steps was the earliest known example of an intramolecular Stetter reaction, using a thiazolium salt to abet the reaction. Surprisingly, it was not until 1995 that another example of an intramolecular Stetter reaction emerged, with Ciganek describing the cyclisation of a suite of appended aldehyde-α,β-unsaturated-ketones, providing 5- and 6-membered annulated benzofuranones and pyranones.[242] The intramolecular process was first rendered asymmetric by Enders *et al.* in 1996, using ketal-derived triazolium precatalyst **92**, Scheme 1.32.[243] The intramolecular cyclisation of **163** resulted in the synthesis of enantiomerically enriched chromanones, **164**, in modest to good yields and enantiospecificities. The cyclisation of salicylaldehyde-derived substrate **163**, (where R^1 = H and R^2 = CH_3) has since become a benchmark test for comparing catalytic efficiency in the Stetter reaction.

Scheme 1.32 Ender's seminal asymmetric intramolecular Stetter reaction



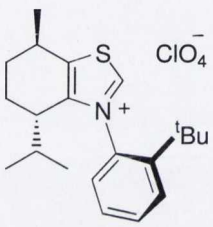
163 **164** 22 - 73%, 41 - 74% *ee* **92**

1.5.1.4 Catalyst systems achieving excellent asymmetric induction in the intramolecular Stetter reaction

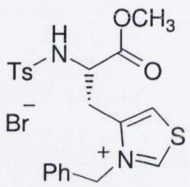
The intramolecular Stetter reaction has been met with far more success and advancements than the intermolecular version. Many chiral triazolium salt precatalysts have promoted highly enantioselective annulations, often in almost quantitative yields. A selection of such precatalysts is depicted below in Figure 1.16. In 2004, Bach

employed the axially chiral thiazolium salt **86** as a promoter for the cyclisation of the benchmark substrate **163**, attaining a product yield of 75% with 50% *ee*.[119] Miller reported modest results in the intramolecular process, using thiazolium salt **165** and peptide-based **166**, achieving asymmetric inductions as high as 80%.[244] Matsumoto and Tomioka developed the C_2-symmetric imidazolinium variant **167**, which, in the presence of a base, supplied reasonable yields (33-74%) and product enantiomeric excess ranging from 53-80%.[245]

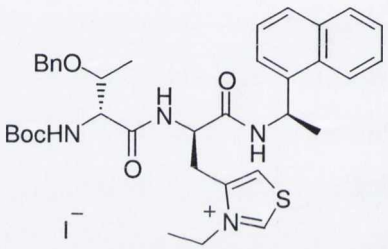
Figure 1.16 Chiral precatalyst systems used in the asymmetric intramolecular Stetter reaction



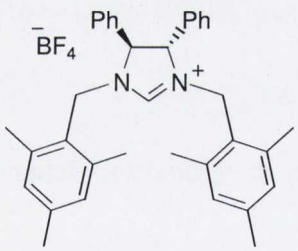
86
Bach (2004)



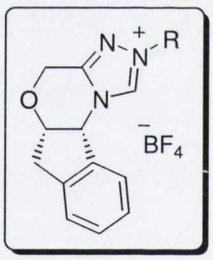
165
Miller (2005)



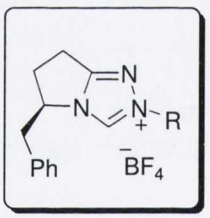
166
Miller (2005)



167
Matsumoto (2006)



168a R = C_6H_5
168b R = 4-CH_3O-C_6H_4
168c R = C_6F_5
168d R = 4-CF_3-C_6H_4
Rovis (2002 - 2010)



169a R = C_6H_5
169b R = 4-CH_3O-C_6H_4
169c R = C_6F_5
169d R = 4-CF_3-C_6H_4
Rovis (2002 - 2010)

In 2002, Rovis disclosed his first of numerous studies on the asymmetric intramolecular Stetter reaction. Triazolium salt precatalysts, **168a**,**b** and **169a**, in the presence of base, afforded high yields and product enantiomeric excesses in the cyclisation of aldehyde-α,β-unsaturated-ketones.[209] Indanol-based precatalysts **168** and pyrrolidine-fused ring systems **169** have found widespread application in the Stetter reaction and since Rovis's primary report on this intramolecular process, he has, in effect, been considered the leader in this area of *Umpolung* chemistry. Following his seminal publication on this process, Rovis investigated many aspects of the reaction, including evaluation of the

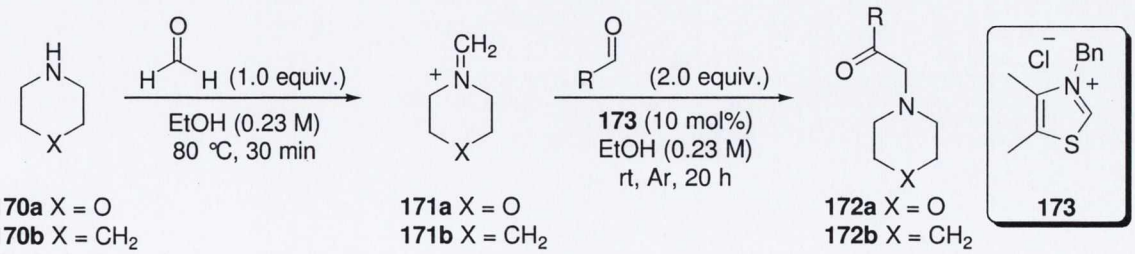
effect of using different Michael acceptors,[246] the construction of quaternary stereocentres using the Stetter reaction,[247] and the effect of pre-existing stereocenters in the Michael acceptor.[248,249] Recently, Rovis has expanded the scope of the intramolecular Stetter reaction to include the synthesis of hydrofuranones *via* desymmetrisation of cyclohexadienones,[250] use of either vinylphosphine oxides or vinylphosphonates as the Michael acceptor,[251] and the synthesis of functionalised cyclopentanones using a multicascade catalytic sequence.[252] It should be noted that other methods of promoting the Stetter reaction involving NHC catalysis, include ROMPgel supported reagents,[253] solid phase supported reagents[254] and ionic liquids promoted by microwave irradiation (whereby the ionic liquid, in the presence of base, acts as both the active catalyst and the reaction medium).[255,256]

1.5.2 Aldehyde-imine coupling reaction

1.5.2.1 Seminal study of the coupling of aldehydes to imine substrates

The aldehyde-imine coupling reaction involves the intermolecular addition of an aldehyde and an imine and provides a facile method for the synthesis of α-amino ketones, which are an important class of biologically relevant molecules.[257,258] This reaction was first revealed in 1988, when Castells and López-Calahorra reported a then novel reaction involving the addition of an iminium ion and an aldehyde, Scheme 1.33.[219]

Scheme 1.33 First reported example of aldehyde-imine addition



170a X = O
170b X = CH_2

171a X = O
171b X = CH_2

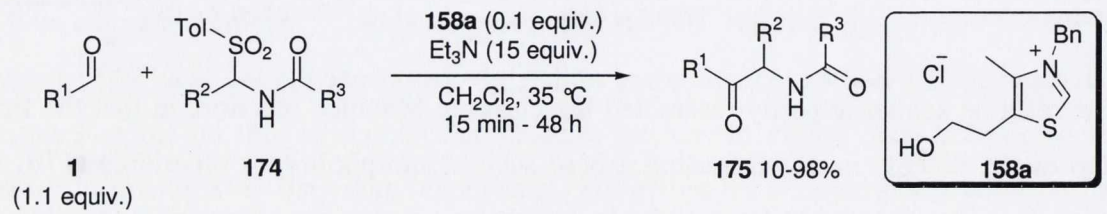
172a X = O
172b X = CH_2

The reaction sequence partly resembled the classical Mannich reaction, in that the first step of the process involved heating a base such as morpholine or piperidine (**170**) in ethanol, in the presence of formaldehyde, which gave rise to the corresponding iminium

ion **171**.[259] The coupling of an array of aldehydes to the *in situ*-generated iminium ions was observed using an achiral thiazolium salt precatalyst, in the presence of triethylamine to provide the α-amino ketone products **172**. Notably, electron-rich aromatic and aliphatic aldehydes were utilised in the reaction and yields of α-amino ketones were attained in the range of 20-47%. Castells and López-Calahorra also reported that temperature played an important role in the reaction process; when higher temperatures were employed the major product was the corresponding α-hydroxy ketone, from the dimerisation of two aldehyde molecules. It was therefore postulated that the α-amino ketone was the kinetically favoured product, whereas under thermodynamic conditions the α-hydroxy ketone prevailed.

Several years later an additional contribution to the aldehyde-imine coupling reaction emerged, with a report stemming from the research laboratories of Merck & Co. Inc.[260] On this occasion, Murry prepared a broad range of α-amido ketones (**175**) using achiral thiazolium salt precatalyst **158a** to promote the addition of aldehydes to *in situ* formed acyl imines - under mild reaction conditions (Scheme 1.34). Tosylsulphonylamides (**174**) were employed as the imine precursors due to their ability, in the presence of base, to eliminate sulphinic acid and liberate the acyl imine substrate. As a result, 15 equivalents of triethylamine were required to ensure complete consumption of starting materials. The reaction conditions accommodated a wide range of aldehyde substrates, encompassing electron-deficient, electron-rich, aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes. The reaction was also found to be very tolerant of the amide portion of the tosylamide, including common amine protecting groups such as Cbz and Boc groups. However, tosylamides derived from aliphatic aldehydes failed under the given reaction conditions due to the known propensity of these substrates to readily isomerise to enamides.[261]

Scheme 1.34 Murry's study of the coupling of aldehydes and acylimine

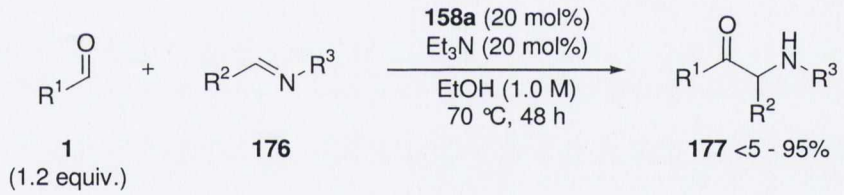


1 (1.1 equiv.) **174** **175** 10-98% **158a**

Murry conducted a series of crossover experiments and concluded that the α-amido ketones were formed under kinetic rather than thermodynamic control, in agreement with the previous study carried out by Castells and López-Calahorra.[219]

Both Castells and Murry used activated imine substrates (iminium salts and acyl imines) in their aldehyde-imine coupling experiments and manipulation of the reaction conditions provided the kinetically favoured products. Contrastingly, S. L. You disclosed the successful cross-coupling of aldehydes with unactivated imines by means of thermodynamic control, whereby less reactive imines were reacted with the Breslow intermediate at higher temperatures resulting in the formation of achiral α-amino ketones (**177**) from a wide range of substrates, see Scheme 1.35.[262] Electronically diverse aromatic imines proved excellent substrates, providing high product yields (5-95%), whereas aliphatic substrates were not tolerated in the reaction process.

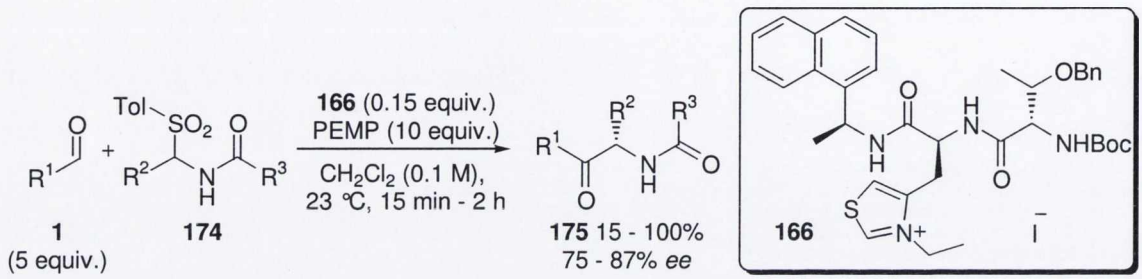
Scheme 1.35 You's thermodynamically controlled aldehyde-imine coupling reaction



Interestingly, to date only one example of an asymmetric intermolecular aldehyde-imine coupling reaction has emerged.[263] Miller reported the use of a thiazolylalanine-containing peptide, **166**, that promoted an efficient and enantioselective coupling of aldehydes to *in situ*-generated acyl imines, Scheme 1.36. Miller established that an excess of hindered base, such as pentamethylpiperidine (PEMP), was necessary for precatalyst activation, and also to ensure complete formation of the acyl imine substrate, as the imine was generated *in situ* from tosylsulphonylamides as per Murry's protocol. Racemisation was problematic under the reaction conditions employed due to the presence of excess base. Accordingly a maximum reaction time of 2 hours was chosen, in order to minimise the erosion of optical purity. The reaction was found to be low-yielding in the presence of benzaldehyde (15% yield after 2 hours, 83% *ee*). A selection of α-amido ketones (**175**) was synthesised using electron-deficient aromatic aldehydes

and electron-rich imines (both aromatic and aliphatic), in moderate yields (excluding benzaldehyde, yields were 57-100%) and with high optical purities (75-87% *ee*).

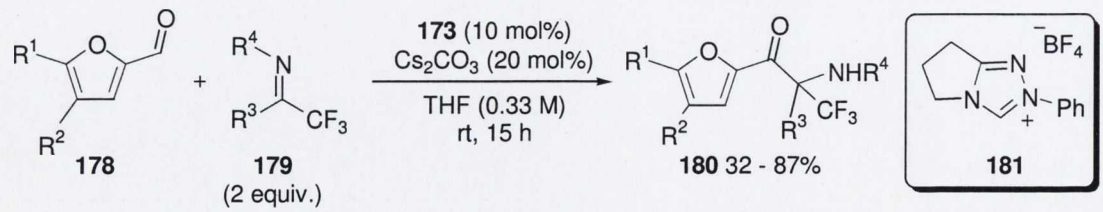
Scheme 1.36 Seminal example of the asymmetric aldehyde-imine addition reaction



1.5.2.2 Achiral aldehyde-ketimine coupling reaction

In 2009, the exploitation of ketimines as electrophiles in the intermolecular aldehyde-imine addition reaction was reported by Enders.[264] From the screening of different aromatic and heteroaromatic aldehydes it was ascertained that benzaldehyde was not reactive enough to serve as the nucleophilic reaction component. Furfuraldehyde, being more reactive than benzaldehyde, was found to be a more suitable candidate in the reaction. Consequently, following optimisation of the reaction protocol, a suite of novel α-amino-α-trifluoromethyl ketones (**180**) derived from furan-carbaldehydes (**178**) was synthesised, using the bicyclic triazolium salt **181**, with yields ranging from moderate to very good (32-87%), Scheme 1.37.

Scheme 1.37 Enders' seminal achiral study of aldehyde-ketimine coupling



It should be noted that the synthesis of such crossed products, α-amino- and α-amido ketones, has found synthetic and practical uses within the chemical industry. Murry *et al.*, of Merck & Co. Inc., incorporated their synthesis of these compounds (**175**, Scheme

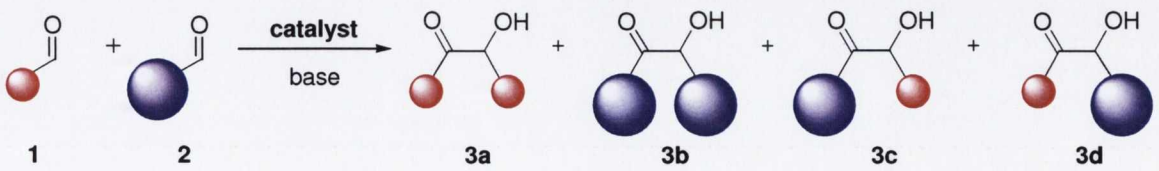
1.34) into a remarkably facile one-pot procedure to create substituted imidazoles, oxazoles and thiazoles.[265] Building upon this result, Lam reported the use of a traceless solid support sulphonyl linker that generated the acyl imine *in situ*, and enabled the synthesis of a range of heterocycles.[266] Recently, Scheidt disclosed the NHC-catalysed addition of acylsilanes to *N*-diphenylphosphinoylated imines, resulting in formation of protected α-amino ketones.[267,268]

1.6 The intermolecular crossed acyloin condensation

1.6.1 The intermolecular crossed acyloin condensation: general outline

The intermolecular crossed acyloin condensation reaction entails the construction of an α-hydroxy ketone *via* the catalytic reaction of two disparate aldehyde substrates. The products, α-hydroxy ketones, from these reactions are potentially important building blocks for the synthesis of heterocycles, natural products, agrochemicals and fine chemicals.[269] In addition, the unsymmetrical nature of the building block allows for access to other important synthetic precursors, such as chiral 1,2-diols and amino alcohols.[270] While significant advances have been made in the NHC-driven intermolecular *homo*benzoin condensation,[197] the intermolecular *crossed* acyloin condensation has not been characterised by comparable success. The crossed process is by far the least developed variant of the benzoin condensation-type reactions that have been discussed, and is inherently the most difficult of these to control from both efficacy and chemoselectivity standpoints.

Scheme 1.38 Reaction scheme of intermolecular crossed acyloin condensation



Scheme 1.38 depicts an intermolecular crossed acyloin condensation between two aldehydes (**1** and **2**), which accordingly generates four possible α-hydroxy ketone products, **3a-3d**. Products **3a** and **3b**, resulting from self-condensation of the aldehydes,

are termed homo-dimers, whereas the crossed products, **3c** and **3d**, arise from crossed coupling of the reactants. The product outcome can include eight possible asymmetric ketones - as each of the four α-hydroxy ketones (**3a-d**) can be formed as the (*R*)- and (*S*)-enantiomers. The challenges associated with chemoselectivity and enantioselectivity are considerable - should a chiral, enantiopure catalyst be employed in the reaction, it must firstly be able to control which aldehyde preferentially forms the Breslow intermediate, while also ensuring that this intermediate predominantly attacks the second aldehyde (which acts as the electrophilic component), thus ensuring chemoselectivity. Secondly, the catalyst must also induce enantioselectivity by ensuring that the Breslow intermediate engages in face selective addition to the second aldehyde component. Several avenues have been explored in attempts to prepare these unsymmetric 1,2-functionalised compounds and these shall be discussed *vide infra*.

1.6.2 Cyanide and NHC-mediated crossed acyloin condensation

1.6.2.1 Cyanide-catalysed crossed coupling reactions

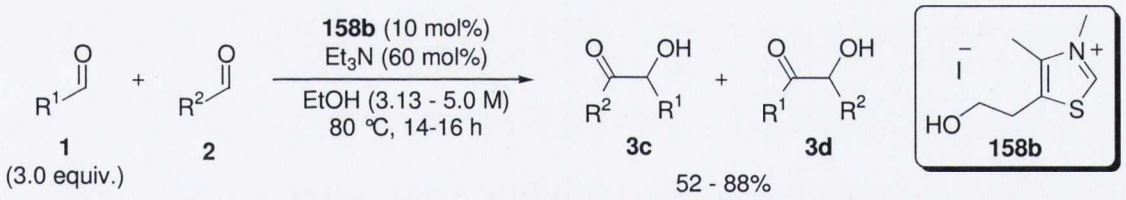
In 1832, Liebig and Wöhler reported the seminal homocoupling of two benzaldehyde molecules, in the presence of a cyanide ion.[2] The first report of a crossed acyloin condensation emerged 50 years later, in 1882. Fischer disclosed the cross-coupling of two different aldehydes; the condensation of benzaldehyde and furfuraldehyde was described, resulting in a 'mixed benzoin'.[271] In 1948, Ide and Buck published a detailed report, studying the mechanism and synthetic scope of the homo- and crossed condensation of aldehydes.[1] Their study concerned the crossed acyloin condensation of aromatic aldehyde partners of contrasting electronic character in the presence of high loadings of cyanide ion. However, they revealed that certain benzoins existed not only in the normal keto form, but also as an enediol, and the isolation of both *cis* and *trans*-enediols was attained in some of these cases.

1.6.2.2 Thiazolium salt-catalysed coupling of aldehydes

Almost 30 years after Ide and Buck's investigations into the cyanide-catalysed acyloin condensation the first truly interpretable intermolecular crossed acyloin condensation reaction was reported.[272] Stetter described an achiral thiazolium salt-mediated crossed

condensation between a range of aromatic and aliphatic aldehydes. Reasonable yields of crossed product could be obtained if the aliphatic aldehyde was used in excess (3.0 equiv.), however, chemoselectivity was both highly variable and substrate dependent. In the study, isomeric crossed acyloin products **3c** and **3d** were 'isolated' together and not separated further. Stetter reported the isolated yield of crossed products **3c** and **3d**, and included alongside this result, the ratio of their formation (Table 1.6). The yields of homo-dimer products, **3a** and **3b**, were not provided. Stetter's report introduced a concept of donor-acceptor reactivity, whereby one aldehyde acts as a donor (nucleophile) and the remaining aldehyde substrate as an acceptor (electrophile). The aldehyde that is initially attacked by the carbene catalyst and consequently forms the Breslow intermediate is classed as the donor aldehyde because in the form of the Breslow intermediate it adds (as a nucleophile) to a second (acceptor) aldehyde. Thus, for compounds of type **3c**, aldehyde **2** (R^2) acts as the donor, whereas for **3d**, the situation is reversed, with **2** assuming the role of the acceptor aldehyde and **1** proceeding as the donor, Table 1.6.

Table 1.6 First example of a thiazolium salt-mediated crossed acyloin reaction



entry	R^1	R^2	yield 3c & 3d (%)	ratio 3c:3d
1	*i*-C_3H_7	C_6H_5	56	35:65
2	*n*-$C_3H_7CHCH_3$	C_6H_5	61	40:60
3	*i*-C_3H_7	2-Cl-C_6H_4	81	100:0
4	*n*-$C_3H_7CHCH_3$	2-Cl-C_6H_4	85	100:0
5	CH_3	2-Cl-C_6H_4	52	0:100
6	*i*-C_3H_7	4-Cl-C_6H_4	75	45:55
7	*i*-C_3H_7	2-furyl	88	95:5
8	*n*-C_3H_7	2-furyl	63	85:15
9	*i*-C_3H_7	2-thienyl	79	100:0
10[a]	*i*-C_3H_7	*n*-C_7H_{15}	56	30:70

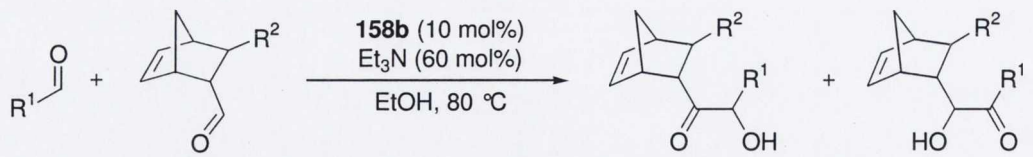
[a]Reaction employed achiral *N*-benzyl substituted thiazolium salt **158a**.

It is evident from Table 1.6 that the reaction between benzaldehyde and aliphatic aldehydes does not have a chemoselective outcome, with modest combined yields of

56% and 61%, and marginal preference for product **3d** (entries 1 and 2). Nonetheless, when *ortho*-chlorobenzaldehyde was used in place of benzaldehyde complete chemoselectivity was achieved - products of type **3c** prevailed, resulting from 2-substituted aldehydes acting as the donor (entries 3 and 4). Interestingly, when acetaldehyde was employed as the aliphatic counterpart the chemoselectivity was reversed with exclusive formation of the opposite cross product **3d** (entry 5). *Para*-substitution of the aromatic aldehyde resulted in poor chemoselectivity (entry 6). 2-furaldehyde and thiophene-2-carbaldehyde were introduced as aromatic substrates and again almost complete chemoselectivity was obtained (entries 7-9). Reaction of a straight chain aliphatic aldehyde and a branched aliphatic analogue provided a modest crossed product return (56%), with moderate chemoselectivity (30:70 **3c**:**3d**, entry 10).

Stetter also disclosed a crossed condensation reaction involving the use of bulky aliphatic norbornene-2-carbaldehydes, such as **182**, in conjunction with a selection of aliphatic aldehydes, Scheme 1.39.[273] The yields of the combined crossed products were reported; unfortunately their ratios and the yields of the homo-condensed products were not. An inherent chemoselective element of this reaction derives from the use of bulky hindered aldehydes (**182**), the self-condensation of which is presumably unfavourable on steric grounds. Combined crossed product yields of **183c** and **183d** in the range of 29-72% were obtained.

Scheme 1.39 Intermolecular crossed acyloin condensation using bulky aldehydes



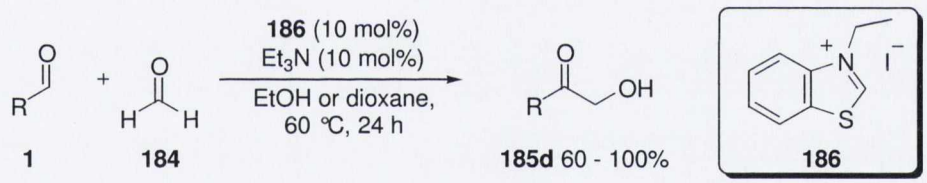
1 **182** **183c** 29 - 72% **183d**

Rétey and Golding supplemented Stetter's pioneering attempts to achieve an intermolecular NHC-catalysed crossed coupling process, reporting the crossed coupling of straight chain aliphatic aldehydes.[274] Using analogous reaction conditions to Stetter and involving an achiral thiazolium salt precatalyst, Golding *et al.* condensed an array of aliphatic aldehydes that contained bulky aromatic and silyl protecting groups. Once again, the yields of the individual crossed products and the homo-dimerisation products

were omitted. Yields of crossed condensation products (**3c** and **3d**) ranging from 29% to 71% were obtained.

Following in the footsteps of Stetter, and contributing to this budding field of *Umpolung* chemistry, Inoue investigated the selective crossed condensation of formaldehyde with various aromatic and aliphatic aldehydes.[275] Inoue had previously described the self-condensation of formaldehyde *via* thiazolium salt catalysis.[276,277] He noted that the triose, dihydroxyacetone, was unexpectedly formed in preference to glycolaldehyde (see **89** and **90**, Figure 1.12). Glycolaldehyde (formoin) was not detected in the product mixture, even in the initial stages of the reaction process. Inoue surmised that the reactivity of the Breslow intermediate was influenced by the structure of the bound aldehyde substrate and he subsequently evaluated the scope of the crossed acyloin condensation using formaldehyde and a range of other aldehydes, as per Scheme 1.40.

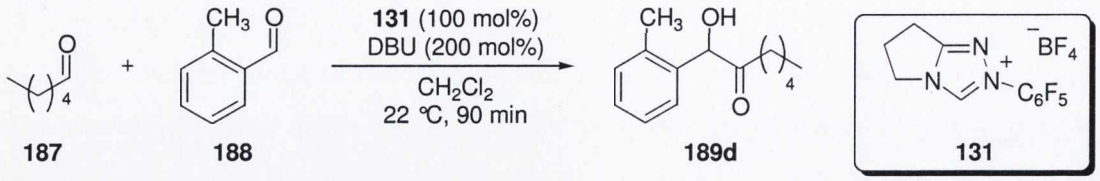
Scheme 1.40 Crossed acyloin condensation using formaldehyde



It was found that the reaction proceeded with excellent chemoselectivity; formaldehyde acted exclusively as the acceptor component, preferentially forming **185d**. By employing a 1:1 ratio of the two aldehyde substrates, the reaction outcome could be controlled to selectively produce only one product.

It should also be noted that as part of a target oriented study of intramolecular crossed acyloin condensation reactions, Miller *et al.* conducted one experiment involving an intermolecular crossed coupling reaction.[202] Using *o*-tolualdehyde and hexanal in the presence of stoichiometric loadings of triazolium ion **131**, crossed product **189d** was obtained as the sole isolatable product in a yield of 16% (Scheme 1.41).

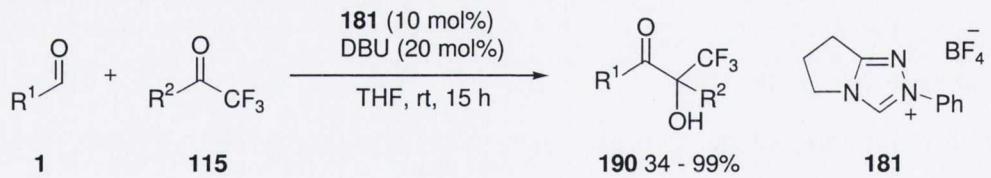
Scheme 1.41 Miller's intermolecular crossed acyloin condensation reaction



1.6.2.3 Aldehyde-trifluoromethyl ketone cross coupling

In 2009, Enders published the first example of NHC-catalysed coupling of aromatic aldehydes with trifluoromethyl ketones.[278] Excellent chemoselectivity could be achieved using the electrophilic trifluoromethyl substrates, in conjunction with unhindered aromatic aldehydes, Scheme 1.42. Enders discovered that employing an excess of base reduced the formation of benzoin (homo-condensation). Most notably, *ortho*-substitution of the benzaldehyde component was poorly tolerated providing a poor yield - most likely due to excessive steric congestion about the catalytic carbene centre. Using unhindered aromatic aldehydes and fluorinated ketones **115**, near-quantitative yields and excellent chemoselectivities were obtained for a wide range of substrates.

Scheme 1.42 Enders' trifluoromethyl ketone coupling with aromatic aldehydes



1.6.2.4 NHC-mediated catalysis of the crossed acyloin condensation: limitations and conclusions

The last 30 years have witnessed only a handful of studies of the NHC-catalysed intermolecular crossed acyloin condensation reaction. In addition, these reports have been restricted with respect to reaction scope. The most apparent difficulty posed by this crossed coupling process is the possibility of forming multiple products - up to eight products can be created within the reaction (if formaldehyde is not one of the components). In order to obtain significant yields of a crossed product it is obligatory

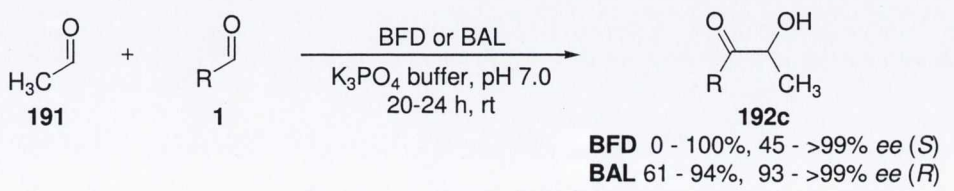
that a chemoselective bias be established within the reaction. In attempts to achieve chemoselectivity, the substrate scope has been limited and often 'tailored' to guarantee a level of chemoselectivity. An additional intricacy of this reaction is the separation and/or purification of the distinct products of the coupling process. For the most part, reports on the crossed acyloin condensation reaction that have appeared in the literature indicate that the different acyloin products were not isolated and the yields of the crossed products are expressed as the combined mass of both possible cross products.[272,273,274] The intermolecular crossed acyloin condensation reaction has yet to be rendered asymmetric, which is salient, considering the widespread interest in asymmetric catalysis of the homocondensation reaction. In conclusion, while significant advances in the (asymmetric) carbene-catalysed homobenzoin condensation have been made recently,[127,128,131] a selective carbene-mediated catalytic methodology, capable of promoting the intermolecular reaction between two different aldehydes in a chemoselective and enantioselective fashion, remains elusive.

1.6.3 Enzymes as catalysts for the intermolecular crossed acyloin condensation

1.6.3.1 Enzyme-mediated crossed acyloin condensation catalysis: acetaldehyde-aldehyde coupling

The ability of enzymes BFD and BAL to provide highly efficient and enantioselective homobenzoin condensation reactions has been briefly described in Section 1.3.3. Given the applicability and versatility exhibited by these enzymes in the self-coupling of a wide variety of aldehydes, it was plausible that these enzymes could perhaps, with equal success, mediate the crossed coupling process. Subsequently, in 2000 Müller and Demir investigated the crossed coupling of a range of aldehydes with acetaldehyde using the enzyme BFD, Scheme 1.43.[279,280]

Scheme 1.43 Enzymatic crossed coupling of acetaldehyde with various aldehydes



BFD 0 - 100%, 45 - >99% *ee* (*S*)
BAL 61 - 94%, 93 - >99% *ee* (*R*)

The reaction scope included substituted aromatic, heteroaromatic and aliphatic aldehydes, and acetaldehyde was utilised as the acyl acceptor in all cases. Best results, with respect to optical purities of the α-hydroxy ketones **192c** were obtained with *meta*-substituted benzaldehydes. Substitution in the 2-position was poorly tolerated (presumably due to steric hindrance) whilst *para*-substitution was only moderately acceptable. It was also determined that BFD did not accept modification of the methyl group of acetaldehyde in the mixed condensation reaction. Although BFD was found to provide highly enantioselective coupling in favour of the (*S*)-enantiomer, it must be highlighted that an excess of *50* equivalents of acetaldehyde was necessary to ensure chemoselective product formation.

Müller and Demir reported further successes of this crossed acetaldehyde-dimerisation process through the application of the enzyme BAL.[176] (Note: BAL was found to be a more efficient promoter of the homobenzoin condensation than BFD).[176] Accordingly, it was revealed that BAL was more versatile than BFD in the crossed coupling process, with acetaldehyde again assuming the role of the acyl acceptor aldehyde. BAL also required only 7 equivalents of acetaldehyde to ensure chemoselectivity. A diverse range of aromatic and heteroaromatic aldehydes was accepted as donor substrates for the formation of **192c** (Scheme 1.43), however the opposite configuration to that provided by BFD prevailed, in the form of the (*R*)-enantiomer. In contrast to BFD, BAL accepted *ortho*-substituted aldehydes, although substrates with a *meta*-substitution were most suited to the enzyme's capabilities. BAL has since demonstrated additional superiority to BFD in the extension of its reaction scope to include the coupling of phenylacetaldehyde to a series of methoxybenzaldehydes,[281] carboligation of mono- and dimethoxy acetaldehydes to aromatic aldehydes[282] and hydroxymethylation of aromatic aldehydes with formaldehyde.[283]

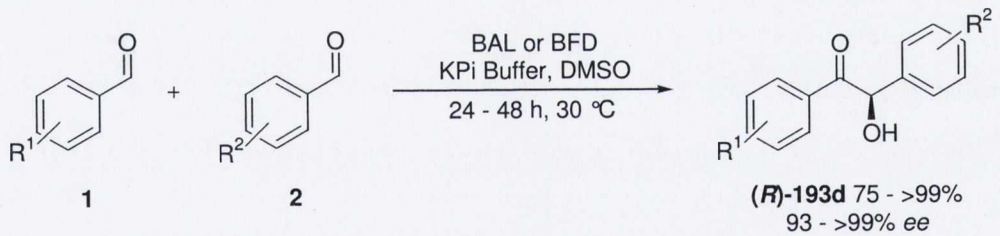
The exploitation of an ancillary enzyme, pyruvate decarboxylase (PDC), has led to increased capacity of the enzyme-catalysed intermolecular crossed acyloin condensation. The predominant physiological task of PDC is the non-oxidative decarboxylation of pyruvate; however it is also capable of enantioselective C-C bond formation.[284] PDC is distinct from BFD and BAL as the carboligation procedure between acetaldehyde and other aldehyde substrates, in the presence of PDC, proceeds with acetaldehyde being the preferred *donor* aldehyde, rather than the usual acceptor substrate.[285] Thus, the

combined use of BFD, BAL or PDC can lead to a diverse range of synthetically useful α-hydroxy ketones *via* an intermolecular crossed acyloin condensation reaction.[286]

1.6.3.2 Enzymatic intermolecular crossed acyloin condensation: expansion of reaction scope, aldehyde-aldehyde coupling

In 2002, Demir and Müller, pioneers of the enzyme-promoted intermolecular homo- and crossed acyloin condensation reactions, developed a highly efficient donor-acceptor asymmetric crossed coupling reaction that extended beyond the scope of acetaldehyde as the sole acceptor unit.[287] Previous studies detailed above had determined that in general *ortho*-substituted aromatic aldehydes were not well tolerated as donor aldehydes, when used in conjunction with acetaldehyde and BAL/BFD. However, when these 2-substituted substrates were evaluated in the crossed reaction in the presence of other aromatic aldehydes, they assumed the role of the acceptor aldehyde. Thus, the first example of the synthesis of asymmetric benzoins with nonidentical moieties, **193d**, was reported. A synopsis of the study is presented in Table 1.7.

Table 1.7 Enzymatic-promoted cross coupling of aromatic aldehydes



1 **2** **(*R*)-193d** 75 - >99%, 93 - >99% *ee*

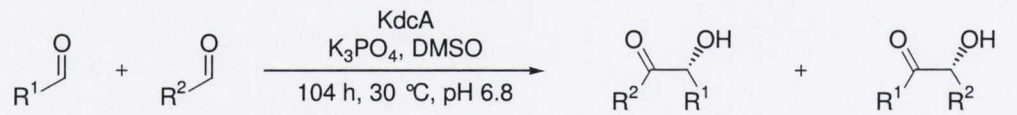
entry	R^1 (donor)	R^2 (acceptor)	enzyme	conv. (%)	selectivity[a] (%)	*ee*[b] (%)
1[c]	3-CN	2-Cl	BFD	>99	>99	90
2	4-Br	2-Cl	BFD	90	95	95
3	4-CF_3	2-Cl	BFD	75	>99	93
4	3,4-CH_2O_2	2-Cl	BAL	98	83	>99
5	3,4,5-$(CH_3O)_3$	2-Cl	BAL	82	97	>99
6	3,5-$(CH_3O)_2$	2-Cl	BAL	>99	95	>99
7	3,5-$(CH_3O)_2$	2,6-F_2	BAL	>99	96	n.d
8	3,5-$(CH_3O)_2$	2,3,5-F_3	BAL	98	92	n.d
9	3,5-$(CH_3O)_2$	2,3,4,5,6-F_5	BAL	>99	>99	n.d

[a]The selectivity is defined as the percent ratio of product in relation to the sum of all acyloins obtained. [b]Determined by HPLC analysis. [c]Compound exhibits a strong tendency towards racemisation.

Initially, the reactivity of BFD and BAL was investigated with various aldehydes (entries 1 - 6). It was deemed that BAL was the superior of the two enzymes, exhibiting a broader substrate scope than BFD, although they both promoted the reaction with excellent product enantioselectivity. (Note: some results not shown.) Müller and Demir subsequently provided evidence that the aldehydes used, in conjunction with BAL, do not serve as selective donors in the presence of only one *o*-substituted hindered acceptor aldehyde (2-chlorobenzaldehyde). An additional series of tests identified three selective acceptors which were combined with the donors used in entries 1-6. Entries 7-9 are representative examples of this study. In general, crossed acyloins were obtained with excellent chemoselectivity; disappointingly the enantioselectivities were not determined.

In 2007, the same research group disclosed the use of another enzyme, branched-chain keto acid decarboxylase, KdcA, for the crossed acyloin condensation reaction.[288] KdcA, derived from *Lactococcus lactis*, is an enzyme that is involved in flavour formation in cheese.[289] Table 1.8 outlines the outcome of Müller's study. At the outset of experimentation the condensation of benzaldehyde and acetaldehyde was considered, and disappointingly crossed products **3c** and **3d** were formed in almost equal quantities, but with exceptional optical purities (entry 1).

Table 1.8 KdcA-promoted cross coupling of aldehydes and 2-keto acids



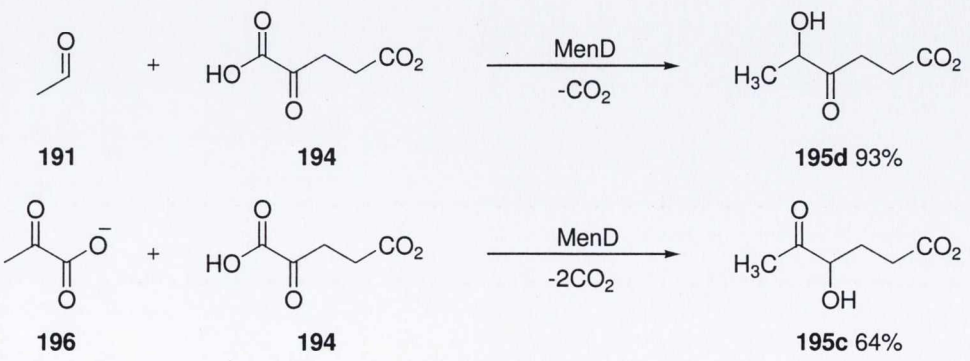
entry	R^1	R^2	yield c (%)	*ee* c (%)	yield d (%)	*ee* d (%)
1	CH_3	C_6H_5	n.d	93	n.d	92
2	C_2H_5	C_6H_5	-	-	n.d	98
3	C_3H_7	C_6H_5	-	-	32	97
4	*i*-C_4H_9	C_6H_5	-	-	25	88
5	cyclopropane	C_6H_5	-	-	14	98
6	CH_3	3,5-Cl_2-C_6H_3	n.d	97	-	-
7[a]	CH_3	$CH_2C_6H_5$	49	n.d	12	n.d
8[a]	CH_3	indole-3-acetaldehyde	23	n.d	-	-

[a]For entries 7 and 8, aldehyde substrates are prone to enolisation and are problematic to use under the given reaction conditions, thus their equivalent 2-keto acids were used and the aldehyde was generated *in situ*.

Surprisingly, the combination of benzaldehyde with larger aliphatic aldehydes gave remarkable results; chemoselectivity shifted to form solely derivatives of type **3d** (aliphatic donor aldehydes), with excellent enantiopurities (entries 2-5) albeit with reduced product yields. In contrast, when 3,5-dichlorobenzaldehyde was reacted with KdcA in the presence of acetaldehyde, acyloin **3c** was selectively formed, whereby acetaldehyde acted as the acceptor substrate. Entries 7 and 8 employed the enolisable substrates phenylacetaldehyde and indole-3-acetaldehyde which led to intractable material. It was found that if the substrate aldehydes were replaced with their corresponding 2-keto acids, (thus the aldehydes were generated *in situ via* loss of CO_2) a more successful reaction could be achieved, with acetaldehyde occupying the role of the acceptor aldehyde. Overall, use of KdcA allows a unique protocol, whereby manipulation and alteration of the product chemoselectivity can be accomplished by judicious selection of the reactants.

Shortly after this preliminary report Müller described a new versatile enzyme catalyst, MenD, which is involved in menaquinone synthesis, and was found to be superior to KdcA.[290] MenD was revealed to be extraordinary for three reasons (i) it could successfully promote the coupling of a selection of substituted aromatic aldehydes with α-ketoglutarate (**194**), attaining high asymmetric inductions (94-98% *ee*), (ii) it was also the only known enzyme to catalyse a Stetter-like 1,4-addition to an α,β-unsaturated carboxylic acid;[291,292] and most interestingly, (iii) MenD displayed a specific and highly unusual reactivity towards pyruvate (**196**) in the presence of α-ketoglutarate (see Scheme 1.44).

Scheme 1.44 Chemoselectivity *via* substrate variation in the presence of MenD



191 **194** **195d** 93%

196 **194** **195c** 64%

In the presence of acetaldehyde and α-ketoglutarate (**194**) MenD promoted the formation of acyloin **195d**, with **194** acting as the donor. However, when pyruvate (**196**) was used in place of acetaldehyde the opposite crossed product **195c** prevailed, whereby **194** acted as the acceptor. This unique reactivity pattern could not be achieved with other substrates, and Müller deemed that this unusual occurrence could perhaps be due to allosteric binding of pyruvate that resulted in a conformational change in the enzyme structure.

1.6.3.3 Limitations of the enzyme-promoted intermolecular crossed acyloin condensation reaction and general conclusions

In the last decade, ThDP-dependent enzymes, such as BFD, BAL, PDC, KdcA and MenD, have been intensively studied with respect to their carboligation activities and have become well-established as promoters of *Umpolung*-induced carbon-carbon bond formations.[293] The enzyme-catalysed crossed coupling of aldehydes has advanced to a far greater degree than NHC-catalysed processes, through the pioneering efforts of Müller *et al.*, with the effect that the enzymatic-crossed coupling of aldehydes offers an easy access to chiral unsymmetric 2-hydroxy ketones from a wide range of substrates. This facile route to synthesising optically pure unsymmetric acyloins has been exploited in the establishment of an industrial-scale biotechnological process for the production of (*R*)-phenyl-acetyl carbinol ((*R*)-PAC), which is the precursor to (-)-ephedrine.[270]

From the comprehensive analyses of the enzymes discussed above, it is evident that manipulation of the chemoselective outcome of enzyme-catalysed crossed coupling reactions is possible *via* judicious selection of a specific enzyme with suitable aldehyde/2-keto acid substrates. There are still however limitations to the enzyme-catalysed process - the cross coupling reactions are not yet of the same calibre as enzyme-mediated homobenzoin condensation reactions, in terms of outstanding product yields and enantioselectivities that have been attained. Additionally, the full scope of the enzyme-induced crossed acyloin condensation reaction has not been evaluated - only very recently the first enzymatic enantioselective aldehyde-ketone cross coupling reaction was reported.[294] This is a relatively unexplored avenue of the crossed acyloin condensation reaction that results in the formation of chiral tertiary alcohols, which are important structural units in bioactive agents.[295] Thus, in conclusion, the enzyme-

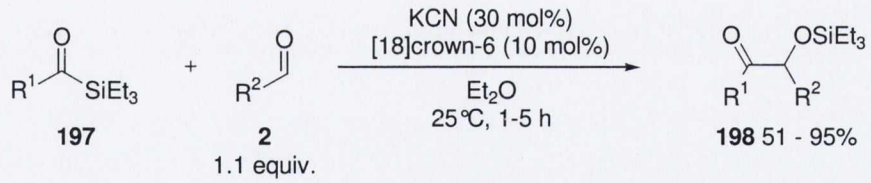
catalysed intermolecular crossed acyloin condensation, although more successful than the NHC-promoted variant, has yet to reach its full potential as a viable and direct route to highly chemo- and enantioselective unsymmetric α-hydroxy ketone synthesis.

1.6.4 Other modes of crossed acyloin condensation catalysis

1.6.4.1 Silyl thiazolium salt-mediated cross-acyloin condensation

The utility of the traditional NHC catalysed acyloin condensation reaction is well documented. Unfortunately, its principal limitation lies in its general inability to couple two different aldehydes. In addition, the product distribution of the crossed coupling reaction is generally determined by the relative stability of the four possible products (**3a-3d**, Scheme 1.38), often meaning that the more energetic crossed-product isomers are inaccessible. In 2003, Johnson disclosed an alternative method for generation of the acyl anion equivalent, which is the key intermediate in an *Umpolung* process.[296] He speculated that by placing the reaction under kinetic control, cyanide-catalysed formation of a siloxy nitrile anion from an acyl silane (**197**) could provide complete regiocontrol within a crossed sila-acyloin condensation reaction, Scheme 1.45.

Scheme 1.45 Johnson's achiral crossed sila-acyloin condensation reaction

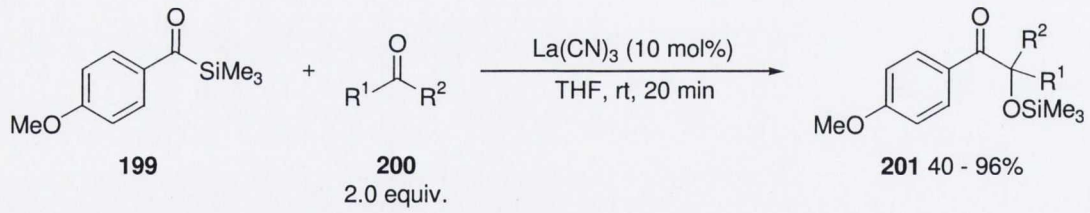


Preliminary investigations revealed that KCN with the ionophere 18-crown-6 provided optimal catalytic conditions. A range of electronically diverse aromatic, heteroaromatic and aliphatic acyl silanes **197** and aldehydes were attempted in the reaction and generated yields as high as 95% of crossed product **198**. Electron-deficient and electron-rich substrates displayed little difference in reactivity and sterically demanding aldehydes were compatible with the reaction conditions employed. The coupling of aromatic silanes with aliphatic aldehydes (and *vice versa*) proceeded smoothly with no evidence of competing homobenzoin adducts. Johnson did however note that

endeavours to induce the coupling of two aliphatic substrates were very low yielding. The reaction was deemed to proceed *via* a variant of the classical benzoin condensation reaction mechanism elucidated by Lapworth[5] and Breslow,[26] with initial nucleophilic addition of a cyanide anion to **197**. The mechanism incorporated a 1,2-Brook rearrangement of the generated tetrahedral intermediate,[297] prior to nucleophilic attack on an aldehyde substrate. 1,4-Silyl migration, followed by retrocyanation provided the carbonyl product **198**.

Shortly after this initial report of α-siloxy ketone synthesis Johnson improved upon the previous reaction protocol. He determined that $La(CN)_3$ was a superior catalyst, no longer requiring the 18-crown-6 additive. Catalyst loadings could be reduced and reaction times were considerably decreased to less than five minutes.[298,299] Most notably, the reaction scope could be expanded to include addition of acyl silanes to α,β-unsaturated aldehydes and also the coupling of two aliphatic partners. Johnson subsequently further developed upon these studies, reporting $La(CN)_3$-catalysed coupling of acyl silanes and ketones.[300,301] *Para*-methoxy silane **199** and a suite of aromatic, heteroaromatic and aliphatic (acyclic and cyclic) ketones (**200**) were successfully coupled using modified reaction conditions (Scheme 1.46).

Scheme 1.46 $La(CN)_3$-catalysed acyl silane-ketone crossed acyloin condensation



For the most part, enolisable ketones were applied in the reaction and fared extremely well, with the major byproduct in all cases being a cyanohydrin (whereby protonation of the acyl anion equivalent occurred). This was presumably due to adventitious water being present in the reaction medium. Johnson discovered that the reaction scope could be expanded to include sterically hindered diaryl ketones and α,β-unsaturated ketones, enones and ynones. Stetter-type 1,4-addition could be avoided if steric hindrance was introduced at the β-position of the enones. Attempts were made to achieve an

asymmetric crossed coupling reaction; disappointingly all avenues explored were unsuccessful. Subsequently, Johnson described a novel kinetic resolution procedure of aryl-methyl ketones *via* CBS-oxazoborolidine reduction.

Other indirect methods that have been examined for catalysis of the crossed acyloin condensation that involve silyl group transfer, (whereby chemoselectivity is derived from the pre-formation of an *Umpolung* reagent), include acyl silane condensation using a metallophosphite catalyst in place of KCN[302] and through the use of aldehyde-thiazolium carbene adducts.[303]

1.6.4.2 Acyl phosphonate catalysis

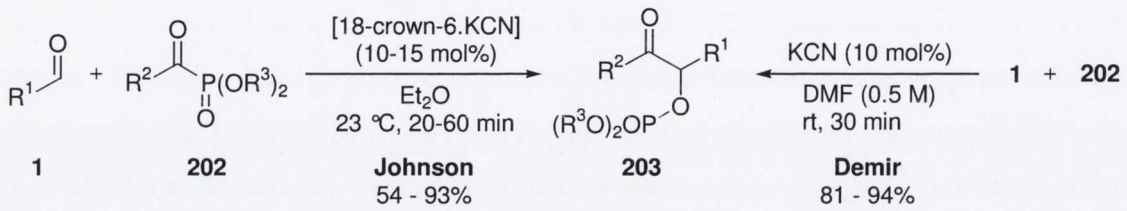
In terms of kinetically controlled crossed acyloin reactions, the use of acyl silanes as acyl anion precursors, based on the nucleophilic Brook rearrangement, was considered to be the most practical and selective method available. However, acyl silanes suffer from tedious preparative operations that often require a strong stoichiometric base or metal nucleophile, and they are primarily synthesised from the corresponding acyl anion.[304] Consequently, acyl phosphonates were recognised as potential contenders for acyl anion precursors, due to their practical and facile one-step synthesis *via* the Michaelis-Arbuzov reaction (involving acyl chlorides and trialkyl phosphites).[305] It was deemed that phosphorus, like silicon, has the ability to migrate from carbon to oxygen and *vice versa*, and is capable of rearrangements that have a close analogy to the 1,2-Brook rearrangement.[306,307] Thus, they could perhaps serve as acyl anion equivalents and promote a crossed condensation reaction.

In 2005, acyl phosphonates were described as novel acyl donors for benzoin type reactions by the research group of Johnson.[308] Demir *et al.* followed very shortly with a similar detailed use of acyl phosphonates as *Umpolung* species in the crossed acyloin condensation reaction.[309] Both achiral studies are summarised in Scheme 1.47, with Demir's reaction conditions obtaining higher product returns overall.

Considering first the study conducted by Johnson, a [18-crown-6/KCN] complex with diethyl ether provided the optimal catalyst/solvent combination, with no requirement for stringently anhydrous reaction conditions. Acyl phosphonates (**202**) and a range of

aromatic, heteroaromatic and aliphatic aldehydes (**1**) were investigated in the coupling reaction. Cleavage of the phosphate group of the products **203** could be achieved using an aqueous amine solution, revealing the unsymmetrically substituted α-hydroxy ketones. Johnson predictably found that reactions involving an aliphatic aldehyde or aliphatic acyl phosphonate were generally unsuccessful, obtaining indefinable decomposition products.

Scheme 1.47 Johnson and Demir's crossed phospha-acyloin condensation



Demir conducted an almost analogous study to Johnson, differing marginally in the reaction conditions utilised, see Scheme 1.47. Overall excellent results were achieved using aromatic acyl phosphonates and aromatic and heteroaromatic aldehydes. Further optimised reaction conditions were reported involving the use of 20 mol% CsF and 30 mol% TMSCN in DMF. These conditions facilitated the crossed condensation of a range of aliphatic aldehydes to aromatic acyl phosphonates (and *vice versa*), generating excellent yields, 64-87%. Once again, coupling of two aliphatic partners was sluggish, providing less than 20% yield of crossed product. Demir also reported the first example of an aldehyde-ketone coupling using benzoyl ethyl phosphonate and trifluoroacetophenone, attaining 87% of coupling product.

In 2009, Demir conducted an in-depth assessment of the scope of the intermolecular aldehyde-ketone coupling reaction using acyl phosphonates.[310] Using the reaction conditions indicated in Scheme 1.47 he evaluated the synthesis of acyloins from a range of aryl and alkyl acyl phosphonates and ketones. Modest to excellent product yields were obtained, (41-95%), and it was observed that increased nucleophilicity of the acyl anion furnished higher product returns in shorter reaction times. It should be noted that electron-deficient ketones were predominantly employed and enolisable protons were generally replaced with a fluorine atom. Whilst a limited number of aliphatic ketones

could be successfully coupled, they required modification of the reaction conditions and/or addition of various cocatalysts.

1.6.4.3 Polymer based catalysis

Polymer-supported reactions consist of a reagent that is immobilised onto a solid support in the presence of unbound reactants that are free in solution. Polymer-supported reagents and catalysts are attracting much attention due to their potential convenience, as they can combine the advantages of substrate supported chemistry with the flexibility of solution phase preparation,[311] in addition to overcoming many operational limitations that conventional solution phase chemistry poses.[312] Such hindrances include ease of monitoring the reaction progress, increased user safety if the reagent on support is toxic or hazardous, and conventional work-up can be avoided as the product (from a clean reaction) can be isolated through simple filtration and solvent removal.[313] Kuriakose and Pillai examined the use of polymer-bound benzaldehyde in the acyloin condensation (self- and crossed coupling).[314] They demonstrated that polymeric benzaldehyde prepared from divinylbenzene (DVB)- and tetraethyleneglycol diacrylate (TTEGDA)-crosslinked polystyrenes (PS), in the presence of KCN, could engage in crossed acyloin condensation reactions with substituted aromatic aldehydes. Using 3-fold excess of the substituted (unbound) aldehyde, they determined that this substrate predominantly acted as the donor aldehyde, whilst the polymer-adjoined benzaldehyde assumed the role of the acceptor congener. They disclosed the results of their study as a percentage condensation of all acyloin products, and it appears that no attempts were made to purify the individual products or determine their respective yields.

1.7 The Benzoin Condensation: Challenges

1.7.1 Limitations and drawbacks associated with the benzoin condensation

The benzoin condensation reaction, being almost 180 years old, has been meticulously investigated.[197] The development of numerous avenues attempting to generate asymmetric α-hydroxy ketones has been described in the above sections. Since the

emergence of the seminal study of the asymmetric NHC-catalysed homo-benzoin condensation in 1966,[109] using a thiazolium salt precatalyst, and Ender's expansion of the methodology to include triazolium precatalysts, only as recently as 1996,[124] the scope of the benzoin condensation has broadened significantly. The homo-dimerisation reaction has been studied in-depth and due to the unfounded success of many triazolium precatalysts few limitations to this process remain.[127,128,131] A general and mainly unavoidable trend in most asymmetric reactions is the poor to modest yields of acyloins derived from sterically hindered electron-rich and aliphatic aldehydes. Additionally, high yields of product (in particular with fast reacting aldehydes) are often accompanied with poor optical purities.

The NHC-promoted intermolecular crossed acyloin condensation reaction is, in contrast to the homo-dimerisation congener, still in its infancy and limitations of this reaction are at present many;

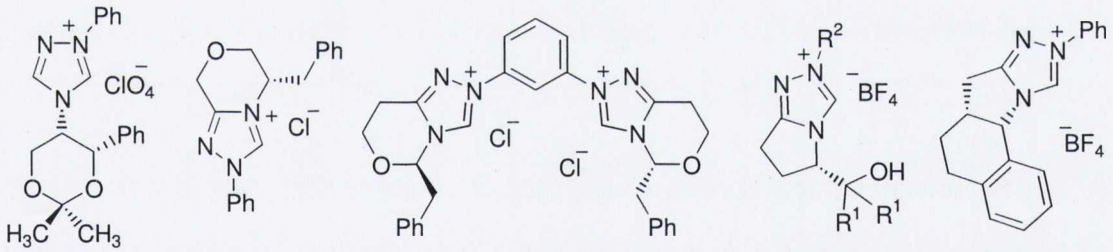
1. First and foremost, the crossed acyloin condensation reaction has yet to be promoted by a chiral NHC-derived carbene.
2. Chemoselectivity can be problematic, resulting in multiple products and consequential low yields. Up to eight possible products can be obtained.
3. A donor-acceptor concept, applicable in the judicious selection of suitable aldehydes partners, has been developed for enzyme-mediated catalysis.[287] Such a principle has not been elucidated for NHC catalysis. In addition, for successful NHC-catalysis an excess of one aldehyde has often been employed to ensure sufficient (chemoselective) product formation.[272,274]
4. Aliphatic aldehydes and ketones have not been comprehensively examined as substrates. The enolisable nature of aliphatic aldehydes renders them unsuitable for cyanide-driven reactions, due to their propensity for participation in undesirable aldol condensation reactions.

At present, there exists a paucity of efficient, chemoselective and enantioselective methods for the generation of α-hydroxy ketones *via* the intermolecular crossed acyloin condensation reaction.

1.7.2 Development of bifunctional NHC precatalysts - hydrogen bonding as a control element

In 2004, Houk performed a detailed computational study of the asymmetric benzoin condensation reaction using various NHC catalysts available at that time.[195] He demonstrated that thiazolium salts are less effective at inducing an enantioselective bias than triazolium variants due to the absence of an *N*-aryl substituent on thiazolium salts. Figure 1.17 depicts a selection of chiral triazolium precatalysts that have been applied in the benzoin condensation or related reactions. The rationale behind their design is based upon the use of the triazolium *N*-aryl substituents and a rigid chiral moiety within the frame of the precatalyst to selectively block three of the four quadrants dividing the space above and below the plane of the triazolium ion. These precatalysts have exhibited particularly efficient stereocontrol in the high optical purities that are obtained using these catalyst systems.

Figure 1.17 Selected chiral bulky NHC catalysts



Since it is unlikely, therefore, that the design of a catalyst of increased steric requirement would offer any significant advantage over these precatalysts, we were encouraged to consider a very different approach to precatalyst design - the development of a chiral azolium ion devised to bring about stereocontrol through the donation of hydrogen bonds. At the outset of this project, to the best of our knowledge, a single example of hydrogen-bonding carbene catalyst had been reported in the literature. Miller *et al.* found that thiazolylalanine-derived catalyst (**166**, Figure 1.16) could promote enantioselective Stetter[244] and intermolecular aldehyde-imine couplings.[263] Only very recently (2008), Ye disclosed the first protic triazolium systems (**118**, Scheme 1.18) for the promotion of enantioselective aza-Morita-Baylis-Hillman[315] and ketene dimerisation

reactions.[147] Additionally, in early 2010, Waser described the synthesis of chiral bifunctional thio(urea) NHCs derived from pyroglutamic acid that were applied in a limited study of the benzoin condensation (using solely benzaldehyde as the aldehyde substrate).[316]

2.1 Synthesis of thiazolium and triazolium salts for use in the benzoin condensation

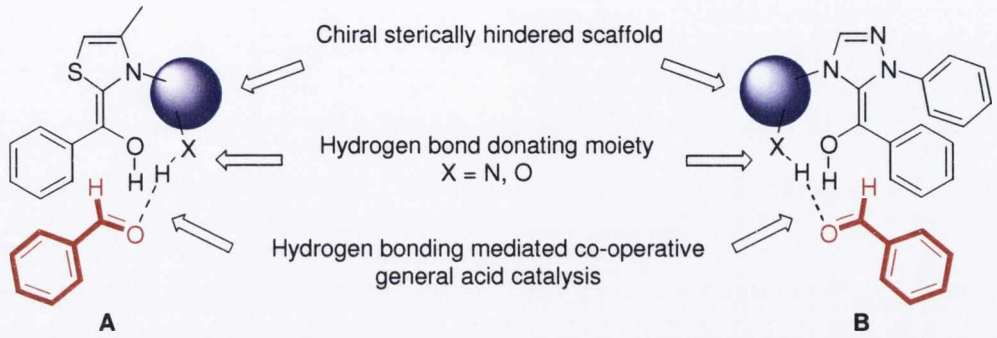
2.1.1 Hydrogen bonding as a tool for asymmetric bifunctional catalysis - rationale for catalyst design

Figure 1.17 depicts several distinguished precatalyst salts that are capable of promoting highly efficient and enantioselective organocatalytic *Umpolung* reactions. It is evident that these catalysts induce a stereochemical bias by taking advantage of chiral steric bulk embedded within their triazolium frameworks and in the appended *N*-aryl substituents of the triazolium rings. Construction of a successful catalyst requires that the chiral moiety and additional components of the catalyst system are designed so as to force a restricted path of access for an aldehyde substrate to the Breslow intermediate. In doing so, a substrate aldehyde is coerced to approach the enamine species from, at best; one trajectory only (*i.e.* of the four quadrants dividing the space above and below the plane of the triazolium ion just one quadrant is available for contact with the carbene.) Significant enantiodiscrimination should be observed if approach of an aldehyde towards one face of the Breslow intermediate is entirely prohibited.

At the outset of this project there did not appear to be any reported studies or catalyst syntheses relating to the use of hydrogen bonding as a method for enhancing catalysis of the benzoin condensation. Intrigued by this dearth in the literature we chose to explore this novel concept. We envisaged that if a hydrogen bond-donating group resided in the area about the catalytic centre (Breslow intermediate) in a well-designed chiral environment, it could perhaps serve as an anchor that would concomitantly activate and guide the second aldehyde substrate towards the Breslow intermediate within the course

of the reaction. A model of the proposed enhanced catalysis of the benzoin condensation is shown in Scheme 2.1.

Scheme 2.1 Rationale for hydrogen bonding as a bifunctional catalytic tool



Scheme 2.1 depicts the Breslow intermediate species that would arise from deprotonation of a thiazolium salt (**A**) or a triazolium salt (**B**) and subsequent reaction with a benzaldehyde molecule. The second benzaldehyde molecule that would react in the benzoin condensation and form the α-hydroxy ketone product (*via* nucleophilic attack of the Breslow intermediate) is indicated in red. We proposed that hydrogen bond donation could be used to co-ordinate the catalyst to the approaching aldehyde, activate the aldehyde towards nucleophilic attack, whilst also directing it in a controlled manner towards the Breslow intermediate. Hydrogen bond donation from the catalyst (in conjunction with donation of a hydrogen bond from the hydroxyl group of the enolamine) would stabilise the increasing negative charge of the resulting oxyanion (*i.e.* general acid catalysis). Co-operative hydrogen bond donation would also rigidify the transition state and aid in the stereochemical outcome of the reaction, if the hydrogen-bond donating group was placed in a chiral environment. In principle, such a dual action (bifunctional) catalyst would incorporate appropriate chiral steric bulk to facilitate enantioselectivity and also possess the potential to activate the aldehyde substrate towards nucleophilic attack by the carbene moiety, *via* hydrogen bond donation. Accordingly, we sought to introduce an amide or a hydroxyl group into a range of novel, chiral thiazolium and triazolium salt catalysts that would serve as hydrogen bond-donating promoters of the benzoin condensation.

2.2 Achiral thiazolium salt precatalyst synthesis

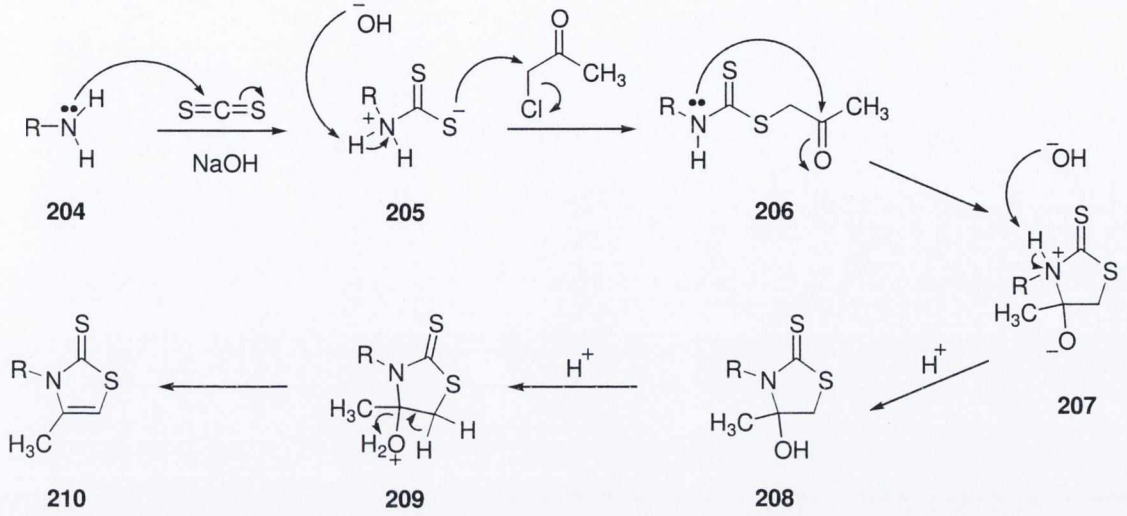
2.2.1 Synthesis of electronically diverse achiral thiazolium salt precatalysts

Thiazolium salts were reported to perform less effectively than their triazolium counterparts in the asymmetric benzoin condensation.[117,118,126] The reason for this was determined experimentally by Houk to be the absence of an attached *N*-aryl substituent on thiazolium salts, (see model A, Scheme 2.1).[195] We aspired to overcome this limitation of thiazolium salts and enhance their potential as facilitators of the asymmetric benzoin condensation *via* hydrogen bond-donation. To initiate our investigations into the synthesis of bifunctional thiazolium salts we decided it would be prudent to generate a library of sterically and electronically diverse simple achiral thiazolium salts. This would permit the assessment, if any, of the influence that the catalysts' steric and electronic properties would have on efficiency of the benzoin condensation. The knowledge gained from this preliminary study could then be employed in the generation of more competent and successful chiral thiazolium salt systems.

Two methods have conventionally been used for the synthesis of thiazolium salts - alkylation of a thiazolium ring[317] or condensation of an *N*-substituted dithioformamide with an α-chloro ketone.[110,318] We chose the latter route for the synthesis of these salts as it allowed the preparation of a more diverse range of products. The condensation of dithioformamides with halogenated ketones to form thiazolium salts can be conducted over two reaction steps, (i) treatment of an amine (**204**) with carbon disulfide, which under basic conditions, results in the formation of a cyclic thiazole-2-thione (**210**) and (ii) ensuing oxidation of the thiazole-2-thione to provide the thiazolium salt **211**. The mechanism of thiazole-2-thione formation is shown below in Scheme 2.2.

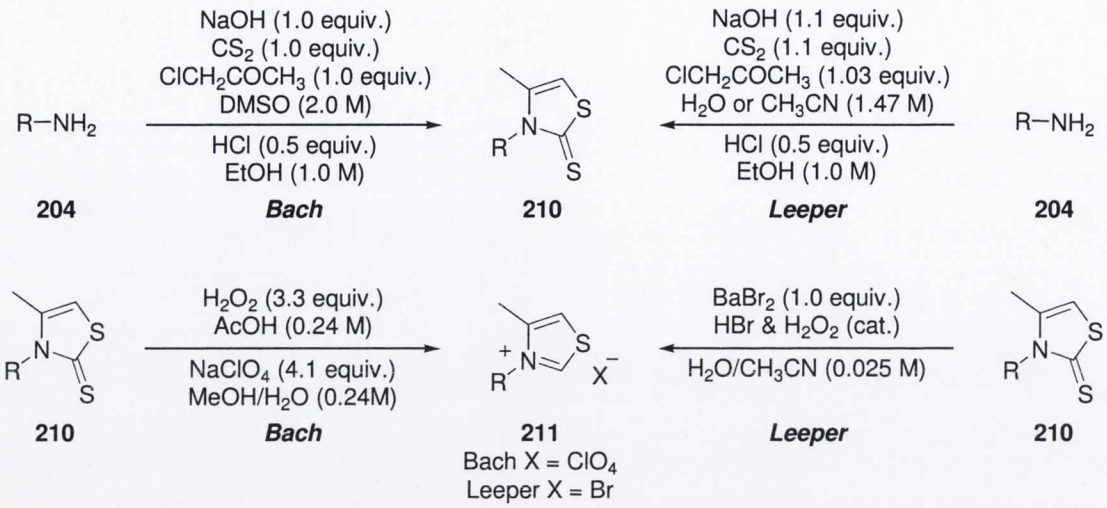
Under basic conditions, the treatment of an amine (**204**) with carbon disulfide creates a dithioformamide species **205**. Nucleophilic addition of **205** to chloroacetone generates **206**, which upon intramolecular cyclisation forms a hydroxy-thiazolidine-2-thione **208**. Refluxing of **208**, under acidic conditions, causes dehydration to occur, furnishing the desired thiazole-2-thione intermediate **210**.

Scheme 2.2 Mechanism of thiazole-2-thione formation



Bach[119] and Leeper[116] have reported two marginally disparate methods for creation of thiazolium salts *via* the oxidation of thiazole-2-thiones **210**. Bach's method entailed the use of hydrogen peroxide and sodium perchlorate, whilst Leeper's protocol involved exposing the thiozole-2-thione to barium bromide and catalytic amounts of hydrogen bromide and hydrogen peroxide. Using both Bach's and Leeper's procedures, the synthesis of a range of achiral thiazolium salts was attempted using electronically diverse substituted anilines and aliphatic amines **204**, as depicted in Table 2.1. The synthesis of the thiazole-2-thione intermediates was undertaken first, using both Bach's and Leeper's procedures. The thiazole-2-thiones **210** were subsequently oxidised to their corresponding thiazolium salts of general type **211**, again using the two methods reported by Bach and Leeper.

Table 2.1 Achiral thiazolium salt synthesis using Bach and Leeper's methods



entry	R	yield 210 Bach (%)	yield 210 Leeper (%)	yield 211 Bach (%)	yield 211 Leeper (%)
1	C_6H_5	60	54	31	29
2	2,4,6-$(CH_3)_3$-C_6H_2	49	41	97	56
3	4-CH_3O-C_6H_4	0	0	-	-
4	2,6-Cl_2-C_6H_3	0	0	-	-
5	2,4,6-Br_3-C_6H_2	0	0	-	-
6	$CH_2C_6H_5$	52	52	65	72
7	*c*-C_6H_{11}	93	13	42	50

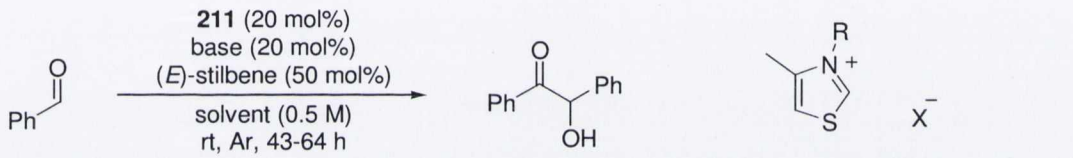
Assessing first the results of the synthesis of thiazole-2-thiones **210**, the method described by Bach proved to be the superior of the two protocols, furnishing enhanced product yields in each case. Under the reaction conditions described by Bach, electron-neutral and electron rich anilines were successfully transformed to their corresponding **210**, in modest yields (60% and 49%, entries 1 and 2). The solubility of the methoxy-substrate in organic solvents proved problematic, leading to the failure of the process with either reaction procedure (entry 3). It is evident that electron-deficient aniline substrates were not compatible with Bach or Leeper's given reaction conditions (entries 4 and 5). This is presumably due to reduced nucleophilicity of the amine group, coupled with steric congestion about the nitrogen centre that prohibited thione creation. Gratifyingly, cyclisation of the aliphatic substrate, cyclohexyl amine, proceeded to near quantitative yield (93%, entry 7). Oxidation of the thiazole-2-thiones **210** to the desired thiazolium ions **211** was carried out, attaining variable yields, 29-97%. When placed in contrast, both oxidation methods were effectively on a par, with Bach's procedure being more successful with aromatic substrates, whilst Leeper's method was more suited to

aliphatic congeners. It is evident that in the two-step reaction procedure electron-rich anilines are more readily converted to their thiazolium salts than are electron-deficient variants.

2.2.2 Preliminary investigations of the benzoin condensation reaction using achiral thiazolium salts

With a selection of four achiral precatalyst systems in hand we investigated the performance of these thiazolium salts in the benzoin condensation. Benzaldehyde (**11**) was used as the aldehyde substrate in the presence of 20 mol% of precatalyst. The results of the study are provided in Table 2.2.

Table 2.2 Preliminary investigations of the achiral benzoin condensation



entry	catalyst	solvent	base	time (h)	conv.[a] (%)	yield[a] (%)
1	**211a**	CH_2Cl_2	NEt_3	64	7	5
2	**211b**	CH_2Cl_2	NEt_3	64	69	40
3	**211a**	MeOH	NEt_3	43	82	38
4	**211b**	MeOH	NEt_3	43	95	48
5	**211b**	THF	NEt_3	43	76	36
6	**211b**	Toluene	NEt_3	43	0	0
7	**211b**	CH_2Cl_2	DBU	43	62	40
8	**211b**	MeOH	DBU	43	59	27
9	**211b**	THF	DBU	43	56	19
10	**211b**	Toluene	DBU	43	15	3
11	**211f**	MeOH	NEt_3	43	59	31
12	**211g**	MeOH	NEt_3	43	44	32

[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

As can be seen from entries 1-4 the *N*-mesityl thiazolium salt **211b** was a more efficient promoter of the benzoin condensation than its phenyl analogue **211a**, in both CH_2Cl_2 and

methanol. Solvent screening indicated that of CH_2Cl_2, methanol, THF and toluene, methanol was the optimal reaction medium for catalysis (entries 2 and 4-6). DBU and triethylamine were assessed as bases, with triethylamine proving superior. Under optimised conditions **211b** delivered a yield of 48% of benzoin (entry 4). The remaining thiazolium precatalysts were assessed under the optimised reaction conditions, resulting in low yields of **15** (entries 3, 11 and 12). Overall, using the optimal reaction conditions, yields in the range of 31-48% of benzoin were possible using the four achiral thiazolium salt precatalysts.

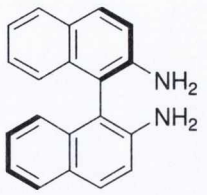
2.3 Synthesis of chiral hydrogen bond-donating thiazolium precatalysts

2.3.1 Generation of BINAM-based thiazolium salt systems

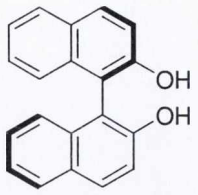
2.3.1.1 Rationale behind catalyst design using BINAM - axial chirality

The most abundant source of chirality in organic chemistry stems from stereogenic centres within a molecule, whereby non-superimposable mirror image forms of the one compound can exist. Yet, some compounds can be considered to be chiral although they do not contain a stereogenic centre; these compounds posses axial chirality. Axial chirality can be defined as the stereoisomerism arising from the non-planar arrangement of four groups in pairs about a chirality axis.[319] Examples of axially chiral compounds include allenes,[320] atropisomeric *ortho*-substituted biphenyl and binaphthyl compounds[321,322] and also dihydroanthracenone compounds.[323] 1,1'-Binaphthyl units that are functionalised at the 2 and 2' positions exhibit axial chirality due to restricted rotation about the transannular bond and are thus C_2 symmetric compounds. Examples of frequently used axially chiral binaphthyl compounds include 2,2'-diamino-1,1'-binaphthalene (BINAM, (*R*)-**212**), 1,1'-binaphthyl-2,2'-diol (BINOL, (*R*)-**213**) and 2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl (BINAP, (*R*)-**214**), Figure 2.1. Compounds (*R*)-**212-214** have been incorporated into many catalyst structures.[324,325,326]

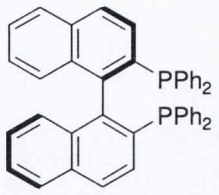
Figure 2.1 Examples of commonly used binaphthyl based compounds



(*R*)-212



(*R*)-213

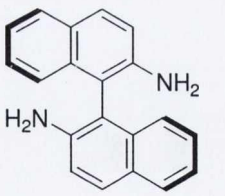


(*R*)-214

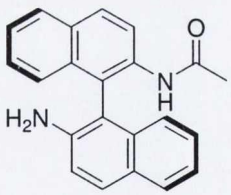
2.3.1.2 Endeavours to create a chiral BINAM-containing thiazolium salt precatalyst

Given that we could synthesise hindered *N*-aryl thiazolium salts and demonstrate that they are active in the benzoin condensation, we next became interested in exploiting the inherent axial chirality of BINAM ((*R*)-**212**) as a starting material for the synthesis of *N*-aryl thiazolium salts. It was our hope that the restricted rotation about the central aryl-aryl bond would provide a sufficiently influential chiral environment in which enantioselective benzoin condensations could take place (see Scheme 2.1). The creation of novel asymmetric thiazolium salts (*R*)-**217a-c** was envisaged, from the reaction of three (*R*)-BINAM-derived amine substrates (**212**, **215** and **216**), as shown in Scheme 2.3.

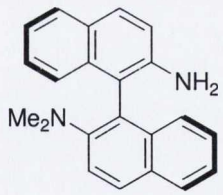
Scheme 2.3 Asymmetric thiazolium BINAM substrates and precatalyst systems



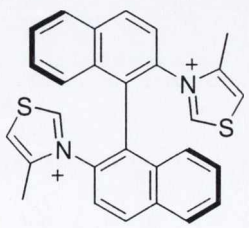
(*R*)-212



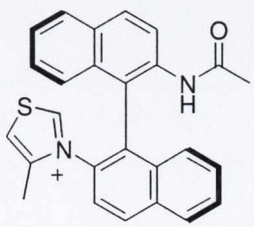
(*R*)-215



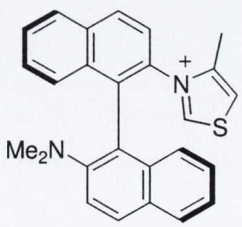
(*R*)-216



(*R*)-217a



(*R*)-217b

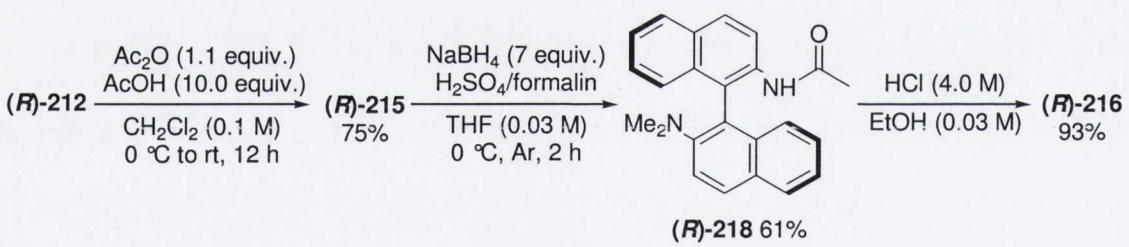


(*R*)-217c

BINAM ((*R*)-(**212**)) is commercially available, and if employed as a substrate, a potentially highly active *bis*-thiazolium salt precatalyst could be designed, (*R*)-**217a**. For generation of a bifunctional hydrogen bond donating thiazolium salt we decided to convert one of the amine groups of (*R*)-**212** to an amide functionality (*i.e.* (*R*)-**215**) - thereby introducing a hydrogen bonding substituent to the vicinity of the thiazolium carbene centre (*i.e.* (*R*)-**217b**). Additionally, in order to verify the contribution of hydrogen bond donation to catalysis of the benzoin condensation we chose to design a precatalyst that was sterically similar to (*R*)-**217b** but was devoid of a hydrogen bonding capability (*i.e.* (*R*)-**217c**).

The synthesis of amine substrates (*R*)-**215** and (*R*)-**216** from (*R*)-**212** is described below in Scheme 2.4. Acetylation of (*R*)-**212** proceeded smoothly to provide the asymmetric amine substrate (*R*)-**215** in 75% yield. Reductive amination of (*R*)-**215** in the presence of formalin afforded (*R*)-**218**, which was consequently hydrolysed to the corresponding tertiary amine (*R*)-**216** in near-quantitative yield (93%).

Scheme 2.4 Synthesis of asymmetric BINAM aniline substrates



With the three asymmetric substrates in hand, the creation of thiazolium salt precatalysts (*R*)-**217a-c** was attempted. The procedure described previously by Bach[119] in Table 2.1 was used for the syntheses. ^{1}H NMR spectroscopy was used to monitor the reaction progress, and although distinct reaction intermediates were determined to have formed within the reaction, the final cyclised products (*R*)-**217a-c** could not be identified. Nucleophilic attack of the amine substrates to CS_2, resulting in formation of a dithiocarbamic acid (**205**, Scheme 2.2), could be verified for each substrate (by the presence of a ^{1}H NMR resonance signal at approximately 10.4 ppm in DMSO, which corresponded to the S-H bond of the dithiocarbamic acid). Addition of the dithiocarbamic acid to chloroacetone and subsequent cyclisation, furnishing a cyclic

hydroxy-thiazolidine-2-thione (**208**, Scheme 2.2), was partially successful for substrates (*R*)-**212** and (*R*)-**216**. This was confirmed by a distinctive pair of doublets at 3.4 and 3.7 ppm (in DMSO) that related to the two diastereotopic methylene protons of the cyclic system. Surprisingly, addition of the dithiocarbamic acid, derived from amine (*R*)-**215**, to chloroacetone was not observed. Modification of reaction parameters (solvent, concentration, temperature, reaction duration and loading of reagents) could not induce product formation of (*R*)-**217a-c** in any case.

In order to eliminate experimental error as grounds for the inability to synthesise these precatalysts, and to confirm that the BINAM substrates were not suitable candidates under this reaction protocol, simpler amines - phenyl and mesityl amines (**204a** and **204b**, Table 2.1) - were employed in the reaction. Amines **204a** and **204b** were concurrently attempted alongside the BINAM substrates, under identical reaction conditions, with ^{1}H spectroscopy methods being used to monitor the reaction progress. Amines **204a,b** could be observed to cleanly progress to the thiazole-2-thione product, with observed formation of the individual reaction intermediates. Contrastingly, the BINAM-based reactions were far more sluggish than those involving **204a** or **204b**, with only partial formation of the individual reaction intermediates. This ruled out experimental error and verified that the BINAM substrates were not compatible with this reaction procedure. A possible reason for the observed tenacity towards formation of BINAM-based thiazolium salts (*R*)-**217a-c** could be due to the presence of a second nitrogen atom on the BINAM substrates (*R*)-**212**, (*R*)-**215** and (*R*)-**216**. The other nitrogen atom, being nucleophilic, could perhaps become inadvertently involved in the reaction process, causing unfavourable side-reactions to occur, such as an intramolecular cyclisation process. No evidence could be found to determine this type of reactivity due to the resultant intractable mixture of reaction intermediates. Alternatively, the BINAM substrates could be excessively hindered due to the presence of their large (almost perpendicular) planar binaphthyl units, which would cause congestion and restricted access to the amine reaction site.

2.3.2 Cyclic diamine-derived thiazolium salts

2.3.2.1 Cyclic diamines as a chiral template for thiazolium salt synthesis

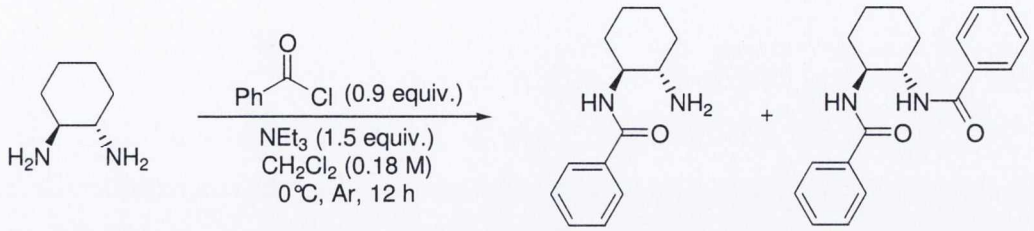
Due to the oversized chiral framework of BINAM, and the resulting failure towards thiazolium salt formation, we considered alternative sources of chiral frameworks that incorporated a capacity for introducing a hydrogen bond-donating moiety. We opted to exploit the chiral aliphatic scaffold of *trans*-1,2-diaminocyclohexane. C_2-Symmetric 1,2-diamines are useful precursors to chiral reagents/auxiliaries for asymmetric synthesis and catalysis.[327,328] Many natural products that possess valuable biological properties contain a 1,2-diaminocyclohexane moiety.[329] In recent years several synthetic diamine derivatives have also been employed as medicinal agents, in particular in chemotherapy. For example, diamine-platinum complexes, containing this scaffold have been designed, such as oxaliplatin and *bis*-neodecanoate diaminoyclohexane platinum (NDDP). These complexes have been determined to possess higher antitumour activity than cisplatin.[330] Notably, *trans*-1,2-diaminocyclohexane is a vicinal diamine, meaning that during thiazolium ring formation, the other amine group could perhaps become involved in unwanted side-reactions. We hoped that this problem would not occur and that the small, rigid, cyclic structure of this molecule could provide a highly successful thiazolium salt precatalyst due to the possibility of positioning a hydrogen bond-donating element adjacent to the thiazolium ring.

2.3.2.2 Synthesis of cyclohexyl diamine-based thiazolium variants

We chose to incorporate an amide substituent as the hydrogen-bond donator. In respect of the decreased size of the cyclohexyl ring (when compared to previously used BINAM) it was considered that a larger amide substituent than the acetyl group of BINAM substrate (*R*)-**215** might be advantageous. If benzamide or a BOC-protected amide was used in the place of a sterically undemanding acetyl group, this might create a bulkier group, capable of increased shielding about the carbene carbon. For this reason the synthesis of phenyl and BOC-protected amides was attempted. Differentiation of the two nitrogen centres of diaminocyclohexane **219**, (Scheme 2.5) typically requires substoichiometric amounts of a derivatising agent and subsequent separation of the diamine starting material from monofunctionalised and difunctionalised diamine

products.[331] Scheme 2.5 outlines the attempted synthesis of mono-acylated diamine **220** using benzoyl chloride as the derivatising agent.

Scheme 2.5 Synthesis of monofunctionalised cyclohexyl diamine **220**



219 **220** 0.5% **221** 43%

Successful discrimination of the two amine groups did not transpire; insignificant levels of monofunctionalisation occurred (0.5%), with near-quantitative formation of the *bis*-acylated diamine **221**. Notably, this difunctionalised compound was highly insoluble in almost every solvent (including DMSO) and as a result precipitated out of the reaction as it formed. Attempts to induce monofunctionalisation included reduction of the reaction concentration, temperature (-15°C), benzoyl chloride loading and also alteration of the solvent and base employed. Unfortunately, none of the avenues explored offered significant yields of product **220**. Attention was turned towards the synthesis of a BOC-protected amine. Using di-*tert*-butyl dicarbonate (Boc_2O) in place of benzoyl chloride, the synthesis of a monofunctionalised diamine was attempted. Once again, such discriminative synthesis was met with frustration as tuning of the reaction conditions did not result in monoacylated product formation. The difunctionalised diamine was selectively generated and was also noted to precipitate out of the reaction when formed. Selective amide hydrolysis was attempted on both *bis*-acylated diamine byproducts; however solubility of the starting material was problematic and deterred such a hydrolysis process. Thus, we decided to focus our efforts on a substitute chiral source for the synthesis of asymmetric bifunctional thiazolium salts.

2.3.3 *Cis*-Amino indanol as a chiral scaffold for thiazolium salt synthesis

2.3.3.1 The potential of the amino indanol frame to induce enantioselectivity

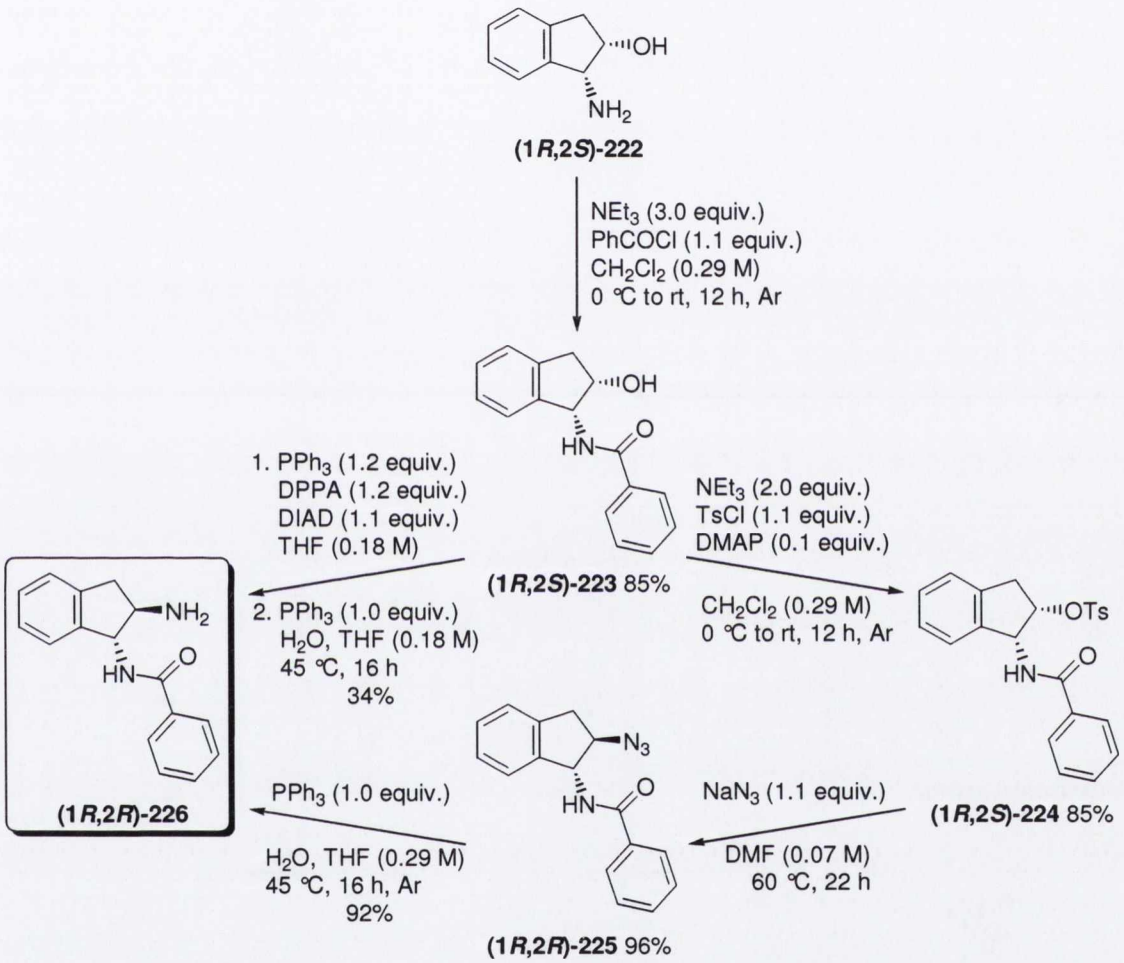
Amino indanol is a fused bicyclic indane system that offers a rigid annulated conformation, and contains contiguous amino and hydroxyl centres. These groups can be readily converted to alternative functionalities and can additionally be orientated in a *cis*- or *trans*-arrangement to each other. Both enantiomerically pure forms of *cis*- and *trans*-amino indanol are commercially available, enabling the preparation of both enantiomers of a target molecule. *cis*-1-Amino-indan-2-ol (**222**, Scheme 2.6), containing a conformationally restricted *cis*-amino indanol moiety, creates an effective discriminative environment in which highly enantioselective and diastereoselective reactions can be performed. Since the discovery of *cis*-amino indanol as a valuable HIV-PR inhibitor ligand in the laboratories of Merck,[332] many asymmetric methodologies have emerged which utilise amino indanol as a constrained phenyl glycinol surrogate.[333] Other examples of the use of the *cis*-amino indanol scaffold in pharmaceutical drug design include the development of a series of potent aggrecanase inhibitors by both DuPont[334,335] and Bristol-Myers Squibb[336,337] for treatment of degenerative joint disease, and the preparation of malarial Plasmepsin inhibitors for treatment of malaria.[338] Additionally, the use of *cis*-amino indanol has been described previously in the design of an array of successful tetracyclic triazolium salt systems, **145**,[208] **153**[212] and **168**,[209] (Sections 1.4 and 1.5). Considering the exceptional achievements of the above-mentioned amino indanol-based NHCs in the intramolecular benzoin condensation and Stetter reactions and also success of the amino indanol frame in the synthesis of important pharmaceutical drugs, we regarded amino indanol as a highly suitable chiral frame for the creation of asymmetric bifunctional thiazolium salt systems.

2.3.3.2 Attempts to create an amino indanol-derived thiazolium salt precatalyst

As was the case in our previous attempts to design bifunctional thiazolium salt precatalysts we chose to integrate an amide substituent as the hydrogen bond-donating moiety; thus we set out to create benzamide species (1*R*,2*R*)-**226**, Scheme 2.6. Benzoylation of *cis*-amino indanol ((1*R*,2*S*)-**222**) with benzoyl choride proceeded

smoothly, furnishing benzoylated alcohol (1*R*,2*S*)-**223** in 85% yield. Note: A small amount of *bis*-acylated byproduct was unavoidable; however selective ester hydrolysis regenerated the desired amide.

Scheme 2.6 Synthesis of amino indanol amine substrate (1*R*,2*R*)-**226**



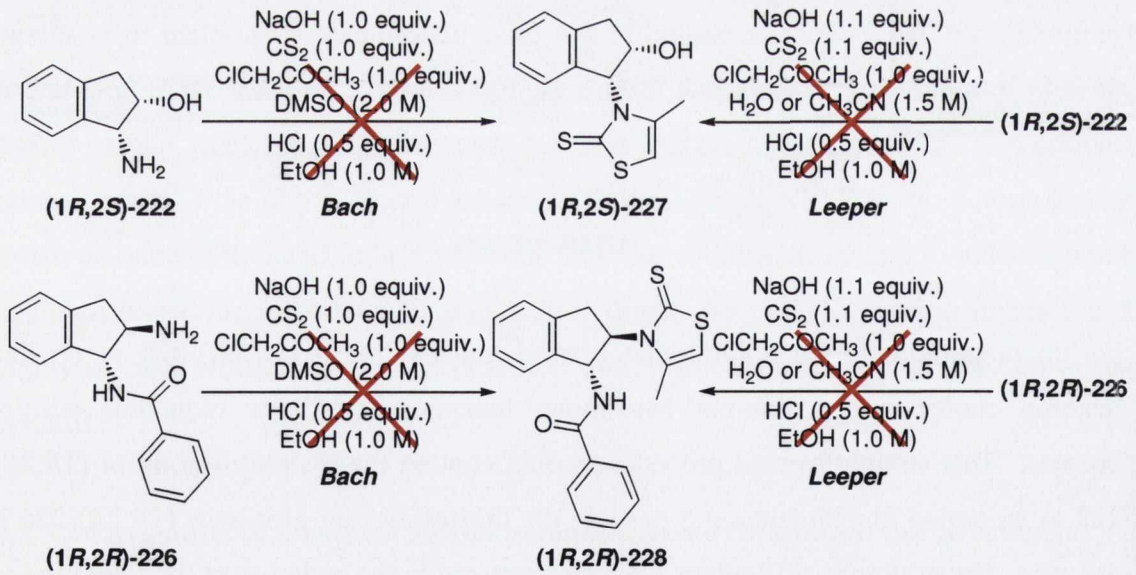
For the preparation of the amino indanol-based amine substrate (1*R*,2*R*)-**226**, an obvious reaction choice was a one-pot Mitsunobu inversion-Staudinger reduction reaction process. This straightforward procedure would convert the hydroxyl group of (1*R*,2*S*)-**223** to an amine functionality and provide the thiazolium salt precursor (1*R*,2*R*)-**226** in one step. Frustratingly, difficulties were encountered in the isolation of the final product which resulted in a reduced yield of 34%. We therefore diverted to a lengthier, yet higher yielding and largely straightforward synthetic pathway for the generation of (1*R*,2*R*)-**226**: tosylation of alcohol (1*R*,2*S*)-**223** furnished (1*R*,2*S*)-**224**, which was then treated with NaN_3 to provide azide (1*R*,2*R*)-**225** with inverted stereochemistry.

Subsequent Staudinger reduction (in one pot) afforded the sought after primary amine (1*R*,2*R*)-**226**, in an acceptable yield of 75%, over the three reaction steps.

We recognised that the hydroxyl group of amino indanol could also serve as a hydrogen bond donating group and were thus interested in using both *cis*- and *trans*-isomers of amino indanol as amine substrates for bifunctional thiazolium salt synthesis. The use of both isomers would allow for comparison of the effects of a *cis* and *trans* arrangement of the thiazolium ring and the hydrogen bonding moiety. Disappointingly, the *trans*-isomer was highly insoluble in most organic solvents making it a particularly recalcitrant starting material.

Cis-Amino indanol ((1*R*,2*S*)-**222**) and primary amine (1*R*,2*R*)-**226** were applied as amine substrates for thiazole-2-thione synthesis. Both Bach's[119] and Leeper's[116] previously described methods were attempted, as outlined in Scheme 2.7. Unfortunately, modification of either reaction protocol did not result in the formation of either thione (1*R*,2*S*)-**227** or (1*R*,2*R*)-**228**.

Scheme 2.7 Attempted amino indanol-based thiazole-2-thione synthesis



A thorough investigation into the syntheses of thiones (1*R*,2*S*)-**227** and (1*R*,2*R*)-**228** was conducted and reaction progress was monitored using ^{1}H NMR spectroscopy. Similar to the synthesis of BINAM thiones, incomplete addition of CS_2 occurred; a ^{1}H NMR

resonance signal was observed at 9.9 ppm (in DMSO) corresponding to formation of the dithioformamide intermediate (**205**, Scheme 2.2). The cyclised adduct after reaction with chloroacetone (*i.e.* hydroxy-thiazolidine-2-thione **208**, Scheme 2.2) was also observed (characterised by the presence of a pair of doublets at 3.2 and 3.5 ppm respectively). We considered adverse interference of the nucleophilic unprotected hydroxy group of *cis*-substrate (1*R*,2*S*)-**222** and the nitrogen atom of the benzamide group of (1*R*,2*R*)-**226** as possible reasons for the inability to form the thiazolium salt intermediates (1*R*,2*S*)-**227** and (1*R*,2*R*)-**228**.

2.3.4 Section 2.3: conclusions

The possibility of generating novel asymmetric bifunctional thiazolium salt systems that would far exceed the capabilities of preceding thiazolium precatalysts was intriguing. We had hoped that addition of a hydrogen bond donating component to these novel thiazolium salt systems would provide highly efficient and enhanced catalysis of the benzoin condensation (in terms of product yield and enantioselectivity). Accordingly, the synthesis of an array of asymmetric thiazolium salts was attempted using three different chiral scaffolds, BINAM, *trans*-1,2-diaminocyclohexane and *cis*-amino indanol. Despite extensive efforts, annulation of related aniline substrates to the intermediate thiazole-2-thiones exceeded our efforts. It was deemed that the BINAM substrate was exceedingly bulky and its excessive steric size prevented thiazole-2-thione formation. The diaminocyclohexane frame was not a viable synthetic choice due to inadequate discrimination of the two amine groups. The amino indanol scaffold was a promising alternative; unfortunately cyclisation to the thiazole-2-thione could not be coerced using this type of substrate. A possible reason for the observed reticence towards thiazole-2-thione synthesis (using BINAM and amino indanol substrates) was considered to be involvement of nearby functional groups, such as hydroxyl, amino and amide groups, within the course of the reaction process. These groups, containg unpaired electrons, could all engage in nucleophilic attack on a reaction intermediate, perhaps leading to intramolecular cyclisation products. This hypothesis could not be verified due to the inseparable mixture of starting material and intermediate products that were obtained. Steric hindrance about the amine group that was involved in thiazolium ring formation, caused by bulky components of the substrate was also

considered. As a result we decided to move away from synthesis of thiazolium salts and focus our attention on the creation of triazolium salt systems.

2.4 Achiral triazolium salt precatalyst synthesis

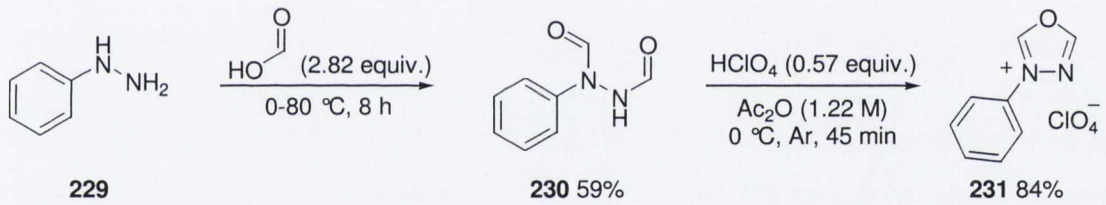
2.4.1 Creation of a suite of first generation achiral triazolium salt catalysts

In the past 15 years, triazolium salts have proven to be far more successful promoters of the enantioselective benzoin condensation than thiazolium salts.[197] Houk proposed that thiazolium salts are less effective than triazolium salts at inducing enantioselective benzoin condensation reactions due to the absence of an *N*-aryl component on thiazolium ions.[195] At the outset of this project, bifunctional triazolium salts, like their thiazolium congeners, had yet to be developed for use in the enantioselective benzoin condensation. At that time, to the best of our knowledge, only one example of a hydrogen bond-donating carbene catalyst was known; Miller's thiazoylalanine-derived precatalyst (**166**, Figure 1.16) had been employed in the Stetter and aza-benzoin condensation reactions.[244,263] Ye[147,315] and Waser[316] later reported the synthesis of an array of bifunctional pyroglutamic acid-derived triazolium salts containing hydrogen bond-donating hydroxyl and (thio)urea groups in 2008 and 2010.

Due to the difficulties encountered with the synthesis of an assortment of chiral thiazolium salts, we decided to diversify into the synthesis of 1,2,4-triazolium salt variants, and investigate the synthetic potential of bifunctional triazolium salt catalysis in the benzoin condensation. Once again, we considered it prudent to begin with the generation of an array of simple, electronically diverse, achiral triazolium salts for assessment in the benzoin condensation. This would allow for development and optimisation of a viable synthetic procedure that would enable the creation of more complex chiral triazolium salts at a later stage. In addition, the factors influencing the benzoin condensation reaction could be examined and optimised prior to the testing of more expensive chiral precatalysts.

In 1967, Boyd reported a novel synthesis of quaternary 1,3,4-oxadiazolium salts using acylated hydrazines and perchloric acid.[339] He subsequently studied the actions of various nucleophiles (mainly amines) in the presence of these salts and revealed a previously undisclosed synthesis of 1,2,4-triazolium salts.[340,341] We opted to use Boyd's methodology for the synthesis of our triazolium precatalysts and set out to create the oxadiazolium salt **231**, as illustrated in Scheme 2.8. Firstly, phenyl hydrazine (**229**) was acylated using formic acid to provide the rotameric diformylhydrazine compound in 59% yield. Cyclisation to provide a quaternary oxadiazolium salt **231** was achieved using perchloric acid and acetic anhydride. Note: oxadiazolium salts are deliquescent; in the presence of water they readily revert, *via* ring fission, to the corresponding diacylated arylhydrazine **230**, changing from a white solid to a red liquid. Thus, **231** was handled and stored under anhydrous conditions.

Scheme 2.8 Synthesis of oxadiazolium salt **231** using Boyd's procedure



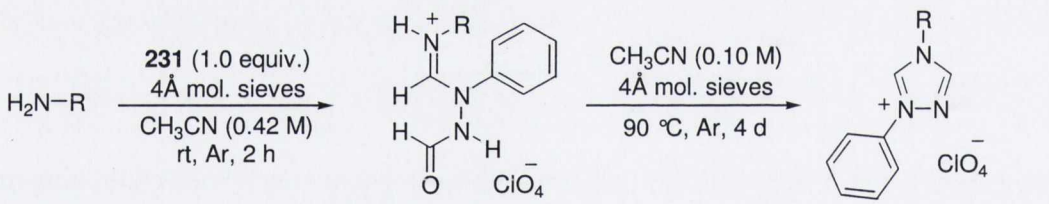
229 **230** 59% **231** 84%

Boyd described a straightforward method for the preparation of triazolium salts - brief heating of **231** in acetic acid, with a marginal excess of aniline, led to separation of the triazolium salt, which could simply be filtered out of the reaction mixture. Boyd indicated that this procedure was compatible with anilines but that preparation of triazolium salts from primary aliphatic amines and oxadiazolium salts, in acetic acid, resulted in the formation of intractable material. Using IR spectroscopy he determined that destructive ring-opening of the oxadiazolium salt *via* hydrolysis occurred under these reaction conditions. To verify this supposition, we attempted the synthesis of several aliphatic amine-derived triazolium salts using Boyd's procedure and obtained meagre product yields between 2 and 6%.

It was clear that an efficient protocol was required for the construction of triazolium salt systems that were derived from a range of aromatic and aliphatic amines. Thus we sought to optimise the reaction conditions and consequently improve the yield of

triazolium salt product. Solvent screening determined (dry) CH_3CN to be the optimal solvent for precatalyst synthesis. THF, CH_2Cl_2, ethanol, methanol and toluene were found to be unsuitable reaction media. Variation of the amine to oxadiazolium salt ratio revealed that using an excess of oxadiazolium salt (2.0 equiv.) increased the amount of cyclised triazolium salt formed, with the excess oxadiazolium salt acting as a drying agent. However, using two equivalents of **231** resulted in augmented levels of by-products and made purification of the triazolium salts rather arduous. To overcome this constraint, molecular sieves were added to assume the role of drying agent, removing any adventitious water present in the reaction and simultaneously abetting cyclisation to **233**. The optimal reaction conditions are depicted in Scheme 2.9 and using these conditions an uncyclised hydrazino-intermediate **232** was isolated and subsequently annulated to provide the triazolium salts **233**. In order to obtain a maximum return of triazolium salt, the unstable oxadiazolium salt **231** was freshly prepared and used directly in the precatalyst synthesis.

Scheme 2.9 Optimised triazolium salt synthesis *via* intermediate **232**



219 R = *c*-$C_6H_{10}NH_2$
204f R = $CH_2C_6H_5$
204g R = *c*-C_6H_{11}

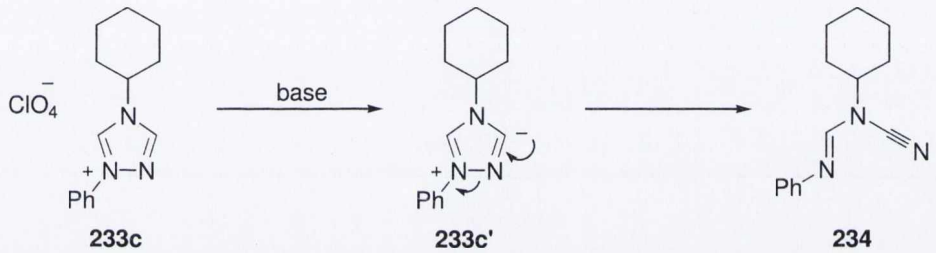
232a R = *c*-$C_6H_{10}NH_2$ 22%
232b R = $CH_2C_6H_5$ n.d.
232c R = *c*-C_6H_{11} 62%

233a R = *c*-$C_6H_{10}NH_2$ 27%
233b R = $CH_2C_6H_5$ 64%
233c R = *c*-C_6H_{11} 78%

Three achiral triazolium salts were prepared from their corresponding amines - racemic *trans*-1,2-diaminocyclohexane (**219**), benzyl amine (**204f**) and cyclohexylamine (**204g**) - in modest to average yields. Note: diamino substrate **219** required a two-fold excess of **231** to provide the *bis*-triazolium analogue **233a** in 27% yield. The yield of the benzyl-containing hydrazino intermediate **232b** was not determined as the crude mixture was found to contain significant levels of the cyclised triazolium ion **233b**. Therefore, it was not purified further and was heated at reflux to obtain the final product **233b** in a yield of 64%.

In 1996, Enders *et al.* reported that carbenes derived from triazolium ions that are devoid of substitution at the C-3 position are less stable catalysts than their C-3 substituted analogues.[124] For example, if deprotonation at the C-5 position of triazolium ion **233c** occurs, a viable carbene catalyst is formed that proceeds to catalyse the benzoin condensation reaction. However, if deprotonation at the C-3 position takes place destructive and irreversible ring opening occurs *via* **233c'** resulting in the formation of a cyanobenzamidine **234**, Scheme 2.10.

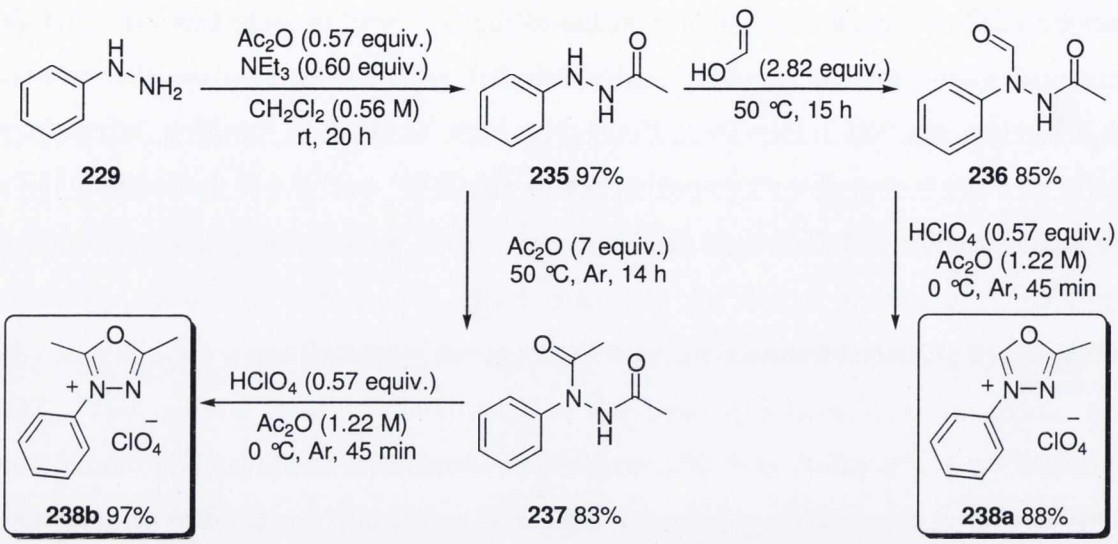
Scheme 2.10 Catalyst decomposition to form a cyanobenzamidine



In order to probe this hypothesis, we synthesised the achiral methylated cyclohexylamine-derived precatalyst **240a**, Scheme 2.12. Additionally, we sought to verify that catalysis of the benzoin condensation is engendered by formation of an *in situ*-generated carbene catalyst, (following deprotonation of the triazolium ring). Accordingly, *bis*-methyl triazolium precatalyst **240b** was designed, containing methyl groups at the two normally available deprotonation sites, Scheme 2.12. Generation of the corresponding oxadiazolium salts **238a,b** was necessary, and the synthetic process is shown first in Scheme 2.11.

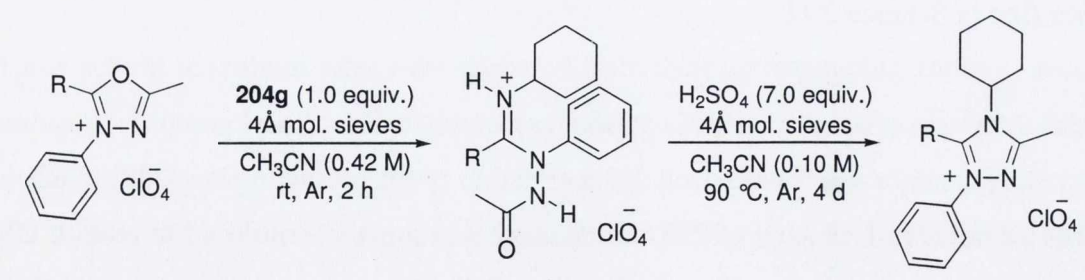
For the synthesis of oxadiazolium salt **238a**, containing a C-5 methyl group, the required hydrazine precursor was synthesised *via* acetylation of phenyl hydrazine (**229**) to afford almost quantitative formation of **235**, which was subsequently formylated to provide **236** (85% yield). Cyclisation to the oxadiazolium salt **238a** proceeded smoothly in 88% yield. The diacetyl hydrazine **237** was generated from **235** using acetic anhydride, and then annulated to the *bis*-methylated oxadiazolium salt **238b** in near-quantitative yield (97%).

Scheme 2.11 Synthesis of C-2 and C-5 methylated oxadiazolium salts **238**



With the requisite oxadiazolium salts **238** now prepared, the previously used synthetic procedure (Scheme 2.9) was applied to create substituted cyclohexylamine-derived triazolium precatalysts **240a,b**, Scheme 2.12. As was found with the previous syntheses, an uncyclised hydrazino-intermediate **239** was obtained in each case and subsequently heated under reflux in the presence of molecular sieves to induce ring formation to **240**. Addition of sulphuric acid was required to facilitate cyclisation of the hindered methylated hydrazino-intermediates **239a,b** to the triazolium ions **240a,b**.

Scheme 2.12 Creation of achiral C-3 and C-5 methylated triazolium salts



238a R = H
238b R = CH_3

239a R = H 81%
239b R = CH_3 82%

240a R = H 63%
240b R = CH_3 77%

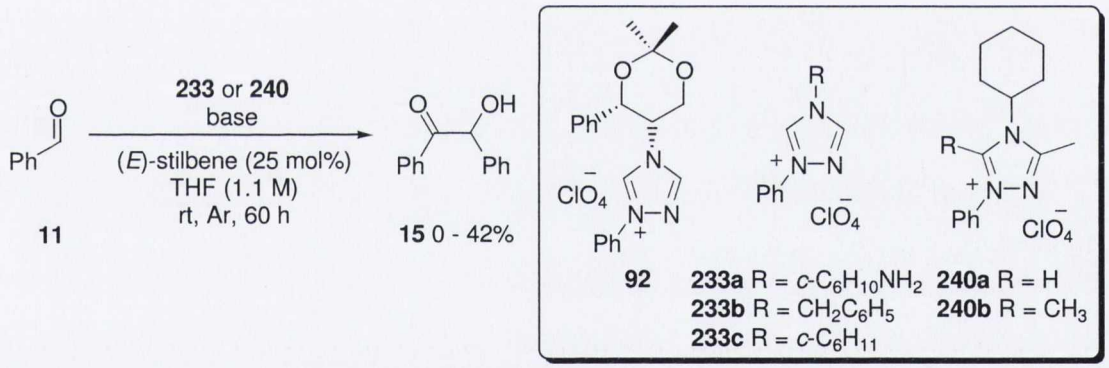
Using an optimised reaction protocol that stemmed from Boyd's initial research we created an array of achiral triazolium salts.[341] The ability of these precatalyst systems to catalyse the benzoin condensation was subsequently investigated.

2.5 Examination of the benzoin condensation reaction using achiral triazolium salts

2.5.1 Initial evaluation of achiral triazolium salts as precatalysts for use in the benzoin condensation

In 1996, Enders reported the first example of a chiral triazolium salt-promoted benzoin condensation.[124] The design of our achiral triazolium ions (**233** and **240**) was similar to Enders' successful chiral ketal-based triazolium salt **92** (Table 2.3). For this reason, we selected Enders' reaction conditions as a starting point for preliminary investigations of the benzoin condensation. Table 2.3 displays the results obtained from our preliminary investigation of the triazolium salt-mediated benzoin condensation using **233** and **240**.

Table 2.3 Screening of achiral triazolium precatalysts **233** and **240**



entry	cat.	loading (mol%)	base	loading (mol%)	conv.[a] (%)	yield[a] (%)
1	-	-	K_2CO_3	0.57	0	0
2	**233a**	1.25	K_2CO_3	0.57	10	7
3	**233b**	1.25	K_2CO_3	0.57	32	24
4	**233c**	1.25	K_2CO_3	0.57	55	35
5	**240a**	1.25	K_2CO_3	0.57	14	8
6	**240b**	1.25	K_2CO_3	0.57	0	0
7	**233c**	1.25	Cs_2CO_3	0.57	41	31
8	**233c**	1.00	Cs_2CO_3	0.80	42	42
9	**233a**	1.25	NEt_3	1.14	0	0
10	**233b**	1.25	NEt_3	1.14	0	0
11	**233c**	1.25	NEt_3	1.14	0	0
12	**240a**	1.25	NEt_3	1.14	0	0
13	**240b**	1.25	NEt_3	1.14	0	0

[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

The reaction failed to proceed in the absence of any catalyst (entry 1), verifying that triazolium salts, in the presence of base, facilitate the reaction process *via* carbene catalysis. The reaction conditions that Enders utilised in his study entailed the use of THF as solvent, 1.25 mol% of precatalyst **92** and 0.57 mol% of K_2CO_3 as base. Under these reaction conditions *bis*-triazolium salt **233a** fared poorly as a mediator of the dimerisation process (entry 2), whilst benzylamine-derived precatalyst **233b** provided a product yield of 24%, (entry 3). The cyclohexylamine derivative **233c** was found to be the most efficient triazolium precatalyst, generating a yield of 35% of benzoin (entry 4). The C-3 methylated cyclohexylamine analogue **240a** was unsuccessful at promoting an efficient process (entry 5) and unsurprisingly, dimethyl triazolium salt **240b** did not offer any benzoin product (entry 6), confirming that catalysis depends on deprotonation of the triazolium ring to form the active carbene catalyst *in situ* (*c.f.* Section 1.1.3.2). Having identified precatalyst **233c** as the optimal achiral promoter of the benzoin condensation (of the salts evaluated), Cs_2CO_3 was investigated as an alternative base to K_2CO_3. Cs_2CO_3 revealed itself to be a more suitable base within the reaction, generating a product yield of 42% after 60 hours (entry 8). Triethylamine was also assessed as a base and surprisingly provided no yield of benzoin (entries 9-13). We found this result surprising as triethylamine is considered as the standard base for use in conjunction with thiazolium salts in these reactions.[110,111,116]

2.5.2 Optimisation of reaction conditions

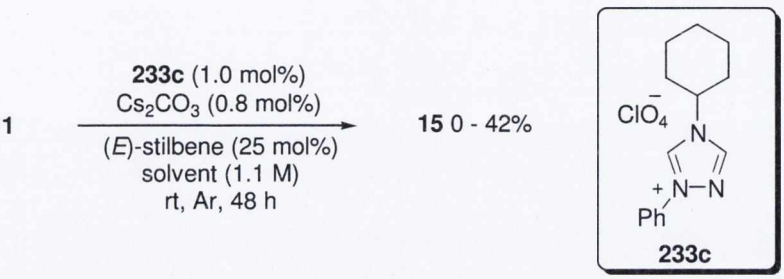
Having determined that the cyclohexylamine-based triazolium ion **233c**, in conjunction with Cs_2CO_3, was an ideal promoter of the benzoin condensation we set about further optimising the reaction conditions. This entailed examining the scope of the reaction with regards to several parameters, such as suitable solvents and bases and also ideal precatalyst and base loadings. The first step in this sequence of analyses was the investigation of the most suitable solvent for the reaction.

2.5.2.1 Solvent screening

A range of solvents were assessed in the benzoin condensation reaction, the results of these studies are displayed in Table 2.4. Using benzaldehyde as the aldehyde substrate and 1.0 mol% of **233c**, THF was clearly identified as the most suitable reaction medium

(entry 1), with CH_2Cl_2, CH_3CN and acetone proving to be less suitable reaction media (entries 2, 4 and 8). *Iso*-propyl ether, toluene, 1,4-dioxane, *t*-butanol, methanol and water (deionised and degassed) did not facilitate benzaldehyde coupling.

Table 2.4 Investigation of the role of solvent in the triazolium ion-mediated benzoin condensation reaction



entry	solvent	conv.[a] (%)	yield[a] (%)	entry	solvent	conv.[a] (%)	yield[a] (%)
1	THF	42	42	6	1,4-dioxane	1	1
2	CH_2Cl_2	7	7	7	^tBuOH	2	2
3	$^iPr_2O$	0	0	8	$(CH_3)_2O$	5	5
4	CH_3CN	7	7	9	CH_3OH	3	1
5	Toluene	1	1	10	H_2O	0	0

[a]Determined by ^1H NMR spectroscopy using (*E*)-stilbene as an internal standard.

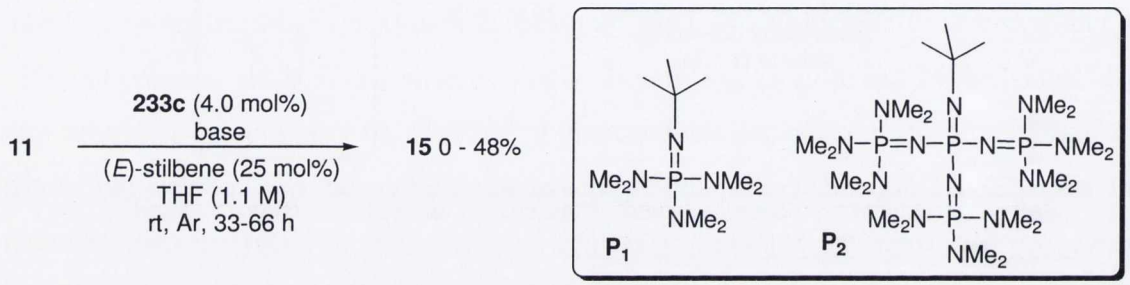
2.5.2.2 Identification of the most proficient bases

With THF determined to be the optimal solvent, we next focused our efforts on examining the effects of different bases. The compatibility of other simple bases (mainly carbonate and organic bases) was evaluated using higher precatalyst and base loadings of 4.0 and 3.2 mol% respectively, to ensure efficient deprotonation of the triazolium precatalyst, Table 2.5.

Li_2CO_3, Na_2CO_3 and $NaHCO_3$ proved completely ineffective at deprotonation of the precatalyst system **233c** (entries 1-3), whereas $KHCO_3$, K_2CO_3 and Rb_2CO_3 furnished promising product yields of 32%, 42% and 48% respectively, under identical reaction conditions (entries 4-6). Cs_2CO_3 disappointingly provided a poor product yield of **15** (24%) after 66 hours, which was surprising considering the higher yields of benzoin obtained at lower catalyst loadings (1.25 and 1.0 mol%, entries 7 and 8, Table 2.3). Cadmium carbonate and potassium hydroxide were unsuitable base choices in the reaction, failing to generate the carbene catalyst (entries 8 and 9). However, somewhat

unexpectedly, a mixture of potassium carbonate and potassium hydroxide was found to serve as a successful and valuable binary base system (entry 10). Amine bases (triethylamine, DMAP and DBU), KHMDS, sodium azide and phosphazene bases (P_1 and P_2) all failed to generate the carbene *in situ* to a catalytically relevant extent (entries 11-17).

Table 2.5 Assessment of the most suitable base for the benzoin condensation



entry	base	loading (mol%)	time (h)	conv.[a] (%)	yield[a] (%)
1	Li_2CO_3	3.2	48	0	0
2	Na_2CO_3	3.2	48	0	0
3	$NaHCO_3$	3.2	48	0	0
4	$KHCO_3$	3.2	48	36	32
5	K_2CO_3	3.2	48	47	42
6	Rb_2CO_3	3.2	48	52	48
7	Cs_2CO_3	3.2	66	23	24
8	$CdCO_3$	3.2	48	0	0
9	KOH	3.2	48	0	0
10	K_2CO_3/KOH	1.6/1.6	48	50	44
11	NEt_3	3.2	60	0	0
12	DMAP	3.2	46	3	2
13	DBU	3.2	33	18	17
14	KHMDS	3.2	48	4	4
15	NaN_3	3.6	48	0	0
16	P_1	3.6	48	7	7
17	P_2	3.6	48	2	2

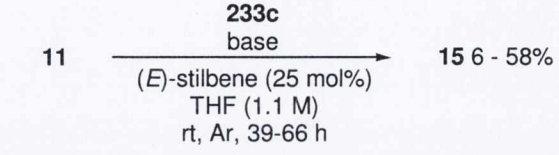
[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

2.5.2.3 Fine-tuning of the reaction protocol

We had now identified a choice of several bases for use in the benzoin condensation reaction; these included carbonate bases K_2CO_3, Rb_2CO_3, Cs_2CO_3 and the binary base mixture of K_2CO_3/KOH. A thorough analysis, involving fine-tuning of the reaction

conditions, using each of these bases, was next undertaken in order to determine the most suitable base (and loading) for the dimerisation process. The results obtained are outlined in Table 2.6.

Table 2.6 Fine tuning of reaction parameters regarding base choice and loading



entry	cat. loading (mol%)	base	loading (mol%)	time (h)	conv.[a] (%)	yield[a] (%)
1	1.00	K_2CO_3	0.80	48	41	38
2	4.00	K_2CO_3	1.80	48	45	34
3	4.00	K_2CO_3	8.00	48	21	22
4	5.00	K_2CO_3	0.57	48	56	25
5	5.00	K_2CO_3	4.00	48	38	37
6	10.0	K_2CO_3	0.57	48	53	30
7	10.0	K_2CO_3	8.00	48	74	58
8	1.00	Cs_2CO_3	0.80	66	43	41
9	2.00	Cs_2CO_3	1.60	66	38	35
10	4.00	Cs_2CO_3	1.80	62	45	42
11	5.00	Cs_2CO_3	4.00	39	49	42
12	10.0	Cs_2CO_3	8.00	61	74	58
13	1.00	Rb_2CO_3	0.50	63	6	6
14	6.00	Rb_2CO_3	2.86	64	54	43
15	10.0	Rb_2CO_3	4.76	64	64	46
16	4.00	K_2CO_3/KOH	0.8/4.8	47	34	32
17	4.00	K_2CO_3/KOH	1.6/3.2	47	40	37
18	4.00	K_2CO_3/KOH	2.4/1.6	47	40	37
19	4.00	K_2CO_3/KOH	2.88/0.32	48	48	41
20	4.00	K_2CO_3/KOH	2.88/0.64	48	48	48
21[b]	4.00	K_2CO_3/KOH	2.88/0.64	48	6	5

[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]C-3 methyl precatalyst **240a** used in place of **233c**.

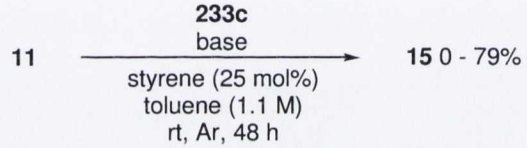
Potassium carbonate was first assessed as a base in the reaction and using 1.0 mol% of precatalyst **233c**, in conjunction with 0.8 mol% K_2CO_3, a yield of 38% of benzoin (**15**) was obtained (entry 1). The precatalyst loading was increased and it was determined that using a large excess of precatalyst to base (or *vice versa*) caused an adverse effect, resulting in reduced yields of **15** (entries 2-4). It was also found that increasing the precatalyst loading to 5.0 mol% did not increase the yield of benzoin (entry 5). When the loading of **233c** was increased to 10.0 mol% (with 8.0 mol% K_2CO_3) a significantly

higher yield of benzoin was furnished, 58% (entry 7). Thus, an ideal ratio of precatalyst to base, which generally mediated higher product yields, was determined experimentally to be 1.0:1.6, taking into account the dibasicity of K_2CO_3, (entries 1, 5 and 7). Variation of the catalyst and base loadings using K_2CO_3 led to conditions under which **15** could be obtained in up to 58% yield (entries 1-7). Cs_2CO_3 was next evaluated as a base in the benzoin condensation and a product yield of 41% was provided when 1.0 mol% **233c** was employed with 0.8 mol% of base (entry 8). As was the case for K_2CO_3, we found that increasing the precatalyst loading from 1.0 mol% to 5.0 mol% did not increase the product yield (entries 9-11). Notably, when 10.0 mol% of **233c** was used, in conjunction with 8.0 mol% Cs_2CO_3, a yield of 58% of benzoin was obtained (entry 12). Rb_2CO_3 was also capable of providing adequate levels of product formation (entries 14 and 15). However, this methodology involving the use of carbonate bases was unsatisfactory due to a difficulty in arriving at a system of acceptable reproducibility (*i.e.* <5% discrepancy in yield between identical runs). Cs_2CO_3, Rb_2CO_3 and to a lesser extent K_2CO_3, are highly deliquescent and were found to be difficult to use reliably, in spite of extreme experimental care being exercised. Despite considerable experimentation involving the rigorous exclusion of air, moisture *etc.*, and completion of >250 iterative runs, a robust and dependable protocol could not be achieved. See Appendix One for experimentation details. Gratifyingly, this quandary was overcome using a dual-base system consisting of K_2CO_3 and KOH. Optimisation of the amounts of the two bases in this unusual mixture and also the precatalyst to base ratio allowed for the development of a reproducible binary base system (entries 16-20). Over a series of repeated experiments **15** could be reliably formed in *ca.* 50% yield using **233c** at 4.0 mol% and a dual-base mixture of K_2CO_3/KOH (2.88/0.64 mol%). This base mixture is unusual in that both K_2CO_3 and KOH are deliquescent but when combined together in the reaction they provide a reliable and reproducible base combination. The reason for this, at this juncture is unclear. Interestingly, when the structurally similar C-3 methylated triazolium salt **240a** was utilised under the optimal reaction conditions a meagre (5%) yield of benzoin was generated, confirming that this precatalyst is not a viable promoter of the benzoin condensation under these reaction conditions (entry 21).

2.5.2.4 Alternative reaction conditions using toluene as solvent

Inspired by a recent study by Enders and Han disclosing the use of KHMDS in toluene solvent to generate carbene catalysts from triazolium salt precursors, we decided to re-examine the use of KHMDS as a base.[128] Our previous investigation of KHMDS as a base in THF solvent had resulted in a paltry yield of 4% of benzoin, (see Table 2.5, entry 14). We subsequently discovered that despite the poor performance of this base in THF solvent, its use in toluene resulted in excellent (>70%) yields of benzoin product if used at 10 mol% in conjunction with an equivalent amount of precatalyst. Optimisation studies were completed using toluene as solvent and the results obtained from assessment of KHMDS (and other bases) are presented in Table 2.7.

Table 2.7 Optimisation studies using toluene as solvent



entry	cat. loading (mol%)	base	loading (mol%)	conv.[a] (%)	yield[a] (%)
1	1.0	KHMDS	1.0	3	3
2	2.0	KHMDS	2.0	4	3
3	4.0	KHMDS	4.0	37	30
4	6.0	KHMDS	6.0	56	36
5	10.0	KHMDS	10.0	98	79
6[b]	10.0	KHMDS	10.0	91	75
7	10.0	P_1	10.0	14	12
8	10.0	P_2	10.0	4	3
9	10.0	NEt_3	10.0	0	0
10	10.0	DBU	10.0	0	0
11	10.0	*t*-BuOK	10.0	6	4

[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b]C-3 methyl precatalyst **240a** used in place of **233c**.

Initial experiments revealed that low precatalyst loadings (1-6 mol%) rendered poor product yields (entries 1-4). Employing 10 mol% loadings of either **233c** or its C-3 methyl analogue **240a** facilitated the formation of substantial levels of benzoin (79% and 75%, entries 5 and 6). Considering these conditions to be most favourable, we assessed alternative bases with this methodology. Use of P_1 led to poor product dimerisation

(12%, entry 7), whilst other bases (P_2, triethylamine, DBU and *t*-BuOK) failed to render sufficient carbene formation (entries 8-11).

2.5.3 Section 2.5: conclusions

An extensive and thorough examination of the achiral benzoin condensation was completed. At the outset we determined that K_2CO_3, Cs_2CO_3 and Rb_2CO_3 with THF as a reaction medium, provided moderate yields of benzoin product. Disappointingly, due to the hygroscopic nature of these carbonates, they could not be used reproducibly in the benzoin condensation. Further optimisation of the reaction conditions led to the development of a dual base system employing 2.88 mol% K_2CO_3 with 0.64 mol% KOH, in conjunction with 4.0 mol% of precatalyst. Although both bases employed are deliquescent this unusual mixture enabled the development of conditions that provided a robust and reliable protocol that consistently generated yields of *ca.* 50% of benzoin using precatalyst **233c**. The reasons for the success of this base combination are unclear at present. However, we can postulate that KOH serves as a drying agent, scavenging adventitious water present in the reaction medium, forming the complex $H_3O_2^-$. The use of the dual base mixture has been reported in the literature - a combination of NaOH or KOH with K_2CO_3 has been used in solid-liquid phase alkylation reactions involving phase transfer catalysis (PTC).[342] Using solid base/organic liquid two-phase systems, diphenylphosphinic hydrazides and heterocyclic amines were *N*-alkylated in good yields.[343,344] The high efficiency of this base system in solid-liquid PTC alkylation was attributed to the limited amount of water in the system, thereby enhancing the reaction rate by effective solvation control. The potassium carbonate apparently prevents aggregation of hydroxide particles in the presence of adventitious water. Alternatively, KOH could possibly serve as a regenerative source of K_2CO_3. Consumption of K_2CO_3 in the reaction process results in the formation of CO_2. However, the nucleophilic hydroxide anion is known to react with oxides. Thus, in the reaction KOH could perhaps react with CO_2 (upon consumption of K_2CO_3) producing potassium bicarbonate, $KHCO_3$. Further reaction of $KHCO_3$ with KOH can produce K_2CO_3, resulting in the regeneration of the base K_2CO_3:

$$KOH + CO_2 \longrightarrow KHCO_3$$

$$KOH + KHCO_3 \longrightarrow K_2CO_3 \qquad [1]$$

Enders reported that decomposition of a triazolium salt can take place if deprotonation occurs at the C-3 position of the triazolium ring, see Scheme 2.10.[124] Using IR and mass spectroscometry techniques, we verified the presence of a cyanobenzamidine substance at the end of a 48 hour benzoin condensation reaction (using precatalyst **233c** and the binary base protocol). We developed C-3 methylated triazolium salt **240a** to verify this supposition and overcome this potential limitation. However, we discovered that **240a** surprisingly performed rather poorly in the benzoin condensation reaction, generating meagre yields of up to 8% of benzoin, (Table 2.3, entry 5 and Table 2.6, entry 21). The reason for the reduced activity of precatalyst **240a** is unclear at this point.

An additional methodology was developed following the disclosure of a study by Enders utilising toluene and KHMDS.[128] Equimolar amounts of precatalyst and base (10 mol%) enabled the formation of significant levels of product (*ca.* 80%). Interestingly, we also found that the C-3 methylated catalyst **240a** exhibited an almost identical reactivity profile to **233c**, under these conditions, indicating that extensive catalyst decomposition *via* deprotonation of **233c** at the C-3 position is not problematic using this system. Thus, at the conclusion of the study we have identified two sets of potentially useful reaction conditions under which we could evaluate chiral triazolium catalysts; one set using 4.0 mol% of precatalyst in THF in the presence of weak bases, and another employing a powerful base at higher precatalyst and base loadings, in a less polar solvent that is more potentially conducive to catalysis involving the donation of hydrogen bonds.

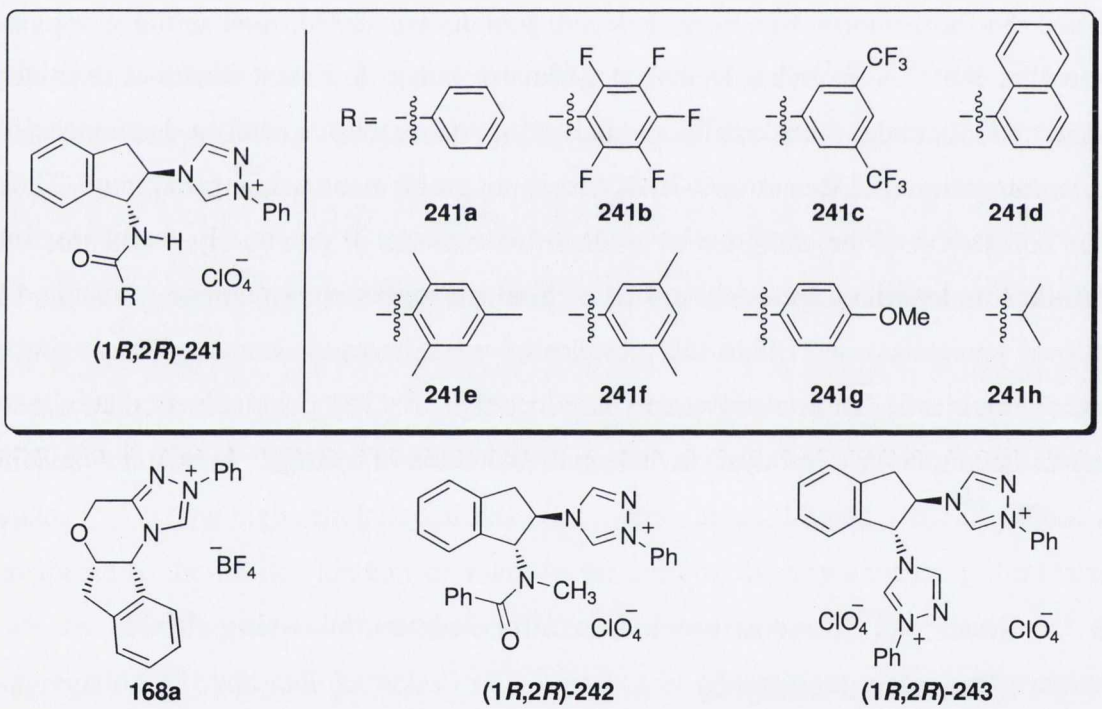
3.1 Studies of the asymmetric benzoin condensation using chiral bifunctional catalysts

3.1.1 Amino indanol-derived chiral bifunctional triazolium salt precatalysts: design rationale

Having identified and optimised two disparate methodologies for the benzoin condensation reaction using achiral triazolium salt **233c**, we moved towards an enantioselective variant of this reaction. Encouraged by the success of Miller's bifunctional thiazoylalanine-derived precatalyst **166** (Figure 1.16), we sought to develop

the first suite of chiral triazolium ion precatalysts incorporating hydrogen bond-donating substituents for catalysis of the enantioselective benzoin condensation. The bicyclic chiral frame of *cis*-amino indanol has been used in the design of many highly successful organocatalytic triazolium salt systems. Eminent research groups, such as those led by Rovis,[209] Suzuki,[212] Bode,[138] Scheidt[140] and Enders,[208] have created efficient amino indanol-derived precatalysts that have been successful in catalysing an array of *Umpolung* reactions, (**168a**, Figure 3.1, is an example of such a precatalyst). For this reason, we decided to use the amino indanol scaffold for construction of a collection of novel chiral bifunctional precatalyst systems (*i.e.*, (1*R*,2*R*)-**241**-**243**, Figure 3.1).

Figure 3.1 Novel amino indanol-derived precatalysts (1*R*,2*R*)-**241**-**243**



Our amino indanol-derived precatalysts differed from those previously synthesised as the triazolium ring was not ring-fused or embedded within the chiral scaffold (as per **168a**, Figure 3.1), but rather appended to it, with free rotation of the triazolium ring. In principle these catalysts would possess the potential to activate the aldehyde substrate towards nucleophilic attack by the carbene moiety *via* general acid catalysis, while simultaneously controlling the stereochemical outcome of the reaction. We designed an assortment of chiral bifunctional precatalysts based on several criteria:

1. The pK_a of the hydrogen bond-donating group should not be lower than that of the triazolium ion - thus, an amide functional group was chosen to serve as the catalyst's 'acidic' component.
2. The acidity of the hydrogen bond donor should be subject to a measure of control *via* variation of the electronic properties of the amide substituent (*i.e.* precatalysts ((1*R*,2*R*)-**241a-c**, **f**, **g**, and **h**) and its contribution to catalysis should be verifiable (*via* comparison of the performance of the bifunctional catalyst to an analogous, non-bifunctional triazolium ion, lacking hydrogen bond donation properties, *i.e.* precatalyst (1*R*,2*R*)-**242**).
3. The steric requirement of the hydrogen bond donor should also be variable (*i.e.* precatalysts (1*R*,2*R*)-**241a**, **d**, **e**, and **h**).
4. At the proof of concept stage, the catalyst should be relatively rigid, but not necessarily conformationally locked, so as to allow for maximum scope for potential cooperation between the nucleophilic and hydrogen bond-donating components.
5. The catalyst should be easily accessible from a readily available, rigid chiral starting material. Hence, (1*R*,2*S*)-*cis*-amino indanol was selected as the appropriate starting material.

We had previously generated an amino indanol-based amine substrate containing a benzamide group, for attempted thiazolium salt synthesis, ((1*R*,2*R*)-**226**, Scheme 2.7). An array of indanol-derived amines similar to (1*R*,2*R*)-**226** was generated, whereby the steric and electronic properties of the amide substituent were modified. The synthesis of these amines and their subsequent conversion to the corresponding triazolium ions are described below.

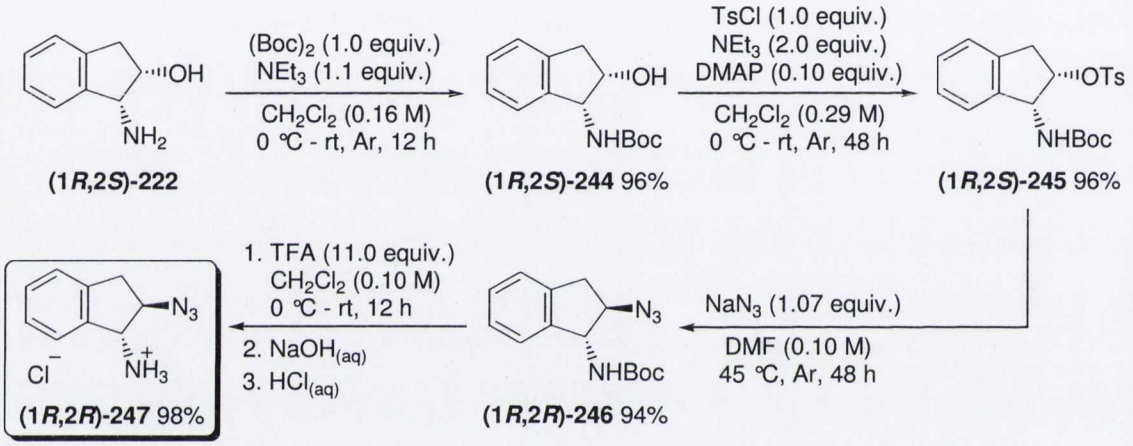
3.2 Synthesis of chiral bifunctional triazolium precatalysts

3.2.1 Synthesis of triazolium salt precursors

The preparation of precatalysts (1*R*,2*R*)-**241-243**, in the main, was an uncomplicated process; a large scale synthesis of a common precursor (1*R*,2*R*)-**247** was firstly

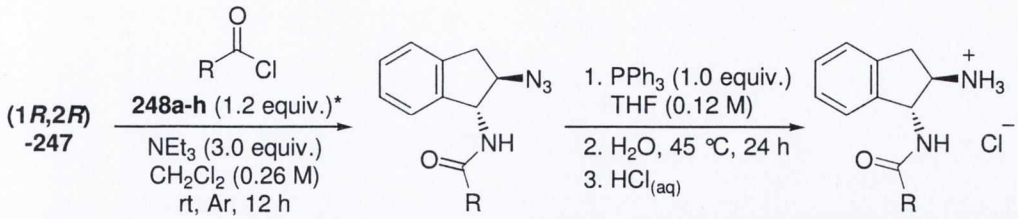
undertaken, as per Scheme 3.1. Boc-protection of (1*R*,2*S*)-*cis*-1-amino-2-indanol (**222**) furnished alcohol (1*R*,2*S*)-**244** in almost quantitative yield, which was tosylated and treated with sodium azide to afford (1*R*,2*R*)-**246** *via* (1*R*,2*S*)-**245**. Azide (1*R*,2*R*)-**246** was formed in 94% yield with inverted stereochemistry. Removal of the protecting group provided the corresponding primary amine - this served as the common precursor to precatalysts (1*R*,2*R*)-**241** and (1*R*,2*R*)-**242** and was isolated as its hydrochloride salt (1*R*,2*R*)-**247** in an excellent yield of 85% over the four reaction steps.

Scheme 3.1 Synthesis of azide (1*R*,2*R*)-**247**, precursor to H bond-donating amines



The next phase of the reaction sequence entailed acylation of (1*R*,2*R*)-**247** with various acid chlorides **248a-h** and azide reduction to the desired amine substrates (1*R*,2*R*)-**250**, Scheme 3.2. The acylation process proceeded smoothly in all cases, save that of the deactivated *para*-methoxy-substituted electrophile **248g**, which required the addition of catalytic DMAP and the use of THF as solvent to obtain high product yield. Staudinger reduction of azides (1*R*,2*R*)-**225** and (1*R*,2*R*)-**249b-h**, using triphenylphosphine and water, gave the precursors (1*R*,2*R*)-**226** and (1*R*,2*R*)-**250b-h** in excellent yields. The required amines, containing various hydrogen bond-donating amide groups, were isolated as their hydrochloride salts for the purposes of straightforward handling and storage.

Scheme 3.2 Generation of hydrogen bond-donating triazolium salt precursors



*248g (1.2 equiv.)
DMAP (5.0 mol%)
THF (0.25 M)

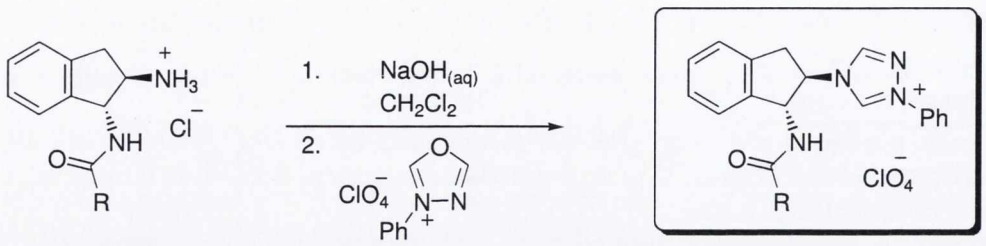
(1*R*,2*R*)-225 R = C_6H_5 96%	**(1*R*,2*R*)-226** R = C_6H_5 92%
(1*R*,2*R*)-249b R = C_6F_5 93%	**(1*R*,2*R*)-250b** R = C_6F_5 91%
(1*R*,2*R*)-249c R = 3,5-$(CF_3)_2$-C_6H_3 92%	**(1*R*,2*R*)-250c** R = 3,5-$(CF_3)_2$-C_6H_3 95%
(1*R*,2*R*)-249d R = 1-naphthyl 89%	**(1*R*,2*R*)-250d** R = 1-naphthyl 93%
(1*R*,2*R*)-249e R = 2,4,6-$(CH_3)_3$-C_6H_2 73%	**(1*R*,2*R*)-250e** R = 2,4,6-$(CH_3)_3$-C_6H_2 56%
(1*R*,2*R*)-249f R = 3,5-$(CH_3)_2$-C_6H_3 92%	**(1*R*,2*R*)-250f** R = 3,5-$(CH_3)_2$-C_6H_3 99%
(1*R*,2*R*)-249g R = 4-CH_3O-C_6H_4 59%	**(1*R*,2*R*)-250g** R = 4-CH_3O-C_6H_4 95%
(1*R*,2*R*)-249h R = C_3H_7 98%	**(1*R*,2*R*)-250h** R = C_3H_7 86%

3.2.2 Generation of a suite of chiral triazolium precatalysts

The final step in the reaction sequence of bifunctional triazolium salt synthesis involved the nucleophilic addition of precursors (1*R*,2*R*)-**226** and (1*R*,2*R*)-**250b-h** to oxadiazolium salt **231**, Scheme 3.3. The hydrochloride salts (1*R*,2*R*)-**226** and (1*R*,2*R*)-**250** were converted to their corresponding free-bases and then reacted with freshly prepared oxadiazolium salt **231** in dry acetonitrile to afford precatalysts (1*R*,2*R*)-**241**. The reaction was not performed in two steps, with the isolation of a hydrazone-type intermediate, as was the case for achiral precatalysts **233** and **240**, (Scheme 2.9 and Scheme 2.11). To avoid loss of product and enhance product yields, this isolation step was excluded. The reaction was stirred at ambient temperature for 90 minutes and then heated at reflux for the indicated time to induce cyclisation of the triazolium ring to form precatalysts (1*R*,2*R*)-**241a-h**.

While this route proved generally reliable, resulting in, for the most part excellent yields, the almost incomplete solubility of both (1*R*,2*R*)-**250f** and its corresponding free-base in a range of organic solvents, disappointingly precluded the formation of triazolium ion (1*R*,2*R*)-**241f**. We were intrigued to find that the triazolium salts could be purified by flash column chromatography without product decomposition. Subsequent recrystallisation provided pure, novel, hydrogen bond-donating precatalysts (1*R*,2*R*)-**241a-e**, **g** and **h**.

Scheme 3.3 Synthesis of novel bifunctional triazolium salts (1*R*,2*R*)-**241**



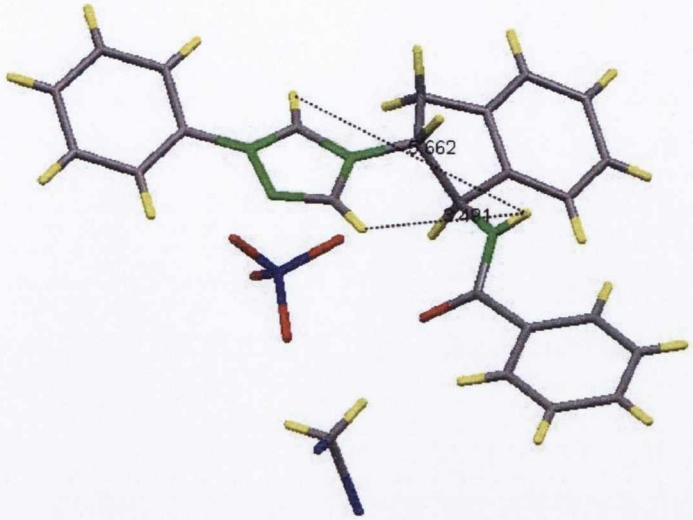
(1*R*,2*R*)-226
(1*R*,2*R*)-250b-h

231 (1.0 equiv.)
CH_3CN (0.08-0.37 M)
4Å mol. sieves
90 °C, Ar, 4-7 d

(1*R*,2*R*)-241a R = C_6H_5 92%
(1*R*,2*R*)-241b R = C_6F_5 42%
(1*R*,2*R*)-241c R = 3,5-$(CF_3)_2$-C_6H_3 88%
(1*R*,2*R*)-241d R = 1-naphthyl 52%
(1*R*,2*R*)-241e R = 2,4,6-$(CH_3)_3$-C_6H_2 48%
(1*R*,2*R*)-241f R = 3,5-$(CH_3)_2$-C_6H_3 0%
(1*R*,2*R*)-241g R = 4-CH_3O-C_6H_4 76%
(1*R*,2*R*)-241h R = C_3H_7 71%

An X-ray crystal structure of phenyl-substituted precatalyst (1*R*,2*R*)-**241a** was obtained, which is depicted below in Figure 3.2. The *trans*-orientation of the amide moiety and the triazolium ring can be clearly observed. In the solid state the C-5 proton of the triazolium ring is orientated away from the amide moiety and is situated between the geminal methylene protons of the indanol ring. The intermolecular distance between the C-5 proton of the triazolium ring (which if deprotonated reveals the carbene catalyst) and the N-H of the amide group was calculated to be 5.662 ♍Å. The C-3 proton (which if deprotonated results in destructive ring-opening of the triazolium ring) is situated closer to the amide group, with a smaller intermolecular distance of 3.491 Å between it and the amide N-H. Although the C-5 proton of the triazolium ring and the amide proton are orientated away from each other in the solid state, in solution rotation of the triazolium ring and amide group will occur, resulting in closer intermolecular distances between these groups in certain conformations. Thus, it is evident that a chiral pocket has been designed whereby the amide substituent resides in the vicinity of the triazolium ring and is capable of engaging in co-operative hydrogen bond donation during the reaction process.

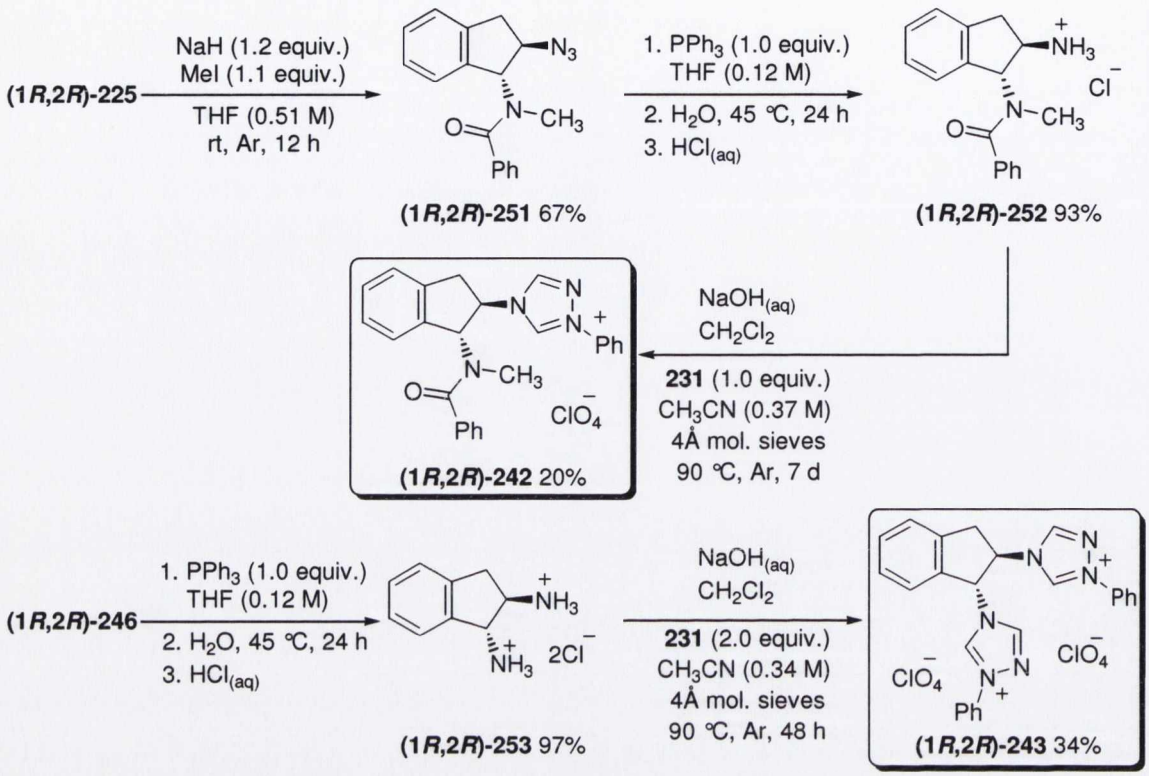
Figure 3.2 X-ray crystal structure of precatalyst (1*R*,2*R*)-**241a**



3.2.3 Creation of chiral triazolium salts lacking hydrogen bond functionality

In order to assess the contribution from hydrogen bonding of precatalysts (1*R*,2*R*)-**241** in catalysis of the benzoin condensation and to determine the efficacy of the bifunctional precatalysts, it was requisite to prepare a precatalyst that was analogous to (1*R*,2*R*)-**241** in its steric and electronic properties but devoid of hydrogen bond-donating capabilities. For this reason, we chose to synthesise *N*-methylated benzamide precatalyst (1*R*,2*R*)-**242**, whereby the hydrogen bond of the benzamide group was replaced with a methyl group. We considered that the small size of the methyl group would have insignificant effects on either the steric requirement or spatial orientation about the amide group. Thus (1*R*,2*R*)-**242** was regarded as being almost identical to precatalyst (1*R*,2*R*)-**241a** but crucially lacking this bifunctional handle. In addition, we decided to create a *bis*-triazolium salt from amino indanol that would be chiral, yet deficient in hydrogen bond-donation capacity. This chiral dual-catalyst (1*R*,2*R*)-**243**, containing two triazolium rings, could perhaps provide highly efficient and enantioselective catalysis of the benzoin condensation as a result of the contiguous orientation of two catalytic centres. Accordingly, we set about creating these non-hydrogen bond-donating chiral precatalysts (1*R*,2*R*)-**242** and (1*R*,2*R*)-**243**, and the reaction process is outlined in Scheme 3.4.

Scheme 3.4 Synthesis of non-hydrogen bond-donating triazolium salts

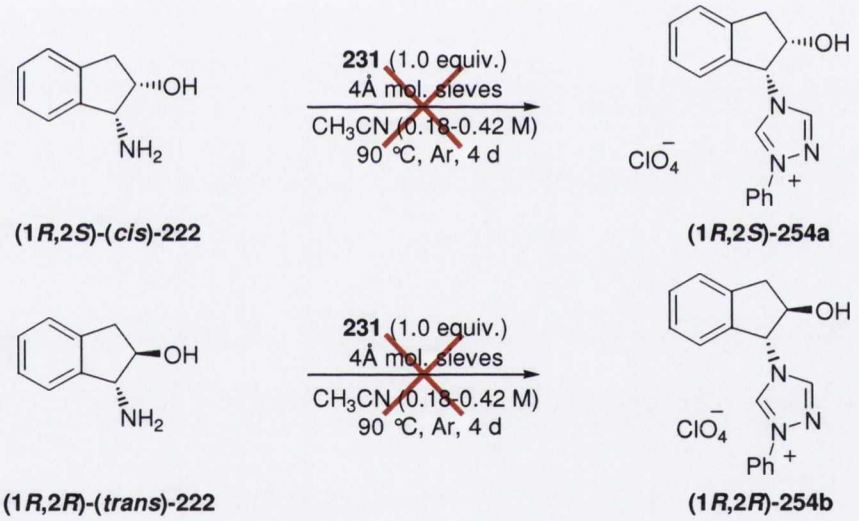


The *N*-methyl precatalyst (1*R*,2*R*)-**242** was prepared *via* the methylation of azide (1*R*,2*R*)-**225** using methyl iodide to provide the rotameric tertiary amide (1*R*,2*R*)-**251** in 67% yield. An analogous sequence of steps to those used previously was employed, involving Staudinger reduction and successive triazolium salt formation. Flash column chromatography followed by preparative thin layer chromatography (TLC) was necessary to isolate and purify the rotameric precatalyst (1*R*,2*R*)-**242** in 20% yield. The *bis*-triazolium salt (1*R*,2*R*)-**243** was generated by firstly subjecting the Boc-protected azide (1*R*,2*R*)-**246** to Staudinger reduction conditions. Reduction of the azide group to an amine functionality concurrently and conveniently resulted in loss of the neighbouring Boc-protection group. During the acidic work-up stage, involving aqueous HCl, cleavage of the Boc-group occurred, furnishing the *bis*-hydrochloride salt (1*R*,2*R*)-**253** in near-quantitative yield (97%). Triazolium salt formation was induced using two equivalents of oxadiazolium salt **231** under the standard conditions, attaining a yield of 34% of the *bis*-triazolium salt precatalyst (1*R*,2*R*)-**243**.

3.2.4 Synthesis of triazolium salts incorporating hydroxyl functionality

In view of the success of numerous triazolium salts as NHC catalysts[197] and previously described pharmaceutical medicines that were designed using amino indanol as a starting material,[332] we decided to take advantage of the inherent hydrogen bond donating properties of the amino indanol molecule. We regarded the hydroxyl group of amino indanol as a potential hydrogen bond donating moiety. Accordingly, we attempted to use the substrate directly in the synthesis of chiral bifunctional triazolium salts **254**, Scheme 3.5. Both (1*R*,2*S*)-*cis*- and (1*R*,2*R*)-*trans*-amino indanol (**222**) were used as amine substrates under the optimised reaction conditions that had readily provided bifunctional precatalysts (1*R*,2*R*)-**241**-**243**.

Scheme 3.5 Generation of triazolium precatalysts with hydroxyl functionality



Gratifyingly, the previously insoluble substrate, *trans*-amino indanol, was soluble at low concentrations of acetonitrile (0.18 M). However, numerous attempts of triazolium salt synthesis led to only modest amounts of both *cis*- and *trans*-precatalyst formation. The products were not formed in sufficient quantity to enable recrystallisation of the crude reaction mixtures and unfortunately column chromatography of these precatalysts was not viable. ^{1}H NMR spectroscopic methods could verify the presence of both *cis*- and *trans*-precatalysts **254** in the crude reactions along with the uncyclised hydrazino-intermediates. ^{1}H NMR resonance signals of both *cis*- and *trans*-**254** were observed at approximately 9.6 and 11.1 ppm respectively in DMSO-d_6, corresponding to the two

protons of the triazolium ring. Additionally, four distinctive resonance signals were noted at approximately 8.4, 9.4, 10.9 and 11.6 ppm respectively, which are characteristic of the uncyclised hydrazino-intermediate. Frustratingly, exhaustive efforts could not provide the desired precatalysts **254**. It was deemed that once again detrimental interaction of the contiguous hydroxyl group caused a destructive effect in precatalyst formation.

3.2.5 Section 3.2: conclusions

The synthesis of novel chiral triazolium perchlorate salts (1*R*,2*R*)-**241**-**243** was completed for evaluation in the benzoin condensation. Seven of these variants comprised a suite of bifunctional precatalysts (1*R*,2*R*)-**241**, containing a diverse selection of amide appendages as hydrogen bond-donating groups. The steric and electronic properties of the amide moieties ranged from electron-rich, electron-neutral, electron-deficient, aromatic, aliphatic, sterically undemanding to sterically challenging. The chiral precatalysts were easily generated over several reaction steps, utilising (1*R*,2*S*)-*cis*-amino indanol (**222**) as the starting material. An analogous non-bifunctional precatalyst (1*R*,2*R*)-**242**, that contained a methyl group in place of a hydrogen bond component was created, for assessment of the effects (if any) that hydrogen bond donation would have in the asymmetric benzoin condensation. Additionally, a *bis*-triazolium salt (1*R*,2*R*)-**243** was synthesised that, although lacking hydrogen bond donation properties, interestingly contained two neighbouring triazolium rings, available for deprotonation to form a dual-carbene catalyst. Precatalysts (1*R*,2*R*)-**241**-**243** were subsequently investigated as promoters of the benzoin condensation.

3.3 Studies of the asymmetric benzoin condensation

3.3.1 Investigation into the asymmetric benzoin condensation using a dual-base methodology: preamble

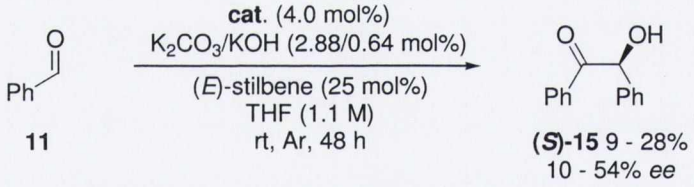
We had previously developed two separate methodologies for catalysis of the benzoin condensation reaction; one method using 4 mol% of precatalyst in THF, in the presence

of a mixture of two weak bases, and the other employing a stronger base at higher precatalyst and base loadings in a less polar solvent that is more potentially conducive to catalysis involving the donation of hydrogen bonds. We were interested in assessing and comparing the two reaction conditions in the asymmetric benzoin condensation. Thus the two reaction conditions were examined separately, starting with the binary base system of K_2CO_3 and KOH.

3.3.1.1 Screening of bifunctional triazolium ions in the benzoin condensation reaction

At the outset we wished to evaluate the performance of the suite of chiral amino-indanol precatalysts (1*R*,2*R*)-**241-243** and determine which precatalyst was the most efficient at promoting the asymmetric benzoin condensation. The precatalysts were screened using benzaldehyde as the aldehyde substrate, under optimised reaction conditions, and the results are shown in Table 3.1.

Table 3.1 Screening of chiral triazolium precatalysts (1*R*,2*R*)-**241-243**



entry	catalyst	loading (mol%)	yield[a] (%)	*ee*[b] (%)
1	(1*R*,2*R*)-**241a**	4.0	25	54
2	(1*R*,2*R*)-**241b**	4.0	16	24
3	(1*R*,2*R*)-**241c**	4.0	11	16
4	(1*R*,2*R*)-**241d**	4.0	27	40
5	(1*R*,2*R*)-**241e**	4.0	27	31
6	(1*R*,2*R*)-**241g**	4.0	16	46
7	(1*R*,2*R*)-**241h**	4.0	28	47
8	(1*R*,2*R*)-**242**	4.0	23	13
9	(1*R*,2*R*)-**243**	2.0	9	10

[a]Isolated yield after column chromatography.
[b]Determined by chiral HPLC using a Chiralpak AD column (4.6 x 250 mm).

The phenyl-substituted amide precatalyst (1*R*,2*R*)-**241a** provided a yield of 25% of (*S*)-benzoin (**15**) in 54% *ee* (entry 1). Somewhat surprisingly, precatalysts (1*R*,2*R*)-**241b**

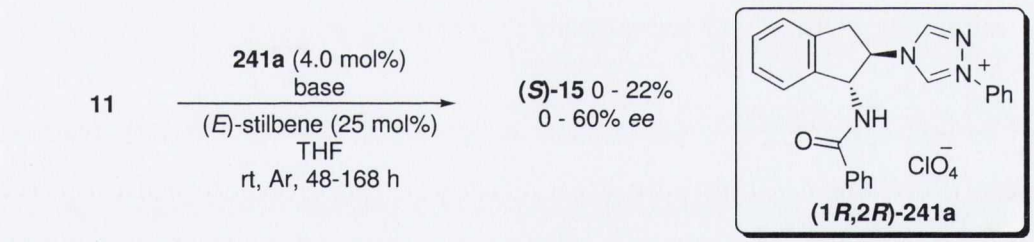
and (1*R*,2*R*)-**241c**, which incorporate electron-withdrawing amide substituents (which we anticipated would facilitate hydrogen bond donation by the catalyst), furnished benzoin product with lower yield and selectivity (entries 2 and 3, respectively). The 1-naphthyl-substituted amide ((1*R*,2*R*)-**241d**) exhibited a reactivity and selectivity profile similar to that observed using (1*R*,2*R*)-**241a** (27% yield, 40% *ee*, entry 4), while catalysis with the hindered mesityl-substituted precatalyst (1*R*,2*R*)-**241e** resulted in reduced product enantioselectivity (entry 5). Precatalyst (1*R*,2*R*)-**241g**, with a relatively electron-rich amide substituent, furnished relatively good levels of enantioselectivity (46% *ee*), albeit at the expense of product yield (16%, entry 6). The aliphatic amide (1*R*,2*R*)-**241h** also proved a useful member of this suite of catalysts; the product yield was higher but the enantioselectivity was lower than that associated with the use of (1*R*,2*R*)-**241a** (entry 7). Thus, on balance it can be seen that while the use of electron deficient amide substituents is not well tolerated by the catalyst, no clear advantages with respect to both product yield and enantioselectivity, associated with the incorporation of analogous electron-rich or bulky groups, could be identified. Most importantly, a comparison of the performance of (1*R*,2*R*)-**241a** with its *N*-methylated analogue ((1*R*,2*R*)-**242**), which is not capable of the donation of hydrogen bonds but is otherwise structurally similar to (1*R*,2*R*)-**241a**, is instructive; the use of (1*R*,2*R*)-**242** afforded benzoin product in a similar yield to that obtained using (1*R*,2*R*)-**241a** but with considerably lower enantioselectivity (54% vs. 13% *ee*, entries 1 and 8, respectively). This strongly indicates that the donation of hydrogen bonds by (1*R*,2*R*)-**241a** is a key control element in the reaction process. It is readily acknowledged that other factors could be important - in particular conformational issues; however, we could find no evidence (^{1}H NMR spectroscopy) for a significant conformational discrepancy between (1*R*,2*R*)-**241a** and (1*R*,2*R*)-**242**. In addition it is noteworthy that (1*R*,2*R*)-**241a** and (1*R*,2*R*)-**242** display almost identical reactivity under these conditions and that all of the secondary amide catalysts evaluated promoted more selective reactions than (1*R*,2*R*)-**242**. This we feel is best explained by the intermediacy of hydrogen-bonded species using precatalysts (1*R*,2*R*)-**241**. To the best of our knowledge, this represents the first example of the use of hydrogen bonding to control the stereochemical outcome of a benzoin condensation reaction. Precatalyst (1*R*,2*R*)-**243** containing two triazolium rings, performed poorly, delivering a low yield of benzoin with decreased enantioselectivity (10% *ee*, entry 9). Notably, 2 mol% of precatalyst (1*R*,2*R*)-**243** was employed, due to its incorporation of two triazolium rings. The low enantioselectivity obtained using

(1*R*,2*R*)-**243** again points towards hydrogen bonding acting as a control element in the stereochemical process.

3.3.1.2 Effect of temperature and concentration in the asymmetric benzoin condensation

With the superiority of (1*R*,2*R*)-**241a** (and also (1*R*,2*R*)-**241d**) identified, attention now turned to optimisation of the reaction conditions. Once again benzaldehyde was employed as the aldehyde substrate and the results of the optimisation study are summarised in Table 3.2. In order to ensure that reproducibility was obtainable under these reaction conditions using precatalyst (1*R*,2*R*)-**241a**, the reaction was repeated - three consecutive experiments were completed at room temperature using precatalyst (1*R*,2*R*)-**241a** and yields of 23-25% and enantioselectivities of 52-54% *ee* were provided (entries 1-3). This verifies that the binary base protocol, in conjunction with precatalyst (1*R*,2*R*)-**241a**, presents a robust and reproducible method.

Table 3.2 Adjustment of optimal reaction conditions using precatalyst **241a**



entry	base	loading (mol%)	time (h)	conc. (M)	yield[a,b] (%)	*ee*[c] (%)
1	K_2CO_3/KOH	2.88/0.64	64	1.1	23(21)	54
2	K_2CO_3/KOH	2.88/0.64	63	1.1	25(24)	52
3	K_2CO_3/KOH	2.88/0.64	48	1.1	25(19)	52
4	K_2CO_3	3.2	70	1.1	18(17)	51
5	K_2CO_3/KOH	2.88/0.64	96	0.1	1	n.d.
6	K_2CO_3/KOH	2.88/0.64	168	0.25	10(8)	52
7	K_2CO_3/KOH	2.88/0.64	48	0.5	16(16)	60
8[d]	K_2CO_3/KOH	2.88/0.64	48	0.5	22(21)	52
9	K_2CO_3/KOH	2.88/0.64	48	2.0	6(4)	37
10[e]	K_2CO_3/KOH	2.88/0.64	48	1.1	0	0

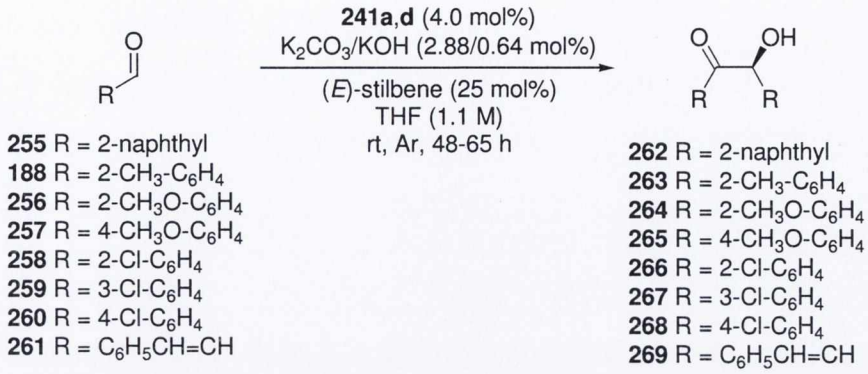
[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]Values in parentheses indicate the isolated yield after column chromatography. [c]Determined by chiral HPLC using a Chiralpak AD column. [d]**241d** used in place of **241a**. [e]Reaction performed at 0 °C.

We also tested K_2CO_3 as a base in the asymmetric reaction to determine if any enhancements of reactivity or selectivity were obtainable. Gratifyingly, the dual-base mixture remained the superior base, with K_2CO_3 furnishing a lower product yield and enantioselectivity (18% yield, 51% *ee*, entry 4). We next evaluated the effect of concentration on the reaction process. At a low concentration of 0.1 M only traces of product were obtained (entry 5), whereas at 0.25 M concentration (1*R*,2*R*)-**241a** provided a yield of 10% with 52% *ee* (entry 6). At 0.5 M concentration product enantiomeric excess improved to 60% (with a concomitant reduction in yield when compared to entry 1). 1-Naphthyl substituted amide (1*R*,2*R*)-**241d** was employed in the reaction at a concentration of 0.5 M and the reaction suffered a similar loss of yield but improved enantioselectivity (22% yield, 52% *ee*, entry 8). However, at the higher concentration of 2.0 M both product yield and selectivity were compromised (entry 9). Finally, the reaction was conducted at 0 °C and resulted in no product formation (entry 10). Although, the best selectivity (60% *ee*) was achieved at a concentration of 0.5 M, optimal reaction conditions were determined to be a concentration of 1.1 M and an ambient temperature. These reaction conditions, offered the maximum product yield, albeit with a marginal loss in selectivity.

3.3.1.3 Evaluation of the substrate scope

With the optimal precatalysts (*i.e.* (1*R*,2*R*)-**241a** and (1*R*,2*R*)-**241d**) and reaction conditions in hand, attention now turned to assessment of the substrate scope, an issue which has severely limited the utility of the benzoin condensation reaction in the past. We were struck by the dearth of material concerning the use of *ortho*-substituted aromatic substrates in catalytic asymmetric benzoin condensations in the literature and thus included them in this study, (the results of which are outlined in Table 3.3). Note: during the evaluation of the substrate scope we encountered a shortage of the phenyl substituted precatalyst (1*R*,2*R*)-**241a** and in some cases (1*R*,2*R*)-**241d** was used in its place due to the similar reactivity and selectivity profile of the two precatalysts.

Table 3.3 Investigation of the reaction scope using different aldehydes



255 R = 2-naphthyl
188 R = 2-CH_3-C_6H_4
256 R = 2-CH_3O-C_6H_4
257 R = 4-CH_3O-C_6H_4
258 R = 2-Cl-C_6H_4
259 R = 3-Cl-C_6H_4
260 R = 4-Cl-C_6H_4
261 R = C_6H_5CH=CH

262 R = 2-naphthyl
263 R = 2-CH_3-C_6H_4
264 R = 2-CH_3O-C_6H_4
265 R = 4-CH_3O-C_6H_4
266 R = 2-Cl-C_6H_4
267 R = 3-Cl-C_6H_4
268 R = 4-Cl-C_6H_4
269 R = C_6H_5CH=CH

entry	catalyst	substrate	time (h)	yield[a,b] (%)	*ee*[c] (%)	Abs. Config.[d]
1	**241d**	**255**	65	37(26)	38	*S*
2	**241a**	**188**	48	0	n.d.	-
3	**241d**	**256**	65	15(7)	52	*S*
4	**241a**	**257**	48	4	n.d.	-
5	**241a**	**258**	48	17(16)	27	*S*
6	**241a**	**259**	48	39(33)	3	*S*
7	**241d**	**260**	65	68(66)	5	*S*
8	**241a**	**261**	48	5	n.d.	-

[a]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]Values in parentheses indicate the isolated yield after column chromatography. [c]Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 x 250 mm). [d]Refers to absolute configuration of the product.

The reaction of 2-naphthaldehyde (**255**) in the presence of 1-naphthyl-containing triazolium salt (1*R*,2*R*)-**241d** produced the aryloin product in 37% yield and 38% *ee* (entry 1). The sterically hindered *o*-tolualdehyde (**188**) furnished no product, in the presence of precatalyst (1*R*,2*R*)-**241a** (entry 2). *o*-Anisaldehyde is a relatively useful substrate, which gave the corresponding aryloin in 15% yield and 52% *ee* (entry 3). The analogous *para*-isomer was not of sufficient activity to afford modest amounts of product under these conditions (entry 4). Concerning the chlorobenzaldehydes **258-260** - in line with previous studies in this reaction - the deactivated *meta*- and *para*-isomers **259** and **260** gave aryloins in relatively good yield but poor enantiomeric excess; however somewhat surprisingly, the trend was reversed in the case of the *o*-chloroisomer **258**. The use of **258** led to the isolation of the corresponding aryloin **266** in poor yield (16%) but comparatively good enantioselectivity, 27% *ee* (entries 5-7). The α,β-unsaturated substrate, cinnamaldehyde, **261** was also attempted in the reaction, but failed to generate substantial aryloin product (entry 8).

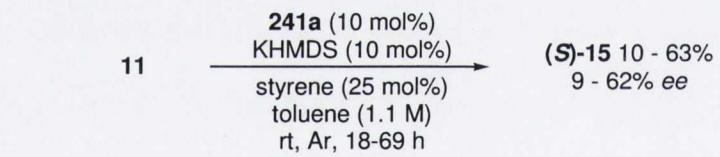
3.3.2 Use of KHMDS as the base

Having examined the scope of the asymmetric benzoin condensation reaction using the combined base system we turned our attention to assessing the efficiency and selectivity of the asymmetric benzoin condensation reaction using KHMDS as the base and toluene as the solvent. The results of these experiments were interesting and are provided in Table 3.4 and 3.5.

3.3.2.1 Importance of the order of addition of reagents

Following the procedure described by Enders[128], and using achiral triazolium ion **233c** in conjunction with KHMDS, we had previously determined ideal precatalyst and base loadings of 10 mol%. However, we wished to ascertain if we could decrease the precatalyst and base loadings without a loss in yield or selectivity, Table 3.4.

Table 3.4 Tuning of optimal reaction conditions using precatalyst (1*R*,2*R*)-**241a**

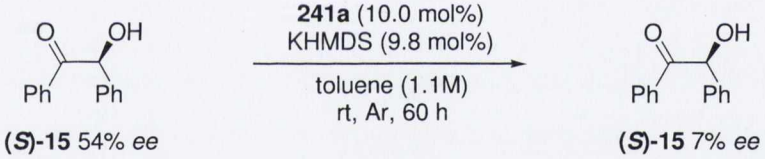


entry	cond.[a]	cat. loading (mol%)	base loading (mol%)	time (h)	yield[b,c] (%)	ee[d] (%)
1	A	5.0	5.0	69	11(11)	19
2	A	10.0	8.0	48	14(5)	61
3	A	10.0	9.0	48	28(19)	47
4	A	10.0	9.8	66	44(40)	32
5	A	10.0	10.0	48	60(58)	31
6[e]	A	10.0	10.0	66	26(19)	42
7	B	10.0	7.0	18	12(11)	58
8	B	10.0	9.0	18	10(8)	54
9	B	10.0	9.0	88	22(21)	45
10	B	10.0	9.8	48	11(9)	57
11	B	10.0	10.0	18	12(12)	62
12	B	10.0	10.0	42	16(16)	57

[a]Refers to conditions. Condition set **A**: KHMDS added last (dropwise over 3 min). Condition set **B**: Benzaldehyde added last (dropwise over 3 min).
[b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.
[c]Values in parentheses indicate the isolated yield after column chromatography.
[d]Determined by chiral HPLC using a Chiralpak AD column (4.6 x 250 mm).
[e]Reaction performed at 0 °C.

The use of 5.0 mol% of precatalyst (1*R*,2*R*)-**241a** and KHMDS indicated that this was not possible, providing poor product yield and enantioselectivity (entry 1, Table 3.4). For our investigations into the benzoin condensation reaction using achiral triazolium ion **233c** the order of addition of reagents involved the sequential addition of toluene, benzaldehyde and lastly KHMDS (drop wise) into a flask containing the precatalyst (condition set A). However, we found that when chiral precatalyst (1*R*,2*R*)-**241a** was utilised in the asymmetric benzoin condensation under condition set A, an inverse correlation between yield and enantioselectivity was observed (entries 2-4), strongly indicative of product racemisation *in situ*. To confirm this, the catalytic process outlined in condition set A was repeated with enantioenriched (*S*)-benzoin (54% *ee*) replacing benzaldehyde as the starting material (Scheme 3.6). After stirring for 60 h, the benzoin was recovered in greatly reduced enantiomeric excess. To the best of our knowledge, such racemisation has not been reported previously in the benzoin condensation.

Scheme 3.6 *In situ* racemisation of benzoin caused by KHMDS



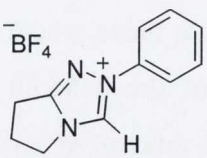
(*S*)-15 54% *ee* → **(*S*)-15** 7% *ee*

In an attempt to circumvent this problem, the asymmetric benzoin condensation was repeated under 'inverse addition' conditions (*i.e.* drop wise addition of benzaldehyde to a stirred mixture of the base and triazolium salt, condition set B). With all the KHMDS consumed prior to the formation of **15**, racemisation was minimised, leading to the isolation of **15** with a maximum *ee* of 62% (entries 7-12). While these reactions were satisfactory from a selectivity standpoint, the isolated yields of the benzoin product diminished considerably. It should be noted that variation of the amount of KHMDS in the reaction did not significantly alter the yield or selectivity and although extension of the duration of the reaction beyond 18 h resulted in increased product yields it inevitably caused partial racemisation of the benzoin product (entries 9, 10 and 12).

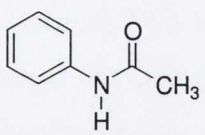
We wished to establish why the reactions carried out using precatalyst (1*R*,2*R*)-**241a** under condition set B were so low yielding. We considered that KHMDS, being a

considerably strong non-nucleophilic base (pK_a ~26, DMSO, 25 °C),[345] was capable of removing the proton of the amide moiety of the precatalyst. An extensive literature search revealed that the pK_a value for deprotonation of the C-5 proton of a simple triazolium ion (**181**, Figure 3.3) was determined to be 17.7 (H_2O, 25 °C).[346] We postulated that the pK_a value for deprotonation of our triazolium salt (1*R*,2*R*)-**241a** would be quite similar to this value. An examination of the pK_a values of secondary amides indicated that the pK_a of the N-H of the amide group of (1*R*,2*R*)-**241a** was approximately 16-18. (The pK_a values of *N*-phenylacetamide (**270**) and *N*-phenylbenzamide (**271**) were found to be 17.6 and 16.5 respectively (H_2O, 25 °C)).[347] With the estimated pK_a values of the amide N-H and the C-5 proton of our triazolium ion being so similar it is possible that upon addition of KHMDS to the reaction vessel, the KHMDS could deprotonate the amide component of the precatalyst, which would presumably result in precatalyst decomposition. Notably, under condition set B the base and precatalyst are stirred for several moments prior to addition of an aldehyde substrate, to ensure complete consumption of KHMDS. We could therefore also posit that the highly reactive carbene catalyst (formed *in situ via* C-5 deprotonation by KHMDS), in the absence of an aldehyde substrate, could proceed to deprotonate an amide substituent of another triazolium precatalyst, again resulting in catalyst decomposition. Thus, the surprisingly similar estimated pK_a values for deprotonation of the C-5 position of the triazolium ring of (1*R*,2*R*)-**241a** and its secondary amide component could rationalise the low yields obtained using this precatalyst under condition set B.

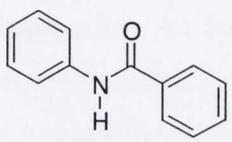
Figure 3.3 pK_a values of triazolium ion **181** and secondary amides



181
pK_a 17.7



270
pK_a 17.6



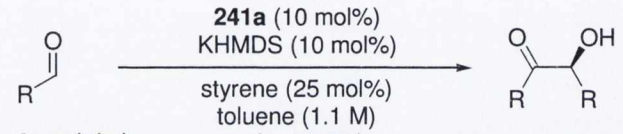
271
pK_a 16.5

3.3.2.2 Evaluation of the substrate scope using KHMDS as the base

We next turned our attention to the question of substrate scope - we evaluated the performance of (1*R*,2*R*)-**241a** in the benzoin condensation, using a range of aromatic

aldehydes (including the frequently-avoided 2-substituted analogues). We used condition set B in our study, which entailed stirring of the base and triazolium ion prior to drop wise addition of the respective aldehyde to the reaction. The results of our study are presented in Table 3.5.

Table 3.5 Investigation of the asymmetric benzoin condensation reaction using different aldehyde substrates and KHMDS as base



255 R = 2-naphthyl
188 R = 2-CH_3-C_6H_4
272 R = 4-CH_3-C_6H_4
256 R = 2-CH_3O-C_6H_4
257 R = 4-CH_3O-C_6H_4
258 R = 2-Cl-C_6H_4
259 R = 3-Cl-C_6H_4
260 R = 4-Cl-C_6H_4
273 R = 2-furanyl

262 R = 2-naphthyl
263 R = 2-CH_3-C_6H_4
274 R = 4-CH_3-C_6H_4
264 R = 2-CH_3O-C_6H_4
265 R = 4-CH_3O-C_6H_4
266 R = 2-Cl-C_6H_4
267 R = 3-Cl-C_6H_4
268 R = 4-Cl-C_6H_4
275 R = furanyl

entry	substrate	time (h)	yield[a] (%)	*ee*[b] (%)	Abs. Config.[c]
1	**255**	16	36	35	*S*
2	**188**	18	0	n.d.	-
3	**272**	18	10	45	*S*
4	**256**	24	29	54	*S*
5	**257**	24	0	n.d.	-
6	**258**	16	8	28	*S*
7	**259**	16	47	1	*S*
8	**260**	16	32	6	*S*
9	**273**	18	49	1	*S*

[a]Isolated yield after column chromatography. [b]Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 x 250 mm). [c]Refers to absolute configuration of the product.

In line with the findings of our previous study involving the use of a dual base mixture of K_2CO_3 and KOH (see Table 3.3) the reaction of 2-naphthaldehyde (**255**) furnished the aryloin product **262** in 36% yield and 35% *ee* (entry 1). The little-used *o*-tolualdehyde proved resistant to the benzoin condensation, completely failing to undergo reaction (entry 2). However, the *para*-isomer **272** resulted in low product formation but improved product enantiomeric excess (entry 3). Regarding the anisaldehydes, the traditionally problematic and deactivated *o*-anisaldehyde substrate underwent a slow

reaction and furnished the corresponding aryloin **264** in 29% yield and 54% *ee* after 24 h, whilst the analogous *p*-isomer did not participate in the reaction process (entries 4 and 5). As expected, 2-chlorobenzaldehyde (**258**) proved difficult to convert with either high selectivity or yield (entry 6), whereas *meta*- and *para*-chlorobenzaldehydes (**259** and **260**) could be transformed into their respective acyloin products but in essentially racemic forms (entries 7 and 8). Furfuraldehyde (**273**) is a substrate that allows the efficient formation of furoin (**275**); however, the enantiomeric excess was again poor (entry 9).

3.3.3 Section 3.3: conclusions

To summarise, we have designed a new class of chiral triazolium ion precatalysts (1*R*,2*R*)-**241** which incorporate protic substituents. These materials catalysed enantioselective benzoin condensations at loadings of 4-10 mol% under two sets of convenient reaction conditions. The maximum product enantiomeric excess obtained was 62% and it was unambiguously demonstrated that for the first time in this reaction class that the donation of hydrogen bonds by the catalyst is a key control element governing the stereochemical outcome of this bimolecular reaction. This offers an alternative to strategies based on the construction of the highly rigid fused systems, which dominate current thinking in this field. Although the bifunctional precatalysts are not yet of sufficient activity and selectivity to be of use on a process scale, the confirmation that hydrogen bond donation can be exploited to bring about augmented stereocontrol in the asymmetric benzoin condensation reaction should open up new vistas in triazolium precatalyst design.

4.1 NHC catalysis of other *Umpolung* reactions; namely the crossed acyloin condensation reaction

The benzoin condensation reaction is one of the oldest carbon-carbon bond forming reactions in organic chemistry - with a rich history dating back to the pioneers Liebig and Wöhler in 1832.[1] For much of the intervening time, the benzoin condensation reaction has proven initially to be an interesting mechanistic challenge[26,42] and later a

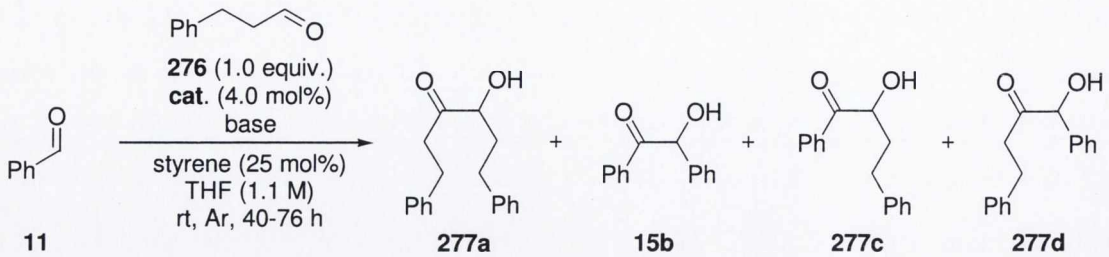
process which inspired the development of numerous *N*-heterocyclic carbene-based catalysts capable of facilitating a remarkable array of reactions proceeding through *Umpolung* intermediates.[145,197,348] While significant advances in the catalysis of the (asymmetric) carbene-catalysed *homo*benzoin condensation reaction have been made recently,[124,126,131] the absence of a selective carbene-mediated catalytic methodology capable of promoting the intermolecular reaction between two different aldehydes in a chemoselective and enantioselective fashion, curtails the utility of this process. The challenges associated with such a crossed acyloin condensation process are considerable - the objective is to exercise control (*via* the catalyst) over the process to an extent that a single major adduct is formed from eight possible products in good yield (4 chiral ketones **3a-d**, each in two enantiomeric forms, see Scheme 1.39). Although Enders recently disclosed the NHC-catalysed coupling of aromatic aldehydes to α,α,α-trifluoromethylacetophenone in moderate to excellent yields,[278] to the best of our knowledge a general carbene-catalysed process capable of promoting chemoselective (and enantioselective) crossed acyloin condensation reactions between two different aldehydes remains elusive.

4.1.1 The crossed acyloin condensation reaction - preliminary experiments

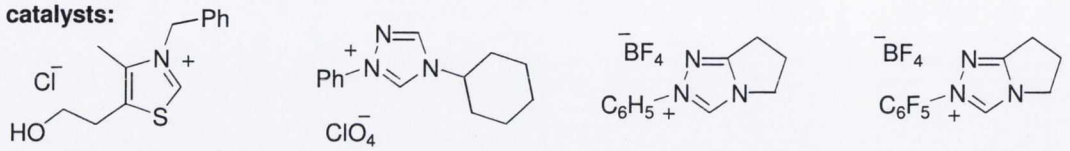
We wished to orient ourselves with respect to the natural bias (if any) a thia- or triazolium-derived carbene catalyst would display towards one of the coupling partners in a crossed acyloin condensation reaction. As a starting point we evaluated the performance of several achiral heteroazolium salt precatalysts in the crossed acyloin condensation reaction between benzaldehyde and the relatively unhindered aliphatic substrate hydrocinnamaldehyde (**276**). The results of these preliminary experiments and the precatalysts utilised are displayed in Table 4.1. Note: the yields of homodimer '**a**' and '**b**' acyloin products account for the 2:1 stoichiometry, to obtain the mol% of these materials divide the yields by two.

Initial results were far from encouraging, with benzyl-substituted thiazolium ion **158a** and triethylamine promoting an unselective and low yielding reaction (entry 1). Triazolium salts **233c** and **181** were equally ineffective at promoting the reaction with significant levels of chemoselectivity; with the highest yield of product being a meagre 14%, that of crossed acyloin product **277d** (entries 2 and 3).

Table 4.1 Screening of achiral precatalysts in the crossed acyloin condensation



catalysts:



158a **233c** **181** **131**

entry	cat.	base	loading (mol%)	time (h)	yield a[a] (%)	yield b[a] (%)	yield c[a] (%)	yield d[a] (%)
1[b]	**158a**	NEt_3	33.0	76	2	4	12	12
2	**233c**	Rb_2CO_3	4.0	76	12	10	0	14
3	**181**	Rb_2CO_3	4.0	40	>2	8	>2	10
4	**131**	Rb_2CO_3	4.0	40	26	20	11	48

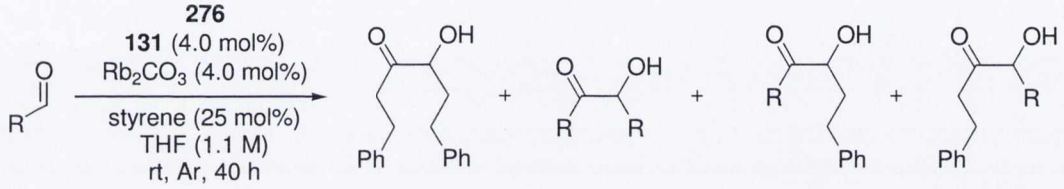
[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of '**a**' and '**b**' products account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2. [b]30 mol% of precatalyst **158a** used.

We were intrigued to read a report from Suzuki's group describing how the judicious modification of *N*-aryl substituents of triazolium ions, to render them more electron-withdrawing in nature, led to higher product yields in the intramolecular benzoin condensation reaction.[212] Notably these reactions involved the use of enolisable substrates that were prone to aldol side reactions. Accordingly, we set about creating the bicylic pentafluorophenyl triazolium ion **131**, adhering to the synthetic procedure outlined by Rovis *et al.*[349] Gratifyingly, **131** proved to be a superior system to **181** under these conditions, furnishing higher yields of all four acyloin products and notably displaying a preference for formation of the crossed acyloin product **277d** (48% yield, entry 4). Overall, the coupling of benzaldehyde and hydrocinnamaldehyde (**276**) proceeded with poor chemoselectivity. While a marked preference for the formation of products derived from initial attack of the catalyst on **276** (*i.e.* **277a** and **277d** *vs.* **277b** and **277c**) was observed, all four possible products (homodimers **277a/b** and crossed products **277c/d**) were formed without any one being present at synthetically useful levels.

4.1.1.1 Evaluation of the crossed coupling of 276 and aromatic aldehydes

We next turned to evaluating the performance of pentafluorophenyl-triazolium ion **131** in the crossed acyloin condensation of hydrocinnamaldehyde and a range of substituted aromatic aldehydes. We wished to determine if reasonable chemoselectivity could be attained by varying the steric and electronic properties of the aldehyde substrates. The results of this study are outlined in Table 4.2.

Table 4.2 Coupling of hydrocinnamaldehyde (**276**) and aromatic aldehydes



260 R = 4-Cl-C_6H_4
259 R = 3-Cl-C_6H_4
258 R = 2-Cl-C_6H_4
278 R = 2-F-C_6H_4
256 R = 2-CH_3O-C_6H_4
188 R = 2-CH_3-C_6H_4
279 R = 2-CF_3-C_6H_4
280 R = 2-Br-C_6H_4
281 R = 2,6-F_2-C_6H_3
273 R = 2-furanyl

entry	R	R (equiv.)	276 (equiv.)	yield a[a] (%)	yield b[a] (%)	yield c[a] (%)	yield d[a] (%)
1	4-Cl-C_6H_4	1.0	1.0	53	44	2	43
2	3-Cl-C_6H_4	1.0	1.0	44	34	6	50
3	2-Cl-C_6H_4	1.0	1.0	8	15	9	51
4	2-F-C_6H_4	1.0	1.0	49	45	17	34
5	2-CH_3O-C_6H_4	1.0	1.0	20	16	21	59
6	2-CH_3-C_6H_4	1.0	1.0	35	0	8	55
7	2-CF_3-C_6H_4	1.0	1.0	8	6	10	81
8	2-Br-C_6H_4	1.0	1.0	0	9	8	49
9[b]	2-Br-C_6H_4	1.0	1.0	4	10	5	73
10[c]	2-Br-C_6H_4	1.0	1.0	5	10	6	76
11[b]	2-Br-C_6H_4	1.3	1.0	>2	6	10	79
12[b]	2-Br-C_6H_4	1.5	1.0	>2	21	11	74
13[b]	2-Br-C_6H_4	1.0	1.3	31	4	7	84
14[b]	2-Br-C_6H_4	1.0	1.5	51	3	7	89
15[b]	2-Br-C_6H_4	1.0	1.7	70	0	10	90
16	2,6-F_2-C_6H_3	1.0	1.0	0	0	5	7
17	2-furanyl	1.0	1.0	>2	18	50	9

[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. . [b]8.0 mol% of precatalyst **131** and Rb_2CO_3 used. [c]10.0 mol% of precatalyst **131** and Rb_2CO_3 used.

The activation of the aromatic aldehyde component with a chlorine atom in either the *meta*- or *para*-position failed to influence chemoselectivity to any appreciable extent, however, use of the *ortho*-substituted analogue (**258**) generated **266d** as the dominant product in a moderate yield of 51% (entries 1-3). Examination of other *ortho*-substituted aldehydes revealed that the electronic characteristics of the aldehydes seem to play a minor role and that the improved chemoselectivity associated with the use of *ortho*-substituted aldehydes is primarily related to the steric requirement of the substituent. For instance, the small but highly electronegative fluorine atom of 2-fluorobenzaldehyde (**278**) does not confer high chemoselectivity (entry 4); however the use of larger units in the *ortho*-position, such as the activating methoxy- and methyl-substituents, allowed relatively selective crossed acyloin condensation reactions to proceed (entries 5 and 6). Interestingly, the deactivated trifluoromethyl-substituent (**279**) suppressed the pathways leading to **277a** and **283b,c** to the extent that crossed acyloin product **283d** was formed in 81% yield (entry 7).

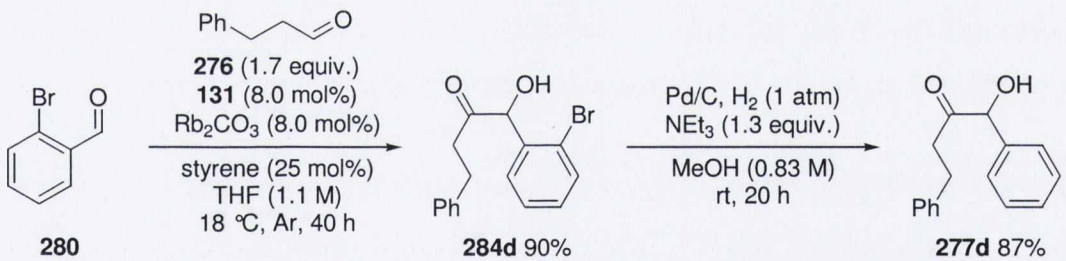
Particularly gratifying was the performance of *ortho*-bromobenzaldehyde **280**; this coupling partner is of potential interest for two reasons. Firstly the bromine atom in the product (*i.e.* **284d**) can serve as a functional handle for further elaboration (radical generation, participation in transition metal catalysed coupling reactions, *etc.*). Secondly, we envisaged that it should be possible to cleanly remove the halogen from the product which allows one to aspire towards the use of an *o*-bromo substituent as a removable tool to control chemoselectivity in these processes; thereby providing access to products (after debromination) which would otherwise be difficult to prepare in good yield *via* carbene-catalysed acyloin condensation chemistry. It was initially found that **280** coupled to **276** with very good chemoselectivity and moderate yield (entry 8). In an attempt to improve upon the yield and chemoselectivity of this crossed acyloin condensation process we increased the precatalyst loading, which gratifyingly furnished significantly higher levels of crossed product **284d** (73% and 76%, entries 9 and 10). Further optimisation of the reaction conditions, involving the use of excess aldehyde, allowed for the synthesis of **284d** in 90% yield by employing a small surplus of **276** (1.7 equiv.) in the presence of 8.0 mol% of precatalyst **131** (entries 11-15).

The 2,6-difluorinated benzaldehyde **281**, being considerably electron-deficient; yet not excessively sterically hindered, failed to take part in an acyloin formation process (entry

16). The results of this study strongly indicate that the steric constraint caused by the substituent on the aromatic ring is mainly responsible for creating a chemoselective bias towards the formation of the '**d**' crossed acyloin product. The electronic properties of the aldehyde component also play a role, but one that is less prominent. Finally, we assessed the coupling of heteroaromatic 2-furaldehyde (**273**) with **276** and unexpectedly attained a reverse chemoselective outcome, with crossed acyloin product **275c** emerging as the major product. This was unusual as the coupling reactions tended to display a preference towards formation of the '**d**' isomer as the main product. The reason for this reverse trend in chemoselectivity is unclear at this juncture.

To demonstrate the potential use of an *ortho*-bromo substituent as a solution to circumvent the inherent lack of chemoselectivity in the crossed acyloin condensation reactions involving aromatic aldehydes, we carried out a coupling experiment using *o*-bromobenzaldehyde (**280**) and hydrocinnamaldehyde (**276**), Scheme 4.1.

Scheme 4.1 Exploitation of a removable 2-bromo substituent

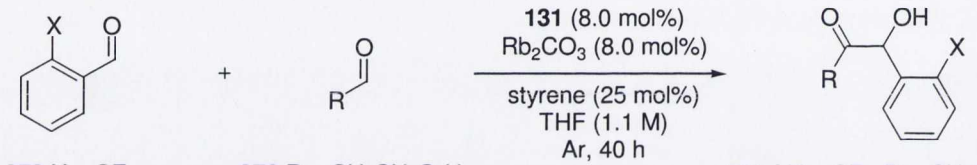


The crossed acyloin condensation adduct **284d** was formed in 90% yield under the standard reaction conditions. Facile debromination under an atmosphere of hydrogen in the presence of Pd/C provided the α-hydroxy ketone **277d** in excellent yield (87%). Note: we had previously attempted to generate crossed acyloin product **277d** using an array of thia- and triazolium salts and achieved considerably poor chemoselectivity (see Table 4.1). Thus, we submit that the *o*-bromo substituent can be employed as a temporary group which can divert the course of an otherwise relatively unselective coupling reaction towards the formation of a single major product. It can then either serve as a functional handle if required or be cleanly removed to give debrominated products not otherwise accessible in high yield directly from a carbene-catalysed acyloin condensation process.

4.1.1.2 Use of *o*-substituted aromatic aldehydes as coupling partners

The scope of the process with respect to 'aliphatic' or '*Umpolung*' aldehyde component was next investigated. *ortho*-Substituted electrophiles **279** and **280** were coupled to a range of unbranched aldehydes **276**, **191** and **286-288** in the presence of **131**. In all examples the '**d**' crossed acyloin product was formed as the major product, for the sake of brevity the yields of the remaining acyloin products ('**a-c**') are omitted.

Table 4.3 Coupling of *o*-aromatic aldehydes and aliphatic substrates



279 X = CF_3
280 X = Br

276 R = $CH_2CH_2C_6H_5$
191 R = CH_3
286 R = CH_2CH_3
287 R = $(CH_2)_3CH_3$
288 R = $CH_2C_6H_5$

283d X = CF_3 R = $CH_2CH_2C_6H_5$
289d X = CF_3 R = CH_3
290d X = Br R = CH_3
291d X = CF_3 R = CH_2CH_3
292d X = Br R = CH_2CH_3
293d X = CF_3 R = $(CH_2)_3CH_3$
294d X = Br R = $(CH_2)_3CH_3$
295d X = CF_3 R = $CH_2C_6H_5$
296d X = Br R = $CH_2C_6H_5$

entry	X	R	R (equiv.)	product	temp. (°C)	yield d[a] (%)
1[b]	CF_3	$CH_2CH_2C_6H_5$	1.7	**283d**	5	61
2	CF_3	$CH_2CH_2C_6H_5$	1.7	**283d**	18	86
3[b]	CF_3	CH_3	1.7	**289d**	18	50
4	CF_3	CH_3	10.0	**289d**	18	78
5[b]	Br	CH_3	1.7	**290d**	18	19
6	CF_3	CH_2CH_3	1.7	**291d**	18	79
7[b]	Br	CH_2CH_3	1.7	**292d**	18	68
8	Br	CH_2CH_3	2.5	**292d**	18	73
9	CF_3	$(CH_2)_3CH_3$	1.7	**293d**	18	84
10	Br	$(CH_2)_3CH_3$	1.7	**294d**	18	77
11	CF_3	$CH_2C_6H_5$	1.7	**295d**	18	81
12	Br	$CH_2C_6H_5$	1.7	**296d**	18	76

[a]Isolated yield. [b]Determined by ^1H NMR spectroscopy using styrene as an internal standard.

We noted that day-to-day changes in the 'ambient' temperature of the laboratory caused fluctuations in the yields of product obtained from identical crossed acyloin experiments. Therefore we assessed the effect of varying the temperature of the reaction and interestingly found that coupling of **279** to **276** (1.7 equiv.) at 5 °C was less

chemoselective than an otherwise identical reaction at 18 °C (entries 1 and 2). In the case of the reaction at the lower temperature (entry 1), crossed acyloin **283d** was still obtained as the major product. However significantly elevated levels of products derived from initial attack of the catalyst on **279** (*i.e.* **283b** (17%) and **283c** (16%)) were detected, indicating that these coupling reactions may proceed under a significant degree of thermodynamic control. Accordingly, subsequent experiments were conducted at the apposite temperature of 18 °C. Acetaldehyde proved a challenging substrate to utilise at ambient temperature due to its low boiling point (20.2 °C), however the use of a tenfold excess (feasible due to the low cost of this reagent) resulted in an excellent isolated yield of 78% of **289d** (entries 3-5). The less volatile aldehyde, propanal (**286**), coupled to **279** and **280** without difficulty, furnishing crossed acyloin yields of 79% and 68% (entries 6 and 7). The yield of the *o*-bromo-crossed acyloin product **292d** could be improved upon by employing 2.5 equivalents of propanal (entry 8). Addition of the unbranched aldehydes, pentanal and phenylacetaldehyde, to aromatic aldehydes **279** and **280** proceeded smoothly under standard conditions, providing good to excellent yields of the coupled products **293d-296d** (entries 9-12).

4.1.2 The asymmetric crossed acyloin condensation reaction - preamble

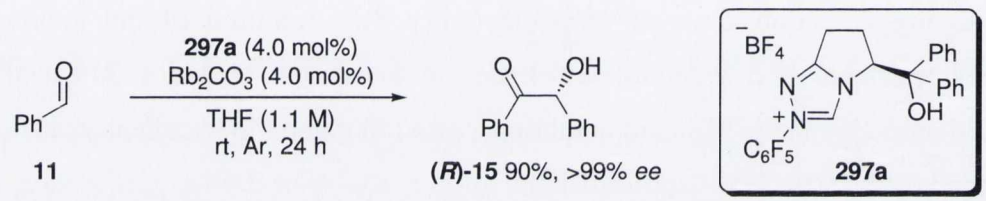
While the methodologies outlined above allow one to carry out highly chemoselective crossed acyloin condensation reactions, the ability to control the stereochemical outcome of these reactions is also a key goal. We reviewed the crossed acyloin condensation reaction in Section 1.5, highlighting the challenges and shortcomings associated with this coupling process. In particular we emphasised that this reaction, surprisingly, has yet to be catalysed in an enantioselective fashion (by means of NHC-catalysis). Thus, we set out to investigate the asymmetric variant of this coupling reaction. We report herein, to the best of our knowledge, the first examples of successful enantioselective and chemoselective carbene-catalysed crossed acyloin condensation reactions.

4.1.2.1 Design of 2nd generation chiral bifunctional triazolium ion precatalysts

Our first course of action taken in this new venture was the creation of a second generation of chiral bifunctional triazolium salt precatalysts, and we based our precatalyst design upon that of achiral triazolium salt **131**, due to its capability to

promote successful crossed acyloin condensation reactions (*vide supra*). We posited that an electron-withdrawing *N*-pentafluorophenyl group would fashion a more acidic triazolium salt (that when deprotonated would reveal a less basic carbene catalyst to that of, for example, amino indanol-derived precatalyst (1*R*,2*R*)-**241a**). Additionally, with the triazolium ring embedded in the rigid frame of **131**, deprotonation of the C-3 position of the triazolium ring was not feasible. Very recently, our group reported the design of a comparable novel bifunctional triazolium salt **297a** that incorporated a chiral protic substituent, and was employed as a precatalyst in the asymmetric benzoin condensation reaction (see Scheme 4.2).[350]

Scheme 4.2 Triazolium salt **297a** used by our group in the benzoin condensation

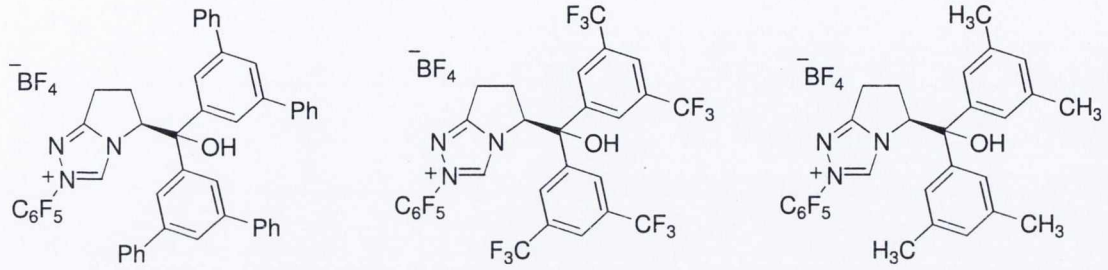


The novel alcohol precatalyst **297a** promoted the asymmetric archetypal benzoin condensation reaction with excellent efficiency and unprecedented enantioselectivity (90% yield, >99% *ee*). **297a** Additionally exhibited exceptional activity in the conversion of a wide range of aromatic aldehydes to the corresponding benzoins - in several cases again with unrivalled enantioselectivity. It was found that the pentafluorophenyl group dramatically enhanced the catalyst efficacy, whilst the hydrogen bond-donating diphenylcarbinol moiety facilitated excellent enantiocontrol.

In view of this significant development in the asymmetric *homo*benzoin condensation reaction, we were prompted to prepare a series of analogous triazolium ion precatalysts (**297b-d**, Figure 4.1), with the intention of assessing the performance of the four precatalysts (**297a-d**) in the asymmetric crossed acyloin condensation reaction. We posited that the rigid, hindered nature of **297a-d**, coupled with the presence of a catalyst hydrogen bond-donating group, would allow the catalysts to potentially distinguish between the two aldehyde electrophiles based on recognition of two substrate properties - steric bulk and Brønsted basicity. We anticipated that variation of the steric and electronic properties of the diarylcarbinol moiety would create an array of successful

chiral triazolium ion precatalysts that were capable of promoting highly chemo- and enantioselective crossed coupling reactions.

Figure 4.1 Novel chiral bifunctional triazolium salt precatalysts **297b-d**

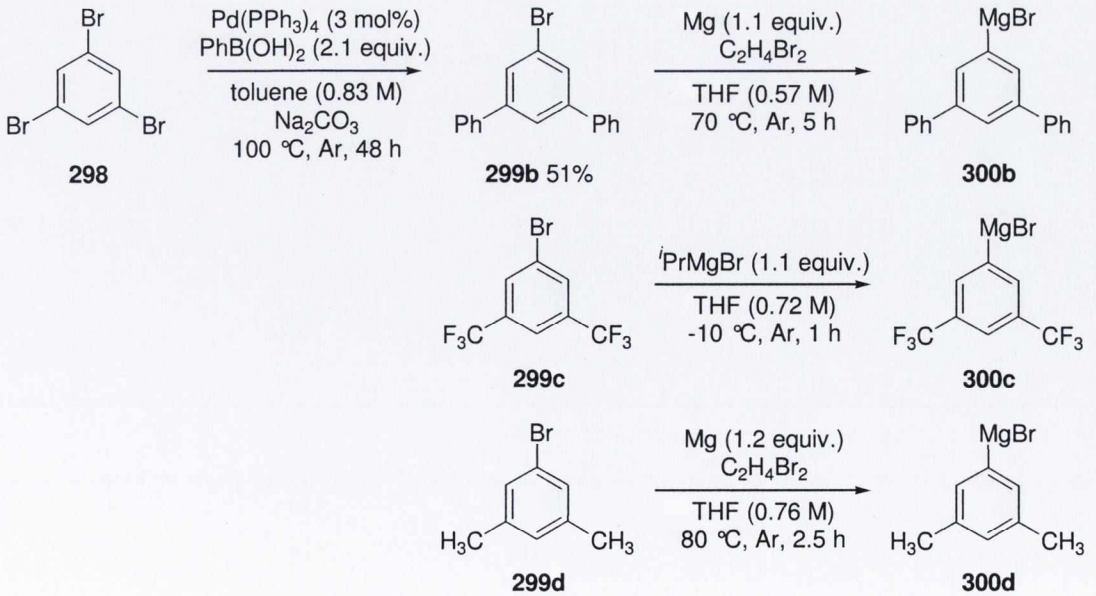


297b **297c** **297d**

4.1.2.2 Preparation of chiral triazolium ions from (*S*)-pyroglutamic acid

The preparation of triazolium ions **297a-d** was a relatively facile process that entailed the synthesis of the requisite Grignard reagents (that would comprise the diarylcarbinol moiety of the precatalysts). Phenylmagnesium bromide (**300a**) was commercially available from Sigma Aldrich and the reaction scheme for synthesis of Grignard reagents **300b-d** is outlined in Scheme 4.3.

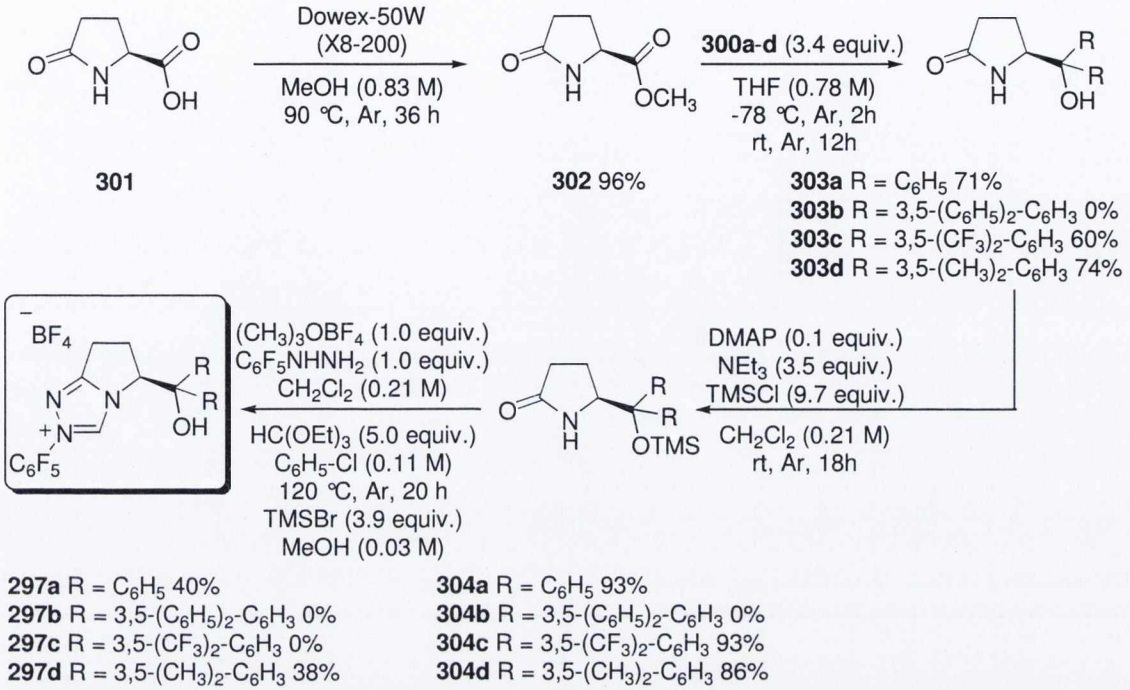
Scheme 4.3 Synthesis of Grignard reagents for generation of chiral precatalysts



In the case of the synthesis of **300b**, the 3,5-diphenyl-bromobenzene precursor (**299b**) was not commercially available and was synthesised accordingly *via* Suzuki coupling of 1,3,5-tribromobenzene (**298**) and phenylboronic acid. The synthesis of the phenyl and methyl substituted Grignard reagents (**300b** and **300d**) was completed using magnesium dust and a catalytic amount of dibromoethane, whereas the fluorinated variant **300c** was generated using *iso*-propyl magnesium bromide. All reactions were assumed to proceed to completion and the formed Grignard reagents were used immediately in the succeeding reaction step with **302** (see Scheme 4.4).

(*S*)-Pyroglutamic acid (**301**) served as the common starting reagent for the synthesis of the four precatalysts, being an inexpensive and commercially available chiral source. Esterification of **301** proceeded smoothly to provide the methyl ester **302** in near-quantitative yield (Scheme 4.4). Reaction of the freshly prepared aryl-magnesium bromides **300** and ester **302** furnished alcohols **303**; notably an excess of the Grignard reagent was employed to ensure efficient conversion to the tertiary alcohol. Disappointingly, alcohol **303b** failed to form *via* Grignard chemistry - the reaction was repeated, generating the Grignard reagent **300b** from magnesium filings (rather than magnesium dust) and also from *iso*-propyl magnesium bromide, all of which failed to produce product. Numerous attempts to generate alcohol **303b** were made, involving modification of the reaction conditions, such as temperature, solvent, concentration, equivalents of reagents and duration of the reaction, none of which favoured formation of the desired product. It was deemed that steric hindrance brought about by the presence of the bulky phenyl rings in the 3- and 5-positions of **299b** prevented product formation.

Scheme 4.4 Synthesis of hydrogen bond-donating triazolium salts **297a-d**

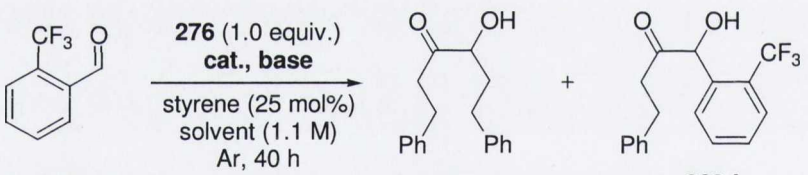


TMS-protection of **303** provided the silylated γ-lactams **304** in excellent yields. The final step in the reaction sequence involved a one-pot triazolium ring formation-alcohol deprotection reaction process. The triazolium ions were generated from successive addition of Meerwein's salt, pentafluorophenyl hydrazine and triethylorthoformate to the reaction. Isolation of the TMS-protected precatalyst was attempted; however several attempts at purification of the crude mixture were unsuccessful. Interestingly, the deprotected precatalysts **297** could be purified using flash column chromatography, whereas the TMS-protected precatalysts were unsuitable for this method due to decomposition on the column. Subsequent recrystallisation provided the pure triazolium salt precatalysts. All endeavours to create the poly-fluorinated triazolium ion **297c** were met with frustration; mass spectrometry verified the presence of the TMS-protected precatalyst. However, upon deprotection of the alcohol moiety using TMSBr, decomposition of the precatalyst to the lactam **303c** occurred. Gratifyingly, precatalysts **297a** and **297d** were attained in modest yields of 40% and 38%.

4.1.2.3 The enantioselective coupling of hydrocinnamaldehyde and *o*-substituted aromatic aldehydes

We proceeded to assess the performance of bifunctional precatalysts **297a,d** in the enantioselective crossed acyloin condensation reaction and our preliminary experiments to determine optimal reaction conditions entailed the coupling of **279** and hydrocinnamaldehyde (**276**), using precatalyst **297a**. The results of this study are outlined in Table 4.4. From the outset it was evident that reactions using the hindered chiral precatalysts were more sluggish and lower yielding than those using achiral precatalyst **131**. Interestingly, formation of products derived from attack of the carbene catalyst on the aromatic aldehyde (*i.e.* **283b** and **283c**) was completely suppressed leading to the formation of only two products - the hydrocinnamaldehyde dimer **277a** and the crossed acyloin product **283d**, (originating from attack of the carbene catalyst on hydrocinnamaldehyde).

Table 4.4 Preliminary experiments of enantioselective coupling of **276** and **279**



279 **277a** **283d**

entry	cat.	loading (mol%)	base	loading (mol%)	temp. (°C)	yield a[a] (%)	yield d[b] (%)	*ee* d[c] (%)
1	**297a**	4.0	Rb_2CO_3	4.0	18	20	45	72
2[d]	**297a**	4.0	NEt_3	6.4	18	25	25	51
3[e]	**297a**	4.0	NEt_3	6.4	18	16	18	24
4	**297a**	4.0	Rb_2CO_3	4.0	35	40	22	65
5	**297a**	10.0	Rb_2CO_3	10.0	0	18	24	73
6	**297a**	10.0	NEt_3	16.0	0	14	19	65
7[f]	**297a**	10.0	Rb_2CO_3	10.0	18	54	73	59
8[g]	**297a**	10.0	Rb_2CO_3	10.0	18	22	58	72
9[f]	**297d**	10.0	Rb_2CO_3	10.0	18	38	44	61

[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. . [b]Isolated yield. [c]Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 x 250 mm). [d]Reaction used toluene as the solvent. [e]Reaction used CH_2Cl_2 as the solvent. [f]Reaction used 2.5 equiv. of **276**. [g]Reaction performed at 0.4 M in THF.

At the outset we conducted a *homo*benzoin condensation reaction using hydrocinnamaldehyde (in the absence of aromatic aldehyde **279**), to determine the reactivity and enantioselectivity obtainable using bifunctional precatalyst **297a** in the presence of hydrocinnamaldehyde (result not shown). A yield of 44% of **277a** was obtained, albeit in essentially racemic form (3% *ee*). We continued our investigation by assessing THF, toluene and CH_2Cl_2 as suitable solvents for the enantioselective coupling of **276** and **279** and identified THF as the most appropriate solvent. Rb_2CO_3 and triethylamine were evaluated as efficient bases in the reaction and it was found that the combination of Rb_2CO_3 and THF allowed for higher chemoselectivity and enantioselectivity in the reaction outcome (entries 1-3).

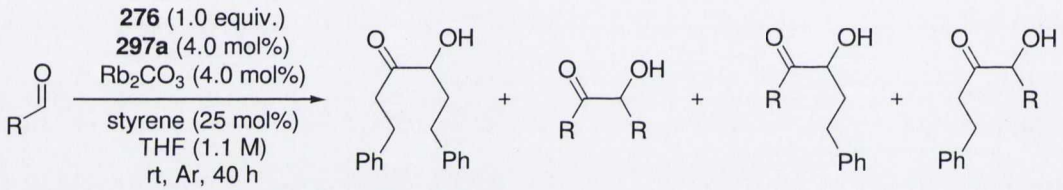
Increasing the temperature to 35 °C had the reverse effect, with inversion of the chemoselectivity to favour formation of the dimer **277a** as the major product. It was also found that elevation of the reaction temperature caused a slight reduction in the enantioselectivity of crossed acyloin **283d** (entry 4). Note: carrying out the coupling reaction at temperatures higher than 35 °C invariably led to lower overall yields due to decomposition. Decreasing the reaction temperature to 0 °C had a destructive effect, furnishing a lower yielding and less chemoselective reaction, although with no change in enantioselectivity of **283d** (73% *ee*, entry 5). When triethylamine was used in place of Rb_2CO_3 (at 0 °C) the reaction was even more sluggish and unselective, providing 19% yield of **283d** with 65% *ee* (entry 6). This once again points towards these coupling reactions proceeding under a significant degree of thermodynamic control.

We performed the coupling reaction at 18 °C, using 10 mol% of precatalyst **297a** and an excess of **276** (2.5 equiv.), and obtained a respectable yield of 73% of **283d**, although with a reduced enantioselectivity of 59% (entry 7). We attributed this loss in optical purity (from 72% to 59% *ee*, entries 2 and 8) to be due to the elevated levels of catalyst and base present in the reaction mixture. We also evaluated the effect of concentration on the reaction - at 0.4 M concentration the reaction yield was compromised; however the chemoselectivity and product enantiomeric excess improved, obtaining 72% *ee* for acyloin **283d** with a concomitant reduction in yield (entry 8). Finally, we examined the performance of precatalyst **297d** under these reaction conditions (10.0 mol% of precatalyst and base, 1.1 M solvent concentration, 2.5 equiv. of **276** and a reaction temperature of 18 °C). The novel precatalyst, possessing a larger diarylcarbinol unit,

was found to be less active than **297a**, but promoted the same reaction with improved enantioselectivity (61% *ee*, entry 9).

Turning next to the question of reaction scope - we evaluated the performance of **297a** in the crossed acyloin condensation reaction of hydrocinnamaldehyde (**276**) and a range of aromatic aldehydes. As expected, reactions involving aromatic aldehydes lacking an *ortho*-substituent were far less chemoselective and as a result the yields of the four acyloin products are provided in Table 4.5. However, the enantioselectivity of only the '**d**' product was obtained. Due to the observed diminution of optical purity when higher loadings of precatalyst and base were employed (Table 4.4) we chose to use 4.0 mol% of both precatalyst and base in the ensuing study.

Table 4.5 Enantioselective coupling of **276** and aromatic aldehydes



11 R = C_6H_5
259 R = 3-Cl-C_6H_4
258 R = 2-Cl-C_6H_4
256 R = 2-CH_3O-C_6H_4
188 R = 2-CH_3-C_6H_4
280 R = 2-Br-C_6H_4

277a | **15b** | **277c** | **277d**
267b | **267c** | **267d**
266b | **266c** | **266d**
264b | **264c** | **264d**
263b | **263c** | **263d**
284b | **284c** | **284d**

entry	R	temp. (°C)	yield a[a] (%)	yield b[a] (%)	yield c[a] (%)	yield d[b] (%)	*ee* d[c] (%)
1	C_6H_5	18	19	28	0	36	54
2[a,d]	C_6H_5	18	36	15	7	41	n.d.
3[a]	C_6H_5	0	16	21	>2	23	n.d.
4	3-Cl-C_6H_4	18	22	34	>2	36	30
5	2-Cl-C_6H_4	18	4	0	0	40	33
6[e]	2-Cl-C_6H_4	18	15	0	0	65	41
7	2-CH_3O-C_6H_4	18	26	5	>2	29	26
8	2-CH_3-C_6H_4	18	36	0	5	10	13
9	2-Br-C_6H_4	18	12	0	5	35	49

[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of '**a**' and '**b**' products account for the 2:1 stoichiometry, to obtain the mol% of these materials divide the yield by 2. [b]Isolated yield. [c]Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 x 250 mm). [d]3.0 equivalents of **276** used. [e]8.0 mol% of precatalyst **297a** used.

The coupling of benzaldehyde and **276** was considerably unselective, furnishing significant amounts of three of the four acyloin products. More promisingly, the enantioselectivity of crossed acyloin **277d** was determined to be 54% *ee* (entry 1). When an excess of hydrocinnamaldehyde was employed (3.0 equiv.) the chemoselectivity improved somewhat, leading to 41% yield of **277d** (entry 2). Conducting the reaction at a reduced temperature (0 °C) did not enhance productivity or chemoselectivity, with a reduction in the yields of all four acyloins (entry 3). It should be noted that the four α-hydroxy ketones **277a,c,d** and **15b** were virtually inseparable by column chromatography, having almost identical R_f values. Exhaustive efforts could not separate the crossed acyloin products from entries 2 and 3 for analysis of their optical purities (using CSP-HPLC techniques).

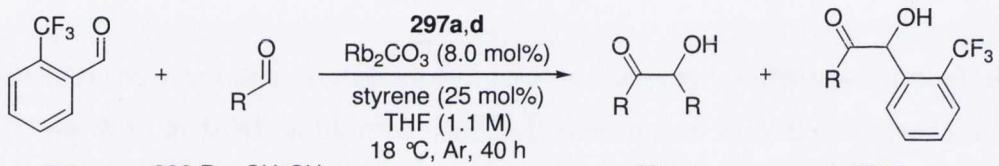
As was found using achiral precatalyst **131**, substitution in the *meta*-position did not induce a chemoselective or enantioselective bias, furnishing **267d** in 36% yield, with 30% *ee* (entry 4). Introduction of a substituent to the *ortho*-position of the aromatic aldehyde (using *o*-chorobenzaldehyde (**258**)), inhibited the formation of acyloins **277a**, and **266b,c** to the extent that crossed acyloin **266d** was almost the sole product obtained, albeit with a modest yield of 40% and 33% *ee* (entry 5). Gratifyingly, the yield of **266d** could be improved to 65% (with 41% *ee*) when a higher loading of 8.0 mol% of the precatalyst was employed (entry 6). Focusing on the use of *ortho*-substituted aromatic aldehydes, the coupling reaction between deactivated *o*-anisaldehyde and **276** was chemoselective, yet neither considerably high yielding or enantioselective (a yield of 29% of **264d** was obtained, with 26% *ee*, entry 7). The hindered and rarely used *o*-tolualdehyde (**188**) fared poorly (although selectively) in the crossed acyloin condensation reaction, furnishing dimer **277a** as the major product (36% yield) and a meagre yield of crossed product **263d** with poor enantioselectivity (10% yield, 13% *ee*, entry 8). We also evaluated *o*-bromobenzaldehyde in the reaction; the reaction proceeded chemoselectively and crossed acyloin product **284d** was generated in modest yield (35%) and with a promising enantioselectivity of 49% (entry 9).

4.1.2.4 Enantioselective coupling of 279 and unbranched aliphatic aldehydes

Having examined the scope of the reaction with respect to the aromatic aldehyde, we also explored the range of the reaction in terms of the electrophile (or *Umpolung*

aldehyde). We wished to ascertain that the enantioselective coupling of *ortho*-trifluoromethyl-benzaldehyde (**279**) was not limited to the use of only hydrocinnamaldehyde, and accordingly we assessed the crossed coupling reactions of **279** and an array of unbranched aliphatic aldehydes. The results of this study are presented below in Table 4.6. Gratifyingly, the use of **279** once again furnished highly chemoselective reactions whereby the formation of '**b**' and '**c**' α-hydroxy ketone products was completely suppressed, with reduction of the reaction outcome to '**a**' and '**d**' acyloins (derived from attack of the carbene catalyst on the aliphatic aldehyde).

Table 4.6 Enantioselective coupling of **279** and unbranched aliphatic aldehydes



279 **286** R = CH_2CH_3; **287** R = $(CH_2)_3CH_3$; **288** R = $CH_2C_6H_5$ **291a** **293a** **295a** **291d** **293d** **295d**

entry	R	R (equiv.)	cat.	cat load. (mol%)	yield a[a] (%)	yield d[b] (%)	*ee* d[c] (%)
1	CH_2CH_3	1.7	**297a**	8.0	14	40	73
2[d]	CH_2CH_3	2.5	**297a**	10.0	34	79	77
3[d]	CH_2CH_3	2.5	**297d**	10.0	14	45	81
4[e]	CH_2CH_3	2.5	**297d**	15.0	12	58	81
5[f]	CH_2CH_3	2.5	**297d**	20.0	17	57	81
6	$(CH_2)_3CH_3$	2.5	**297a**	8.0	66	86	71
7	$CH_2C_6H_5$	2.5	**297a**	8.0	0	61	66

[a]Determined by ^1H NMR spectroscopy using styrene as an internal standard. Note: yields of '**a**' product account for the 2:1 stoichiometry, to obtain the mol% of this material divide the yield by 2. [b]Isolated yield. [c]Determined by chiral HPLC using either a Chiralpak AD, OD-H or OJ-H column (4.6 x 250 mm). [d]10.0 mol% of Rb_2CO_3 used. [e]15.0 mol% of Rb_2CO_3 used. [f]20.0 mol% of Rb_2CO_3 used. Note: entries 4 and 5 were experiments carried out by Mr. S. Gundala.

At the outset we found that the crossed coupling reaction of the fluorinated aromatic aldehyde **279** and propanal (**286**), using 8.0 mol% of precatalyst **297a**, was relatively low yielding, providing a yield of 40% of the crossed acyloin product **291d**, although with a gratifying enantiomeric excess of 73% (entry 1). The substrates could be coaxed towards a higher yield of acyloin **291d** by increasing the precatalyst loading to 10.0 mol% and using an excess of 2.5 equiv. of propanal, furnishing 79% yield of **291d**, with 77% *ee* (entry 2). Under these same conditions we evaluated the bulkier bifunctional

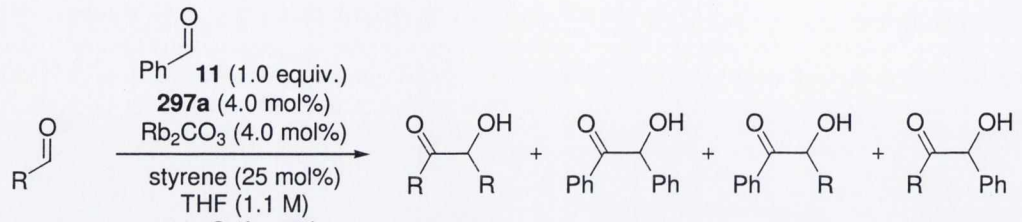
precatalyst **297d** in the crossed acyloin process of **279** and propanal. Once again we found that precatalyst **297d** was less active than **297a**, promoting the same reaction with improved enantioselectivity (81% *ee*), albeit at the expense of product yield (entry 3). Attempts to enhance the yield of crossed acyloin **291d**, using 15 mol% and 20 mol% of precatalyst **297d** were made (entries 4 and 5). Unfortunately, the maximum yield of **291d** achievable using a 'catalytic' amount of triazolium ion **297d** was 58%, with no reduction in enantioselectivity. Note: entries 4 and 5 were conducted by Mr. S. Gundala. The higher homologue and less volatile aldehyde, pentanal (**287**) coupled efficiently to **279**, generating a satisfactory yield of 86% of the crossed acyloin product **293d** with an enantiomeric excess of 71% *ee* (entry 6). We were also pleased to observe that phenylacetaldehyde (**288**) underwent a highly chemoselective reaction, providing exclusive formation of crossed product **295d** with acceptable enantioselectivity (66% *ee*, entry 7).

4.1.2.5 Investigation of the asymmetric crossed coupling of two different aromatic aldehydes

The crossed coupling processes involving *ortho*-substituted aromatic aldehydes and aliphatic variants, in the presence of precatalysts **131** and **297a**, have enabled us to achieve highly chemoselective and enantioselective crossed acyloin condensation reactions. However, we wished to determine if a chemoselective bias be could identified in the crossed coupling of aromatic aldehydes with aromatic partners. Accordingly, we assessed the outcome of the coupling of benzaldehyde (**11**) with a range of aromatic aldehydes of varying electronic and steric properties. It was found that these reactions, involving aromatic aldehydes in place of aliphatic analogues, were faster and as a result the reactions were quenched after 20 h instead of the customary 40 h. Note: our group had previously reported that a yield of 90% of benzoin ((*R*)-**15**) could be obtained after 24 h under identical reaction conditions to those applied below and utilising bifunctional triazolium salt **297a**.[350] The results obtained from this crossed acyloin condensation study are shown in Table 4.7. As mentioned previously, we found to our dismay that these aromatic acyloin products had almost identical R_f values and were extremely difficult to isolate by way of column chromatography. The products were oils and therefore could not be recrystallised. Additionally, short-path vacuum distillation using a Kugelrohr apparatus was not a viable method of purification. As a result, the yields

reported below were obtained using ^{1}H NMR spectroscopy techniques, employing styrene as an internal standard. Furthermore, the enantiomeric excesses of the respective products were not obtained.

Table 4.7 Enantioselective crossed coupling of aromatic aldehydes



260 R = 4-Cl-C_6H_4 — **268a** — **15b** — **312c** — **312d**
257 R = 4-CH_3O-C_6H_4 — **265a** — **313c** — **313d**
305 R = 4-NO_2-C_6H_4 — **308a** — **308c** — **308d**
258 R = 2-Cl-C_6H_4 — **266a** — **314c** — **314d**
256 R = 2-CH_3O-C_6H_4 — **264a** — **315c** — **315d**
188 R = 2-CH_3-C_6H_4 — **263a** — **316c** — **316d**
306 R = 2-pyridyl — **309a** — **309c** — **309d**
191 R = CH_3 — **310a** — **310c** — **310d**
307 R = *c*-C_6H_{11} — **311a** — **311c** — **311d**

entry	R	yield a[a] (%)	yield b[a] (%)	yield c[a] (%)	yield d[a] (%)
1	4-Cl-C_6H_4	30	39	15	20
2	4-CH_3O-C_6H_4	26	58	13	13
3	4-NO_2-C_6H_4	0	0	0	0
4	2-Cl-C_6H_4	0	42	41	0
5	2-CH_3O-C_6H_4	0	50	35	5
6	2-CH_3-C_6H_4	0	82	5	0
7	2-pyridyl	0	56	23	0
8	CH_3	16	42	2	35
9	*c*-C_6H_{11}	0	80	0	10

[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of '**a**' and '**b**' products account for the 2:1 stoichiometry, to obtain the mol% of these materials divide the yield by 2.

We first examined the utility of *p*-chlorobenzaldehyde (**260**) and found it to be non-selective in the crossed coupling reaction, with high conversion of both aromatic aldehydes and generation of significant yields of the four acyloin products (entry 1). The reaction of benzaldehyde (**11**) and the deactivated *p*-anisaldehyde substrate (**257**) favoured reaction of the Breslow intermediate (originating from addition of the catalyst to benzaldehyde) with another molecule of **11**, such that the benzoin dimer **15b** (resulting from *homo*benzoin condensation reaction) was formed as the main product

(entry 2). The electron-deficient *p*-nitrobenzaldehyde was not tolerated in the reaction process, failing to furnish acyloin product (entry 3).

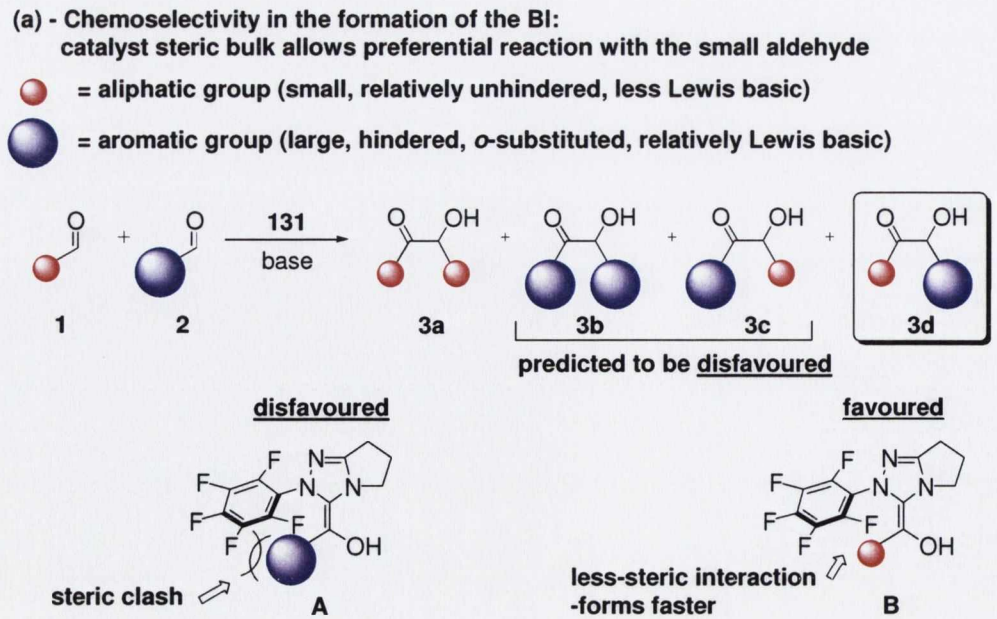
A chemoselective bias was achieved when *o*-chlorobenzaldehyde was employed in the coupling process, with the formation of only two products (**15b** and **314c**), notably those that arise from attack of the carbene catalyst on benzaldehyde (entry 4). We posit that steric hindrance brought about by substitution in the 2-position precludes attack of the carbene on *o*-chlorobenzaldehyde, resulting in the catalyst being predisposed to add to benzaldehyde. The Breslow intermediate formed from addition to benzaldehyde did not demonstrate a preference for addition to either aldehyde, resulting in the formation of almost equal amounts of **15b** and **314c**. A similar trend was observed when *o*-anisaldehyde (**256**) was used in the coupling reaction, with the inhibition of the formation of '**a**' and '**d**' acyloin products that are derived from attack of the carbene on **256** (entry 5). The little utilised *o*-tolualdehyde (**188**) proved resistant to the crossed acyloin condensation process, with benzoin (**15b**) emerging as the major product (entry 6). We employed 2-pyridine carboxaldehyde (**306**) in the reaction and once again achieved a chemoselective bias whereby addition of the catalyst to benzaldehyde occurred, resulting in formation of benzoin and crossed acyloin product **309c** (entry 7).

We diverted from the use of substituted aromatic aldehydes and included in this study two aliphatic aldehydes. The coupling of acetaldehyde and benzaldehyde was attempted (entry 8), and most interestingly, we observed a trend whereby chemoselectivity somewhat reverted back to that obtained prior to this study - benzoin (**15b**) and crossed acyloin **310d** were provided as the major products (meaning that addition of the catalyst to *both* aldehydes occurred). However, the two distinct Breslow-intermediates, formed from reaction with both aldehydes, displayed a preference to add to benzaldehyde over acetaldehyde, giving rise to the chemoselective formation of **15b** and **310d**. Employment of cyclohexanecarbaldehyde (**307**) in the crossed acyloin condensation led to a similar chemoselective outcome, with formation of benzoin as the major product, but markedly with a 10% yield of crossed acyloin product **311d** (entry 9). Thus, from this study we can deduce that coupling of benzaldehyde and an *ortho*-substituted aromatic aldehyde invariably leads to the formation of benzoin (**15b**) and the crossed acyloin '**c**' product. A reverse trend is observed when an aliphatic aldehyde is coupled with benzaldehyde, leading to the generation of **15b** and the crossed acyloin '**d**' product.

4.1.2.6 Rationale for chemoselectivity obtained using precatalysts 131 and 297a

The question regarding the origin of the chemoselectivity observed in the above studies is both intriguing and difficult to definitively answer at this juncture. It was experimentally determined that achiral triazolium ion **131** and bifunctional precatalyst **297a** exhibited a similar chemoselective bias in the coupling reactions - the use of a hindered *ortho*-substituted aromatic aldehyde in conjunction with a less hindered aliphatic analogue invariably led to formation of the crossed acyloin '**d**' product as the predominant product. Our rationale is outlined below and is approached from two standpoints: (a) selectivity arising from which aldehyde is involved in formation of the Breslow intermediate and (b) the subsequent selective addition of the Breslow intermediate to an aldehyde (Scheme 4.5 and Figure 4.2). By comparing the performance of the pentafluorophenyl-substituted precatalyst **131** and the *N*-phenyl variant **181** (Table 4.1, entries 3 and 4) we could assume that a large factor contributing to the observed chemoselectivity of **131** and **297a** was the presence of the bulky pentafluorophenyl moiety on both precatalysts. In addition, superior chemoselectivity was obtained using the sterically demanding bifunctional precatalyst **297a**, albeit with reduced product yields.

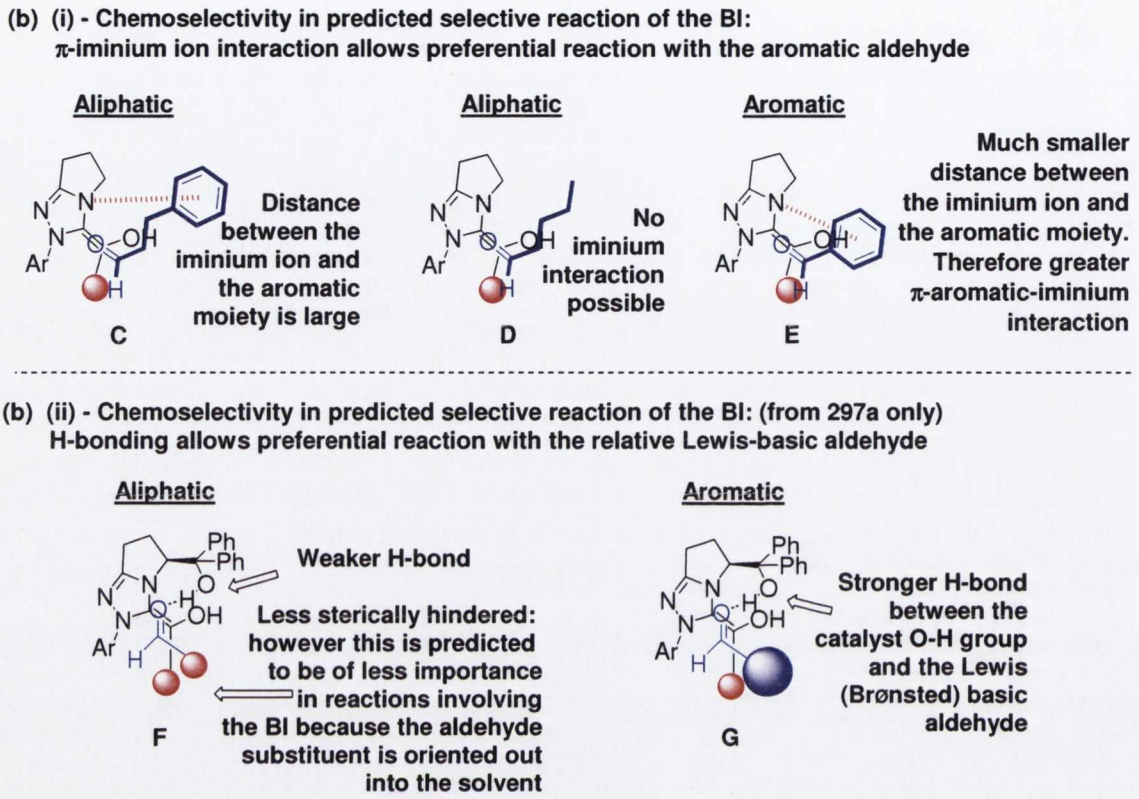
Scheme 4.5 Proposal for chemoselective outcome arising from formation of the Breslow intermediate



Scheme 4.5 depicts the two Breslow intermediates (**A** and **B**) that are generated from addition of achiral precatalyst **131** to each aldehyde, notably with the enolamine intermediates adopting the more energetically favourable *E*-conformation.[195] Regarding model **A**, it is reasonable to assume that the bulky aromatic aldehyde sterically clashes with the nearby *N*-pentafluorophenyl group of the catalyst, and as a result retards the rate of attack of the carbene on the aromatic aldehyde. This leads to increased concentrations of the Breslow intermediate derived from initial attack of the catalyst on the aliphatic aldehyde (model **B**). One could also presume that the benzaldehyde carbonyl moiety, having access to the π-electrons of the aromatic ring, is electronically less well desposed towards attack by the catalyst (*i.e.* it is also less electrophilic than the aliphatic aldehyde on electronic grounds).

What is unclear, is why this intermediate, model **B**, (rather counter intuitively) then prefers to react with the presumably more hindered *o*-substituted benzaldehyde over another molecule of aliphatic aldehyde. A possible explanation for the preference of both precatalysts to predominantly produce the '**d**' acyloin product is an attractive π-iminium interaction which lowers the energy of the developing transition state as the enolamine attacks the aromatic aldehyde (Figure 4.2, models **C**, **D** and **E**).[195,314] Model **C** depicts how this favourable interaction would be greatly reduced if an aliphatic aldehyde (such as hydrocinnamaldehyde) were to add to the Breslow intermediate, due to the larger distance from the iminium ion to the aromatic moiety. In addition, for aliphatic aldehydes lacking an aromatic side chain, such as propanal and pentanal, this π-iminium interaction would naturally be impossible and would clearly be absent (model **D**). The attractive π-iminium interaction between an aromatic aldehyde and the Breslow intermediate is shown in model **E**.

Figure 4.2 Proposals for chemoselectivity arising from selective addition to the Breslow intermediate

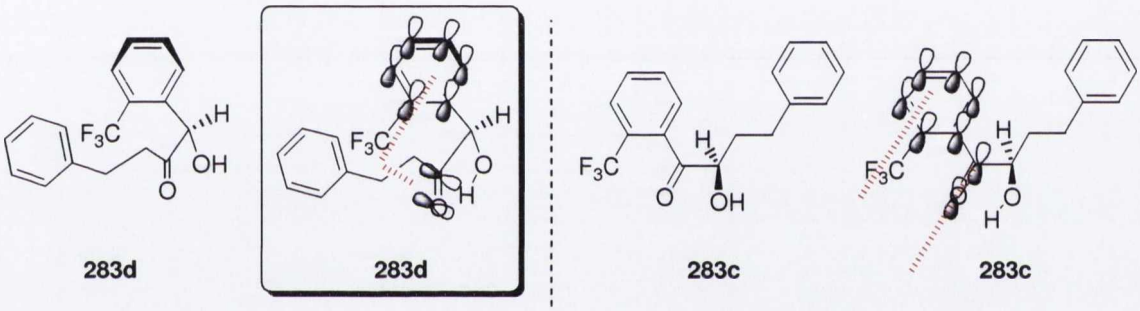


We could also posit that the chemoselective outcome (from using bifunctional precatalyst **297a**) arises from a dual control that the carbene catalyst exhibits in the reaction process. It could be considered that a stabilising (and selectively formed) hydrogen bond between the more (Brønsted) basic aromatic aldehyde carbonyl oxygen and the enolamine hydroxyl group could exist. This hydrogen bond-donation is depicted in models **F** and **G** above (Figure 4.2). It can also be assumed, given the supporting evidence uncovered as this study progressed, that a degree of thermodynamic product control is responsible for the observed chemoselectivity. Based on the well-established mechanistic picture of acyloin/benzoin condensations,[42,197] it is also reasonable to assume that the properties of the Breslow intermediate should also be dependant to a significant extent on the nature of the catalyst it is derived from.

Thus, it is difficult to justify exactly why the Breslow intermediate (model **B**, Scheme 4.5) formed from addition of the carbene catalyst to the aliphatic aldehyde) prefers to attack the hindered aromatic aldehyde over another molecule of aliphatic aldehyde. In a

natural product synthesis study involving an intramolecular acyloin condensation step Miller has suggested that a stabilising interaction between orthogonally aligned carbonyl and aromatic moieties (known to exist in α-phenyl ketones in cases where it is sterically permitted) may influence the chemoselective outcome of acyloin condensation reactions between aliphatic and aromatic aldehyde components.[202] Crossed acyloin products **283c** and **283d** are shown in Figure 4.3 and their relevant aromatic and carbonyl π-systems are illustrated alongside. It is evident that this stabilising alliance can only occur for α-arylketone crossed product **283d** due to the difference in alignment of the π-faces of the phenyl ring and the carbonyl group in both the products.

Figure 4.3 α-phenylketone stereoelectronic effect of crossed acyloin products

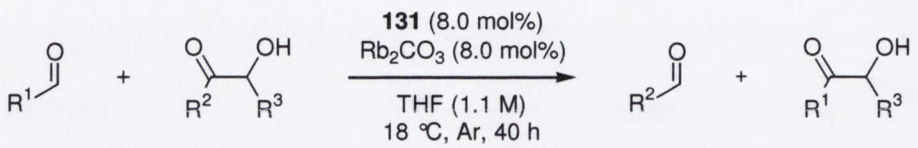


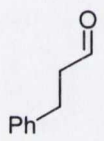
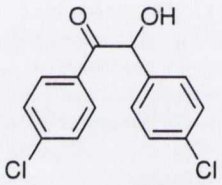
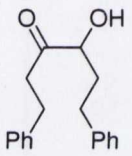
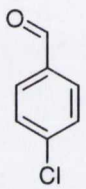
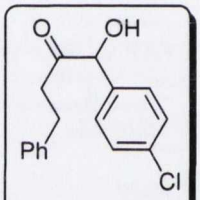
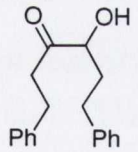
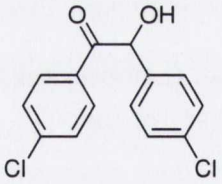
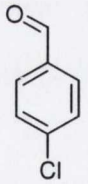
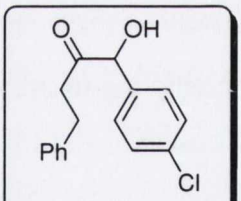
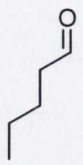
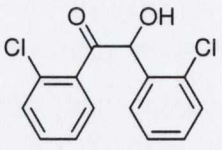
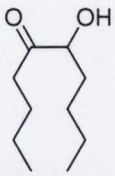
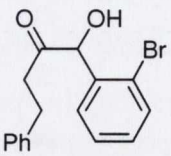
It is tempting to draw parallels in this study, *i.e.* that the observed preference for the α-arylketone crossed product (*i.e.* the '**d**' crossed acyloin product) over the α-substituted aromatic ketone analogue (*i.e.* the '**c**' crossed product) is related to the contribution of this interaction, which presumably results in greater reversibility of the latter cross-product over the former, and hence the greater stability of the crossed acyloin '**d**' product over the '**c**' isomer.

In an attempt to further shed light on the origins of the observed chemoselectivity a number of crossover experiments were carried out by Mr. S. Gundala. The results of these experiments are outlined in Table 4.8. In the first instance, it was pertinent to establish if there was a degree of reversibility in these coupling processes. The reaction of aliphatic aldehyde **276** and a homodimer derived from a *para*-substituted aromatic aldehyde (*i.e.* **268b**) with the achiral precatalyst **131** under our standard conditions was investigated (entry 1). Interestingly, this experiment afforded significant amounts of the

cross-product **268d**, along with free aldehyde **260** (which also stems from a retro-acyloin reaction) and additionally the homodimer **277a**. The experiment was repeated and the aliphatic aldehyde **276** was replaced with its homodimer **277a** (entry 2). Again retroacyloin of **268b** was observed but in this case no coupling to form cross-product **268d** occurred. These results indicate that the *p*-substituted benzoin **268b** is able to revert to its parent aldehyde under the reaction conditions, whereas the homodimer **277a** derived from hydrocinnamaldehyde is not.

Table 4.8 Crossover experiments under optimised conditions using achiral **131**



Entry	Starting Materials		Products		
1	 **276**	 **268b** (0.5 equiv.)	 **277a** 40%	 **260** 1%	 **268d** 15%
2	 **277a**	 **268b**	 **260** 5%		 **268d not detected**
3	 **287**	 **266b**	 **317a** 10%		**317d not detected**
4	 **284d**		**No reaction**		

To probe this further, the *ortho*-isomer of benzoin **268b** (*i.e.* **266b**) was treated with an aliphatic aldehyde **276** in the presence of the catalyst. Gratifyingly, no cross product **266d** was detected in this experiment, only the slow dimerisation of **276** (entry 3). Thus it would appear that the *o*-substituted aromatic acyloin **266b** is more stable towards the catalyst than its *p*-isomer **268b**, which, together with the rather slow rate of dimerisation of *o*-substituted aromatic aldehydes and hydrocinnamaldehyde (**276**) and the reluctance of the 'aliphatic' homodimer **277a** to undergo a retro-acyloin reaction, goes some way towards explaining the chemoselectivity observed in these processes. Finally, exposure of the cross product **284d** (derived from reaction of *o*-bromobenzaldehyde and hydrocinnamaldehyde) to the catalyst under standard reaction conditions failed to product any products (entry 4). This points towards the irreversible formation of the crossed acyloin '**d**' product that will not undergo a retro-acyloin reaction.

From evaluation of the results of our studies of the crossed acyloin condensation reaction and the cross-over experiments conducted by Mr. S. Gundala a number of conclusions that can be drawn from these reactions:

1. 'Aliphatic' and *o*-substituted benzaldehydes dimerize, but do so only slowly. This was evident from the low levels of '**a**' and '**b**' homodimer products obtained in Table 4.2, Table 4.3 and Table 4.6. This is central to attaining high chemoselectivity in these processes.
2. The homodimers derived from 'aliphatic' aldehydes do not participate in retro-acyloin chemistry under these conditions and are essentially formed irreversibly (entry 2, Table 4.8).
3. Unhindered benzoins (*i.e.* homodimers of aromatic aldehydes) will participate in retro-acyloin chemistry under these conditions, whereas *o*-substituted isomers will not (entries 1 and 3, Table 4.8).
4. The α-arylketone cross-product (acyloin '**d**', the major product under our reaction conditions) from the reaction of an aliphatic and an aromatic aldehyde undergoes a retroacyloin reaction either slowly or not at all (entry 4, Table 4.8).

Overall it is clear that the crossed-coupling process is facilitated by the slow dimerisation of the aliphatic aldehyde and *o*-substituted benzaldehydes. We would propose that it is reasonable to assume that initial attack of the carbene on the aliphatic aldehyde is preferred on electronic grounds - *i.e.* the more electron rich aromatic

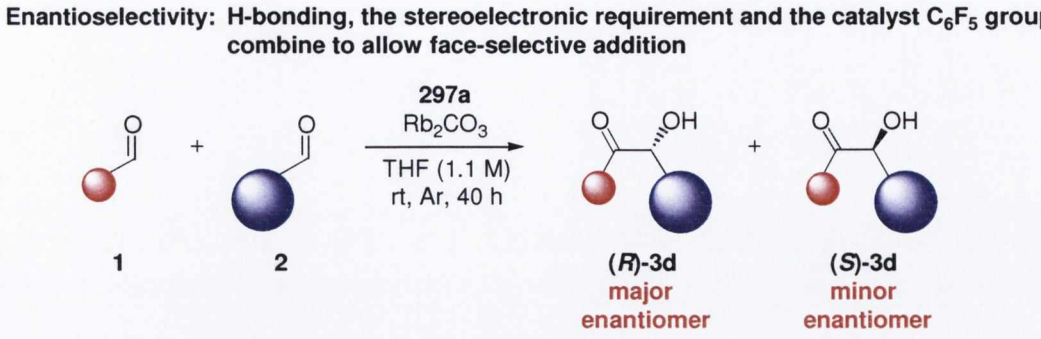
aldehyde carbonyl moieties make for poorer electrophiles in the first step of the catalytic cycle. This is supported by the observation that the use of more activated, halogen-substituted benzaldehydes generates greater levels of homobenzoin products, derived from attack of the Breslow intermediate on benzaldehyde (entries 1-4, Table 4.2). In the case of *o*-substituted benzaldehydes this preference for the aliphatic partner as the initial site of attack would obviously be exaggerated for steric reasons; this argument can be underlined by the decreasing amount of homobenzoins ('**b**' product) detected with increasing size of the *ortho*-halogen substituent (*o*-F, *o*-Cl, *o*-Br with 45%, 15% and 9% yields of homocoupled '**b**' product, see entries 3, 4 and 8, Table 4.2).

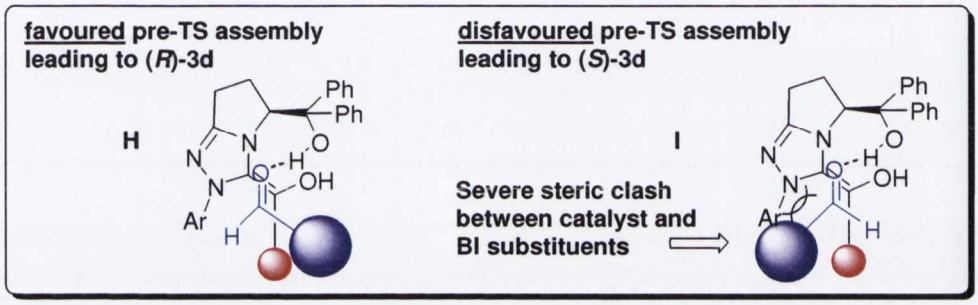
What can be safely inferred is that chemoselectivity in these processes is not governed by a single factor alone but rather a confluence of factors depending on the catalyst employed and the steric and electronic nature of the reactants. That being said, it is clear that one can achieve high selectivity in the diverse array of crossed acyloin condensation reactions examined in this study by using precatalysts **131** and **297a** in the presence of an aromatic aldehyde incorporating an *ortho*-substituent.

4.1.2.7 Rationale for enantioselectivity observed using precatalyst 297a

The matter of the absolute configuration of the crossed acyloin products must now be addressed. In this work, the absolute configuration of the products was not elucidated because the acyloin products were novel compounds, devoid of literature data concerning their stereochemical and structural properties. The products themselves were oils and thus X-ray crystallography was not a viable method for determination of their absolute configurations. However, a rational approach to this issue would be to consider the influence of the steric requirement of the catalyst and the contribution of the hydrogen bond-donating moiety in determining the stereochemical outcome of the products. Such a premise is outlined in Scheme 4.6.

Scheme 4.6 Rationale for enantioselectivity using dual-control precatalyst **297a**





Models **H** and **I** above depict the addition of the Breslow intermediate to either face of the aromatic aldehyde and surmises that the major enantiomer formed using precatalyst **297a** is the (*R*)-enantiomer. A hydrogen bond which stabilises developing negative charge on the aldehyde being attacked by the Breslow intermediate is assumed (general acid catalysis). Model **I** displays the severe steric strain that would incur between the bulky pentafluorophenyl moiety attached to the triazolium ring and the sterically demanding aromatic side-chain of the electrophilic aldehyde upon addition of the Breslow intermediate to the *re*-face of the aromatic aldehyde. The favoured pre-transition state assembly is that of model **H** where this steric clash is avoided and the aromatic aldehyde is not as constricted in its approach towards the Breslow intermediate. Therefore, the selective and more facile addition of the Breslow intermediate to the *si*-face of the electrophilic aromatic aldehyde, coupled with assistive hydrogen bond-donation from the catalyst, would lead one to postulate that the crossed α-hydroxy ketone products would contain a (*R*)-configuration.

To strengthen this argument, we have previously described how precatalyst **297a** was initially developed for use in the enantioselective homobenzoin condensation reaction

and it was determined that precatalyst **297a** generated homoacyloin '**b**' products that possessed a (*R*)-configuration.[350] The step that determines the stereochemical outcome of a benzoin condensation reaction process is the addition of the Breslow intermediate to the second (electrophilic) aldehyde. Thus, the stereochemistry of the acyloin product arises from face-selective addition of the Breslow intermediate to the second aldehyde. Similar to our crossed acyloin condensation reactions discussed above, the study of the homobenzoin condensation reaction conducted by our group using **297a** involved the face-selective addition of an *aromatic* aldehyde to the Breslow intermediate. Therefore, one could simply suppose that the stereochemical outcome of our crossed acyloin condensation reactions would surely also give rise to the (*R*)-enantiomer.

Another point to consider is the essentially racemic result attained when a homo-acyloin condensation reaction was conducted using hydrocinnamaldehyde (**276**), in the presence of **297a** (3% *ee*). This indicates that a bias was not found in relation to which face of the approaching second molecule of **276** was attacked in the reaction process. This is presumably due to the reduced steric demand of hydrocinnamaldehyde in relation to that of, for example, *o*-trifluoromethyl-benzaldehyde **279**. Therefore, at this point we could confidently ascertain that the *si*-face of the aromatic partners of our coupling reactions is attacked by the Breslow intermediate which consequently provides the (*R*)-configuration of our crossed acyloin '**d**' products.

4.1.3 Section 4.1: conclusions

In summary, we have developed the first efficient, chemoselective intermolecular crossed acyloin condensation reactions involving triazolium ion precatalysts. The methodology is of a very broad scope: hindered, activated and electron-rich aromatic aldehydes are compatible, as are aliphatic aldehydes. Importantly, unlike the previous benchmark study involving thiazolium catalysts, in these reactions the expected product from the crossed coupling of two aldehydes can be confidently predicted, and the methodology is complementary to that most often associated with enzymatic catalysis of the enzymes BAL and BFD (with the exception of some pyruvate decarboxylases capable of accepting aliphatic aldehydes as donors in place of their natural α-ketoacid substrates)[288,290] as it consistently furnishes the opposite (in an *Umpolung* context) crossed product in high yield. We also touched upon the use of an *o*-bromo substituent

as a temporary chemoselectivity-controlling group which can subsequently be removed conveniently in high yield. The feasibility of highly enantioselective crossed acyloin condensation reactions has also been demonstrated, in particular with reference to the coupling of *o*-trifluoromethyl-benzaldehyde and a range of unbranched aliphatic aldehydes. Our work has demonstrated for the first time that chiral protic bifunctional triazolium salts are efficient promoters of the enantioselective crossed acyloin condensation reaction. Future work may involve further development of modified chiral catalysts to promote the enantioselective version of this coupling reaction. Another aspect that begs further investigation is the unexpected formation of the 'opposite' crossed acyloin '**c**' product that was formed from the coupling of hydrocinnamaldehyde and 2-furaldehyde (*i.e.* product **275c**, entry 17, Table 4.2). This unanticipated result could perhaps be examined as future work in this project, in an attempt to exploit a chemoselective formation of the '**c**' crossed acyloin product.

4.2 Studies on the asymmetric catalysis of other NHC-promoted reactions

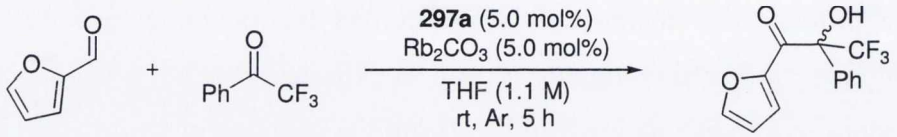
Investigative studies of the crossed acyloin condensation reaction have been conducted, which entailed the assessment of the reaction scope. Unprecedented endeavours to promote an enantioselective variant of this reaction were successful, attaining highly chemo- and enantioselective reactions with a variety of aldehyde substrates. Although the crossed acyloin condensation reaction has yet to reach its full potential, being merely in its infancy in investigative terms, we decided to diversify into the evaluation of other NHC-promoted reactions that have yet to be catalysed in an enantioselective fashion. This section describes preliminary exploratory studies of four disparate reactions that utilise the *Umpolung* of the classical carbonyl reactivity.

4.2.1 The first asymmetric NHC-assisted aldehyde-ketone crossed condensation

Very recently Enders disclosed the NHC-catalysed coupling of α,α,α-trifluoromethylacetophenone to an array of aromatic aldehydes.[278] Although this was the first example of an intermolecular aldehyde-ketone crossed coupling reaction, there

does not appear to be any examples of an asymmetric (NHC-catalysed) variant of this reaction. We report herein the first example of an NHC-assisted enantioselective aldehyde-ketone crossed acyloin condensation, using α,α,α-trifluoromethylacetophenone (**318**) and 2-furaldehyde (Scheme 4.7).

Scheme 4.7 The first example of an asymmetric aldehyde-ketone coupling reaction



273 **318** (2.0 equiv.) **319** 4%

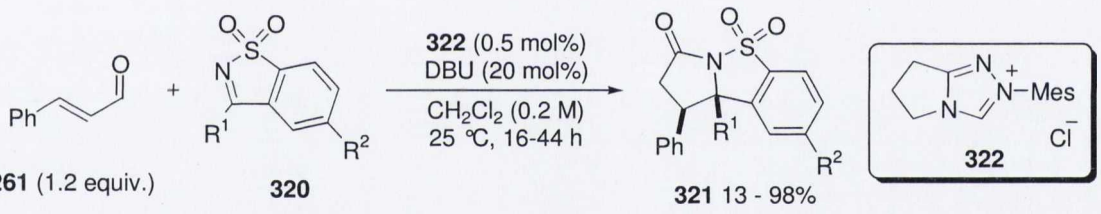
An initial crossed coupling experiment involving the addition of both 2-furaldehyde and **318** to the reaction medium at the start of the experiment furnished solely the α-hydroxy ketone, furoin (**275b**), arising from self-condensation of **273**, with no evidence of the crossed product **319**. Note: our group determined previously that **273** undergoes a *homo*benzoin condensation reaction, furnishing furoin in near quantitative yield over several hours, using the reaction conditions outlined above in Scheme 4.7.[350] Taking this into consideration, we modified our experimental procedure, slowly adding 2-furaldehyde to the reaction, in 4.0 mol% aliquots, at 20 minute intervals. After 5 h a sample of the reaction was analysed by ^{1}H NMR spectroscopy (upon addition of 0.60 equiv. of **273**) and a ratio of 8:1 of products furoin:**319** was observed. The reaction mixture was purified and the novel α-hydroxy ketone was isolated as a yellow oil. Disappointingly, there was insufficient sample remaining for chiral HPLC analysis of **319**; therefore the enantiomeric excess of the crossed acyloin product was not determined. We could speculate that in our attempt to reduce furoin formation, catalyst decomposition occurred which would account for the low yield of this reaction.

4.2.2 Annulation of α,β-unsaturated aldehydes and unsaturated cyclic *N*-sulphonyl imines

The nucleophilic addition of α,β-unsaturated aldehydes (enals) to a variety of electrophiles (by means of NHC catalysis) allows the facile preparation of a wide range of annulated products, including trisubstituted cyclopentenes, γ-lactams and bicyclic β-

lactams.[221] In particular, the addition of enals to aldimines and ketimines has encountered many difficulties arising from the lability of ketimine derivatives, which complicates their preparation and handling. Despite considerable efforts from both Bode's and Scheidt's research groups, NHC-catalysed additions of α,β-unsaturated aldehydes to imine electrophiles have been limited to the use of aromatic aldehydes derived from *N*-sulphonyl imines,[351] azomethine imines[352] and *N*-phenyl nitrones.[353] However, in 2008 Bode *et al.* reported the simple and convenient synthesis of tertiary amine derivatives *via* the formal addition of α,β-unsaturated aldehydes (homoenolate equivalents) to chemically stable, yet highly reactive, sulphonyl ketimines derived from saccharin.[142] This significant study enabled the diastereoselective formation of γ-lactams and was for the most part conducted using an achiral *N*-mesityl-containing triazolium ion **322**, using the conditions outlined in Scheme 4.8.

Scheme 4.8 NHC-catalysed annulation of **261** and various sulphonyl ketimines

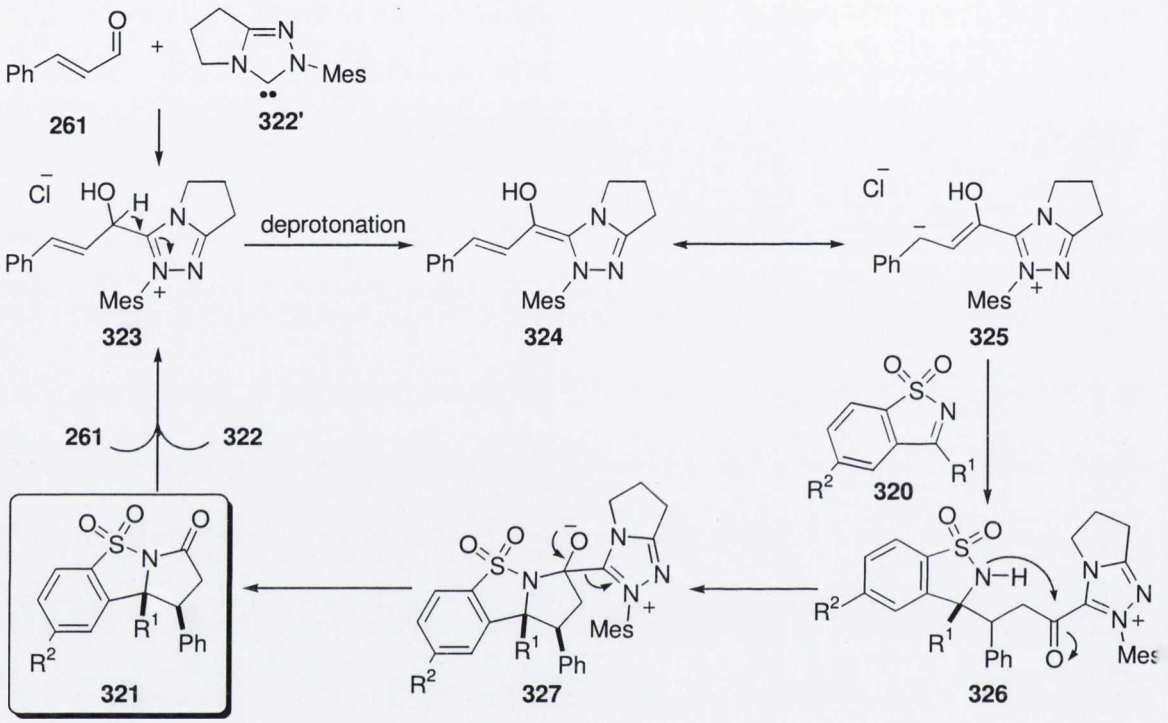


Electronically diverse aromatic and heteroaromatic ketimines were tolerated in the reaction with cinnamaldehyde (**261**), furnishing near quantitative yields of **321**. In most cases the *cis*-product predominated, although an electron-deficient aromatic substituent (R^1) resulted in a small preference for the *trans*-product. The reaction was found to proceed smoothly at ambient temperature, using a mere 0.5 mol% of precatalyst **322**, providing, on the whole, excellent yields of the annulated tertiary amines **321**. The mechanism of the reaction is displayed below in Scheme 4.9 using **261** and **320**.

Addition of carbene **322'** to cinnamaldehyde **261** furnished a hydroxy-species **323**, which upon deprotonation provided the diene homoenolate equivalent **324**. Interconversion of **324** and **325** was possible. Homoenolate addition to imine **320** occured forming adduct **326** and subsequent annulation *via* intramolecular nucleophilic

addition of the amine group generated the tertiary amine **327**. Expulsion of the catalyst (**322**) to re-enter the catalytic cycle created the final product, γ-lactam **321**.

Scheme 4.9 Proposed mechanism for the NHC-catalysed annulation of enals and cyclic sulphonyl ketimines

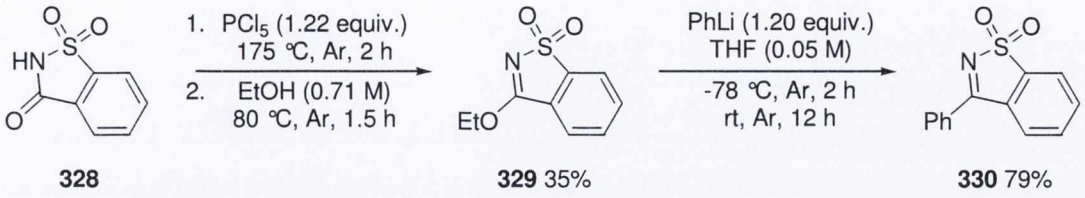


While Bode included three examples of an asymmetric variant of the reaction using chiral triazolium salts (at 15 mol% loadings), no further elaboration of an enantioselective study has been completed. Thus we chose to conduct a preliminary investigation into the asymmetric version of this annulation process.

Evaluation of the reaction required the synthesis of a benchmark ketimine substrate; saccharin was employed as the starting reagent and the phenyl ketimine substrate **330** was prepared over two steps following the procedure outlined by Bode (see Scheme 4.10).[142] Saccharin (**328**) was heated in the presence of the chlorinating agent PCl_5, and ensuing nucleophilic substitution provided the *O*-ethoxy-saccharin intermediate **329** in 35% yield. The second reaction step involved the use of the organolithium reagent,

phenyllithium, which upon arylation of **329**, furnished the desired ketimine substrate **330** in a respectable yield of 79%.

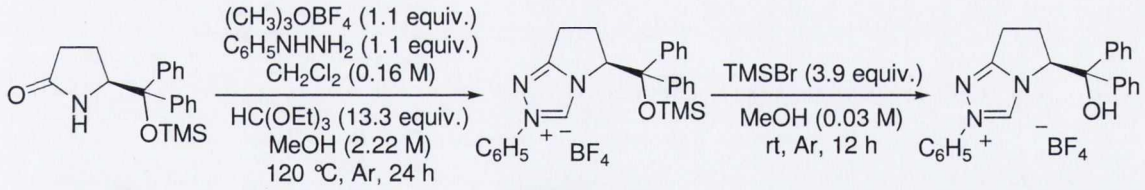
Scheme 4.10 Synthesis of cyclic sulphonyl ketimine substrate **330**



328 **329** 35% **330** 79%

We also created a second chiral bifunctional triazolium salt precatalyst, **118a**, containing an *N*-phenyl moiety in place of the *N*-pentafluorophenyl group. The synthesis of this precatalyst is presented below in Scheme 4.11. The protic bifunctional precatalyst **118a** was readily prepared over two reaction steps, involving triazolium ring formation from the TMS-protected γ-lactam to provide the bulky alcohol protected triazolium ion **97c**. Subsequent removal of the protecting group furnishing the desired precatalyst **118a** in 91% yield.

Scheme 4.11 Synthesis of *N*-phenyl pyroglutamic acid-derived salt **118a**



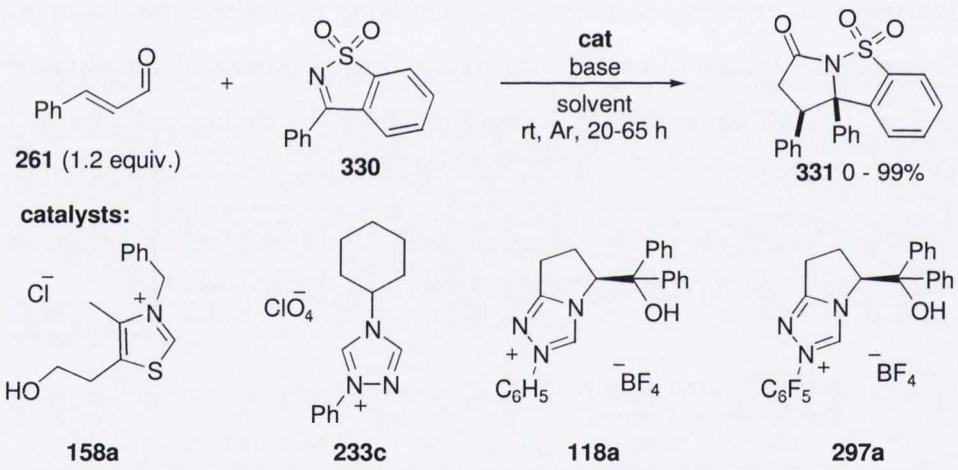
(*S*)-304a **(*S*)-97c** 43% **(*S*)-118a** 91%

4.2.2.1 Asymmetric catalysis of the reaction of cinnamaldehyde and 325

It must be emphasised that most prior reports of NHC-catalysed additions of enals to electrophiles such as aldehydes, imines or ketones, employed imidazolium salts as precatalysts for homoenolate generation.[354,355,356] As a result, we initiated our investigation into this homoenolate addition reaction using achiral thia- and triazolium precatalysts **158a** and **233c**, to determine whether these heterazolium salts would be effective promoters of the reaction. Most interestingly, our experiments generated solely the *cis*-product and the results of our study are presented in Table 4.9.

Achiral thiazolium salt **158a**, in conjunction with triethylamine, was ineffective in providing an annulation reaction (entry 1). On the other hand, when 10 mol% of achiral triazolium ion **233c** and 8.0 mol% of Rb_2CO_3 were employed in the reaction process, quantitative conversion to *cis*-**331** was accomplished after 44 h (entry 2). We next evaluated the chiral bifunctional pyroglutamic acid-derived precatalysts **118a** and **297a** in the annulation process, beginning with the reaction conditions employed by Bode. These parameters entailed the use of increased precatalyst and base loadings (15.0 and 20.0 mol% respectively), high dilutions and employing dichloromethane as the solvent and DBU as the base. Surprisingly, both triazolium ions failed to generate the γ-lactam product (entries 3 and 4).

Table 4.9 Enantioselective annulation of **261** and sulphonyl ketimine **330**



entry	cat.	loading (mol%)	b se	loading (mol%)	solvent	conc. (M)	time (h)	yield[a] (%)	ee[b] (%)
1	**158a**	10.0	NEt_3	10.0	THF	0.70	65	0	n/a
2	**233c**	10.0	Rb_2CO_3	8.0	THF	0.80	44	99	n/a
3	**118a**	15.0	DBU	20.0	CH_2Cl_2	0.10	18	0	0
4	**297a**	15.0	DBU	20.0	CH_2Cl_2	0.10	18	0	0
5	**118a**	4.0	Rb_2CO_3	3.2	THF	0.10	25	0	0
6	**118a**	4.0	Rb_2CO_3	3.2	THF	0.87	23	0	0
7	**297a**	4.0	Rb_2CO_3	3.2	THF	0.87	23	0	0
8	**118a**	10.0	Rb_2CO_3	8.0	THF	0.87	31	21	56
9	**297a**	10.0	Rb_2CO_3	8.0	THF	0.87	20	0	0
10	**297a**	2.0	NEt_3	6.0	CH_2Cl_2	0.56	40	0	0
11	**297a**	2.0	NEt_3	6.0	CH_2Cl_2	0.70	23	0	0

[a]Isolated yield. [b]Determined by chiral HPLC using a Chiralpak AD-H column (4.6 x 250 mm).

We reverted to using THF as the reaction medium, and assessed the performance of **118a** and **297a** (4.0 mol%) at different concentrations. At both high and low concentrations, these reaction conditions failed to furnish a productive reaction (entries 5-7), indicating that an insufficient quantity of precatalyst had been utilised. We increased the precatalyst loading to 10.0 mol% and using a concentration of 0.87 M, gratifyingly obtained a yield of 21% (after column chromatography) using **118a** (entry 8). Note: the absolute configuration of *cis*-**331** was not determined, although a promising enantioselectivity of 56% *ee* was attained, with no indication of the *trans*-diastereoisomer being present. Unexpectedly, the *N*-pentafluorophenyl-containing salt **297a**, in the presence of Rb_2CO_3, did not deliver any of the γ-lactam (entry 9). Endeavours to attain an intermolecular cyclisation process using **297a** and triethylamine (in dichloromethane) were, to our dismay, unsuccessful (entries 10 and 11).

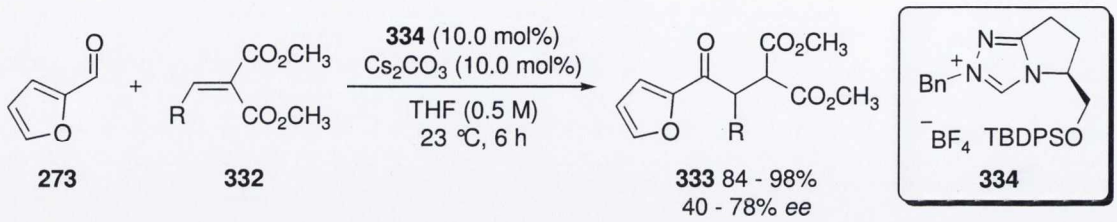
Thus, in conclusion, we have investigated the NHC-catalysed annulation of cinnamaldehyde and the cyclic sulphonyl ketimine **330**. We found that the achiral triazolium ion **233c**, when used with Rb_2CO_3 as base, provided quantitative conversion to the γ-lactam *cis*-**331**. We assessed the performance of chiral bifunctional precatalysts **118a** and **297a** under Bode's reported reaction conditions and failed to generate the desired product. Modification of the reaction parameters enabled the formation of *cis*-**331** in 21% yield and 56% *ee* using **118a**. Interestingly, the pentafluorophenyl variant **297a** failed to furnish the γ-lactam product under identical reaction conditions. The reason for the aversion of **297a** towards homoenolate generation is unclear at this juncture.

4.2.3 The intermolecular Stetter reaction using activated arylidenemalonate Michael acceptors

Among the various NHC-catalysed carbon-carbon bond-forming processes, the Stetter reaction enjoys first-rank status, as it allows conjugate nucleophilic acylation reactions *via Umpolung* chemistry. Although a number of efficient protocols for inter- and intramolecular Stetter reactions have been developed of late,[251,357,,358] high asymmetric inductions in the classical intermolecular Stetter reaction continue to remain a challenge. Recently, Enders disclosed results on the asymmetric intermolecular Stetter reaction

involving aromatic heterocyclic aldehydes and the activated Michael acceptors, arylidenemalonates, as depicted in Scheme 4.12.[359]

Scheme 4.12 Intermolecular Stetter reaction utilising arylidenemalonates **327**



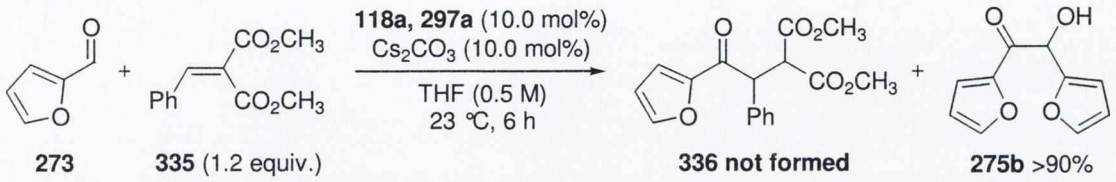
273 **332** **333** 84 - 98%, 40 - 78% *ee* **334**

The asymmetric Michael addition of the electron-rich 2-furfuraldehyde (**273**) to arylidenemalonates (**332**) was promoted by the chiral bulky alcohol-protected pyroglutamic acid-derived precatalyst **334**. The ketomalonates **333** were obtained in yields of 84-98% and with moderate to good enantioselectivities. Both electron-rich and electron-deficient aromatic substituents (R groups) were tolerated in the reaction, although notably Enders did not employ any *o*-substituted arylidenemalonates. It was determined that the *N*-benzyl substituent and the bulky *t*-butyldiphenylsilyl (TBDPS) group of **334** were crucial to the facilitation of the asymmetric Stetter reaction; the use of analogous pyroglutamic acid-derived precatalysts that either lacked an *N*-benzyl moiety or contained a side chain of dissimilar steric size to that of the TBDPS group were ineffective in providing the desired Stetter products, furnishing the *homo*benzoin condensation adduct, furoin, as the sole product.

We set out to investigate the intermolecular Stetter reaction using chiral bifunctional precatalysts **118a** and **297a**, and the Michael acceptor substrate, dimethyl benzyildenemalonate (**335**) as per Scheme 4.13. **335** Was easily prepared by microwave-induced Knoevenagel condensation of benzaldehyde and dimethylmalonate.[360] Disappointingly, all endeavours to provide the keto diester product **336** invariably led to the formation of the benzoin condensation product, furoin (**275b**), using both bifunctional precatalysts. Modification of the reaction parameters, such as using dichloromethane as the solvent, variation of the concentration and the precatalyst and base loadings and using an excess of **335** (7.0 equiv.) could not entice the reaction to provide the Stetter product **336**. In each case furoin was provided in greater

than 90% yield, with no evidence of the Stetter product. Therefore, we decided to cease further investigation of this intermolecular Stetter reaction.

Scheme 4.13 Asymmetric nucleophilic acylation of benzylidenemalonate **335**

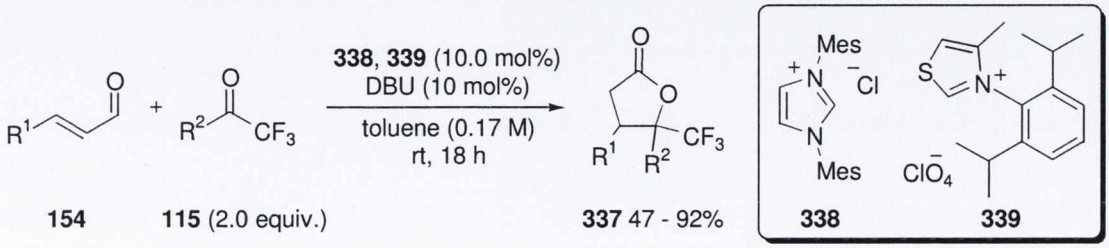


273 **335** (1.2 equiv.) **336 not formed** **275b** >90%

4.2.4 Stereoselective synthesis of trifluoromethylated γ-butyrolactones

Fluorinated organic compounds have found widespread applications as active ingredients in medicinal drugs, crop protection agents, in materials science or in the area of catalysis and are therefore gaining increasing importance in the life sciences. [361,362,363] In spite of recent significant progress, new methods for the synthesis of organofluorine compounds, such as fluorinated aromatic or trifluoromethyl-substituted compounds, are highly sought after.[364] In 2004, Glorius reported the conjugate addition of α,β-unsaturated aldehydes to trifluoromethylacetophenone, resulting in the formation of trifluoromethylated γ-butyrolactones, albeit, with low stereoselectivities.[355] Recently, Glorius furthered upon his investigations of the synthesis of trifluoromethylated γ-butyrolactones, comparing the performance of achiral imidazolium, triazolium and thiazolium salt precatalysts in the addition reaction and attained much higher product diastereoselectivities.[365] The reaction procedure is depicted below in Scheme 4.14, and the two precatalysts that provided the optimal yields and diastereoselectivities are included.

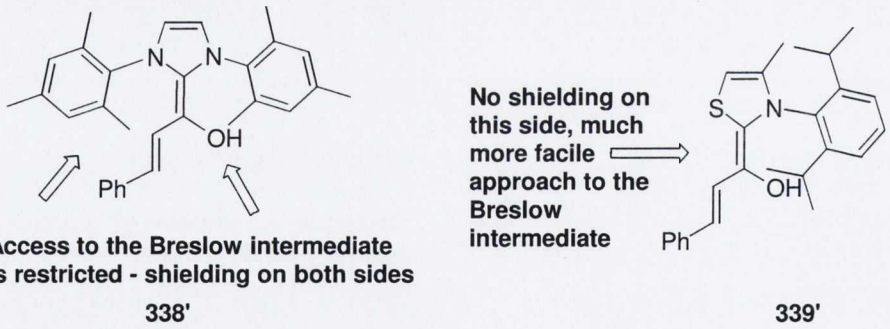
Scheme 4.14 Diastereoselective synthesis of trifluoromethylated γ-butyrolactones



154 **115** (2.0 equiv.) **337** 47 - 92% **338** **339**

Initial experimentation involved the annulation of cinnamaldehyde and trifluoromethylacetophenone. Imidazolium salt **338** was employed in the reaction, and furnished excellent yields of **337** (where R^1 and R^2 = Ph), displaying a small preference for formation of the *cis*-isomer (2:1 *cis*:*trans*). Glorius also assessed a commercially available triazolium salt in the reaction and attained only modest levels of γ-butryolactone product. A range of thiazolium salts were evaluated in the reaction, some of which did not promote the annulation process. The best results were obtained using the sterically demanding aryl-substituted thiazolium salt **339** (Scheme 4.14). Contrary to the outcome using using precatalyst **338**, thiazolium salt **339** generated **337**, with predominantly *trans*-stereochemistry (1:8 *cis*:*trans*) and in an exceptional overall yield (94%). Glorius speculated that the change in selectivity from using 1,3-disubstituted imidazolium salt **338** to 3-aryl-substituted thiazolium ion **339** originated from the fundamentally different steric demand of the two systems. He claimed that opposite to **338**, the Breslow intermediate that would arise from thiazolium salt **339** would only be shielded on one side, thus allowing the stereoselective approach of the electrophilic ketone **115** (see Scheme 4.15). This, he considered, enabled the exceedingly more diastereoselective formation of **337** using thiazolium salt **339**.

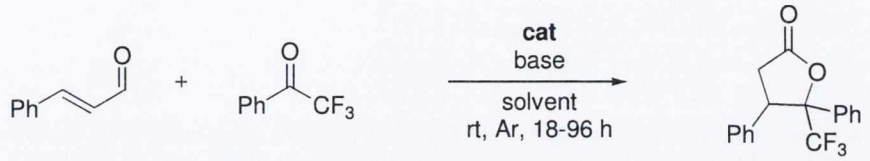
Scheme 4.15 Depictions of Breslow intermediates from precatalysts **338** and **339**



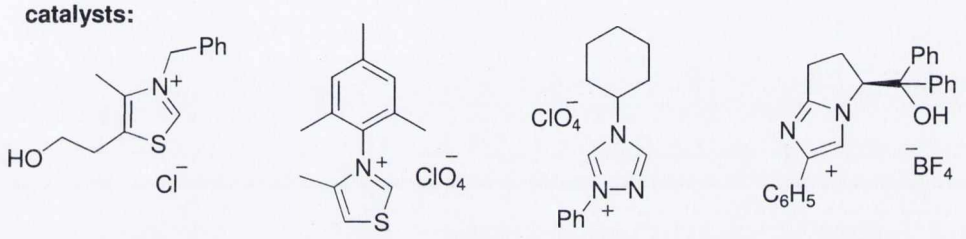
The reaction scope was investigated using the reaction conditions outlined in Scheme 4.14. A range of cinnamaldehyde derivatives were reacted with several substituted trifluormethyl ketones, obtaining good to excellent yields of **337**. In each case, *cis*-**337** prevailed when imidazolium salt **338** was employed, whilst use of thiazolium salt **339** provided the *trans*-isomer. It was also highlighted that the selectivity obtained using thiazolium ion **339** was greater in each case than the selectivity generated by

imidazolium salt **338**. We noted that an enantioselective version of this reaction had not been attempted and accordingly set about investigating this annulation process; the results of this study are presented in Table 4.10.

Table 4.10 Attempts at enantioselective γ-butryolactone formation



catalysts:



entry	cat.	loading (mol%)	base	loading (mol%)	solvent	conc. (M)	time (h)	yield[a] (%)	dr (*cis*:*trans*)
1	**158a**	10.0	NEt_3	10.0	THF	0.70	65	0	-
2	**211b**	10.0	DBU	10.0	toluene	0.68	96	>2	-
3	**233c**	10.0	Rb_2CO_3	8.0	THF	0.80	96	26	1.1:1.0
4	**118a**	4.0	Rb_2CO_3	3.2	THF	0.17	25	>2	-
5[b]	**118a**	10.0	Rb_2CO_3	8.0	THF	1.10	31	34	1.2:1.0
6	**118a**	10.0	DBU	10.0	toluene	0.17	18	0	-

[a]Isolated yield. [b]An optical purity of 30% *ee* for *cis*-**340** was determined by chiral HPLC using a Chiralpak AD-H column (4.6 x 250 mm).

We first assessed the ability of simple achiral thiazolium and triazolium ion precatalysts to promote the γ-butryolactone formation process. Both benzyl- and mesityl-substituted thiazolium ions **158a** and **211b** were unsuccessful at facilitating the reaction (entries 1 and 2). Triazolium salt **233c** enabled the addition of **261** to **318**, furnishing a yield of 26% of **340**, with poor diastereoselectivity (1.1:1.0 *cis*:*trans*). Chiral bifunctional precatalyst **118a** was attempted in the reaction process, and it was determined that a loading of 4.0 mol% was inadequate, failing to generate the γ-butryolactone product (entry 4). By increasing the amount of **118a** present in the reaction to 10.0 mol% (and changing the concentration of the reaction to 1.1 M) we were gratifyingly able to generate the fluorinated product **340** in a modest yield of 34% (entry 5). Once again the diastereomeric ratio of the isomeric products was low (1.2:1.0 *cis*:*trans*). We also

evaluated **118a** under the reaction conditions used by Glorius and surprisingly did not generate any product (entry 6). We attempted the isolation of the two isomeric products of both achiral and chiral experiments (entries 3 and 5). Following multiple attempts at purification *via* column chromatography we obtained a pure sample of *cis*-**340** and determined the enantioselectivity of the product to be 30% *ee*. Although we could isolate the *cis*-product from the crude reaction mixture, exhaustive efforts frustratingly did not permit isolation of the *trans*-isomer.

We decided at this point to stop further investigation into this reaction process as the diastereomeric ratios attainable using precatalyst **118a** were not of a significantly useful magnitude.

4.2.5 Section 4.2: conclusions

To conclude, we have extended the utility of our chiral bifunctional pyroglutamic acid-derived triazolium ions **118a** and **297a**, to include preliminary investigative studies of three NHC-catalysed reactions, two of which involved homoenolate generation and subsequent addition to electrophilic species. For the reactions entailing homoenolate addition (*i.e.* addition of cinnamaldehyde derivatives to cyclic sulphonyl ketimines and trifluoromethylacetophenones) the *N*-phenyl-containing triazolium salt **118a** identified itself as the superior promoter of the reaction processes, providing modest yields and enantioselectivies of the annulation products. The essentially analogous but electron-deficient *N*-pentafluorophenyl-substituted triazolium ion **297a** was unable to facilitate the reaction processes. This clearly relates to the difference in electronic properties (and hence activity) of the generated carbenes; the fluorinated triazolium salt **297a**, being more electron-deficient than **118a**, was unable to generate the homoenolate equivalent (Breslow intermediate of cinnamaldehyde) under the various reaction conditions we employed. Thus, in summary, we completed opening studies of four NHC-catalysed reactions that had yet to be evaluated from an enantioselective standpoint. Although the bifunctional precatalysts were not of sufficient activity and selectivity to be of significant use in these reactions, we have opened the door for further asymmetric investigations into these NHC-catalysed transformations.

5.1 General Experimental Data

Proton Nuclear Magnetic Resonance spectra were recorded on 400 MHz and 600 MHz spectrometers in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d_6 referenced relative to residual DMSO (H) (δ = 2.51 ppm) and CD_3CN referenced relative to residual CH_3CN (δ = 1.96 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz and 150 MHz) with total proton decoupling. Fluorine NMR spectra were recorded on a 376 MHz spectrometer. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a diamond Perkin Elmer Spectrum 100 FT-IR spectrometer using a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Ether and THF were distilled from sodium. Toluene, chlorobenzene, methylene chloride and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was performed using Daicel CHIRALCEL AD (4.6 mm x 25 cm), CHIRALCEL OD-H (4.6 mm x 25 cm) and CHIRALCEL OJ-H (4.6 mm x 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. Unless otherwise specified, all reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon.

5.2 Experimental Data for Section 2

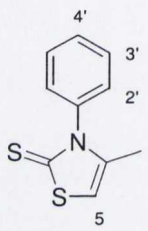
5.2.2 Experimental Data for Section 2.2

5.2.2.1 Procedure A: General procedure for preparation of thiazole-2-thiones

The relevant amine (10.00 mmol) was charged to a 25 cm^3 round bottomed flask and the reaction flask was sealed with a rubber septum seal and placed under an atmosphere of Argon. DMSO (5.00 cm^3) and NaOH solution (20 M, 500 µL, 10.00 mmol) were added

via syringe to the reaction vessel and the reaction was cooled to 0 °C. Carbon disulfide (600 μL, 10.00 mmol) was added to the flask and the reaction was stirred at ambient temperature for 30 min. The reaction was cooled to 0 °C once again and chloroacetone (800 μL, 10.00 mmol) was charged to the flask. The reaction was warmed to ambient temperature and stirred for 2 h, after which deionised water (10 cm^3) was added to the reaction. A precipitate formed which was filtered and subsequently dissolved in ethanol (10 cm^3). HCl (32% (*v*/*v*), 550 μL) was added and the mixture was heated at reflux (80 °C) for 1 h. Upon cooling a precipitate formed and filtration gave the crude thiazole-2-thione product. Recrystallisation from hot ethanol provided the pure thiazole-2-thione product as needle-like crystals.

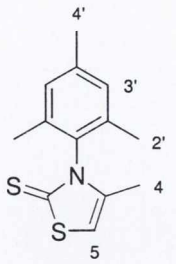
5.2.2.2 4-Methyl-3-phenyl-3*H*-thiazole-2-thione (210a)



Procedure A was followed using aniline (**204a**) (970 μL, 10.00 mmol) with NaOH solution (20 M, 500 μL, 10.00 mmol), carbon disulfide (600 μL, 10.00 mmol) and chloroacetone (800 μL, 10.00 mmol) in DMSO (5.00 cm^3). The precipitate was dissolved in ethanol (10 cm^3) and HCl (32% (*v*/*v*), 550 μL) was added. Upon cooling a precipitate formed and filtration gave orange crystals. Recrystallisation from hot ethanol gave **210a** (1.24 g, 60%) as yellow-brown crystals, m.p. 152-153 °C, lit.,[366] 150-151 °C.

δ_H (400 MHz, $CDCl_3$): 1.96 (s, 3H, CH_3), 6.37 (s, 1H, H-5), 7.27 (d, 2H, J 7.1, H-2'), 7.58-7.62 (m, 3H, H-3' and H-4').

5.2.2.3 4-Methyl-3-(2,4,6-tri-methyl-phenyl)-3*H*-thiazole-2-thione (210b)



Procedure A was followed using 2,4,6-tri-methylaniline (**204b**) (1.40 cm^3, 10.00 mmol) with NaOH solution (20 M, 500 µL, 10.00 mmol), carbon disulfide (600 µL, 10.00 mmol) and chloroacetone (800 µL, 10.00 mmol) in DMSO (5.00 cm^3). A slurry was obtained which was dissolved directly in ethanol (10 cm^3) and HCl (32% (*v*/*v*), 550 µL) was added. Upon cooling a precipitate formed and filtration gave off-white crystals. Recrystallisation from hot ethanol gave **210b** (1.22 g, 49%) as off-white crystals. No melting point is available but all spectra are consistent with literature data.[365]

δ_H (400 MHz, DMSO-d_6): 1.81 (s, 3H, CH_3-4'), 1.92 (s, 6H, CH_3-2'), 2.21 (s, 3H, CH_3-4), 6.93 (s, 1H, H-5), 7.08 (s, 2H, H-3')

ν_{max} (neat)/cm^{-1}: 3129, 2975, 2916, 2828, 1590, 1429, 1285, 1059 (C-N-C), 962, 856, 842.

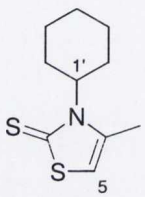
5.2.2.4 3-Benzyl-4-methyl-3*H*-thiazole-2-thione (210f)

Procedure A was followed using benzyl amine (**204f**) (1.09 cm^3, 10.00 mmol) with NaOH solution (20 M, 500 µL, 10.00 mmol), carbon disulfide (600 µL, 10.00 mmol) and chloroacetone (800 µL, 10.00 mmol) in DMSO (5.00 cm^3). The precipitate was dissolved in ethanol (10 cm^3) and HCl (32% (*v*/*v*), 550 µL) was added. Upon cooling a

precipitate formed and filtration gave a brown solid. Recrystallisation from hot ethanol gave pure **210f** (1.15 g, 52%) as a pale brown crystals, m.p. 88-89 °C, lit.,[367] 89-90 °C.

δ_H (400 MHz, $CDCl_3$): 2.17 (s, 3H, CH_3), 5.55 (s, 2H, H-1''), 6.28 (s, 1H, H-5), 7.21 (d, 2H, J 7.8, H-2'), 7.30-7.37 (m, 3H, H-3' and H-4').

5.2.2.5 3-Cyclohexyl-4-methyl-3*H*-thiazole-2-thione (210g)



Procedure A was followed using cyclohexylamine (**204g**) (1.14 cm^3, 10.00 mmol) with NaOH solution (20 M, 500 µL, 10.00 mmol), carbon disulfide (600 µL, 10.00 mmol) and chloroacetone (800 µL, 10.00 mmol) in DMSO (5.00 cm^3). The precipitate was dissolved in ethanol (10 cm^3) and HCl (32% (*v/v*), 550 µL) was added. Upon cooling a precipitate formed and filtration gave a cream solid. Recrystallisation from hot ethanol gave pure **210g** (1.98 g, 93%) as a white solid, m.p. 97-98 °C, lit.,[368] 98-99 °C.

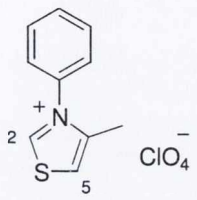
δ_H (400 MHz, DMSO-d_6): 1.33-1.40 (m, 3H, alk), 1.65-1.96 (m, 7H, alk), 2.25-2.33 (m, 1H, H-1'), 2.26 (s, 3H, CH_3), 6.68 (s, 1H, H-5).

5.2.2.6 Procedure B: General procedure for preparation of thiazolium salts from thiazole-2-thiones

The relevant thiazole-2-thione (1.50 mmol) was placed in a 50 cm^3 round bottomed flask and acetic acid (10 cm^3) was added. Hydrogen peroxide (27.5% (*v/v*), 430 µL, 4.95 mmol) was charged to the reaction vessel and the reaction was stirred at room temperature for 45 min. Toluene was added to the reaction to form an azeotrope and the solvent was removed under reduced pressure. The remaining residue was dissolved in methanol (810 µL). To the reaction mixture was added a solution of sodium perchlorate (758 mg, 6.19 mmol) in a mixture of methanol and water (2:1 (*v/v*), 4.00 cm^3). The

reaction mixture was stirred at 0 °C for 1 h, with resultant formation of a precipitate. Filtration of the precipitate provided the crude product and recrystallisation from hot methanol gave the pure thiazolium salt.

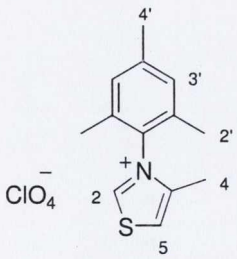
5.2.2.7 4-Methyl-3-phenyl-thiazol-3-ium perchlorate (211a)



Procedure B was followed using thiazole-2-thione **210a** (311 mg, 1.50 mmol), H_2O_2 (27.5% (*v*/*v*), 430 µL, 4.95 mmol), methanol (810 µL) and a solution of $NaClO_4$ (758 mg, 6.19 mmol) in a mixture of methanol and water (2:1 (*v*/*v*), 4.00 cm^3). Recrystallisation from hot methanol yielded pure **211a** (129 mg, 31%) as dark brown crystals, m.p. 189-190 °C, lit.,[15] 189-190 °C.

δ_H (400 MHz, DMSO-d_6): 2.33 (s, 3H, CH_3), 7.71-7.76 (m, 5H, Ar), 8.20 (s, 1H, H-5), 10.40 (s, 1H, H-2).

5.2.2.8 4-Methyl-3-(2,4,6-tri-methyl-phenyl)-thiazol-3-ium perchlorate (211b)



Procedure B was followed using thiazole-2-thione **210b** (1.21 g, 4.87 mmol), H_2O_2 (27.5% (*v*/*v*), 1.47 cm^3, 15.46 mmol), methanol (3.40 cm^3) and a solution of $NaClO_4$ (2.46 g, 20.07 mmol) in a mixture of methanol and water (2:1 (*v*/*v*), 16.7 cm^3). Recrystallisation from hot methanol gave pure **211b** (1.50 g, 97%) as off-white crystals, m.p. 170-171 °C. No melting point is available but all spectra are consistent with literature data.[365]

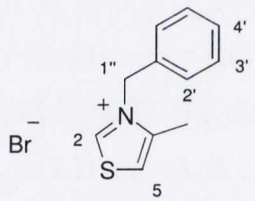
δ_H (400 MHz, DMSO-d_6): 1.92 (s, 6H, CH_3-2'), 2.18 (s, 3H, CH_3-4'), 2.37 (s, 3H, CH_3-4), 7.23 (s, 2H, H-3'), 8.36 (s, 1H, H-5), 10.42 (s, 1H, H-2)

δ_C (100 MHz, DMSO-d_6): 12.5, 16.7, 20.6, 123.2, 129.7, 132.4(q), 133.8(q), 141.1(q), 145.7(q), 161.2

ν_{max} (neat)/cm^{-1}: 3086, 1639, 1605, 1564, 1481, 1436, 1228 (C-N-C), 914, 870, 830

HRMS (*m/z* - ES): Found: 218.1005 (M^+ - ClO_4. $C_{13}H_{16}NS$ requires 218.1003).

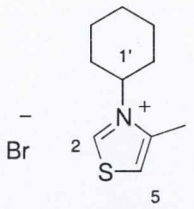
5.2.2.9 3-Benzyl-4-methyl-thiazol-3-ium bromide (211f)



Procedure B was followed using thiazole-2-thione **210f** (332 mg, 1.50 mmol), H_2O_2 (27.5% (*v/v*), 430 µL, 4.95 mmol), methanol (810 µL) and a solution of $NaClO_4$ (758 mg, 6.19 mmol) in a mixture of methanol and water (2:1 (*v/v*), 4.00 cm^3). Recrystallisation from hot methanol yielded pure **211f** (263 mg, 65%) as pale yellow crystals, m.p. 188-189 °C, lit.,[369] 188-189 °C.

δ_H (400 MHz, DMSO-d_6): 2.43 (s, 3H, CH_3), 5.77 (s, 2H, H-1''), 7.32 (d, 2H, J 7.4, H-2'), 7.41-7.49 (m, 3H, H-3' and H-4'), 8.07 (s, 1H, H-5), 10.18 (s, 1H, H-2).

5.2.2.10 3-Cyclohexyl-4-methyl-thiazol-3-ium bromide (211g)



Procedure B was followed using thiazole-2-thione **210g** (320 mg, 1.50 mmol), H_2O_2 (27.5% (*v*/*v*), 430 μL, 4.95 mmol), methanol (810 μL) and a solution of $NaClO_4$ (758 mg, 6.19 mmol) in a mixture of methanol and water (2:1 (*v*/*v*), 4.00 cm^3). Recrystallisation from hot methanol yielded pure **211g** (165 mg, 42%) as pale yellow crystals, m.p. 168-170 °C.

δ_H (400 MHz, DMSO-d_6): 1.20-1.30 (m, 1H, alk), 1.43-1.53 (m, 2H, alk), 1.68-1.89 (m, 6H, alk), 2.09-2.12 (m, 1H, alk), 2.61 (s, 3H, CH_3), 4.46-4.54 (m, 1H, H-1'), 8.06 (s, 1H, H-5), 10.25 (s, 1H, H-2)

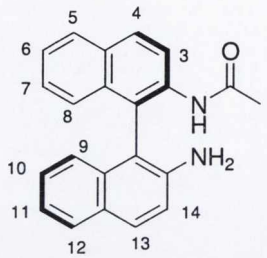
δ_C (100 MHz, DMSO-d_6): 12.9, 24.3, 24.7(2C), 32.5(2C), 61.8, 121.6, 146.0(q), 156.9. Note: 2 CH_2 signals coalescing at 24.7 and also at 32.5 ppm.

ν_{max} (nujol)/cm^{-1}: 3459, 2922, 1660 (C=N), 1574, 1457, 1378, 928, 880, 722

HRMS (*m*/*z* - ES): Found: 182.1000 (M^+ - Br. $C_{10}H_{16}NS$ requires 182.1003).

5.2.3 Experimental data for Section 2.3

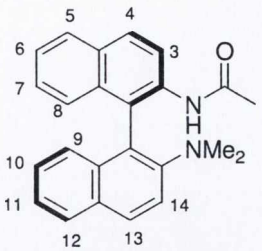
5.2.3.1 (*R*)-(+)-*N*-acetyl-1,1'-binaphthyl-2,2'-diamine (215)



A 100 cm^3 round bottomed flask containing a stirring bar was charged with (*R*)-(+)-binaphthyl-diamine (**212**) (1.00 g, 3.52 mmol) and the reaction vessel was placed under an atmosphere of Argon (balloon). CH_2Cl_2 (35 cm^3) was added *via* syringe followed by addition of acetic acid (2.11 cm^3, 35.17 mmol) and the resulting solution was cooled to 0 °C. Acetic anhydride (365 μL, 3.87 mmol) was added drop wise *via* syringe and the reaction was left to warm to room temperature overnight. The resulting clear colourless solution was brought to pH 9 using NaOH solution (2.0 M) and was extracted with CH_2Cl_2 (3 x 15 cm^3). The organic layers were combined and dried over $MgSO_4$ and concentrated providing the crude product as an off-white solid. Purification by column chromatography (2:1 hexane-EtOAc, R_f 0.2) gave (*R*)-**215** (862 mg, 75%) as a white solid, m.p. 241-242 °C, lit.,[370] 240-241 °C.

δ_H (600 MHz, DMSO-d_6): 1.81 (s, 3H, CH_3), 4.71 (s (broad), 2H, NH_2), 6.64 (d, 1H, J 8.3, H-9), 7.00 (d, 1H, J 8.7, H-8), 7.09-7.11 (app. t, 1H, H-10), 7.13-7.15 (app. t, 1H, H-11), 7.23 (d, 1H, J 8.7 H-14), 7.26-7.28 (app. t, 1H, H-7), 7.43-7.46 (app. t, 1H, H-6), 7.78 (d, 1H, J 7.9, H-12), 7.81 (d, 1H, J 8.7, H-13), 7.98 (d, 1H, J 7.9, H-5), 8.02 (d, 1H, J 8.3, H-4), 8.08 (d, 1H, J 8.3, H-3), 8.50 (s, 1H, N-H).

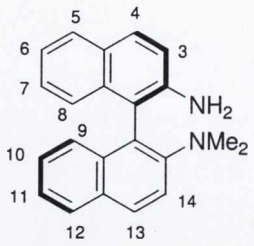
5.2.3.2 (*R*)-(+)-*N*-acetyl-*N'*, *N'*,-dimethyl-1,1'-binaphthyl-2,2'-diamine (218)



A 250 cm^3 round bottom flask was charged with H_2SO_4 (20%, 2.15 cm^3) and THF (43 cm^3). The solution was cooled to 0 °C and formalin (40%, 2.15 cm^3, 25.74 mmol) was added *via* syringe. A solution of amine (*R*)-**215** (700 mg, 2.15 mmol) dissolved in THF (43 cm^3) was added slowly to the reaction while concurrently adding $NaBH_4$ (571 mg, 15.01 mmol). The reaction was stirred at 0 °C for 1.25 h. The pH was raised to 7 using NaOH solution (2.0 M) and the reaction was concentrated under reduced pressure to *ca.* 20 cm^3. The resulting solution was extracted with CH_2Cl_2 (3 x 10 cm^3) and the organic layers were combined and dried over $MgSO_4$. Filtration followed by removal of solvent *in vacuo* gave a yellow solid. Purification by column chromatography (3:2 hexane-EtOAc, R_f 0.4) gave (*R*)-**218** (465 mg, 61%) as a pale yellow solid, m.p. 191-192 °C, lit.,[370] 189-191 °C.

δ_H (400 MHz, $CDCl_3$): 1.89 (s, 3H, CH_3), 2.60 (s, 6H, $2CH_3$), 6.95 (d, 1H, J 8.5 H-9), 7.13 (d, 1H, J 7.5, H-8), 7.17-7.21 (app. t, 1H, H-11), 7.23-7.27 (app. t, 1H, H-7), 7.34-7.47 (app. t, 1H, H-10), 7.40-7.44 (app. t, 1H, H-6), 7.52-7.54 (app. d, 2H, H-13 and H-14), 7.87 (d, 1H, J 8.0, H-12), 7.91 (d, 1H, J 8.5, H-5), 7.99-8.01 (m, 2H, H-3 and N-H), 8.48 (d, 1H, J 9.0, H-4).

5.2.3.3 (*R*)-(+)-*N*, *N*-dimethyl-1,1'-binaphthyl-2,2'-diamine (216)



To a 100 cm^3 round bottom flask containing (*R*)-**218** (461 mg, 1.30 mmol) was added a mixture of ethanol (38 cm^3) and HCl solution (4.0 M, 13.8 cm^3, 55.20 mmol). The resulting clear solution was heated at reflux (80 °C) for 12 h and the reaction was cooled to ambient temperature. Ethanol was removed under reduced pressure and the resulting solution was washed with CH_2Cl_2 (3 x 10 cm^3). The organic layers were combined, dried over $MgSO_4$ and filtered. Removal of solvent *in vacuo* gave crude product as an off-white solid. Purification by column chromatography (2:1 hexane-EtOAc, R_f 0.6) gave (*R*)-**216** (378 mg, 93%) as a white solid, m.p. 116-117 °C, lit.,[370] 116-118 °C.

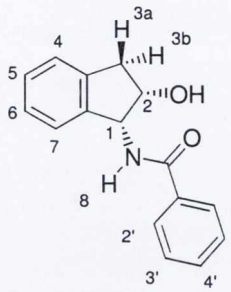
δ_H (400 MHz, $CDCl_3$): 2.66 (s, 6H, $2CH_3$), 4.06 (s (broad), 2H, NH_2), 7.01 (d, 1H, J 8.5, H-9), 7.14-7.26 (m, 5H, H-3, H-4, H-6, H-7 and H-11), 7.33-7.37 (app. t, 1H, H-10), 7.62 (d, 1H, J 7.5, H-12), 7.80-7.87 (m, 3H, H-8, H-13 and H-14), 7.94 (d, 1H, J 9.0, H-5).

5.2.3.4 Procedure C: General procedure for acylation of amino indanol substrates (amide formation)

An oven-dried 50 cm^3 round bottomed flask containing a stirring bar was charged with the relevant amine (6.56 mmol). The flask was fitted with a septum seal and placed under an Argon atmosphere (balloon). Dry CH_2Cl_2 (14 cm^3) was added *via* syringe and the resulting solution cooled to 0 °C. Triethylamine (2.74 cm^3, 19.67 mmol) was charged to the reaction and the reaction was stirred at 0 °C for 20 min. A solution of benzoyl chloride (800 μL, 6.89 mmol) in CH_2Cl_2 (7.9 cm^3) was added drop wise over 2.5 h using a pressure equalising dropping funnel while stirring at 0 °C. The reaction was left to warm to room temperature overnight. The pH was raised to *ca.* 12 using

NaOH solution (2.0 M). The resulting solution was washed with CH_2Cl_2 (3 x 10 cm^3) and the organic layers combined and dried over $MgSO_4$. Removal of solvent under reduced pressure and purification of the crude product by column chromatography gave the pure amide product.

5.2.3.5 (1*R*,2*S*)-*cis*-*N*-(2-Hydroxy-indan-1-yl)benzamide (223)



Procedure C was followed using (1*R*,2*S*)-*cis*-1-amino-2-indanol (**222**) (979 mg, 6.56 mmol), CH_2Cl_2 (14 cm^3), triethylamine (2.74 cm^3, 19.67 mmol) and a solution of benzoyl chloride (800 μL, 6.89 mmol) in CH_2Cl_2 (7.90 cm^3). Removal of solvent *in vacuo* gave a white solid. Purification by column chromatography (8:1 CH_2Cl_2-EtOAc, R_f = 0.4) gave (1*R*,2*S*)-**223** (1.41 g, 85%) as a white solid, m.p. 155-156 °C, lit.,[371] 155-156 °C; $[\alpha]_D^{20}$ = -32.2 (*c* 1.00 in $CHCl_3$).

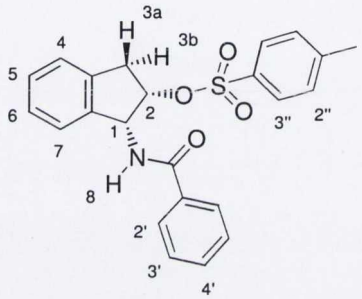
δ_H (400 MHz, $CDCl_3$): 2.18 (s, 1H, OH), 3.01 (dd, 1H, J 16.4, 2.0, H-3a), 3.27 (dd, 1H, J 16.4, 5.3, H-3b), 4.79-4.80 (app. t, 1H, H-2), 5.63 (dd, 1H, J 8.0, 5.3, H-1), 6.85 (d, 1H, J 8.0, H-8), 7.29-7.32 (m, 3H, H-4 to H-6), 7.38 (d, 1H, J 6.5, H-7), 7.48-7.50 (app. t, 2H, H-3'), 7.54 (t, 1H, J 7.5, H-4'), 7.87 (d, 2H, J 7.0, H-2').

5.2.3.6 Procedure D: General procedure for tosylation of alcohols

To a 50 cm^3 round bottomed flask, equipped with a magnetic stirring bar, was added the relevant alcohol (2.86 mmol). A septum seal was fitted and the reaction was placed under an atmosphere of Argon (balloon) and charged with CH_2Cl_2 (12 cm^3). The reaction was cooled to 0 °C and triethylamine (796 μL, 5.72 mmol), tosyl chloride (545

mg, 2.86 mmol) and 4-dimethylaminopyridine (35 mg, 0.29 mmol) were added sequentially. The mixture was warmed to ambient temperature and stirred for 24 h. The resulting solution was diluted with CH_2Cl_2 (20 cm^3) and washed with HCl (5% (*v/v*), 10 cm^3), $NaHCO_3$ (5% (*w/v*), 10 cm^3) and brine (10 cm^3). The organic extract was then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography provided the pure tosylated product.

5.2.3.7 (1*R*,2*S*)-Toluene-4-sulphonic acid-1-benzoyl-amino-indan-2-yl ester (224)



Procedure D was followed using amino indanol substrate (1*R*,2*S*)-**223** (724 mg, 2.86 mmol), CH_2Cl_2 (12 cm^3), triethylamine (796 μL, 5.72 mmol), tosyl chloride (545 mg, 2.86 mmol) and 4-dimethylaminopyridine (35 mg, 0.29 mmol). Purification of the organic extract (white solid) by column chromatography (CH_2Cl_2, R_f = 0.3) gave (1*R*,2*S*)-**224** (1.03 g, 85%) as a white solid, m.p. 193-194 °C; $[\alpha]_D^{20}$ = -80.4 (*c* 1.00 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.36 (s, 3H, CH_3), 3.27 (d, 2H, J 2.0, H-3a and H-3b), 5.41-5.44 (m, 1H, H-2), 5.85 (dd, 1H, J 9.0, 4.5, H-1), 6.55 (d, 1H, J 9.0, H-8), 7.14 (d, 2H, J 8.0, H-3''), 7.26-7.33 (m, 4H, H-4 to H-7), 7.46-7.50 (app. t, 2H, H-3'), 7.56 (t, 1H, J 7.3, H-4'), 7.70 (d, 2H, J 8.0, H-2''), 7.74 (d, 2H, J 7.0, H-2')

δ_C (100 MHz, $CDCl_3$): 21.2, 37.8, 55.9, 83.6, 123.0, 124.8, 126.7, 127.1, 127.2, 128.1(2C), 129.5, 131.5, 133.0(q), 133.1(q), 138.0(q),

139.1(q), 144.5(q), 166.7(q), (C=O). Note 2C resonances coalescing at 128.1 ppm.

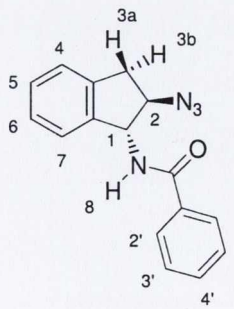
ν_{max} (nujol)/cm^{-1}: 3311 (N-H), 2922, 2726, 1639 (C=O), 1463, 1377, 1340, 1181, 926, 818, 729

HRMS (*m/z* -ES): Found: 430.1089 (M^+ + Na. $C_{23}H_{21}NO_4SNa$ requires 430.1900).

5.2.3.8 Procedure E: General procedure for the formation of azides from tosylated alcohols

The relevant toluene sulphonic acid derivative (3.68 mmol) was placed in a 100 cm^3 round bottomed flask containing a stirring bar and DMF (37 cm^3) was added. Sodium azide (256 mg, 3.94 mmol) was added and the reaction was sealed with a septum and put under an atmosphere of Argon (balloon). The solution was heated at 60 °C for 22 h. The resulting clear solution was cooled to room temperature and EtOAc (30 cm^3) was added. The reaction was extracted with ice-cold water (3 x 100 cm^3) and finally with ice-cold brine (100 cm^3). The organic solvent was dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude azide. Purification by column chromatography provided the pure azide product.

5.2.3.9 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-benzamide (225)



Procedure E was followed using (1*R*,2*S*)-**224** (1.50 g, 3.68 mmol), DMF (37 cm^3) and sodium azide (256 mg, 3.94 mmol). Purification by column chromatography (7:3

CH_2Cl_2-hexane, R_f 0.2) yielded (1*R*,2*R*)-**225** (983 mg, 96%) as a white solid, m.p. 170-171 °C; $[\alpha]_D^{20} = -28.8$ (*c* 0.94 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.97 (dd, 1H, J 16.1, 6.5, H-3b), 3.35 (dd, 1H, J 16.1, 7.3, H-3a), 4.22-4.27 (m, 1H, H-2), 5.63 (dd, 1H, J 8.0, 6.0, H-1), 6.43 (d, 1H, J 8.0, H-8), 7.28-7.36 (m, 4H, H-4 to H-7), 7.45-7.49 (app. t, 2H, H-3'), 7.54 (t, 1H, J 7.4, H-4'), 7.83 (d, 2H, J 7.4, H-2')

δ_C (100 MHz, $CDCl_3$): 36.3, 60.3, 68.1, 124.3, 125.1, 127.1, 127.8, 128.7, 129.0, 131.9, 133.9(q), 139.7(q), 139.8(q), 167.5(q), (C=O)

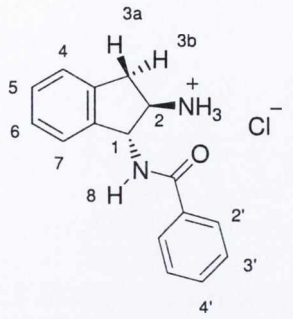
ν_{max} (neat)/cm^{-1}: 3262, 3070, 2911, 2099 (N_3), 1638 (C=O), 1526, 1342, 743

HRMS (*m/z* - ES): Found 301.1065 (M^+ + Na. $C_{16}H_{14}N_4ONa$ requires 301.1071).

5.2.3.10 Procedure F: General procedure for Staudinger reduction of amino indanol-containing azides

To a 50 cm^3 round bottomed flask, equipped with a stirring bar, was added the relevant azide (3.83 mmol) and triphenylphosphine (1.01 g, 3.83 mmol). The reaction was placed under an atmosphere of Argon and THF (32 cm^3) was added *via* syringe. The resulting clear colourless solution was stirred at 45 °C for 14.5 h. Deionised water (8.00 cm^3) was added and the reaction was stirred at 45 °C for an additional 24 h. The solvent was removed under reduced pressure to give a yellow oil. This was dissolved in CH_2Cl_2 (40 cm^3) and HCl solution (3.0 M, 160 cm^3) was added, forming a white solid which dissolved slowly into the aqueous layer. The aqueous layer was separated and washed with CH_2Cl_2 (4 x 25 cm^3). Concentration of the aqueous layer *in vacuo* gave a solid and recrystallisation from hot methanol produced the pure hydrochloride salt.

5.2.3.11 (1*R*,2*R*)-*trans*-1-Benzoylamino-indan-2-yl ammonium hydrochloride (226)



Procedure F was followed using amino indanol-derived azide (1*R*,2*R*)-**225** (1.07 g, 3.83 mmol), triphenylphosphine (1.01 g, 3.83 mmol) and THF (32 cm^3). Recrystallisation from hot methanol produced the hydrochloride salt (1*R*,2*R*)-**226** (1.02 g, 92%) as a white solid, m.p. 285-287 °C; $[\alpha]_D^{20}$ = -19.8 (*c* 0.88 in MeOH).

δ_H (400 MHz, DMSO-d_6): 3.00 (dd, 1H, J 15.7, 8.8, H-3a), 3.36 (dd, 1H, J 15.7, 7.7, H-3b), 3.96 (ddd, 1H, J 8.8, 7.7, 7.7, H-2), 5.70 (dd, 1H, J 8.8, 7.7, H-1), 7.20 (d, 1H, J 7.7, H-7), 7.26-7.33 (m, 3H, H-4 to H-6), 7.51-7.53 (app. t, 2H, H-3'), 7.57 (t, 1H, J 7.2, H-4'), 7.98 (d, 2H, J 7.8, H-2'), 8.55, (s (broad), 3H, NH_3), 9.01 (d, 1H, J 8.8, H-8)

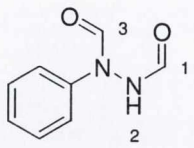
δ_C (100 MHz, DMSO-d_6): 34.6, 56.4, 57.6, 123.7, 124.8, 127.4, 127.6, 128.2, 128.3, 131.5, 134.0(q), 138.4(q), 141.0(q), 166.9(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3323 (N-H), 2860 (NH_3^+), 2768, 1636 (C=O), 1526, 1492, 748, 731, 694

HRMS (*m/z* - ES): Found 253.1345 (M^+ - Cl. $C_{16}H_{17}N_2O$ requires 253.1341).

5.2.4 Experimental data for Section 2.4

5.2.4.1 *N,N'*-Diformyl-*N*-phenylhydrazine (230)



To a 25 cm^3 round bottomed flask, equipped with a magnetic stirring bar, was added phenyl hydrazine (**229**) (2.00 cm^3, 20.33 mmol). The reaction was cooled to 0 °C and treated with formic acid (2.20 cm^3, 57.32 mmol) turning the solution a crimson colour. The reaction was fitted with a reflux condenser and heated at reflux (80 °C) for 8 h and left to cool to room temperature overnight. The resulting mixture was triturated with ether and filtered to give a cream solid. Recrystallisation from hot ethanol gave **230** (1.97 g, 59%) as an off-white crystalline solid, m.p. 125-126 °C, lit.,[372] 125-126 °C. No reference spectroscopic data was available for this compound. The ^1H and ^{13}C NMR spectra of this compound indicate the presence of 4 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.05:0.10:0.35:0.50.

δ_H (600 MHz DMSO-d_6): 7.22-7.52 (m, 5H, Ar), 8.13 (d, 0.10H, J 8.3, H-1), 8.28 (s, 0.50H, H-3), 8.29 (s, 0.35H, H-3), 8.37-8.39 (m, 0.05H and 0.35H, H-1), 8.53 (s, 0.05H, H-3), 8.80 (s, 0.50H, H-1), 8.93 (s, 0.10H, H-3), 10.27 (d, 0.10H, J 8.2, H-2), 10.69-10.76 (m, 0.05H and 0.50H, H-2), 11.07 (s, 0.35H, H-2)

δ_C (150 MHz DMSO-d_6): 119.6, 120.1, 121.0, 121.4, 125.9, 126.0, 126.1, 126.3, 128.9, 129.1, 129.5, 129.6, 139.3(q), 139.4(q), 140.2(q), 140.5(q), 159.5, 159.9, 161.4, 161.6, 163.8, 164.1, 167.1, 167.2

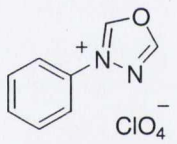
ν_{max} (neat)/cm^{-1}: 3161, 2929, 1658 (C=O), 1590, 1346, 753, 691

HRMS (*m/z* - ES): Found: 187.0485 (M^+ + Na. $C_8H_8N_2O_2Na$ requires 187.0483).

5.2.4.2 Procedure G: General procedure for the synthesis of oxadiazolium salts 231 and 238

To an oven-dried 50 cm^3 round bottomed flask equipped with a magnetic stirring bar was added the relevant phenyl hydrazide (13.29 mmol). The flask was placed under an atmosphere of Argon and cooled to 0 °C. Acetic anhydride (10.90 cm^3) was added *via* syringe and perchloric acid (70% (*v*/*v*), 1.09 cm^3, 7.58 mmol) was added drop wise to the reaction over 15 min. The reaction was stirred at ambient temperature for 30 min during which a precipitate formed. The reaction was triturated with ether and the solid was filtered under a stream of Argon to give the crude oxadiazolium salt. Note: these salts were too unstable to be characterised fully using NMR spectroscopy; product reverted back to starting material *via* hydrolysis (caused by water present in DMSO solvent), and were therefore used without further purification.

5.2.4.3 3-Phenyl-[1,3,4]oxadiazol-3-ium perchlorate (231)



Procedure G was followed using *N*,*N*'-diformyl-*N*-phenylhydrazine (**230**) (2.18 g, 13.29 mmol), acetic anhydride (10.90 cm^3) and perchloric acid (70% (*v*/*v*), 1.09 cm^3, 7.58 mmol). Vacuum filtration of the precipitate under a stream of Ar gave crude **231** (2.75 g, 84%) as a white solid, m.p. 135-136 °C (dec.), lit.,[373] 135-136 °C (dec).

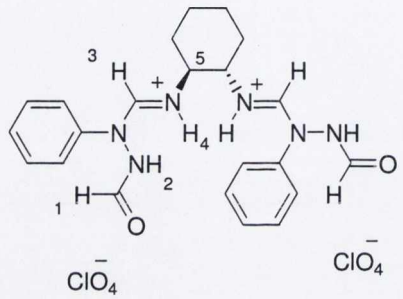
ν_{max} (neat)/cm^{-1}: 3066, 1691 (C=N), 1328, 1058 (C-O-C), 767, 684.

5.2.4.4 Procedure H: General procedure for the preparation of hydrazino intermediates; precursors to achiral triazolium salts

To an oven-dried 10 cm^3 round bottomed flask, equipped with a small magnetic stirring bar and oven-dried molecular sieves (4Å, 100 mg), was added the relevant oxadiazolium salt (0.75 mmol) and the reaction was put under an atmosphere of Ar. A solution of the required amine (0.37 mmol) in CH_3CN (1.80 cm^3) was added *via* syringe. (Note:

exothermic reaction.) The resulting solution slowly formed a white precipitate. The reaction was stirred at ambient temperature for 2 h after which ether was added to the reaction to encourage further formation of the precipitate. Filtration of the precipitate under a stream of Ar gave the desired pure hydrazino-product.

5.2.4.5 Cyclohexyl-1,2-(*N'*, *N'*-diformyl-*N*-phenyl-hydrazinomethylene) ammonium; perchlorate (232a)



Procedure H was followed using oxadiazolium salt **231** (183 mg, 0.75 mmol), oven-dried molecular sieves (4Å, 100 mg) and a solution of *trans*-1,2-diamine-cyclohexane (**219**) (45 μL, 0.37 mmol) in CH_3CN (1.80 cm^3). Filtration of the reaction under a stream of Ar furnished pure **232a** (49 mg, 22%) as a pale orange solid, m.p. 197-198 °C.

δ_H (400 MHz, DMSO-d_6): 1.23-1.34 (m, 2H, alk), 1.50-1.62 (m, 2H, alk), 1.78-1.87 (m, 2H, alk), 2.03-2.13 (m, 2H, alk), 3.78-3.86 (m, 2H, H-5), 7.43-7.58 (m, 10H, Ar), 8.35 (s, 2H, H-1), 8.91 (d, 2H, J 9.0, H-3), 10.26-1.30 (m, 2H, H-4), 11.74 (s, 2H, H-2)

δ_C (100 MHz, DMSO-d_6): 23.7, 31.7, 60.2, 120.0, 128.3, 129.8, 130.4, 154.2(q), 159.6 (C=O)

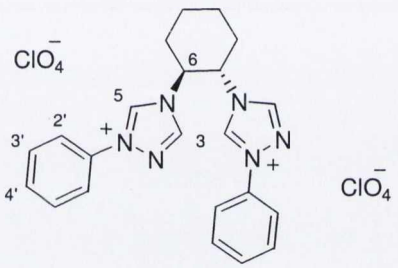
ν_{max} (neat)/cm^{-1}: 3231 (N-H), 3027, 2998, 2937, 2907, 1719 (C=O), 1681 (C=N), 1370, 750, 687

HRMS (*m/z* - ES): Found 408.2280 (M^{2+} -2ClO_4. $C_{22}H_{28}N_6O_2$ requires 408.2274).

5.2.4.6 Procedure I: General procedure for synthesis of achiral triazolium salts from hydrazino-intermediates

To a 10 cm^3 round bottomed flask, equipped with a magnetic stirring bar and oven-dried molecular sieves (4Å, 100 mg), was added the relevant hydrazino-intermediate (0.08 mmol) and the reaction was put under an atmosphere of Argon. CH_3CN (800 μL) was added *via* syringe. The flask was fitted with a reflux condenser and heated at reflux (90 °C) for 4 d under an atmosphere of Ar. The crude reaction was filtered under a stream of Ar to remove the molecular sieves. Removal of the solvent under reduced pressure gave the crude product. Recrystallisation from hot CH_3CN provided the pure triazolium salt.

5.2.4.7 Cyclohexyl-1,2-di-(1-phenyl-4*H*-[1,2,4]triazol-1-ium) perchlorate (233a)



Procedure I was followed using oven-dried molecular sieves (4Å, 100 mg), hydrazino-intermediate **232a** (50 mg, 0.08 mmol) and CH_3CN (800 μL). Recrystallisation from hot CH_3CN yielded **233a** (13 mg, 27%) as off-white fine needles, m.p. 209-210 °C.

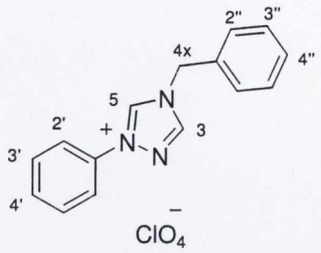
δ_H (400 MHz, DMSO-d_6): 1.51-1.59 (m, 4H, alk), 1.99-2.05 (m, 2H, alk), 2.21-2.28 (m, 2H, alk), 5.11-5.13 (m, 2H, H-6), 7.64 (t, 2H, J 7.3, H-4'), 7.72-7.76 (app. t, 4H, H-3'), 7.91 (d, 4H, J 8.0, H-2'), 9.46 (s, 2H, H-3), 11.01 (s, 2H, H-5)

δ_C (100 MHz, DMSO-d_6): 23.5, 31.8, 60.9, 120.5, 130.2, 130.8, 134.9(q), 141.0, 144.1

ν_{max} (neat)/cm^{-1}: 3130, 3119, 2956, 2940, 2867, 1478, 1082 (C-N-C), 1061, 753, 746, 681

HRMS (*m/z* - ES): Found 372.2062 (M^{2+} -2ClO_4. $C_{22}H_{24}N_6$ requires 372.2062).

5.2.4.8 4-Benzyl-1-phenyl-4*H*-[1,2,4]triazol-1-ium; perchlorate (233b)



Procedure H was followed using oven-dried molecular sieves (4Å, 600 mg), oxadiazolium salt **231** (498 mg, 2.02 mmol) and a solution of benzylamine (**204f**) (220 µL, 2.02 mmol) in CH_3CN (4.80 cm^3). Filtration of the precipitate under a stream of Ar gave crude **232b** which contained a significant amount of cyclised triazolium salt **233b**. Purification of the hydrazino-intermediate was not performed and procedure I ensued using oven-dried molecular sieves (4Å, 600 mg), crude hydrazino-intermediate product and CH_3CN (20 cm^3). Recrystallisation of the off-white solid from hot CH_3CN gave pure **233b** (434 mg, 64%) as white crystals, m.p. 188-190 °C.

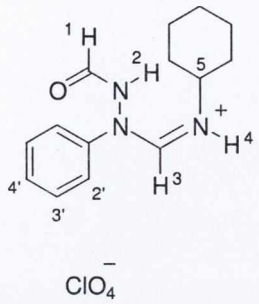
δ_H (400 MHz, DMSO-d_6): 5.59 (s, 2H, H-4x), 7.43-7.51 (m, 3H, H-3'' and H-4''), 7.56 (d, 2H, J 7.0, H-2''), 7.63 (t, 1H, J 7.0, H-4'), 7.69-7.73 (app. t, 2H, H-3'), 7.92 (d, 2H, J 8.0, H-2'), 9.53 (s, 1H, H-3), 10.97 (s, 1H, H-5)

δ_C (100 MHz, DMSO-d_6): 51.0, 120.8, 128.8, 129.0, 129.1, 130.1, 130.6, 133.3(q), 135.0(q), 141.8, 145.0

ν_{max} (neat)/cm^{-1}: 3133, 3073, 1569, 1487, 1452, 1404, 1076 (C-N-C), 1058, 761, 711, 699, 683, 666

HRMS (*m/z* - ES): Found 236.1180 (M^+ -ClO_4. $C_{15}H_{14}N_3$ requires 236.1188).

5.2.4.9 Cyclohexyl-(*N'*-formyl-*N*-phenyl-hydrazinomethylene)-ammonium; perchlorate (232c)



Procedure H was followed using oven-dried molecular sieves (4Å, 600 mg), oxadiazolium salt **231** (498 mg, 2.02 mmol) and a solution of cyclohexylamine (**204g**) (230 µL, 2.02 mmol) in CH_3CN (4.80 cm^3). Filtration of the precipitate under a stream of Ar gave pure **232c** (433 mg, 62%) as a white solid, m.p. 187-188 °C (dec.).

δ_H (400 MHz, DMSO-d_6): 1.09-1.15 (m, 1H, alk), 1.22-1.31 (m, 2H, alk), 1.40-1.49 (m, 2H, alk), 1.61-1.65 (app. d, 1H, alk), 1.78-1.81 (app. d, 2H, alk), 1.90-1.93 (app. d, 2H, alk), 3.63-3.70 (m, 1H, H-5), 7.39 (t, 1H, J 6.8, H-4'), 7.51-7.56 (m, 4H, H-2' and H-3'), 8.34 (s, 1H, H-1), 9.09 (d, 1H, J 13.6, H-3), 10.32 (dd, 1H, J 13.6, 7.8, H-4), 11.59 (s, 1H, H-2)

δ_C (100 MHz, DMSO-d_6): 24.5 (2C), 32.2, 57.7, 119.6, 127.7, 129.7, 140.1(q), 153.6, 159.9. 10C signals should be noted, 2C coalescing at 24.5ppm.

ν_{max} (neat)/cm^{-1}: 3237 (N-H), 2937, 2905, 1723 (C=O), 1683 (C=N), 1375, 761, 693

HRMS (*m/z* - ES): Found 246.1597 (M^+ -ClO_4. $C_{14}H_{20}N_3O$ requires 246.1606).

5.2.4.10 4-Cyclohexyl-1-phenyl-4*H*-[1,2,4]triazol-1-ium; perchlorate (233c)

Procedure I was followed using oven-dried molecular sieves (4Å, 600 mg), hydrazino intermediate **232c** (433 mg, 1.25 mmol) and CH_3CN (10 cm^3). Recrystallisation of the crude residue from hot CH_3CN gave pure **233c** (320 mg, 78%) as white crystals, m.p. 248-250 °C.

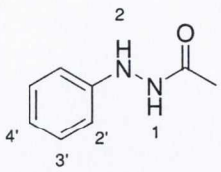
δ_H (400 MHz, DMSO-d_6): 1.09-1.19 (m, 1H, alk), 1.30-1.40 (m, 2H, alk), 1.60-1.82 (m, 5H, alk), 2.15-2.18 (app. d, 2H, alk), 4.32-4.39 (m, 1H, H-6), 7.53 (t, 1H, J 7.1, H-4'), 7.61-7.65 (m, 2H, H-3'), 7.85 (d, 2H, J 8.0, H-2'), 9.47 (s, 1H, H-3), 10.79 (s, 1H, H-5)

δ_C (100 MHz, DMSO-d_6): 24.2, 24.4, 32.0, 58.4, 120.7, 130.1, 130.5, 135.1(q), 140.5, 143.9

ν_{max} (neat)/cm^{-1}: 3125, 2940, 2860, 1486, 1092 (C-N-C), 1064, 761, 685

HRMS (*m/z* - ES): Found 228.1510 (M^+ -ClO_4. $C_{14}H_{18}N_3$ requires 228.1501).

5.2.4.11 Acetic Acid *N*-phenyl-hydrazide (235)



To a 100 cm^3 reaction vessel, equipped with a magnetic stirring bar, was added phenyl hydrazine (**229**) (3.00 cm^3, 30.49 mmol) and the flask was placed under an atmosphere of Ar. CH_2Cl_2 (20 cm^3) was charged to the reaction and the flask was cooled to 0 °C. Triethylamine (2.60 cm^3, 18.29 mmol) was added *via* syringe. After 15 min of stirring at 0 °C the vessel was equipped with an oven-dried 100 cm^3 pressure equalising dropping funnel and the reaction returned to an atmosphere of Ar. A solution of acetic anhydride (1.50 cm^3, 16.16 mmol) in CH_2Cl_2 (35 cm^3) was charged to the dropping funnel. The solution was added to the reaction drop wise at 0 °C over 8 h and left to equilibrate to ambient temperature overnight. NaOH solution (2.0 M, 25 cm^3) was added until the pH of the aqueous layer was 12. The organic layer was separated and the aqueous phase was washed further with CH_2Cl_2 (4 x 25 cm^3). The organic extracts were combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (1:1 EtOAc-hexane, R_f 0.2) gave **235** (2.36 g, 97%) as an off-white solid, m.p. 121-122 °C. No reference spectroscopic data was available for this compound. The ^1H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.12:0.88.

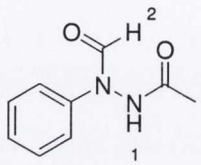
δ_H (600 MHz, DMSO-d_6): 1.86 (s, 0.36H, CH_3), 1.90 (s, 2.64H, CH_3), 6.70-6.71 (m, 2.64H, H-2' and H-4'), 6.74-6.77 (app. t, 0.36H, H-2' and H-4'), 7.12-7.15 (app. t, 1.76H, H-3'), 7.18-7.21 (app. t, 0.24H, H-3'), 7.63 (d, 0.88H, J 2.3, H-2), 7.95 (app. s, 0.12H, H-2), 8.91 (app. s, 0.12H, H-1), 9.59 (d, 0.88H, J 2.3, H-1)

δ_C (150 MHz, DMSO-d_6): 19.2, 20.7, 111.7, 112.1, 118.3, 118.8, 128.7, 129.0, 148.8(q), 149.3(q), 168.9(q), (C=O), 175.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3281, 3029, 1640 (C=O), 1594, 1372, 754, 691

HRMS (*m/z* - ES): Found 173.0697 (M^+ +Na. $C_8H_{10}N_2ONa$ requires 173.0691).

5.2.4.12 *N'*-Acetyl-*N*-formyl-*N*-phenylhydrazine (236)



To a 25 cm^3 round bottomed flask, equipped with a magnetic stirring bar, was added acetic acid *N*-phenyl-hydrazide (**235**) (2.30 g, 15.32 mmol). The reaction was cooled to 0 °C and treated with formic acid (1.63 cm^3, 43.20 mmol) turning the solution a crimson colour. The reaction was fitted with a reflux condenser and heated at 50 °C for 15 h and left to cool to room temperature overnight. The resulting mixture was triturated with ether and a precipitate formed. Filtration of the precipitate and subsequent washing with ether gave pure **236** (2.32 g, 85%) as a white solid, m.p. 83-85 °C, lit.,[372] 86-87 °C. No reference spectroscopic data was available for this compound. The ^{1}H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.40:0.60.

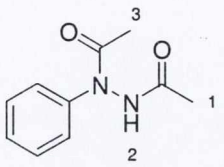
δ_H (600 MHz, DMSO-d_6): 2.00 (s, 1.80H, CH_3), 2.04 (s, 1.20H, CH_3), 7.20-7.50 (m, 5H, Ar), 8.27 (s, 0.40H, H-2), 8.80 (s, 0.60H, H-2), 10.52 (s, 0.60H, H-1), 10.95 (s, 0.40H, H-1)

δ_C (150 MHz, DMSO-d_6): 20.36, 20.41, 119.3, 120.7, 125.5, 125.6, 128.7, 129.3, 139.7(q), 140.9(q), 159.6, 164.1, 168.3(q), (C=O), 169.8(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3474, 3374 (N-H), 3172, 2968, 1692 (HC=O), 1660 (CH_3C=O), 1590, 763, 683

HRMS (*m/z* - ES): Found 201.0641 (M^+ +Na. $C_9H_{10}N_2O_2Na$ requires 201.0640).

5.2.4.13 *N,N'*-diacetyl-*N*-phenylhydrazine (237)



To a 10 cm^3 round bottomed flask, equipped with a small magnetic stirring bar, was added acetic acid *N*-phenyl-hydrazide (**235**) (653 mg, 4.35 mmol) and acetic anhydride (3.00 cm^3, 31.74 mmol). The suspension was placed under an atmosphere of Ar and heated to 50 °C for 14 h. The reaction was cooled to room temperature and a precipitate formed. Ether (1 cm^3) and hexane (1 cm^3) were added to encourage formation of the precipitate. Filtration of precipitate under a stream of Ar gave pure **237** (694 mg, 83%) as a white solid, m.p. 107-109 °C, lit.,[374] 107-108 °C. No reference spectroscopic data was available for this compound. The ^1H NMR spectrum of this compound indicates the presence of two rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.20:0.80. The ^{13}C spectrum indicates the major rotamer only.

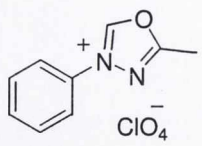
δ_H (600 MHz, DMSO-d_6): 1.98 (s, 3H, CH_3-1), 2.08 (s, 3H, CH_3-3), 7.20-7.45 (m, 5H, Ar), 10.39 (s, 0.20H, H-2), 10.88 (s, 0.80H, H-2)

δ_C (150 MHz, DMSO-d_6): 20.4, 21.6, 123.4, 125.7, 128.4, 141.5(q), 168.8(q), (C=O), 171.2(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3278, 3009, 1692 (C=O), 1667 (C=O), 1516, 1490, 1364, 1287, 759, 695

HRMS (*m/z* - ES): Found 215.0803 (M^+ +Na. $C_{10}H_{12}N_2O_2Na$ requires 215.0796).

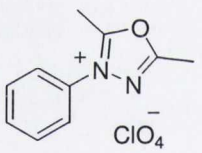
5.2.4.14 5-Methyl-3-phenyl-[1,3,4]oxadiazol-3-ium perchlorate (238a)



Procedure G was followed using *N*'-acetyl-*N*-formyl-*N*-phenylhydrazine (**236**) (930 mg, 5.22 mmol), acetic anhydride (4.30 cm^3) and perchloric acid (70% (*v*/*v*), 430 μL, 2.98 mmol). Filtration under a stream of Ar gave **238a** (1.20 g, 88%) as a white solid, m.p. 139-140 °C (dec), lit.,[339] 140-141 °C (dec). Note **238a** was too unstable to be characterised fully using NMR spectroscopy; product reverted back to starting material *via* hydrolysis due to water present in DMSO solvent.

ν_{max} (neat)/cm^{-1}: 3075, 2946, 1624 (C=N), 1068 (C-O-C), 768, 686.

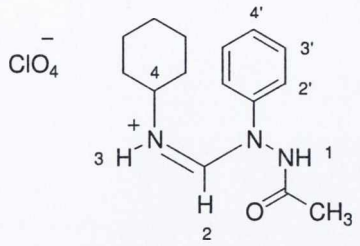
5.2.4.15 2,5-Dimethyl-3-phenyl-[1,3,4]oxadiazol-3-ium perchlorate (238b)



Procedure G was followed using *N*,*N*'-diacetyl-*N*-phenylhydrazine (**237**) (589 mg, 3.06 mmol), acetic anhydride (2.50 cm^3) and perchloric acid (70% (*v*/*v*), 250 μL, 1.75 mmol). Filtration under a stream of Ar gave **238b** (815 mg, 97%) as a white solid, m.p. 112-113 °C, lit.,[373] 113-114 °C, (dec). Note **238b** was too unstable to be characterised fully using NMR spectroscopy; product reverted back to starting material *via* hydrolysis due to water present in DMSO solvent.

ν_{max} (neat)/cm^{-1}: 2943, 1629 (C=N), 1375, 1303, 1219, 1083 (C-O-C), 781, 689.

5.2.4.16 (*N'*-Acetyl-*N*-phenyl-hydrazinomethylene)-cyclohexyl-ammonium; perchlorate (239a)



Procedure H was followed using oven-dried molecular sieves (4Å, 3.00 g), oxadiazolium salt **238a** (1.20 g, 4.62 mmol), cyclohexylamine (**204g**) (500 μL, 4.40 mmol) and CH_3CN (11 cm^3). Purification of the resulting product *via* filtration under a stream of Ar gave **239a** (1.27 g, 81%) as a white solid, m.p. 230-231 °C.

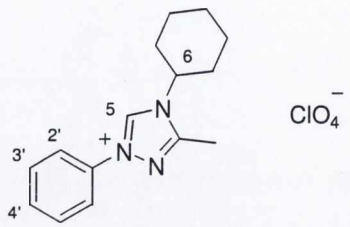
δ_H (400 MHz, DMSO-d_6): 1.06-1.16 (m, 1H, alk), 1.23-1.32 (m, 2H, alk), 1.41-1.51 (m, 2H, alk), 1.63-1.66 (app. d, 1H, alk), 1.80-1.83 (app. d, 2H, alk), 1.90-1.94 (m, 2H, alk), 2.09 (s, 3H, CH_3), 3.63-3.69 (m, 1H, H-4), 7.38 (t, 1H, J 7.0, H-4'), 7.47-7.55 (m, 4H, H-2' and H-3'), 9.05 (d, 1H, J 13.4, H-2), 10.24 (dd, 1H, J 13.4, 8.1, H-3), 11.43 (s, 1H, H-1)

δ_C (100 MHz, DMSO-d_6): 21.5, 24.97, 24.99, 32.7, 58.2, 120.0, 128.1, 130.1, 140.8(q), 154.3, 168.6(q) (C=O)

ν_{max} (neat)/cm^{-1}: 3235 (N-H), 2931, 2857, 1725 (C=O), 1686 (C=N), 1372, 762, 693

HRMS (*m/z* - ES): Found 260.1764 (M^+ -ClO_4. $C_{15}H_{22}N_3O$ requires 260.1763).

5.2.4.17 4-Cyclohexyl-3-methyl-1-phenyl-4*H*-[1,2,4]triazol-1-ium; perchlorate (240a)



Procedure I was followed using oven-dried molecular sieves (4Å, 6.30 g), hydrazino-intermediate **239a** (2.27 g, 6.31 mmol), CH_3CN (63 cm^3) and H_2SO_4 (2.40 cm^3, 44.16 mmol). Recrystallisation of the crude product from hot CH_3CN gave pure **240a** (1.36 g, 63%) as white crystals, m.p. 198-199 °C.

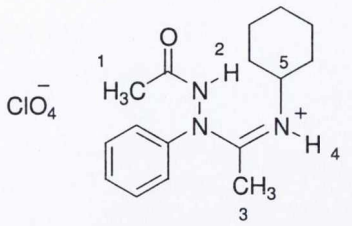
δ_H (400 MHz, DMSO-d_6): 1.18-1.29 (m, 1H, alk), 1.44-1.54 (m, 2H, alk), 1.72-1.82 (m, 3H, alk), 1.89-1.92 (app. d, 2H, alk), 2.19-2.22 (app. d, 2H, alk), 2.73 (s, 3H, CH_3), 4.36-4.44 (m, 1H, H-6), 7.61 (t, 1H, J 7.4, H-4'), 7.68-7.73 (app. t, 2H, H-3'), 7.94 (d, 2H, J 8.2, H-2'), 10.79 (s, 1H, H-5)

δ_C (100 MHz, DMSO-d_6): 10.6, 24.95, 25.0, 32.7, 57.5, 120.9, 130.5, 130.7, 135.5(q), 140.7, 153.7(q)

ν_{max} (neat)/cm^{-1}: 3132, 3101, 2949, 2928, 1584, 1470, 1074 (C-N-C), 766, 680

HRMS (*m/z* - ES): Found 242.1653 (M^+ -ClO_4. $C_{15}H_{20}N_3$ requires 242.1657).

5.2.4.18 [1-(Acetyl-*N*-hydrazino)-ethylidene]-cyclohexyl-ammonium; perchlorate (239b)



Procedure H was followed using oven-dried molecular sieves (4Å, 6.30 g), oxadiazolium salt **238b** (927 mg, 3.38 mmol), cyclohexylamine (**204g**) (390 µL, 3.39 mmol) and CH_3CN (8.50 cm^3). Purification of the resulting product *via* filtration under a stream of Ar gave pure **239b** (1.04 g, 82%) as a white solid, m.p. 202-203 °C.

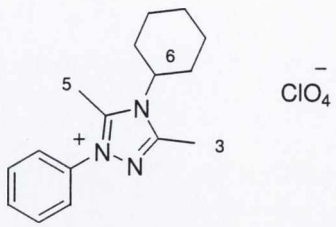
δ_H (600 MHz, DMSO-d_6): 1.10-1.12 (m, 1H, alk), 1.30-1.37 (m, 2H, alk), 1.51-1.53 (m, 2H, alk), 1.63-1.65 (app. d, 1H, alk), 1.77-1.79 (app. d, 2H, alk), 1.84-1.86 (m, 2H, alk), 1.96 (s, 3H, CH_3-1), 2.28 (s, 3H, CH_3-3), 3.67-3.72 (m, 1H, H-5), 7.47-7.57 (m, 5H, Ar), 9.35 (d, 1H, J 7.0, H-4), 11.18 (s, 1H, H-2)

δ_C (150 MHz, DMSO-d_6): 16.2, 21.6, 24.7, 24.9, 31.9, 55.1, 127.1, 130.2, 130.3, 140.7(q), 164.6(q), (C=N), 168.6(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3318 (N-H), 3295, 2934, 2853, 1703 (C=O), 1636 (C=N), 1491, 798, 708

HRMS (*m/z* - ES): Found 274.1928 (M^+ -ClO_4. $C_{16}H_{24}N_3O$ requires 274.1919).

5.2.4.19 4-Cyclohexyl-3,5-dimethyl-1-phenyl-4H-[1,2,4]triazol-1-ium; perchlorate (240b)



Procedure I was followed using oven-dried molecular sieves (4Å, 1.80 g), hydrazino-intermediate **239b** (700 mg, 1.86 mmol), CH_3CN (19 cm^3) and H_2SO_4 (700 µL, 13.03 mmol). Recrystallisation of the crude product from hot CH_3CN gave pure **240b** (510 mg, 77%) as a white solid, m.p. 183-184 °C.

δ_H (400 MHz, DMSO-d_6): 1.26-1.36 (m, 1H, alk), 1.45-1.55 (m, 2H, alk), 1.66-1.70 (app. d, 2H, alk), 1.86-2.09 (m, 5H, alk), 2.73 (s, 3H, CH_3-3), 2.75 (s, 3H, CH_3-5), 4.39-4.45 (m, 1H, H-6), 7.15-7.71 (m, 5H, Ar)

δ_C (100 MHz, DMSO-d_6): 11.9, 12.0, 24.2, 25.0, 29.6, 58.7, 125.7, 129.9, 131.0, 134.7(q), 151.8(q), 151.9(q)

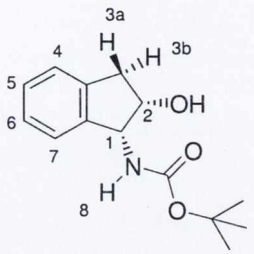
ν_{max} (neat)/cm^{-1}: 2935, 2861, 1584, 1494, 1373, 1084 (C-N-C), 773, 697

HRMS (*m/z* - ES): Found 256.1813 (M^+ -ClO_4. $C_{16}H_{22}N_3$ requires 256.1814).

5.3 Experimental data for Section 3

5.3.2 Experimental data for Section 3.2

5.3.2.1 (1*R*,2*S*)-*cis*-(2-Hydroxy-indan-1-yl)-carbamic acid *tert*-butyl ester (244)



An oven-dried 1000 cm^3 reaction vessel containing a large stirring bar and (1*R*,2*S*)-1-amino-indan-2-ol (**222**) (7.00 g, 46.92 mmol) was fitted with a rubber septum seal and placed under an atmosphere of Ar. To this was added CH_2Cl_2 (140 cm^3) and the resulting solution was cooled to 0 °C. Triethylamine (7.18 cm^3, 51.61 mmol) was added *via* syringe and the reaction was stirred for 20 min. A 250 cm^3 pressure equalising dropping funnel was attached to the flask and a solution of di-*tert*-butyl dicarbonate (97%, 10.56 g, 46.92 mmol) in CH_2Cl_2 (153 cm^3) was added to the dropping funnel. The reaction was returned to an Argon atmosphere and the solution was added drop wise to the reaction at 0 °C over 8 h and the resulting clear colourless solution was left to stir at room temperature overnight. CH_2Cl_2 (250 cm^3) and deionised water (300 cm^3) were then added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 x 200 cm^3). The organic layers were combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to give (1*R*,2*S*)-**244** (11.23 g, 96%) as an off-white solid, not purified further, m.p. 76-77 °C; $[\alpha]_D^{20}$ = -13.6 (*c* 3.00 in $CHCl_3$).

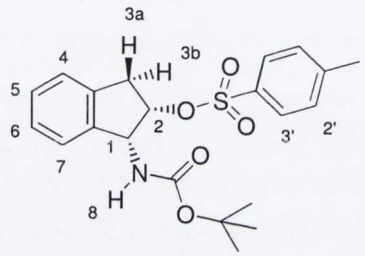
δ_H (400 MHz, $CDCl_3$): 1.53 (s, 9H, $3CH_3$), 2.30 (s, 1H, OH), 2.92 (dd, 1H, J 16.6, 2.0, H-3a), 3.11 (dd, 1H, J = 16.6, 5.0, H-3b), 4.59-4.61 (m, 1H, H-2), 5.07-5.22 (m, 2H, H-1 and H-8), 7.26-7.31 (m, 4H, H-4 to H-7)

δ_C (100 MHz, $CDCl_3$): 28.0, 38.9, 58.4, 73.2, 79.4, 124.0, 124.9, 126.7, 127.7, 139.4(q), 140.4(q), 155.9(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3429 (O-H), 3350 (N-H), 2983, 2933, 1688 (C=O), 1522, 1389, 1167 (C-O-C), 735

HRMS (*m/z* - ES): Found 272.1251 (M^+ + Na. $C_{14}H_{19}NO_3Na$ requires 272.1263).

5.3.2.2 (1*R*,2*S*)-*cis*-Toluene-4-sulphonic acid-1-*tert*-butoxycarbonylamino-indan-2-yl ester (245)



Procedure D was followed using (1*R*,2*S*)-**244** (11.69 g, 46.92 mmol), CH_2Cl_2 (164 cm^3), triethylamine (13.06 cm^3, 93.84 mmol), tosyl chloride (8.94 g, 46.92 mmol) and 4-dimethylaminopyridine (573 mg, 4.69 mmol). Removal of the solvent under reduced pressure provided pure (1*R*,2*S*)-**245** (18.17 g, 96%) as an off-white solid, not purified further, m.p. 162-163 °C; $[\alpha]_D^{20}$ = -108.8 (*c* 0.53 in $CHCl_3$).

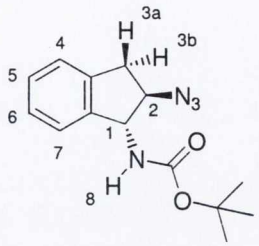
δ_H (400 MHz, $CDCl_3$): 1.50 (s, 9H, $3CH_3$), 2.48 (s, 3H, CH_3), 3.11 (d, 2H, J 2.5, H-3a and H-3b), 5.03 (d, 1H, J 9.5, H-8), 5.24 (t of d, 1H, J 5.0, 2.5, H-2), 5.30 (dd, 1H, J 9.5, 5.0, H-1), 7.20-7.27 (m, 4H, H-4 to H-7), 7.36 (d, 2H, J 8.0, H-2'), 7.80 (d, 2H, J 8.0, H-3')

δ_C (100 MHz, $CDCl_3$): 21.3, 27.9, 37.0, 57.1, 79.5(q), 83.2, 123.2, 124.6, 127.0, 127.4, 127.9, 129.5, 133.2(q), 137.7(q), 139.4(q), 144.4(q), 155.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3362, 2981, 2934, 1683 (C=O), 1520, 1349 (SO_2-O-), 1178 (SO_2-O-), 1161 (C-O-C), 818, 753

HRMS (*m/z* - ES): Found 426.1369 (M^+ + Na. $C_{21}H_{25}NO_5NaS$ requires 426.1351).

5.3.2.3 (1*R*,2*R*)-*trans*-(2-Azido-indan-1-yl)-carbamic acid *tert*-butyl ester (246)



Procedure E was followed using toluene sulphonic acid-derivative (1*R*,2*S*)-**245** (18.24 g, 45.21 mmol), DMF (452 cm^3) and sodium azide (3.15 g, 48.37 mmol). Removal of the solvent removed *in vacuo* gave (1*R*,2*R*)-**246** (11.66 g, 94%) as a cream solid, not purified further, m.p. 145-146 °C; $[\alpha]_D^{20}$ = -2.4 (*c* 2.00 in $CHCl_3$). The ^1H NMR spectrum of this compound indicates the presence of 2 rotameric species at room temperature in $CDCl_3$ - the ratio of these was found to be 0.10:0.90. The ^{13}C spectrum indicates the major rotamer only.

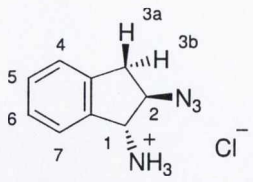
δ_H (600 MHz, $CDCl_3$): 1.53 (s, 8.10H, $3CH_3$), 1.59 (s, 0.90H, $3CH_3$), 2.87 (dd, 1H, J 15.8, 7.2, H-3b), 3.26 (dd, 1H, J 15.8, 7.4, H-3a), 4.05-4.10 (m, 1H, H-2), 4.55 (s, 0.10H, H-8), 4.81 (s (broad), 0.90H, H-8), 5.04 (s, 0.10H, H-1), 5.15 (s (broad), 0.90H, H-1), 7.23 (d, 1H, J 6.8, H-7), 7.29-7.30 (m, 3H, H-4 to H-6)

δ_C (150 MHz, $CDCl_3$): 28.3, 35.7, 61.1, 68.4, 80.0(q), 123.9, 124.8, 127.4, 128.6, 138.9(q), 140.0(q), 155.2(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3337, 2983, 2913, 2096 (N_3), 1690 (C=O), 1519, 1368, 1169 (C-O-C), 747

HRMS (*m/z* - ES): Found 297.1321 (M^+ + Na. $C_{14}H_{18}N_4O_2Na$ requires 297.1327).

5.3.2.4 (1*R*,2*R*)-*trans*-2-Azido-indan-1-yl-ammonium chloride (247)



A 250 cm^3 round bottomed flask equipped with a magnetic stirring bar was charged with (1*R*,2*R*)-**246** (9.13 g, 33.28 mmol) and CH_2Cl_2 (130 cm^3). The reaction was cooled to 0 °C and trifluoroacetic acid (28 cm^3, 366.04 mmol) was added drop wise over 30 min. The resulting solution was warmed to ambient temperature and left to sir overnight. NaOH solution (2.0 M, 75 cm^3) was added to raise the pH to 10. The organic layer was removed and the remaining aqueous layer was extracted with CH_2Cl_2 (4 x 50 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield a brown liquid. The crude amine was dissolved in HCl solution (8.0 M, 100 cm^3) and the solvent was removed *in vacuo* to yield (1*R*,2*R*)-**247** (6.87 g, 98%) as a pale yellow solid, not purified further, m.p. 194-195 °C; $[\alpha]_D^{20}$ = -78.0 (*c* 0.90 in MeOH).

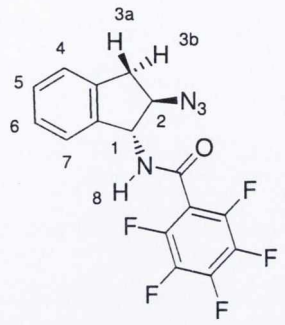
δ_H (600 MHz, DMSO-d_6): 2.96 (dd, 1H, J 16.3, 5.5, H-3b), 3.52 (dd, 1H, J 16.3, 7.3, H-3a), 4.47-4.49 (m, 1H, H-2), 4.60-4.61 (m, 1H, H-1), 7.33-7.39 (m, 3H, H-4 to H-6), 7.63 (d, 1H, J 7.3, H-7), 8.83 (s, (broad), 3H, NH_3)

δ_C (150 MHz, DMSO-d_6): 36.2, 59.3, 64.4, 125.0, 125.2, 127.3, 129.6, 136.4(q), 140.4(q)

ν_{max} (neat)/cm^{-1}: 2837 (NH_3^+), 2715, 2118 (N_3), 1608, 1521, 1459, 748

HRMS (*m/z* - ES): Found 175.0992 (M^+ - Cl. $C_9H_{11}N_4$ requires 175.0984).

5.3.2.5 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-2,3,4,5,6-pentafluoro-benzamide (249b)



Procedure C was followed using azide (1*R*,2*R*)-**247** (762 mg, 3.62 mmol), CH_2Cl_2 (6.00 cm^3), triethylamine (2.51 cm^3, 18.03 mmol) and a solution of acid chloride **248b** (600 μL, 4.34 mmol) in CH_2Cl_2 (8.00 cm^3). Purification by column chromatography (1:1 CH_2Cl_2-hexane, R_f 0.2) gave (1*R*,2*R*)-**249b** (1.24 g, 93%) as a white solid, m.p. 211-212 °C; $[\alpha]_D^{20}$ = -27.9 (*c* 0.63 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6): 2.85 (dd, 1H, J 15.4, 8.8, H-3a), 3.30 (dd, 1H, J 15.4, 7.7, H-3b), 4.27-4.31 (app. q, 1H, H-2), 5.41-5.43 (dd, 1H, J 8.8, 7.7, H-1), 7.19 (d, 1H, J 4.4, H-7), 7.30-7.31 (m, 3H, H-4 to H-6), 9.62 (d, 1H, J 7.7, H-8)

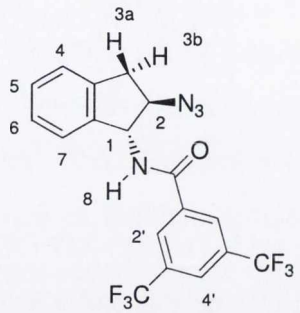
δ_C (150 MHz, DMSO-d_6): 35.3, 59.4, 66.7 112.0 (t, qC, J 20.8), 123.4, 124.8, 127.3, 128.5, 136.0 (d of t, qC, J 250.5, 14.7), 139.0(q), 139.5(q), 140.4 (d of m, qC, J 257.7), 142.2 (d of m, qC, J 251.7), 157.0(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -159.98 (app. t, 2F), -150.13 (t, 1F, J 18.4), -140.48 (d, 2F, J 18.3)

ν_{max} (neat)/cm^{-1}: 3266, 2968, 2934, 2105 (N_3), 1655 (C=O), 1499 (C-F), 1077, 988 (C-F), 752

HRMS (*m/z* - ES): Found 391.0579 (M^+ + Na. $C_{16}H_9N_4OF_5Na$ requires 391.0594).

5.3.2.6 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-3,5-*bis*-trifluoromethyl-benzamide (249c)



Procedure C was followed using (1*R*,2*R*)-**247** (1.20 g, 5.70 mmol), CH_2Cl_2 (10 cm^3), triethylamine (2.38 cm^3, 17.09 mmol) and a solution of acid chloride **248c** (1.23 cm^3, 6.84 mmol) in CH_2Cl_2 (8.00 cm^3). Purification by column chromatography (6:4 CH_2Cl_2-hexane, R_f 0.3) gave (1*R*,2*R*)-**249c** (2.17 g, 92%) as a white solid, m.p. 207-208 °C; $[\alpha]_D^{20}$ = -20.7 (*c* 0.97 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6): 2.89 (dd, 1H, J 15.7, 7.7, H-3a), 3.37 (dd, 1H, J 15.7, 7.3, H-3b), 4.39-4.43 (m, 1H, H-2), 5.54-5.57 (m, 1H, H-1), 7.26-7.33 (m, 4H, H-4 to H-7), 8.35 (s, 1H, H-4'), 8.60 (s, 2H, H-2'), 9.49 (d, 1H, J 8.4, H-8)

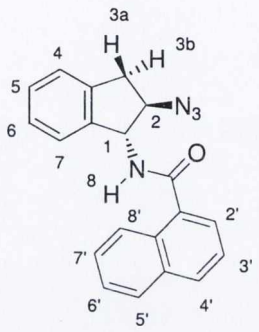
δ_C (150 MHz, DMSO-d_6): 35.4, 59.7, 66.9, 120.4 (q, quartet, J 272.9), 124.2, 124.7, 125.1 (septet, J 3.3), 127.2, 128.2 (quartet, J 3.0), 128.4, 130.2(q, quartet, J 33.2), 136.1(q), 139.3(q), 140.0(q), 163.6(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -61.76

ν_{max} (neat)/cm^{-1}: 3257, 3094, 2928, 2105 (N_3), 1645 (C=O), 1547, 1272 (C-F), 1124 (C-F), 910, 847, 701, 680

HRMS (*m/z* - ES): Found 437.0807 (M^+ + Na. $C_{18}H_{12}N_4OF_6Na$ requires 437.0813).

5.3.2.7 (1*R*,2*R*)-*trans*-Naphthalene-1-carboxylic acid (2-azido-indan-1-yl)-amide (249d)



Procedure C was followed using (1*R*,2*R*)-**247** (1.50 g, 7.12 mmol), CH_2Cl_2 (10 cm^3), triethylamine (2.97 cm^3, 21.36 mmol) and a solution of acid chloride **248d** (1.28 cm^3, 8.55 mmol) in CH_2Cl_2 (15 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.4) gave (1*R*,2*R*)-**249d** (2.08 g, 89%) as an off-white solid, m.p. 204-205 °C; $[\alpha]_D^{20}$ = -41.3 (*c* 0.93 in $CHCl_3$).

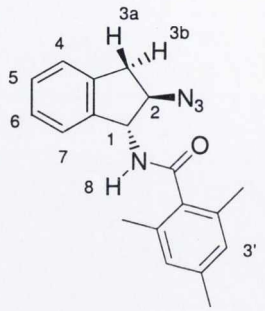
δ_H (600 MHz, DMSO-d_6): 2.85 (dd, 1H, J 15.4, 8.4, H-3a), 3.30 (dd, 1H, J 15.4, 7.8, H-3b), 4.38-4.42 (app. q, 1H, H-2), 5.58-5.61 (app. t, 1H, H-1), 7.29-7.33 (m, 3H, H-4 to H-6), 7.34 (d, 1H, J 6.6, H-7), 7.57-7.63 (m, 3H, H-3', H-6' and H-7'), 7.68 (d, 1H, J 7.7, H-2'), 8.00 (d, 1H, J 7.7, H-5'), 8.04 (d, 1H, J 8.8, H-4'), 8.29 (d, 1H, J 8.8, H-8'), 9.17 (d, 1H, J 7.7, H-8)

δ_C (150 MHz, DMSO-d_6): 35.3, 59.3, 66.7, 123.6, 124.7, 124.9, 125.25, 125.29, 126.3, 126.8, 127.2, 128.1, 128.2, 129.7(q), 130.0, 133.1(q), 134.2(q), 138.8(q), 140.8(q), 168.9(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3238, 3047, 2926, 2888, 2098 (N_3), 1646, 1527, 1519, 773, 753

HRMS (*m/z* - ES): Found 351.1210 (M^+ + Na. $C_{20}H_{16}N_4ONa$ requires 351.1222).

5.3.2.8 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-2,4,6-trimethyl-benzamide (249e)



Procedure C was followed using (1*R*,2*R*)-**247** (1.00 g, 4.75 mmol), CH_2Cl_2 (8.00 cm^3), triethylamine (3.96 cm^3, 28.48 mmol) and a solution of acid chloride **248e** (2.67 g, 14.62 mmol) in CH_2Cl_2 (10 cm^3). Purification by column chromatography (1:1 CH_2Cl_2-hexane, R_f 0.1) gave (1*R*,2*R*)-**249e** (1.11 g, 73%) as a red-brown solid, m.p. 149-150 °C; $[\alpha]_D^{20}$ = -61.3 (*c* 1.03 in $CHCl_3$).

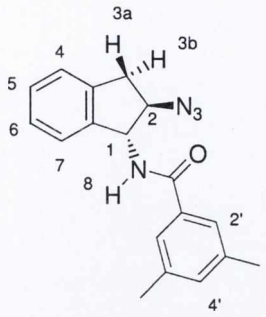
δ_H (400 MHz, $CDCl_3$): 2.29 (s, 3H, CH_3), 2.39 (s, 6H, $2CH_3$), 2.98 (dd, 1H, J 15.7, 7.0, H-3b), 3.32 (dd, 1H, J 15.7, 7.5, H-3a), 4.12 (ddd, 1H, J 7.5, 7.0, 6.5, H-2), 5.60 (dd, 1H, J 8.0, 6.5, H-1), 5.92 (d, 1H, J 8.0, H-8), 6.87 (s, 2H, H-3'), 7.26-7.33 (m, 4H, H-4 to H-7)

δ_C (100 MHz, $CDCl_3$): 18.9, 20.7, 35.8, 59.3, 67.9, 123.7, 124.6, 127.3, 127.8, 128.5, 133.7(q), 133.9(q), 138.3(q), 138.9(q), 139.3(q), 170.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3242, 2951, 2912, 2099 (N_3), 1639 (C=O), 1518, 1458, 1260, 856, 748, 704, 682

HRMS (*m/z* - ES): Found 321.1725 (M^+ + H. $C_{19}H_{21}N_4O$ requires 321.1715).

5.3.2.9 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-3,5-dimethyl-benzamide (249f)



Procedure C was followed using (1*R*,2*R*)-**247** (1.10 g, 5.22 mmol), CH_2Cl_2 (10 cm^3), triethylamine (4.36 cm^3, 31.33 mmol) and a solution of acid chloride **248f** (2.81 g, 16.64 mmol) in CH_2Cl_2 (10 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.1) gave (1*R*,2*R*)-**249f** (1.47 g, 92%) as a yellow solid, m.p. 178-180 °C; $[\alpha]_D^{20}$ = -20.5 (*c* 0.74 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 2.38 (s, 6H, $2CH_3$), 2.96 (dd, 1H, J 16.1, 6.5, H-3b), 3.34 (dd, 1H, J 16.1, 7.5, H-3a), 4.20-4.25 (app. q, 1H, H-2), 5.62-5.66 (app. t, 1H, H-1), 6.35 (d, 1H, J 7.5, H-8), 7.18 (s, 1H, H-4'), 7.29-7.33 (m, 4H, H-4 to H-7), 7.43 (s, 2H, H-2')

δ_C (100 MHz, $CDCl_3$): 20.8, 35.8, 59.8, 67.7, 123.9, 124.4, 124.6, 127.3, 128.5, 133.0, 133.4(q), 138.0(q), 139.3(q), 139.5(q), 167.4(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3248, 3044, 2914, 2100 (N_3), 1640 (C=O), 1601, 1532, 1459, 861, 744, 683

HRMS (*m/z* - ES): Found 307.1559 (M^+ + H. $C_{18}H_{19}N_4O$ requires 307.1559).

5.3.2.10 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-4-methoxy-benzamide (249g)

Procedure C was followed using (1*R*,2*R*)-**247** (1.20 g, 5.70 mmol), THF (10 cm^3), triethylamine (2.38 cm^3, 17.09 mmol), 4-dimethylaminopyridine (35 mg, 0.29 mmol) and a solution of acid chloride **248g** (930 μL, 6.84 mmol) in THF (13 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.3) gave (1*R*,2*R*)-**249g** (1.04 g, 59%) as an off-white solid, m.p. 174-175 °C; $[\alpha]_D^{20}$ = -26.1 (*c* 0.76 in $CHCl_3$).

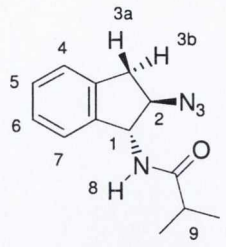
δ_H (600 MHz, DMSO-d_6): 2.81 (dd, 1H, J 15.4, 8.8, H-3a), 3.30 (dd, 1H, J 15.4, 7.7, H-3b), 3.81 (s, 3H, OCH_3), 4.36-4.39 (app. q, 1H, H-2), 5.47 (dd, 1H, J 8.8, 7.7, H-1), 7.01 (d, 2H, J 8.8, H-3'), 7.13 (d, 1H, J 6.6, H-7), 7.22-7.27 (m, 3H, H-4 to H-6), 7.88 (d, 2H, J 8.8, H-2'), 8.85 (d, 1H, J 7.7, H-8)

δ_C (150 MHz, DMSO-d_6): 35.2, 55.4, 59.2, 66.7, 113.5, 123.7, 124.6, 126.2(q), 127.1, 128.0, 129.2, 138.9(q), 141.1(q), 161.8(q), 166.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3279, 3025, 2913, 2847 (C-O-CH_3), 2097 (N_3), 1634 (C=O), 1507, 1259 (C-O-C), 844, 750

HRMS (*m/z* - ES): Found 331.1164 (M^+ + Na. $C_{17}H_{16}N_4O_2Na$ requires 331.1171).

5.3.2.11 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-isobutyramide (249h)



Procedure C was followed using (1*R*,2*R*)-**247** (1.00 g, 4.75 mmol), CH_2Cl_2 (8.00 cm^3), triethylamine (1.98 cm^3, 14.24 mmol) and a solution of acid chloride **248h** (600 μL, 5.70 mmol) in CH_2Cl_2 (8.00 cm^3). Purification by column chromatography (0.95:0.05 CH_2Cl_2-hexane, R_f 0.2) gave (1*R*,2*R*)-**249h** (1.14 g, 98%) as a white solid, m.p. 177-178 °C; $[\alpha]_D^{20}$ = -15.3 (*c* 0.87 in $CHCl_3$).

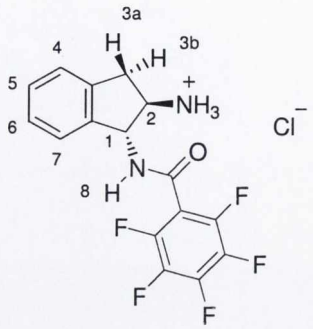
δ_H (600 MHz, DMSO-d_6): 1.07 (d, 3H, J 6.6, CH_3), 1.11 (d, 3H, J 7.0, CH_3), 2.44-2.48 (m, 1H, H-9), 2.77 (dd, 1H, J 15.5, 8.4, H-3a), 3.24 (dd, 1H, J 15.5, 7.5, H-3b), 4.17-4.21 (app. q, 1H, H-2), 5.25-5.27 (app. t, 1H, H-1), 7.10 (d, 1H, J 7.0, H-7), 7.24-7.28 (m, 3H, H-4 to H-6), 8.32 (d, 1H, J 8.4, H-8)

δ_C (150 MHz, DMSO-d_6): 19.2, 19.6, 34.1, 35.2, 58.6, 66.7, 123.5, 124.6, 127.1, 128.0, 138.8(q), 141.0(q), 176.5(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3269, 2973, 2877, 2100 (N_3), 1644 (C=O), 1524, 1460, 745

HRMS (*m/z* - ES): Found 267.1209 (M^+ + Na. $C_{13}H_{16}N_4ONa$ requires 267.1222).

5.3.2.12 (1*R*,2*R*)-*trans*-1-Pentafluorobenzoylamino-indan-2-yl-ammonium chloride (250b)



Procedure F was followed using (1*R*,2*R*)-**249b** (1.14 g, 3.09 mmol), triphenylphosphine (810 mg, 3.09 mmol), THF (28 cm^3) and water (4.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250b** (1.06 g, 91%) as a white solid, m.p. 277-279 °C; $[\alpha]_D^{20}$ = -26.7 (*c* 0.99 in MeOH).

δ_H (600 MHz, DMSO-d_6): 3.04 (dd, 1H, J 15.8, 7.5, H-3b), 3.39 (dd, 1H, J 15.8, 8.3, H-3a), 3.87-3.91 (app. q, 1H, H-2), 5.62-5.65 (app. t, 1H, H-1), 7.27 (d, 1H, J 4.9, H-7), 7.32-7.36 (m, 3H, H-4 to H-6), 8.69 (s (broad), 3H, NH_3), 9.66 (d, 1H, J 7.9, H-8)

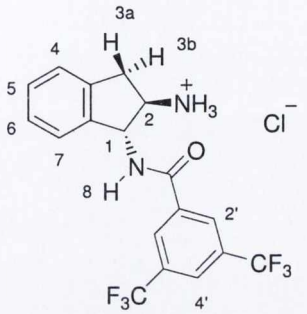
δ_C (150 MHz, DMSO-d_6): 35.3, 56.3, 58.5, 112.1 (t, qC, J 20.1), 124.1, 125.3, 127.9, 129.0, 136.5 (d of t, qC, J 249.9, 16.2), 139.2(q), 140.0(q), 140.7 (d of m, qC, J 254.1), 142.7 (d of m, qC, J 250.7), 157.5(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -161.80 (dd, 2F, J 22.0, 16.5), -152.66 (t, 1F, J 22.0), -141.40 (d, 2F, J 16.5)

ν_{max} (neat)/cm^{-1}: 3299 (N-H), 2856 (NH_3^+), 1661 (C=O), 1552, 1518 (N-H), 1496 (C-F), 994 (C-F), 768, 738, 713

HRMS (*m/z* - ES): Found 343.0858 (M^+ - Cl. $C_{16}H_{12}N_2OF_5$ requires 343.0870).

5.3.2.13 (1*R*,2*R*)-*trans*-1-(3,5-*Bis*-trifluoromethyl-benzoylamino)-indan-2-yl-ammonium chloride (250c)



Procedure F was followed using (1*R*,2*R*)-**249c** (2.16 g, 5.22 mmol), triphenylphosphine (1.37 g, 5.22 mmol), THF (44 cm^3) and water (6.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250c** (2.11 g, 95%) as a white solid, m.p. 301-303 °C; $[\alpha]_D^{20}$ = -4.7 (*c* 1.11 in MeOH).

δ_H (600 MHz, DMSO-d_6): 3.06 (dd, 1H, J 15.7, 9.2, H-3a), 3.37 (dd, 1H, J 15.7, 7.9, H-3b), 3.97-4.03 (m, 1H, H-2), 5.75-5.77 (app. t, 1H, H-1), 7.26-7.40 (m, 4H, H-4 to H-7), 8.36 (s, 1H, H-4'), 8.63 (s, 2H, H-2'), 8.74 (broad s, 3H, NH_3), 9.57 (d, 1H, J 8.3, H-8)

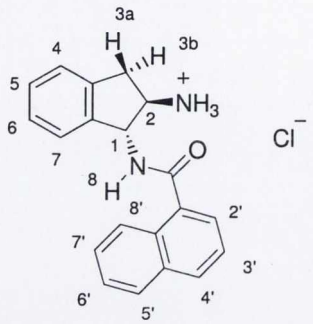
δ_C (150 MHz, DMSO-d_6): 34.4, 56.6, 57.8, 120.4 (quartet, qC, J 273.7), 123.9, 124.8, 124.9 (septet, J 3.3), 127.4, 128.4, 128.5 (quartet, J 3.8), 130.1 (quartet, qC, J 33.1), 136.5(q), 138.5(q), 140.2(q), 164.2(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -61.76

ν_{max} (neat)/cm^{-1}: 3280 (N-H), 2861 (NH_3^+), 1646 (C=O), 1621, 1544, 1278 (C-F), 1124 (C-F), 847, 742, 682

HRMS (*m/z* - ES): Found 389.1071 (M^+ - Cl. $C_{18}H_{15}N_2OF_6$ requires 389.1089).

5.3.2.14 (1*R*,2*R*)-*trans*-1-[(Naphthalene-1-carbonyl)-amino]-indan-2-yl-ammonium chloride (250d)



Procedure F was followed using (1*R*,2*R*)-**249d** (1.99 g, 6.05 mmol), triphenylphosphine (1.59 g, 6.05 mmol), THF (50 cm^3) and water (5.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250d** (1.92 g, 93%) as a white solid, m.p. 293-295 °C; $[\alpha]_D^{20}$ = -72.2 (*c* 1.68 in MeOH).

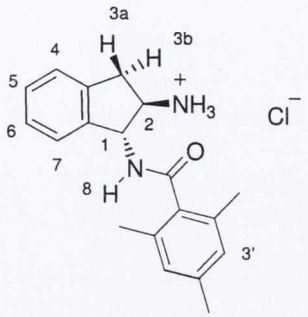
δ_H (600 MHz, DMSO-d_6): 3.03 (dd, 1H, J 15.8, 8.7, H-3a), 3.38 (dd, 1H, J 15.8, 8.3, H-3b), 3.94-4.01 (app. q, 1H, H-2), 5.76-5.79 (app. t, 1H, H-1), 7.33-7.36 (m, 4H, H-4 to H-7), 7.59-7.65 (m, 3H, H-3', H-6' and H-7'), 7.88 (d, 1H, J 6.4, H-2'), 8.01 (d, 1H, J 7.9, H-5'), 8.07 (d, 1H, J 8.3, H-4'), 8.43 (d, 1H, J 8.3, H-8'), 8.66 (s (broad), 3H, NH_3), 9.12 (d, 1H, J 8.3, H-8)

δ_C (150 MHz, DMSO-d_6): 35.1, 56.7, 58.0, 124.1, 125.1, 125.2, 126.0, 126.4, 126.6, 127.1, 127.8, 128.6, 128.7, 130.1(q), 130.6, 133.5(q), 134.2(q), 138.8(q), 141.1(q), 169.5(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3290 (N-H), 2981, 2857 (NH_3^+), 1633 (C=O), 1522, 1329, 1305, 1260, 1169, 783, 734

HRMS (*m/z* - ES): Found 303.1493 (M^+ - Cl. $C_{20}H_{19}N_2O$ requires 303.1497).

5.3.2.15 (1*R*,2*R*)-*trans*-1-(2,4,6-Trimethyl-benzoylamino)-indan-2-yl-ammonium chloride (250e)



Procedure F was followed using (1*R*,2*R*)-**249e** (1.12 g, 3.48 mmol), triphenylphosphine (914 mg, 3.48 mmol), THF (29 cm^3) and water (4.00 cm^3). Concentration of the aqueous layer produced a pale brown solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250e** (642 mg, 56%) as an off-white solid, m.p. 278-280 °C; $[\alpha]_D^{20}$ = -37.5 (*c* 0.70 in MeOH).

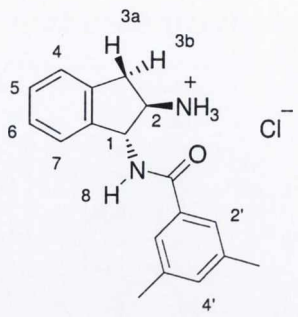
δ_H (600 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 2.27 (s, 6H, $2CH_3$), 2.99 (dd, 1H, J 16.6, 6.4, H-3b), 3.42 (dd, 1H, J 16.6, 8.1, H-3a), 3.87-3.90 (app. q, 1H, H-2), 5.57-5.59 (app. t. 1H, H-1), 6.87 (s, 2H, H-3'), 7.30-7.32 (m, 3H, H-4 to H-6), 7.37 (d, 1H, J 6.4, H-7), 8.53 (s (broad), 3H, NH_3), 8.85 (d, 1H, J 7.5, H-8)

δ_C (150 MHz, DMSO-d_6): 19.1, 20.6, 35.4, 56.1, 58.2, 124.4, 124.8, 127.3, 127.7, 128.4, 133.8(q), 134.9(q), 137.4(q), 139.0(q), 140.5(q), 169.7(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3251 (N-H), 2915 (NH_3^+), 1634 (C=O), 1612, 1517, 1477, 1375, 848, 746

HRMS (*m/z* - ES): Found 295.1815 (M^+ - Cl. $C_{19}H_{23}N_2O$ requires 295.1810).

5.3.2.16 (1*R*,2*R*)-*trans*-1-(3,5-Dimethyl-benzoylamino)-indan-2-yl-ammonium chloride (250f)



Procedure F was followed using (1*R*,2*R*)-**249f** (1.39 g, 4.53 mmol), triphenylphosphine (1.19 g, 4.53 mmol), THF (38 cm^3) and water (5.00 cm^3). Concentration of the aqueous layer produced a yellow solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250f** (1.43 g, 99%) as a pale yellow solid, m.p. 265-266 °C (dec.); $[\alpha]_D^{20} = -31.9$ (*c* 0.91 in MeOH).

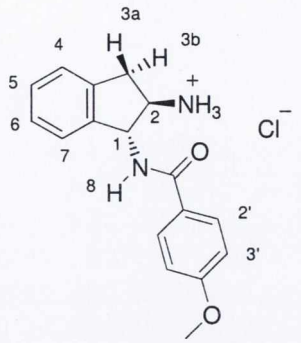
δ_H (600 MHz, DMSO-d_6): 2.33 (s, 6H, $2CH_3$), 2.97 (dd, 1H, J 15.8, 9.0, H-3a), 3.35 (dd, 1H, J 15.8, 7.9, H-3b), 3.97-3.99 (app. q, 1H, H-2), 5.67-5.70 (app. t, 1H, H-1), 7.16 (d, 1H, J 7.2, H-7), 7.20 (s, 1H, H-4'), 7.24-7.31 (m, 3H, H-4 to H-6), 7.59 (s, 2H, H-2'), 8.64 (broad s, 3H, NH_3), 8.90 (d, 1H, J 8.3, H-8)

δ_C (150 MHz, DMSO-d_6): 20.8, 34.5, 56.3, 57.5, 123.6, 124.6, 125.2, 127.3, 128.0, 132.6, 134.0(q), 137.2(q), 138.3(q), 140.9(q), 167.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3306 (N-H), 2947, 2920, 2838 (NH_3^+), 1641 (C=O), 1601, 1521, 1475, 1343, 863, 769, 750, 691

HRMS (*m/z* - ES): Found 281.1662 (M^+ - Cl. $C_{18}H_{21}N_2O$ requires 281.1654).

5.3.2.17 (1*R*,2*R*)-*trans*-1-(4-Methoxy-benzoylamino)-indan-2-yl-ammonium chloride (250g)



Procedure F was followed using (1*R*,2*R*)-**249g** (938 mg, 3.04 mmol), triphenylphosphine (798 mg, 3.04 mmol), THF (25 cm^3) and water (4.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250g** (925 mg, 95%) as a white solid, m.p. 272-273 °C; $[\alpha]_D^{20}$ = -10.5 (*c* 0.87 in MeOH).

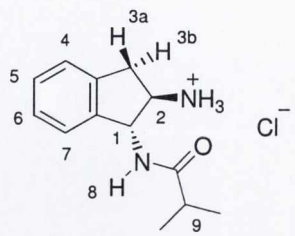
δ_H (600 MHz, DMSO-d_6): 2.98 (dd, 1H, J 15.7, 8.9, H-3a), 3.35 (dd, 1H, J 15.7, 7.6, H-3b), 3.84 (s, 3H, OCH_3), 3.94-3.97 (app. q, 1H, H-2), 5.68-5.71 (app. t, 1H, H-1), 7.04 (d, 2H, J 7.7, H-3'), 7.18 (d, 1H, J 6.4, H-7), 7.27-7.31 (m, 3H, H-4 to H-6), 7.95 (d, 2H, J 7.7, H-2'), 8.49 (s (broad), 3H, NH_3), 8.87 (d, 1H, J 7.2, H-8)

δ_C (150 MHz, DMSO-d_6): 34.6, 55.4, 56.7, 57.7, 113.5, 123.8, 124.7, 126.2(q), 127.4, 128.2, 129.4, 138.4(q), 141.0(q), 161.8(q), 166.4(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3323 (N-H), 2933, 2866 (NH_3^+ and C-O-CH_3), 1629 (C=O), 1608, 1533, 1505, 1251 (C-O-C), 842, 742

HRMS (*m/z* - ES): Found 283.1450 (M^+ - Cl. $C_{17}H_{19}N_2O_2$ requires 283.1447).

5.3.2.18 (1*R*,2*R*)-*trans*-1-(Isobutyrylamino)-indan-2-yl-ammonium chloride (250h)



Procedure F was followed using (1*R*,2*R*)-**249h** (0.98 g, 4.01 mmol), triphenylphosphine (1.05 g, 4.01 mmol), THF (33 cm^3) and water (5.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**250h** (878 mg, 86%) as a white solid, m.p. 274-276 °C; $[\alpha]_D^{20}$ = -28.1 (*c* 0.76 in MeOH).

δ_H (600 MHz, DMSO-d_6): 1.10 (d, 3H, J 6.8, CH_3), 1.12 (d, 3H, J 6.8, CH_3), 2.46-2.51 (m, 1H, H-9), 2.99 (dd, 1H, J 15.8, 8.7, H-3a), 3.30 (dd, 1H, J 15.8, 8.3, H-3b), 3.74 (ddd, 1H, J 8.7, 8.3, 7.9, H-2), 5.39 (dd, 1H, J 7.9, 7.9, H-1), 7.11 (d, 1H, J 6.0, H-7), 7.26-7.28 (m, 3H, H-4 to H-6), 8.41 (d, 1H, J 7.9, H-8), 8.65 (s (broad), 3H, NH_3)

δ_C (150 MHz, DMSO-d_6): 19.5, 20.3, 34.4, 34.9, 56.9, 57.4, 124.0, 125.0, 127.7, 128.5, 138.8(q), 141.3(q), 177.4(q), (C=O)

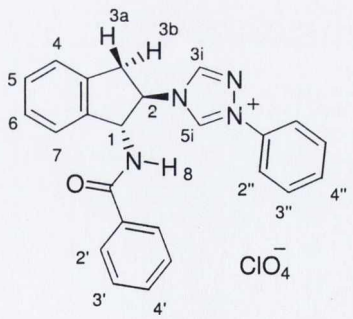
ν_{max} (neat)/cm^{-1}: 3301 (N-H), 2966, 2831 (NH_3^+), 1643 (C=O), 1596, 1522, 1474, 1354, 746

HRMS (*m/z* - ES): Found 219.1488 (M^+ - Cl. $C_{13}H_{19}N_2O$ requires 219.1497).

5.3.2.19 Procedure J: General procedure for the preparation of bifunctional chiral triazolium salts using oxadiazolium salt 231

To an oven-dried 25 cm^3 round bottomed flask, equipped with a magnetic stirring bar and oven-dried molecular sieves (4Å, 2.26 g), was added oxadiazolium salt **231** (2.32 mmol) and the reaction was put under an atmosphere of Argon. The relevant hydrochloride salt was free-based by dissolving the salt in NaOH solution (2.0 M, 5.00 cm^3) and extracting the solution with CH_2Cl_2 (4 x 10 cm^3). The organic extracts were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the free-base amine. A solution of the requisite amine (2.21 mmol) in CH_3CN (10.3 cm^3) was added to the reaction *via* syringe. The resulting solution was stirred for 90 min at ambient temperature. The flask was fitted with a reflux condenser and heated at reflux (90 °C) for the indicated time under an atmosphere of Ar. The crude reaction was filtered under a stream of Argon to remove the molecular sieves. Subsequent removal of the solvent under reduced pressure gave the crude product. Purification *via* column chromatography or recrystallisation from cold $CHCl_3$ and diisopropyl ether provided the pure triazolium salt.

5.3.2.20 (1*R*,2*R*)-*trans*-4-(1-Benzoylamino-indan-2-yl)-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241a)



Procedure J was followed using oven-dried molecular sieves (4Å, 2.26 g), oxadiazolium salt **231** (571 mg, 2.32 mmol) and (1*R*,2*R*)-**226** (as free-base amine, 556 mg, 2.21 mmol) in CH_3CN (10.3 cm^3). After heating at reflux for 5 d under an atmosphere of Ar the crude reaction was filtered under a stream of Ar to remove the molecular sieves. Removal of the solvent *in vacuo* yielded a pale brown solid. Recrystallisation from cold

$CHCl_3$ and diisopropyl ether gave (1*R*,2*R*)-**241a** (979 mg, 92%) as an off-white solid, m.p. 121-123 °C; $[\alpha]_D^{20}$ = -70.6 (*c* 1.42 in MeOH).

δ_H (600 MHz, DMSO-d_6): 3.61 (dd, 1H, J 15.8, 9.4, H-3a), 3.73 (dd, 1H, J 15.8, 8.7, H-3b), 5.34 (ddd, 1H, J 9.4, 8.7, 7.9, H-2), 6.13 (dd, 1H, J 8.3, 7.9, H-1), 7.34 (d, 1H, J 7.2, H-7), 7.37-7.45 (m, 3H, H-4 to H-6), 7.49-7.51 (app. t, 2H, H-3'), 7.57 (t, 1H, J 7.3, H-4'), 7.66 (t, 1H, J 7.5, H-4''), 7.73-7.76 (app. t, 2H, H-3''), 7.92 (d, 2H, J 7.5, H-2'), 7.96 (d, 2H, J 7.9, H-2''), 9.24 (d, 1H, J 8.3, H-8), 9.75 (s, 1H, H-3i), 11.22 (s, 1H, H-5i)

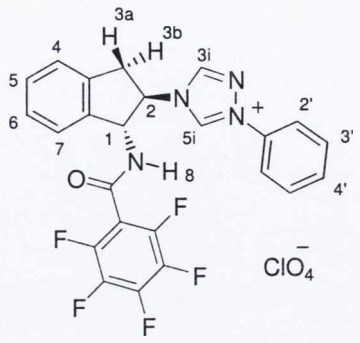
δ_C (150 MHz, DMSO-d_6): 36.4, 60.1, 65.4, 120.6, 123.9, 124.7, 127.6, 127.7, 128.3, 128.6, 130.3, 130.6, 131.7, 133.5(q), 134.9(q), 137.7(q), 139.2(q), 141.4, 144.7, 167.4(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3350, 3125, 3074, 2925, 1646 (C=O), 1601, 1570, 1522, 1486, 1305, 1075, (C-N-C), 757, 687

HRMS (*m/z* - ES): Found 381.1722 (M^+ - ClO_4. $C_{24}H_{21}N_4O$ requires 381.1715).

CHN Analysis: Found C: 53.15%; H: 3.95%; N: 10.01%. $C_{24}H_{21}ClN_4O_5.CH_2Cl_2$ requires C: 53.07%; H: 4.10; N: 9.90.

5.3.2.21 (1*R*,2*R*)-*trans*-4-(1-Pentafluorobenzoylamino-indan-2-yl)-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241b)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.30 g), oxadiazolium salt **231** (330 mg, 1.34 mmol) and (1*R*,2*R*)-**250b** (as free-base amine, 458 mg, 1.34 mmol) in CH_3CN (7.00 cm^3). The reaction was heated at reflux for 4 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (1:1 EtOAc-hexane, R_f 0.2) gave (1*R*,2*R*)-**241b** (321 mg, 42%) as a yellow solid, m.p. 101-102 °C; $[\alpha]_D^{20}$ = -40.8 (*c* 2.42 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6): 3.66 (dd, 1H, J 15.8, 9.4, H-3a), 3.71 (dd, 1H, J 15.8, 8.7, H-3b), 5.28 (ddd, 1H, J 9.4, 8.7, 8.3, H-2), 6.09 (dd, 1H, J 8.3, 7.9, H-1), 7.33-7.34 (m, 1H, H-7), 7.44-7.47 (m, 3H, H-4 to H-6), 7.69 (t, 1H, J 7.5, H-4'), 7.75-7.77 (app. t, 2H, H-3'), 7.96 (d, 2H, J 7.9, H-2'), 9.70 (s, 1H, H-3i), 9.85 (d, 1H, J 7.9, H-8), 11.29 (s, 1H, H-5i)

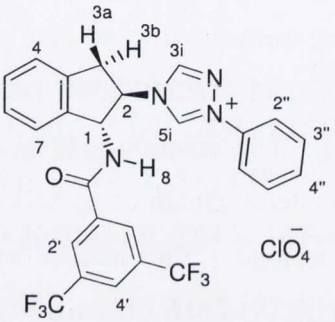
δ_C (150 MHz, DMSO-d_6): 36.1, 60.6, 65.3, 111.4 (t, qC, J 33.6), 120.5, 123.6, 125.0, 127.9, 129.1, 130.3, 130.7, 134.9(q), 136.1 (d of m, qC, J 250.9), 137.7(q), 137.9(q), 140.6 (d of m, qC, J 252.1), 141.3, 142.4 (d of m, qC, J 247.6), 144.6, 157.8(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -161.68 (app. t, 2F), -152.30 (t, 1F, J 23.0), -141.65 (d, 2F, J 27.6)

ν_{max} (neat)/cm^{-1}: 3290 (N-H), 3127, 3077, 2925, 1657 (C=O), 1570, 1542, 1516, 1501 (C-F), 1461, 1072 (C-N-C), 990 (C-F), 756, 686

HRMS (*m/z* - ES): Found 471.1238 (M^+ - ClO_4. $C_{24}H_{16}N_4OF_5$ requires 471.1244).

5.3.2.22 (1*R*,2*R*)-*trans*-4-[1-(3,5-*Bis*trifluoromethyl-benzoylamino)-indan-2-yl]-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241c)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.10 g), oxadiazolium salt **231** (285 mg, 1.16 mmol) and (1*R*,2*R*)-**250c** (as free-base amine, 427 mg, 1.10 mmol) in CH_3CN (10 cm^3). The reaction was heated at reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.3) gave (1*R*,2*R*)-**241c** (597 mg, 88%) as a yellow solid, m.p. 127-128 °C; $[\alpha]_D^{20}$ = -78.9 (*c* 1.62 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6): 3.64 (dd, 1H, J 15.8, 9.2, H-3a), 3.75 (dd, 1H, J 15.8, 8.8, H-3b), 5.34 (ddd, 1H, J 9.2, 8.8, 8.1, H-2), 6.18 (dd, 1H, J 8.1, 7.3, H-1), 7.40-7.48 (m, 4H, H-4 to H-7), 7.66 (t, 1H, J 7.3, H-4''), 7.73-7.76 (app. t, 2H, H-3''), 7.96 (d, 2H, J 8.1, H-2''), 8.37 (s, 1H, H-4'), 8.57 (s, 2H, H-2'), 9.74 (d, 1H, J 7.3, H-8), 9.78 (s, 1H, H-3i) 11.20 (s, 1H, H-5i)

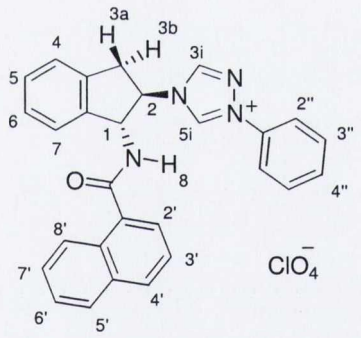
δ_C (150 MHz, DMSO-d_6): 36.7, 60.8, 65.9, 120.7 (quartet, qC, J 273.1), 120.9, 124.6, 125.1, 125.5 (septet, J 2.7), 128.1, 128.8 (quartet, J 4.1), 129.2, 130.4 (quartet, qC, J 33.3), 130.6, 131.0, 135.3(q), 136.3(q), 138.3(q), 138.9(q), 141.8, 145.1, 164.9(q), (C=O)

δ_F (376 MHz, DMSO-d_6): -61.76

ν_{max} (neat)/cm^{-1}: 3318 (N-H), 3133, 3076, 1655 (C=O), 1621, 1570, 1534, 1461, 1277 (C-F), 1128 (C-F), 1069 (C-N-C), 759, 681

HRMS (*m/z* - ES): Found 517.1473 (M^+ - ClO_4. $C_{26}H_{19}N_4OF_6$ requires 517.1463).

5.3.2.23 (1*R*,2*R*)-*trans*-4-{1-[(Naphthalene-1-carbonyl)-amino]-indan-2-yl}-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241d)



Procedure J was followed using oven-dried molecular sieves (4Å, 2.20 g), oxadiazolium salt **231** (582 mg, 2.36 mmol) and (1*R*,2*R*)-**250d** (as free-base amine, 680 mg, 2.25 mmol) in CH_3CN (30 cm^3). The reaction was heated at reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 hexane-EtOAc, R_f 0.1) gave (1*R*,2*R*)-**241d** (620 mg, 52%) as an off-white solid, m.p. 159-160 °C; $[\alpha]_D^{20}$ = -113.2 (*c* 0.71 in MeOH).

δ_H (600 MHz, DMSO-d_6): 3.67 (dd, 1H, J 15.6, 9.4, H-3a), 3.73 (dd, 1H, J 15.6, 8.3, H-3b), 5.32-5.37 (app. q, 1H, H-2), 6.18-6.21 (app. t, 1H,

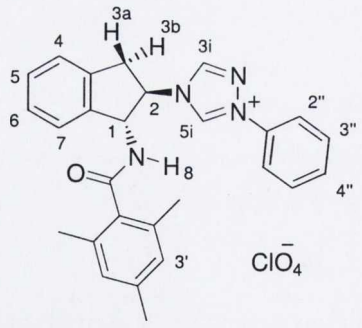
H-1), 7.42-7.51 (m, 5H, H-4 to H-7 and H-5'), 7.56-7.61 (m, 2H, H-3' and H-6'), 7.69 (t, 1H, J 7.5, H-4''), 7.76-7.79 (app. t, 2H, H-3''), 7.85 (d, 1H, J 6.8, H-2'), 7.99-8.02 (m, 3H, H-7' and H-2''), 8.07 (d, 1H, J 8.3, H-4'), 8.12 (d, 1H, J 8.3, H-8'), 9.38 (d, 1H, J 7.9, H-8), 9.86 (s, 1H, H-3i), 11.35 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 36.5, 60.6, 65.9, 120.9, 124.3, 125.15, 125.19, 125.5, 126.5, 126.6, 127.1, 128.1, 128.6, 129.0, 130.0(q), 130.7, 130.9, 131.1, 133.47(q), 133.52(q), 135.3(q), 138.1(q), 139.3(q), 141.9, 145.2, 170.1(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3294 (N-H), 3136, 3104, 1640 (C=O), 1593, 1569, 1530, 1505, 1485, 1078 (C-N-C), 769

HRMS (*m/z* - ES): Found 431.1868 (M^+ - ClO_4. $C_{28}H_{23}N_4O$ requires 431.1872).

5.3.2.24 (1*R*,2*R*)-*trans*-1-Phenyl-4-[1-(2,4,6-trimethyl-benzoylamino)-indan-2-yl]-4*H*-[1,2,4]triazol-1-ium perchlorate (241e)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.60 g), oxadiazolium salt **231** (416 mg, 1.69 mmol) and (1*R*,2*R*)-**250e** (as free-base amine, 473 mg, 1.61 mmol) in CH_3CN (15 cm^3). The reaction was heated at reflux for 5 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3

hexane-EtOAc, R_f 0.2) gave (1*R*,2*R*)-**241e** (403 mg, 48%) as a pale green solid, m.p. 143-144 °C; $[\alpha]_D^{20}$ = -94.1 (*c* 2.22 in $CHCl_3$).

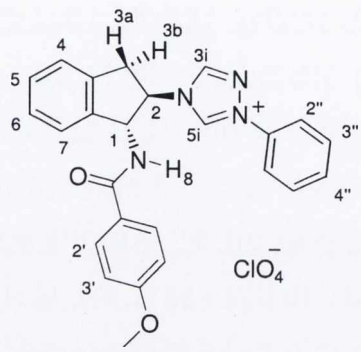
δ_H (600 MHz, DMSO-d_6): 2.18 (s, 6H, $2CH_3$), 2.24 (s, 3H, CH_3), 3.57 (dd, 1H, J 15.7, 9.6, H-3a), 3.68 (dd, 1H, J 15.7, 8.3, H-3b), 5.24-5.29 (app. q, 1H, H-2), 6.18-6.21 (app. t, 1H, H-1), 6.88 (s, 2H, H-3'), 7.35-7.36 (m, 1H, H-7), 7.40-7.43 (m, 3H, H-4 to H-6), 7.68 (t, 1H, J 7.5, H-4''), 7.75-7.78 (app. t, 2H, H-3''), 7.96 (d, 2H, J 7.9, H-2''), 9.13 (d, 1H, J 7.9, H-8), 9.77 (s, 1H, H-3i) 11.38 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 18.9, 20.6, 36.5, 59.6, 65.4, 120.5, 123.6, 124.9, 127.7, 127.8, 128.7, 130.3, 130.8, 133.4(q), 134.7(q), 134.8(q), 137.57(q), 137.60(q), 138.8(q), 141.5, 144.9, 170.3(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3284 (N-H), 3128, 3029, 2922, 1639 (C=O), 1610, 1569, 1501, 1487, 1460, 1379, 1084 (C-N-C), 852, 755

HRMS (*m/z* - ES): Found 423.2195 (M^+ - ClO_4. $C_{27}H_{27}N_4O$ requires 423.2185).

5.3.2.25 (1*R*,2*R*)-*trans*-4-[1-(4-Methoxy-benzoylamino)-indan-2-yl]-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241g)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.40 g), oxadiazolium salt **231** (355 mg, 1.44 mmol) and (1*R*,2*R*)-**250g** (as free-base amine, 388 mg, 1.37 mmol) in CH_3CN (14 cm^3). The reaction was heated at reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.2) gave (1*R*,2*R*)-**241g** (533 mg, 76%) as a pink solid, m.p. 123-124 °C; $[\alpha]_D^{20}$ = -88.9 (*c* 0.72 in $CHCl_3$).

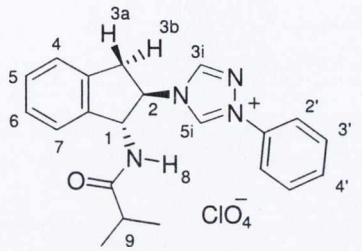
δ_H (600 MHz, DMSO-d_6): 3.59 (dd, 1H, J 16.1, 9.6, H-3a), 3.72 (dd, 1H, J 16.1, 8.3, H-3b), 3.82 (s, 3H, OCH_3), 5.31 (ddd, 1H, J 9.6, 8.7, 8.3, H-2), 6.11 (dd, 1H, J 8.7, 8.3, H-1), 7.02 (d, 2H, J 8.7, H-3'), 7.32 (d, 1H, J 7.2, H-7), 7.37-7.44 (m, 3H, H-4 to H-6), 7.66 (t, 1H, J 7.3, H-4''), 7.73-7.75 (app. t, 2H, H-3''), 7.90 (d, 2H, J 8.7, H-2'), 7.95 (d, 2H, J 7.5, H-2''), 9.09 (d, 1H, J 8.3, H-8), 9.74 (s, 1H, H-3i), 11.21 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 36.4, 55.4, 60.1, 65.6, 113.5, 120.6, 123.9, 124.7, 125.7(q), 127.7, 128.6, 129.5, 130.3, 130.7, 135.0(q), 137.7(q), 139.4(q), 141.4, 144.7, 162.0(q) (C-O-C), 166.9(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3363 (N-H), 3123, 3074, 2841 (C-O-CH_3), 1640 (C=O), 1605, 1571, 1498, 1460, 1253 (C-O-CH_3), 1075 (C-N-C), 757, 687

HRMS (*m/z* - ES): Found 411.1822 (M^+ - ClO_4. $C_{25}H_{23}N_4O_2$ requires 411.1821).

5.3.2.26 (1*R*,2*R*)-*trans*-4-(1-Isobutyrylamino)-indan-2-yl]-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (241h)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.60 g), oxadiazolium salt **231** (420 mg, 1.71 mmol) and (1*R*,2*R*)-**250h** (as free-base amine, 354 mg, 1.62 mmol) in CH_3CN (11 cm^3). The reaction was heated at reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.3) gave (1*R*,2*R*)-**241h** (515 mg, 71%) as a pale brown solid, m.p. 86-87 °C; $[\alpha]_D^{20}$ = -2.3 (*c* 0.53 in $CHCl_3$).

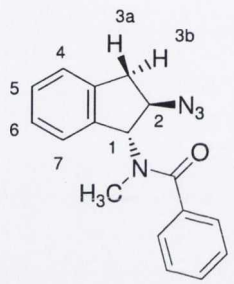
δ_H (600 MHz, DMSO-d_6): 1.02 (d, 3H, J 6.6, CH_3), 1.07 (d, 3H, J 6.6, CH_3), 2.47-2.51 (m, 1H, (under DMSO resonance), H-9), 3.56 (dd, 1H, J 16.0, 9.5, H-3a), 3.66 (dd, 1H, J 16.0, 8.4, H-3b), 5.09-5.13 (app. q, 1H, H-2), 5.82-5.85 (app. t, 1H, H-1), 7.27 (d, 1H, J 7.3, H-7), 7.38-7.42 (m, 3H, H-4 to H-6), 7.67 (t, 1H, J 7.3, H-4'), 7.74-7.76 (app. t, 2H, H-3'), 7.95 (d, 2H, J 7.3, H-2'), 8.62 (d, 1H, J 8.1, H-8), 9.67 (s, 1H, H-3i), 11.20 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 19.3, 19.6, 33.9, 36.0, 59.5, 66.0, 120.5, 123.7, 124.8, 127.7, 128.7, 130.0, 130.7, 134.9(q), 137.7(q), 138.9(q), 141.3, 144.6, 177.7(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3349 (N-H), 3125, 2972, 1649 (C=O), 1570, 1520 (N-H), 1487, 1460, 1386, 1070 (C-N-C), 756, 687

HRMS (*m/z* - ES): Found 347.1875 (M^+ - ClO_4. $C_{21}H_{23}N_4O$ requires 347.1872).

5.3.2.27 (1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-*N*-methyl-benzamide (251)



To an oven-dried 25 cm^3 round bottomed flask, equipped with a magnetic stirring bar, was added amide (1*R*,2*R*)-**225** (1.20 g, 4.31 mmol) and the reaction was put under an atmosphere of Argon (balloon). THF (6.50 cm^3) was charged to the flask *via* syringe and the reaction was cooled to 0 °C. Sodium hydride (60% suspension, 198 mg, 4.96 mmol) was added quickly from a clock glass, the reaction was returned to an atmosphere of Ar and stirred for 30 min at 0 °C. Methyl iodide (300 µL, 4.74 mmol) was added *via* syringe and the reaction was stirred at room temperature overnight. Deionised water (15 cm^3) and EtOAc (40 cm^3) were added and the organic layer removed. The aqueous layer was extracted with EtOAc (4 x 10 cm^3) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow-brown oil. Purification by column chromatography (8:2 CH_2Cl_2-hexane, R_f 0.2) gave (1*R*,2*R*)-**251** (847 mg, 67%) as a yellow oil, $[\alpha]_D^{20}$ = -92.6 (*c* 1.10 in $CHCl_3$). The ^1H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.40:0.60.

δ_H (400 MHz, DMSO-d_6): 2.67 (s, 1.2H, N-CH_3), 2.69 (dd, 0.6H, J 15.6, 9.5, H-3a), 2.79 (s, 1.8H, N-CH_3), 2.84 (dd, 0.4H, J 15.6, 9.5, H-3a), 3.21 (dd, 0.6H, J 15.6, 8.0, H-3b), 3.39-3.36 (m, 0.4H, (under H_2O resonance), H-3b), 4.60-4.66 (m, 1H, H-2),

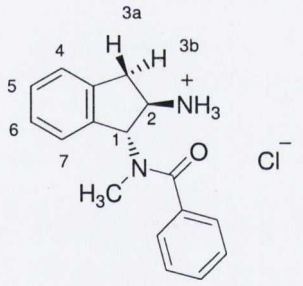
5.09 (d, 0.6H, J 7.8, H-1), 6.15 (d, 0.4H, J 7.8, H-1), 7.25-7.35 (m, 4H, H-4 to H-7), 7.44-7.55 (m, 5H, Ar)

δ_C (100 MHz, DMSO-d_6): 28.2, 32.9, 34.5, 35.5, 63.0, 63.2, 64.0, 69.1, 123.3, 123.7, 125.1, 125.2, 126.4, 126.8, 127.3, 127.6, 128.4, 128.5, 128.67, 128.71, 129.6, 129.7, 136.2(q), 136.4(q), 137.4(q), 137.8(q), 138.7(q), 139.7(q), 171.5(q), (C=O), 171.6(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3026, 2921, 2097 (N_3), 1635 (C=O), 1396, 1263, 748, 700

HRMS (*m/z* - ES): Found 293.1404 (M^+ + H. $C_{17}H_{17}N_4O$ requires 293.1402).

5.3.2.28 (1*R*,2*R*)-*trans*-1-(Benzoyl-methyl-amino)-indan-2-yl-ammonium chloride (252)



Procedure F was followed using azide (1*R*,2*R*)-**251** (850 mg, 2.91 mmol), triphenylphosphine (763 mg, 2.91 mmol), THF (24 cm^3) and water (4.00 cm^3). Concentration of the aqueous layer produced an off-white solid which was purified by washing with diethylether to yield (1*R*,2*R*)-**252** (817 mg, 93%) as an off-white solid, m.p. 254-255 °C; $[\alpha]_D^{20}$ = -66.4 (*c* 1.15 in MeOH). The ^1H and ^{13}C NMR spectra of this compound indicate the presence of two rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.33:0.67.

δ_H (600 MHz, DMSO-d_6): 2.68 (s, 2.01H, N-CH_3), 2.77 (s, 0.99H, N-CH_3), 2.79-2.84 (m, 0.33H, H-3a), 2.98 (dd, 0.67H, J 15.0, 9.2, H-3a), 3.26-3.30 (m, 0.33H, H-3b), 3.38 (dd, 0.67H, J 15.0, 7.2, H-3b),

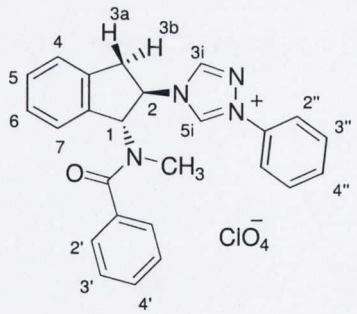
4.09-4.14 (m, 1H, H-2), 5.33 (d, 0.33H, J 8.0, H-1), 6.27 (d, 0.67H, J 8.0, H-1), 7.22-7.70 (m, 9H, H-4 to H-7 and Ar), 8.68 (s (broad), 0.99H, NH_3), 8.83 (s (broad), 2.01H, NH_3)

δ_C (150 MHz, DMSO-d_6): 28.5, 33.4, 34.3, 34.8, 53.0, 53.2, 62.5, 67.3, 123.5, 123.7, 125.4, 125.5, 126.90, 126.93, 127.8, 128.0, 128.5, 128.7, 129.0, 129.1, 129.5, 130.0, 136.7(q), 136.9(q), 138.0(q), 138.2(q), 138.8(q), 139.5(q), 171.8(q), (C=O), 172.5(q), (C=O)

ν_{max} (neat)/cm^{-1}: 2924, 2851 (NH_3^+), 1622 (C=O), 1598, 1481, 1386, 751, 731, 697

HRMS (*m/z* - ES): Found 267.1506 (M^+ - Cl. $C_{17}H_{19}N_2O$ requires 267.1497).

5.3.2.29 (1*R*,2*R*)-*trans*-4-[1-(Benzoyl-methyl-amino)-indan-2-yl]-1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate (242)



Procedure J was followed using oven-dried molecular sieves (4Å, 1.80 g), oxadiazolium salt **231** (476 mg, 1.93 mmol), and (1*R*,2*R*)-**252** (as free-base amine, 490 mg, 1.84 mmol) in CH_3CN (5.00 cm^3). The reaction was heated at reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by preparative thin layer chromatography (7:3 EtOAc-hexane, R_f 0.2) gave (1*R*,2*R*)-**242** (182 mg, 20%) as an orange solid, m.p. 155-156 °C; $[\alpha]_D^{20}$ = -53.0 (*c* 0.82 in $CHCl_3$). The ^1H NMR spectrum

of this compound indicates the presence of 2 rotameric species at rt in CD_3CN - the ratio of these was found to be 0.20:0.80, the ^{13}C NMR spectrum indicates the major rotamer only.

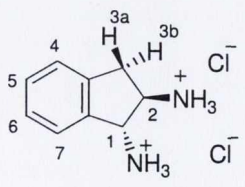
δ_H (600 MHz, CD_3CN): 2.83-2.97 (m, 3H, N-CH_3), 3.31 (s (broad), 0.20H, H-3a), 3.55 (s (broad), 0.80H, H-3a), 3.67 (s (broad), 0.20H, H-3b), 3.90 (s (broad), 0.80H, H-3b), 5.43-5.47 (app. q, 1H, H-2), 5.88 (s (broad), 0.20H, H-1), 6.65 (s (broad), 0.80H, H-1), 7.16-7.62 (m, 9H, H-4 to H-7 and H-2' to H-4'), 7.73-7.88 (m, 5H, H-2'', H-3'' and H-4''), 8.80 (s (broad), 0.20H, H-3i), 9.16 (s (broad), 0.80H, H-3i), 9.78 (s (broad), 0.20H, H-5i), 10.25 (s (broad), 0.80H, H-5i)

δ_C (150 MHz, CD_3CN): 34.3, 37.7, 63.5, 66.0, 122.0, 125.6, 126.4, 128.4, 129.1, 129.4, 130.3, 131.2, 131.4, 132.1, 136.0(q), 136.6(q), 137.0(q), 139.7(q), 141.4, 145.4, 174.6(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3131, 3068, 1623 (C=O), 1600, 1571, 1479, 1403, 1084 (C-N-C), 760, 689

HRMS (*m/z* - ES): Found 395.1873 (M^+ - ClO_4. $C_{25}H_{23}N_4O$ requires 395.1872).

5.3.2.30 (1*R*,2*R*)-*trans*-Indan-1,2-diammonium chloride (253)



Procedure F was followed using boc-protected azide (1*R*,2*R*)-**246** (1.50 g, 5.47 mmol), triphenylphosphine (1.43 g, 5.47 mmol), THF (46 cm^3) and water (4.00 cm^3). Concentration of the aqueous layer produced a white solid which was purified by

washing with diethylether to yield (1*R*,2*R*)-**253** (1.17 g, 97%) as a white solid, m.p. 295-296 °C (dec.); $[\alpha]_D^{20}$ = -11.6 (*c* 0.50 in MeOH).

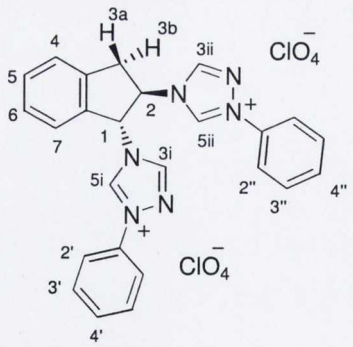
δ_H (600 MHz, DMSO-d_6): 3.07 (dd, 1H, J 16.3, 7.3, H-3b), 3.43 (dd, 1H, J 16.3, 8.4, H-3a), 4.02-4.06 (app. q, 1H, H-2), 4.94 (d, 1H, J 6.6, H-1), 7.37-7.43 (m, 3H, H-4 to H-6), 7.63 (d, 1H, J 7.3, H-7), 8.82 (s (broad), 3H, NH_3), 9.04 (s (broad), 3H, NH_3)

δ_C (150 MHz, DMSO-d_6): 35.1, 54.5, 58.0, 124.6, 125.0, 127.6, 129.6, 136.2(q), 139.5(q)

ν_{max} (neat)/cm^{-1}: 3034, 2967, 2816 (NH_3^+), 2579, 2484, 1594, 1562, 1507, 750

HRMS (*m/z* - ES): Found 149.1080 (M^+ - 2HCl + H. $C_9H_{13}N_2$ requires 149.1079).

5.3.2.31 (1*R*,2*R*)-*trans*-*N*,*N*-Indan-1,2-yl-di-(1-phenyl-4*H*-[1,2,4]triazol-1-ium perchlorate) (243)



Procedure J was followed using oven-dried molecular sieves (4Å, 2.00 g), oxadiazolium salt **231** (2.15 g, 8.71 mmol), and (1*R*,2*R*)-**253** (as free-base amine, 646 mg, 4.36 mmol) in CH_3CN (13 cm^3). H_2SO_4 (1.00 cm^3, 18.40 mmol) was added to the reaction *via* syringe and the reaction was heated at reflux for 5 d. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a brown oily residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.3) followed by recrystallisation

from hot EtOAc gave (1*R*,2*R*)-**243** (895 mg, 34%) as an off-white solid, m.p. 74-75 °C (dec.); $[\alpha]_D^{20} = -62.2$ (*c* 0.50 in MeOH).

δ_H (600 MHz, DMSO-d_6): 3.84 (dd, 1H, J 16.5, 8.7, H-3b), 3.93 (dd, 1H, J 16.5, 9.0, H-3a), 5.90-5.94 (app. q, 1H, H-2), 6.85 (d, 1H, J 7.9, H-1), 7.50-7.52 (m, 2H, H-5 and H-7), 7.59-7.62 (m, 2H, H-4 and H-6), 7.67-7.71 (m, 2H, H-4' and H-4''), 7.74-7.78 (m, 4H, H-3' and H-3''), 7.95-7.96 (m, 4H, H-2' and H-2''), 9.62 (s, 1H, H-3i), 9.69 (s, 1H, H-3ii), 11.05 (s, 1H, H-5i), 11.15 (s, 1H, H-5ii)

δ_C (150 MHz, DMSO-d_6): 37.1, 64.4, 68.0, 120.4, 120.5, 124.9, 125.2, 128.5, 130.3, 130.4, 130.7, 130.76, 130.79, 134.5(q), 134.8(q), 134.9(q), 139.1(q), 141.59, 141.63, 144.4, 144.7

ν_{max} (neat)/cm^{-1}: 3126, 3038, 1597, 1564, 1487, 1460, 1083 (C-N-C), 768, 746, 688

HRMS (*m/z* - ES): Found 405.1829 (M^+ - H - $2ClO_4$. $C_{25}H_{21}N_6$ requires 405.1828).

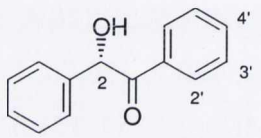
5.3.3 Experimental data for Section 3.3

5.3.3.1 Procedure K: General procedure for organocatalysed-benzoin condensation reactions using KHMDS as base

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added the appropriate precatalyst (0.11 mmol), and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was washed in CH_2Cl_2 with aq. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The aldehyde was distilled under vacuum and used directly. Toluene was charged to the reaction, followed by addition *via* syringe of KHMDS (0.5 M solution in toluene, 220 μL, 0.11 mmol) over

5 min. The reaction was stirred for 15 min and the required aldehyde (1.10 mmol) was added drop wise to the reaction over 5 min. The reaction was stirred at room temperature for 16 h (unless otherwise indicated). To quench the reaction EtOAc (6.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The organic layer was removed and the aqueous layer was washed with EtOAc (4 x 6.0 cm^3). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified using column chromatography. Note: The internal standard styrene (31.5 μL, 0.28 mmol) was added to the reaction prior to the work-up.

5.3.3.2 (*S*)-2-Hydroxy-1,2-diphenyl-ethanone (15) (Table 3.4, entry 11)

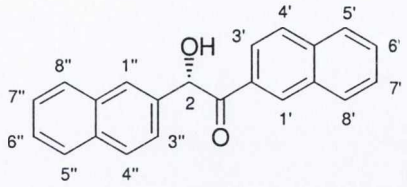


Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (670 μL), KHMDS (0.5M solution in toluene, 220 μL, 0.11 mmol) and benzaldehyde (**11**) (112 μL, 1.10 mmol). The reaction was stirred at room temperature for 18 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave (*S*)-**15** (13.6 mg, 12%) as a white solid, m.p. 131-132 °C, lit.,[375] 132-133 °C, 62% *ee*. $[\alpha]_D^{20}$ = +62.8 (*c* 0.20 in MeOH), lit.,[376] $[\alpha]_D^{20}$: +146.5 (*c* 1.00 in MeOH), for *S* enantiomer with 90% *ee*.

CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 21.4 min (minor enantiomer) and 29.1 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.58 (d, 1H, J 5.8, OH), 5.98 (d, 1H, J 5.8, H-2), 7.29-7.38 (m, 5H, Ar) 7.41-7.44 (app. t, 2H, H-3'), 7.53 (t, 1H, J 7.0, H-4'), 7.93 (d, 2H, J 7.1, H-2').

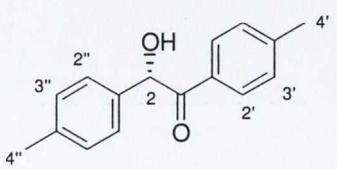
5.3.3.3 (*S*)-2-Hydroxy-1,2-di-naphthalen-2-yl-ethanone (262) (Table 3.5, entry 1)



Procedure K was followed using precatalyst gave (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (400 μL), KHMDS (0.5M solution in toluene, 220 μL, 0.11 mmol,) and 2-naphthaldehyde (**255**) (171.8 mg, 1.10 mmol) in toluene (380 μL). The reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave (*S*)-**262** (62.6 mg, 36%) as a pale yellow solid, m.p. 127-128 °C, lit.,[377] 127-128 °C, 35% *ee*. $[\alpha]_D^{20}$ = -6.8 (*c* 0.63 in $CHCl_3$), lit.,[176] $[\alpha]_D^{20}$: +21.0 (*c* 1.10 in $CHCl_3$), for *R* enantiomer with 99% *ee*.
CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 8/2, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 28.1 min (minor enantiomer) and 47.7 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.75 (s (broad), 1H, OH), 6.30 (s, 1H, H-2), 7.47-7.50 (m, 3H, H-6'' to H-8''), 7.52-7.55 (app. t, 1H, H-7'), 7.58-7.61 (app. t, 1H, H-6'), 7.78-7.85 (m, 5H, H-4', H-5' and H-3'' to H-5''), 7.89 (d, 1H, J 8.5, H-8'), 7.94 (s, 1H, H-1''), 8.01 (d, 1H, J 8.5, H-3'), 8.53 (s, 1H, H-1').

5.3.3.4 (*S*)-2-Hydroxy-1,2-*bis*-(4-methylphenyl)ethanone (274) (Table 3.5, entry 3)



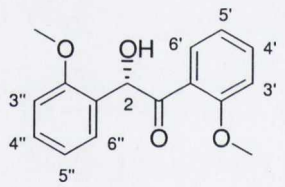
Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (650 μL), KHMDS (0.5M solution in toluene, 220 μL, 0.11 mmol)

and *p*-tolualdehyde (**272**) (130 μL, 1.10 mmol). The reaction was stirred at room temperature for 18 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave (*S*)-**274** (12.8 mg, 10%) as a yellow solid, m.p. 90-91 °C, lit.,[378] 89-90 °C, 45% *ee*. $[\alpha]_D^{20}$ = +51.3 (*c* 0.18 in MeOH), lit.,[126] $[\alpha]_D^{20}$: -130.8 (*c* 1.00 in MeOH), for *R* enantiomer with 82% *ee*.

CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 29.3 min (minor enantiomer) and 33.8 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 2.31 (s, 3H, CH_3-4''), 2.38 (s, 3H, CH_3-4'), 4.60 (s (broad), 1H, OH), 5.92 (s (broad), 1H, H-2), 7.13-7.34 (m, 6H, (overlapping with $CHCl_3$ resonance), H-3', H-2'' and H-3''), 7.83 (d, 2H, J 8.0, H-2').

5.3.3.5 (*S*)-2-Hydroxy-1,2-*bis*-(2-methoxy-phenyl)ethanone (264) (Table 3.5, entry 4)

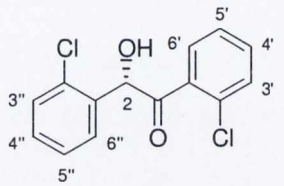


Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (480 μL), KHMDS (0.5M solution in toluene, 220 μL, 0.11 mmol) and *o*-anisaldehyde (**256**) (149.8 mg, 1.10 mmol) in toluene (300 μL). The reaction was stirred at room temperature for 24 h. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave (*S*)-**264** (42.9 mg, 29%) as an off-white solid, m.p. 98-99 °C, lit.,[379] 98-99 °C, 54% *ee*. $[\alpha]_D^{20}$ = +39.1 (*c* 0.43 in $CHCl_3$), lit.,[119] $[\alpha]_D^{20}$: +123.0 (*c* 1.00 in $CHCl_3$), for *S* enantiomer with 98% *ee*.

CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 30.8 min (major enantiomer) and 43.7 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 3.74 (s, 3H, OCH_3-2''), 3.75 (s, 3H, OCH_3-2'), 4.50 (s (broad), 1H, OH), 6.13 (s, 1H, H-2), 6.76-6.81 (app. t, 2H, H-3' and H-3''), 6.84-6.88 (app. t, 1H, H-5''), 6.93-6.97 (app. t, 1H, H-5'), 7.17-7.22 (m, 2H, H-4'' and H-6''), 7.37-7.41 (app. t, 1H, H-4'), 7.70 (d, 1H, J 7.5, H-6').

5.3.3.6 (*S*)-1,2-*Bis*-(2-chloro-phenyl)-2-hydroxy-ethanone (266) (Table 3.5, entry 6)

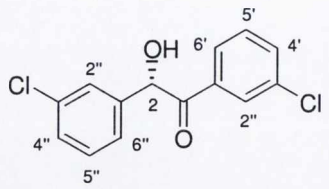


Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (660 µL), KHMDS (0.5M solution in toluene, 220 µL, 0.11 mmol) and *o*-chlorobenzaldehyde (**258**) (124 µL, 1.10 mmol). The reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave (*S*)-**266** (11.6 mg, 8%) as a colourless solid, m.p. 61-62 °C, lit.,[378] 63-64 °C, 28% *ee*. $[\alpha]_D^{20}$ = +9.3 (*c* 0.17 in $CHCl_3$), lit.,[176] $[\alpha]_D^{20}$: -46.0 (*c* 1.00 in $CHCl_3$), for *R* enantiomer with 97% *ee*.

CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.8 min (major enantiomer) and 25.8 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 3.30 (s (broad), 1H, OH), 6.31 (s, 1H, H-2), 7.15-7.23 (m, 5H, H-4', H-5', H-4'' to H-6''), 7.31-7.34 (m, 3H, H-3', H-6' and H-3'').

5.3.3.7 (*S*)-1,2-*Bis*-(3-chloro-phenyl)-2-hydroxy-ethanone (267) (Table 3.5, entry 7)

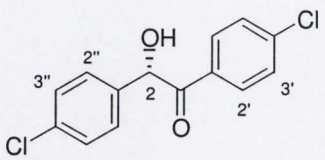


Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (660 µL), KHMDS (0.5M solution in toluene, 220 µL, 0.11 mmol) and *m*-chlorobenzaldehyde (**259**) (125 µL, 1.10 mmol). The reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave (*S*)-**267** (73.1 mg, 47%) as an off-white solid, m.p. 75-76 °C, lit.,[378] 76-77 °C, 1% *ee*. $[\alpha]_D^{20}$ = +2.4 (*c* 0.73 in $CHCl_3$), lit.,[176] $[\alpha]_D^{20}$: -31.0 (*c* 1.20 in $CHCl_3$), for *R* enantiomer with 99% *ee*.

CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.7 min (minor enantiomer) and 26.9 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.50 (d, 1H, J 5.5, OH), 5.90 (d, 1H, J 5.5, H-2), 7.23-7.41 (m, 5H, H-5', H-2'', H-4'', to H-6''), 7.53 (d, 1H, J 8.0, H-4'), 7.76 (d, 1H, J 7.5, H-6'), 7.93 (s, 1H, H-2').

5.3.3.8 (*S*)-1,2-*Bis*-(4-chloro-phenyl)-2-hydroxy-ethanone (268) (Table 3.5, entry 8)



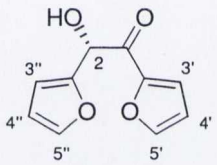
Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (400 µL), KHMDS (0.5M solution in toluene, 220 µL, 0.11 mmol) and *p*-chlorobenzaldehyde (**260**) (154.6 mg, 1.10 mmol) in toluene (380 µL). The reaction was stirred at room temperature for 16 h. Purification by column

chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave (*S*)-**268** (48.8 mg, 32%) as an off-white solid, m.p. 88-89 °C, lit.,[378] 87-88 °C, 6% *ee*. $[\alpha]_D^{20}$ = +1.4 (*c* 0.49 in MeOH), lit.,[124] $[\alpha]_D^{20}$: -12.3 (*c* 1.00 in MeOH), for *R* enantiomer with 29% *ee*.

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.6 mL min^{-1}, RT, UV detection at 220 nm, retention times: 34.7 min (major enantiomer) and 37.8 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.49 (s (broad), 1H, OH), 5.90 (s, 1H, H-2), 7.26-7.29 (m (overlapping with $CHCl_3$ resonance), 2H, H-3''), 7.32 (d, 2H, J 8.0, H-2''), 7.40 (d, 2H, J 7.8, H-3'), 7.84 (d, 2H, J 7.8, H-2').

5.3.3.9 (*S*)-1,2-Di-furan-2-yl-2-hydroxy-ethanone (275) (Table 3.5, entry 9)



Procedure K was followed using precatalyst (1*R*,2*R*)-**241a** (52.9 mg, 0.11 mmol), with addition of toluene (690 µL), KHMDS (0.5M solution in toluene, 220 µL, 0.11 mmol) and 2-furaldehyde (**273**) (91 µL, 1.10 mmol). The reaction was stirred at room temperature for 18 h. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave (*S*)-**275** (51.3 mg, 49%) as a pale yellow solid, m.p. 134-135 °C, lit.,[179] 135-136 °C, 1% *ee*. $[\alpha]_D^{20}$ = +0.6 (*c* 0.51 in MeOH), lit.,[176] $[\alpha]_D^{20}$: -21.6 (*c* 0.10 in MeOH), for *R* enantiomer with 92% *ee*.

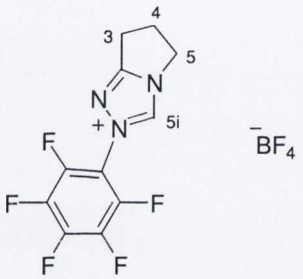
CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 33.3 min (major enantiomer) and 40.9 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.22 (s (broad), 1H, OH), 5.82 (s (broad), 1H, H-2), 6.37 (dd, 1H, J 3.3, 1.5, H-4''), 6.42 (d, 1H, J 3.3, H-5''), 6.56 (dd, 1H, J 3.5, 1.5, H-4'), 7.26 (d, 1H, J 3.5, H-5'), 7.40 (d, 1H, J 1.5, H-3''), 7.64 (app. s, 1H, H-3').

5.4 Experimental data for Section 4

5.4.1 Experimental data for Section 4.1

5.4.1.1 2-Pentafluorophenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoro borate (131)

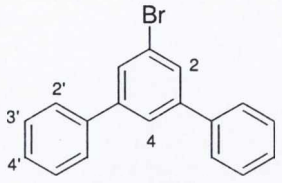


An oven-dried 500 cm^3 round bottomed flask, equipped with a magnetic stirrer, was put under an atmosphere of Argon (balloon). To the reaction vessel was added 2-pyrrolidinone (2.00 g, 26.32 mmol) and CH_2Cl_2 (130 cm^3). Trimethyloxonium tetrafluoroborate (3.89 g 26.32 mmol) was added to the flask and the reaction was stirred under Ar for 12 h. Pentafluorophenyl hydrazine (5.21 g, 26.32 mmol) was added to the clear solution and the reaction was stirred at room temperature for a further 2 h. Concentration of the crude reaction *in vacuo* produced a pale orange solid. The crude reaction was heated under vacuum at 110 °C for 2 h. Triethylorthoformate (21.9 cm^3, 131.61 mmol) was charged to the reaction which was subsequently heated at 110 °C for 1 h (under Ar). Upon cooling to ambient temperature a precipitate appeared. The solid was filtered and washed with toluene (60 cm^3) to give a white solid, pure **131** (4.68 g, 49%), m.p. 248-249 °C, lit.,[249] 248-253 °C.

δ_H (600 MHz, DMSO-d_6): 2.73-2.78 (m, 2H, H-4), 3.23-3.31 (m, 2H, H-5), 4.46-4.49 (m, 2H, H-3), 10.53 (s, 1H, H-5i)

δ_F (376 MHz, DMSO-d_6): -160.64 (app. t, 2F), -148.81 (t, 1F, J 23.0), -146.47 (d, 2F, J 18.4).

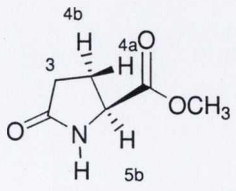
5.4.1.2 5-Bromo-*m*-terphenyl (299b)



To an oven-dried 100 cm^3 round bottomed flask, equipped with a magnetic stirrer, was added 1,3,5-tribromobenzene (**298**) (1.18 g, 3.75 mmol) and $Pd(PPh_3)_4$ (130 mg, 0.11 mmol). The flask was equipped with a reflux condenser, sealed with a rubber septum and placed under an atmosphere of Ar. Subsequently, a solution of phenylboronic acid (972 mg, 7.98 mmol) in toluene (17 cm^3) and a Na_2CO_3 solution (1.0 M, 14 cm^3, degassed) were added to the reaction vessel *via* syringe and the mixture was heated at reflux (100 °C) for 48 h. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude brown liquid was partitioned between CH_2Cl_2 (15 cm^3) and H_2O (15 cm^3). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 cm^3 aliquots). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo* to give a brown oil. Purification by column chromatography (hexane, R_f 0.4) yielded **299b** as a white solid (589 mg, 51%), m.p. 105-107 °C, lit.,[380] 105-106 °C.

δ_H (400 MHz, $CDCl_3$): 7.40 (t, 2H, J 7.3, H-4'), 7.48-7.51 (app. t, 4H, H-3'), 7.63 (d, 4H, J 8.1, H-2'), 7.73 (s, 3H, H-2 and H-4).

5.4.1.3 (5*S*)-Oxopyrrolidine-2-carboxylic acid methyl ester (302)



To an oven-dried 250 cm^3 round bottomed flask was charged (*S*)-pyroglutamic acid (**301**) (10.00 g, 77.45 mmol) and DOWEX-50W resin (X8-200, 5.00 g). Methanol (HPLC grade, 93 cm^3) was added to the flask, which was then equipped with a reflux

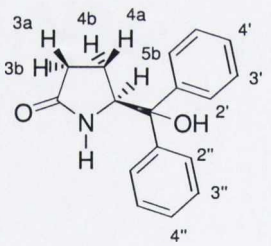
condenser and placed under an atmosphere of Argon (balloon). The reaction was heated at reflux (90 °C) for 36 h. Filtration to remove the solid and consequent concentration of the filtrate *in vacuo* yielded a colourless oil. Purification by column chromatography (9:1 EtOAc-hexane, R_f 0.1) gave (*S*)-**302** (10.64 g, 96%) as a pale yellow oil; $[\alpha]_D^{20}$ = -2.4 (c 1.00 in CH_2Cl_2), lit.,[381] $[\alpha]_D^{20}$ = -7.0 (*c* 1.00 in CH_2Cl_2), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): 2.13-2.21 (m, 1H, H-4a), 2.25-2.48 (m, 3H, H-3 and H-4b), 3.73 (s, 3H, O-CH_3), 4.22 (dd, 1H, J 8.8, 5.0, H-5b), 7.35 (s (broad), 1H, N-H)

δ_C (150 MHz, $CDCl_3$): 24.8, 29.3, 52.5, 55.5, 172.7(q), (C=O), 178.5(q), (C=O)

HRMS (*m/z* - ES): Found 166.0477 (M^+ + Na. $C_6H_9NO_3Na$ requires 166.0480).

5.4.1.4 (5*S*)-(Hydroxy-diphenyl-methyl)-pyrrolidin-2-one (303a)

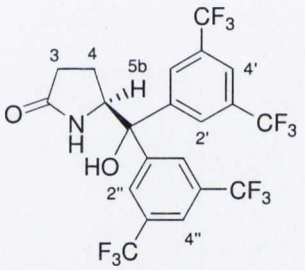


To an oven-dried 250 cm^3 round bottomed flask, equipped with a magnetic stirrer, was added methyl ester (*S*)-**302** (7.49 g, 52.33 mmol) and the reaction was put under an atmosphere of Ar. THF (41 cm^3) was added *via* syringe and the reaction was cooled to -78 °C. Phenylmagnesium bromide (**300a**) (3.0 M solution in diethylether, 60 cm^3, 180.00 mmol) was added slowly over 20 min and the reaction was stirred for an additional 60 min at -78 °C. The reaction was left stirring overnight to warm to room temperature. The reaction mixture was cooled to 0 °C and quenched with HCl (5% (*v/v*), 60 cm^3). The aqueous layer was extracted with CH_2Cl_2 (5 x 200 cm^3). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give an off-white solid. Recrystallisation from CH_2Cl_2 and Et_2O gave (*S*)-**303a** (9.93 g, 71%) as a white

solid, m.p. 192-193 °C, lit.,[382] 191-192 °C; $[\alpha]_D^{20}$ = -79.1 (*c* 1.30 in $CHCl_3$), lit.,[382] $[\alpha]_D^{20}$ = -80.8 (*c* 1.30 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): 1.94-2.01 (m, 1H, H-4a), 2.11-2.17 (m, 1H, H-4b), 2.24-2.30 (m, 1H, H-3a), 2.33-2.39 (m, 1H, H-3b), 2.74 (s (broad), 1H, OH), 4.74 (dd, 1H, J 8.3, 5.0, H-5b), 5.47 (s (broad), 1H, N-H), 7.23 (t, 1H, J 7.3, H-4''), 7.26 (t, 1H, J 7.3, H-4'), 7.31-7.34 (app. t, 2H, H-3''), 7.35-7.38 (app. t, 2H, H-3'), 7.46 (d, 2H, J 7.5, H-2''), 7.50 (d, 2H, J 8.3, H-2').

5.4.1.5 (5*S*)-*Bis*-(3,5-*bis*-trifluoromethyl-phenyl)-hydroxy-methyl)-pyrrolidin-2-one (303c)



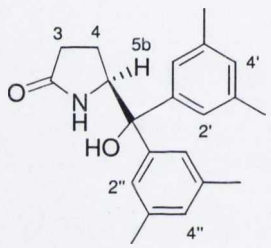
An oven-dried 100 cm^3 round bottomed flask was placed under an atmosphere of Ar. 3,5-*Bis*-(trifluoromethyl)-bromobenzene (**299c**) (1.00 cm^3, 5.80 mmol) and THF (600 µL) were charged to the reaction vessel and the reaction was cooled to -15 °C. A solution of isopropyl magnesium bromide (1.0 M in THF, 6.40 cm^3, 6.38 mmol) was added slowly *via* syringe. The reaction was stirred at -10 °C for 1 h and the yellow solution was then cooled to -50 °C. Methyl ester (*S*)-**302** (241 mg, 1.69 mmol) was added slowly over 10 min and the reaction was stirred for 1 h at -50 °C and left to warm to room temperature overnight. The reaction mixture was quenched by slow addition of HCl (5% (*v/v*), 5.0 cm^3) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (5 x 5 cm^3). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow-orange solid. Purification by column chromatography (4:6 EtOAc:hexane, R_f 0.3) yielded (*S*)-**303c** (547 mg, 60%) as an off-white solid, m.p. 155-

156 °C, lit.,[315] 157-158 °C; $[\alpha]_D^{20}$ = -49.3 (*c* 0.50 in CH_2Cl_2), lit.,[315] $[\alpha]_D^{20}$ = -57.2 (*c* 0.50 in CH_2Cl_2), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): 1.88-1.94 (m, 2H, H-4), 2.16-2.35 (m, 2H, H-3), 4.29 (s (broad), 1H, OH), 4.85 (dd, 1H, J 8.3, 6.0, H-5b), 6.38 (s, 1H, N-H), 7.82 (s, 1H, H-4''), 7.85 (s, 1H, H-4'), 7.94 (s, 2H, H-2'), 8.03 (s, 2H, H- 2'')

δ_F (376 MHz, $CDCl_3$): -62.88, -62.86.

5.4.1.6 (5*S*)-[*Bis*-(3,5-dimethyl-phenyl)-hydroxy-methyl]-pyrrolidin-2-one (303d)



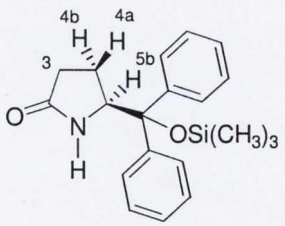
Mg filings (859 mg, 35.33 mmol) were freshly ground using a mortar and pestle and placed under Argon in an oven-dried 100 cm^3 round bottomed flask. THF (38 cm^3) and 3,5-dimethyl-bromobenzene (**299d**) (4.00 cm^3, 29.44 mmol) were charged to the reaction. Dibromoethane (2 drops) was added to the reaction after which it was equipped with a reflux condenser. The vessel was heated using a heat gun for 10 sec to initiate the reaction, which was then heated at reflux (80 °C) for 2 h. The reaction was cooled to 0 °C and methyl ester (*S*)-**302** (1.00 cm^3, 8.56 mmol) was added slowly over 20 min. The reaction was stirred overnight and allowed to warm to room temperature. The reaction mixture was quenched by slow addition of HCl (5% (*v/v*), 20 cm^3) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (5 x 15 cm^3). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow-orange solid. Purification by column chromatography (6:4 EtOAc:hexane, R_f 0.2) yielded (*S*)-**303d** (2.05 g, 74%) as an off-white solid, m.p. 79-80 °C, lit.,[315] 79-80 °C; $[\alpha]_D^{20}$ = -81.2 (*c* 1.00 in $CHCl_3$), lit.,[315] $[\alpha]_D^{20}$ = -82.3 (*c* 1.00 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): 1.97-2.03 (m, 1H, H-4), 2.12-2.17 (m, 1H, H-4), 2.29-2.42 (m, 14H, H-3, CH_3-3' and CH_3-3''), 4.73 (dd, 1H, J 7.9, 5.7, H-5b), 5.50 (s (broad), 1H, N-H), 6.89 (s, 1H, H-4'), 6.91 (s, 1H, H-4''), 7.07 (s, 2H, H-2'), 7.10 (s, 2H, H-2'').

5.4.1.7 Procedure L: General procedure for the synthesis of trimethyl-silylated lactams (*S*)-304a,c,d

To an oven-dried 25 cm^3 round bottomed flask, equipped with a magnetic stirrer, was added the relevant lactam (0.88 mmol) and 4-dimethylaminopyridine (10.7 mg, 0.09 mmol). The flask was fitted with a rubber septum seal and put under an atmosphere of Argon. CH_2Cl_2 (8.75 cm^3) was injected *via* syringe and the reaction was cooled to 0 °C. Triethylamine (426 μL, 3.06 mmol) was charged to the flask and the reaction was stirred for 20 min. Trimethylsilane chloride (1.07 cm^3, 8.48 mmol) was added to the reaction slowly over 30 min. The reaction was left to stir overnight at ambient temperature. The reaction was quenched *via* slow addition of deionised water (10 cm^3). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 cm^3 aliquots). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography provided the TMS-protected lactam product.

5.4.1.8 (5*S*)-(Diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (304a)

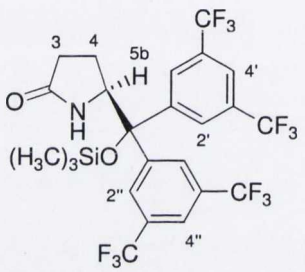


Procedure L was followed using lactam (*S*)-**303a** (234 mg, 0.88 mmol), 4-dimethylaminopyridine (10.7 mg, 0.09 mmol), CH_2Cl_2 (8.75 cm^3), triethylamine (426 μL, 3.06 mmol) and trimethylsilane chloride (1.07 cm^3, 8.48 mmol). Purification of the resultant brown residue by column chromatography (6:4 EtOAc:hexane, R_f 0.4) provided (*S*)-**304a** (278 mg, 93%) as a white solid, m.p. 120-121 °C, lit.,[129] 120-122 °C;

$[\alpha]_D^{20}$ = -76.3 (*c* 0.50 in $CHCl_3$), lit.,[129] $[\alpha]_D^{20}$ = -81.6 (*c* 0.50 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): -0.10 (s, 9H, $Si(CH_3)_3$, 128-1.38 (m, 1H, H-4a), 1.94-2.02 (m, 1H, H-4b), 2.07-2.16 (m, 2H, H-3), 4.64 (dd, 1H, J 7.8, 4.3, H-5b), 5.89 (s (broad), 1H, N-H), 7.32-7.37 (m, 10H, Ar).

5.4.1.9 (5*S*)-*Bis*-(3,5-*bis*-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (304c)

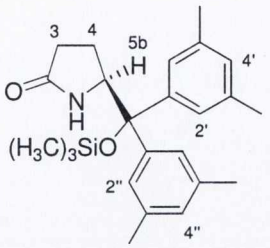


Procedure L was followed using lactam (*S*)-**303c** (2.56 g, 4.75 mmol), 4-dimethylaminopyridine (58.0 mg, 0.48 mmol), CH_2Cl_2 (24 cm^3), triethylamine (2.31 cm^3, 16.61 mmol) and trimethylsilane chloride (5.82 cm^3, 46.03 mmol). Purification of the resultant brown residue by column chromatography (2:8 EtOAc:hexane, R_f 0.2) yielded (*S*)-**304c** (2.70 g, 93%) as a white solid, m.p. 130-131 °C, lit.,[315] 129-130 °C; $[\alpha]_D^{20}$ = -56.2 (*c* 0.75 in CH_2Cl_2), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, $CDCl_3$): -0.05 (s, 9H, $Si(CH_3)_3$, 1.49-1.52 (m, 1H, H-3b), 1.90-1.97 (m, 1H, H-4b), 2.09-2.17 (m, 2H, H-3a and H-4a), 4.72 (dd, 1H, J 5.9, 4.5, H-5b), 6.13 (s, 1H, N-H), 7.70 (s, 2H, H-2''), 7.79 (s, 2H, H-2'), 7.90 (s, 1H, H-4''), 7.94 (s, 1H, H-4')

δ_F (376 MHz, $CDCl_3$): -63.48. Note: coalescence of both ^{19}F signals.

5.4.1.10 (5*S*)-[*Bis*-(3,5-dimethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidin-2-one (304d)



Procedure L was followed using lactam (*S*)-**303d** (1.40 g, 4.33 mmol), 4-dimethylaminopyridine (52.9 mg, 0.43 mmol), CH_2Cl_2 (20 cm^3), triethylamine (2.11 cm^3, 15.14 mmol) and trimethylsilane chloride (5.31 cm^3, 41.96 mmol). Purification of the resultant yellow solid by column chromatography (4:6 EtOAc:hexane, R_f 0.3) yielded (*S*)-**304d** (1.47 g, 86%) as a white solid, m.p. 81-82 °C, lit.,[315] 82-83 °C; $[\alpha]_D^{20}$ = -75.7 (*c* 1.00 in $CHCl_3$), lit.,[315] $[\alpha]_D^{20}$ = -78.0 (*c* 1.00 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

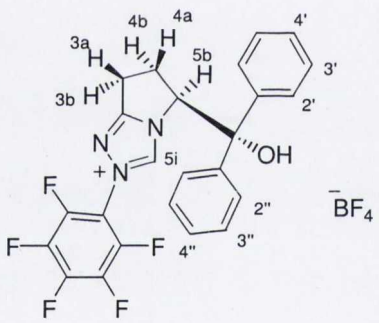
δ_H (600 MHz, $CDCl_3$): -0.07 (s, 9H, $Si(CH_3)_3$), 1.56-1.62 (m, 1H, H-4), 2.01-2.09 (m, 3H, H-3 and H-4), 2.30 (s, 6H, CH_3-3''), 2.33 (s, 6H, CH_3-3'), 4.59-4.60 (m, 1H, H-5b), 5.77 (s (broad), 1H, N-H), 6.91 (s, 2H, H-2'), 6.93 (s, 1H, H-4'), 6.95 (s, 2H, H-2''), 6.96 (s, 1H, H-4'').

5.4.1.11 Procedure M: General procedure for synthesis of chiral bifunctional triazolium salts, with *in situ* deprotection of alcohol group

To an oven-dried 250 cm^3 round bottomed flask, equipped with a magnetic stirring bar, was added the appropriate TMS-protected lactam (5.89 mmol) and the reaction was put under an atmosphere of Argon. CH_2Cl_2 (28 cm^3) was injected *via* a syringe to give a clear solution. Trimethyloxonium tetrafluoroborate (871 mg, 5.89 mmol) was added and the reaction was returned to an atmosphere of Ar. The reaction was stirred for 12 h resulting in a pale orange suspension. Pentafluorophenyl hydrazine (1.17 g, 5.89 mmol) was added to the reaction. After 2 h of stirring at room temperature the orange solution was concentrated *in vacuo*. The crude reaction was equipped with a reflux condenser

and put under an atmosphere of Argon. Chlorobenzene (56 cm^3) and triethyl orthoformate (2.45 cm^3, 14.73 mmol) were charged to the vessel and the reaction was heated at reflux (120 °C) for 12 h. Additional triethylorthoformate (2.45 cm^3, 14.73 mmol) was added and the reflux (130 °C) was continued for a further 12 h. Upon cooling, the reaction mixture was concentrated *in vacuo* resulting in a brown residue. The reaction vessel was fitted with a rubber septum seal and placed under an atmosphere of Ar. MeOH (203 cm^3) was injected *via* syringe. To the resulting solution was added a solution of TMSBr in MeOH (10% (*v*/*v*), 2.94 cm^3, 22.74 mmol of TMSBr in 26.5 cm^3 MeOH). The reaction mixture was stirred at room temperature for 24 h. Removal of solvent under reduced pressure with ensuing purification by column chromatography and/or recrystallisation from EtOAc gave the pure triazolium salt.

5.4.1.12 (5*S*)-(Hydroxy-diphenyl-methyl)-2-pentafluorphenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoro borate (297a)



Procedure M was followed using TMS-protected lactam (*S*)-**304a** (2.00 g, 5.89 mmol), CH_2Cl_2 (28 cm^3), trimethyloxonium tetrafluoroborate (871 mg, 5.89 mmol), pentafluorophenyl hydrazine (1.17 g, 5.89 mmol), chlorobenzene (56 cm^3) and 2 aliquots of triethyl orthoformate (2.45 cm^3, 14.73 mmol). The *in situ* deprotection reaction required MeOH (203 cm^3) and a solution of TMSBr in MeOH (10% (*v*/*v*), 2.94 cm^3, 22.74 mmol of TMSBr in 26.5 cm^3 of MeOH). Removal of solvent under reduced pressure and recrystallisation from EtOAc gave (*S*)-**297a** (1.29 g, 40%) as pale yellow needles, m.p. 224-226 °C, lit.,[350] 225-226 °C; $[\alpha]_D^{20}$ = -183.2 (*c* 1.00 in $CHCl_3$), lit.,[350] $[\alpha]_D^{20}$ = -205.5 (*c* 1.00 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

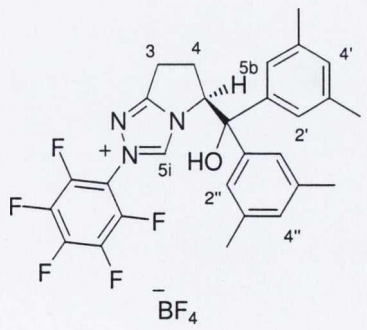
δ_H (600 MHz, DMSO-d_6): 2.62-2.71 (m, 1H, H-4a), 2.89-2.95 (m, 1H, H-3a), 3.02-3.08 (m, 1H, H-4b), 3.18-3.23 (m, 1H, H-3b), 6.16 (dd, 1H, J 8.7, 2.6, H-5b), 6.80 (s, 1H, OH), 7.31 (t, 1H, J 7.3, H-4'), 7.36-7.40 (m, 3H, H-3' and H-4''), 7.44-7.48 (m, 4H, H-2' and H-3''), 7.76 (d, 2H, J 7.2, H-2''), 9.63 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 21.8, 30.0, 68.5, 79.1(q), 111.4 (t, qC, J 11.6), 126.56, 126.57, 128.0, 128.4, 128.8, 129.2, 136.9 (d of t, qC, J 250.0, 14.1), 142.0 (d of m, qC, J 259.7), 142.3 (d of m, qC, J 259.8), 143.2(q), 143.5, 143.8(q), 165.0(q)

δ_F (376 MHz, DMSO-d_6): -160.62 (app. t, 2F), -148.24 (t, 1F, J 22.9), -145.97 (d, 2F, J 18.3)

HRMS (*m/z* - ES): Found 458.1288 (M^+ - BF_4. $C_{24}H_{17}N_3OF_5$ requires 458.1292).

5.4.1.13 (5*S*)-[*Bis*-(3,5-dimethylphenyl)-hydroxy-methyl]-2-pentafluorophenyl 6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (297d)



Procedure M was followed using TMS protected lactam (*S*)-**304d** (500 mg, 1.27 mmol), CH_2Cl_2 (6.00 cm^3), trimethyloxonium tetrafluoroborate (187 mg, 1.27 mmol), pentafluorophenyl hydrazine (251 mg, 1.27 mmol), chlorobenzene (12 cm^3) and two aliquots of triethyl orthoformate (530 µL, 3.16 mmol). The *in situ* deprotection step

required MeOH (37 cm^3) and a solution of TMSBr in MeOH (10% (*v/v*), 630 μL, 4.88 mmol of TMSBr in 5.70 cm^3 of MeOH). Removal of the solvent under reduced pressure gave a red-brown residue. Purification by column chromatography (95:5 EtOAc:isopropanol, R_f 0.4) and subsequent recrystallisation from EtOAc gave a pale yellow solid, pure (*S*)-**297d** (292 mg, 38%), m.p. 165-167 °C, (dec.); $[\alpha]_D^{20}$ = -168.0 (*c* 1.39 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, DMSO-d_6): 2.27 (s, 6H CH_3-3''), 2.29 (s, 6H, CH_3-3'), 2.68-2.71 (m 1H, H-4a), 2.92-2.98 (m, 1H, H-3a), 3.01-3.07 (m, 1H, H-4b), 3.17-3.21 (m, 1H, H-3b), 6.05 (dd, 1H, J 8.7, 1.9, H-5b), 6.59 (s, 1H, OH), 6.95 (s, 1H, H-4''), 6.98 (s, 1H, H-4'), 7.07 (s, 2H, H-2''), 7.13 (s, 2H, H-2'), 9.38 (s, 1H, H-5i)

δ_C (150 MHz, DMSO-d_6): 21.0, 21.1, 21.4, 29.7, 68.4, 78.5(q), 111.0 (t, qC, J 12.8), 123.6, 123.7, 129.0, 129.4, 136.5 (d of m, qC, J 250.0), 137.4,(q), 137.8(q), 141.6 (d of m, qC, J 255.4), 142.1 (d of m, qC, J 255.6), 142.9(q), 143.1(q), 143.2, 164.7(q)

δ_F (376 MHz, DMSO-d_6): -157.48 (app. t, 2F), -145.05 (t, 1F, J 24.9), -143.15 (d, 2F, J 22.1)

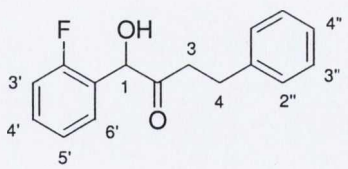
ν_{max} (neat)/cm^{-1}: 3399 (O-H), 3215, 3034, 2956, 2919, 1635, 1594, 1526 (C-F), 1504, 1486, 1068 (C-N-C), 999 (C-F), 866, 856, 810, 730

HRMS (*m/z* - ES): Found 514.1918 (M^+ - BF_4. $C_{28}H_{25}N_3OF_5$ requires 514.1918).

5.4.1.14 Procedure N: General procedure for organocatalysed-crossed acyloin condensation reactions

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added Rb_2CO_3 (99.8%, anhydrous, 10.2 mg, 0.04 mmol) that had been finely ground using a mortar and pestle. The reaction vessel was put under a vacuum and heated with a heat gun for 4 one-minute intervals. When cooled to ambient temperature the appropriate precatalyst (0.04 mmol) was added and the flask was fitted with a septum seal. The reaction was evacuated for 1 min and put under an atmosphere of Ar. The required aldehydes were distilled under vacuum and used directly. THF was charged to the reaction, followed by consecutive addition of each aldehyde (1.10 mmol). The reaction was stirred at 18 °C for 40 h (unless otherwise indicated). To quench the reaction CH_2Cl_2 (3.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The lower organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 x 3.0 cm^3). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified using column chromatography. Note: The internal standard styrene (31.5 μL, 0.28 mmol) was added to the reaction prior to the work-up.

5.4.1.15 1-(2-Fluoro-phenyl)-1-hydroxy-4-phenyl-butan-2-one (282d) (Table 4.2, entry 4)



Procedure N was followed using precatalyst **131** (16.0 mg, 0.04 mmol) and Rb_2CO_3 (10.2 mg, 0.04 mmol), with addition of THF (740 μL), hydrocinnamaldehyde (**276**) (145 μL, 1.10 mmol) and *o*-fluorobenzaldehyde (**278**) (116 μL, 1.10 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave **282d** (74.1 mg, 26%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 2.66-2.71 (m, 1H, H-3), 2.77-2.82 (m, 1H, H-3), 2.85-2.89 (m, 1H, H-4), 2.93-2.98 (m, 1H, H-4), 4.29 (s (broad), 1H, OH), 5.40 (s, 1H, H-1), 7.09-7.29 (m, 8H, H-4' to H-6' and H-2'' to H-4''), 7.34 (d, 1H, J 6.4, H-3')

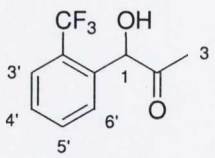
δ_C (150 MHz, $CDCl_3$): 29.6, 39.2, 73.4 (d, J 3.3), 115.8 (d, J 20.9), 124.8 (d, J 3.3), 125.1 (d, qC, J 14.3), 126.3, 128.2, 128.5, 128.9 (d, J 3.3), 130.4 (d, J 8.8), 140.1(q), 159.6 (d, qC, J 247.6), 207.8(q), (C=O)

δ_F (376 MHz, $CDCl_3$): -129.68

ν_{max} (neat)/cm^{-1}: 3459 (O-H), 3064, 3028, 2926, 2857, 1717 (C=O), 1611, 1587, 1490, 1455, 1277, 1232, 1056, 756, 698

HRMS (*m/z* - ES): Found 281.0944 (M^+ + Na. $C_{16}H_{15}O_2NaF$ requires 281.0954).

5.4.1.16 1-Hydroxy-1-(2-trifluoromethyl-phenyl)-propan-2-one (289d) (Table 4.3, entry 4)



Procedure N was followed using precatalyst **131** (31.9 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (240 μL), *o*-trifluoromethyl-benzaldehyde (**279**) (145 μL, 1.10 mmol) and acetaldehyde (**191**) (617 μL, 11.00 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.25) gave **289d** (187.3 mg, 78%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 2.20 (s, 3H, H-3), 4.41 (s (broad), 1H, OH), 5.52 (s, 1H, H-1), 7.29 (d, 1H, J 7.2, H-6'), 7.49-7.52 (app. t, 1H, H-4'), 7.59-7.62 (app. t, 1H, H-5'), 7.77 (d, 1H, J 7.9, H-3')

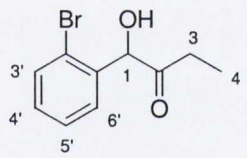
δ_C (150 MHz, $CDCl_3$): 25.4, 74.9 (quartet, J 2.2), 121.4 (quartet, qC, J 274.3), 126.2 (quartet, J 5.5), 128.7 (quartet, qC, J 30.8), 128.8, 128.9, 132.7, 136.7(q), 206.2(q), (C=O)

δ_F (376 MHz, $CDCl_3$): -57.70

ν_{max} (neat)/cm^{-1}: 3454 (O-H), 2971, 2902, 1717 (C=O), 1608, 1586, 1497, 1454, 1311 (C-F), 1158 (C-F), 1108 (C-F), 1036, 768, 672

HRMS (*m/z* - ES): Found 241.0456 (M^+ + Na. $C_{10}H_9O_2NaF_3$ requires 241.0452).

5.4.1.17 1-(2-Bromo-phenyl)-1-hydroxy-butan-2-one (292d) (Table 4.3, entry 8)



Procedure N was followed using precatalyst **131** (31.9 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (670 µL), *o*-bromobenzaldehyde (**280**) (128 µL, 1.10 mmol) and propanal (**286**) (200 µL, 2.75 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.20) gave **292d** (195.6 mg, 73%) as a yellow oil.

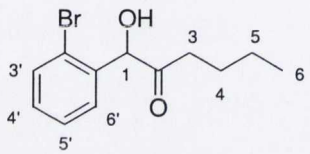
δ_H (600 MHz, $CDCl_3$): 1.07 (t, 3H, J 7.2, H-4), 2.33 (d of q, 1H, J 17.8, 7.2, H-3), 2.52 (d of q, 1H, J 17.8, 7.2, H-3), 4.44 (d, 1H, J 2.8, OH), 5.63 (d, 1H, J 2.8, H-1), 7.22-7.26 (m, 2H, H-4' and H-6'), 7.34-7.37 (app. t, 1H, H-5'), 7.63 (d, 1H, J 7.9, H-3')

δ_C (150 MHz, $CDCl_3$): 7.6, 31.4, 78.1, 123.8(q), 128.1, 129.1, 130.1, 133.4, 137.8(q), 209.4(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3455 (O-H), 3064, 2979, 2939, 1714 (C=O), 1589, 1567, 1470, 1438, 1378, 1351, 1087, 1021, 974, 754, 724, 666

HRMS (*m/z* - ES): Found 264.9831 (M^+ + Na. $C_{10}H_{11}O_2NaBr$ requires 264.9840).

5.4.1.18 1-(2-Bromo-phenyl)-1-hydroxy-hexan-2-one (294d) (Table 4.3, entry 10)



Procedure N was followed using precatalyst **131** (31.9 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (640 μL), *o*-bromobenzaldehyde (**280**) (128 μL, 1.10 mmol) and pentanal (**287**) (199 μL, 1.87 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.23) gave **294d** (229.7 mg, 77%) as a yellow oil.

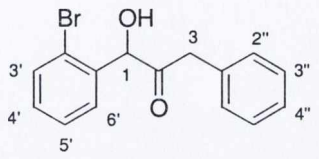
δ_H (600 MHz, $CDCl_3$): 0.84 (t, 3H, J 7.5, H-6), 1.21-1.29 (m, 2H, H-5), 1.49-1.62 (m, 2H, H-4), 2.31 (d of t, 1H, J 8.0, 6.8, H-3), 2.48 (d of t, 1H, J 8.0, 6.8, H-3), 4.45, (s (broad), 1H, OH), 5.62 (s, 1H, H-1), 7.22-7.25 (m, 2H, H-4' and H-6'), 7.34-7.37 (app. t, 1H, H-5'), 7.63 (d, 1H, J 7.5, H-3')

δ_C (150 MHz, $CDCl_3$): 13.6, 22.1, 25.8, 37.7, 78.2, 123.9(q), 128.1, 129.1, 130.1, 133.4, 137.6(q), 209.0(q) (C=O)

ν_{max} (neat)/cm^{-1}: 3455 (O-H), 3066, 2958, 2931, 2873, 1713 (C=O), 1589, 1569, 1468, 1438, 1379, 1022, 754, 671

HRMS (*m/z* - ES): Found 293.0163 (M^+ + Na. $C_{12}H_{15}O_2NaBr$ requires 293.0153).

5.4.1.19 1-(2-Bromo-phenyl)-1-hydroxy-3-phenyl-propan-2-one (296d) (Table 4.3, entry 12)



Procedure N was followed using precatalyst **131** (31.9 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (660 μL), *o*-bromobenzaldehyde (**280**) (128 μL, 1.10 mmol) and phenylacetaldehyde (**288**) (209 μL, 1.87 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.22) gave **296d** (254.5 mg, 76%) as a yellow oil.

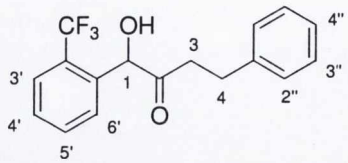
δ_H (600 MHz, $CDCl_3$): 3.69 (d, 1H, J 15.6, H-3), 3.76 (d, 1H, J 15.6, H-3), 4.34 (s (broad), 1H, OH), 5.74 (s, 1H, H-1), 7.06 (d, 2H, J 6.4, H-2''), 7.22 (d, 1H, J 7.5, H-6'), 7.24-7.29 (m, 4H, H-4', H-3'' and H-4''), 7.33-7.35 (app. t, 1H, H-5'), 7.67 (d, 1H, J 8.1, H-3')

δ_C (150 MHz, $CDCl_3$): 44.8, 78.2, 124.1(q), 127.3, 128.2, 128.6, 129.3, 129.6, 130.4, 132.6(q), 133.5, 137.0(q), 206.3(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3457 (O-H), 3063, 3030, 2923, 1717 (C=O), 1586, 1568, 1496, 1471, 1454, 1022, 752, 723, 701

HRMS (*m/z* - ES): Found 327.0010 (M^+ + Na. $C_{15}H_{13}O_2NaBr$ requires 326.9997).

5.4.1.20 1-Hydroxy-4-phenyl-1-(2-trifluoromethyl-phenyl)-butan-2-one (283d) (Table 4.4, entry 9)



Procedure N was followed using precatalyst (*S*)-**297a** (60.0 mg, 0.11 mmol) and Rb_2CO_3 (25.4 mg, 0.11 mmol), with addition of THF (2.43 cm^3), *o*-trifluoromethyl-benzaldehyde (**279**) (145 μL, 1.10 mmol) and hydrocinnamaldehyde (**276**) (145 μL, 1.10 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.25) gave **283d** (196.7 mg, 58%) as a yellow oil, 72% *ee*. $[\alpha]_D^{20}$ = -76.7 (c 1.33 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 96/4, 0.4 mL min^{-1}, RT, UV detection at 220 nm, retention times: 49.4 min (major enantiomer) and 54.9 min (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 2.53-2.58 (m, 1H, H-4), 2.70-2.75 (m, 1H, H-4), 2.86-2.95 (m, 2H, H-3), 4.39 (s (broad), 1H, OH), 5.48 (s, 1H, H-1), 7.06 (d, 2H, J 7.5, H-2''), 7.12 (d, 1H, J 7.5, H-6'), 7.18 (t, 1H, J 7.4, H-4''), 7.23-7.26 (app. t, 2H, H-3''), 7.45-7.51 (m 2H, H-4' and H-5'), 7.74 (d, 1H, J 7.5, H-3')

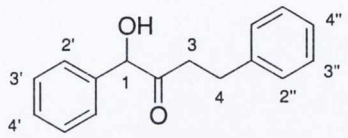
δ_C (150 MHz, $CDCl_3$): 29.3, 39.4, 74.5, 121.3 (quartet, qC, J 274.1), 126.1 (quartet, J 5.5), 126.2, 128.0, 128.4, 128.5 (quartet, qC, J 30.2), 128.6, 128.8, 132.5, 136.3(q), 139.8(q), 207.6(q), (C=O)

δ_F (376 MHz, $CDCl_3$): -57.60

ν_{max} (neat)/cm^{-1}: 3456 (O-H), 3031, 2930, 1717 (C=O), 1605, 1497, 1454, 1311 (C-F), 1159 (C-F), 1108 (C-F), 1034, 768, 747, 696

HRMS (*m/z* - ES): Found 331.0923 (M^+ + Na. $C_{17}H_{15}O_2NaF_3$ requires 331.0922).

5.4.1.21 1-Hydroxy-1,4-diphenyl-butan-2-one (277d) (Table 4.5, entry 1)



Procedure N was followed using precatalyst (*S*)-**297a** (24.0 mg, 0.04 mmol) and Rb_2CO_3 (10.2 mg, 0.04 mmol), with addition of THF (710 μL), benzaldehyde (**11**) (112 μL, 1.10 mmol) and hydrocinnamaldehyde (**276**) (145 μL, 1.10 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.25) gave **277d** (95.2 mg, 36%) as a white solid, m.p. 63-65 °C, 54% *ee*. $[\alpha]_D^{20}$ = -61.4 (c 0.95 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.6 mL min^{-1}, RT, UV detection at 220 nm, retention times: 27.4 min (minor enantiomer) and 28.7 min (major enantiomer).

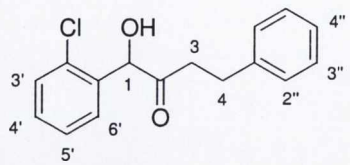
δ_H (600 MHz, $CDCl_3$): 2.63-2.75 (m, 2H, H-3), 2.79-2.84 (m, 1H, H-4), 2.89-2.94 (m, 1H, H-4), 4.31 (s (broad), 1H, OH), 5.07 (s, 1H, H-1), 7.06 (d, 2H, J 7.2, H-2''), 7.19 (t, 1H, J 7.3, H-4''), 7.25-7.27 (app. t, 2H, H-3''), 7.29 (d, 2H, J 7.2, H-2'), 7.35-7.40 (m, 3H, H-3' and H-4')

δ_C (150 MHz, $CDCl_3$): 29.7, 39.5, 79.2, 126.3, 127.4, 128.2, 128.5, 128.7, 129.1, 137.8(q), 140.2(q), 208.6(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3427 (O-H), 3084, 3028, 2923, 1713 (C=O), 1601, 1495, 1452, 1062 (C-O), 748, 715

HRMS (*m/z* - ES): Found 263.1050 (M^+ + Na. $C_{16}H_{16}O_2Na$ requires 263.1048).

5.4.1.22 1-(2-Chloro-phenyl)-1-hydroxy-4-phenyl-butan-2-one (266d) (Table 4.5, entry 6)



Procedure N was followed using precatalyst (*S*)-**297a** (48.0 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (700 μL), *o*-chlorobenzaldehyde (**258**) (124 μL, 1.10 mmol) and hydrocinnamaldehyde (**276**) (145 μL, 1.10 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.36) gave **266d** (196.4 mg, 65%) as a yellow oil, 41% *ee*. $[\alpha]_D^{20}$ = -59.4 (c 1.24 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 96/4, 0.4 mL min^{-1}, RT, UV detection at 220 nm, retention times: 86.4 min (major enantiomer) and 107.2 min (minor enantiomer).

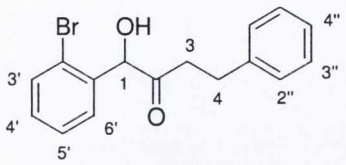
δ_H (600 MHz, $CDCl_3$): 2.64-2.70 (m, 1H, H-3), 2.79-2.83 (m, 1H, H-3), 2.84-2.89 (m, 1H, H-4), 2.92-2.97 (m, 1H, H-4), 4.36 (s (broad), 1H, OH), 5.58 (s, 1H, H-1), 7.08 (d, 2H, J 7.5, H-2''), 7.18-7.22 (app. t, 2H, H-6' and H-4''), 7.24-7.27 (app. t, 2H, H-3''), 7.28-7.31 (m, 2H, H-4' and H-5'), 7.43 (d, 1H, J 7.5, H-3')

δ_C (150 MHz, $CDCl_3$): 29.6, 39.4, 76.2, 126.3, 127.5, 128.2, 128.5, 129.1, 129.9, 130.1, 133.5(q), 135.6(q), 140.1(q), 207.9 (q), (C=O)

ν_{max} (neat)/cm^{-1}: 3456 (O-H), 3063, 3028, 2926, 1714 (C=O), 1593, 1604, 1574, 1475, 1454, 1440, 1032, 751, 699

HRMS (*m/z* - ES): Found 297.0666 (M^+ + Na. $C_{16}H_{15}O_2NaCl$ requires 297.0658).

5.4.1.23 1-(2-Bromo-phenyl)-1-hydroxy-4-phenyl-butan-2-one (284d) (Table 4.5, entry 9)



Procedure N was followed using precatalyst (*S*)-**297a** (24.0 mg, 0.04 mmol) and Rb_2CO_3 (10.2 mg, 0.04 mmol), with addition of THF (700 μL), *o*-bromobenzaldehyde (**280**) (128 μL, 1.10 mmol) and hydrocinnamaldehyde (**276**) (145 μL, 1.10 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.26) gave **284d** (122.9 mg, 35%) as a yellow oil, 49% *ee*. $[\alpha]_D^{20} = -53.9$ (c 1.21 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 96/4, 0.4 mL min^{-1}, RT, UV detection at 220 nm, retention times: 94.5 min (major enantiomer) and 124.5 min (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 2.64-2.70 (m, 1H, H-3), 2.82-2.88 (m, 2H, H-3 and H-4), 2.93-2.98 (m, 1H, H-4), 4.39 (s (broad), 1H, OH), 5.59 (s, 1H, H-1), 7.09 (d, 2H, J 7.3, H-2''), 7.17-7.23 (m, 3H, H-4' to H-6'), 7.24-7.27 (app. t, 2H, H-3''), 7.28 (t, 1H, J 7.3, H-4''), 7.61 (d, 1H, J 8.1, H-3')

δ_C (150 MHz, $CDCl_3$): 29.5, 39.4, 78.3, 123.7(q), 126.2, 128.0, 128.1, 128.4, 129.0, 130.0, 133.3, 137.1(q), 139.9(q), 207.8(q), (C=O)

ν_{max} (neat)/cm^{-1}: 3456 (O-H), 3063, 3028, 2925, 1713 (C=O), 1536, 1496, 1454, 1024, 749, 698, 672

HRMS (*m/z* - ES): Found 341.0152 (M^+ + Na. $C_{16}H_{15}O_2NaBr$ requires 341.0153).

5.4.1.24 1-Hydroxy-1-(2-trifluoromethyl-phenyl)-butan-2-one (291d) (Table 4.6, entry 3)

Procedure N was followed using precatalyst (*S*)-**297d** (66.1 mg, 0.11 mmol) and Rb_2CO_3 (25.4 mg, 0.11 mmol), with addition of THF (660 μL), *o*-trifluoromethyl-benzaldehyde (**279**) (145 μL, 1.10 mmol) and propanal (**286**) (200 μL, 2.75 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.30) gave **291d** (115.6 mg, 45%) as a yellow oil, 81% *ee*. $[\alpha]_D^{20}$ = -178.2 (c 1.14 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 99/1, 0.3 mL min^{-1}, RT, UV detection at 220 nm, retention times: 55.9 min (major enantiomer) and 64.4 min (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 1.05 (t, 3H, J 7.2, H-4), 2.23 (d of q, 1H, J 18.2, 7.2, H-3), 2.39 (d of q, 1H, J 18.2, 7.2, H-3), 4.45 (s (broad), 1H, OH), 5.51 (s, 1H, H-1), 7.26 (d, 1H, J 7.9, H-6'), 7.48-7.50 (app. t, 1H, H-4'), 7.58-7.60 (app. t, 1H, H-5'), 7.76 (d, 1H, J 7.9, H-3')

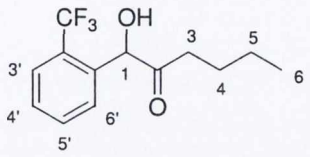
δ_C (150 MHz, $CDCl_3$): 7.5, 31.4, 74.3, (quartet, J 2.2), 121.4 (quartet, qC, J 274.0), 126.2 (quartet, J 5.5), 128.7 (quartet, qC, J 30.6), 128.8, 128.9, 132.6, 137.1(q), 209.3(q), (C=O)

δ_F (376 MHz, $CDCl_3$): -57.65

ν_{max} (neat)/cm^{-1}: 3460 (O-H), 2981, 2922, 2854, 1718 (C=O), 1608, 1586, 1497, 1455, 1311 (C-F), 1159 (C-F), 1102 (C-F), 1058, 1033, 768, 657

HRMS (*m/z* - ES): Found 255.0618 (M^+ + Na. $C_{11}H_{11}O_2NaF_3$ requires 255.0609).

5.4.1.25 1-Hydroxy-1-(2-trifluoromethyl-phenyl)-hexan-2-one (293d) (Table 4.6, entry 6)



Procedure N was followed using precatalyst (*S*)-**297a** (60.0 mg, 0.11 mmol) and Rb_2CO_3 (25.4 mg, 0.11 mmol), with addition of THF (560 μL), *o*-trifluoromethyl-benzaldehyde (**279**) (145 μL, 1.10 mmol) and pentanal (**287**) (292 μL, 2.75 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.14) gave **293d** (245.7 mg, 86%) as a yellow oil, 71% *ee*. $[\alpha]_D^{20}$ = -146.4 (c 2.44 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 98.5/1.5, 0.3 mL min^{-1}, RT, UV detection at 220 nm, retention times: 31.6 min (major enantiomer) and 36.1 min (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 0.83 (t, 3H, J 7.3, H-6), 1.18-1.29 (m 2H, H-5), 1.48-1.60 (m, 2H, H-4), 2.20-2.26 (m 1H, H-3), 2.37-2.42 (m 1H, H-3), 4.45 (s (broad), 1H, OH), 5.50 (s, 1H, H-1), 7.26 (d, 1H, J 7.5, H-6'), 7.48-7.51 (app. t, 1H, H-4'), 7.58-7.61 (app. t, 1H, H-5'), 7.77 (d, 1H, J 7.9, H-3')

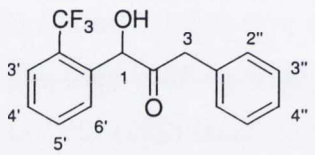
δ_C (150 MHz, $CDCl_3$): 13.6, 22.0, 25.6, 37.7, 74.4 (quartet, J 2.3), 121.5 (qC, quartet, J 274.3), 126.2 (quartet, J 5.7), 128.7 (qC, quartet, J 30.4), 128.8, 129.0, 132.6 (quartet, J 1.3), 136.9 (qC, quartet, J 1.4), 208.9(q), (C=O)

δ_F (376 MHz, $CDCl_3$): -57.62

ν_{max} (neat)/cm^{-1}: 3464 (O-H), 2961, 2935, 2875, 1716 (C=O), 1608, 1587, 1455, 1311 (C-F), 1159 (C-F), 1113 (C-F), 1033 (C-F), 768, 658

HRMS (*m/z* - ES): Found 283.0923 (M^+ + Na. $C_{13}H_{15}O_2NaF_3$ requires 283.0922).

5.4.1.26 1-Hydroxy-3-phenyl-1-(2-trifluoromethyl-phenyl)-propan-2-one (295d) (Table 4.6, entry 7)



Procedure N was followed using precatalyst (*S*)-**297a** (48.0 mg, 0.09 mmol) and Rb_2CO_3 (20.3 mg, 0.09 mmol), with addition of THF (550 μL), *o*-trifluoromethyl-benzaldehyde (**279**) (145 μL, 1.10 mmol) and phenylacetaldehyde (**288**) (307 μL, 2.75 mmol). The reaction was stirred at 18 °C for 40 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.26) gave **295d** (197.5 mg, 61%) as a yellow oil, 66% *ee*. $[\alpha]_D^{20}$ = -78.7 (c 1.00 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 96/4, 0.4 mL min^{-1}, RT, UV detection at 220 nm, retention times: 50.7 min (major enantiomer) and 56.4 min (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 3.59 (d, 1H, J 15.8, H-3), 3.67 (d, 1H, J 15.8, H-3), 4.33 (s (broad), 1H, OH), 5.64 (s, 1H, H-1), 7.02 (d, 2H, J 6.8, H-2''), 7.23-7.28 (m, 4H, H-6', H-3'' and H-4''), 7.50-7.53 (app. t, 1H, H-4'), 7.55-7.57 (app. t, 1H, H-5'), 7.80 (d, 1H, J 7.9, H-3')

δ_C (150 MHz, $CDCl_3$): 44.6, 74.5 (quartet, J 2.2), 121.5 (quartet, qC, J 274.1), 126.3 (quartet, J 5.5), 127.3, 128.6, 129.0, 129.1 (quartet,

qC, J 34.1), 129.3, 129.4, 132.5(q), 132.6, 136.2(q), 206.2(q), (C=O)

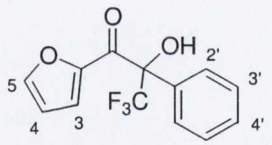
δ_F (376 MHz, $CDCl_3$): -57.53

ν_{max} (neat)/cm^{-1}: 3456 (O-H), 3067, 3033, 2929, 1721 (C=O), 1606, 1586, 1497, 1455, 1311 (C-F), 1158 (C-F), 1114 (C-F), 1033 (C-F), 768, 699, 660

HRMS (*m/z* - ES): Found 317.0767 (M^+ + Na. $C_{16}H_{13}O_2NaF_3$ requires 317.0765).

5.4.2 Experimental data for Section 4.2

5.4.2.1 3,3,3-Trifluoro-1-furan-2-yl-2-hydroxy-2-phenyl-propan-1-one (319)



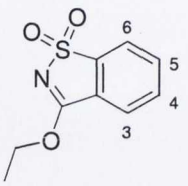
Procedure N was followed using precatalyst (*S*)-**297a** (13.6 mg, 0.03 mmol) and Rb_2CO_3 (5.8 mg, 0.03 mmol), with addition of THF (120 μL) and α,α,α-trifluoroacetophenone (**318**) (136 μL, 1.00 mmol). A solution of 2-furaldehyde (**273**) (41 μL, 0.50 mmol) in THF (160 μL) was prepared. An aliquot of this solution (8 μL, 0.02 mmol (4.0 mol% of **273**)) was added to the reaction vessel every 20 min for 5 h. Purification by column chromatography (9:1 hexane-CH_2Cl_2, R_f 0.2) gave pure **319** (3.0 mg, 4%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 5.08 (s (broad), 1H, OH), 6.46 (dd, 1H, J 3.7, 1.4, H-4), 7.01 (d, 1H, J 3.7, H-5), 7.43-7.45 (app. t, 3H, H-3' and H-4'), 7.57 (d, 2H, J 7.3, H-2'), 7.62 (d, 1H, J 1.4, H-3)

δ_C (100 MHz, $CDCl_3$): 81.0 (quartet, qC, J 29.0), 112.7, 120.5 (quartet, qC, J 286.3), 124.0, 127.0, 128.8, 129.5, 134.4(q), 148.4, 148.8(q) 181.1(q), (C=O)

HRMS (*m/z* - ES): Found 293.0397 (M^+ + Na. $C_{13}H_9O_3NaF_3$ requires 293.0401).

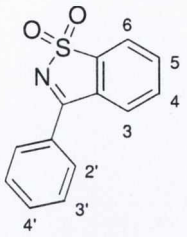
5.4.2.2 3-Ethoxy-1,2-benzoisothiazole 1,1-dioxide (329)



To a 100 cm^3 round bottomed flask, equipped with a magnetic stirrer, was added saccharin (**328**) (5.00 g, 27.29 mmol) and PCl_5 (6.91 g, 33.16 mmol). The flask was fitted with a reflux condenser and heated gently until the reaction became an oil. The reaction was then heated at 175 °C for 90 min. The side product $POCl_3$ was removed under reduced pressure. The resulting yellow residue was cooled and ethanol (38 cm^3) added. The reaction was heated at reflux for 90 min and when cooled to ambient temperature a precipitate formed. Vacuum filtration gave **329** (2.01 g, 35%) as white crystals, m.p. 217-219 °C, lit.,[142] 216-219 °C.

δ_H (400 MHz, $CDCl_3$): 1.54 (t, 3H, J 7.0, CH_3), 4.67 (q, 2H, J 7.0, CH_2), 7.71-7.81 (m, 3H, H-3 to H-5), 7.91 (d, 1H, J 7.5, H-6).

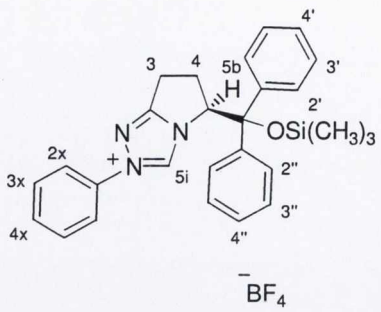
5.4.2.3 3-Phenyl-1,2-benzoisothiazole 1,1-dioxide (330)



In a 500 cm^3 oven-dried round bottomed flask, equipped with a magnetic stirrer, was placed ethoxy saccharin (**329**) (2.01 g, 9.51 mmol) and the reaction was put under an atmosphere of Ar. THF (190 cm^3) was charged to the flask and the reaction was cooled to -78 °C. Phenyl lithium (1.8 M solution in dibutylether, 6.34 cm^3, 11.42 mmol) was added slowly *via* syringe. The yellow solution was stirred for 2 h at -78 °C and left to warm to ambient temperature overnight. The reaction was quenched *via* addition of a saturated solution of NH_4Cl (60 cm^3) at 0 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (6 x 30 cm^3 aliquots). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give a yellow solid. Recrystallisation from hot EtOAc gave **330** (1.82 g, 79%) as white crystals, m.p. 165-166 °C, lit.,[142] 166-167 °C.

δ_H (400 MHz, $CDCl_3$): 7.62-7.66 (app. t, 2H, H-3'), 7.71-7.84 (m, 3H, H-4, H-5 and H-4'), 7.93 (d, 1H, J 6.7, H-3), 7.98 (d, 2H, J 7.0, H-2'), 8.03 (d, 1H, J 6.8, H-6).

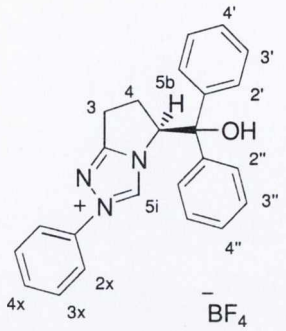
5.4.2.4 (5*S*)-(Diphenyl-trimethylsilanyloxy-methyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoro borate (97c)



Procedure M was followed using TMS-protected lactam (*S*)-**304a** (2.30 g, 6.78 mmol), CH_2Cl_2 (42 cm^3), trimethyloxonium tetrafluoroborate (1.09 g, 7.38 mmol), phenyl hydrazine (**229**) (727 μL, 7.38 mmol), MeOH (3.10 cm^3) and triethyl orthoformate (15 cm^3, 90.10 mmol). After heating at reflux for 24 h the reaction was cooled to ambient temperature and the solvent was removed under reduced pressure to give a red-brown liquid. Upon addition of EtOAc a precipitate appeared. Recrystallisation of the solid from methanol gave (*S*)-**97c** (1.52 g, 43%) as pale yellow crystals, m.p. 197-198 °C, lit.,[129] 196-198 °C; $[\alpha]_D^{20}$ = -117.7 (*c* 0.50 in CH_3CN), lit.,[129] $[\alpha]_D^{20}$ = -113.8 (*c* 0.50 in CH_3CN), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, $CDCl_3$): -0.07 (s, 9H, $Si(CH_3)_3$), 2.04-2.13 (m, 1H, H-4), 2.77-2.82 (m, 1H, H-4), 2.86-2.93 (m, 1H, H-3), 3.26-3.37 (m, 1H, H-3), 6.12 (m, 1H, H-5b), 7.27-7.29 (m, 2H, H-4' and H-4''), 7.35-7.48 (m, 8H, H-2', H-3', H-2'' and H-3''), 7.59-7.61 (m, 3H, H-3x and H-4x), 7.69-7.73 (m, 2H, H-2x), 8.89 (s, 1H, H-5i).

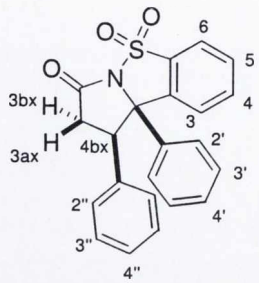
5.4.2.5 (5*S*)-(Hydroxy-diphenyl-methyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoro borate (118a)



To an oven-dried 500 cm^3 round bottomed flask, equipped with a magnetic stirrer, was added TMS-protected precatalyst (*S*)-**97c** (1.10 g, 2.09 mmol) and MeOH (HPLC grade, 209 cm^3). The reaction was put under an atmosphere of Argon and to it was added *via* syringe a solution of TMSBr (10% (*v/v*), 1.04 cm^3, 8.05 mmol of TMSBr in 9.37 cm^3 MeOH). The reaction was stirred at ambient temperature for 24 h. Concentration of the reaction under reduced pressure gave a pale yellow solid, pure (*S*)-**118a** (864 mg, 91%), m.p. 180-181 °C, lit.,[350] 177-180 °C; $[\alpha]_D^{20}$ = -65.0 (*c* 0.50 in CH_3CN), lit.,[350] $[\alpha]_D^{20}$ = -58.6 (*c* 0.50 in CH_3CN), for *S* enantiomer with 100% *ee*.

δ_H (600 MHz, DMSO-d_6): 2.59-2.62 (m, 1H, H-4b), 2.91-3.01 (m, 2H, H-3b and H-4a), 3.13-3.18 (m, 1H, H-3a), 6.13 (dd, 1H, J 8.4, 2.7, H-5b), 6.56 (s, 1H, OH), 7.29 (t, 1H, J 7.3, H-4'), 7.36-7.39 (m, 3H, H-3' and H-4''), 7.44-7.47 (app. t, 2H, H-3''), 7.52 (d, 2H, J 7.3, H-2'), 7.58 (d, 2H, J 8.1, H-2''), 7.62 (t, 1H, J 7.3, H-4x), 7.66-7.68 (app. t, 2H, H-3x), 7.78 (d, 2H, J 7.3, H-2x), 9.58 (s, 1H, H-5i).

5.4.2.6 5,5-Dioxo-1,9b-diphenyl-1,2,5,9b-tetrahydro-5λ^6-benzopyrrolo[1,2-*b*]isothiazol-3-one (331) (Table 4.9, entry 8)

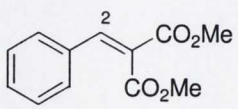


Procedure N was followed using precatalyst (*S*)-**118a** (22.8 mg, 0.05 mmol), Rb_2CO_3 (9.2 mg, 0.04 mmol) and **330** (121.6 mg, 0.50 mmol), with addition of THF (380 μL) and cinnamaldehyde (**261**) (76 μL, 0.60 mmol). The reaction was stirred at room temperature for 31 h. The crude product was purified using column chromatography (1:1 hexane-CH_2Cl_2, R_f 0.2) to give pure **331** (39.5 mg, 21%) as a white solid, m.p. 251-253 °C, lit.,[142] 253-253.5 °C, 56% *ee*. $[\alpha]_D^{20}$ = +33.8 (*c* 0.40 in $CHCl_3$).

CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 33.3 min (major enantiomer) and 39.8 (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 2.87 (dd, 1H, J 16.8, 7.5, H-3bx), 3.07 (dd, 1H, J 16.8, 13.6, H-3ax), 4.13 (dd, 1H, J 13.6, 7.5, H-4bx), 6.84 (d, 2H, J 7.5, H-2''), 7.14 (d, 2H, J 7.0, H-2'), 7.23-7.32 (m, 5H, H-3', H-4' and H-3''), 7.35 (t, 1H, J 7.5, H-4''), 7.59-7.65 (m, 1H, H-5), 7.73-7.76 (app. d, 2H, H-3 and H-4), 7.79 (d, 1H, J 8.0, H-6).

5.4.2.7 2-Benzylidene-malonic acid dimethyl ester (335)



To an oven-dried 10 cm^3 microwave reaction vessel was added benzaldehyde (**11**) (2.50 cm^3, 24.62 mmol), dimethyl malonate (2.81 cm^3, 24.62 mmol) and piperidine (122 μL,

1.23 mmol). The tube was sealed with a cap and subjected to microwave irradiation, 60W, at 95 °C for 10 min. The resulting pale yellow liquid was purified by column chromatography (95:5 hexane-EtOAc, R_f 0.2) to give **335** (3.20 g, 59%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 3.87 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 7.38-7.46 (m, 5H, Ar), 7.80 (s, 1H, H-2).

HRMS (*m/z* - ES): Found 243.0639 (M^+ + Na. $C_{12}H_{12}O_4Na$ requires 243.0633).

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Appendix One

Experiments to optimise the benzoin condensation reaction protocol involving the use of carbonate bases

Achiral Cyclohexylamine Triazolium Perchlorate (233c) Catalyst Results

Expt SOT210:

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	K_2CO_3	0.568	THF	60	1.9	54.8	35.4	4.0 ml reaction scale
C	1.25	TEA	0.568	THF	60	0.5	0	0	Rxns extracted & vacced down

Expt SOT213:

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	5.00	K_2CO_3	0.568	THF	0	1.7	n/a	n/a	2.0ml reaction scale
B	10.00	K_2CO_3	0.568	THF	0	0.4	n/a	n/a	Reactions extracted & vacced down
A	5.00	K_2CO_3	0.568	THF	24	1	21.3	20.8	catalyst used from expt SOT164, 171 & 179
B	10.00	K_2CO_3	0.568	THF	24	0.2	18.6	16.9	
A	5.00	K_2CO_3	0.568	THF	51	0.7	55.9	38.8	
B	10.00	K_2CO_3	0.568	THF	51	0.4	52.9	29.6	

Expt SOT270:

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	K_2CO_3	0.568 (d)	THF	0	1.5	n/a	n/a	1.0ml reaction scale
A	1.25	K_2CO_3	0.568 (d)	THF	13	0	0	0	Reaction not extracted & vacced
A	1.25	K_2CO_3	0.568 (d)	THF	60	2.8	4.8	4.7	At T_{94hrs} base increased to 1.5mol% total & stirred for 67hrs
A	1.25	K_2CO_3	0.568 (d)	THF	93	2	4.4	4.1	Cat used from expt SOT234(1b)
A	1.25	K_2CO_3	0.568 (d)	THF	159 (65)	0.8	45.9	42.9	Rxn A clear susp
A	1.25	K_2CO_3	0.568 (d)	THF	161 (67)	0.5	47	46.2	

Expt SOT271:

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	K_2CO_3	1.000	THF	0	1.3	n/a	n/a	1.0ml reaction scale
A	1.25	K_2CO_3	1.000	THF	36	1.6	1.7	1.6	Reaction A not extracted & vacced down but rxn B was
A	1.25	K_2CO_3	1.000	THF	61	1.1	5.6	5.9	At T_{68hrs} 10uL D.I. water added to rxn A & stirred for 65hrs
A	1.25	K_2CO_3	1.000	THF	133 (65)	1.2	12.3	12.6	Rxn A pale yellow susp

Expt SOT272:

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	K_2CO_3	0.568	THF	0	1.2	n/a	n/a	4.0ml reaction scale
A	1.25	K_2CO_3	0.568	THF	16	3.1	1.6	1.5	Reaction not extracted & vacced down
A	1.25	K_2CO_3	0.568	THF	89	2.5	13.7	11.7	Base not dried??
									Benzaldehyde added ~10min after THF addn

Expt SOT275: Base Run

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	K_2CO_3	1.0 (d)	THF	0	1.6	n/a	n/a	1.0ml reaction scale
B	1.25	Na_2CO_3	1.000	THF	0	1.5	n/a	n/a	Reaction not extracted & vacced down
C	**1.25**	**Cs_2CO_3**	**1.000**	**THF**	**0**	**1.1**	**n/a**	**n/a**	Cat used from expt SOT234(1b)
D	1.25	$NaHCO_3$	1.000	THF	0	1.5	n/a	n/a	Dry TEA and DBU used in 10% THF soln
E	1.25	TEA	1.000	THF	0	1.6	n/a	n/a	No carbonates were dried apart from K_2CO_3
F	1.25	DBU	1.000	THF	0	0.8	n/a	n/a	Benzaldehyde added ~5min after THF addn
A	1.25	K_2CO_3	1.0 (d)	THF	12	1.5	9.9	8.7	Rxn A & C pale yellow, small amt ppt
B	1.25	Na_2CO_3	1.000	THF	12	0.8	0	0	Rxn B, D & E clear with ppt.
C	**1.25**	**Cs_2CO_3**	**1.000**	**THF**	**12**	**0.3**	**26.3**	**25.2**	
D	1.25	$NaHCO_3$	1.000	THF	12	1.2	1	1	
E	1.25	TEA	1.000	THF	12	0.2	0	0	
F	1.25	DBU	1.000	THF	12	0.8	11.5	11.3	
A	1.25	K_2CO_3	1.0 (d)	THF	33	1.6	12.3	11.2	
B	1.25	Na_2CO_3	1.000	THF	33	~0	0	0	
C	**1.25**	**Cs_2CO_3**	**1.000**	**THF**	**33**	**1.4**	**42.2**	**41.6**	
D	1.25	$NaHCO_3$	1.000	THF	33	1.5	0	0	
E	1.25	TEA	1.000	THF	33	1.4	0	0	
F	1.25	DBU	1.000	THF	33	0.8	18	16.9	

Expt SOT276: Change in base loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.25	Cs_2CO_3	0.500	THF	0	1.6	n/a	n/a	1.0ml reaction scale
A	1.25	Cs_2CO_3	0.500	THF	64	1.7	0	0	Reaction not extracted & vacced down
A	1.25	Cs_2CO_3	0.500	THF	~10 days	1.2	0	0	Cat used from expt SOT234(1b)

Expt SOT277: Change in base and catalyst loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde not washed, but distilled
A	1.00	Cs_2CO_3	0.5 (d)	THF	0	3	n/a	n/a	1.0ml reaction scale
B	1.00	Cs_2CO_3	1.0 (d)	THF	0	2.1	n/a	n/a	Reaction A, B & C not extracted & vacced down
C	1.00	Cs_2CO_3	1.0 (w)	THF	0	2	n/a	n/a	Carbonate heated gunned on vac line
D	1.00	Cs_2CO_3	5.0 (d)	THF	0	2	n/a	n/a	Carbonate used in rxns A, B & D were dried, C not dried
A	1.00	Cs_2CO_3	0.5 (d)	THF	14	2.5	0	0	Cat used from expt SOT234(1b)
B	1.00	Cs_2CO_3	1.0 (d)	THF	14	3.3	0	0	Benzaldehyde distilled ~10 hrs before addn.
C	1.00	Cs_2CO_3	1.0 (w)	THF	14	2.8	0	0	Rxn pale yellow susp, rxn B & C yellow susp, rxn D dark yellow
D	1.00	Cs_2CO_3	5.0 (d)	THF	14	2.8	0	0	susp
A	1.00	Cs_2CO_3	0.5 (d)	THF	37.5	2.5	3.7	3.9	
B	1.00	Cs_2CO_3	1.0 (d)	THF	37.5	3.3	1.9	2.1	
C	1.00	Cs_2CO_3	1.0 (w)	THF	37.5	3.9	1.9	2.1	
D	1.00	Cs_2CO_3	5.0 (d)	THF	37.5	3.9	1.9	2.1	
A	1.00	Cs_2CO_3	0.5 (d)	THF	62.5	3.3	6.5	7	
B	1.00	Cs_2CO_3	1.0 (d)	THF	62.5	3.6	2.7	3.1	
C	1.00	Cs_2CO_3	1.0 (w)	THF	62.5	4.3	0	0	
D	1.00	Cs_2CO_3	5.0 (d)	THF	62.5	4.3	0	0	

Expt SOT280: New method of washing benzaldehyde, change in base/cat loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Benzaldehyde stirred with solid Na_2CO_3, dried**
A	1.25	Cs_2CO_3	1.0 (w)	THF	0	0	n/a	n/a	**over $MgSO_4$ filtered and then distilled under Ar**
B	5.00	Cs_2CO_3	4.0 (w)	THF	0	0	n/a	n/a	1.0ml reaction scale
A	1.25	Cs_2CO_3	1.0 (w)	THF	14	1.3	2.5	2.3	Reaction A & B not extracted & vacced down
B	5.00	Cs_2CO_3	4.0 (w)	THF	14	0	21.7	21.8	Carbonate not heated gunned on vac line, dried 2days before
A	1.25	Cs_2CO_3	1.0 (w)	THF	39	2.4?	1.6	1.5	Cat used from expt SOT234(1a)
B	5.00	Cs_2CO_3	4.0 (w)	THF	39	0	20	17.5	**Note: At T_{134hrs} an additional 5mol% cat added to rxn B**
A	1.25	Cs_2CO_3	1.0 (w)	THF	111	2	0	0	Rxns A & B yellow susp
B	5.00	Cs_2CO_3	4.0 (w)	THF	111	0	21.2	18.9	
A	1.25	Cs_2CO_3	1.0 (w)	THF	134	2.5	0	n/a	
B	5.00	Cs_2CO_3	4.0 (w)	THF	134	0	23	20.4	
B	10.00	Cs_2CO_3	1.0 (w)	THF	135 (269)	2	57.5	47.9	
B	10.00	Cs_2CO_3	4.0 (w)	THF	17 (151)	2.2	46.4	40.9	
B	10.00	Cs_2CO_3	1.0 (w)	THF	39 (173)	2.5	52.4	46.4	
B	10.00	Cs_2CO_3	4.0 (w)	THF	63 (197)	1.4	50.6	43.9	

Expt SOT281: Change of cat and base loading (Cs_2CO_3)

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde stirred with solid Na_2CO_3, dried
A	1.00	Cs_2CO_3	0.8 (d)	THF	0	n/a	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
B	1.00	Cs_2CO_3	0.8 (d)	THF	0	0	n/a	n/a	1.0ml reaction scale
C	1.00	Cs_2CO_3	0.8 (d)	THF	0	2	n/a	n/a	Reactions not extracted & vacced down
D	2.00	Cs_2CO_3	1.6 (d)	THF	0	1	n/a	n/a	Carbonate heated gunned on vac line
E	2.00	Cs_2CO_3	1.6 (d)	THF	0	1.3	n/a	n/a	Cat used from expt SOT234(1a)
A	1.00	Cs_2CO_3	0.8 (d)	THF	66	1	43.3	41.3	Note Cs_2CO_3 sample tube fell over when adding to rxn D and
B	1.00	Cs_2CO_3	0.8 (d)	THF	66	0.7	40.5	30.7	some carbonate lost. Rxn proceeded as was.
C	1.00	Cs_2CO_3	0.8 (d)	THF	66	1.3	1.4	1.3	
D	2.00	Cs_2CO_3	1.6 (d)	THF	66	3.3	38	34.7	
E	2.00	Cs_2CO_3	1.6 (d)	THF	66	2	38.4	34.8	

Expt SOT282: Rxn at -10 'C with achiral cat

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxn done at -10'C**
A	1.00	Cs_2CO_3	0.8 (d)	THF	61	0.9	0	0	Benzaldehyde stirred with solid Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under Ar
									1.0ml reaction scale
									Rxn A pale yellow soln

Expt SOT283: Change cat and base loading (Cs_2CO_3 - dry)

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde stirred with solid Na_2CO_3, dried
A	10.00	Cs_2CO_3	8.0 (d)	THF	0	1.4	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
B	1.00	Cs_2CO_3	5.0 (d)	THF	0	1.2	n/a	n/a	1.0ml reaction scale
C	1.00	Cs_2CO_3	0.80 (d)	THF	0	1	n/a	n/a	Reactions not extracted & vacced down
D	1.00	Cs_2CO_3	0.80 (d)	THF	0	1.4	n/a	n/a	Carbonate heated gunned on vac line
E	1.00	Cs_2CO_3	0.80 (d)	THF	0	0	n/a	n/a	Cat used from expt SOT234(1a)
A	10.00	Cs_2CO_3	8.0 (d)	THF	14	1.3	51.2	39	Rxns C and D duplicates
B	1.00	Cs_2CO_3	5.0 (d)	THF	14	0	14.8	14.2	Rxn E contained ~0.100g 4A mol. Sieves
C	1.00	Cs_2CO_3	0.80 (d)	THF	14	2.4	12.8	12.7	After 133hrs rxn A dark yellow susp
D	1.00	Cs_2CO_3	0.80 (d)	THF	14	0.9	25	24.7	After 133hrs rxn b colourless susp
E	1.00	Cs_2CO_3	0.80 (d)	THF	14	1.3	3.9	2.9	After 133hrs rxn C colourless almost soln
A	10.00	Cs_2CO_3	8.0 (d)	THF	37	0.8	72.7	51.9	After 133hrs rxn D pale yellow almost soln
B	1.00	Cs_2CO_3	5.0 (d)	THF	37	0.7	12.2	11.8	After 133hrs rxn E clear colourless soln
C	1.00	Cs_2CO_3	0.80 (d)	THF	37	1	42	41.8	
D	1.00	Cs_2CO_3	0.80 (d)	THF	37	0.7	40.8	41.4	
E	1.00	Cs_2CO_3	0.80 (d)	THF	37	0.4	7	5.3	
A	10.00	Cs_2CO_3	8.0 (d)	THF	61	0	74.3	57.6	
B	1.00	Cs_2CO_3	5.0 (d)	THF	61	0.6	12.3	11.7	
C	1.00	Cs_2CO_3	0.80 (d)	THF	61	1.3	41.2	40.5	
D	1.00	Cs_2CO_3	0.80 (d)	THF	61	0.7	42.2	41.4	
E	1.00	Cs_2CO_3	0.80 (d)	THF	61	0.4	5.4	4.1	
A	10.00	Cs_2CO_3	8.0 (d)	THF	133	1.2	76.2	55.2	
B	1.00	Cs_2CO_3	5.0 (d)	THF	133	0.6	9.4	8.7	
C	1.00	Cs_2CO_3	0.80 (d)	THF	133	0.6	37.2	35.2	
D	1.00	Cs_2CO_3	0.80 (d)	THF	133	1.4	41.6	40.4	
E	1.00	Cs_2CO_3	0.80 (d)	THF	133	0.6	6.4	5.2	

Expt SOT287: Solvent Run

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde stirred with solid Na_2CO_3, dried
A	1.00	Cs_2CO_3	0.8 (d)	THF	0	1.2	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
B	1.00	Cs_2CO_3	0.8 (d)	DCM	0	1.2	n/a	n/a	1.0ml reaction scale
C	1.00	Cs_2CO_3	0.8 (d)	i-Propyl Ether	0	0.9	n/a	n/a	Reactions not extracted & vacced down
D	1.00	Cs_2CO_3	0.8 (d)	CH_3CN	0	1.5	n/a	n/a	Carbonate heated gunned on vac line
E	1.00	Cs_2CO_3	0.8 (d)	Toluene	0	1.1	n/a	n/a	Cat used from expt SOT234(1a)
F	1.00	Cs_2CO_3	0.8 (d)	Dioxane	0	1.5	n/a	n/a	Rxns B, D & E contained freshly distilled solvent
G	1.00	Cs_2CO_3	0.8 (d)	t-Butanol	0	2.2	n/a	n/a	Rxns C & F contained solvent from sure-sealed bottles
H	1.00	Cs_2CO_3	0.8 (d)	HPLC Acetone	0	1.9	n/a	n/a	D.I. Water degassed for ~40min on high vac line
I	1.00	Cs_2CO_3	0.8 (d)	H_20 (degassed)	0	0	n/a	n/a	Note: t-Butanol sample was not homogeneous so T_0 off
A	1.00	Cs_2CO_3	0.8 (d)	THF	48	2.5	0	0	Note: H_2O and benzaldehyde were immiscible so T_0 off
B	1.00	Cs_2CO_3	0.8 (d)	DCM	48	2.1	0.8	0.7	Benzaldehyde added ~30min after THF addn
C	1.00	Cs_2CO_3	0.8 (d)	i-Propyl Ether	48	2.4	0	0	Rxns A, B, E, F, & H clear colourless solns, rxns C & D clear
D	1.00	Cs_2CO_3	0.8 (d)	CH_3CN	48	1.6	6.5	7.2	with white ppt, rxn G thick emulsion & rxn I contained 2
E	1.00	Cs_2CO_3	0.8 (d)	Toluene	48	2.4	0.8	0.8	immiscible layers at T_0
F	1.00	Cs_2CO_3	0.8 (d)	Dioxane	48	1.7	0.6	0.7	At T_{48}hrs Rxn A & B dark yellow soln, rxn C, D, F, pale yellow
G	1.00	Cs_2CO_3	0.8 (d)	t-Butanol	48	1.1	2.4	2.8	susp, rxn E yellow soln, rxn G clear susp, rxh H yellow susp,

H	1.00	Cs_2CO_3	0.8 (d)	HPLC Acetone	48	2.7	4.9	5.4	rxn I 2 layers
I	1.00	Cs_2CO_3	0.8 (d)	H_20 (degassed)	48	0	0	0	

Expt SOT289: Duplicate reactions and new method of washing benzaldehyde

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Benzaldehyde stirred in DCM with aq $NaHCO_3$, dried**
A	1.00	Cs_2CO_3	0.800	THF	0	2.1	n/a	n/a	**over $MgSO_4$ filtered and then distilled under Ar**
B	1.00	Cs_2CO_3	0.800	THF	0	0.7	n/a	n/a	1.0ml reaction scale
A	1.00	Cs_2CO_3	0.800	THF	87.5	0.9	5.7	4.7	Reaction A & B not extracted & vacced down
B	1.00	Cs_2CO_3	0.800	THF	87.5	0.76	15.5	12.2	Rxns A & B yellow susp
A	1.00	Cs_2CO_3	0.800	THF	93.5	0.7	12.4	10.6	Rxns A & B duplicate reactions
B	1.00	Cs_2CO_3	0.800	THF	93.5	0.8	15.1	10.3	Benzaldehyde added ~15min after THF addn

Expt SOT291: Cs_2CO_3 base and impure C-3 Me catalyst 240a

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Note: 2,5-diphenylfuran used as internal standard**
A	1.00	Cs_2CO_3	0.8 (d)	THF	0	0	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.6	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.8	n/a	n/a	2.0ml reaction scale
A	1.00	Cs_2CO_3	0.8 (d)	THF	29	0	21.5	21	Reaction A & B not extracted & vacced down
B	1.00	Cs_2CO_3	0.8 (d)	THF	29	0.6	25.6	24.7	Cat used from expt SOT234(2)
C	1.00	Cs_2CO_3	0.8 (d)	THF	29	0.6	0	0	Rxns A & B duplicate reactions
A	1.00	Cs_2CO_3	0.8 (d)	THF	67.25	1.2	20.2	19.7	**Rxn C contained cat from expt SOT269 (impure)**
B	1.00	Cs_2CO_3	0.8 (d)	THF	67.25	0	40.3	37.1	**(C-3 cyclohexylamine catalyst - ~50% impure)**
C	1.00	Cs_2CO_3	0.8 (d)	THF	67.25	0.5	0	0	Benzaldehyde added ~15min after THF addn
A	1.00	Cs_2CO_3	0.8 (d)	THF	144.75	1.3	16.9	15.7	Rxns A & B dark yellow susp, rxn C red-brown soln
B	1.00	Cs_2CO_3	0.8 (d)	THF	144.75	~1	41.1	43.3	
C	1.00	Cs_2CO_3	0.8 (d)	THF	144.75	-	-	-	

Expt SOT292: Cs_2CO_3 base, CH_3CN solvent and impure C-3 Me catalyst 240a

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	0	0.9	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	0	0.5	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	0	1.3	n/a	n/a	2.0ml reaction scale
A	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	29	0.7	2.6	2.4	Reactions not extracted & vacced down
B	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	29	0.7	2	0	Rxns A & B duplicate reactions
C	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	29	0.6	0	0	**Rxn C contained cat from expt SOT269 (impure)**
A	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	67.25	0	0	0	**(C-3 cyclohexylamine catalyst - ~50% impure)**
B	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	67.25	0	3.7	3.4	Benzaldehyde added ~15min after THF addn
C	1.00	Cs_2CO_3	0.8 (d)	**CH_3CN**	67.25	0.7	0	0	Rxns A & B yellow susp, rxn C red-brown soln

Expt SOT294: Difference if reaction scaled up from 1ml to 2ml

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	Cs_2CO_3	0.800	THF	0	~0	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	Cs_2CO_3	0.800	THF	0	0	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
A	1.00	Cs_2CO_3	0.800	THF	61.25	1.6	0	0	Rxn A 1.0ml scale, rxn B 2.0ml scale
B	1.00	Cs_2CO_3	0.800	THF	61.25	1.6	11.3	10.5	Reaction A & B not extracted & vacced down

Expt SOT295: - Different order of addn of reagents

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.8	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.9	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	DBU	1.600	THF	0	0.8	n/a	n/a	Rxn A 1.0ml scale, rxns B & C 2.0ml scale
A	1.00	Cs_2CO_3	0.8 (d)	THF	48	2	0.6	0.6	Int Std, cat & carbonate put in rbf under Ar o/n
B	1.00	Cs_2CO_3	0.8 (d)	THF	48	1.8	1.1	0.9	Next morn THF added, then DBU, ~10min later behzald added
C	1.00	DBU	1.600	THF	48	1.1	0	0	DBU used was distilled ~2 weeks in advance & stored
A	1.00	Cs_2CO_3	0.8 (d)	THF	68	2.2	0.7	0.6	over dry 4A mol sieves under Ar
B	1.00	Cs_2CO_3	0.8 (d)	THF	68	1.6	0.6	0.5	**Rxns sealed with brand new septa not glass stopper**
C	1.00	DBU	1.600	THF	68	1.2	0	0	THF obtained from Prof. Senge's lab
									"Dry" carbonate dried on high vac line & heat gunned
									Rxn A & B dark yellow almost soln, rxn C orange soln

Expt SOT296: Retro-Benzoin Reaction - Standard Conditions - as per SOT218

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	Cs_2CO_3	0.8 (d)	THF	0	n/a	0	n/a	Rxn 2.0ml scale
A	1.00	Cs_2CO_3	0.8 (d)	THF	68	n/a	1	n/a	Reaction not extracted & vacced down
A	1.00	Cs_2CO_3	0.8 (d)	THF	144	n/a	3.4	n/a	Cat used from expt SOT234(2)
									THF obtained from Prof. Senge's lab

Calculations of catalyst and base loading made relative to benzaldehyde formation

Expt SOT298: Wet vs Dry Carbonate

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	K_2CO_3	0.8 (w)	THF	0	~0	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	K_2CO_3	0.8 (d)	THF	0	0.8	n/a	n/a	over $MgSO_4$ filtered and then distilled **twice** under Ar
C	1.00	Cs_2CO_3	0.8 (w)	THF	0	0.5	n/a	n/a	Rxn 2.0ml scale
D	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.5	n/a	n/a	Reactions not extracted & vacced down
A	1.00	K_2CO_3	0.8 (w)	THF	65	0.6	2.5	2.2	New THF still made up that day
B	1.00	K_2CO_3	0.8 (d)	THF	65	0.4	33	30.9	"Wet" carbonate was untouched
C	1.00	Cs_2CO_3	0.8 (w)	THF	65	0.4	24.2	21.8	"Dry" carbonates were dried on high vac line & heat gunned
D	1.00	Cs_2CO_3	0.8 (d)	THF	65	1.1	15	13.9	Benzaldehyde added ~2min later
D	1.00	Cs_2CO_3	0.8 (d)	THF	144	1.5	28.2	26.2	Rxn A yellow soln, rxn B, C & D yellow susp
									Rxn A seal cracked, not resealed

Expt SOT300: Wet vs Dry Carbonate and Reproducibility Study

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: 2,5-diphenylfuran used as internal standard
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.2	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried

B	1.00	K_2CO_3	0.8 (d)	THF	0	0.7	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	K_2CO_3	0.8 (d)	THF	0	0.8	n/a	n/a	Rxn 2.0ml scale
A	1.00	K_2CO_3	0.8 (w)	THF	63.5	1.4	9.2	8.6	"Wet" carbonate was untouched
B	1.00	K_2CO_3	0.8 (d)	THF	63.5	1.1	39.8	37.9	"Dry" carbonates were dried on high vac line & heat gunned
C	1.00	K_2CO_3	0.8 (d)	THF	63.5	0.9	19.9	19.1	Rxns B & C duplicates
									Note: In rxn A error in addition of benzaldehyde occurred so
									rxns were repeated (SOT301)
									Benzaldehyde added ~5min later, 3 rxns yellow susps

Expt SOT301: Wet vs Dry Carbonate and Reproducibility Study

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: (E)-stilbene used as internal standard
A	1.00	K_2CO_3	0.8 (w)	THF	0	0.7	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	K_2CO_3	0.8 (d)	THF	0	0.7	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	K_2CO_3	0.8 (d)	THF	0	1.1	n/a	n/a	Rxn 2.0ml scale
D	1.00	Cs_2CO_3	0.8 (w)	THF	0	0.5	n/a	n/a	Reaction A & B not extracted & vacced down
E	1.00	Cs_2CO_3	0.8 (d)	THF	0	0.7	n/a	n/a	Cat used from expt SOT234(2)
A	1.00	K_2CO_3	0.8 (w)	THF	39	0.3	26.1	23.1	"Wet" carbonate was untouched
B	1.00	K_2CO_3	0.8 (d)	THF	39	1.8	0	0	"Dry" carbonates were dried on high vac line & heat gunned
C	1.00	K_2CO_3	0.8 (d)	THF	39	0.4	30.5	28.6	Note: Rxns B & C duplicates
D	1.00	Cs_2CO_3	0.8 (w)	THF	39	0	39.7	37.7	Benzaldehyde added ~15min later
E	1.00	Cs_2CO_3	0.8 (d)	THF	39	0	27.1	24.9	Rxns A, B, C & E seals cracked, resealed.
A	1.00	K_2CO_3	0.8 (w)	THF	65	0.4	34.2	30.8	Rxn A, C & D almost colurless susp, Rxn B & E yellow susp
B	1.00	K_2CO_3	0.8 (d)	THF	65	1.5	2.5	2.2	
C	1.00	K_2CO_3	0.8 (d)	THF	65	0.6	30.8	28.1	
D	1.00	Cs_2CO_3	0.8 (w)	THF	65	0.1	40.1	35.3	
E	1.00	Cs_2CO_3	0.8 (d)	THF	65	0.7	29.8	26.7	

Expt SOT302: K_2CO_3 vs Cs_2CO_3 (Wet)

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: (E)-stilbene used as internal standard
A	1.00	K_2CO_3	0.8 (w)	THF	0	0.6	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	K_2CO_3	0.8 (w)	THF	0	0.4	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	Cs_2CO_3	0.8 (w)	THF	0	0.7	n/a	n/a	Rxn 2.0ml scale
D	1.00	Cs_2CO_3	0.8 (w)	THF	0	0.5	n/a	n/a	Reactions A & B and C & D duplicates
A	1.00	K_2CO_3	0.8 (w)	THF	66.5	0.8	41.3	37.7	Reactions not extracted & vacced down
B	1.00	K_2CO_3	0.8 (w)	THF	66.5	0.8	36	33.9	Benzaldehyde added ~15min after THF addn
C	1.00	Cs_2CO_3	0.8 (w)	THF	66.5	1.3	5.2	4.5	Rxn A seal cracked, resealed after ~10min
D	1.00	Cs_2CO_3	0.8 (w)	THF	66.5	0.6	42	38.6	Rxn A almost colourless susp, rxn B, C & D pale yellow susp

Expt SOT303: Changing Base Loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: (E)-stilbene used as internal standard
A	1.25	K_2CO_3	0.568 (w)	THF	0	0.6	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.25	K_2CO_3	0.568 (w)	THF	0	0.4	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.25	Cs_2CO_3	0.568 (w)	THF	0	0.8	n/a	n/a	Rxn 2.0ml scale
D	1.25	Cs_2CO_3	0.568 (w)	THF	0	0.4	n/a	n/a	Reactions A & B and C & D duplicates
A	1.25	K_2CO_3	0.568 (w)	THF	41.5	0.5	7.6	6.9	Benzaldehyde added ~30min after THF addn
B	1.25	K_2CO_3	0.568 (w)	THF	41.5	0.4	32.4	30	Rxn B & D seal cracked, resealed after ~10min
C	1.25	Cs_2CO_3	0.568 (w)	THF	41.5	1.3	0	0	Rxn A pale yellow susp, Rxns B & D almost colourless
D	1.25	Cs_2CO_3	0.568 (w)	THF	41.5	1	9.1	8.5	& Rxn C dark yellow susp.

Expt SOT304: Change of Base Loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Note: (E)-stilbene used as internal standard
A	1.00	K_2CO_3	0.4 (w)	THF	0	0.6	n/a	n/a	Benzaldehyde stirred with aq $NaHCO_3$, dried
B	1.00	K_2CO_3	0.4 (w)	THF	0	0.34	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
C	1.00	Cs_2CO_3	0.4 (w)	THF	0	1	n/a	n/a	Rxn 2.0ml scale
D	1.00	Cs_2CO_3	0.4 (w)	THF	0	0.2	n/a	n/a	Reactions A & B and C & D duplicates
A	1.00	K_2CO_3	0.4 (w)	THF	41.5	1.2	0	0	Reaction A & B not extracted & vacced down
B	1.00	K_2CO_3	0.4 (w)	THF	41.5	0.38	25.6	24.1	Benzaldehyde added ~30min after THF addn
C	1.00	Cs_2CO_3	0.4 (w)	THF	41.5	2.3	2	1.9	Rxn C seal cracked, resealed after ~15min
D	1.00	Cs_2CO_3	0.4 (w)	THF	41.5	0.3	24.9	23.2	Rxn A&C dark yellow susp. Rxn B & D cloudy almost colourless

Expt SOT321: Achiral testing, variation of base and cat loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Benzaldehyde stirred with aq **Na_2CO_3**, dried
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.4	n/a	n/a	over $MgSO_4$ filtered and then distilled under Ar
A	1.00	K_2CO_3	0.8 (w)	THF	64	0.69	37.5	34.8	Rxn 2.0ml scale
									Benzaldehyde added ~30min after THF addn

Expt SOT329: Achiral testing, variation of base and cat loading

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxn done in carousel, equal stirring**
A	1.00	K_2CO_3	0.8 (w)	THF	62	1.11	3.1	2.7	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under Ar

Expt SOT331: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring**
A	1.00	K_2CO_3	0.8 (w)	THF	0	0.68	n/a	n/a	Note: (E)-stilbene used as internal standard
B	1.00	K_2CO_3	0.8 (w)	THF	0	~0	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.8 (w)	THF	61.67	2.07	0	0	over $MgSO_4$ filtered and then distilled under Ar **(~3hrs later)**
B	1.00	K_2CO_3	0.8 (w)	THF	61.67	2.48	3.9	3.5	Rxn 1.0ml scale
									Some benzaldehyde stuck to sides of carousel flasks

Expt SOT332: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring**
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.75	n/a	n/a	Note: (E)-stilbene used as internal standard
B	1.00	K_2CO_3	0.8 (w)	THF	0	0.87	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.8 (w)	THF	89	2.34	0	0	over $MgSO_4$ filtered and then distilled under Ar

B	1.00	K_2CO_3	0.8 (w)	THF	89	1.39	1.52	1.41	Rxn 1.0ml scale
									Rxns A & B not extracted and vacced down
									Benzaldehyde added ~30min after THF addn
									Rxns A & B dark yellow susp.
									Some benzaldehyde stuck to sides of carousel flasks

Expt SOT333: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring**
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.43	n/a	n/a	Note: (E)-stilbene used as internal standard
B	1.00	K_2CO_3	0.8 (w)	THF	0	1.47	n/a	n/a	**Benzaldehyde not washed, distilled & used immediately**
A	1.00	K_2CO_3	0.8 (w)	THF	66	1.69	1.1	1.1	Rxn 1.0ml scale
B	1.00	K_2CO_3	0.8 (w)	THF	66	1.58	4	3.7	Rxns A & B not extracted and vacced down
Note: Three days later new THF still prepared, THF in this reaction possibly wet??									Benzaldehyde added ~30min after THF addn
									Rxns A & B clear yellow solns

Expt SOT337: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring, rpm = 340**
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.48	n/a	n/a	Some benzaldehyde stuck to sides of flask of rxn A
B	1.00	K_2CO_3	0.8 (w)	THF	0	0.3	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.8 (w)	THF	114	1.34	1.8	1.4	over $MgSO_4$ filtered and then distilled under Ar **(twice)**
B	1.00	K_2CO_3	0.8 (w)	THF	114	1.46	8.4	7.9	Rxn 1.0ml scale
Note: New THF still prepared two days prior to reaction									Rxns A & B not extracted and vacced down

Expt SOT338: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring, rpm = 370**
A	1.00	K_2CO_3	0.8 (w)	THF	0	1.2	n/a	n/a	**K_2CO_3 ground in mortar & pestle prior to weighing**
B	1.00	K_2CO_3	0.8 (w)	THF	0	1.49	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.8 (w)	THF	91	1.94	1.8	1.7	over $MgSO_4$ filtered and then distilled under Ar **(twice)**
B	1.00	K_2CO_3	0.8 (w)	THF	91	2.94	1.5	1.4	Rxn 1.0ml scale
									Benzaldehyde added ~30min after THF addn

Expt SOT339: Reproducibility Studies

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring, rpm = 360**
A	1.00	K_2CO_3	**0.8 (w, n)**	THF	0	0.9	n/a	n/a	**New anhydrous K_2CO_3 99.995% used**
B	1.00	K_2CO_3	**0.8 (w, n)**	THF	0	0.27	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	**0.8 (w, n)**	THF	65	1.4	2.8	2.9	over $MgSO_4$ filtered and then distilled under Ar **(twice)**
B	1.00	K_2CO_3	**0.8 (w, n)**	THF	65	2.36	1.8	1.7	Rxn 1.0ml scale
									Benzaldehyde added ~60min after THF addn

Expt SOT340: Reproducibility Studies, CaH in THF Still

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in 5ml rbr.f.s**
A	1.00	K_2CO_3	0.8 (w, n)	THF	0	neg	n/a	n/a	**New anhydrous K_2CO_3 99.995% used**
B	1.00	K_2CO_3	0.8 (w, n)	THF	0	neg	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.8 (w, n)	THF	60	0.27	0	0	over $MgSO_4$ filtered and then distilled under Ar
B	1.00	K_2CO_3	0.8 (w, n)	THF	60	1.82	0	0	Rxn 1.0ml scale
									Benzaldehyde added ~40min after THF addn
									Rxn B seal cracked, resealed after ~20min
									Rxns A & B were pale yellow solns

Expt SOT351: Reproducibility Studies, No CaH in THF Still

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in carousel, equal stirring**
A	5.00	K_2CO_3	4.0 (w, n)	THF **(No CaH)**	47.5	2.5	20	14.4	New anhydrous K_2CO_3 99.995% used
B	5.00	K_2CO_3	4.0 (w, n)	THF **(No CaH)**	47.5	2.8	6.5	5.8	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	K_2CO_3	3.2 (w, n)	THF **(No CaH)**	47.5	5.7	3	3	over $MgSO_4$ filtered and then distilled under Ar
D	4.00	K_2CO_3	3.2 (w, n)	THF **(No CaH)**	47.5	2.8	20.5	19	Rxn 1.0ml scale
									New THF still prepared without CaH on day of rxn
									THF still leaked at collecting tap, water present??

Expt SOT355: Reproducibility Studies, No CaH in THF Still, K_2CO_3 not ground

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	5.00	K_2CO_3	4.000	THF **(No CaH)**	0	Neg	n/a	n/a	New anhydrous K_2CO_3 99.995% used
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	Neg	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	5.00	K_2CO_3	4.000	THF **(No CaH)**	64	2.7	2.9	2.4	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	64	4.7	1.3	1	Rxn 1.0ml scale

Expt SOT356: Use of para-chloro benzaldehyde

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	Neg	n/a	n/a	Note: (E)-stilbene used as internal standard
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	19	1.44	16.8	9.9	Chloro-Benzaldehyde stirred with NaOH in DCM, dried
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	68.5	0.82	64.5	44	over $MgSO_4$ filtered and solvent removed
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	114	Neg	68.4	23.2	Rxn 2.0ml scale
									Rxn was dark yellow susp
									New anhydrous K_2CO_3 99.995% used, ground
									Overlapping peaks at stilbene std peak so results not valid

Expt SOT357: Reproducibility Studies, No CaH in THF Still, K_2CO_3 ground and 2.0ml rxn scale

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	0.95	n/a	n/a	Note: (E)-stilbene used as internal standard
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	Neg	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	49	??	47	40.5	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	49	1.16	47.1	41.7	Rxn 2.0ml scale
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	70	0.74	51.4	48.5	Rxns were dark yellow susp
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	70	0.94	57	49.8	**New anhydrous K_2CO_3 99.995% used, ground**
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	142.5	1.34	54	46.2	
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	142.5	1.16	61.6	51.5	

Expt SOT358: Rxns done at 35'C

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	1.00	K_2CO_3	0.800	THF **(No CaH)**	0	Neg	n/a	n/a	Note: (E)-stilbene used as internal standard
B	5.00	K_2CO_3	4.000	THF **(No CaH)**	0	Neg	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	1.00	K_2CO_3	0.800	THF **(No CaH)**	19	1.47	19.8	18.1	over $MgSO_4$ filtered and then distilled under Ar
B	5.00	K_2CO_3	4.000	THF **(No CaH)**	19	1.59	32.9	31.2	Rxn 2.0ml scale
A	1.00	K_2CO_3	0.800	THF **(No CaH)**	68.5	1.39	17.3	15.7	Rxns were dark yellow susp
B	5.00	K_2CO_3	4.000	THF **(No CaH)**	68.5	0.69	28.3	24.5	**New anhydrous K_2CO_3 99.995% used, ground yesterday**
A	1.00	K_2CO_3	0.800	THF **(No CaH)**	114	1.46	16.3	15	
B	5.00	K_2CO_3	4.000	THF **(No CaH)**	114	0.72	26.3	23.4	

Expt SOT359: Reproducibility Studies, No CaH in THF Still, K_2CO_3 ground, repeat of SOT357

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	0.52	n/a	n/a	**New anhydrous K_2CO_3 99.995% used, ground 3days prev**
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	0	0.12	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	K_2CO_3	3.200	THF **(No CaH)**	65	1.61	29.3	25.6	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	K_2CO_3	3.200	THF **(No CaH)**	65	2.4	19.5	17.7	Rxn 2.0ml scale
									THF was blue-green, alot of uncoated Na present in still

Expt SOT360: New THF, Rxns A & B 99.9% HPLC THF, no sure seal, Rxns C & D Biotech Grade THF, sure seal 99.9%

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF (No CaH)	70	1.5	31.3	26.2	Note: (E)-stilbene used as internal standard
B	4.00	K_2CO_3	3.200	THF (No CaH)	70	0.1	49	41.8	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	K_2CO_3	3.200	THF (No CaH)	70	0.46	38.8	34.3	over $MgSO_4$ filtered and then distilled under Ar
D	4.00	K_2CO_3	3.200	THF (No CaH)	70	0.6	33.2	28.4	Rxn 2.0ml scale
									Rxns A & B turned yellow instrantly when adding benz
									Rxns C & D turned yellow ~20min after adding benz
									New anhydrous K_2CO_3 99.995% used, ground on the day
									99.9% HPLC THF, max 0.05% peroxides, no sureseal
									Biotech Grade 99.9% THF, unopened sureseal bottle
									Rxns were dark yellow susp, rxn B slighlty paler yellow

Expt SOT362: Addition of 1% and 5% D.I. Water to reactions

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF (1% H_2O)	24	3.1	23.1	21.8	Note: (E)-stilbene used as internal standard
B	4.00	K_2CO_3	3.200	THF (5% H_2O)	24	Neg	3.1	2.7	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	K_2CO_3	3.200	THF (1% H_2O)	70	3.3	43.7	40.1	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	K_2CO_3	3.200	THF (5% H_2O)	70	3.8	10.1	9	Rxn 2.0ml scale
									New anhydrous K_2CO_3 99.995% used, ground yest
									Rxns A (1% H_2O) turned yellow instrantly when adding benz
									Rxns B (5% H_2O) turned yellow ~30min after adding benz
									Rxn A almost colourless soln b4 T_0, at 70hrs pale yellow susp
									Rxn B clear soln b4 T_0,70hrs dark yellow soln,some immis liqud

Expt SOT364: Reproducibility of standard conditions

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF	69	2.35	15.8	12.4	Note: (E)-stilbene used as internal standard
B	4.00	K_2CO_3	3.200	THF	69	2.24	21.6	18.5	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under Ar
									Rxn 2.0ml scale
									New anhydrous K_2CO_3 99.995% used, ground today
									1.5ml THF added & 0.5ml used to rinse down sides of flasks
									After ~15min rxn A had gone yellow, rxn B not
									Rxn top removed by accident from rxn A o/n, rxn dark orange

Expt SOT365: Use of Enders cat:base ratio, 2.2:1 cat:base & reproducibility

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	1.818	THF	37	1.42	29.1	28	Note: (E)-stilbene used as internal standard
B	4.00	K_2CO_3	1.818	THF	37	2.35	14.2	11.9	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	K_2CO_3	1.818	THF	61	1.38	29.2	26.6	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	K_2CO_3	1.818	THF	61	3.59	14.3	13.2	Rxn 2.0ml scale
									New anhydrous K_2CO_3 99.995% used, ground today
									1.3ml THF added & 0.7ml used to rinse down sides of flasks
									Rxn A & B yellow susp, rxn A slightly darker

Expt SOT366: Use of Enders cat:base ratio, 2.2:1 cat:base Cs_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	**Cs_2CO_3**	1.818	THF	47	4.2	3.8	3.4	Note: (E)-stilbene used as internal standard
B	4.00	**Cs_2CO_3**	1.818	THF	47	2.48	29.7	28.3	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	**Cs_2CO_3**	1.818	THF	62	7.93	1.9	1.7	over $MgSO_4$ filtered and then distilled under Ar
B	4.00	**Cs_2CO_3**	1.818	THF	62	4.35	45	41.9	Rxn 2.0ml scale
A	4.00	**Cs_2CO_3**	1.818	THF	120	7.44	4.8	4	**Cs_2CO_3 (very wet) ground, weighed immediately**
B	4.00	**Cs_2CO_3**	1.818	THF	120	2.3	54.4	49.6	1.3ml warm THF added,0.7ml used to rinse down sides of flass
									Rxn A & B yellow susp, rxn A slightly darker

Expt SOT367: 2-Naphthaldehyde (solid) used

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF	50	~2.5	15.8	12.8	Note: (E)-stilbene used as internal standard
A	4.00	K_2CO_3	3.200	THF	68	2.73	13.8	12.1	Naphthaldehyde washed in DCM with 2M NaOH, dried over
									$MgSO_4$, filtered solvent removed
									Rxn 2.27ml scale, ~0.5% Benzoic A present in aldehyde
									New anhydrous K_2CO_3 99.995% used, ground today
									Balloon put in top of rxn to see if air leaking in over time, after
									24hrs balloon had gone down

Expt SOT368: Older conditions, benzaldehyde distilled under vac, K_2CO_3 & Cs_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in carousel, equal stirring, rpm = 380
A	4.00	K_2CO_3	3.200	THF	50	5.21	4	3.5	Note: (E)-stilbene used as internal standard

B	4.00	K_2CO_3	3.200	THF	50	2.16	13.2	11.7	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	Cs_2CO_3	3.200	THF	50	3.32	20	18.8	over $MgSO_4$ filtered and then distilled under **vac**
A	4.00	K_2CO_3	3.200	THF	67.5	4.73	0.9	1	**Rxn 2.27ml scale**
B	4.00	K_2CO_3	3.200	THF	67.5	3.08	11	10	**Both carbonates (wet) ground on day of rxn**
C	4.00	Cs_2CO_3	3.200	THF	67.5	2.94	15.7	13.4	1.3ml warm THF added, 0.8ml used to rinse down sides of flasks
									Rxns A & B turned yellow instantly, rxn C ~15min later
									Balloon in 3 rxns, rxn A went down after ~24hrs
									Rxn A dark orange, rxn B dark yellow susp, rxn C bright yellow susp with a lot less ppt than A or B

Expt SOT371: Enders 2.2:1 cat: K_2CO_3 ratio, exclusion of oxygen & septum sealed rxns

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in 5ml rbfs with septa seals**
A	4.00	K_2CO_3	1.818	THF	44	5.73	0	0	**Rxns evacuated on high vac line (~4min) prior to THF addn**
B	4.00	K_2CO_3	1.818	THF	44	4.83	0	0	**Rxn C not evacuated or flushes with Ar, air in reaction flask**
C (Air)	4.00	K_2CO_3	1.818	THF	44	7.71	1	0.9	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under **vac**
									Rxn 2.0ml scale
									New anhydrous K_2CO_3 99.995% used, ground today
									Rxns A & B yellow-orange susp, rxn C slightly paler susp

Expt SOT372: Enders 2.2:1 cat: K_2CO_3 ratio, exclusion of oxygen & septum sealed rxns

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in 5ml rbfs with septa seals**
A	4.00	K_2CO_3	1.818	THF	44	6.08	5	4.6	**Rxns evacuated on high vac line (~4min) prior to THF addn**
B	4.00	K_2CO_3	1.818	THF	44	4.9	3	2.8	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under **vac**
									Rxn 2.0ml scale
									New anhydrous K_2CO_3 99.995% used, ground today
									Balloon continously went down on rxn A
									Rxns A & B bright yellow with ppt, rxn A slightly darker

Expt SOT373: Old 4.0:3.2 cat: K_2CO_3 ratio, exclusion of oxygen & septum sealed rxns, addn of (1%) water and use of KHMDS

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Rxns done in 5ml rbfs with septa seals**
A (1% H_2O	4.00	K_2CO_3	3.200	THF	64	3.66	4.3	4.1	**Rxns evacuated on high vac line (~4min) prior to THF addn**
B (1% H_2O	4.00	K_2CO_3	3.200	THF	64	2.86	4.8	4.4	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	K_2CO_3	3.200	THF	64	1.43	39.5	31.6	over $MgSO_4$ filtered and then distilled under **vac**
D	4.00	KHMDS	3.200	THF	64	1.53	0	0	Rxn 2.0ml scale
E (1% H_2O	4.00	K_2CO_3	3.200	THF	64	2.51	2.1	1.9	**New anhydrous K_2CO_3 99.995% used, ground today**
									Fresh untouched K_2CO_3 used in rxn E (ground up)
									Rxns A, B & E yellow susp, rxns C & D pale yellow susp
									Rxns A & B were duplicates
									THF left over xmas under Ar, unclear if wet?? (Rxn done 09 Jan)
									20uL degassed DI water added to rxns A,B and E
									KHMDS (in toluene) slightly gone off? Bottle cloudy.

Expt SOT379: Repeat of SOT373, duplicates with and without 1% water added

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals
A	4.00	K_2CO_3	3.200	THF	40	5.11	3.9	3.7	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	40	4.68	5.8	5.3	Benzaldehyde stirred with aq Na_2CO_3, dried
C (1% H_2O	4.00	K_2CO_3	3.200	THF	40	4.26	2.8	2.5	over $MgSO_4$ filtered and then distilled under **vac**
D (1% H_2O	4.00	K_2CO_3	3.200	THF	40	2.58	6.1	5.5	Rxn 2.0ml scale, warm THF added
									New fresh anhydrous K_2CO_3 99.995% used, ground today
									Rxns A&B dark yellow-orange susp,rxns C&D bright yellow susp
									Rxns A & B and C & D were duplicates
									New THF still prepared 4 days previously
									20uL degassed DI water added to rxns C and E

Expt SOT382: Repeat of SOT373, using fresh unground and unused K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals
A	4.00	K_2CO_3	3.200	THF	0	<0.45	n/a	n/a	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	0	<0.50	n/a	n/a	**Benz not washed with aq Na_2CO_3,distilled under vac directly**
A	4.00	K_2CO_3	3.200	THF	48	2.12	18.5	16.7	Balloon on rxn A deflated partially
B	4.00	K_2CO_3	3.200	THF	48	1.11	14.6	13.3	Rxn 2.0ml scale, warm THF added
A	4.00	K_2CO_3	3.200	THF	80	4.29	16.9	14.7	**New fresh anhydrous K_2CO_3 99.995% used, ground today**
B	4.00	K_2CO_3	3.200	THF	80	4.33	17.7	16.2	Rxns A & B were medium yellow susps, also duplicates

Expt SOT383: Exact repeat of SOT382, using fresh unground and unused K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with **brand new balloons**
A	4.00	K_2CO_3	3.200	THF	0	0.55	n/a	n/a	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	0	n/a	n/a	n/a	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	K_2CO_3	3.200	THF	24	0.22	27.7	27.9	over $MgSO_4$ filtered and then distilled under **vac**
B	4.00	K_2CO_3	3.200	THF	24	n/a	n/a	n/a	Rxn 2.0ml scale, warm THF added
A	4.00	K_2CO_3	3.200	THF	48	3.24	28.7	27.8	**New fresh anhydrous K_2CO_3 99.995% used, ground today**
B	4.00	K_2CO_3	3.200	THF	48	3.57	10	9	Rxns A dark yellow/orange susp, rxn B pale yellow susp
A	4.00	K_2CO_3	3.200	THF	60	n/a	n/a	n/a	Rxns A & B duplicates
B	4.00	K_2CO_3	3.200	THF	60	0.91	10.2	9.2	NMRs taken on rxn A, rxn B untouched til 48hrs

Expt SOT385: Exact repeat of SOT383, using Cs_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with **brand new balloons**
A	4.00	K_2CO_3	3.200	THF	68	2.17	31.9	30.7	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	68	2.77	33.3	33.4	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	K_2CO_3	3.200	THF	68	1.58	27.7	25.2	over $MgSO_4$ filtered and then distilled under **vac**
D	4.00	Cs_2CO_3	3.200	THF	68	1.49	25.5	23.9	Rxn 2.0ml scale, warm THF added
E	4.00	Cs_2CO_3	3.200	THF	68	3.29	7.2	6.9	**New fresh anhydrous K_2CO_3 99.995% used, ground today**
									Fresh unopened Cs_2CO_3 99.995% used, ground today
									Rxns A-C med yellow susp, rxns D & E dark yellow susp
									Rxns A-C and rxns D & E were duplicates
									Balloons on rxns A & B deflated.

Expt SOT388: Exact repeat of SOT385, using 0.5% degassed H_20 and larger stirring bars

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with **brand new balloons**
A	4.00	K_2CO_3	3.200	THF	48	1.98	28	26.6	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	48	5.94	0.9	0.7	Benzaldehyde stirred with aq Na_2CO_3, dried
(0.5% H_2	4.00	Cs_2CO_3	3.200	THF	48	1.96	6.6	6.5	over $MgSO_4$ filtered and then distilled under **vac**
(0.5% H_2	4.00	Cs_2CO_3	3.200	THF	48	3.13	1.9	1.7	Rxn 2.0ml scale, warm THF added
									New fresh anhydrous K_2CO_3 99.995% used, ground today
									Rxn A & C yellow susp, rxn B & D fstk orange susp
									Rxns A & B and C & D were duplicates
									10uL degassed DI water added to rxns C and D

Expt SOT389: Exact repeat of SOT385, using 0.5% degassed H_20 and larger stirring bars

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with **brand new balloons**
A	4.00	DBU	2.900	THF	48	1	8.5	7	Rxns evacuated on high vac line (~4min) prior to THF addn
B	4.00	DBU	2.900	THF	48	1.5	10.7	9	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under **vac**
									Rxn 2.0ml scale, warm THF added
									Balloon on rxn B deflated
									Both rxns pale yellow small amt ppt
									Rxn A & B duplicates

Expt SOT390: Exact repeat of SOT385, ~30% yield

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with **brand new balloons**
A	4.00	K_2CO_3	3.200	THF	65	4.5	2.4	2	Rxns evacuated on high vac line (~8min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	65	1.5	31.6	28	Benzaldehyde stirred with aq Na_2CO_3, dried
									over $MgSO_4$ filtered and then distilled under **vac**
									Rxn 2.0ml scale, warm THF added
									New fresh anhydrous K_2CO_3 99.995% used, ground today
									Rxn A dark yellow susp, rxn B yellow susp
									Rxns A & B duplicates
									New identical fat smaller stirring bars used (now standard!)
									Balloon on rxn A deflated several times

Expt SOT393: Carbonate Base Test

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	**K_2CO_3**	3.200	THF	48	0.8	36.5	**35**	Rxns evacuated on high vac line (~8min) prior to THF addn
B	4.00	**Cs_2CO_3**	3.200	THF	48	1.23	22.5	**23.4**	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	Na_2CO_3	3.200	THF	48	0	0	0	over $MgSO_4$ filtered and then distilled under **vac**
D	4.00	Li_2CO_3	3.200	THF	48	1.04	0	0	Rxn 2.0ml scale, warm THF added
E	4.00	**Rb_2CO_3**	3.200	THF	48	0.84	25	**25.4**	**Brand new unopened carbonates used & ground up.K_2CO_3**
A	4.00	K_2CO_3	3.200	THF	66	1.67	40.2	36	**and Cs_2CO_3 were presviosly opened, fresh samples ground**
B	4.00	Cs_2CO_3	3.200	THF	66	1.67	22.9	23.7	Carbonates stored under Ar until evacuated on line
C	4.00	Na_2CO_3	3.200	THF	66	0.99	0	0	Balloon on rxn E partially deflated
D	4.00	Li_2CO_3	3.200	THF	66	1.49	0	0	Rxns A, B & E yellow susps, rxns C & D white susp
E	4.00	Rb_2CO_3	3.200	THF	66	1.22	25.4	25.1	**New identical fat smaller stirring bars used (now standard!)**

Expt SOT395: Repeat of SOT393 - Carbonate Base Run Test

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	**K_2CO_3**	3.200	THF	48	1.47	37.3	**34.8**	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	**Cs_2CO_3**	3.200	THF	48	1.4	18.7	**19.9**	Benzaldehyde stirred with aq Na_2CO_3, dried
C	4.00	Na_2CO_3	3.200	THF	48	0.77	0	0	over $MgSO_4$ filtered and then distilled under **vac**
D	4.00	Li_2CO_3	3.200	THF	48	0.8	0	0	Rxn 2.0ml scale, warm THF added
E	4.00	**Rb_2CO_3**	3.200	THF	48	1.48	51.7	**48.3**	**Brand new unopened carbonates used & ground up.K_2CO_3**
									and Cs_2CO_3 were presviosly opened, fresh samples ground
									Carbonates stored under Ar until evacuated on line
									Balloon on rxn B continually deflated
									Rxns A, B & E yellow susps, rxns C & D white susp
									New identical fat smaller stirring bars used (now standard!)

Expt SOT397: Change of Base and catalyst loading using Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	63	1.96	40.7	39.2	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	63	2.17	38.5	33.5	Benzaldehyde stirred with aq Na_2CO_3, dried
C	1.00	Rb_2CO_3	0.500	THF	63	0.95	6	6	over $MgSO_4$ filtered and then distilled under **vac**
D	1.00	Rb_2CO_3	0.500	THF	63	0.5	5.3	5.2	Rxn 2.0ml scale, warm THF added
									New fresh Rb_2CO_3 99.8% used, ground today
									Rb_2CO_3 could be seen to liquify when weighing out
									Rxns A & B yellow susps, rxns C & D clear yellow soln
									Rxns A & B and C & D duplicates

Expt SOT400: Change of catalyst to base loading using Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	48	3.05	13.4	11.2	Rxns evacuated on high vac line (~5min) prior to THF addn
C	4.00	Rb_2CO_3	1.667	THF	48	4.39	27.8	25	Benzaldehyde stirred with aq Na_2CO_3, dried
D	4.00	Rb_2CO_3	1.818	THF	48	2.81	26.6	24.2	over $MgSO_4$ filtered and then distilled under **vac**
E	4.00	Rb_2CO_3	1.905	THF	48	2.09	32.5	28.8	Rxn 2.0ml scale, warm THF added
									Rb_2CO_3 99.8% ground & used previously stored o/n in oven
									Carbonates stored under Ar until evacuated on line

Expt SOT401: Change of catalyst to base loading using Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	64	2.99	29.2	26.4	Rxns evacuated on high vac line (~5min) prior to THF addn
C	**4.00**	Rb_2CO_3	**1.905**	THF	64	2.01	37.4	31.5	Benzaldehyde stirred with aq Na_2CO_3, dried
D	**6.00**	Rb_2CO_3	**2.857**	THF	64	1.52	53.6	42.8	over $MgSO_4$ filtered and then distilled under **vac**
E	**10.00**	Rb_2CO_3	**4.762**	THF	64	4.29	64.3	45.7	Rxn 2.0ml scale, warm THF added
									Rb_2CO_3 99.8% ground & used previously, in oven for 3days
									New THF still prepared on day of reactions

Expt SOT402: Wet vs. Dry Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	**Rb_2CO_3 (w)**	3.200	THF	48	3.25	3.1	2.9	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	**Rb_2CO_3 (d)**	3.200	THF	48	0.76	22.3	21	Benzaldehyde stirred with aq Na_2CO_3, dried
C (1% H_2O	4.00	**Rb_2CO_3 (d)**	3.200	THF	48	0.31	5.6	5.3	over $MgSO_4$ filtered and then distilled under **vac**
									Rxn 2.0ml scale, warm THF added
									Rb_2CO_3 99.8% ground & used previously, in oven for 8days
									Rb_2CO_3 rxn A weighed out into rbf and left sealed o/n in air
									Exposure time weighing carb 8mins rxns B & C

Expt SOT404: Oven dried vs oven-dried and heat gunned Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	47	1.05	20.2	20.9	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	47	<0.68	29.7	29.7	Benzaldehyde stirred with aq Na_2CO_3, dried
A	4.00	Rb_2CO_3	3.200	THF	67	n/a	n/a	n/a	over $MgSO_4$ filtered and then distilled under **vac**
B	4.00	Rb_2CO_3	3.200	THF	67	0.73	27.5	25.3	Rxn 2.0ml scale, warm THF added
A	4.00	Rb_2CO_3	3.200	THF	112	n/a	n/a	n/a	**Rb_2CO_3 99.8% ground & used previously, in oven for 8days**
B	4.00	Rb_2CO_3	3.200	THF	112	0.85	27.6	25.1	**Rb_2CO_3 rxn A heat gunned 4x1 min intervals on vac line**
									Total exposure time weighing carb 7 mins

Expt SOT407: Oven dried and heat gunned Rb_2CO_3 with and without mol. Sieves

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	61.5	0.59	31.8	29.8	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	61.5	0.77	0	0	Benzaldehyde stirred with aq Na_2CO_3, dried
0.5g Mol. Sieves added to rxn B									over $MgSO_4$ filtered and then distilled under **vac (now std)**
Both balloons half deflated									Rxn 2.0ml scale, warm THF added
									Rb_2CO_3 99.8% ground & used previously, in oven for 2days
									Rb_2CO_3 rxn A&B heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 8 mins

Expt SOT410: Oven dried and heat gunned (long and shoer) Rb_2CO_3 with and without mol. Sieves

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	3.200	THF	48	0.94	34.9	32.2	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	48	<1.89	0	0	Rxn C heat gunned over course of the day, ~8hrs
C	4.00	Rb_2CO_3	3.200	THF	48	<1.26	34.7	33.9	0.5g Mol. Sieves added to rxn B
Rxn A short heat gun (4 x 1min intervals)									Rxn 2.0ml scale, warm THF added
Rxn B with 0.5g mol sieves short heat gun (4 x 1min intervals)									**Rb_2CO_3 99.8% ground & used previously, in oven for 4days**
Rxn C long heat gun, heated for 1min intervals over ~8hrs									**Rb_2CO_3 rxn A&B heat gunned 4x1 min intervals on vac line**
									Total exposure time weighing carb 8 mins

Expt SOT413: Oven dried and heat gunned (long and short) Rb_2CO_3 with and without mol. Sieves

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	K_2CO_3	3.200	THF	48	1.95	15	14.5	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	48	0.68	35.4	32.3	**Rxn A & C freshly ground new carbonates used**
C	4.00	Rb_2CO_3	3.200	THF	48	2.33	36.5	34.8	Rxn 2.0ml scale, warm THF added
									Rb_2CO_3 rxn B ground & used previously, in oven for 7days
									Rxns A & B heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 8 mins

Expt SOT417: Change in cat:base ratio using oven dried K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	K_2CO_3	3.200	THF	43	4.4	16.8	14.7	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	48	1	62.3	55.5	Rxn 2.0ml scale, **cold** THF added
C	4.00	Rb_2CO_3	2.800	THF	48	1.2	61.9	55.4	**Both carbs ground & used previously, in oven for 7days**
D	4.00	Rb_2CO_3	2.400	THF	48	2.16	62.2	**58.6**	**All rxns heat gunned 4x1 min intervals on vac line**
E	4.00	Rb_2CO_3	2.100	THF	48	1.38	60.2	53.7	Exposure time weighing carb for each 8 mins, (A), (BCD), (DEF)
F	4.00	Rb_2CO_3	1.800	THF	48	3.62	52.3	48.3	
G	4.00	Rb_2CO_3	1.500	THF	48	5.52	0	0	

Expt SOT424: Optimum conditions to date using oven dried Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	2.400	THF	45.5	1.92	34	30.8	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	2.400	THF	45.4	1.66	34.9	32.8	Rxn 2.0ml scale
									Rb_2CO_3 ground & used previously, in oven for 7days
									All rxns heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 10 mins
									New THF still prepared on day,when cooled was blue/green
									Balloon on rxn C half deflated after 24hrs

Expt SOT425: Trying to get reproducibility using oven dried Rb_2CO_3 in rbf and carousel reduced volume flask

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_2	2.400	THF	48	0.74	57.4	52.6	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	2.400	THF	48	0.58	32.5	30.1	**Rxn C done in reduced volume flask in carousel**
C	4.00	Rb_2CO_3	2.400	THF	48	3.78	0	0	Rb_2CO_3 ground & used previously, in oven for 8days
									All rxns heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 15 mins

Expt SOT442: Trying to get reproducibility using oven dried K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_2	2.400	THF	48	2.2	42.3	35.4	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	2.400	THF	48	0.82	51.3	39.6	Rxn A & B done in duplicate
A	4.00	Rb_2CO_2	2.400	THF	68	1.51	40	37.6	Rb_2CO_3 ground & used previously, in oven for 12 days
B	4.00	Rb_2CO_3	2.400	THF	68	1	49.8	46.7	All rxns heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 13 mins

Expt SOT444: Trying to get reproducibility of 50% using oven dried K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_3	2.400	THF	65	1.08	42.6	37.8	Rxns evacuated on high vac line (~5min) prior to THF addn
									Rxn A & B done in duplicate
									Rb_2CO_3 ground & used previously, in oven for 4 days
									All rxns heat gunned 4x1 min intervals on vac line
									Total exposure time weighing carb 7 mins
									Rxn 2.0ml scale, cold THF added

Expt SOT445: Trying to get reproducibility of 50%, using recrystallised and redried catalyts and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	Rb_2CO_2	2.400	THF	89	3.73	37.9	32.6	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_2	2.400	THF	89	??	36.7	29.3	Rb_2CO_3 ground & used previously, in oven for 14 days
C	4.00	Rb_2CO_2	2.400	THF	89	7.22	3.3	2.7	**All rxns heat gunned for 4 x 1min intervals on vac line**
									Total exposure time weighing carb 9 mins
									Rxn 2.0ml scale, cold THF added
									Rxns A&B duplicates, new x-allised cat, dried 24hrs on high vac
									Rxn C "old" catalyst not dried or recrystallised

Expt SOT446: Reproducibility of 50% obtained in base run using recrystallised and redried catalyts

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	K_2CO_2	2.400	THF	48	7.17	7.1	7	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	**Rb_2CO_2 new**	2.400	THF	48	0.61	41.7	39.5	Rb_2CO_3 ground & used previously, in oven for 5 days (rxn C)
C	4.00	**Rb_2CO_2 old**	2.400	THF	48	1.17	38.4	36.1	**Rxns not heat gunned, just evacuated for 4mins on vac line**
D	4.00	$CdCO_2$	2.400	THF	48	3.96	0	0	Total exposure time weighing carb 9 mins
									Rxn 2.0ml scale, cold THF added
									Fresh new carbonates used in rxns A, B & D, all ground up
									Balloon on rxns A & D deflated and partly rxn B

Expt SOT448: Reaction using $KHCO_3$ and KHMDS as base

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
A	4.00	**$KHCO_3$**	**3.200**	THF	48	2.86	36.1	32	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	**KHMDS**	3.200	THF	48	1.34	4.4	4.4	New $KHCO_3$ ground & used freshly that day
A	4.00	**$KHCO_3$**	**3.200**	THF	90	4.87	33.3	28.1	**10% soln KHMDS (in toluene) made up in THF.**
B	4.00	**KHMDS**	3.200	THF	90	0.78	6.1	5.9	Rxn 2.0ml scale, warm THF added
A	4.00	**$KHCO_3$**	**3.200**	THF	160	7.7	27.7	22.5	
B	4.00	**KHMDS**	3.200	THF	160	0.94	5.9	5.7	

Note: Potassium hydrogen carbonate used, this is monobasic, unlike K_2CO_3. Therefore only half the std base used

Expt SOT449: Chiral crystalline vs ppted catalyst and achiral cat at 1.1M and 2.2M soln with $KHCO_3$

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns done in 5ml rbfs with septa seals with brand new balloons
C	4.00	$KHCO_3$	3.600	**THF (1.1M)**	48	2.31	31.4	30.6	Rxns evacuated on high vac line (~5min) prior to THF addn
D	4.00	$KHCO_3$	3.600	**THF (2.2M)**	48	1.87	33.8	30.7	$KHCO_3$ ground 9 days previously used
C	4.00	$KHCO_3$	3.600	**THF (1.1M)**	117	4.84	26.4	21.5	**Rxns heat gunned 4x1min intervals**
D	4.00	$KHCO_3$	3.600	**THF (2.2M)**	117	2.65	40.6	34.6	**Rxn C 1.1M soln,rxn D 2.2M soln(4.4mmol benz in 2.0ml THF**
									Rxn 2.0ml scale, warm THF added

Note: THF still needed to be changed, still purple but yellow residue on sides of flask

Expt SOT450: Use of New THF and columned new cat vs crystalline & achiral standard catalyst 233c

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn B used SOT439A (columned), rxn B 240(5) (crystalline)
A	1.25	K_2CO_3	1.000	THF	48	1.73	15.3	14.9	Rxns evacuated on high vac line (~5min) prior to THF addn
									K_2CO_3 ground 25 days previously used
									Rxns heat gunned 4x1min intervals
									2.0ml dry anhydrous inhibitor-free THF (unopened) used
									Rxn A used crystalline cat ((SOT381(1))

Expt SOT451: Comparison of 98-100% lab grade vs 99.995% (anhydrous) K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Fresh lab grade 98-100% K_2CO_3 (rxn A), 99.995% ahydr K_2CO_3
A	4.00	K_2CO_3	3.200	THF	48	1.31	24.5	18.8	(rxn B) and Rb_2CO_3 (rxn C), all ground freshly
B	4.00	K_2CO_3	3.200	THF	48	0	39.1	30.4	Rxns evacuated on high vac line (~5min) prior to THF addn
C	4.00	Rb_2CO_3	3.200	THF	48	0	29.1	22.4	**Rxns NOT heat gunned 4x1min intervals**
									New THF still prepared 5 days previously, added cool temp

Expt SOT452: Effect of drying K_2CO_3 and Rb_2CO_3 on vac line over several hours or via heat gunning

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns A & B used ppt cat, rxns C & D crystalline cat SOT381 1&2
A	4.00	K_2CO_3	3.200	THF	48	2.72	3.6	3.1	Rxns A & C carb hair dried for 30sec regularly over 4hrs
B	4.00	K_2CO_3	3.200	THF	48	6.05	2.1	1.8	Rxns B & D carb heat gunned 4x1min intervals
C	4.00	K_2CO_3	3.200	THF	48	2.1	25	22	Rxns evacuated on high vac line (~5min) prior to THF addn
D	4.00	K_2CO_3	3.200	THF	48	0.42	22.3	20.4	Luke warm THF from still used

Expt SOT455: Variaton of catalyst state - ppt, aziotroped or recrystallised

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns A orig ppt cat, rxn B aziotroped & high vac line cat, rxns C
A	4.00	K_2CO_3	3.200	THF	48	3.19	21.4	18.4	& D recrystallised cat
B	4.00	K_2CO_3	3.200	THF	48	0.57	37.8	34.8	K_2CO_3 ground 7 days previously used in rxns A - C
C	4.00	K_2CO_3	3.200	THF	48	1.1	21.8	19.9	Rxns heat gunned 3x1min intervals
D	4.00	Rb_2CO_3	3.200	THF	48	0.44	49.1	46.9	Rb_2CO_3 ~30days in oven used in rxn D
A	4.00	K_2CO_3	3.200	THF	142	~0.37	21.3	17.6	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	K_2CO_3	3.200	THF	142	1.49	37.1	32.8	Cool THF from still used
C	4.00	K_2CO_3	3.200	THF	142	2.43	21.3	18.8	
D	4.00	Rb_2CO_3	3.200	THF	142	1.86	48.1	46.3	

Expt SOT458: Achiral cat using NaN_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Achiral crystalline catalst used in rxn A
A	4.00	NaN_3	3.600	THF	48	0.62	0	0	3.6mol% NaN_3 used in rxn A as base
									Rxns evacuated on high vac line (~5min) prior to THF addn

Expt SOT459: Aziotroped achiral cat using K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn A crystalline cat, rxn B ~33% aziotroped cat, 66%

A	4.00	K_2CO_3	3.200	THF	48	3.65	2.9	2.4	crystalline cat, rxns C & D used aziotroped chiral cat
B	4.00	Rb_2CO_3	3.200	THF	48	1.52	45.3	39	Rb_2CO_3 ~50days in oven used in rxns B &D. K_2CO_3 fresh
A	4.00	K_2CO_3	3.200	THF	64	3.82	2.4	2.1	Rxns evacuated on high vac line (~5min) prior to THF addn
B	4.00	Rb_2CO_3	3.200	THF	64	1.15	45.3	39.6	Cool THF from still used
									Balloon on rxn A deflated & after ~1hr was dark yellow susp

Expt SOT465: Achiral crystalline cat with K_2CO_3 and Rb_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn A-C used crystalline achiral cat
A	4.00	K_2CO_3	3.200	THF	63	2.31	46.3	41.9	Rb_2CO_3 ~55days in oven used in rxns B &D. K_2CO_3 fresh
B	4.00	Rb_2CO_3	3.200	THF	63	0.84	29.1	27	Rxns evacuated on high vac line (~5min) prior to THF addn
C	4.00	Rb_2CO_3	4.000	THF	63	0.22	24.6	24.4	

Expt SOT466: Achiral cat with new and old K_2CO_3 and DBU

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	**Fresh K_2CO_3 used in rxn A, K_2CO_3 that had been previously**
A	4.00	K_2CO_3	3.200	THF	48	1.54	46.1	44.1	**used ~6/7 times & stored under Ar used in rxn B**
B	4.00	Rb_2CO_3	3.200	THF	48	1.75	39	34.3	Rxns evacuated on high vac line (~5min) prior to THF addn
C	4.00	DBU	3.200	THF	48	0.63	6.7	6.1	Carbonates heat gunned as per usual proc

Expt SOT468: Reproducibility using achiral cat by putting reaction on at different times of the day

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn A put on at 12:30hrs, rxn B at 15:00hrs
A	4.00	K_2CO_3	3.200	THF	48	2.95	41.1	37	K_2CO_3 ~1month old used in both rxns
B	4.00	K_2CO_3	3.200	THF	48	0.62	44.9	36.2	Rxns evacuated on high vac line (~5min) prior to THF addn
									Carbonates heat gunned as per usual proc

Expt SOT474: Two different standards of crystalline cat and variation of cat:base ratio

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn A used Louise's very square crystalline catalyst
A	4.00	K_2CO_3	3.200	THF	48.5	~2.45	37.2	34.3	K_2CO_3 ~15days old used, used twice previously used
B	4.00	K_2CO_3	3.200	THF	48.5	~1.81	43	38.5	Rxns evacuated on high vac line (~5min), **pulled at 4psi**
C	4.00	K_2CO_3	4.000	THF	48.5	1.42	16.7	14.8	Carbonates heat gunned as per usual proc
D	4.00	K_2CO_3	2.000	THF	48.5	2.94	34.2	31.1	Cold THF from still used
E	4.00	K_2CO_3	1.600	THF	48.5	4.72	17.9	16.8	Rxn A & B 1:1.6 cat:base ratio
A	4.00	K_2CO_3	3.200	THF	117	1.93	40.1	34	Rxn C 1:2 cat:base ratio
B	4.00	K_2CO_3	3.200	THF	117	2.44	43.2	34.6	Rxn D 1:1 cat:base ratio
C	4.00	K_2CO_3	4.000	THF	117	0.11	16.6	14.1	Rxn E 1:0.8 cat:base ration
D	4.00	K_2CO_3	2.000	THF	117	~2.0	33	27.2	**Assumed results for rxns C & E not valid**
E	4.00	K_2CO_3	1.600	THF	117	4.62	15.9	13.1	

Expt SOT476: Variation of cat:base ratio

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	K_2CO_3 ~15days old used, used 4times previously
A	4.00	K_2CO_3	3.200	THF	61.5	0.87	38.5	33.6	When weighing K_2CO_3 top of sample tube became liquid
B	4.00	K_2CO_3	4.000	THF	61.5	0.44	36.5	34.4	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
C	4.00	K_2CO_3	2.100	THF	61.5	7.18	1.3	1.1	Carbonates heat gunned as per usual proc
D	4.00	K_2CO_3	1.900	THF	61.5	5.23	28.2	23.9	Cold THF from still used
E	4.00	K_2CO_3	1.000	THF	61.5	3.2	28.1	25.3	Cat:base ratio: Rxn A 1:1.6, rxn B 1:2, rxn C 1:1.05, rxn D
A	8.00	K_2CO_3	6.400	THF	60/121.5	3.63	52.7	43.8	1:0.95 and rxn E 1:0.5
Air got into rxn C, assume result not valid									4.0mol% cat and 3.2mol% K_2CO_3 added to rxn A at 61.5hrs

Expt SOT478: Variation of cat:base ratio using fresh K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Fresh K_2CO_3 ground up and used in expt
A	4.00	K_2CO_3	3.200	THF	48	1.55	46.5	43.2	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
B	4.00	K_2CO_3	8.000	THF	48	0.31	21.2	21.5	Carbonates heat gunned as per usual proc
C	4.00	K_2CO_3	2.600	THF	48	2.87	2	1.7	Cold THF from still used
D	4.00	K_2CO_3	2.200	THF	48	2.6	41.8	37.7	**Old once used septa used as no new septa available**
E	4.00	K_2CO_3	1.600	THF	48	~3.85 (?)	39.3	39.3	Cat:bse ratio: Rxn A 1:1.6, rxn B 1:4, rxn C 1:1.3, rxn D 1:1.1
Air got into rxn C, assume result not valid									and rxn E 1:0.8

Expt SOT479: Achiral catalyst using fresh K_2CO_3 and DBU in DCM

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Fresh K_2CO_3 ground up and used in expt
A	4.00	K_2CO_3	3.200	THF	48	3.14	6.8	6.8	Rxn A evacuated on high vac line (~5min), **pulled at 0psi**
B	4.00	DBU	6.400	**DCM**	48	1.22	0	0	Cold THF from still used
									Old once used septa used as no new septa available

Expt SOT480: Achiral and chiral cat using K_2CO_3, and achiral cat with DBU and 10%KOH in K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Chiral rxn B done on 1.1mmol scale instead of 2.2mmol
A	4.00	K_2CO_3	3.200	THF	48	3.9	2.9	2.4	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
C	4.00	DBU	20.000	THF	48	2.91	0	0	Carbonates heat gunned as per usual proc
D	4.00	K_2CO_3/KOH	2.88/0.32	THF	48	1.61	47.8	48.4	Fresh carbonate & KOH weighed out & used
D	4.00	K_2CO_3/KOH	2.88/0.32	THF	66	1.95	45.9	41.4	**Rxn D contained 3.6mol% K_2CO_3 & 0.4mol% KOH**
									Old once used septa used as no new septa available

Expt SOT484: Achiral cat using K_2CO_3, 10%KOH in K_2CO_3 100% KOH and P_2 Base

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxn C KOH was a clear liquid when heat gunned
A	4.00	K_2CO_3	3.200	THF	48	3.6	29.1	26.6	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
B	4.00	K_2CO_3/KOH	2.88/0.32	THF	48	1.89	34.1	29.4	Carbonates heat gunned as per usual proc
C	4.00	KOH	3.200	THF	48	7.59	0	0	Fresh carbonate & KOH weighed out & used
D	4.00	P2	3.200	THF	48	1.11	2.4	2.3	**P_2 base is phosazene P_2 t-butyl base**

Expt SOT486: Achiral catalyst 233c and C-3 Methylated achiral cat 240a using K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate 4days old used in expt
A	4.00	K_2CO_3	3.200	THF	62	1.96	39.9	35.6	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
B	4.00	K_2CO_3/KOH	3.200	THF	62	1.89	5.4	4.9	Carbonates heat gunned as per usual proc
									Rxn B achiral C-3 Me Canary catalyst 240a

Expt SOT487: Achiral catalyst 233c and C-3 Methylated achiral cats 240a using K_2CO_3, KOH and DBU

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up & used
A	4.00	K_2CO_3	3.200	THF	69	2.83	33.6	30.3	Rxns evacuated on high vac line (~5min), **pulled at 0psi**
B	4.00	K_2CO_3/KOH	2.88/0.32	THF	69	4.21	4.5	4.1	Carbonates heat gunned as per usual proc
C	4.00	K_2CO_3/KOH	1.6/1.6	THF	69	2.77	41.9	40.1	**Rxns D & E achiral C-3 Me catalyst 240a**
									Benzaldehyde not washed prior to distillation

Expt SOT492: Variation of K_2CO_3 and KOH ratio

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up & used
A	4.00	K_2CO_3	3.200	THF	47	2.29	44.3	43.7	Rxns evacuated on high vac line (~5min), pulled at 0psi
B	4.00	KOH	6.400	THF	47	2.5	0	0	Carbonates heat gunned as per usual proc, **not rxn B**
C	4.00	K_2CO_3/KOH	2.88/0.64	THF	47	1.26	48.4	41.9	In all rxns cat:base ratio is 1:1.6
D	4.00	K_2CO_3/KOH	2.4/1.6	THF	47	1.87	40.1	36.9	
E	4.00	K_2CO_3/KOH	1.6/3.2	THF	47	1.71	12.1	11.2	
F	4.00	K_2CO_3/KOH	0.8/4.8	THF	47	2.03	34.1	31.6	

Expt SOT496: Achiral cat 233c with 10% KOH in K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH used 2days previously
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	64	2.32	37.2	29.9	Rxns evacuated on high vac line (~5min), pulled at 0psi
									Carbonates heat gunned as per usual proc
									Rxn B worked up at 65hrs

Expt SOT497: 10% and 50% KOH in K_2CO_3 in THF and DCM

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	61	2.43	50	43.9	Rxns evacuated on high vac line (~5min), pulled at 0psi
B	4.00	K_2CO_3/KOH	2.88/0.64	DCM	61	4.7	13.3	12.5	Carbonates heat gunned as per usual proc
C	4.00	K_2CO_3/KOH	1.62/0.36	THF	61	4.56	25.4	21.5	Cold THF added to rxns from still
D	4.00	K_2CO_3/KOH	1.62/0.36	DCM	61	4.98	9.8	8.8	Cat:base ratio rxns A & B 1:1.6 and rxns C & D 1:0.9

Expt SOT498: Achiral cat 233c with 10% KOH in K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH that was 4days old used, used once prev
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	64.5	3.42	36.8	31.5	Rxns evacuated on high vac line (~5min), **pulled at 1psi**
									Carbonates for rxn A heat gunned as per usual proc

Expt SOT500: Achiral cat 233c using 10% KOH in K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up & used
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	52	1.48	37.1	35.2	Rxns evacuated on high vac line (~5min), **pulled at 0 & 1 psi**
									Carbonates for rxns A-H heat gunned as per usual proc
									Cool THF added to rxns from still

Expt SOT501: Achiral cat using P_1 Base

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Rxns evacuated on high vac line (~5min), **pulled at 0 & 1 psi**
A	4.00	P_1 Base	3.600	THF	48	1.68	6.8	6.6	Cool THF added to rxn from still

Expt SOT502: Achiral cat using 10% KOH in K_2CO_3

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up & used
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	49	0.05	45.1	36.1	Rxn evacuated on high vac line (~5min), pulled at 0 psi
									Carbonates for rxn A heat gunned as per usual proc

Expt SOT505: Achiral cat evaluation

Reaction	Cat (mol%)	Base	Base (mol%)	Solvent	Time (hr)	% Benzoic A	% Conv	% Yield	Carbonate and KOH freshly ground up & used
A	4.00	K_2CO_3/KOH	2.88/0.64	THF	48	1.49	31.6	27.7	Rxns evacuated on high vac line (~5min), pulled at 0 psi

Appendix Two

X-ray crystallography data for amino indanol-derived precatalyst (*1R*,2*R*)-**241a**

Table 1. Crystal data and structure refinement for m1.

Identification code	shelxl	
Empirical formula	C50 H46 Cl6 N8 O10	
Formula weight	1131.65	
Temperature	150(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 11.223(6) Å	α= 90°.
	b = 7.430(4) Å	β= 91.586(8)°.
	c = 15.471(9) Å	γ = 90°.
Volume	1289.6(12) $Å^3$	
Z	1	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	0.400 mm^{-1}	
F(000)	584	
Crystal size	0.20 x 0.10 x 0.05 mm^3	
Theta range for data collection	1.82 to 25.00°.	
Index ranges	-13<=h<=13, -4<=k<=8, -18<=l<=18	
Reflections collected	6284	
Independent reflections	3525 [R(int) = 0.0333]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8208	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3525 / 1 / 334	
Goodness-of-fit on F^2	1.091	
Final R indices [I>2sigma(I)]	R1 = 0.0527, wR2 = 0.1397	
R indices (all data)	R1 = 0.0560, wR2 = 0.1427	
Absolute structure parameter	-0.02(9)	
Largest diff. peak and hole	0.700 and -0.495 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for m1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8319(3)	3535(5)	6277(2)	29(1)
N(1)	9843(3)	1534(5)	6312(2)	23(1)
N(2)	8812(3)	1087(6)	8306(2)	23(1)
N(3)	6862(3)	1370(8)	8417(2)	40(1)
N(4)	7405(3)	1237(5)	9218(2)	23(1)
C(1)	8597(4)	1939(7)	3137(3)	30(1)
C(2)	9695(4)	1600(6)	3543(3)	27(1)
C(3)	9830(4)	1747(6)	4428(3)	25(1)
C(4)	8862(4)	2251(6)	4927(3)	23(1)
C(5)	7753(4)	2601(6)	4517(3)	27(1)
C(6)	7633(4)	2452(7)	3630(3)	29(1)
C(7)	13666(4)	1926(8)	6719(3)	37(1)
C(8)	12461(4)	2295(7)	6575(3)	30(1)
C(9)	11663(4)	1822(6)	7210(2)	23(1)
C(10)	10312(4)	1982(6)	7173(2)	21(1)
C(11)	9960(4)	663(6)	7909(2)	25(1)
C(12)	11016(4)	660(7)	8555(3)	26(1)
C(13)	12052(4)	1012(7)	7985(2)	25(1)
C(14)	13253(4)	661(7)	8128(3)	32(1)
C(15)	14061(4)	1097(9)	7490(3)	38(1)
C(16)	5563(4)	1978(7)	9935(3)	29(1)
C(17)	4862(4)	1873(7)	10662(3)	33(1)
C(18)	5306(4)	1067(8)	11425(3)	33(1)
C(19)	6456(4)	373(7)	11460(3)	33(1)
C(20)	7165(4)	441(7)	10734(3)	27(1)
C(21)	6707(3)	1238(7)	9977(2)	24(1)
C(22)	8974(4)	2502(7)	5890(3)	25(1)
C(23)	7728(4)	1294(10)	7885(3)	42(1)
C(24)	8570(3)	1077(6)	9145(2)	22(1)
Cl(1)	8841(1)	6155(2)	8910(1)	25(1)
O(2)	9364(3)	7481(5)	9498(2)	37(1)
O(3)	8015(3)	5054(6)	9354(2)	43(1)
O(4)	9792(3)	5061(6)	8576(3)	52(1)

O(5)	8236(3)	7081(6)	8203(2)	50(1)
Cl(3)	6993(2)	8937(2)	5777(1)	60(1)
Cl(2)	5381(1)	5890(3)	5912(1)	80(1)
C(50)	6651(5)	6962(9)	6373(4)	52(2)

Table 3. Bond lengths [Å] and angles [°] for m1.

O(1)-C(22)	1.231(6)
N(1)-C(22)	1.364(6)
N(1)-C(10)	1.457(5)
N(1)-H(1)	0.8800
N(2)-C(24)	1.334(5)
N(2)-C(23)	1.373(5)
N(2)-C(11)	1.477(5)
N(3)-C(23)	1.292(6)
N(3)-N(4)	1.370(4)
N(4)-C(24)	1.322(5)
N(4)-C(21)	1.429(5)
C(1)-C(2)	1.390(6)
C(1)-C(6)	1.394(7)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.378(6)
C(2)-H(2)	0.9500
C(3)-C(4)	1.401(6)
C(3)-H(3)	0.9500
C(4)-C(5)	1.405(6)
C(4)-C(22)	1.503(6)
C(5)-C(6)	1.379(6)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-C(8)	1.391(7)
C(7)-C(15)	1.403(7)
C(7)-H(7)	0.9500
C(8)-C(9)	1.393(6)
C(8)-H(8)	0.9500
C(9)-C(13)	1.400(6)

C(9)-C(10)	1.521(6)
C(10)-C(11)	1.561(6)
C(10)-H(10)	1.0000
C(11)-C(12)	1.528(5)
C(11)-H(11)	1.0000
C(12)-C(13)	1.501(6)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.385(6)
C(14)-C(15)	1.396(7)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-C(17)	1.392(6)
C(16)-C(21)	1.397(6)
C(16)-H(16)	0.9500
C(17)-C(18)	1.403(7)
C(17)-H(17)	0.9500
C(18)-C(19)	1.389(7)
C(18)-H(18)	0.9500
C(19)-C(20)	1.396(6)
C(19)-H(19)	0.9500
C(20)-C(21)	1.397(6)
C(20)-H(20)	0.9500
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500
Cl(1)-O(3)	1.426(4)
Cl(1)-O(5)	1.447(4)
Cl(1)-O(4)	1.448(4)
Cl(1)-O(2)	1.453(3)
Cl(3)-C(50)	1.781(6)
Cl(2)-C(50)	1.766(6)
C(50)-H(50A)	0.9900
C(50)-H(50B)	0.9900

C(22)-N(1)-C(10)	123.6(4)
C(22)-N(1)-H(1)	118.1
C(10)-N(1)-H(1)	118.3
C(24)-N(2)-C(23)	105.2(3)

C(24)-N(2)-C(11)	127.3(3)
C(23)-N(2)-C(11)	126.8(3)
C(23)-N(3)-N(4)	104.5(3)
C(24)-N(4)-N(3)	110.3(3)
C(24)-N(4)-C(21)	129.5(3)
N(3)-N(4)-C(21)	120.2(3)
C(2)-C(1)-C(6)	119.6(4)
C(2)-C(1)-H(1A)	120.2
C(6)-C(1)-H(1A)	120.2
C(3)-C(2)-C(1)	120.3(4)
C(3)-C(2)-H(2)	119.8
C(1)-C(2)-H(2)	119.8
C(2)-C(3)-C(4)	120.3(4)
C(2)-C(3)-H(3)	119.9
C(4)-C(3)-H(3)	119.9
C(3)-C(4)-C(5)	119.4(4)
C(3)-C(4)-C(22)	122.3(4)
C(5)-C(4)-C(22)	118.2(4)
C(6)-C(5)-C(4)	119.7(4)
C(6)-C(5)-H(5)	120.2
C(4)-C(5)-H(5)	120.2
C(5)-C(6)-C(1)	120.7(4)
C(5)-C(6)-H(6)	119.7
C(1)-C(6)-H(6)	119.7
C(8)-C(7)-C(15)	120.4(4)
C(8)-C(7)-H(7)	119.8
C(15)-C(7)-H(7)	119.8
C(7)-C(8)-C(9)	118.5(4)
C(7)-C(8)-H(8)	120.7
C(9)-C(8)-H(8)	120.7
C(8)-C(9)-C(13)	121.5(4)
C(8)-C(9)-C(10)	127.8(4)
C(13)-C(9)-C(10)	110.7(4)
N(1)-C(10)-C(9)	110.6(3)
N(1)-C(10)-C(11)	115.5(4)
C(9)-C(10)-C(11)	101.3(3)
N(1)-C(10)-H(10)	109.7
C(9)-C(10)-H(10)	109.7

C(11)-C(10)-H(10)	109.7
N(2)-C(11)-C(12)	113.4(3)
N(2)-C(11)-C(10)	114.2(4)
C(12)-C(11)-C(10)	105.7(3)
N(2)-C(11)-H(11)	107.7
C(12)-C(11)-H(11)	107.7
C(10)-C(11)-H(11)	107.7
C(13)-C(12)-C(11)	102.4(3)
C(13)-C(12)-H(12A)	111.3
C(11)-C(12)-H(12A)	111.3
C(13)-C(12)-H(12B)	111.3
C(11)-C(12)-H(12B)	111.3
H(12A)-C(12)-H(12B)	109.2
C(14)-C(13)-C(9)	119.7(4)
C(14)-C(13)-C(12)	129.8(4)
C(9)-C(13)-C(12)	110.4(4)
C(13)-C(14)-C(15)	119.5(4)
C(13)-C(14)-H(14)	120.3
C(15)-C(14)-H(14)	120.3
C(14)-C(15)-C(7)	120.4(4)
C(14)-C(15)-H(15)	119.8
C(7)-C(15)-H(15)	119.8
C(17)-C(16)-C(21)	118.7(4)
C(17)-C(16)-H(16)	120.6
C(21)-C(16)-H(16)	120.6
C(16)-C(17)-C(18)	120.5(4)
C(16)-C(17)-H(17)	119.8
C(18)-C(17)-H(17)	119.8
C(19)-C(18)-C(17)	120.0(4)
C(19)-C(18)-H(18)	120.0
C(17)-C(18)-H(18)	120.0
C(18)-C(19)-C(20)	120.3(4)
C(18)-C(19)-H(19)	119.8
C(20)-C(19)-H(19)	119.8
C(19)-C(20)-C(21)	119.0(4)
C(19)-C(20)-H(20)	120.5
C(21)-C(20)-H(20)	120.5
C(16)-C(21)-C(20)	121.5(4)

C(16)-C(21)-N(4)	119.1(4)
C(20)-C(21)-N(4)	119.4(4)
O(1)-C(22)-N(1)	121.6(4)
O(1)-C(22)-C(4)	121.7(4)
N(1)-C(22)-C(4)	116.7(4)
N(3)-C(23)-N(2)	112.0(4)
N(3)-C(23)-H(23)	124.0
N(2)-C(23)-H(23)	124.0
N(4)-C(24)-N(2)	108.1(3)
N(4)-C(24)-H(24)	126.0
N(2)-C(24)-H(24)	126.0
O(3)-Cl(1)-O(5)	109.8(2)
O(3)-Cl(1)-O(4)	110.2(3)
O(5)-Cl(1)-O(4)	109.4(2)
O(3)-Cl(1)-O(2)	110.1(2)
O(5)-Cl(1)-O(2)	108.9(2)
O(4)-Cl(1)-O(2)	108.4(2)
Cl(2)-C(50)-Cl(3)	110.2(3)
Cl(2)-C(50)-H(50A)	109.6
Cl(3)-C(50)-H(50A)	109.6
Cl(2)-C(50)-H(50B)	109.6
Cl(3)-C(50)-H(50B)	109.6
H(50A)-C(50)-H(50B)	108.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for m1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(2)	27(2)	30(2)	-3(2)	-1(1)	5(2)
N(1)	27(2)	16(2)	24(2)	-4(2)	-8(1)	2(2)
N(2)	25(2)	18(2)	27(2)	1(2)	-9(1)	-6(2)
N(3)	30(2)	62(3)	26(2)	10(2)	-8(1)	-1(2)
N(4)	23(2)	15(2)	29(2)	3(2)	-6(1)	-3(2)
C(1)	39(3)	30(3)	20(2)	4(2)	-7(2)	-8(2)
C(2)	34(2)	19(3)	27(2)	4(2)	-2(2)	-4(2)
C(3)	25(2)	17(2)	32(2)	1(2)	-4(2)	-1(2)
C(4)	29(2)	17(2)	23(2)	2(2)	-5(2)	-2(2)
C(5)	25(2)	19(2)	35(2)	6(2)	-3(2)	-1(2)
C(6)	32(2)	25(3)	28(2)	6(2)	-14(2)	0(2)
C(7)	26(2)	34(3)	50(3)	-9(3)	2(2)	-7(2)
C(8)	34(3)	21(3)	36(2)	0(2)	-2(2)	-3(2)
C(9)	25(2)	18(2)	26(2)	-6(2)	-5(2)	-1(2)
C(10)	26(2)	14(2)	25(2)	0(2)	-5(2)	-4(2)
C(11)	27(2)	20(2)	27(2)	-3(2)	-3(2)	-2(2)
C(12)	28(2)	25(3)	25(2)	3(2)	-8(2)	3(2)
C(13)	28(2)	18(2)	30(2)	-8(2)	-6(2)	-1(2)
C(14)	31(2)	28(3)	35(2)	-3(2)	-14(2)	-1(2)
C(15)	20(2)	42(3)	50(3)	-13(3)	-7(2)	-2(3)
C(16)	27(2)	24(3)	37(2)	4(2)	-8(2)	-1(2)
C(17)	27(2)	26(3)	47(3)	-5(2)	1(2)	0(2)
C(18)	38(3)	29(3)	33(2)	-2(3)	4(2)	-6(3)
C(19)	41(3)	31(3)	28(2)	1(2)	-8(2)	-2(2)
C(20)	25(2)	21(3)	34(2)	-1(2)	-7(2)	4(2)
C(21)	26(2)	16(2)	29(2)	-1(2)	-4(2)	-4(2)
C(22)	24(2)	20(2)	31(2)	1(2)	-2(2)	-5(2)
C(23)	27(2)	62(4)	35(2)	5(3)	-8(2)	-8(3)
C(24)	29(2)	10(2)	26(2)	-3(2)	-7(2)	-2(2)
Cl(1)	33(1)	16(1)	25(1)	1(1)	-1(1)	-1(1)
O(2)	63(2)	21(2)	27(2)	-1(2)	-8(2)	-6(2)

O(3)	47(2)	34(2)	50(2)	5(2)	9(2)	-7(2)
O(4)	47(2)	47(3)	64(2)	-11(2)	19(2)	11(2)
O(5)	61(3)	41(2)	47(2)	20(2)	-26(2)	-11(2)
Cl(3)	76(1)	44(1)	60(1)	8(1)	-2(1)	-18(1)
Cl(2)	39(1)	56(1)	144(2)	3(1)	-1(1)	-14(1)
C(50)	46(3)	38(4)	71(4)	8(3)	0(3)	-3(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for m1.

	x	y	z	U(eq)
H(1)	10139	591	6048	27
H(1A)	8504	1822	2528	36
H(2)	10357	1265	3208	32
H(3)	10581	1505	4701	30
H(5)	7090	2939	4849	32
H(6)	6885	2702	3353	34
H(7)	14224	2237	6293	44
H(8)	12188	2857	6054	36
H(10)	10073	3236	7326	26
H(11)	9895	-571	7653	30
H(12A)	10935	1620	8993	31
H(12B)	11096	-517	8850	31
H(14)	13526	129	8655	38
H(15)	14883	830	7579	45
H(16)	5269	2542	9421	35
H(17)	4076	2351	10641	40
H(18)	4821	995	11917	40
H(19)	6760	-150	11981	40
H(20)	7948	-47	10754	32
H(23)	7626	1373	7274	50
H(24)	9138	973	9610	26
H(50A)	7338	6127	6371	62
H(50B)	6499	7288	6981	62

Table 6. Torsion angles [°] for m1.

C(23)-N(3)-N(4)-C(24)	-0.4(7)
C(23)-N(3)-N(4)-C(21)	-178.8(5)
C(6)-C(1)-C(2)-C(3)	0.8(7)
C(1)-C(2)-C(3)-C(4)	-0.4(7)
C(2)-C(3)-C(4)-C(5)	0.1(7)
C(2)-C(3)-C(4)-C(22)	-177.5(4)
C(3)-C(4)-C(5)-C(6)	-0.3(7)
C(22)-C(4)-C(5)-C(6)	177.5(4)
C(4)-C(5)-C(6)-C(1)	0.7(7)
C(2)-C(1)-C(6)-C(5)	-0.9(8)
C(15)-C(7)-C(8)-C(9)	-0.1(7)
C(7)-C(8)-C(9)-C(13)	0.7(7)
C(7)-C(8)-C(9)-C(10)	-175.8(5)
C(22)-N(1)-C(10)-C(9)	-136.3(4)
C(22)-N(1)-C(10)-C(11)	109.5(5)
C(8)-C(9)-C(10)-N(1)	38.3(6)
C(13)-C(9)-C(10)-N(1)	-138.5(4)
C(8)-C(9)-C(10)-C(11)	161.3(5)
C(13)-C(9)-C(10)-C(11)	-15.6(5)
C(24)-N(2)-C(11)-C(12)	-15.3(7)
C(23)-N(2)-C(11)-C(12)	175.8(5)
C(24)-N(2)-C(11)-C(10)	-136.6(4)
C(23)-N(2)-C(11)-C(10)	54.5(7)
N(1)-C(10)-C(11)-N(2)	-86.9(4)
C(9)-C(10)-C(11)-N(2)	153.7(3)
N(1)-C(10)-C(11)-C(12)	147.7(4)
C(9)-C(10)-C(11)-C(12)	28.2(4)
N(2)-C(11)-C(12)-C(13)	-156.3(4)
C(10)-C(11)-C(12)-C(13)	-30.4(5)
C(8)-C(9)-C(13)-C(14)	-0.2(7)
C(10)-C(9)-C(13)-C(14)	176.8(4)
C(8)-C(9)-C(13)-C(12)	179.6(4)
C(10)-C(9)-C(13)-C(12)	-3.3(5)
C(11)-C(12)-C(13)-C(14)	-159.0(5)
C(11)-C(12)-C(13)-C(9)	21.2(5)
C(9)-C(13)-C(14)-C(15)	-0.9(8)

C(12)-C(13)-C(14)-C(15)	179.3(5)
C(13)-C(14)-C(15)-C(7)	1.6(8)
C(8)-C(7)-C(15)-C(14)	-1.1(8)
C(21)-C(16)-C(17)-C(18)	1.1(8)
C(16)-C(17)-C(18)-C(19)	0.3(8)
C(17)-C(18)-C(19)-C(20)	-1.3(8)
C(18)-C(19)-C(20)-C(21)	0.9(7)
C(17)-C(16)-C(21)-C(20)	-1.5(7)
C(17)-C(16)-C(21)-N(4)	176.1(4)
C(19)-C(20)-C(21)-C(16)	0.6(7)
C(19)-C(20)-C(21)-N(4)	-177.0(4)
C(24)-N(4)-C(21)-C(16)	159.9(5)
N(3)-N(4)-C(21)-C(16)	-22.0(7)
C(24)-N(4)-C(21)-C(20)	-22.4(7)
N(3)-N(4)-C(21)-C(20)	155.7(5)
C(10)-N(1)-C(22)-O(1)	-18.6(7)
C(10)-N(1)-C(22)-C(4)	161.1(4)
C(3)-C(4)-C(22)-O(1)	152.4(5)
C(5)-C(4)-C(22)-O(1)	-25.2(7)
C(3)-C(4)-C(22)-N(1)	-27.2(6)
C(5)-C(4)-C(22)-N(1)	155.1(4)
N(4)-N(3)-C(23)-N(2)	1.0(8)
C(24)-N(2)-C(23)-N(3)	-1.3(7)
C(11)-N(2)-C(23)-N(3)	169.5(5)
N(3)-N(4)-C(24)-N(2)	-0.5(6)
C(21)-N(4)-C(24)-N(2)	177.8(5)
C(23)-N(2)-C(24)-N(4)	1.1(6)
C(11)-N(2)-C(24)-N(4)	-169.7(4)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for m1 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)