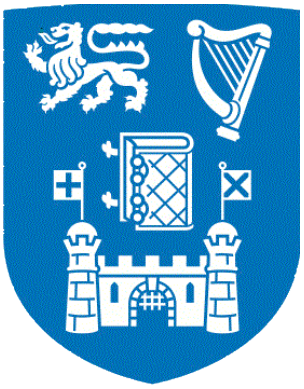
N-Heterocyclic Carbene-Catalysed Transformations: the Crossed Benzoin Condensation and Oxidative Aldehyde Esterifications



A thesis submitted to

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for the degree of

Doctor of Philosophy

by

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Under the supervision of

Prof. Stephen Connon

2015

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others.

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Eoghan Delany

1. E. G. Delany, C.-L. Fagan, S. Gundala, A. Mari, T. Broja, K. Zeitler and S. J. Connon, *Chem. Commun.*, 2013, **49**, 6510.
2. E. G. Delany, C.-L. Fagan, S. Gundala, K. Zeitler and S. J. Connon, *Chem. Commun.*, 2013, **49**, 6513.
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Chapter 2 Development of a Chemoselective NHC-Catalysed Intermolecular Crossed Benzoin Condensation

Chapter 3 Studies on the Asymmetric Intermolecular Crossed Benzoin Condensation as Catalysed by a Suite of Chiral Bifunctional *N*-Heterocyclic Carbenes

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Finally, to Laura: no words can sum up how you have helped me reach this point. Thank you for everything you have done and put up with in the last ten years; I got there in the end.

Abstract

The focus of this thesis is the development of a suite of heteroazolium ion-based salts as precursors to *N*-heterocyclic carbene (NHC) catalysts for a range of transformations involving aldehyde substrates. It has been demonstrated that, under basic conditions, a novel triazolium ion-based precatalyst can promote the chemoselective crossed benzoin condensation between *ortho*-substituted benzaldehydes and a range of aromatic aldehyde coupling partners in excellent yield. The chemoselectivity of the methodology was found to be reliant on a careful balance of catalyst and substrate control, with an *ortho*-bromine atom serving as a temporary directing group to aid the catalyst in differentiating between the two aromatic aldehydes. It has then been shown how this *ortho*-bromine atom can be conveniently and quickly removed *via* transition metal-catalysed reduction (to allow access to a further range of cross-benzoin adducts) or utilised as a functional handle for further transformations.

Extension of this methodology to develop the first asymmetric crossed benzoin condensation between two disparate aromatic aldehydes revealed how the resulting cross-benzoin products are subject to base- and carbene-mediated racemisation under the reaction conditions. It was demonstrated that the optical purity of these adducts is negatively impacted by these pathways and how, through careful optimisation of the reaction conditions and employment of carefully selected *ortho*-substituted aromatic aldehydes, the first ever highly enantioselective crossed benzoin condensation was subsequently reported.

Finally, a highly efficient, broad scope, additive-free mild protocol for the oxidative carbene-catalysed esterification of aldehydes has been developed. Benzoin (and neither the Breslow intermediate nor the NHC–aldehyde tetrahedral adduct) has been unambiguously identified as the oxidised species in aerobic NHC-catalysed aldehyde esterifications. The first organocatalytic aerobic oxidative cleavage of cyclic 1,2-diketones is reported. These reactions proceed in either aqueous or alcoholic media and are promoted by a simple *N*-heterocyclic carbene catalyst derived from a 1,2,4-triazolium ion.

Abbreviations

Ar	Aryl
BAL	Benzaldehyde lyase
BFD	Benzoylformate decarboxylase
Bn	Benzyl
bpz	bipyrazine
^{t}BuOK	Potassium *tert*-butoxide
Cbz	Carboxybenzyl
CsOAc	Caesium acetate
CSP	Chiral stationary phase
DABCO	1,4-diazabicyclo[2.2.2]octane
DIBAL-H	Di*iso*butylaluminium hydride
DIPEA	*N*,*N*-di*iso*propylethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance
Equiv./equiv.	Equivalent
EWG	Electron-withdrawing group
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
KHMDS	Potassium hexamethyldisilazane
KOAc	Potassium acetate
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
m	*Meta*
MeCN	Acetonitrile
Mes	Mesityl or (2,4,6-trimethyl)-phenyl
MTBE	Methyl-*tert*-butyl ether
m/z	Mass/charge
n/a	Not applicable
n/d	Not determined

NHC	*N*-heterocyclic carbene
NMI	*N*-methylimidazole
NMR	Nuclear magnetic resonance
o	*Ortho*
p	*Para*
Ph	Phenyl
precat.	Precatalyst
psi	Pounds per square inch
rt	Room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
ThDP	Thiamine diphosphate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
TMSCN	Trimethylsilyl cyanide
v/v	Volume/volume

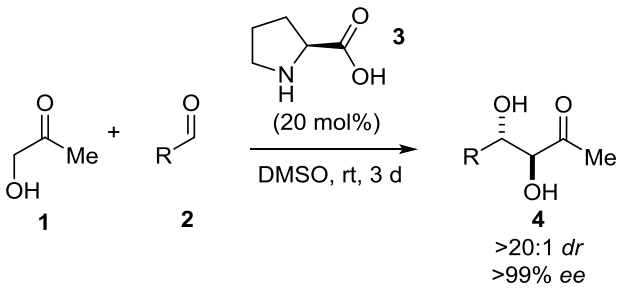
Chapter 1 Introduction

1.0 Organocatalysis: a brief introduction

Organocatalysis has become a familiar area of organic chemistry in recent decades that has developed into a subdivision of synthetic chemistry in its own right. Interest and attraction to the field is founded primarily upon the fact that many organocatalytic reactions can replicate (and in certain cases even surpass) the efficacy and selectivity of established synthetic protocols.[1] Further advantages derive from the ease of access to organocatalysts, with the naturally-occuring amino acid L-proline being perhaps the most recognisable example of a readily available, simple molecule capable of catalysing a diverse range of transformations,[2] as well as significant reductions in toxicity, air/moisture sensitivity and cost relative to many transition metal-catalysed processes.

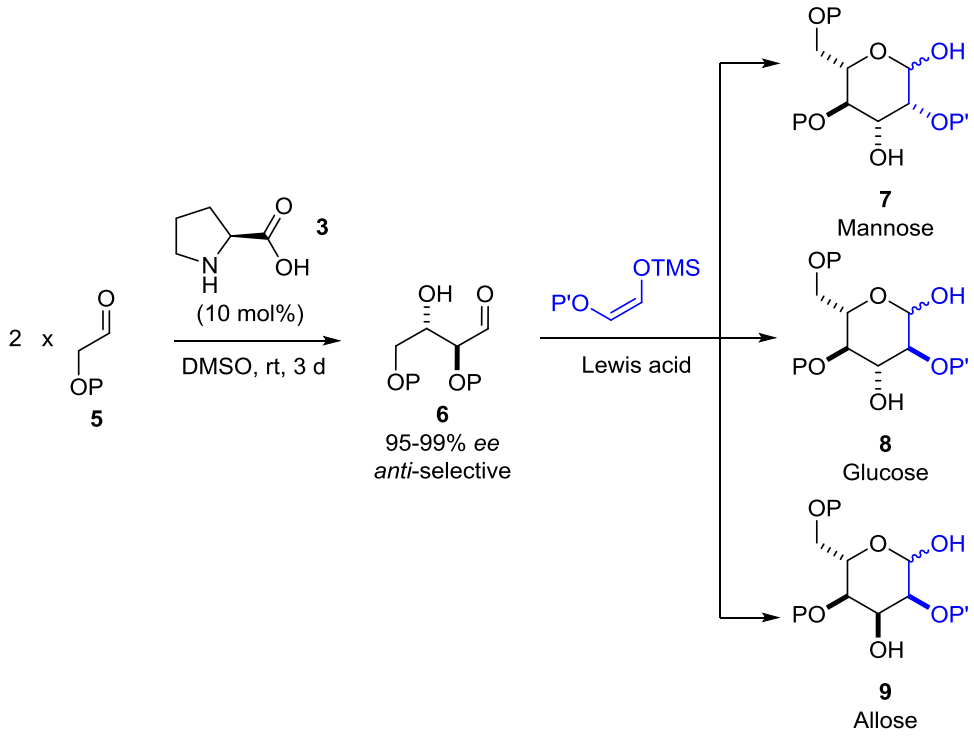
Of course, while the rapid emergence of organocatalysis in this manner has occurred principally in the last two decades, it is important to note that the use of organic molecules as catalysts has been documented sporadically in the previous century. However, it was only through demonstration of their ability to efficiently catalyse asymmetric transformations that the field has come to be accepted as an applicable synthetic tool in the construction of complex molecular scaffolds.[3] In this regard, two independent reports from Hajos and Parish and Weichert *et al*. paved the way in 1974, utilising L-proline to effect an intramolecular aldol reaction for the enantioselective synthesis of the Wieland-Miescher ketone.[4,5,6,7] Although well-received, the underlying enamine-based catalytic action of proline was not exploited for further reactions until 2000, with the work of Barbas, Lerner and List when they published their enantioselective intermolecular aldol reaction, again catalysed by **3** (Scheme 1.1).[8]

Scheme 1.1 L-proline-catalysed enantioselective aldol reaction as conducted by List



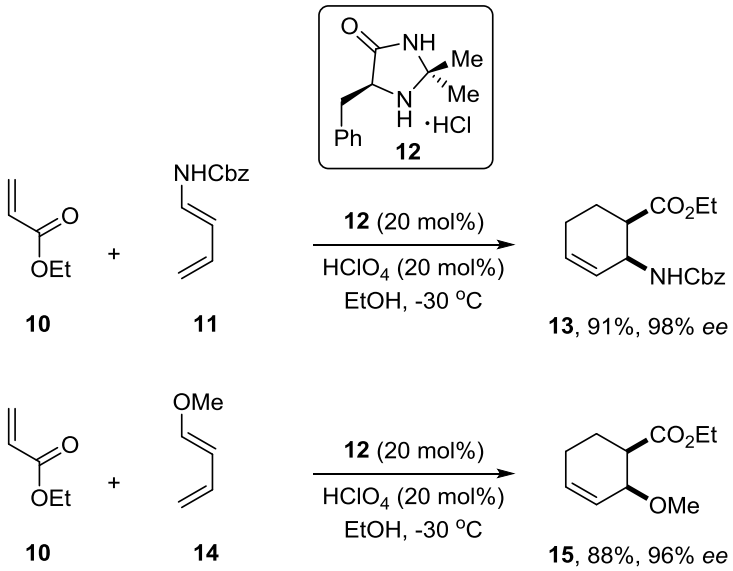
In the intervening years, a wider range of generic organocatalytic activation modes were developed – the enantioselective Strecker reaction and an organocatalytic kinetic resolution of alcohols using hydrogen-bonding chiral urea- and thiourea-based organocatalysts,[9-11] while MacMillan modified List's procedure to develop the shortest reported stereoselective synthetic route (at the time) to protected monosaccharides (**7**-**9**, Scheme 1.2).[12a]

Scheme 1.2 Organocatalytic protected hexose synthesis reported by MacMillan



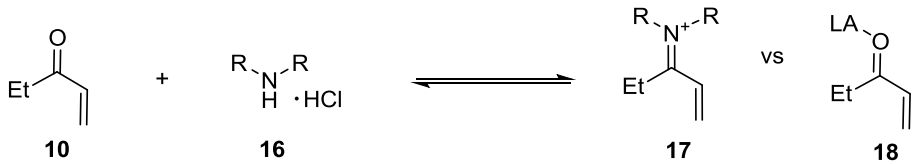
Conversely, in 2000 MacMillan *et al.* further introduced the concept of iminium ion activation, employing chiral imidazolidinones to catalyse a range of asymmetric transformations, chief among them the asymmetric Diels-Alder reaction (Scheme 1.3).[12b]

Scheme 1.3 Asymmetric Diels-Alder reaction mediated by a chiral imidazolidinone



MacMillan postulated that, in an analogous manner to Lewis acid activation of a carbonyl group, *in situ* reversible formation of an iminium ion using the imidazolidinone organocatalyst **12** aids not only a lowering in energy of the LUMO, but equally establishment of a rigid chiral environment for formation of the Diels-Alder product (Scheme 1.4). Later generations of this imidazolidinone catalyst structure have proved amenable to use in a diverse range of reactions including, but not limited to, Mukaiyama-Michael reactions,[13] Friedel-Crafts alkylations,[14] epoxidations[15] and conjugate hydride reductions.[16,17] Indeed, such is the synthetic versatility of imidazolidinones as organocatalysts, they are now commonly referred to as "MacMillan organocatalysts".

Scheme 1.4 MacMillan's proposed carbonyl activation mode through iminium ion formation



These pioneering developments by List and MacMillan, amongst others, rapidly laid the foundation for the subsequent emergence of organocatalysis as one of the main branches of enantioselective synthesis (the others previously accepted as being enzymatic catalysis

and organometallic catalysis).[3] In addition, the mechanistic insights they established allowed identification of broad suites of new suitable organocatalysts such as alternative amino acids,[18] cinchona alkaloids,[19] phase-transfer agents[20] and carbenes.

1.1 Carbenes

1.1.1 General overview

A carbene is an electrically-neutral species of general structure R_2C: in which the carbon atom is covalently bonded to two univalent groups (or a single divalent group) and possesses two non-bonding valence electrons. The term 'carbene' itself technically describes H_2C:, otherwise known as methylene, the archetype carbene whose isolation was first attempted in 1835 by Dumas and Peligot.[21] Noting the abundance of small molecules containing a solitary carbon throughout the world (methane, carbon dioxide, carbon monoxide, etc.), they postulated that a facile laboratory synthesis of methylene would be achievable *via* dehydration of methanol through treatment with sulfuric acid. While these (and subsequent) efforts failed, Guether did succeed in the *in situ* generation and trapping of dichlorocarbene (Cl_2C:) almost 30 years later through base-catalysed elimination of HCl from chloroform.[22] However, by the 1960s, it was widely accepted that the stability and lifetime of carbenes was such that physical isolation was impossible. Despite this, over the course of the next century they became recognised as species of valuable synthetic utility and important intermediates in a range of reactions. Büchner,[23] Curtius[24] and Staudinger[25] were among early pioneers of their synthetic application, while Fischer[26] and Schrock[27] were later instrumental in their incorporation into transition metal complexes and catalysts.

1.1.2 Singlet vs triplet carbenes

Carbenes themselves can be typically categorised as either singlet or triplet carbenes, a distinction made based upon the electronic configuration of the constituent electrons. Given that they possess only two coordinate substituents, the carbene centre can adopt either a linear or bent geometry. A linear alignment, as with an alkyne, would bestow sp-hybridisation upon the carbene with the bonding electrons being accommodated in the sp-orbitals and the non-bonding electrons, due to electron repulsion, occupying separate degenerate (but higher energy) p-orbitals (Figure 1.1).

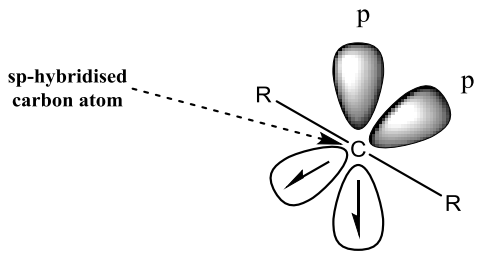


Figure 1.1 Orbital depiction of a linear carbene

However, in reality there are very few examples of linear carbenes, with most instead adopting a bent geometry and bond angles of between 100-150^{o}, suggesting a trigonal (sp^2) hybridisation state.[28] Such a carbene would therefore possess three degenerate sp^2-orbitals and one (higher energy) p-orbital. The distribution of the six electrons in this case can be achieved in one of two possible manners:

i. All electrons can be paired, each pair occupying one of the three sp^2-orbitals and leaving the higher energy p-orbital vacant (Figure 1.2A). Carbenes adopting such a configuration are termed singlet carbenes.

ii. Two electrons can remain unpaired, one occupying an sp^2-orbital and the other occupying the p-orbital (Figure 1.2B). Carbenes adopting such a configuration are termed triplet carbenes.

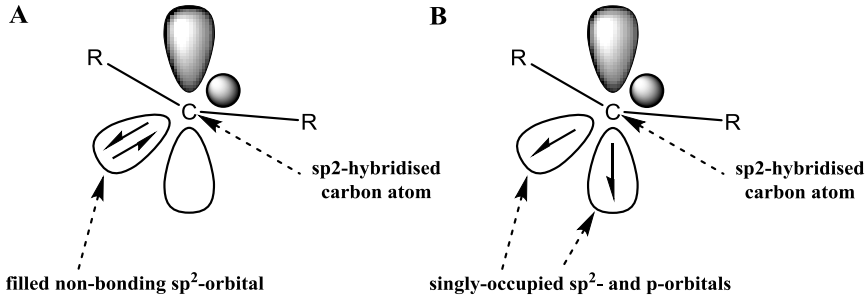


Figure 1.2 Orbital depiction of singlet (**A**) and triplet (**B**) carbenes

There are several factors determining whether a carbene adopts a singlet or triplet spin state upon formation. As a basic principle, most carbenes are more stable in the triplet state due to the energy required to overcome electronic repulsions in pairing two

electrons (singlet state) exceeding that necessary to promote a single electron into a higher energy p-orbital (triplet state). In most cases, this energy difference is approximately 40 kJ/mol.[28] Of course, the nature of its coordinate substituents can also influence the preferred spin state significantly. For instance, dichlorocarbene (Cl_2C:) adopts a singlet spin state as its ground state and indeed, such carbenes all have substituents possessing lone pairs adjacent to the carbon centre as recognised by Harrison in 1971.[29] The presence of these adjacent lone pairs enables them to interact with p-orbital of the carbene, hybridising to produce a new (lower energy) orbital in which to accommodate two electrons (Figure 1.3). In this instance, this stabilisation induces pairing of the non-bonding electrons as the electronic repulsions are offset by the hybridisation. As the energy diagram indicates, the electrophilicity of carbenes with electron-donating substituents is considerably reduced due to the increase in the energy of the LUMO. Indeed, as will be pertinent later, certain carbene species, such as diamino carbenes, can actually display strong nucleophilic characteristics.

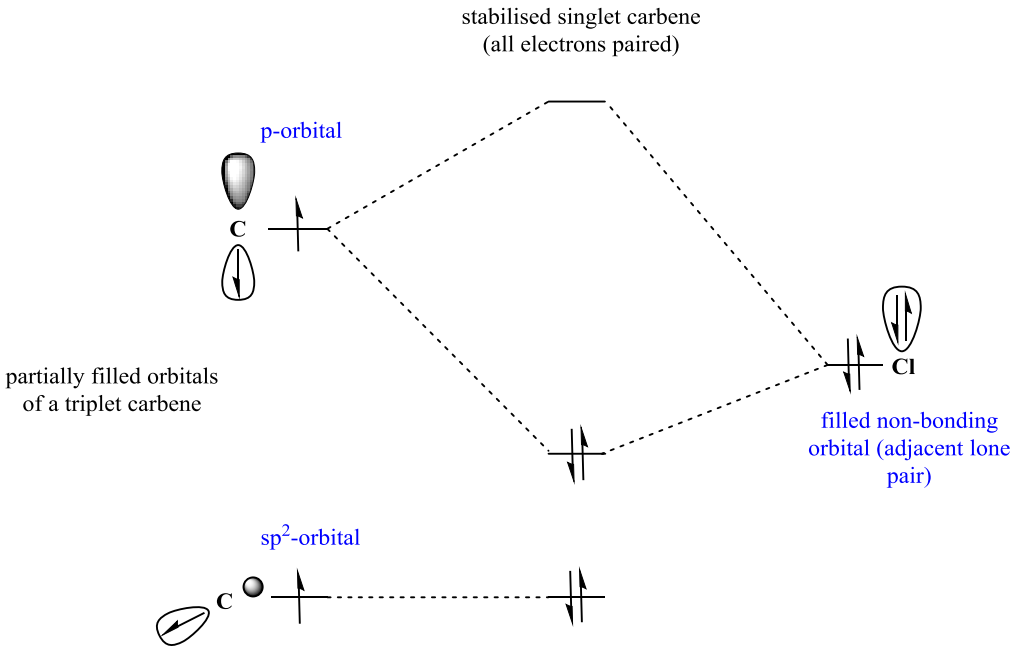


Figure 1.3 Stabilisation of triplet carbene orbitals by adjacent lone pairs

The steric bulk of the substituents can also dictate the carbene ground state. As singlet carbenes possess two paired non-bonding electrons in a single sp^2-orbital, the electronic repulsions encountered with neighbouring substituents will exceed the analogous

repulsions experienced in a triplet carbene where the sp^2-orbital houses a solitary electron (Figure 1.4).

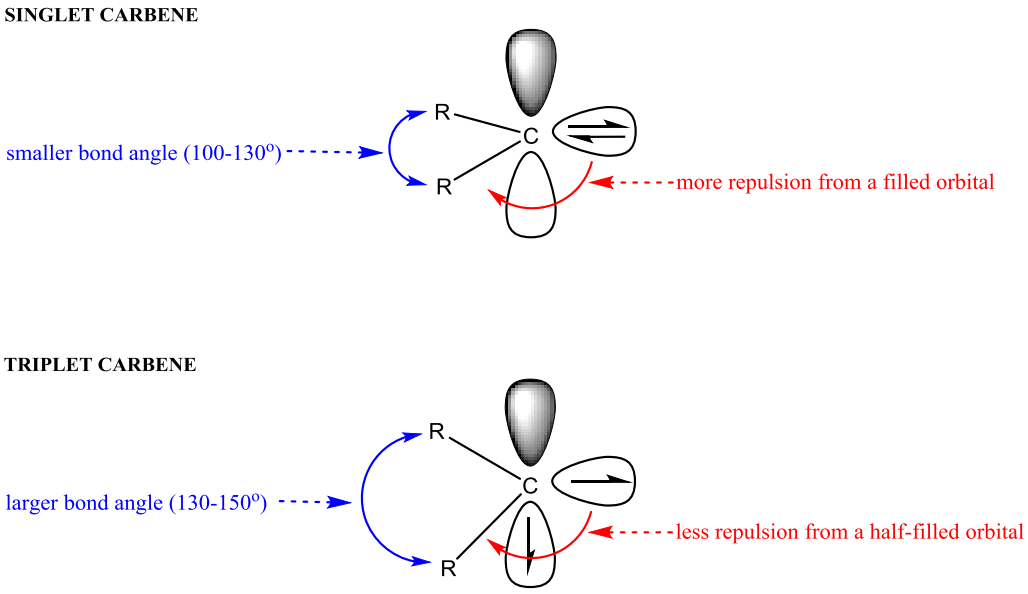


Figure 1.4 Effect of electron repulsions upon bond angles in carbenes

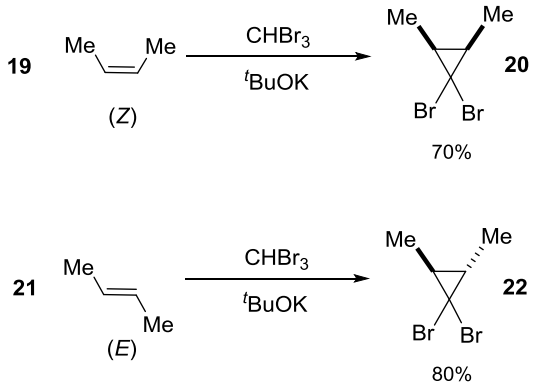
As a result, bond angles between substituents in singlet carbenes tend to be smaller than those in triplet carbenes. Thus, substituents of considerable steric bulk will tend to repel one another and increase the size of the bond angle between the two. Larger bond angles being characteristic of triplet carbenes, it stands to reason that carbenes flanked by bulky substituents will try to adopt a triplet spin state.[30,31]

1.1.3 Typical reactivity of singlet and triplet carbenes

Being an electron-deficient species, the typical reactivity of a carbene is similar to that of a carbocation in that they will both seek to complete the valency of their outer electron shell through reaction with a nucleophile. However, unlike carbocations, the uncharged nature of a carbene means that it also reacts with species that may not (under normal circumstances) ordinarily be considered as nucleophiles. While carbocations also interact with nucleophiles they are far more selective than carbenes (typically electron-rich alkenes or lone pairs). Carbenes, on the other hand, may even abstract electrons from the HOMO of a simple alkane in addition to lone pairs or π-bonds. However, this is generally not restrictive, and three main carbene reaction types can be identified as: cyclopropanations, C-H insertions and rearrangements.[32]

Both singlet and triplet carbenes will react with alkenes in a cyclopropanation reaction, arguably the most important reaction associated with carbenes and certainly the most common method for formation of cyclopropanes.[28] There is a stark contrast in the mechanism by which both do so, however, as evident from the stereochemical outcome of the reaction. Skell demonstrated this initially in 1956 in treating bromoform with ^{t}BuOK in the presence of *cis*- or *trans*-butene (**19** and **21**, Scheme 1.5).[33] The resulting carbene, dibromocarbene, is stabilised by the bromine substituents and therefore occupies a singlet ground state. As a result, its addition to the alkene occurs in a concerted manner (as both electrons occupy the same sp^2-orbital) and so the geometry of the final products **20** and **22** reflects that of their parent alkene – the cyclopropane derived from the (*Z*)-alkene maintains both methyl groups in a *cis* relationship, while the reverse is true for the cyclopropane derived from the (*E*)-alkene. In both cases, Skell reported less than 1% formation of the alternative isomer. Thus, as singlet carbenes add in a concerted fashion, the reaction is deemed to be *stereospecific*.

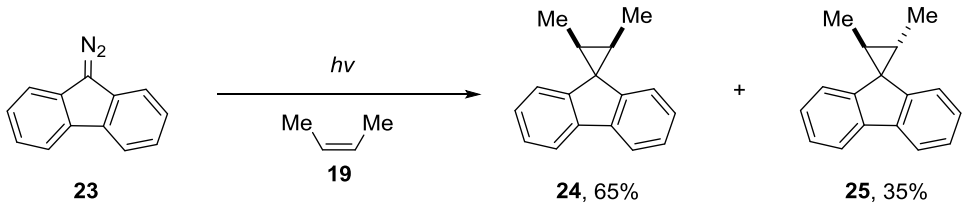
Scheme 1.5 Stereochemistry of cyclopropanations using singlet carbenes (Skell, 1956)



We can contrast this with the work of Doering and Jones[34] several years later and their investigations into the cycloaddition of diazofluorene (**23**) to **19** (Scheme 1.6). Thermal decomposition of diazoalkenes occurs readily, with loss of nitrogen being entropically favourable and initially generating a singlet carbene. However, fluorenylidene (the carbene formally derived from diazofluorene) has the unusual property that its triplet ground state lies only 4.6 kJ/mol lower in energy than its singlet state and so photochemistry can be used to enable an intersystem crossing that allows subsequent generation of the triplet carbene.[35] The reaction displays a stereochemical outcome that

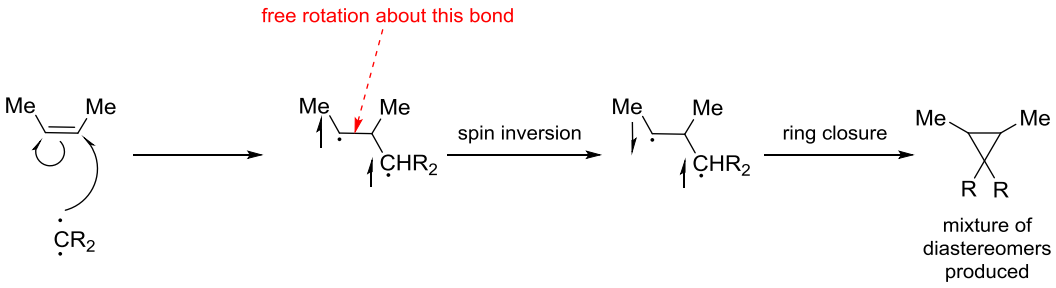
differs hugely from that reported by Skell and so clearly, the reaction must proceed through an alternative, non-concerted mechanistic pathway.

Scheme 1.6 Stereochemistry of cyclopropanations using triplet carbenes (Jones, 1963)



Indeed, the electronic spin configuration of a triplet carbene renders a concerted pathway impossible as (as indicated in Scheme 1.7) following initial radical addition of the carbene to the alkene, the diradical intermediate must undergo a spin inversion of one of its unpaired electrons prior to formation of the second C-C bond. Spin-flipping results only through collisions with other molecules in the system and is quite slow relative to bond rotation within the molecule so that the stereochemistry of the parent alkene is no longer retained faithfully upon closure of the ring. However, depending on the stability of the relative diastereomers, triplet carbene cyclopropanations can sometimes be said to be *stereoselective*.

Scheme 1.7 Mechanistic pathway for triplet carbene addition to an alkene



Carbenes can also participate in insertion reactions with C-H bonds to form new carbon-carbon bonds. Given the importance of such connections in the construction of larger molecular skeletons, such reactions represent another significant synthetic application of carbenes. While triplet carbene insertions are proposed to follow an abstraction-recombination, two-step radical pathway that mirrors that of their addition to alkenes, in practice very few such insertions have been observed.[28,36,37] Instead, Doering and Kirmse

established that most carbene C-H insertions were direct, single barrier concerted processes characteristic of singlet carbene behaviour.[38] While 'arrows' can be used to describe the electron movement of such a transformation, the concerted nature of the reaction means an orbital view is most effective in understanding the stereochemical outcomes (Figure 1.5). Side-on approach of the singlet carbene enables interaction between its empty p-orbital and the filled C-H σ-bond (**A**). Concurrent overlap is possible between the carbene's sp^2-orbital, housing two electrons, and the empty C-H σ^*-bond (**B**) so that a three-membered transition state results (**X**) prior to formation of the product.

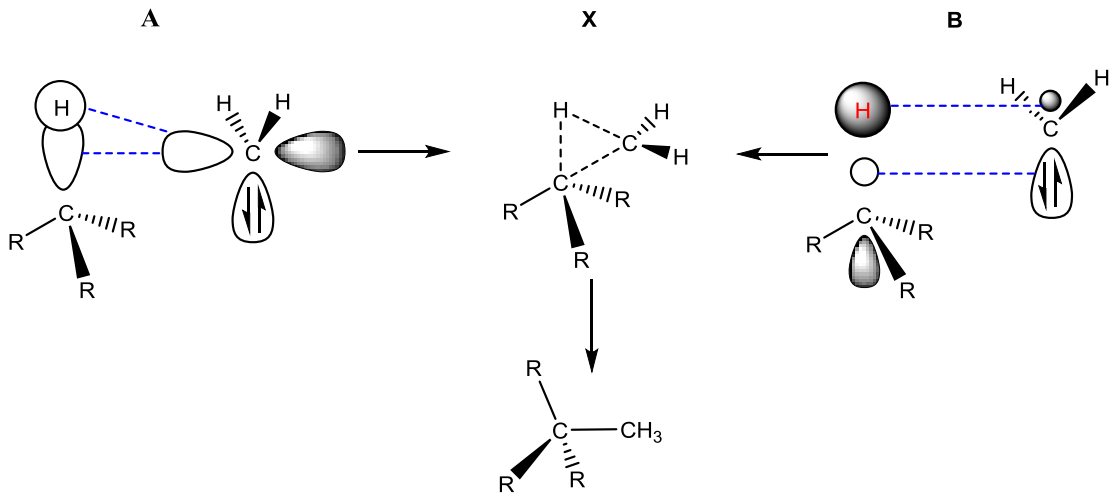


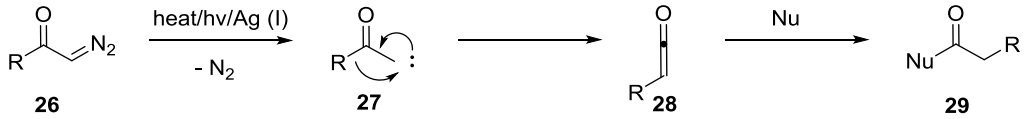
Figure 1.5 Orbital view of singlet carbene C-H insertion reaction

The most significant aspect of this orbital view is that if the insertion occurs at a stereocentre there is retention of stereochemistry. Several natural product syntheses have exploited this stereospecificity, notably Lee[39] in assembling the structural core of the natural antibiotic platensimycin and Cane's synthesis of pentalenolactone.[40]

The third primary reaction carbenes participate in is that of rearrangements. In a fashion similar to carbocations, C-H insertions by carbenes can occur intramolecularly provided a β-proton is present to undergo a 1,2-hydride shift. However, the generation of a carbene within molecules lacking such a proton can instead result in migration of other suitable groups and thus, a rearrangement of the carbon skeleton. The Wolff rearrangement[41] (Scheme 1.8) represents perhaps the most famous exploitation of a carbene rearrangement,[42] with heat-induced elimination of nitrogen gas from an α-

diazocarbonyl (**26**) generating a ketocarbene intermediate (**27**) that rapidly undergoes a 1,2 alkyl/aryl shift to produce a ketene (**28**). Subsequent use of various nucleophiles allows synthesis of a wide range of compounds such as amides and esters (through use of amine or alcohol nucleophiles respectively) or even [2+2] cycloaddition products through reaction with an olefin.[43] Further exploitation of the rearrangement capabilities of carbenes can be found in the homologation of carboxylic acids, such as the Arndt-Eistert reaction,[44] and ring-contractions when the starting α-diazocarbonyl is cyclic.[45,46,47,48]

Scheme 1.8 The Wolff rearrangement



1.1.4 'Wanzlick' carbenes

Regardless of their characteristics, carbenes are acknowledged as being exceptionally reactive and unstable towards air and moisture. However, as previously noted, efforts to isolate stable (persistent) carbenes began as far back as 1835[21] and have continued ever since. Roth[49] has defined a persistent or 'Wanzlick' carbene as one which is "stable, exhibiting a life-span, in both solution and in a pure isolated form". In this regard, early pioneering work by Wanzlick,[50] Arduengo[51] and more recently Bertrand[52] in particular has enabled the synthesis of an impressive array of persistent carbene structures in the past three decades, a selection of which are highlighted in Figure 1.6 and include acyclic diaminocarbenes **30**,[53,54] aminooxy- and thiocarbenes (**31** and **32**),[55] (amino)(phosphine)carbenes **33**,[56,57] cyclic diphosphinocarbenes **34**,[58] phosphinosilylcarbenes **35**,[59] phosphinophosphoniocarbenes **36**,[60,61] and sulphenylpentafluorothiocarbenes **37**.[62]

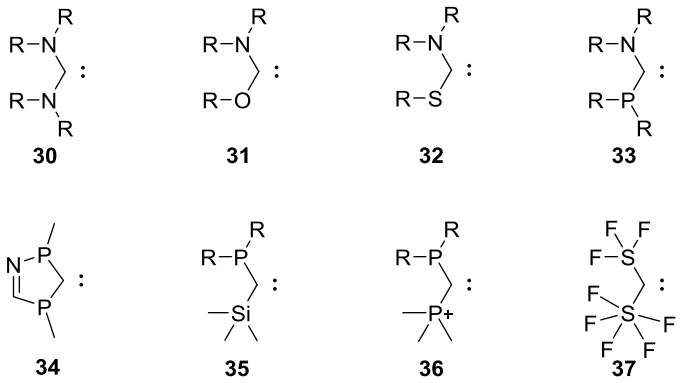


Figure 1.6 Some common N, P, S and Si-based carbenes

Although Bertrand was first to report the isolation of a persistent carbene in the form of phosphinocarbene (**38**, Figure 1.7) in 1988,[52a] it has been demonstrated to react like phosphaacetylene **39** and is viewed as not possessing predominantly carbene character.[63] Recent literature has, however, given weight to counter-argument[64] and Bertrand has since succeeded in the synthesis of a stable *P*,*N*-heterocyclic carbene, although its isolation in a pure form was not achieved.[65] Thus, isolation of the first 'true' persistent carbene is accredited to A. J. Arduengo III who succeeded in synthesising **40** in 1991.[51] **40** is a diaminocarbene and, more concisely, an *N*-heterocyclic carbene (NHC), the most extensive sub-group of persistent carbenes throughout the literature. It is this type of carbene that shall be the primary focus of this thesis.

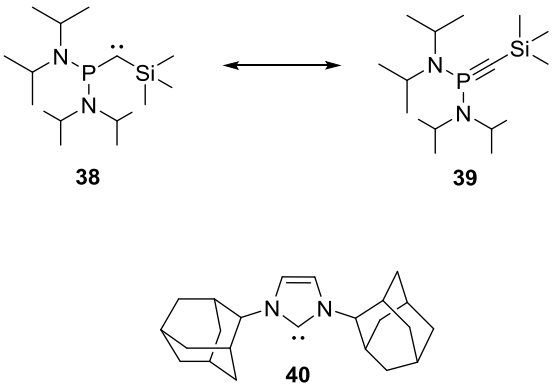


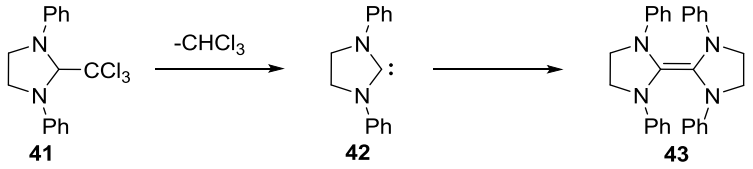
Figure 1.7 The first stable carbenes isolated by Bertrand (**38**) and Arduengo (**40**)

1.1.5 *N*-Heterocyclic Carbenes

1.1.5.1 Historical overview

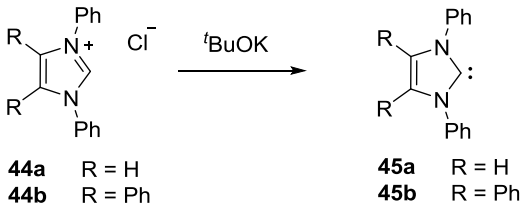
In 1980, Linus Pauling[66] proposed that the stability of singlet carbenes could be augmented by creating an electronically neutral environment at the carbene centre. Two decades previously, however, Wanzlick had identified the fact that the stability of carbenes was enhanced by amino groups adjacent to the carbene, leading to the first synthesis of aminocarbenes (See Figure 1.6) and subsequently NHCs.[67,68,69] The spin multiplicity of NHCs has been confirmed as a singlet ground state[70] and thus the stability of such carbenes revolves around the synergistic 'push-pull' effect of the nitrogen atoms – their inductive electronegativity withdraws electron-density from the carbene centre while the presence of their lone pairs allows them to concurrently donate electron density into the empty carbene p-orbital, creating the requisite electroneutrality postulated by Pauling. Much of Wanzlick's research upon NHCs focused upon the electron-rich imidazoline ring. In 1962, he attempted the derivatisation of the 1,3-diphenylimidazolidin-2-ylidene (**42**) *via* thermal elimination of chloroform from the parent imidazolidine (**41**, Scheme 1.9). The isolation of **42** seemed impossible at the time, however, due to its pronounced reactivity that led to its rapid dimerisation to yield **43**.[71]

Scheme 1.9 Attempted isolation of imidazolidin-2-ylidene **42** by Wanzlick



While Wanzlick's efforts revolved primarily around imidazolidine structures similar to **41**, he did succeed in avoiding carbene dimerisation through use of an analogous imidazole.[72,73] Using potassium *tert*-butoxide to deprotonate imidazolium salts **44** (Scheme 1.10), Wanzlick could generate the resulting carbenes (**45a** and **45b**) and simultaneously avoid the formation of a dimeric alkene, although physical isolation of a crystalline sample of either carbene proved beyond his efforts.

Scheme 1.10 Generation of a stable imidazolylidene by Wanzlick



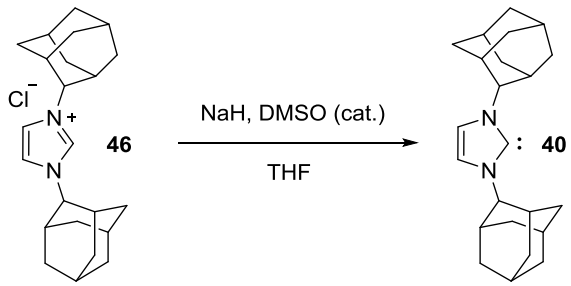
44a R = H
44b R = Ph

45a R = H
45b R = Ph

Despite the ability to generate NHC carbenes, Wanzlick never succeeded in a physical isolation of a stable carbene, the ultimate goal of his life's research efforts. It was somewhat fitting, yet ironic, that Bertrand should report the synthesis and isolation of his phosphinocarbene (**38**, Figure 1.7) in 1988 (the year in which Wanzlick died) despite the debate surrounding its legitimacy as a true carbene. It is for his work in the field that persistent carbenes are sometime referred to as 'Wanzlick carbenes' in his honour.[32]

As previously discussed, it was instead Arduengo who is reputed to have prepared the first crystalline stable carbene in 1991.[51,71] Like Wanzlick, he focused his research upon NHCs, succeeding in employing sodium hydride to cleanly deprotonate the adamantyl-substituted imidazolium salt **46** in the catalytic presence of DMSO (Scheme 1.11). Under these conditions, the aforementioned carbene **40** was isolated as a colourless crystalline solid in almost quantitative yield. While Arduengo attributed a degree of the carbene's stability to electron-rich π-system of the imidazole ring, he also rationalised that electronic factors alone were not enough to allow for its isolation and that the steric bulk of the adamantyl substituents shielded the carbene centre and allowed its endurance.

Scheme 1.11 Arduengo's isolation of the first crystalline carbene **40**



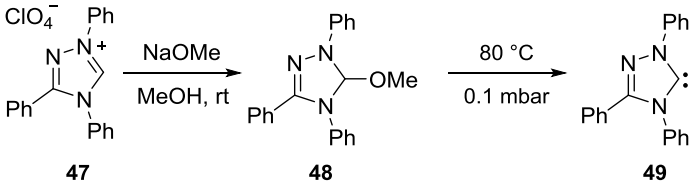
In the following years, Arduengo prepared and reported the isolation of a wide variety of NHCs.[74,75,76] Upon re-examination of the work of Wanzlick, he further attempted the

synthesis of **45b**, a structure which had eluded Wanzlick himself. Correcting some of the procedures employed by Wanzlick, he succeeded in its isolation and deemed it to be far more stable than previously suggested. He published his work under the title "1,3,4,5-Tetraphenylimidazol-2-ylidene: The Realization of Wanzlick's Dream"[77] as a tribute to the late chemist.

1.1.5.2 Common *N*-heterocyclic carbene structures

While Wanzlick utilised imidazoline core structures in establishing the field of NHC chemistry, the developments of the past three decades have seen present research move firmly away from their use. Since Arduengo's breakthrough, a thoroughly extensive structural range of ion-based heterocyclic carbene salt precursors have been prepared. In addition to imidazolium salts, thiazolium salts had long been identified as carbene precursors, most notably by Breslow[78] who proposed that the catalytic action of thiamine chloride (vitamin B_1) in the benzoin condensation (discovered fifteen years previously by Ugai *et al.*[79]) relied on deprotonation of the thiazolium ring, under basic conditions, generating a thiazolylidene *in situ*. However, the most significant synthetic development came in 1995 when Enders and Teles[80] reported the synthesis of the novel triazolium salt carbene precursor 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ium perchloroate (**47**, Scheme 1.12) which underwent reaction with methoxide ion to afford adduct **48**. Subsequent thermal elimination at 80 ^{o}C generated the corresponding stable triazolylidene **49**, which later also became the first commercially available carbene.[81] Crystal structure analysis revealed the N-C-N bond angle to be 100^{o} (contrasting a regular pentagonal five-membered ring, which has a bond angle of 108^{o}), suggesting a singlet spin multiplicity,[82] while the bond lengths between both nitrogen atoms and the central carbon were found to be 1.351 and 1.373 Å, much shorter than expected for a single bond and indicating a strong interaction between the filled p-orbitals of both the nitrogen atoms and the empty p-orbital of the carbene.[81]

Scheme 1.12 The first commercially available triazolylidene reported by Enders and Teles



The development of triazolium ion-based NHC precursors, in conjunction with the synthesis of novel bicyclic triazolium carbene salts by Rovis *et al.*,[83] has seen triazolylidenes become the most prolific form of carbene within the NHC field due to their enhanced stability, attributable to the incorporation of the extra nitrogen into the heterocyclic ring which further augments the previously-discussed 'push-pull' synergistic effect. Figure 1.8 highlights selected examples of the numerous triazolium structures throughout the literature.[83,84,85,86,87] In the presence of a base, deprotonation of the triazolium ring gives rise to the corresponding carbene in each case.

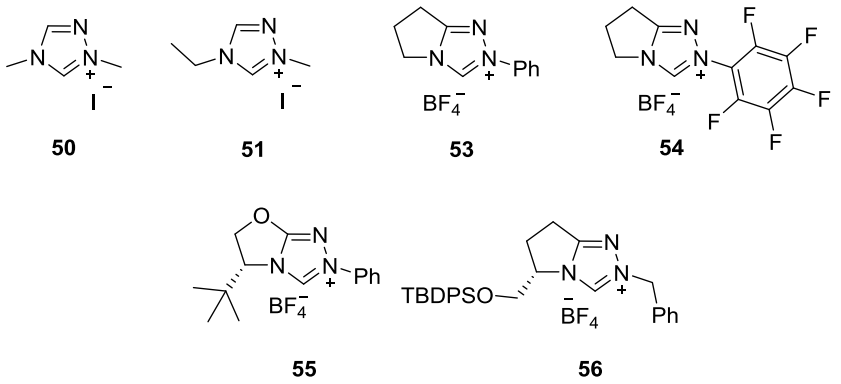


Figure 1.8 Selected examples of triazolium salt precursors to triazolylidenes

Of course, while these examples are representative of the great progress achieved in the preparation of persistent singlet NHC carbenes, the same cannot be said for triplet carbenes of any kind. In this regard, there is a significant dearth in the literature. Tomioka succeeded in 2001 in isolating a triplet *bis*(9-anthranyl)carbene which, by the author's own admission, was "fairly stable" with a half-life of just 19 minutes.[88] Tomioka then subsequently improved upon his previous work by synthesis of a triplet diphenylcarbene incorporating bulky *ortho* substituents (bromine and trifluoromethyl moieties) to shield the carbene centre and reduce the rate of dimerization to the olefin.[89]

Again, however, the stability of the carbene upon exposure to an external atmosphere was low, with a half-life of 40 minutes.

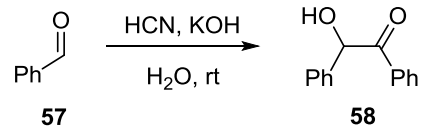
1.2 NHCs and the benzoin condensation

Although the first reported use of NHCs in an organocatalytic capacity dates back over 70 years ago,[78] there has been a tremendous growth in their application this field of since the publications by Arduengo *et al.* and Enders *et al* during the 1990s.[90,91] One of the primary advantages associated with their use in this manner, aside from cost and toxicity, is their ability to reverse the normal polarity or reactivity of a particular reactant during the course of a reaction, otherwise termed an *umpolung* reaction by Seebach.[92] In addition, other transformations such as transesterifications[93] and oxidations are possible, while chiral NHCs open up the possibility of effecting these reactions asymmetrically. Perhaps the most famous and well-studied example of this is the benzoin condensation.

1.2.1 Wöhler and von Liebig: discovery of the benzoin condensation

The benzoin condensation is widely recognised as one of the oldest carbon-carbon bond forming reactions in organic chemistry. In 1832, during research on bitter almond oil (comprised of benzaldehyde with traces of hydrocyanic acid), Wohler and von Liebig observed the formation of benzoin (**58**) whilst attempting to synthesise cyanohydrins from benzaldehyde (**57**) through treatment of this oil with potassium hydroxide (Scheme 1.13). [94]

Scheme 1.13 The benzoin condensation as discovered by Wohler and von Liebig

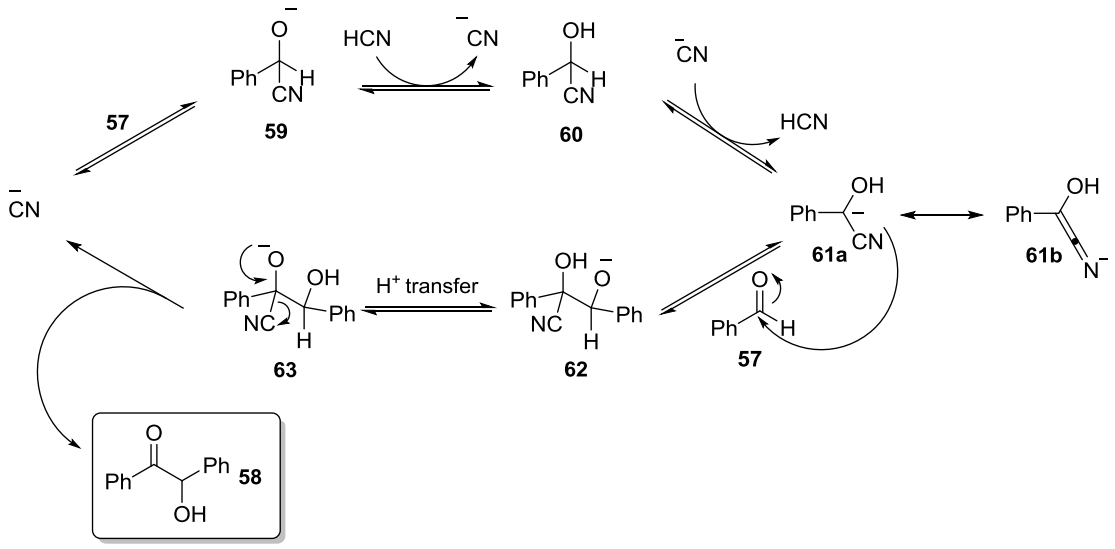


57 **58**

A mechanism to explain the formation of benzoin rather than the intended cyanohydrin was not published for more than 70 years after the original report. Zinin showed in 1839 that the cyanide-mediated reaction could be carried out catalytically,[95,96] highlighting the role played by the cyanide anion, and in 1904 Lapworth proposed a plausible mechanism based upon this observation (Scheme 1.14).[97] He suggested that initial nucleophilic

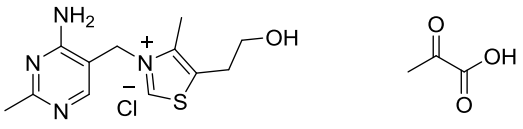
attack by cyanide upon **57** generates oxyanion **59**, protonation of which (either by the solvent or hydrogen cyanide) produces cyanohydrin **60**. However, subsequent deprotonation of the proton α to the heteroatom gives rise to **61a** - an acyl anion equivalent - which can also be viewed as the vinylidene amide **61b**. At this juncture we can see the synthetic utility of *umpolung* reactivity, with **57** representing a good example of an electrophile which, upon exposure to cyanide, is converted into a powerful nucleophile. Further nucleophilic attack of **61a** upon another molecule of **57** forms a second oxyanion *i.e.* **62**. A final proton transfer allows formation of the tetrahedral intermediate **63** which collapses, yielding benzoin and re-generating the cyanide catalyst.

Scheme 1.14 Lapworth's proposed mechanism for the cyanide-catalysed benzoin condensation



1.2.2 The *N*-heterocyclic carbene-catalysed benzoin condensation

Although Ugai, as noted previously, is accredited with achieving the first reported usage of an NHC to catalyse the benzoin condensation[79] it was previously well-established that several biological processes within living organisms proceed through the *in vivo* formation of acyl anion equivalents.[98] Common to all of these is the presence of thiamine (**64**, Figure 1.9), or vitamin B_1, in the form of the coenzyme thiamine diphosphate, whose prime metabolic substrate is pyruvic acid (**65**).

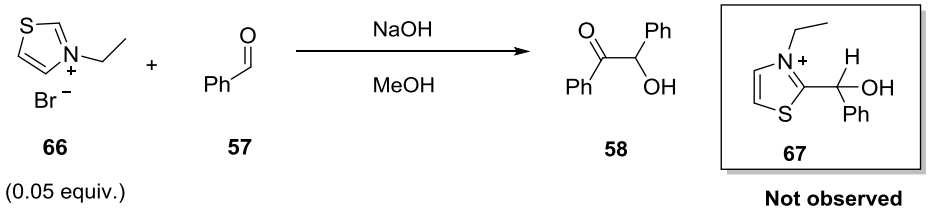


64 65

Figure 1.9 Thiamine hydrochloride (vitamin B_1) and pyruvic acid

Its ability to catalyse this range of biological transformations involving **65** initiated investigations into its analogous ability to mediate other reactions proceeding *via* acyl anion equivalents, such as the benzoin condensation. Kröhnke had paved the way in this regard, demonstrating how pyridinium salts could react with aldehydes in the presence of a base to form hydroxy compounds through formation of a ylid intermediate.[99] Ugai hypothesised that the similarities between pyridine and thiazole should enable condensation of thiazolium compounds with aldehydes. However, upon heating an alcoholic solution of thiazolium salt **66** in the presence of one equivalent of sodium hydroxide and **57**, he observed the formation of benzoin (**58**) rather than the desired hydroxyl compound *i.e.* **67** (Scheme 1.15)

Scheme 1.15 Thiazolium salt-catalysed benzoin condensation



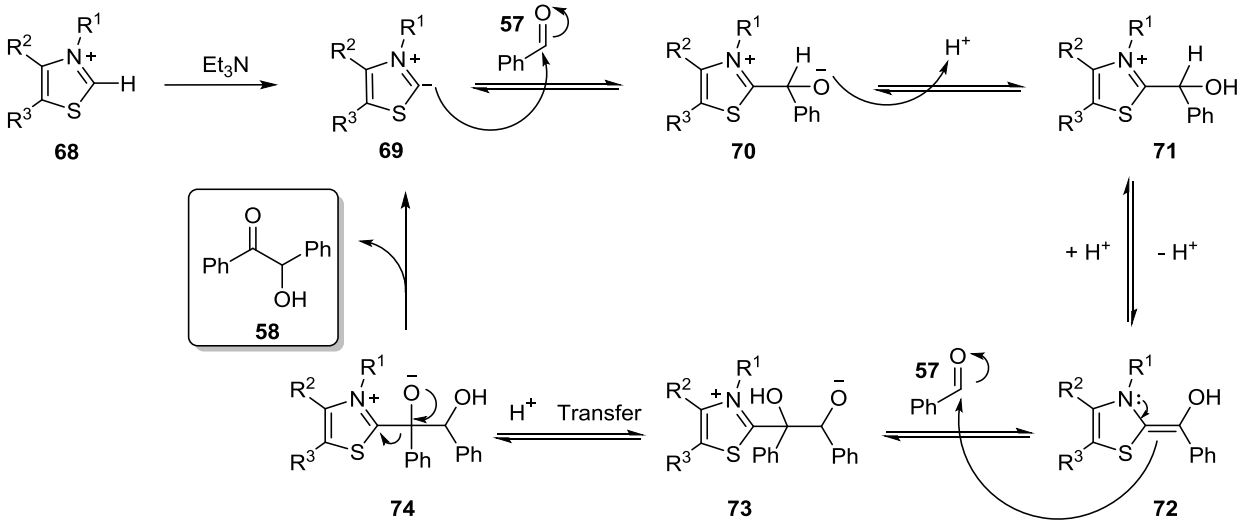
With this work it quickly became recognised that, due to the presence of the thiazolium ring within the structure of thiamine, vitamin B_1 (amongst other thiazolium salts) could be used to effect the conversion of aldehydes into their corresponding acyloins.[100,101,102,103]

1.2.2.1 Mechanism of the thiamine-mediated benzoin condensation

Breslow, in 1958, after an incorrect proposal two years earlier,[104] published the now widely-accepted mechanism *via* which thiazolium salts (and, by extension, other hetercyclic ion-based carbene precursors) catalyse the synthesis of benzoin.[78] He had

noted that, upon standing in neutral D_2O for several hours, thiamine hydrochloride undergoes proton-deuterium exchange at five sites in the molecule (including the OH and NH_3^+ moieties). The C-2 position within the thiazolium ring was demonstrated to be one of these sites through IR and NMR evidence. It was further shown that thiazolium salts are in equilibrium with their corresponding anions at this C-2 position under mild conditions and Breslow used this observation to postulate that the catalytic mode of operation of thiamine in the benzoin condensation was similar to that of cyanide, proposing the mechanism as detailed in Scheme 1.16. The base (Et_3N) deprotonates the 2-position of the thiazolium salt (**68**) to generate the catalytically-active species **69**. Reversible nucleophilic attack upon benzaldehyde (**57**) generates alkylated thiazolium derivative **71** *via* intermediate **70**. Similar to the cyanide-catalysed version of the reaction, the presence of the thiazolium ring increases the acidity of the α-proton and thus its removal forms the resonance-stabilised hydroxylenamine intermediate **72**, an *umpolung* species also termed the Breslow intermediate. At the time of its publication, however, Breslow referred to it as an 'active aldehyde' and attempted its isolation without success. The nucleophilic character of the Breslow intermediate enables further attack upon a second molecule of benzaldeyde to form **73**. A final proton transfer allows the elimination of the NHC and benzoin (**58**) from **74**. Through this mechanism, the NHC is free to re-enter the catalytic cycle and initiate the reaction again.

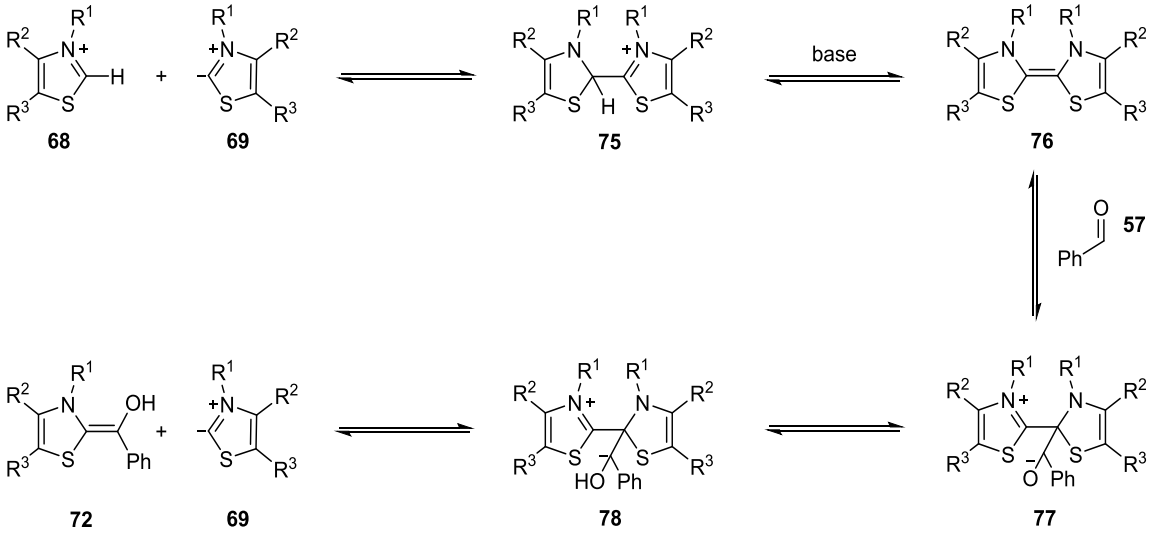
Scheme 1.16 Mechanism of the thiazolylidene-catalysed benzoin reaction as proposed by Breslow



1.2.2.2 Lemal and Castells: postulated thiazolylidene dimer-based mechanism and alternative proposals

Following Breslow's mechanistic proposal, various studies have been undertaken to ascertain its validity.[105,106,107,108] Other studies have conversely advocated alternative mechanisms, chief among them that published by Lemal *et al*. suggesting the formation of a carbene dimer which acts as the catalytically-active species (Scheme 1.17),[109] while Castells and co-workers proposed an alternative dimer mechanism in 1986 (Scheme 1.18).[110] The two differed only in their interpretation of how the dimer **76** proceeded to form benzoin, with Lemal suggesting a fragmentation of **78** produced the original carbene species **69** and the Breslow intermediate **72**.

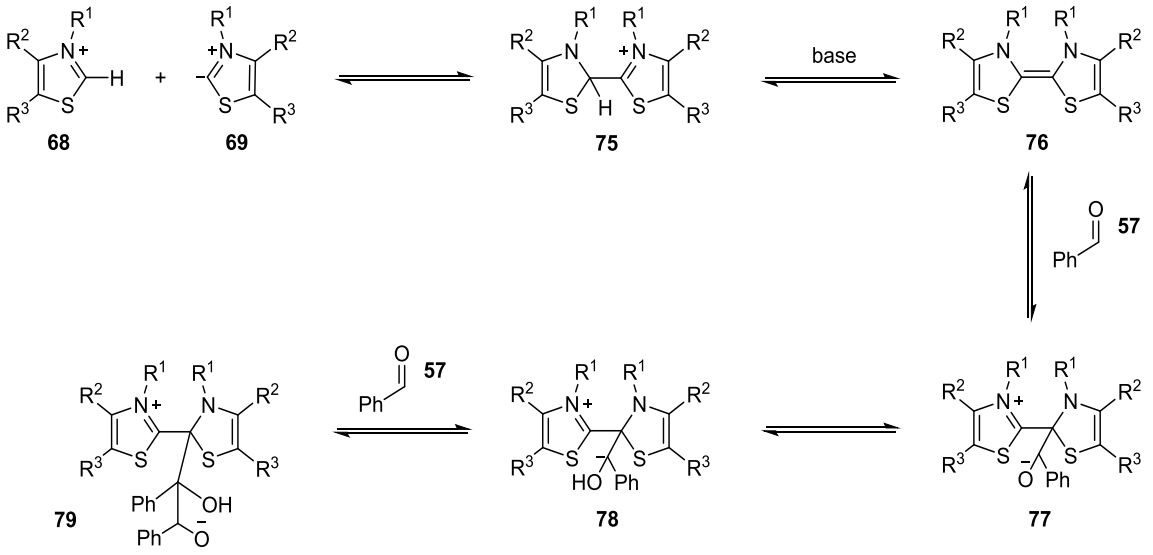
Scheme 1.17 Lemal's carbene dimer-catalysed benzoin condensation



Castells' postulated mechanism involved no fragmentation of **78** but simply its nucleophilic attack upon the second benzaldehyde molecule to form oxyanion **79** which, following proton transfer, collapses to regenerate the dimer and release benzoin. However, while it has been shown that such dimers can indeed catalyse the benzoin condensation,[111] as well as the fact that dimer formation would explain certain results in the field (for example, why the reaction still proceeds in a protic solvent medium), spectroscopic and kinetic investigations have since dismissed the plausibility of the theory.[106,107,112] Despite this, the validity of Breslow's proposed mechanism remains intermittently under scrutiny with modern techniques and studies allowing deeper

understanding to come forth. As recently as 2015, Rehbein *et al*. used EPR and computational data to identify a radical pair derived from the Breslow intermediate *via* a single electron transfer that they suggest may represent a second key intermediate in the process.[251]

Scheme 1.18 Castells' carbene dimer-catalysed benzoin condensation

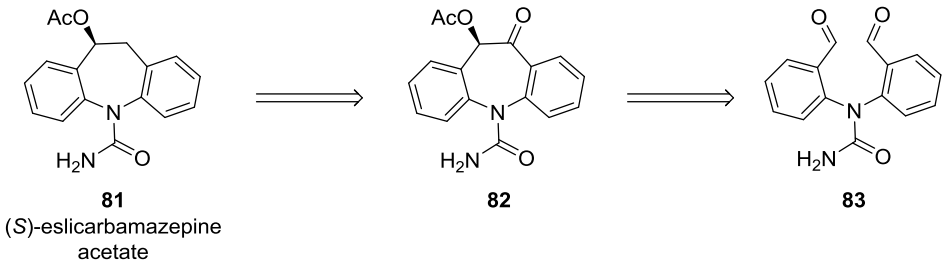


1.3 Crossed acyloin condensations employing NHC organocatalysts

With the advent of NHCs there have been significant advances made in their application in the *homo*-benzoin condensation.[90] In stark contrast, although the last few years have seen considerable progress, the *crossed* acyloin condensation (*i.e.* between two non-identical coupling partners) presently remains beyond complete synthetic control. The condensation of two such aldehydes allows access to unsymmetrical α-hydroxy ketones (also termed acyloins); which serve as building blocks of great utility in the construction of range of compounds, including heterocycles, natural products, agrochemicals and pharmaceuticals,[113] while further reduction or reductive amination also yields unsymmetrical 1,2-diols and amino alcohols respectively.[114] Scheme 1.19 depicts prodrug (*S*)-eslicarbamazepine acetate (**81**), used in the treatment of epilepsy, which is metabolised *in vivo* to the active anticonvulsant (*S*)-(+)-licarbamazepine. A possible retrosynthesis of **81** could reveal the unsymmetrical *O*-acyl α-hydroxy ketone (**82**), the formation of which could be achieved through a site-selective crossed acyloin condensation of dialdehyde **83**. Further examples of compounds bearing an α-hydroxy

ketone moiety within their structure include the potential anticancer drug class epothilones and antidepressants.[115,116]

Scheme 1.19 Possible retrosynthesis of eslicarbamazepine acetate



1.3.1 Intermolecular NHC-catalysed crossed acyloin condensation

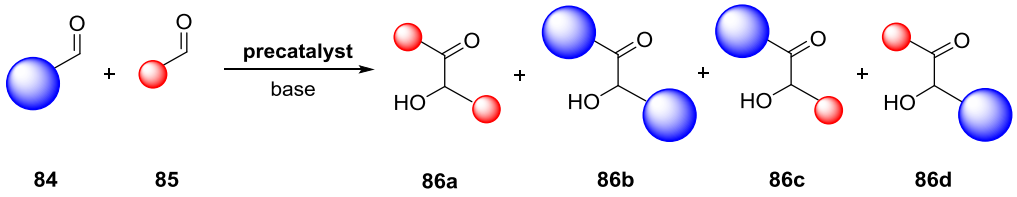
Since 1976, with the work of Cookson and Lane,[117] the NHC-catalysed *intramolecular* crossed acyloin condensation has been studied extensively; numerous reports detail the formation of cyclic α-hydroxy ketones (the product of such condensations) in excellent yield with high regio- and enantioselectivity through employment of a wide range of heteroazolium salt precatalysts.[118-127] However, the intramolecular nature of the process aids in reducing the number of possible products formed in the reaction. The NHC-catalysed *intermolecular* crossed acyloin condensation also produces α-hydroxy ketones, but of an acyclic nature. Due to their high synthetic utility, the development of routes to acyloin compounds *via* metal-catalysed heteroatom transfer and organocatalytic α-oxidation chemistry has been extensively investigated.[128] Often the conditions necessary to effect these transformations are harsh and intolerant of other functionalities present within a molecule. It stands to reason that an NHC-mediated pathway, conducted under much milder conditions, represents a far more convenient and synthetically advantageous method for the synthesis of these acyclic adducts. The increased complexity of the chemoselective outcomes means that the primary research efforts to develop NHC-based protocols addressing this issue are relatively recent.

1.3.1.1 Chemoselective considerations of the crossed acyloin condensation

As detailed in Scheme 1.20, an intermolecular crossed acyloin condesnation between two non-identical aldehydes generates four possible products – two homodimers (**86a** and **86b**), produced *via* self-condensation of each aldehyde, and two heterodimers (**86c** and

86d), arising from the desired cross-condensation of the aldehydes. Considering the chiral nature of the product acyloins, a total of eight possible products can be formed in one pot and so the key elements of a methodology exerting control over the reaction are appreciable – a suitable catalyst must select one aldehyde as the initial electrophile, thereby forming one Breslow intermediate exclusively, and then ensure that subsequent nucleophilic attack occurs solely upon the second coupling partner. Furthermore, a chiral catalyst must exercise such chemoselective control while also influencing the stereochemical outcome of the reaction with regard to the cross-acyloin product.

Scheme 1.20 Challenges associated with the intermolecular crossed acyloin condensation

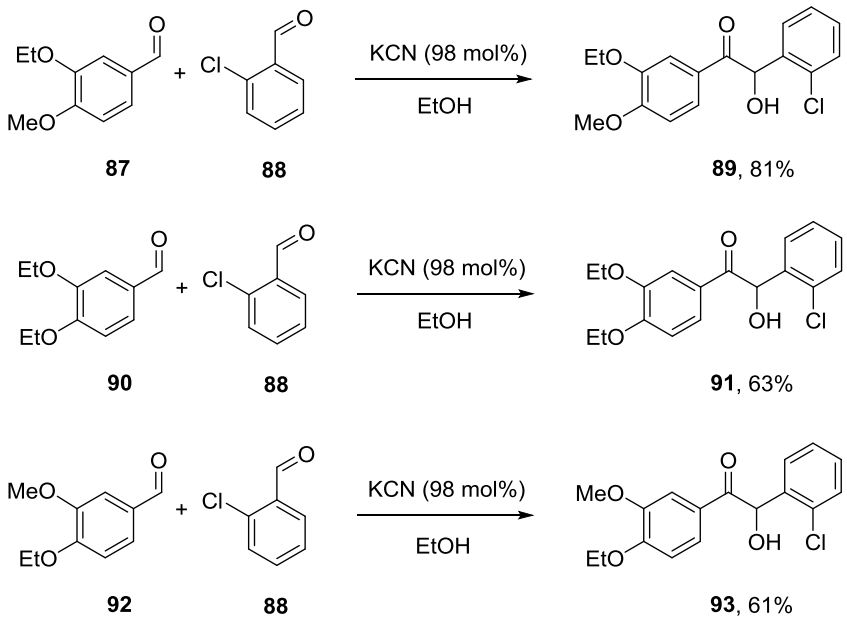


1.3.1.2 Seminal studies: cyanide- and thiazolylidene-catalysed crossed acyloin condensations

In 1882, Fischer reported the first attempted cyanide-catalysed cross-condensation to produce a cross-benzoin product (for the purposes of this thesis, a cross-benzoin is defined as being the product of the condensation between two non-identical aromatic aldehydes and is regarded as a sub-class of cross-acyloins, which encompasse all combinations of aliphatic and aromatic moieties).[130] His research focused upon the reaction between benzaldehyde and furfuraldehdye, while over 60 years later Buck *et al*. carried out a more detailed examination of the mechanism and governing electronic factors of the cross-benzoin condensation (Scheme 1.21).[131] No general chemoselectivity trends were proposed – for example, in the presence of a near-stoichiometric amount of potassium cyanide, 2-chlorobenzaldehyde (**88**) was cross-coupled with a variety of 3,4-substituted benzaldehydes (**87**, **90** and **92**) in moderate to good yield. One aspect of the study that remains pertainent today is that the absence of an *ortho*-substituted benzaldehyde coupling partner resulted in lower isolated yields (40-50%) of cross-benzoin adducts. At the time, these reactions were believed to be under thermodynamic

control and considered to generate the α-hydroxy ketone with the more electron-deficient aryl ring adjacent to the hydroxyl group as the major product.

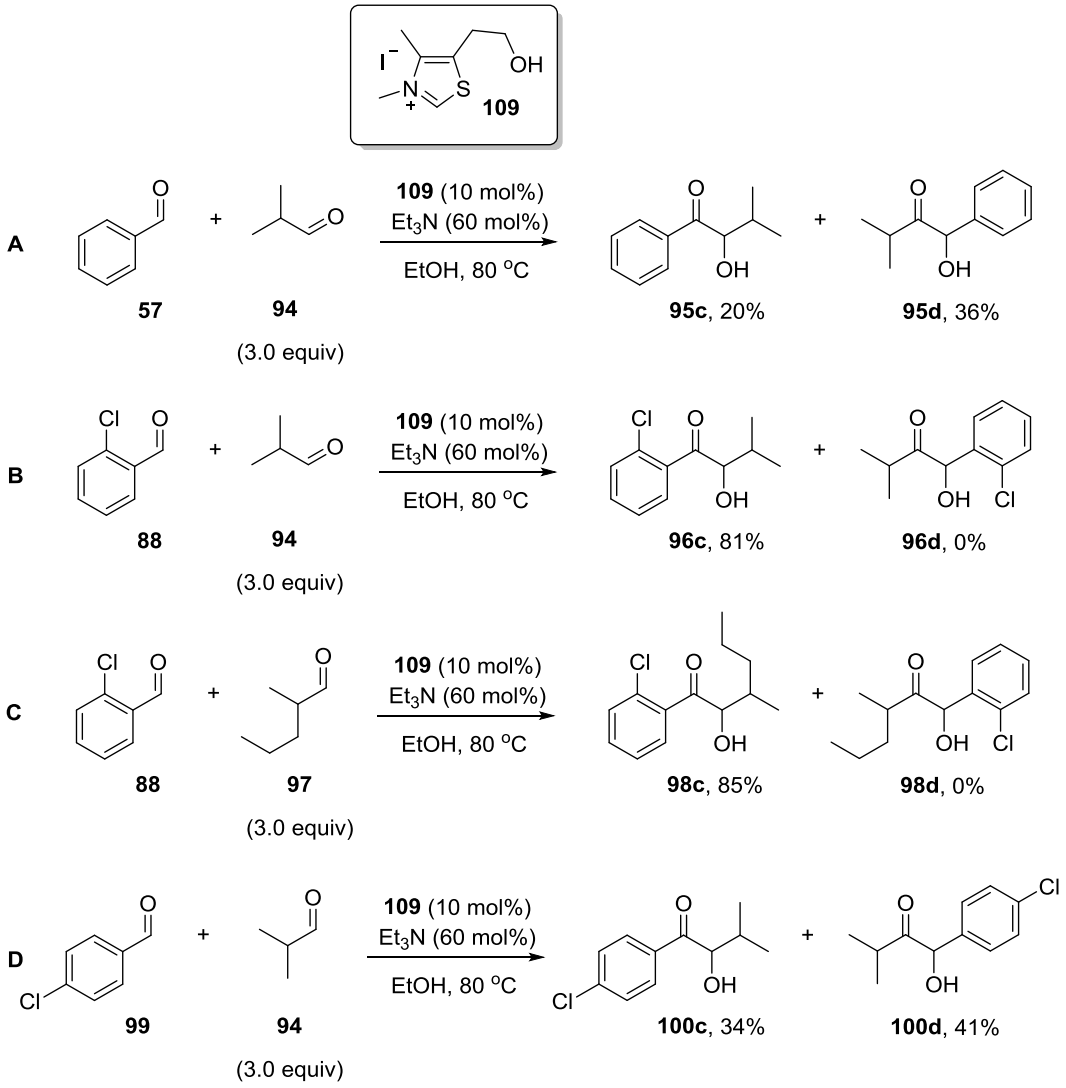
Scheme 1.21 The crossed acyloin condensation carried out by Buck *et al.*



Despite these pioneering studies by Fischer and Buck, a further 30 years elapsed before the emergence of a systematic study upon the intermolecular crossed acyloin condensation by Stetter.[132] His study employed thiazolium salts as precatalysts for the preparation of acyloin and benzoin compounds on a synthetically-useful scale, using the aliphatic aldehyde in a three-fold excess to afford good yields of cross-acyloin products (Scheme 1.22). However, Stetter reported only the combined isolated yield of both cross-products together and made no reference to any further purification of these adducts being carried out. Furthermore, no yields were provided for the homodimers of both aldehydes. Despite this, the work again highlighted a feature of cross-acyloin condensations that Buck had also observed – that the presence of an *ortho*-substitued benzaldehyde as one coupling partner tended to positively influence the carbene catalyst's ability to direct a chemoselective reaction (see **B** and **C**). The condensation between non-*ortho*-substituted benzaldehydes and aliphatic aldehydes gave rise to modest combined yields and lacked any degree of chemoselectivity (see **A** and **D**). An interesting further observation was that when **88** and acetaldehyde were employed as the aldehyde coupling partners, Stetter reported a complete reversal in the chemoselective

outcome of the reaction in that the cross-benzoin with the aryl ring adjacent to the hydroxyl group was the major product.

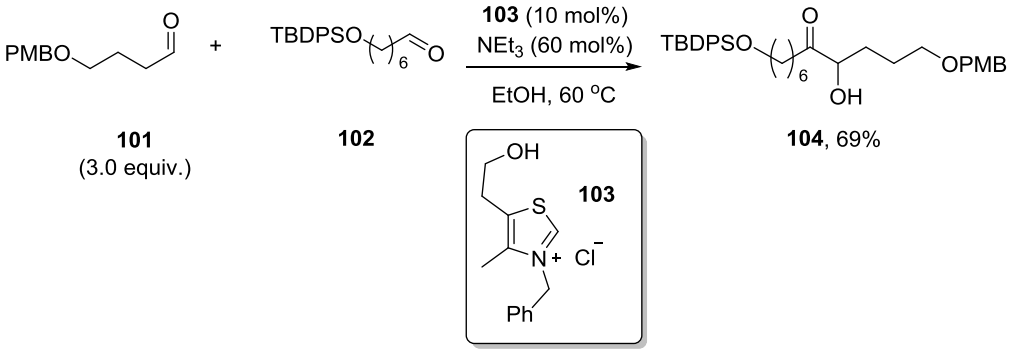
Scheme 1.22 Intermolecular crossed acyloin condensation carried out by Stetter



In 2011 Connon *et al.* corrected an error in Stetter's data regarding the identity of the cross-acyloin product formed under the conditions outlined in **B** and **C**, clarifying that **96d** and **98d** were in fact the sole products of the reaction (81% and 85% yield respectively).[138] Use of 2-furfuraldehyde and 2-thiophenecarbaldehyde as the aromatic component also enabled Stetter to achieve good chemoselectivities with this methodology. He would employ the same catalyst three years later in an intermolecular crossed acyloin condensation between bulky substituted norbornene-2-carbaldehydes and various aliphatic aldehydes.[133] While he again reported combined isolated yields of both cross-products, no product ratios were given.

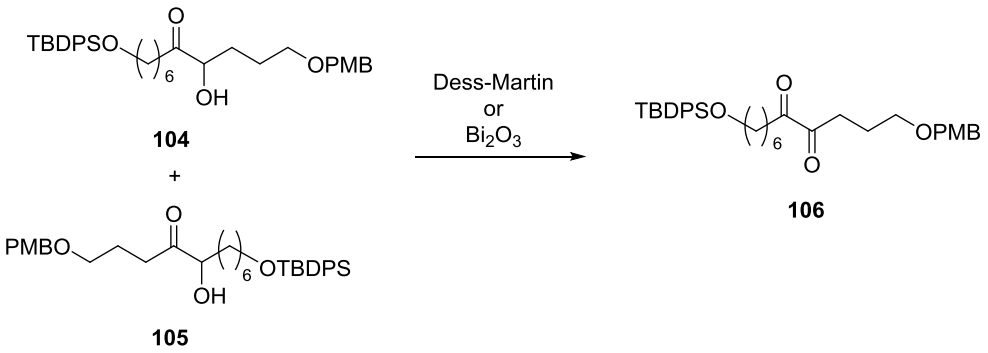
Such an omission of product ratio was also present in the work of Golding *et al*. in 2001 when they examined the cross-condensation of straight-chain aliphatic aldehydes with a thiazolium salt.[134] Seeking to synthesise non-symmetrical 1,2-dioximes for further synthesis of supramolecular cobaloximes as models for vitamin B_{12}-dependent enzymatic reactions, they chose to access these compounds through an NHC-catalysed crossed acyloin condensation. The authors employed identical conditions to those utilised by Stetter above, most notably maintaining a 3:1 ratio of the starting aldehyde substrates. In the presence of thiazolium salt **103** and base, poor to moderate isolated yields of cross-acyloin products could be obtained. For example, use of unhindered aliphatic aldehydes **101** and **102** enabled generation of **104** in 69% yield (Scheme 1.23).

Scheme 1.23 Thiazolylidene-catalysed crossed acyloin condensation conducted by Golding *et al.*



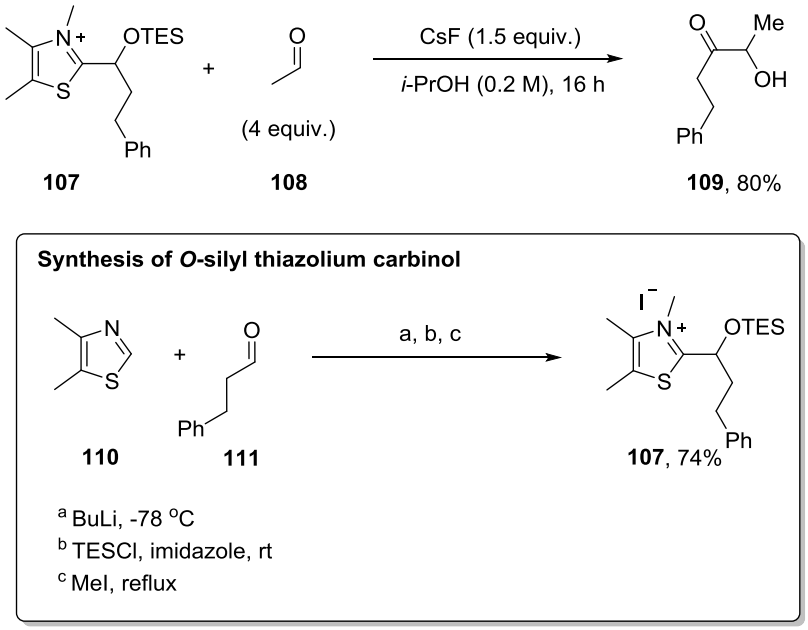
The observed chemoselectivity of the reaction was rationalised by a statistical argument – *in situ* generation of the relevant Breslow intermediates occurs in an approximate 3:1 ratio favouring that derived from **101** relative to that derived from **102**. This ratio is further biased by an approximately 3:1 ratio of starting materials on a mole:mole basis and so although the primary reaction product (on the basis of this argument) is the homodimer of **101**, the Breslow intermediate derived from the minor aldehyde (**102**) is more likely to give rise to cross-product **104** in up to 86% yield. However, despite this, isolated yields of other cross-acyloin adducts derived from alternate coupling partners remained moderate, and occasion were as low as 29%. The chemoselectivity of the reaction in general was of little consequence overall as a subsequent one-pot Dess-Martin oxidation of both cross-product isomers **104c** and **104d** (or use of bismuth (III) oxide in a 2-ethyoxyethanol/acetic acid solvent system) was employed to generate unsymmetrical 1,2-diketones (**105**) as precursors for the desired 1,2-dioximes (Scheme 1.24).

Scheme 1.24 Oxidation of cross-acyloins by Golding *et al.*



One of the primary problems encountered when attempting to cross-couple aliphatic aldehydes within an NHC-based system is moderating the basicity of the conditons to enable sufficient levels of the carbene to be generated *in situ* while suppressing the occurance of aldol side reactions. In 2009, Scheidt *et al*. unveiled a novel (but not catalytic) way to circumvent this problem and direct the chemoselective outcome of a cross-condensation between two disparate aliphatic aldehydes through use of *O*-silyl thiazolium carbinols *i.e.* silylated precursors of the Breslow intermediate (*e.g.* **107**, Scheme 1.25) in the presence of caesium fluoride.[151] Using a 3,4-dimethylthiazole (**110**) precursor and various aliphatic aldehydes, Scheidt could achieve formation of these thiazolium carbinols in three synthetically facile steps with yields up to 74%. Subsequent exposure to an excess of CsF in the presence of 4 equivalents of an aliphatic aldehyde coupling partner allowed isolation of a range of cross-acyloin products. Fluorine-catalysed addition of the thiazolium carbinol derived from **111** (**107**) to acetaldehyde (**108**) provided **109** in 80% yield, with Scheidt proposing that desilylation of **107** by CsF allows a formal 1,2-proton shift to generate the Breslow intermediate, which then reacts with the aliphatic aldehyde in the usual manner.

Scheme 1.25 Intermolecular cross-acyloin condensation by fluoride-promoted addition of *O*-silyl thiazolium carbinols conducted by Scheidt *et al*.



1.3.1.3 Triazolylidene-mediated intermolecular crossed acyloin condensations

The first reported example of a triazolylidene-catalysed crossed acyloin condensation in the literature did not appear until 2007. Indeed, even at that point it only formed part of Miller's investigations into the intramolecular acyloin condensation and his synthesis of *trans*-resorcylide (**112**, Figure 1.11),[120] notable for its use of the pentafluorophenyl-substituted triazolium salt **54** (in the presence of DBU) to achieve the cyclisation of the ring. Further transformations enabled the final synthesis of the product.

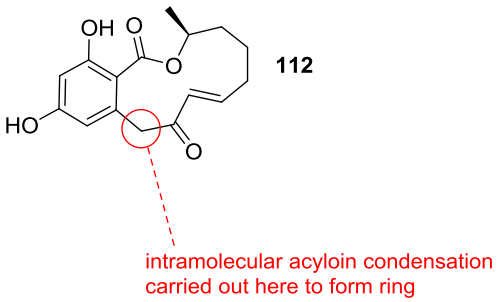
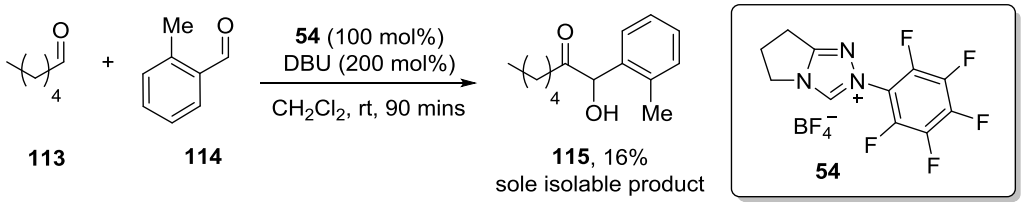


Figure 1.11 The structure of *trans*-resorcylide, indicating the site of Miller's NHC-catalysed acyloin condensation to form the ring

In addition to achieving this ring-closure through an NHC-mediated crossed acyloin pathway, Miller further questioned whether the regioselectivity of this process was dictated by thermodynamic or kinetic control and conducted an examination of the factors influencing this regioselectivity. The authors subsequently conducted a cross-condensation between *n*-hexanal (**113**) and 2-tolualdehyde (**114**) in the presence of an excess of DBU and stoichiometric loading of triazolium precatalyst **54** (Scheme 1.26).

Scheme 1.26 Intermolecular crossed acyloin condensation carried out by Miller *et al.*



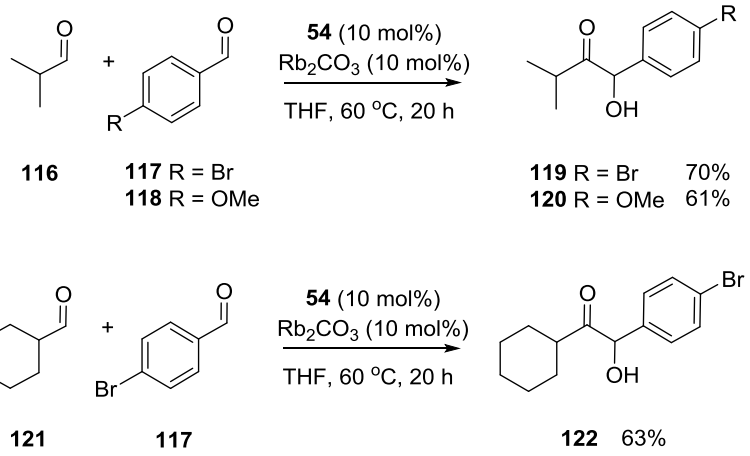
113 **114** **115**, 16% sole isolable product **54**

Cross-acyloin **115** was the sole reaction product, isolated in just 16% yield after column chromatography, while the analogous reaction using benzaldehyde (**57**) instead of **114** produced a complex mixture of three different acyloin products. This led Miller to conclude that the presence of the *ortho*-methyl substituent *may* preclude formation of the Breslow intermediate derived from initial attack by the triazolylidene upon **114** due to steric hinderance. However, considering the reaction was a means of macrocyclisation, he also acknowledged that conformational restrictions may favour intial attack of the carbene catalyst upon the aliphatic aldehyde component.

Following these reports, Zeitler and Connon have since collaborated to carry out the most thorough investigations to date of the triazolylidene-mediated cross-coupling between two disparate aldehydes. In 2010, they examined the catalyst and substrate features which influence the chemoselectivity of the reaction.[138] It was determined that in cross-condensations between aliphatic and aromatic aldehydes, the use of the pentafluorophenyl-substituted triazolium salt **54** enabled establishment of a far more chemoselective process than use of an alternative thiazolium ion-based precatalyst. Other factors deemed of significance were the use of *ortho*-substituted benzaldehydes or a π-excessive heterocycle substituted at the 2-position as the aromatic coupling partner. The seeming reliance upon an *ortho*-substituent was alleviated somewhat through the use of **54** and branched aliphatic aldehydes, which tended to participate in moderately

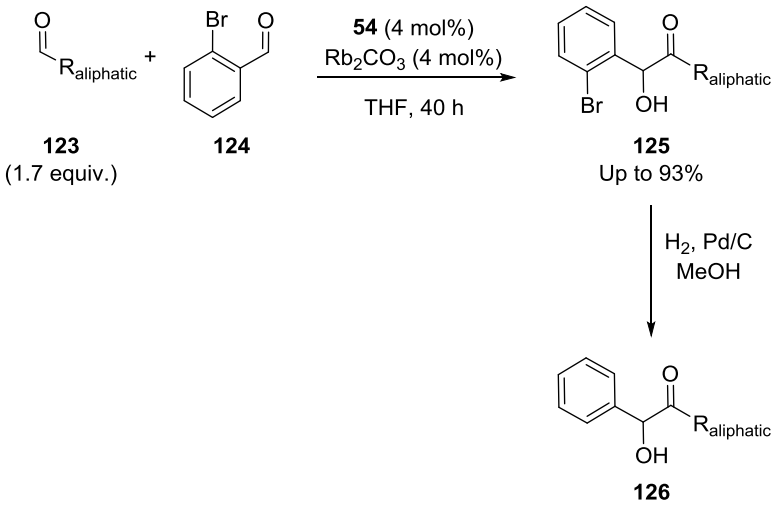
chemoseletive processes despite the absence of an *ortho*-substituted benzaldehyde (Scheme 1.27).

Scheme 1.27 Chemoselective crossed acyloin condensations of unhindered benzaldehydes



The same authors then published a further examination of the crossed acyloin condensation between aliphatic and aromatic aldehydes using triazolium catalyst **54** the following year (Scheme 1.28).[139] To date, this study remains the most in-depth analysis of the reaction available in the literature. The chemoselectivity of the reaction was again heavily reliant upon the presence of an *ortho*-substituent on the benzaldehyde ring, although the substrate scope with regard to the aliphatic aldehyde (**123**) was excellent, with both branched and unbranched variants amenable to condensation. 2-Bromobenzaldehyde **124** was chosen as the aromatic coupling partner and enabled production of cross-acyloin **125** in up to 93% isolated yield in certain cases in the presence of an excess (1.7 equivalents) of the aliphatic aldehyde. However, the authors also extended the synthetic utility of their protocol by demonstrating that the requirement for the *ortho*-bromine atom in seeking to establish a catalytic bias for one cross-benzoin product was not restrictive – further hydrodebromination meant that its subsequent removal could be achieved and thus it could be viewed as a functional handle that aids in directing a chemoselective process and is then either removed or utilised for further transformations. The most significant aspect of such a reduction meant that cross-acyloins of general type **126**, formally derived from aliphatic aldehydes and benzaldehyde, were accessible in high yield.

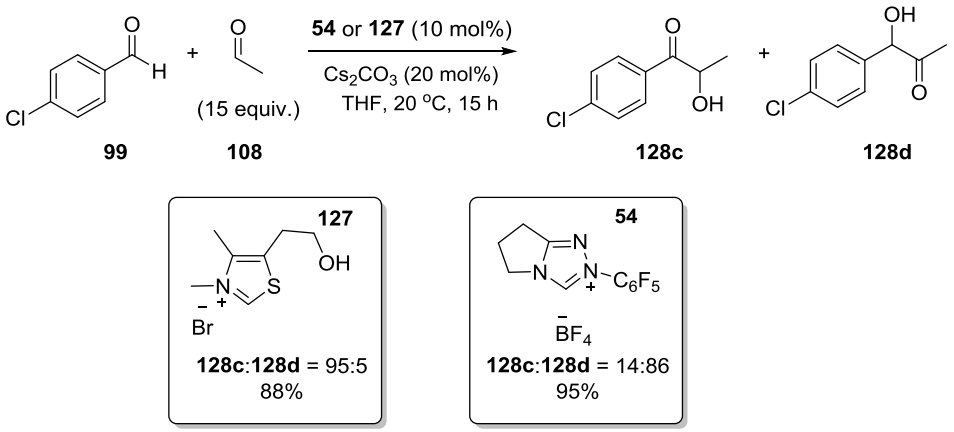
Scheme 1.28 Chemoselective crossed acyloin condensation and subsequent hydrodebromination by Connon *et al.*



The origin of the chemoselectivity of the reaction was then investigated through a series of crossover experiments. They concluded that self-condensation of both the aliphatic and *ortho*-substituted aromatic aldehydes occurs very slowly and is central to attaining high chemoselectivity in the reaction. Homodimers derived from aliphatic aldehydes were also deemed not to participate in retro-acyloin process and were essentially formed irreversibly. Furthermore, homodimers derived from unhindered aromatic aldehydes (*i.e.* non-*ortho*-substituted benzaldehydes) do participate in the retro-acyloin reaction while *ortho*-substituted benzaldehydes will not do so under identical reaction conditions. The major cross-acyloin product in the reaction was shown to either undergo a retro-acyloin condensation either slowly or not at all, while cross-acyloins derived from unhindered aromatic aldehydes are subject to far greater degree of thermodynamic control. Thus, given the energy differences between acyloin products is likely to be quite small, this leads to a less selective process due to reversible formation of at least three products in one pot.

Following the publication of these results, Yang *et al*. disclosed their own studies upon the intermolecular crossed acyloin condensation between a large excess of acetaldehyde **108** and various aromatic aldehydes.[140] Interestingly, while their efforts focused primarily upon the use of **54** as the carbene precursor, they found that the selectivity of the reaction could be switched *via* alternative use of the thiazolium salt precatalyst **127** (Scheme 1.29).

Scheme 1.29 Switch in regioselectivity of the intermolecular crossed acyloin condensation observed by Yang *et al.*

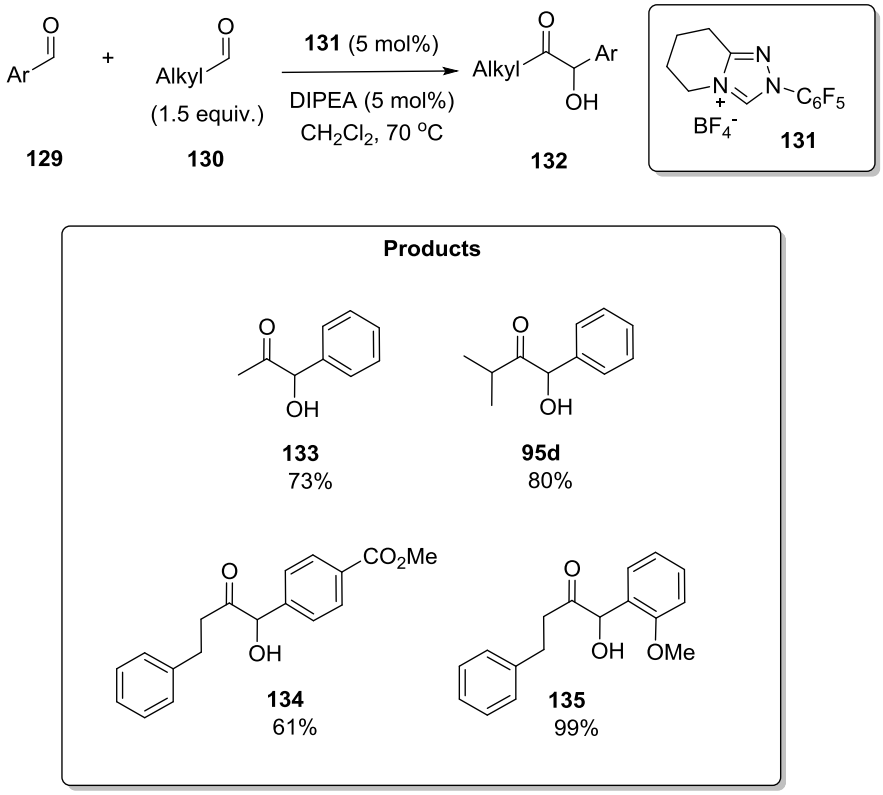


The origin of this observed regioselectivity switch with use of alternative precatalysts remains unknown. The authors postulated that attack of the carbene derived from **127** upon **99** would generate the most resonance-stabilised Breslow intermediate. Subsequent attack by the Breslow intermediate upon an incoming molecule of **108** would allow release of the more thermodynamically stable cross-acyloin adduct **128c**. Conversely, the more sterically-demanding triazolylidene catalyst, derived from **54**, would disfavour intial attack upon the aromatic aldehyde and would instead add preferentially to **108**. The authors also suggested that the electronic characteristics of the aromatic aldehyde may influence the selectivity of the reaction. In the presence of **127**, for example, the selectivity was found to be better when using electron-deficient benzaldehydes. However, electron-rich benzaldehydes gave rise to a more selective process in conjunction with triazolium precatalyst **54** and base.

In 2014, Yang again employed a large excess of an aliphatic aldehyde as one coupling partner in an NHC-catalysed crossed acyloin condensation using 10 mol% of *N*-pentafluorophenyl-substituted precatalyst **54**.[252] The authors demonstrated how its derivative carbene was highly robust and remained active in solution when catalysing the cross-condensation between *iso*butyraldehyde (**94**) and 4-chlorobenzaldehyde (**99**). Utilising 15 equivalents of **94**, upon completion of the reaction **99** could be recharged to the flask up to 5 times and subjected to further cross-acyloin coupling without the addition of further precatalyst. The accumulated percentage yield of 93% was coupled with an excellent chemoselectivity for cross-acyloin adduct **100d** (up to 98%).

Gravel *et al*. have also developed an NHC-based methodology less reliant upon the *ortho*-substituted benzaldehydes employed by Connon *et al*. through the synthesis of the piperidinone-derived triazolium precatalyst **131** (Scheme 1.30).[152] Low catalytic loadings and the presence of one equivalent of DIPEA rendered the cross-condensation between aliphatic and aromatic aldehydes highly chemoselective, albeit utilising an excess of the aliphatic partner. The scope of the reaction with regard to both substrates was broad, including a wide range of benzaldehydes containing electron-withdrawing and -donating substituents as well as branched and unbranched aliphatic aldehydes. However, in keeping with previously established trends, the use of an *ortho*-substituted benzaldehyde correlated to the most chemoselective reported cross-condensation (up to 99% yield of **135**).

Scheme 1.30 Chemoselective crossed acyloin condensation reported by Gravel *et al*.



Gravel further investigated the origin of this observed chemoselectivity using **131** through a combination of density functional theory (DFT) and experimental data.[153] The authors concluded that the formation of cross-acyloins **132** was due to kinetically-controlled chemoselectivity. Major contributing factors in this regard include the rapid and preferential formation of an NHC adduct with aliphatic aldehydes, a rate-limiting

carbon-carbon bond formation step benefiting from a stabilising π-stacking/π-cation interaction and steric penalties paid by competing pathways. In comparison, the reaction energy profile for precatalyst **54** was found to be remarkably similar, despite experimental data showing that it promoted a less chemoselective reaction. Interestingly, implementation of conditions favouring kinetic control did not improve the chemoselectivity of the NHC derived from **54**. Instead, equilibrating conditions (*i.e.* thermodynamic control) showed preference for the same cross-acyloin product kinetically favoured by **131**. Several of these conclusions had been proposed in a separate DFT investigation conducted by Bi *et al*. only one month previously.[154]

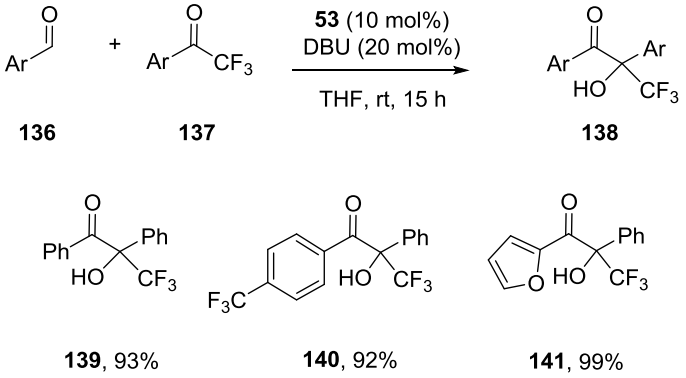
1.3.1.4 Alternative cross-coupling partners

Among the advances in the cross-coupling of two non-identical aldehydes in recent years, other research efforts have also focused upon the coupling of aldehydes with alternative coupling partners, specifically ketones and α-ketoesters. Johnson has shown how this can be achieved using α-siloxyketones in the presence of the cyanide ion in benzoin-type additions.[141,142] However, the primary examples employing NHCs are Enders *et al.* in 2009 and Zeitler *et al*. in 2012.

Enders initially disclosed the NHC-catalysed coupling of aromatic aldehydes with various trifluoromethyl ketones (**136**, Scheme 1.31).[143,144] Using phenyl-substituted triazolium salt **53**, the resulting α-hydroxy-α-trifluoromethyl ketones **138**, bearing a quaternary stereocentre, were produced with excellent chemoselectivity and in good to excellent yields in the presence of an excess of base. The substrate scope of the reaction was broad, with electron-neutral and -deficient benzaldehydes undergoing highly efficient and chemoselective cross-coupling with 2,2,2-trifluoroacetophenone (see **139** and **140** for representative examples), while 2-furfuraldehyde underwent almost full conversion to **141**. Electron-rich benzaldehydes were also amenable to transformation, although the reaction rate was considerable slower. However, in keeping with previous observations, the chemoselectivity of the protocol was negatively impacted when *ortho*-substituted benzaldehydes were employed as the aldehyde component as such substrates serve as poor electrophiles for initial attack by the carbene. Enders also extended this methodology to enable asymmetric synthesis of these α-hydroxy-α-trifluoromethyl ketones through use of a chiral NHC precursor salt (see Scheme 1.44 below). Although

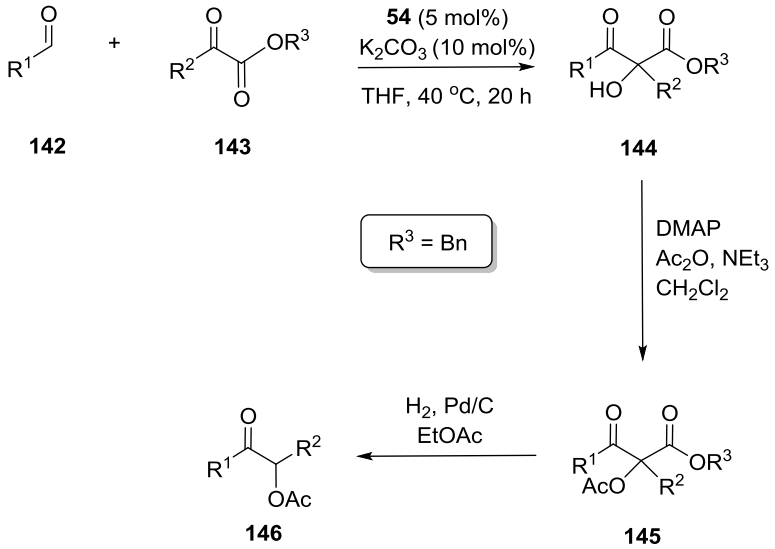
the optical purity of the cross-benzoin derivatives was moderate to good (up to 83% *ee*), recrystallisation allowed their isolation in >99% optical purity in selected cases.

Scheme 1.31 Cross-coupling of aromatic ketones with trifluoromethyl ketones



In 2012, Zeitler *et al*. envisioned the possibility to cross-couple both aliphatic and aromatic aldehydes with α-ketoesters (**143**, Scheme 1.32).[145] Again, catalytic loadings of triazolium precatalyst **54** in conjunction with an excess of base afforded densely functionalised α-hydroxy-β-ketoesters (**144**) with a quaternary stereocentre.

Scheme 1.32 NHC-mediated crossed acyloin coupling between aldehydes and α-ketoesters



The scope of the reaction was found to be very broad with regard to both coupling partners and, like Enders, they also developed an asymmetric version of the reaction

through synthesis and use of a chiral triazolium catalyst (see **206**, Scheme 1.41 below), although optical purities were modest (up to 76% *ee*). However, the authors emphasised that the true synthetic value of the methodology was that when R^3 = Bn, subsequent acylation of the hydroxyl moiety (yielding **145**) and decarboxylation allowed access to acetylated acyloins (**146**). It was demonstrated that unsymmetrical aliphatic acyloins, normally unaccessible through conventional NHC-mediated pathways, could be synthesised using these means.

More recently, Anand *et al.* expanded upon Enders' idea to employ an electrophilic coupling partner incapable of forming the Breslow intermediate when they reported a highly chemoselective cross-acyloin-type condensation using aromatic aldehydes in conjunction with trifluoroacetaldehyde ethyl hemiacetal (described as an "aldehyde equivalent") in the presence of **53** and base.[150]

1.4 The intermolecular crossed benzoin condensation

The recent advances detailed above highlight that extensive efforts have been aimed at overcoming the chemoselectivity issues surrounding crossed acyloin coupling using NHCs. However, the crossed condensation between two aromatic aldehydes *i.e.* the crossed benzoin condensation, has received comparably minimal attention in this regard. Indeed, although Fischer and Buck (credited with the first investigations into cross condensations[130,131]) selected two non-identical aromatic aldehydes substrates (see Section 1.3.1.2) there have since only been two reported examples of efforts to address the NHC-catalysed cross-benzoin condensation.

1.4.1 Chemoselectivity challenges associated with cross-coupling of two non-identical aromatic aldehydes

The chemoselectivity issues surrounding a crossed benzoin condensation mirror those outlined above (see Scheme 1.20) in that the possibility arises of four possible products in one pot, a number which doubles if one considers enantiomers. However, further complicating the issue is the presence of two aromatic aldehydes. Observed chemoselective outcomes in the crossed acyloin condensation, where initial NHC attack occurs upon the aliphatic aldehyde, were attributed to electronic effects *i.e.* the fact that aliphatic aldehydes are naturally more reactive than their aromatic counterparts.[139]

However, in the absence any aliphatic aldehyde, the NHC catalyst must now be able to differentiate between two considerably more similar aldehydes. Furthermore, as disclosed by Connon *et al.*,[139] benzoins derived from aromatic aldehydes are subject to a much greater degree of thermodynamic control and so, with the relative energies of each benzoin product likely to be quite similar, reversible formation may lead to a complex mixture of products before complete consumption of both starting aldehydes has been achieved.

1.4.2 Intermolecular cross-coupling of aromatic aldehydes using benzaldehyde lyase

While a selective process for the NHC-catalysed cross-coupling of aromatic aldehydes has yet to be extensively investigated, enzymatic catalysis has previously been employed with great success in this area. Müller and Pohl *et al*. had shown, in collaboration, that the synthesis of enantiopure benzoins could be achieved through the use of either of the thiamine diphosphate-dependent enzymes BAL[146] or BFD.[147] Aromatic homobenzoins were synthesised in excellent yield and enantioselectivity (>99% *ee*), while they also demonstrated how the same conditions could be utilised to develop a chemo- and enantioselective intermolecular crossed acyloin condensation using a range of aromatic aldehydes and acetaldehyde. The same groups collaborated further to publish the first example of a selective crossed benzoin condensation,[148] describing a donor-acceptor concept for the synthesis of cross-benzoins. Using BAL, they could cross-couple two non-identical aromatic aldehydes with confidence as to which substrate would serve as a donor (initially adding the enzyme) and which would act as a subsequent acceptor. They chose to conduct their study using 2-chlorobenzaldehyde (**88**), 2-tolualdehyde and 2-anisaldehyde, as well as a range of other aromatic aldehydes, as they envisaged that despite the previously described inability of these aldehydes to form symmetrical benzoins in the BFD-catalysed reaction,[148a] they might still be able to serve as acceptor aldehydes. While selectivities of cross-benzoins formed through use of 2-tolualdehyde and 2-anisaldehyde were modest, initial screening studies indicated that the BFD-catalysed crossed condensation between benzaldehyde and **88** could be carried out with 90% formation of **147** (Scheme 1.33).

Scheme 1.33 BFD-catalysed crossed benzoin condensation between **57** and **88**

57 **88** **147** 90%

The authors subsequently cross-coupled an extensive range of aldehyde partners with excellent results. The scope of the reaction was very broad, with various 3- and 4-substituted benzaldehydes (termed the donors) proving amenable to condensation with **88** in the presence of BAL or BFD with excellent stereochemical control. Furthermore, various di-, tri- and pentafluoro-substituted acceptor aldehydes could also be employed with good to excellent yields, although no enantiomeric excesses were determined for these adducts (**154-156**, Figure 1.12).

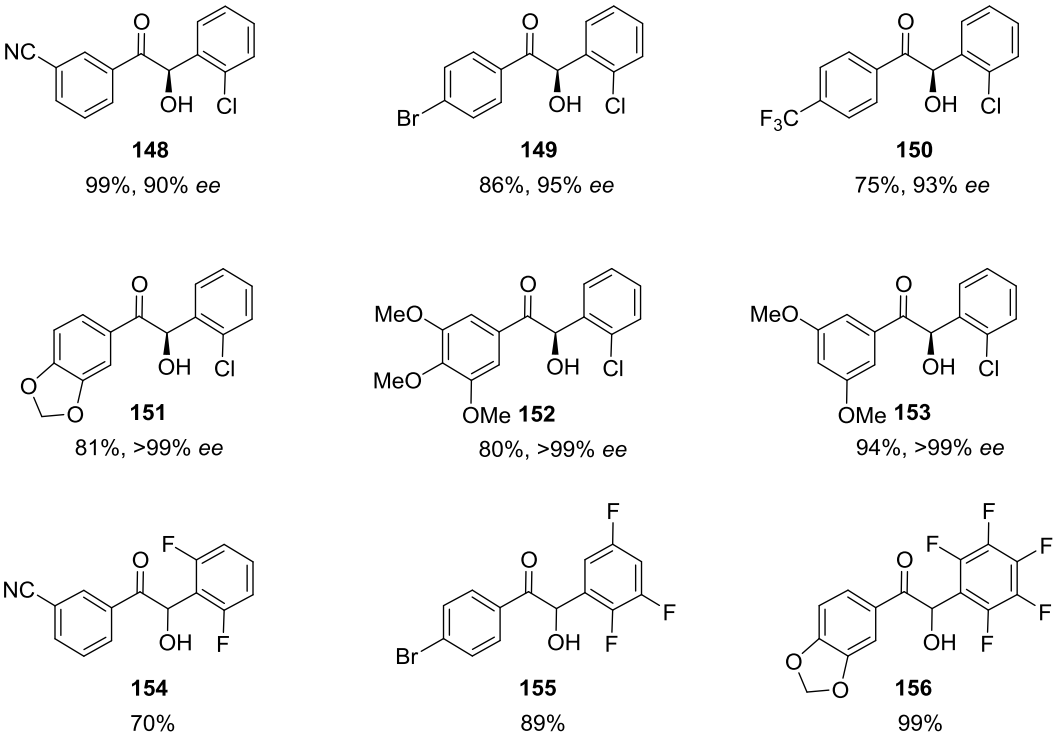
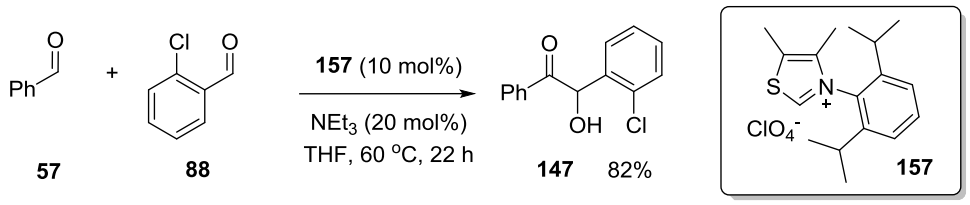


Figure 1.12 Selected cross-benzoins synthesised through BAL- or BFD-catalysed crossed benzoin condensation

1.4.3 Cross-coupling of two non-identical aromatic aldehydes using a thiazolium ion-based precatalyst

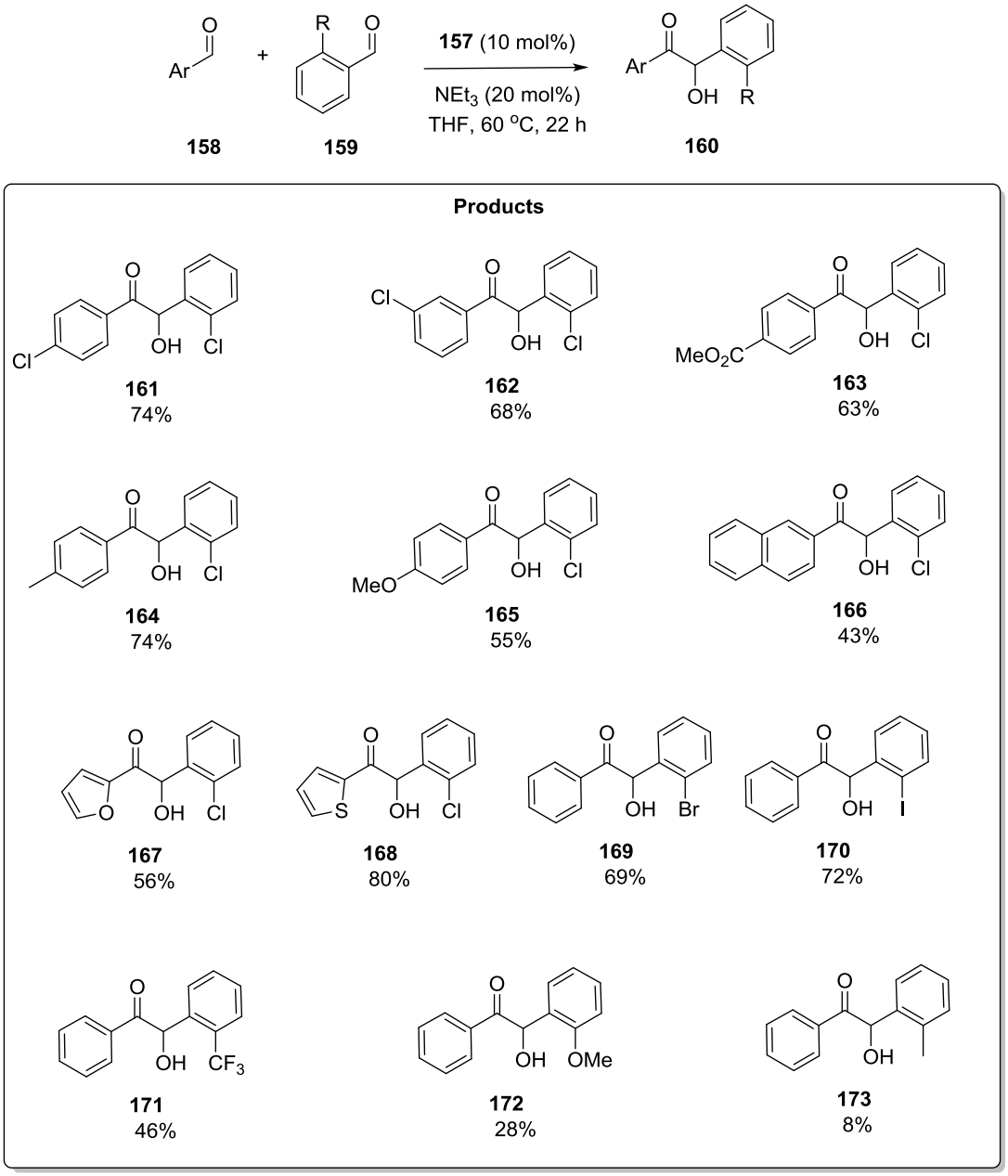
For several years the work of Müller and Pohl remained the sole modern study of the intermolecular cross-benzoin condensation between two separate aromatic aldehydes. Zeitler *et al*. would eventually demonstrate how their linear acetylation/decarboxylation treatment of α-hydroxy-β-ketoesters could be used to form an acetylated cross-benzoin formally derived from the condensation between 2-thiophenecarbaldehyde and benzaldehyde.[145] However, prior to this, in 2011, Glorius published an extremely thorough investigation into the catalytic capabilities of a range of structurally-related thiazolylidenes.[149] Using tools developed for the analysis of NHCs as transition metal ligands, they were able to explore the electronic and steric properties of these NHCs. They subsequently demonstrated how their findings could be used to employ the di*iso*propyl-substituted NHC derived from **157** in directing a chemoselective intermolecular cross-benzoin condensation between **57** and **88** with **147** isolated in 82% yield (Scheme 1.34).

Scheme 1.34 Chemoselective thiazolylidene-catalysed cross-benzoin condensation carried out by Glorius *et al.*



Glorius further showed how the methodology could be used to synthesise a wider range of cross-benzoin adducts. However, while the scope of the reaction was broad with regard to both aldehyde coupling partners, isolated yields were modest and never exceeded the 82% reported for the original reaction (Scheme 1.35). Furthermore, product yields for other benzoin products formed within the reaction pot were not reported.

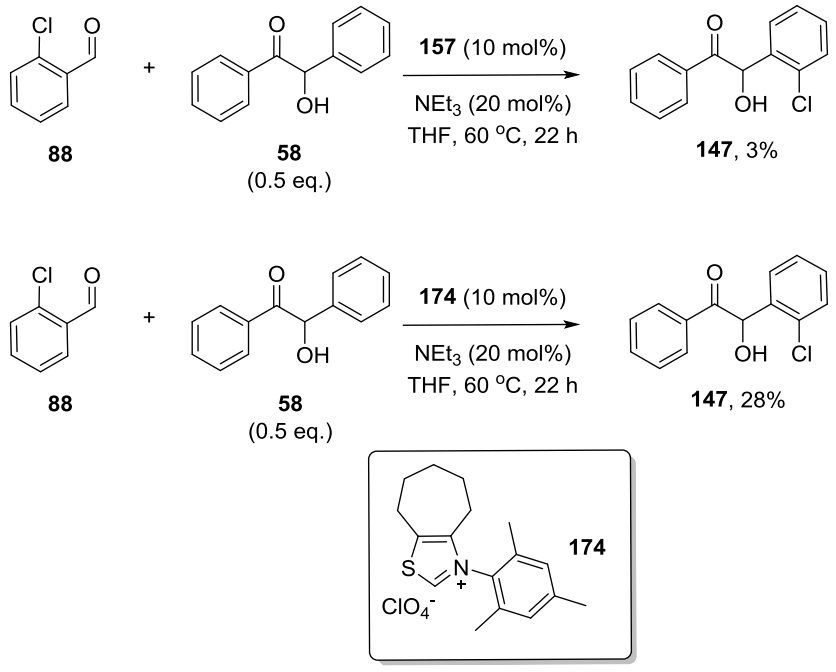
Scheme 1.35 Scope of thiazolylidene-catalysed cross-benzoin condensation



Glorius postulated that the observed selectivity of the reaction was attributed solely to the steric and electronic characteristics of the *ortho*-substituted aldehyde, suggesting that initial nucleophilic attack of the NHC occurrs primarily on the non-*ortho*-substituted coupling partner due to the steric hinderance of the *ortho* moiety. However, although the Breslow intermediate then faces two possible reaction partners, it favours attack upon the *ortho*-substituted aldehyde due to electronic effects according to Glorius. They assumed that the principal electron-withdrawing effect of the chlorine atom creates a better electrophile for the Breslow intermediate (which itself is also a better nucleophile in the

absence of a halide) and so the cross-condensation is feasible. This conjecture was supported by the fact that ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed that benzoin was never observed in more than 2% yield throughout the course of the reaction. The study concluded with an examination of the influence of the retro-benzoin condensation pathway upon the selectivity of the reaction. Treating **88** with 0.5 equivalents of benzoin in the presence of **157** led to the formation of just 3% of cross-benzoin **147**, while the alternative use of the mesityl-substituted precatalyst **174** under the optimized conditions allowed its formation in 28% yield (Scheme 1.35). The group thus concluded that the increased steric demands of the *iso*propyl groups on the *N*-aryl ring of precatalyst **157** contributed to a significant decrease in its capacity to catalyse the retro-benzoin condensation pathway. Coupled with the lack of formation of benzoin, this suggested that there existed a difference in the thermodynamic stability of both the homo- and cross-benzoin products that might be responsible for the degradation of the more labile homobenzoin, resulting in a selective cross-benzoin formation step that liberates the NHC and completes the catalytic cycle.

Scheme 1.35 Crossover experiments conducted by Glorius *et al*.



While Glorius' work represented a significant advance in controlling the chemoselectivity of the intermolecular crossed benzoin condensation, the modest yields reported for many cross-benzoin products emphasised the fact that a solution to the

problem remains elusive. Furthermore, no efforts were made to expand the synthetic utility of the methodology by developing an asymmetric variant. In this regard, the use of a thiazolium salt precatalyst is not ideal, as has been extensively documented in studies upon the asymmetric benzoin condensation.

1.5 The asymmetric benzoin condensation

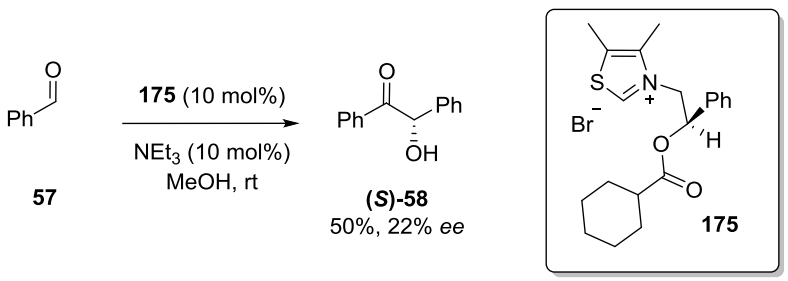
Section 1.3 details the synthetic utility and versatility of benzoins of both a symmetrical and unsymmetrical nature. However, while their value as a building block in the construction of larger, more complex molecules is in no doubt, the ability to construct enantiomerically enriched α-hydroxy ketones adds even further to their subsequent value. Although previous sections have touched upon several relatively recent methods to achieve this, in the context of NHC catalysis of the benzoin condensation scientists have been involved in efforts to accomplish enantioselective formation of α-hydroxy ketones for almost 50 years.

1.5.1 Chiral thiazolium ion precatalysts

1.5.1.1 Sheehan's seminal studies

Although Ugai reported on the catalytic ability of thiamine (in the presence of base) in the benzoin condensation in 1943, it was over 20 years later before the first reported example of an asymmetric version of the reaction was disclosed. In 1966, Sheehan detailed how a 10 mol% loading of chiral thiazolium salt precatalyst **175** (Scheme 1.36), in the presence of an equimolar loading of TEA, could promote the benzoin condensation in 50% yield with very modest enantioselectivity (22% *ee*).[155]

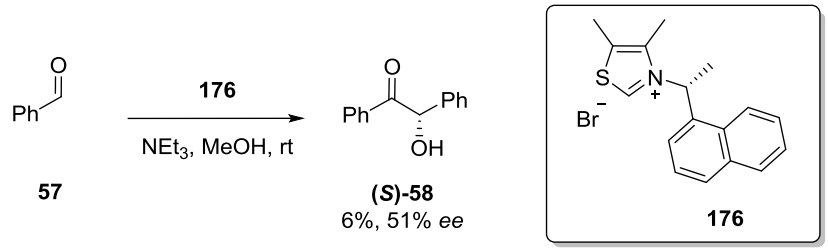
Scheme 1.36 Sheehan's pioneering asymmetric benzoin condensation



1.5.1.2 Second generation thiazolium salt-based precatalysts

Sheehan was the sole early pioneer of the asymmetric benzoin condensation, publishing a second generation thiazolium ion-based precatalyst eight years later in 1974.[156] Although **176**, possessing a bulky naphthyl group (Scheme 1.37), offered a significant improvement upon **175** in terms of enantioselectivity with (*S*)-**58** being isolated with an optical purity of 51%, isolated yields were poor.

Scheme 1.37 Second generation chiral thiazolium salt utilised in the asymmetric benzoin condensation by Sheehan



While other thiazolium salt precatalysts were subsequently reported over the following 20 years, progress towards an asymmetric benzoin condensation was limited. In general, these catalysts either brought about moderate levels of enantioselectivity with exceptionally low yields or synthetically-useful yields with poor enantiomeric excesses, but could never marry the two together. Tagaki examined the catalytic ability of three carbenes derived from thiazolium salts possessing menthol-based chiral side groups in a micellar two-phase media.[157] The carbenes derived from **177** and **178** (Figure 1.13) were found to be highly active and enabled the authors to isolate benzoin in 78% and 82% yield respectively but with poor enantioselectivity. Conversely, the NHC derived from **179** was rather inactive but allowed isolation of benzoin in 35% *ee*. Zhao would later use Sheehan's precatalysts under the micellar conditions described by Tagaki but again could only obtain benzoin in 20-30% yield and up to 47% *ee*.[158] Prior to this, in 1993 López-Calahorra unveiled a bridged *bis*-thiazolium salt **180** which promoted the most enantioselective benzoin condensation reported at that point (87% *ee*), although yields were just 4%. Further investigation of the activity of these bridged thiazolylidenes by the same author was met with disappointment however, with benzoin formed in 12% yield and poor optical purities using precatalyst **181**.[159] More recently (although the field had by then moved away from the use of thiazolium ion-based chiral precatalysts) Benaglia

synthesised the C_2-symmetric *bis*-thiazolium salt **182** and found the derivative carbene to catalyse the reaction in a moderate yield with poor enantioselectivity.[160] In 1997 Leeper *et al.* introduced the concept of rigidity into the thiazolium core structure through the synthesis of bicyclic salts **183-185** and the polycyclic salt **186**.[161] Disappointingly, the enantioselective outcome of the benzoin condensation in the presence of these precatalysts offered no improvement on the literature benchmark. This was further confirmed by Rawal in 1998 when he designed bicyclic thiazolium salts (not shown) that produced benzoin with 30% optical purity.[162] Bach *et al*., in 2004, designed the axially chiral *N*-aryl thiazolium ion **187**. Although the derivative carbene was quite active, benzoin formed in 85% yield, the enantioselectivity of the reaction was again modest (40% *ee*).

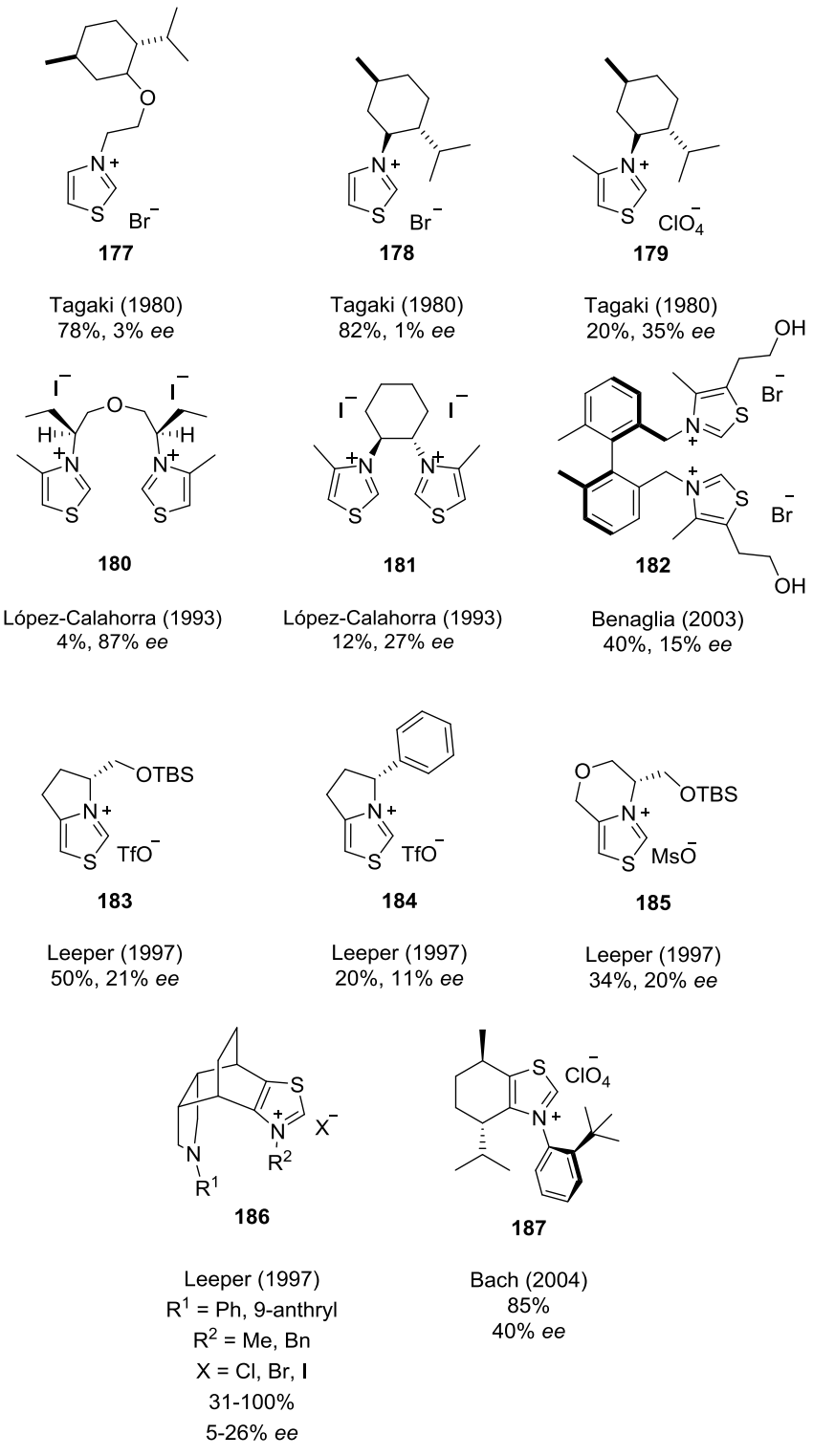


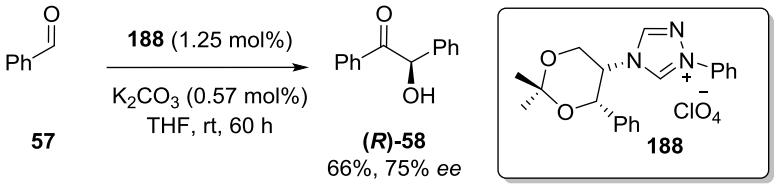
Figure 1.13 Chiral thiazolium salts employed in the asymmetric benzoin condensation

1.5.2 The advent of triazolium salts for the asymmetric benzoin condensation

1.5.2.1 Enders' pioneering studies

In 1996, Enders and Teles *et al.* examined the effect of the various heterocyclic carbenes upon the outcome of the formoin condensation.[164a] Their study produced results that correlated well with previous reports published by Castells and López-Calahorra[163] in that the use of thiazolium salt precatalysts lead to mixture of aldoses and ketoses rather than the homobenzoin condensation product, formoin. It was observed that use of imidazolium salts under identical reaction conditions produced a similar outcome. 1,2,4-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 catalytic loadings. The major product in these reactions was glycoaldehyde (formoin) and no dihydroxyacetone was detected. These findings prompted Enders to synthesise a variety of chiral triazolium salts for the asymmetric benzoin condensation, the most successful of which was the perchlorate salt **188** (Scheme 1.38). At a relatively low organocatalytic loading of 1.25 mol% and in the presence of K_2CO_3 as a base, Enders *et al.* could effect an asymmetric benzoin condensation with 66% yield and 75% *ee*.[165b]

Scheme 1.38 The first triazolylidene-catalysed asymmetric benzoin condensation



For the first time, Enders extended the scope of this developed methodology to include a range of substituted benzaldehydes, achieving their self-condensation in yields of 22-72% and although enantiomeric excesses as high as 86% for the (*R*)-enantiomer were obtained, the optical purity of the products tended to fluctuate depending on the identity of the aldehyde starting material. The proposed transition state model (Figure 1.14) for this process suggested that the phenyl ring of the dioxane moiety shields the *re*-face of the Breslow intermediate, thus directing attack upon the incoming second aldehyde to occur from the less hindered *si*-face. The second aldehyde itself approaches the Breslow

intermediate with its *si*-face, thus leading to formation of the (*R*)-enantiomer, in keeping with experimental observations.

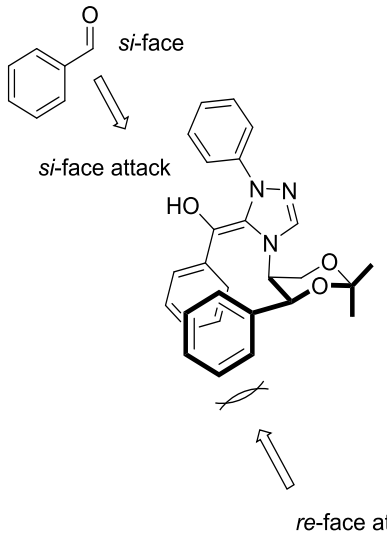
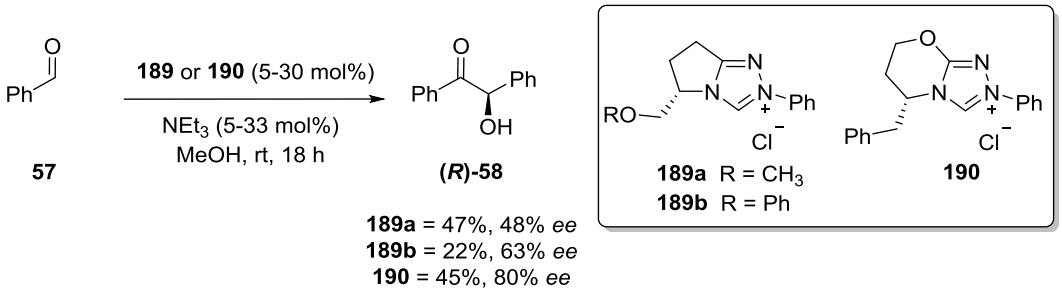


Figure 1.14 Transition state model explaining formation of (*R*)-enantiomer proposed by Enders

1.5.2.2 Rigid chirality: the fused ring system

Having previously synthesised bicyclic thiazolium salts for evaluation in the asymmetric benzoin condensation, Leeper then pioneered the development of triazolium salts of a similar structure.[161c] Although precatalysts **189a** and **189b** offered no remarkable improvement upon Leeper's previous results using thiazolium salts, precatalyst **190** enabled him to synthesise benzoin with an optical purity of 80%, the highest levels reported to that date using triazolium ion-based precatalysts (Scheme 1.39).

Scheme 1.39 Leeper's bicyclic triazolium precatalysts **189** and **190**

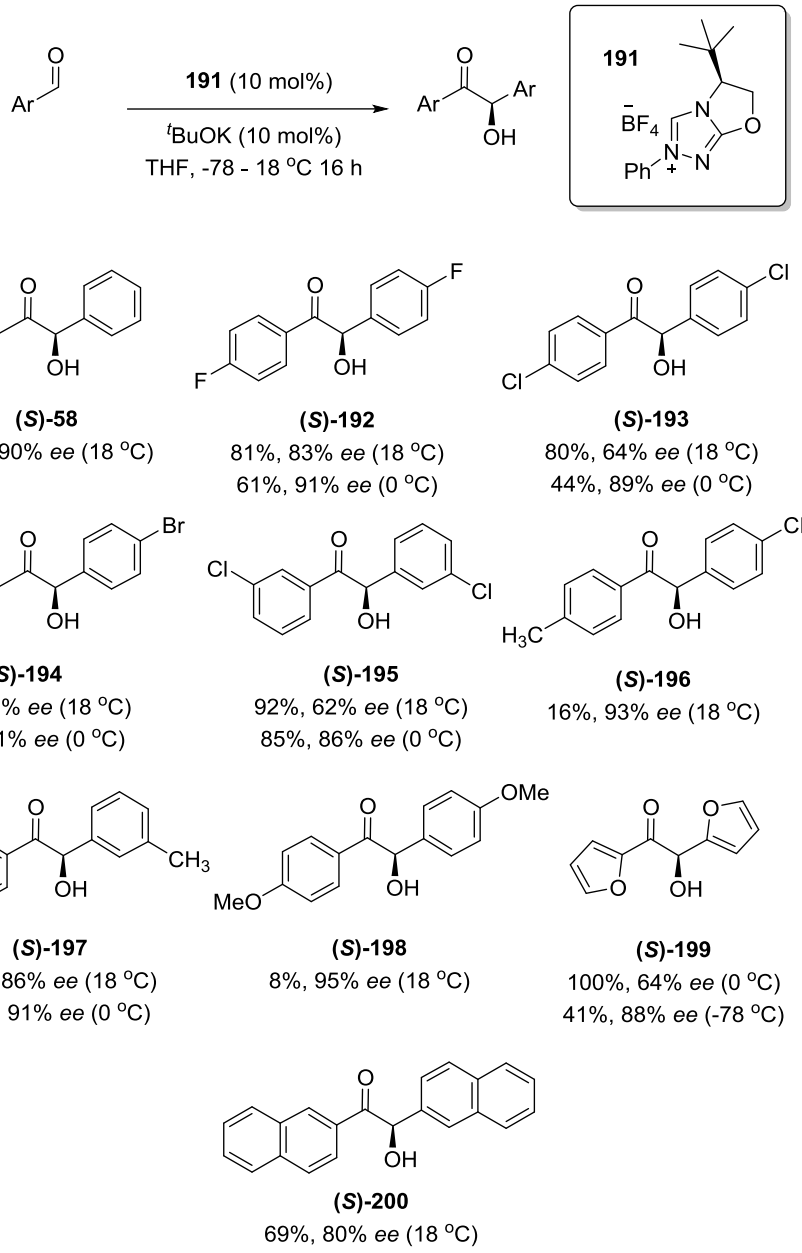


In view of this, the authors compared the performances of thiazolium and triazolium salts as precatalysts of the asymmetric benzoin condensation and concluded that the primary difference between the two derives from the fact that the *N*-phenyl group of the latter is much bulkier than a sulfur atom. This *N*-phenyl group is almost perpendicular to the plane of the heterocyclic ring in the Breslow intermediate, leading to steric interactions with the incoming benzaldehyde molecule. Another striking observation was that benzoin produced by triazolylidenes was of the opposite absolute configuration to that produced by thiazolylidenes. This was rationalised using molecular mechanic studies in which the carbonyl group of the incoming benzaldehyde is *anti* to the olefin of the Breslow intermediate. When the reaction is catalysed by a thiazolylidene, the phenyl ring of the benzaldehyde molecule has a slight preference for lying below the sulfur atom of the heterocycle. Conversely, in the case of triazolylidenes, this phenyl ring would have an unfavourable steric interaction with the *N*-phenyl ring of the catalyst, which occupies an equivalent orientation. Thus, the aldehyde proton occupies this position instead.

Inspired by these results, in 2002 Enders developed another chiral, bicyclic triazolium salt derived from (*S*)-*tert*-leucine (**191**, Scheme 1.39).[86] In its presence, (*S*)-benzoin was formed in 83% yield with an excellent enantioselectivity (90% *ee*). This result improved upon all previous studies of the asymmetric benzoin condensation, although again enantiomeric excesses tended to fluctuate when substituted benzaldehydes were employed (53-95% *ee*). In general, it was evident that the presence of electron-withdrawing substituents impacted negatively upon the obtained enantiomeric excess, while the reverse was true for substrates incorporating electron-donating substituents. Reducing the temperature to 0 ^{o}C allowed the authors to circumvent this issue to some degree, albeit at the expense of products yields.

Enders again proposed a transition state model to explain formation of (*S*)-benzoin by the novel catalyst (Figure 1.15). He postulated that the *si*-face of the Breslow intermediate would be sterically shielded by the *tert*-butyl group of the bicyclic catalyst. Therefore, attack upon the incoming second aldehyde would occur upon its *re*-face, giving rise to the (*S*)-enantiomer (**TS1**). Additionally, there may be a degree of pre-organisation about the transition state through π-stacking with the phenyl ring of the enolamine, as well as the hydroxy group *via* H-bridge activation of the aldehyde. The (*E*/*Z*) geometry of the Breslow intermediate has not yet been verified, however, and so the validity of the model

Scheme 1.39 Asymmetric benzoin condensation using Enders' (*S*)-*tert*-leucine derived triazolium salt



remains in question. Despite this, the corresponding (*E*)-isomer of the Breslow intermediate would favour a *si*-*si*-attack, resulting in the (*R*)-enantiomer, which is not observed experimentally. The authors attributed this to an unfavourable steric interaction between the phenyl substituent of the enolamine and that of the approaching aldehyde (**TS2**), which raises the energy of this transition state. Houk and Dudding later determined the most stable transition state to be **TS3** using computational methods in 2004.[165] In this transition state, no π-stacking occurs but the phenyl ring of the approaching aldehyde can reside in an open pocket of the catalyst with minimum steric

repulsion. In keeping with experimental data, this proposed transition state leads to the (*S*)-configuration.

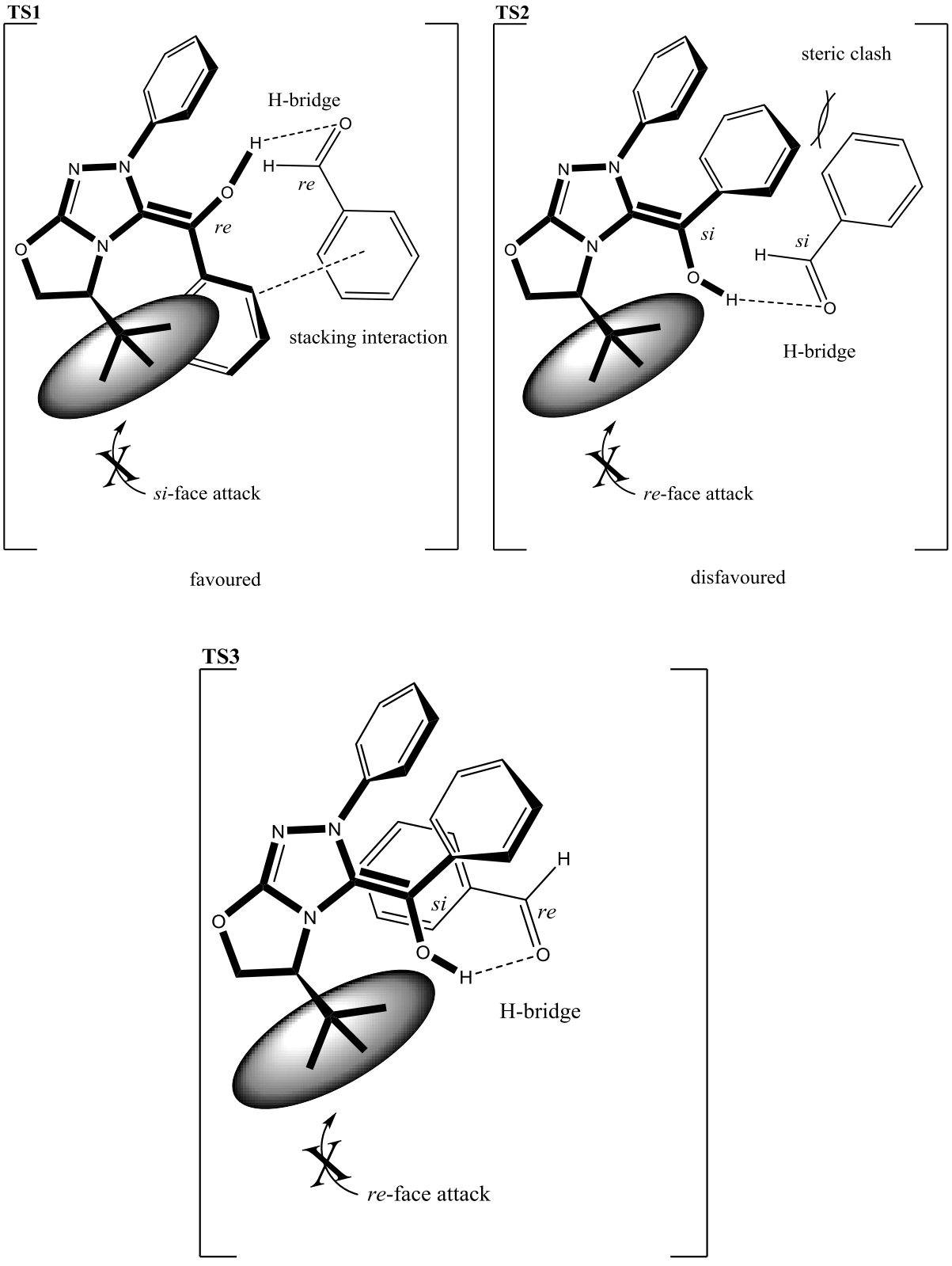
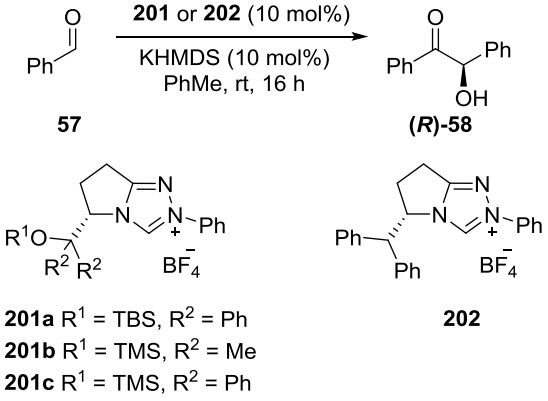


Figure 1.15 Possible transitions states proposed by Enders *et al.* and Houk *et al.*

1.5.2.3 Chiral triazolium precatalysts derived from pyroglutamic acid

Prompted by the use of bicyclic triazolium salts bearing a diphenyl(trialkylsilyloxy)-methyl substituent in the Staudinger reaction by Ye *et al.*,[166] Enders continued his pioneering studies of the asymmetric benzoin condensation in 2008 by disclosing the synthesis of chiral triazolium salts derived from (*S*)-pyroglutamic acid and their performance as precatalysts of the benzoin condensation.[167] Salts **201** and **202**, in the presence of KHMDS in toluene, produced benzoin with excellent optical purity under mild conditions (Scheme 1.40), with **201c** giving rise to the most enantioselective reaction (66% isolated yield, 95% *ee*). The influence of the silyloxy group in the observed enantioinduction was highlighted when, under the same conditions, precatalyst **202** enabled formation of benzoin in 90% yield but with just 5% *ee*.

Scheme 1.40 Asymmetric benzoin condensation catalysed by chiral triazolium salts derived from (*S*)-pyroglutamic acid



The scope of the reaction with respect to the aldehyde again proved to be quite broad and in keeping with observed trends from previous studies, in which activated aldehydes (*i.e.* possessing electronegative ring substituents) underwent condensation at a rate considerably faster than their deactivated analogues. However, this was off-set by lower enantiomeric excesses, while the reverse was found to be true for deactivated aromatic aldehydes.

In 2008, four years after Castells and Benagalia disclosed studies examining the catalytic capabilities of *bis*-thiazolylidenes in the asymmetric benzoin condensation,[159,160] You *et al*. reasoned that *bis*-triazolylidenes would give rise to an improved catalytic

performance in the asymmetric benzoin condensation. Through molecular modelling investigations, the authors determined that the greater conjugation of such species relative to *mono*-triazolylidenes would correlate to a greater stability, thus a higher concentration of the active catalytic species in solution and an enhancement of catalyst turnover and efficiency.[168] Furthermore, computational calculations allowed the authors to discern that two triazolylidene rings tethered *via* a phenyl ring would exist in a perfectly co-planar geometry and perhaps provide a strict chiral catalytic environment to mediate the reaction. Their hypotheses were proved correct when the synthesis and use of a chiral *bis*-triazolium salt under basic conditions resulted in 95% yield of benzoin with 95% enantiopurity.

You's work represented the most enantioselective literature example published at the time. All examples of thiazolium and triazolium ion-based precatalysts up until this point sought to achieve enantioinduction through steric hinderance. The plane of the carbene catalyst can be viewed in four quadrants, three of which were selectively blocked off using rigid chiral groups (Figure 1.16[259]). Triazolium ion-based precatalysts are distinctly advantageous in this regard as functionality can be introduced on either side of the catalytic centre (**203**). Conversely, thiazolium salts possess a divalent sulfur atom and so the extent of structural diversity allowed within their structure is more limited (**204**). Furthermore, the additional scope for substitution in triazolium salts allows greater modulation of the electronic character of the carbene centre.

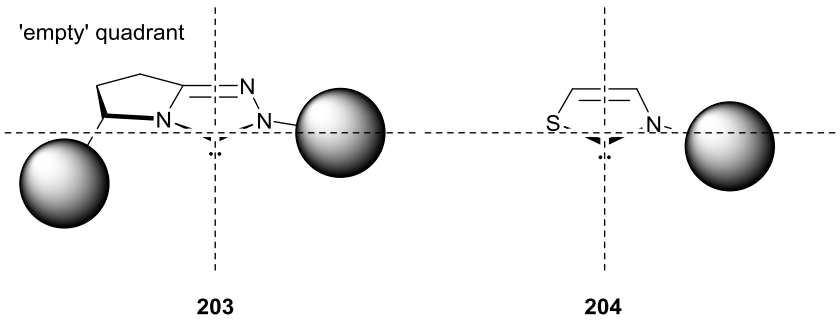


Figure 1.16 Steric-based rationale for the design of chiral triazolium precatalysts

However, by 2008, Connon and co-workers extended the design of triazolium salts beyond monofunctionality with the incorporation of hydrogen-bonding moieties into the chiral moiety. They envisaged that such bifunctional catalysts could activate one or both aldehydes towards attack (by either the carbene or the Breslow intermediate) while

maintaining the chiral environment, thus enabling both high product yields and enantiomeric excesses to be obtained concurrently. The importance of hydrogen-bonding interactions was emphasised through the synthesis of the novel amino indanol-derived triazolium salts **205a** and **205b**.[169] Under optimised conditions, **205a** could be employed to generate benzoin in 62% *ee* (Figure 1.17).

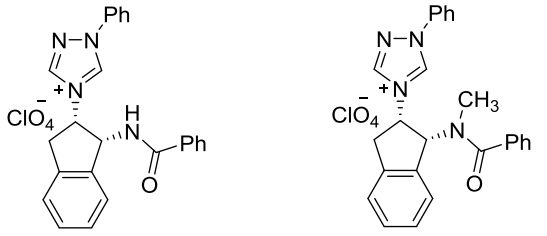
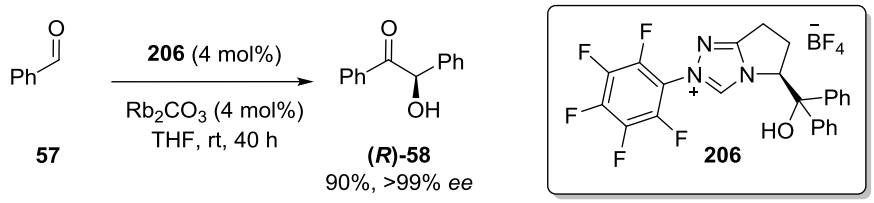


Figure 1.17 Amino indanol-derived triazolium precatalysts designed by Connon *et al.* as precatalysts in the asymmetric benzoin condensation

Conversely, precatalyst **205b** (which is incapable of participating in hydrogen-bonding interactions with aldehydes) yielded benzoin with a dramatically reduced optical purity of 13% *ee*. These results confirmed that the concept of hydrogen-bonding in asymmetric induction of the benzoin condensation was significant, despite the optical purity of the product being lower than the benchmark established by You *et al.*

Given the fact that the triazolium ring of **205a** is not fused and thereby allows free rotation of the chiral moiety, Connon *et al.* then redesigned these precatalysts to include successful features from previous carbene catalysts, notably the rigid bicyclic structure utilised by Enders. In a subsequent publication,[171] the authors disclosed the design of the *N*-pentafluorophenyl-substituted precatalyst **206** which was similarly derived from (*S*)-pyroglutamic acid. In the presence of the heterogenous base rubidium carbonate, 4 mol% of **206** could be utilised to produce benzoin in 90% yield with complete enantioselectivity (>99% *ee*, Scheme 1.41). The pentafluorophenyl ring was deemed crucial in achieving these yields as it renders the triazolium ring more electron-deficient, thus facilitating deprotonation of the triazolium ring by the base and ensuring sufficient levels of carbene present in solution. This effect was emphasised by the fact that the analogous *N*-phenyl precatalyst generated benzoin with equal levels of enantioselectivity, but in just 29% yield.

Scheme 1.41 Asymmetric benzoin condensation catalysed by Connon's bifunctional triazolylidene catalyst



Despite Connon *et al*. solving the long-standing challenge of an enantioselective NHC-catalysed benzoin condensation, a selected few efforts have continued to design and develop new heteroazolium ion-based precatalysts. Waser[171] maintained the presence of hydrogen-bonding moieties, introducing urea and thiourea groups into the triazolium structure, and produced benzoin with excellent optical purity (90% *ee*) but with much lower yields, while Rafinski *et al.* synthesised camphor-derived triazolium salts that could mediate the reaction in excellent yields but with moderate enantioselectivity in 2014.[172]

1.5.3 The asymmetric intermolecular crossed benzoin condensation

1.5.3.1 The NHC-catalysed asymmetric intermolecular crossed benzoin condensation

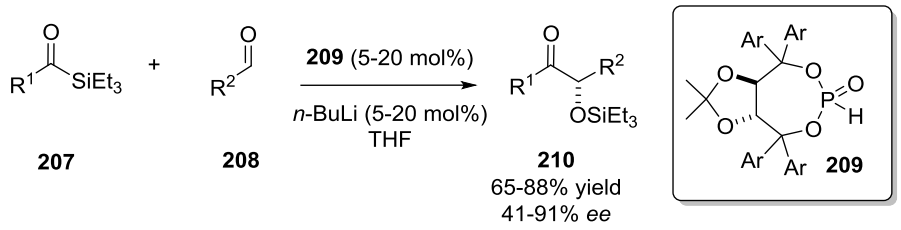
Given the dearth of studies relating to the achiral NHC-mediated intermolecular crossed benzoin condensation (see Section 1.4), it is no surprise that the literature is devoid of any studies seeking to address the asymmetric formation of these cross-benzoins. Thus, development of such a methodology remains a key target for scientists invested in this field of carbene-based organocatalysis. A suitable catalyst would be required to not only differentiate between two aromatic aldehydes in some manner but also to induce face-selective approach of the second aldehyde coupling partner upon the Breslow intermediate. Several examples do exist of NHC-catalysed enantioselective synthesis of cross-benzoin derivatives through intramolecular condensations of ketoaldehydes where both the ketone and aldehyde component are α to an aromatic ring.[121,126,127,173,174] While NHC organocatalysis has yet to provide a solution to this problem in an intermolecular

context, other research efforts have disclosed alternative methods to achieve enantioselective formation of cross-benzoin derivatives. These are discussed below.

1.5.3.2 Alternative approaches for enantioselective intermolecular synthesis of cross-benzoin derivatives

Figure 1.12 (Section 1.4.2) previously details selected examples of cross-benzoins synthesised by Müller and Pohl using BAL or BFD and to date this report remains the most successful and efficient method of effecting a direct intermolecular crossed benzoin condensation. However, using a chiral metallophoshite catalyst, Johnson *et al.*[175] developed the first non-enzymatic enantioselective version of the reaction with the synthesis of cross-silyl benzoin adducts (Scheme 1.42). The reaction scope allowed alkyl, aryl and heterocyclic substrates to be cross-coupled with good to excellent yields and good to excellent enantiomeric excesses.

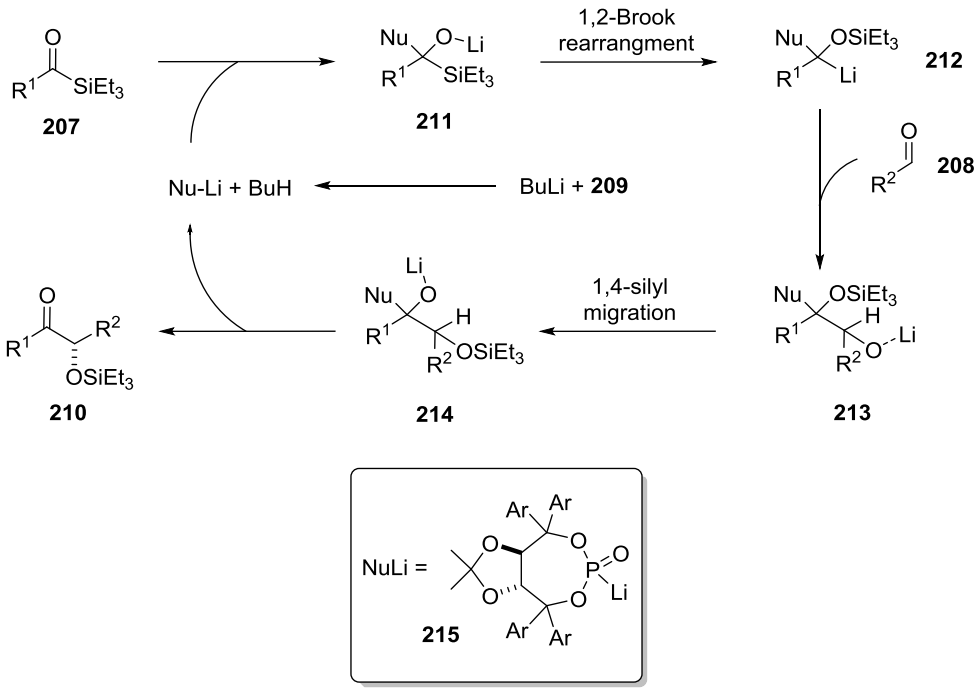
Scheme 1.42 Enantioselective cross-silyl benzoin reaction conducted by Johnson *et al.*



207 **208** **210**
65-88% yield
41-91% *ee*

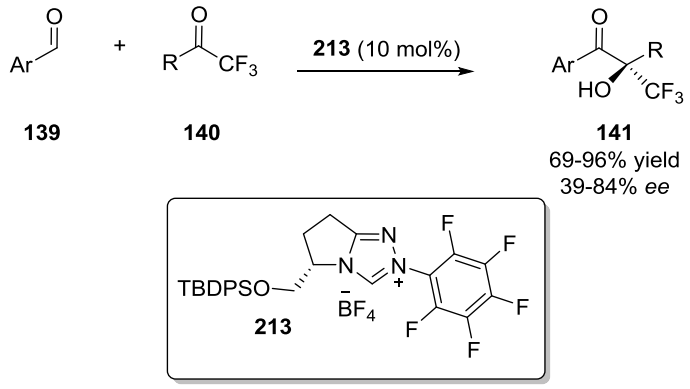
The proposed mechanism (Scheme 1.43) behind the reaction revolves around initial deprotonation of **209** by *n*-BuLi forming **215** followed by attack upon **207**, generating intermediate **211**. A subsequent 1,2-Brook rearrangement forms the *O*-silylated acyl anion equivalent **212** which undergoes nucleophilic addition to **208** and allows a 1,4-silyl migration to yield **214** *via* **213**. Collapse of the tetrahedral intermediate regenerates the catalyst and eliminates the optically active cross-silyl benzoin product **210**.

Scheme 1.43 Proposed mechanism for the enantioselective cross-silyl benzoin reaction



Following his disclosure of the NHC-mediated cross-condensation of aromatic aldehydes and trifluoromethyl ketones (see Scheme 1.31),[143] Enders also later developed an enantioselective version of the reaction mediated by a triazolium salt bearing a chiral *O*-silyl-substituted chiral arm.[144] Although the enantioselectivity of reactions employing these precatalysts was modest (up to 83% *ee*), recrystallisation allowed the α-hydroxy-α-trifluoromethyl ketones to be further isolated in >99% *ee* (Scheme 1.44).

Scheme 1.44 Enders' enantioselective cross-condensation between aromatic aldehydes and trifluoromethyl ketones



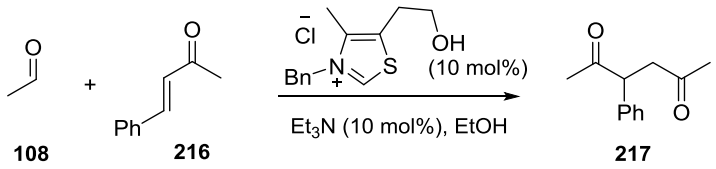
1.6 Alternative fates of the Breslow intermediate: variants on the benzoin condensation

While efforts have continued to extend the scope of the benzoin condensation and develop a truly chemoselective method for cross-coupling two different aldehydes, the nucleophilic character of the Breslow intermediate can also be exploited in a variety of alternative reaction outcomes depending on either the reaction partner employed or the structure of the starting aldehyde. In contrast to the benzoin condensation, these alternative pathways are relatively recent developments. They are introduced briefly below.

1.6.1 The Stetter reaction: overview

In 1973, Stetter disclosed a novel means for accessing synthetically useful 1,4-dicarbonyl compounds **215** and related derivatives through the coupling of an aldehyde and Michael acceptor in an cyanide-mediated reaction.[176] Three years later he further demonstrated how NHCs could be employed to catalyse the same reaction between acetaldehyde **108** and the Michael acceptor **216** (Scheme 1.45).[177] Using this methodology enabled Stetter to report the synthesis of a wide range of 1,4-dicarbonyl compounds.[178,179] The formation of such adducts means it has become a synthetically valuable tool; corresponding 1,3- and 1,5-dicarbonyl compounds are easily accessed through a Claisen condensation or Michael addition respectively while 1,4-analogues pose a more difficult challenge due to the fact that they require generation of an acyl anion equivalent.

Scheme 1.45 The NHC-catalysed Stetter reaction

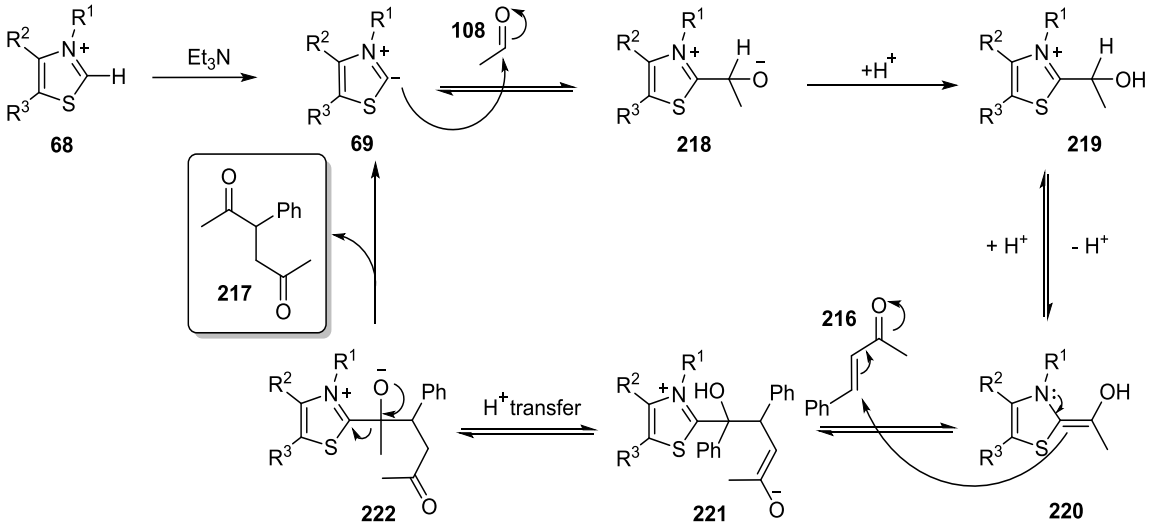


108 216 217

As with the benzoin condensation, the Stetter reaction is an example of *umpolung* chemistry and indeed the two are closely related in terms of mechanism. The classic Stetter reaction proceeds through initial deprotonation of the thiazolium salt by TEA (Scheme 1.46) to generate the NHC catalyst *in situ*. Addition of this carbene to **108**

initiates subsequent formation of the Breslow intermediate **220** (as previously detailed), upon which a choice of reaction pathways then presents itself – 1,2-nucleophilic addition (*i.e.* the benzoin condensation) or 1,4-nucleophilic addition to the Michael acceptor. Competition arises between these two pathways, with the benzoin condensation being the faster of the two. The 1,4-dicarbonyl product of the Stetter reaction represents a thermodynamic 'sink', however, with proton transfer from the tetrahedral intermediate formed upon nucleophilic attack of the carbene on the aldehyde being an irreversible step under the conditions promoting the Stetter reaction.[265] In contrast, the benzoin condensation is an entirely reversible process and so its formation does not interfere with the Stetter pathway. Thus, 1,4-addition of the Breslow intermediate generates enolate **221** which, following proton exchange and keto-enol tautomerisation, forms tetrahedral intermediate **222** which collapses to release the Stetter product **217** and allow the NHC to re-enter the catalytic cycle.

Scheme 1.46 Mechanism of the thiazolylidene-catalysed Stetter reaction



1.6.1.1 The intermolecular Stetter reaction

The scope of the Stetter reaction allows both intermolecular and intramolecular additions to be achieved. Stetter, having first reported the transformation, was its most prominent early pioneer and investigated a wide range of substrates and thiazolium salt precatalysts for the reaction.[180] The archetypal Stetter reaction is that between an aldehyde and an α,β-unsaturated carbonyl compound and generally proceeds efficiently in the presence of

aliphatic, aromatic and heterocyclic aldehydes with 1,4-diketones, 1,4-ketocarboxylic esters and 4-ketocarbonitriles all produced in good to excellent yields (Figure 1.18).[180]

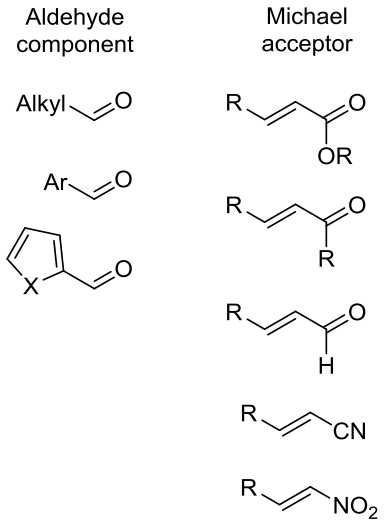
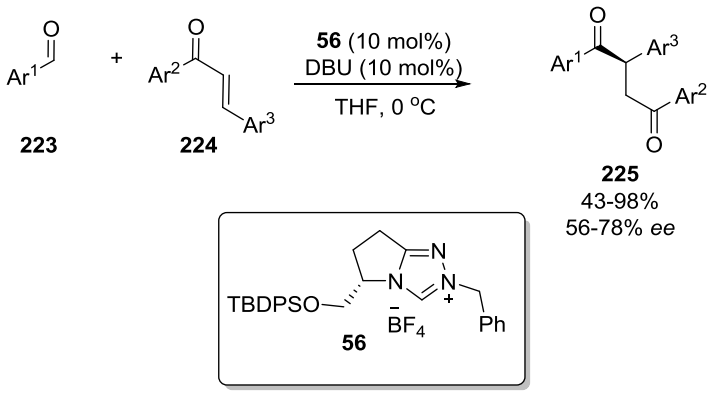


Figure 1.18 Scope of the Stetter reaction

1.6.1.2 Chiral NHC catalysts for the intermolecular asymmetric Stetter reaction

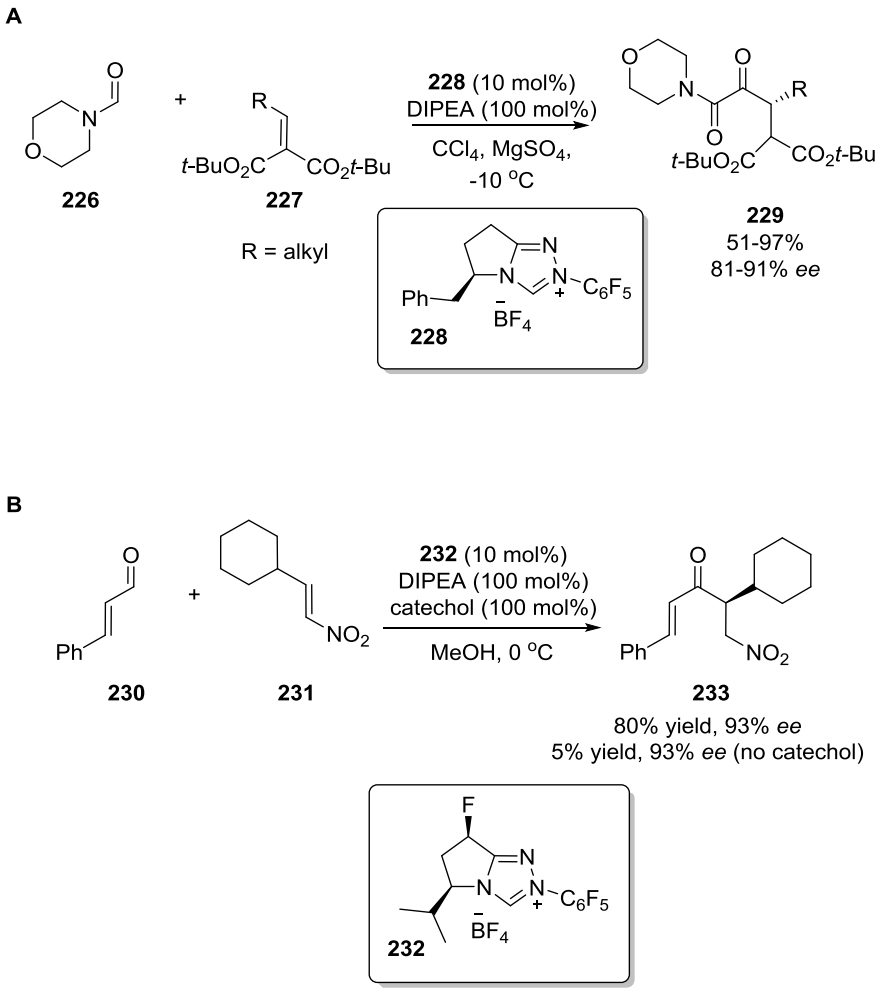
The most interesting studies on the Stetter reaction arguably focus upon enantioselective formation of the resulting 1,4-dicarbonyl compounds. Interestingly, it was not until 2008 that the first example of an enantioselective variant of the reaction was published by Enders,[181] although the same author had previously reported a single example of an intermolecular Stetter reaction catalysed by a thiazolium-derived carbene with moderate yield and enantioselectivity.[182] Using catalytic loadings of novel chiral trizolium salt **56** in the presence of DBU, Enders could effect the addition of aromatic aldehydes **223** to chalcones **224** in moderate to excellent yields and with moderate enantioselectivity (Scheme 1.47).

Scheme 1.47 Enantioselective Stetter reaction catalysed by a chiral triazolium salt disclosed by Enders *et al*. in 2008



Following Enders' work, Rovis succeeded in the development of numerous NHC catalytic systems for the promotion of highly enantioselective Stetter reactions utilising a wide array of substrates.[183] Chief among these has been the NHC-catalysed addition of glyoxamide **226** to activated Michael acceptors **227** and addition of heteroaromatic aldehydes and enals (**230**) to aliphatic nitroolefins **231** (Scheme 1.48, **A** and **B**). The dramatic increase in yield due to the stoichiometric addition of catechol in this latter example was attributed to the fact that catechol facilitates the rate-limiting proton transfer step leading to the formation of the Breslow intermediate. Rovis has continued to pioneer many developments in this area of NHC organocatalysis, extending the scope of the reaction to enable a one-pot synthesis of enantiopure lactams[184] and even finding application in the total synthesis of natural products.[185] However, relative to the extensive volume of studies devoted to the asymmetric benzoin condensation following Enders' seminal work, investigations into the NHC-catalysed asymmetric intermolecular Stetter reaction are comparatively rare.[186] Indeed, it is a fair comment to say that the asymmetric variants of the intramolecular reaction have received more attention and have met with far more success.[187] This is primarily due to the fact that reactivity and chemoselectivity problems are significantly reduced in such cases. Furthermore, it has been reported that certain triazolylidene carbene catalysts can form stable adducts with some Michael acceptors, leading to their unsuitability in catalysis.[188]

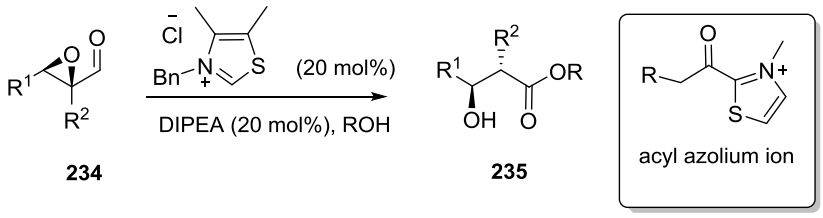
Scheme 1.48 NHC-catalysed symmetric intermolecular Stetter reactions reported by Rovis *et al.*



1.6.2 Internal redox chemistry

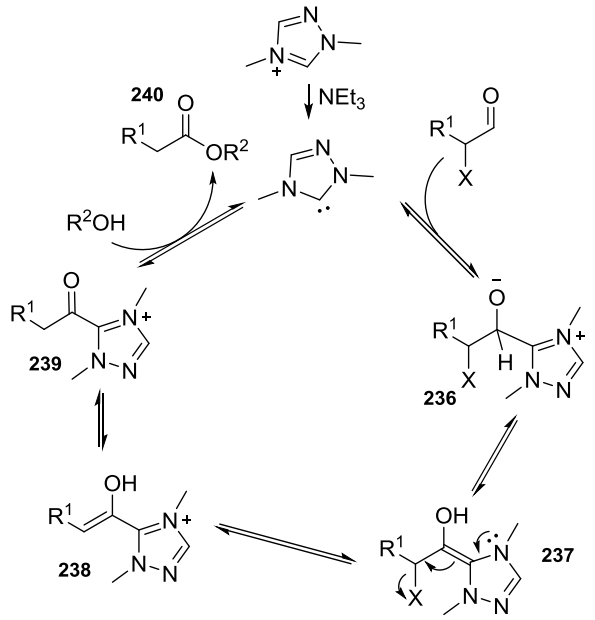
The presence of a suitable group in the α-position of an aldehyde can induce a change in the characteristics of the Breslow intermediate. In 2004, Bode *et al.*[189] exploited this through their synthesis of β-hydroxyesters of general type **235** from epoxyaldehydes (**234**) using a thiazolium salt precatalyst (Scheme 1.49). This internal redox reaction revolves around the NHC-catalysed generation of an acyl azolium ion. The redox aspect of the reaction derives from the fact that the epoxide is reduced to an alcohol while the aldehyde is oxidised to an ester and so the reaction is redox-neutral. In the same year, Rovis unveiled a similar reaction that depended upon the presence of a halogen atom in the α-position.[190]

Scheme 1.49 NHC-catalysed β-hydroxyester synthesis



The proposed catalytic cycle (Scheme 1.50) illustrates how the nitrogen lone pair can induce the breaking of the C-X bond within the Breslow intermediate **237**, with subsequent tautomerisation from the resulting enol **238** to the acyl azolium ion **239**, an excellent electrophile that can undergo reaction with (for instance) an alcohol to eliminate the triazolylidene carbene and produce the ester product **240**.

Scheme 1.50 NHC-catalysed internal redox reaction mechanism



1.6.3 'Homoenolate' Chemistry

A homoenolate is any reactive intermediate that is homologous to an enolate and specifically can refer to a species of general type **241** possessing an anionic or nucleophilic carbon β to a carbonyl group (Figure 1.19). Alternatively, it may be viewed as a cyclopropyl alkoxide of general type **242**.[191]

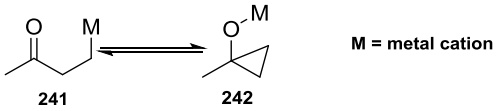
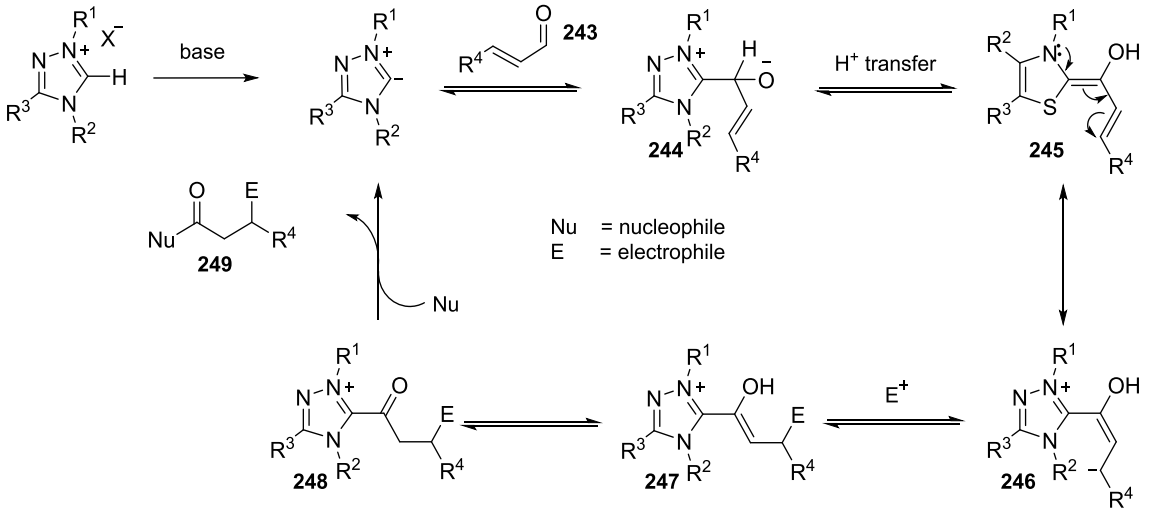


Figure 1.19 A homoenolate species in equilibrium with a cyclopropyl alkoxide

Bode[192] and Glorius[193] pioneered the development of NHC-derived homoenolates in 2004 when they independently reported that, in a manner similar to the generation of the Breslow intermediate from an aldehyde and an NHC, an 'extended' Breslow intermediate can be formed when an α,β-unsaturated aldehyde **243** is employed instead (Scheme 1.51). The extended conjugation of **245** renders it nucleophilic at the β-carbon through resonance form **246**; and hence it is a homoenolate. The steric bulk of the aldehyde means that reaction at the α-carbon is disfavoured and so **245** may undergo nucleophilic attack upon an electrophile to generate enol **247**. Subsequent tautomerisation to the carboxylate equivalent **248** provides a means of carbene elimination in the presence of a nucleophile to yield the product **249** and allows the triazolylidene carbene to re-enter the catalytic cycle.

Scheme 1.51 Mechanism of the homoenolate reaction



A wide range of electrophiles and nucleophiles are compatible with the process, such as Michael acceptors[194], alcohols[195] and single molecules containing both electrophilic and nucleophilic components.[192] Bode's pioneering studies demonstrated that using substrates fulfilling the latter criteria, ring-closures could be effected with yields in excess of 90%.

1.7 NHC-catalysed oxidative aldehyde transformations

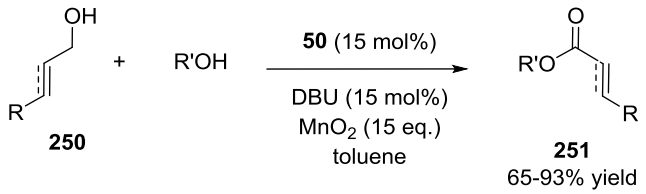
1.7.1 Aerobic oxidation of aldehydes in NHC-catalysed esterifications

The importance of the ester functional group throughout organic synthesis and a range of other disciplines is beyond quantification.[196] The most common means of ester formation is through stoichiometric activation of a carboxylic acid as an acyl halide, anhydride or activated ester with subsequent acyl transfer to a nucleophilic alcohol. Recently, interest has grown rapidly in the development of an alternative oxidative esterification of aldehydes using NHCs.

1.7.1.1 Aldehyde esterifications in the presence of an external oxidant

The first reported example of an NHC-catalysed esterification of an aldehyde in the presence of an external oxidant is Scheidt *et al.* in 2007.[197] In the presence of the dimethyl-substituted triazolium salt **50**, DBU and a large excess of MnO_2, a proposed tandem oxidation of allylic, propargylic and benzylic alcohols (**250**) to their corresponding esters (**251**) was achieved in up to 93% isolated yield (Scheme 1.52).

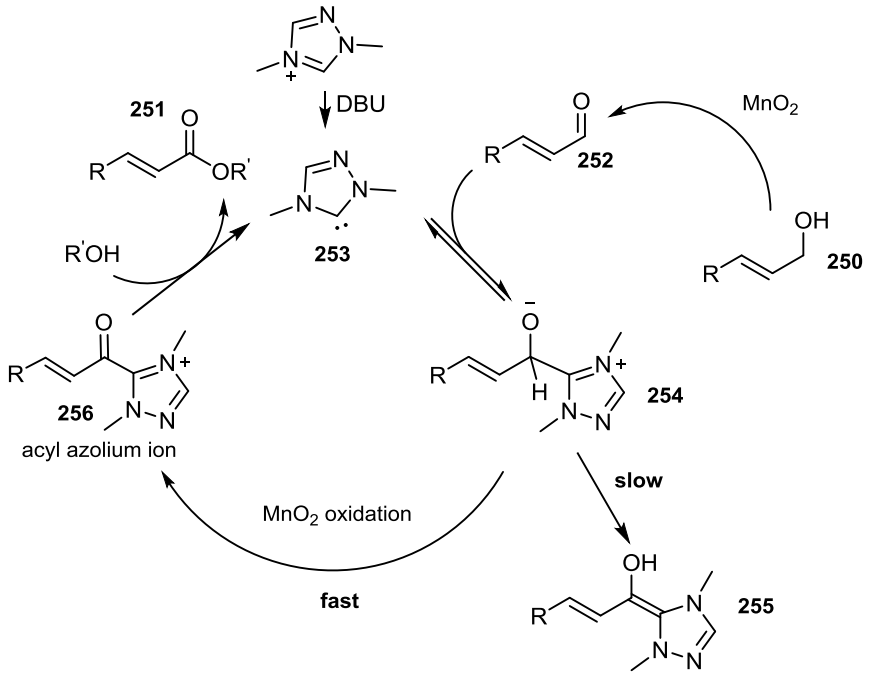
Scheme 1.52 First reported NHC-catalysed aldehyde esterification by Scheidt *et al*.



Scheidt's proposed mechanism (Scheme 1.53) involves initial oxidation of the alcohol (**250**) by MnO_2 *in situ* to generate aldehyde **252**. Concurrently, deprotonation of **50** by DBU produces the active carbene **253** which subsequently attacks **252** to yield the tetrahedral intermediate **254**. At this point, relatively slow formation of the Breslow intermediate **255** is suppressed by rapid oxidation of **254** to the acyl azolium ion **256**. Here we see the true synthetic utility of Scheidt's methodology – the NHC serves to activate the aldehyde through generation of an extremely reactive electrophilic intermediate, allowing access to products otherwise inaccessible through direct means

using an aldehyde substrate. Rapid acylation of the alcohol R'OH by the activated ester then completes the oxidation to **251**.

Scheme 1.53 Proposed mechanistic pathway for Scheidt's tandem oxidation process

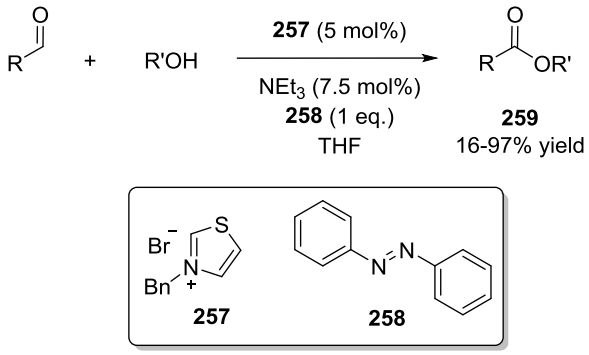


While the scope of Scheidt's methodology was restricted to allylic, propargylic and benzylic alcohols, the process accommodated a more extensive range of nucleophilic alcohol partners. Further employment of a chiral triazolium precatalyst also allowed the desymmetrisation of a *meso* 1,2-diol when it was utilised as the nucleophilic component.

Scheidt would later disclose the findings of a further study in 2008 in which the NHC-catalysed oxidation of unactivated aldehydes to esters under the same conditions was reported.[198] Again, the scope of the reaction was broad and epimerisable aldehydes could be transformed without loss of stereochemical information. However, prior to this, Connon *et al.* had developed the first synthetically useful protocol of broad scope for the oxidative esterification of aldehydes with equimolar amounts of primary and secondary alcohols through NHC catalysis.[199] Using a thiazolium salt precatalyst (**257**, Scheme 1.54) and the external oxidant azobenzene (**258**), a range of aromatic and unsaturated aldehydes could be converted to their corresponding esters; with the reaction displaying a high tolerance for a variety of different alcohol components. Interestingly, *ortho*-substituted benzaldehydes furnished the highest yields (2-tolualdehyde providing the

corresponding methyl ester in 97% isolated yield), for reasons that were unclear. Conversely, use of aliphatic aldehydes proved problematic, giving rise to yields as low as 16% on occasion. Lack of control over the aldol side reaction was likely to be a significant contributing factor in this regard.

Scheme 1.54 Connon *et al*'s NHC-catalysed aldehyde esterification



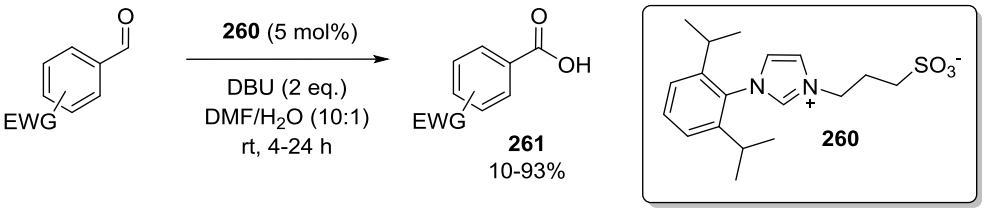
Since the publication of these studies, numerous investigations have been carried out to explore the depth of this reaction with regard to all components. A variety of external oxidants (in addition to those above) have been shown to efficiently oxidise the Breslow intermediate to the key acyl azolium intermediate, including nitrobenzene,[200] TEMPO,[201] diphenoquinone[202] and phenazine.[203] Boydston *et al*. have also used an anodic electrochemical oxidation to replace the need for a stoichiometric external oxidant.[204] Furthermore, derivatisation of aldehydes to thioesters and carboxylic acids through use of thiols and water respectively as the nucleophile has also been reported,[203,205] while Zhao has astutely demonstrated how the technology can be applied to a kinetic resolution of tertiary alcohols, providing access to highly enantiopure 3-hydroxy-3-substituted oxindoles.[206]

1.7.1.2 Aldehyde esterifications using either O_2 or air as the oxidant

By comparison, studies pertaining to the analogous aldehyde oxidations in the absence of external oxidants are far less common. As a general comment, many systems operating without the need for added stoichiometric oxidants depend upon a cooperative metal/NHC catalysis that employs molecular oxygen as the terminal oxidant to re-oxidise the metal centre. For example, in 2010 Gois *et al.* reported an oxidative aldehyde esterification utilising boronic acids in an NHC-iron complex-catalysed pathway.[207a]

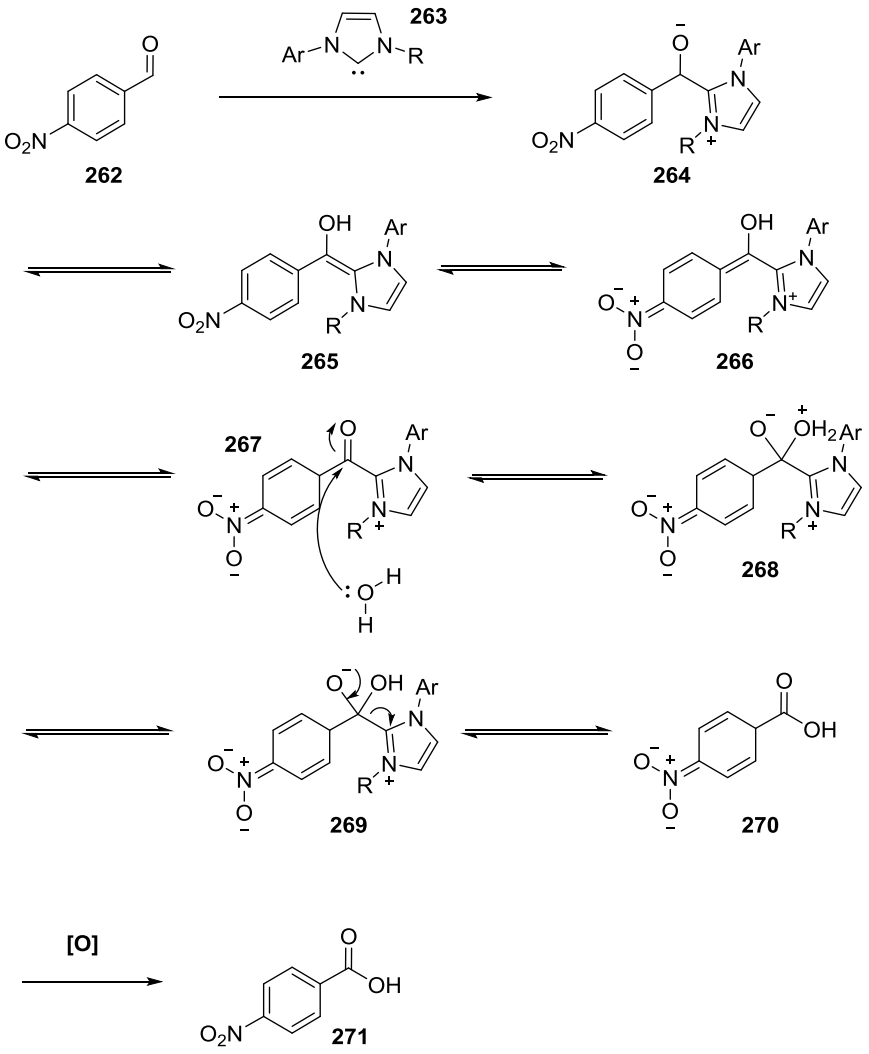
Three years later, in 2013, Studer *et al.* disclosed a similar transformation, esterifying various aromatic and heteroaromatic aldehydes in the presence of alcohols *via* a methodology employing co-operative NHC and ruthenium redox catalysis.[207b] The $Ru(bpz)_3(PF_6)_2$ complex was shown to be compatible with free NHCs and, using air as the terminal oxidant for regeneration of the ruthenium co-catalyst, a range of aldehydes could be esterified in good to excellent yields. Furthermore, in the absence of the ruthenium co-catalyst and alcohol, the corresponding acids could also be formed in equivalent yields. Further examples of such systems operating with use of a co-catalyst include the employment of a flavin derivative as reported by Yashima *et al.*[208] However, methodologies operating strictly under aerobic oxidation conditions are scarce and are commonly reliant upon the use of specific starting substrates. Yoshida *et al*. were the first to detail the use of the novel sulfoxyalkyl-substituted NHC **260** in the catalytic aerobic oxidation of aromatic aldehydes (Scheme 1.55). Various aromatic aldehydes bearing electron-withdrawing substituents were converted to the corresponding carboxylic acids (**261**).

Scheme 1.55 Aerobic aldeyde carboxylation using an imidiazolium precatalyst



The proposed mechanism of the transformation remains open to debate however; Yoshida posited the mechanism detailed in Scheme 1.56 which is reliant upon the presence of anion-stabilising groups such as the nitro moiety. Deprotonation of **260** generates the active carbene **263** which undergoes the usual addition to the aldehyde and forms the Breslow intermediate **265** *in situ*. Yoshida suggested that an equilibrium exists between resonance form **266** and the dearomatised acyl imidazolium intermediate **267** (which is facilitated by the electron-withdrawing ability of the nitro group). Nucleophilic attack of water upon this acyl azolium affords the carboxylic acid **270** and regenerates the carbene catalyst. Re-aromatisation of **270** with dissolved oxygen yields the final product **271**.

Scheme 1.56 Yoshida's proposed mechanism for his NHC-catalysed aerobic carboxylation



While this mechanism is viable in the above case of 4-nitrobenzaldehyde, Yoshida offered no suggestion as to whether a similar pathway is in operation when the identity of the aromatic aldehyde is changed. For example, 3-nitrobenzaldehyde would no longer be able to form **269** and so the mechanistic rationale falters. A similar situation arises for 4-fluoro and 4-chlorobenzaldehyde, which both undergo oxidation under the reaction conditions with 92% and 55% yield respectively.

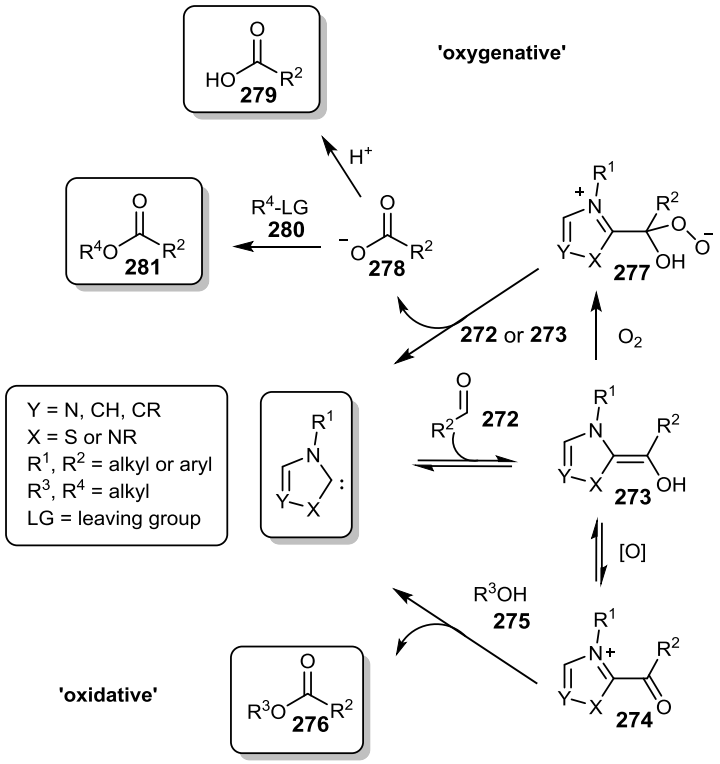
Following this publication, further examples of external oxidant-free systems for NHC-catalysed oxidations are rare. Two are worth consideration however, both proposing a mechanistic pathway relevant to the work detailed in this thesis. In 2011, Liu *et al.*[209] successfully esterified α,β-unsaturated aldehydes using a bicyclic imidazolium salt

precatalyst using either air or MnO_2 as an oxidant. Isotope labelling studies enabled them to propose what is now termed an oxygenative esterification pathway for formation of the product. Two years later, in 2013, the oxidative coupling of aldehydes with carbodiimides to produce *N*-acylureas using NHCs was published by Ukaji.[210] Again, although no isotope labelling was carried out, the authors proposed a mechanism for the reaction that was heavily reliant upon the oxygenative pathways previously proposed by Liu.

1.7.2 Proposed oxidative/oxygenative pathways for the aerobic oxidation of aldehydes through NHC catalysis

Two primary pathways for the direct conversion of an aldehyde to an ester are proposed in the literature and can be classified as being either 'oxidative' or 'oxygenative' (Scheme 1.57).[211] Oxidative transformations are purported to involve the addition of the carbene catalyst to the aldehyde **272** to form the Breslow intermediate **273**, which is then converted by an external oxidant to an electrophilic acyl azolium ion **274**. This species can then transfer the acyl group to an alcohol **275** to afford the ester product **276** whilst releasing the carbene to re-enter the catalytic cycle. In the presence of molecular oxygen, rather than an added stoichiometric oxidant, it has been proposed that a separate oxidative fate for the Breslow intermediate involving addition of O_2 to **273** to afford the internal peroxy Zwitterion **277**[210] is possible; which then reacts with either the substrate aldehyde **272** (*via* peroxyacid intermediates) or another molecule of **273** to generate a carboxylate ion **278**,[209] which can either be trapped by a proton or an alkyl halide[209,210] **280** to afford either the acid **279** or ester **281** respectively.

Scheme 1.57 NHC-mediated aldehyde esterifications using either an external oxidant or molecular oxygen: current mechanistic rationales.

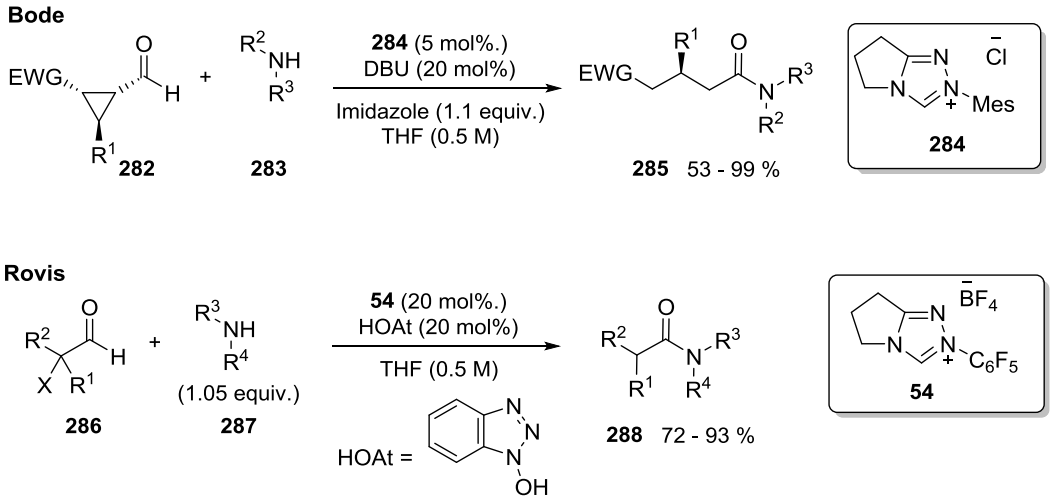


1.7.3 Aerobic oxidation of aldehydes in NHC-catalysed amidations

Considering the significance of the amide functional group both in both natural and synthetic molecules, there is a distinct dearth of reports in the literature in relation to direct amidation of aldehydes using NHCs. The principal methodologies reported for effecting such transformations rely primarily upon the use of transition metal catalysis[212] and an external oxidant. NHC-catalysed amidations again depend upon *in situ* generation of the aforementioned acyl azolium ion from the Breslow intermediate, either through an internal redox pathway or addition of an external oxidant, with subsequent nucleophilic attack from an amine. Bode[213] and Rovis[214] again pioneered early progress in this area, both employing starting aldehyde substrates capable of undergoing internal redox reactions (Scheme 1.58). Both methodologies employ the use of a co-catalyst to initiate a second catalytic cycle *in situ* to generate an acyl imidazole and an activated carboxylate respectively from the acyl azolium intermediate, which then undergo attack from the amine to yield the amide product. Alternative NHC-catalysed pathways for amide synthesis exploit *in situ* activated hexafluoroisopropyl ester formation through external oxidation of the Breslow intermediate as reported again by Studer *et al.*,[215]

attack of the Breslow intermediate upon nitroso-containing compounds[216] or oxidation of the Breslow intermediate using *N*-chlorosuccinimide as reported by Yamada *et al.*[205]

Scheme 1.58 Alternative aldehyde amidation strategies as demonstrated by Bode and Rovis**.**



1.7.4 Scope and limitations associated with current methodologies

A major drawback associated with NHC-catalysed oxidative transformations is that the most efficient catalytic pathways depend entirely upon the formation of the acyl azolium ion *in situ*, either through addition of an external oxidant or internal redox reactions of functionalised aldehydes possessing a reducible bond in the α-position. Many external oxidants are extremely toxic and so their use on a larger or commercial scale is undesirable. Access to specifically-functionalised aldehydes required for internal redox strategies may not always be possible either. In contrast, molecular oxygen represents an inexpensive, environmentally-friendly and ubiquitous oxidant.[208] Its successful application to NHC-catalysed esterifications/amidations in generating the acyl azolium ion would prove a highly significant development within the field of NHC organocatalysis. Although Anand *et al.*[217] recently succeeded in aerobically esterifying aldehydes in the absence of any external oxidant, the procedure employed the use of often biologically-active and potentially hazardous boronic acids rather than alcohols. Thus, the need remains for the development of a general NHC-catalysed aldehyde esterification methodology, using molecular oxygen as a terminal oxidant, in the presence of alcohol and base. The reaction should demonstrate a tolerance of a wide

range of aromatic aldehydes and would ideally also be effective in the esterification of typically unreactive aliphatic aldehydes. Equally, application of the same technology (or a modification) to the synthesis of amides directly from aldehydes is desirable.

Chapter 2 Development of a Chemoselective NHC-Catalysed Intermolecular Crossed Benzoin Condensation

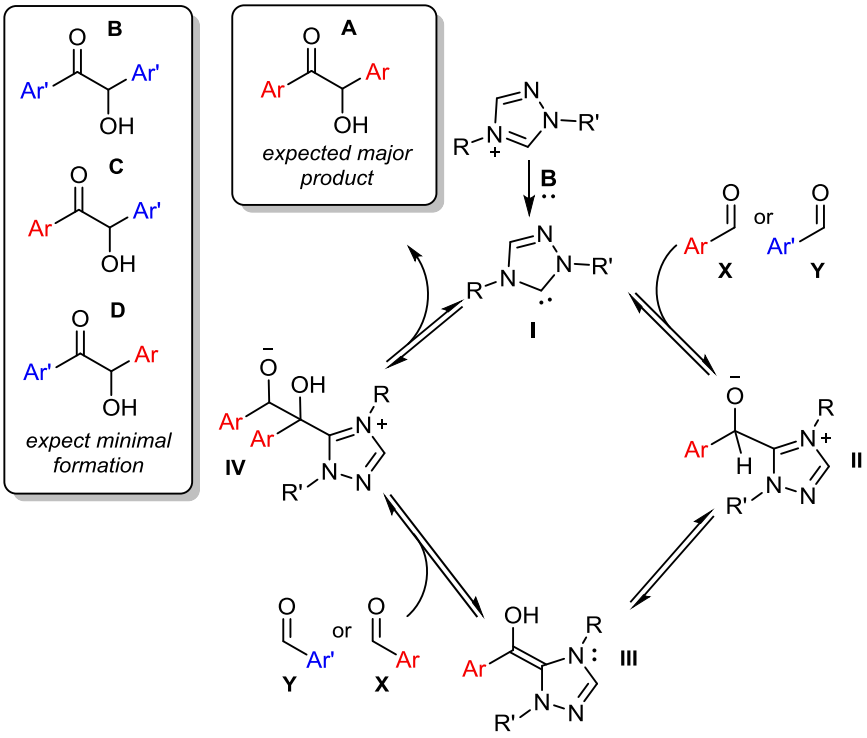
2.1 Intermolecular crossed benzoin condensations: initial considerations

In seeking to develop an efficient methodology for the intermolecular crossed condensation of two disparate aromatic aldehydes, it was necessary to give due consideration to several issues that may arise during the catalytic cycle. Firstly, the fundamental question of how the two different aldehydes could act as electrophiles in two separate steps of the reaction pathway needed to be addressed. In this regard it seems intuitive that, in a triazolylidene-catalysed crossed benzoin condensation (Scheme 2.1), should aldehyde **X** function as the electrophile in the Breslow intermediate-forming step (**I** → **III**) then the electrophilicity of **X** should again be of greater magnitude than that of aldehyde **Y** in the presence of a powerful nucleophile such as the Breslow intermediate (*i.e.* **III** → **IV**). Thus, we could logically expect homodimer **A** to be the main product of any attempted crossed condensation between two such aldehydes rather than the desired cross-products **C** or **D**. However, given the pathway is reversible the relative stabilities of each benzoin adduct may also influence the chemoselective outcome of the reaction and so it would be necessary to establish a set of reaction conditions conducive to selective formation of a sole product.

In trying to circumvent these obstacles, we envisaged that the reliance on an electronic differentiation between two aromatic aldehydes alone by a suitable carbene catalyst would prove insufficient in establishing a chemoselective process. It has been firmly established by Zeitler *et al*. that a strong interplay exists between catalyst and substrate control in crossed acyloin condensations.[138] In particular, they demonstrated that *ortho*-substituted benzaldehydes display a strong propensity to participate in chemoselective crossed couplings. Our research group, in collaboration with Zeitler, exploited these findings in the design of the first chemoselective intermolecular crossed acyloin condensation using 2-bromobenzaldehyde as the aromatic component.[139] Glorius further employed 2-chlorobenzaldehyde to effect moderately chemoselective crossed benzoin condensations in the presence of a thiazolylidene catalyst (see Scheme 1.34).[149] Using these reports as primary starting points in developing an efficient protocol for the NHC-mediated cross-coupling of two different aldehydes, we hypothesised that use of a specifically-designed thiazolium or triazolium salt in the presence of two non-identical

aromatic aldehydes, one being an *ortho*-substituted benzaldehyde, could potentially enable us to develop a chemoselectively-superior methodology to that of Glorius for the intermolecular crossed benzoin condensation.

Scheme 2.1 General chemoselectivity considerations of the triazolylidene-catalysed benzoin condensation

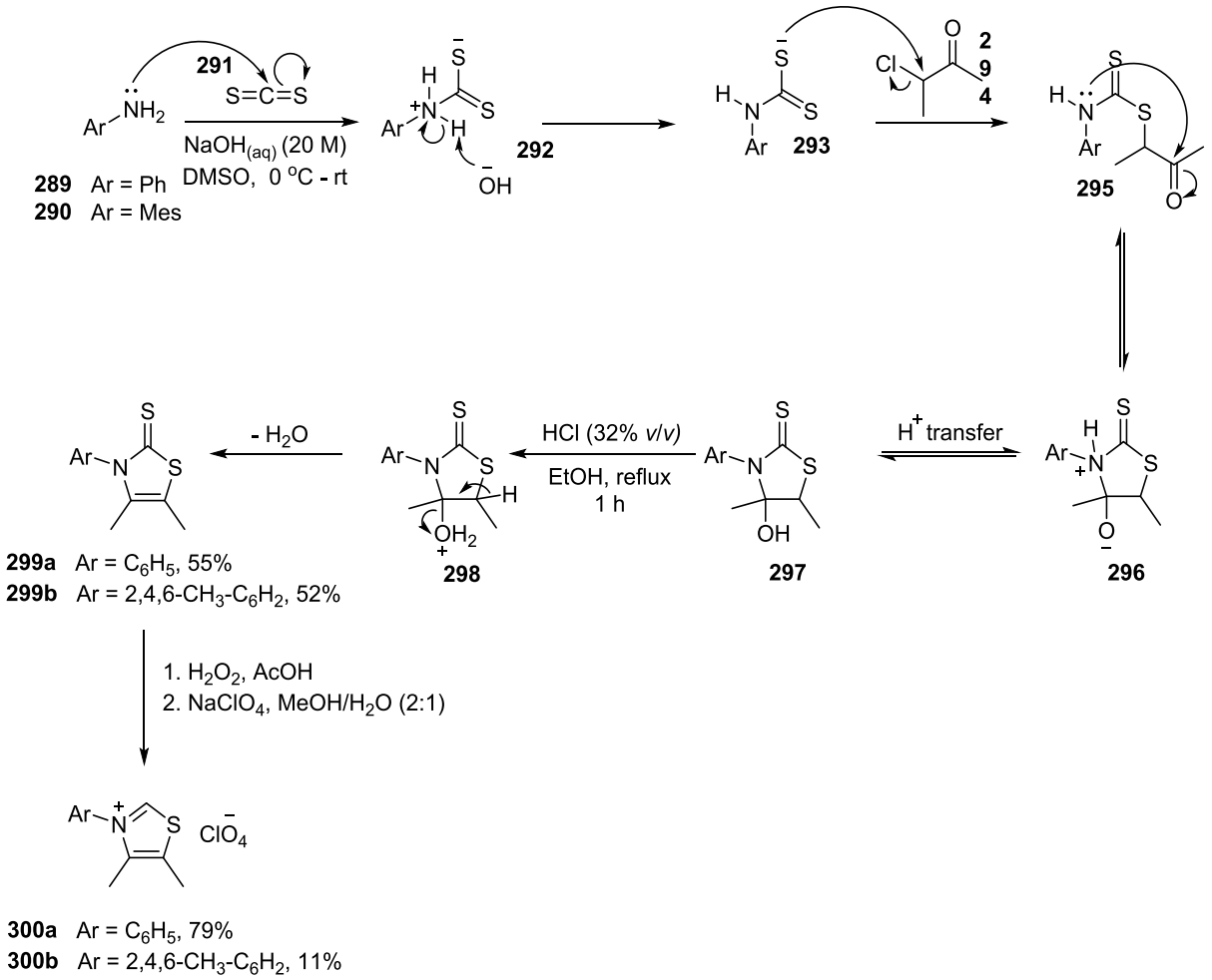


2.2 Synthesis of achiral heteroazolium salts

We began this endeavour by synthesising a range of triazolium and thiazolium salts of various steric and electronic characteristics by varying the precatalyst *N*-alkyl/aryl group. Thiazolium salts are traditionally synthesised *via* one of two means – alkylation of a preformed thiazolium ring[218] or condensation of an *N*-substituted dithioformamide with an α-chloro ketone.[149,156,219] Using the latter method, we synthesised thiazolium precatalysts **300a** and **300b** as per Scheme 2.2. Under basic conditions, initial treatment of the relevant aniline (**289** or **290**) with carbon disulphide (**291**) results in dithioformamide intermediate **293** which, in the presence of 3-chloro-2-butanone (**294**), generates **295** through an S_N2 nucleophilic substitution. Following intramolecular cyclisation to form the hydroxyl-thiazolidine-2-thione **297**, subsequent acid-induced dehydration allows isolation of the relevant thione (*i.e.* **299a** or **299b**). Using hydrogen

peroxide and sodium perchlorate, under reaction conditions devised by Bach *et al.*,[220] oxidation of the relevant thione yields the derivative thiazolium salts **300a** or **300b** in low to good yield.

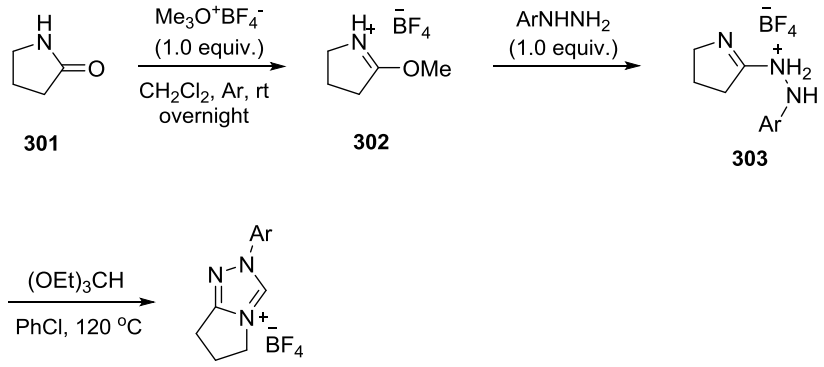
Scheme 2.2 Mechanism of thiazole-2-thione formation and oxidation to yield thiazolium salts



In the design of a suite of triazolium precatalysts, we endeavoured to vary only the steric and electronic properties of the *N*-aryl moiety. This would allow for development and optimisation of a viable synthetic procedure that could be extended to devise a more intricate asymmetric methodology. Similar to their thiazolium relatives, triazolium salts can be synthesised *via* two primary methods; either alkylation of an existing triazole ring or (for more rigid bicyclic structures) using Rovis' seminal method.[83] Previous reports from our group[138,139,145,169,170] have demonstrated these bicyclic structures to be particularly efficient when employed to mediate the intermolecular acyloin condensation

under basic conditions and so we chose to focus primarily on the construction of triazolium scaffolds of this nature. Scheme 2.3 details Rovis' procedure used for the synthesis of these achiral precatalyst salts.

Scheme 2.3 Synthesis of triazolium salts using the method described Rovis *et al*.



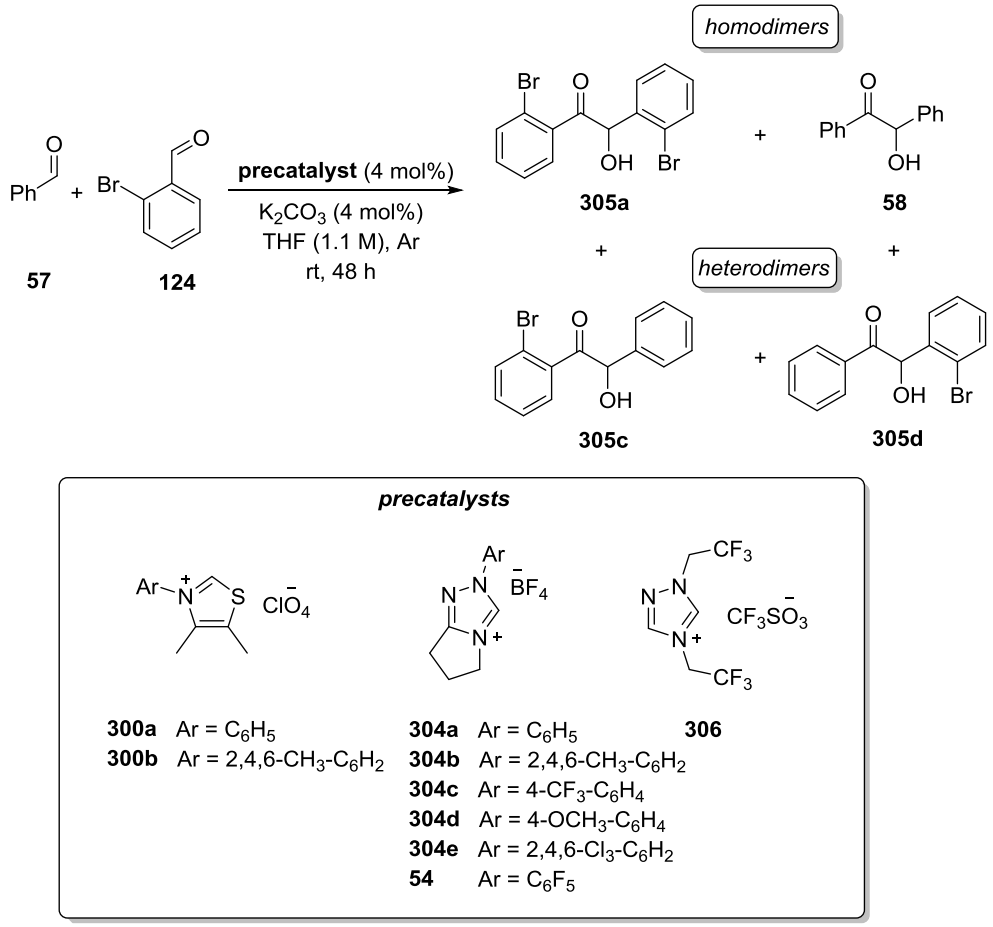
304a Ar = C_6H_5, 82%
304b Ar = 2,4,6-CH_3-C_6H_2
304c Ar = 4-CF_3-C_6H_4, 22%
304d Ar = 4-OCH_3-C_6H_4, 25%
304e Ar = 2,4,6-Cl_3-C_6H_2, 73%
54 Ar = C_6F_5, 69%

Addition of the relevant aryl hydrazine to the amidate **302**, derived from treatment of 2-pyrrolidinone (**301**) with trimethyloxonium tetrafluoroborate (commonly referred to as Meerwin's reagent/salt), provides the hydrazinium tetrafluoroborate **303**. Cyclisation of this intermediate can be carried out under reflux conditions in the presence of an excess of triethyl orthoformate to provide the final triazolium salts **304a-f** in moderate to good yields. In the case of catalyst **304b**, the crude hydrazinium salt could be obtained as per the literature procedure,[221] however, although following identical conditions employed in the synthesis of all other analogues, the desired product could not be isolated despite extensive repetition and/or modification of the procedure. All reactions detailed in this thesis using mesityl-substituted triazolium salt **304b** as an NHC precatalyst were conducted using a sample kindly provided by the research group of Prof. Andrew D. Smith (University of St. Andrew's).

2.3 Preliminary studies on the intermolecular crossed benzoin condensation using achiral heteroazolium salts

Seeking to determine if an inherent natural bias for formation of one of the four possible benzoin adducts in the intermolecular crossed benzoin condensation would be displayed in the presence of a carbene derived from our family of heteroazolium salts, we began by evaluating their performance in the cross-condensation between equimolar amounts of benzaldehyde (**57**) and 2-bromobenzaldehyde (**124**) under conditions previously employed by our group (Table 2.1). As expected, in the presence of 4 mol% K_2CO_3 but the absence of precatalyst, no conversion to any of the four adducts **305a**, **58**, **305c** and **305d** is observed after 48 hours (entry 1). Surprisingly, thiazolium salts **300a** or **300b** failed to induce a reaction of any kind, with both starting aldehydes being observed quantitatively *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture after 48 hours (entries 2 and 3). It is likely that the pK_a of the thiazolium ring in both cases was too high for sufficient levels of carbene to be generated by the mild carbonate base. A similar reasoning can be applied to the use of triazolium precatalyst **304a** and its even less acidic (but more sterically hindered) counterpart **304b**, where very low levels of conversion were observed (entries 4 and 5). Employing precatalyst **304c**, possessing an electron-withdrawing trifluoromethyl group in the *para* position of the *N*-aryl ring, led to an expected rise in conversion due to the increased acidity of the triazolium ring; however, the lack of any steric influence in the *N*-aryl *ortho* positions corresponded to an unselective reaction (entry 6). Conversely, the electron-rich carbene derived from **304d** failed to promote the reaction at all, again attributable to the fact that the parent triazolium ring is not acidic enough to undergo deprotonation due to the presence of the electron-donating methoxy substituent. When the reaction was mediated by the highly electron-deficient carbene derived from **54**, conversion of the starting aldehydes was almost complete. While the reaction again lacked any true chemoselectivity, there was an apparent bias for formation of cross-benzoin adduct **305d**, produced in 66% crude yield (entry 8). Increasing the steric bulk of the *ortho*-substituents on the *N*-aryl ring but maintaining a degree of its electron-deficiency through use of the 2,4,6-trichlorophenyl-substituted precatalyst **304e** also provided excellent an conversion rate with a slight improvement in the selectivity of the reaction (entry 9).

Table 2.1 Screening of achiral catalysts in the crossed benzoin condensation



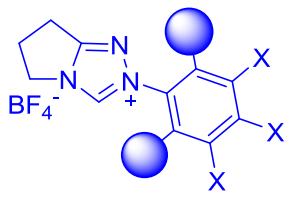
entry	precatalyst	yield **305a** (%)[a]	yield **58** (%)[a]	yield **305c** (%)[a]	yield **305d** (%)[a]
1	/	0	0	0	0
2	**300a**	0	0	0	0
3	**300b**	0	0	0	0
4	**304a**	1	2	2	3
5	**304b**	0	1	0	1
6	**304c**	0	8	1	49
7	**304d**	0	0	0	0
8	**54**	4	21	11	66
9	**304e**	0	18	2	80
10	**306**	0	32	15	56

[a]Yield determined by ^{1}H NMR spectroscopy using styrene (0.25 equiv.) as an internal standard. Note: yields of **305a** and **58** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2.

Finally, to highlight the crucial role played by *N*-aryl-substituted triazolium salts, novel alkyl-substituted triazolium salt **306** (synthesised by Dr. Claire-Louise Fagan within our group) was employed under identical reactions conditions. The corresponding carbene proved to be exceptionally active but, due to the unhindered rotation of the alkyl substituents, was unable to promote a chemoselective reaction.

2.4 Rational design of novel achiral triazolium precatalysts based upon preliminary findings

While these preliminary findings offered no immediate or obvious solution to developing a chemoselective process, we were encouraged by certain results. It was clear that decreasing the electron density at the carbene centre through the introduction of electron-withdrawing substituents on the *N*-aryl ring corresponded to higher conversions (see entries 8-10), irrespective of the overall chemoselective bias of the reaction for formation of a particular benzoin product. This can be attributed to the fact that electron-deficient triazolium salts are more amenable to deprotonation (in basic solution) and so there is a higher concentration of carbene *in situ* when they are employed. Furthermore, although by no means definitive, we noted that increasing the steric bulk of the *ortho* substituents on the *N*-aryl ring appeared to minimise formation of products derived from initial attack of the carbene upon **124** *i.e.* **305a** and **305c** (see entries 5 and 9). We envisaged that potentially combining these favourable electronic and steric properties in the design of a novel triazolium ion-based precatalyst would ultimately enable us to gain chemoselective control over the reaction. An ideal precatalyst would possess an *N*-aryl substituent containing bulky *ortho* functionalities and further electron-withdrawing moieties to enable generation of catalytically-useful levels of carbene *in situ* (Figure 2.1).



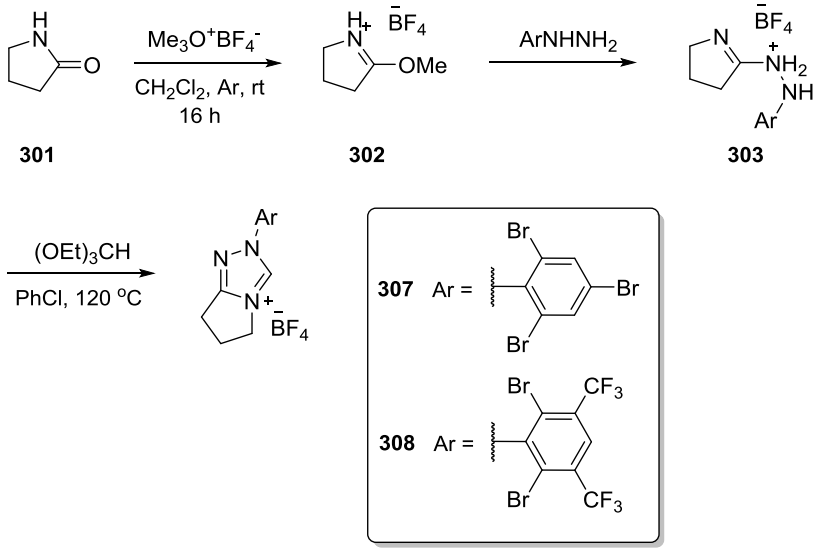
X = electron-withdrawing group

Figure 2.1 Postulated design of an efficient triazolium ion-based precatalyst for the intermolecular crossed benzoin condensation

2.4.1 Synthesis of novel achiral triazolium salts

We set about the synthesis of novel triazolium salts incorporating the requisite steric bulk and electron-deficient characteristics detailed above. We considered that installation of bromine atoms in the *ortho* positions of the *N*-aryl ring would provide not only an increased steric presence (relative to precatalyst **304e**) but also a degree of electronegativity, effectively 'killing two birds with one stone' and allowing us to employ further electron-withdrawing groups in the remaining three positions on the ring. Thus, in accordance with Rovis' procedure, we synthesised the novel triazolium salts **307** (possessing an *N*-2,4,6-tribromophenyl moiety) and **308** (possessing a more complex *N*-2,6-dibromo-3,5-*bis*(trifluoromethyl)phenyl pendant) (Scheme 2.4). It should be noted at this point that at the time of its synthesis, precatalyst **307** was (to the best of our knowledge) not reported in the literature and thus was considered novel. However, Smith and O'Donoghue have recently disclosed a report examining the effect of *ortho*-substituents in *N*-aryl triazolium salts when employed in proton transfer reactions in which precatalyst **307** has been synthesised and reported for the first time in available literature.[222]

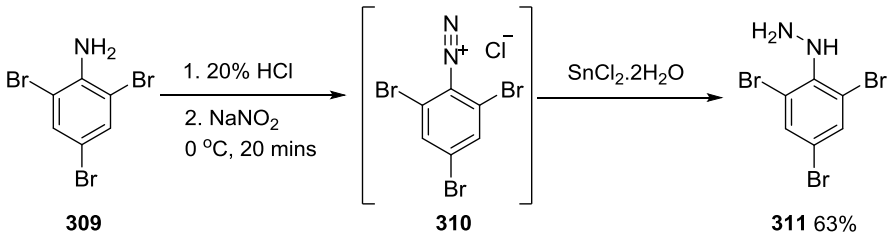
Scheme 2.4 Synthesis of novel triazolium salt precatalysts for the intermolecular crossed benzoin condensation



The most prominent obstacle hindering the synthesis of precatalysts **307** and **308** was obtaining the relevant aryl hydrazine precursors, neither of which is readily available

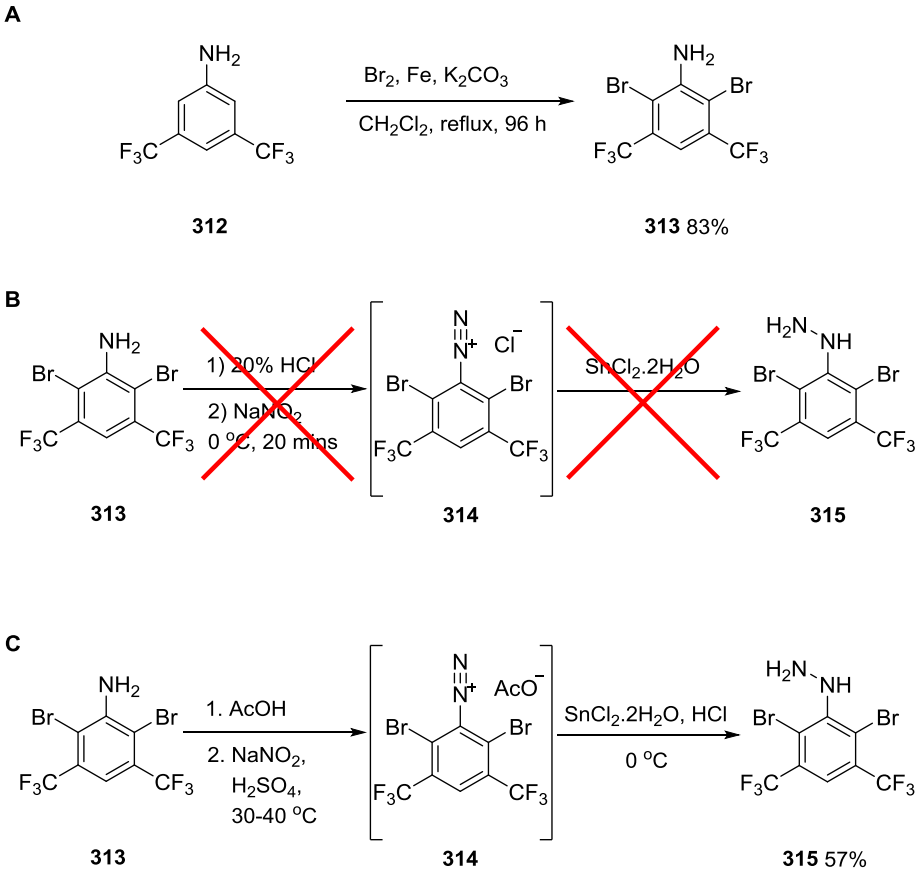
from commercial sources. We therefore prepared them from their parent aniline analogues *via* generation of a diazonium salt *in situ*, subsequent reduction of which would furnish the desired hydrazine Accordingly, conventional diazotisation of 2,4,6-tribromoaniline (**309**) at reduced temperatures in the presence of hydrochloric acid and an aqueous solution of sodium nitrite followed by treatment with stannous (II) chloride afforded (2,4,6-tribromophenyl)hydrazine (**311**) in moderate yield following basic work-up and recrystallisation from hexane (Scheme 2.5).

Scheme 2.5 Synthesis of (2,4,6-tribromophenyl)hydrazine



Accessing (2,6-dibromo-3,5-*bis*-trifluoromethyl-phenyl)-hydrazine proved far more cumbersome however, with the parent amine (2,6-dibromo-3,5-*bis*-trifluoromethyl)aniline (**313**, Scheme 2.6A) also being commercially unavailable. Thankfully, bromination of 3,5-*bis*(trifluoromethyl)aniline (**312**) allowed **313** to be synthesised in good yields under relatively mild conditions. We were therefore disappointed to find that, under the conditions outlined in Scheme 2.5, the attempted tin-mediated reduction of the diazonium intermediate **314** returned only starting material (Scheme 2.6B). Reflecting upon this, we postulated that the electron-deficiency of the ring was sufficient to discourage the amine's attack upon the nitroso species that would otherwise enable formation of the diazonium **314**. We envisaged that more forcing conditions could be implemented to effect the transformation, given the relative robustness of the substituents on the ring. Thus, dissolution of **313** in glacial acetic acid followed by treatment with a solution of sodium nitrite in concentrated sulphuric acid and then reduction using a solution of stannous (II) chloride in concentrated hydrochloric acid enabled isolation of **315** in moderate yields after a basic work-up and recrystallisation from hexane (Scheme 2.6C).

Scheme 2.6 Synthesis of (2,6-dibromo-3,5-*bis*-trifluoromethyl)aniline (**313**) and subsequent reduction to (2,6-dibromo-3,5-*bis*-trifluoromethyl-phenyl)-hydrazine (**315**)

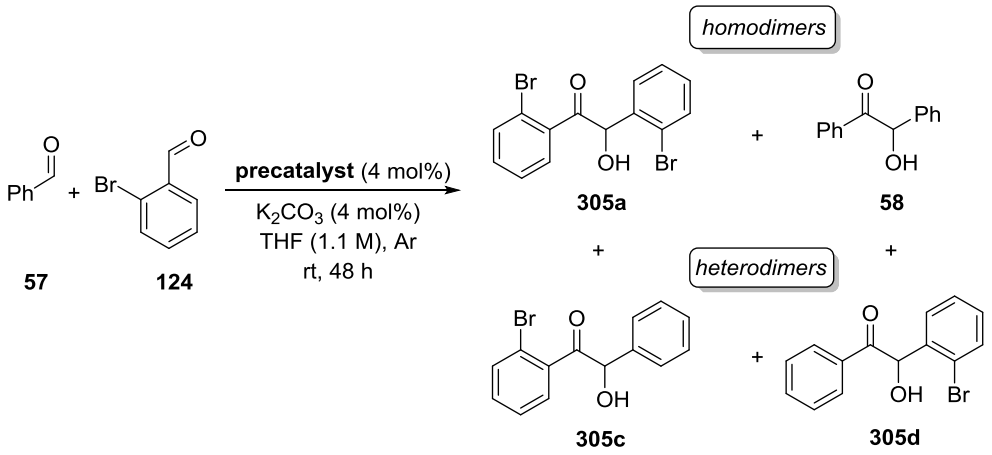


2.4.2 Evaluation of novel achiral triazolium salts in the intermolecular crossed benzoin condensation

With the desired triazolium salts in hand, we set about evaluating their influence upon the chemoselectivity of the intermolecular crossed benzoin condensation between **57** and **124** under our previously-employed reaction conditions (Table 2.2). Although activity levels were poor when tribromophenyl-substituted precatalyst **307** was utilised (presumably due to the lower electronegativity of the bromine atoms relative to fluorine or chlorine) we were pleased to observe a 15:1 chemoselectivity ratio in favour of **305d** over **305a** and **58** (entry 1). To our delight, in the presence of 4 mol% **308** and K_2CO_3, **305d** was produced in 97% crude yield after a 48 hour reaction time. Benzoin (**58**) was observed in just 2% yield, while a minor crude yield of **305c** was also recorded (entry 2). This result verified our conjecture that a combination of steric bulk and electron-

deficienty adjacent to the carbene centre would facilitate chemoselective control over the reaction.

Table 2.2 Screening of triazolium salts **307** and **308** in the crossed benzoin condensation



entry	precatalyst	yield **305a** (%)[a]	yield **58** (%)[a]	yield **305c** (%)[a]	yield **305d** (%)[a]
1	**307**	1	1	0	15
2	**308**	0	2	1	97

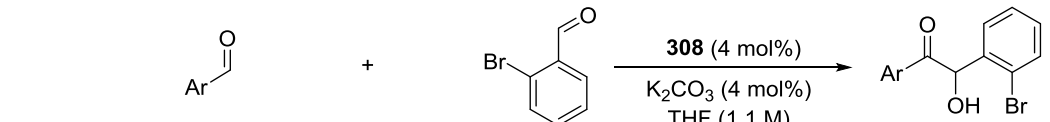
[a]Yield determined by ^{1}H NMR spectroscopy using styrene (0.25 equiv.) as an internal standard. Note: yields of **305a** and **58** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2.

2.5 Crossed benzoin condensation: substrate scope of the non-*ortho*-substituted aromatic aldehyde

With the optimum catalyst in hand, we set about evaluating the scope of the reaction with regard to the non-*ortho*-substituted coupling partner using a range of aromatic aldehydes (Table 2.3). Electron-neutral benzaldehydes (*i.e.* **57**, **316**-**319**) were coupled with **124** to provide the corresponding cross-benzoins (*i.e.* **305d**, **331**-**334**) in moderate to excellent isolated yields in the catalytic presence of **308** and K_2CO_3, with only 4-tolualdehyde (**318**) leading to a slow reaction rate due to the slight inductive effect of the methyl substituent upon the carbonyl group. Activated benzaldehydes proved similarly

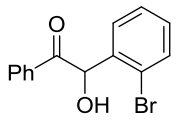
amenable to the transformation, with 3-fluorobenzaldehyde (**320**) providing a 93% isolated yield of its relevant cross-benzoin (**335**). Perhaps due to increased steric hinderance, increasing the size of the *meta* halogen substituent on the starting aldehyde coupling partner negatively impacts the reaction rate. Thus, 3-chlorobenzaldehyde (**321**) and 3-iodobenzaldehyde (**322**) led to an isolated yield of their cross-benzoin products (**336** and **337**) in 81% and 51% respectively. In the case of **322**, this yield could be improved slightly to 60% by the alternative use of trichlorophenyl-substituted precatalyst **304e**. 4-Fluorobenzaldehyde and 4-chlorobenzaldehyde (**323** and **324**) could also be cross-coupled in good isolated yields while unsurprisingly, the use of deactivated benzaldehydes also led to a decrease in the rate of reaction. Although use of 3-methoxybenzaldehyde (**325**) provided its corresponding cross-benzoin product **340** in 82% yield under our optimised conditions, 3-isopropoxybenzaldehyde (**326**) required elevated reaction temperatures to achieve a comparable result. The use of 3-(dimethylamino)-benzaldehyde (**327**) initially resulted in a poor isolated yield of corresponding benzoin adduct (**342**). Seeking to improve this through an increase in reaction temperature proved futile. Thankfully, alternative use of precatalyst **304e** again allowed this yield to be increased to a moderate and synthetically useful 74%. Gratifyingly, 6-methoxy-naphthalene-2-carbaldehyde (**328**) underwent cross-coupling with **124** in 80% isolated yield of **343** without the need for elevated temperatures, albeit at an extended reaction time. Finally, a selection of heterocyclic aromatic aldehydes could also be utilised in the transformation. Initially, thiophene-2-carbaldeyde (**329**) proved a poor coupling partner, with a slow reaction rate leading to just 18% of the desired product **344** observed *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture, while carrying out the reaction at 55 ^{o}C failed to alleviate this problem. However, once again use of precatalyst **304e** enabled us to somewhat overcome this, with **344** being isolated in a moderate 76% yield. It has previously been reported that homo-coupling of 2-furfuraldehyde (**330**) proceeds rapidly with excellent isolated yields of furoin.[86,170] Initial results in attempting to employ this substrate under our reaction conditions were consistent with these previous observations, with ^{1}H NMR spectroscopic analysis indicating the presence of the homobenzoin in 86% crude yield and just 10% of the desired cross-benzoin product (**345**). Suspecting that this homobenzoin may represent a thermodynamic "sink", we repeated the reaction at 55 ^{o}C and to our delight, were able to isolate **345** in 83% yield.

Table 2.3 Substrate scope: non-*ortho*-substituted aromatic aldehyde

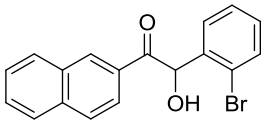


57 Ar = C_6H_5
316 Ar = 2-napthyl
317 Ar = 3-CH_3-C_6H_4
318 Ar = 4-CH_3-C_6H_4
319 Ar = 3-C_6H_5-C_6H_4
320 Ar = 3-F-C_6H_4
321 Ar = 3-Cl-C_6H_4
322 Ar = 3-I-C_6H_4
323 Ar = 4-F-C_6H_4
324 Ar = 4-Cl-C_6H_4
325 Ar = 3-OCH_3-C_6H_4
326 Ar = 3-[$(CH_3)_2$CH]O-C_6H_4
327 Ar = 3-$(CH_3)_2$N-C_6H_4
328 Ar = 6-OCH_3-2-napthyl
329 Ar = 2-thienyl
330 Ar = 2-furanyl

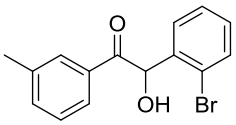
Products[a]



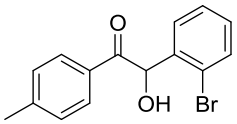
305d
93%



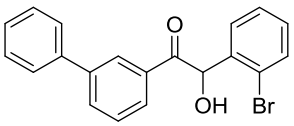
331
90% (72 h)



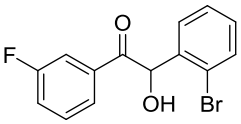
332
88%



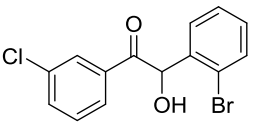
333
55% (55 °C)



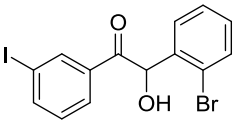
334
87% (55 °C)



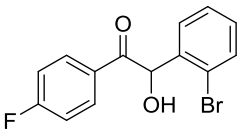
335
93%



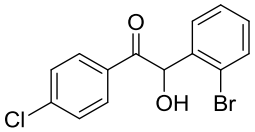
336
81% (64 h)



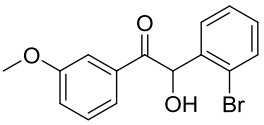
337
53%
60% (precat. **305e**)



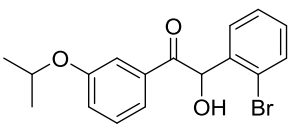
338
86%



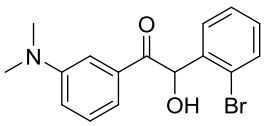
339
83% (55 °C)



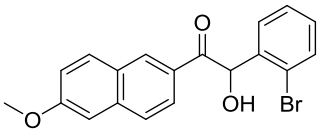
340
82%



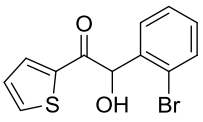
341
83% (55 °C)



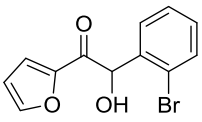
342
47%
51% (55 °C)
74% (precat. **305e**)



343
80% (96 h)



344
18%
31% (55 °C)
76% (precat. **305e**)

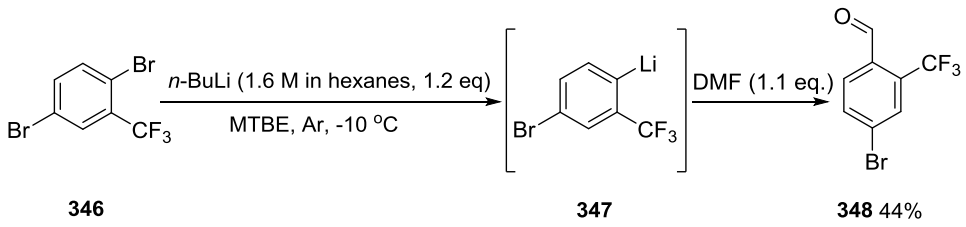


345
10%
83% (55 °C)

2.6 Crossed benzoin condensation: substrate scope of the *ortho*-substituted aromatic aldehyde

Having examined the scope of the reaction with regard to one coupling partner, we then turned our attention to evaluating the feasibility of cross-coupling a variety of *ortho*-substituted aldehydes with **57** using our devised methodology (Table 2.4). In this regard, we chose to employ a selection of commercially available aldehydes. However, seeking to emphasise the synthetic utility of the process we had established, we also prepared a further set of *ortho*-substituted benzaldehydes to examine the tolerance of our methodology with regard to more functionalised benzaldehydes. To this end, treatment of 2,5-dibromotrifluoromethylbenzene (**346**) with a slight excess of *n*-BuLi under strictly anhydrous conditions allowed generation of the lithiate intermediate **347** through lithium-halogen exchange. Subsequent addition of 1.1 equivalents of DMF and acidic work-up allows isolation of 4-bromo-2-(trifluoromethyl)benzaldehyde (**348**) in moderate yield (Scheme 2.7)

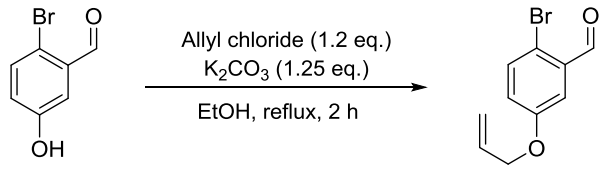
Scheme 2.7 Synthesis of 4-bromo-2-(trifluoromethyl)benzaldehyde



346 **347** **348** 44%

Cognisant of the fact that benzaldehydes bearing hydroxy groups may interfere with the viability of the carbene-catalysed crossed benzoin reaction (it being sensitive to changes in pK_a) we also sought to somewhat overcome this limitation through use of the *O*-allyl-substituted benzaldehyde **349**. Envisaging the removal of the allyl protecting group to be possible following cross-coupling, **349** was prepared *via* treatment of 2-bromo-5-hydroxybenzaldehyde (**350**) with allyl chloride under basic and reflux conditions (Scheme 2.8).

Scheme 2.8 Protection of 2-bromo-5-hydroxybenzaldehyde using allyl chloride

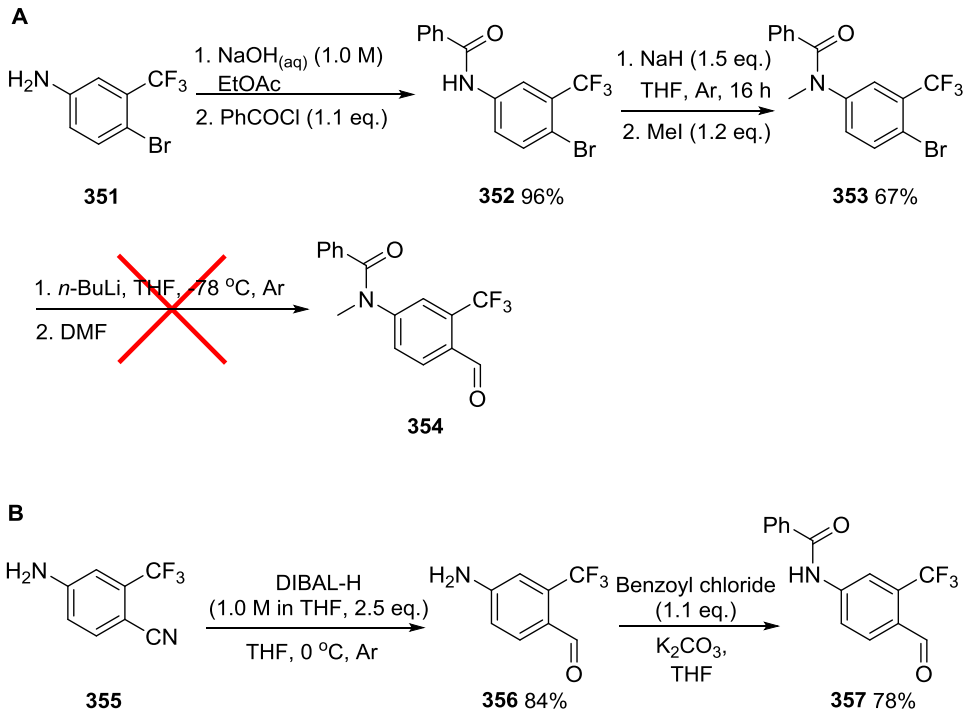


349 **350** 96%

The amide functionality features heavily in many small or complex synthetic and natural molecules. It is ubiquitous in life, with proteins fulfilling countless roles throughout the body of a living organism. It is also a significant motif for medicinal chemists, with an estimated 25% of known drugs containing a carboxamide group.[223] Recognising this, as well as the privileged role of the CF_3 group in medicinal chemistry due to its ability to enhance the efficacy of a drug,[224-226] we also designed a pathway for the synthesis of *N*-(4-formyl-3-trifluoromethyl-phenyl)-benzamide (**357**, Scheme 2.8). Our original strategy (**A**) involved acylation of 4-bromo-3-(trifluoromethyl)aniline (**351**), yielding amide **352** which was then alkylated to produce the *N*-methyl derivative **353**. Attempts to derive the desired aldehyde (**354**) through *in situ* generation of a lithiated derivative and subsequent nucleophilic attack upon DMF met with failure however, with a complex mixture of products resulting, likely a result of the ability of the amide to direct *ortho*-lithiation upon treatment with butyllithium. We therefore revised our approach (**B**), choosing instead to install the aldehyde functionality first. Gratifyingly, reduction of 4-amino-2-(trifluoromethyl)benzonitrile (**355**) using a solution of DIBAL-H followed by acylation with benzoyl chloride allowed isolation of the desired aldehyde in good yield.

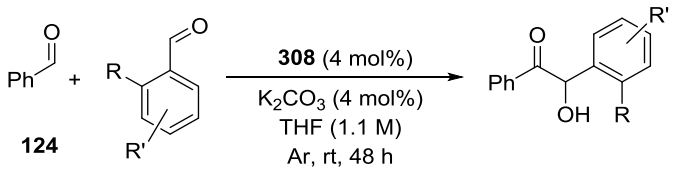
With our selected substrates in hand, we set about employing them in the intermolecular crossed benzoin condensation mediated by **308** under basic reaction conditions (Table 2.4). Pleasingly, all proved compatible with our protocol. 2-Chlorobenzaldehyde (**88**) and 2-iodobenzaldehyde (**358**) could be successfully employed with isolated yields of 80% and 79% of their corresponding cross-benzoin products respectively (entries 1 and 2). A degree of homo-coupling in the case of **88** is observed, presumably due to the decreased steric bulk of the chlorine atom. Conversely, the increased hinderance of the iodo-substituent means the reaction proceeds somewhat slower but maintains an excellent chemoselectivity. 2-(trifluoromethyl)benzaldehyde (**359**) provided its relevant cross-benzoin product in 84% isolated yield (entry 3), while its *para*-bromo-substituted analogue (*i.e.* **348**) also did so in 81% yield (entry 4). Similarly, a wider variety of

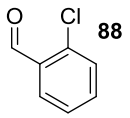
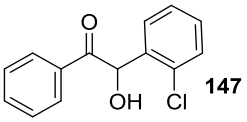
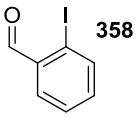
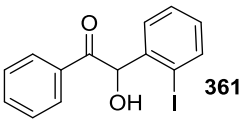
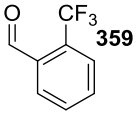
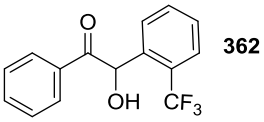
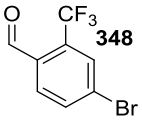
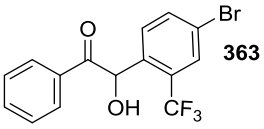
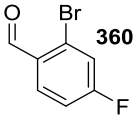
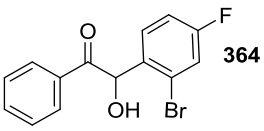
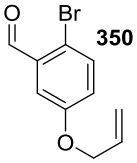
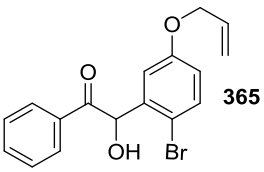
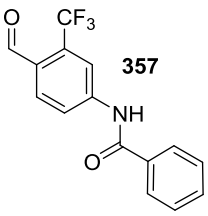
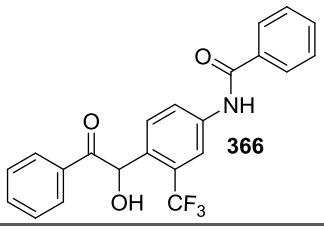
Scheme 2.8 Preparation of *N*-(4-formyl-3-trifluoromethyl-phenyl)-benzamide



disubstituted benzaldehydes proved amenable to transformation. Although introduction of a fluorine atom into the *para* position of 2-bromobenzaldehyde (*i.e.* **360**, entry 5) led to increased levels of the homo-coupled benzoin derived from **360** (observed in 15% yield through ^{1}H NMR spectroscopic analysis of the crude reaction mixture) and thus problems purifying the desired product *via* flash chromatography, we were still pleased to isolate the desired cross-benzoin **364** in a synthetically useful yield of 65%. A comparable result was obtained when using the *O*-allyl-substituted benzaldehyde (**350**, entry 6). In this case, the deactivation of the aryl ring through addition of the protected alcohol led to a concurrent reduction in the reaction rate but still allowed isolation of **365** in 57% yield. Finally, we were pleased to find that more complex functionalities could be installed on the phenyl ring of the coupling partner without significantly impacting the viability of the reaction, with employment of **357** (entry 7) in our catalytic system returning a moderate isolated yield of 74% of its corresponding cross-benzoin **366**.

Table 2.4 Substrate scope: *ortho*-substituted aromatic aldehyde



entry	substrate	product	yield[a] (%)
1	 **88**	 **147**	80[b]
2	 **358**	 **361**	79
3	 **359**	 **362**	84
4	 **348**	 **363**	81
5	 **360**	 **364**	65[c]
6	 **350**	 **365**	57
7	 **357**	 **366**	74

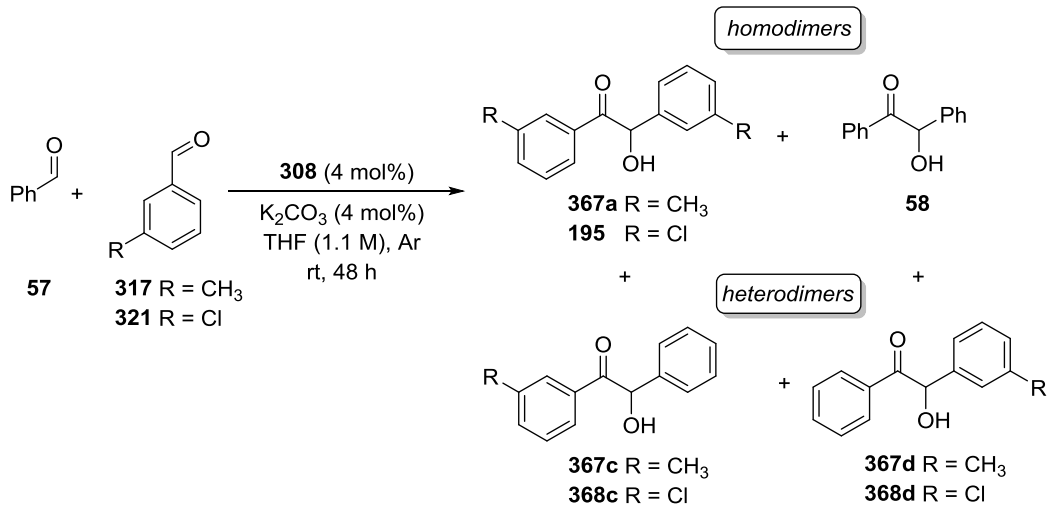
[a]Isolated yield. [b]Homobenzoin derived from **88** also formed in 14% yield. [c]Homobenzoin derived from **360** also formed in 15% yield.

2.7 Assessing the chemoselective importance of the *ortho*-substituent

While these results were gratifying (particularly the reaction scope with regard to the identity of both coupling partners), the necessity for the use of at least one *ortho*-substituted benzaldehyde represented an obvious limitation to its synthetic utility.

Conscious of this, we sought to quantify the importance of the *ortho*-bromine atom with regard to the ability of our novel catalyst to direct formation of one sole cross-benzoin product derived from two disparate aromatic aldehydes. We therefore attempted to cross-couple **57** with 3-tolualdehyde (**317**) or 3-chlorobenzaldehyde (**321**) under our optimised reaction conditions (Table 2.5), monitoring the reaction by ^{1}H NMR spectroscopic analysis of the crude reaction mixture to establish whether any natural bias existed for formation of either of the heterodimers **367c**/**368c** or **367d**/**368d**.

Table 2.5 Cross-coupling of two aromatic aldehydes: absence of *ortho*-substitution



entry	substrate	yield **367a/195** (%)[a]	yield **58** (%)[a]	yield **367a/368c** (%)[a]	yield **367d/368d** (%)[a]
1	**317**	12	17	32	30
2	**321**	20	15	29	38

[a]Yield determined by ^{1}H NMR spectroscopy using styrene (0.25 eq) as an internal standard. Note: yields of **305a** and **305b** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2.

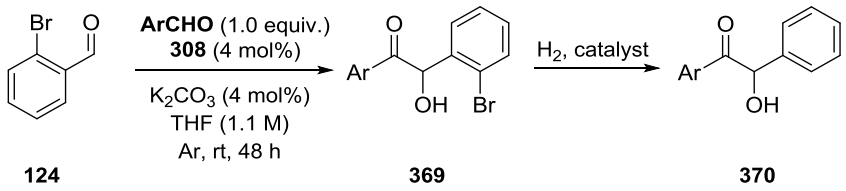
Disappointingly, the presence of an *ortho*-substituent on at least one benzaldehyde ring appears necessary for the carbene derived from **308** to induce chemoselective formation of just one cross-benzoin product. As the data in Table 2.5 indicates, in its absence no

distinct preference exists for formation of any of the four possible products, a finding concurrent with previous studies from within our group.[139]

2.7.1 Exploitation of the *ortho*-bromine as removable functional handle

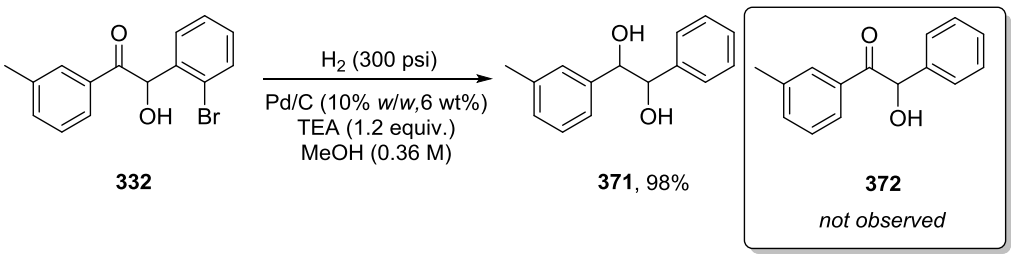
Although discouraged by these results, we envisaged the possibility to exploit the use of the *ortho*-bromo substituent as a removable directing group and thus, circumvent the lack of chemoselectivity in its absence. In the presence of a suitable transition metal catalyst, hydrodebromination of a cross-benzoin adduct (**369**, Scheme 2.9), formed under our standard reaction conditions, could conceivably provide debrominated cross-benzoin products (*i.e.* **370**) otherwise inaccessible through conventional NHC-catalysed means.

Scheme 2.9 Exploitation of a removable *ortho*-bromo substituent



Accordingly, we began this endeavour by exposing the 3-methyl substituted cross-benzoin **332** to a high pressure hydrogen atmosphere in the presence of Pd/C and TEA (Scheme 2.10). To our surprise, following work-up we observed almost quantitative conversion of the starting adduct, not to the desired cross-benzoin **372**, but to the unsymmetrical diol **371**.

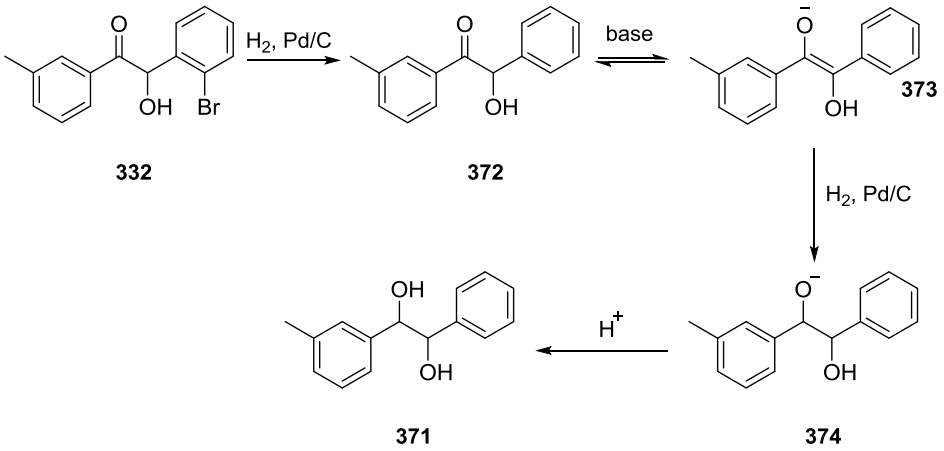
Scheme 2.10 Attempted hydrodebromination of **332** using a palladium catalyst



While reduction of aromatic ketones to their corresponding alcohols using molecular hydrogen over Pd/C was reported by Ley *et al*. in 2006,[227] the alcohol was obtained as

the minor reaction product (13% yield) with complete reduction to the alkane the major outcome of the reaction (87% isolated yield). On the other hand, palladium is not sufficiently active to mediate the reduction of aliphatic ketones to their alcohols under a hydrogen atmosphere and platinium or Raney nickel are more commonly employed to achieve such transformations.[228] However, with further consideration, we concluded that (following hydrogenative debromination) direct reduction of the carbonyl was not the underlying pathway responsible for formation of **371** as above, but rather base-mediated generation of the enolate (**373**) *in situ* and its subsequent reduction under the hydrogenative conditions (Scheme 2.11).

Scheme 2.11 Proposed mechanism behind the palladium-catalysed formation of **371**



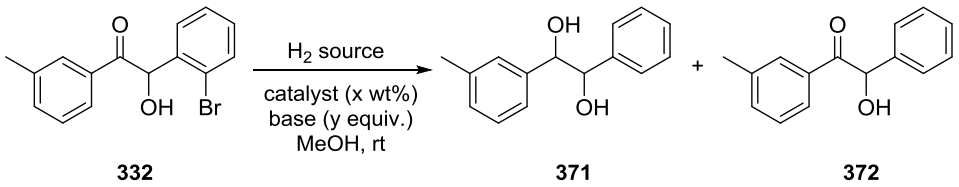
Although this pathway represents a novel (and very much unintended) method for synthesising unsymmetrical aromatic diols, it was clear that its underlying activity would impact upon our ultimate goal of preparing unsymmetrical cross-benzoin derivatives *via* debromination of adducts formed through our NHC-catalysed pathway. We looked to overcome this problem by employing cross-benzoin **332** as a model substrate and subjecting it to a variety of alternative hydrogenation conditions in the hope that this over-reduction could be avoided (Table 2.6). We commenced our optimisation studies by employing the same palladium over charcoal catalyst (10% *w*/*w*) but reducing the hydrogen pressure to just 15 psi and concurrently the basicity of the system. We surmised that use of a weaker base, such as $NaHCO_3$, may deter the formation of the enolate *in situ*, thereby avoiding over-reduction, yet still enable neutralisation of HBr formed through debromination of the cross-benzoin substrate. Under these conditions, we observed the presence of the desired product **372** in 41% yield *via* ^{1}H NMR

spectroscopic analysis of the crude reaction mixture, as well as 56% crude yield of diol **371**, after 20 hours (entry 1), suggesting that while $NaHCO_3$ does indeed reduce the rate of enolate formation, this is insufficient to prevent a degree of over-reduction to the diol **371**. A decrease in the reaction time to 4 hours under the same conditions resulted in formation of **372** in 72% crude yield, while pleasingly **371** was not observed (entry 2). Seeking to improve this yield, we then increased the reaction time to 6 hours but, under the same reaction conditons, were disappointed to see that this allowed a threshold for the formation of **371** to be crossed, as it was observed in 15% crude yield (entry 3). With use of *tetrakis*(triphenylphosphine)palladium(0) and ammonium formate as a H_2 source a complex crude reaction mixture resulted upon work-up, with no observed presence of either **371** or **372** (entry 4). With the failure of these experiments to alleviate the problem, we decided to attempt to discourage enolisation entirely by omission of a base from the reaction system. Conscious of the production of HBr, we compensated for this omission through an increase in the loading of the Pd/C catalyst to 25 wt%. Gratifyingly, under these conditions **372** was observed in 90% crude yield after 20 hours, with no concurrent production of **371** (entry 5), using ammonium formate as a source of molecular hydrogen. Increasing the reaction temperature to 60 ^{o}C correlated to a dramatic decrease in the time required for conversion of **332** to **372**, the desired cross-benzoin observed in 96% crude yield after just 40 minutes reaction time (entry 6).

2.7.2 Reductive hydrodebromination of cross-benzoin adducts in the presence of Pd/C

Having devised a practical and efficient set of conditions for the reductive hydrodebromination of **332**, we then set about examining the scope of this reaction by subjecting a wider array of cross-benzoin adducts to this protocol (Table 2.7). To our delight, the methodology proved to be extremely tolerant of substrates of various steric and electronic characteristics. Cross-benzoin substrate **332** underwent conversion to **373** in 94% isolated yield after 40 minutes (entry 1). Similarly, further electron-neutral adducts (*i.e.* **331** and **334**) were smoothly debrominated in excellent yield (entries 2 and 3), while employing fluorine-substituted cross-benzoins (*i.e.* **335** and **338**) allowed debrominated analogues **378** and **379** to be isolated in 80% and 83% yield respectively (entries 4 and 5). Deactivated substrates (*i.e.* **340**-**342**) were equally amenable to the transformation in consistently excellent yields (entries 6-8). Particularly pleasing is the isolation of **381** in quantitative yield (entry 9) given the initial propensity for 2-

Table 2.6 Avoiding over-reduction: alternative hydrogenation conditions



332 **371** **372**

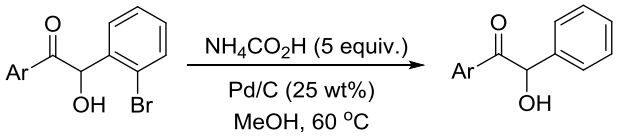
entry	H_2 source	catalyst	x	base	y	yield **371** (%)[a]	yield **372** (%)[a]
1[b]	H_2 (15 psi)	Pd/C	6	$NaHCO_3$	6.5	56	41
2[c]	H_2 (15 psi)	Pd/C	6	$NaHCO_3$	6.5	0	72
3[d]	H_2 (15 psi)	Pd/C	6	$NaHCO_3$	6.5	15	55
4[e,f]	$NH_4^+HCO_2^-$	$Pd(PPh_3)_4$	10	NEt_3	2	0	0
5[b]	$NH_4^+HCO_2^-$	Pd/C	25	/	n/a	0	90
6[g,h]	$NH_4^+HCO_2^-$	Pd/C	25	/	n/a	0	96

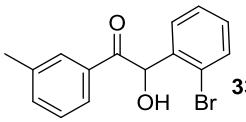
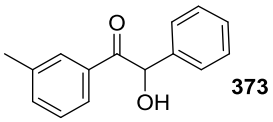
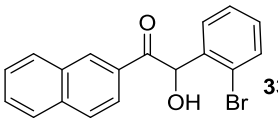
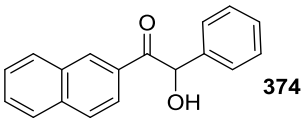
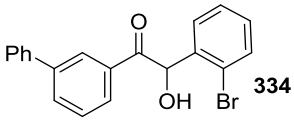
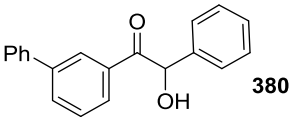
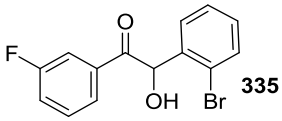
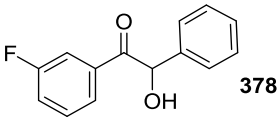
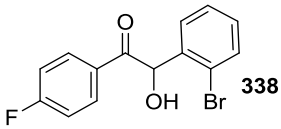
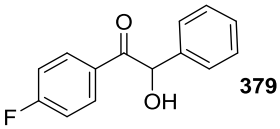
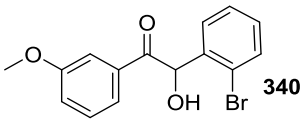
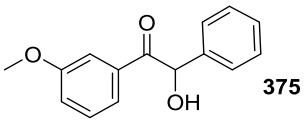
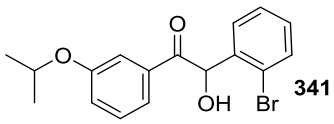
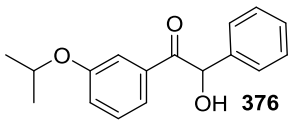
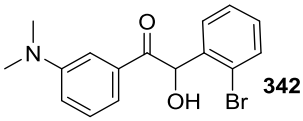
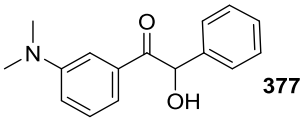
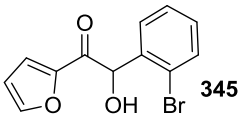
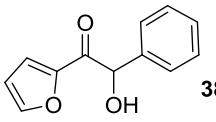
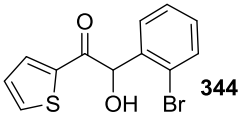
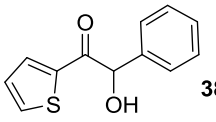
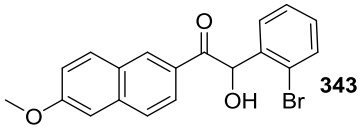
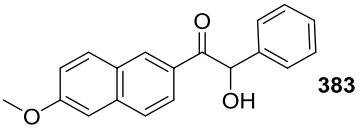
[a]Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b]20 h reaction time. [c]4 h reaction time. [d]6 h reaction time. [e]24 h reaction time. [f]Reaction conducted at 80 °C in MeCN/DMF (1:1). [g]Reaction conducted at 60 °C. [h]40 min reaction time.

furfuraldehyde's self-condensation when attempting its cross-condensation with **124** in the presence of the carbene derived from **308** (see Table 2.3, entry 21). Exchanging the furan ring for thiophene (*i.e.* use of **344** instead of **345**) leads to a stark decrease in the reaction rate, with no observation of the desired debrominated product **382** after 1 hour (entry 10), although given the fact sulfur is a known poison for many palladium-mediated chemistry this is perhaps not surprising. Finally, the 6-methoxy-substituted napthyl-based substrate **343** also proved resistant to reduction within the same timeframe (entry 11).

In this manner, we would propose that the *ortho*-bromo substituent can serve as a temporary directing group to direct (in conjunction with our novel NHC catalyst) the

Table 2.7 Reductive hydrodebromination of cross-benzoin adducts



entry	substrate	product	time (min)	yield (%)[a]
1	 **332**	 **373**	40	94
2	 **331**	 **374**	60	93
3	 **334**	 **380**	35	88
4	 **335**	 **378**	20	80
5	 **338**	 **379**	30	83
6	 **340**	 **375**	30	85
7	 **341**	 **376**	20	98
8	 **342**	 **377**	10	95
9	 **345**	 **381**	90	100
10	 **344**	 **382**	60	0
11	 **343**	 **383**	60	0

[a]Isolated yield.

chemoselectivity of an otherwise unselective reaction. It can then be used as a functional handle for further transformations or, if not required, be cleanly removed to yield debrominated products *otherwise inaccessible in synthetically useful yields through a carbene-catalysed cross-benzoin condensation*.

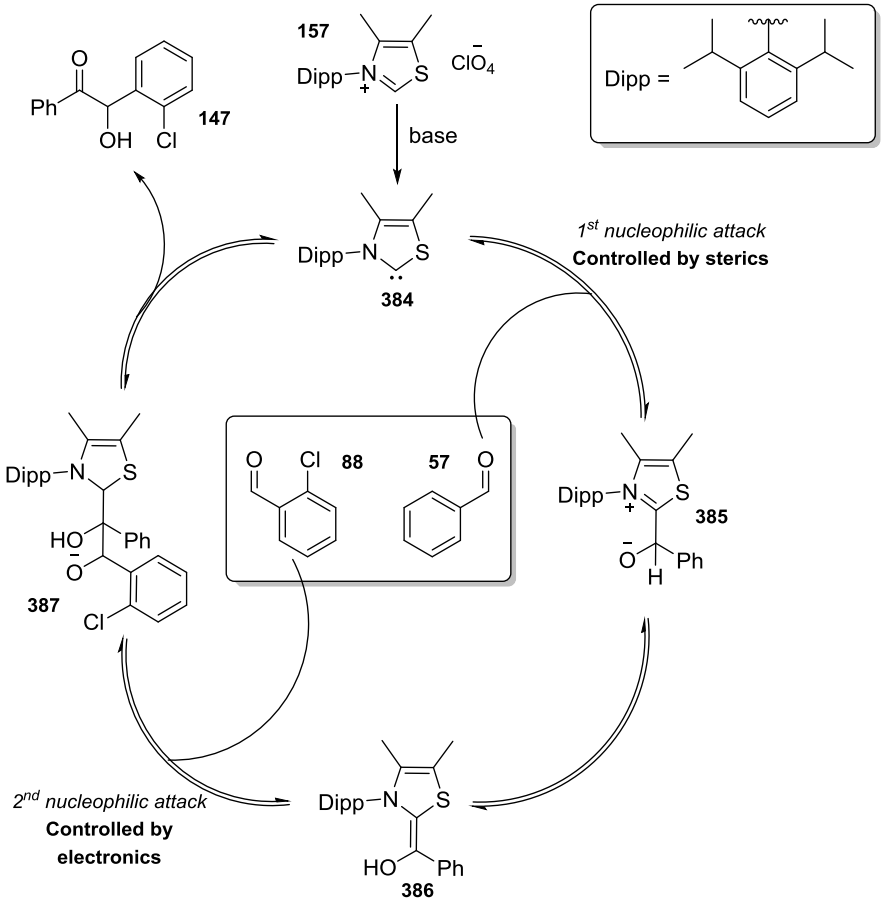
2.8 Rationalising the observed chemoselectivity using precatalyst 308

2.8.1 Initial considerations

At first, our efforts to explain the preferred formation of cross-benzoin **305d** in our prototype reaction (as catalysed by the carbene derived from **308**) were influenced by Glorius' work in 2011.[149] The reasoning for formation of cross-benzoin **147** in the presence of a base and thiazolium salt **157** assumed that the preferred initial attack of the NHC (**384**, Scheme 2.12) upon the carbonyl moiety of **57** was controlled primarily by the steric characteristics (rather than the electronic make-up) of both aromatic aldehydes; with the *ortho*-chloro atom substituent hindering attack of the carbene upon the carbonyl moiety of **88** and thereby leaving formation of the more nucleophilic Breslow intermediate **386** more energetically favourable. Conversely, the observed preference for nucleophilic attack of this Breslow intermediate upon the carbonyl moiety of **88** (rather than that of **57**) is dictated primarily by electronics as the Breslow intermediate is sterically less hindered than the original parent carbene.

With the literature offering no alternative proposal to either verify or contradict this mechanistic postulate, the correlation between our experimental data and Glorius' proposed mechanism led us to reason that the highly chemoselective bias of our developed methodology for formation of **305d** was based upon similar principles. Our screening of a variety of triazolium ion-based precatalyst structures (see Tables 2.1 and 2.2) had indicated that increasing the steric bulk of the 2,6-substituents on the *N*-aryl ring decreased the carbene's propensity to attack the carbonyl moiety of 2-bromobenzaldehyde first, a trend suggestive of a sterically-controlled process. Furthermore, second nucleophilic attack of the resulting Breslow intermediate upon 2-bromobenzaldehyde supports general chemical intuition, in that the more nucleophilic Breslow intermediate could be expected to add to the more electrophilic aldehyde.

Scheme 2.12 Glorius' proposed mechanistic pathways for a selective crossed benzoin condensation



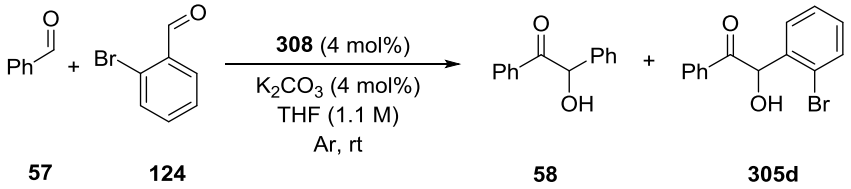
However, in proposing that the carbonyl group of **124** is sterically shielded to some degree by the presence of the *ortho*-bromine atom on the aromatic ring, we also acknowledged the alternative possibility that the bias of our catalyst for formation of **305d** in the crossed benzoin condensation was due to it being a thermodynamically-controlled pathway. In this regard, initial formation of benzoin as the kinetic reaction product (due to it being the least sterically hindered of the four possible adducts) is conceivable, with a subsequent NHC-catalysed retro-benzoin condensation pathway allowing generation of the potentially more stable cross-benzoin **305d** over time.

2.8.2 ^{1}H NMR spectroscopic analysis: kinetic vs thermodynamic product formation

In order to evaluate these hypotheses further, we conducted a typical cross-condensation between **57** and **124**, mediated by **308** in the presence of base, and monitored the

progress of the reaction at various time intervals *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Table 2.8). After 5 minutes, **305d** is detectable in 3% yield with no concurrent production of **58** (entry 1). Similar observations were made at various time points throughout the course of the reaction; yields of the cross-benzoin adduct increased in an approximately time-dependent fashion without an observable presence of **58** (entries 2-8). Indeed, it is only after 14 hours that formation of benzoin becomes evident (entry 9). We were therefore confident that under these conditions, **305d** represents the kinetic reaction product and not the thermodynamic reaction product.

Table 2.8 *In situ* ^{1}H NMR spectroscopic analysis of the intermolecular crossed benzoin condensation between **57** and **124**

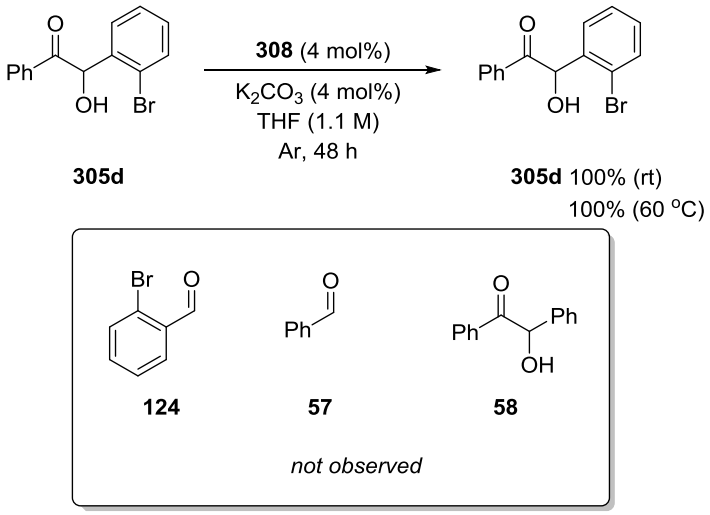


entry	time (min)	yield **58** (%)[a]	yield **305d** (%)[a]
1	5	0	3
2	10	0	4
3	15	0	4
4	20	0	5
5	30	0	8
6	60	0	11
7	120	0	19
8	240	0	29
9	840	2	61

[a]Yield determined by ^{1}H NMR spectroscopy using styrene (0.25 equiv.) as an internal standard. Note: yields of **58** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2.

Following this, in an attempt to quantify the ability of the carbene derived from **308** to promote the destruction of cross-benzoin **305d**, we exposed a pure sample of **305d** to our reaction conditions (Scheme 2.13). Interestingly, after 48 hours the starting material was present (*via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture) in quantitative yield with no detection of any species derived from the action of an NHC-mediated retro-benzoin condensation process (*i.e.* **57**, **58** or **124**) at ambient temperature. Increasing the temperature of the reaction to 60 ^{o}C also failed to lead to observable transformation of **305d** into its parent aldehydes.

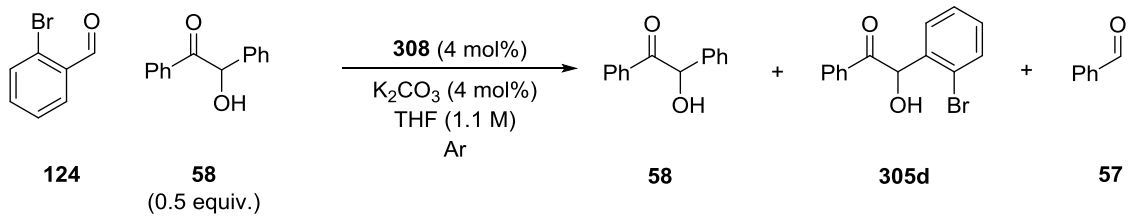
Scheme 2.13 Quantifying the reversibility of **305d** formation *via* an NHC-mediated pathway



Similarly, utilising 0.5 equivalents of **58** (*in lieu* of **305d**) in the presence of **124** under these reaction conditions returned both starting materials in 100% crude yield (entry 1, Table 2.9). However, increasing the reaction temperature to 60 ^{o}C enabled us to observe species (*i.e.* **57** and **305d**) whose presence can only be rationalised through the operation of an NHC-mediated retro-benzoin condensation pathway (entry 2), indicating that formation of benzoin within the system may be a reversible and thermodynamically-controlled pathway. By employing alternative triazolium precatalyst salts (entries 3 and 4) we found that the reversible formation of benzoin in the presence of the corresponding NHCs was accentuated by reducing the sterics of the *N*-aryl ring. Under such conditions, the final ratio of products appeared heavily influenced by the size of the *N*-aryl ring (*e.g.* both homo- and cross-benzoin dimers are observable *in situ* when employing the smaller

N-pentafluorophenyl-substituted triazolium ion precatalyst **54**), in parallel with results obtained in our original optimisation studies (see Table 2.1)

Table 2.9 Assessing the reversibility of benzoin formation under standard conditions



124 **58** (0.5 equiv.) **58** **305d** **57**

entry	time (h)	temp. (^{o}C)	yield **58** (%)[a]	yield **57** (%)[a]	yield **305d** (%)[a]
1	48	rt	100	0	0
2	18	60	97	1	2
3[b]	18	60	84	2	13[c]
4[d]	18	60	92	2	2[e]

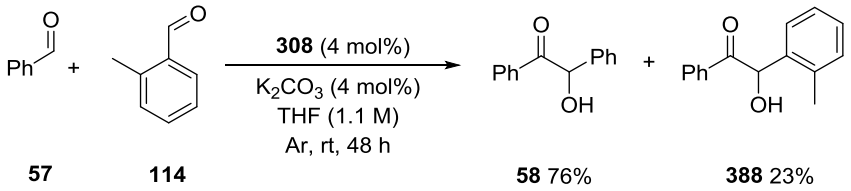
[a]Yield determined by ^{1}H NMR spectroscopy using styrene (0.25 equiv.) as an internal standard. [b]Precatalyst **304e** employed. [c]Formation of **305c** was also observed in 4% crude yield. [d]Precatalyst **54** employed. [e]Formation of benzoin adducts **305a** and **305c** was also observed in 8% and 5% crude yield respectively.

2.8.3 Examining the electrophilicity of 2-bromobenzaldehyde and benzaldehyde

With these results we somewhat satisfied ourselves that formation of **305d** in the crossed benzoin condensation between **124** and **57** in the presense of **308** was a kinetically-controlled reaction pathway that occurs irreversibly at ambient temperature. Thus, it stands to reason that the extent of the *ortho*-bromine atom's electronic effect upon the carbonyl of **124** may be sufficient enough to compensate for any steric obstruction it poses to the Breslow intermediate's nucleophilic attack. In order to confirm the enhanced electrophilicity of **124** over **57** in the presence of a nucleophile, we conducted a series of experiments to support this postulate. Accordingly, we attempted an intermolecular cross-condensation between **57** and 2-tolualdehyde (**114**, Scheme 2.14), in the presence of **308** and base, envisaging that although the steric bulk of the *ortho*-methyl group

would mirror that of the *ortho*-bromine atom of **124** to some degree, its slight deactivating effect upon the carbonyl would disfavour chemoselective formation of the cross benzoin adduct **388**. To our delight, our intuitions proved correct, with **58** isolated in 76% yield while **388** was formed in just 23% after 48 hours.

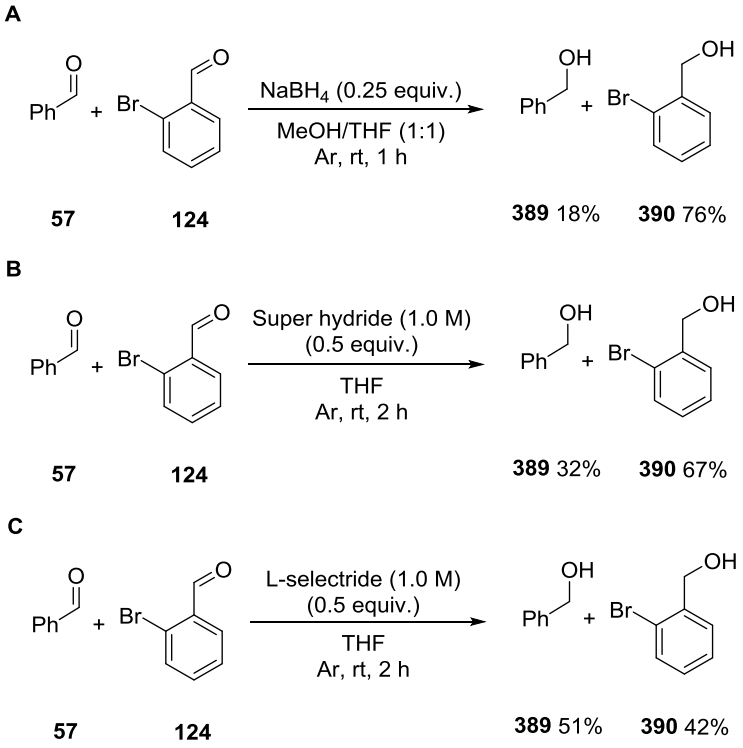
Scheme 2.14 Attempted NHC-catalysed intermolecular crossed benzoin condensation of **57** and **114**



57 **114** **58** 76% **388** 23%

We then sought to further explain the superior electrophilicity of **124** over **57** through a range of competition experiments in the presence of a range of nucleophiles. We hypothesised that the steric characteristics of the nucleophile would dictate which aldehyde would be subject to nucleophilic attack *i.e.* the larger the nucleophile, the less favoured its attack on the carbonyl moiety of **124** would be. In a mixture of stoichiometric amounts of **124** and **57**, stereotypical carbonyl reduction using 0.25 equivalents of sodium borohydride ($NaBH_4$) resulted primarily in the production of alcohol **390**, observed *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture after 1 hour (**A**, Scheme 2.15). Increasing the steric bulk of the reductant by using lithium triethylborohydride (Super Hydride®) led to a decrease in the propensity for attack of the hydride upon **124**, with **390** produced in 67% yield and benzyl alcohol (**389**) formed in 32% yield (**B**). Further augmentation of the size of the reducing agent when employing lithium tri-*sec*-butyl(hydrido)borate (L-selectride®) resulted in nearly equal formation of both alcohol products, with hydride-induced reduction of the less hindered benzaldehyde (*i.e.* **57**) marginally preferred (**C**).

Scheme 2.15 Electrophilicity competition experiments: carbonyl reduction



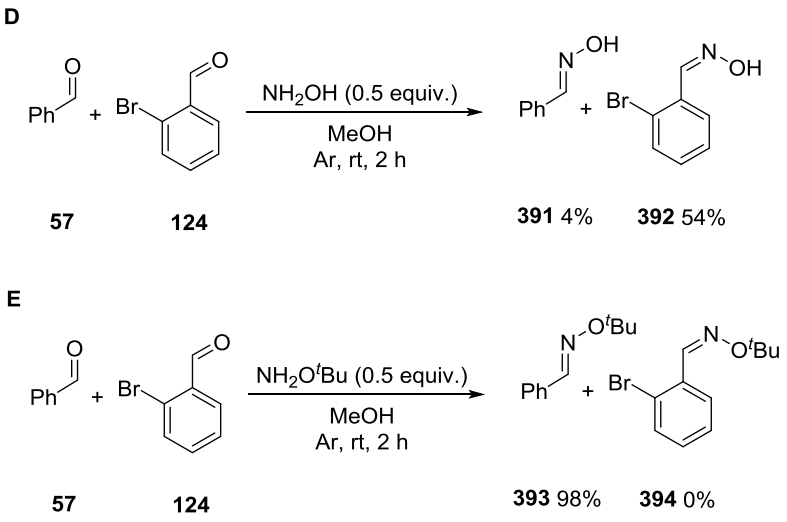
Note: yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using conversion of starting aldehydes and styrene (0.25 equiv.) as an internal standard.

To ensure that the nature of the nucleophile employed in our study was not restricted to boron-based reducing agents, we also exposed both **57** and **124** to a stoichiometric amount of hydroxylamine (NH_2OH) *in situ* and monitored the observed conversion to their oxime derivatives **391** and **392** (Scheme 2.16). Again, the unhindered steric nature of NH_2OH correlated to preferential nucleophilic attack upon **124** over the course of a two hour reaction timeframe (**D**), while in the presence of the more hindered *O*-*tert*-butyl hydroxylamine there was a marked reversal in the selectivity of the reaction, with 98% conversion of **57** to **393** (**E**).

Finally, to introduce a degree of parity with the Breslow intermediate, we employed the carbon-based nucleophile TMSCN which provides access to *O*-silylated cyanohydrins (Scheme 2.17) through nucleophilic addition to a carbonyl moiety. In keeping with our previous observations, activation of the carbonyl group of **124** by the presence of the *ortho*-bromine atom dictates that it is primarily subjected to nucleophilic attack by TMSCN under these conditions, with **396** present in a five-fold excess over **395** after 2 hours (**F**). To further support these findings, analogous employment of the unactivated

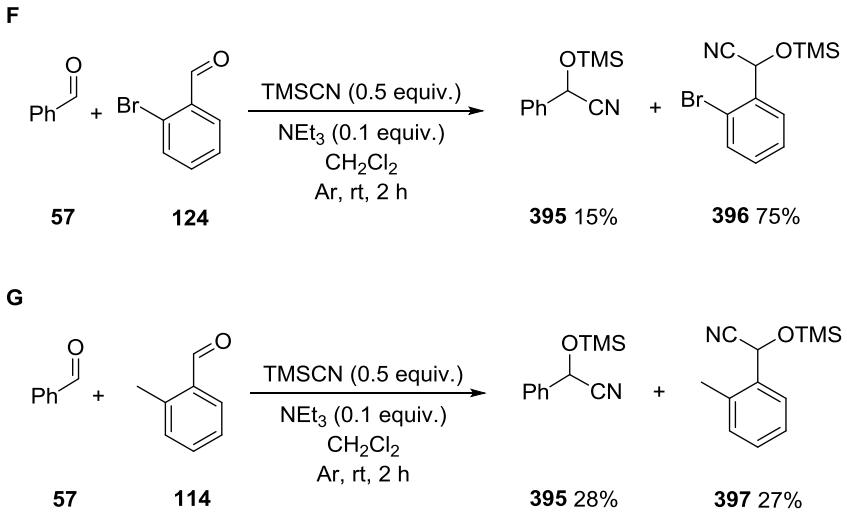
aldehyde **114** under the same reaction conditions led to an almost equal propensity for attack of the nucleophile upon either aromatic aldehyde (**G**).

Scheme 2.16 Electrophilicity competition experiments: hydrazone formation



Note: yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using conversion of starting aldehydes and styrene (0.25 equiv.) as an internal standard.

Scheme 2.17 Electrophilicity competition experiments



Note: yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using conversion of starting aldehydes and styrene (0.25 equiv.) as an internal standard.

2.8.4 Proposed mechanistic rationale for observed chemoselectivity using precatalyst 308

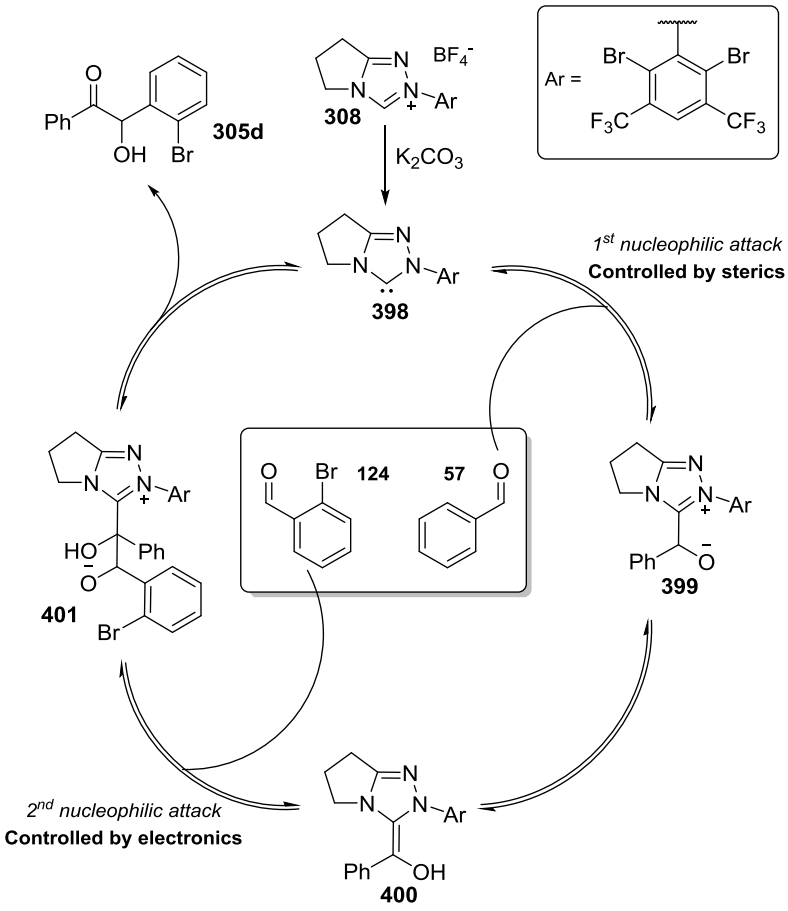
Considering the data presented above, we propose a mechanistic pathway very much in keeping with that postulated by Glorius (Scheme 2.18). Following generation of the triazolylidene catalyst **398** through base-mediated deprotonation of the parent triazolium ion (**308**), addition of the carbene to the carbonyl moiety of the less sterically-hindered aromatic aldehyde forms the 3-(hydroxybenzyl)azolium intermediate **399**. Subsequent derivatisation of the Breslow intermediate (**400**) occurs through a proton exchange and enables a second nucleophilic attack to take place. Unlike the original carbene, however, the Breslow intermediate is sterically less imposing at the site of subsequent carbon-carbon bond formation and so the electronic effect of the *ortho*-bromine atom upon the carbonyl compensates for potential steric repulsions incurred upon nucleophilic addition. Thus, as shown in our competition experiments detailed above, the electrophilicity of **124** supersedes that of **57** in the presence of sufficiently unhindered nucleophiles and so attack upon its carbonyl moiety by the Breslow intermediate is the primary outcome, forming the tetrahedral adduct **401**. Rapid and irreversible elimination of the NHC from this adduct gives rise to the desired cross-benzoin **305d** as the major reaction product. Under our employed reaction conditions, **305d** is shown not to participate readily in a retro-benzoin condensation pathway and so its formation is essentially irreversible. A reasoning behind the irreversibility of this pathway is open to debate and may arise from a hydrogen-bonding interaction of the lone pairs on the *ortho*-bromine atom and the OH moiety, which stabilises the adduct towards the retro-benzoin condensation pathway under the aprotic and anhydrous reactions employed in this study.

2.8.5 Mechanistic studies upon the rate and equilibria constants of triazolylidene-mediated processes: alternative considerations

Recently, however, several noteworthy reports have emerged which offer extensive mechanistic insights into a variety of triazolylidene-catalysed reaction pathways. While none of the data presented in these studies has thus far culminated in an alternative mechanistic proposal to explain the chemoselective preference of such reaction systems for formation of cross-benzoin adducts such as **305d**, in the context of this thesis they pose several questions that require addressing in future work.

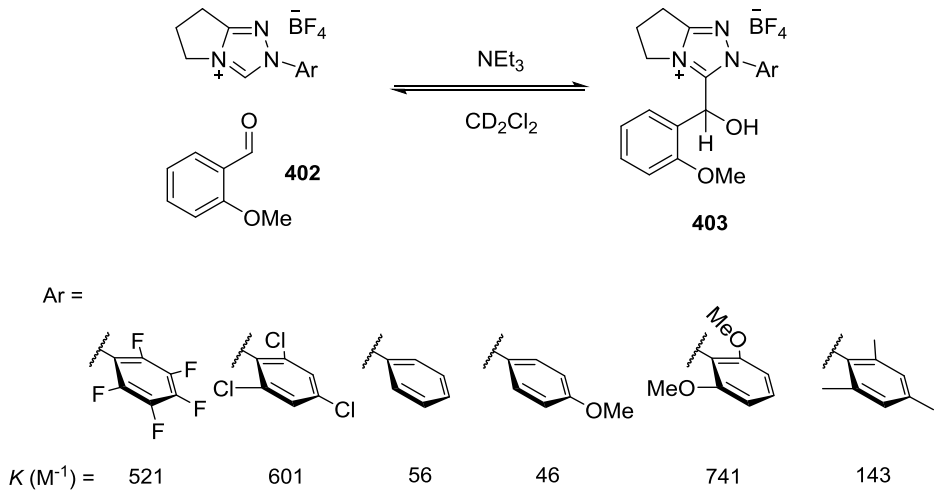
In seeking to quantify the effect of *N*-mesityl triazolium salts in NHC-mediated reactions, Bode carried out an NHC-catalysed benzoin condensation in the presence of a

Scheme 2.18 Proposed mechanistic pathway to explain formation of cross-benzoin 305d



deuterium source (deuterated methanol, CD_3OD).[229] Under these conditions, Bode not only observed the formation of deuterated benzoin but also of deuterated benzaldehyde and suggested that Breslow intermediates derived from benzaldehydes are formed reversibly. Later, in 2013, Smith *et al*. extended the focus of Bode's work beyond *N*-mesityl triazolium salts when they conducted a study upon the general effect of the triazolium unit's *N*-aryl substituent in the Stetter and benzoin reactions.[261] Examining the equilbrium constants (*K*) for the nucleophilic attack of various triazolylidene carbenes upon the deactivated carbonyl of 2-anisaldehyde (**402**, Scheme 2.19) to form the 3-(hydroxybenzyl)azolium Breslow intermediate precursor **403**, it was found that the presence of a 2,6-substitution pattern in the *N*-aryl ring corresponds to much larger *K* values.

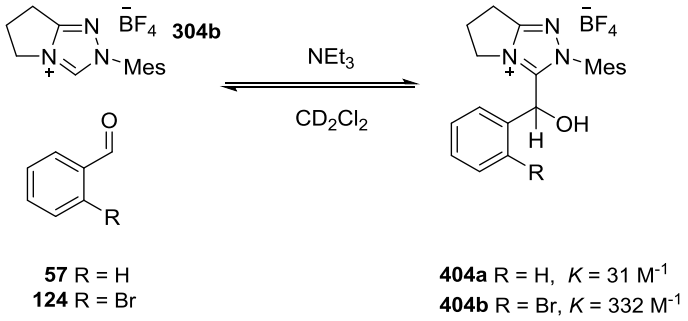
Scheme 2.19 Determination of equilibrium constants for the addition of triazolium salts to 2-anisaldehyde



Smith explained this observation simplistically, suggesting that a 2,6-substituted *N*-aryl ring generates a more stable 3-(hydroxybenzyl)azolium salt due to the orthogonality of the *N*-aryl ring, leading to a greater ability to accommodate the 3-(hydroxybenzyl) substituent. This proposed orthogonality in *N*-mesityl-substituted triazolium salts had been previously verified by Mayr through computational and X-ray crystallographic studies.[230] Cavollo further demonstrated how the orientation of the *N*-aryl group was determined through a balance of the conjugation energy gained in a co-planar geometry and minimisation of steric repulsions by adopting an orthogonal alignment. *N*-phenyl salts were shown to adopt this co-planar geometry, while *N*-mesityl salts were almost perpendicular to the heterocyclic ring.[231] Smith's work further established (through deuterium exchange experiments) that while the formation of electron-rich 3-(hydroxybenzyl)azoliums with a 2,6-substitution pattern occurred relatively quickly, subsequent deprotonation to form the Breslow intermediate proceeded much faster in electron-deficient analogues, reflective of the pK_a value of the original triazolium salt. Indeed, within Smith's system the rate of proton-deuterium exchange for various *N*-aryl-substituted triazolium precatalysts generally paralleled the rate of product formation in the Stetter and benzoin condensations mediated by the same precatalysts in basic conditions, leading the author's to conclude that deprotonation of **403** to form the Breslow intermediate was the rate-determining step of the reaction, in accordance with Rovis' previous proposals.[232]

More recently, in 2015, Smith *et al*. disclosed the most comprehensive mechanistic investigation to date into the interaction of triazolylidene species and *ortho*-substituted benzaldehydes.[233] The results of this study were remarkable in the context of previously reported chemoselectivities in an extensive range of crossed acyloin condensations and were brought to our attention soon after work on this thesis was begun. Acknowledging the pronounced use of benzaldehydes possessing heteroatoms in the *ortho* positions in several chemoselective NHC-catalysed crossed acyloin reactions, the authors sought to determine the specific rate and equilibria constants (*K*) for the addition of NHCs to *ortho*-substituted benzaldehydes. In regard to our work detailed above, the addition of the carbene derived from *N*-mesityl triazolium salt **304b** to the carbonyl of **124** proceeded faster than the corresponding addition involving **57** (Scheme 2.20).

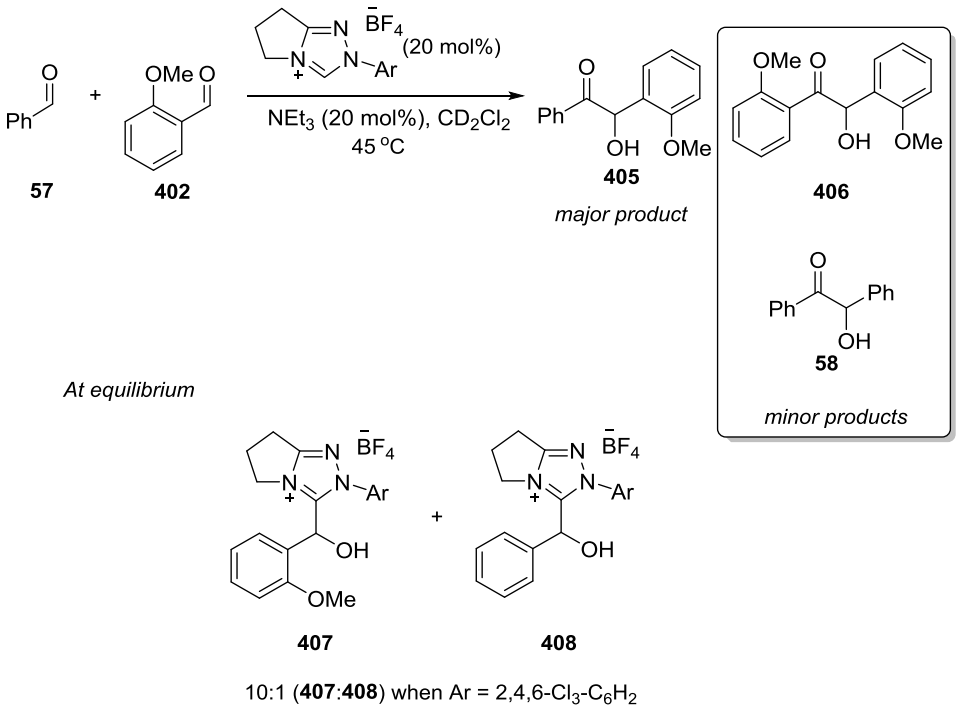
Scheme 2.20 Measured equilibrium constants for addition of an *N*-mesityl triazolylidene to 2-bromobenzaldehyde and benzaldehyde by Smith *et al*.



The study found that, regardless of its identity, the installation of a heteroatom in the *ortho* position of the benzaldehyde ring corresponded to a dramatic increase in the equilibrium constant for formation of 3-(hydroxybenzyl)azolium salts (*i.e.* **404**). Such a result is obviously in direct conflict with both ours and Glorius' postulated mechanistic pathway, which deemed the first nucleophilic attack of the NHC to be primarily determined by the steric characteristics of both aromatic aldehydes rather than their electronic properties. However, a representative NHC-catalysed cross-condensation experiment conducted by Smith found the chemoselective outcome of the reaction to be consistent with Glorius' results (Scheme 2.21). Significantly, in doing so Smith demonstrated that at equilibrium the formation of 3-(hydroxybenzyl)azolium **407** (derived from initital attack of the NHC upon **402**) was favoured over **408**. While a definitive explanation behind the preference for this first addition of the NHC to the *ortho*-substituted aldehyde remained elusive, the authors suggested that interaction of the

heteroatom lone pair with the σ*- or π*-orbital of the carbonyl may induce it to twist out of conjugation with the aromatic ring and thus increase its reactivity towards nucleophiles. Alternatively, interaction between this lone pair and the OH moiety of the 3-(hydroxybenzyl)azolium may induce increased stability of this adduct.

Scheme 2.21 Intermolecular crossed benzoin condensation conducted by Smith *et al*.



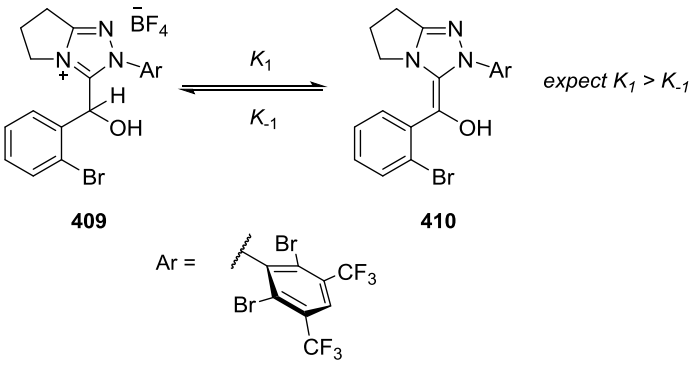
Considering these reports, two points of note could be of relevance to our system:

1. The presence of a 2,6-substitution pattern in the *N*-aryl ring of **308** suggests that addition of the subsequent carbene to the *ortho*-substituted benzaldehyde could also occur rapidly.
2. The electronegative nature of the *ortho*-bromine atom in **308** is such that the proposed rate-limiting step within the cross-benzoin condensation (*i.e.* deprotonation of the 3-(hydroxybenzyl)azolium adduct to form the Breslow intermediate) would still proceed relatively quickly.

The selectivity observed in our crossover experiments is in keeping with those reported by Glorius and Smith in that products derived from initial attack of the carbene upon the carbonyl of the *ortho*-substituted benzaldehyde are formed in negligible yield. However, no data is available to quantify the affinity of the carbene derived from **308** for addition

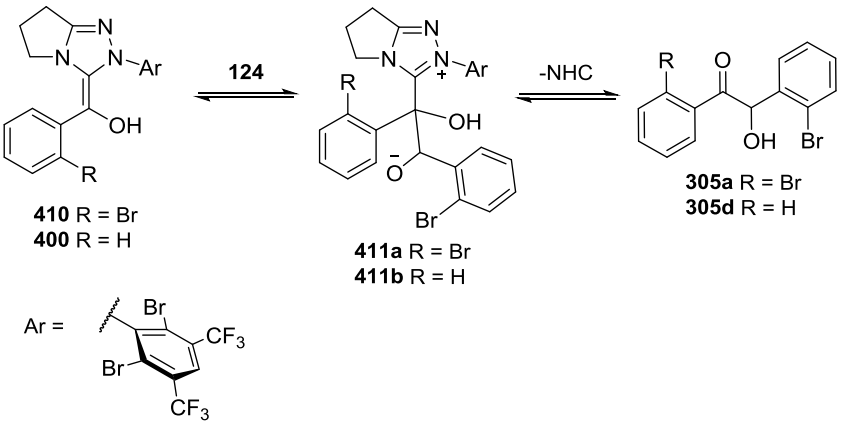
to the carbonyl of **124** and so it is both difficult and speculative to attempt to extend the applicability of this study to our methodology. Given Smith's observations, such a significant difference in the tendency for specific triazolylidenes to initially add to the carbonyl of *ortho*-substituted aldehydes would mean that the chemoselectivity of an NHC-catalysed crossed benzoin condensation must be determined at a later point in the reaction. Smith's report suggests that deprotonation of the 3-(hydroxybenzyl)azolium adduct to form the Breslow intermediate represents a plausible (albeit unlikely) origin for this selectivity. In this regard, it was determined that (in general) the presence of both *ortho*-substituents and heteroatoms, as well as an electron-deficient *N*-aryl ring, helped increase the value of the equilibrium constant (K_1) for this step (Scheme 2.22). However, Smith found electron-donating *ortho*-substituents to actually decrease the magnitude of K_1 and increase the value of K_{-1} and so it follows that the electron-deficient nature of **409** would likely increase the value of K_1. With this it therefore becomes highly improbable that the selectivity of our methodology is determined at this point as we have combined the three elements Smith prioritises in formation of **409** (*ortho*-substitution, heteroatom presence and electron-deficiency), presumably aiding its deprotonation to form **410** also and yet products derived from this pathway are formed in a minority.

Scheme 2.22 Comparison of possible equilibrium constants for formation of the Breslow intermediate using precatalyst **308** under Smith's postulates



Therefore, under such conditions, it is conceivable that the chemoselective outcome of the reaction could be determined at either (a) forward reaction of the Breslow intermediate (*i.e.* **410** or **400** → **411**, Scheme 2.23) or (b) dissociation of the resulting tetrahedral intermediate (*i.e.* **411** → **305a** or **305d**).

Scheme 2.23 Potential origins of chemoselectivity using precatalyst **308** under Smith's postulates



Considering (a), the nucleophilic character of **410** would be diminished (relative to **400**) due to the electronegative effect of the *ortho*-bromine atom. Coupled with its size, it would be entirely plausible that, using Smith's postulates, chemoselective formation of the cross-benzoin **305d** is attributable to the fact that **400** is sufficiently nucleophilic and unimpeded to carry out a further attack upon a second aldehyde while **410** is not. Conversely, although slow dissociation of the NHC from tetrahedral adduct **411a** relative to **411b** would also represent a valid explanation for the observed chemoselectivity of the reaction, the accumulation of intermediates such as these has never been observed *via* ^{1}H NMR spectroscopic analysis of crude reaction mixtures throughout the duration of this study. This is in keeping with Smith's work, as well as earlier reports conducted by Leeper and White on the thiazolylidene-mediated benzoin condensation.[234]

2.8.6 Alternative mechanistic considerations

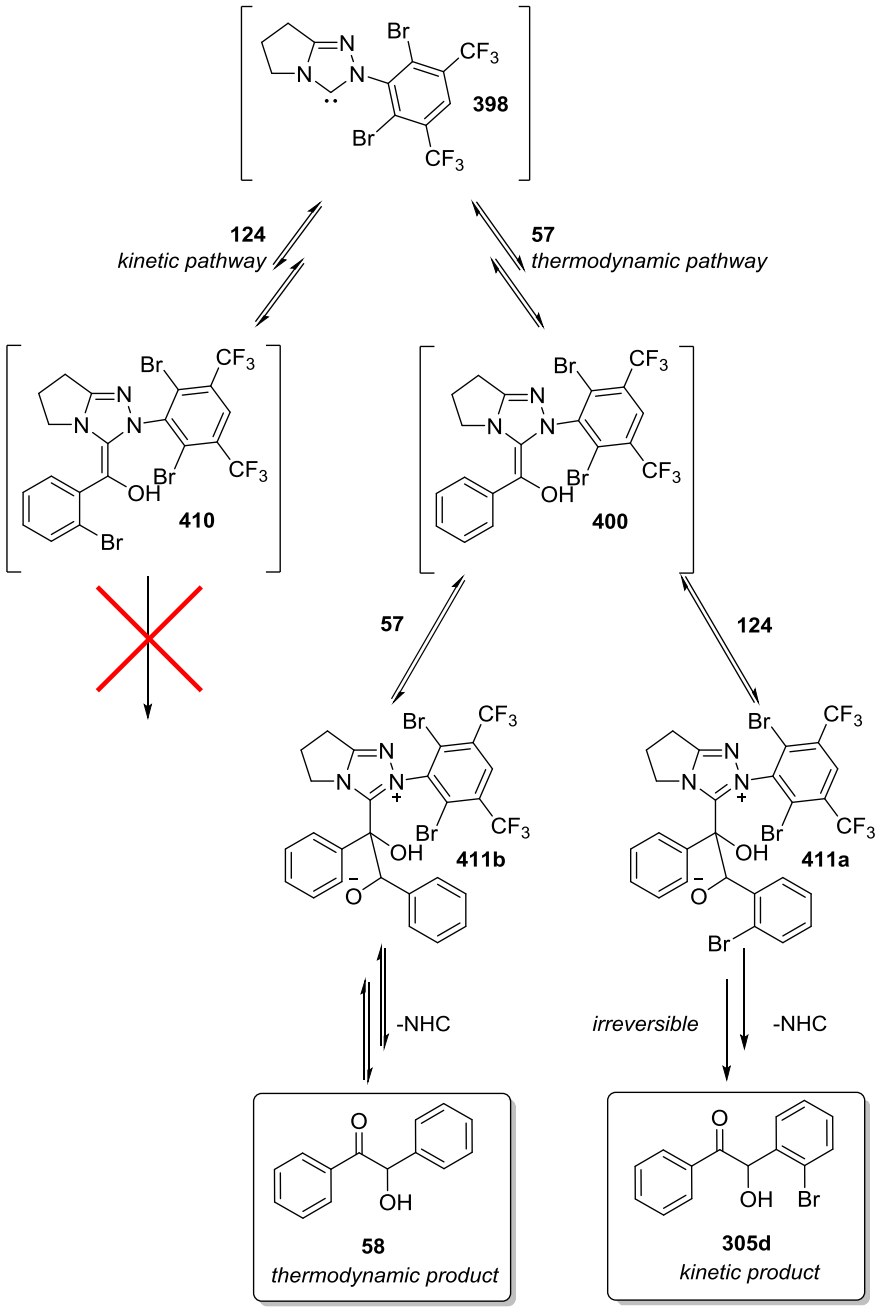
Acknowledging the potential implications of Smith's report for our previously proposed mechanism for the NHC-catalysed crossed benzoin condensation, it is of course conceivable that the chemoselective formation of **305d** occurs due to a combination of thermodynamic and kinetic reaction factors detailed in Scheme 2.24: following base-mediated generation of **398** from its parent triazolium ion **308**, addition of the carbene to the carbonyl moiety of **124** occurs rapidly, generating the kinetic Breslow intermediate **410**. This pathway could represent an impasse as the nucleophilic ability of **410** in the context of this reaction is perhaps compromised by the presence of the electronegative bromine atom, in addition to its steric bulk. Intermediate **410** would then revert to its

parent aldehyde and triazolylidene **398**. Alternative addition of **398** to the carbonyl of **57** generates the thermodynamic and reactive Breslow intermediate **400** which, when faced with a further choice of electrophilic coupling partners, undergoes nucleophilic attack upon the more activated aromatic aldehyde **124** to form the tetrahedral adduct **411a**. Rapid and irreversible elimination of the NHC from this adduct would again give rise to the desired cross-benzoin **305d** as the kinetic product. In this manner, we can see how the electrophilicity of both aromatic aldehydes (as opposed to steric hinderance) remains the dictating factor for the nucleophilic attack of the Breslow intermediate upon the carbonyl of the second aldehyde. However, considering Smith's recent disclosures, the point at which the chemoselectivity of the reaction is determined (when employing our triazolium ion precatalyst **308**) is in need of much more stringent verification than that posited here. Indeed, it may be the case that the complexity of the reaction renders this beyond current analytical methods and, although several literature reports have detailed syntheses of isolable Breslow intermediate analogues,[243-246] without its physical isolation it is likely that the basis for the chemoselective outcome of many NHC-catalysed reactions will remain hypothetical.

2.9 Conclusions

In conclusion, through careful optimisation and design of a novel triazolium salt precatalyst we have developed the first highly chemoselective method for the intermolecular crossed benzoin condensation between two non-identical disparate aldehydes. Using moderate catalytic loadings of the precatalyst and an equimolar loading of heterogenous base, a wide range of substituted aromatic aldehydes could be cross-coupled with 2-bromobenzaldehyde in high yield and excellent chemoselectivity under our devised reaction conditions. Similarly, the substrate scope of the reaction with regard to the *ortho*-substituted aromatic aldehyde was found to be broad. Disappointingly, the presence of an *ortho*-substituent was deemed necessary for our catalyst to direct a chemoselective process. However, through optimisation of a palladium-catalysed hydrodebromination process, the preparation of cross-benzoin adducts otherwise inaccessible through conventional NHC-catalysed means could be achieved rapidly and in excellent yield.

Scheme 2.24 Postulated kinetic and thermodynamic control of the crossed benzoin condensation mediated by NHC **398**



Finally, a rationale explaining (in part) the observed selectivity of our novel triazolylidene catalyst was proposed through extensive mechanistic and competition studies. It was suggested that formation of the Breslow intermediate derived from attack of the carbene upon benzaldehyde occurs due to its carbonyl moiety being sterically unhindered in comparison to that of 2-bromobenzaldeyde. However, subsequent nucleophilic attack of the derived Breslow intermediate upon the carbonyl of 2-bromobenzaldehyde was posited to be the favoured pathway due to the activating effect

of the *ortho*-bromine substituent. The formation of cross-benzoin **305d** through this pathway was deemed to be irreversible under our reaction conditions and hence the observed chemoselective outcome of this NHC-catalysed condensation. We also acknowledged the recent publication disclosed by Smith *et al*. by postulating an alternative reaction mechanism, based upon their findings regarding the effect of *ortho*-substituents upon rates of NHC addition to aromatic aldehydes, which could also explain our results. However, with regard to our system, this pathway would require significant further validation by means of in-depth analysis.

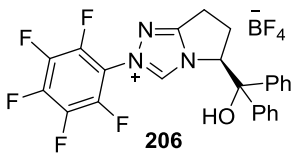
Chapter 3 Studies on the Asymmetric Intermolecular Crossed Benzoin Condensation as Catalysed by a Suite of Chiral Bifunctional *N*-Heterocyclic Carbenes

3.1 Expanding beyond the achiral intermolecular crossed benzoin condensation

Having established and optimised a method for the chemoselective NHC-catalysed crossed benzoin condensation using the achiral triazolium salt **308**, we then endeavoured to develop an asymmetric variant of this process. With the mechanistic insights outlined in the previous chapter, this extension of our methodology to enable enantioselective cross-benzoin formation represented a considerable synthetic challenge. Through introduction of a chiral moiety into the rigid bicyclic structure of our triazolium core, it was entirely plausible that the increased steric bulk would impact its ability to direct the chemoselective outcome of the reaction, or further still negate its catalytic activity entirely.

3.2 Pyroglutamic acid-derived chiral bifunctional triazolium salts precatalysts: design rationale

Previous studies from our group have demonstrated the proficiency of bifunctional chiral triazolium ion precatalysts incorporating hydrogen bond-donating substituents in promoting enantioselective benzoin and crossed acyloin condensations under basic conditions. [139,169] Chief among these has been the *N*-pentafluorophenyl-substituted precatalyst **206** (Figure 3.1), synthesised from (*S*)-pyroglutamic acid, with a chiral arm bearing a hydrogen-donating tertiary alcohol.



206

Figure 3.1 A bifunctional hydrogen-bonding chiral triazolium ion precatalyst for the asymmetric benzoin condensation

As reported previously by our group (see Section 1.5.2.3), (*R*)-benzoin was synthesised in 90% yield and >99% optical purity when **206** was employed as an NHC precatalyst in

the homobenzoin condensation, while a brief study examining its influence upon the enantioselectivity of the crossed acyloin condensation found it capable of promoting synthesis of cross-acyloin adducts with 79% yield and 77% *ee*. Encouraged by this, we decided to employ this general scaffold in the construction of a suite of novel chiral bifunctional precatalysts (**206** and **412a-g**, Figure 3.2). Increasing the steric bulk of the chiral arm through use of suitably substituted phenyl moieties had previously been demonstrated to offer very little reward (in terms of an improved enantioselective process)[139] and so we chose only to vary the identity of the *N*-aryl ring in deriving this new precatalyst library.

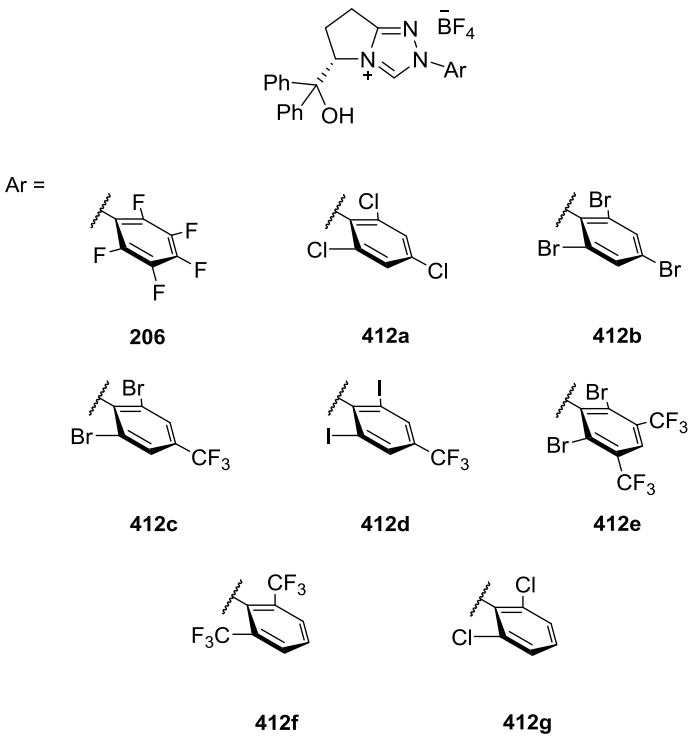


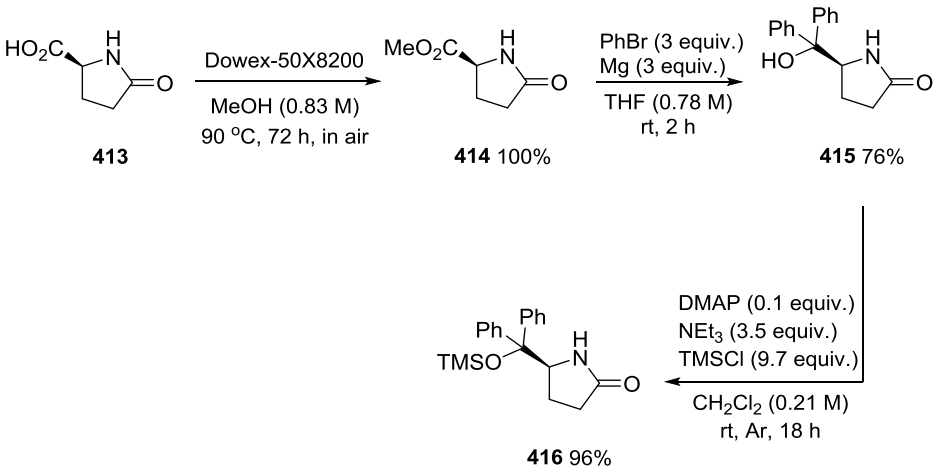
Figure 3.2 Chiral bifunctional triazolium precatalysts **206** and **412a-g**

3.3 Synthesis of chiral bifunctional triazolium salts

3.3.1 Synthesis of chiral lactam precursors

The synthesis of these novel chiral salts requires preparation of an *O*-silyl chiral lactam precursor (as outlined in Scheme 3.1) and utilises (*S*)-pyroglutamic acid (**413**) as a common starting reagent, an inexpensive and commercially available source of chirality.

Scheme 3.1 Synthetic route for preparation of chiral lactam precursors

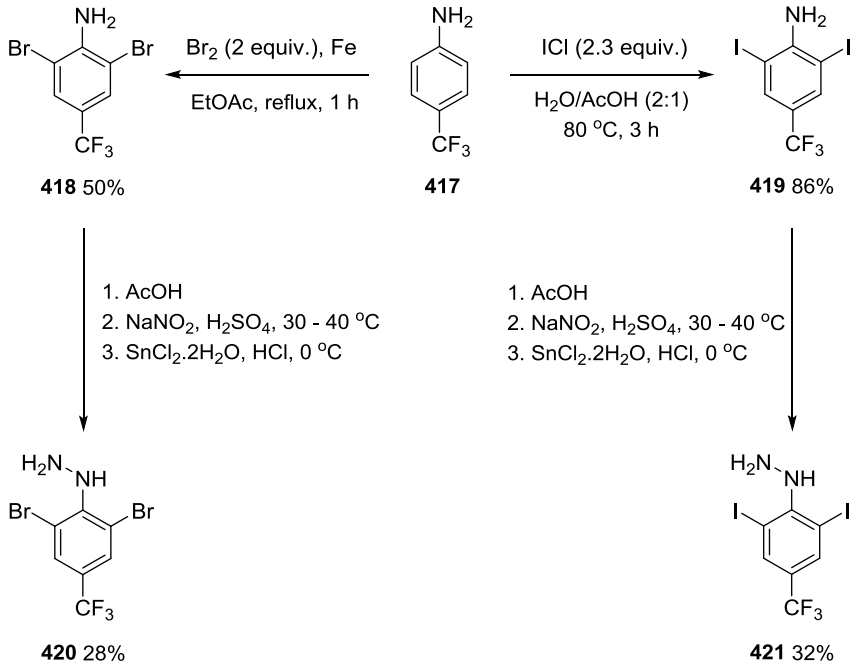


Esterification of **413** to its corresponding methyl ester **414** was smoothly carried out with quantitative yield, while Grignard chemistry was subsequently employed to afford the tertiary alcohol **415** in 76% yield. Finally, silylation of the OH moiety furnished the TMS-protected γ-lactam **416** in excellent yield.

3.3.2 Preparation of substituted arylhydrazine precursors

As with their achiral analogues, a desire to vary the structure of the *N*-aryl ring in our family of chiral triazolium salts demanded that we be able to access substituted arylhydrazine precursors for their synthesis. Again, while (2,4,6-trichlorophenyl)hydrazine (see precatalyst **412a**) was commercially available, precatalysts **412b**-**g** required the use of arylhydrazines not so readily at hand. (2,4,6-tribromophenyl)Hydrazine (**311**) and (2,6-dibromo-3,5-*bis*-trifluoromethyl-phenyl)-hydrazine (**315**) were prepared as described in Chapter 2 (Schemes 2.5 and 2.6). Further syntheses of the previously unreported arylhydrazines (2,6-dibromo-4-trifluoromethyl-phenyl)-hydrazine (**420**) and (2,6-diiodo-4-trifluoromethyl-phenyl)-hydrazine (**421**) were achieved according to the procedures outlined in Scheme 3.2, with both being derived from commercially available 4-(trifluoromethyl)aniline (**417**). Initial treatment with either molecular bromine, in the presence of iron filings, or iodine monochloride (a source of I^+) under acidic conditions provides the corresponding 2,6-halo-substituted anilines **418** and **419** in moderate and excellent yield respectively. Subsequent diazotisation and *in situ* tin-mediated reduction allows isolation of both desired arylhydrazines in low yield following basic work-up and recrystallisation from hexane.

Scheme 3.2 Synthesis of substituted anilines and arylhydrazines as precursors to precatalysts **412c** and **412d**

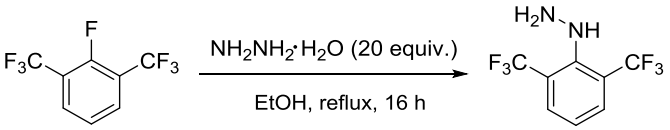


418 50% **417** **419** 86%

420 28% **421** 32%

Conversely, while 2,6-*bis*(trifluoromethyl)aniline is available from commercial sources, its high cost and the inefficiency of the diazotisation-reduction protocol meant we were reluctant to attempt the synthesis of the corresponding hydrazine *via* this method. Instead, we opted to achieve this through a nucleophilic aromatic substitution of the fluorinated precursor 2-fluoro-1,3-bis(trifluoromethyl)benzene (**422**, Scheme 3.3). Gratifyingly, reflux of **422** in the presence of a large excess of hydrazine monohydrate ($NH_2NH_2{\cdot}H_2O$) in EtOH provided (2,6-*bis*(trifluoromethyl)phenyl)hydrazine (**423**) in a moderate 50% yield.

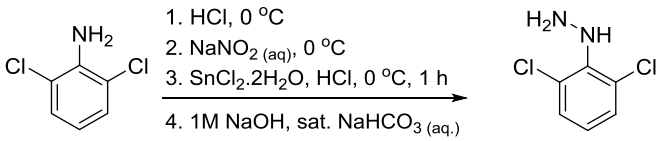
Scheme 3.3 Preparation of (2,6-*bis*(trifluoromethyl)phenyl)hydrazine *via* nucleophilic aromatic substitution



422 **423** 50%

Finally, (2,6-dichlorophenyl)hydrazine (**425**) was prepared from its parent aniline (**424**) *via* treatment with hydrochloric acid at 0 ^{o}C and subsequent addition of an aqeous sodium nitrite solution to form the diazonium salt *in situ*. Further reduction using stannous chloride and basic work-up enables isolation of **425** in poor yields following recrystallisation (Scheme 3.4).

Scheme 3.4 Preparation of (2,6-dichlorophenyl)hydrazine



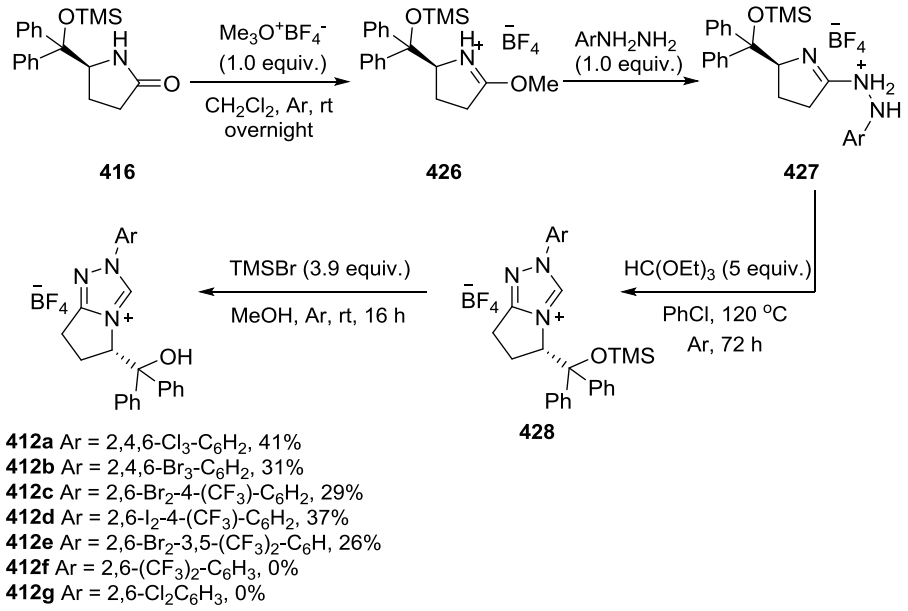
424 **425** 17%

3.3.3 Generation of a suite of chiral triazolium precatalysts possessing a hydroxy functionality

With the requisite arylhydrazine precursors in hand, the final step in the synthesis of our suite of chiral precatalysts involved a one-pot triazolium ring formation and subsequent alcohol deprotection in a procedure similar to that employed in the preparation of achiral analogues previously. Generation of the triazolium ion-based salt was achieved through successive treatment of the TMS-protected γ-lactam **416** with stoichiometric amounts of Meerwein's salt, the relevant arylhydrazine and an excess of triethyl orthoformate to effect the ring closure (Scheme 3.5). While the isolation of the TMS-protected precatalysts **428** has previously been attempted in our group, they have been shown to decompose readily on silica and resist efforts at their purification *via* recrystallisation. Thus, deprotection of **428** is carried out without purification of the crude reaction mixture. Thankfully, deprotected precatalysts **412** are generally stable to flash column chromatography and can be isolated in this manner with further recrystallisation if required. Following this procedure enabled us to obtain pure triazolium salts **412a**-**e** in low to moderate yields. Disappointingly, however, all endeavours to prepare **412f** and **412g** met with failure; following flash column chromatography, the obtained tan solids (in both cases) were observed to visibly decompose to dark brown semi-solids upon exposure to the external atmosphere and while mass spectrometry confirmed the presence of both desired products, pure samples of either precatalyst were unobtainable

for characterisation. Whether the absence of a *para* substituent on the *N*-aryl ring in these structures contributes to a dramatic increase in the air/moisture sensitivity of these species was not investigated further.

Scheme 3.5 Synthetic route for preparation of novel bifunctional chiral triazolium salts **412a-g**



3.4 The NHC-mediated asymmetric crossed benzoin condensation between two non-identical aromatic aldehydes

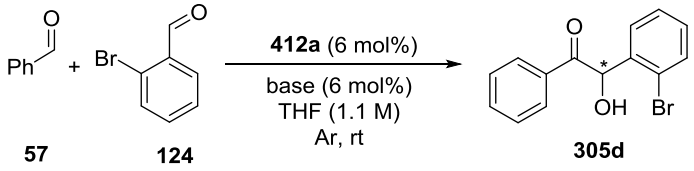
3.4.1 Preliminary experiments: optimisation of the base component

With the necessary precatalysts in hand, we began by establishing a set of reaction conditions amenable to promoting an NHC-catalysed asymmetric cross-benzoin condensation between two non-identical aromatic aldehydes. Through our previous studies, we were conscious of the fact that employment of an *ortho*-substituted benzaldehyde as one coupling partner could aid in establishment of a chemoselective process. We therefore again turned our attention to the cross-condensation between benzaldehyde (**57**) and 2-bromobenzaldehyde (**124**), focusing initially on enantioselective synthesis of **305d** rather than seeking to establish a highly chemoselective reaction. Aware that (under the basic reaction conditions) avoiding enolisation of the newly-formed stereocentre within the cross-benzoin product may prove

a considerable challenge, we set about screening a wide range of bases in the hope of identifying a suitable candidate for asymmetric cross-benzoin formation (Table 3.1). Thus, in the presence of 6 mol% of K_2CO_3 and *N*-trichlorophenyl-substituted precatalyst **412a**, **305d** was isolated in 71% yield with just 5% optical purity (entry 1). However, reducing the reaction time to 17 hours allowed us to isolate **305d** in 60% yield with an enantiopurity of 64% *ee* (entry 2), suggesting that the basic reaction conditions do indeed induce racemisation of the stereocentre. A slight reduction in the strength of the base through use of lithium carbonate slows this rate of racemisation but also impacts upon the reaction rate, such that **305d** is isolated in just 6% yield after 48 hours (entry 3). Interestingly, both rubidium carbonate and casesium carbonate appeared to promote both moderate yields and a moderately enantioselective reaction within an identical timeframe (entries 4 and 5). Strangely, however, reducing the reaction time to 18 hours but maintaining a 6 mol% base loading of Cs_2CO_3 leads to a pronounced loss in optical purity of the isolated product but significantly higher yields (entry 6). Further reduction of the reaction time but still utilising identical condtions produced erratic results, **305d** formed in 29% yield after 4 hours with an optical purity of 44% yet isolated in 45% yield and 43% *ee* after just 2 hours (entries 7 and 8). Conversely, increasing the reaction time 6 days leads to total racemisation of the product (entry 9).

In a similar manner, further use of a heterogeneous base in potassium benzoate ($KC_6H_4CO_2$) produced results that equally defied logical explanation. In its presence (6 mol%), after 48 hours we obtained **305d** in 47% yield with 51% optical purity (entry 10). Reducing the reaction time to 4 hours decreases this isolated yield to 22% yield but allows an improvement in the enantioselectivity of the process, the desired product having an optical purity of 63% (entry 11). After 2 hours, however, the isolated yield of **305d** was 21% but we failed to observe an increase in its optical purity (57%, entry 12), while this value decreased further when the reaction was quenched after just 1 hour (entry 13). We also examined the effect of acetate bases upon the efficiency and enantioselectivity of the reaction, with a 6 mol% base loading of KOAc allowing us to isolate **305d** in 60% yield and 38% *ee* (entry 14). As with previous findings, a shorter reaction time promoted a more enantioselective process with moderate yields without ever allowing us to produce **305d** in entirely enantiopure form. After 20 hours, the desired cross-benzoin was formed 62% yield with 58% optical purity (entry 15), while halting the reaction after 4 hours and 2 hours increased this enantioenrichment to 61% *ee*

Table 3.1 Asymmetric cross-benzoin condensation: initial studies



57 124 305d

entry	base	time (h)	yield (%)[a]	*ee* (%)[b]
1	K_2CO_3	48	76	5
2	K_2CO_3	17	60	64
3	Li_2CO_3	48	6	40
4	Rb_2CO_3	48	66	50
5	Cs_2CO_3	48	62	52
6	Cs_2CO_3	18	83	25
7	Cs_2CO_3	4	29	44
8	Cs_2CO_3	2	45	43
9	Cs_2CO_3	144	82	0
10	$KC_6H_4CO_2$	48	47	51
11	$KC_6H_4CO_2$	4	22	63
12	$KC_6H_4CO_2$	2	21	57
13	$KC_6H_4CO_2$	1	8	50
14	KOAc	48	60	38
15	KOAc	20	62	58
16	KOAc	4	58	61
17	KOAc	2	58	63
18	KOAc	1	40	69
19	KOAc	0.5	13	63
20	CsOAc	48	53	45
21	CsOAc	2	52	59
22	CsOAc	1	48	63
23[c]	K_2CO_3	2	85	15

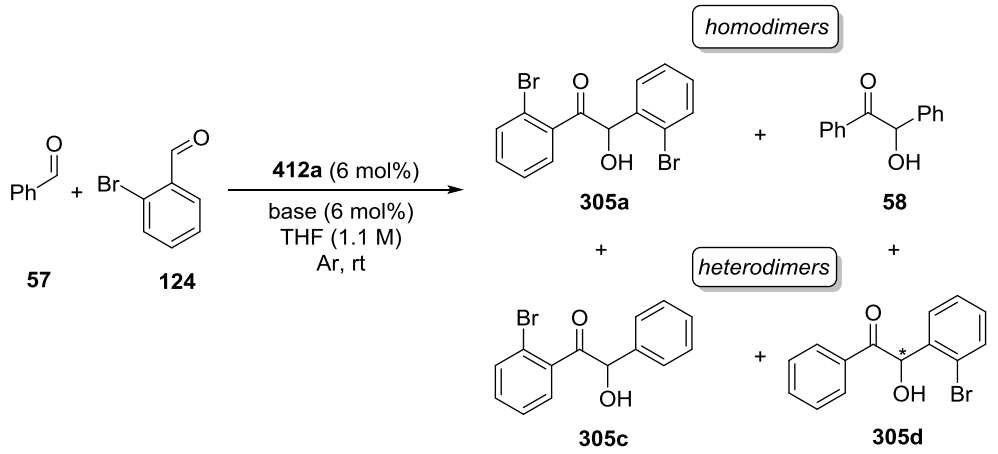
[a]Isolated yield. [b]Determined *via* HPLC analysis. [c]Reaction carried out on a 3.3 mmol scale as opposed to 1.1 mmol scale.

and 63% *ee* respectively (entries 16 and 17). Our most successful experiment (in terms of asymmetry) as part of this optimisation study was achieved when 6 mol% of KOAc was employed with an equimolar catalytic loading of **412a** and the reaction was quenched after 1 hour. Under these conditions, **305d** was isolated in 40% yield with an optical purity of 69% (entry 18). Again, however, halving this reaction time further led to a marginal decrease in the enantioselectivity of the protocol (entry 19). No such unusual values were observed when the identity of the counterion was changed through alternative use of CsOAc, with **305d** being produced in moderate isolated yield (48-53%) regardless of the extent of the reaction and the enantioselectivity of the reaction improving with shorter reaction times (entries 20-22). At this point, despite the reproducibility of our methods, given the fluctuation in the optical purity of **305d** at a range of reaction timepoints we began to postulate that the heterogeneous nature of carbonate/benzoate/acetate bases and THF was hampering our efforts to gain enantiocontrol over the process and would continue to produce erratic future results. This was confirmed through a three-fold increase the reaction scale upon which, using 6 mol% K_2CO_3 in the presence of **412a**, the cross-condensation between **124** and **57** proceeded with 85% isolated yield of **305d** which had a corresponding optical purity of just 15% (entry 23). Contrasting this with entry 2, we determined that a heterogeneous system was counter-productive in seeking to develop a truly enantioselective methodology.

3.4.2 Preliminary experiments: homogeneous base screening

With these preliminary results to hand, we decided to screen a series of nitrogenous bases, with conjugate acids of various pK_a values,[262-264] in the presence of **412a** in THF and examine their influence upon the efficiency and enantioselectivity of the cross-condensation between **124** and **57**. We envisaged that their homogeneity would result in an improvement of the stereochemical outcome of the reaction (Table 3.2). Use of DABCO (conjugate acid pK_a 8.8) allowed the isolation of **305d** in 25% yield after just 1 hour with a corresponding *ee* of 67% (entry 4). Pleasingly, we found no change in the enantiomeric excess of the isolated product over the course of a 2-4 hour timescale when a 6 mol% base loading of DABCO is employed, while yields of **305d** increase in an approximately time-dependent fashion, with ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicating its formation in 60% yield after 4 hours, albeit with significant concurrent formation of **58** (entries 1-4). Similar results were obtained

Table 3.2 Asymmetric cross-benzoin condensation: initial studies



entry	base	time (h)	yield **305a** (%)[a]	yield **58** (%)[a]	yield **305c** (%)[a]	yield **305d** (%)[a,b]	*ee* **305d** (%)[c]
1	DABCO	1	0	28	0	30 (25)	67
2	DABCO	2	0	38	0	49 (45)	67
3	DABCO	3	0	40	0	59 (55)	67
4	DABCO	4	0	40	0	60 (57)	67
5	DIPEA	1	0	14	0	20 (14)	67
6	DIPEA	2	0	18	0	34 (30)	67
7	DIPEA	3	0	22	0	48 (45)	67
8	DIPEA	4	0	27	0	65 (63)	67
9	DIPEA	24	n/d	n/d	n/d	63 (60)	51
10	DMAP	4	0	1	0	16 (9)	67
11	NMI	20	0	0	0	6 (n/d)	n/d
12	DBU	1	0	34	9	48 (n/d)	n/d
13	DBU	2	0	35	0	59 (57)	57

[a]Determined *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (0.25 equiv.) as an internal standard. [b]Value in parentheses represents isolated yield. [c]Determined *via* CSP-HPLC analysis.

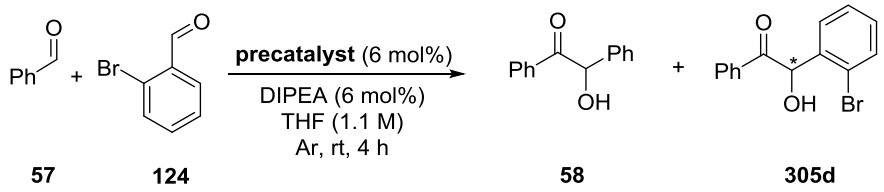
through the use of DIPEA (Hunig's base, conjugate acid pK_a 10.8), with a consistent product optical purity of 67% observed across a 1-4 hour reaction timeframe, with **305d** being isolated in 63% yield after 4 hours, although **58** was still observed in moderate crude yield (entries 5-8). However, employing DIPEA and allowing the reaction to proceed for 24 hours induces a degree of racemisation, with **305d** obtained in 60% isolated yield but with 51% *ee* (entry 9). Surprisingly, employing DMAP (conjugate acid

pK_a 9.7) resulted in a slower reaction rate, despite its higher basicity than DABCO (entry 10). This observation may be linked to its alternative use as a nucleophilic catalyst, which may hinder the reaction. Pleasingly, however, the optical purity of **305d** isolated from under these reaction conditions was again 67%. Use of NMI (conjugate acid pK_a 7.1) also correlated to a slow reaction rate due to its lower basicity, with just 6% yield of **305d** observed after 20 hours (entry 11). Finally, DBU (conjugate acid pK_a *ca* 13) induced a significantly faster reaction rate due to its superior ability to deprotonate the triazolium salt precatalyst, with 48% production of **305d** observable after just 1 hour (entry 12). A 2 hour reaction time allowed the isolation of **305d** in 57% yield but with just 57% *ee* (entry 13).

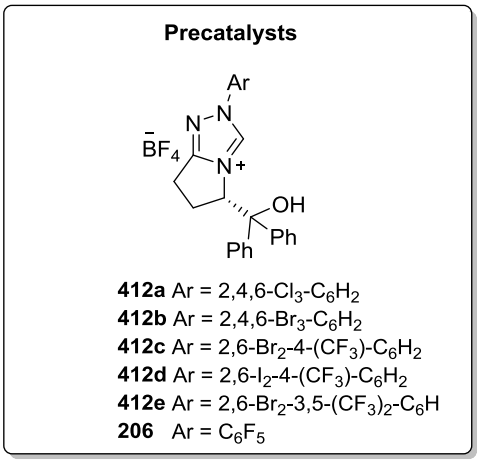
3.4.3 Screening of chiral bifunctional triazolium salts in the asymmetric crossed benzoin condensation

Although the chemoselective outcome of the reaction remained relatively modest, we were confident that we had established a reaction timeframe and suitable base (DIPEA) which provided accurate and reproducible results. We then set about evaluating the influence of each member of our family of triazolium precatalysts upon the chemo- and enantioselectivity of the crossed benzoin condensation between **57** and **124** (Table 3.3) in the presence of DIPEA. As previously detailed, at 6 mol% loading the carbene derived from **412a** catalyses the reaction in 63% yield and 67% *ee* after a 4 hour reaction time in THF (entry 1). To our surprise, reducing the nucleophilicity of the carbene (but equally, the steric bulk of the *N*-aryl ring) through the use of precatalyst **206** under the same conditions provided **305d** in just 26% isolated yield in racemic form (entry 2). In addition, we isolated (*R*)-**58** as the major reaction product in 74% yield and >99% *ee*. We were pleased to observe that use of triazolium salt **412b**, possessing a bulkier *N*-aryl side ring but a more electron-rich carbene centre, led to an improvement in the chemo- and face selectivity of the reaction with **305d** being produced in 72% *ee*, although the reaction proceeded in a much slower manner as a result, with just 23% and 4% isolated yields of **305d** and **58** respectively (entry 3). Intrigued by this observation, we postulated that the presence of a sterically demanding substituent in the *ortho*-positions of the *N*-aryl ring might serve to not only aid the catalyst in directing the chemoselectivity of the reaction but also improve its ability to distinguish between different faces of the aromatic aldehydes. However, the reduced acidity of the triazolium

Table 3.3 Asymmetric crossed benzoin condensation: catalyst evaluation



57 **124** **58** **305d**



entry	precatalyst	yield **58** (%)[a]	yield **305d** (%)[a]	*ee* **305d** (%)[b]
1	**412a**	23	63	67
2	**206**	74 (>99)[c]	26	0
3	**412b**	4	23	72
4	**412c**	7	28	75
5	**412d**	1	3	60
6	**412e**	11	38	68

[a] Isolated yields. [b]Determined *via* HPLC analysis. Note: yields of **58** account for the 2:1 reaction stoichiometry. [c]Value in parentheses represents the optical purity of (*R*)-**58** as determined by CSP-HPLC analysis.

ring in **412b** consequently impacts upon the levels of carbene generated *in situ* and thus, the isolated yields of the desired cross-product. With these postulates in mind, we envisaged employment of **412c**-**e**, each possessing *N*-aryl rings with bulky *ortho*-substituents and electron-withdrawing trifluoromethyl moieties, might succeed in promoting higher yields and improved chemo- and enantioselectivity under these reaction conditions. Our rationale proved somewhat correct; through the use of **412c**, which allowed the generation of **305d** with an optical purity of 75% *ee*, but in just 28% isolated yield, while levels of benzoin in the crude material were again relatively

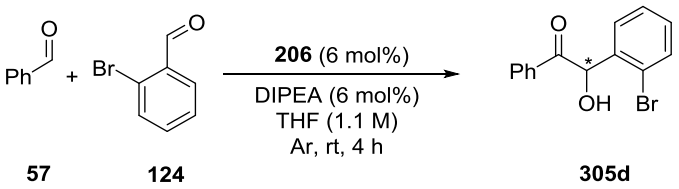
significant (entry 4). The iodo-substituted salt **412d** offered no significant improvement, the reduced electronegativity but increased steric bulk of iodine corresponding to slow reaction rates with just a 3% isolated yield of **305d** and moderate optical purity (entry 5). Following our success in mediating an achiral intermolecular crossed benzoin condensation between **57** and **124** with achiral precatalyst **308**, we disappointed to find that under our reaction conditions, although inducing an accelerated reaction rate relative to **412c** and **412d**, use of chiral precatalyst **412e** resulted in isolation of **305d** in 38% yield and 68% *ee* without significant suppression of benzoin formation (entry 6).

Seeking to gain more insight into the complete lack of enantioselectivity for formation of **305d** when the reaction is mediated by **206** in the presence of DIPEA, we decided to monitor the change in the optical purity of **305d** formed under these reaction conditions as a function of time (Table 3.4). We found that, although the pentafluorophenyl-substituted carbene derived from **206** induces enantioselective formation of **305d** to a minor degree, there is a general inherent lack of face selectivity from the outset of the reaction. After just 5 minutes, **305d** can be isolated from the reaction mixture with just 6% optical purity (entry 1). This value is reduced to 5% *ee* when the reaction is allowed to proceed for 15 minutes (entry 2) and we were able to observe the gradual racemisation of the product under the reaction conditions over time (entries 3-5) such that at 4 hours, as previously detailed, the isolated cross-benzoin product was optically inactive (entry 6).

3.4.3.1 Assigning the absolute configuration: reductive hydrodebromination of the obtained cross-benzoin adduct 305d

The observation that precatalyst **206**, containing the smaller (but more electronegative) *N*-aryl ring (relative to **412a-e**), induces a marked preference for the formation of **58** in good yields and with excellent enantioselectivity (see Table 3.3, entry 2) with concurrent production of cross-benzoin **305d** as a racemate *in the same pot* is remarkable. Given that, under identical reaction conditions, **412a** establishes a bias for generation of **305d** as the major reaction product with modest enantioselectivity (see Table 3.3, entry 1), it became clear to us that the installation of the bromine atom in the *ortho*-position of one benzaldehyde ring not only serves as a potential means to aid the carbene catalyst in directing a chemoselective reaction, but also results in a change the absolute configuration of the obtained cross-benzoin product (relative to benzoin). Indeed, reduction of the brominated cross-benzoin adduct using a palladium catalyst under a

Table 3.4 Monitoring the enantioselectivity of the crossed benzoin condensation mediated by **206** and base as a function of time



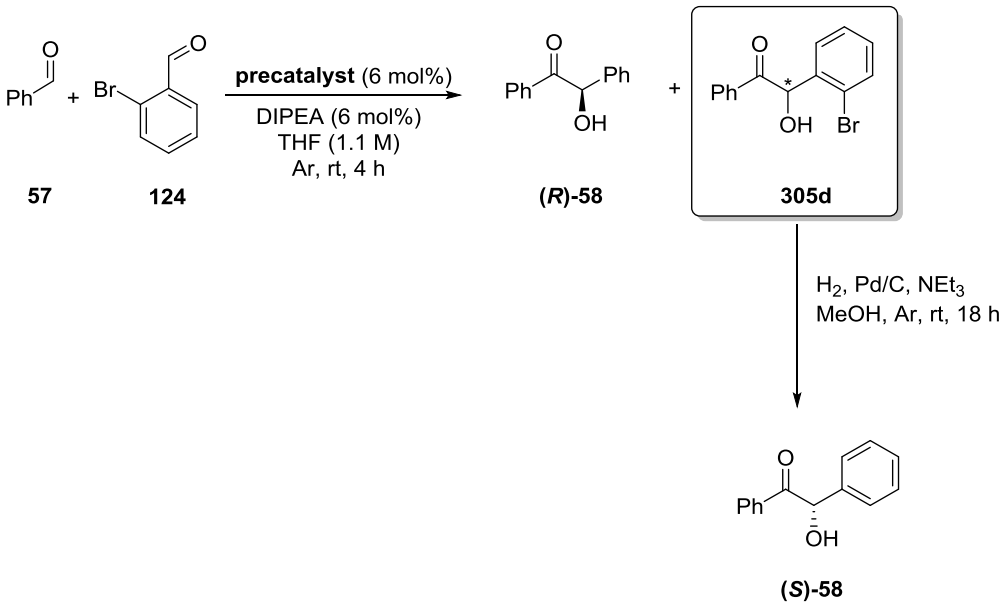
57 **124** **305d**

entry	time (min)	*ee* (%)[a]
1	5	6
2	15	5
3	60	5
4	120	3
5	180	2
6	240	0

[a]Determined *via* CSP-HPLC analysis.

hydrogen atmosphere and subsequent HPLC analysis revealed an extraordinary detail: under our reaction conditions, the formation of **58** in the presence of **412a** and **412b** and base proceeds with a distinct bias for (*R*)-**58**, while cross-benzoin **305d** is produced in an enantioenriched (*S*)-form (Table 3.5). As previously outlined, the carbene derived from precatalyst **206** directs formation of (*R*)-**58** with >99% *ee* while **305d** is concurrently formed racemically (entry 1). In addition to producing **305d** in 63% yield and 67% *ee* (*S*), use of precatalyst **412a** also leads to formation of (*R*)-**58** in 23% yield and 80% *ee* (entry 2). Just as increasing the size of the *ortho*-substituents on the precatalyst *N*-aryl ring correlates to a more enantioselective formation of (*S*)-**305d** under our reaction conditions, we observe an analogous reduction in the optical purity of **58** when utilising precatalyst **412b**, (*R*)-**58** synthesised in 4% yield with 78% *ee* (entry 3).

Table 3.5 Asymmetric NHC-catalysed crossed benzoin condensation and subsequent hydrodebromination of brominated cross-benzoin adducts



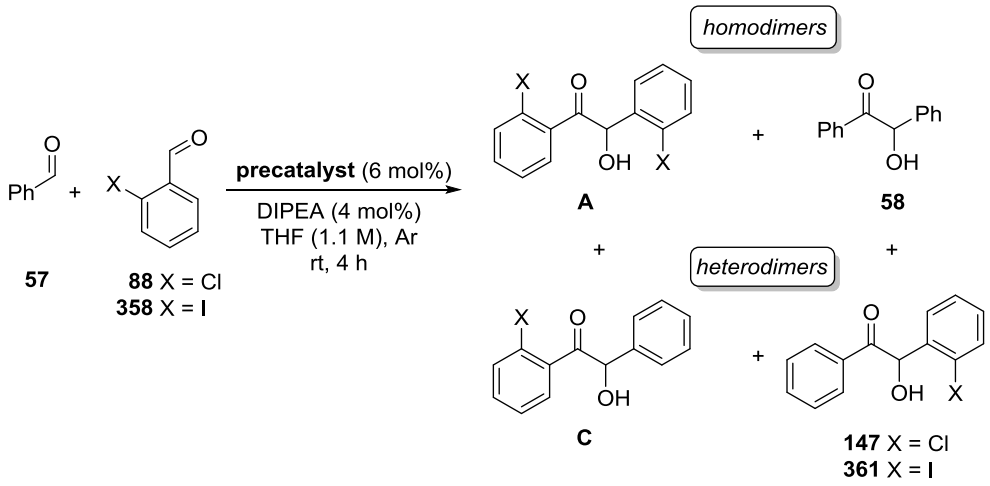
entry	precatalyst	yield **58** (%)[a]	*ee* **58** (%)[b]	yield **305** (%)[a]	*ee* **305d** (%)[b]
1	**206**	74	>99 (*R*)	26	0
2	**412a**	23	80 (*R*)	63	67 (*S*)
3	**412b**	4	78 (*R*)	23	72 (*S*)

[a]Isolated yields. [b]Determined *via* CSP-HPLC analysis, no racemisation of **305d** during hydrogenlysis is assumed.

3.4.3.2 Effect of the *ortho* group upon face selectivity

Prompted by these results, we endeavoured to determine whether this trend was reliant solely upon the steric characteristics of the catalyst or if the identity of the *ortho*-substituted aldehyde also influenced the enantioselectivity of the reaction. We therefore evaluated the effect selected precatalysts had on both the chemo- and enantioselectivity of the crossed condensation between benzaldehyde **57** and 2-chlorobenzaldehyde (**88**) and 2-iodobenzaldehyde (**358**) respectively under identical reaction conditions (Table 3.6).

Table 3.6 Asymmetric cross-benzoin condensation: effect of the *ortho*-substituent upon enantioselectivity



entry	precatalyst	X	yield **A** (%)[a]	yield **58** (%)[b,c]	yield **C** (%)[a]	yield **147**/**361** (%)[b]	*ee* **147**/**361** (%)[d]
1	**206**	Cl	11	52 (>99)	2	44	44 (*R*)
2	**412a**	Cl	8	32 (80)	1	49	40 (*S*)
3	**412b**	Cl	6	17 (78)	1	28	53 (*S*)
4	**206**	I	0	65 (n/d)	0	35	58 (*S*)
5	**412a**	I	0	42 (n/d)	0	43	72 (*S*)
6	**412b**	I	0	32 (n/d)	0	27	74 (*S*)

[a]Determined *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene as an internal standard. [b]Isolated yields. [c]Value in parentheses represents enantiomeric excess of (*R*)-**58** as determined *via* CSP-HPLC analysis. [d]Determined *via* CSP-HPLC analysis.

In the presence of 6 mol% of precatalyst **206** and DIPEA, the cross-coupling between **57** and **88** proceeds with the resulting cross-benzoin adduct (*R*)-**147** formed in 44% yield and with an optical purity of 44%. Again, however, in the same pot, (*R*)-**58** represented the major reaction product, present in 52% yield and >99% *ee* (entry 1). Remarkably, use of **412a** as the carbene precursor results in a complete change in the absolute configuration of the cross-benzoin adduct relative to benzoin, with (*S*)-**147** produced in 49% yield and 40% *ee*. Formation of (*R*)-**58** under these conditions is less pronounced (32% yield), isolated with an optical purity of 80% (entry 2). In keeping with previous observations, employing precatalyst **412b** results in a further improvement in the

enantioselectivity of the reaction, with (*S*)-**147** produced with 53% *ee* but in just 28% yield. The chemoselectivity outcome of this reaction is also quite poor, with 24% isolated yield of (*R*)-**58** and a corresponding 78% optical purity (entry 3). The pronounced loss of chemoselectivity in the condensation between **57** and **88** (relative to that between **57** and **124**) may be rationalised through the less considerable steric bulk of the *ortho*-chlorine substituent. This is reflected in the minor production of both the **A** and **C** benzoin products when X = Cl (entries 1-3), a feature not observed in Table 3.2. Utilising **358** as the *ortho*-substituted coupling partner also results in equally low levels of chemoselectivity; when the reaction is mediated by the carbene derived from **206**, (*R)*-**58** is again the primary reaction product, formed in 65% yield, whereas the desired cross-benzoin adduct **361** is produced in just 35% isolated yield (entry 4). However, in complete contrast to analogous use of **88** under these reaction conditions, **361** was formed with an optical purity of 58% as the (*S*)-enantiomer (compare with entry 1). Subsequent use of precatalyst **412a** results in a further improvement of the enantioselective outcome of this particular condensation, (*S*)-**361** isolated with 72% *ee* (entry 5). Distinct chemoselectivity issues arise here, with (*R*)-**58** and (*S*)-**361** present in 42% and 43% yield respectively. Increasing the size of the precatalyst's *N*-aryl ring negatively impacts this chemoselectivity further, to the extent that the carbene derived from **412b** will preferentially induce formation of (*R*)-**58** (32% yield) over the cross-benzoin (*S*)-**361** (27% yield, entry 6), albeit with further improvement in the enantioselectivity of the system. Again, the increasing preference for second nucleophilic attack by the Breslow intermediate upon **57** as opposed to the more activated **358** with increasing catalyst size may generally be attributed to the sheer size of the *ortho*-iodo substituent, which will certainly hinder nucleophilic approach upon the carbonyl moiety of the second aldehyde.

The results obtained in Table 3.5 and Table 3.6 are indicative of a clear trend – that, in general, the use of an *ortho*-halo-substituted benzaldehyde as one coupling partner will cause a shift in the enantioselective outcome of cross-condensations mediated by our novel chiral triazolium ion precatalysts under basic conditions. Furthermore, as the steric bulk of both this *ortho*-halogen atom and the carbene's *N*-aryl ring increase, the enantioselective outcome of the reaction (regarding the desired cross-benzoin products) improves.

3.4.4 Rationalising the observed influence of selected precatalysts upon the enantioselectivity of the reaction

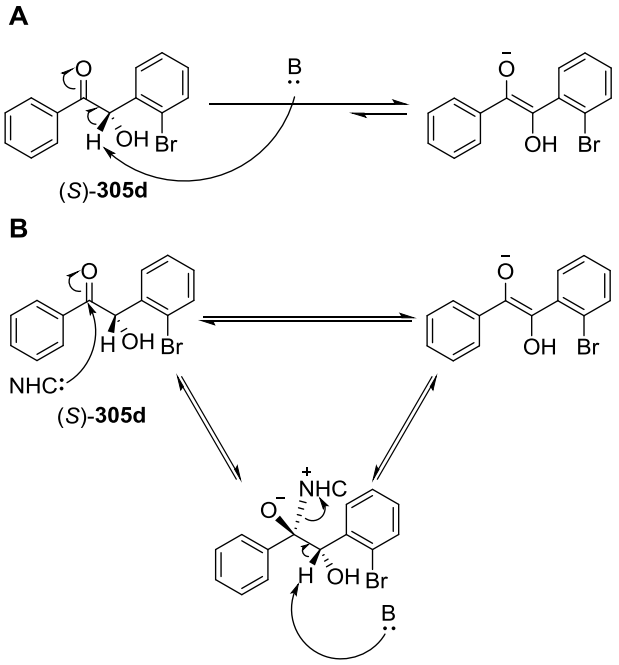
Despite these findings, our efforts to develop an asymmetric variant of the intermolecular cross-benzoin condensation were unsuccessful to that point. While we envisaged that utilising 2-iodobenzaldeyde as the *ortho*-substituted component (given its size) would offer the greatest hope of achieving a totally selective formation of a cross-benzoin adduct, we were discouraged by the lack of chemoselectivity observed in its presence. Conversely, use of 2-bromobenzaldehyde gave rise to comparable process from an enantioselectivity standpoint (see Table 3.3, entry 3 vs Table 3.6, entry 6) but also provided the desired cross-benzoin adduct as the main reaction product (albeit in a rather poor reaction from a chemoselectivity perspective). We therefore satisfied ourselves that it was the most adequate coupling partner to hand proceeding forward.

In order to develop a truly enantioselective protocol for the crossed benzoin condensation, we first had to understand why, if the size of the precatalyst *N*-aryl ring has a direct effect upon the observed enantioselectivity of the reaction, the use of precatalysts **412c-e** did not correlate directly to a significantly improved methodology. We reasoned that, due to the fact that (for example) the steric and spacial constraints around the carbene centre in precatalysts **412b**, **412c** and **412e** are identical (owing to the presence of the *ortho*-bromine atoms in each), the answer must lie in the electronic characteristics of each precatalyst. The additional trifluoromethyl moieties incorporated into salts **412c** and **412e** allow for more facile deprotonation of the triazolium ring in the presence of a base and thus, a greater concentration of active carbene in solution relative to **412b**. We further proposed that cross-benzoin **305d**, possessing an electronegative bromine atom, would have a pK_a lower than that of benzoin and so, under our reaction conditions, may therefore be subject to racemisation not only through base-mediated enolisation, but also carbene-mediated enolisation (whether through α-proton deprotonation or an E2-type elimination, **A** and **B**, Scheme 3.6).

3.4.4.1 Quantifying the racemisation of enantioenriched 305d through base-mediated enolisation: deuterium studies

Initially, however, we were aware from previous experience that the solubility of benzoin in THF at a 1.1 M concentration was poor compared to its brominated analogue **305d**.

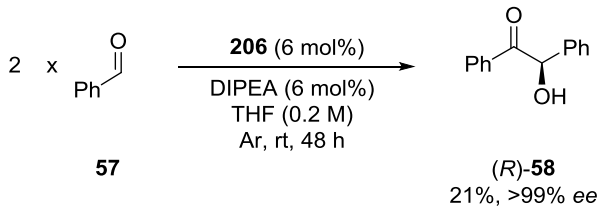
Scheme 3.6 Proposed racemisation pathways of **305d** by both base and carbene



We became interested in discerning if the contrast between the observed optical purities for samples of **58** and **305d** obtained under reaction conditions employing precatalyst **206** arose from this proposal; the cross-benzoin adduct remains in solution throughout the course of the reaction and while benzoin itself precipitates at higher concentrations and thus avoids base-induced racemisation of the stereocentre. To test this hypothesis, we carried out a typical benzoin condensation in the presence of precatalyst **206** and DIPEA at a 0.2 M reaction concentration (Scheme 3.7), envisaging that by maintaining the solubility of **58** we would possibly observe racemisation of the stereocentre over time. After 48 hours, we were pleased to observe no precipitation of any kind within the reaction flask. However, following quenching and work-up, we isolated (*R*)-**58** in 21% yield with >99% *ee*, suggesting that the poor solubility of benzoin in THF is not responsible for its resistance to racemisation under our reaction conditions.

Following this, we turned our attention to examining the enolisability of **305d** under the reaction conditions and initially exposed a sample of enantioenriched (*S*)-**305d** to our typical reaction conditions in the presence of 5 equivalents of deuterated methanol. We sought to monitor the corresponding deuterium incorporation into **305d** *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture as the proposed enolate tautomerises to its keto form. However, the large excess of CD_3OD resulted in the quenching of the **58**

Scheme 3.7 Benzoin condensation in the presence of precatalyst **206** at a lower reaction concentration

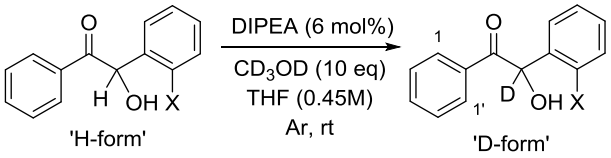


reaction through deuteration of the carbene *in situ* and we failed to observe any such incorporation. Therefore, we instead exposed both **305d** and **58** separately to a 6 mol% loading of DIPEA in THF in the presence of 10 equivalents of CD_3OD and monitored the rate of deuterium incorporation as a function of time (Table 3.7). For accuracy and reproducibility, it was necessary to operate at a lower concentration (0.45 M) to that which we had previously used as **58** displays poor solubility in THF at 1.1 M concentration (as per our typical reaction conditions). As expected, at t_0 there is no incorporation of deuterium to be observed when **305d** is exposed to these conditions (entry 1). To our delight, however, at t = 2 hours we were able to record a 4% D-incorporation into **305d** (entry 2). This deuterium uptake continued throughout the timeframe of the reaction, with 6%, 9% and 12% incorporation observed at t = 5 hours, 20 hours and 44 hours respectively (entries 3-5). In contrast, although the rate of D-incorporation using **305d** appears slow, under identical conditions **58** displays no observable D-uptake at all within the same timeframe (entries 6-9).

3.4.4.2 Quantifying catalyst-mediated racemisation of 305d: plausibility of an E2-type elimination pathway

With these results, we were confident that in parallel with inducing a change in the absolute configuration selectivity of our methodology, the presence of the *ortho*-bromine atom also facilitates a lowering of the acidity of the α-proton of (*S*)-**305** and thus, a corresponding reduction in its optical purity over time through accelerated rates of enolisation under the basic conditions of our reaction. Gratifyingly, it also enabled us to formulate a hypothetical means by which **58** and **305d** can be formed in the same pot (by the same catalyst) but with such contrasting degrees of enantioselectivity. We sought to further support this model argument by studying the effect of various carbenes upon

Table 3.7 Base-mediated enolisation: deuterium studies

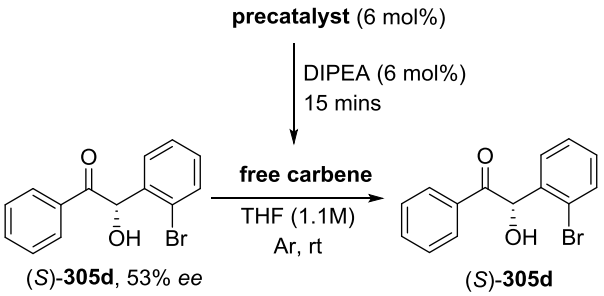


entry	X	time (h)	H%[a]
1	Br	0	100
2	Br	2	96
3	Br	5	95
4	Br	20	91
5	Br	44	88
6	H	0	100
7	H	2	100
8	H	5	100
9	H	20	100

[a]Determined *via* ^{1}H NMR spectroscopic analysis of the crude reaction using protons 1 and 1' as an internal reference.

enantioenriched **305d** (Table 3.8). By dissolving the relevant precatalyst in basic solution and subsequently adding a sample of **305d** (of known optical purity) we could observe the change in this value at a specific time interval following exposure to the relevant carbene. After stirring 6 mol% of precatalyst **206** in the presence of DIPEA in THF for 15 minutes, addition of (*S*)-**305d** (53% *ee*) leads to rapid onset of racemisation of the stereocentre. 15 minutes following exposure, the optical purity of the sample has depleted to 38% *ee* (entry 1). Similarly, but in a less pronounced manner, the use of precatalyst **412a** under identical conditions returned (*S*)-**305d** in 47% *ee* after 15 minutes reaction time (entry 2). The use of the less acidic and more hindered precatalyst **412b** allowed re-isolation of (*S*)-**305d** without any observable loss of optical purity after 15 minutes (entry 3). Finally, the carbene derived from **412c** is demonstrated to represent a medium between its *N*-pentafluorophenyl and *N*-trichlorophenyl analogues, with (*S*)-**305d** recovered in 43% *ee* after the same time period (entry 4). Although **412b** represents the most electron-rich of the four employed carbenes, it appears that the size of the

Table 3.8 Carbene-mediated racemisation studies



entry	precatalyst	time (h)	*ee* (%)[a]
1	**206**	0.25	38
2	**412a**	0.25	47
3	**412b**	0.25	53
4	**412c**	0.25	43

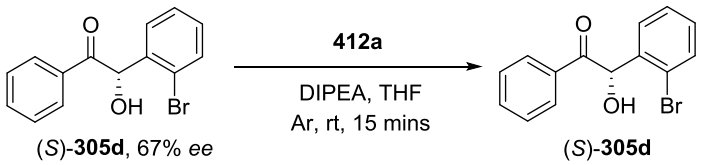
[a]Determined *via* CSP-HPLC analysis.

precatalyst *N*-aryl ring and the pK_a of the triazolium ring (and hence the concentration of carbene generated in solution) are more relevant factors in the racemisation of **305d** by the carbene. This proposal can also be extended to account for the failure of carbenes derived from precatalysts **412c**-**e**, possessing both steric bulk and electron-withdrawing groups on the *N*-aryl ring, to offer any significant enantioselective improvement in mediating this crossed benzoin condensation – both the face selectivity of the Breslow intermediate (when carrying out nucleophilic attack upon the **124**) and racemisation of **305d** *in situ* by the carbene depend on a delicate balance and confluence of factors, most notably the steric properties of the *N*-aryl ring, the electronic character of the carbene centre and how the dual influence of the elements affect the nucleophilicity of the carbene.

Despite the observation that the action of the free carbene contributes to the racemisation of the enantioenriched cross-benzoin product, the means by which it occurs still required further clarification. While it was likely that concurrent α-deprotonation and E2-type elimination are in operation, we sought to shed further light on this mechanism. As a typical E2 elimination displays a dependence on the concentration of both the base and substrate, we envisaged that we could exploit this through variation of the starting

concentration of both the precatalyst and enantioenriched (*S*)-**305d** (67% *ee*) and subsequently measuring the degree of racemisation under our reaction conditions (Table 3.9). We were pleased to observe that we could identify a correlation between the extent of racemisation and the concentration of both the precatalyst and the starting cross-benzoin adduct. Initially holding the molarity of (*S*)-**305d** constant at 0.9 mol L^{-1} and employing **412a** in 0.027 mol L^{-1}, we recovered the enantioenriched product with 59% *ee*, an optical purity loss of 9% after 15 mins (entry 1). Subsequently doubling the concentration of the precatalyst in solution resulted in a further decrease in the optical purity of the re-isolated cross-benzoin (entry 2), while again increasing its starting molarity corresponded to further increases in the rate of racemisation, (*S*)-**305d** isolated with 44% *ee* after 15 minutes under these conditions (entry 3). Conversely, maintaining a steady concentration of the precatalyst (0.055 mol L^{-1}) while varying that of the starting cross-benzoin substrate highlighted a similar concentration dependency (entries 4-6).

Table 3.9 Concentration variance in identifying of an E2-type racemisation mechanism



(*S*)-**305d**, 67% *ee* (*S*)-**305d**

entry	[**412a**] (mol L^{-1})	[(*S*)-**305d**] (mol L^{-1})	*ee* (%)[a]
1	0.027	0.9	59
2	0.055	0.9	48
3	0.11	0.9	44
4	0.055	0.225	55
5	0.055	0.45	51
6	0.055	0.9	48

[a.] Determined *via* CSP-HPLC analysis.

The data obtained from this series of experiments suggests that while deprotonation of the α-proton by the free carbene remains a plausible source of the observed racemisation of the stereocentre over time, the dependence of the extent of racemisation upon both the

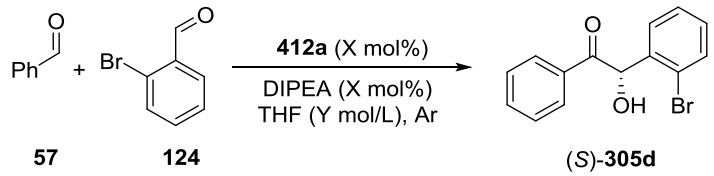
concentration of the precatalyst and cross-benzoin substrate suggests that the E2-type mechanism portrayed in Scheme 3.6 may also play a significant role in the racemisation of the stereocentre in (*S*)-**305d**.

3.4.5 Further optimisation of reaction conditions

With these insights into the factors affecting the enantioselectivity of our protocol, we then began an examination of the influence of other parameters within the system in an effort to circumvent this problem of *in situ* product racemisation. We focused our attention upon the temperature, substrate concentration and catalytic/base loadings of the reaction (Table 3.10). Accordingly, when we reduced the catalytic loading of precatalyst **412a** we observed a concurrent reduction in the reaction rate, with an 18% isolated yield of (*S*)-**305d** after 4 hours (entry 1). Disappointingly, however, the optical purity of the product was slightly inferior to that obtained using a 6 mol% loading of precatalyst. Conversely, doubling the catalytic loading of **412a** to 12 mol% improved the isolated yield of the desired cross-benzoin to 73% (entry 2), but again the enantioselectivity of the reaction was modest. Halving the starting concentration of starting aldehydes from 1.1 M to 0.55 M also resulted in poor isolated yields, (*S*)-**305d** obtained in 19% yield and 67% *ee* (entry 3). Conducting the reaction under our usual conditions but adding **57** in regular aliquots over a 1 hour period results in an 32% isolated yield of (*S*)-**305d** with 69% *ee* (entry 4).

Although these efforts to improve the enantioselectivity of our methodology provided no significant results, we were confident that a considerable decrease in the temperature of the reaction would promote both access to only the most stable reaction transition state and concurrently disfavour racemisation of the newly-formed stereocentre. We were therefore surprised to find that a considerable lowering of the temperature gave rise (in general) to the process with the poorest enantioselectivity. Initially, acknowledging that carrying out the reaction at -30 ^{o}C would impact the reaction rate, we were pleased to obtain (*S*)-**305d** with an optical purity of 67% after 24 hours, albeit in just 12% isolated yield (entry 5). We were then somewhat at a loss to explain how, at the same temperature but having shortened this reaction time to 4 hours, we could isolate the desired cross-benzoin adduct in an identical yield but with a significantly reduced enantioenrichment (47% *ee*, entry 6). Further lowering of the catalytic loading of **412a** corresponded to an even further loss in the enantioselectivity of the reaction, (*S*)-**305d**

Table 3.10 Further optimisation of reaction conditions



57 **124** (*S*)-**305d**

entry	X	Y	temp. (^{o}C)	time (h)	yield (%)[a]	*ee* (%)[b]
1	2	1.1	rt	4	18	60
2	12	1.1	rt	4	73	49
3	6	0.55	rt	4	19	67
4[c]	6	1.1	rt	4	32	69
5	6	1.1	-30	24	12	67
6	6	1.1	-30	4	12	47
7	2	1.1	-30	4	8	24
8	10	1.1	-30	4	14	33
9	6	1.1	0	24	34	67
10	6	1.1	0	7	17	45
11	6	1.1	0	4	15	57
12	2	1.1	60	4	43	25

[a]Isolated yield [b]Determined *via* CSP-HPLC analysis. [c]**57** added in 5 μL aliquots over a 1 h period.

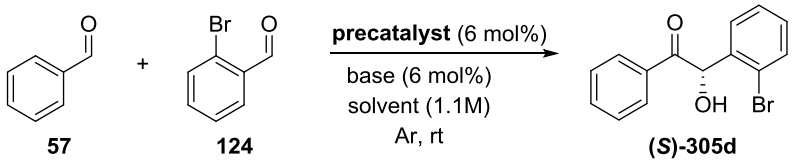
being produced in 8% isolated yield with just 24% *ee* after 4 hours (entry 7). Conversely increasing the catalytic loading of the precatalyst to 10 mol% enabled minor improvement in the yield and the optical purity of (*S*)-**305d** (entry 8). Conducting the reaction at 0 ^{o}C offered marginal improvement in both the efficiency and enantioselectivity of the protocol. A 24 hour reaction timeframe provided (*S*)-**305d** in 34% isolated yield and 67% optical purity, while strangely the same reaction conducted over a 7 hour period allowed production of the desired cross-benzoin with 45% optical purity (entries 9 and 10). To further complicate the issue, shortening the reaction to 4 hours sees the optical purity of the isolated increase to 57% (entry 11). Although we anticipated no major increase in the enantioselectivity of the reaction, we also examined the enantioselective outcome of the reaction under reflux conditions with a reduced

catalytic loading to compensate for this temperature increase (entry 12); (*S*)-**305d** formed with just 25% *ee*, in line with our expected observations.

It is perhaps fair comment to state that no definite trends or patterns with regard to the influence of these parameters upon the enantioselectivity of the reaction can be extracted from these results. The reasons behind this remain unknown, and perhaps the nature of the reaction is far more complex than we perceive. Indeed, it seems remarkable that conducting the same reaction at -30 ^{o}C and at 60 ^{o}C (*i.e.* entries 7 and 12) can result in an almost identical enantioselective outcome.

Although variations in concentration and temperature failed to improve the enantioselectivity of our methodology, recognising that the cross-benzoin product is subject to racemisation through base- and catalyst-mediated enolisation did allow us to modify our catalytic system given the knowledge that a polar aprotic solvent, such as THF, will favour promotion of these pathways. However, Breslow's proposed mechanism for the NHC-catalysed reaction (see Scheme 1.16) highlights how the initial formation of the cross-benzoin proceeds through charged intermediates, the stability and lifetime of which will be increased in the presence of polar solvents. We envisaged that in screening a variety of non-polar solvents to counteract our proposed racemisation pathways, the rate of the reaction would decline significantly. We further acknowledged that in reducing the polarity of our system, solubility issues in respect to the triazolium salts would be arise. We therefore began screening the effect of various solvents (Table 3.8) upon the chemo- and enantioselective outcome of the intermolecular cross-condensation between **57** and **124** in the presence of our chiral triazolium precatalysts and base (Table 3.10). In a 4:1 THF/*n*-hexane solution, (*S*)-**305** is produced in just 19% isolated yield and 54% *ee* after 18 hours employing 6 mol% of precatalyst **412a** and DIPEA. Alternatively, conducting the reaction in a 4:1 THF/MTBE solvent system increased the isolated yield of (*S*)-**305d** to 56% over the same timeframe but was accompanied by a significant reduction in optical purity (entry 2). Pleasingly, a 10:1 mixture of PhMe:CH_2Cl_2 allowed isolation of (*S*)-**305d** in 54% yield with 66% *ee* after 18 hours reaction time (entry 3). While the solubility of the **412a** in conjunction with DIPEA was too low in toluene alone to allow the reaction to be carried out efficiently, a 7.5:1 PhMe:THF mixture resulted in formation of (*S*)-**305d** in a moderate 63% isolated yield and 75% *ee* after 20 hours when 1.25 equivalents of **124** were employed (entry 4). Gratifyingly, under these new conditions, concurrent formation of **58** was suppressed to

Table 3.11 Asymmetric cross-benzoin condensation: solvent screening



57 **124** **(*S*)-305d**

entry	precat.	base	solvent	time (h)	yield (%)[a]	*ee* (%)[b]
1	**412a**	DIPEA	THF:*n*-hexane (4:1)	18	19	54
2	**412a**	DIPEA	THF:MTBE (4:1)	18	56	33
3	**412a**	DIPEA	PhMe:CH_2Cl_2 (10:1)	18	54	66
4[c]	**412a**	DIPEA	PhMe:THF (7.5:1)	20	63[d]	75
5	**412a**	DIPEA	PhMe:THF (7.5:1)	4	40	75
6	**412b**	KHMDS	PhMe:THF (7.5:1)	18	27	85
7[e]	**412b**	KHMDS	PhMe:THF (7.5:1)	20	52	57
8[f]	**412a**	KHMDS	PhMe:THF (7.5:1)	72	2	72
9[f]	**412b**	KHMDS	PhMe:THF (7.5:1)	72	5	80
10[g]	**412a**	KHMDS	PhMe:THF (7.5:1)	24	6	79
11[h,i]	**412a**	KHMDS	PhMe:THF (7.5:1)	18	94	0

[a]Isolated yield. [b]Determined *via* HPLC analysis. [c]1.25 equivalents of **124** used [d]**58** also observed in 5% yield *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] Reaction carried out using 12 mol% of both precatalyst and base. [f]Reaction performed at -40 °C. [g]Reaction performed at 0 °C. [h]Reaction carried out using 12 mol% KHMDS. [i]1.5 equivalents of **124** used.

just 5% yield as determined *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture, perhaps indicating that a reduction in the polarity of the system promotes a more selective reaction pathway. Reduction of the reaction time still allowed isolation the desired product in 40% yield but disappointingly, we observed no improvement in the enantioselective outcome of the reaction (entry 5), suggesting that while the use of non-polar solvents succeeds in alleviating the problems associated with product racemisation, there may be an inherent lack of face selectivity when the reaction is mediated by **412a**. Seeking to overcome this slow reaction rate, we decided to employ precatalyst **412b** in toluene alone and utilised KHMDS (6 mol%) to generate a higher concentration of the corresponding carbene *in situ*, as well as avoid solubility issues. Using these modified conditions, we obtained (*S*)-**305d** with an optical purity of 85% *ee*, albeit accompanied by a slow rate of product formation (27% isolated yield, entry 6). Further modifications

to this system proved unsuccessful – doubling the catalyst and base loading was accompanied by a corresponding improvement in yield (52%) after 20 hours but a reduction in the enantiomeric excess of (*S*)-**305d** (57% *ee*, entry 7), while lowering the reaction temperature caused the reaction rate to drop sharply. At -40 ^{o}C, employing precatalyst **412a** resulted in isolation of (*S*)-**305d** in just 2% yield after 72 hours with a corresponding optical purity of 72% *ee* (entry 8). Under identical conditions, **412b** offered slight improvements upon these results, forming (*S*)-**305d** in 5% yield and 80% *ee* (entry 9). Increasing the temperature to 0 ^{o}C allowed us to obtain (*S*)-**305d** in 6% yield and 79% *ee* in the presence of **412a** and KHMDS (entry 10). Conversely, doubling the loading of KHMDS and employing 1.5 equivalents of **124** enabled chemoselective production of (*S*)-**305d** in 94% isolated yield, but in entirely racemic form (entry 11).

3.5 Asymmetric crossed benzoin condensation: substrate scope of non-*ortho*-substituted aromatic aldehyde

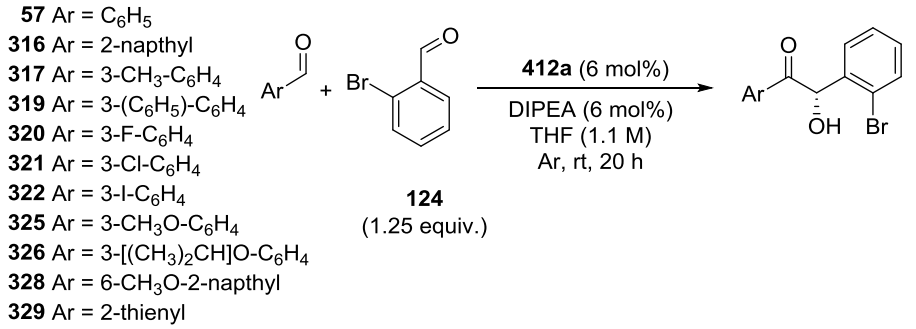
Our results up until this point emphasised one feature about the reaction in particular – that marrying both high yields and optical purities may prove an unachievable and unrealistic target. The pair represents two opposite ends of a "see-saw" effect in that the optimal reaction conditions to maximise yields of (*S*)-**305d** also encourage racemisation; on the contrary, a reaction system promoting a more enantioselective cross-benzoin condensation relies on a non-polar environment and a bulky, less active carbene precursor salt, discouraging synthetically useful yields of the desired adduct. Acknowledging the above, we decided to strike a compromise between the two extremes and screen a range of substituted benzaldehydes in the asymmetric intermolecular cross-condensation with **124** using our best conditions (Table 3.9). We therefore employed precatalyst **412a**, in the presence of DIPEA and 1.25 equivalents of **124**, in a 7.5:1 PhMe:THF solvent system (*i.e.* Table 3.8, entry 4), conditions which we felt enabled moderate chemoselective production of the desired cross-product without significantly impacting the enantioselectivity of the reaction. As noted above, under these conditions **57** can be coupled with **124** in 63% isolated yield and 75% *ee* (entry 1). However, consistent with a process subject to racemisation *via* an E2-type elimination mechanism, reducing the concentration of the reaction enables us to increase this value to 80% *ee*, although as expected the yield is negatively impacted (entry 2). We must acknowledge that the simple base-mediated racemisation may also be a second order process and so

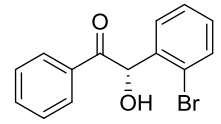
this result may not be entirely indicative of an E2-type pathway. Interestingly, 2-naphthaldehyde (**316**) proves exceptionally active when employed as the non-*ortho*-substituted coupling partner under our conditions, (*S*)-**331** visibly precipitating from solution after just 1 hour; however the product is present in racemic form after 20 hours (entry 3). Thankfully, quenching the reaction after 2 hours still enables isolation of (*S*)-**331** in a moderate 62% yield and with good optical purity (84% *ee*, entry 4). Indeed, electron-neutral benzaldehydes prove the most suitable coupling partners in our hands, with 3-tolualdehyde (**317**) undergoing asymmetric condensation with **124** in 66% isolated yield, (*S*)-**332** formed with 83% *ee* (entry 5). Biphenyl-3-carbaldehyde (**319**) condenses in a much slower manner, undoubtedly due to the increased sterics of the additional phenyl ring, but still allows access to (*S*)-**334** in 57% yield and modest enantiopurity (77% *ee*, entry 6). In keeping with the observations of previous studies,[86,164] the optical purity of cross-benzoins derived in from activated benzaldehydes (*i.e.* **320**-**322**) is significantly impacted (entries 7-9). Through our previous postulates, we can attribute this to the accentuation of the acidity of the α-proton of the products (*S*)-**335**-**337**. In addition, the chemoselectivity of the process is reduced when employing **320** and **321** due to accelerated formation of the corresponding homobenzoin products derived from these aldehydes, such that (*S*)-**335** and (*S*)-**336** are formed in just 47% and 48% yield respectively. Conversely, electron-rich benzaldehydes tend to participate in slow but extremely chemoselective reactions, as their propensity for self-condensation is less pronounced. Accordingly, (*S*)-**340** can be obtained in 48% yield through cross-coupling between 3-anisaldehyde (**325**) and **124** with 83% *ee* after 20 hours (entry 10), while 3-isopropoxybenzaldehyde (**326**) participates in the condensation with isolation of its corresponding cross-benzoin (*S*)-**341** in 42% yield with a modest enantioselective outcome (76% *ee*, entry 11). Methoxy-substituted naphthaldehyde **328** proves less adequate as a substrate, leading to 56% yield of its desired cross-benzoin (*S*)-**343** and 67% *ee* (entry 12). Finally, we were pleased to find that the heterocyclic aldehyde 2-thiophenecarbaldehyde (**329**) could be coupled with **124** in 76% yield and 71% *ee* (entry 13).

Seeking to enable a further improvement of selected enantioselectivity values, we attempted to recrystallise enantioenriched (*S*)-**331** (84% *ee*) from hexane, envisaging results similar to those reported by Enders in the asymmetric synthesis of α-trifluoromethylated benzoin derivatives.[144] However, it seems that the tendency towards

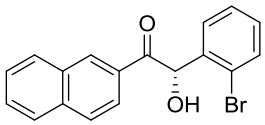
enolisation of these adducts is such that even the heating required for dissolution promotes extensive tautomerisation, with **331** crystallising in racemic form.

Table 3.9 Substrate scope: non-*ortho*-substituted benzaldehyde

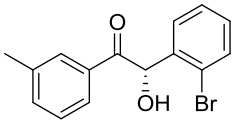




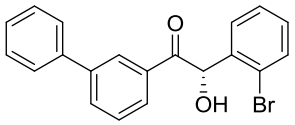
(*S*)-**305d**
63%, 75% *ee*
40%, 80% *ee* (0.55 M)



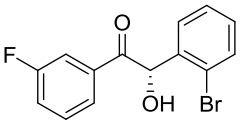
(*S*)-**331**
76%, 0% *ee*
62%, 84% *ee* (2 h)



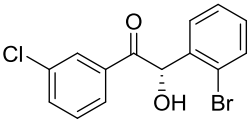
(*S*)-**332**
66%, 83% *ee*



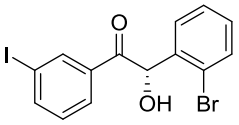
(*S*)-**334**
57%, 77% *ee*



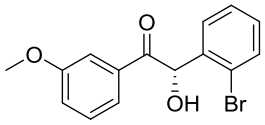
(*S*)-**335**
47%, 66% *ee*



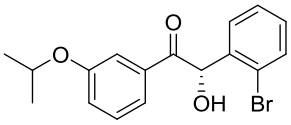
(*S*)-**336**
48%, 45% *ee*



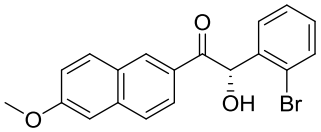
(*S*)-**337**
79%, 52% *ee*



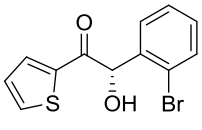
(*S*)-**340**
48%, 83% *ee*



(*S*)-**341**
42%, 76% *ee*



(*S*)-**343**
56%, 67% *ee*



(*S*)-**344**
76%, 71% *ee*

3.6 Re-evaluation of the *ortho*-substituted aldehyde: development of an enantioselective system through α-proton chelation

Since our efforts to marry both high yields and enantioselectivity had encountered this impasse, we dedicated ourselves to devising a system that would enable enantioselective

formation of a cross-benzoin product, irrespective of yields. Having already extensively evaluated a range of reaction conditions and precatalyst designs, we focused our attention instead on our choice of *ortho*-substituted benzaldehyde. Conscious of the fact that removal of the cross-benzoin α-proton was in some way responsible for their modest optical purities, we postulated that installation of an *ortho*-substituent capable of deterring deprotonation might be a viable strategy to overcome this obstacle. In this regard, we took inspiration from the pK_a values of the *ortho*-substituted phenol series where, despite the superior electronegativity of fluorine, the pK_a of 2-fluorophenol (**430**, Figure 3.3) is actually higher than that of halo-analogues 2-chlorophenol or 2-bromophenol (pK_a 8.73 *vs* 8.56 and 8.45 respectively). This is primarily attributed to the fact that fluorine can favourably hydrogen-bond with the acidic proton (O-H-F) to form a chelating intramolecular five-membered ring to a greater extent than chlorine, while the larger atomic radius of bromine prevents it from participating in this arrangement.

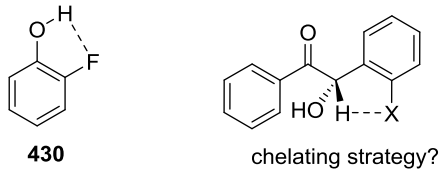


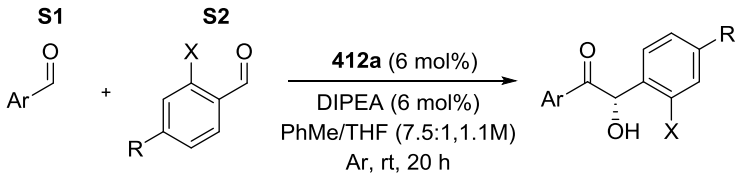
Figure 3.3 Chelation ability of 2-fluorophenol and potential replication in cross-benzoins

We postulated that such an interaction would be potentially achievable in a cross-benzoin product and, in an analogous manner, could lead to decrease in the acidity of the α-proton. Thus, under our previously established conditions, we attempted to cross-couple **57** and 2-fluorobenzaldehyde (**431**) in the presence of precatalyst **412a** (6 mol%) and DIPEA (6 mol%) (Table 10, entry 1). We envisaged that the small steric presence of an *ortho*-fluorine (relative to bromine) would render the process unselective and we were proven correct, with all four possible cross-benzoins observed in approximately 20% yield each *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Attempts to separate these adducts through flash chromatography were unsuccessful.

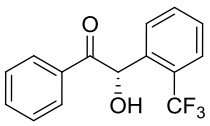
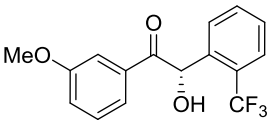
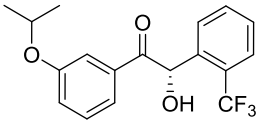
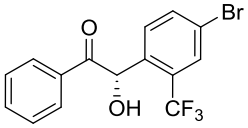
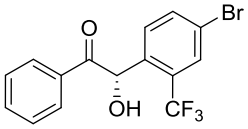
However, we noted how a similar trend in pK_a values emerges for both 2-(trifluoromethyl)phenol and 3-(trifluoromethyl)phenol (pK_a 8.95 and 8.68 respectively).

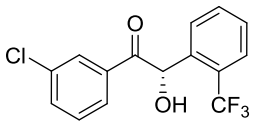
Thus, we repeated the attempted cross-condensation with **57** as before, employing 2-(trifluoromethyl)benzaldehyde (**359**) in anticipation that its greater steric bulk would

Table 3.10 Development of an enantioselective intermolecular crossed benzoin condensation



431, X = F, R = H
359, X = CF_3, R = H
348, X = CF_3, R = Br

entry	S1	S2	product	yield (%)[a]	*ee* (%)[b]
1	**57**	**431**	n/a	unselective	n/d
2	**57**	**359**	 (*S*)-**362**	34	92
3	**325**	**359**	 (*S*)-**432**	6	90
4	**326**	**359**	 (*S*)-**433**	17	90
5	**57**	**348**	 (*S*)-**434**	58	4
6[d]	**57**	**348**	 (*S*)-**434**	10	50

7	**322**	**359**	 (*S*)-**435**	12	80

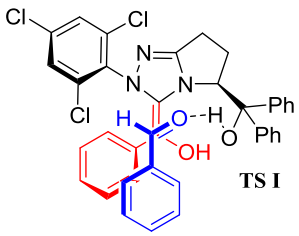
[a]Isolated yield. [b]Determined *via* CSP-HPLC analysis. [c]Reaction time reduced to 4 h.

enable the catalyst to firstly direct a chemoselective reaction and secondly an enantioselective process. To our delight, despite the slow reaction rate, we were able to isolate (*S*)-**362** in 34% yield and 92% *ee* after 20 hours (entry 2), which, to the best of our knowledge, represents the first ever highly enantioselective intermolecular cross-benzoin condensation between two non-identical aromatic aldehydes as catalysed by a chiral NHC. **359** Participates in the reaction quite slowly relative to **124** and indeed this general trend may be applicable to all crossed benzoin condensations it participates in – further cross-condensation under the reaction conditions with **325** provided cross-benzoin adduct (*S*)-**432** in just 6% yield but with an enantioenrichment of 90% *ee* (entry 3). Similarly, using deactivated aromatic aldehyde **326**, (*S*)-**433** could be isolated in 17% yield and 90% *ee* (entry 4). Subsequent attempts to increase yields but maintain the *ortho*-CF_3 moiety presence in the final cross-benzoin product through use of aldehyde **348** met with failure as after 20 hours, with highly functionalised cross-benzoin (*S*)-**434** isolated in 58% yield but with just 4% optical purity (entry 5). Conversely, reducing the reaction time to 4 hours saw just 10% formation of (*S*)-**434** in 50% *ee* (entry 6). Similarly, use of a more activated non-*ortho*-substituted benzaldehyde in the form of **322** negatively impacts the optical purity of the desired cross-benzoin product *in situ*, (*S*)-**435** isolated in 12% yield with an 80% enantiomeric excess (entry 7). Evidently, the installation of electron-withdrawing substitutents again lowers the pK_a of the α-proton to the extent that our proposed chelating effect to alleviate product racemisation is negated under these conditions.

3.7 Rationalising the observed enantioselectivity employing precatalyst 412a in the asymmetric crossed benzoin condensation

At this point in our studies, we had established an understanding of the primary factors dictating and influencing the optical purity of isolated cross-benzoins formed using our NHC-catalysed methodology. The issue of the change in absolute configuration of benzoin products observed in the presence or absence of an *ortho*-substituted

benzaldehyde remained unanswered however. In 2004, Houk and Dudding published a report detailing computational predictions for the benzoin condensation in the presence of various thiazolium and triazolium precatalysts.[165] Their work outlined the various diastereomeric combinations of the Breslow intermediate-benzaldehyde transition states that give rise to formation of either (*S*)- or (*R*)-benzoin. Using this as a reference point, we were able to construct our own hypothetical model transition states to explain how the introduction of an *ortho*-substituent may induce a reversal in face selectivity with regard to attack of the Breslow intermediate upon the second aromatic aldehyde when employing the carbene derived from precatalyst **412a**. We originally worked on the assumption that a favourable π-stacking interaction between the catalyst *N*-aryl group and the aromatic ring of the enolamine will predominantly generate an (*E*)-alkene within the Breslow intermediate. In asymmetric formation of both **58** and cross-benzoin **305d** (for example), the carbonyl moiety of benzaldehyde undergoes initial attack by the NHC and thus we have no legitimate reason to assume that this geometry would be subject to change in either case. The only variable factor is the identity of the second aromatic aldehyde. Our research group have previously postulated that (in the course of the archetypal benzoin condensation) the hydrogen-bonding chiral moiety present within precatalyst **412a** will stabilise the developing negative charge on the aldehyde undergoing nucleophilic attack by the Breslow intermediate through general acid catalysis. In the formation of **58** (Figure 3.4), as the (*E*)-enolamine (Breslow intermediate) approaches a second molecule of benzaldehyde from below (as drawn), the presence of the 2,6-chlorine atoms on the *N*-aryl ring of the catalyst and the phenyl ring of the enolamine offer a degree of steric hinderance and so the benzaldehyde aromatic ring will be orientate itself in the *gauche* conformation as shown to avoid a steric clash. Such a *gauche* arrangement allows the developing charges on both the oxygen atom of the carbonyl and the nitrogen atom of the triazole ring to be located in close proximity to one another and results in the (*si*)-face of the (*E*)-enolamine attacking upon the (*si*)-face of the incoming carbonyl group (**TS I**). This results in hypothetical formation of (*R*)-benzoin (according to Houk and Dudding), a proposal that originally fit well with our observed experimental results, with the carbene catalyst derived from **412a** enabling formation of (*R*)-benzoin with 80% *ee* (see Table 3.5, entry 2).



(*E*),(*si*)-enolamine-(*si*)-aldehyde = (*R*)-**58**

Figure 3.4 Previously proposed transition state model for formation of (*R*)-**58** in the presence of the carbene derived from novel chiral triazolium precatalyst **412a** – for clarity, the orientation of the (2,4,6-trichloro)phenyl ring has been adjusted

With more recent consideration, however, the validity of this model must be re-evaluated. Houk and Dudding's calculations had demonstrated how the lowest energy transition state was that in which the aldehyde phenyl ring was *anti* to the bulky chiral arm, which is not the case in **TS I**. More poignantly though, through the introduction of an *ortho* substituent of the second aromatic aldehyde, while the energy of the analogous transition state that enables general acid catalysis to be achieved (**TS II**, Figure 3.5) is likely to be comparatively higher than that of **TS I** due to the steric bulk of the *ortho* substituent, it would not appear sufficiently so to induce a complete reversal in the enantioselective outcome of the reaction. This is further supported by the fact that the transition state for formation of the (*S*)-product through general acid catalysis (**TS III**) would be characterised by a more severe steric strain between the bulky trichlorophenyl ring, the enolamine phenyl ring and the aromatic ring of the incoming *ortho*-substituted aldehyde.

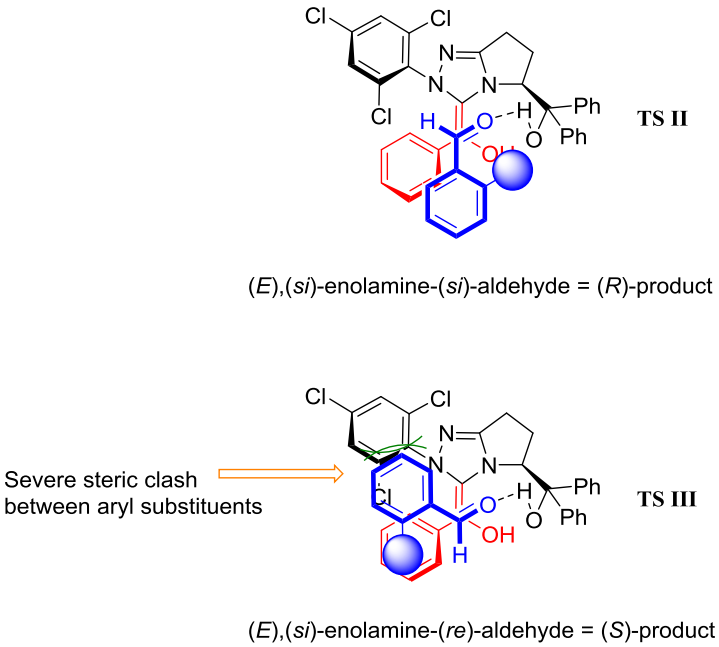


Figure 3.5 Proposed transition state models for formation of (*R*) and (*S*)-cross-benzoin products through general acid catalysis the presence of the carbene derived from novel chiral triazolium precatalyst **412a**

We therefore propose an alternative model to explain the formation of both (*R*)-**58** and (*S*)-cross-benzoin products utilising our hydrogen-bonding triazolium ion-based precatalysts. Instead of participating in a stabilisation of the transition state through general acid catalysis, we suggest that a hydrogen-bonding interaction between the hydroxy group of the chiral moiety and that of the enolamine fixes the (*E*)-alkene geometry of the Breslow intermediate and enables establishment of a 7-membered ring interaction within the transition state as it attacks upon the second aromatic aldehyde. In the formation of **58** (**TS IV**, Figure 3.6), a computationally measured distance (using a low level MM2 method) of 2.2 Å between these hydroxy groups supports the notion that a hydrogen-bonding interaction between the two could take place. In doing so, approach of the carbene from below the benzaldehyde molecule (as drawn) is obstructed and the 'empty' quadrant around the carbene is now located below the 5-membered aliphatic ring. Houk and Dudding's calculations propose that the lowest energy diastereomeric transition state is **TS IV** (Figure 3.6). Although in a *syn* conformation, the aldehyde phenyl ring is *anti* to both the phenyl substituent of the enolamine and the *N*-aryl ring of the catalyst, an orientation cited by the authors as being the decisive factor in determining **TS IV** as the lowest energy model. Despite the separation of the developing charges enforced by the *syn* conformation, a hydrogen-bonding interaction between the

aldehyde and the enol and a concurrent π-iminium interaction between the benzaldehyde ring and the nitrogen atom of the triazole ring mean these developing charges are stabilised. This (*E*),(*re*)-enolamine-(*si*)-aldehyde arrangement results in predominant formation of (*R*)-**58**.

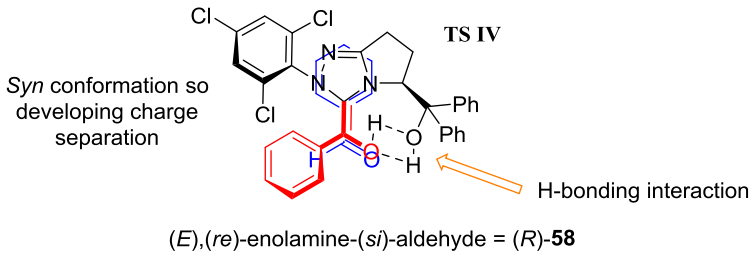


Figure 3.6 Proposed favoured transition state model for formation of (*R*)-**58** in the presence of the carbene derived from novel chiral triazolium precatalyst **412a**

Similarly, an analogous attack of the Breslow intermediate upon the (*si*)-face of the carbonyl of the *ortho*-substituted aldehyde (leading to formation of the (*R*)-cross-benzoin) *via* a higher energy *syn* conformation may also occur (**TS V**, Figure 3.7). However, the energy of this transition state is likely to be augmented further, relative to **TS IV**, due to an unfavourable steric clash between the *ortho* substituent and the chlorine atoms located on the *N*-aryl ring. Of course, there is still a degree of freedom through 180^{o} rotation of the aromatic ring to allow the *ortho* substituent to be orientated away from the chlorine atoms and out into the solvent, which perhaps explains why the enantioselectivity of the reaction in the presence of our precatalyst is modest. Figure 3.7 may also highlight how larger *ortho* substituents (such as chlorine and bromine atoms) in the *N*-aryl ring can discourage orientation of the second aldehyde's aromatic ring into the 'western' hemisphere (as drawn) of the Breslow intermediate to a much greater extent than the *ortho*-fluorine atoms present in precatalyst **206** (and thus, by extension, disfavour predominant formation of the (*R*)-product).

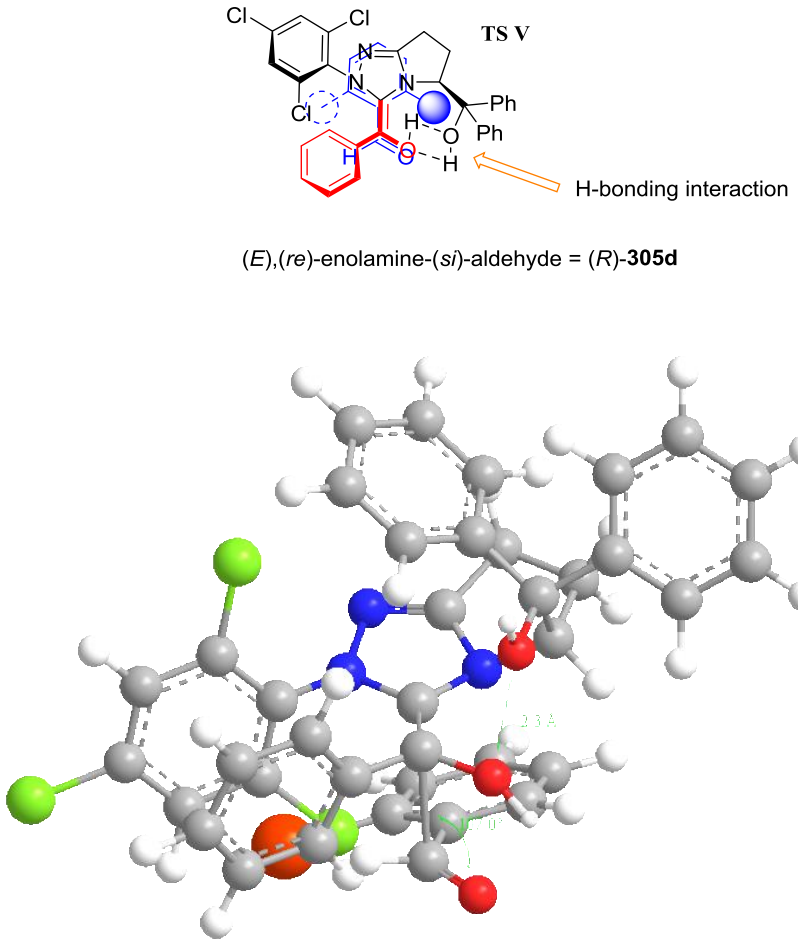
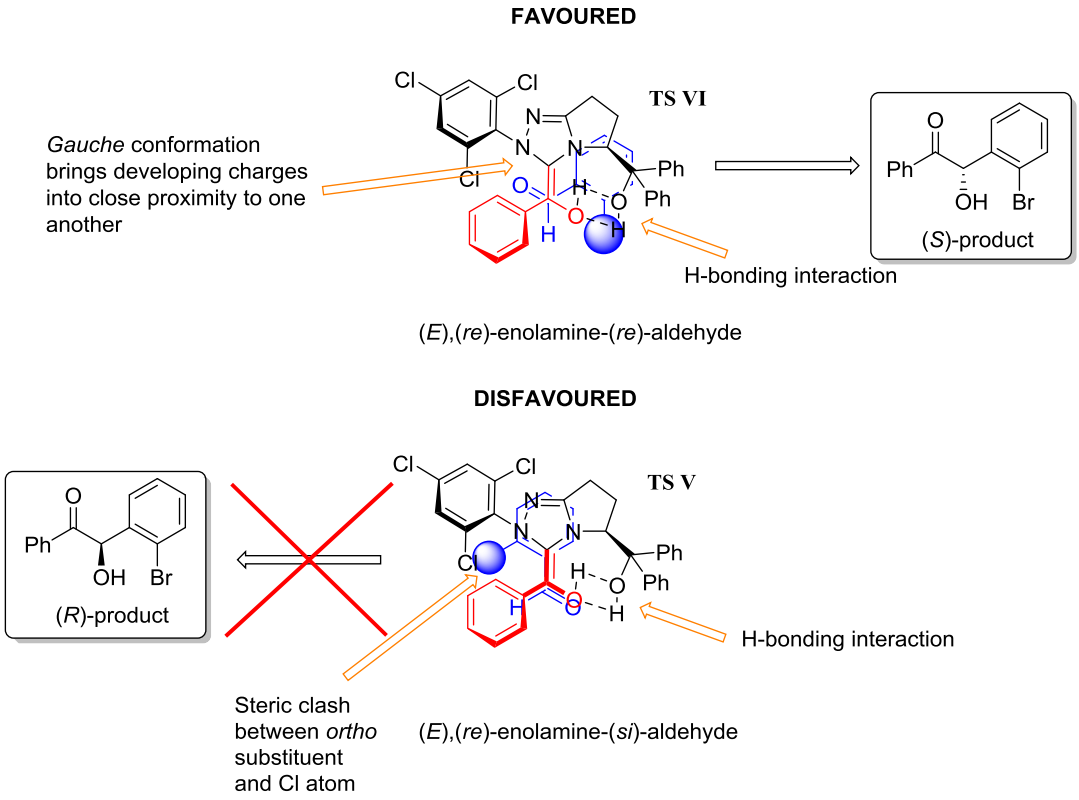


Figure 3.7 Proposed disfavoured transition state model for formation of the (*R*)-cross-benzoin adduct in the presence of the carbene derived from novel chiral triazolium precatalyst **412a**

Considering the above, we suggest that the lowest energy transition state possible that minimises the steric hinderance caused by the *ortho* substituent while maintaining the developing charges in close proximity to one another is **TS VI** (Figure 3.8). Here, attack of the Breslow intermediate upon the *ortho*-substituted aldehyde again occurs from above (as drawn), but does so upon the (*re*)-face of the carbonyl moiety, thereby allowing the lowest energy *gauche* conformation to be achieved while maintaining the bulky aromatic substituents in an *anti* relationship to one another. In addition to the close proximity of the developing charges on the oxygen and nitrogen atoms, the large aromatic ring of the aldehyde is also positioned in the 'empty' quadrant around the carbene environment. Such an arrangement results in predominant formation of the (*S*)-product, as is observed experimentally.



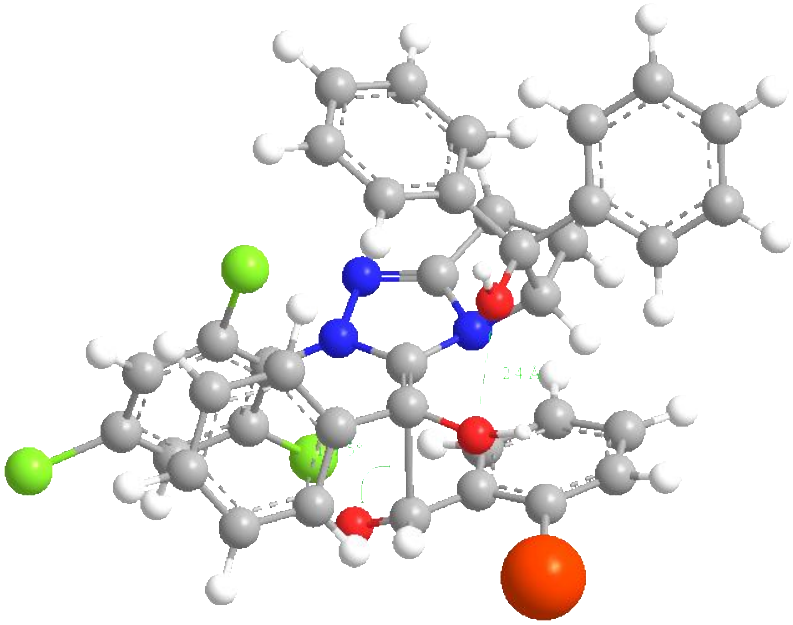


Figure 3.8 Proposed favoured and disfavoured transition state models for formation of cross-benzoin products in the presence of the carbene derived from novel chiral triazolium precatalyst **412a**

Of course, such are the complexities of this reaction and the possibility that other interactions and/or van der Waals forces are involved that it is entirely possible that this model is an incorrect representation of the true situation. However, we are not in a position to accurately identify such factors and the above treatment is derived from a combination of general chemical intuition and published literature in an attempt to explain our findings. A much more stringent computational examination would provide a substantial insight into the relative energies of all transition states and allow concrete comparisons with experimental data to be made.

3.8 Conclusions

In conclusion, we have carried out the first extensive study into the asymmetric intermolecular cross-benzoin condensation between two non-identical aromatic aldehydes as catalysed by chiral NHCs. The presence of at least one *ortho*-substituted benzaldehyde proved crucial in enabling the NHC to direct a moderately chemoselective reaction. Using a catalytic loading of a novel chiral triazolium precatalyst salt and base, our initial efforts to develop a fully asymmetric version of the reaction met with failure, but in doing so enabled us to investigate the underlying processes that compromise the observed optical purity values of the obtained cross-benzoin products. In this regard, we have revealed how, in the presence of carbene and base, these cross-benzoin adducts are subject to racemisation *via* base- or catalyst-mediated racemisation. The favourability of these pathways is greatly enhanced through the presence of electron-withdrawing substituents on the aryl rings of the cross-benzoin and hence the reason why previous studies investigating homobenzoin condensations have observed irregular and fluctuating enantiomeric excess values when employing activated benzaldehydes. Benzoin itself appears resistant to such racemisation in the presence of catalyst and base and so we propose that the archetypal benzoin condensation is no longer a suitable model reaction for the evaluation of the catalytic potential utility of a chiral carbene in mediating crossed acyloin condensations.

Through investigation of these pathways, we were subsequently able to modify and tailor our reaction conditions to minimise their negative impact upon the enantioselective outcome of the reaction, thus allowing us to synthesise a range of crossed benzoins in moderate yields with moderate-good enantioselectivity. Furthermore, careful planning and choice of the substrate aldehyde coupling partners employed allowed us to develop

the first highly enantioselective intermolecular cross-benzoin condensation using an NHC catalyst. Finally, we also detailed how the enantioselectivity of the reaction is heavily dependent upon the identity of the *ortho*-substituted benzaldehyde, with general trends suggesting that the larger the substituent, the greater the enantioselectivity of the process. A similar trend was observed when considering the size of the precatalyst *N*-aryl ring. Finally, a stereochemical rationale was put forward which, although in need of computational verification, fits well with our obtained experimental data.

Chapter 4 NHC-Catalysed Aerobic Aldehyde Esterifications in the Absence of External Oxidants or Co-Catalysts

4.1 NHC-catalysed aerobic esterifications: preamble

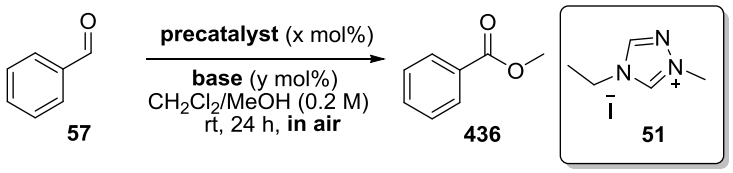
Our research group had previously postulated that the development of an NHC/magnetite nanoparticle bifunctional oxidative system (the NHC effecting the esterification of an aldehyde as previously discussed whilst 'tethered' to the nanoparticle, which provides an oxidative surface capable of catalysing formation of an acyl azolium ion from the Breslow intermediate) would represent a marked improvement upon existing methodologies with regards to efficiency, toxicity issues and (given the magnetic nature of the nanoparticle), simple recovery of the catalyst. Unpublished studies previously carried out within the group yielded positive results in terms of the ability of the NHC/magnetite catalytic system to catalyse the reaction as anticipated. However, the removal of the nanoparticle (in an attempt to determine its role in the oxidation of the Breslow intermediate) gave rise to remarkable results. It was observed that the esterification of benzaldehyde (**57**) in methanol, as catalysed by the NHC, under these aerobic conditions, could still occur *in the absence of the nanoparticle*. These initial studies were conducted by Dr. Alessandra Mari.

4.2 Preliminary experiments

It was subsequently decided to explore the scope and mechanism of this reaction. Initially, care was taken to establish the validity of these observations through an extensive second round of experimentation. Results from this study, assessing the esterification of **57** under basic conditions in the presence of the novel triazolium ion **51**, are detailed in Table 4.1. It became apparent at an early stage of our investigations that O_2 exclusion precluded ester formation, suggesting it potentially acts as an oxidant of the Breslow intermediate as previously described (Scheme 1.57). Sealing the reaction vessel to ensure neither solvent evaporation nor further influx of O_2 to the system results in a lower yield of 73% (entry 1). Conversely, allowing extensive O_2 access by not sealing the vessel has a detrimental effect (entry 2) due to the volatile nature of CH_2Cl_2. The apparent need to strike a balance between O_2 concentrations within the system and deter solvent evaporation is highlighted by the experiments outlined in entries 3 and 4, where limited exposure of the reaction to the external atmosphere produces methyl benzoate

(**436**) in 87% and 85% yield respectively at ambient temperature. Increasing the initial concentration of **57** *in situ* results in generation of **436** in moderate yields (entries 5 and 6), while larger reaction scales prove to have a negative effect, with benzoin being the dominant product in the crude reaction mixture (entry 7). This is attributed to the reduction of headspace within the flask, therefore reducing the O_2 levels within the system. Gratifyingly, exchange of CH_2Cl_2 for the less volatile THF resulted in a significant increase in activity, allowing product formation in an excellent 96% yield (entry 8). The use of methanol as the sole solvent (entry 9) provides **436** in 68% yield, supporting the suggestion that the role of THF in aiding oxygen diffusion into the system may be extremely significant.

Table 4.1 NHC-mediated oxidative esterification: preliminary experiments



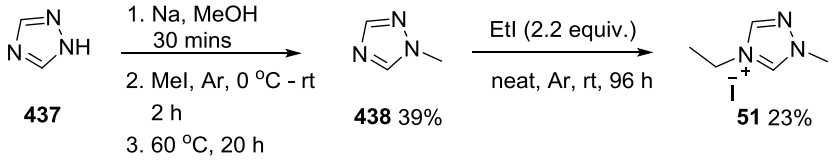
entry	precatalyst	x (mol%)	base	y (mol%)	solv. (*v/v*)	yield (%)[a]
1	**51**	15	DBU	110	1:1	73[b]
2	**51**	15	DBU	110	1:1	47[c]
3	**51**	15	DBU	110	1:1	87[d]
4	**51**	15	DBU	110	1:1	85[e]
5	**51**	15	DBU	110	1:1	65[f]
6	**51**	15	DBU	110	1:1	54[g]
7	**51**	15	DBU	110	1:1	18[h,i]
8	**51**	15	DBU	110	1:1	96[j]
9	**51**	15	DBU	110	n/a	68[k]

[a]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard. [b]Reaction vessel sealed. [c]Reaction vessel unsealed and exposed to external environment. [d]Reaction vessel sealed but opened and re-sealed at 1 h, 2 h, 17 h and 24 h. [e]Reaction carried out in 10 mL round-bottomed flask fitted with a septum punctured with a needle. [f][**57**] = 1.0 M. [g][**57**] = 0.5 M. [h]Reaction scale = 10 mL solvent (as opposed to 5 mL). [i]Also observed the formation of benzoin (**58**) in 26 % yield. [j]CH_2Cl_2 exchanged for THF.

4.3 Optimisation of reaction conditions

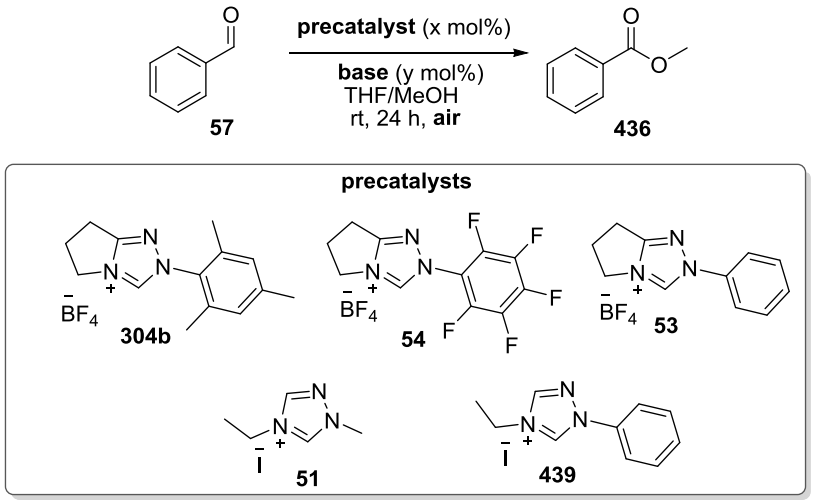
Repetition of entry 8 above in a tertiary round of experimentation provided a reproducible protocol enabling subsequent investigations determining the other factors (besides O_2 concentrations within the system) influencing the efficiency of this catalytic process; particularly the precatalyst structure and electronic characteristics. This allowed optimisation of the procedure (Table 4.2). As noted, precatalyst **304b** was gratefully received from the research group of Prof. Andrew Smith (University of St. Andrews). Precatalysts **53** and **54** were synthesised according to previously detailed literature procedures[83] while **439** was prepared by Dr. Mari. The synthesis of novel triazolium salt **51** was achieved through successive alkylations of 1,2,4-triazole as outlined in Scheme 4.1.

Scheme 4.1 Synthesis of novel triazolium ion **51**



57 Could be esterified to a conveniently detectable extent in methanolic THF (1:1 *v*/*v*) in the presence of triazolium precatalysts (15 mol%) and a small excess of base (DBU, 110 mol%) under an air atmosphere (Table 4.2). The importance of the precatalyst in this transformation is evident however - in the absence of the triazolium ion no conversion to methyl benzoate (**436**) is observed (entry 1). In the presence of the *N*-mesityl substituted triazolium ion **304b**, **436** is formed in moderate yield after a 24 hour reaction time at ambient temperature (entry 2). Increasing the acidity of the carbene precursor through use of **54**[235] resulted in a marginal decline in product yield (entry 3), which decreased further when employing the less hindered and acidic phenyl-substituted carbene derived from **53** (entry 4). A more hindered, open-chain analogue of precatalyst **53** (*i.e.* **439**) was completely inactive under these conditions (entry 5). The exchange of the *N*-phenyl substituent for a methyl group (*i.e.* precatalyst **51**) is evidently significant in the observed difference in activity between **51** and **439**, with **51** producing **436** in 96% yield as previously detailed (entry 6).

Table 4.2 NHC-mediated oxidative esterification: optimisation of reaction conditions



entry	precatalyst	x (mol%)	base	y (mol%)	solv. (*v/v*)[a]	yield (%)[b]
1	-	0	DBU	110	1:1	0
2	**305b**	15	DBU	110	1:1	61
3	**54**	15	DBU	110	1:1	56
4	**53**	15	DBU	110	1:1	48
5	**439**	15	DBU	110	1:1	0
6	**51**	15	DBU	110	1:1	96
7	**51**	5	DBU	110	1:1	74
8	**51**	15	DBU	15	1:1	17
9	**51**	15	DBU	50	1:1	54
10	**51**	15	NEt_3	110	1:1	9
11	**51**	15	DMAP	110	1:1	12
12	**51**	15	DABCO	110	1:1	0
13	**51**	15	K_2CO_3	110	1:1	60
14	**51**	15	DBU	110	12:1	44
15	**51**	15	DBU	110	6:1	61

[a]THF held constant (2.5 mL). [b]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard.

Having established precatalyst **51** as being markedly superior, the various reaction parameters were then investigated. A reduction of the loading of the triazolium ion to 5 mol% had a congruent effect upon product yields (entry 7). It was surprising to find that the oxidation process also strongly depends on both the loading (entries 8 and 9) and the identity (entries 10-13) of the base employed – with DBU emerging comfortably superior to the others evaluated in this study. The esterification can also be carried out using considerably less methanolic solvent (entries 14-15), at the expense of reaction rate.

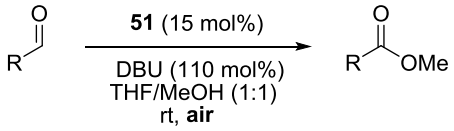
4.4 NHC-mediated aldehyde esterification: reaction scope

4.4.1 Substrate scope: aldehyde component

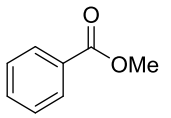
Having optimised the protocol, the compatibility of the process with different aldehyde substrates (Table 4.3) was then evaluated. In keeping with our initial results, electron-neutral (*i.e.* **57** and **316**, entries 1-2) aromatic aldehydes could be converted to the corresponding methyl esters in excellent isolated yield in the presence of **51**, DBU, methanol and air. Deactivated (*i.e.* **318** and **440**, entries 3-4) aromatic aldehydes also proved to be excellent substrates under the optimised reaction conditions, albeit with slower reaction rates. Contrary to initial expectations, the use of activated aromatic aldehydes produced unusual yet interesting results: while 3-chlorobenzaldehyde (**321**) proved an excellent substrate, the esterification of its *para*-substituted (and less hindered) isomer **324** did not proceed with such efficacy. The 3-methoxy-substituted variant **325** proceeded with lower (albeit synthetically useful) yields (entries 5-7). In contrast to our group's previous experience regarding catalysis of the corresponding reaction using stoichiometric oxidants (see Section 1.7.1.1),[199] *ortho*-substitution is not well tolerated: 2-Tolualdehyde (**114**) and 2-chlorobenzaldehyde (**88**) underwent conversion to **449** and **450** in low to moderate yields respectively (entries 8-9), this trend most striking with the activated yet hindered 2-(trifluoromethyl)benzaldehyde (**359**) which could not be transformed into the desired ester **451** under these conditions (entry 10).

Table 4.3 Substrate scope: aldehyde component

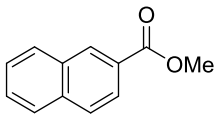
57 R = C_6H_5
316 R = 2-naphthyl
318 R = 4-CH_3-C_6H_4
440 R = 4-(CH_3O)-C_6H_4
321 R = 3-Cl-C_6H_4
324 R = 4-Cl-C_6H_4
325 R = 3-(CH_3O)-C_6H_4
114 R = 2-CH_3-C_6H_4
88 R = 2-Cl-C_6H_4
359 R = 2-CF_3-C_6H_4
329 R = 2-thenyl
441 R = 3-pyridyl
442 R = 2-(C_6H_4)-CH_2CH_2



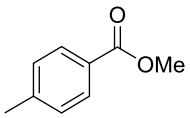
Products



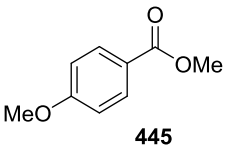
436
94% (24 h)



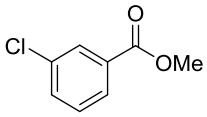
443
90% (12 h)



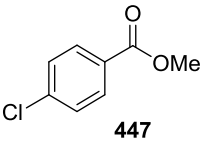
444
92% (30 h)



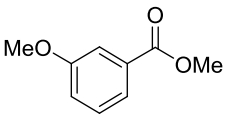
445
90% (92 h)



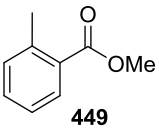
446
92% (24 h)



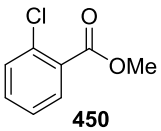
447
72% (12 h)



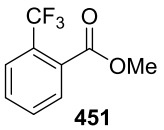
448
77% (68 h)[a]



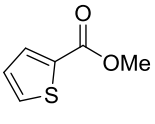
449
28% (24 h)[b]



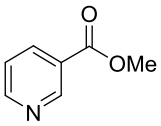
450
53% (24 h)



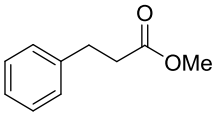
451
0% (24 h)



452
65% (18 h)



453
93% (0.3 h)



454
15% (24 h)[b]

[a]Reaction carried out at 45 °C. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard.

From a synthetic utility point of view, it was pleasing to observe that substrates incorporating oxidisable heterocyclic functionalities (*i.e.* **441** and **329**) could be converted to their methyl ester analogues in good-excellent yields, with the latter substrate undergoing relatively rapid esterification (entries 11-12). Goswami and Hazra had previously reported the aerobic esterification of heterocyclic aromatic aldehydes involving thiamine hydrochloride and NEt_3 (2.0 equiv.) in MeOH (heating under reflux

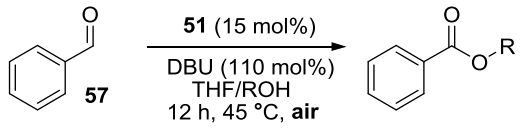
was required to ensure high yields).[236] In contrast to the fast, clean esterification of **441** involving **51**, the exposure of the unbranched aliphatic aldehyde **442** to these reaction conditions resulted in a poor yield of the ester **454** as a component of a complex product mixture (entry 13), most likely due to competing aldol side reactions.

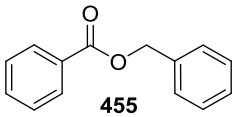
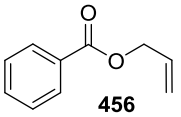
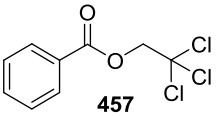
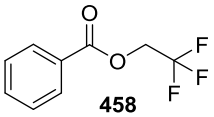
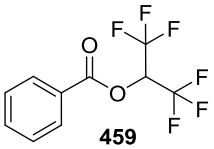
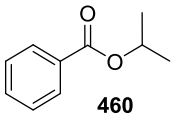
4.4.2 Substrate scope: alcohol component

Having demonstrated the synthetic versatility of the reaction with regard to the aldehyde substrate, attention then turned to the alcohol component. The esterification of **57** using **51** and DBU in the presence of a variety of alcohols at 45 ^{o}C is detailed in Table 4.4. Focus was placed primarily upon those alcohols forming esters amenable to deprotection by methods other than specific acid or base-catalysed hydrolysis. Initial studies utilised such alcohols in a 1:1 (*v/v*) ratio with THF (condition set A). Benzyl alcohol proved to be an excellent substrate in this regard, allowing isolation of benzyl benzoate (**455**) in 94% yield (entry 1). Allyl alcohol was equally suitable for the esterification, providing **446** in similar efficacy (entry 2). It was envisaged that the use of more acidic alcohols might result in a concurrent increase in yields due to facile deprotonation under the basic reaction environment. This hypothesis proved incorrect however, with 2,2,2-trichloroethanol generating **447** in moderate yields (entry 3), while the corresponding trifluoro-analogue failed to yield **448** at all (entry 4). A similar result was observed when employing 1,1,1,3,3,3-hexafluoro*iso*propanol (entry 5). The more sterically hindered and less acidic *iso*propanol also proved resistant to esterification (entry 6).

Recognising the need for versatility with regard to the identity of the alcohol in our catalytic system, efforts then began to overcome the issues arising with alcohols of lower pK_a values. It was speculated that, by employing such alcohols in a 1:1 (*v/v*) ratio with THF, their greater acidity impedes carbene generation *in situ*, with only the alcohol itself undergoing deprotonation by the base (or any carbene being formed immediately being reprotonated by the alcohol). Thus, it was perceived that by reducing the level of alcohol within the system it may be possible to promote both carbene formation and alcohol deprotonation simultaneously and obtain the relevant ester product. Gratifyingly, this conjecture proved correct. Through variation of alcohol concentrations within the system, it was determined that moderate yields could be obtained when 1.2 equivalents of alcohol were employed (Table 2.4, condition set B). The formation of the

Table 4.4 Reaction scope: alcohol component.



entry	product	alcohol pK_a	condition set[a]	yield (%)[b,c]
1	 **455**	15.4	A	94
2	 **456**	15.5	A	87
3[d]	 **457**	12.3	A B	64 58
4[d]	 **458**	12.4	A B	0 54
5[d]	 **459**	11.2	A B	0 25[e]
6[d]	 **460**	17.1	A	0

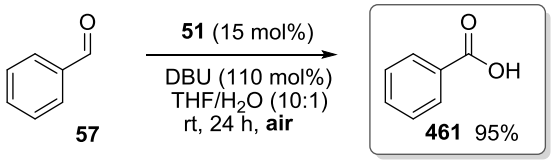
[a]Condition set A: THF/ROH (1:1 *v*/*v*). Condition set B: THF solvent, ROH (3.0 equiv.). [b]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (114 μL, 1 mmol, 1 equiv.) as an internal standard. [c]Yield of isolated product given in parentheses. [d]Reaction at rt. [e]Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture only.

trichloroethanol-derived ester **457** proceeded in *ca.* 60% yield irrespective of the conditions employed, with 1.2 equivalents providing 58% yield (entry 3). It was rewarding to observe that the trifluoroethanol analogue **458** could be formed in similar yields (entry 4) and, whilst not synthetically useful, the production of **459** in 25% yield (entry 5) is particularly satisfactory as supplementary evidence to support this hypothesis. The acidity of this alcohol is perhaps too high to be truly compatible with the protocol.

Reconciling obtained yields of **457** and **458** with the pK_a values of their respective alcohol parents proves difficult, particularly when considering condition set A. It is suggested that the volatility of 2,2,2-trifluoroethanol (b.p. 58 ^oC) may be the primary reason for these observations – both it and 2,2,2-trichloroethanol have similar effects in deterring carbene generation (through their practically identical pK_a values). The volatility of 2,2,2-trifluoroethanol means that the alcohol concentration within the system decreases as the reaction proceeds so that carbene generation becomes increasingly favourable. However, the amount of alcohol subsequently available for esterification is quite limited. Conversely, in the presence of 2,2,2-trichloroethanol, carbene generation is slower but the level of alcohol remains constant throughout the course of the reaction. Reducing the alcohol concentration (condition set B) favours carbene generation *in situ*, allowing a mutual increase in the reaction rate that renders the volatility of the alcohol less problematic.

Yoshida *et al.*[237] have previously disclosed the imidazolium ion-derived carbene-mediated aerobic oxidation of aromatic aldehydes to carboxylic acids in the presence of water. The method was efficacious only with activated aldehyde substrates: for instance, benzaldehyde underwent conversion to benzoic acid with <10% yield. In contrast, in the presence of precatalyst **51** and DBU, **57** could be cleanly oxidised to the acid **461** in THF/H_2O (10:1 *v/v*) in excellent isolated yield (Scheme 4.2) following simple acid/base work-up.

Scheme 4.2 The efficient NHC-catalysed aerobic oxidation of benzaldehyde



4.5 Oxidative or oxygenative? Elucidating the reaction pathway

The development of this protocol represents the most efficient NHC-mediated *aerobic* oxidative esterification methodology involving alcohols in the literature. Having established the breadth of the reaction scope, we then sought to elucidate the reaction mechanism. The results of the studies outlined in Tables 4.1 – 4.4 are difficult to

reconcile with either of the mechanisms proposed in the literature (shown in Scheme 1.57). For instance, the 'oxygenative' esterification reaction requires alkyl transfer from an electrophile (such as an alkyl halide). The 'oxidative' esterification mechanism is also unsatisfactory here, as the sensitivity of the process described in this work to the steric bulk of the nucleophilic and electrophilic reaction components is not consistent with that observed previously[199] (*e.g.* in esterifications involving azobenzene as an oxidant, 2-tolualdehyde (**114**) and *iso*propanol served as excellent electrophilic and nucleophilic components respectively, while in the current study both are poor substrates) which strongly indicates that the aerobic oxidative esterifications outlined above do not proceed via acyl azolium ion intermediates.

4.5.1 Mechanistic studies

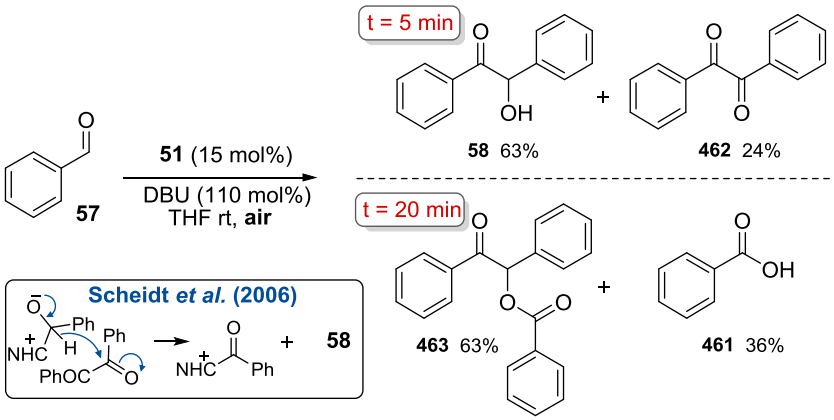
At this point, aware of time constraints due to perceived competition from other research groups active in this field, investigations became a collaborative effort between several members of our research group. Although the majority of the reactions detailed below represent my own work, important contributions have been made by others in an effort to elucidate the reaction mechanism in a swift and thorough fashion. Where this is the case, their work has been clearly identified and acknowledged.

Given that the esterifications do not proceed in the absence of oxygen, a series of alternative structures were postulated in our search for the species which is oxidised in these reactions, with benzoin (**58**) speculated to be the most likely candidate as the slow, base-catalysed aerobic oxidation of which to benzil (**462**, see Scheme 4.3) by O_2 is known.[238] While never isolated/observed in any of the reactions outlined above, **462** is highly electrophilic and it is plausible it would undergo rapid destruction in the presence of the relatively unhindered carbene derived from **51** and methanol. Additionally, although the sensitivity of the esterifications to steric factors did not match that of known processes involving acyl azolium ions, it was (in our experience[138,139,145,169,170]) consistent with the influence of substrate steric bulk on the efficiency of triazolium-catalyssed benzoin condensation. This observation, although perhaps reasonably weak evidence upon which to base the hypothesis, nevertheless encouraged further investigations.

The exploration of this hypothesis began by subjecting benzaldehyde (**57**) to the esterification conditions in the absence of methanol; upon which it was observed that the

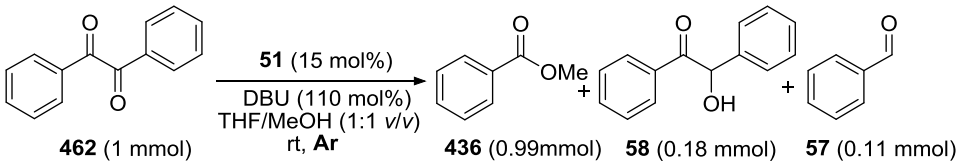
formation of both **58** and **462** occurred after just 5 min reaction time (Scheme 4.3).[239] After 20 min, both these species have been replaced by a hydroacylation product **463** (in good yield) and the acid **461** (presumably formed due to the presence of adventitious water). Scheidt *et al.*[195] have previously reported the formation of **463** in the NHC-mediated reaction between **57** and **462**, rationalising this in terms of a hydride transfer process between the carbene-aldehyde adduct and **462** to generate an acyl azolium ion and benzoin. To the best of our knowledge, the reaction outlined in Scheme 4.3 is the first example of the efficient NHC-mediated formation of a hydroacylation product from an aldehyde alone in the presence of air. This reaction, which represents the 'gateway' reaction for subsequent mechanistic study reactions, was carried out by Dr. Claire-Louise Fagan.

Scheme 4.3 The observation of benzil as an oxidised intermediate in the absence of MeOH.



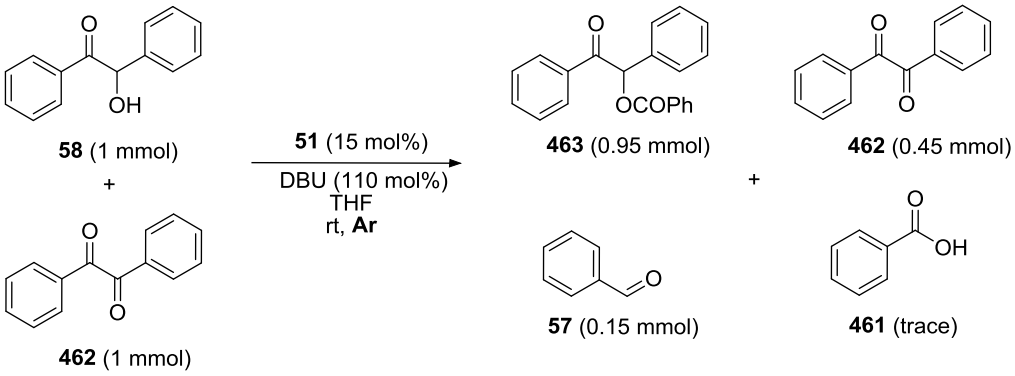
In seeking to establish if **462** is indeed a catalytically relevant intermediate in the presence of alcohol, it was exposed to methanol and the carbene under an argon atmosphere, upon which rapid conversion of **462** to methyl benzoate (**436**), **58** and **57** at ambient temperature (Scheme 4.4) was observed.[240]

Scheme 4.4 The NHC-mediated conversion of benzil to methyl benzoate in the absence of O_2



Similarly, the carbene-catalysed reaction of **58** with an equivalent amount of **462** *in the absence* of both air and MeOH generated the hydroacylation product **463** as the major constituent of the crude reaction mixture (Scheme 4.5), indicating that benzoin may also be able to play the role the nucleophilic alcohol in these reactions.

Scheme 4.5 The NHC-mediated reaction of benzil (**462**) with benzoin (**58**) in the abence of O_2

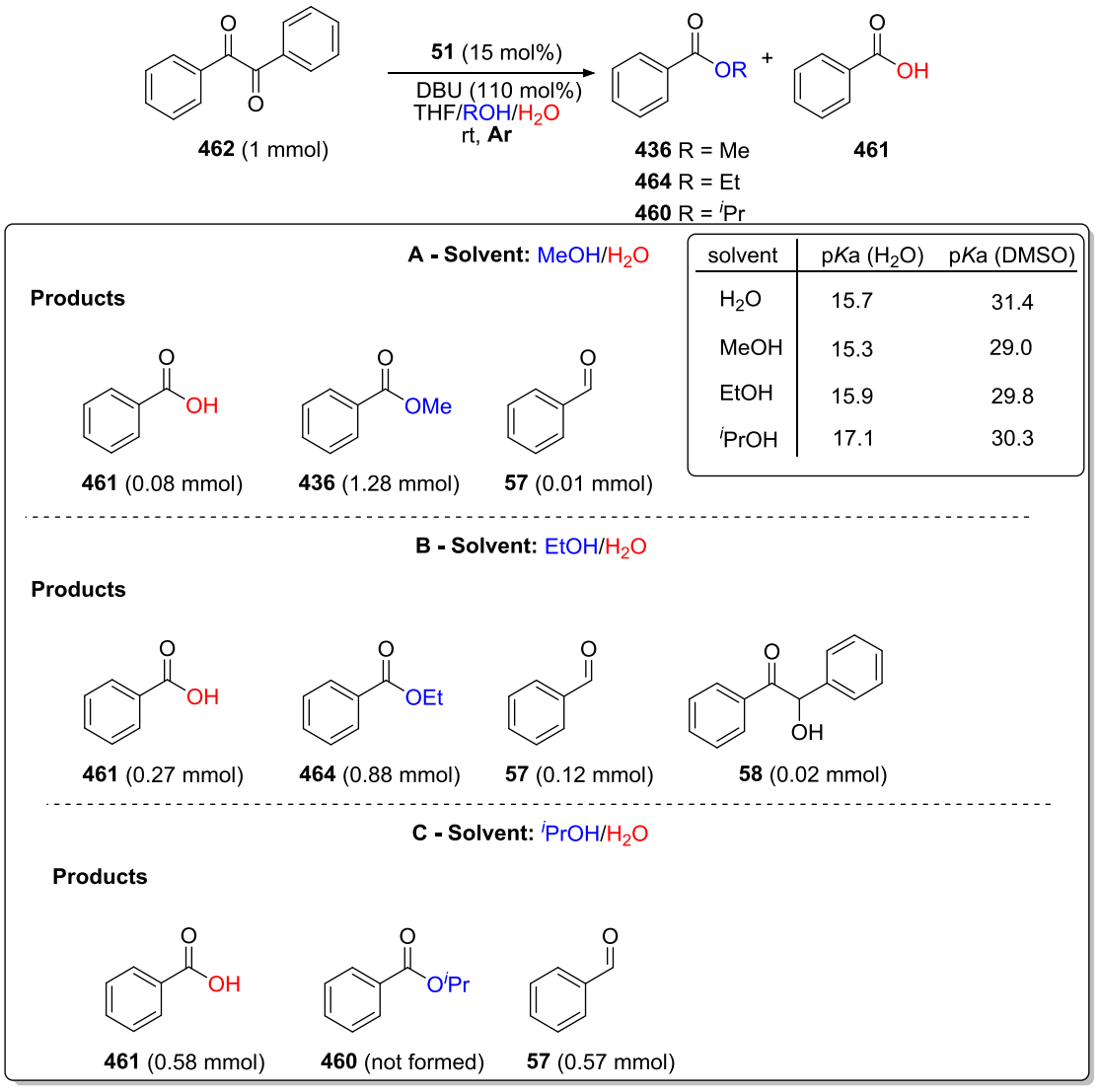


From the above, it must be acknowledged that hydroacylation product **463** can also serve as an acylating agent. Further studies into this possibility, carried out by Dr. Sivaji Gundala, showed conclusively that **463** can indeed be cleanly converted to **436** in excellent yields (89%) in the presence of **51** and DBU. However, it is noted that formation of **463** *in situ* is relatively slow compared to that of benzil (**462**) and that it is conspicuously absent in ^{1}H NMR spectra of reactions involving methanol or various other alcohols. Thus it is proposed that **462** serves as principal reactive intermediate in the reaction.

Finally, in order to gain some insight regarding the origins of the influence of the alcohol structure on the reaction efficiency, benzil (**462**) was reacted in the presence of **51** under

anaerobic conditions in competition experiments using alcohol and water solvent mixtures, yielding either the ester or acid product respectively. We expected products derived from nucleophilic attack of the less hindered water molecule to dominate over the ester analogues stemming from the more hindered alcohols. Surprisingly, the 1:1 solvent mixture of methanol and water generated the methyl ester **436** as the major product (Scheme 4.5A; only low levels of acid **461** and aldehyde **57** observed). The use of ethanol as a co-solvent also diverted this process towards the generation of ester **464** (Scheme 4.5B), however, acid formation was more favourable here (together with small amounts of **57** and **58**). In aqueous *iso*propanol conversion is incomplete. No esterification occurs: oxidation to **461** and reversion back to **57** are the major fates of **462** (Scheme 4.5C).

Scheme 4.5 Alcohol and water competition experiments



It appears that the factors which govern the selectivity of these processes are not simply related to either acidity or steric bulk alone, but a confluence of factors: a weak correlation between the acidity and propensity for ester formation was found, while the outcome of the experiment involving *iso*propanol is difficult to rationalise based on its pK_a alone.

4.5.2 Proposed pathway

This data, along with other results not mentioned here, allow the proposal of a mechanistic rationale as shown in Figure 4.1. The carbene **465** reacts with **57** to form the Breslow intermediate **466**, which, on addition to another molecule of **57** results in the rapid formation of **58**, which is oxidised by air in the presence of base to benzil (**462**). Since our results are not consistent with acyl triazolium ion formation, we would propose that the electrophilic diketone **462** is attacked by carbene **465** to give the tetrahedral intermediate **467**, which is converted to **468** (presumably under the influence of intramolecular general base catalysis). The hemiacetal **468**[241] can then collapse to reform the Breslow intermediate (*i.e.* **466**) and methyl benzoate **436**. The formation of the hindered hemiacetal **468** would be likely to depend on both the steric bulk and the pK_a of the alcohol. In the absence of added alcohol, it is possible that a similar process occurs involving **58** as the nucleophile, which affords the hydroacylation product **463**. In the presence of MeOH **463** is converted to **436** *via* **469**. The formation of benzoin (**58**) from benzil (**462**) in the absence of oxygen (but presence of methanol) also requires explanation: we would suggest that - by analogy with a proposal by Fantin *et al*.[241] in a distinct but related transformation – attack by the Breslow intermediate (*i.e.* **466**) on **462** would yield **470** (which was isolated by Fantin *et al*.). In the presence of excess base and methanol, the cleavage of **470** to yield **436** and **58** *via* hemiacetal **471** is conceivable.

4.6 Expanding the scope of the reaction to effect NHC-catalysed aerobic aldehyde amidations

In conjunction with our studies on NHC-mediated aldehyde esterifications, we also recognised the potential to replace the alcohol as the nucleophile within the system with an amine, thereby ultimately forming a synthetically valuable amide bond. Prior to determining a mechanistic pathway by which the aldehyde esterification proceeds, it was felt that such a strategy would prove successful. Initial studies involving an excess of

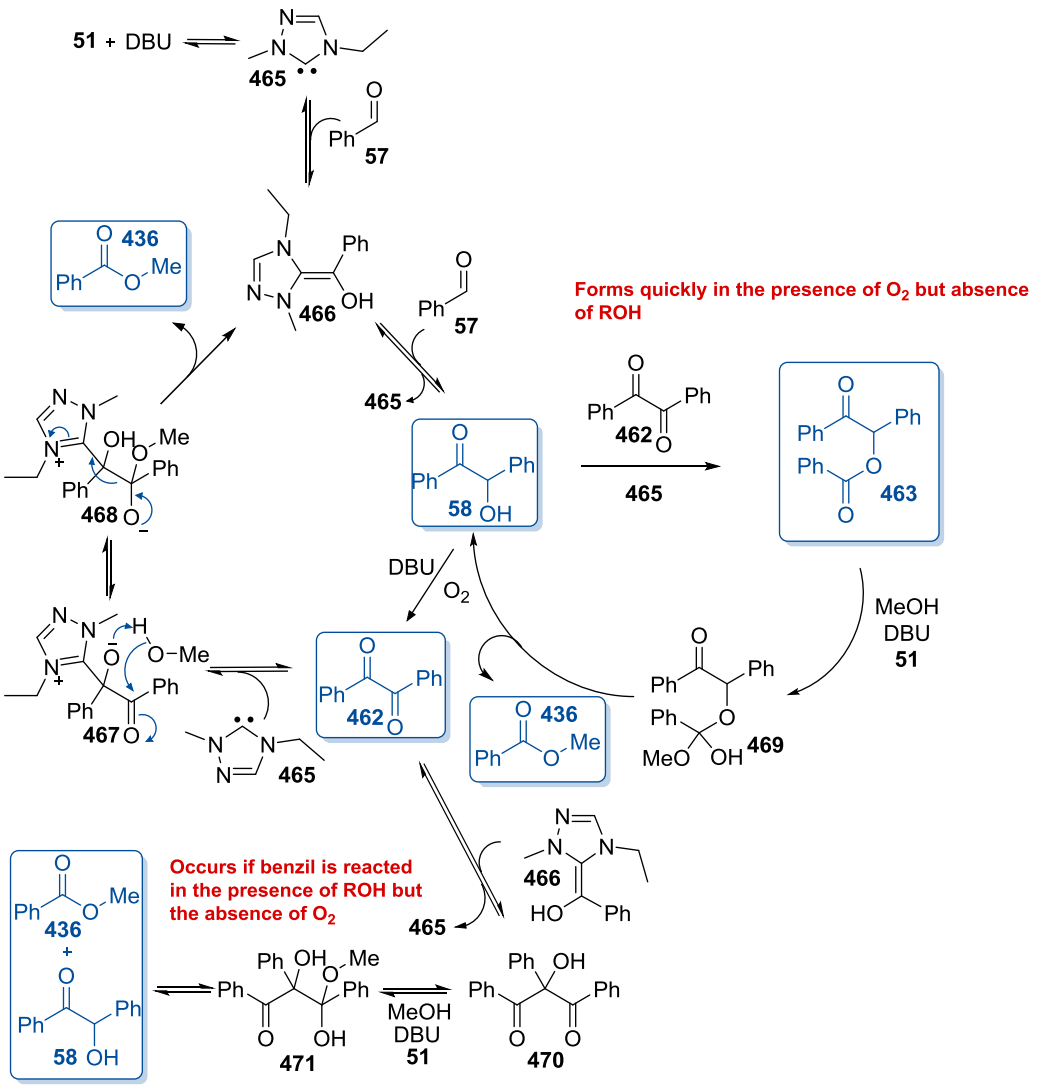
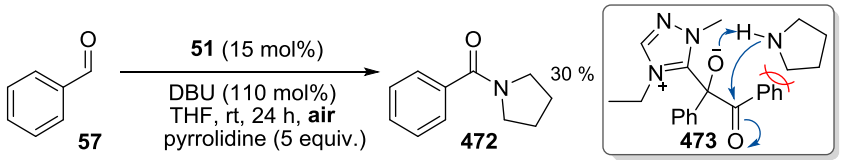


Figure 4.1 Mechanistic rationale for the NHC-catalysed oxidative esterification of **9** with MeOH in air. All highlighted compounds have been either isolated or detected *in situ* by ^{1}H NMR spectroscopy

pyrrolidine provided phenyl-pyrrolidin-1-yl-methanone (**472**) in an isolated yield of 32% (Scheme 4.6). This result lends further support to the proposed mechanistic model (Figure 4.1) as pyrrolidine represents a more nucleophilic reagent than methanol. However, attack of the more hindered amine on the very bulky ketone **473** may be more difficult. In addition, this reaction would be hampered by considerably less efficient general base catalysis of the attack on the ketone involving the considerably less acidic amine. Work within our group, presently being carried out by Dr. Vikas Kumar, aims at developing a successful methodology to effect such amidations based around the premise of this study.

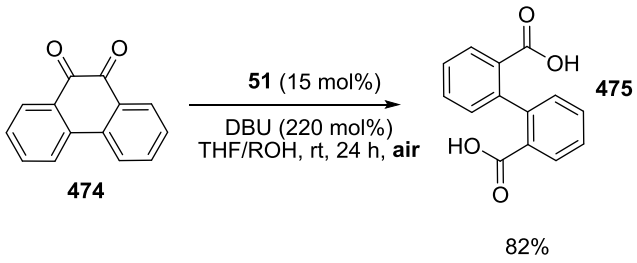
Scheme 4.6 The NHC-mediated amidation of **57**



4.7 Expansion of the protocol: NHC-catalysed oxidative cleavage of 1,2-diketones

The results of this novel study, specifically the identification of benzil as the key intermediate, allowed us to identify the use of 1,2-diketones to generate the corresponding ester/acid derivatives with a concurrent carbon-carbon bond cleavage, a synthetically attractive manipulation. Predicting problematic issues involving enolate chemistry using aliphatic 1,2-diketones, we envisaged the reaction amenable to effecting ring-opening reactions of aromatic 1,2-diketones of general type **474** (Scheme 4.7):

Scheme 4.7 Ring-opening esterifications/acidifications of aromatic 1,2-diketones

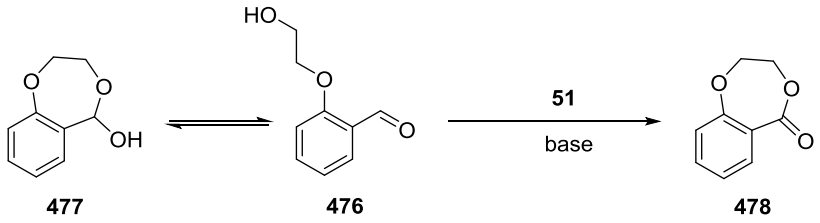


Our predictions were proven to be accurate, with Dr. Sivaji Gundala and Dr. Claire-Louise Fagan able to demonstrate that, using water as the nucleophile, diacids of general structure **475** could be isolated in good yield. Initial results based upon the use of MeOH in these studies had met with problems through the presence of adventitious water – acid production was significant and hampered the synthesis of the analogous ester. Therefore, altering our approach solely towards the production of the carboxylic acid by exchange of H_2O for MeOH, we were grateful for its isolation in 82% yield under reaction conditions employing a 20:1 (*v/v*) ratio between THF and H_2O. DBU loading was increased to 220 mol% to account for the presence of two acid moieties within the product. Subsequent investigations have shown the substrate scope of this process to be very reliant upon the nature of the structure of the 1,2-diketone: fused aromatic rings tend to react slower,

presumably due to sterics, than those joined by a single bond (of type **474**) whilst as envisaged aliphatic aldehydes undergo extensive aldol chemistry under the basic reaction conditions. In an excellent exploitation of this novel protocol, we also reported the first example of a one-pot synthesis of an anhydride from a 1,2-diketone using NHC catalysis.[242]

4.8 Intramolecular lactone formation through NHC-catalysed oxidative esterifications

As a further attempt to extend the applicability of our methodology, we also postulated that the use of an *ortho*-substituted benzaldehyde such as **476** (which exists in solution in equilibrium with its lactol/hemiacetal form **477**) could allow formation of a new alkyl lactone ring through its oxidative esterification to produce **478** (Scheme 4.8).

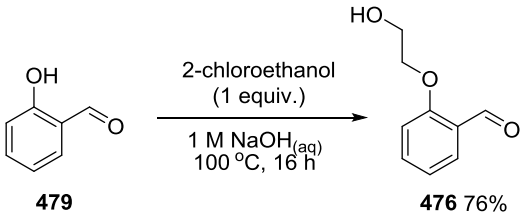


Scheme 4.8 Postulated lactone formation through oxidative esterification

However, we envisaged problems in successfully achieving this transformation, specifically that in the absence of an added alcohol nucleophilic component solubility issues with the precatalyst were likely to arise in a strictly THF-based solvent medium. Furthermore, the equilibrium between the lactol (**477**) and aldehyde (**476**) would likely affect the rate of the esterification, given that the lactol will not participate in any form of synthetically useful interaction with an NHC. Finally, we have previously demonstrated how employing *ortho*-substituted benzaldehydes in our oxidative esterification protocol results in reduced isolated yields of their methyl ester derivatives. Based upon our proposed mechanism (Figure 4.1), this is attributable to the well-documented reluctance for such substrates to participate in a homobenzoin condensation and so the problem will likely hamper efforts to achieve lactone formation *via* an NHC-catalysed oxidative esterification pathway. Nevertheless, the treatment of salicylaldehyde (**479**) with 2-

chloroethanol under basic and reflux conditions provided **476** in good yield (Scheme 4.9).

Scheme 4.9 Synthesis of **476**

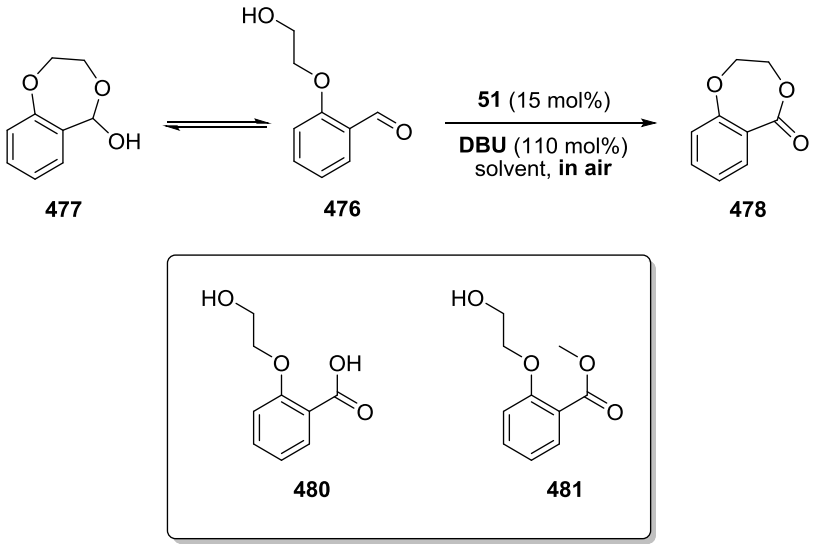


479 **476** 76%

We proceeded to employ **476** as a substrate in our NHC-mediated oxidative esterification in the presence of precatalyst **51** and DBU (Table 4.5). Having previously determined that the presence of *iso*propanol deters formation of its corresponding ester within the system, we initially employed it in as part of 1:1 (*v*/*v*) solvent medium with THF to aid dissolution of the precatalyst. While this was not wholly effective in this regard we were pleased that, using a 15 mol% catalytic loading of **51** (in conjunction with 1.1 equivalents of DBU), we could isolate the desired lactone product **478** after a 66 hour reaction time. However, the reaction rate was quite slow with just 36% yield obtained (entry 1). Increasing the temperature of the reaction to 45 ^{o}C and reducing the reaction time to 24 hours under otherwise identical conditions did not improve this result significantly; **478** being isolated in 38% yield (entry 2), while the carboxylic acid derivative of **476** (*i.e.* **480**) was also observed in 32% yield *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Seeking to encourage complete dissolution of the triazolium ion-based precatalyst to increase yields, we chose to then employ methanol as a co-solvent in the reaction, envisaging that the intramolecular esterification of **476** would proceed faster than the intermolecular analogue between **476** and methanol under our conditions. Initially, this was done on a 1:1 (*v*:*v*) basis with THF (entry 3) but disappointingly ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated no presence of the desired product. Instead, we observed a mixture of **476**, **480** and the methyl ester **481** after 24 hours. Subsequently lowering the concentration of the alcohol component within the system also failed to enable any considerable product formation – in a 5:1 (*v*/*v*) THF/*i*-PrOH solvent medium, **478** was isolated in just 19% yield after 24 hours (entry 4), while conducting the reaction in a 5:1 (*v*/*v*) THF/MeOH system resulted in a mixture of just **476** and **480** after 24 hours (entry 5). In both of these entries, the

solubility of the precatalyst was poor and we postulate this is the primary reason behind the low yields in either case.

Table 4.5 Intramolecular oxidative esterification using precatalyst **51**



entry	solvent (*v/v*)	time (h)	yield **478** (%)[a]	yield **480** (%)[b]	yield **481** (%)[b]
1	THF/*i*-PrOH (1:1)	66	36	n/d	n/a
2[c]	THF/*i*-PrOH (1:1)	24	38	32	n/a
3	THF/MeOH (1:1)	24	0	21	16
4	THF/*i*-PrOH (5:1)	24	19	n/d	n/a
5	THF/MeOH (5:1)	24	0	10	0

[a]Isolated yield. [b]Determined *via* ^{1}H NMR spectroscopic analysis of the crude reaction mixture using styrene (0.25 equiv.) as an internal standard. [c]Reaction conducted at 45 ^{o}C.

With these results offering no positive outcome in terms of yield, we ceased our investigations into the scope of this transformation. However, the possibility remains that future work may build upon the foundations laid with this data. Certainly, the extent of modification of the system parameters presented above here is quite limited and is entirely plausible that a protocol can be developed to effect this NHC-catalysed oxidative lactonisation in a successful manner.

4.9 Conclusions

In summary, we have discovered, developed and optimised a novel NHC-catalysed esterification of aldehydes involving alcohols and air (*i.e.* oxygen) as the oxidant. The primary attraction of such a process is the non-reliance upon external and often toxic oxidants, making the technology potentially viable on larger industrial scales. Furthermore, the mild conditions would be amenable to a wide range of functionalities. Initial optimisation studies revealed the reaction displays a significant reliance upon numerous factors, primarily access of air to the system and the identity of the NHC precatalyst. The novel dialkyl triazolium salt **51** proved to be the most efficient catalyst in this regard, whilst the base loading and alcohol concentrations were also shown to have a considerable impact upon reaction rates. The strong dependence upon the base loading suggests that it plays a role not only in carbene generation but deprotonation of the alcohol nucleophile. The substrate scope of the process was gratifyingly broad, with only *ortho*-substituted benzaldehydes proving resistant to extensive esterification. Otherwise unhindered aromatic aldehydes (including heterocyclic analogues) can be converted to the corresponding methyl esters in good to excellent yields at ambient temperature. Equally, a range of primary alcohols can be utilised; including synthetically relevant benzyl-, allyl- and trichloroethyl-alcohols, while hindered alcohols give poor results. Alcohols of lower pK_a values (in the range of 9 – 13) were found to have detrimental effects upon product yields when employed in a 1:1 (*v/v*) ratio with THF. This observation was rationalised on the basis of impedance of carbene generation through the accentuated acidity of these nucleophiles and was overcome by a reduction in alcohol concentration to produce the corresponding esters in moderate yields. Furthermore, in aqueous solvent the reaction generates benzoic acid (**461**) from benzaldehyde (**57**) in excellent yield, whilst the analogous amidation reaction does not produce synthetically useful yields but does further support the proposed mechanistic pathway.

An extensive array of mechanistic studies were carried out, a selection of which are detailed in this work, in order to elucidate this mechanistic pathway. The reactions have been shown to be mechanistically distinct from other either NHC-catalysed 'oxidative' (*i.e.* involving stoichiometric oxidants) or 'oxygenative' esterifications (which require an electrophilic additive to trap the carboxylate product) in that the species which reacts with oxygen in the air is not the Breslow intermediate, but the aryloin (or more accurately, it's enolate). Benzil, generated through the base-catalysed oxidation of benzoin, has been proposed as the relevant

intermediate through which the mechanism proceeds. The reluctance of *ortho*-substituted aromatic aldehydes to undergo the process lends further weight to this proposal, as does the similar observations when employing sterically hindered alcohols such as *iso*propanol. Although the analogous aldehyde amidations did not proceed to any significant extent, the reliance of the pathway upon general base catalysis for deprotonation of the amine nucleophile is consistent with their poor yields.

Finally, extending the synthetic utility of this methodology, we developed an NHC-catalysed protocol for the oxidative cleavage of aromatic 1,2-diketones in moderate to good yields. The possibility of effecting oxidative lactonisations by alternatively employing a lactol substrate was also investigated and although the derivative lactone could be isolated, yields were poor and were hampered by the poor solubility of the precatalyst and the production of carboxylic acid derivatives at elevated temperatures.

5.0 Experimental

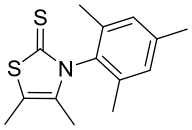
5.1 General experimental data

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Melting points were determined using a standard melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker Avance III 400 MHz (400.23 MHz) spectrometer using the solvent peak as internal reference ($CDCl_3$: δ H 7.26; δ C 77.0 and DMSO-d_6: δ H 2.51; δ C 39.5). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), quart (quartet), quint (quintet), sept (septet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). Carbon NMR spectra were recorded on the same instrument at 100.61 Hz with total proton decoupling. Fluorine NMR spectra were recorded on the same instrument at 376.5 Hz. Mass spectra (MS ESI) were recorded using a Finnigan MAT 95 or Varian MAT 311A. Electron Impact mass spectra were recorded on the same machine in EI mode. TLC analysis was performed on precoated silica gel $60F_{254}$ slides, and visualised by $KMnO_4$ staining. Flash chromatography was carried out using silica gel, particle size 0.2-0.063 mm, and using the indicated mobile phase as correlated with TLC analysis. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. THF was distilled from sodium/benzophenone under argon. Dichloromethane and toluene were distilled over calcium hydride under argon. Liquid aldehydes were distilled under vacuum prior to use. Solid aldehydes were washed acid-free with 10% aq. K_2CO_3-solution prior to use. Methanol, ethanol, *iso*propanol and allyl alcohol were distilled from sodium under argon. Benzyl alcohol was purified *via* flash chromatography using a gradual solvent gradient of CH_2Cl_2:MeOH to remove residual benzaldehyde and benzyl benzoate.

5.2 Experimental data for Chapter 2

5.2.1 Synthesis of achiral thiazolium salts

5.2.1.1 4,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-3*H*-thiazole-2-thione (299b)[149]

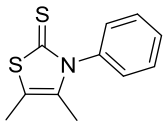


2,4,6-trimethylaniline (1.40 mL, 10.00 mmol, 1.00 equiv.) was charged to a 25 mL round-bottom flask equipped with a magnetic stirring bar. DMSO (5 mL) and a 20 M aqueous NaOH solution (0.5 mL, 10.00 mL, 1.00 equiv.) were added *via* syringe and the vessel cooled to 0 ^{o}C. Carbon disulfide (0.6 mL, 10.00 mmol, 1.00 equiv.) was added *via* syringe before the solution was allowed to warm to room temperature and stir for a further 1 hour. It was then cooled to 0 ^{o}C again and 3-chloro-2-butanone (1 mL, 10.00 mmol, 1.00 equiv.) added *via* syringe. The reaction was again warmed to room temperature and stirred for 2 hours before adding H_2O (10 mL), filtering the resulting precipitate and dissolving it in EtOH (10 mL). HCl (36.5%, 0.55 mL) was added and the reaction refluxed at 80 ^{o}C for 1 hour. Upon cooling, a precipitate formed that was allowed to stand at 4 ^{o}C overnight. It was then filtered and recrystallised from hot ethanol to give the title product as white needle-like crystals (1.33 g, 51%).

δ_H (400 MHz, DMSO-d_6): 1.73 (s, 3H, CH_3), 1.93 (s, 6H, CH_3), 2.22 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 7.06 (s, 2H, *m*-H).

HRMS (*m/z*-ESI$^+$): Found 264.0875 ($[M + H]^+$, $C_{14}H_{18}NS_2$ requires 264.0881).

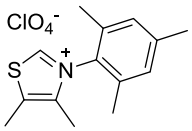
5.2.1.2 4,5-Dimethyl-3-phenyl-3*H*-thiazole-2-thione (299a)[149,260]



Prepared as per **299b** except utilising aniline (0.97 mL, 10 mmol, 1.00 equiv.) instead of 2,4,6-trimethylaniline. Recrystallised from hot EtOH to give the title product as white needle-like crystals in (1.22 g, 55%). M.p. 102-104 ^{o}C (lit. 98 ^{o}C).

δ_H (400 MHz, $CDCl_3$): 1.88 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 7.26 (obscured, 2H, *m*-H), 7.51-7.60 (m, 3H, *o*-H and *p*-H).

5.2.1.3 4,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-thiazol-3-ium perchlorate (300b)[149]



4,5-Dimethyl-3-(2,4,6-trimethyl-phenyl)-3*H*-thiazole-2-thione (**299b**, 0.83 g, 3.20 mmol, 1.00 equiv.) was dissolved in glacial acetic acid (13.45 mL) in 100 mL round-bottom flask equipped with magnetic stirring bar. H_2O_2 (0.93 mL, 3.96 mmol, 1.20 equiv.) was added and the solution stirred at room temperature for 45 minutes. Toluene (20 mL) was then added and the mixture concentrated *in vacuo*. The resulting residue was dissolved in MeOH (10 mL) and cooled to 0 ^{o}C before adding a solution of $NaClO_4^-$ (1.89 g, 13.44 mmol, 4.20 equiv.) in MeOH/H_2O (2:1, 30 mL). The reaction was stirred at 0 ^{o}C for 30 minutes after which H_2O (10 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography using a CH_2Cl_2/MeOH mobile phase (gradient 50:1 → 1:1). The title product was obtained as an oil that solidified to a beige solid upon trituration in ether (393 mg, 11%). M.p. 131-133 ^{o}C.

δ_H (400 MHz, DMSO-d_6): 1.92 (s, 6H, CH_3), 2.06 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.22 (s, 2H, *m*-H), 10.27 (s, 1H, CH).

HRMS (*m/z*-ESI$^+$): Found 232.1149 (M^+, $C_{14}H_{18}NS$ requires 232.1160).

5.2.1.4 4,5-Dimethyl-3-phenyl-thiazol-3-ium perchlorate (300a)

4,5-Dimethyl-3-phenyl-3*H*-thiazole-2-thione (**299a**, 0.93 g, 4.20 mmol, 1.00 equiv.) was dissolved in glacial acetic acid (17.55 mL) in 100 mL round-bottom flask equipped with magnetic stirring bar. H_2O_2 (1.22 mL, 5.20 mmol, 1.20 equiv.) was added and the solution stirred at room temperature for 45 minutes. Toluene (20 mL) was then added and the mixture concentrated *in vacuo*. The resulting residue was dissolved in MeOH (10 mL) and cooled to 0 ^oC before adding a solution of $NaClO_4$ (2.46 g, 17.49 mmol, 4.20 equiv.) in MeOH/H_2O (2:1, 30 mL). The reaction was stirred at 0 ^oC for 30 minutes after which H_2O (10 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography using a CH_2Cl_2/MeOH mobile phase (gradient 50:1 → 1:1). The title product was obtained as an oil that solidified to a beige solid upon trituration in ether (630 mg, 79%). R_f = 0.05 (50:1, CH_2Cl_2:MeOH). M.p. 108-110 ^oC.

δ_H (400 MHz, DMSO-d_6): 2.21 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 7.71 (s, 5H, CH), 10.27 (s, 1H, CH).

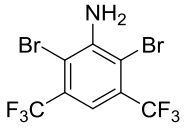
δ_C (100 MHz, $CDCl_3$): 12.4, 12.5, 126.6, 130.5, 131.8, 133,2 (q), 137.5 (q), 142.6 (q), 157.5 (q).

ν_{max} (neat)/cm^{-1} 3519, 3087, 1594, 1581, 1492, 1437, 1251, 1076, 770. 698.

HRMS (*m/z*-ESI^+): Found 190.0699 (M^+, $C_{11}H_{12}NS$ requires 190.0690).

5.2.2 Synthesis of substituted anilines

5.2.2.1 2,6-Dibromo-3,5-bis(trifluoromethyl)phenylamine (313)[249]

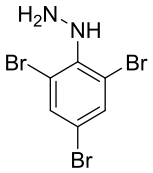


To a mixture of 3,5-bis(trifluoromethyl)aniline (2.04 mL/3 g, 13.2 mmol, 1.00 equiv.), K_2CO_3 (2.32 g, 16.7 mmol) and iron filings (384 mg) in a 500 mL round-bottom flask, equipped with a magnetic stirring bar, was added CH_2Cl_2 (300 mL). A solution of Br_2 (3 mL, 41.3 mmol, 3.13 equiv.) in CH_2Cl_2 (30 mL) was added dropwise with stirring and the mixture heated at reflux for 3 days. Upon cooling, a saturated aqueous Na_2CO_3 solution (200 mL) was added the organic layer extracted with Et_2O (2 x 100 mL). After drying over $MgSO_4$ and filtering, the organic extracts were concentrated *in vacuo* to give the crude product as a red solid which was purified *via* flash chromatography (100% hexane). The title compound was obtained as a white solid (2.45 g, 48%). M.p. 76 ^oC (lit. 75 – 76 ^oC).

δ_H (400 MHz, $CDCl_3$): 5.23 (s, 2H, NH_2), 7.36 (s, 1H, *p*-H).

5.2.3 Synthesis of substituted arylhydrazines

5.2.3.1 (2,4,6-tribromophenyl)hydrazine (311)[250]



1,3,5-tribromoaniline (3.0 g, 9.1 mmol, 1.00 equiv.) was charged to a 250 mL round-bottom flask equipped with a large magnetic stirring bar and cooled to -25 ^oC. Hydrochloric acid (36.5%, 12 mL) was added before a 3.2 M aqueous solution of $NaNO_2$ (0.66 g, 9.57 mmol, 1.05 equiv.) was added dropwise with stirring and the solution turned yellow. Stirring was continued for 15 minutes before rapid addition of a 3.6 M solution of $SnCl_2.2H_2O$ (4.926 g, 21.83 mmol, 2.40 equiv.) in hydrochloric acid (36.5%,

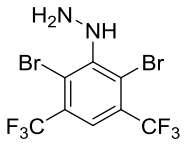
6 mL). A thick white slurry developed which required swirling by hand for 5 minutes. Follwing this, the solution was warmed to 0 ^{o}C and stirred vigourously for 1 hour. The white solid was filtered, washed with water and dried extensively in air before being collected and transferred to an Erlenmeyer flask. A magnetic stirring bar was charged to the flask followed by a 40% aqeous solution of NaOH (30 mL). The mixture was stirred at ambient temperature for 1 hour before filtering the obtained solid again and drying further in air. Recrystallisation from hot EtOH yielded the titled compound as tan needle-like crystals (1.41 g, 45%). M.p. 143 ^{o}C. R_f = 0.17 (9:1, hexanes:EtOAc).

δ_H (400 MHz, DMSO-d_6): 4.33 (s, 2H, NH_2), 5.78 (s, 1H, NH), 7.74 (s, 2H, *m*-H).

5.2.3.2 Procedure A: General procedure for the synthesis of arylhydrazine precursors to triazolium ion precatalysts

To a 500 mL round-bottom flask equipped with a magnetic stirring bar was charged the relevant aniline precursor. Glacial acetic acid was added to create a 0.8 M solution which was stirred gently at room temperature for 2 minutes. A 1.7 M solution of sodium nitrite (1.09 equiv.) in sulfuric acid was then added dropwise, ensuring that the temperature did not exceed 40 ^{o}C. A red or yellow colour was observed upon formation of the diazonium species *in situ*. The solution was then cooled to 0 ^{o}C and stirred for 15 minutes before rapid addition of a 3.86 M solution of stannous chloride dihydrate (3.34 equiv.) in hydrochloric acid (note: a thick white slurry results that can cause stirring to halt; it is recommended that the rate of stirring is increased prior to addition). Stirring was continued at 0 ^{o}C for 15 minutes before allowing the solution to warm to room temperature and stir for a further 1 hour. It was then filtered and the resulting white solid dried *via* suction filtration for 2 hours. This solid was charged to a 250 mL Erlenmeyer flask equipped with a magnetic stirring bar and 2 M NaOH (30 mL) added. The suspension was stirred at room temperature for 15 minutes before extracting with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a pale yellow solid. Recrystallisation from hexane yields the desired arylhydrazine.

5.2.3.3 (2,6-Dibromo-3,5-bis(trifluoromethyl)phenyl)hydrazine (315)



Prepared according **procedure A** using 2,6-dibromo-3,5-bis-trifluoromethyl-phenylamine (2.45 g, 6.33 mmol, 1.00 equiv.) as white needle-like crystals (1.27 g, 50%). M.p. 122 ^{o}C. R_f = 0.13 (9:1, hexanes:EtOAc).

δ_H (400 MHz, $CDCl_3$): 4.02 (s, 2H, NH_2), 5.90 (s, 1H, NH), 7.69 (s, 1H, *p*-H)

δ_C (100 MHz, $CDCl_3$): 118.0 (quart., J_{CF} 273.8, q, -CF_3), 119.8 (q), 120.8 (quart., J_{CF} 5.8, q), 130.5 (quart., J_{CF} 32.5, q), 150.2.

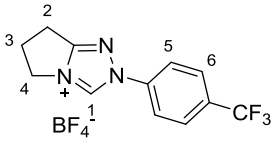
δ_F (376 MHz, $CDCl_3$): -62.19, -62.16.

ν_{max} (neat)/cm^{-1} 3369, 3268, 3103, 1586, 1497, 1413, 1350, 1279, 1176, 1113, 1053, 937, 900, 799, 725, 661.

HRMS (*m/z*-ESI$^+$): Found 400.8728 ([M + H]$^+$, $C_8H_5Br_2F_6N_2$ requires 400.8718).

5.2.4 Synthesis of achiral triazolium salts

5.2.4.1 2-(4-Trifluoromethyl-phenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (304c)



To a flame-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was added 2-pyrrolidinone (0.58 g, 6.85 mmol, 1.00 equiv.) and CH_2Cl_2 (40 mL). Trimethyloxonium tetrafluoroborate (1.013 g, 6.85 mmol, 1.00 equiv.) was added

quickly in one portion, the vessel flushed with argon and sealed. The mixture was stirred overnight at room temperature before adding 4-(trifluoromethyl)phenyl hydrazine (1.206 g, 6.85 mmol, 1.00 equiv.) and stirring for a further 9 hours. The solvent was then removed *in vacuo* and MeOH/triethyl orthoformate (1:7, 16 mL) was added and the solution refluxed overnight at 110 ^{o}C. After concentrating *in vacuo*, the crude product was precipitated through addition of EtOAc at 0 ^{o}C. Recrystallisation from hot methanol gave a light yellow solid (462 mg, 22%). M.p. 148-149 ^{o}C.

δ_H (400 MHz, DMSO-d_6): 2.69 (quint., *J* 7.5, 2H, H-3), 3.19 (app. t, 2H, H-2), 4.39 (t, *J* 7.5, 2H, H-4), 8.07-8.12 (m, 4H, H-5 and H-6), 10.81 (s, 1H, H-1).

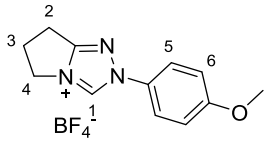
δ_C (100 MHz, DMSO-d_6): 21.7, 27.1, 47.5, 121.8, 122.6 (quart., J_{CF} 271.3, q, -CF_3), 128.0 (m), 130.2 (quart., J_{CF} 33.0, q), 138.9 (q), 139.7 (q), 163.8 (C=N).

δ_F (376 MHz, DMSO-d_6): -61.25, -148.35.

ν_{max} (neat)/cm^{-1} 3153, 1614, 1595, 1530, 1386, 1322, 1230, 1176, 1133, 1068, 1012, 972, 859, 833.

HRMS (*m/z*-ESI$^+$): Found 254.0902 (M^+, $C_{12}H_{11}N_3F_3$ requires 254.0905).

5.2.4.2 2-(4-Methoxy-phenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (304d)[83]



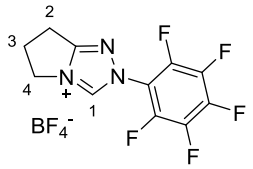
To a 100 mL round-bottom flask equipped with a magnetic stirring bar was charged 2-pyrrolidinone (1.53 g, 18.0 mmol, 1.00 equiv.) and CH_2Cl_2 (40 mL). Trimethyloxonium tetrafluoroborate (2.95 g, 18.0 mmol, 1.00 equiv.) was added in one portion and the vessel flushed with argon and sealed. The mixture was stirred overnight at room temperature before adding 4-(methoxy)phenyl hydrazine (purchased as the

corresponding hydrochloride salt which was free-based prior to use in aqueous 1 M KOH; 3.14 g (HCl salt), 18.0 mmol, 1.00 equiv.) dissolved in CH_2Cl_2 (10 mL). The reaction was stirred further at room temperature for 24 hours under argon before concentrating *in vacuo*. MeOH/triethyl orthoformate (1:4, 50 mL) was then added and the solution refluxed at 110 ^oC for 48 hours. The solvent was again removed *in vacuo* before precipitating the title product from toluene at 0 ^oC as an off-white solid (1.36 g, 25%). M.p. 155-157 ^oC (lit. 155-157 ^oC).

δ_H (400 MHz, DMSO-d_6): 2.86 (quint., *J* 7.3, 2H, H-3), 3.24 (t, *J* 7.7, 2H, H-2), 3.89 (s, 3H, CH_3), 4.64 (t, *J* 7.5, 2H, H-4), 7.03 (d, *J* 9.0, 2H, H-6), 7.72 (d, *J* 9.0, 2H, H-5), 10.00 (s, 1H, CH).

HRMS (*m/z*-ESI$^+$): Found 216.1126 (M^+, $C_{12}H_{14}N_3O$ requires 216.1137).

5.2.4.3 2-Pentafluorophenyl-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (54)

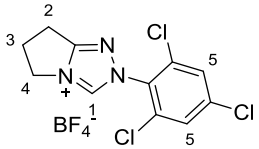


Prepared according to the procedure employed by Rovis *et al.*[83]

δ_H (600 MHz, DMSO-d_6): 2.73-2.78 (m, 2H, H-3), 3.23-3.31 (m, 2H, H-2), 4.46-4.49 (m, 2H, H-4), 10.53 (s, 1H, H-1).

HRMS (*m/z*-ESI$^+$): Found 276.0554 (M^+, $C_{11}H_7N_3F_5$ requires 276.0560).

5.2.4.4 2-(2,4,6-Trichlorophenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (304e)

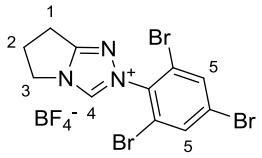


Prepared according to the procedure employed by Bode *et al.*[229] M.p. 244 ^{o}C.

δ_H (400 MHz, DMSO-d_6): 2.71 (quint., *J* 7.2, 2H, H-3), 3.24 (obscured, 2H, H-2), 4.51 (t, *J* 6.8, 2H, H-4), 8.14 (s, 2H, H-5), 10.43 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 21.9, 27.0, 48.6, 129.9 (q), 130.9 (q), 134.0, 138.5 (q), 143.9 (q), 164.4 (C=N).

5.2.4.5 2-(2,4,6-Tribromophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (307)



To a flame-dried 100 mL round-bottom flask charged with a magnetic stirring bar was added 2-pyrrolidinone (0.25 g, 2.9 mmol, 1.00 equiv.). The flask was flushed with argon and sealed under an inert atmosphere using a rubber septum and an argon-filled balloon. CH_2Cl_2 (15 mL) was added *via* syringe followed by rapid addition of trimethyloxonium tetrafluoroborate (Meerwein's salt, 0.42 g, 2.9 mmol, 1.00 equiv.) under a gentle flow of argon. The reaction was stirred overnight at room temperature before adding (2,4,6-tribromo)phenyl hydrazine (**311**, 0.9 g, 2.9 mmol, 1.00 equiv.) and stirring for a further 16 hours at room temperature. The solvent was then removed *in vacuo* and the vessel cooled to 0 ^{o}C. Chlorobenzene (10 mL) was added and the mixture stirred for 5 mins. It was then filtered to yield the hydrazone intermediate as a white solid which was dried under vacuum. This was then charged to a 25 mL round-bottom flask equipped with a reflux condenser. The vessel was placed under argon and chlorobenzene (3 mL) and triethyl orthoformate (5 mL) were added *via* syringe. The reaction was refluxed at 120 ^{o}C for 16 hours. The desired triazolium salt precipitated as the reaction proceeded and, upon cooling, further precipitation was induced through addition of toluene (5 mL) and stirring the suspension at 0^{o}C. The title product was obtained as an off-white (0.122 g, 11%). M.p. 246 – 248 ^{o}C.

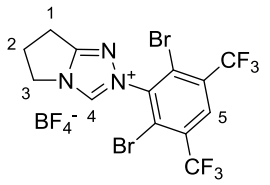
δ_H (400 MHz, DMSO-d_6): 2.70 (quint., *J* 7.3, 2H, H-2), 3.24 (obscured, 2H, H-1), 4.51 (t, *J* 7.5, 2H, H-3), 8.36 (s, 2H, H-5), 10.48 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 21.9, 27.0, 48.7, 123.6, 127.4 (q), 134.0 (q), 135.9, 143.6 (q), 164.2 (C=N).

ν_{max} (neat)/cm^{-1} 3479, 3078, 1672, 1594, 1429, 1375, 1256, 1191, 1029, 970, 853, 753, 724, 644.

HRMS (*m/z*-ESI^+): Found 419.8353 (M^+, $C_{11}H_9N_3Br_3$ requires 477.8989).

5.2.4.6 2-(2,6-Dibromo-3,5-bis(trifluoromethyl)phenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (308)



To a flame-dried 100 mL round-bottom flask charged with a magnetic stirring bar was added 2-pyrrolidinone (0.6 g, 6.7 mmol, 1.00 equiv.). The flask was flushed with argon and sealed under an inert atmosphere using a rubber septum and an argon-filled balloon. CH_2Cl_2 (60 mL) was added *via* syringe followed by rapid addition of trimethyloxonium tetrafluoroborate (Meerwein's salt, 1.06 g, 6.7 mmol, 1.00 equiv.) under a gentle flow of argon. The reaction was stirred overnight at room temperature before adding 2,6-dibromo-3,5-bis(trifluoromethyl)phenyl hydrazine (**315**, 2.9 g, 6.7 mmol, 1.00 equiv.) and stirring for a further 24 hours at room temperature. The solvent was then removed *in vacuo* to obtain the crude hydrazone intermediate as a pale orange solid. This was used without further purification, being dissolved in a mixture of chlorobenzene, triethyl orthoformate and methanol (1:2:0.5 ratio, 27 mL) and refluxed at 110 ^oC for 24 hours. Upon ice-cooling, a white solid precipitated from the solution. Filtration and subsequent ^1H NMR spectroscopic analysis revealed this to be the pure hydrazone intermediate. After drying in air, this was again redissolved in chlorobenze, triethyl orthoformate and methanol and again refluxed at 110 ^oC for 24 hours. A solid precipitated over the course

of the reaction which was filtered and washed with cold ethyl acetate to yield the title product as an off-white solid (1.647 g, 43%). M.p. 272.5 ^{o}C.

δ_H (400 MHz, DMSO-d_6): 2.78 (quint., *J* 7.5, 2H, H-2), 3.31 (obscured, 2H, H-1), 4.55 (app. t, 2H, H-3), 8.40 (s, 1H, H-5), 10.48 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 21.5, 26.6, 48.6, 121.6 (quart., J_{CF} 274.2, q, -CF_3), 126.8 (q), 130.0 (quart., J_{CF} 6.0), 130.1 (quart., J_{CF} 33.4, q), 138.6 (q), 143.9, 164.2 (C=N).

δ_F (376 MHz, DMSO-d_6): -61.98, - 148.34.

ν_{max} (neat)/cm^{-1} 3124, 3092, 1598, 1335, 1287, 1278, 1257, 1188, 1144, 1060, 1045, 975, 721.

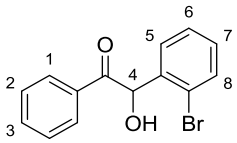
HRMS (*m/z*-ESI$^+$): Found 477.8980 (M^+, $C_{13}H_8N_3Br_2F_6$ requires 477.8989).

5.2.5 Procedure B: General procedure for achiral NHC-catalysed crossed aromatic-aromatic benzoin condensation employing 2-bromobenzaldehyde

A flame-dried 5 mL round-bottom flask containing a magnetic stirring bar was charged with K_2CO_3 (5.7 mg, 0.044 mmol) and placed under vacuum. The flask was heated to 650 ^{o}C for two separate 2 minute intervals before allowing to cool. The vacuum was released and the relevant azolium salt precatalyst was added quickly in one portion. The flask was flushed with argon gas and sealed under an inert atmosphere using a rubber septum and an argon-filled balloon. THF (1.1M) was added *via* syringe and the suspension stirred for 15 minutes. A colour change was generally observed upon formation of the carbene *in situ*. 2-Bromobenzaldehyde (128 μL, 1.1 mmol, 1.00 equiv.) was then added *via* syringe, followed by the relevant aldehyde coupling partner (1.1 mmol, 1.00 equiv.). The septum was replaced with a glass stopper under a gentle flow of argon and the vessel sealed to the external atmosphere using parafilm. The reaction was stirred at room temperature for 48 hours before quenching with H_2O (5 mL) and extracting with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified *via* flash chromatography.

5.2.5.1 2-(2-Bromophenyl)-2-hydroxy-1-phenylethan-1-one (305d)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (298 mg, 93%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.27. M.p. 74 – 76 ^oC.

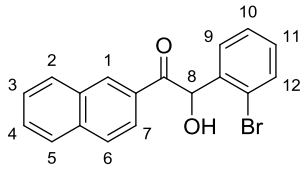
δ_H (400 MHz, $CDCl_3$): 4.51 (d, *J* 5.6, 1H, OH), 6.34 (d, *J* 5.6, 1H, H-4), 7.04 (dd, *J* 7.7, 1.8, 1H, H-5), 7.10 (td, *J* 7.7, 1.8, 1H, H-6), 7.17 (td, *J* 7.5, 1.2, 1H, H-7), 7.37 (app. t, 2H, H-2), 7.50 (t, *J* 7.5, 1H, H-3), 7.59 (dd, *J* 8.0, 1.2, 1H, H-8), 7.89 (dd, *J* 7.3, 1.2, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.3, 124.2 (q), 128.3, 128.8, 129.0, 129.2, 130.2, 133.1 (q), 133.6, 134.1, 138.4 (q), 198.7 (C=O).

ν_{max} (neat)/cm^{-1} 3479, 2924, 1669, 1595, 1446, 1245, 1193, 1083, 969, 760, 703, 681.

HRMS (*m/z*-ESΙ): Found 288.9878 ($C_{14}H_{10}BrO_2$ requires 288.9864).

5.2.5.2 2-(2-Bromophenyl)-2-hydroxy-1-(naphthalen-2-yl)ethan-1-one (331)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 2-naphthaldehyde (172 mg, 1.1 mmol, 1.00 equiv.). Upon concentration *in vacuo* the crude product crystallised to give a yellow solid which was suspended in hexane and filtered. Further washing with hexane yielded an off-white solid (100 mg) yield. The filtrate was again concentrated *in vacuo* and further purified *via* flash chromatography (hexanes:EtOAc, 9:1) to give a white solid (238 mg), resulting in 338 mg (90%) as the total yield. R_f = 0.23. M.p. 128 – 130 ^oC.

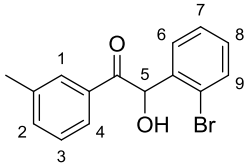
δ_H (600 MHz, $CDCl_3$): 4.63 (d, *J* 5.6, 1H, OH), 6.53 (d, *J* 5.6, 1H, H-8), 7.10-7.13 (m, 2H, H-10 and H-11), 7.18-7.21 (m, 1H, H-9), 7.52-7.54 (m, 1H, H-3), 7.58-7.60 (m, 1H, H-4), 7.62 (dd, *J* 7.7, 0.7, 1H, H-12), 7.8 (d, *J* 7.9, 1H, H-5), 7.84 (d, *J* 8.8, 1H, H-6), 7.90 (d, *J* 8.1, 1H, H-2), 7.97 (dd, *J* 7.7, 1.7, 1H, H-7), 8.52 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.3, 124.0, 124.2 (q), 127.0, 127.7, 128.4, 128.7, 129.1, 129.2, 129.2, 129.8, 130.2, 130.3 (q), 131.3, 132.2 (q), 133.7, 135.9 (q), 138.6 (q), 198.7 (C=O).

ν_{max} (neat)/cm^{-1} 3448, 3057, 2925, 1665, 1621, 1598, 1584, 1470, 1440, 1380, 1350, 1279, 1229, 1182, 1127, 1117, 1071, 1022, 981, 937, 865, 803, 760, 744.

HRMS (*m/z*-ESI^+): Found 362.9997 ($[M + Na]^+$, $C_{18}H_{13}BrO_2Na$ requires 362.9997).

5.2.5.3 2-(2-Bromophenyl)-2-hydroxy-1-(3-tolyl)ethan-1-one (332)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 3-tolualdehyde (130 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (292 mg, 87%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.26. M.p. 86 ^{o}C.

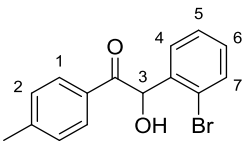
δ_H (400 MHz, $CDCl_3$): 2.34 (s, 3H, CH_3), 4.53 (d, *J* 5.6, 1H, OH), 6.34 (d, *J* 5.6, 1H, H-5), 7.04 (dd, *J* 7.7, 1.7, 1H, H-6), 7.10-7.14, (m, 1H, H-7), 7.17 (td, *J* 7.7, 1.2, 1H, H-8), 7.26 (obscured, 1H, H-3), 7.31 (d, *J* 7.6, 1H, H-2), 7.59 (dd, *J* 7.9, 1.3, 1H, H-9), 7.66 (d, *J* 7.6, 1H, H-4), 7.78 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 21.2, 75.2, 124.2 (q), 126.2, 128.3, 128.6, 129.2, 129.4, 130.2, 133.1 (q), 133.6, 135.0, 138.5 (q), 138.7 (q), 198.9 (C=O).

ν_{max} (neat)/cm^{-1} 3431, 2921, 1665, 1582, 1468, 1432, 1372, 1272, 1186, 1114, 1073, 1022, 975, 890. 816, 786, 757, 706, 680.

HRMS (*m/z*-ESI$^-$): Found 303.0034 ($C_{15}H_{12}BrO_2$ requires 303.0021).

5.2.5.4 2-(2-Bromophenyl)-2-hydroxy-1-(4-tolyl)ethan-1-one (333)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 4-tolualdehyde (130 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (168 mg, 50%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.26. M.p. 65 ^{o}C.

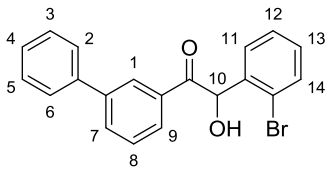
δ_H (400 MHz, $CDCl_3$): 2.34 (s, 3H, CH_3), 4.55 (d, *J* 5.7, 1H, OH), 6.31 (d, *J* 5.7, 1H, H-3), 7.03 (dd, *J* 7.7, 1.8, 1H, H-4), 7.09 (td, *J* 7.7, 1.8, 1H, H-5), 7.16-7.20 (m, 3H, H-2 and H-6), 7.59 (dd, *J* 7.9, 1.2, 1H, H-7), 7.79 (d, *J* 8.3, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 21.7, 75.1, 124.2 (q), 128.3, 129.1, 129.2, 129.5, 130.1, 130.5 (q), 133.6, 138.7 (q), 145.2 (q), 198.3 (C=O).

ν_{max} (neat)/cm^{-1} 3465, 3058, 2966, 2921, 1674, 1603, 1409, 1291, 1240, 1087, 976, 853, 803, 753, 723.

HRMS (*m/z*-ESI$^-$): Found 303.0017 ($C_{15}H_{12}O_2Br$ requires 303.0021).

5.2.5.5 1-([1,1'-Biphenyl]-3-yl)-2-(2-bromophenyl)-2-hydroxyethan-1-one (334)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and biphenyl-3-carbaldehyde (179 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (351 mg, 87%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.23. M.p. 72 ^oC.

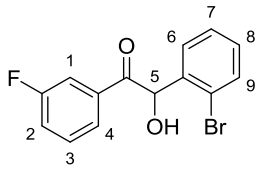
δ_H (600 MHz, $CDCl_3$): 4.59 (d, *J* 5.3, 1H, OH), 6.45 (d, *J* 5.3, 1H, H-10), 7.14 (d, *J* 7.6, 1H, H-11), 7.17 (app. t, 1H, H-12), 7.25 (t, *J* 7.5, 1H, H-13), 7.40 (t, *J* 7.3, 1H, H-4), 7.47-7.52 (m, 3H, H-3 and H-8), 7.56 (d, *J* 8.3, 2H, H-2), 7.67 (d, *J* 7.9, 1H, H-14), 7.78 (d, *J* 7.7, 1H, H-7), 7.91 (d, *J* 7.9, 1H, H-9), 8.20 (d, *J* 1.2, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.5, 124.2 (q), 127.1, 127.6, 127.7, 128.0, 128.4, 129.3, 129.3, 130.3, 132.7, 133.6 (q), 133.7, 138.5 (q), 139.6 (q), 141.9 (q), 198.7 (C=O).

ν_{max} (neat)/cm^{-1} 3471, 2912, 1674, 1622, 1579, 1474, 1291, 1227, 1187, 1090, 1021, 978, 756, 688.

HRMS (*m/z*-ESI$^+$): Found 389.0144 ([M + H]$^+$, $C_{20}H_{16}BrO_2$ requires 389.0148).

5.2.5.6 2-(2-Bromophenyl)-1-(3-fluorophenyl)-2-hydroxyethan-1-one (335)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 3-fluorobenzaldehyde (117 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a yellow oil (316 mg, 87%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.25.

δ_H (400 MHz, $CDCl_3$): 4.40 (d, *J* 5.6, 1H, OH), 6.31 (d, *J* 5.6, 1H, H-5), 7.04 (dd, *J* 7.7, 1.7, 1H, H-6), 7.12-7.17 (m, 1H, H-7), 7.20-7.24 (m, 2H, H-3 and H-8), 7.34-7.39 (m, 1H, H-4), 7.60-7.67 (m, 3H, H-1, H-2 and H-9).

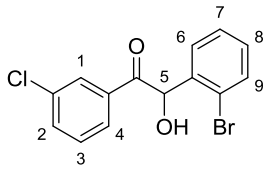
δ_C (100 MHz, $CDCl_3$): 75.6, 115.6 (d, J_{CF} 22.8), 121.2 (d, J_{CF} 21.8), 124.2 (q), 124.7 (d, J_{CF} 3.1), 128.4, 129.2, 130.4, 130.5 (d, J_{CF} 7.7), 133.8, 135.2 (d, J_{CF} 6.5, q), 137.9 (q), 162.7 (d, J_{CF} 249.3, q), 197.8 (C=O, d, J_{CF} 2.3).

δ_F (376 MHz, $CDCl_3$): -110.88 (dt, J_{HF} 8.8, 3.2)

ν_{max} (neat)/cm^{-1} 3450, 3072, 2925, 1683, 1587, 1440, 1258, 1079, 1015, 889, 785, 755.

HRMS (*m/z*-ESI$^-$): Found 306.9776 ($C_{14}H_9BrFO_2$ requires 306.9770).

5.2.5.7 2-(2-Bromophenyl)-1-(3-chlorophenyl)-2-hydroxyethan-1-one (336)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 4-chlorobenzaldehyde (124 μL, 1.1 mmol, 1.00 equiv.) at 55 ^{o}C. The title product was obtained as a pale yellow oil (290 mg, 81%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.24. Upon standing for several hours, this oil gradually solidified to a pale yellow solid. M.p. 93 ^{o}C.

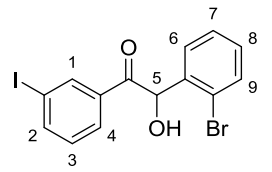
δ_H (400 MHz, $CDCl_3$): 4.39 (d, *J* 5.7, 1H, OH), 6.31 (d, *J* 5.7, 1H, H-5), 7.03 (dd, *J* 7.7, 1.8, 1H, H-6), 7.12 (td, *J* 7.8, 1.6, 1H, H-7), 7.20 (obscured, 1H, H-8), 7.30 (t, *J* 7.9, 1H, H-3), 7.47 (d, *J* 7.9, 1H, H-4), 7.60 (d, *J* 7.9, 1H, H-9), 7.72 (d, *J* 7.8, 1H, H-2), 7.94 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.7, 124.1 (q), 126.9, 128.4, 128.9, 129.2, 130.1, 130.5, 133.8, 134.0, 134.7 (q), 135.2 (q), 137.8 (q), 197.8 (C=O).

ν_{max} (neat)/cm^{-1} 3492, 3069, 2904, 1677, 1565, 1469, 1419, 1353, 1285, 1234, 1185, 1118, 1086, 1021, 975, 871, 798, 750, 708, 672.

HRMS (*m/z*-ESI$^-$): Found 322.9468 ($C_{14}H_9BrClO_2$ requires 322.9474).

5.2.5.8 2-(2-Bromophenyl)-1-(3-iodophenyl)-2-hydroxyethan-1-one (337)



Prepared according to **procedure B** using **304e** (17 mg, 0.044 mmol) and 3-iodobenzaldehyde (272 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (275 mg, 60%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.26. M.p. 86 ^{o}C.

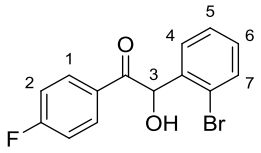
δ_H (400 MHz, $CDCl_3$): 4.41 (d, *J* 5.6, 1H, OH), 6.31 (d, *J* 5.6, 1H, H-5), 7.05 (dd, *J* 7.6, 1.5, 1H, H-6), 7.11-717 (m, 2H, H-7 and H-8), 7.21 (obscured, 1H, H-3), 7.61 (d, *J* 7.9, 1H, H-9), 7.81-7.85 (m, 2H, H-2 and H-4), 8.32 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.3, 94.4 (q, C-I), 124.1 (q), 127.9, 128.4, 129.2, 130.4, 130.5, 133.8, 134.8, 137.7, 137.8 (q), 142.8, 197.6 (C=O).

ν_{max} (neat)/cm^{-1} 3492, 3067, 2905, 1674, 1583, 1557, 1354, 1284, 1233, 1183, 1087, 1019, 971, 862, 795, 756, 726, 693, 672, 639.

HRMS (*m/z*-ESI$^-$): Found 414.8841 ($C_{14}H_9BrIO_2$ requires 414.8836).

5.2.5.10 2-(2-Bromophenyl)-1-(4-fluorophenyl)-2-hydroxyethan-1-one (338)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 4-fluorobenzaldehyde (117 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a pale yellow solid (296 mg, 87%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.30. M.p. 82.5 – 84 ^{o}C.

δ_H (400 MHz, $CDCl_3$): 4.47 (d, *J* 5.4, 1H, OH), 6.30 (d, *J* 5.4, 1H, H-3), 7.03-7.09 (m, 3H, H-2 and H-4), 7.12 (td, *J* 7.7, 1.7, 1H, H-5), 7.19-7.23 (m, 1H, H-6), 7.60 (dd, *J* 7.9, 1.0, 1H, H-7), 7.92 (dd, *J* 8.7, 3.4, 2H, H-1).

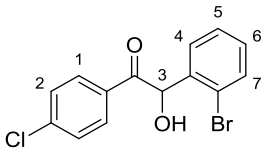
δ_C (100 MHz, $CDCl_3$): 75.2, 116.1 (d, J_{CF} 22.1), 124.1 (q), 128.4, 129.2, 129.5 (d, J_{CF} 3.1, q) 130.4, 131.7, 131.8 133.7, 138.3 (q), 166.1 (d, J_{CF} 257.8, q), 197.2 (C=O).

δ_F (376 MHz, $CDCl_3$): -105.52 (tt, J_{FH} 8.2, 5.3).

ν_{max} (neat)/cm^{-1} 3429, 2923, 1665, 1585, 1470, 1431, 1374, 1274, 1183, 1075, 978, 892, 787, 761, 725, 709, 682.

HRMS (*m/z*-ESI⁻): Found 306.9761 ($C_{14}H_9O_2FBr$ requires 306.9770).

5.2.5.11 2-(2-Bromophenyl)-1-(4-chlorophenyl)-2-hydroxyethan-1-one (339)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 4-chlorobenzaldehyde (155 mg, 1.1 mmol, 1.00 equiv.) at 55 °C. The title product was obtained as a pale yellow oil (297 mg, 83%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.26. Upon standing for several hours, this oil gradually solidified to a pale yellow solid. M.p. 54 °C.

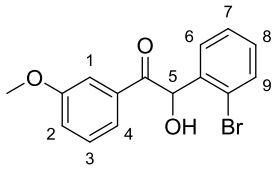
δ_H (400 MHz, $CDCl_3$): 4.45 (d, *J* 5.6, 1H, OH), 6.30 (d, *J* 5.6, 1H, H-3), 7.02 (dd, *J* 7.6, 1.9, 1H, H-4), 7.12 (td, *J* 7.6, 1.9, 1H, H-5), 7.19 (td, *J* 7.5, 1.4, 1H, H-6), 7.35-7.38 (m, 2H, H-2), 7.60 (dd, *J* 7.9, 1.3, 1H, H-7), 7.83-7.85 (m, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 75.4, 124.2 (q), 128.4, 129.2, 129.2, 130.3, 130.4, 131.4 (q), 133.7, 138.1 (q), 140.7 (q), 197.7 (C=O).

ν_{max} (neat)/cm^{-1} 3436, 3376, 3086, 2926, 1686, 1677, 1587, 1570, 1469, 1433, 1401, 1268, 1249, 1205, 1188, 1178, 1091, 1079, 1022, 969, 860, 810, 763, 739, 718, 638.

HRMS (*m/z*-ESI⁻): Found 322.9482 ($C_{14}H_{11}BrClO_2$ requires 322.9474).

5.2.5.12 2-(2-Bromophenyl)-1-(3-methoxyphenyl)-2-hydroxyethan-1-one (340)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 3-anisaldehyde (134 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (290 mg, 82%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.26. M.p. 67 – 68 °C.

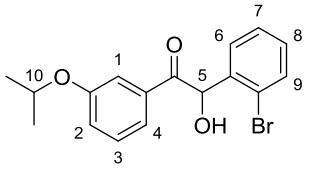
δ_H (400 MHz, $CDCl_3$): 3.79 (s, 3H, CH_3), 4.50 (d, *J* 5.7, 1H, OH), 6.34 (d, *J* 5.7, 1H, H-5), 7.04-7.07 (m, 2H, H-2 and H-6), 7.10 (td, *J* 7.7, 1.3, 1H, H-7), 7.18 (t, *J* 7.5, 1H, H-8), 7.26 (t, *J* 7.9, 1H, H-3), 7.43 (s, 1H, H-1), 7.47 (d, *J* 7.6, 1H, H-4), 7.60 (d, *J* 7.9, 1H, H-9).

δ_C (100 MHz, $CDCl_3$): 55.5, 75.4, 112.7, 121.1, 121.6, 124.2 (q), 128.4, 129.2, 129.8, 130.2, 133.6, 134.3 (q), 138.5 (q), 159.7 (q), 198.5 (C=O).

ν_{max} (neat)/cm^{-1} 3430, 2943, 1675, 1593, 1463, 1427, 1389, 1336, 1259, 1176, 1117, 1082, 1009, 875, 763, 719, 675.

HRMS (*m/z*-ESI⁻): Found 318.9974 ($C_{15}H_{14}BrO_3$ requires 318.9970).

5.2.5.13 2-(2-Bromophenyl)-1-(3-*iso*propoxyphenyl)-2-hydroxyethan-1-one (341)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 3-*iso*propoxybenzaldehyde (187 μL, 1.1 mmol, 1.00 equiv.) at 55 °C. The title product was

obtained as a yellow solid (330 mg, 86%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.28. M.p. 66 - 67 ^oC.

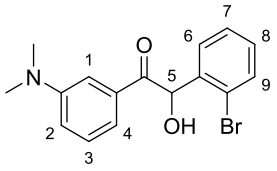
δ_H (400 MHz, $CDCl_3$): 1.22 (d, *J* 6.0, 3H, CH_3), 1.30 (d, *J* 6.0, 3H, CH_3), 4.49-4.58 (m, 2H, H-10 and OH), 6.31 (d, *J* 5.5, 1H, H-5), 7.01-7.05 (m, 2H, H-2 and H-6), 7.10-7.14 (m, 1H, H-7), 7.18 (app. t, 1H, H-8), 7.24 (app. t, *J* 7.9, 1H, H-3), 7.38 (s, 1H, H-1), 7.44 (d, *J* 7.6, 1H, H-4), 7.59 (d, *J* = 7.5, 1H, H-9).

δ_C (100 MHz, $CDCl_3$): 21.7, 22.0, 70.2, 75.4, 114.5, 121.3, 122.9, 124.2 (q), 128.4, 129.2, 129.8, 130.2, 133.6, 134.2 (q), 138.6 (q), 158.1 (q), 198.5 (C=O).

ν_{max} (neat)/cm^{-1} 3423, 2984, 2937, 1675, 1575, 1469, 1434, 1378, 1273, 1194, 1108, 1067, 1019, 953, 874, 761, 719, 674.

HRMS (*m/z*-ESI$^-$): Found 347.0269 ($C_{17}H_{16}BrO_3$ requires 347.0283).

5.2.5.14 2-(2-Bromophenyl)-1-(3-(dimethylamino)phenyl)-2-hydroxyethan-1-one (342)



Prepared according to **procedure B** using **304e** (17 mg, 0.044 mmol) and 3-(dimethylamino)benzaldehyde (160 μL, 1.1 mmol, 1.00 equiv.). The title product precipitated as a bright yellow solid (272 mg, 74%) following filtration of the crude reaction mixture. R_f = 0.26 (9:1, hexanes:EtOAc). M.p. 137 - 139 ^oC.

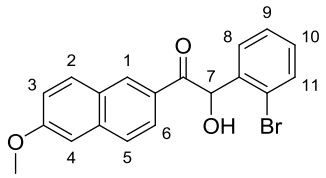
δ_H (400 MHz, $CDCl_3$): 2.95 (s, 6H, CH_3), 4.57 (d, *J* 5.5, 1H, OH), 6.35 (d, *J* 5.5, 1H, H-5), 6.89 (d, *J* 6.4, 1H, H-2), 7.05 (dd, *J* 7.7, 1.8, 1H, H-6), 7.10-7.14 (m, 1H, H-7), 7.18-7.27 (m, 4H, H-1, H-3, H-4 and H-8), 7.60 (dd, *J* 7.9, 1.2, 1H, H-9).

δ_C (100 MHz, $CDCl_3$): 40.4, 75.2, 112.1, 116.9, 117.8, 124.3 (q), 128.4, 129.2, 129.3, 130.1, 133.5, 133.7 (q), 138.9 (q), 150.4 (q), 199.3 (C=O).

ν_{max} (neat)/cm^{-1} 3400, 2849, 1660, 1597, 1568, 1474, 1421, 1314, 1356, 1290, 1237, 1187, 1084, 981, 957, 852, 758, 719, 673.

HRMS (*m/z*-ESI): Found 332.0283 ($C_{16}H_{15}BrNO_2$ requires 332.0286).

5.2.5.15 2-(2-Bromophenyl)-2-hydroxy-1-(6-methoxynaphthalen-2-yl)ethan-1-one (343)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 6-methoxynaphthaldehyde (205 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (327 mg, 80%) following flash chromatography (hexanes:EtOAc, 9:1), R_f = 0.18. M.p. 84 ^oC.

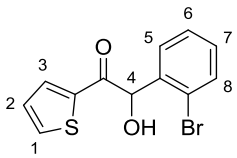
δ_H (600 MHz, $CDCl_3$): 4.61 (d, *J* 5.6, 1H, OH), 6.51 (d, *J* 5.6, 1H, H-7), 7.11-7.16 (m, 3H, H-3, H-8 and H-9), 7.19-7.23 (m, 2H, H-4 and H-10), 7.65 (d, *J* 7.9, 1H, H-11), 7.73 (d, *J* 8.7, 1H, H-5), 7.81 (d, *J* 8.7, 1H, H-2), 7.96 (d, *J* 8.7, 1H, H-6), 8.46 (s, 1H, H-1).

δ_C (150 MHz, $CDCl_3$): 55.5, 75.1, 105.7, 120.0, 124.1 (q), 124.8, 127.3, 127.6 (q), 128.3 (q), 128.4, 129.2, 130.2, 131.2, 131.5, 133.6, 137.8 (q), 138.9 (q), 160. 3 (q), 198.2 (C=O).

ν_{max} (neat)/cm^{-1} 3459, 2937, 1673, 1622, 1476, 1396, 1275, 1171, 1083, 1025, 984, 853, 760, 704.

HRMS (*m/z*-ESI$^+$): Found 393.0090 ([M + Na]$^+$, $C_{19}H_{15}BrO_3Na$ requires 393.0097)

5.2.5.16 2-(2-Bromophenyl)-2-hydroxy-1-(thiophen-2-yl)ethan-1-one (344)



Prepared according to **procedure B** using **304e** (17 mg, 0.044 mmol) and 2-thiophenecarbaldehyde (103 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a yellow solid (242 mg, 74%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.29. M.p. 87 ^{o}C.

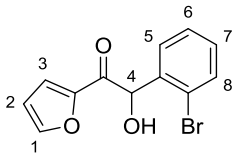
δ_H (400 MHz, $CDCl_3$): 4.41 (d, *J* 5.5, 1H, OH), 6.18 (d, *J* 5.5, 1H, H-4), 7.03 (app. t, 1H, H-6), 7.14-7.19 (m, 2H, H-1 and H-5), 7.26 (app. t, 1H, H-2), 7.61-7.67 (m, 3H, H-3, H-7 and H-8).

δ_C (100 MHz, $CDCl_3$): 75.8, 124.2 (q), 128.4, 128.5, 129.5, 130.4, 133.6, 133.9, 135.2, 138.7 (q), 139.4 (q), 191.2 (C=O).

ν_{max} (neat)/cm^{-1} 3413, 3096, 3084, 2901, 1638, 1471, 1407, 1244, 1189, 1051, 1018, 934, 864, 815, 743, 662.

HRMS (*m/z*-ESI$^+$): Found 296.9586 ([M + H]$^+$, $C_{12}H_{10}BrO_2S$ requires 296.9579).

5.2.5.17 2-(2-Bromophenyl)-1-(furan-2-yl)-2-hydroxyethan-1-one (345)



Prepared according to **procedure B** using **308** (25 mg, 0.044 mmol) and 2-furaldehyde (91 μL, 1.1 mmol, 1.00 equiv.) at 55 ^{o}C. The title product was obtained as a low-melting yellow solid (253 mg, 83%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.13.

δ_H (400 MHz, $CDCl_3$): 4.36 (d, *J* 5.5, 1H, OH), 6.13 (d, *J* 5.5, 1H, H-4), 6.46 (dd, *J* 3.7, 1.7, 1H, H-2), 7.13-7.19 (m, 2H, H-5 and H-6), 7.22-7.27 (m, 2H, H-3 and H-7), 7.55 (d, *J* 1.1, 1H, H-1), 7.59 (dd, *J* 8.0, 0.8, 1H, H-8).

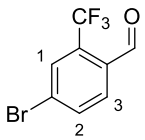
δ_C (100 MHz, $CDCl_3$): 75.1, 112.5, 120.2, 124.2 (q), 128.2, 129.4, 130.2, 133.5, 138.2 (q), 147.8, 149.5 (q), 186.6 (C=O).

ν_{max} (neat)/cm^{-1} 3433, 3133, 3925, 1669, 1462, 1382, 1290, 1019, 981, 756.

HRMS (*m/z*-ESI$^+$): Found 262.9706 ($[M + H]^+$, $C_{12}H_8BrO_2$ requires 262.9702).

5.2.6 Synthesis of *ortho*-substituted aromatic aldehyde substrates for use in the NHC-catalysed crossed-benzoin condensation

5.2.6.1 4-Bromo-2-(trifluoromethyl)benzaldehyde (348)[254]



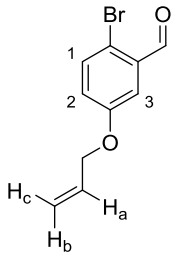
A 100 mL round-bottom flask equipped with a magnetic stirring bar was flushed with argon and fitted with a rubber septum. The vessel was cooled to -25 ^{o}C and anhydrous MTBE (25 mL) was added *via* syringe. *n*-Butyllithium (1.6 M in hexanes; 12.25 mL, 19.6 mmol, 1.20 equiv.) was then syringed into the solution in a dropwise fashion with stirring. 2,5-dibromotrifluoromethylbenzene (5 g, 16.3 mmol, 1.00 equiv.) was dissolved

in anhydrous MTBE (15 mL) before being added *via* syringe to the reaction. Stirring was continued for 30 minutes. Dimethylformamide (DMF, 1.38 mL, 17.9 mmol, 1.10 equiv.) was then added *via* syringe and the reaction stirred for a further 40 minutes before warming to room temperature. H_2O (30 mL) and 6 M HCl (10 mL) were added separately. The organic layer was extracted, washed with H_2O (3 x 15 mL) before being dried over $MgSO_4$ and filtered. Concentration *in vacuo* provided the title compound as white crystals (1.8 g, 44%). M.p. 57 ^oC (lit. 48-50 ^oC).

δ_H (400 MHz, $CDCl_3$): 7.83 (d, *J* 8.3, 1H, H-2), 7.92 (s, 1H, H-1), 7.97 (d, *J* 8.3, 1H, H-3), 10.33 (s, 1H, CHO).

HRMS (*m/z*-EI^+): Found 250.9321 ($C_8H_3BrF_3O$ requires 250.9319).

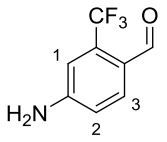
5.2.6.2 5-(allyloxy)-2-bromobenzaldehyde (350)



6-bromo-3-hydroxybenzaldehyde (1 g, 5 mmol, 1.00 equiv.) was charged to a 50 mL round-bottom flask and dissolved in EtOH (7 mL). A magnetic stirring bar was added, followed by K_2CO_3 (0.9 g, 6.25 mmol, 1.25 equiv.) and the flask fitted with a reflux condenser. Allyl chloride (0.49 mL, 6 mmol, 1.20 equiv.) was then added *via* syringe and the reaction refluxed for 2 hours. Upon cooling, the solution was filtered through a celite plug, concentrated *in vacuo* and the crude product purified using flash chromatography (9:1, hexanes:EtOAc). The title product was obtained as a red liquid that solidified upon cooling in an ice bath (1.14 g, 96%).

δ_H (400 MHz, $CDCl_3$): 4.55 (dt, *J* 5.3, 1.3 2H, CH_2), 5.28-5.31 (m, 1H, H_b), 5.38-5.43 (dd, *J* 17.3, 1.5, 1H, H_c), 5.96-6.06 (m, 1H, H_a), 7.02 (dd, *J* 8.8, 3.1, 1H, H-2), 7.40 (d, *J* 3.1, 1H, H-3), 7.50 (d, *J* 8.8, 1H, H-1), 10.29 (s, 1H, CHO).

5.2.6.3 4-amino-2-(trifluoromethyl)benzaldehyde (356)



4-amino-2-(trifluoromethyl)benzonitrile (2.5 g, 13.4 mmol, 1.00 equiv.) was dissolved in dry THF (7.5 mL) in a flame-dried 100 mL round-bottom flask equipped with a magnetic stirring bar under an inert argon atmosphere. The vessel was cooled to 0 ^{o}C and di*iso*butylaluminium hydride (DIBAL-H, 1.0 M in CH_2Cl_2, 33.6 mL, 33.6 mmol, 2.50 equiv.) was added dropwise *via* syringe. The solution turned yellow and was allowed to warm to room temperature before stirring for 15 mins, after which it was carefully transferred to separate 250 mL round-bottom flask containing a 3 M aqueous solution of potassium sodium tartrate (Rochelle salt, 32.5 mL). The organic layer was extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in EtOAc (12.5 mL) and stirred vigorously (using a magnetic stirring bar). 1.0 M HCl (12.5 mL) was added and stirring continued for 5 minutes. The solution was then basified to ~ pH 9 using 1.0 M NaOH before extracting the organic layer with EtOAc (1 x 50 mL). This was then washed with brine (35 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the titled product as an orange solid (2.55 g, 84%) that was dried under vacuum for several hours. M.p. > 250 ^{o}C. R_f = 0.21 (4:1, hexanes:EtOAc).

δ_H (400 MHz, $CDCl_3$): 4.45 (bs, 2H, NH_2), 6.78 (dd, *J* 8.5, 1.9, 1H, H-2), 6.91 (d, *J* 2.2, 1H, H-1), 7.95 (d, *J* 8.5, 1H, H-3), 10.12 (d, *J* 1.6, CHO).

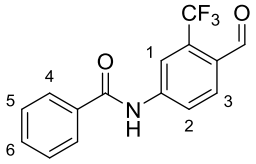
δ_C (100 MHz, $CDCl_3$): 110.7 (quart., J_{CF} 6.1), 115.5, 120.7 (d, J_{CF} 1.2, q), 124.3 (quart., J_{CF} 274.5, q, -CF_3), 131.6 (quart., J_{CF} 31.3, q), 133.5, 154.8 (q), 186.6 (t, J_{CF} 1.8, C=O).

δ_F (376 MHz, $CDCl_3$): -56.21 (d, J_{FH} 1.4).

ν_{max} (neat)/cm^{-1} 3459, 3359, 3239, 2913, 2824, 2687, 1570, 1350, 1266, 1156, 1114, 1040, 909, 867, 830, 809, 652.

HRMS (*m/z*-ESI⁻): Found 188.0331 ($C_8H_6F_3NO_2$ requires 188.0323).

5.2.6.4 N-(4-Formyl-3-trifluoromethyl-phenyl)-benzamide (357)



4-amino-2-(trifluoromethyl)benzaldehyde (2.5 g, 13.2 mmol, 1.00 equiv.) was charged to a 250 mL round-bottom flask equipped with a magnetic stirring bar and dissolved in THF (80 mL). K_2CO_3 (2.00 g, 14.5 mmol, 1.10 equiv.) was added in one portion and the suspension stirred for 1 minute before adding benzoyl chloride (2.04 mL, 14.5 mmol, 1.10 equiv.). The reaction was stirred at room temperature for 1 hour before concentrating *in vacuo* and re-dissolving in EtOAc (80 mL). This solution washed washed with 1.0 M AcOH (2 x 30 mL), H_2O (1 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 50 mL). It was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product which was suspended in cold CH_2Cl_2 (10 mL). This suspension was filtered and washed with cold Et_2O (5 mL) to yield the title product as a pale yellow solid (3.02 g, 78%). M.p. 165 ^oC. R_f = 0.29 (4:1, hexanes:EtOAc).

δ_H (400 MHz, $CDCl_3$): 7.53 (t, *J* 7.4, 2H, H-5), 7.60 (app. t, 1H, H-6), 7.96 (d, *J* 7.7, 2H, H-4), 8.11 (d, *J* 8.5, 1H, H-3), 8.28 (d, *J* 8.5, 1H, H-2), 8.40 (s, 1H, H-1), 10.14 (s, 1H, CHO), 10.87 (s, 1H, NH).

δ_C (100 MHz, $CDCl_3$): 117.6 (quart., J_{CF} 6.4, q), 123.1, 124.0 (quart., J_{CF} 273.7, q, -CF_3), 128.4, 129.0, 130.0 (quart., J_{CF} 32.4, q), 132.7 (d, *J* 2.2), 134.4 (q), 144.9 (q), 166.8 (C=O), 188.6 (C=O).

δ_F (376 MHz, $CDCl_3$): -55.95.

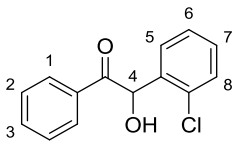
ν_{max} (neat)/cm^{-1} 3340, 3196, 3116, 3082, 2907, 2818, 1677, 1591, 1530, 1503, 1322, 1246, 1163, 1117, 1046, 894, 848, 813, 688, 631.

HRMS (*m/z*-ESI⁻): Found 292.0591 ($C_{15}H_{10}F_3NO_2$ requires 292.0585).

5.2.7 Procedure C: General procedure for achiral NHC-catalysed crossed aromatic-aromatic benzoin condensation employing various *ortho*-substituted benzaldehydes

A flame-dried 5 mL round-bottom flask containing a magnetic stirring bar was charged with K_2CO_3 (5.7 mg, 0.044 mmol) and placed under vacuum. The flask was heated to 650 ^oC for two separate 2 minute intervals before allowing to cool. The vacuum was released and the relevant triazolium salt precatalyst was added quickly in one portion. The flask was flushed with argon gas and sealed under an inert atmosphere using a rubber septum and an argon-filled balloon. THF (1.1M) was added *via* syringe and the suspension stirred for 15 minutes. A colour change was generally observed upon formation of the carbene *in situ* (red for precatalyst **X**). The relevant *ortho*-substituted benzaldehyde (1.1 mmol, 1.00 equiv.) was then added *via* syringe, followed by benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The septum was replaced with a glass stopper under a gentle flow of argon and the vessel sealed to the external atmosphere using parafilm. The reaction was stirred at room temperature for 48 hours before quenching with H_2O (5 mL) and extracting with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified *via* flash chromatography.

5.2.7.1 2-(2-Chlorophenyl)-2-hydroxy-1-phenylethan-1-one (147)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 2-chlorobenzaldehyde (124 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (217 mg, 80%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.27. M.p. 70-72 ^oC.

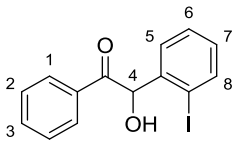
δ_H (400 MHz, $CDCl_3$): 4.53 (d, *J* 5.8, 1H, OH), 6.35 (d, *J* 5.8, 1H, H-4), 7.09 (d, *J* 7.4, 1H, H-5), 7.14-7.22 (m, 2H, H-6 and H-7), 7.36-7.41 (m, 3H, H-2 and H-8), 7.49 (t, *J* 7.4, 1H, H-3), 7.89 (d, *J* 7.6, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 72.8, 127.7, 128.8, 128.9, 129.2, 130.0, 130.3, 133.1 (q), 133.6 (q), 134.1, 136.7 (q), 198.7 (C=O).

ν_{max} (neat)/cm^{-1} 3479, 2958, 2913, 1669, 1595, 1445, 1392, 1358, 1314, 1240, 1178, 1089, 1035, 970, 851, 759, 713, 678, 628.

HRMS (*m/z*-ESI$^-$): Found 244.0291 ($C_{14}H_9ClO_2$ requires 244.0297).

5.2.7.2 2-(2-Iodophenyl)-2-hydroxy-1-phenylethan-1-one (361)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 2-iodobenzaldehyde (255 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (294 mg, 79%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.27. M.p. 104 ^oC.

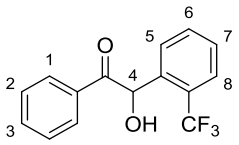
δ_H (400 MHz, $CDCl_3$): 4.47 (d, *J* 5.5, 1H, OH), 6.21 (d, *J* 5.5, 1H, H-4), 6.93-6.99 (m, 2H, H-5 and H-6), 7.19 (app. t, 1H, H-7), 7.37 (t, *J* 7.7, 2H, H-2), 7.50 (t, *J* 7.4, 1H, H-3), 7.87-7.91 (m, 3H, H-1 and H-8).

δ_C (100 MHz, $CDCl_3$): 75.3, 100.8 (C-I, q) 124.1, 122.9, 128.4, 129.2, 130.4, 130.5, 133.8, 134.8 (q), 137.7, 137.8 (q), 142.8, 197.6 (C=O).

ν_{max} (neat)/cm^{-1} 3479, 3057, 2912, 1669, 1579, 1447, 1363, 1311, 1244, 1186, 1084, 1007, 970, 844, 759, 724, 695, 674.

HRMS (*m/z*-ESI$^+$): 360.9695 ([M$^+$ + Na]$^+$, $C_{14}H_{11}IO_2Na$ requires 360.9696)

5.2.7.3 2-Hydroxy-1-phenyl-2-(2-(trifluoromethyl)phenyl)ethan-1-one (362)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 2-(trifluoromethyl)benzaldehyde (145 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (259 mg, 84%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.25. M.p. 83 – 84 ^oC.

δ_H (400 MHz, $CDCl_3$): 4.49 (d, *J* 5.5, 1H, OH), 6.23 (d, *J* 5.5, 1H, H-4), 7.05-7.08 (m, 1H, H-5), 7.35-7.42 (m, 4H, H-2, H-6 and H-7), 7.48 (t, *J* 7.4, 1H, H-3), 7.74-7.77 (m, 1H, H-8), 7.83-7.85 (m, 2H, H-1).

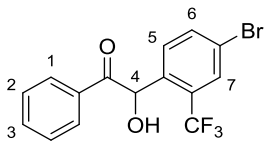
δ_C (100 MHz, $CDCl_3$): 71.8 (quart., J_{CF} 1.5), 124.3 (quart., J_{CF} 275.2, q, -CF_3), 126.7 (quart., J_{CF} 5.7, q), 128.7 (quart., J_{CF} 36.6, q), 128.8, 129.1, 129.2, 132.8, 133.1, 134.1, 137.3 (quart., J_{CF} 1.6, q), 198.6 (C=O).

δ_F (376 MHz, $CDCl_3$): -57.68.

ν_{max} (neat)/cm^{-1} 3483, 2939, 1673, 1582, 1451, 1369, 1304, 1241, 1158, 1117, 1058, 1033, 969, 852, 768, 693, 670.

HRMS (*m/z*-ESI$^+$): Found 303.0609 ([M + H]$^+$, $C_{15}H_{12}F_3O_2$ requires 303.0603).

5.2.7.4 2-(4-Bromo-2-(trifluoromethyl)phenyl)-2-hydroxy-1-phenylethan-1-one (363)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 4-bromo-2-(trifluoromethyl)benzaldehyde (**348**, 278 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a yellow oil (320 mg, 81%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.29.

δ_H (400 MHz, $CDCl_3$): 4.47 (d, *J* 5.4, 1H, OH), 6.17 (d, *J* 5.4, 1H, H-4), 6.92 (d, *J* 8.4, 1H, H-5), 7.37 (app. t, 2H, H-2), 7.50-7.55 (m, 2H, H-3 and H-6), 7.81 (dd, *J* 8.5, 1.1, 2H, H-1), 7.88 (s, 1H, H-7).

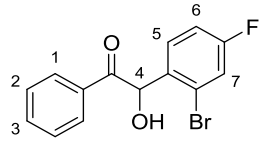
δ_C (100 MHz, $CDCl_3$): 71.2 (quart., J_{CF} 1.8), 122.9 (q), 123.3 (quart., J_{CF} 275.2, q, $-CF_3$), 128.9, 129.0, 130.0 (quart., J_{CF} 6.0), 130.3 (quart., J_{CF} 31.4, q), 130.8, 132.8, 134.4, 135.9 (quart., J_{CF} 1.0, q), 136.4 (quart., J_{CF} 1.1, q), 198.1 (C=O).

δ_F (376 MHz, $CDCl_3$): -58.07.

ν_{max} (neat)/cm^{-1} 3444, 3072, 2959, 1683, 1596, 1403, 1300, 1162, 1121, 1046, 973, 832, 706, 682.

HRMS (*m/z*-ESI⁻): Found 356.9741 ($C_{15}H_9BrF_3O$ requires 356.9744).

5.2.7.5 2-(2-Bromo-4-fluorophenyl)-2-hydroxy-1-phenylethan-1-one (364)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 2-bromo-4-fluorobenzaldehyde (223 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a

white solid (221 mg, 65%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.20. M.p. 75 ^oC.

δ_H (400 MHz, $CDCl_3$): 4.50 (d, *J* 5.6, 1H, OH), 6.30 (d, *J* 5.6, 1H, H-4), 6.90-6.95 (m, 1H, H-6), 7.01-7.06 (m, 1H, H-5), 7.33 (dd, *J* 8.22, 2.5, 1H, H-7), 7.38 (app. t, 2H, H-2), 7.52 (d, *J* 7.4, 1H, H-3), 7.87 (d, *J* 7.2, 2H, H-1).

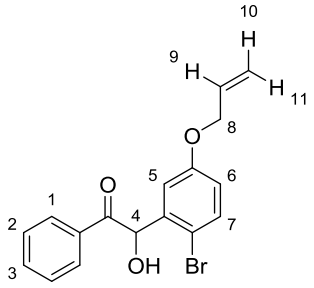
δ_C (100 MHz, $CDCl_3$): 74.5, 115.7 (d, J_{CF} 21.2), 120.8 (d, J_{CF} 24.4), 124.4 (d, J_{CF} 9.7, q), 128.8, 128.9, 130.3 (d, J_{CF} 8.7), 133.0 (q), 134.3, 134.6 (d, J_{CF} 3.8, q), 162.1 (d, J_{CF} 253.3, q), 198.6 (C=O).

δ_F (376 MHz, $CDCl_3$): -110.25 (dt, J_{FH} 8.1, 5.9).

ν_{max} (neat)/cm^{-1} 3263, 3087, 2923, 1687, 1592, 1483, 1220, 1082, 974, 864, 819, 751, 678.

HRMS (*m/z*-ESI⁻): Found 306.9766 ($C_{14}H_9O_2FBr$ requires 309.9770).

5.2.7.6 2-(5-(Allyloxy)-2-bromophenyl)-2-hydroxy-1-phenylethan-1-one (365)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and 5-(allyloxy)-2-bromobenzaldehyde (**350**, 265 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a pale yellow oil (218 mg, 57%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.20. M.p. 59 ^oC.

δ_H (400 MHz, $CDCl_3$): 4.33-4.41 (m, 2H, H-8), 4.48 (br. s, 1H, OH), 5.19 (dd, *J* 10.5, 1.2, 1H, H-10), 5.26 (dd, *J* 17.4, 1.2, 1H, H-11), 5.85-

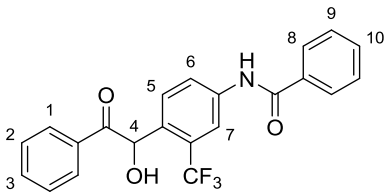
5.94 (m, 1H, H-9), 6.29 (s, 1H, H-4), 6.57 (d, *J* 2.9, 1H, H-5), 6.69 (dd, *J* 8.8, 2.9, 1H, H-6), 7.38 (app. t, 2H, H-2), 7.46 (d, *J* 8.8, 1H, H-7), 7.51 (t, *J* 7.4, 1H, H-3), 7.90 (d, *J* 7.5, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 69.0, 75.3, 114.6 (q), 115.2, 117.1, 118.1, 128.8, 129.0, 132.2 (q), 133.0 (q), 134.1, 134.2, 139.2, 158.4 (q), 198.7 (C=O).

ν_{max} (neat)/cm^{-1} 3485, 3068, 2954, 2881, 1670, 1591, 1469, 1410, 1287, 1230, 1160, 1079, 1003, 978, 932, 682.

HRMS (*m/z*-ESI⁻): Found 345.0120 ($C_{17}H_{14}O_3Br$ requires 345.0126).

5.2.7.7 *N*-(4-(1-hydroxy-2-oxo-2-phenylethyl)-3-(trifluoromethyl)phenyl)benzamide (366)



Prepared according to **procedure C** using **308** (25 mg, 0.044 mmol) and *N*-(4-formyl-3-(trifluoromethyl)phenyl)benzamide (**357**, 323 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (325 mg, 74%) following flash chromatography (4:1, hexanes:EtOAc), R_f = 0.19. M.p. 66 - 68 ^oC.

δ_H (400 MHz, $CDCl_3$): 4.50 (d, *J* 5.4, 1H, OH), 6.20 (d, *J* 5.4, 1H, H-4), 7.05 (d, *J* 8.6, 1H, H-5), 7.36 (app. t, 2H, H-2), 7.46-7.58 (m, 4H, H-3, H-9 and H-10), 7.71 (dd, *J* 8.6, 2.0, 1H, H-6), 7.81-7.91 (m, 5H, H-1, H-8 and NH), 8.06 (d, *J* 2.0, 1H, H-7).

δ_C (100 MHz, $CDCl_3$): 71.4, 118.0 (quart., J_{CF} 5.8, q), 123.7, 123.9 (quart., J_{CF} 276.3, q, -CF_3), 127.0, 128.9, 128.9, 129.1, 129.5 (quart.,

J_{CF} 30.5, q), 130.3, 132.3, 132.8 (quart., J_{CF} 1.1, q) 133.1, 134.1 (q), 134.2, 138.5 (q), 165.9 (C=O), 198.6 (C=O).

δ_F (376 MHz, $CDCl_3$): -57.95.

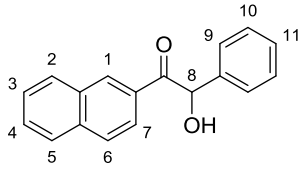
ν_{max} (neat)/cm^{-1} 3381, 3062, 2976, 1674, 1596, 1530, 1419, 1317, 1262, 1160, 1114, 972, 688.

HRMS (*m/z*-ESI$^+$): Found 422.0993 ($[M^+ + Na]^+$, $C_{22}H_{16}NO_3F_3Na$ requires 422.0980).

5.2.8 Procedure D: General procedure for the hydrodebromination of aromatic benzoins

To a flame-dried 50 mL round-bottom flask equipped with a magnetic stirring bar was charged the relevant aromatic benzoin (0.34 mmol, 1.00 equiv.), MeOH (10 mL), palladium on activated charcoal (10% Pd basis, 25 wt%) and ammonium formate (100 mg, 1.6 mmol, 5.00 equiv.). The flask was fitted with a reflux condenser, flushed with argon and sealed with a rubber septum. The mixture was refluxed at 60 ^oC with stirring and the progress of the reaction monitored *via* TLC. Upon consumption of the starting material, the reaction was allowed to cool and filtered to remove the Pd/C. The filtrate was concentrated *in vacuo* before adding CH_2Cl_2 (10 mL) and H_2O (5 mL). The layers were separated and the aqueous layer extracted once further with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* once more to yield the desired product.

5.2.8.1 2-Hydroxy-1-(naphthalen-2-yl)-2-phenylethan-1-one (374)



Prepared according to **procedure D** using 2-(2-bromophenyl)-2-hydroxy-1-(naphthalen-2-yl)ethan-1-one (**331**, 116 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 1 hour, the

title product was obtained as a white solid (83 mg, 93%). R_f = 0.16 (9:1, hexanes:EtOAc). M.p. 139-141 ^oC.

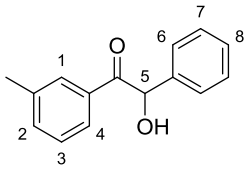
δ_H (400 MHz, $CDCl_3$): 4.63 (br. s, 1H, OH), 6.11 (s, 1H, H-8), 7.24-7.27 (obscured, 1H, H-11), 7.30 (app. t, 2H, H-10), 7.39 (d, *J* 7.3, 2H, H-9), 7.51 (app. t, 2H, H-3), 7.57 (app. t, 1H, H-4), 7.81-7.84 (m, 1H, H-5 and H-6), 8.12 (d, *J* 8.1, 1H, H-2), 7.95 (d, *J* 8.7, 1.4, 1H, H-7), 8.45 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 76.3, 124.2, 127.0, 127.7, 127.8, 128.6, 128.6, 129.0, 129.1, 129.7, 130.8 (q), 131.3, 132.2 (q), 135.8 (q), 139.1 (q), 198.9 (C=O).

ν_{max} (neat)/cm^{-1} 3413, 3056, 2902, 1677, 1622, 1388, 1263, 1172, 1078, 1005, 794, 749, 692.

HRMS (*m/z*-ESI⁻): Found 261.0905 ($C_{18}H_{13}O_2$ requires 261.0916).

5.2.8.2 2-Hydroxy-2-phenyl-1-(3-tolyl)ethan-1-one (372)



Prepared according to **procedure D** using 2-(2-bromophenyl)-2-hydroxy-1-(3-tolyl)ethan-1-one (332, 104 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 40 minutes, the title product was obtained as a clear oil (72 mg, 94%). Upon standing for several hours, this oil gradually solidified to a white solid. R_f = 0.18 (9:1, hexanes:EtOAc). M.p. 55-56 ^oC.

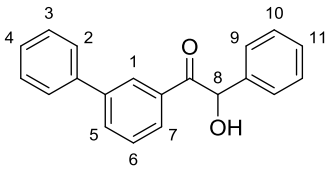
δ_H (400 MHz, $CDCl_3$): 2.33 (s, 3H, CH_3), 4.53 (d, *J* 6.2, 1H, OH), 5.92 (d, *J* 6.2, 1H, H-5), 7.23-7.32 (m, 7H, H-2, H-3, H-6, H-7 and H-8), 7.66 (d, *J* 7.8, 1H, H-4), 7.73 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 21.3, 76.1, 126.4, 127.7, 128.5, 128.5, 129.1, 129.6, 133.5 (q), 134.7, 138.6 (q), 139.1 (q), 199.1 (C=O).

ν_{max} (neat)/cm^{-1} 3450, 3033, 2960, 2922, 2859, 1673, 1263, 1165, 1023, 784, 749, 690.

HRMS (*m/z*-ESI⁻): Found 225.0921 ($C_{15}H_{13}O_2$ requires 225.0916).

5.2.8.3 1-Biphenyl-3-yl-2-hydroxy-2-phenyl-ethanone (380)



Prepared according to **procedure D** using 1-([1,1'-biphenyl]-3-yl)-2-(2-bromophenyl)-2-hydroxyethan-1-one (**334**, 125 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 30 minutes, the title product was obtained as a low-melting pale yellow solid (86 mg, 88%). R_f = 0.16 (9:1, hexanes:EtOAc).

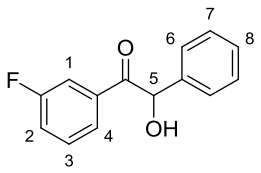
δ_H (400 MHz, $CDCl_3$): 4.57 (br. s, 1H, OH), 5.98 (d, *J* 2.9, 1H, H-8), 7.27-7.50 (m, 11H, H-2, H-3, H-4, H-7, H-9, H-10 and H-11), 7.72 (d, *J* 7.8, 1H, H-5), 7.85 (d, *J* 7.9, 1H, H-7), 8.13 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 76.4, 127.0, 127.8, 127.8, 127.9, 128.6, 128.9, 129.1, 129.2, 132.5, 133.9 (q), 139.0 (q), 139.7 (q), 141.8 (q), 198.9 (C=O).

ν_{max} (neat)/cm^{-1} 3439, 3060, 3032, 2922, 1678, 1452, 1298, 1234, 1179, 1072, 979, 752, 694.

HRMS (*m/z*-ESI⁻): Found 287.1080 ($C_{20}H_{15}O_2$ requires 287.1072).

5.2.8.4 1-(3-Fluoro-phenyl)-2-hydroxy-2-phenyl-ethanone (378)



Prepared according to **procedure D** using 2-(2-bromophenyl)-1-(3-fluorophenyl)-2-hydroxyethan-1-one (**335**, 104 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 20 minutes, the title product was obtained as a white solid (63 mg, 80%). R_f = 0.20 (9:1, hexanes:EtOAc). M.p. 105-107 ^{o}C.

δ_H (400 MHz, $CDCl_3$): 4.44 (br. s, 1H, OH), 5.90 (s, 1H, H-5), 7.19 (dd, *J* 8.3, 2.3, 1H, H-3), 7.29-7.40 (m, 6H, H-4, H-6, H-7 and H-8), 7.58-7.62 (m, 1H, H-2), 7.66 (d, *J* 7.8, 1H, H-1).

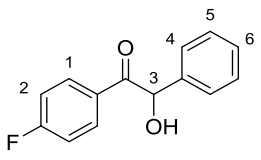
δ_C (100 MHz, $CDCl_3$): 76.5, 115.8 (d, J_{CF} 22.5), 120.9 (d, J_{CF} 21.3), 124.8 (d, J_{CF} 3.1), 127.8, 128.8, 129.3, 130.3 (d, J_{CF} 7.7), 135.5 (d, J_{CF} 6.5, q), 138.5 (q), 162.6 (d, J_{CF} 247.3, q), 197.9 (d, J_{CF} 2.2, C=O).

δ_F (376 MHz, $CDCl_3$): -111.05 (dt, J_{FH} 8.6, 5.7)

ν_{max} (neat)/cm^{-1} 3437, 3071, 2936, 1677, 1585, 1486, 1444, 1250, 1222, 1155, 1066, 1066, 794, 755, 696, 671.

HRMS (*m/z*-ESI$^-$): Found 229.0660 ($C_{14}H_{10}O_2F$ requires 229.0665).

5.2.8.5 1-(4-Fluoro-phenyl)-2-hydroxy-2-phenyl-ethanone (379)



Prepared according to **procedure D** using 2-(2-bromophenyl)-1-(4-fluorophenyl)-2-hydroxyethan-1-one (**338**, 104 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 30 minutes, the title product was obtained as a white solid (65 mg, 83%). R_f = 0.17 (9:1, hexanes:EtOAc). M.p. 82-84 ^{o}C.

δ_H (400 MHz, $CDCl_3$): 4.49 (br. s, 1H, OH), 5.88 (s, 1H, H-3), 7.03 (t, *J* 8.7, 2H, H-5), 7.26-7.35 (m, 5H, H-2, H-4 and H-6), 7.92-7.95 (m, 2H, H-1).

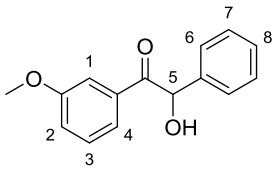
δ_C (100 MHz, $CDCl_3$): 76.2, 116.0 (d, J_{CF} 22.0), 127.1 (q), 127.7, 128.1 129.2, 131.9 (d, J_{CF} 9.5), 138.8 (q), 166.0 (d, J_{CF} 256.8, q), 197.3 (C=O).

δ_F (376 MHz, $CDCl_3$): -103.00 (m).

ν_{max} (neat)/cm^{-1} 3450, 3064, 3033, 2901, 1674, 1595, 1503, 1229, 1156, 1076, 974, 832, 757, 698.

HRMS (*m/z*-ESI$^-$): Found 229.0654 ($C_{14}H_{10}O_2F$ requires 229.0665).

5.2.8.6 2-Hydroxy-1-(3-methoxyphenyl)-2-phenylethan-1-one (375)



Prepared according to **procedure D** using 2-(2-bromophenyl)-2-hydroxy-1-(3-methoxyphenyl)ethan-1-one (**340**, 109 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 30 minutes, the title product was obtained as a pale yellow oil (70 mg, 85%). Upon standing for several hours, this oil gradually solidified to a pale yellow solid. R_f = 0.13 (9:1, hexanes:EtOAc). M.p. 45 ^oC.

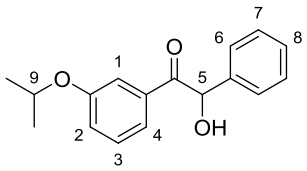
δ_H (400 MHz, $CDCl_3$): 3.78 (s, 3H, CH_3), 4.50 (d, *J* 6.0, 1H, OH), 5.90 (d, *J* 6.0, 1H, H-5), 6.77-6.86 (m, 1H, H-3), 7.03 (dd, *J* 8.3, 2.2, 1H, H-2), 7.20-7.32 (m, 5H, H-6, H-7 and H-8), 7.43 (s, 1H, H-1), 7.45 (d, *J* 7.6, 1H, H-4).

δ_C (100 MHz, $CDCl_3$): 55.4, 76.3, 113.3, 120.4, 121.7, 127.1, 127.7, 128.2, 128.6, 129.1, 134.7 (q), 139.0 (q), 159.7 (q), 198.8 (C=O).

ν_{max} (neat)/cm^{-1} 3409, 3065, 3003, 2907, 2836, 1677, 1582, 1487, 1432, 1261, 1224, 1042, 981, 877, 790, 758, 698, 603.

HRMS (*m/z*-ESI⁻): Found 241.0865 ($C_{15}H_{13}O_2$ requires 241.0865).

5.2.8.7 2-Hydroxy-1-(3-isopropoxyphenyl)-2-phenylethan-1-one (376)



Prepared according to **procedure D** using 2-(2-bromophenyl)-2-hydroxy-1-(3-isopropoxyphenyl)ethan-1-one (**341**, 119 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 20 minutes, the title product was obtained as a yellow oil (90 mg, 98%). R_f = 0.16 (9:1, hexanes:EtOAc).

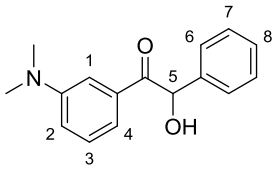
δ_H (400 MHz, $CDCl_3$): 1.25 (d, *J* 6.0, 3H, CH_3), 1.29 (d, *J* 6.0, 3H, CH_3), 4.45-4.53 (m, 2H, H-9 and OH), 5.89 (s, 1H, H-5), 7.00 (dd, *J* 8.3, 1.6, 1H, H-3), 7.23-7.32 (m, 6H, H-2, H-6, H-7 and H-8), 7.40-7.47 (m, 2H, H-1 and H-4).

δ_C (100 MHz, $CDCl_3$): 21.7, 21.9, 70.2, 76.3, 115.2, 121.4, 122.2, 127.7, 128.5, 129.1, 129.7, 134.7 (q), 139.1 (q), 158.0 (q), 198.8 (C=O).

ν_{max} (neat)/cm^{-1} 3444, 3066, 3033, 2978, 2931, 1679, 1582, 1486, 1444, 1256, 1111, 952, 756, 698.

HRMS (*m/z*-ESI⁻): Found 269.1183 ($C_{17}H_{17}O_3$ requires 269.1178).

5.2.8.8 1-(3-(Dimethylamino)phenyl)-2-hydroxy-2-phenylethan-1-one (377)



Prepared according to **procedure D** using 2-(2-bromophenyl)-1-(3-(dimethylamino)phenyl)-2-hydroxyethan-1-one (**342**, 114 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 10 minutes, the title product was obtained as a pale yellow oil (82 mg, 95%). R_f = 0.11 (9:1, hexanes:EtOAc).

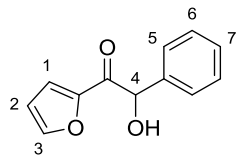
δ_H (400 MHz, $CDCl_3$): 2.92 (s, 6H, CH_3), 4.58 (br. s, 1H, OH), 5.91 (s, 1H, H-5), 6.81-6.86 (m, 1H, H-3), 7.20-7.34 (m, 8H, H-1, H-2, H-4, H-6, H-7 and H-8).

δ_C (100 MHz, $CDCl_3$): 40.3, 76.2, 112.2, 117.3, 117.6, 127.7, 128.4, 129.0, 129.1, 134.1 (q), 137.4 (q), 150.4 (q), 199.5 (C=O).

ν_{max} (neat)/cm^{-1} 3443, 3064, 3031, 2890, 2807, 1667, 1597, 1499, 1352, 1232, 1064, 1026, 983, 947, 760, 697.

HRMS (*m/z*-ESI$^+$): Found 256.1332 ($[M + H]^+$, $C_{16}H_{18}NO_2$ requires 256.1338).

5.2.8.9 1-Furan-2-yl-2-hydroxy-2-phenyl-ethanone (381)



Prepared according to **procedure D** using 2-(2-bromophenyl)-1-(furan-2-yl)-2-hydroxyethan-1-one (**345**, 96 mg, 0.34 mmol, 1.00 equiv.). After refluxing for 1 hour, a further portion of ammonium formate (100 mg, 5 equiv.) was added and refluxing continued for a further 30 mins, upon which the title product was obtained as a tan solid (69 mg, 100%). R_f = 0.13 (9:1, hexanes:EtOAc). M.p. 127 ^oC.

δ_H (400 MHz, $CDCl_3$): 4.36 (br. s, 1H, OH), 5.75 (s, 1H, H-4), 6.48 (dd, *J* 3.7, 1.5, 1H, H-2), 7.19 (d, *J* 3.7, 1H, H-3), 7.27-7.41 (m, 5H, H-5, H-6 and H-7), 7.57 (s, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 76.1, 112.6, 119.9, 127.7, 128.6, 128.9, 138.7 (q), 147.3, 149.9 (q), 187.4 (C=O).

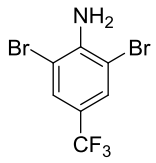
ν_{max} (neat)/cm^{-1} 3423, 3121, 2958, 1660, 1458, 1399, 1270, 1157, 1039, 976, 908, 811, 754, 726, 694.

HRMS (*m/z*-ESI⁻): Found 201.0562 ($C_{12}H_9O_3$ requires 201.0552).

5.3 Experimental data for Chapter 3

5.3.1 Synthesis of substituted anilines

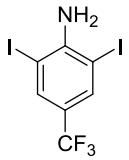
5.3.1.1 2,6-Dibromo-4-(trifluoromethyl)aniline (418)[247]



To a 250 mL round-bottom flask equipped with a magnetic stirring bar was charged 4-(trifluoromethyl)aniline (2.3 mL/3 g, 18.6 mmol, 1.00 equiv.), iron filings (190 mg) and ethyl acetate (20 mL). Br_2 (1.92 mL, 37.2 mmol, 2.00 equiv.) was added dropwise at 30 – 50 °C. The solution was then heated at reflux for 1 hour before being concentrated *in vacuo*, redissolved in Et_2O and basefied to pH 14 with 2 M NaOH. The organic layer was separated and the aqueous layer washed with Et_2O (2 x 50 mL). The organic extracts were then combined, washed with H_2O (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification *via* flash chromatography (100% hexane) yielded a colourless oil. Scratching the bottom of the vessel with a glass pipette caused solidification, producing the title compound as a white solid (3.00 g, 50%). M.p. 37 °C (lit. 37-39 °C).

δ_H (400 MHz, $CDCl_3$): 4.78 (s, 2H, NH_2), 7.62 (s, 2H, *m*-H).

5.3.1.2 2,6-Diiodo-4-(trifluoromethyl)aniline (419)[248]

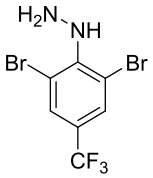


In a 250 mL round-bottom flask equipped with a magnetic stirring bar was charged 4-(trifluoromethyl)aniline (1.54 mL/2 g, 12 mmol, 1.00 equiv.) and acetic acid (12.5 mL). A solution of iodine monochloride (4.5 g, 27 mmol, 2.27 equiv.) in acetic acid (15 mL) was added dropwise followed by immediate addition of H_2O (50 mL). The resulting suspension was heated gradually to 80 ^oC, stirred at this temperature for 3 hours and, upon cooling, basefied with a 40% NaOH solution to pH 11. The product was then extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with a saturated aqueous sodium thiosulfate solution, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a light brown solid. Trituration with cold hexane provided the title compound as a white solid (4.28 g, 86%). M.p. 97 ^oC (lit. 96 ^oC).

δ_H (400 MHz, $CDCl_3$): 4.95 (s, 2H, NH_2), 7.84 (s, 2H, *m*-H).

5.3.2 Synthesis of substituted arylhydrazines

5.3.2.1 (2,6-Dibromo-4-trifluoromethyl-phenyl)hydrazine (420)[247]

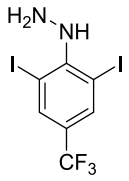


Prepared according to **procedure A** using 2,6-dibromo-4-trifluoromethyl-phenylamine (3.32 g, 10.4 mmol) as white needle-like crystals (0.973 g, 28%). M.p. 65-66 ^oC. (lit. 65-67 ^oC).

δ_H (400 MHz, $CDCl_3$): 4.03 (s, 2H, NH_2), 5.78 (s, 1H, NH) 7.71 (s, 2H, *m*-H).

HRMS (*m/z*-ESI$^+$): Found 332.8848 ([M + H]$^+$, $C_7H_6Br_2F_3N_2$ requires 332.8844).

5.3.2.2 (2,6-Diiodo-4-(trifluoromethyl)-phenyl)hydrazine (421)



Prepared according to **procedure A** using 2,6-diiodo-4-trifluoromethyl-phenylamine (2.42 g, 5.8 mmol) as white needle-like crystals (0.81 g, 32%). M.p. 94-95 ^oC. R_f = 0.17 (9:1, hexanes:EtOAc).

δ_H (400 MHz, $CDCl_3$): 3.96 (s, 2H, NH_2), 5.52 (s, 1H, NH), 7.99 (s, 2H, *m*-H).

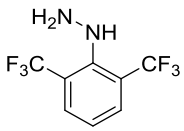
δ_C (100 MHz, $CDCl_3$): 79.5 (q, C-I), 118.2 (quart., J_{CF} 273.6, q, -CF_3), 122.0 (quart., J_{CF} 33.8, q), 136.3 (quart., J_{CF} 3.7), 148.9 (q).

δ_F (376 MHz, $CDCl_3$): -61.40.

ν_{max} (neat)/cm^{-1} 3410, 3323, 3088, 1784, 1604, 1545, 1464, 1387, 1307, 1110, 1088, 933, 886, 739, 700, 655, 619.

HRMS (*m/z*-ESI$^+$): Found 428.8572 ([M + H]$^+$, $C_7H_6I_2F_3N_2$ requires 428.8567).

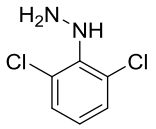
5.3.2.3 (2,6-bis(trifluoromethyl)phenyl)hydrazine (423)



Prepared according to a modified procedure from the thesis of Dr. Daniel DiRocco (Rovis Group, Colorado State Univesity), kindly shared with us: to a solution of 2-fluoro-1,3-bis(trifluoromethyl)benzene (4.00 g, 17.23 mmol, 1.00 equiv.) in ethanol (50 mL) was added hydrazine monohydrate (16.8 mL, 0.258 mol, 20.0 equiv.) and the mixture refluxed overnight. Water (100 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were concentrated in vacuo and purified *via* flash column chromatography (98:2, petroleum ether:EtOAc) to yield the title compound as a pale yellow oil (2.08 g, 50%).

δ_H (400 MHz, $CDCl_3$): 3.99 (br. s, 2H, NH_2), 5.47 (br. s, 1H, NH), 7.11-7.17 (m, 1H, *p*-H), 7.76 (d, *J* 7.9, 2H, *m*-H).

5.3.2.4 (2,6-Dichlorophenyl)hydrazine (425)[253]

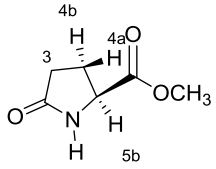


A solution of 2,6-dichloroaniline (2.00 g, 12.34 mmol, 1.00 equiv.) in HCl (36.5%, 10 mL) was cooled to 0 ^oC and a 3 M aqueous solution of $NaNO_2$ (1.02 g, 14.8 mmol, 1.20 equiv.) was added dropwise. The solution turned orange and was stirred for 15 mins before cold filtration to remove the precipitate. The filtrate was then stirred vigorously at 0 ^oC and a 3 M solution of $SnCl_2.2H_2O$ (6.9 g, 30 mmol, 2.43 equiv.) in HCl (36.5%, 10 mL) was added in one portion. The pale yellow slurry was stirred at 0 ^oC for 1 hour before filtering and drying the resulting solid extensively in air. This solid was then added to a solution of brine (30 mL), 1 M NaOH (13.2 mL) and a saturated aqueous $NaHCO_3$ solution (24 mL) in an Erlenmeyer flask and the resulting mixture swirled by hand. The product was extracted with CH_2Cl_2 (1 x 100 mL, 1 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a pale yellow solid. Recrystallisation from hot hexane/ethyl acetate (6:1) yielded the title product as white needle-like crystals (0.18 g, 17%). M.p. 96 ^oC (lit. 95 ^oC)

δ_H (400 MHz, $CDCl_3$): 3.94 (br. s, 2H, NH_2), 5.56 (br. s, 1H, NH), 6.86 (td, *J* 8.2, 1.8, 1H, *p*-H), 7.24-7.26 (m, 2H, *m*-H).

5.3.3 Preparation of TMS-protected lactam precursors to chiral bifunctional triazolium ion-based precatalysts

5.3.3.1 (5*S*)-oxopyrrolidine-2-carboxylic acid methyl ester (414)[268]



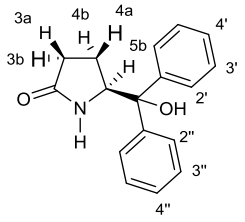
To an oven-dried 250 mL round bottomed flask was charged *L*-pyroglutamic acid (10.00 g, 77.447 mmol) and Dowex-50W (X8-200) resin (5.00 g). Methanol (HPLC grade) was added to the flask, which was then equipped with a reflux condenser and placed under an atmosphere of Argon. The reaction was heated under reflux at 90 °C for 72 h. The solution was filtered to remove the solid resin and concentration of the filtrate *in vacuo* yielded the title product as a pale yellow oil (11.08 g, 100%). $[\alpha]_D^{20}$ = -2.4 (c 1.00 in CH_2Cl_2), lit. $[\alpha]_D^{20}$ = -6.95 (*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, *J* 8.8, 5.0, 1H, H-5b), 7.35 (br. s, 1H, N-H).

δ_C (150 MHz, $CDCl_3$): 24.8, 29.3, 52.5, 55.5, 172.7 (C=O), 178.5 (C=O).

HRMS (*m/z*-ESI$^+$): Found 166.0477 ($[M^+ + Na]^+$ $C_6H_9NO_3Na$ requires 166.0480).

5.3.3.2 (5*S*)-(Hydroxy-diphenyl-methyl)-pyrrolidin-2-one (415)[269,270]



An oven-dried 500 mL round bottomed flask equipped with a magnetic stirrer was charged with magnesium (3.28 g, 0.175 mol, 3.00 equiv.) and THF (15 mL) was added. Bromobenzene (15.12 mL 0.175 mol, 3.00 equiv.) was added slowly over 5 minutes in 1 mL aliquots with stirring. Gentle heating was provided by holding the flask with one hand and once 3 mL of bromobenzene had been added, formation of the Grignard reagent was observed *in situ* as the solution turned dark brown. Bromobenzene was continually added in 1 mL aliquots. Once 7 mL of bromobenzene had been added, a further 15 mL THF was syringed into the reaction mixture and the remaining bromobenzene was added in 1 mL aliquots. The reaction was then heated to 80 ^{o}C for 1 hour to ensure complete formation of the Grignard reagent. Upon cooling, **414** (4.7 g, 36.0 mmol, 1.00 equiv.) was charged to a pressure-equalised dropping funnel and dissolved in THF (150 mL). This solution was added in a dropwise manner over the course of 30 minutes. The reaction was allowed to stir at room temperature for 2 hours before it was cooled to 0 ^{o}C and excess phenylmagnesium bromide quenched with 5% (*v/v*) HCl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give an off-white solid. Recrystallisation from CH_2Cl_2 and Et_2O gave the title compound as a white solid (5.37 g, 76%). M.p. 192-194 °C (lit. 191-192 ^{o}C). $[\alpha]_D^{20}$ = -79.1 (*c* 1.30 in $CHCl_3$), lit. $[\alpha]_D^{20}$ = -80.8 (*c* 1.30 in $CHCl_3$), for *S*-enantiomer with 100% *ee*.

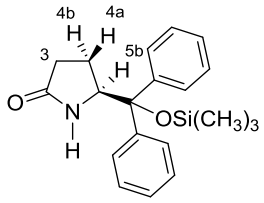
δ_H (600 MHz, $CDCl_3$): 1.94-2.01 (m, 1H, H-4a), 2.11-2.17 (m, 1H, H-4b), 2.24-2.30 (m, 1H, H-3a), 2.33-2.39 (m, 1H, H-3b), 2.74 (br. s, 1H, OH), 4.74 (dd, *J* 8.3, 5.0, 1H, H-5b), 5.47 (br. s, 1H, N-H), 7.23 (t, *J* 7.3, 1H, H-4''), 7.26 (t, *J* 7.3, 1H, H-4'), 7.33 (app. t, 2H, H-3''), 7.37 (app. t, 2H, H-3'), 7.46 (d, *J* 7.5, 2H, H-2''), 7.50 (d, *J* 8.3, 2H, H-2').

δ_C (150 MHz, $CDCl_3$): 21.5, 30.1, 60.5, 78.6 (q), 125.5, 125.7, 127.0, 127.4, 128.2, 128.7, 143.0 (q), 145.1 (q), 179.1 (C=O)

HRMS (*m/z*-ESI$^+$): Found 290.1145 ([M + Na]$^+$, $C_{17}H_{17}NO_2Na$ requires 290.1157).

5.3.3.3 (5*S*)-(Diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one

(416)[271,272]



An oven-dried 25 mL round bottomed flask equipped with a magnetic stirrer was charged with **348** (0.470 g, 1.750 mmol, 1.00 equiv.) and dimethylaminopyridine (22.0 mg, 0.175 mmol, 0.10 equiv.). The flask was sealed with a rubber septum seal and put under an atmosphere of Argon. CH_2Cl_2 (18.0 mL) was injected *via* a syringe and the reaction cooled to 0 ^oC. Triethylamine (1.0 mL, 3.06 mmol, 9.00 equiv.) was charged and the reaction stirred for 20 min. Trimethylsilane chloride (1.10 mL, 8.5 mmol, 18.0 equiv.) 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 mL). The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 x 10 mL aliquots). The organic layers were combined, dried ($MgSO_4$) and solvent removed under reduced pressure to give a brown residue. Purification by column chromatography (6:4 EtOAc:hexane, R_f 0.4) yielded **349** as a white solid (0.285 g, 96%). M.p. 120-121 °C (lit. 120-122 ^oC) $[\alpha]_D^{20}$ = -76.3 (*c* 0.50 in $CHCl_3$), lit. $[\alpha]_D^{20}$ = -81.6 (*c* 0.50 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 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, *J* 7.8, 4.3, 1H, H-5b), 5.89 (bs, 1H, N-H), 7.32-7.37 (m, 10H, Ar).

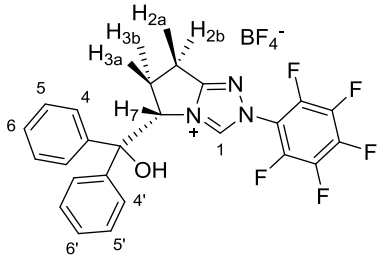
δ_C (100 MHz, $CDCl_3$): 1.9, 22.3, 29.2, 60.3, 82.7 (q), 127.8, 128.0, 128.1, 128.2, 142.9 (q), 143.1 (q), 178.7 (C=O).

HRMS (*m/z*-ESI$^+$): Found 362.1551 ($[M + Na]^+$, $C_{20}H_{25}NO_2NaSi$ requires 362.1552).

5.3.4 Procedure E: general procedure for the synthesis of chiral triazolium salts

5-(Diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (**416**, 1.00 equiv.) was charged to 250 mL round-bottom flask, equipped with a magnetic stirring bar, the vessel flushed with argon and fitted with a rubber septum. CH_2Cl_2 was added *via* syringe, followed quickly by trimethyloxonium tetrafluoroborate (Meerwein salt, 1.00 equiv.) in one portion. The solution was stirred under argon for 18 h at room temperature before the addition of the relevant arylhydrazine (1.00 equiv.) and stirring continued for a further 24 h. The solution was then concentrated *in vacuo* to yield the hydrazone intermediate as a white fluffy solid. This was dissolved in chlorobenzene and the vessel set up for reflux under argon. Triethyl orthoformate (4.3 equiv.) was added *via* syringe and the solution refluxed at 120 ^oC for 24 h. A further aliquot of triethyl orthoformate (4.3 equiv.) was added and refluxing continued for a further 48 h. Upon cooling, the dark brown solution was concentrated *in vacuo* and the oily residue dissolved in MeOH. The vessel was again flushed with argon and fitted with a rubber septum. Bromotrimethylsilane (TMS-Br, 3.5 equiv. as a 10% v/v solution in MeOH) was added *via* syringe and the solution stirred under argon for 24 h at room temperature. Upon concentration, the dark brown residue was subjected to flash chromatography as outlined below to obtain the final compound.

5.3.4.1 (*S*)-5-(Hydroxy-diphenyl-methyl)-2-pentafluorophenyl-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (206)

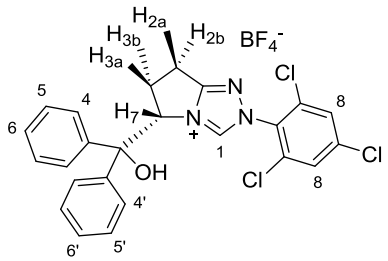


Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (1.27 g, 3.7 mmol, 1.00 equiv.), Meerwein salt (0.71 g, 3.7 mmol, 1.00 equiv.), CH_2Cl_2 (30 mL), pentafluorophenylhydrazine (0.74 g, 3.7 mmol, 1.00 equiv.), chlorobenzene (35 mL), triethyl orthoformate (2 x 2.7 mL, 26 mmol, 8.60 equiv.), TMS-Br (1.7 mL, 13.1 mmol. 3.50 equiv.) and MeOH (100 mL). Purified *via* flash chromatography using EtOAc:MeOH (9:1). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a light tan crystalline

solid (806 mg, 38 %). All spectral data obtained for this compound was in agreement with previous literature published within our group.[169]

δ_H (600 MHz, DMSO-d_6): 2.62-2.71 (m, 1H, H-3a), 2.89-2.95 (m, 1H, H-2a), 3.02-3.08 (m, 1H, H-3b), 3.18-3.23 (m, 1H, H-2b), 6.16 (dd, 1H, *J* 8.7, 2.6, H-7), 6.80 (s, 1H, OH), 7.31 (t, 1H, *J* 7.3, H-6), 7.36-7.40 (m, 3H, H-5 and H-6'), 7.44-7.48 (m, 4H, H-4 and H-5'), 7.76 (d, 2H, *J* 7.2, H-4'), 9.63 (s, 1H, H-1)

5.3.4.2 (*S*)-5-(Hydroxy-diphenyl-methyl)-2-(2,4,6-trichloro-phenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (412a)



Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (1.27 g, 3.7 mmol, 1.00 equiv.), Meerwein salt (0.71 g, 3.7 mmol, 1.00 equiv.), CH_2Cl_2 (30 mL), 2,4,6-trichlorophenyl hydrazine (0.79 g, 3.7 mmol, 1.00 equiv.), chlorobenzene (35 mL), triethyl orthoformate (2 x 2.7 mL, 26 mmol, 8.6 equiv.), TMS-Br (1.7 mL, 13.1 mmol, 3.5 equiv.) and MeOH (100 mL). Purified *via* flash chromatography using a solvent gradient of EtOAc:hexanes (9:1) to EtOAc:MeOH (9:1). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a yellow crystalline solid (854 mg, 41 %). M.p. 182-184 ^oC. R_f = 0.4 (9:1, EtOAc:MeOH). $[\alpha]_D^{20}$ = -168.4 (*c* 1.40 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, DMSO-d_6): 2.64-2.74 (m, 1H, H-3a), 2.82-2.86 (m, 1H, H-2a), 3.08-3.21 (m, 2H, H-2b and H-3b), 6.16 (d, *J* 7.3, 1H, H-7), 6.79 (s, 1H, OH), 7.28-7.31 (m, 2H, H-6 and H-6'),

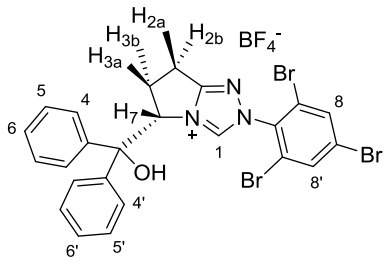
7.35-7.41 (m, 6H, H-4, H-5 and H-5'), 7.44 (d, *J* 7.6, 2H, H-4'), 8.11 (s, 2H, H-8), 9.45 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 21.9, 30.3, 68.5, 79.3 (q), 126.6, 126.8, 128.2, 128.4, 128.9, 129.2, 129.7, 130.7 (q), 134.0 (q), 138.6, 143.3 (q), 143.5 (q), 164.8 (C=N).

ν_{max} (neat)/cm^{-1} 3187, 2951, 1729, 1671, 1593, 1572, 1559, 1448, 1413, 1374, 1245, 1192, 1152, 959, 855, 823, 768, 700.

HRMS (*m/z*-ESI$^+$): Found 470.0574 (M^+, $C_{24}H_{19}Cl_3N_3O$ requires 470.0594).

5.3.4.3 (*S*)-5-(Hydroxy-diphenyl-methyl)-2-(2,4,6-tribromo-phenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (412b)



Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (1.42 g, 4.2 mmol, 1.00 equiv.), Meerwein salt (0.80 g, 4.2 mmol, 1.00 equiv.), CH_2Cl_2 (60 mL), 2,4,6-tribromophenyl hydrazine (1.44 g, 4.2 mmol, 1.00 equiv.), chlorobenzene (40 mL), triethyl orthoformate (2 x 3 mL, 29 mmol, 8.60 eq), TMS-Br (1.90 mL, 14.7 mmol, 3.50 equiv.) and MeOH (120 mL). Purified twice *via* flash chromatography using 1) 100 % EtOAc to EtOAc:MeOH (9:1) and 2) EtOAc:MeOH (9:1). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a light tan crystalline solid (913 mg, 31 %). M.p. 190 – 192 ^oC. R_f = 0.34 (9:1, EtOAc:MeOH). $[\alpha]_D^{20}$ = -175.2 (*c* 1.40 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, DMSO-d_6): 2.68-2.73 (m, 2H, H-2a and H-3a), 3.08-3.23 (m, 2H, H-2b and H-3b), 6.24 (d, *J* 8.0, 1H, H-7), 6.76 (s, 1H, OH),

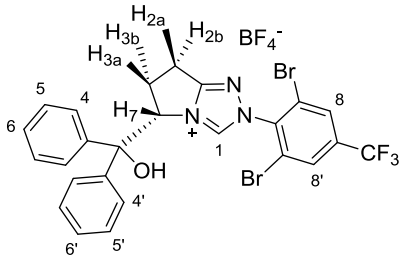
7.26-7.31 (m, 2H, H-6 and H-6'), 7.34-7.43 (m, 6H, H-4, H-5 and H-5'), 7.45 (d, *J* 7.51, 2H, H-4'), 8.30 (s, 1H, H-8), 8.32 (s, 1H, H-8'), 9.39 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 21.9, 30.4, 68.6, 79.3 (q), 123.6 (q), 123.9 (q), 126.6, 126.8, 127.4 (q), 128.2, 128.4, 129.0, 129.2, 133.8 (q), 135.6, 142.8 (q), 143.4, 143.5 (q), 164.6 (C=N).

ν_{max} (neat)/cm^{-1} 3243, 1668, 1592, 1553, 1494, 1445, 1405, 1371, 1250, 1190, 1066, 1012, 963, 856, 750, 699, 654, 627.

HRMS (*m/z*-ESI^+): Found 601.9080 (M^+, $C_{24}H_{19}Br_3N_3O$ requires 601.9073).

5.3.4.4 (*S*)-2-(2,6-Dibromo-4-trifluoromethyl-phenyl)-5-(hydroxy-diphenyl-methyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (412c)



Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (0.99 g, 2.9 mmol, 1.00 equiv.), Meerwein salt (0.43 g, 2.9 mmol, 1.00 equiv.), CH_2Cl_2 (25 mL), 2,6-dibromo-4-(trifluoromethyl)phenyl hydrazine (0.97 g, 2.9 mmol, 1.00 equiv.), chlorobenzene (35 mL), triethyl orthoformate (2 x 2.1 mL, 25 mmol. 8.60 equiv.), TMS-Br (1.34 mL, 10.2 mmol, 3.50 equiv.) and MeOH (90 mL). Purified twice *via* flash chromatography using 1) 100 % EtOAc to EtOAc:MeOH (9:1) and 2) EtOAc:MeOH (9:1). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a light tan crystalline solid in 577 mg (29 %) yield. M.p. 187 ^oC. R_f = 0.38 (9:1, EtOAc:MeOH). $[\alpha]_D^{20}$ = -189.3 (*c* 1.40 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, DMSO-d_6): 2.70 (t, *J* 10.8, 1H, H-3a), 2.92-2.98 (m, 1H, H-2a), 3.12 (m, 2H, H-2b and H-3b), 6.27 (d, *J* 7.3, 1H, H-7), 6.79 (s, 1H, OH), 7.26-7.32 (m, 2H, H-6 and H-6'), 7.34 (t, *J* 7.8, 2H, H-5), 7.37 (app. t, 2H, H-5'), 7.43 (d, *J* 7.6, 2H, H-4), 7.47 (d, *J* 7.6, 2H, H-4'), 8.44 (s, 1H, H-8), 8.46 (s, 1H, H-8'), 9.37 (s, 1H, H-1).

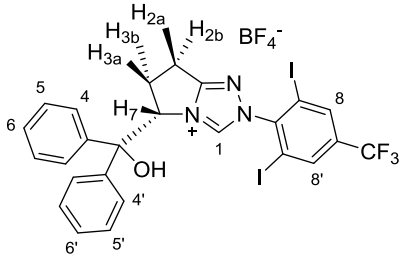
δ_C (100 MHz, DMSO-d_6): 21.9, 30.5, 63.2, 68.7, 79.4 (q), 118.1 (quart., J_{CF} 272.8, q, -CF_3), 124.1 (q), 124.3 (q), 126.6, 126.8, 128.2, 128.4, 129.0, 129.2, 130.5 (quart., J_{CF} 3.9), 134.2 (quart., J_{CF} 33.6, q), 137.8 (d, J_{CF} 1.2, q), 142.8 (q), 143.4, 143.5 (q), 164.8 (C=N).

δ_F (376 MHz, DMSO-d_6): -61.52.

ν_{max} (neat)/cm^{-1} 3215, 3060, 2972, 1668, 1593, 1493, 1449, 1389, 1307, 1136, 1100, 962, 881, 751, 700, 656, 623.

HRMS (*m/z*-ESI^+): Found 591.9859 (M^+, $C_{25}H_{19}Br_2F_3N_3O$ requires 591.9841).

5.3.4.5 (*S*)-2-(2,6-Diiodo-4-trifluoromethyl-phenyl)-5-(hydroxy-diphenyl-methyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (412d)



Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (1.11 g, 3.3 mmol, 1.00 equiv.), Meerwein salt (0.48 g, 3.3 mmol, 1.00 equiv.), CH_2Cl_2 (30 mL), 2,6-diiodo-4-(trifluoromethyl)phenyl hydrazine (1.4 g, 3.3 mmol, 1.00 equiv.), chlorobenzene (40 mL), triethyl orthoformate (2 x 2.33 mL, 28

mmol, 8.60 equiv.), TMS-Br (1.51 mL, 11.5 mmol, 3.50 equiv.) and MeOH (100 mL). Purified twice *via* flash chromatography using 1) 100 % EtOAc to EtOAc:MeOH (9:1) and 2) EtOAc:MeOH (9:1). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a light tan crystalline solid (948 mg, 37 %). M.p. 196 ^oC. R_f = 0.47 (9:1, EtOAc:MeOH). $[\alpha]_D^{20}$ = -162.0 (*c* 1.40 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, DMSO-d_6): 2.71 (t, *J* 10.8, 1H, H-3a), 2.97-3.01 (m, 1H, H-2a), 3.03-3.14 (m, 1H, H-3b), 3.23 (obscured, 1H, H-2b), 6.37 (d, *J* 8.1, 1H, H-7), 6.75 (s, 1H, OH), 7.27-7.32 (m, 2H, H-6 and H-6'), 7.34 (app. t, 2H, H-5), 7.38 (app. t, 2H, H-5'), 7.46 (d, *J* 7.7, 2H, H-4), 7.51 (d, *J* 7.7, 2H, H-4'), 8.41 (s, 1H, H-8), 8.44 (s, 1H, H-8'), 9.38 (s, 1H, H-1).

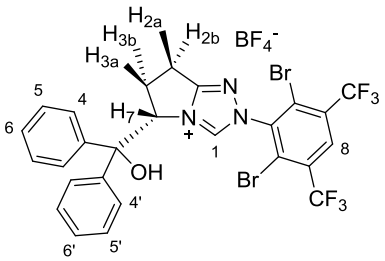
δ_C (100 MHz, DMSO-d_6): 21.8, 30.6, 68.6, 79.4 (q), 100.3 (q), 101.2 (q), 121.8 (quart., J_{CF} 271.4, -CF_3), 126.7, 126.9, 128.1, 128.3, 129.1, 129.2, 134.1 (quart., J_{CF} 32.7, q), 136.4 (quart., J_{CF} 7.7), 142.1 (q), 143.3, 144.8 (q), 144.1 (q), 164.5 (C=N).

δ_F (376 MHz, DMSO-d_6): -61.92, -62.05.

ν_{max} (neat)/cm^{-1} 3255, 3057, 2974, 1587, 1497, 1448, 1383, 1306, 1133, 1077, 963, 884, 757, 700, 653, 629.

HRMS (*m/z*-ESI$^+$): Found 687.9565 (M^+, $C_{25}H_{19}F_3I_2N_3O$ requires 687.9564).

5.3.4.6 (*S*)-2-(2,6-Dibromo-3,5-bis-trifluoromethyl-phenyl)-5-(hydroxy-diphenyl-methyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium tetrafluoroborate (412e)



Prepared according **procedure E** using (*S*)-5-(diphenyl-trimethylsilanyloxy-methyl)-pyrrolidin-2-one (0.93 g, 2.7 mmol, 1.00 equiv.), Meerwein salt (0.40 g, 2.7 mmol, 1.00 equiv.), CH_2Cl_2 (25 mL), 2,6-dibromo-3,5-*bis*(trifluoromethyl)phenyl hydrazine (1.1 g, 2.7 mmol, 1.00 equiv.), chlorobenzene (40 mL), triethyl orthoformate (2 x 1.93 mL, 23 mmol, 8.60 equiv.), TMS-Br (1.25 mL, 9.5 mmol, 3.50 equiv.) and MeOH (100 mL). Purified *via* flash chromatography using a solvent gradient of 100 % EtOAc to EtOAc:MeOH (97:3). Concentration *in vacuo* yielded a tan residue that was redissolved in CH_2Cl_2 and re-concentrated to produce a light tan crystalline solid (568 mg, 28 %). M.p. 147 ^oC. R_f = 0.35 (9:1, EtOAc:MeOH). $[\alpha]_D^{20}$ = -193.8 (*c* 1.40 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, DMSO-d_6): 2.74 (app. t, 1H, H-3a), 2.97-3.20 (m, 3H, H-2a, H-2b and H-3b), 6.32 (d, *J* 7.6, 1H, H-7), 6.79 (s, 1H, OH), 7.28-7.38 (m, 4H, H-5, H-6 and H-6'), 7.39 (app. t, 2H, H-5'), 7.46 (d, *J* 7.9, 2H, H-4), 7.49 (d, *J* 7.9, H-4'), 8.37 (s, 1H, H-8), 9.24 (s, 1H, H-1).

δ_C (100 MHz, DMSO-d_6): 22.1, 30.5, 63.2, 68.9, 79.5 (q), 122.0 (quart., J_{CF} 272.9, -CF_3), 126.6, 126.8, 127.1 (q), 127.6 (q), 128.2, 128.4, 128.8 (quart., J_{CF} 30.7, q) 129.1, 129.2, 129.9 (quart., J_{CF} 30.7, q), 138.9 (q), 143.3 (q), 143.3, 143.7 (q), 165.1 (C=N).

δ_F (376 MHz, DMSO-d_6): -61.91, -62.04.

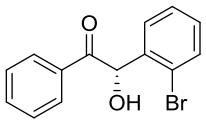
ν_{max} (neat)/cm^{-1} 3283, 2936, 1596, 1333, 1282, 1260, 1190, 1145, 1040, 701.

HRMS (*m/z*-ESI$^+$): Found 659.9717 (M^+, $C_{25}H_{19}F_3I_2N_3O$ requires 659.9721).

5.3.5 Procedure F: General procedure for the asymmetric NHC-catalysed crossed aromatic-aromatic benzoin condensation between two non-identical aromatic aldehydes

A flame-dried 5 mL round-bottom flask containing a magnetic stirring bar was charged with the relevant chiral triazolium ion precatalyst (0.066 mmol, 6 mol%), flushed with argon gas and sealed under an inert atmosphere using a rubber septum and an argon-filled balloon. Toluene and THF (7.5:1, 1.1 M) and DIPEA (11.5 μL, 0.066 mmol, 6 mol%) were added *via* syringe and the suspension stirred for 5 minutes. The relevant *ortho*-substituted aromatic benzaldehyde was then added *via* syringe, followed by the relevant aldehyde coupling partner (1.1 mmol, 1.00 equiv.). The septum was replaced with a glass stopper under a gentle flow of argon and the vessel sealed to the external atmosphere using parafilm. The reaction was stirred at room temperature for 20 hours before quenching with H_2O (5 mL) and extracting with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified *via* flash chromatography.

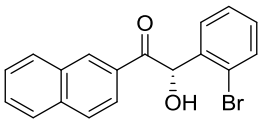
5.3.5.1 (*S*)-2-(2-Bromophenyl)-2-hydroxy-1-phenylethan-1-one ((*S*)-305d)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (202 mg, 63%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{27}$ = + 2.31^o (*c* 0.3, $CHCl_3$) for 75% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 12.9 min (major enantiomer) and 30.1 min (minor enantiomer).

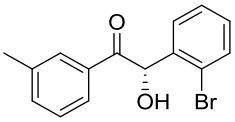
5.3.5.2 (*S*)-2-(2-Bromophenyl)-2-hydroxy-1-(naphthalen-2-yl)ethan-1-one ((*S*)-331)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 2-naphthaldehyde (172 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (233 mg, 62%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 1.49° (*c* 0.15, $CHCl_3$) for 84% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 85/15, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 17.5 min (major enantiomer) and 46.2 min (minor enantiomer).

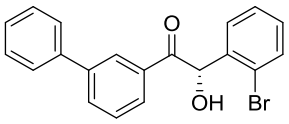
5.3.5.3 (*S*)-2-(2-Bromophenyl)-2-hydroxy-1-(3-tolyl)ethan-1-one ((*S*)-332)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-tolualdehyde (130 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (222 mg, 66%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 2.60° (*c* 0.79, $CHCl_3$) for 83% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 13.0 min (major enantiomer) and 30.0 min (minor enantiomer).

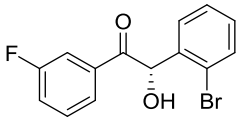
5.3.5.4 (*S*)-1-([1,1'-Biphenyl]-3-yl)-2-(2-bromophenyl)-2-hydroxyethan-1-one ((*S*)-334)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and biphenyl-3-carbaldehyde (179 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (230 mg, 57%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 2.09° (*c* 0.3, $CHCl_3$) for 77% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 20.4 min (major enantiomer) and 58.3 min (minor enantiomer).

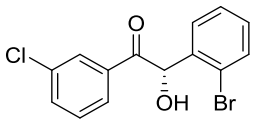
5.3.5.5 2-(2-Bromophenyl)-1-(3-fluorophenyl)-2-hydroxyethan-1-one ((*S*)-335)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-fluorobenzaldehyde (117 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a yellow oil (160 mg, 47%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 1.63° (*c* 0.29, $CHCl_3$) for 66% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 14.5 min (major enantiomer) and 44.9 min (minor enantiomer).

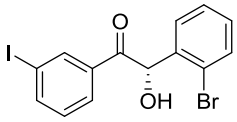
5.3.5.6 2-(2-Bromophenyl)-1-(3-chlorophenyl)-2-hydroxyethan-1-one ((*S*)-336)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-chlorobenzaldehyde (124 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (172 mg, 48%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 1.00° (*c* 0.25, $CHCl_3$) for 45% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 14.9 min (major enantiomer) and 48.3 min (minor enantiomer).

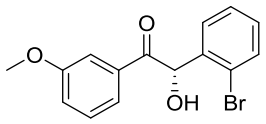
5.3.5.7 2-(2-Bromophenyl)-1-(3-iodophenyl)-2-hydroxyethan-1-one ((*S*)-337)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-iodobenzaldehyde (272 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (172 mg, 48%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 0.92° (*c* 0.35, $CHCl_3$) for 52% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 15.2 min (major enantiomer) and 50.7 min (minor enantiomer).

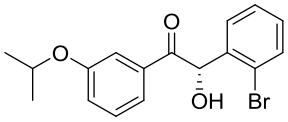
5.3.5.8 (*S*)-2-(2-Bromophenyl)-1-(3-methoxyphenyl)-2-hydroxyethan-1-one ((*S*)-340)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-anisaldehyde (134 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as white solid (170 mg, 48%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 2.31° (*c* 0.5, $CHCl_3$) for 83% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 16.8 min (major enantiomer) and 38.2 min (minor enantiomer).

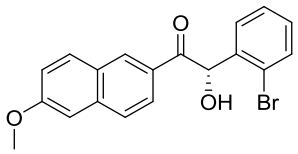
5.3.5.9 (*S*)-2-(2-Bromophenyl)-1-(3-*iso*propoxyphenyl)-2-hydroxyethan-1-one ((*S*)-341)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 3-*iso*propoxybenzaldehyde (187 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (161 mg, 42%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{29}$ = + 1.95° (*c* 0.6, $CHCl_3$) for 76% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 12.8 min (major enantiomer) and 34.8 min (minor enantiomer).

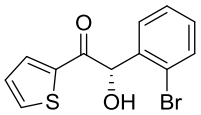
5.3.5.10 (*S*)-2-(2-Bromophenyl)-2-hydroxy-1-(6-methoxynaphthalen-2-yl)ethan-1-one ((*S*)-343)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 6-methoxynaphthaldehyde (205 mg, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (229 mg, 56%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{29}$ = + 1.19° (*c* 0.23, $CHCl_3$) for 67% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 85/15, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 22.7 min (major enantiomer) and 51.4 min (minor enantiomer).

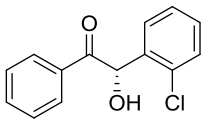
5.3.5.11 (*S*)-2-(2-Bromophenyl)-2-hydroxy-1-(thiophen-2-yl)ethan-1-one ((*S*)-344)



Prepared according to **procedure F** using **412a** (36 mg), 2-bromobenzaldehyde (160 μL, 1.38 mmol, 1.25 equiv.) and 2-thiophenecarbaldehyde (103 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a yellow solid (248 mg, 76%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{28}$ = + 2.60° (*c* 0.68, $CHCl_3$) for 71% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 16.5 min (major enantiomer) and 33.8 min (minor enantiomer).

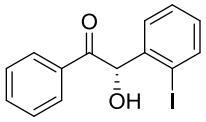
5.3.5.12 (*S*)-2-(2-Chlorophenyl)-2-hydroxy-1-phenylethan-1-one ((*S*)-147)



Prepared according to **procedure F** (in THF exclusively) using **412b** (45 mg), 2-chlorobenzaldehyde (124 μL, 1.1 mmol, 1.25 equiv.) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (76 mg, 28%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{20}$ = + 2.17 (*c* 0.3, $CHCl_3$) for 53% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 12.8 min (major enantiomer) and 22.2 min (minor enantiomer)

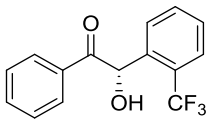
5.3.5.13 (*S*)-2-(2-Iodophenyl)-2-hydroxy-1-phenylethan-1-one ((*S*)-361)



Prepared according to **procedure F** (in THF exclusively) using **412b** (45 mg), 2-iodobenzaldehyde (272 mg, 1.1 mmol, 1.0 equiv.) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (91 mg, 27%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{20}$ = + 3.12 (*c* 0.3, $CHCl_3$) for 74% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 14.3 min (major enantiomer) and 47.4 min (minor enantiomer).

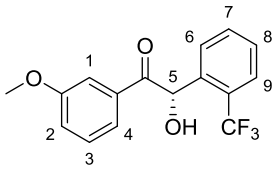
5.3.5.14 (*S*)-2-Hydroxy-1-phenyl-2-(2-(trifluoromethyl)phenyl)ethan-1-one ((*S*)-362)



Prepared according to **procedure F** using **412a** (36 mg), 2-(trifluoro)benzaldehyde (145 μL, 1.1 mmol, 1.0 equiv.) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (105 mg, 34%) following flash chromatography (9:1, hexanes:EtOAc). $[\alpha]_D^{24}$ = + 0.78° (*c* 0.15, $CHCl_3$) for 92% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 7.9 min (major enantiomer) and 13.3 min (minor enantiomer).

5.3.5.15 (*S*)-2-hydroxy-1-(3-methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)ethan-1-one ((*S*)-432)



Prepared according to **procedure F** using **412a** (36 mg), 2-(trifluoromethyl)benzaldehyde (145 μL, 1.1 mmol, 1.25 equiv.) and 3-anisaldehyde (134 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (21 mg, 6%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.18. M.p. 78 °C. $[\alpha]_D^{24}$ = + 1.75° (*c* 0.01, $CHCl_3$) for 90% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 9.2 min (major enantiomer) and 15.8 min (minor enantiomer).

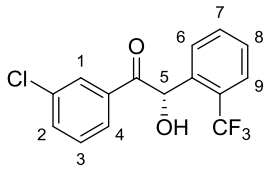
δ_H (400 MHz, $CDCl_3$): 3.74 (s, 3H, CH_3), 4.47 (d, *J* 5.4, 1H, OH), 6.21 (d, *J* 5.4, 1H, H-5), 7.03-7.06 (m, 2H, H-2 and H-6), 7.27 (obscured, 1H, H-3), 7.37-7.44 (m, 4H, H-1, H-7, H-8 and H-4), 7.75 (d, *J* 6.8, 1H, H-9).

δ_C (100 MHz, $CDCl_3$): 55.3, 71.9 (quart., J_{CF} 1.8), 120.2 (quart., J_{CF} 274.3, q, -CF_3), 121.1, 121.7 (d, J_{CF} 0.7), 126.6 (quart., J_{CF} 5.8, q), 128.8, 129.1, 129.8, 132.8 (d, J_{CF} 0.8), 134.3 (q), 137.4 (q), 159.8 (q), 198.4 (C=O).

ν_{max} (neat)/cm^{-1} 3470, 3080, 2967, 2840, 1685, 1599, 1458, 1306, 1261, 1153, 1109, 1035, 1011, 875, 804, 778, 705, 674, 608.

HRMS (*m/z*-ESI⁻): Found 308.0750 ($C_{16}H_{13}F_3O_3$ requires 309.0739).

5.3.5.16 (*S*)-1-(3-chlorophenyl)-2-hydroxy-2-(2-(trifluoromethyl)phenyl)ethan-1-one ((*S*)-435)



Prepared according to **procedure F** using **412a** (36 mg), 2-(trifluoromethyl)benzaldehyde (145 μL, 1.1 mmol, 1.25 equiv.) and 3-chlorobenzaldehyde (124 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained as a white solid (42 mg, 12%) following flash chromatography (9:1, hexanes:EtOAc), R_f = 0.24. M.p. 78-80 °C. $[\alpha]_D^{24}$ = + 0.36° (*c* 0.1, $CHCl_3$) for 80% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 9/1, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 7.5 min (major enantiomer) and 16.2 min (minor enantiomer).

δ_H (400 MHz, $CDCl_3$): 4.35 (d, *J* 5.5, 1H, OH), 6.19 (d, *J* 5.5, 1H, H-5), 7.04 (app. t, 1H, H-6), 7.27 (app. t, 1H, H-7), 7.42 (m, 3H, H-3, H-8 and H-9), 7.63 (d, *J* 7.8, 1H, H-2), 7.76 (app. t, 1H, H-4), 7.88 (s, 1H, H-1).

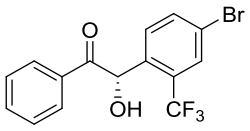
δ_C (100 MHz, $CDCl_3$): 71.9 (quart., J_{CF} 1.6), 120.1 (quart., J_{CF} 274.2, q, -CF_3), 126.8 (quart., J_{CF}, 5.8, q), 127.0 (d, J_{CF} 1.1), 129.0, 129.1,

129.1, 130.1, 132.9 (quart., J_{CF} 0.8), 134.7 (q), 135.3 (q), 136.7 (quart., J_{CF} 1.3, q), 197.6 (C=O).

ν_{max} (neat)/cm^{-1} 3481, 3073, 2964, 1684, 1572, 1427, 1396, 1309, 1259, 1144, 1110, 1034, 997, 903, 869, 766, 702, 671, 642, 604.

HRMS (*m/z*-ESI⁻): Found 313.024883 ($C_{15}H_{10}ClF_3O_2$ requires 313.024865).

5.3.5.17 (*S*)-1-(3-Chloro-phenyl)-2-hydroxy-2-(2-trifluoromethyl-phenyl)-ethanone ((*S*)-434)



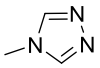
Prepared according to **procedure F** using **412a** (36 mg), 4-bromo-2-(trifluoromethyl)benzaldehyde (278 μL, 1.1 mmol, 1.00 equiv.) and benzaldehyde (112 μL, 1.1 mmol, 1.00 equiv.). The title product was obtained (41 mg, 12%) following flash chromatography (95:5, hexanes:EtOAc). $[\alpha]_D^{24}$ = - 2.42° (*c* 0.01, $CHCl_3$) for 50% *ee*.

CSP-HPLC analysis: Chiralcel OD-H (4.6 mm x 25 mm), *n*-hexane/IPA: 98/2, 1 mL min^{-1}, RT UV detection at 254 nm, retention times: 35.7 min (major enantiomer) and 38.5 min (minor enantiomer).

5.4 Experimental data for Chapter 4

5.4.1 Synthesis of triazolium precatalyst 51

5.4.1.1 1-Methyl-1*H*-1,2,4-triazole (438)

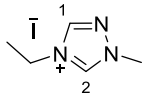


To a flame-dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged MeOH (80 mL) and sodium (3.30 g). The solution was stirred for 5 minutes before 1,2,4-triazole (10 g, 1.55 mol, 1.00 equiv.) was added and the mixture stirred at

room temperature until the solid had dissolved. The vessel was then placed under a protective atmosphere of argon and cooled to 0 ^{o}C in a H_2O/ice bath. Iodomethane (9.04 mL, 20.61 g, 1.55 mol, 1.00 equiv.) was added dropwise *via* syringe. Stirring was continued for 5 minutes at 0 ^{o}C before warming to room temperature and stirring for a further 2 hours under argon before refluxing at 60 ^{o}C for 20 h. Upon cooling, the solvent was removed *in vacuo* and H_2O (60 mL) was added. The product was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to yield the title product as a yellow liquid (4.67 g, 39%) that was dried under vacuum for several hours.

δ_H (400 MHz, $CDCl_3$):	3.80 (s, 3H, CH_3), 7.78 (s, 1H, CH), 7.93 (s, 1H, CH).
δ_C (100 MHz, $CDCl_3$):	39.8, 142.8, 151.9.
ν_{max} (neat)/cm^{-1}	3112, 2921, 2880, 1648, 1509, 1270, 1011.
HRMS (*m/z*-ESI$^+$):	Found 84.0564 ([M + H]$^+$, $C_3H_6N_3$ requires 84.0562).

5.4.1.2 4-Ethyl-1-methyl-4*H*-[1,2,4]triazol-1-ium iodide (439)



To a flame-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged 1-methyl-1*H*-1,2,4-triazole (**438**, 4.2 g, 0.051 mol, 1.00 equiv.). The vessel was placed under a protective atmosphere of argon and ethyl iodide (17.3 g, 8.9 mL, 0.11 mol, 2.17 equiv.) was added *via* syringe. The flask was covered with aluminium foil and the reaction mixture stirred for 96 h at room temperature under argon. The resulting precipitate was filtered, washed with Et_2O (3 x 20 mL) and recrystallised from 1% CH_2Cl_2/MeOH to yield the title product as a white crystalline solid (3.07g, 23%). M.p. 137-139 ^{o}C. R_f = 0.41 (4:1, CH_2Cl_2:MeOH).

δ_H (400 MHz, DMSO-d_6): 1.42 (t, *J* 7.3, 3H, CH_3), 4.03 (s, 3H, CH_3), 4.20 (q, *J* 7.3, 2H, CH_2), 9.18 (s, 1H, H-1) 10.03 (s, 1H, H-2).

δ_C (100 MHz, DMSO-d_6): 15.0, 39.0, 43.4, 143.1, 144.7.

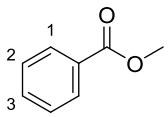
ν_{max} (neat)/cm^{-1} 3423, 3028, 1773, 1583, 1164, 990, 730, 720, 653.

HRMS (*m/z*-ESI$^+$): Found 112.0874 (M^+, $C_5H_{10}N_3$ requires 112.0875).

5.4.2 Procedure G: general procedure for the aerobic oxidation of aromatic aldehydes to their methyl ester derivatives in the presence of triazolium ion precatalyst 51

To a 25 mL vial equipped with a magnetic stirring bar was charged triazolium precatalyst **51** (36 mg, 0.15 mmol). THF (2.5 mL) and MeOH (2.5 mL) were added *via* syringe, followed by DBU (165 μL, 1.1 mmol). The solution was stirred at room temperature for 5 minutes before sealing the vial with a plastic lid perforated with 4 holes (each 1 cm apart) to allow air to access the reaction. The relevant aldehyde was then added *via* syringe and the solution stirred at room temperature for the specified length of time. Upon completion, the solvent was removed *in vacuo* and the crude product purified *via* flash column chromatography to yield the relevant ester product.

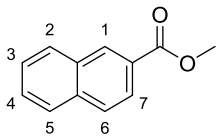
5.4.2.1 Methyl benzoate (436)



Prepared according to **procedure G** (24 h) using benzaldehyde (102 μL, 1 mmol). The title compound was obtained as a colourless oil (128 mg, 94%) following purification *via* flash chromatography (85:15, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 3.92 (s, 3H, CH_3), 7.44 (dd, *J* 7.8, 7.3, 2H, H-2), 7.56 (t, *J* 7.3, 1H, H-3), 8.04 (d, *J* 8.4, 2H, H-1).

5.4.2.2 Methyl 2-naphthoate (443)[255]

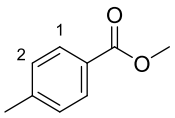


Prepared according to **procedure G** (12 h) using 2-naphthaldehyde (156 mg, 1 mmol). The title compound was obtained as a white solid (167 mg, 90%) following purification *via* flash chromatography (9:1, hexanes:Et_2O). M.p. 74-75 ^oC. (lit. 74.5-75.5 ^oC).

δ_H (400 MHz, $CDCl_3$): 3.97 (s, 3H, CH_3), 7.49-7.58 (m, 2H, H-3 and H-4), 7.85 (d, *J* 8.0, 2H, H-5 and H-6), 7.93 (d, *J* 8.0, 1H, H-2), 8.06 (d, *J* 9.7, 1H, H-7), 8.60 (s, 1H, H-1).

HRMS (*m/z*-EI): Found 186.0688 ($C_{12}H_{10}O_2$ requires 186.0681).

5.4.2.3 Methyl 4-methylbenzoate (444)[256]

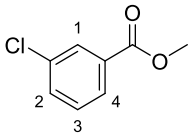


Prepared according to **procedure G** (30 h) using 4-tolualdehyde (118 μL, 1 mmol). The title compound was obtained as a white solid (138 mg, 92%) following purification *via* flash chromatography (9:1, hexanes:EtOAc). M.p. 33-35 ^oC (lit. 33-34 ^oC).

δ_H (400 MHz, $CDCl_3$): 2.38 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.24 (d, *J* 8.1, 2H, H-2), 7.92 (d, *J* 8.1, 2H, H-1).

HRMS (*m/z*-EI): Found 150.0680 ($C_9H_{10}O_2$ requires 150.0681).

5.4.2.4 Methyl 3-chlorobenzoate (446)

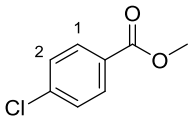


Prepared according to **procedure G** (24 h) using 3-chlorobenzaldehyde (113 μL, 1 mmol). The title compound was obtained as a colourless oil (157 mg, 92%) following purification *via* flash chromatography (85:15, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 3.90 (s, 3H, CH_3), 7.38 (app. t, 1H, H-3), 7.50 (d, *J* 8.0, 1H, H-2), 7.95 (d, *J* 7.8, 1H, H-4), 7.99 (s, 1H, H-1).

HRMS (*m/z*-EI): Found 170.0133 ($C_8H_7O_2Cl$ requires 170.0135).

5.4.2.5 Methyl 4-chlorobenzoate (447)[256]

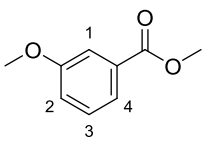


Prepared according to **procedure G** (12 h) using 4-chlorobenzaldehyde (141 mg, 1 mmol). The title compound was obtained as a white solid (123 mg, 72%) following purification *via* flash chromatography (9:1, hexanes:EtOAc). M.p. 44-45 ^oC (lit. 43 ^oC).

δ_H (400 MHz, $CDCl_3$): 3.88 (s, 3H, CH_3), 7.38 (d, *J* 8.5, 2H, H-2), 7.94 (d, *J* 8.5, 2H, H-1).

HRMS (*m/z*-EI): Found 170.0141 ($C_8H_7O_2Cl$ requires 170.0135).

5.4.2.6 Methyl 3-(methoxy)benzoate (448)

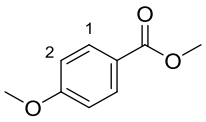


Prepared according to **procedure F** (68 h, 45 ^{o}C in 10 mL round-bottomed flask) using 3-anisaldehyde (122 μL, 1 mmol). The title compound was obtained as a pale yellow oil (128 mg, 77%) following purification *via* flash chromatography (3:1, hexanes:CH_2Cl_2).

δ_H (400 MHz, $CDCl_3$): 3.82 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.07 (d, *J* 10.8, 1H, H-2), 7.32 (app. t, 1H, H-3), 7.54 (s, 1H, H-1), 7.61 (d, *J* 7.7, 1H, H-4).

HRMS (*m/z*-ESI$^-$): Found 165.0552 ($C_9H_9O_3$ requires 165.0552).

5.4.2.7 Methyl 4-(methoxy)benzoate (445)[257]

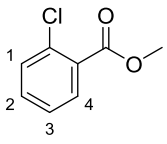


Prepared according to **procedure F** (92 h) using 4-anisaldehyde (122 μL, 1 mmol). The title compound was obtained as a white solid (150 mg, 90%) following purification *via* flash chromatography (9:1, hexanes:EtOAc). M.p. 52-53 ^{o}C (lit. 48-49 ^{o}C).

δ_H (400 MHz, $CDCl_3$): 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.90 (d, *J* 8.9, 2H, H-2), 7.98 (d, *J* 8.9, 2H, H-1).

HRMS (*m/z*-EI): Found 166.0635 ($C_9H_{10}O_3$ requires 166.0630).

5.4.2.8 Methyl 2-chlorobenzoate (450)

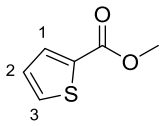


Prepared according to **procedure F** (24 h) using 2-chlorobenzaldehyde (113 μL, 1.0 mmol). The title compound was obtained as a pale yellow oil (90 mg, 53%) following purification *via* flash chromatography (3:1, hexanes:CH_2Cl_2).

δ_H (400 MHz, $CDCl_3$): 3.91 (s, 3H, CH_3), 7.30 (app. t, 1H, H-3), 7.37-7.44 (m, 2H, H-1 and H-2), 7.81 (d, *J* 7.76, 1H, H-4).

HRMS (*m/z*-EI): Found 170.0135 ($C_8H_7O_2Cl$ requires 170.0135).

5.4.2.9 Methyl 2-thiophene 2-carboxylate (452)

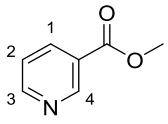


Prepared according to **procedure F** (18 h) using thiophene-2-carbaldehyde (94 μL, 1 mmol). The title compound was obtained as a pale yellow oil (92 mg, 65%) following purification *via* flash chromatography (4:1, hexanes:EtOAc).

δ_H (400 MHz, $CDCl_3$): 3.87 (s, 3H, CH_3), 7.07 (t, *J* 4.1, 1H, H-2), 7.52 (d, *J* 4.9, 1H, H-3), 7.77 (d, *J* 3.8, 1H, H-1).

HRMS (*m/z*-EI): Found 142.0090 ($C_6H_6O_2S$ requires 142.0089).

5.4.2.10 Methyl 3-nicotinate (453)[258]



Prepared according to **procedure F** (20 min) using 3-pyridinecarboxaldehyde (94 μL, 1 mmol). The title compound was obtained as a white solid (126 mg, 93%) following purification *via* flash chromatography (7:3, hexanes:EtOAc). M.p. 41-43 ^oC (lit. 38-39 ^oC).

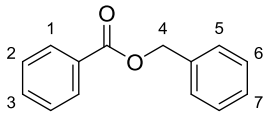
δ_H (400 MHz, $CDCl_3$): 3.92 (s, 3H, CH_3), 7.38 (app. t, 1H, H-2), 8.27 (d, *J* 7.9, 1H, H-3), 8.74 (s, 1H, H-1), 9.19 (s, 1H, H-4).

HRMS (*m/z*-ESI^+): Found 138.0553 ($[M + H]^+$, $C_7H_8NO_2$ requires 138.0555).

5.4.3 Procedure H: General procedure for the aerobic oxidation of benzaldehyde to various ester derivatives in the presence of triazolium ion precatalyst 51

To a 25 mL vial equipped with a magnetic stirring bar was charged triazolium precatalyst **51** (36 mg, 0.15 mmol, 15 mol%). THF (2.5 mL) and the relevant alcohol were added *via* syringe, followed by DBU (165 μL, 1.1 mmol, 1.10 equiv.). The solution was stirred at room temperature for 5 minutes before sealing the vial with a plastic lid perforated with 4 holes (each 1 cm apart) to allow air to access the reaction. Benzaldehyde (102 μL, 1.0 mmol, 1.00 equiv.) was then added *via* syringe and the solution stirred at room temperature for the specified length of time. Upon completion, the solvent was removed *in vacuo* and the crude product purified *via* flash column chromatography to yield the relevant ester product.

5.4.3.1 Benzyl benzoate (455)

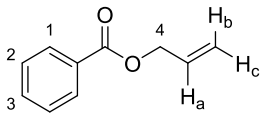


Prepared according to **procedure H** (24 h, 45^{o}C in a 10 mL round-bottomed flask) using benzyl alcohol (2.5 mL). The title compound was obtained as a pale yellow oil (200 mg, 94 %) following purification *via* flash chromatography (9:1, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 5.35 (app. d, 2H, H-4), 7.34-7.47 (m, 7H, H-2, H-5, H-6 and H-7), 7.55 (app. t, 1H, H-3), 8.10 (d, *J* 7.0 , 2H, H-1).

HRMS (*m/z*-EI): Found 212.0845 ($C_{14}H_{12}O_2$ requires 212.0837).

5.4.3.2 Allyl benzoate (456)

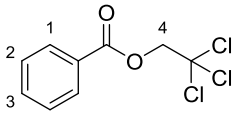


Prepared according to **procedure H** (24 h, 45 ^{o}C in a 10 mL round-bottomed flask) using allyl alcohol (2.5 mL). The title compound was obtained as a pale yellow oil (141 mg, 87 %) following purification *via* flash chromatography (9:1, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 4.81 (d, *J* 5.6, 2H, H-4), 5.27 (d, *J* 10.4, 1H, H_b), 5.41 (d, *J* 17.2, 1H, H_c), 5.98-6.07 (m, 1H, H_a), 7.43 (t, *J* 7.5, 2H, H-2), 7.55 (t, *J* 7.5, 1H, H-3), 8.05 (d, *J* 7.5, 2H, H-1).

HRMS (*m/z*-EI): Found 162.0680 ($C_{10}H_{10}O_2$ requires 162.0681).

5.4.3.3 2,2,2-Trichloroethyl benzoate (457)

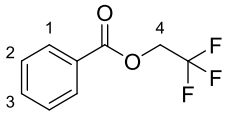


Prepared according to **procedure H** using 2,2,2-trichloroethanol (115 μL, 1.2 mmol, 1.2 equiv). The title compound was obtained as a pale yellow oil (147 mg, 58 %) following purification *via* flash chromatography (9:1, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 4.95 (s, 2H, H-4), 7.48 (t, *J* 7.8, 2H, H-2), 7.59 (t, *J* 7.8, 1H, H-3), 8.11 (d, *J* 8.1 Hz, 2H, H-1).

HRMS (*m/z*-EI): Found 251.9520 ($C_9H_7O_2Cl_3$ requires 251.9512).

5.4.3.4 2,2,2-Trifluoroethyl benzoate (458)



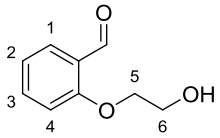
Prepared according to **procedure H** (24 h) using 2,2,2-trifluoroethanol (90 μL, 1.2 mmol, 1.2 equiv). The title compound was obtained as a pale yellow oil (110 mg, 54 %) following purification *via* flash chromatography (9:1, hexanes:Et_2O).

δ_H (400 MHz, $CDCl_3$): 4.71 (q, *J* 8.4, 2H, H-4), 7.47 (t, *J* 7.7, 2H), 7.61 (t, *J* 7.7, 1H, H-3), 8.06 (d, *J* 7.7, 2H, H-1).

δ_F (375 MHz, $CDCl_3$): -73.71 (d, *J* 8.4).

HRMS (*m/z*-EI): Found 204.0397 ($C_9H_7F_3O_2$ requires 204.0398).

5.4.4 Synthesis of 2-(2-Hydroxyethoxy)benzaldehyde (476)[266]

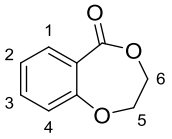


To a 1 M aqueous solution of NaOH (0.4 g, 10 mmol, 1.00 equiv.) in a 50 mL round-bottom flask equipped with a magnetic stirring bar was added salicylaldehyde (1.06 mL, 10 mmol, 1.00 equiv.) *via* syringe in a dropwise manner. 2-chloroethanol (0.68 mL, 10 mmol, 1.00 equiv.) was then also added dropwise *via* syringe and the reaction heated at 100 ^oC for 16 hours. The vessel was then cooled to 0 ^oC and basified with 2 M $NaOH_{(aq)}$ to pH 10. The product was extracted with CH_2Cl_2 (2 x 30 mL) before drying over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a dark brown residue. The crude product was purified *via* flash column chromatography using a hexanes:EtOAc solvent gradient (4:1 → 1:1) to yield the title product as a low-melting pale yellow solid (1.26 g, 76%). M.p. 38 ^oC (lit. 37 ^oC).

δ_H (400 MHz, $CDCl_3$): 2.99 (br. s, 1H, OH), 4.02 (t, *J* 4.5, 2H, H-6), 4.20 (t, *J* 4.5, 2H, H-5), 6.94-7.08 (m, 2H, H-2 and H-4),

7.47-7.57 (m, 1H, H-3), 7.79 (dd, *J* 7.7, 1.7, 1H, H-1), 10.42 (d, *J* 0.6, 1H, CHO).

5.4.5 Synthesis of 2*H*-Benzo[*e*][1,4]dioxepin-5(3*H*)-one (478)[267] *via* oxidative lactonisation in the presence of triazolium precatalyst 51



To a 25 mL vial equipped with a magnetic stirring bar was charged triazolium precatalyst **51** (36 mg, 0.15 mmol, 15 mol%). THF (2.5 mL) and *i*-PrOH (2.5 mL) were added *via* syringe, followed by DBU (165 μL, 1.1 mmol, 1.10 equiv.). The solution was stirred at room temperature for 5 minutes before 2-(2-hydroxyethoxy)benzaldehyde (**476**, 166 mg, 1 mmol, 1.00 equiv.) was added and the vial sealed with a plastic lid perforated with 4 holes (each 1 cm apart) to allow air to access the reaction. The reaction was stirred for 66 hours before the solvent was removed *in vacuo* and the crude product purified *via* flash column chromatography (4:1, hexanes:EtOAc) to yield the title product as a pale yellow oil (62 mg, 36%).

δ_H (400 MHz, $CDCl_3$): 4.46-4.48 (m, 2H, H-5), 4.51-4.53 (m, 2H, H-6), 7.00 (d, *J* 8.2, 1H, H-4), 7.10-7.14 (m, 1H, H-2), 7.48-7.52 (m, 1H, H-3), 7.88 (dd, *J* 8.0, 1.6, 1H, H-1).

HRMS (*m/z*-EI): Found 164.0475 ($C_9H_8O_3$ requires 164.0473).

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