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N-Heterocyclic Carbene-Mediated Reactions; Controlling the Fate of the Breslow Intermediate

Trinity College Dublin

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

Doctor of Philosophy

by

Claire-Louise Fagan

Under the supervision of

Prof. Stephen Connon

May 2015

Declaration

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Abstract

We have developed a highly efficient, broad scope, additive-free mild protocol for the oxidative carbene-catalysed esterification of aldehydes. We have unambiguously identified benzoin as the oxidised species in these aerobic NHC-catalysed aldehyde esterifications proving that these reactions are mechanistically distinct from previously reported, similar esterifications. We also reported the first carbene-catalysed aerobic oxidative cleavage of cyclic 1,2-diketones and consequently exploited this novel organocatalytic process using similar reaction conditions to allow for the one-pot synthesis of an anhydride.

We designed and carried out synthetic routes in order to obtain novel monofunctional and bifunctional triazolium salts of a chiral nature. We successfully synthesised two novel monofunctional enantiopure triazoloium salts incorporating a) an azide and b) a triazole ring. We also explored the synthesis of a novel electron-poor aliphatic-substituted achiral triazolium salt. A highly chemoselective process was observed when this novel triazolium ion-based precatalyst was employed in the coupling of an aromatic aldehyde and an aliphatic aldehyde, allowing access to a wide range of asymmetric α-hydroxyketones in unprecedented yields.

It has been shown for the first time that the use of various 2-pyridinecarboxaldehydes in the NHC-mediated crossed acyloin condensation can also lead to a highly chemoselective process. We have studied the carbon-carbon bond forming and complimentary bond breaking reactions in the presence of these aldehydes to determine the origins for the observed chemoselectivity. Having developed a process rendering such high chemoselectivity has allowed us to synthesise an alkaloid from the plant, *Lobelia inflata*, medically, the most important of the *Lobelia* family, in a high yield in just three steps.

We have also shown for the first time that relatively electron deficient triazolium ion-based precatalysts promote highly chemoselective crossed acyloin condensation reactions between aldehydes and α-ketoesters to afford densely functionalised products incorporating a quaternary stereocentre of considerable synthetic potential.

To the best of our knowledge, we are now the first research group to gain complete control over chemoselectivity within the crossed acyloin condensation, as we have devised several

distinct protocols that allow for the formation of both crossed acyloin products in extremely high yields.

Abbreviations

AcOH	Acetic acid
Aliph	Aliphatic
Ar	Aryl
Atm	Atmosphere
BAL	Benzaldehyde lyase
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
cat.	Catalyst
CSP	Chiral stationary phase
DBU	1,8-Diazabicyclo[5.4.0]undec-7ene
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMSO	Dimethyl sulphoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
HPLC	High Performance Liquid Chromatography
^{i}Pr	*iso*propyl

^{i}PrOH	2-propanol
IR	Infra red
K_2CO_3	Potassium carbonate
KHMDS	Potassium bis(trimethylsilyl)amide
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
NEt_3	Triethylamine
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
Ph	Phenyl
Precat.	Precatalyst
rt	Room temperature
^{t}Bu	*tert*-Butyl
^{t}BuOK	Potassium *tert*-butoxide
TBDPSO	*tert*-Butyldiphenylsiloxy
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
Temp.	Temperature
TES	Triethylsilyl ether
ThDP	Thiamine diphosphate
THF	Tetrahydrofuran
TMS	Trimethylsilyl

Ts	Tosyl
m/z	Mass/Charge
v/v	Volume/Volume

1. Introduction

1.1 Carbenes

1.1.1 Definition and historical perspective

Carbenes are members of a class of highly reactive molecules and are defined as a neutral organic species consisting of a carbon atom with only six electrons in its valence shell. The first assumption of a carbene was made in 1835 by Dumas *et al.*,[1] who postulated that an intermediate species was formed *via* the dehydration of methanol in the presence of phosphorous pentoxide to produce the carbene $:CH_2$, otherwise referred to as methylene. In 1862, Guether[2] proposed that the species dichlorocarbene ($:CCl_2$) was an intermediate formed *in situ* during the base-mediated hydrolysis of chloroform. A second period of carbene research was carried out in the early 1900s, primarily by Curtius,[3] Buchner[4] and Staudinger *et al.*[5] in which they demonstrated the unambiguous existence of the intermediate species. Carbenes evolved from being considered mere chemical curiosities to becoming recognised as important reactive intermediates. Successful studies carried out by Doering *et al.*,[6] in 1954, and Fischer,[7] in 1965, on the use of these intermediates in chemical reactions established carbenes as being of extremely high synthetic value.

1.1.2 A comparison of singlet and triplet carbenes

Carbenes may exist in two different ground states; a singlet state and a triplet state.[8] This duality arises from the two possible electronic spin states that a carbene may possess. Given that a carbene has six valence electrons, and the two bonds of the carbene utilises four of these, there remains two non-bonding electrons to be distributed throughout the orbitals. These two non-bonding electrons may exist in either two different orbitals with parallel spins (unpaired) or in the same orbital with opposite spins (paired) as shown in Figure 1.1 .

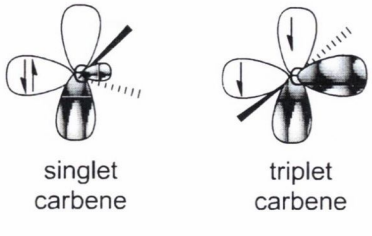


Figure 1.1 Singlet and triplet carbenes

Triplet carbenes are those in which the non-bonding electrons are unpaired. The triplet carbene is sp-hybridised, due to the two half-filled degenerate p-orbitals, causing the species to adopt a linear geometry. However, singlet carbenes possess paired electrons and are sp^2-hybridised causing the singlet carbene to exist in a trigonal shape.[9] Singlet and triplet carbenes exhibit very different reactivity. As triplet carbenes possess two singly occupied orbitals, they are generally regarded as exhibiting radical-like reactivity, whereas, singlet carbenes exhibit an ambiphilic character due to their σ-type lone pair and vacant p-orbital.[10]

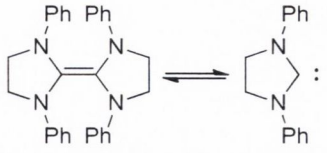
The electronic state that the carbene possesses is determined by the electronic and steric properties of the substituents that are bonded to the divalent carbon.[11] Steric effects largely dictate the formation of a triplet carbene. Increasing the steric bulk of the substituents attached to the carbon centre leads to the broadening of the bond angles, thus, forcing the carbene to adopt a linear geometry.[12,13] In contrast, electronic factors play an important role in the formation of the singlet carbene. The carbene exists in a singlet state if it is bonded to σ-withdrawing substituents due to the stabilisation of the filled non-bonding orbital which increases its s-character. In 1960, Pauling[14] reported that a combination of inductive and mesomeric effects, induced by the two substituents, plays an important role in the stabilisation of the singlet carbene. The use of either two π-donor σ-attractor substituents, resulting in a 'pull, pull' mesomeric and 'push, push' inductive substitution pattern or the use of two π-donor σ-attractor substituents, resulting in a 'push, push' mesomeric and 'pull, pull' inductive substitution pattern are two ways a stable singlet carbene can be stabilised. The best example where the latter situation occurs is observed in *N*-heterocyclic carbenes. The excellent stability of these carbenes can be accounted for by two synergistic factors: the donation of the adjacent nitrogen lone pair into the empty p-orbital of the carbon and the inductive effect of the electronegative nitrogen atoms.

1.2 N-Heterocyclic carbenes

1.2.1 Discovery and structure of NHCs

In 1960, Wanzlick *et al.*[15] were the first to intensively investigate NHC-mediated transformations. They proposed that these carbenes are influenced both by steric and, particularly, electronic factors, such as π-donation into the carbene p-orbital. At the time of these investigations it was not yet proven that stable NHCs could be isolated. The studies

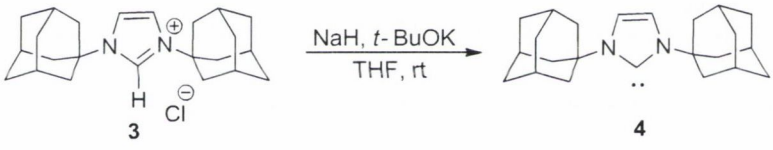
carried out by Wanzlick[16] involved the use of electron rich olefins such as the imidazolidin-2-ylidene (**1**), which exists in equilibrium with the carbene species **2** (Scheme 1.1).



1 **2**

Scheme 1.1 Equilibrium leading to the dimeric carbene **2** as reported by Wanzlick[16]

In 1991 Arduengo *et al.*[17] published a landmark study on the isolation of NHCs with exceptional stability. The first NHC obtained and characterised by Arduengo and his research group resulted from the deprotonation of the hindered imidazolium salt **3** to produce the NHC **4** (Scheme 1.2), which was isolated as colourless crystals. The analysis of the crystal structure of **4** revealed that this NHC possesses structural features similar to those of a singlet carbene. The stability of **4** was accredited to a combination of steric and electronic factors such as the π-donor ability of the amino group and the steric bulk afforded by the two adamantyl substituents.



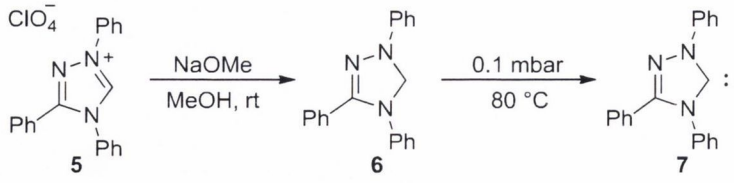
3 **4**

Scheme 1.2 Preparation of the first stable carbene **4** as described by Arduengo *et al.*[17]

Arduengo *et al.*[18] and, subsequently, Kuhn *et al.*[19] synthesised a series of both aryl and alkyl imidazole-carbenes. The successful synthesis of alkyl carbenes lacking steric hindrance proved the feasibility of attaching small substituents to the dimeric carbene. In 1943, Ugai *et al.* [20] proved that NHCs bearing heteroatoms other than nitrogen were also accessible when he prepared NHCs containing sulphur. These combined studies paved the way for a wide range of NHCs to be synthesised and studied.

Inspired by the successful synthesis of imidazole-based carbenes, Enders and Teles[21] studied the triazole heterocycle as an alternative structural framework. In 1995 they reported the first isolation of triazole-based carbene **7** which was synthesised from triazolium salt **5** as the starting material. The addition of a stoichiometric amount of sodium methoxide to **5** followed by thermal α-elimination of methanol *in vacuo* from **6** generated carbene **7** as shown in

Scheme 1.3. Carbene **7** was shown to possess the same properties as those of a singlet carbene and was the first NHC to become commercially available.



Scheme 1.3 Synthesis of the stable triazole-carbene **7** as reported by Enders and Teles[21]

1.2.2 Versatility of NHCs in contemporary chemistry

NHCs have found a range of applications in some of the most important catalytic transformations in all areas of chemistry.[22] Additionally, the inexpensive synthesis of azolium salts has led to the prominence of NHCs in the chemical industry.[23–25] Due to their unique properties, NHCs have a strong coordination ability allowing them to form adducts with transition metals and p-block elements. Furthermore, NHCs are capable of coordinating to carbon-based electrophiles, rendering them as excellent organocatalysts.

One of the most important applications of NHCs is their use as ancillary ligands in homogeneous transition-metal catalysis.[26] Currently NHCs compete with both phosphine- and cyclopentadiene-based species as the ligands of choice across organometallic chemistry.[27] Since 1995, when Hermann *et al.*[28] reported the NHC-mediated Mizoroki-Heck reaction, NHCs have been involved in a myriad of important processes including iridium- and ruthenium-mediated hydrogenations,[29–31] rhodium-catalysed hydrosilylations,[32,33] gold-catalysed activation of π-bonds[34] and palladium catalysed cross-couplings.[35] However, one of the most significant transformations involving the use of NHCs and transition metals is accredited to Shrock[36] and Grubbs and coworkers[37] for the ruthenium-catalysed olefin metathesis for which they were awarded the Nobel Prize in Chemistry in 2005.

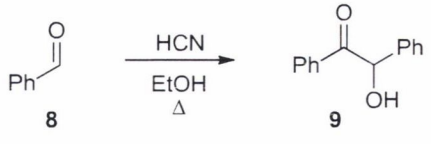
NHCs can also act as ligands and coordinate with p-block elements to render adducts that exhibit interesting properties and reactivity which are different from those typical of the two species when they are not interacting in a complex.[38] It has been proven, for example, that the coordinative interactions between NHCs and bulky, electrophilic boranes form complexes capable of splitting hydrogen and other small molecules.[39] Another interesting aspect of NHC coordinative chemistry with p-block elements is the stabilisation of non-metals in their zero oxidation state. Robinson and coworkers[40] recently reported the use of bulky NHCs in the

presence of phosphorus to obtain the novel diatomic species, P_2, which was found to be similar in structure to N_2. The same author also disclosed the first complex to feature silicon in its ground oxidative state.[41] Hence, the study of NHCs in combination with p-block elements has allowed previously inaccessible species to be isolated.

NHCs have recently been employed as organocatalysts for a variety of chemical transformations in both molecular chemistry and polymerisation reactions. Their ability to promote a chemical process arises from the affinity of the carbene towards a carbonyl group.[42] NHCs have recently been employed in the presence of cyclic esters to promote ring-opening polymerisations.[43] They have also been shown to promote chain-growth polymerisation processes in the presence of ethylene and propylene oxides.[44] However, the most diverse array of NHC-mediated processes arises from the nucleophilic attack of carbenes on aldehydes to promote a process which results in the polarity reversal, also known as *Umpolung*, of the carbonyl group.[45] This change in polarity allows access to an unconventional yet highly useful mode of reactivity of carbonyl groups which is the basis for several important reactions such as the Stetter reaction and the benzoin condensation.[46]

1.3 The benzoin condensation

The benzoin condensation is an eminent carbon-carbon bond-forming reaction involving aldehydes, which react under nucleophilic catalysis to produce an α-hydroxyketone, also referred to as an acyloin. An example of the benzoin condensation involving benzaldehyde (**8**) is reported in Scheme 1.4.



8 **9**

Scheme 1.4 The benzoin condensation reported by Liebig and Wohler[47]

1.3.1 Cyanide-mediated catalysis of the benzoin condensation

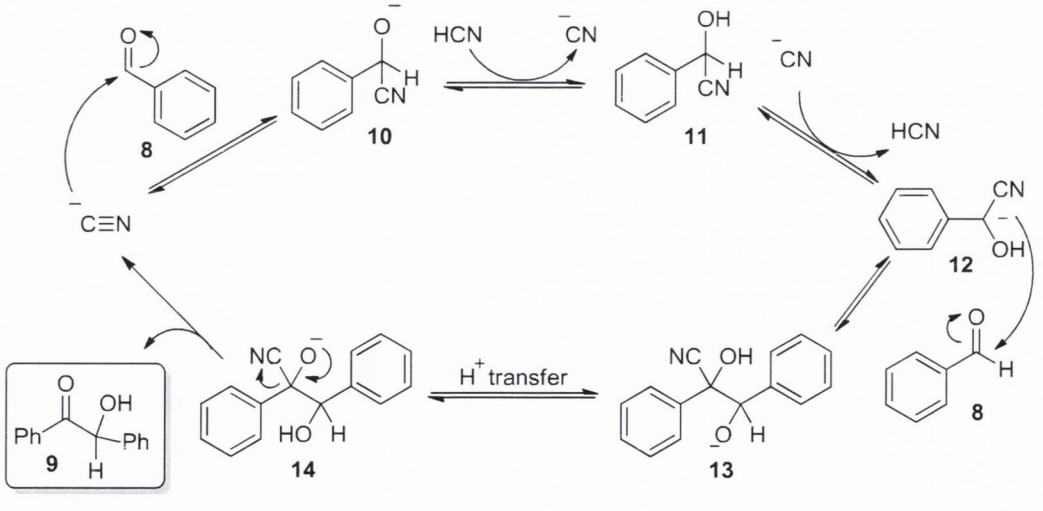
1.3.1.1 Historical perspective

It was German chemists, Liebig and Wohler in 1832, who first reported the self-condensation of benzaldehyde **8** resulting in the synthesis of benzoin **9**. This historic reaction was discovered while carrying out research studies on the generation of cyanohydrins in the

presence of the cyanide ion. Their seminal studies established that the use of aromatic aldehydes in the presence of the cyanide ion resulted in the formation of α-hydroxyketones.[47]

1.3.1.2 Mechanism

Lapworth[48] investigated the mechanism of the cyanide-mediated benzoin condensation seventy years after Liebig and Wohler's first report. By studying the reaction involving the use of benzaldehyde (**8**), he proposed that the reaction is initiated by the cyanide ion acting as a nucleophile and attacking the electrophilic carbon of the carbonyl group in **8** to form the cyanohydrin **11** *via* the tetrahedral intermediate **10**. The key step is represented by the acid-base reaction between the acidic proton present in cyanohydrin **11** and the cyanide ion (acting as a base) which results in the formation of **12** which is referred to as an acyl anion equivalent. The nucleophilic carbanion present in this intermediate species is found on the same carbon atom which originally possessed an electrophilic character in the carbonyl group of aldehyde **8**. For this reason intermediate **12** is referred to as an *Umpolung* species and has the formal character of a nucleophilic carbonyl centre. The carbanionic intermediate subsequently attacks a second benzaldehyde molecule to form the unstable oxyanion **13**. The ensuing proton transfer, followed by elimination of the cyanide ion from intermediate **14**, allows for the formation of the α-hydroxyketone **9** (also called benzoin) as the product and the regeneration of the cyanide ion (Scheme 1.5).



Scheme 1.5 Mechanism of the cyanide catalysed benzoin condensation reported by Lapworth

1.3.2 The NHC-catalysed benzoin condensation

1.3.2.1 Discovery of Thiamine (vitamin B1) as a promoter of the benzoin condensation

Thiamine (**15a)** is classified as a B-complex vitamin and, thus, is also referred to as Vitamin B_1. Thiamine is present in all living organisms and its phosphate derivatives, such as thiamine diphosphate (ThDP - **15b)**, are involved in a plethora of crucial cellular processes. ThDP in particular is a coenzyme responsible for, amongst others, the oxidative decarboxylation of pyruvic acid to acetyl-coenzyme A, the generation of acetoin from pyruvic acid and the transketolase reaction.[49] Biological studies concluded that thiamine, which bears a thiazolium salt moiety, promotes these biochemical transformations *via Umpolung* processes resulting in the generation of acyl anion equivalents which add to electrophilic carbonyl centres.[50]

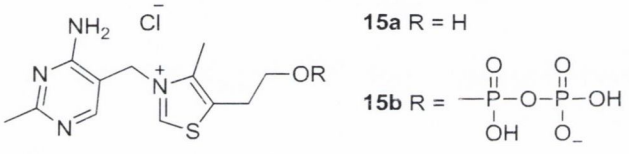
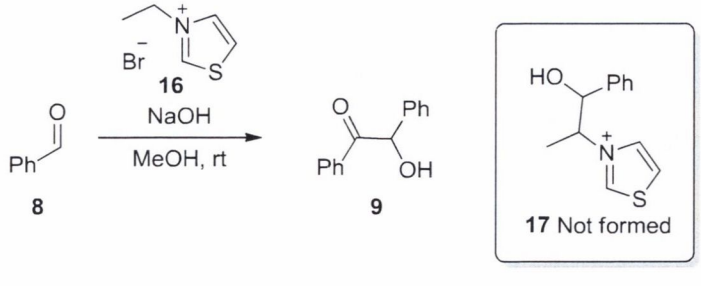


Figure 1.2 Structures of Thiamine (**15a**) and Thiamine diphosphate (ThDP – **15b**)

The concept that thiazolium salts were involved in nucleophilic catalysis encouraged the pioneering work of Ugai,[20] who in 1943, reported the earliest application of a NHC in the benzoin condensation. Based on previous studies involving the reaction of pyridinium salts with aldehydes to form hydroxy compounds,[51] Ugai predicted that thiazolium salts were capable of reacting with aldehydes. He therefore carried out studies on the reaction of benzaldehyde **8** in a basic methanolic solution of thiazolium salt **16** only to serendipitously discover that, benzoin **9** was formed rather than the anticipated product **17**.



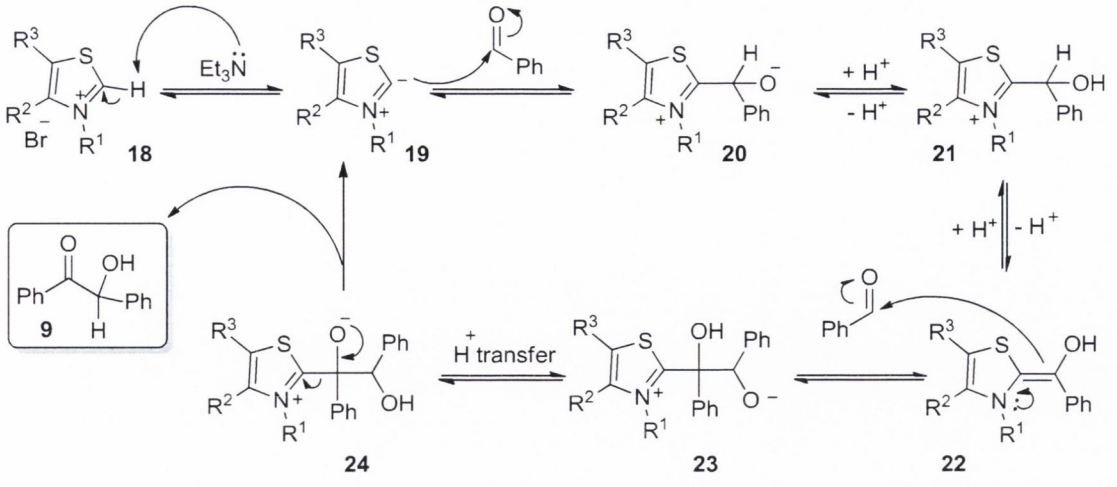
Scheme 1.6 Benzoin condensation of benzaldehyde in the presence of thiazolium salt **16** as observed by Ugai et al.

In 1953 Mizuhara *et al.*,[52] in a bid to mimic biological processes in the presence of thiazolium salts (including thiamine), reported the formation of acetoin upon the incubation of pyruvate with thiamine in an alkaline media. Furthermore, they demonstrated that thiazolium salts were capable of promoting the formation of furoin from furaldehyde in a protein-free model system. From their studies, they concluded that thiamine (**15a**) was responsible for promoting a multitude of the reactions commonly observed in biological systems and that the thiazolium moiety of thiamine is essential for its activity in enzyme biocatalysed processes.

1.3.2.2 Mechanism

Until 1958 the overall mechanism of the thiazolium salt-mediated benzoin condensation and thiamine-catalysed biological transformations remained speculative. In that year Breslow[53] contributed significantly in shedding light upon the mechanistic picture of these reactions with his investigation of the role of thiazolium salts in the benzoin condensation. He discovered that the hydrogen atom, present at the 2-position of the thiazolium salt core, underwent facile exchange with deuterium of D_2O. Upon observing this dissociation, Breslow proposed that a thiazole-carbene, generated *in situ* from the thiazolium salt in thiamine, was the active species responsible for the catalysis of the benzoin condensation.

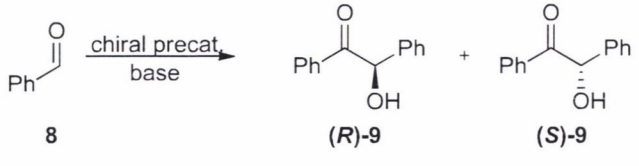
Following his discoveries, Breslow proposed a mechanistic model for the reaction under scrutiny in which a base, triethylamine (NEt_3), deprotonates the acidic hydrogen at the 2-position of the thiazolium salt **18** resulting in the formation of the ylide **19**, a highly reactive carbene species, which subsequently acts as the catalytic species promoting the entire condensation reaction as shown in Scheme 1.7. The crucial species **19** attacks the carbonyl carbon of the aldehyde (following a process which is analogous to that proposed for the cyanide-catalysed reaction, as illustrated in Scheme 1.6), to produce carbanion **20**. The protonation of the oxyanion present in **20** leads to the reversible formation of intermediate **21**. Upon the loss of the acidic proton adjacent to the phenyl group, the hydroxyl-enamine **22** is formed. This *Umpolung* species, also known as the Breslow intermediate, attacks another molecule of benzaldehyde to form intermediate **23**. The reversible proton transfer allows for the formation of intermediate **24** which, upon elimination of the thiazolium carbanion, allows for the regeneration of the catalytic species **19** and the formation of the benzoin product **9**. Through this now widely accepted mechanism, Breslow demonstrated that the thiazolium salt **18** itself acts as a precatalyst in this transformation and that the catalytic carbanionic species **19** is formed *in situ* upon deprotonation of **18**.



Scheme 1.7 Mechanism of the thiazolium catalysed benzoin reaction as described by Breslow

1.4 The NHC-catalysed asymmetric benzoin condensation

The generation of a new stereocentre in the benzoin product (Scheme 1.8), prompted the investigation into the development of an enantioselective benzoin condensation. The mechanism disclosed by Breslow, which highlighted the triazole carbene as the active catalyst, was encouraging for the use of NHCs as possible chiral catalysts to carry out this asymmetric process as they provided an ideal molecular platform for the introduction of elements of chirality. The following Sections highlight the development of NHCs derived from chiral thiazolium salts and chiral triazolium salts, which were employed as catalysts in the stereoselective benzoin condensation.

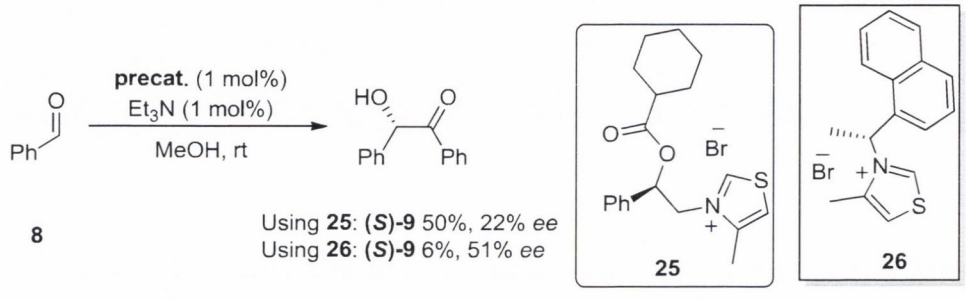


Scheme 1.8 Rationale for the use of chiral catalysts promoting the asymmetric benzoin condensation

1.4.1 Chiral thiazolium ion-based precatalysts

It was Sheehan and Hunnemann[54] who, in 1966, pioneered the introduction of elements of chirality in thiazolium salt precatalysts in order to perform an enantioselective benzoin condensation. This seminal work was carried out using the thiazolium-based precatalyst **25** (Scheme 1.9) however, disappointingly for the authors, low yields (50%) and poor

enantioselectivity (22% *ee*) were obtained. Despite the lack of efficiency in providing enantioselective induction using thiazolium salt **25** as a precatalyst, the study was conclusive in ascertaining that the enantiomeric enrichment of the product resulted from the interaction with precatalyst **25**, as it is the only species in the reaction capable of providing a stereoselective induction. Following this study, the author concluded that it was conceivable to improve the stereoselective outcome of the transformation by tuning the electronic and steric properties of chiral thiazolium species leading to NHC catalysts.



Scheme 1.9 Asymmetric benzoin condensations reported by Sheehan *et al.*[54, 55]

Sheehan *et al.*[55] later synthesised a second generation thiazolium salt **26** that was used in the enantioselective benzoin condensation. Under otherwise identical reaction conditions, precatalyst **26** proved to be more proficient in promoting the formation of the enantiomerically enriched benzoin product **(*S*)-9** when compared to **25**: product **(*S*)-9** was obtained with an enantiomeric excess of 51%. However, this improved enantioselectivity came at a cost as yields diminished considerably to 6%. Research was carried out in the following years by several groups all with the aim of developing thiazolium precatalyst analogues in order to obtain high levels of enantiomeric excess. In 1980 Tagaki[56] developed the enantiomerically pure thiazolium salt **27** bearing a menthyl group, however, this variation of Sheehan's precatalyst did not result in improved performance and in the presence of **27** product **(*S*)-9** was only generated in 35% *ee* (Figure 1.3). In 1993 López-Calahorra *et al.*[57] reported the synthesis of two chiral *bis*-thiazolium salts, **28** and **29**, however, despite the novelty of these structures, these precatalysts performed poorly in the enantioselective benzoin condensation. In the presence of **28** the benzoin product **(*S*)-9** was achieved in an excellent 87% yield but with a low enantiomeric excess of 4%. Upon introducing an enantiomerically pure cyclohexyl moiety into the bridged system, the **(*S*)-9** was obtained with an improved enantiomeric excess of 27%, albeit in a low 12% yield.

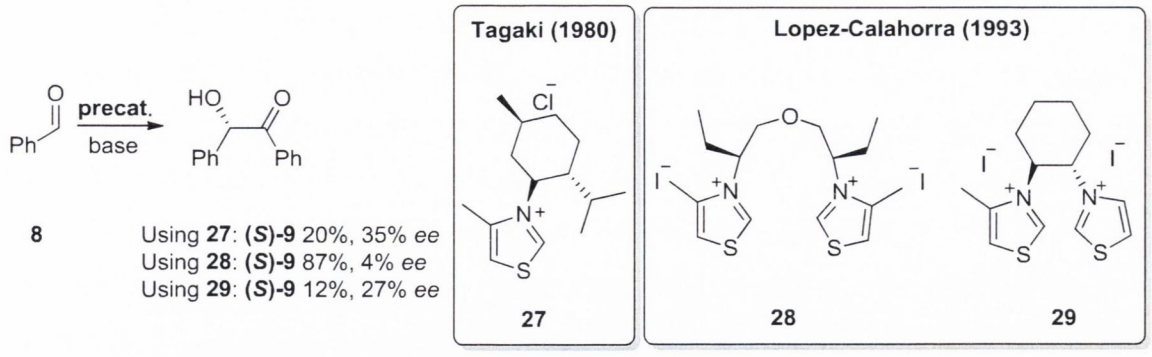
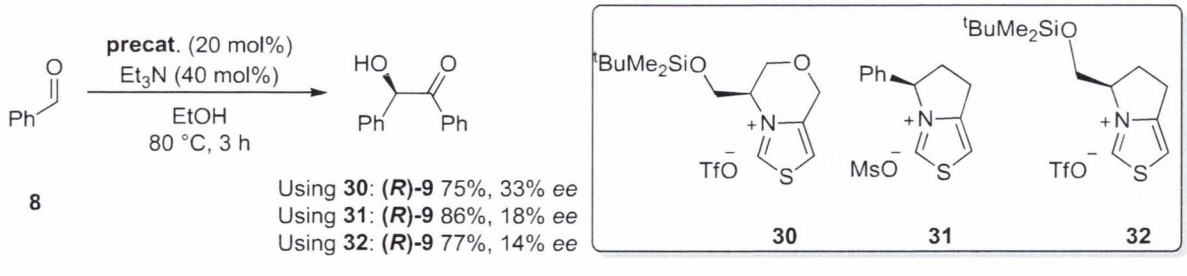


Figure 1.3 Thiazolium precatalysts used to promote the enantioselective benzoin condensation

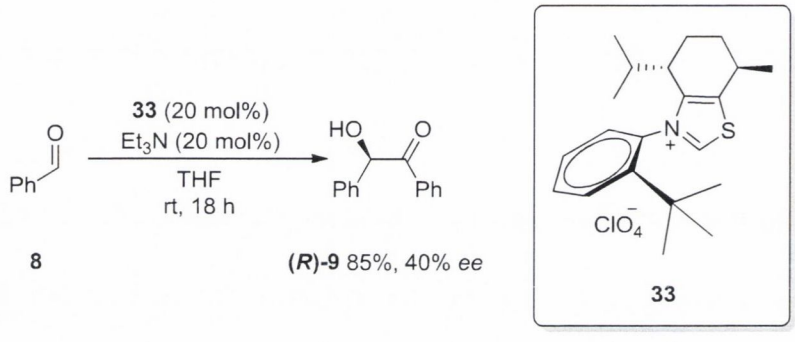
Leeper and coworkers[58] were the first to disclose the rational design of chiral bicyclic thiazolium salts and their use as precatalysts for the asymmetric benzoin condensation. Theye postulated that the free rotation of the chiral substituent attached to the thiazolium moiety was detrimental to obtaining a stereoselective transformation. To prove this suggestion, Leeper designed a series of rigid bicyclic thiazolium salts (**30** – **32**) and employed them as precatalysts in the benzoin condensation, as illustrated in Scheme 1.10. Despite obtaining the benzoin product (***R***)-**9** in notably high yields, these precatalysts performed poorly in terms of asymmetric induction when compared to Sheehan's precatalyst **26**. Despite the disappointing results obtained with benzaldehyde, Leeper reported the hitherto use of aliphatic aldehydes (*e.g.* butyraldehyde) as substrates of the asymmetric acyloin condensation. The products arising from the dimerisation of aliphatic aldehydes were obtained in moderate to high yields along with modest levels of enantiocontrol.



Scheme 1.10 Chiral, bicyclic thiazolium precatalysts employed by Leeper in the asymmetric benzoin condensation

Based on the same concept pioneered by Leeper, Bach and coworkers[59] sought to develop axially chiral catalysts bearing sterically encumbered aryl substituents attached to the

nitrogen of the thiazolium moiety. Consequently, Bach and coworkers designed a series of thiazolium salts (*e.g.* **33**) which they postulated could act as axially chiral precatalysts by virtue of their aryl substituents which possessed a limited rotation along the N-C_{aryl} bond and resulted in the creation of a stereogenic axis. In the presence of the diastereomerically pure precatalyst **33**, the benzoin product **(*R*)-9** was obtained in 85% yield with 40% *ee* (Scheme 1.11). Whilst Bach's novel approach of axial chirality proved to be viable, the asymmetric induction provided by thiazolium precatalysts such as **33** in promoting the benzoin condensation was considerably lower than that of Sheehan's catalyst (*i.e.* **26**, Scheme 1.9).



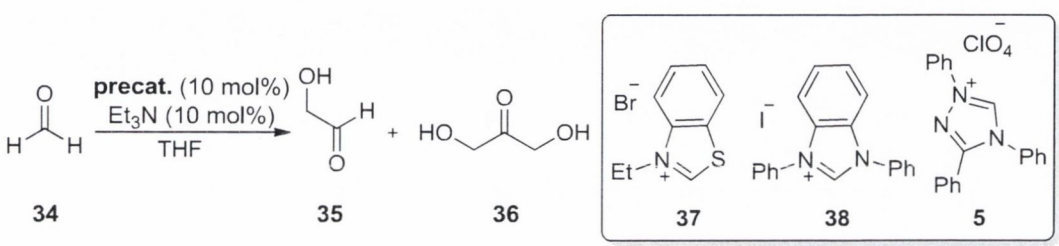
Scheme 1.11 Benzoin condensation promoted by the axially chiral salt **33** developed by Bach[59]

1.4.2 The development of chiral triazolium ion-based precatalysts

The first benzoin condensation promoted by a triazolium ion-derived carbene was carried out by Enders *et al.* who, in 1996, proved the superiority of triazolium precatalysts over their thiazolium analogues in promoting the dimerisation of benzaldehyde (**8**). Inspired by earlier studies carried out by López-Calahorra and coworkers[60] who reported the use of formaldehyde **34** as a substrate for the acyloin condensation promoted by a thiazole-based carbene, Enders studied the 'formoin condensation' in the presence of various NHCs in order to compare the performance of thiazolium, imidazolium and triazolium ion-derived carbenes as promoters of this process.[61] Enders' investigation resulted in identifying the superiority of the NHC derived from achiral triazolium salt **5** in catalysing the formation of glycolaldehyde (**35**, also called 'formoin') when compared to analogous thiazolium- and imidazolium-based NHCs. The author reported that, while **35** was the major product generated in the presence of triazolium salt **5**, high to moderate yields of dihydroxyacetone (**36**) together with other carbohydrates were formed in the presence of imidazolium and thiazolium salts such as **37** and **38** as illustrated in Table 1.1.

Enders concluded that the superiority of triazolium precatalysts compared to thiazolium precatalysts in promoting the dimerisation of **34** is due to the increased stability of triazolium ylides in comparison to their thiazolium counterparts, therefore allowing the elimination of **35** to occur faster than the addition of a third molecule of **34** that leads to the undesired formation of **36**.

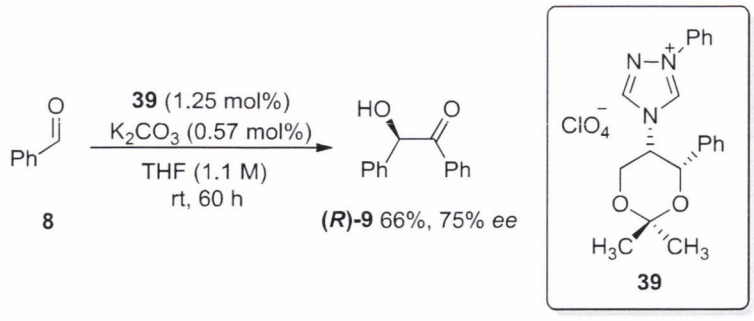
Table 1.1 Studies on the dimerisation of formaldehyde in the presence of different NHCs as reported by Enders *et al.*[59]



Entry	Precatalyst	Yield 35 (%)	Yield 36 (%)
1	**37**	<2	65
2	**38**	4	34
3	**5**	59	0

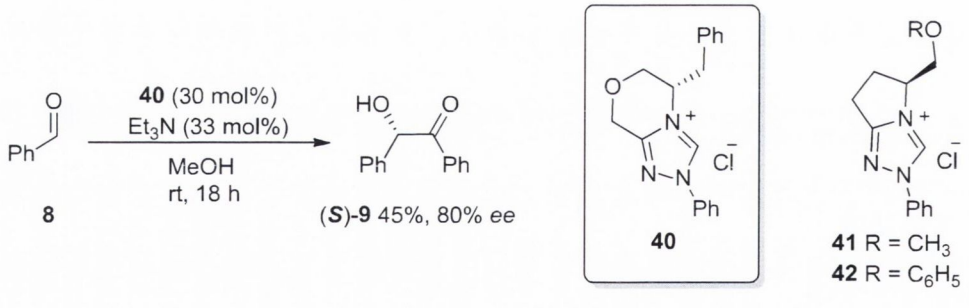
Encouraged by these preliminary results which highlighted the superiority of triazolium salt-based catalysis, Enders *et al.* reported the first chiral triazolium precatalyst **39** for the asymmetric benzoin condensation.[62] In the presence of a remarkably low precatalyst loading (1.25 mol%) (***R***)-**9** was generated in 66% yield with a unprecedented enantiomeric excess of 75%, as illustrated in Scheme 1.12. At this time, this was the highest reported *ee* for **9** obtained as the product of a NHC-mediated benzoin condensation.

The same precatalyst **39** was used to promote the self condensation of various substituted aromatic aldehydes with broad ranging product yields (22-72%). The enantioselective excesses obtained where highly substrate-dependant (20-86% *ee*), with highest optical purities obtained for acyloin products derived from electron-rich aromatic aldehydes.



Scheme 1.12 The first asymmetric triazolium salt-mediated benzoin condensation reported by Enders *et al.*[62]

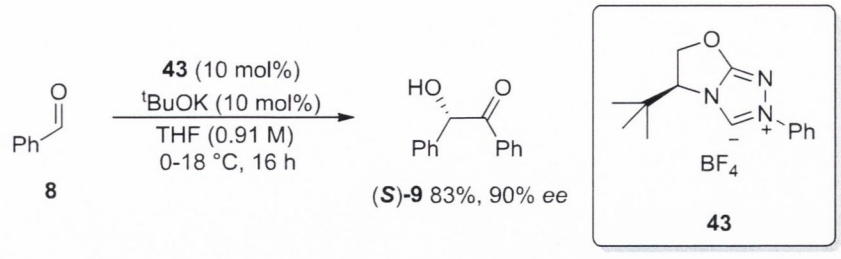
Further contributions to the triazolium salt-promoted asymmetric benzoin condensation were made by Leeper and his group.[63] Based on the earlier studies on rigid thiazolium precatalysts, Leeper synthesised a range of chiral bicyclic 1,2,4-triazolium precatalysts such as **40** - **42** (Scheme 1.13) which proved to be far superior in the asymmetric benzoin condensation than their thiazolium analogues. NHCs derived from triazolium precatalysts **41** and **42** promoted the formation of benzoin product (***R***)-**9** with optical purities of up to 63%; lower than those reported by Enders with the use of **39**. However, the use of Leeper's triazolium salt **40** led to the benzoin product (***S***)-**9** being formed in moderate yields and with an optical purity comparable to that achieved by Enders, albeit in its opposite enantiomeric form as illustrated in Scheme 1.13.



Scheme 1.13 Chiral, bicyclic triazolium precatalysts reported by Leeper[63]

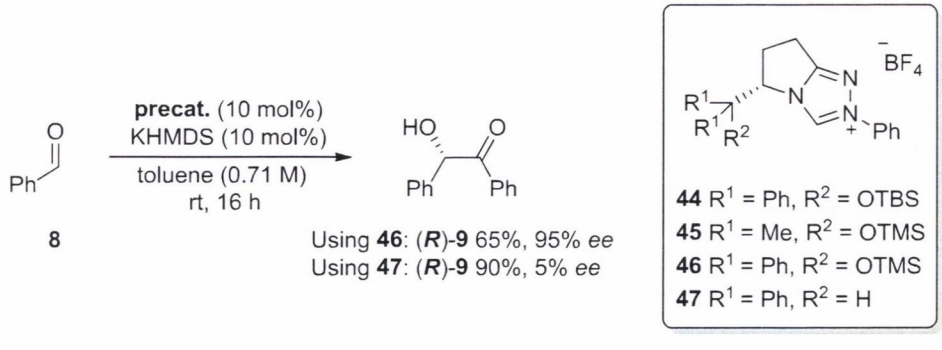
Inspired by Leeper's novel bicyclic triazolium precatalysts, Enders *et al.*[64] further developed the utility of triazolium precatalysts when, in 2002, they employed the fused triazolium precatalyst **43** as a promoter of the benzoin condensation. Under optimised conditions (***S***)-**9** was formed in excellent yields and a remarkable 90% *ee*. The benzoin condensation performed in the presence of **43** was of broad substrate scope; a wide range of variably substituted aromatic aldehydes were dimerised in the presence of this precatalyst to render

the corresponding acyloin products with levels of enantiopurity as high as 95%, (Scheme 1.14).



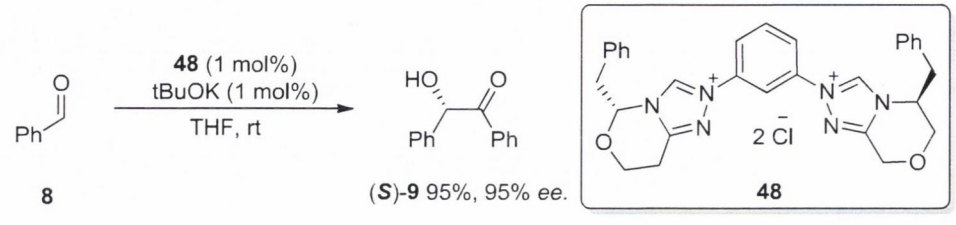
Scheme 1.14 Asymmetric benzoin condensations using the enantiomerically pure, bicyclic precatalyst **43**

In 2008, the same author reported further modifications to the design of precatalyst **43** by introducing sterically demanding silylether groups in place of the previously widely employed methyl substituents. These modifications lead to the synthesis of precatalysts such as **44** - **47**, as shown in Scheme 1.16. Of this novel group of precatalysts, the NHC derived from **46** proved to be more effective than its analogues in promoting the asymmetric benzoin condensation and catalysed the formation of (***R***)-**9** in 65% yield and with an impressive 95% *ee*. The investigation of the substrate scope for this transformation, using precatalyst **46**, revealed that heteroaromatic aldehydes and substituted aromatic aldehydes afforded α-hydroxyketone products in comparable yields and with moderate to high levels of enantiomeric excess. Notably, when the less sterically hindered triazolium salt **47** was used to promote the reaction, product **(*R*)-9** was formed in higher yields (90%) albeit a much lower enantiomeric excess (5% *ee*). Following this result, Enders theorised that the high asymmetric inductions are not solely dependent on the catalyst's rigid bicyclic framework and that the presence of sterically demanding substituents is essential.



Scheme 1.15 A series of fused chiral triazolium precatalysts synthesised and evaluated by Enders[64]

Another notable example, where bicyclic triazolium salts are employed as precatalysts in the asymmetric benzoin condensation, was reported by You and coworkers[65] who prepared a range of *bis*-triazolium salts, with the most successful analogue being **48**. The active NHC-based catalyst derived from **48** was able to promote the dimerisation of benzaldehyde to render **(*S*)-9** in an excellent 95% yield and with 95% *ee*, using a precatalyst loading as low as 1 mol%.



8 (*S*)-**9** 95%, 95% *ee*. **48**

Scheme 1.16 Example of high product *ee* in the asymmetric benzoin condensation promoted by *bis*-triazolium salts designed by You and coworkers[65]

The evaluation of **48** in terms of substrate scope also proved successful and electron-rich aromatic aldehydes, which were usually problematic substrates in previously reported acyloin condensations (*i.e.* they often participated in enantioselective, but poor-yielding reactions), fared extremely well in this asymmetric process with good to moderate yields of the corresponding acyloins being obtained and with impressively high levels of enantiopurity (83 – 95% *ee*). Precatalyst **48** proved to be far more efficient than any of its competitors when employed in the benzoin condensation - thereby establishing a benchmark for future asymmetric acyloin condensation studies.

1.4.3 The study of bifunctional triazolium ion-based precatalysts: hydrogen bonding as a control element

The structurally and electronically diverse NHC catalysts discussed thus far have highlighted the requisite properties the catalysts (derived from their parent precatalysts) must possess in order to efficiently promote an enantioselective benzoin condensation. The triazolium scaffold has proven to be far superior to its thiazolium counterpart in promoting the process as the former presents more sites where structural (and electronic) modifications can be introduced to increase the steric bulk surrounding the catalyst.

In 2004 Houk and coworkers[66] carried out computational studies on the asymmetric benzoin condensation to prove the importance of steric bulk embedded within the NHC catalyst. The imperative stereocentre is created during the carbon-carbon bond formation between the

Breslow intermediate **22** (Scheme 1.7) and the second aldehyde **8**, hence the stereocontrol exerted by the NHC catalyst on this transition state is crucial for an enantioselective process to occur. Houk's studies explained the success of triazolium ion-based precatalysts, which allow a substituent to be positioned on the nitrogen adjacent to the carbene centre, thus, exerting far more control over the enantioselective outcome of the process than the far less sterically encumbered thiazolium precatalyst. In Figure 1.3 the rationale is depicted for the superiority of triazolium ion-based precatalysts compared to their thiazolium variants. Houk stated that the chiral substituent, or the fused aliphatic ring, effectively blocks the top face (as drawn) of the Breslow intermediate with the *N*-aryl ring occupying two of other three quadrants. This leaves only one quadrant free to accommodate the large aldehyde phenyl substituent in the reaction transition state, leading to facial control from both the aldehyde and Breslow intermediate's perspective. If the Breslow intermediate adopts an (*E*)-geometry, then multiple steric clashes occur (case **A**). To avoid this steric clash, the second benzaldehyde molecule is attacked by the enolamine from its *re* face (case **B**). This *re* transition state is also favoured by the π-iminium ion interaction between the Breslow intermediate at the approaching aldehyde. In contrast to cases **A** and **B**, the geometry of the transition states in cases **C** and **D** are equally favoured, due to lack of a repulsive steric interaction, resulting in a poor enantioselective process to occur when a thiazolium ion-based precatalyst is employed.

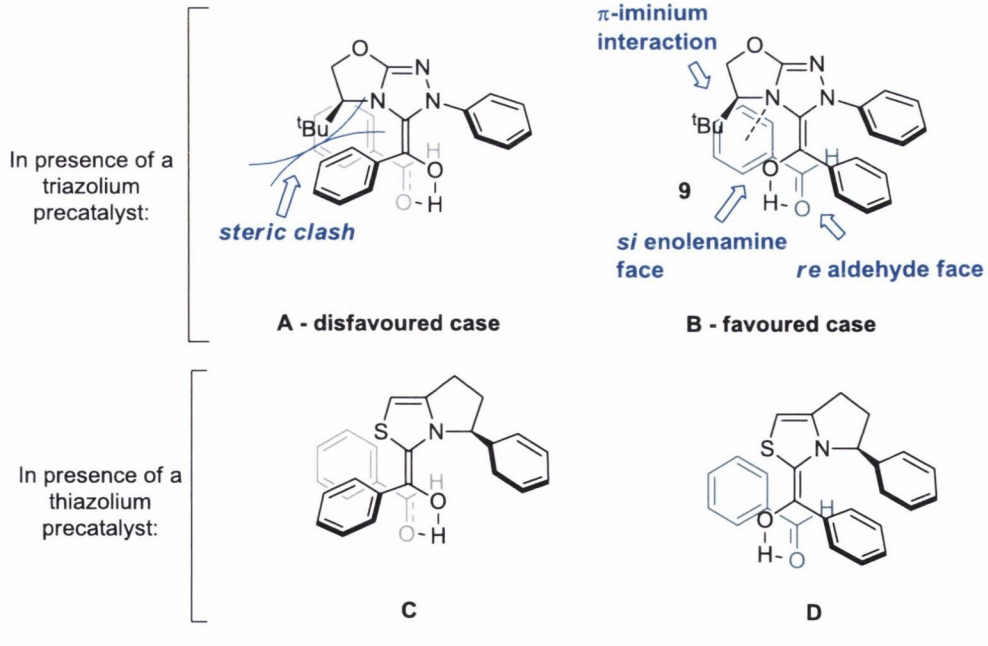
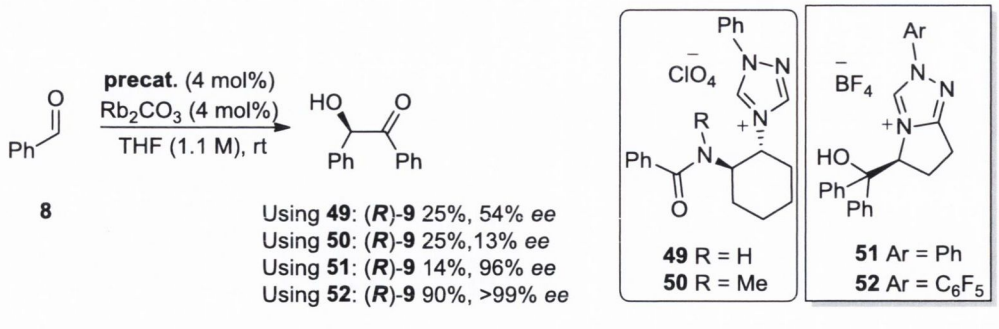


Figure 1.3 Rationale for superiority of triazolium precatalyst to thiazolium

At the time of Houk's studies it was understood that the stereoselective outcome of benzoin condensations was exclusively due to the steric requirements of the face-selective addition of the approaching aldehyde to the Breslow intermediate. Influenced by the important pieces of evidence regarding the mechanism of the asymmetric benzoin condensation, and taking the cue from other organocatalytic transformations where hydrogen-bonding interactions play an important role, Connon and co-workers suggested a novel approach towards this transformation. They proposed that the facial selectivity of the attack on the second aldehyde molecule by the Breslow intermediate could be promoted by using hydrogen-bonding interactions as a method for the induction of stereocontrol.[67] The authors postulated that a hydrogen bond donating group, present on the catalyst, should coordinate to the approaching aldehyde, thereby increasing the electrophilicity at the carbonyl group whilst also assisting the controlled approach of aldehydes towards the Breslow intermediate. Such a hydrogen bond-donating group would therefore complement the function of the steric-bulk and lead to a higher level of asymmetric induction *via* a bifunctional process. Based on this concept, Connon was the first to report the synthesis of a bifunctional triazolium precatalyst and its evaluation in the asymmetric benzoin condensation.

In order to assess the role of hydrogen bond donation in the asymmetric benzoin condensation, Connon and coworkers studied the dimerisation of benzaldehyde (**8**), and compared the hydrogen bond donating amide precatalyst **49** to its *N*-methylated counterpart **50** devoid of hydrogen bond donating groups. The marked decrease in optical purity for product (***R***)-**9**, observed when triazolium salt **50** was used as precatalyst, was a direct confirmation that hydrogen bond-donation is involved in promoting the asymmetric transformation.



Scheme 1.17 Bifunctional triazolium precatalysts reported by Connon and co-workers[67, 68]

Whilst the enantiomeric excess obtained by using **49** was not synthetically useful, this proof of concept encouraged Connon and coworkers[68] to optimise the steric and electronic

properties of triazolium-based precatalysts in order to enhance their hydrogen bond donating abilities. This resulted in the synthesis of precatalyst **51** which, by virtue of its rigid, bicyclic framework and a hydrogen bond donating alcohol, proved to be far superior than **49** in promoting an enantioselective process. The use of precatalyst **51**, in the presence of Rb_2CO_3 as the base forming the active NHC species, could promote the formation of product (***R***)-**9** with excellent enantiomeric excess albeit diminished yield. The authors speculated that the protonation of the NHC by the benzoin product was the reason for this low yield, hence they modified the precatalyst by introducing an electron-withdrawing pentafluorophenyl group **52** which could prevent this unwanted process. Gratifyingly, the finely-tuned precatalyst **52** promoted the benzoin condensation to render product (***R***)-**9** in enantiopure form and in excellent yields, the highest levels of both enantiomeric excess and efficiency achieved to date. Besides benzaldehyde (**8**), the NHC species derived from **52** was also capable of catalysing the dimerisation of a wide range of aromatic aldehydes to their corresponding acyloins with unprecedented enantioselectivities as high as 97% *ee*.

Following the rewarding results reported by Connon, Waser and coworkers[69] explored thiourea substituents on the triazolium precatalyst as a source of hydrogen bond donation. The desired triazolium ion-based precatalyst presented both a thiourea moiety and a pentafluoroaryl substituent, however, its synthesis was hampered by the incompatibility of these groups with the synthetic route chosen by Waser and coworkders. The authors therefore decided to prepare precatalyst **53** bearing a phenyl group as the substituent on the triazolium moiety. The use of precatalyst **53**, the most successful among the library of thiourea based catalysts prepared by Waser, resulted in benzoin product **(*R*)-9** being formed in 90% *ee*, however, a poor yield of just 17% was reported. Collectively, these studies, carried out by Connon and subsequently Waser, highlight that hydrogen bonding is a useful tool for the successful stereochemical control of benzoin condensation reactions, however, the electron-withdrawing pentafluorophenyl group is also necessary to allow access to the benzoin product **9** in high yields.

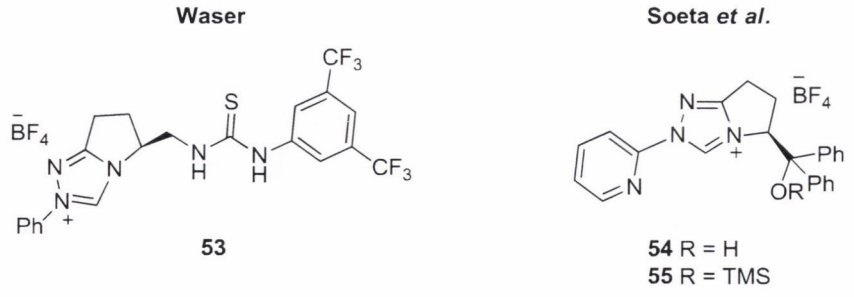


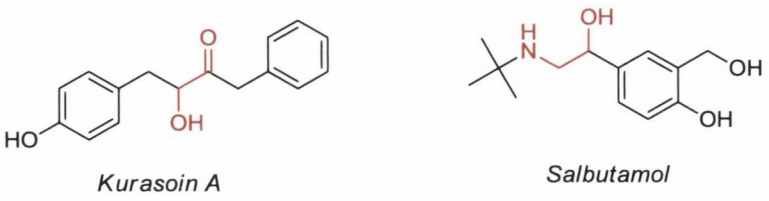
Figure 1.4 Bifunctional triazolium precatalysts reported by Waser and coworkers[69] and Soeta *et al.*[70]

Figure 1.4 Bifunctional triazolium precatalysts reported by Waser and coworkers[69] and Soeta *et al.*[70]

Soeta *et al.*[70] recently disclosed the use of a chiral triazolium ion-based precatalyst, bearing a pyridine moiety in place of a pentafluorophenyl group, as a promoter of the asymmetric benzoin condensation. The authors postulated that the pyridine substituent would allow intramolecular hydrogen bonding to occur between the nitrogen, on the pyridine ring, and the hydroxyl group of the Breslow intermediate. They expected this hydrogen bonding to give rise to an extremely rigid Breslow intermediate therefore providing an ideal platform for which an enantioselective process can occur. In the presence of the precatalyst **54**, where two sources of hydrogen bonding (intra- and intermolecular) are available on the precatalyst, (***R***)-**9** was obtained with 98% *ee* and in 65% yield. Protection of the precatalyst's hydroxyl moiety, to allow for only the intramolecular hydrogen bonding to occur, led to improved efficacy as **55** promoted the reaction with 99% *ee* and in 75% yield. Whilst the use of the pyridine moiety as a source of hydrogen bonding and the concept of a 'rigid' Breslow intermediate was a novel approach, Soeta's precatalysts did not rival Connon's pentafluorophenyl bearing precatalyst **52** in terms of efficiency.

1.5 The intermolecular crossed acyloin condensation

While there is no doubt that α-hydroxyketones derived from homo-condensation of aldehydes are extremely useful building blocks in synthetic and pharmaceutical chemistry, the potential applications of asymmetric α-hydroxyketones that result from acyloin condensations involving two different aldehyde substrates is even more vast and allows for a wider range of synthetic precursors to be obtained. These unsymmetrical acyloin frameworks are the key structural motif for agrichemicals, natural products and pharmaceuticals.[71] They are also precursors of important drugs such as Kurasoin A,[72] used in the treatment of cancer, and Salbutamol,[73] used to treat the symptoms of asthma (Figure 1.5)

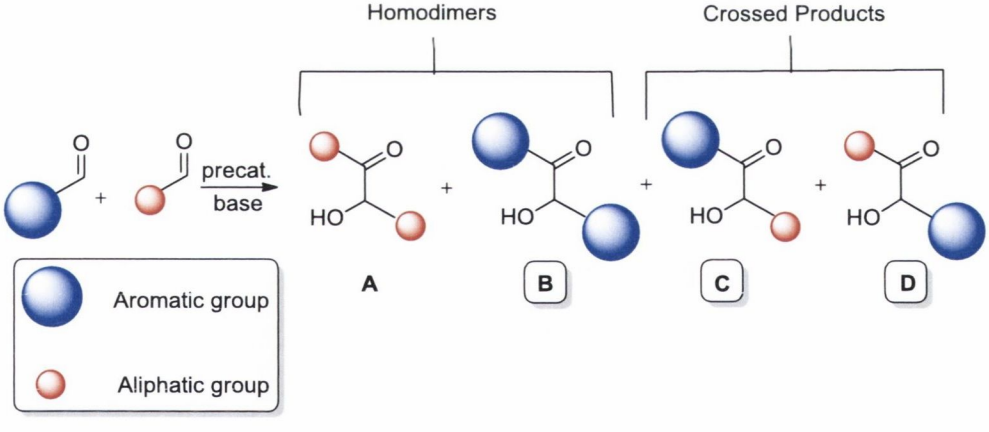


Kurasoin A *Salbutamol*

Figure 1.5 Kurasoin A and Salbutamol derived from unsymmetrical α-hydroxyketones

The main challenge associated with intermolecular crossed acyloin condensations is that, as a second aldehyde is being introduced as the reagent, the number of possible products increases from two to four as illustrated in

Scheme 1.18; two homodimers **A** and **B** and two crossed products **C** and **D**. Hence, a chemoselective bias must be established within this process in order for one cross product (**C** or **D**) to be obtained in high yields, and access to these highly synthetically pliable molecules is clearly curtailed if little or no chemoselectivity is observed. Currently, crossed acyloin condensations are being widely explored, with a focus on precatalyst design and substrate chemoselectivity in order to increase the synthetic use of this undoubtedly beneficial, direct carbon-carbon bond forming process.



Scheme 1.18 Possible products that can be formed in the cross coupling of two different aldehydes

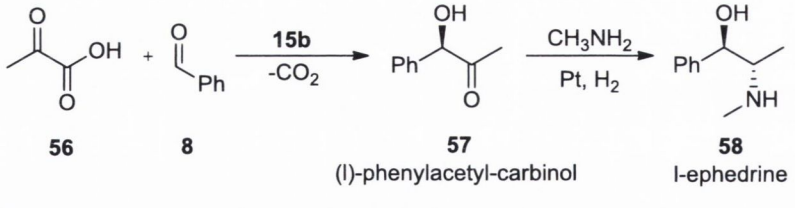
1.5.1 Catalysis by cyanide ions

The first report of a crossed acyloin condensation occurred in the presence of cyanide ions when Fischer,[74] in 1882, demonstrated the condensation between furfuraldehyde and benzaldehyde to obtain a crossed benzoin product. It was only 50 years later when the

process was revisited by Buck *et al.*[75] who studied the crossed benzoin condensation in the presence of cyanide ions using, as reagents, aldehydes having contrasting electronic properties. Despite his efforts, Buck was unsuccessful in discerning the factors that governed the chemoselectivity of the process. An important limitation of these studies was that only aromatic aldehydes were considered while the crossed acyloin condensation involving aliphatic aldehydes was completely excluded.

1.5.2 Catalysis by enzymes

α-Hydroxyketones are a frequent *motif* present in the stucture of many biologically active compounds. In nature, these acyloins are accessed *via* enzyme-promoted processes, making the use of isolated enzymes an attractive option for the synthesis of chemospecific acyloins. In 1921 Neuberg *et al.*[76,77] serendipitously discovered the formation of L-phenylacetyl-carbinol (**57**) during the phytochemical transformation of benzaldehyde (**8**) to benzyl alcohol in the presence of fermenting yeast and glucose. To their surprise they obtained acyloin product **57** along with low quantities of benzyl alcohol. Almost 30 years later Hanc and Kakac[78] reported that the fermentation of glucose, by yeast cells, produces pyruvic acid **56** which is decarboxylated by the thiamine diphosphate (ThDP - **15b**, Figure 1.2) present in yeast cells, to give activated acetaldehyde. The authors stated that upon addition of benzaldehyde **15b** was also responsible for catalysing the carbon-carbon bond forming reaction bewtween the two substrates. The generation of **57** by ThDP-dependent yeast was one of the first industrial biotransformations to be reported and is still used as the initial step in synthesising the stimulant drug l-ephedrine **58** (Scheme 1.19).

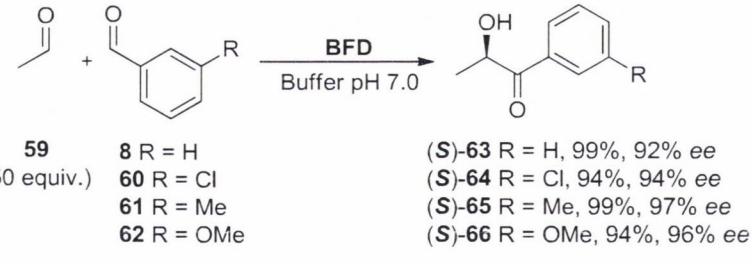


Scheme 1.19 Pyruvate decarboxylation and subsequent asymmetric carboligation catalysed by yeast cells in the synthesis of L-ephedrine

Acyloin formation catalysed by ThDP, present in yeast, encourgaed many researchers to explore the substrate scope of this crossed acyloin condensation. Ward and coworkers[79] demonstrated that a range of substituted benzaldehydes were capable of reacting with **57** to form the corresponding (*R*)-acetyl aromatic carbinols, when in the presence of *S. Cerevisiae* (Baker's yeast). They discovered that the highest yields were obtained when methyl,

trifluoromethyl- or chloro-substituents were present in the *para* position with yields diminshing when these substituents occupied the *meta* postion. The poorest yields were obtained when *ortho*-substituted aromatic aldehydes were employed, and no product was formed in the presence of two different aliphatic aldehydes such as cinamaldehyde in conjunction with acetaldehyde.

In 1999 Demir and Müller[80] reported the first example of an enzyme mediated formation of enantiopure benzoin, in its *R* configuration, using benzoylformate decarboxylase (BFD), a ThDP-dependent enzyme present in bacteria such as *Pseudomonas putida* and *Pseudomonas aeruginosa*. BFD is capable of generating benzaldehyde (**8**) *via* the decarboxylation of benzylformate and subsequently catalyses the formation of (***R***)-**9** *via* asymmetric ligation. Demir *et al.* discovered that BFD was also capable of catalysing the dimerisation of a broad spectrum of aldehydes to render their corresponding acyloins, hence the authors decided to investigate the performance of BFD in the crossed acyloin condensation between a range of aldehydes and acetaldehyde (**59**).[81,82] Upon studyng the carboligation of benzaldehyde and **59**, the authors discovered that the enzyme accepts the aromatic aldehyde as the initial 'donor' substrate, and acetaldehyde as the subsequent 'acceptor' substrate, to yield (*S*)-2-hydroxy-1-phenylpropanone ((***S***)-**63**) in 99% yield and with 92% *ee* (Scheme 1.20).

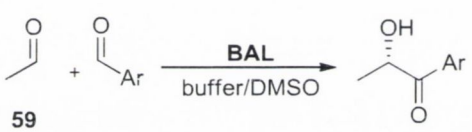


Scheme 1.20 Crossed acyloin condensation of benzaldehyde and *meta*-substituted benzaldehydes with acetaldehyde (**59**) catalysed by BFD

It must be noted that these results were only obtained when 50 equivalents of acetaldehyde were employed. A broad spectrum of *meta*-substitued aromatic aldehydes were ideal donor candidates for this process and their corresponding crossed acyloin products ((***S***)-(**64-66**)) were generated with enantiomeric enrichement as high as 99% *ee* and in excellent yields. However, the performance of BFD as a catalyst of this process was limited by the use of aromatic substrates bearing substituents in the *para* or *ortho* position, significantly more so in the latter case.

Demir *et al.*[83] subsequently examined the use of a similar enzyme, Benzaldehyde lyase (BAL) found in *Pseudomonas florescens* as a potential catalyst in the crossed acyloin condensation. They discovered that this enzyme catalysed the formation of (*R*)-2-hydroxy-1-phenylpropanone (**63**), in the presence of 7 equivalents of acetaldehyde (**59**), in enantiopure form and in 96% yield (Table 1.2, entry 1). This enzyme proved to be far more versatile than BFD and accepted mono- (entries 2 - 4) and di-substituted (entry 5) aromatic aldehydes and catalysed the asymmetric ligation of these substrates with acetaldehyde in high yield and with high levels of enantiomeric enrichment as illustrated in Table 1.2. Most notably this enzyme accepted aldehydes that were found to be problematic in previous enzyme mediated crossed acyloin condensations such as *ortho* substituted aromatic aldehydes (entry 2) and heteroaromatic aldehydes (entry 6) and promoted the formation of their corresponding acyloin products in almost enantiopure form.

Table 1.2 Cross coupling of aromatic aldehydes with acetaldehyde catalysed by BAL



59
(7 equiv.)

Entry	Ar	Product	Yield (%)	*ee* (%)
1	C_6H_5	(***R***)-**63**	94	>99
2	2-F-C_6H_5	(***R***)-**67**	64	97
3	3-OMe-C_6H_5	(***R***)-**66**	80	>99
4	4-Cl-C_6H_5	(***R***)-**68**	88	>99
5	2,4-F_2-C_6H_5	(***R***)-**69**	65	97
6	2-Furyl	(***R***)-**70**	61	>99

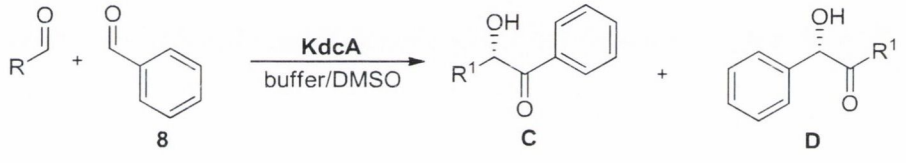
However, heteroaromatic aldehydes bearing a nitrogen atom and hydroxy substituted aromatic aldehydes were not accepted by the enzyme. Furthermore, the use of sterically demanding substrates such as vanillin, isovanillin and 3,5-dimethoxybenzaldehyde led to little or no formation of the corresponding acyloin.

In 2007 Müller and coworkers[84] explored the use of another enzyme as a catalyst in the acyloin crossed condensation. Keto acid decarboxylase (KdcA) is derived from *Lactococcus lactis* and is involved in catalysing the formation of flavour compounds found in cheese.[85]

The authors applied this enzyme to the ligase reaction between benzaldehyde (**8**) and acetaldehyde, however, only poor chemoselectivity was observed. The two crossed products **63c** and **63d** were genererated in almost equal amounts with high levels of optical purity (Table 1.3, entry 1). The authors discovered that chemoselectivity improved remarkably when larger aliphatic aldehydes were employed with only one possible crossed product (of chemoselectivity **D**) being generated, in almost enantiopure form, albeit in low yields (Table 1.3, entries 2 - 4). It is not reported if any homodimers were observed.

The use of Kdca allowed acyloins to be obtained with high levels of enantiomeric enrichment but in diminutive yields. However, a unique approach was established; product chemoselectivity can be achieved *via* adjustment and alteration of substrate properties.

Table 1.3 KdcA catalysed carboligation of benzaldehyde and various aliphatic aldehydes



Entry	R	Product	Yield C (%)	Yield D (%)	*ee* C (%)	*ee* D (%)
1	CH_3	**63**	n.d	n.d	93	92
2	C_3H_7	**71**	-	32	-	97
3	*i*-C_3H_7	**72**	-	25	-	88
4	cyclopropyl	**73**	-	14	-	98

ThDP-dependent enzymes PDC, BFD, BAL and KdCA have been established as effective and versatile biocatalysts for the asymmetric chemoligation of aldehydes, yet there are still limitations associated with the enzyme-catalysed crossed acyloin condensation. The studies previously discussed highlight the importance of specific enzyme selection in combination with tolerated substrates in order to achieve a chemo- and enantioselective process. Whilst the homo-acyloin condensation has proved successful in the presence of these biocatalysts, it is evident that low product yields and poor substrate tolerance make current methods for enzyme-catalysed crossed acyloin condensation of limited synthetic value.

1.5.3 NHC-catalysed variants

1.5.3.1 Thiazolium salts

Initial studies on thiazolium salts focused solely on the homocoupling of aldehydes, as discussed in Section 1.3.2. Stetter *et al.*[86] are credited with the first report of a crossed acyloin condensation carried out in the presence of a thiazolium salt. Thirty years after Buck's disclosure of the cyanide-mediated crossed acyloin condensation, Stetter studied the condensation of a mixture of disparate aldehydes in the presence of the achiral thiazolium precatalyst **74.**

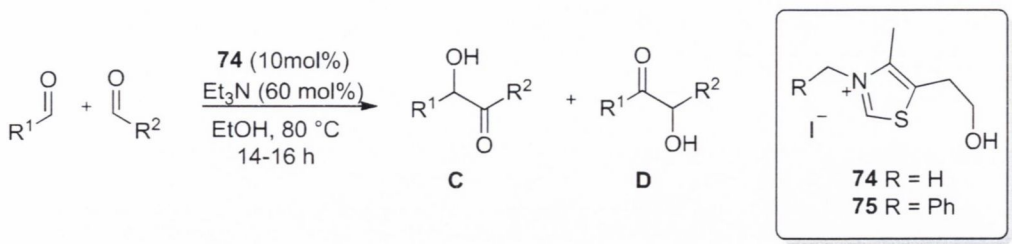
1.5.3.1.1 Substrate Scope

1.5.3.1.1.1 Cross coupling of aromatic alehydes with aliphatic aldehydes

Stetter was also the first to discover aliphatic aldehydes as potential substrates for the crossed acyloin condensation and investigated their reactivity in the presence of thiazolium salts **74** and **75**. The author revealed that when an aliphatic aldehyde present in three-fold excess was allowed to react with an aromatic aldehyde, satisfactory yields were obtained. The two crossed products that were generated were isolated as an inseparable mixture and the ratios of product formation were reported (Table 1.44, entries 1 - 8). This study found the process to be highly substrate dependent; with chemoselectivity being higher using either an aromatic aldehyde possessing a chlorine substituent in the *ortho* position (entries 2 and 3), or a π-excessive heterocyclic aldehyde (entries 5 - 7). It was also noted that, when acetaldehyde was employed, the opposite chemoselectivity was observed (Table 1.4, entry 3) as **78d** was the sole crossed product obtained. Subsequently, Stetter explored the coupling of two different aliphatic aldehydes (entry 8) in the presence of *N*-benzyl substituted thiazolium precatalyst **75**. The author proposed that an element of chemoselective bias should occur if one of the aldehydes is sterically demanding, hence omit the possibility of self-condensation, however, **83c** and **83d** were obtained in a combined mediocre yield of 56%.

The precatalyst **74** was also used to promote the coupling of various hindered aliphatic norbornene-2-carbaldehydes with a range of smaller aliphatic aldehydes. Stetter did not report the yields of any homo-coupled products and, whilst the combined yields of the crossed acyloins (as high as 72%) were disclosed, the product ratios were not.

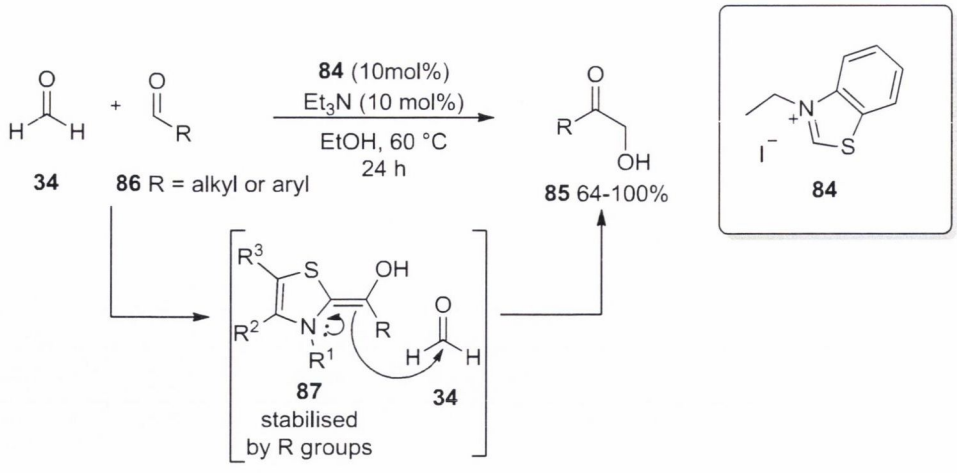
Table 1.4 The first reported NHC-catalysed crossed acyloin condensation



Entry	R^1	R^2	Product	Yield C + D (%)	Ratio C:D
1	*i*-C_3H_7	C_6H_5	**76**	56	35:65
2	*i*-C_3H_7	2-Cl-C_6H_5	**77**	81	100:0
3	CH_3	2-Cl-C_6H_5	**78**	52	0:100
4	*i*-C_3H_7	4-Cl-C_6H_5	**79**	75	45:55
5	*i*-C_3H_7	2-thienyl	**80**	79	100:0
6	*i*-C_3H_7	2-furyl	**81**	88	95:5
7	*n*-C_3H_7	2-furyl	**82**	63	85:15
8[a]	*i*-C_3H_7	*n*- C_7H_{15}	**83**	56	30:70

[a]Reaction carried out in presence of triazolium ion-based precatalyst **75**.

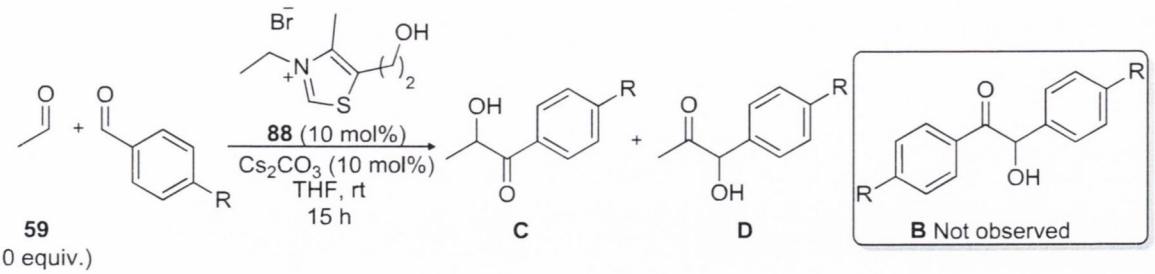
In 1984, Inoue and coworkers[87] supplemented Stetter's studies on the NHC-catalysed crossed acyloin condensation reporting the use of 3-ethylbenzylthiazolium bromide (**84**) as a precatalyst in this process. The NHC derived from precatalyst **84** promoted the coupling of formaldehyde (**34**) with another aldehyde to form crossed product **85** almost exclusively (Scheme 1.21). A broad range of aldehydes, both aliphatic and aromatic, were accepted in conjunction with **34**. The author proposed that the NHC reacts exclusively with the partner aldehyde (**86**), and not formaldehyde (**34**), as the Breslow intermediate **87** is far more stabilised by virtue of the alkyl or aryl groups present on this species. This intermediate **87** then attacks the extremely electrophilic aldehyde **34** to generate the acyloin product **85**. Inoue highlighted that the difference in electrophilicity between the partner aldehydes strongly influences the chemoselectivity of the process.



Scheme 1.21 A chemoselective process developed by Inoue whereby formaldehyde is employed as a substrate

In 2010 Yang and coworkers[88] proved that high yields can be achieved in the cross coupling of acetaldehyde (**59**) with *meta*-substituted aromatic aldehydes when a large excess of the aliphatic substrate is employed. They postulated that high yields of cross product and improved chemoselectivity are obtained when formation of the self-condensation of the aromatic substrates leading to product **B** is suppressed. To achieve this, 10 equivalents of **59** were employed with 1 equivalent of aromatic aldehyde. Product yields were highest when an electron-withdrawing chlorine atom was placed in the *para* position of benzaldehyde and **68c** was formed as the major product (Table 1.5, entry 1). Regioselectivity remained high when *para*-tolualdehyde (entry 2) and *para*-anisaldehyde (entry 3) were employed as **89c** and **90c** were formed as the major products, however, yields diminished considerably in the presence of the latter aldehyde. Notably, the authors stated that when a triazolium ion-based precatalyst was employed, under the same reaction conditions, product yields were unaffected, however, reversed regioselectivity was observed. The authors surmised that the less sterically hindered thiazolium precatalyst **88** reacts with the aromatic aldehyde to generate the corresponding Breslow intermediate, whilst nucleophilic attack of the sterically demanding triazolium precatalyst on **59** affords the alternative Breslow intermediate.

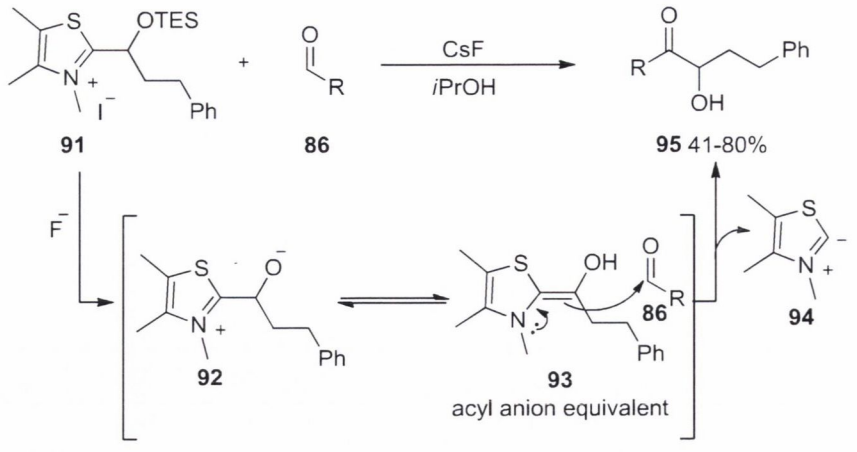
Table 1.5 Crossed acyloin condensation carried out in the presence of thiazolium ion-based precatalyst **88** and excess aliphatic aldehyde **59**



Entry	R	Product	Yield of C + D (%)	Ratio C:D
1	Cl	**68**	88	95:5
2	Me	**89**	78	91:9
3	OMe	**90**	45	92:8

1.5.3.1.1.2 Cross coupling of different aliphatic aldehydes

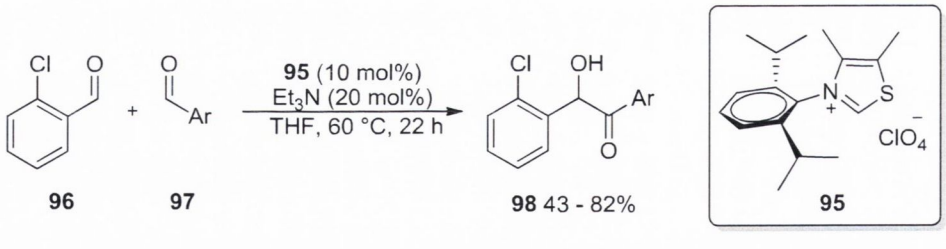
Inspired by Breslow's mechanism (Scheme 1.7), Scheidt and coworkers[89] took the approach of applying a 'pre-formed' Breslow intermediate to this process in order to generate a crossed aliphatic-aliphatic acyloin product. He achieved this by employing *O*-silyl thiazolium carbinols such as **91**, which upon desilylation by cesium fluoride, underwent a 1,2-proton shift to generate the acyl anion equivalent **92** (Breslow intermediate). Attack of this intermediate **93** on the various aliphatic aldehydes **86**, followed by elimination of the NHC **94**, rendered the corresponding unsymmetrical α-hydroxyketone products **95** in good to high yields (41 – 80%) as shown in Scheme 1.22. A wide range of aliphatic aldehydes and *O*-silyl thiazolium carbinols were tolerated. Whilst this was an innovative advance towards aliphatic-aliphatic cross-couplings, it is limited by the requirement for a stoichiometric amount of the pre-formed Breslow intermediate.



Scheme 1.22 Novel route towards chemoselective aliphatic-aliphatic cross couplings reported by Scheidt and coworkers[89]

1.5.3.1.1.3 Cross coupling of different aromatic aldehydes

In 2011 Glorius and coworkers[90] reported the first cross benzoin condensation between two different aromatic aldehydes in the presence of a NHC-based catalyst. The research group synthesised the sterically demanding *N*-diisopropylphenyl based triazolium-ion precatalyst **95** and applied this to the cross coupling between *ortho*-chlorobenzaldehyde (**96**) and various aromatic aldehydes (**97**) as shown in Scheme 1.23. The corresponding asymmetric benzoins (**98**) were synthesised in moderate to good yields, however, one major limitation of this reaction was that only *ortho*-halo substituted aldehydes, such as **96**, were tolerated by the catalyst.



Scheme 1.23 The first selective crossed benzoin condensation reported by Glorius and coworkers[90]

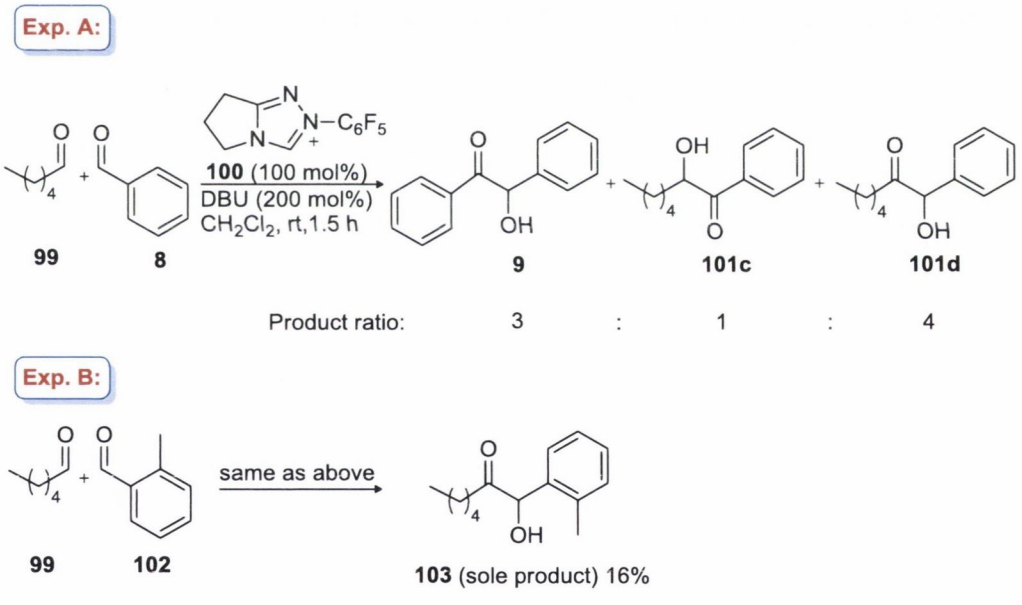
1.5.3.2 Triazolium salts

As previously discussed, triazolium salts proved to be far superior catalyst systems to their thiazolium analogues in promoting the benzoin condensation, so naturally many research groups turned their attention towards evaluating these precatalysts in the crossed acyloin condensation. As this area of research is in its infancy, a general protocol for the coupling of

two different aromatic aldehydes or two different aliphatic aldehyes in the presence of a triazolium precatalyst remains elusive. At present, only reports of triazolium ylide-catalysed intermolecular crossed acyloin condensations involving the cross coupling of an aliphatic partner with an aromatic partner exist and hence the following Section will focus on the coupling of these substrates.

1.5.3.2.1 Substrate Scope

In 2007, Miller and coworkers[91] carried out studies on the macrocylisation of dialdehydes, one being aliphatic and the other being aromatic, in the presence of achiral triazolium ion-based precatalyst **100**. In a bid to determine which aldehyde, *i.e* aliphatic or aromatic, is initially attacked by the NHC catalyst, Miller designed an experiment to examine the intermolecular crossed acyloin condensation between benzaldehyde (**8**) and hexanal (**99**) in the presence of **100** (Scheme 1.24, Exp. A).



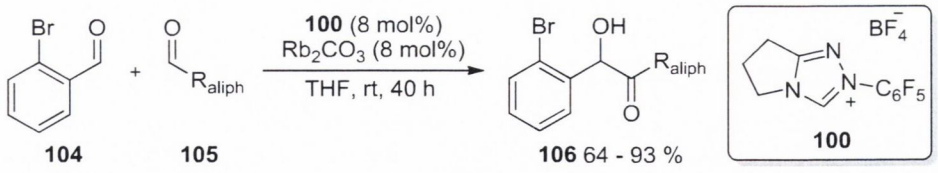
Scheme 1.24 First intermolecular crossed acyloin condensation reported by Miller and coworkers[91]

They observed an unselective process; the two crossed products **101c** and **101d** were formed along with homodimer **9**, implying that the NHC, derived from **100**, was capable of attacking both aldehydes. The authors also studied the condensation between hexanal and *ortho*-tolualdehyde (**102**) under the same reaction conditions and observed the formation of one product, **103** as illustrated in Scheme 1.24 (Exp. B). Miller concluded that sterics may preclude the carbene, derived from precatalyst **100**, from formation of the Breslow

intermediate at the bulky *ortho*-substituted benzaldehyde. Whilst Miller's seminal studies highlighted the important role that sterics may play in promoting a chemoselective process, his particular protocol was of little synthetic value as the crossed acyloin product **103** was formed in an extremely low yield of 16%.

In 2010, Connon and Zeitler[92] carried out an investigation on the influence of catalyst structure and substrate properties on chemoselectivity in the crossed acyloin condensation reaction. The authors compared the triazolium ion-based prectalyst **100** to Stetter's thiazolium precatalyst **74** (Table 1.4) in a number of cross coupling reactions previously carried out by Stetter. A few general trends emerged from these studies: precatalyst **100** is far more effective than its thiazolium counterpart **74** in promoting the cross coupling of two different aldehydes, and thiazolium precatalyst **74** only mediates a selective reaction when *ortho*-substituted benzaldehydes are employed as the aromatic substrate. This study highlighted the superiority of triazolium precatalyst **100** and the importance of substrate features in obtaining chemoslectivity in this process.

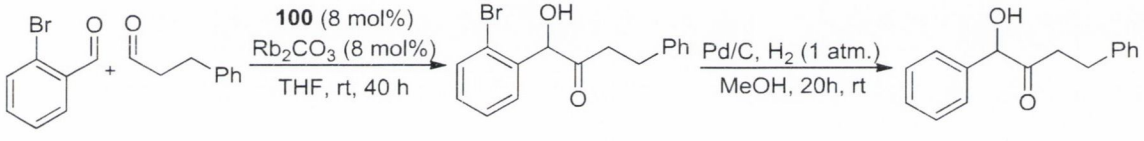
In the same year Connon and coworkers[93] reported the first highly chemoselective crossed acyloin condensation reactions that allow access to a range of unsymmetrical acyloins to be obtained in high yields. Inspired by both Stetter and Miller's observations of the effect of sterics on promoting a chemoselective process, Connon and coworkers theorised that high chemoselectivity should be observed in the condensation between an aliphatic aldehyde and an aromatic aldehyde if an extremely bulky atom is placed in the *ortho* position of benzaldehyde. The authors decided to employ a halogen atom as an ideal temporary directing group that could easily be removed from the final acyloin product *via* hydrogenolysis. During preliminary experiments *ortho*-bromobenzaldehyde (**104**) proved to be the superior candidate for the aromatic aldehyde as upon reacting with hydrocinnamaldehyde in the presence of precatalyst **100**, the corresponding crossed acyloin was obtained in 90% yield. As a control experiment, benzaldehyde was employed as the aromatic partner under the same reaction conditions and poor chemoselectivity was observed with all four possible products formed. The evaluation of **104** in terms of compatibility with other aliphatic substrates (**105**), branched and unbranched, in the presence of **100**, led the corresponding acyloins (**106**) being obtained in good to high yields as illustrated in Scheme 1.25.



104 **105** **106** 64 - 93 % **100**

Scheme 1.25 Cross coupling of aliphatic aldehydes with *ortho*-bromobenzaldehyde reported by Connon and coworkers[93]

The aromatic aldehyde **104** reacted with hydrocinamaldehyde (**107**) in the presence of **100** to render the corresponding adduct **108** in an excellent yield of 90%. This α-hydroxyketone was consequently debrominated, in the presence of Pd/C, under an atmosphere of hydrogen to render the corresponding adducts **109** in uniformly a high yield (90%). The scope of the aromatic aldehyde was also broad, as a variety of *ortho*-bromobenzaldehydes bearing electron-neutral, electron-donating and electron-withdrawing substituents were accepted in this process.



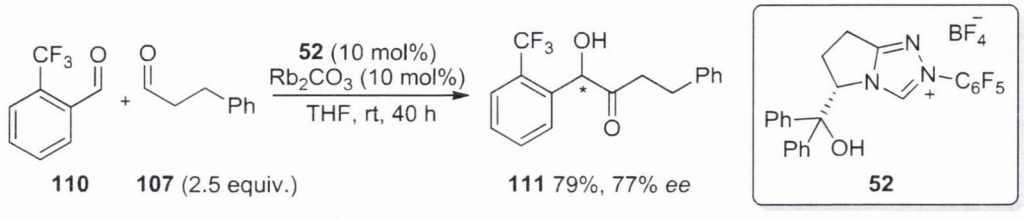
104 **107** (1.7 equiv.) **108** 90% **109** 90%

Scheme 1.26 Cross coupling of substituted *ortho*-bromobenzaldehyde **104** with **107** subsequently followed by debromination

Connon and coworkers carried out a number of experiments in order to elucidate the origins of the observed chemoselectivity. Upon analysing the reversibility of these condensation reactions, the authors discovered that homodimers formed from unhindered aromatic aldehydes, such as benzaldehyde (**8**), are generated quickly and are ameanable to retroacyloin reactions in the presence of the NHC catalyst. Crossed acyloins formed from these aldehydes also underwent retroacyloin reactions and hence are observed in lower yields. In contrast, *ortho*-substituted aromatic aldehydes and aliphatic aldehydes were found to dimerise slowly and the corresponding homodimers are formed irreversibly. Hence, cross coupling of these two aldehydes occurs faster than the dimerisation of either aldehyde. The crossed acyloins generated when an *ortho*-substituted aldehyde was present were also found to form irreversibly. The authors continued to explain that the reason for one cross product, as opposed to two, is due to a combination of electronic and steric factors. The NHC, derived from the triazolium precatalyst **100**, is more likely to attack the aliphatic aldehyde **107**

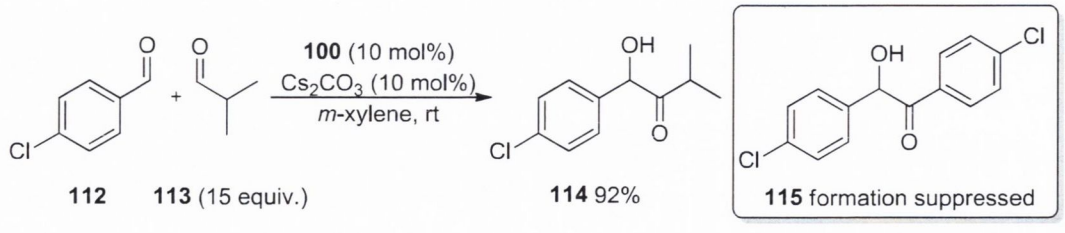
initially as the carbonyl of this aldehyde is more electrophilic than that of *ortho*-bromobenzaldehdye (**104**). This preference of initial attack is also amplified by steric reasons.

The authors also applied this methodology to the asymmetric crossed acyloin condensation. They employed *ortho*-trifluoromethylbenzaldehyde (**110**) as the aromatic partner and upon reacting with **107**, in the presence of the enantiopure precatalyst **52**, the crossed product **111** was obtained in 78% yield and with 77% *ee,* as depicted in Scheme 1.27.



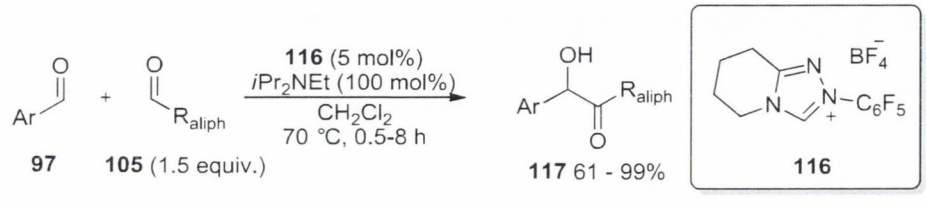
Scheme 1.27 Asymmetric crossed acyloin condensation performed by Connon and coworkers[93]

Yang and coworkers[94] reported that in a crossed intermolecular condensation reaction, the aliphatic to aromatic aldehyde ratio is a critical reaction parameter in observing a chemoselective process. They carried out preliminary studies on isobutyraldehyde (**113**) and *para*-chlorobenzaldehyde (**112**), a problematic substrate in previous studies due to its rapid dimerisation to form its homodimer **115**, in the presence of an NHC. However, Yang discovered that upon using this aromatic aldehyde **112** in conjunction with 15 equivalents of **113**, in the presence of **100**, formation of the homodimer **115** is suppressed allowing the corresponding crossed product **114** to be formed in 92% yield as reported in Scheme 1.28. The authors discovered that this methodology was applicable to a wide range of aromatic aldehydes of contrasting electronic nature and a variety of aliphatic aldehydes and in the presence of **100**, unsymmetrical acyloins were obtained in good to high yields (61 – 98%).



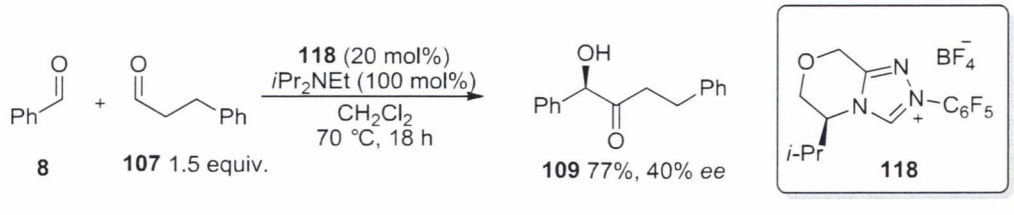
Scheme 1.28 Crossed acyloin condensation in presence of 15 equivalents of isobutaraldehyde (**113**) as reported by Yang and coworkers[93]

Recently, Gravel and coworkers[95] reported the first highly chemoselective crossed acyloin condensation that exploits catalyst properties rather than substrate control. Gravel and coworkers synthesised an achiral triazolium salt bearing a fused piperidine ring (**116**), therefore expanding the ring size of the prevailing fused pyrrole ring (such as that of precatalyst **100**), as reported in previous studies. A study comparing the two catalysts **116** and **100** highlighted that the six-membered ring is optimal as chemoselectivity is lost when the commonly employed precatalyst **100**, bearing the five-membered ring, is employed. Upon elevation of reaction temperature to 70 °C, the NHC derived from **116** catalysed the condensation between benzaldehyde and a range of aliphatic aldehydes (**105**) to generate the corresponding crossed acyloin products in high yields (68 – 89%). Chemoselectivity remained consistent when various substituted aromatic aldehydes (**97**) were employed in conjunction with hydrocinamaldehyde and in the presence of **116**, the corresponding adducts **117** were formed in gratifying yields (61 – 99%), as illustrated in Scheme 1.29.



Scheme 1.29 Cross coupling of aliphatic aldehydes with aromatic aldehydes in presence of novel triazolium precatalyst bearing a six-membered fused ring

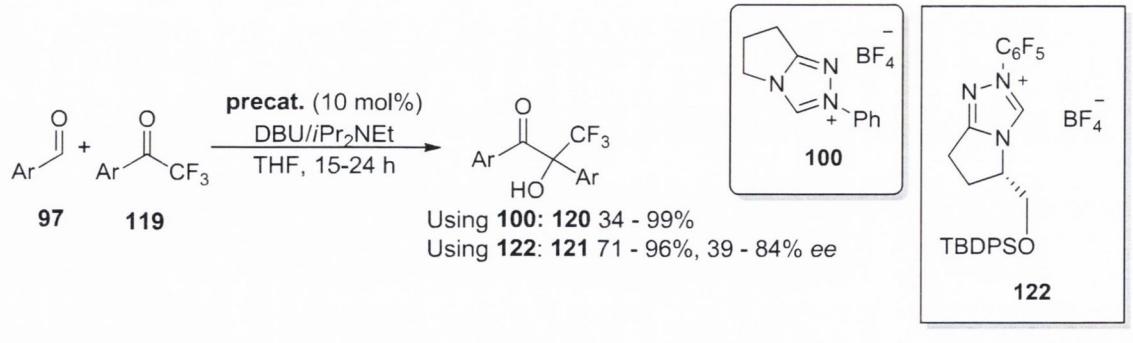
Gravel also employed an enantiopure six-membered fused ring based triazolium precatalyst to the asymmetric crossed acyloin condensation. Upon reacting **8** with **107** in the presence of the morpholine-based triazolium precatalyst **118**, high levels of chemoselectivity were achieved, however, with poor enantiocontrol (Scheme 1.30). The specific origin of chemoselectivity in this process remains unknown.



Scheme 1.30 Enantioselective crossed acyloin condensation in the presence of morpholine-based triazolium precatalyst **118**

1.5.3.2.2 Chemoselectivity: a general overview

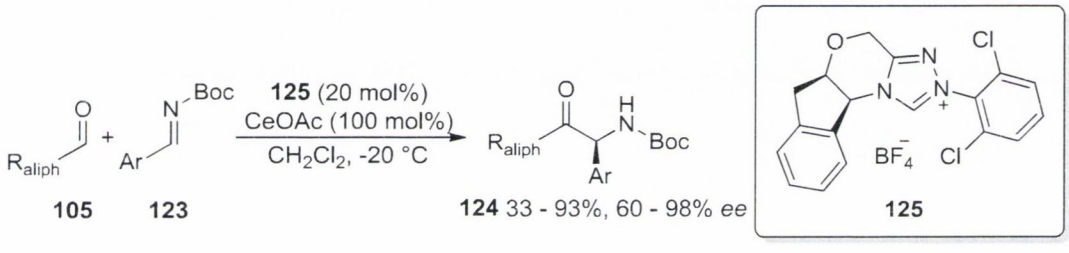
To this point intermolecular crosssed acyloin condensation reactions between two different aldehydes in the presence of a triazolium ion-based precatalyst have been discussed. However, Enders *et al.*[96] demonstrated that 'alternative' substrates can serve as electrophilic reaction partners in this process to allow chemoselectivity to be achieved. The authors published the condensation reaction between various aromatic aldehydes and trifluormethyl ketones (**119**) in the presence of triazolium precatalyts **100**. During initial studies involving the use of benzaldehyde as the aromatic substrate, one crossed product was obtained *albeit* in the presence of benzoin (**9**). Upon employing an excess of DBU, homodimerisation of benzaldehyde was supressed allowing the corresponding crossed acyloins (**120**) to be obtained in high yields. The ketones **119** serve as ideal reaction partners in this process as they are sufficiently electrophilic enough to be attacked by the Breslow intermediate, however, as they are ketones, the possibility of initial attack on these substrates by the NHC is eliminated and the NHC will only attack the aldehyde substrate. A range of aromatic aldehydes were accepted in this condensation and the corresponding products (**119**) were attained in the highest yields (99%) when heteroaromatic aldehydes were employed. In contrast, sterically demanding *ortho*-substituted aromtic aldehydes were tolerated poorly and the corresponding acyloin products were obtained in low yields. Enders and co-workers[97] subsequently reported an asymmetric variant of this process; moderate to high levels of enantiopurity were achieved for the cross coupling of **119** with heteroaromatic aldehydes in the presence of the enantiopure precatalyst **122** as illustrated in Scheme 1.31.



Scheme 1.31 Cross coupling of aromatic aldehydes with highly electrophilic trifluoromethyl ketones as reported by Enders *et al.*[96]

Another variation of the cross benzoin condensation is the cross-aza benzoin condensation that employs an imine as a reaction partner. This concept has a distinct advantage; the

difference in electrophilicity between the aldehyde and the imine substrate is far greater than that between two aldehyde substrates, therefore increasing the possibility of a chemoselective outcome in this process. Based on earlier studies,[98,99,100] reporting the cross coupling of imines with aldehydes in the presence of a NHC, Rovis and coworkers[101] reported the first asymmetric cross-aza benzoin condensation. In the presence of enantiopure chiral precatalyst **125**, cross coupling of aliphatic aldehydes with *N*-Boc protected imines (**123**) rendered the corresponding α-imido ketones (**124**) in moderate to high yields and with high enantiomeric excess, as reported in Scheme 1.32. However, there were limitations in regards to both substrate partners; the use of β-branched aldehydes resulted in low yields being obtained (33%) whilst α-branched aldehydes were not tolerated at all by the catalyst. The use of imines bearing a heterocycle negatively affected the enantioselectivity of the process and imines possessing an *ortho*-substituted phenyl group were not accepted at all.



Scheme 1.32 First enantioselective cross coupling of *N*-Boc protected imines with aliphatic aldehydes in the presence of enantiopure precatalyst **125**, reported by Rovis and coworkers[101]

1.5.4 Limitations associated with the process

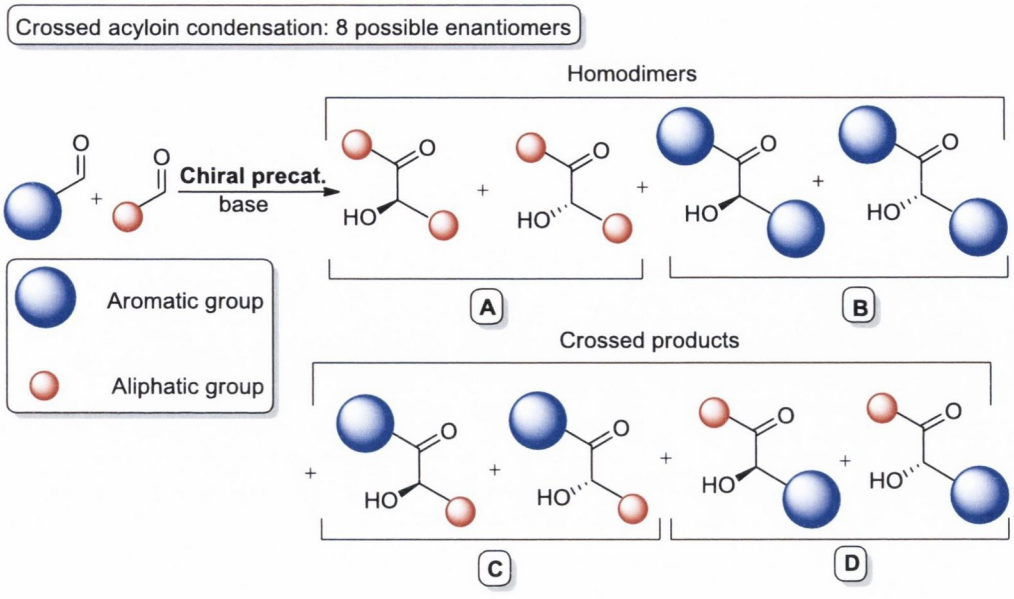
In recent decades, NHCs have developed from poorly-performing thiazolium salts to complicated bifunctional triazolium structures capable of carrying out the homobenzoin condensation with almost maximum efficiency. While extensive studies have been carried out to obtain α-hydroxyketones resulting from a crossed acyloin condensation process, very few have succeeded in reporting a general approach towards a chemo- and enantioselective crossed acyloin condensation that does not involve either a directing group on one partner aldehyde or harsh reaction conditions such as elevated temperatures or large equivalents of one substrate. As highlighted in the previously discussed reports, there are many challenges associated with this process, such as chemoselectivity, enantioselectivity and substrate scope, that must be overcome in order for a successful protocol to be established.

1.5.4.1 Chemoselectivity

A major problem that must be addressed in the crossed acyloin condensation is establishing selectivity in the process to ensure that one product is obtained in high yield. When two different aldehydes are allowed to react in the presence of an achiral NHC catalyst, there are four possible outcomes as illustrated previously in Scheme 1.18; two homodimers **A** and **B** and two crossed products **C** and **D**. Hence, it is essential that a chemoselective bias be established within this process in order for one cross product (**C** or **D**) to be obtained in high yields. As discussed, endeavours in achieving this chemoselective bias have resulted in the use of 'tailored' substrates or large excesses of aliphatic aldehydes in order to suppress the formation of the problematic homodimer **B**. It is necessary to design a catalyst that selectively attacks one aldehyde partner with which it will form the Breslow intermediate, while ensuring that this intermediate preferentially attacks the second aldehyde.

1.5.4.2 Enantioselectivity

If a chiral catalyst is added to the equation, the result is that the four potential products (**A** – **D**) will each yield two enantiomers (*R* or *S*) as illustrated in Scheme 1.33. Hence it is crucial to design a catalyst that is capable of exerting stereocontrol over the reaction, ensuring that the Breslow intermediate attacks the second aldehyde in a face-selective manner, in combination with exerting a chemoselective bias, as discussed above, therefore allowing a single enantiopure product to be synthesised.



Scheme 1.33 The coupling of two different aldehydes in the presence of a chiral precatalyst leads to four potential products being formed; each yielding two enantiomers

1.5.4.3 Substrate scope

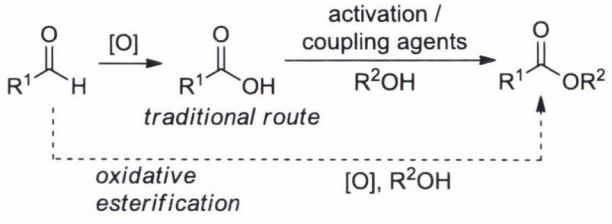
Another challenge of the crossed acyloin condensation occurs when attempting to couple aldehydes of significantly different electrophilicity. The more electrophilic substrate can be expected to more readily form the Breslow intermediate as well as undergo the carbon-carbon bond forming step far faster than the partner substrate, resulting in poor chemoselectivity, thus making the choice of substrates that take part in the condensation reaction of crucial importance. A further intricacy of this process is the enolisable nature of many aliphatic aldehydes in the presence of base, thus these aldehydes are more prone to participating in an aldol condensation rather than a desired cross coupling reaction.

In conclusion, an elegant methodology that accepts a broad substrate scope to allow access to highly synthetically useful, enantiopure, crossed acyloin products remains elusive.

1.6 NHC-mediated oxidative esterification of aldehydes

Esters are a general class of molecules which are so commonplace that their undoubted synthetic importance defies quantification.[102,103] The ester functional group is most commonly accessed *via* a two-step synthetic process involving the initial activation of a carboxylic acid as an acyl halide, anhydride or activated ester followed by the subsequent nucleophilic attack of an alcohol, as illustrated in Scheme 1.34. Recently, interest has grown

steadily towards the development of alternative synthetic methodologies that allow access to ester functionalities *via* one-pot NHC-catalysed oxidative esterifications of aldehydes in the presence of alcohols as nucleophiles.[104]

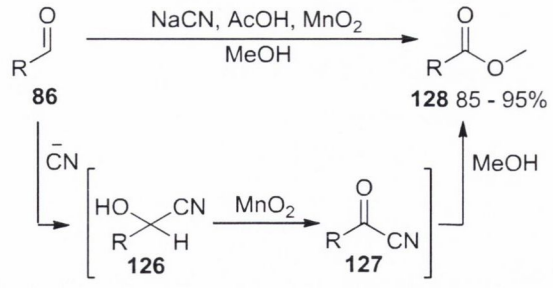


Scheme 1.34 Synthesis of esters from aldehydes; traditional route vs. direct oxidative method

While NHC-based catalysis normally involves *Umpolung* chemistry, as described for the benzoin condensation (see Section 1.3.2.2), the Breslow intermediate common to NHC-based catalytic processes is also amenable to alternative fates; one being oxidation. This oxidative process is commonly encountered in the complex biological process whereby the NHC, generated from the deprotonation of Thiamine Diphosphate (**15b**), catalyses the decarboxylation and subsequent esterification of pyruvate to acetyl-coenzyme A in the presence of the important oxidising coenzyme lipoic acid.[105] Taking the cue from this biotransformation, synthetic organic chemists have developed a steadily growing interest towards the development of oxidative esterification processes involving aldehydes and alcohols which are catalysed by NHCs *via* the *in situ* formation of Breslow intermediates and their subsequent oxidation by means of either a stoichiometric external oxidant (oxidative process) or oxygen (oxygenative process).[106]

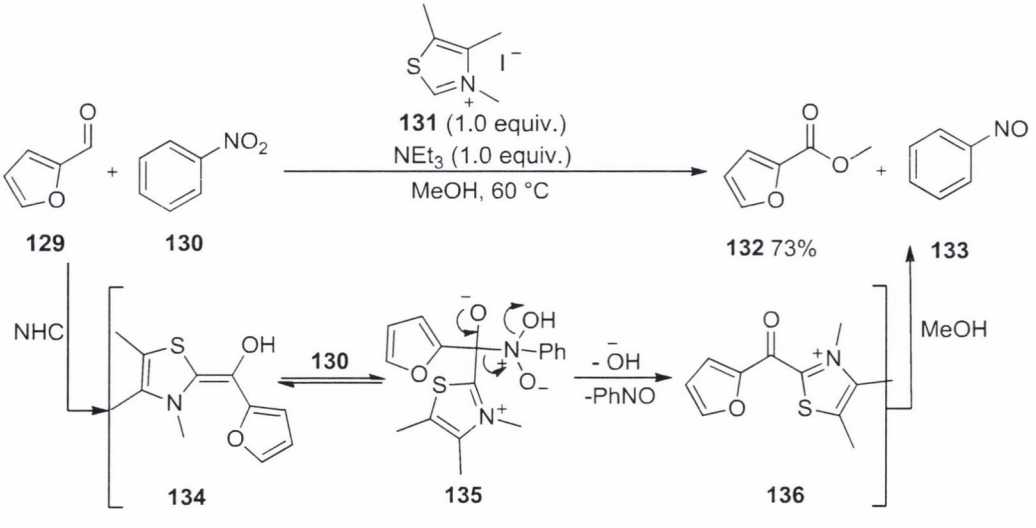
1.6.1 Use of (super) stoichiometric oxidants

A seminal study carried out by Corey *et al.*[107] in 1968 described the cyanide ion-catalysed oxidative esterification of aldehydes (*i.e.* **86**) in the presence of an alcohol and oxidising agent MnO_2. The overall reaction proceeded *via* a one-pot, two step process involving the in-situ formation of cyanohydrin intermediate **126** as illustrated in Scheme 1.35.



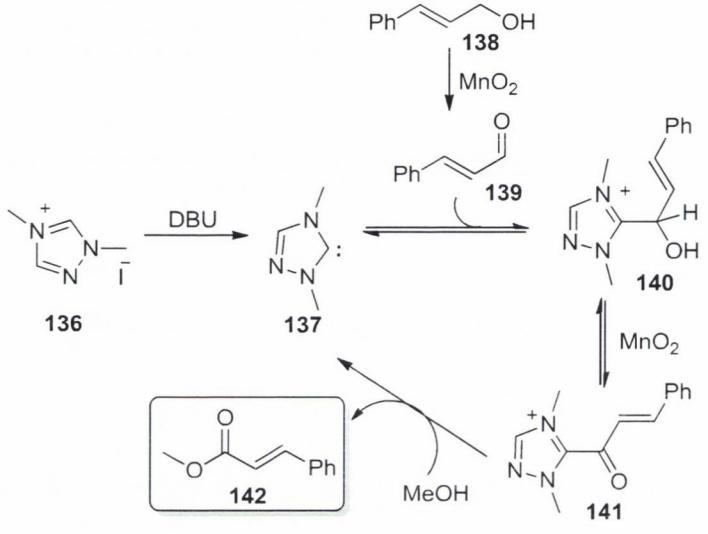
Scheme 1.35 The oxidative esterification of aldehydes in the presence of cyanide ions, reported by Corey *et al.*[107]

Since NHCs share numerous similarities with the cyanide ion in terms of their reactivity with aldehydes,[108] chemists began to investigate the possibility of substituting the cyanide ion with NHC species as catalysts for oxidative esterification processes similar to those reported by Corey. In 1981, Castells *et al.*[109] described the oxidative esterification of 2-furaldehyde (**129**) in the presence of nitrobenzene (**130**) as the oxidising agent and thiazolium-ion precatalyst **131**, both in stoichiometric loadings, as depicted in Scheme 1.36. Upon completion of the reaction, the authors obtained the desired methyl ester **132** and nitrosobenzene **133** as the by-product. The mechanism is believed to occur *via* nucleophilic addition of the Breslow intermediate (**134**), formed upon the attack of the *in situ* formed NHC on aldehyde **129**, to the nitrogen atom of nitrobenzene (**130**). The ensuing proton transfer generates the unstable species **135** which, upon release of a hydroxide anion and **133**, forms the acyl heteroazolium ion **136** that can react with methanol to yield the methyl ester **132**.



Scheme 1.36 NHC-mediated oxidative esterification of aldehyde **129** using **130** as an oxidising agent, as reported by Castells *et al.*[109]

In 2006 Scheidt and coworkers[110] investigated the catalytic performance of a range of azolium-based precatalysts in the conversion of cinnamyl alcohol (**138**) to methyl cinnamate (**142**) in the presence of MnO_2 and methanol. It was reported that when thiazolium, benzimidazolium and imidazolium ion-based precatalysts were employed, the ester product was formed in little or no yield, however, the use of triazolium ion-based precatalyst **136** led to the conversion of alcohol **138** to methyl ester **142** in 93% yield.



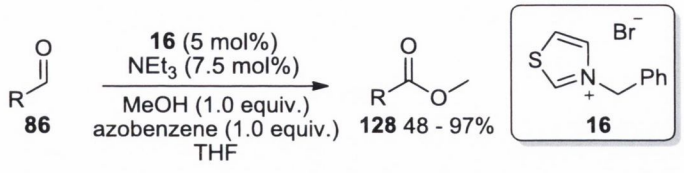
Scheme 1.37 Mechanism for oxidative esterification proposed by Scheidt

Scheidt and coworkers proposed a mechanism for this process which involved two oxidation steps, as outlined in Scheme 1.37. Initially, MnO_2 assists the *in situ* oxidation of alcohol **138** to aldehyde **139** which subsequently reacts with NHC **137** (generated upon deprotonation of the triazolium salt **136**) to form the Breslow intermediate **140**. A diversion from the usual benzoin condensation pathway occurs when intermediate **140** is rapidly oxidised by MnO_2 to the acyl azolium salt **141**. This species then reacts with methanol to afford ester **142** and regenerates carbene **137**, which re-enters the catalytic cycle.

1.6.1.1 Substrate scope

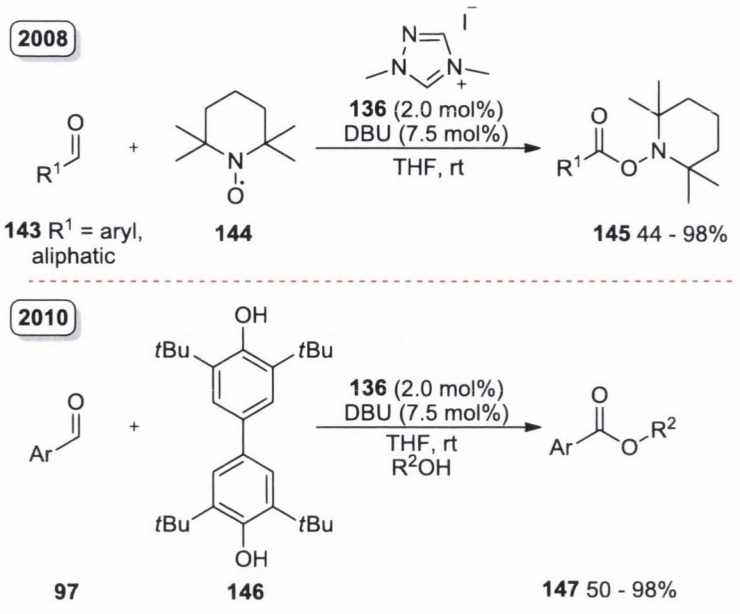
In a bid to broaden the synthetic utility of the NHC-mediated oxidative esterification of aldehydes, Connon and coworkers[111] evaluated the substrate scope for this reaction. In the presence of thiazolium ion-based precatalyst **16**, in 5 mol% loading, and the oxidant azobenzene in stoichiometric quantity, aromatic and aliphatic branched aldehydes were reacted with one equivalent of methanol to generate the corresponding methyl esters (*i.e.*

128) in moderate to good yields (Scheme 1.38). The authors reported that unbranched aliphatic aldehydes were not compatible with this protocol.



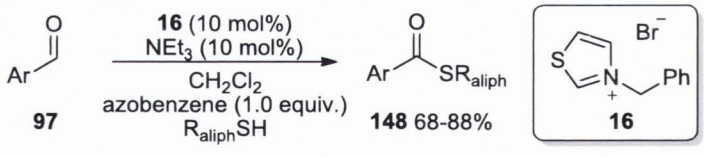
Scheme 1.38 Evaluation of substrate scope for the NHC-mediated oxidative esterification of aldehydes, reported by Connon and coworkers[111]

In 2008, Studer and coworkers[112] employed 2,2,6,6-tertramethyl piperidine *N*-oxyl radical (TEMPO, **144**) as both the oxidant and nucleophile in the NHC-mediated oxidative esterification of aldehydes in the presence of precatalyst **136**. This reaction occurred *via* the formation of a radical cation species to form ester products (*i.e.* **145**). Various aromatic and aliphatic aldehydes were compatible with the NHC-based catalyst in this process, however, aliphatic aldehydes performed poorly and their use resulted in low yields (44%) of ester product being obtained (Scheme 1.39). Following this preliminary report, the same author in 2010 reported a similar protocol[113] involving precatalyst **136** and the readily available oxidating agent 3,3',5,5'-tetra-*tert*-butyldiphenoquinone (**146**) which, in this case, did not act as the nucleophile. The oxidative esterification of aromatic aldehydes in the presence of various alcohols as illustrated in Scheme 1.39 could be obtained in good to excellent yields, however, aliphatic aldehydes proved to be recalcitrant substrates for this transformation.



Scheme 1.39 Use of single-electron transfer oxidants in the NHC-mediated esterification of aldehydes, as reported by Studer and coworkers[113]

In a bid to mimic the catalytic process promoted by the enzyme pyruvate dehydrogenase in the formation of acetyl-coenzyme A, Murata and coworkders[114] studied the oxidative thioesterification of aromatic aldehydes (*i.e.* **97**). Various thioesters **148** could be formed by reacting aldehydes and aliphatic thiols in the presence of azobenzene as the oxidising agent and thiazolium precatalyst **16** (Scheme 1.40). Electron-deficient aromatic aldehydes were better tolerated in this transformation compared to electron-rich aromatic aldehydes and resulted in the highest yields (88%) of thioester (*i.e.* **148**) being formed.

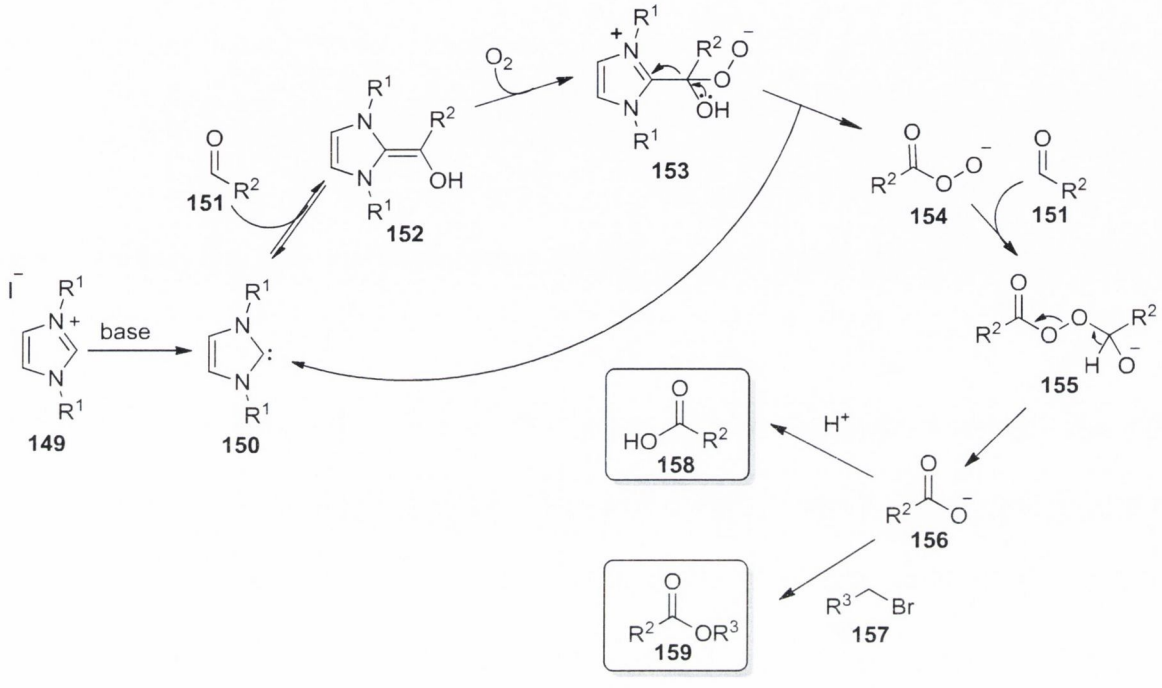


Scheme 1.40 NHC-catalysed oxidative thioesterification of aromatic aldehydes reported by Murata and coworkers[114]

1.6.2 Use of O_2 as the oxidant

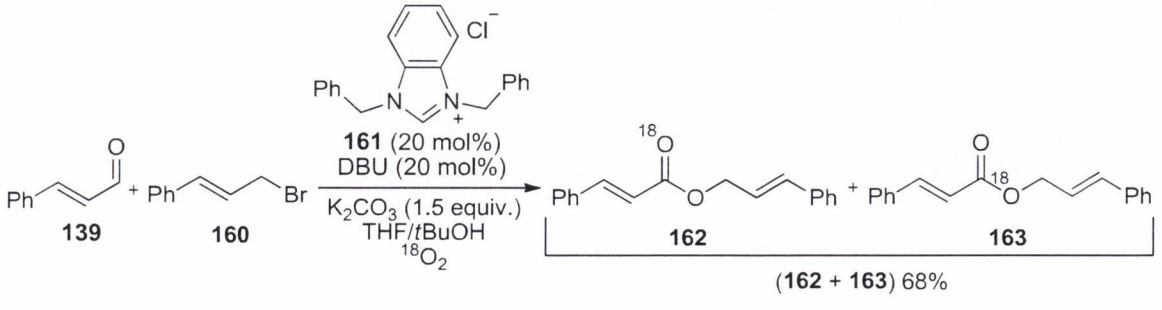
In the presence of molecular oxygen as the stoichiometric oxidant, it has been proposed that a separate oxidative fate for the Breslow intermediate occurs. Mechanistic studies on this process have reported that addition of O_2 to the Breslow intermediate **152** affords the peroxy Zwitterionic species **153**[115] as shown in Scheme 1.41. The ensuing fragmentation of intermediate **153** subsequently regenerates the NHC and yields the peroxycarboxylate **154**

which then reacts with a second equivalent of aldehyde **151** (*via* the peroxyester intermediate **155**) to generate the carboxylate ion **156**.[116] This species can ultimately act as a base to afford carboxylic acids (i.e. **158**) upon protonation or react with alkyl halides (i.e. **157**) to yield esters such as **159**.



Scheme 1.41 Mechanism of the NHC-promoted oxygenative aldehyde oxidation

To support this mechanism, Liu and coworkers[117] used $^{18}O_2$ as an oxidant in the NHC-catalysed oxygenative esterification of cinnamaldehyde (**139**) in the presence of cinnamyl bromide (**160**) as depicted in Scheme 1.42. The result obtained with this experiment was in agreement with the postulated mechanism described above since, in the presence of precatalyst **161**, isotopically labelled esters **162** and **163** could be formed in a 1:1.25 ratio and a combined yield of 68%.

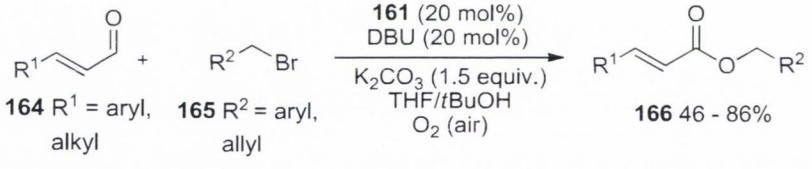


Scheme 1.42 Isotopic labelling experiment using $^{18}O_2$ as the oxidant, carried out by Liu

Zhang[118] and Nair[119] independently reported the NHC-mediated oxidation of aryl and cinnamyl aldehydes to carboxylic acids using carbon dioxide instead of molecular oxygen. However, these studies were questioned by Bode, who suggested that exogeneous molecular oxygen is the oxidant in these processes. Bode and coworkers[120] repeated the authors' experiments using O_2 as the stoichiometric oxidant, both in the presence and absence of CO_2. Similar yields of acid product were reported with and without CO_2 therefore proving that O_2 is indeed the oxidant in these transformations.

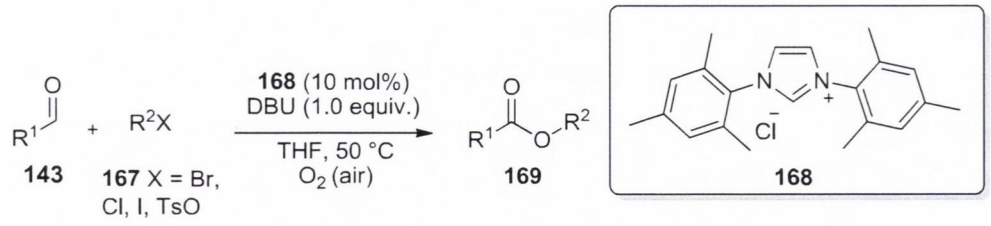
1.6.2.1 Substrate scope

In addition to the isotopic labelling experiments mentioned above, Liu and corkers[117] also studied the esterification of a wide range of cinnamyl aldehydes **164** in the presence of different aryl and allyl bromides **165**. In these reactions the use of atmospheric oxygen as the oxidising agent in the presence of precatalyst **161** could lead to the formation of the corresponding esters **166** in moderate to good yields (Scheme 1.43). The use of aromatic aldehydes in this protocol resulted in poor product yields which could be significantly improved only by using MnO_2 as the oxidant.



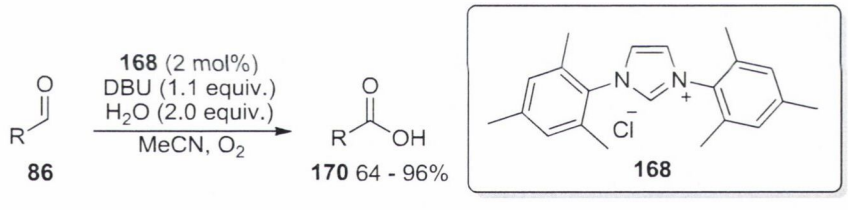
Scheme 1.43 NHC-mediated oxidative esterification of aldehydes **164** in the presence of aryl and allyl bromides **165**, as reported by Liu

Hui and co-workers[116] reported the use of alternative electrophiles **167** in the oxygenative esterification of aldehydes in the presence of the imidazolium ion-based precatalyst **168** and using atmospheric oxygen as the oxidant. A wide range of aromatic and aliphatic aldehydes were coupled with various unactivated alkyl halides and tosylates (**167**) to generate the corresponding ester products **169** in good to excellent yields as illustrated in Scheme 1.44. The use of aromatic substrates bearing electron-withdrawing substituents led to higher yields of ester product **169** being obtained, while electron-rich aromatic aldehydes performed poorly in this transformation, giving rise to lower product yields. A variety of electrophiles could be tolerated in this protocol such as those bearing iodine, tosylate and chloride as the leaving group.



Scheme 1.44 Oxygenative esterification of aldehydes in the presence of imidazolium precatalyst **168**

More recently Blechert and coworkers[121] reported a protocol for the NHC-mediated oxidation of aldehydes to their corresponding acids, in the presence of molecular oxygen, employing a wide range of aldehyde substrates (Scheme 1.45). This process employed water as the nucleophile. Contrary to their poor performance in similar processes as reported in earlier studies, the use of electron rich aromatic aldehydes in the protocol developed by Blechert led to the formation of carboxylic acids (**170**) in moderate to excellent yields (64 – 96%). Aliphatic and α,β-unsaturated aldehydes also performed extremely well generating the acid products in uniformly high yields (68 – 91%). Notably the authors reported that by using atmospheric oxygen instead of O_2, no repercussion on product yields could be observed.



Scheme 1.45 NHC-mediated oxidation of aldehydes to their corresponding acids as reported by Blechert and coworkers[121]

1.6.3 Challenges

The potential of NHC-mediated oxidative esterification reactions using aldehydes and an oxidising agent in stoichiometric loadings, has recently begun to be appreciated as a synthetic tool in natural product synthesis.[122,123] A major drawback associated with this protocol, however, is the use of highly toxic oxidising agents which renders these types of synthetic processes of little practical use on larger scales as carried out at a pharmaceutical industry level. In contrast, the use of molecular oxygen as an alternative inexpensive, non-toxic and environmentally-friendly oxidising agent for 'oxygenative' esterifications of aldehydes has the potential to circumvent the limited applicabilities of metal-based and organic oxidising agents.[124] Protocols involving the use of molecular oxygen have proved relatively successful,

especially in the synthesis of carboxylic acids from aldehydes. However, 'oxygenative' esterification processes leading to the formation of ester products using alkyl halides are rarely reported as being high yielding, mainly because these reactions are extremely sensitive to moisture and carboxylic acid is always formed as an unwanted side product in these transformations. [121] Anand and coworkers[125] reported the aerobic esterification of aldehydes, a protocol that does not employ an external oxidant. However, this procedure used boronic acids in place of alcohols. Therefore the development of an NHC-mediated, aerobic aldehyde esterification, that tolerates a broad substrate scope would prove a highly significant development in the area of NHC organocatalysis.

1.7 Aims and Objectives

From above, it is clear that there have been numerous studies carried out on the reaction between aldehydes and NHC catalysts. It has been established that the initial interaction between these two species leads to the generation of the very important Breslow Intermediate. The Breslow Intermediate is then subject to various fates depending on the substrates and the reaction conditions that are present. However, these fates are not fully understood and often the outcome of the various reactions is not predictable. For example it is unclear when two aldehydes are allowed to react in the presence of an NHC catalyst, which aldehyde will react with the catalyst and which, if either, will react with the Breslow Intermediate. An elegant methodology that accepts a broad substrate scope to allow access to highly synthetically useful, enantiopure, crossed acyloin products remains elusive. Hence the aim of this project, as described in the following chapters, is to understand the factors that govern both Breslow Intermediate formation and subsequent Breslow Intermediate reaction. Once we understand these, we hope to predict the fate of the Breslow Intermediate and eventually obtain the medically useful, final products from these reactions in high yields.

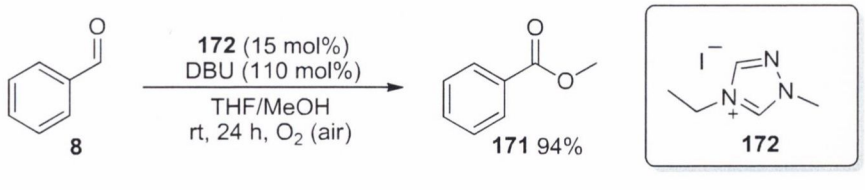
2. Aerobic oxidative transformations catalysed by a triazolium ion-based precatalyst

2.1 Aerobic oxidative esterifications of aldehydes: aims and objectives

Our research group carried out an investigation into the use of magnetite nanoparticles as a co-catalyst for the NHC-mediated oxidative esterification of aldehydes. It was postulated that the NHC/magnetite catalyst would provide a surface capable of catalysing the oxidation of the Breslow intermediate whilst the magnetic nature of the nanoparticle would also allow for simple recovery of the 'tethered' catalyst, thus presenting a far more efficient process than those reported previously. In a bid to determine what role the nanoparticle plays in this process, the nanoparticle was removed and the 'detached' triazolium ion-based precatalyst was added to the reaction. It was observed that, in the absence of the nanoparticle, partial esterification of benzaldehyde (**8**) in methanol under aerobic conditions took place. These preliminary studies were performed by Ms. Alessandra Mari. After reproducing the result several times, our research group embarked on a study to determine the factors which influence the efficiency of this catalytic process.

2.1.1 A preamble to the preliminary optimisation of reaction conditions

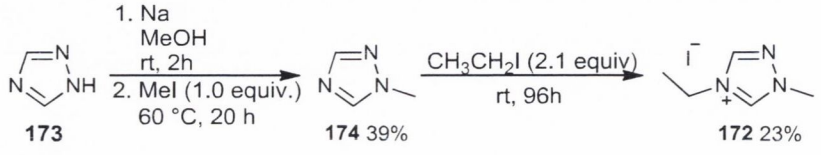
Preliminary experiments, carried out by Mr. Eoghan Delany, revealed that ester formation was prevented in the absence of air, suggesting that atmospheric oxygen acts as the oxidant in this process, as described in previous reports (see Section 1.6). Further experiments revealed that **8** could be esterified to a detectable extent in methanolic THF (1:1 *v*/*v*) in the presence of triazolium ion-based precatalysts (15 mol%) and a small excess of base (DBU, 110 mol%) under an O_2 (air) atmosphere.



Scheme 2.1 Oxidative esterification of benzaldehyde (**8**) in the presence of triazolium precatalyst **162**

Mr E. Delany subsequently examined the influence of the precatalyst structure on the efficiency of the process. It was observed that in the absence of triazolium ions, no

conversion of **8** to methyl benzoate (**171**) occurred. A variety of triazolium salts were examined under the optimised reaction conditions and the NHC, derived from precatalyst **172**, proved far superior in promoting this process, allowing ester formation to occur in 96% yield (Scheme 2.1). The triazolium salt **172** was easily synthesised from commercially available 1,2,4-triazole (**173**). Methylation of **173** followed by an *N*-alkylation of **174** with ethyl iodide furnished precatalyst **172** in low yield (Scheme 2.2).



Scheme 2.2 Synthesis of triazolium ion-based precatalyst **172**

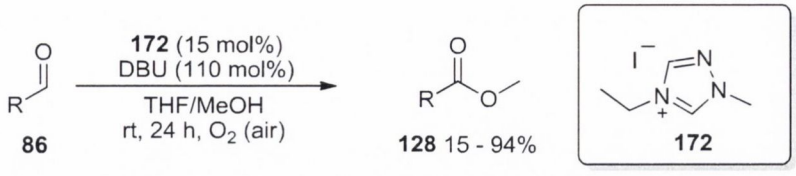
Having established the NHC derived from precatalyst **172** as the superior catalyst in this process, our research group proceeded to determine the influence of the other reaction components on the process. THF could be exchanged for CH_2Cl_2, however, with an attendant loss in product yield to 87%. Notably, when methanol was employed as the sole solvent, ester product formation occurred in a diminished yield of 68%; suggesting that THF is capable of aiding oxygen diffusion into the system. Reduction of the loading of the triazolium ion **172** to 5 mol% led to a similar reduction in efficacy, as the ester product **171** was obtained in 74% yield. It was also discovered that the oxidation process also strongly depends on both the loading and the identity of the base. DBU present in 110 mol% resulted in the highest yields (94%) of ester product **171** being obtained. In contrast, the use of TEA, DMAP and DABCO (also present in 110 mol%) led to the formation of little or no ester product.

2.1.2 Evaluation of substrate scope

2.1.2.1 The aldehyde component

With a useful protocol in hand, the compatibility of the new process with different aldehydes (**86**) was next investigated by Mr. E. Delany and Dr. Sivaji Gundala. It was found that electron-neutral (such as benzaldehyde) and deactivated aromatic aldehydes (such as *para*-tolualdehyde) could be converted to the corresponding methyl esters (**128**) in excellent isolated yield in the presence of **172**, DBU, methanol and air as shown in Scheme 2.3. Activated benzaldehydes such as *meta*-chlorobenzaldehyde proved an excellent substrate, while, interestingly, the esterification of its *para*-substituted (and less hindered) isomer proceeded in a diminished yield. Disappointingly, both aliphatic and *ortho*-substituted

aromatic aldehydes were not well tolerated as the corresponding ester products **128** were obtained in yields as low as 15%.



Scheme 2.3 Substrate scope: aldehyde component

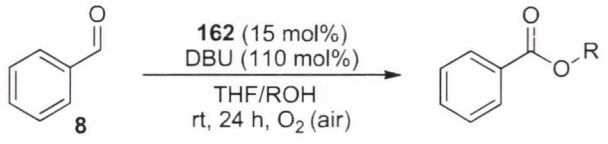
2.1.2.2 The alcohol component

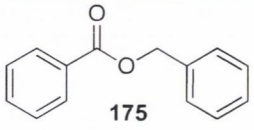
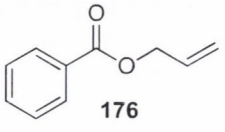
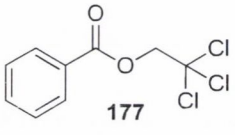
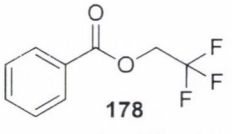
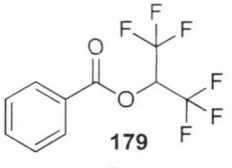
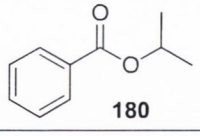
Having demonstrated the broad substrate scope of this reaction with regards to the aldehyde component, we next turned our attention to the alcohol component. The esterification of benzaldehyde (**8**) was carried out in the presence of **172**, DBU and a series of alcohols, at 45 °C, as illustrated in Table 2.1.

Initial studies were carried out using a 1:1 THF/alcohol solvent mixture (Table 2.1, condition set A). The use of benzyl alcohol allowed the corresponding ester **175** to be obtained in an excellent 94% yield (entry 1). Whilst the use of allyl alcohol led to uniformly high yields of ester product **176** being obtained (entry 2), it was postulated that alcohols of lower pK_a would undergo facile deprotonation, under the basic reaction conditions, and would therefore result in increased product yields. However, upon employing acidic alcohols, the opposite occurred (entries 3 - 6). The use of 2,2,2-trichloroethanol resulted in a moderate yield (64%) of the corresponding ester product **177** being formed while the use of 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoro*iso*propanol failed to yield any ester product.

In a bid to improve the synthetic utility of this process, efforts began to resolve the issues arising from the use of alcohols of lower pK_a. It was postulated that in the presence of a 1:1 ratio of alcohol to THF, the pH of the reaction media was lowered to an extent that the *in situ* carbene generation is hampered. We reasoned that reducing the volume of alcohol in the system would allow the deprotonation of both the triazolium salt (to generate the NHC) and the alcohol to occur in an environment of suitable pH.

Table 2.1 Reaction scope: alcohol component



Entry	Alcohol pK_a	Condition set[a]	Product	Yield (%)
1	15.4	A B	 **175**	94 72
2	15.5	A B	 **176**	87 69
3[b]	12.3	A B	 **177**	64 61
4[b]	12.4	A B	 **178**	0 55
5[b]	11.2	A B	 **179**	0 25[c]
6[b]	17.1	B	 **180**	0

[a]Carried out at 45 °C. Condition set A: THF/ROH (1:1 *v/v*). Condition set B: THF solvent, ROH (3.0 equiv.), rt. [b]Reaction performed at rt. [c]Yield determined by ^{1}H NMR spectroscopy only

We examined the process in the presence of just 3 equivalents of alcohol in THF solvent (Table 2.1, condition set B). Both the benzylic and allylic alcohols provided the corresponding products **175** and **176** in good yield. It was found that formation of the trichloroethanol-derived **177** proceeded in *ca.* 60% yield irrespective of the conditions employed.

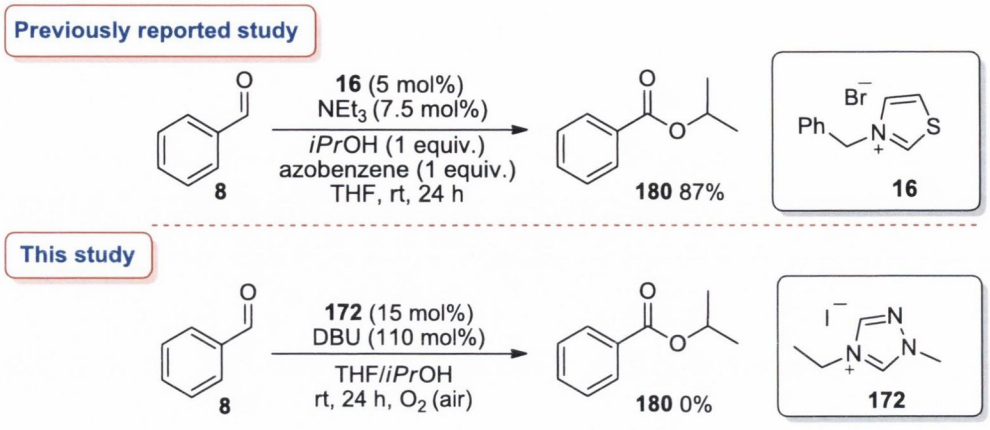
Though 2,2,2-trichloroethanol and 2,2,2-trifluoroethanol possess practically identical pK_a values (entries 3 and 4), the obtained yields of the corresponding ester products **177** and **178** differ dramatically under condition set A. It is speculated that the lack of formation of **178**,

under this condition set, is due to the volatility of its parent alcohol which has a low boiling point of 58 °C. Under condition set A, the evaporation of 2,2,2-trifluoroethanol from the system does lead to carbene generation becoming more favourable however, at the expense of a limited amount of alcohol available to act as the nucleophile in the reaction. In comparison, carbene generation is slower when 2,2,2-trichloroethanol is employed, under condition set A, however, the amount of alcohol remains consistent. Considering condition set B necessitated a low volume of alcohol, the reactions employing the volatile flouro- substituted alcohols and *iso*propanol were carried out at room temperature (entries 4 – 6). Gratifyingly, when the reactions were carried out under condition set B and at room temperature, the trifluoro-analogue **178** was synthesised in 54% yield. The use of hexafluoro*iso*propanol under the same reaction conditions resulted in the formation of the corresponding ester product **179** *albeit* in low yield (25%) as perhaps the pK_a of this alcohol is too low to be compatible with the system (entry 5). Whilst this low yield of **179** is not synthetically useful, it provides evidence to support our hypothesis. The more hindered and less acidic *iso*propanol proved resistant to esterification: ester **180** could not be generated (entry 6).

2.1.3 Mechanistic insight

To the best of our knowledge, this methodology described in the previous Section, represents the most efficient NHC-mediated aerobic oxidative esterification process using alcohols and air as the sole oxidant in the literature. With the breadth of the reaction scope established, we attempted to divine some information regarding the reaction mechanism. The results of our studies (outlined in Section 2.1.2) are not readily reconciled with either 'oxidative' or 'oxygenative' mechanisms proposed in the literature (Scheme 1.37 and Scheme 1.41). 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 due to the steric bulk of both the nucleophilic and electrophilic reaction components, is not consistent with that observed in a previous study, reported by our research group,[111] involving the use of azobenzene as a stoichiometric reactant. In these esterifications involving azobenzene as an oxidant, bulky reagents such as *ortho*-tolualdehyde and *iso*propanol served as excellent coupling partners with methanol and benzaldehyde, respectively. For example, the reaction between **8** and *iso*propanol allowed the ester product **180** to be formed in 87% yield, while in this study no ester product was formed from the reaction between these two substrates (Scheme 2.4). This strongly indicates that our

aerobic oxidative esterifications outlined above do not proceed *via* acyl azolium ion intermediates.

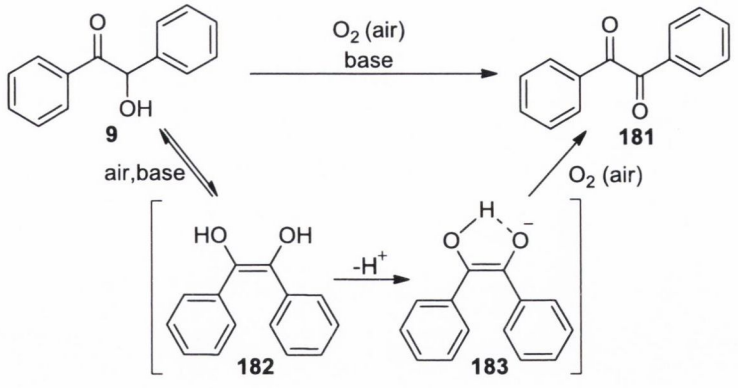


Scheme 2.4 Comparison of NHC-mediated esterifications of **8** in the presence of *iso*propanol; the former employing stoichiometric azobenzene as the oxidant and the latter employing O_2 (air) as the oxidant

2.1.3.1 Serendipity: observation of benzoin

Since the esterifications do not proceed in the absence of O_2, we were forced to consider alternative species which are oxidised in these reactions. Serendipitously, in a bid to examine the rate of ester product formation, the reaction between **8** and MeOH (Scheme 2.1) was analysed by ^{1}H NMR spectroscopy after 5 minutes reaction time. To our surprise low yields of benzoin product (**9**) were observed. Hence we postulated that benzoin was the likely candidate being oxidised in this process – the slow, base-catalysed aerobic oxidation of which to benzil (**181**) by O_2 is known.[126] The keto-enol tautomeric equilibrium that occurs in the presence of air and base facilitates formation of the enol **182**. Deprotonation of **182** forms the enediolate intermediate **183** which further reacts with oxygen to form **181**, as illustrated in Scheme 2.5.[127]

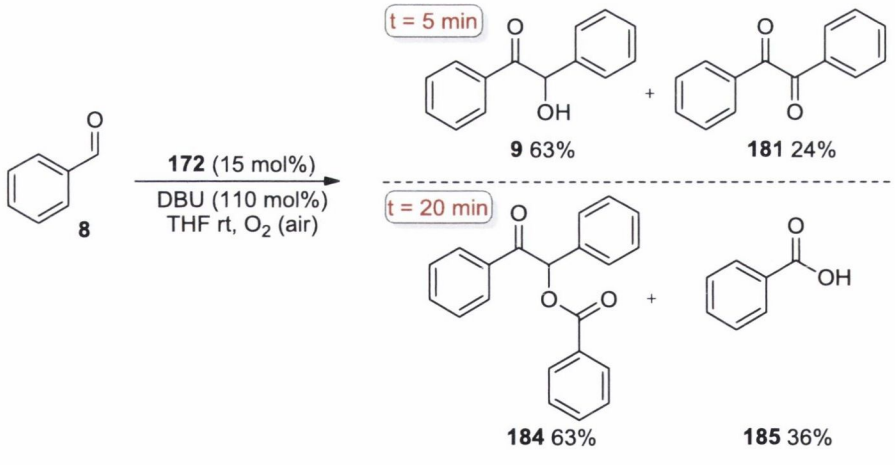
While **181** was never isolated/observed in any of the reactions outlined above, it is a highly electrophilic species: therefore its rapid destruction in the presence of the relatively unhindered carbene, derived from triazolium precatalyst **172**, and methanol was not implausible. In addition, while the sensitivity of the esterifications to steric factors (Scheme 2.4) did not match that of known processes involving acyl azolium ions, it was consistent with the influence of steric bulk on the benzoin condensation,[128,129,130] which encouraged us to further investigate this hypothesis.



Scheme 2.5 Base-catalysed aerobic oxidation of benzoin (**9**) to benzil (**181**)

2.1.3.2 Preliminary experiments

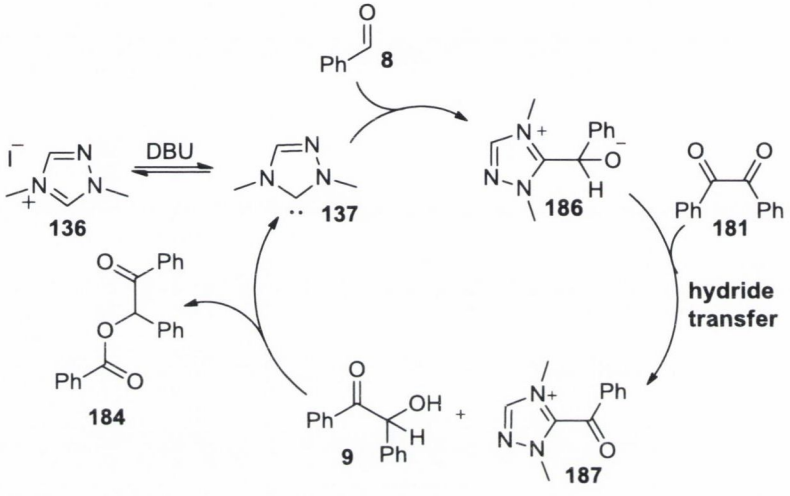
In order to prove this hypothesis, we began by subjecting benzaldehyde (**8**) to the esterification conditions in the absence of methanol. Gratifyingly, we observed the formation of both **9** and **181** after just 5 min (Scheme 2.6). After 20 min, both these species were replaced by a hydroacylation product **184** in good yield and the acid **185**, presumably formed due to the presence of adventitious water. (Note: yields were calculated by ^{1}H NMR spectroscopy using styrene as an internal standard.)



Scheme 2.6 The observation of benzil (**181**), a hydroacylation product **184** and the acid **185** in the absence of methanol

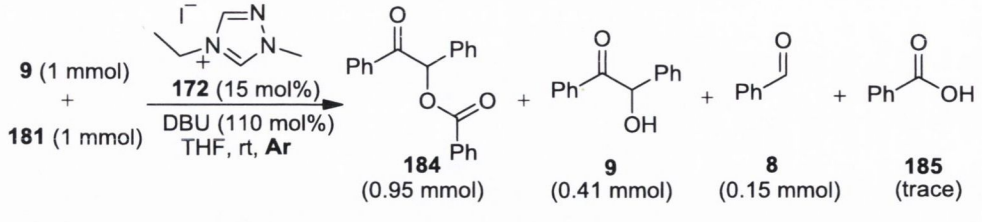
Scheidt *et al.*[131] have previously reported the formation of **184** in the NHC-mediated reaction between benzaldehyde (**8**) and benzil (**181**). This reaction is the first example of the efficient anaerobic NHC-mediated formation of a hydroacylation product from an aldehyde. They

rationalised this process in terms of a hydride transfer process between the intermediate **186** (formed from the reaction between carbene **137** and **8**) and benzil (**181**) to form benzoin product **9** (or more specifically its enol whilst present in a basic environment). The resulting product **9** can then undergo an acylation reaction with the species **187**, formed *in situ*, to generate the hydroacylated product **184** and carbene **137**, which re-enters the catalytic cycle as shown in Scheme 2.7. In the same study, Scheidt also reported that the intermediate **186** can also be formed from the collapse of **9** upon attack of the NHC **137** on the electrophilic moiety of **9**.



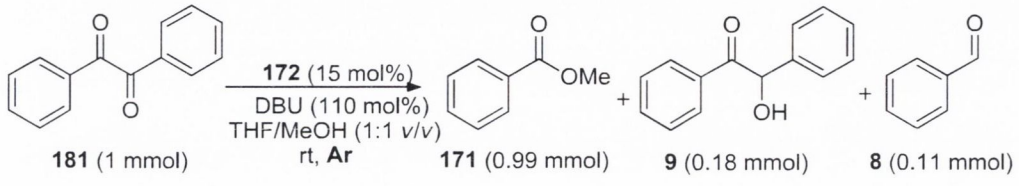
Scheme 2.7 First example of the aerobic NHC-mediated formation of a hydroacylation product from an aldehyde, as reported by Scheidt

We wished to investigate the role of intermediates **181** and **184** in our NHC-mediated esterification of aldehydes. A reaction was carried out, using precatalyst **172**, between **9** and an equivalent amount of **181** in the absence of both air and MeOH. The hydroacylation product **184** was observed as the major constituent of the crude reaction mixture as illustrated in Scheme 2.8, indicating that benzoin may also be able to play the role of the nucleophilic alcohol in these reactions.



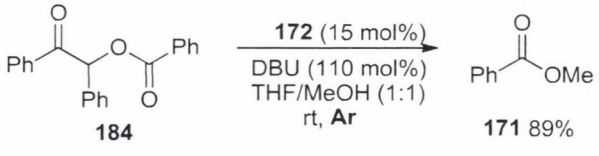
Scheme 2.8 Reaction between benzoin (**9**) and benzil (**181**) in the absence of methanol and air

We also attempted to establish if benzil (**181**) is a catalytically relevant intermediate in the presence of alcohol. Accordingly, an experiment was conducted where **181** was exposed to methanol and the NHC, generated from precatalyst **172**, under an argon atmosphere. Under these conditions and at ambient temperature, rapid conversion of **181** to methyl benzoate (**171**) was observed along with the presence of **9** and aldehyde **8** as shown in Scheme 2.9.



Scheme 2.9 Reaction of benzil with methanol in the presence of precatalyst **172**

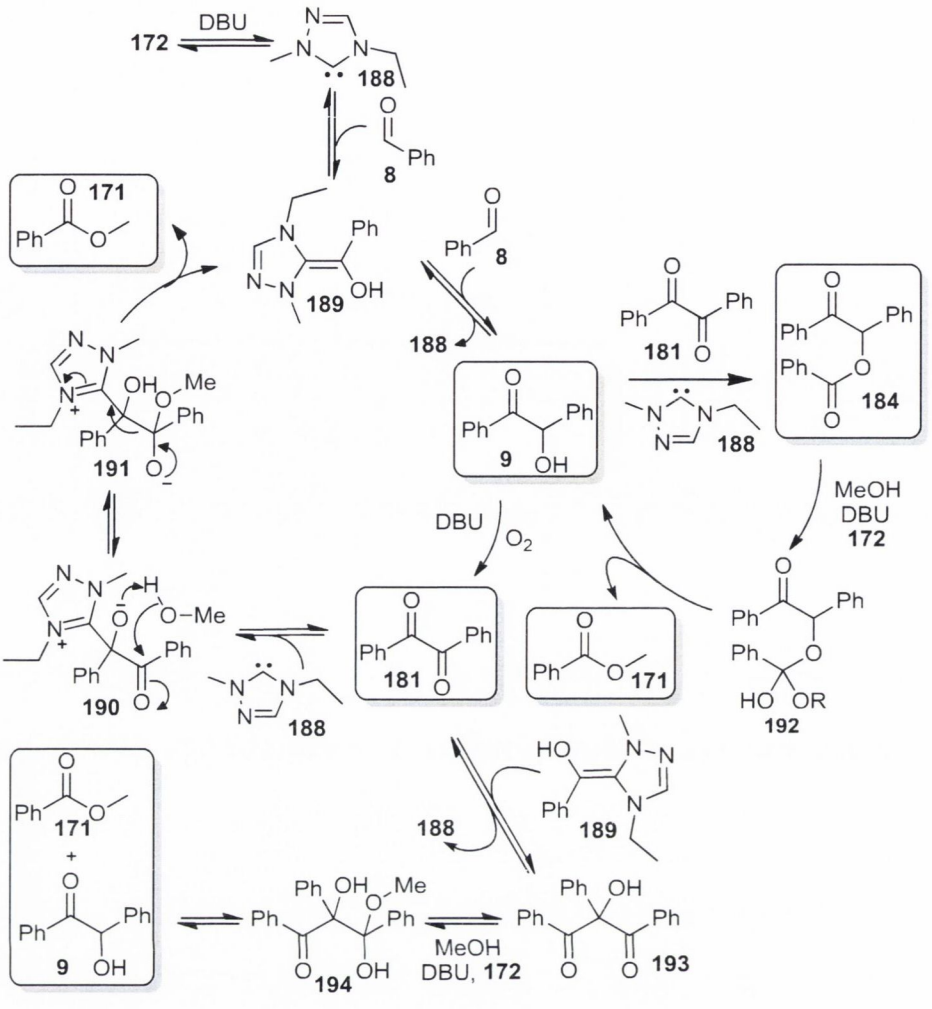
However, the hydroacylation product **184** was found to be conspicuously absent in the ^{1}H NMR spectra of reactions involving methanol or other smaller alcohols. Therefore the stability of **184** under anaerobic reaction conditions was assessed by Dr. S. Gundala, as shown in Scheme 2.10. In the presence of precatalyst **172**, DBU and methanol, smooth acyl transfer to afford methyl benzoate **171** in excellent yield was observed.



Scheme 2.10 Collapse of hydroacylation species **184** to generate methyl benzoate (**171**), in the presence of NHC carbene and methanol

2.1.3.3 A proposed mechanism: benzoin is the oxidised species

These studies allow the proposal of a mechanistic rationale, different to those mentioned previously in Section 1.6. The carbene **188** reacts with aldehyde **8** to form the enaminol **189** which, on addition to another molecule of **8** results in the rapid formation of **9** which is oxidised by air in the presence of base to benzil (**181**).



Scheme 2.11 Proposed mechanism for NHC-mediated oxidative esterification of benzaldehyde (**8**)

Since our results are not consistent with acyl azolium ion formation, we would propose that the electrophilic diketone **181** is attacked by NHC **188** to give the tetrahedral intermediate **190**, which is converted to **191** *via* intramolecular general base catalysis. The hemiacetal **191** can then collapse to reform the enaminol **189** and methyl benzoate **171**. The formation of the hindered hemiacetal **191** 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 **9** as the nucleophile, which affords the hydroacylation product **184**. In the presence of MeOH **184** is quickly converted to **9** *via* **192**.

The formation of benzoin (**9**) from benzil (**181**) in the absence of O_2 (but presence of methanol) also requires explanation: we would suggest that - by analogy with a recent proposal, reported by Massi,[132] in a distinct but related transformation – attack by the

enaminol **189** on diketone **181** would yield **193**. In the presence of excess base and methanol, the cleavage of **193** to yield ester **171** and **9** *via* hemiacetal **194** is conceivable.

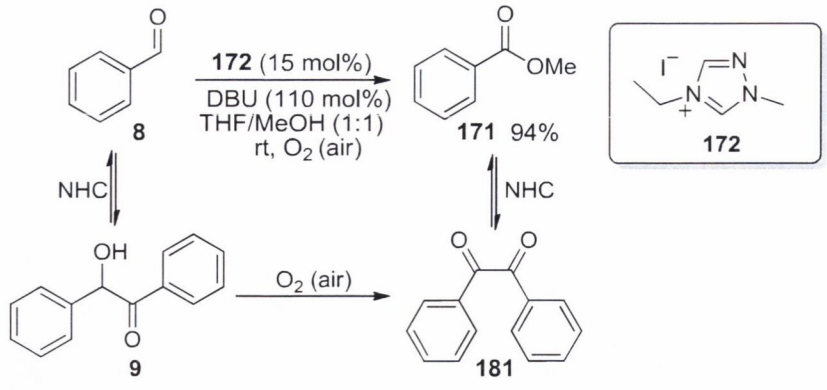
2.2 Aerobic oxidative cleavage of 1,2-diketones

The oxidative cleavage of 1,2-diols (*i.e.* 'breaking' of a carbon-carbon bond) is a time-honoured synthetic tool of enormous importance and is just as important and synthetically useful as its complimentary process: the formation of carbon-carbon bonds. By contrast, the corresponding oxidative cleavage of 1,2-diketones to yield carboxylic acids has received considerably less attention. There are a number of methods available for this transformation involving the use of stoichiometric oxidants such as oxone™,[133] calcium perchlorate,[134] CuCl/pyridine/O_2[135] and sodium percarbonate/alkaline H_2O_2.[136,137] However, the majority of these protocols were performed at elevated temperatures with the use super stoichiometric amounts of metal salts leading to the possible release of toxic substances. The photochemical aerobic oxidation of phenathrene on silica gel is also possible, but yields multiple products.[138]

To the best of our knowledge, no catalytic version of this reaction is known, although a single example of the oxidative esterification of a 1,2-diketone catalysed by dichloroethoxyoxyvanadium in ethanol (under an O_2 atmosphere) has been reported by Momose *et al.*[139] Therefore an elegant methodology that allows for the catalytic cleavage of 1,2-diketones to generate highly synthetically useful 1,2-dicarboxylic acids or esters, in the absence of transition metals, remains elusive.

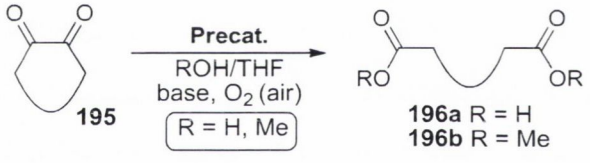
2.2.1 Preliminary experiments: proof of concept

In Section 2.1, we discussed the detection (and confirmation of the intermediacy) of benzil (**181**) in the aerobic oxidative esterification of benzaldehyde (**8**) to methylbenzoate (**171**) catalysed by the carbene derived from the triazolium ion **172** in the presence of stoichiometric DBU and methanol as illustrated in Scheme 2.12.



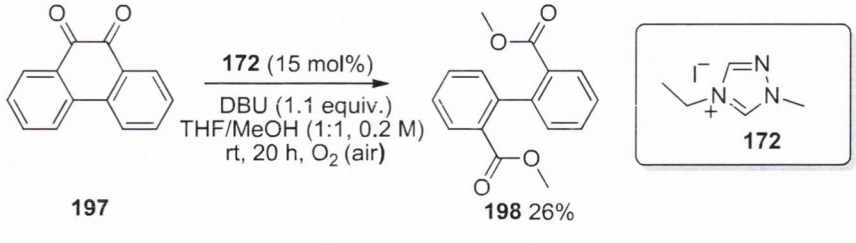
Scheme 2.12 Rationale for NHC-mediated oxidative cleavage of 1,2-diketones, based on previous work carried out by our research group

This led us to propose that if one exposed a cyclic 1,2-diketone **195** (instead of an aldehyde) to similar conditions it could bring about an organocatalytic oxidative cleavage reaction to give either dicarboxylic acids (*i.e.* **196a**) or diesters (*i.e.* **196b**), depending on the protic nucleophile used (Scheme 2.13). In the absence of evidence to the contrary, these distinct but related oxidative cleavage transformations could be potentially rationalised in a similar fashion.



Scheme 2.13 Proposed organocatalytic cleavage of 1,2-diketones

To test this hypothesis, a preliminary experiment was executed whereby phenanthrene-9,10-dione (**197**) was reacted with methanol in air in the presence of precatalyst **172** and DBU (Table 1). In 1:1 THF:MeOH at ambient temperature we were pleased to obtain the ring-opened diester **198**, albeit in a low yield of 26%.

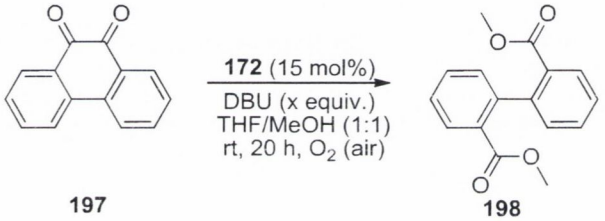


Scheme 2.14 Preliminary experiment for oxidative cleavage of phenanthrene-9,10-dione (**197**) to generate 1,2-dicarboxylic ester **198** in the presence of precatalyst **172**

2.2.2 Optimisation of the general reaction conditions

Attempts were made to increase the synthetic utility of this reaction. Increasing the reaction concentration to either 0.5 or 1.0 M had only marginal influence on efficiency (Table 2.2, entries 1 and 2) and thus for operational convenience 0.2 M was selected as the concentration of choice for further studies. Increasing the loading of base from 1.1 equivalents to 2.2 equivalents improved the product yield to 41% (entry 3), however, the use of elevated reaction temperatures had no effect on product yield (entries 4 and 5).

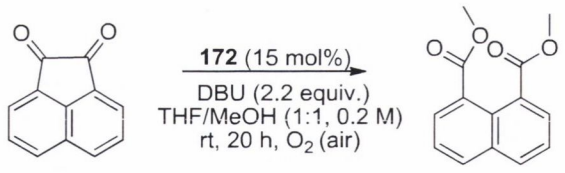
Table 2.2 Optimisation of reaction conditions for the NHC-mediated oxidative cleavage of **197** to the corresponding 1,2-diester **198**



197 **198**

Entry	x	Temp (°C)	Conc (M)	Yield 198 (%)
1	1.1	rt	0.5	28
2	1.1	rt	1.0	31
3	2.2	rt	0.2	41
4	2.2	30	0.2	41
5	2.2	40	0.2	41

These optimised reaction conditions did not afford synthetically useful yields of the diester product **198**. In a bid to investigate the applicability of these reactions conditions in the oxidative cleavage of other cyclic 1,2-diketones, we employed acenaphthenequinone (**199**) as a substrate in this process. However, to our disappointment, the corresponding diester product **200** was also generated in a modest yield of 42% when employed under the optimised reaction conditions.



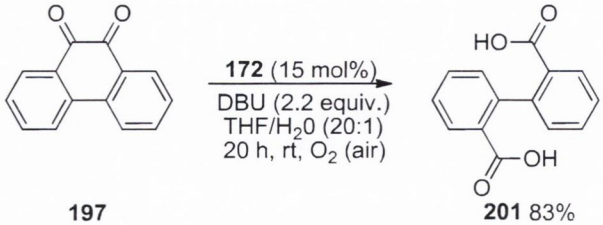
199 **200** 42%

Scheme 2.15 NHC-mediated oxidative cleavage of acenaphthenequinone (**199**) to dicarboxylic ester **200** in the presence of methanol

The moderate yields obtained for diester products **198** and **200** were disappointing when compared to the high yield of methyl benzoate (**171**) obtained in our previous study (Section 2.1). We observed that diacid formation was also occurring in the above reactions which are carried out in air, so the intervention of adventitious water was difficult to prevent. However, taking the cue from this observation, we postulated that water may be a more suitable nucleophile in these reactions than the bulkier methanol molecule. Hence we next investigated the corresponding transformations involving water as the nucleophile.

2.2.2.1 Optimised reaction conditions for the synthesis of a dicarboxylic acid

Speculating that reactions involving 1:1 THF:H_2O would not be optimal from both carbene-generation and substrate-solubility standpoints, a 5:1 THF:H_2O mixture was employed. Under these conditions the diacid **201** was generated in a low yield of 12%. Further reduction in the contribution of the protic solvent allowed the eventual preparation of the cleaved diacid **201** in 83% yield in a 20:1 THF:H_2O solvent mixture, as illustrated in Scheme 2.16 (Note: these experiments were conducted by Dr. S. Gundala and Mr. E. Delany).

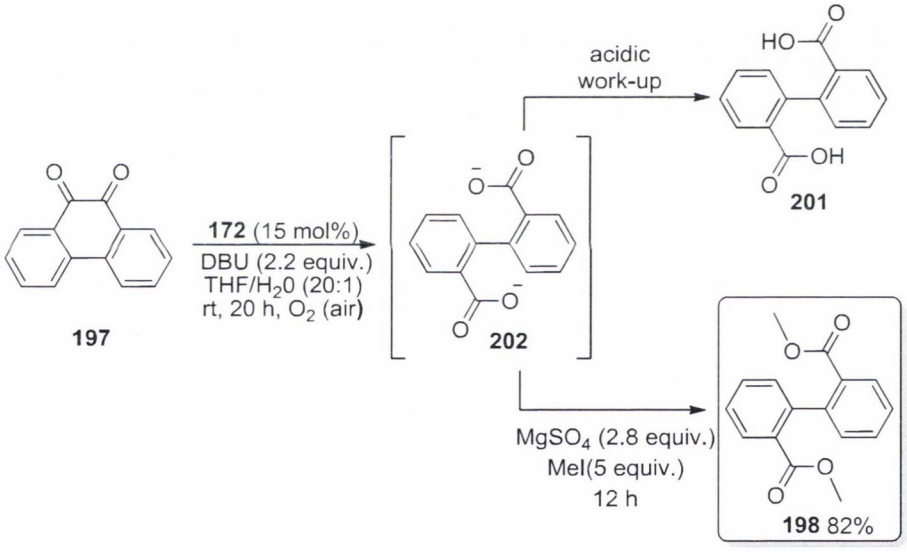


197 **201** 83%

Scheme 2.16 NHC-mediated oxidative cleavage of cyclic 1,2 diketone **197** employing water as the nucleophile

2.2.2.2 Optimised reaction conditions for the synthesis of a dicarboxylic acid ester

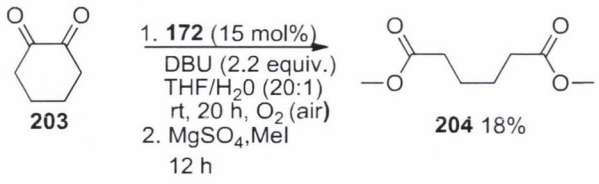
While the aqueous protocol leading to dicarboxylic acids proved the most effective in our preliminary studies, we were interested in extending this methodology of oxidative cleavage of cyclic 1,2-diketones to produce diesters. We postulated that employing water as the nucleophile would still allow for the most efficient C-C bond-breaking process to occur generating the corresponding 1,2-dicarboxylate **202**, as before. However, rather than forming the diacid **201**, (formed upon protonation from the acidic work-up) we speculated that removal of the water and addition of an electrophilic alkylating agent would allow the diester to be obtained. To test this theory, we employed $MgSO_4$ to sequester the water from the solvent after the carbon-carbon bond-breaking process was complete, and the dicarboxylate products were then esterified *via* the addition of MeI. Gratifyingly, under these conditions **197** was converted to its corresponding diester product **198** in 82% yield.



Scheme 2.17 NHC-mediated oxidative cleavage of phenanthrene-9,10-dione (**197**) to its corresponding dicarboxylic acid ester (**198**)

2.2.3 Evaluation of substrate scope: 1,2-diketones

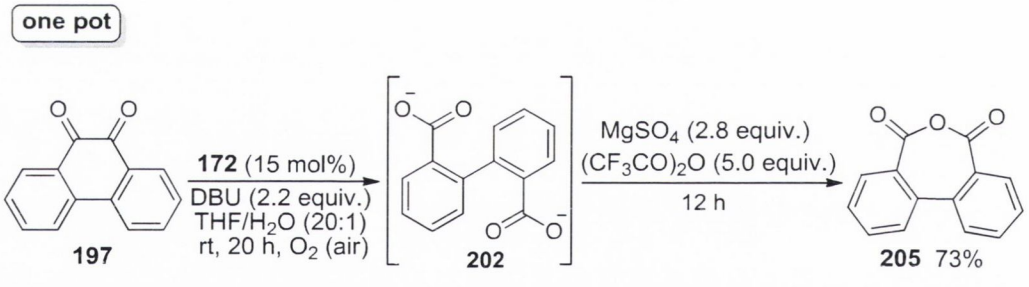
Under the optimised conditions, Dr. S. Gundala and Mr. E. Delany demonstrated that a variety of cyclic 1,2-diketones could be converted to their corresponding biaryldiesters in high yield. Perhaps unsurprisingly (under these basic conditions), oxidative cleavage of the enolisable 1,2-dione **203** proved more challenging: this reaction was not clean, however, the acyclic diester **204** could be isolated in low (yet appreciable) yield.



Scheme 2.18 NHC-mediated oxidative cleavage of enolisable 1,2-cyclohexanedione (**203**) to adipic acid dimethyl ester (**204**)

2.2.4 Chemoselective conversion of a 1,2-diketone to an anhydride

We postulated that we could further exploit this organocatalytic process to synthesise an anhydride, in one-pot, from the cyclic 1,2-diketone **197** *via* the carboxylate **202**. The α-diketone **197** was first oxidatively cleaved in the presence of the carbene derived from **172** in an aqueous medium to generate the corresponding dicarboxylate **202** *in situ* as shown in Scheme 2.19. When this reaction was complete, addition of magnesium sulfate was necessary to sequester the water in the reaction. Gratifyingly, addition of trifluoroacetic anhydride (TFAA) led to the cyclisation of the *in situ*- formed dicarboxylate **202** to afford the anhydride **205** in good isolated yield (73%). To the best of our knowledge, such a one-pot sequence starting from a 1,2-diketone is unprecedented in the literature.



Scheme 2.19 One pot chemoselective conversion of 1,2-diketone **197** to anhydride **205**

2.3 Conclusions

In summary, we have developed an efficient NHC-catalysed esterification of aldehydes involving alcohols and air (*i.e.* oxygen) as the oxidant. No other added stoichiometric oxidants or catalysts to activate molecular oxygen are required. Unhindered aromatic aldehydes (including heterocyclic analogues) can be converted to the corresponding methyl esters in good to excellent yields at ambient temperature. These reactions have also shown to be mechanistically distinct from other NHC-catalysed 'oxidative' or 'oxygenative' esterifications (see Section 1.6) in that the species which reacts with oxygen, in the air, is *not* the Breslow intermediate, but the benzoin (or

more accurately, its enolate). Currently, investigations to further develop the scope and utility of these reactions are underway in our research laboratory.

These studies, whereby benzil (formed from the aerobic oxidation of benzoin in basic media) can be attacked by both the carbene and the alcohol nucleophile to give an adduct which collapses to form the Breslow intermediate and the carboxylic acid ester, encouraged us to investigate the NHC-mediated oxidative cleavage of 1,2-diketones. As a result a new, organocatalytic oxidative cleavage reaction of cyclic 1,2-diketones has been developed. The use of either water as the nucleophile allows the generation of a diacid in high yield under mild conditions. However, while the corresponding methanolytic transformation occurs, it is less productive. Coupling an *in situ* esterification with the more efficient acid-generating reaction allows the formation of esters in good yields from a variety of cyclic diketones. The process is promoted by an NHC derived from a readily prepared, simple triazolium ion precursor, and no strong stoichiometric oxidants are required. If TFAA and a drying agent are added to the reaction mixture after completion of oxidative cleavage, cyclisation to form the cyclic anhydride occurs in good overall yield.

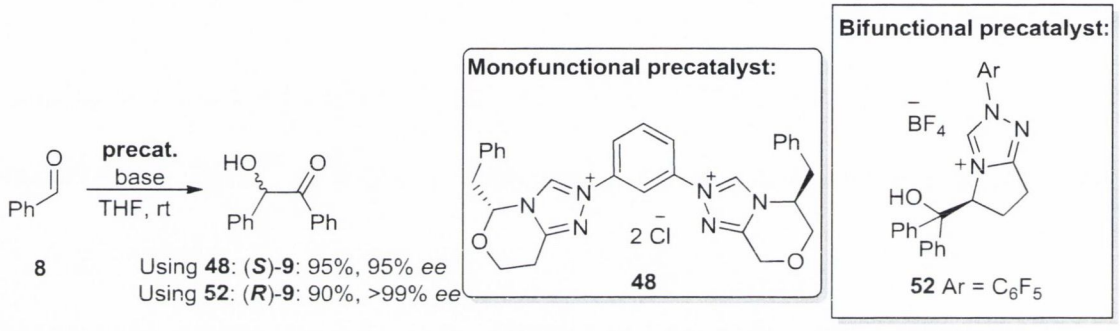
2.4 Future work

We have developed an efficient protocol that allows for the esterification of aldehydes in the presence of alcohols. We would like to expand the substrate scope of this reaction further and our research group is currently investigating imines as substrates in the place of aldehydes. We have also proposed a unique mechanism for the oxidation of aldehydes under the described conditions. Upon analysing one of the intermediate species in this reaction (benzil), we developed a protocol that allows for the oxidative cleavage of cyclic diketones. Therefore we are investigating other substrates, similar in structure to the various intermediates described in the mechanism, to examine their performance in the presence of an NHC catalyst.

3. The design of novel chiral triazolium salts

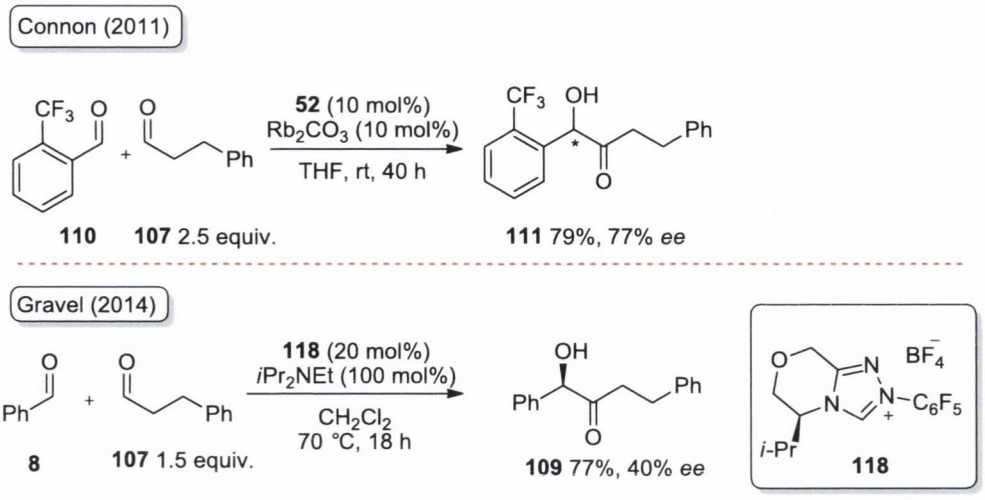
3.1 Rationale behind the synthesis of novel chiral triazolium salts: a comparison between monofunctional and bifunctional triazolium ion-based precatalysts

As discussed previously in Section 1.4, there are a variety of chiral triazolium salts that have proven to be successful when employed as precatalysts in the archetypal benzoin condensation. In the presence of these chiral precatalysts, such as **48** and **52**, the benzoin product **9** can be obtained in high yields and with high levels of enantioenrichment for any of the two possible stereoisomers (Scheme 3.1).[65,68]



Scheme 3.1 Monofunctional triazolium ion-based precatalyst **48** (reported by You)[65] and bifunctional triazolium ion-based precatalyst **52** (reported by Connon)[68] can both promote the formation of benzoin product **9** in high yields and with excellent enantiocontrol

However, when employed in crossed acyloin condensations, the NHCs derived from chiral triazolium salts are not capable of promoting the reaction with the same efficiency and enantioselectivity.[93] In the presence of precatalyst **52**, highest yields and *ee* values were obtained when *ortho*-substituted aromatic aldehyde **110** was employed with hydrocinnamaldehyde (**107**), as illustrated in Scheme 3.2. However, despite the use of this 'tailored' substrate, the results obtained did not rival those observed in the benzoin condensation. Gravel also reported the asymmetric crossed acyloin condensation in the presence of a monofunctional triazolium ion-based precatalyst **118**, however, low *ee* values were observed.



Scheme 3.2 The use of enantiopure triazolium ion-based precatalysts in the asymmetric crossed acyloin condensation

As highlighted in reports discussed previously (Section 1.5), there are numerous challenges associated with the asymmetric crossed acyloin condensation reaction; such as chemoselectivity, enantioselectivity and substrate scope limitations that must be overcome in order for a successful protocol to be established. In order to gain insight into the factors that influence a chemo- and enantioselective process, it is necessary to address precatalyst design and synthesise novel *ad hoc* chiral triazolium ion-based precatalysts with the ultimate aim of generating crossed acyloin products in high yields and with uniformly high *ee* values.

In order to achieve the desired stereochemical control, it is essential to design precatalysts that feature elements of chirality and steric bulk embedded within its framework. As the triazolium scaffold, in comparison to its thiazolium counterpart, presents more sites where structural modifications (steric and electronic) can be introduced, it was decided to design and synthesise a range of triazolium ion-based precatalysts structurally similar to the chiral triazolium salt **52** previously employed by our research group in the benzoin condensation (Figure 3.1). It emerged from previous studies that the electron withdrawing pentafluorophenyl group was of paramount importance to prevent protonation of the NHC, by either the benzoin product or the conjugate acid of the base employed, and therefore dramatically enhances catalyst efficiency; it was therefore decided to retain this structural feature in the new series of triazolium ion-based precatalysts that we aimed to synthesise (Figure 3.1). Tuneable elements of chirality and of steric bulk were deemed necessary to obtain asymmetric catalysis in the acyloin condensation reaction. Consequently, we envisaged that by introducing a variable substituent in close proximity to the chiral centre on

the novel triazolium salts, it was possible to monitor and compare their performance with that of precatalyst **52** in the crossed acyloin condensation.

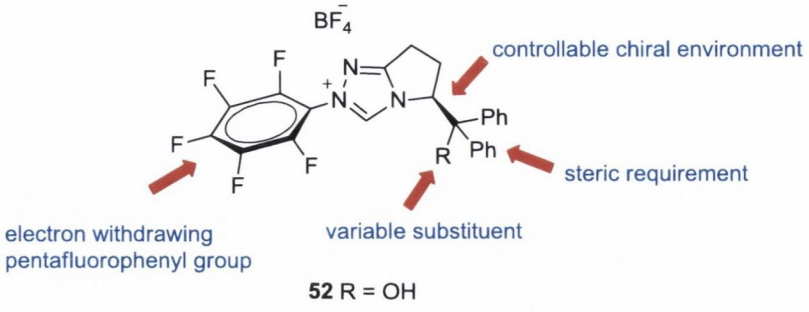


Figure 3.1 Structural design of novel triazolium ion-based precatalysts for the asymmetric acyloin condensation similar to that of precatalyst **52** previously employed by our research group

Whilst the bifunctional precatalyst **52**, having hydrogen bond donating capability, has proved to be extremely efficient when applied to the benzoin condensation (Scheme 3.1), a plethora of monofunctional precatalysts (such as triazolium salt **48** as reported by You *et al.*) have also proven to be as proficient when employed in this reaction. Whilst Connon *et al.* demonstrated that the bifunctionality of the NHC, derived from **52**, was beneficial to its catalytic performances, it was decided to investigate whether the presence of substituents lacking hydrogen bond donating abilities but having different steric requirements could also bring about highly enantioselective benzoin and acyloin condensation reactions.

In order to assess the importance of steric effects for the catalytic abilities of triazole-NHCs, it was decided to synthesise monofunctional chiral precatalysts **206** and **207** (Figure 3.2), which feature the same structural backbone as bifunctional precatalyst **52**, yet lack the hydroxyl group which was substituted by moieties devoid of hydrogen bonding capabilities and having remarkably different steric requirements: precatalyst **206** possess a relatively small and linear azido group, while precatalyst **207** is much more sterically encumbered having a freely rotating and larger triazole substituent. A comparison of precatalysts **52**, **206** and **207** in the benzoin condensation could shed light on the catalytic role of hydrogen bond donation and the relevance of steric bulk in promoting the benzoin (and acyloin) condensations while allowing enantiodiscrimination to occur (Section 1.4)[66] by controlling the orientation of the aromatic aldehyde approaching the Breslow intermediate.

The design of alternative chiral bifunctional triazolium salts (also structurally similar to **52**), which upon deprotonation, could be capable of activating and directing the approaching aldehyde to the Breslow intermediate, was also taken into consideration as an alternative strategy to promote chemo- and stereoselective crossed acyloin condensations in high yields. Accordingly, we sought to introduce a hydrogen bond donating moiety different than the hydroxyl group of **52**. Precatalyst **208** was considered for this purpose; its structure presented a secondary amide group which could serve as a tuneable alternative hydrogen bond donating moiety and could also allow for the incorporation of substituents having different steric bulk (Figure 3.2).

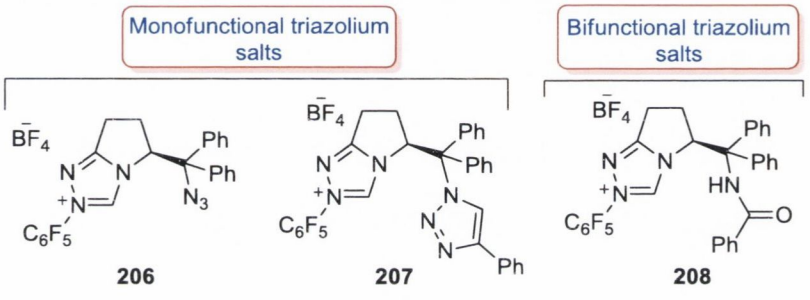
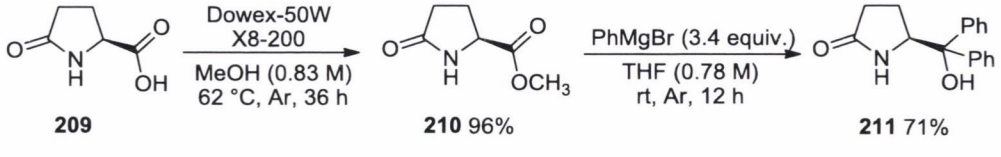


Figure 3.2 Target novel enantiopure triazolium salts

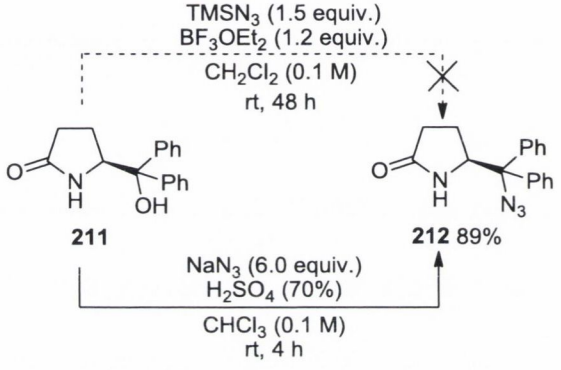
3.2 Synthesis of a common intermediate for target triazolium salts

When planning the synthesis of triazolium salts **206**, **207**, and **208** we decided to retain some of the synthetic steps previously employed for the synthesis of precatalyst **52**; thus, we employed the inexpensive (*S*)-pyroglutamic acid (**209**) as the enantiomerically pure starting material which, in the presence of methanol and a strongly acidic resin (Dowex50W X8-200), underwent esterification to produce the methyl ester **210** in almost quantitative yields. This intermediate was subsequently reacted with freshly prepared phenylmagnesium bromide to obtain the γ-lactam **211** in 71% yield.



Scheme 3.3 Synthesis of the enantiopure γ-lactam **211** as previously reported in our research group

From **211** we envisaged the synthesis of the azide-bearing lactam **212** which would act as the precursor in the synthetic pathways to triazolium salts **206**, **207** and **208**. Initially, the conversion of the tertiary alcohol **211** to the corresponding azide was attempted in the presence of trimethylsilyl azide and boron trifluoride (Scheme 3.4),[140] however, to our disappointment, only starting material could be recovered. We tentatively assumed that the lack of reactivity of **211** was due to the presence of two phenyl substituents (α- to the tertiary alcohol) which were preventing the interaction between the alcohol substituent and the bulky trimethylsilyl azide reagent, therefore another route to obtaining the azide was examined.



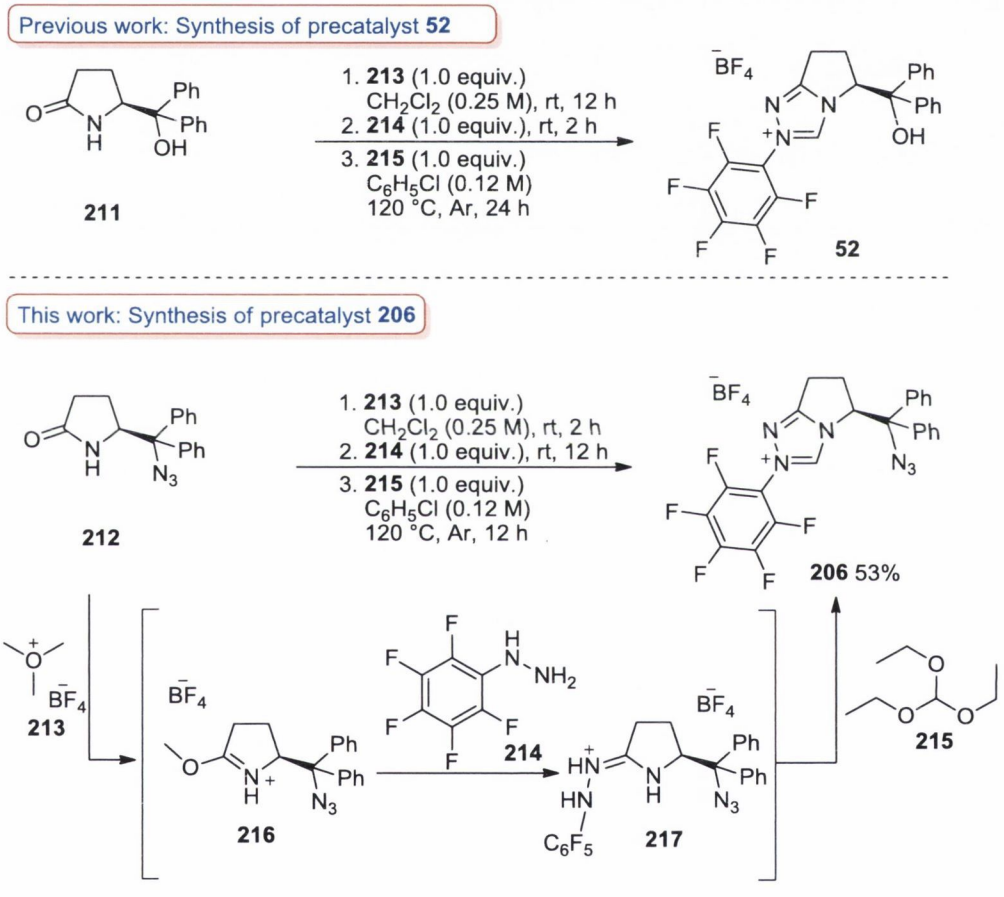
Scheme 3.4 Synthetic routes to the azido intermediate **212**

We decided to convert the alcohol of **211** to an azido group by treating it with hydrazoic acid, generated *in situ* by reacting sodium azide with sulfuric acid.[141] Initially the reaction was carried out in the presence of a 50% aqueous solution of sulfuric acid; whilst this resulted in the formation of **212**, the yield obtained (34%) was not synthetically useful. Hence, it was decided to increase the concentration of acid present in the reaction and accordingly, various reactions in the presence of aqueous solutions of sulfuric acid ranging from 50% to 80% (*v/v*) were performed to optimise the yield of the reaction. A protocol was found which involved the use of a 70% aqueous sulfuric acid solution and which led to **212** in yields as high as 89%, as illustrated in Scheme 3.4. Further increases in acid concentration resulted in product decomposition.

3.2.1 Synthesis of an azido-bearing chiral triazolium salt

In order to synthesise precatalyst **206** from intermediate **212** it was decided to follow the same synthetic route reported by Connon *et al.* for the synthesis of bifunctional precatalyst **52** which involved the use of trimethyloxonium tetrafluoroborate (**213**), pentafluorophenyl hydrazine (**214**) and triethylorthoformate (**215**) in a sequential one-pot procedure as shown in

Scheme 3.5.[142] The chiral γ-lactam **212** is initially alkylated by Meerwein's salt **213** to generate *in situ* the electrophilic intermediate **216** which, upon addition of hydrazine **214** reacts to yield the pentafluorophenyl substituted salt **217**. The removal of solvent *in vacuo* is followed by addition of chlorobenzene as a higher boiling solvent and triethyl orthoformate (**215**), which reacts with **217**, yields the triazolium salt **206**. Nevertheless, adherance to the procedure previously reported resulted in very poor yields of **206**: the process needed to be reconsidered in order to access the desired **206** in acceptable yields and since the overall three-step reaction takes place *in situ*, each step in this synthetic route was carefully monitored by ^{1}H NMR spectroscopy.



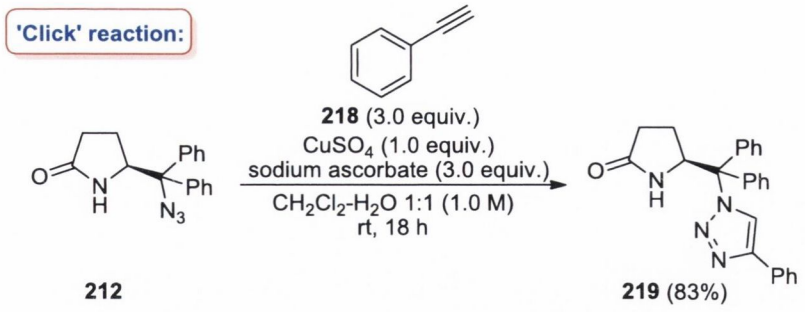
Scheme 3.5 Synthesis of the azido-based enantiopure triazolium salt **206**

From this spectroscopic analysis it was possible to notice that when the azide precursor **212** was employed as starting material, the reaction times necessary for each step to go to completion were remarkably different than those previously reported by Connon *et al.* for a similar compound. We discovered that after the addition of Meerwein's salt **213**, intermediate **216** was formed in reaction times as short as 2 hours compared to the previously reported 12

hours, as shown in Scheme 3.5. On the contrary, the second step which involves the nucleophilic attack of hydrazine **214** on the electrophilic intermediate **216** was found to be much slower in this case and quantitative formation of salt **217** occurred after 12 hours instead of the previously reported 2 hours. Finally, the cyclisation reaction leading to the desired precatalyst **206** could be accomplished over 12 hours: a reaction time halved when compared to the previously reported 24 hours for a similar transformation. Having established a successful and high-yielding synthetic process for **206**, we focused our efforts on developing a purification procedure for this precatalyst, which turned out to be problematic. Attempts to recrystallise the product from the crude mixture using solvents such as ethyl acetate and methanol, as previously used for purifying similar salts (e.g. **52**) proved to be unsuccessful. Purification by column chromatography was not viable either as product decomposition took place on silica gel and hence, it was essential to find an optimal solvent suited for the recrystallisation of **206** from the crude mixture. Much to our delight, **206** was isolated in moderate yield of 53% using 2-propanol as a solvent for recrystallisation.

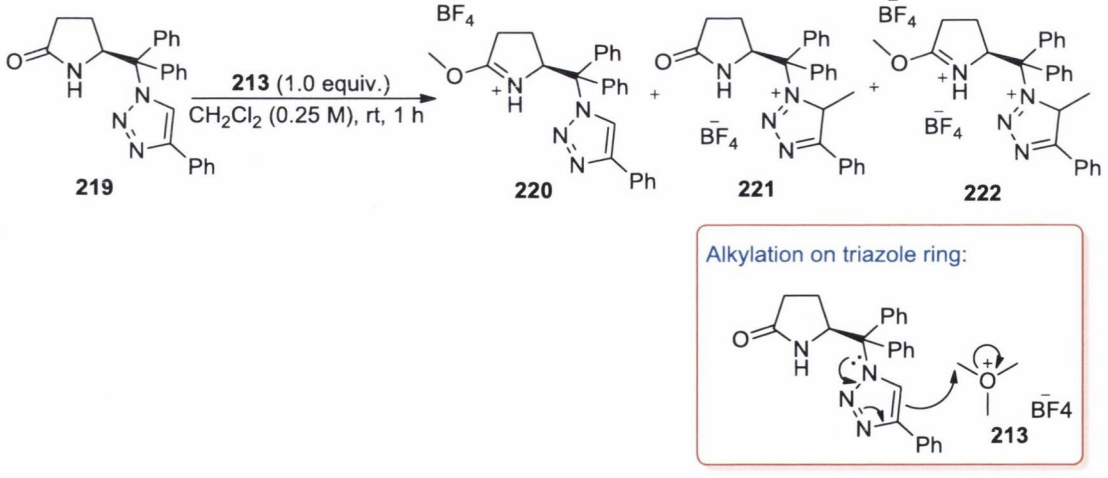
3.2.2 Synthesis of a triazole-substituted chiral triazolium salt

In an effort to synthesise the triazole-bearing chiral triazolium salt **207** we decided that a 'click' reaction,[143] in the presence of phenylacetylene (**218**), could be the most accessible route to install the triazole ring on the γ-lactam **219** from the azide precursor **212**. However, the triazole-substituted lactam **219** could only be formed in a mere 22% yield using this strategy, whereby **212** was subjected to 5 mol% copper sulphate and 15 mol% sodium ascorbate in the presence of 1.1 equivalents of **218**. In an effort to increase the yield of product **219**, we decided to optimise reaction conditions by using alkyne **219** and sodium ascorbate in super-stoichiometric quantities (*i.e.* 3 equivalents). To our delight, this modification led to the formation of **219** in 83% yield (Scheme 3.6).



Scheme 3.6 Synthesis of a triazole-substituted precursor **219** of precatalyst **207** *via* a 'click' reaction on the azide moiety of **212**

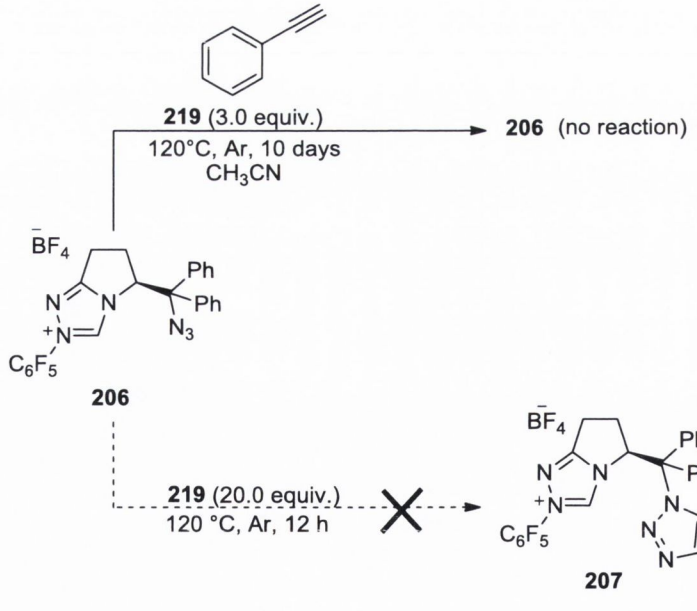
With the aim of obtaining precatalyst **207**, compound **219** was subsequently subjected to the same reaction conditions employed previously for the synthesis of azido-based triazolium salt **206**. It was disappointing to observe using ^{1}H NMR spectroscopy that methylation, in the presence of the Meerwein's salt **213**, occurred simultaneously on both the triazole ring and the carbonyl group of the γ-lactam. The reaction time of the methylation process was reduced to just 1 hour in order to observe if methylation occurred at the carbonyl moiety initially. However, it was evident that alkylation occurred at both possible sites simultaneously to generate a complex mixture of inseparable alkylated salts; **220**, **221** and **222** (along with decomposed products of **221** and **222**) as shown in Scheme 3.7. Because of this inconvenience, it was deemed necessary to devise another synthetic route that allowed the preparation of the desired triazolium salt **207**.



Scheme 3.7 Alkylation of the triazole-based γ-lactam **219** using Meerwein's salt **213** leads to the formation of undesired by-products **221** and **222**

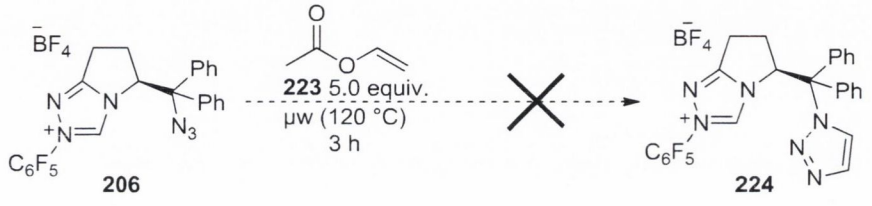
The synthesis of precatalyst **207** seemed feasible by using a 'click' reaction between the azide-based triazolium salt **206** and phenylacetylene (**219**). Initially this 'click' process was carried out under identical reaction conditions used to obtain the triazole-substituted γ-lactam **219** from the azide **212** (Scheme 3.6). However, triazolium salt **206** was not stable under the aqueous conditions employed in this reaction leading to decomposition-related by-products. The use of a solvent mixture of methanol and toluene was not feasible either since neither the starting material **206** nor the desired product **207** could be detected using ^{1}H NMR spectroscopic analysis.

Prompted by these stability issues in protic solvents, we opted to carry out the reaction in acetonitrile. However, after carefully monitoring the reaction by ^{1}H NMR spectroscopy, product formation was not observed and after 10 days we obtained 100% starting material (Scheme 3.8). We surmised that a more suitable reaction medium was necessary, hence we decided to carry out a neat thermal 'click' process by allowing precatalyst **206** to react with larger excesses of phenylacetylene (**219**) acting as the solvent. Unfortunately, upon analysis of the crude reaction mixture using ^{1}H NMR spectroscopic methods, neither **206** nor **207** could be found and an unidentifiable dark brown solid was formed as the product of the reaction, presumably due to thermal polymerisation of **219**.[144]



Scheme 3.8 Attempted synthesis of triazole-substituted triazolium salt **207** from azide-based triazolium salt **206**

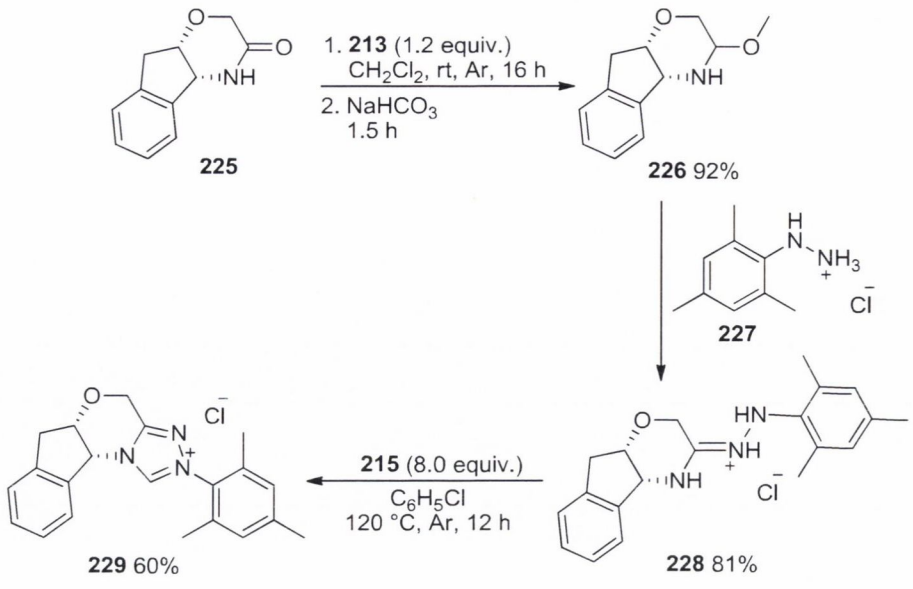
Encouraged by previously published work by Jensen *et al.*[145] showing that 1,2,3-triazoles could be synthesised by reacting primary or tertiary azides and vinyl acetate (**223**) in the presence of microwave irradiation, we decided to investigate this protocol in the synthesis of an alternative triazolium salt **224**. To our dismay, we were unsuccessful in synthesising the triazolium salt **224** using Jensen's procedure and we tentatively attributed our failure to possible decomposition of **206** under the harsh irradiation conditions (Scheme 3.9).



Scheme 3.9 Attempted synthesis of triazolium salt **224** by means of microwave irradiation

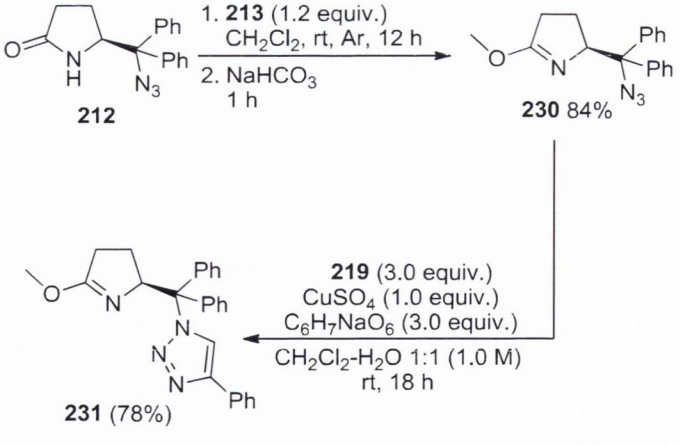
We concluded that the synthesis of a triazole-substituted triazolium salt using the azide precatalyst **206** as a precursor was not viable and consequently we re-examined the synthetic pathway leading to **207** and investigated an alternative route devoid of the problematic alkylation step of a triazole intermediate.

Taking the cue from a previously reported methodology by Bode and co-workers[146] for the synthesis of various triazolium salts, we decided to investigate whether their reaction conditions were applicable to one of our intermediates. Interestingly, the authors were able to alkylate the lactam present in compound **225** using the Meerwein's salt **213** and subsequently were able to generate the neutral hemi-aminal product **226** by treating *in situ* the methylated salt with sodium bicarbonate. The neutral species **226** (arguably more amenable to purification by column chromatography than the parent tetrafluoroborate salt) was then treated with the mesityl-based hydrazinium chloride **227** to generate the salt **228** which cyclised in the presence of triethyl orthoformate (**215**) to generate triazolium salt **229** (Scheme 3.10).



Scheme 3.10 Synthesis of triazolium ion-based precatalyst **229** as reported by Bode

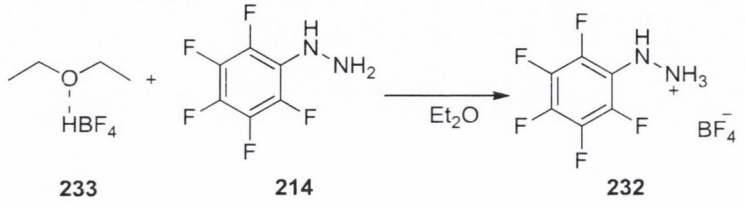
We postulated that this protocol would allow for the methylation of the easily accessible azide precursor **212** to form a tetrafluoroborate salt that could be neutralised *in situ* with sodium bicarbonate to yield **230** which could later undergo a 'click' reaction to generate the desired triazole-substituted γ-lactam **231** as shown in Scheme 3.11. Gratifyingly, this strategy could afford the desired product; the addition of sodium bicarbonate led to the formation of product **230**, which could be purified by column chromatorgraphy, and the subsequent 'click' reaction generated the triazole-based product **231** in a satisfying 78% yield.



Scheme 3.11 Synthesis of triazole-substituted γ-lactam **231**

With the desired product **231** in hand, we focused our synthetic efforts on the final steps aimed at preparing precatalyst **207**: the addition of a pentafluorophenyl hydrazine moiety and

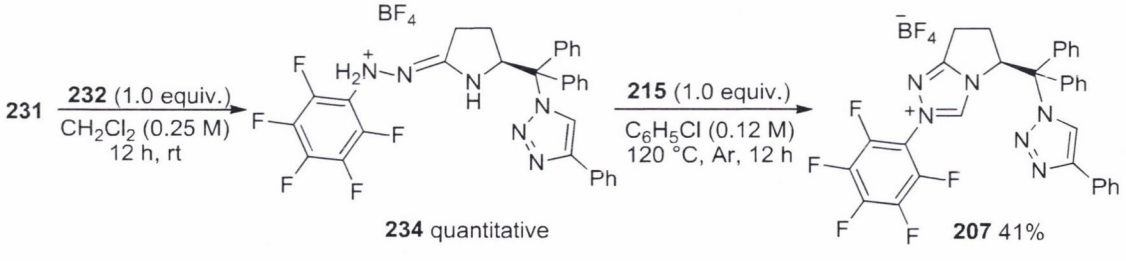
the ensuing triethyl orthoformate-promoted cyclisation reaction. The necessity of having a hydrazinium salt (as reported by Bode) capable of reacting with **231** meant it was essential that compound **232** be synthesised (Scheme 3.12). Previous investigations by our German collaborators (Zeitler *et al.*) were extremely helpful since they had developed a procedure aimed at synthesising the desired pentafluorophenyl hydrazinium salt **232** by reacting tetrafluoroborate diethyl ether complex (**233**) with pentafluorophenyl hydrazine (**214**) to generate **232**, which precipitated from solution instantaneously (Scheme 3.12).



233 **214** **232**

Scheme 3.12 Synthesis of pentafluorophenyl hydrazinium salt **232**

Hence we employed the same procedure to generate **232**, which we subsequently reacted with the previously formed triazole **231** to form the pentafluorophenyl-substituted salt **234** and upon removal of the solvent *in vacuo* this species was exposed to triethylorthoformate (**215**) in chlorobenzene (Scheme 3.13). Analysis by ^{1}H NMR spectroscopy confirmed that successful cyclisation had occurred and the desired triazolium salt **207** had formed. Gratifyingly, its purification could be accomplished by using 2-propanol as the solvent for recrystallisation to obtain the triazolium salt **207** in 41% yield.



234 quantitative **207** 41%

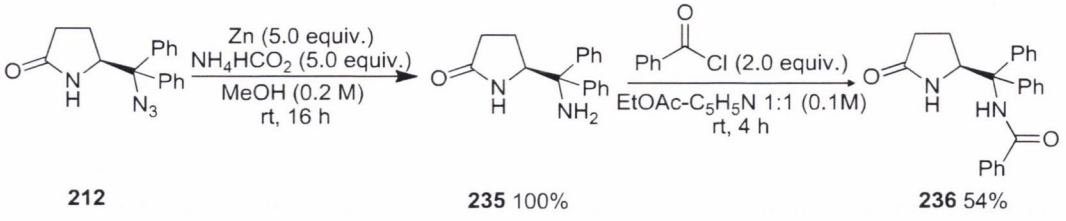
Scheme 3.13 Synthesis of the triazolium salt **207**

3.3 Synthetic routes towards bifunctional triazolium salt precatalysts

3.3.1 Attempted synthesis of an amide-based triazolium precatalyst

In order to incorporate an amide into the triazolium precatalyst structure, we opted to employ the previously synthesised azide-based γ-lactam **212** as the precursor to generate the

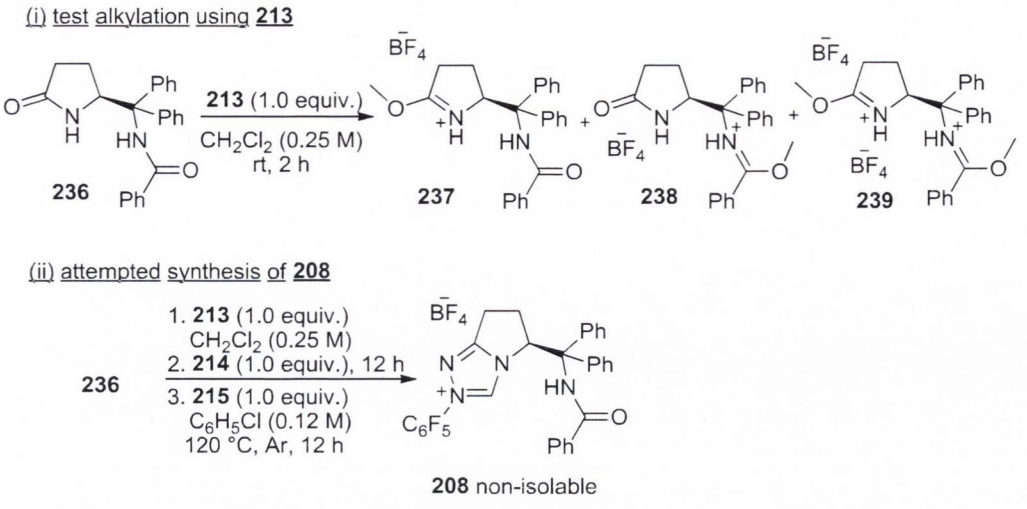
corresponding amine **235**, from which we postulated the amide-based γ-lactam **236** would be readily accessible (Scheme 3.14).



212 **235** 100% **236** 54%

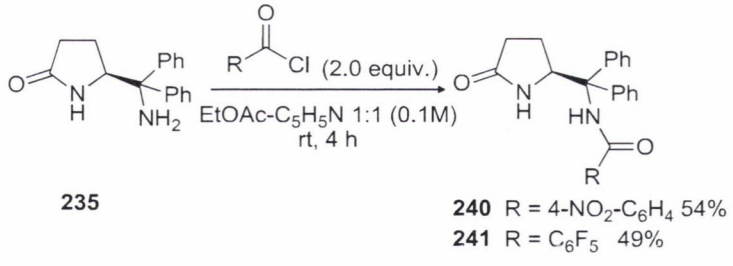
Scheme 3.14 Synthesis of amide-substituted γ-lactam **236** from azide precursor **212**

In the presence of zinc and an excess of ammonium formate the azido group of **212** was quantitatively reduced to afford the corresponding amine **235**.[147] This compound was used directly for the ensuing acylation reaction and was thus treated with pyridine in the presence of a two-fold excess of benzoyl chloride which led to the formation of **236** in a moderate 54% yield. With the amide-substituted intermediate **236** in hand we were prompted to investigate the next step towards the synthesis of the desired triazolium salt **208**; the chemoselective alkylation of the lactam group using Meerwein's salt **213**. While we acknowledged that the presence of two amide groups could lead to chemoselectivity-related issues for this reaction, we concluded that the more sterically hindered amide substituent might be less prone to alkylation than the arguably more accessible lactam, hence we carried out the methylation reaction on **236** using previously employed reaction conditions while closely monitoring the course of the reaction using ^{1}H NMR spectroscopy. It was possible to observe that methylation using **213** lacked the desired chemoselectivity and that by-products **238** and **240** were also formed together with **237**, albeit at a slower rate (Scheme 3.15). Further optimisation of the reaction proved to be inconclusive, nonetheless the formation of **237** was encouraging and prompted us to investigate the feasibility of the synthetic route previously employed to access the azido-substituted salt **206** (Scheme 3.5). Whilst it was possible to identify the formation of the desired triazolium salt **208** by ^{1}H NMR spectroscopic analysis, the presence of large amounts of by-products **238** and **239** did not allow the isolation of pure **208** by recrystallisation.



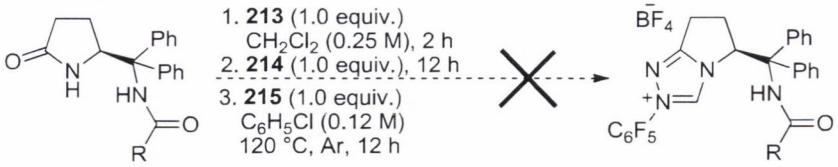
Scheme 3.15 Attempted synthesis of amide-substituted triazole salt **208**

Taking into consideration the chemoselectivity issues involved in the amide alkylation using Meerwein's salt **213**, we opted to reconsider the structure of our intended bifunctional triazolium ion-based precatalyst so that it would bear an amide group less prone to alkylation by virtue of its more electron deficient character. Accordingly, we chose to synthesise amide precursors **240** and **241** by treating amine **235** with either *para*-nitro benzoyl chloride or pentafluoro benzoyl chloride, respectively (Scheme 3.16).



Scheme 3.16 Synthesis of electron deficient amides **240** and **241**

With the electron-deficient amide-bearing γ-lactams **240** and **241** in hand, we subsequently evaluated their suitability for use in a chemoselective alkylation using Meerwein's salt **213** under reaction conditions identical to those attempted previously. The analysis using ^{1}H NMR spectroscopic techniques demonstrated that the alkylations of **240** and **241** were considerably more regioselective processes than previously found using amide **236**. Despite the formation of alkylated by-products in low yields, it was decided to pursue the canonical synthetic route for the formation of triazolium salts **242** and **243** which involved the reaction with hydrazine **214** and the final cyclisation reaction (Scheme 3.17).



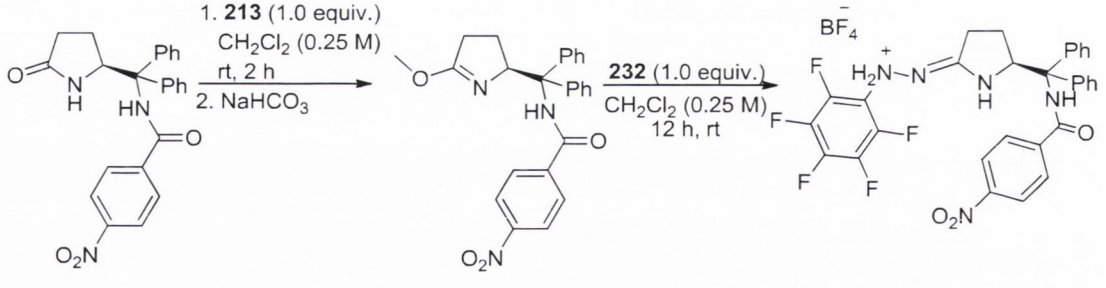
240 R = 4-NO_2-C_6H_4
241 R = C_6F_5

242 R = 4-NO_2-C_6H_4
243 R = C_6F_5

Scheme 3.17 Attempted synthesis of triazolium salts **242** and **243**

To our disappointment, we noticed that additional by-products were generated in the final two steps and in addition we subsequently encountered problems with the purification of these novel triazolium salts. We therefore resorted to the synthetic methodology reported by Bode that proved to be successful for the synthesis of triazolium precatalyst **207** (*vide supra*) and investigated its applicability in the synthesis of triazolium salt **242** from amide **240**. Upon alkylation and neutralisation of precursor **240**, we were able to purify the neutral desired alkylated product **244** in 42% isolated yield. This reacted smoothly with the pentafluorohydrazinium salt **232**, leading to the formation of **245** in quantitative yields.

To our disappointment, the subsequent cyclisation reaction using triethyl orthoformate (**215**) failed to deliver the desired triazolium salt **242** and numerous unidentifiable by-products were formed as indicated by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

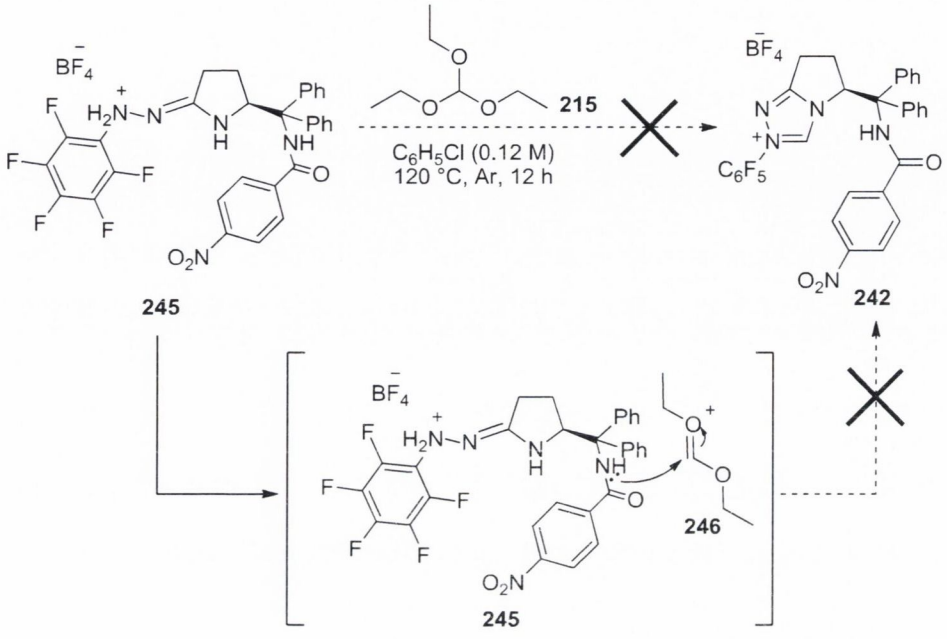


240 **244** 42% **245** quantitative

Scheme 3.18 Synthesis of the amide bearing triazolium salt **245** following the procedure introduced by Bode *et al.*

Extensive experimentation was carried out in order to improve the efficacy of this final cyclisation reaction, which also included the use of trimethyl orthoformate as an alternative reagent, however, all of the attempts failed to result in the clean formation of the desired precatalyst **242**. We tentatively explained the formation of by-products to be the result of the reaction between ethyl formate (**246**, formed *in situ* upon heating **215**) and the amide group of **245** (Scheme 3.19). We therefore concluded that the structure of the amide-based

triazolium salts **208**, **242** and **243** were not compatible with any of the synthetic pathways attempted due to the amide groups being too reactive under the conditions employed, thus generating multiple by-products.



Scheme 3.19 Attempted cyclisation reaction of intermediate **245** using triethyl orthoformate (**215**)

3.4 Conclusions

In conclusion, we aimed to synthesise a range of novel triazolium ion-based precatalysts that we could directly compare with the performance of the hydroxy-substituted triazolium ion-based precatalyst **52** in both the benzoin condensation and the acyloin condensation. We wished to discern the factors leading to chemoselective and enantioselective processes in NHC-mediated condensation reactions with the ultimate goal of generating crossed acyloin products in both high yields and with high levels of chemoselectivity and enantiomeric control.

We have successfully synthesised two novel monofunctional triazolium salts (**206** and **207**) Whilst the synthetic process leading to the azido-based triazolium salt **206** was devoid of any major issues, the preparation of the triazole-substituted counterpart **207** proved to be far more challenging and could only be addressed after tedious experimentation.

The synthesis of a range of novel bifunctional triazolium salts bearing an amide substituent, capable of hydrogen bond donation was also attempted. However, despite extensive

experimentation we failed to achieve the synthesis of such triazolium salts and we were able to conclude that the structural framework of a triazolium salt bearing an amide group is not compatible with the synthetic pathways attempted.

3.5 Future work

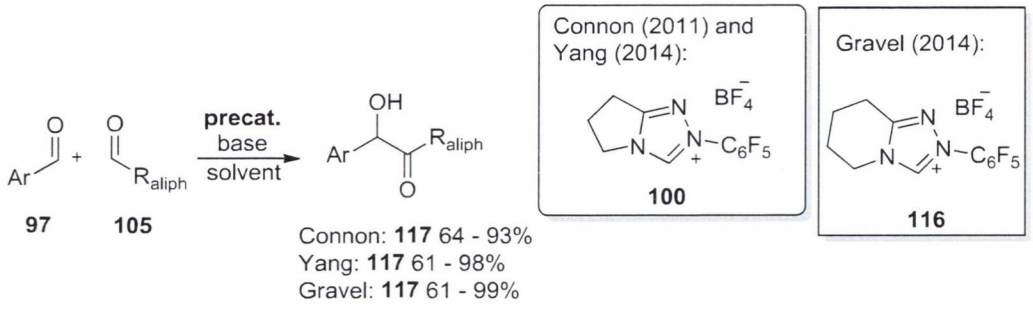
Further work is currently being carried out by fellow co-workers in our research group to evaluate the catalytic performance of triazolium salts **206** and **207** in the coupling reaction between two aldehyde molecules in order to provide an insight into the role that hydrogen bonding and sterics may play in this reaction. We also wish to test the performance of these novel chiral triazolium-ion based precatalyst in various other NHC-mediated reactions.

There is also ongoing research being carried out by our research group into the synthesis of novel bifunctional triazolium salts bearing alternative hydrogen bond donating substituents that are tolerant of the reaction conditions described above. In addition, our research group is also synthesising novel bifunctional triazolium salts that bear an alternative electron-poor aryl ring, in place of the pentafluorophenyl group, to investigate the performance of a range of NHC catalysts, possessing varied pKa's, in the cross coupling reaction between two different aldehydes.

4. Synthesis and study of electron-deficient achiral triazolium ion-based precatalysts for use in chemoselective crossed acyloin condensations

The coupling of two different aldehyde molecules is perhaps the most atom-economical method for the preparation of crossed acyloin products. Yet, for the last 180 years, due to an inherent chemoselectivity problem and low yields of these acyloin products being obtained, this reaction has been deemed of little synthetic value. As mentioned earlier (Section 1.5.4.1), when two different aldehyde molecules react there is a possibility of four different acyloin products being formed and rarely does a single α-hydroxyketone dominate. This issue arises as the more electrophilic aldehyde is likely to be attacked faster by both the NHC catalyst (to form the Breslow intermediate) and the Breslow intermediate itself, to form the corresponding dimer product. Hence, an unchemoselective process is observed.

As previously discussed in Section 1.5.3, there are a variety of achiral (and chiral) triazolium ion-based precatalysts that have been employed in crossed acyloin condensation reactions. Many of these precatalysts differ structurally and from those that performed moderately well in these condensation processes, few general trends have emerged as to what constitutes success in precatalyst design, except that NHCs derived from triazolium salts are far superior in catalysing an acyloin condensation than those derived from their thiazolium counterparts.[92] The studies that have reported a NHC-mediated condensation reaction between an aliphatic aldehyde and an aromatic aldehyde all employed pentafluorophenyl-substituted triazolium salts, as shown in Scheme 4.1.[93–95] It was previously reported by our research group that electron-poor NHCs promote the formation of acyloin products in high yields in comparison to the more electron-rich phenyl-substituted NHCs.[93]

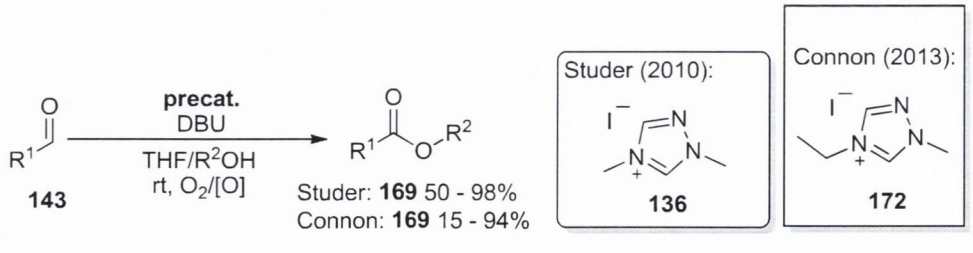


Scheme 4.1 NHC-mediated coupling reaction between various aromatic and aliphatic aldehydes in the presence of pentafluoro-substituted triazolium salts **100** and **116**

During our studies on the crossed acyloin condensation, we noticed that there were very few reports involving the use of alternative electron-poor salts in the literature *i.e.* triazolium ion-based precatalysts that veer away from the archetypal precatalyst structure bearing an electron-withdrawing phenyl substituent such as that of **100** and **116**. Intrigued by this dearth in the literature and in anticipation of discovering what underlying factors govern a chemoselective crossed acyloin process, we decided to explore the design of novel electron-poor triazolium ion-based precatalysts and evaluate their performance in the crossed acyloin condensation.

4.1 Rationale behind the synthesis of an achiral triazolium ion-based precatalyst containing a trifluoroethyl group

To initiate our investigations into the role that electron-poor NHC catalysts may play in the crossed acyloin condensation, we decided that it would be prudent to generate an achiral electron-poor triazolium salt. We were intrigued by the lack of reports in literature of electron-poor triazolium salts that bear two aliphatic substituents, rather than one aliphatic and one aromatic substituent. The general scaffold of an aliphatic-substituted triazolium salt (**136** and **172**) has been employed in studies reporting NHC-mediated oxidative esterifications of aldehydes as illustrated in Scheme 4.2, [148,149] however, NHCs of this structure have not been reported as efficient catalysts of the crossed acyloin condensation. It is reasonable to assume that this is due to reprotonation of the electron-rich carbene by the alcohol of the acyloin product, or the conjugate acid of the base employed, leading to a highly inefficient protocol.

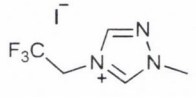


Scheme 4.2 NHC-mediated oxidative esterifications of aldehydes in the presence of 1,2,4-triazolium salts **136** and **172**[113,148,149]

We envisaged that the presence of an electron-withdrawing aliphatic substituents would be likely to facilitate carbene formation (*i.e.* make the salt more acidic) and also make the carbene less basic, therefore the NHC would be less susceptible to reprotonation by either the

acyloin product or the conjugate acid of the base employed. It was essential to synthesise a triazolium ion-based precatalyst that bears electron-withdrawing substituents that are catalytically inert and that also prevent reprotonation of the corresponding NHC catalyst in the reaction media. Inspired by the success of the pentafluorophenyl-substituted achiral triazolium salt **100** previously employed by our research group, we envisaged synthesising a novel electron-poor aliphatic-substituted achiral triazolium salt bearing electron-withdrawing fluorine atoms.

Hence, we decided to explore the synthesis of triazolium salt **247** (Figure 4.1), bearing a trifluoroethyl group in place of the ethyl substituent on precatalyst **172**, and examine the performance of this novel aliphatic substituted ion-based triazolium precatalyst in the crossed acyloin condensation.

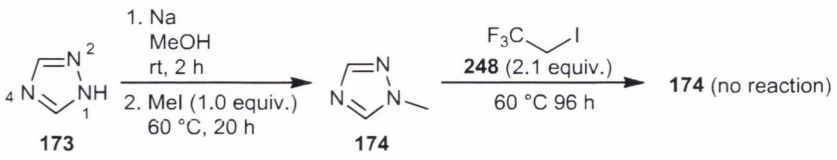


247

Figure 4.1 Target aliphatic-substituted triazolium salt **247**: electron-poor variant of triazolium precatalyst **172**

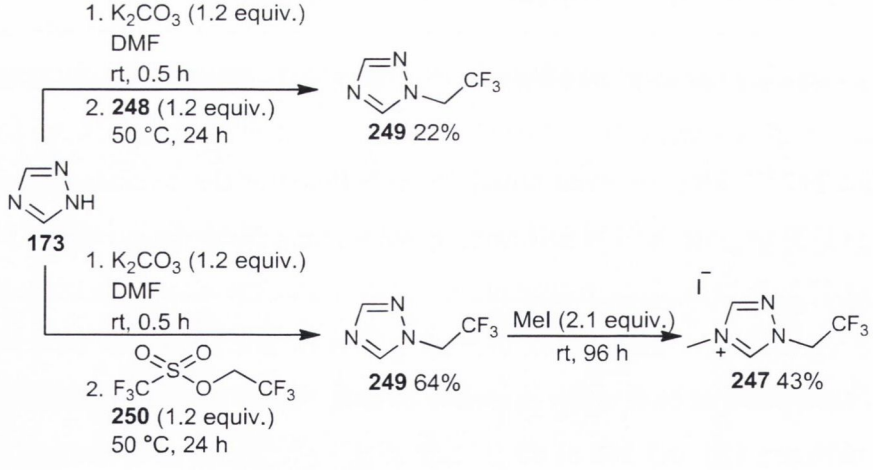
4.2 Synthesis of a mono-trifluoroethyl-based triazolium salt

We decided to employ the same synthetic route, previously reported by our research group, for the synthesis of the aliphatic-substituted achiral triazolium salt **172** as for the target triazolium salt **247**.[148] This involved initial *N*-methylation at the secondary amine (N-1) of 1,2,4-triazole (**173**) to generate **174** followed by subsequent *N*-ethylation at N-4 to furnish the triazolium salt **172** (Scheme 2.2). However, in our synthetic route towards triazolium salt **247** we employed iodotrifluoroethane (**248**), in place of iodoethane and to our disappointment, no *N*-alkylation took place at N-4 in the presence of **248**; only **174** was obtained. We repeated the reaction between **174** and **248** at 60 °C however, once again, only starting material was detected, as shown in Scheme 4.3.



Scheme 4.3 Attempted synthesis of triazolium precatalyst **247** from commercially available **173**

We postulated that alkylation at N-4 of **174** using **248** was problematic and that trifluoroethylation at the secondary amine (N-1) of **173** would be far more facile. However, in the presence of sodium methoxide (generated *in situ* from reaction of sodium metal with methanol), *N*-alkylation of the primary amine was not observed. We subsequently followed a procedure reported by Szarek[150] who studied the *N*-alkylation at N-1 on 1,2,4-triazoles, at elevated temperatures, in the presence of potassium carbonate and a wide range of alkylating agents. Whilst formation of **249** was observed, the yield was not synthetically useful, therefore we sought to employ a more 'active' alkylating agent than **248**. Gratifyingly, in the presence of 2,2,2-trifluoroethyl trifluoromethanesulfonate (**250**) and potassium carbonate, the *N*-alkylated product **249** was generated in 64% yield, as illustrated in Scheme 4.4. Upon obtaining **249** we proceeded with the addition of a methyl group to generate precatalyst **247**. To our delight, upon addition of iodomethane, triazolium salt **247** was formed in 43% yield.



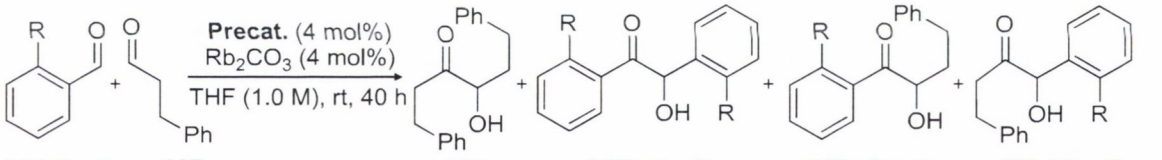
Scheme 4.4 Synthesis of aliphatic-substituted triazolium salt **247**

4.2.1 Initial evaluation of the mono-trifluoroethyl-based triazolium salt for use in the intermolecular cross-coupling of aldehydes

With triazolium salt **247** in hand, we aimed to assess the influence of the electron-withdrawing aliphatic substituent on **247** in the crossed acyloin condensation in comparison

to the prevalent triazolium ion-based precatalyst **100**. We decided it would be prudent to compare the novel triazolium salt **247** in a condensation reaction, previously reported by our research group, where little chemoselectivity was observed when precatalyst **100** was employed in order to observe if **247** was a superior precatalyst.[93] Therefore, we studied the reaction of hydrocinnamaldehyde (**107**) with *ortho*-fluorobenzaldehyde (**251**) and *ortho*-methoxybenzaldehyde (**252**) in the presence of the novel precatalyst **247**. As depicted in Table 4.1 and as previously reported by our research group,[93] the NHC, derived from deprotonation of precatalyst **100**, did not promote a chemoselective process when these substrates, **251** and **252**, were employed (entries 1 and 3). We then employed the novel precatalyst **247** under identical conditions and, to our disappointment, discovered that little or no crossed acyloin products were generated and large quantities of aldehyde remained in the reaction vessel (entries 2 and 4). We concluded that precatalyst **247** was not sufficiently active and that another, more electron-poor variant should be synthesised.

Table 4.1 Comparison of triazolium precatalysts **100** and **247** in the condensation reaction between hydrocinnamaldehyde (**107**) and **251** or **252**



251 R = F
252 R = OMe

107

253a

253b R = F
254b R = OMe

253c R = F
254c R = OMe

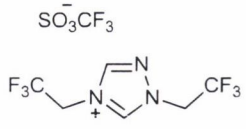
253d R = F
254d R = OMe

Entry	Precat.	Aldehyde	Product	Yield 253a (%)	Yield B (%)	Yield C (%)	Yield D(%)
1[a]	**100**	**251**	**253**	52	45	14	34
2	**247**	**251**	**253**	0	0	0	5
3[a]	**100**	**252**	**254**	20	16	21	59
4	**247**	**252**	**254**	0	0	0	<2

[a]Yields previously reported by Connon *et al.*

4.3 Synthesis of a *bis*-trifluoroethyl-based triazolium salt

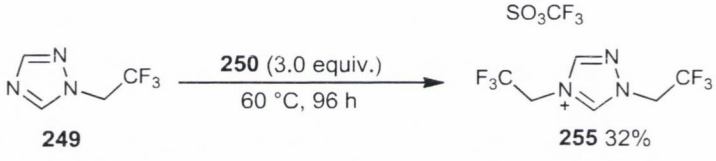
Despite the results obtained above, we postulated that a more electron-poor NHC, derived from the deprotonation of a triazolium ion-based precatalyst similar in structure to **247**, would catalyse the crossed acyloin reaction with greater efficiency. Hence it was decided to synthesise a triazolium salt bearing two trifluoroethyl substituents (**255**) as shown in Figure 4.2.



255

Figure 4.2 Target triazolium salt **255** bearing two trifluoroethyl-substituents

We employed the *N*-alkylated precursor **249** generated during the synthesis of precatalyst **247**. The precursor **249** was allowed to react in presence of the alkylating reagent **250** at room temperature however, no reaction was observed and only starting material was detected by ^{1}H NMR spectroscopic methods. We considered the requirement for heat in the previous alkylating step (for the synthesis of **249**, Scheme 4.4) when **250** was employed so we repeated the reaction at 60 °C and under these conditions, the novel *bis*-trifluoroethyl-based triazolium salt **255** was generated in 32% yield as shown in Scheme 4.5.



249 **255** 32%

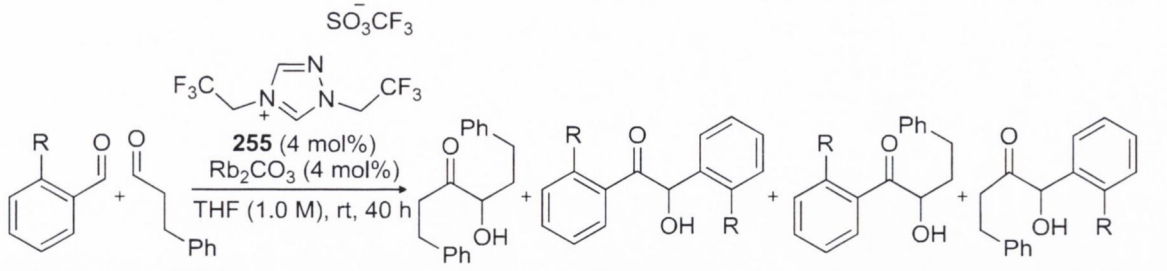
Scheme 4.5 Synthesis of *bis*-trifluoroethyl-substituted triazolium salt **255**

4.4 Examination of the intermolecular crossed condensation reaction using *bis*-trifluoroethyl-based triazolium salt 255

4.4.1 Preliminary experiments: evaluation of the *bis*-trifluoroethyl-based triazolium salt 255 for use in the intermolecular cross-coupling of aldehydes

We applied the novel precatalyst **255** to the same crossed acyloin reactions described above, where little chemoselectivity was observed when precatalyst **100** was employed, and the results we obtained were quite surprising. As previously discussed; when precatalyst **100** was employed (Table 4.2) the reaction proceeded to generate acyloin products **253d** and **254d** in moderate yields but with very little chemoselectivity; all four possible products were formed. In contrast, when the novel precatalyst **255** was employed, lower yields of product **253d** and **254d** were generated however, the process was extremely selective and these low yields of acyloin product were as a result of unreacted starting material and not the formation of other acyloin products.

Table 4.2 Evaluation of precatalyst **255** in the crossed condensation reaction



251 R = F **252** R = OMe | **107** | **253a** | **253b** R = F **254b** R = OMe | **253c** R = F **254c** R = OMe | **253d** R = F **254d** R = OMe

Entry	Aldehyde	Product	Yield 253a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	**251**	**253**	0	0	0	13
2	**252**	**254**	0	0	0	6

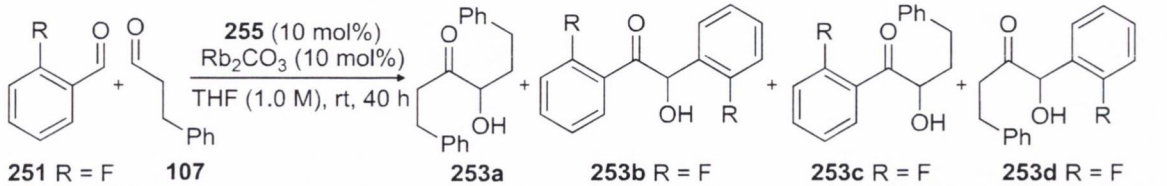
[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard.

We postulated that optimisation of the reaction conditions would facilitate the NHC-mediated process and allow access to the desired crossed acyloin products in higher yields.

4.4.2 Optimisation of reaction conditions

Precatalyst loading was the first parameter investigated in these optimisation studies; we repeated the two experiments mentioned above at a higher precatalyst and base loading of 10 mol% and were pleased to observe a uniformly selective process and a dramatic increase in product yield (Table 4.3, entries 1 and 2).

Table 4.3 Evaluation of precatalyst **255** (10 mol% loading) in the crossed condensation reaction



251 R = F **252** R = OMe | **107** | **253a** | **253b** R = F **254b** R = OMe | **253c** R = F **254c** R = OMe | **253d** R = F **254d** R = OMe

Entry	Aldehyde	Product	Yield 253a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	**251**	**253**	0	<2	0	54
2	**252**	**254**	0	0	0	38

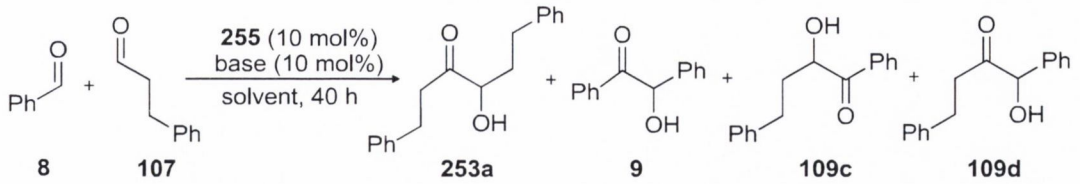
[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard.

Upon achieving these high levels of chemoselectivity with these sterically hindered substrates in the presence of **255** we wished to evaluate the performance of this precatalyst in the presence of an unactivated aromatic aldehyde, hence we examined the condensation reaction between hydrocinnamaldehyde (**107**) and benzaldehyde (**8**). We observed that this reaction also proceeded in a chemoselective manner; acyloin product **109d** was rendered in 47% yield, whilst the other potential acyloin products were formed in little or no yield (Table 4.4, entry 1). Whilst we were pleased to observe such a chemoselective process in the presence precatalyst **255**, the obtained yields of acyloin product **109d** were not synthetically useful and as high quantitites of aldehyde (**8** and **107**) remained, it was essential to further optimise the reaction conditions to generate this crossed product in higher yields.

Subsequently the influence of base on the reaction between **8** and **107** (in the presence of precatalyst **255**) was examined (Table 4.4). In the presence of DBU no product was formed as perhaps this base is not compatible with the electron-poor triazolium salt **255** (Table 4.4, entry 2). When TEA was employed, product yields diminished to 38% (entry 3); hence we speculated that a slightly stronger base was essential in obtaining higher product yields. Gratifyingly, in the presence of DIPEA, the acyloin product **109d** was obtained in 63% yield (entry 4). We next focused our efforts on examining the effect of elevated base loadings on this protocol, however, the use of DIPEA in 20 mol% and 40 mol% failed to generate the acyloin product in higher yields (entries 5 and 6).

We also investigated the most suitable solvent for this reaction. Similar yields of **109d** were obtained when the reaction was carried out in CH_2Cl_2 and toluene, however, these yields were lower than those obtained when THF was employed (Table 4.4, entries 7 and 8). Chloroform also proved to be a less useful reaction medium (entry 9). With THF determined to be the optimal solvent, we set about further optimising the reaction conditions with respect to temperature. The reaction was carried out at 30 °C and a rise in product yield was noted (entry 10). Encouraged by this result, we subsequently performed the coupling reaction at 40 °C and were pleased to observe that the crossed acyloin product **109d** was generated in an extremely high yield of 98% (entry 11).

Table 4.4 Optimisation of the reaction conditions



8 **107** **253a** **9** **109c** **109d**

Entry	Base	Base loading (mol%)	Cat. loading (mol%)	Solvent	Temp. (°C)	Yield 253a (%)[a]	Yield 9 (%)[a]	Yield 109c (%)[a]	Yield 109d (%)[a]
1	Rb_2CO_3	10	10	THF	18	0	<2	0	47
2	DBU	10	10	THF	18	0	0	0	0
3	TEA	10	10	THF	18	0	0	0	38
4	DIPEA	10	10	THF	18	0	<2	0	63
5	DIPEA	20	10	THF	18	0	<2	0	63
6	DIPEA	40	10	THF	18	0	<2	0	63
7	DIPEA	10	10	CH_2Cl_2	18	0	<2	0	46
8	DIPEA	10	10	toluene	18	0	<2	0	47
9	DIPEA	10	10	$CHCl_3$	18	0	<2	0	33
10	DIPEA	10	10	THF	30	0	<2	0	76
11	DIPEA	10	10	THF	40	0	<2	0	98
12	DIPEA	5	5	THF	40	0	<2	0	49

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard.

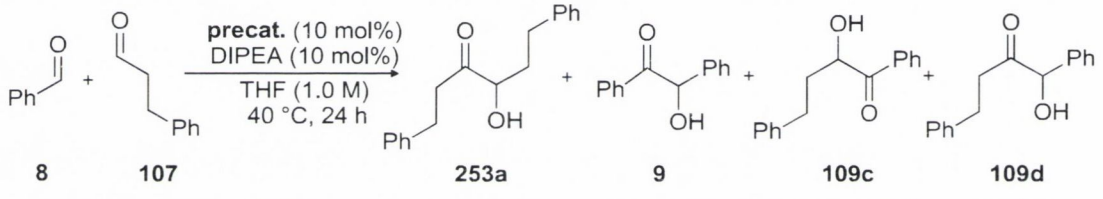
We wished to further fine tune the reaction parameters and postulated that the effect of elevated temperatures on this reaction was so significant, that perhaps lower precatalyst and base loadings could be employed without compromising product yields. However, in the presence of 5 mol% of **255** and DIPEA product yield was halved; implying that higher precatalyst and base loadings are essential for achieving high products yields (entry 12). We monitored the reaction by ^{1}H NMR spectroscopic methods under the optimised reaction conditions (at 40 °C and in the presence of 10 mol% precatalyst and base) and observed that the reaction proceeded to completion after 24 h.

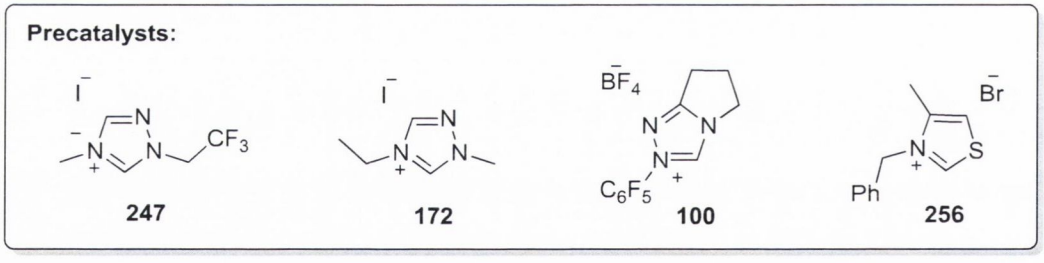
4.4.3 Screening of achiral NHC precatalysts under optimised reaction conditions

With a useful protocol in hand, we wished to assess and compare the performance of a variety of azolium salts under these optimised reaction conditions to determine if the NHC derived from triazolium ion-based precatalyst **255** was the most proficient in catalysing the acyloin condensation reaction in a chemoselective manner (Table 4.5). Quite surprisingly when the previously synthesised trifluoroethyl-substituted precatalyst **247** was employed

under the optimised reaction conditions the acyloin product **109d** was generated in half the yield of that when its *bis*-trifluoroethyl counterpart was used, but the process still proceeded with equally high levels of chemoselectivity (Table 4.5, entry 1). When precatalyst **172** was employed, no acyloin product was formed as presumably the NHC (derived from **172**) is either too electron rich or is not formed in sufficient amounts *in situ* to be rendered useful in this process (entry 2). High yields of acyloin product **109d** were achieved when pentafluorophenyl-substituted precatalyst **100** was employed whilst the use of thiazolium salt **256** led to a poor chemoselective process being observed (entries 3 and 4). Hence, from these studies, we observed that none of the azolium ion-based precatalysts outperformed precatalyst **255** when employed in the cross coupling reaction between aldehydes **8** and **107**.

Table 4.5 Screening of azolium ion-based precatalysts in the coupling reaction between aldehydes **8** and **107**





Entry	Precat.	Yield 253a (%)[a]	Yield 9 (%)[a]	Yield 109c (%)[a]	Yield 109d (%)[a]
1	**247**	0	9	0	44
2	**172**	0	0	0	0
3	**100**	12	10	0	75
4	**256**	36	21	0	28

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard.

4.4.4 Evaluation of substrate scope

With a useful protocol in hand, we turned our attention towards evaluating the behaviour of different aromatic and aliphatic aldehydes in this process. Due to the observation of

uniformly high yields of acyloin product **109d** obtained when triazolium ion-based precatalysts **100** and **255** were employed, we decided to screen a variety of aldehydes in the presence of both precatalysts to observe if precatalyst **255** was in fact superior to **100** in the crossed acyloin condensation across a range of substrates.

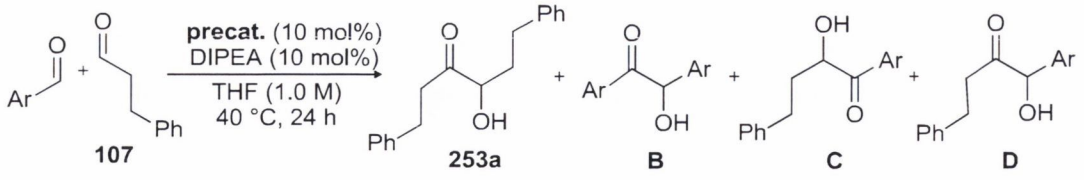
4.4.4.1 The aromatic aldehyde

We evaluated the performance of both the *bis*-trifluoroethyl triazolium salt **255** and the pentafluorophenyl-substituted triazolium salt **100** in the crossed condensation reaction between hydrocinnamaldehyde (**107**) and a wide range of aromatic aldehydes. We wished to determine if high levels of chemoselectivity could be achieved, in the presence of **255**, by varying the electronic and steric properties of the aromatic aldehyde partner.

We decided to compare the performance of the two precatalysts, under the optimised reaction conditions, in the presence of the functionalised aromatic aldehydes (**251** and **252**) employed earlier in our studies. Consistent with results reported previously by our research group,[93] the use of aldehyde **251** in the presence of precatalyst **100** led to an unchemoselective process (entry 1). In contrast, the same reaction carried out in the presence of novel precatalyst **255** was found to be highly chemoselective; acyloin product **253d** was furnished in 97% yield (entry 2). Under the optimised reaction conditions and in the presence of **100**, the *ortho*-methoxyphenyl-substituted acyloin product **254d** was generated in a relatively high yield of 75% (entry 3), yet the same reaction proceeded in a more cheomoselective fashion when precatalyst **255** was employed (entry 4). We observed that starting material remained after the allocated reaction time so we increased the temperature to 60 °C and gratifyingly, the product **254d** was obtained in quantitative yield (entry 6).

We subsequently executed experiments using *ortho*-, *para*- and *meta*-chlorobenzaldehyde to examine the tolerance of these various *isomers* by the two triazolium ion-based precatalysts. Interestingly, the position of the chlorine substituent on the benzaldehyde ring had a significant effect on the chemoselectivity of this reaction when precatalyst **100** was employed. *ortho*-Chlorobenzaldehyde was a suitable substrate in this reaction however, the use of the corresponding *meta*- and *para*-substituted aldehydes had a detrimental effect on the selectivity of this reaction; implying that when precatalyst **100** is employed, the process is highly sensitive to both electronic and steric factors (entries 7, 9 and 11). Gratifyingly, these factors were not an issue when our novel precatalyst **255** was employed as quantitative yields of acyloin products **257d**, **258d** and **259d** were obtained (entries 8, 10 and 12)

Table 4.6 Evaluation of the aromatic aldehyde



Entry	Precat.	Aromatic aldehyde	Prod.	Yield 253a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	**100**	2-F-C_6H_5	**253**	19	18	12	50
2	**255**	2-F-C_6H_5	**253**	0	3	0	97
3	**100**	2-MeO-C_6H_5	**254**	7	3	9	75
4	**255**	2-MeO-C_6H_5	**254**	0	0	0	89
5[b]	**100**	2-MeO-C_6H_5	**254**	4	0	7	89
6[b]	**255**	2-MeO-C_6H_5	**254**	0	0	0	>99
7	**100**	2-Cl-C_6H_5	**257**	6	5	9	81
8	**255**	2-Cl-C_6H_5	**257**	0	0	0	>99
9	**100**	3-Cl-C_6H_5	**258**	18	19	16	44
10	**255**	3-Cl-C_6H_5	**258**	0	0	0	>99
11	**100**	4-Cl-C_6H_5	**259**	20	19	16	64
12	**255**	4-Cl-C_6H_5	**259**	0	0	0	>99
13	**100**	4-CH_3-C_6H_5	**260**	10	13	0	73
14	**255**	4-CH_3-C_6H_5	**260**	0	<2	0	98
15	**100**	4-MeO-C_6H_5	**261**	30	8	0	49
16	**255**	4-MeO-C_6H_5	**261**	0	0	0	46
17[b]	**100**	4-MeO-C_6H_5	**261**	32	7	0	56
18[b]	**255**	4-MeO-C_6H_5	**261**	0	0	0	50
19[b,c]	**100**	4-MeO-C_6H_5	**261**	30	14	0	56
20[b,c]	**255**	4-MeO-C_6H_5	**261**	0	0	0	93
21	**100**	4-CO_2Me-C_6H_5	**262**	17	17	13	52
22	**255**	4-CO_2Me-C_6H_5	**262**	0	4	0	96
23	**100**	2-napthyl	**263**	8	8	6	78
24	**255**	2-napthyl	**263**	0	0	0	98
25	**100**	1-napthyl	**264**	4	1	0	92
26	**255**	1-napthyl	**264**	0	0	0	<99

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard. [b]Reaction executed at 60 °C. [c]Allowed to react for 40 h.

We also compared the performance of the two precatalysts in reactions involving more electron-rich aldehydes (entries 13-20). Once again our novel triazolium ion-based precatalyst proved the far superior promoter of the two triazolium salts. When precatalyst **255** was employed, the acyloin product **260d** was furnished in 92% yield, in stark contrast to the yield obtained in the presence of precatalyst **100** (entries 13 and 14). Low yields of acyloin **261d** were obtained in the presence of both precatalysts, as *para*-anisaldehyde appeared to react at a very slow rate (entries 15 and 16). We speculated that increasing the temperature of

the reaction to 60 °C may encourage the aldehyde to react with the partner substrate **107** at a faster rate. We observed an increase in product yield of **261d**, however, after 24 hours the yields obtained were still low in comparison to the yields of acyloin products achieved when other aromatic aldehyde substrates were utilised (entries 17 and 18). When precatalyst **100** was employed, the generation of acyloin product **261d** was hampered by the dimerisation of *para*- anisaldehyde to form **261b** in 30% yield (entry 90). However, in the presence of our novel precatalyst **255** the low yields obtained were not due to the formation of alternative acyloin products (such as **261b**) but rather a slow reaction rate. Hence we allowed the two aldehydes to react in the presence of precatalyst **255** at 60 °C and gratifyingly, acyloin **261d** was obtained in 93% yield after 40 hours (entry 20).

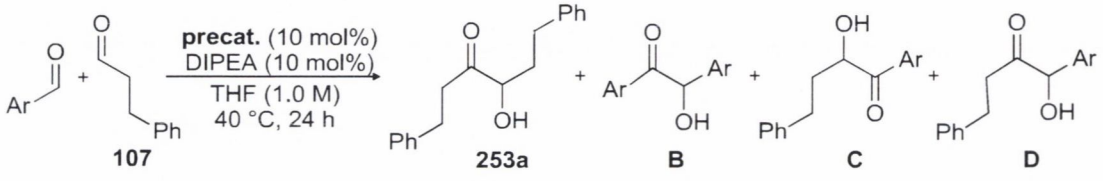
The evaluation of an ester-substituted aromatic aldehyde was also undertaken (entries 21 and 22). Whilst the acyloin product **262d** was generated in high yields in the presence of both triazolium ion-based precatalysts, the NHC derived from our novel precatalyst still remained superior in promoting a chemoselective process. Having demonstrated the high tolerance of precatalyst **255** to different substituted benzaldehydes possessing very differing steric and electronic properties, we were curious if this protocol would also accept 2- and 1-napthaldehyde (entries 23-26). Once again, we observed that precatalyst **255** outperformed **100** as acyloin products **263d** and **264d** were obtained in almost quantitative yields in the presence of **255** (entries 24 and 26).

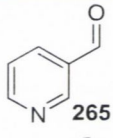
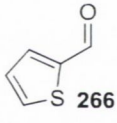
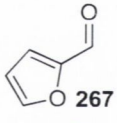
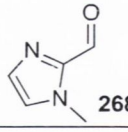
We thought it prudent to also test the compatibility of precatalyst **255** with different heteroaromatic aldehydes (Table 4.7). We initiated these studies by examining the performance of the two precatalysts, **100** and **255**, in the coupling reaction between 3-pyridinecarboxaldehyde (**265**) and **107** (entries 1 and 2). When precatalyst **100** was employed, little chemoselectivity was observed in comparison to the equivalent reaction carried out in the presence of precatalyst **255**, in which **269d** was furnished in 92% yield. A similar outcome was observed when 2-thiophenecarboxaldehyde (**266**) was employed in this process, however, degradation of **270d** on silica gel during purification led to a reduced isolated yield (entry 4).

We noted that the less aromatic aldehyde 2-furfuraldehyde (**267**) was not tolerated by our protocol involving the use of precatalyst **255** and for the first time in this study, precatalyst **100** outperformed **255** in generating high yields of the **D** acyloin product (entries 5 and 6). We were surprised to observe that relatively high yields of **271b** were generated in the

presence of **255** and postulated that this occurrence was due to the decrease in aromaticity of the aryl substrate. Hence, we decided to evaluate the tolerance of an aryl partner, in this process, that is even less aromatic in nature than **267**. We discovered that **272d** was generated in 41% yield in the presence of precatalyst **100** (entry 7) and, in contrast, this acyloin product was not formed when **255** was employed as all of aldehyde **268** dimerised to form **272b** (entry 8).

Table 4.7 Evaluation of heteroaromatic aldehydes



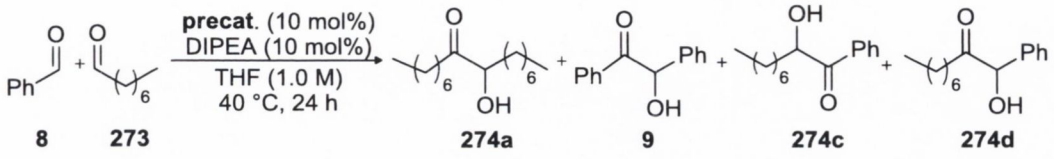
Entry	Precat.	Heteroaromatic aldehyde	Product	Yield 253a (%)	Yield B (%)	Yield C (%)	Yield D (%)
1	**100**	 **265**	**269**	14	18	11	52
2	**255**		**269**	0	5	0	92
3	**100**	 **266**	**270**	18	18	14	50
4	**255**		**270**	0	8	0	85
5	**100**	 **267**	**271**	13	11	25	49
6	**255**		**271**	0	32	0	36
7	**100**	 **268**	**272**	8	8	37	41
8	**255**		**272**	0	100	0	0

4.4.4.2 The aliphatic aldehyde

We wished to ascertain if the use different aliphatic aldehydes in the presence of precatalyst **255** would also lead to a highly chemoselective process. Hence, we studied the coupling reaction between benzaldehyde (**8**) and octanal (**273**) as shown in Table 4.8 (entries 1-4). Under the optimised reaction conditions we observed that **274d** was generated in comparable yields in the presence of both triazolium salts; **100** and **255** (entries 1 and 2). However, in the presence of precatalyst **255**, starting material remained (entry 2) hence we repeated the reaction at 60 °C in the presence of both triazolium salts. When precatalyst **100** was employed, the yield of acyloin product **274d** increased to 84% (entry 3) however, the NHC

derived from our novel precatalyst **255** proved superior once again and catalysed the formation of **274d** in 96% yield (entry 4).

Table 4.8 Evaluation of aliphatic aldehyde **273** with benzaldehyde (**8**)

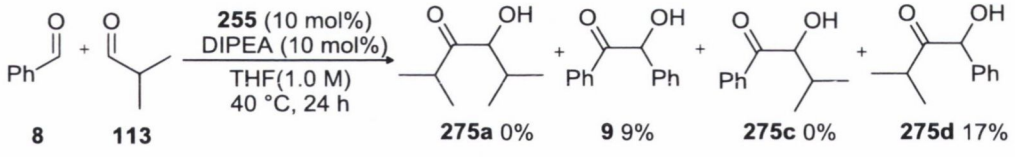


8 **273** **274a** **9** **274c** **274d**

Entry	Precat.	Yield 274a (%)[a]	Yield 9 (%)[a]	Yield 274c (%)[a]	Yield 274d (%)
1	**100**	11	14	0	74
2	**255**	0	3	0	79
3[b]	**100**	8	8	0	84
4[b]	**255**	0	4	0	96

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard. [b]Reaction carried out at 60 °C.

We also wished to examine the tolerance that precatalyst **255** has for a sterically hindered branched aliphatic aldehyde. We were surprised to observe a lack of crossed acyloin product **275d** when *iso*-butaraldehyde (**113**) was employed, suggesting that precatalyst **255** is extremely sensitive to the steric properties of the aliphatic aldehyde (Scheme 4.6).



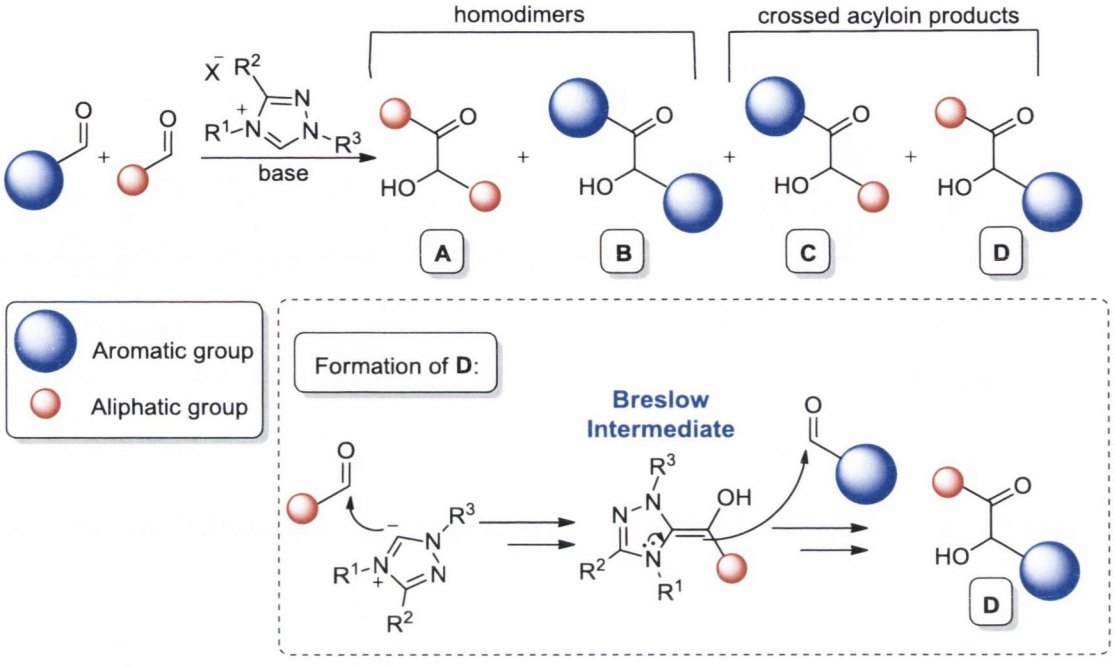
8 **113** **275a** 0% **9** 9% **275c** 0% **275d** 17%

Scheme 4.6 Evaluation of branched aliphatic aldehyde **113** with benzaldehyde (**8**) in the presence of precatalyst **255**

4.4.5 A chemoselective crossed acyloin condensation; a mechanistic rationale

It is clear from these investigations that the use of precatalyst **255** in the crossed acyloin condensation allows for the favourable formation of the **D** acyloin product. Upon cursory analysis of the mechanism of this reaction described earlier (Section 1.5), the **D** acyloin product is generated *via* initial nucleophilic attack of the NHC catalyst on the aliphatic

aldehyde followed by attack of the newly formed Breslow intermediate on the aromatic aldehyde, as depicted in Scheme 4.7.



Scheme 4.7 Formation of **D** acyloin product in the crossed acyloin condensation

From previous studies reported in Section 1.5.3.2 that employed precatalyst **100** it is evident that the NHC, formed from deprotonation of **100**, usually has a higher affinity for the carbonyl moiety of the aliphatic aldehyde rather than that of the aromatic aldehyde due to steric reasons (Figure 4.3).[93] The interaction between the smaller aliphatic aldehyde and the NHC catalyst is favoured as there is little steric hindrance between the pentafluorophenyl group and the aliphatic substituent of the aldehyde. In contrast, formation of the Breslow intermediate resulting from interaction of the catalyst with the aromatic aldehyde is disfavoured due to the steric clash between the aromatic moiety of the aldehyde and the aryl ring on the catalyst as depicted in Figure 4.3. Note: *A*-values are often employed for the assessment of the relative steric size of functional groups.[151] According to their *A*-values, the steric demand of a phenyl group ($A_{C_6H_5} \sim 2.87$) is far greater than that of a straight chained ethyl group ($A_{CH_2CH_3} \sim 1.79$).[152]

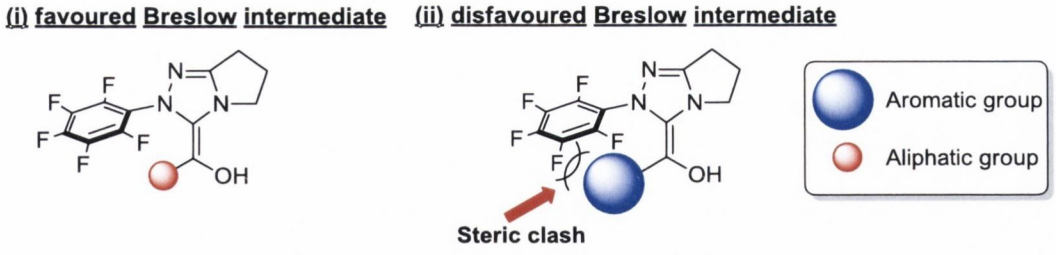


Figure 4.3 Rationale for the chemoselective outcome arising from Breslow intermediate formation

The corresponding Breslow intermediate (generated upon reaction of the NHC and the aliphatic aldehyde) has a higher affinity for the aromatic aldehyde than the aliphatic aldehyde due to an attractive π-iminium interaction between the Breslow intermediate and the aromatic moiety of the aldehyde (Figure 4.4). This favourable interaction lowers the energy of the developing transition state as the Breslow intermediate attacks the aromatic aldehyde.[66,153] When an aliphatic aldehyde lacking an aromatic group is employed, no iminium interaction can occur. When the aliphatic aldehyde possesses an aryl ring, the interaction would be reduced as there is a larger distance between the iminium ion and the aromatic group.

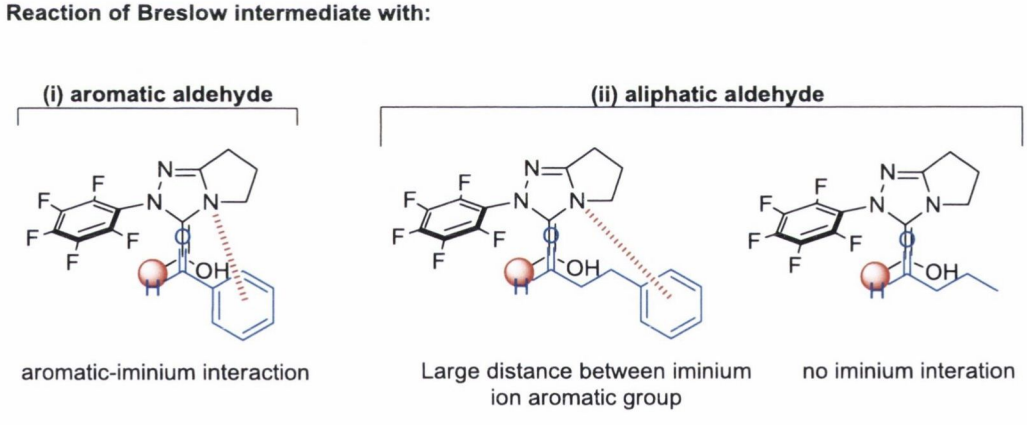


Figure 4.4 Explanation for chemoselectivity observed upon attack of Breslow intermediate on aromatic aldehyde

Based on this mechanistic picture, we can deduce that sterics play a large role in the formation of the Breslow intermediate, whilst formation of the acyloin product depends largely on electronic factors such as π-iminium interactions. However, rarely is a highly chemoselective process observed and it has been reported in literature that the NHC derived from **100** is often capable of attacking the aromatic aldehyde and once this occurs a chemoselective bias cannot occur. This explains why aldehyde substrates are often 'tailored'

to this reaction as the use of bulkier aromatic aldehydes reduces the possibility of nucleophilic attack of the NHC on the carbonyl moiety of the aromatic aldehyde.

Upon examination of the substrate scope of this protocol employing precatalyst **255**, we found the results quite surprising yet extremely interesting. We observed that this protocol is extremely sensitive to the use of bulky aliphatic substrates. When the aliphatic aldehyde is sterically demanding, we postulate that NHC catalyst (derived from deprotonation of **255**) cannot access the carbonyl moiety of the aldehyde and hence Breslow intermediate formation and subsequent product generation cannot occur (according to their *A*-values, the steric demand of an *iso*-propyl group ($A_{CH(CH_3)_2} \sim 2.21$) is higher than that of an ethyl group ($A_{CH_2CH_3} \sim 1.79$)).[152] In a similar fashion, it is understandable why the NHC catalyst does not attack the aromatic aldehyde; as perhaps steric hindrance also plays a role here.

Thus far we can deduce that the NHC, derived from **255**, prefers to attack the aliphatic aldehyde (if not blocked by steric interactions) to generate the corresponding Breslow intermediate. This Breslow intermediate will subsequently only attack the carbonyl moiety of the aromatic aldehyde (due to the favourable π-iminium interaction) and not that of the aliphatic aldehyde leading to extremely high yields of acyloin product **D** being formed.

We speculate that the origins of chemoselectivity observed in this process arise from the freely rotating trifluoroethyl groups present on **255**. It is reasonable to assume that these freely rotating aliphatic groups prevent any bulky substrates from approaching the carbene centre, from either orientation, and only the carbonyl moiety of an unhindered, non-branched aldehyde is accessible by the catalyst as shown in Figure 4.5. Hence, this NHC catalyst is capable of distinguishing between the two aldehyde electrophiles based on the recognition of steric bulk of the substrate. As explained previously, the Breslow intermediate has a preference for attacking the aromatic aldehyde so it is essential that a chemoselective bias be established in the initial stage of the process (*i.e.* Breslow intermediate formation) so that only one Breslow intermediate is formed and this can subsequently attack the aromatic aldehyde.

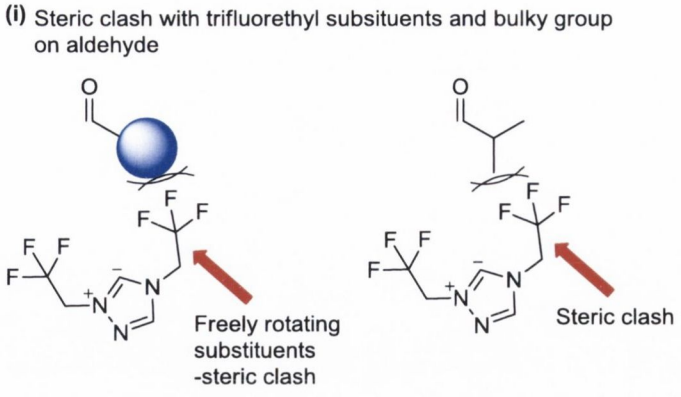


Figure 4.5 Freely-rotating trifluoroethyl substituents prevent nucleophilic attack on bulky aldehydes (*i.e.* aromatic or branched aliphatic aldehydes)

Moreover the NHC, derived from precatalyst **255**, is far superior to alternative aliphatic-substituted triazole-NHCs (*i.e.* **172**), that may also be capable of inducing a steric bias in the crossed acyloin condensation, as the electron-withdrawing trifluoroethyl groups prevent reprotonation of the NHC by either the acyloin product or the amine conjugate acid.

We discovered that this protocol is compatible with a wide range of aromatic aldehydes, with different electronic and steric properties, to consistently allow for the formation of **D** acyloin products. However, a decrease in aromaticity of the aryl substrate led to increased yields of homodimer products of type **B** being formed. It can be assumed that there is not a large difference in size between 2-thiophenecarboxaldehyde (**266**), 2-furfuraldehyde (**267**) and 1-methyl-2-imidazolecarboxaldehdye (**268**). Yet, in the presence of **266**, the **D** acyloin product is furnished in high yields, however, formation of the **B** acyloin product occurs in the presence of aldehydes **267** and **268**. This suggests that in these cases, the NHC is capable of attacking the aromatic aldehyde and perhaps this is occurrence is not governed by a single factor alone but rather a combination of steric and electronic factors.

As discussed, we postulate that high levels of chemoselectivity are observed in the presence of precatalyst **255** due to the steric hindrance, originating from the two freely rotating trifluoroethyl groups, preventing any interaction between the NHC and the aromatic aldehyde. In order to prove our hypothesis, we postulated that benzoin cannot be reversibly formed in the presence of this precatalyst as steric hindrance would prevent attack of the NHC, generated *in situ*, on the carbonyl moiety of benzoin (Figure 4.6). In contrast, it has been reported in previous studies that benzoin formation is reversible in the presence of precatalyst **100**, suggesting that the NHC derived from this precatalyst can access the

carbonyl moiety despite the presence of the two aromatic groups present on benzoin products. Perhaps this is due to the rigid pentafluorophenyl ring, causing a limited environment of steric bulk surrounding the NHC and therefore the NHC is capable of attacking the benzoin product.

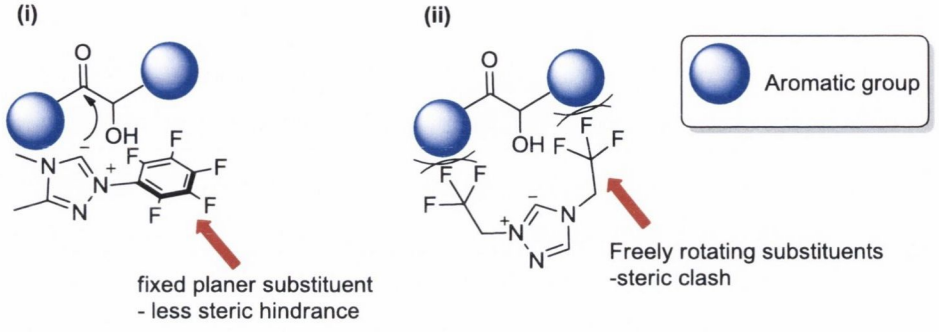
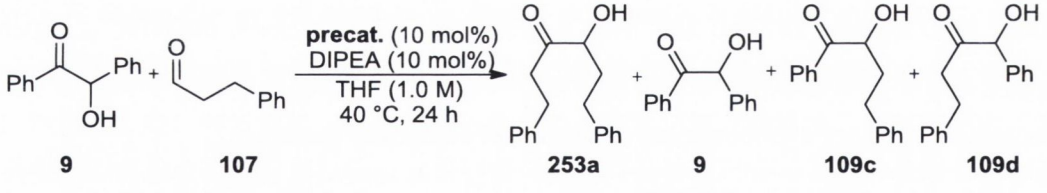


Figure 4.6 Rationale for reversible benzoin formation in the presence of NHC, generated from deprotonation of **100**

Hence we subjected benzoin product **9** to the same reaction parameters discussed previously, in the presence of **255**. We also carried out the same reaction using precatalyst **100** as a control experiment to observe if under this new set of conditions, reversible formation of **9** still occurred.

Table 4.9 Evaluation of reversible formation of benzoin in presence of precatalysts **100** and **255**



9 **107** **253a** **9** **109c** **109d**

Entry	Precat.	Yield 253a (%)[a]	Yield 9 (%)[a]	Yield 109c (%)[a]	Yield 109d (%)[a]
1	**100**	57	84	0	16
2	**255**	<2	100	0	0

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (114 μL, 1.00 mmol, 0.5 equiv.) as an internal standard.

Consistent with previous studies, the reversible formation of benzoin was observed in the presence of **100** to generate benzaldehyde (**8**) which consequently reacted with hydrocinnamaldehyde (**107**) to furnish **109d** in 16% yield (Table 4.9, entry 1). However, this

was not the case in the presence of **255**; quantitative yields of benzoin product were observed, suggesting that no retroacyloin occurred (entry 2). This study further proves our hypothesis that steric hindrance, introduced by the two trifluoroethyl groups, prevents attack on bulky substrates.

4.5 Conclusions

We have synthesised a novel triazolium ion-based precatalyst **255**, that now fills the void of electron-poor aliphatic-substituted triazolium salts in literature. With this triazolium salt in hand, we have developed a highly synthetically useful protocol that allows access to a wide range of crossed acyloin products in extremely high and unprecedented yields. This protocol accepts a variety of aromatic aldehydes and unbranched aliphatic aldehydes of differing electronic and steric properties to yield the corresponding crossed α-hydroxyketones. To the best of our knowledge there is no report in literature, concerning NHC catalysis, that allows access to such a variety of crossed products in such high yields.

Perhaps more importantly, the development of this novel precatalyst has allowed us to gain insight into what factors influence a chemoselective crossed acyloin condensation. In the presence of this precatalyst we have discovered that sterics plays an important role in the formation of the Breslow intermediate. We have also contributed to the current theory that steric factors are somewhat insignificant in the reaction between the Breslow intermediate and the second aldehyde and that this interaction is highly dependent on the electronic properties of the aldehyde *i.e.* the Breslow intermediate favours attack on the aromatic aldehyde.

Whilst this protocol may appear quite limited in the presence of "less" aromatic aryl aldehydes, it may be possible to exploit this in the generation or aromatic-aromatic crossed acyloin products. We have observed that the NHC, derived from **255**, is capable of attacking furfuraldehyde (**267**) and 1-methyl-2-imidazole carboxaldehde (**268**) to form the Breslow intermediate. As the only other reaction partner available was an aliphatic aldehyde, which the Breslow intermediate has less of an affinity for, the same aromatic aldehyde was attacked to generate the homo-benzoin product of type **B**. However, if another aldehyde "more" aromatic in nature was available we postulate that Breslow intermediate formation would occur between the less aromatic aldehyde and the NHC and the corresponding Breslow intermediate would consequently attack the more aromatic aldehyde. While partial solutions

are available for the selective coupling of aliphatic and aromatic aldehydes, a general NHC-mediated method for accessing crossed aromatic benzoins (*i.e.* between two different aromatic aldehydes) has remained elusive. This theory, if successful, would allow for the first triazole-NHC-mediated aromatic-aromatic condensation reaction to be reported.

4.6 Future work

As described above, there is currently research being carried out by our collaborators (Zeitler and coworkers) into developing a methodology for accessing aromatic-aromatic crossed acyloin producte and into expanding the substrate scope using aliphatic aldehydes in the presence of this novel triazolium salt. We would also like to employ this novel aliphatic NHC triazolium ion-based precatalyst in other NHC-mediated reactions to prove our theory that the two freely rotating trifluroethyl groups, due to sterics, establish substrate selectivity within the reaction. If this is the case our ultimate goal is to synthesise a chiral triazolium salt that bears similar electronic and steric properties to this triazolium ion-based precatalyst in the hope to obtain crossed α-hydroxyketones in extremely high yields with high equally high levels of enantiopurity.

5. The study of heteroaromatic aldehydes in the intermolecular crossed acyloin condensation

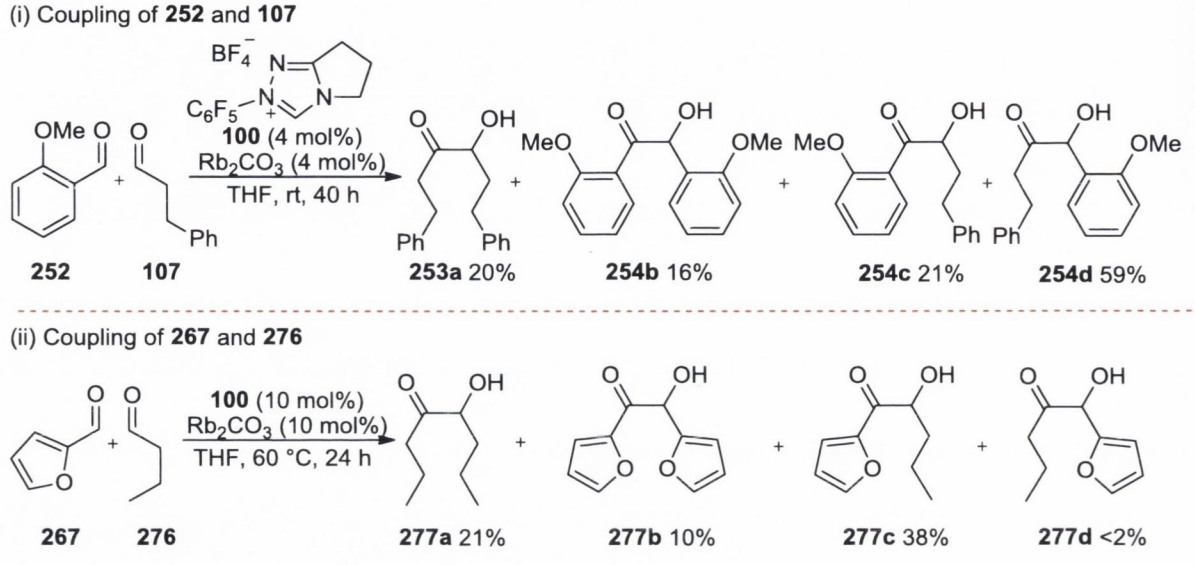
Though several studies have been carried out in recent decades in which significant advances in the NHC-catalysed homobenzoin condensation have been made, reports of NHC-mediated crossed condensations that allow access to the formation of a single major product still remain elusive. In order to obtain significant yields of a crossed acyloin product it is necessary that a chemoselective bias be established; either by successful precatalyst design or the use of 'tailored' substrates.[93]

We have previously studied the crossed acyloin condensation with respect to novel precatalyst design (Section 4.0) but we were also interested in studying this reaction with regards to substrate scope, with the aim of achieving not only high levels of chemoselectivity, but more importantly gaining an insight into the factors which influence both Breslow intermediate formation and subsequent reaction, in order to ascertain how to develop a chemoselective process.

5.1 Rationale behind the evaluation of heteroaromatic aldehydes in the crossed acyloin condensation

Our research group previously reported two separate investigations on the influence of both substrate and catalyst structure on the chemoselective outcome of the crossed acyloin condensation. As previously discussed (Scheme 4.7), when an aromatic and an aliphatic aldehyde are employed, the NHC-based catalyst (generated *in situ* upon deprotonation of the parent triazolium salt) usually has a preference for attack on the carbonyl moiety of the aliphatic aldehyde, rather than the aromatic aldehyde, due to steric factors (Figure 4.3). The newly formed Breslow intermediate subsequently prefers to attack the carbonyl group of the aromatic aldehyde, rather than the aliphatic aldehyde due to a favourable π-iminium interaction between the nitrogen atom of the Breslow intermediate and the approaching aromatic aldehyde (Figure 4.4). This occurrence results in the formation of the crossed acyloin product of type **D**, *i.e.* the α-hydroxyketone where the alcohol moiety is alpha to the aromatic group. However, during two studies previously carried out by Connon *et al.* on the coupling of a variety of aromatic aldehydes with aliphatic aldehydes, in the presence of the pentafluorophenyl-substituted triazolium salt **100**, small amounts of the acyloin product of

the opposite chemoselectivity were also observed when particular aromatic substrates were employed; a) in one report, the use of *ortho*-anisaldehyde (**252**) led to the formation of **254c** in 21% yield,[154] b) in the second report the heteroaromatic aldehyde, 2-furaldehyde (**267**), was employed and the crossed product **277c** was generated in 38% yield, however, isolation of this product proved impossible due to rapid oxidation of the product (Scheme 5.1). [92]



Scheme 5.1 Observation of **C** acyloin products (*i.e.* **254c** and **277c**) in reports previously carried out by Connon *et al.*

Whilst the yields of these acyloin products were not synthetically useful, the studies implied that certain aromatic aldehydes are capable of reacting with an aliphatic substrate, in the crossed acyloin condensation, to form the **C** acyloin product *i.e.* the α-hydroxyketone where the alcohol moiety is alpha to the aliphatic group. We appreciated that α-hydroxyketones of this particular chemoselectivity are of equal synthetic importance to those of the opposite and frequently studied chemoselectivity (*i.e.* the **D** acyloin product), however, at the outset of this experiment, only one study on the NHC-mediated crossed acyloin condensation that allows access to the **C** acyloin product was reported; Yang[88] revealed that for this chemoselective process to occur it was necessary that 10 equivalents of acetaldehyde and *para*-substituted aromatic aldehydes be employed (Table 1.5). Intrigued by the paucity of these particular studies in the literature (*i.e.* those that report access to α-hydroxyketones where the alcohol moiety is alpha to the aliphatic group) and encouraged by the results obtained previously by our research group (Scheme 5.1), we set out to explore the influence that heteroaromatic and

methoxy-bearing aromatic aldehydes have on chemoselectivity when employed in the crossed acyloin condensation.

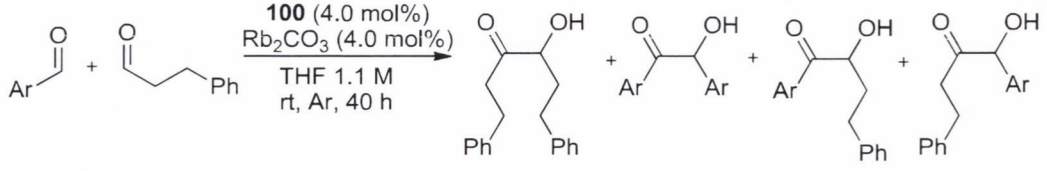
5.2 Preliminary results

We initiated our studies by evaluating the performance of a variety of heteroaromatic and methoxy-bearing aromatic aldehydes in the crossed acyloin condensation under identical reaction conditions employed previously by our research group *i.e.* in the presence of precatalyst **100**, at ambient temperature and a 1:1 ratio of aldehyde substrates (Table 5.1).

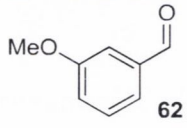
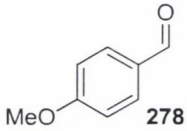
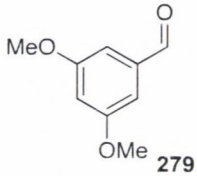
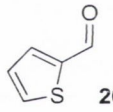
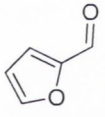
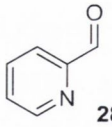
Disappointingly, when the methoxy-substituent was present in the *para* or *meta* position, very little of the corresponding **C** acyloin products (*i.e.* **281c** and **261c**) were observed (Table 5.1, entries 1 and 2). We postulated that the use of a di-substituted variant of **62** may lead to a chemoselective process, however, in the presence of aldehyde **279** the acyloin product **282c** was formed in extremely low yields (entry 3).

We also wished to investigate the performance of heteroaromatic aldehydes in this process. Hence we employed 2-thiophenecarboxaldehyde (**266**), 2-furfuraldehyde (**267**) and 2-pyridinecarboxaldehyde (**280**). We observed that almost no acyloin product **270c** was generated when aldehyde **266** was employed (entry 4). Quite surprisingly, the use of aldehyde **267** led to very low quantities of **271c** being formed, (entry 5), in comparison to when it was employed previously by our research group (at 60 °C and in the presence of butyraldehyde). To our delight, the use of aldehyde **280** resulted in generation of acyloin product **283c** in a relatively high yield of 41% and interestingly, the product of opposite chemoselectivity, **283d**, was not observed (entry 6).

Table 5.1 Crossed acyloin condensation in presence of precatalyst **100**; preliminary studies



107 253a B C D

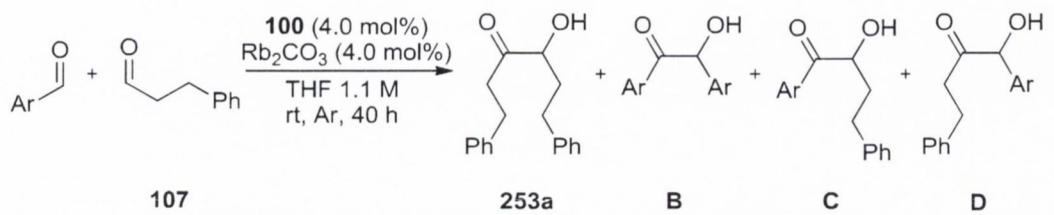
Entry	Aromatic aldehyde	Product	Yield 253a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	 62	**281**	14	22	14	27
2	 278	**261**	24	18	3	45
3	 279	**282**	7	19	8	53
4	 266	**270**	15	24	<2	46
5	 267	**271**	3	14	5	52
6	 280	**283**	23	12	46	0

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard.

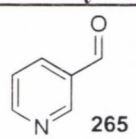
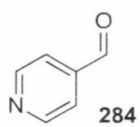
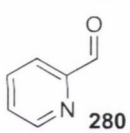
Encouraged by the results obtained when aldehyde **280** was employed, we postulated that perhaps the use of other aldehydes bearing the pyridine moiety may also lead to the formation of acyloin products of this particular chemoselectivity and hence, we examined the crossed acyloin condensation using 3- and 4-pyridinecarboxyaldehyde (Table 5.2). The results we obtained were remarkable; the use of **265** resulted in preferential formation of the **D** acyloin

product (*i.e.* **269d**, entry 1) while the use of **284** led to higher yields of the corresponding homodimer (**285b**) being obtained (entry 2).

Table 5.2 Evaluation of heteroaromatic aldehydes bearing a pyridine moiety in the crossed acyloin condensation

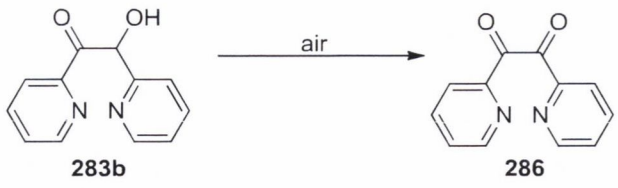


107 253a B C D

Entry	Aromatic aldehyde	Product	Yield 253a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	 265	**269**	21	11	9	55
2	 284	**285**	45	50	0	0
3[b]	 280	**283**	4	8	88	0

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard. [b]2 equivalents of aromatic aldehyde were employed.

We were also curious to record the result obtained when employing a surplus of aldehyde **280**, hence we carried out the condensation process with 2 equivalents of **282** and 1 equivalent of **107** which, to our delight, rendered **283c** in 88% yield (entry 3). The results outlined in Table 5.2 imply that the position of the nitrogen atom on the pyridine ring plays a large role in determining the chemoselective outcome of this crossed acyloin condensation. It is worth noting that when aldehydes **280** and **284** were employed, the corresponding homodimers (**283b** and **285b**) rapidly oxidised in the presence of air to generate the corresponding pyridil compounds.



283b **286**

Scheme 5.2 Rapid oxidation of **283b** in air to generate corresponding pyridil compound (**286**)

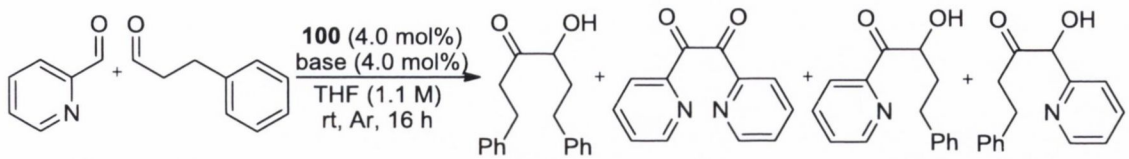
5.3 Optimisation of reaction conditions

Having established a useful protocol whereby the use of aldehyde **280** leads to the generation of the acyloin product **283c**, with opposite chemoselectivity to that usually observed in the crossed acyloin condensation, we next turned our attention towards optimisation of the reaction parameters. Despite the high yields of **283c** formed in the presence of 2 equivalents of aldehyde **280**, our priority is to understand the origin of chemoselectivity when this particular heteroaromatic aldehyde is employed and hence, we decided to continue our studies with 1 equivalent of both aromatic and aliphatic aldehydes.

The choice of base reported was rubidium carbonate, however, due to the difficult handling of this particular base we opted to carry out trial experiments in the presence of a variety of bases with the aim of optimising the reaction conditions to obtain **283c** in higher yields (Table 5.3). The use of inexpensive K_2CO_3 led to a slight increase in the amount of acyloin product generated (entry 1). There was no marked difference on product yield when DBU was employed (entry 2), whilst the use of KOAc led to higher yields of pyridil (**286**) being observed (entry 3). Gratifyingly, in the presence of DIPEA, **283c** was formed in 57% yield (entry 4).

We were also curious of the effect of increased catalyst and base loading on this system. However, after carrying out experiments comparing 4 mol% loading of catalyst and base to 8 mol% loading of catalyst and base, in the presence of hydrocinnamaldehyde (**107**) and 2-pyridinecarboxaldehyde (**280**), we concluded that product yields remained the same under both reaction conditions (entry 5).

Table 5.3 Screening of bases in the coupling reaction between **280** and **107**

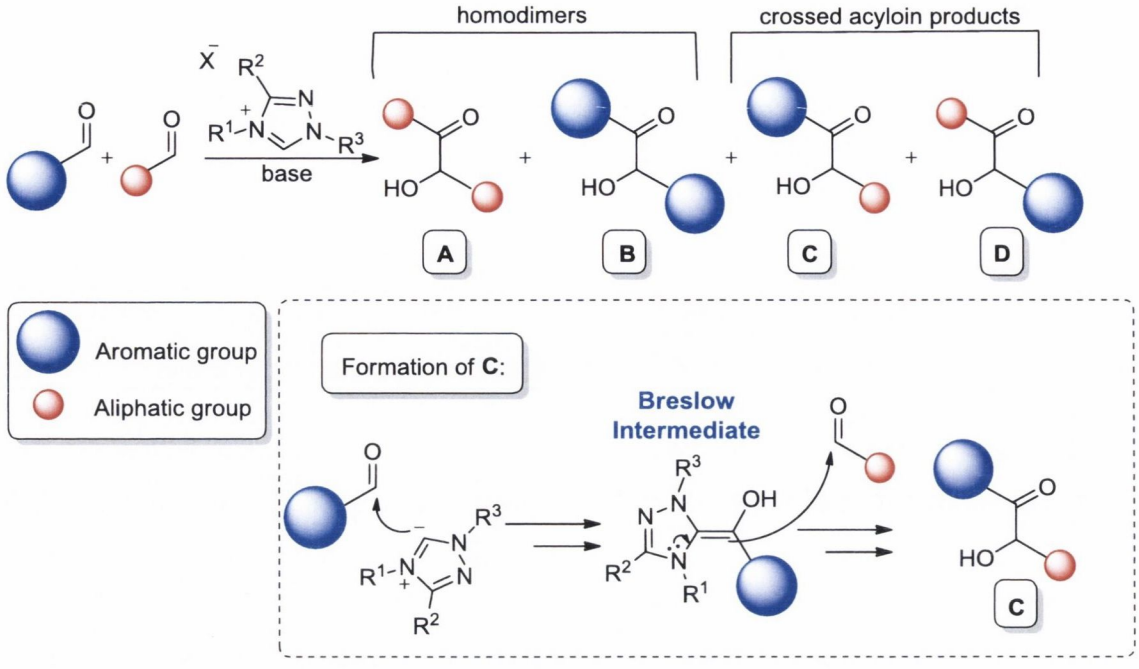


280 **107** **253a** **286** **283c** **283d**

Entry	Base	Yield 253a (%)[a]	Yield 286 (%)[a]	Yield 283c (%)[a]	Yield 283d (%)[a]
1	K_2CO_3	24	24	51	0
2	DBU	18	29	41	0
3	KOAc	22	36	27	0
4	DIPEA	15	21	57	0
5[b]	DIPEA	14	20	58	0

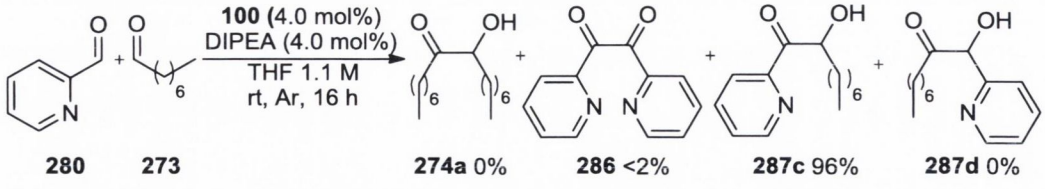
[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard. [b]Reaction carried out in the presence of 8 mol% loading of triazolium salt **100** and base

The results obtained thus far were analysed to determine what other parameters could be optimised to increase product yields. We noticed that in the reactions executed above, relatively high yields of the homodimer **253a** were observed so we considered the role that the aliphatic aldehyde **107** plays in this process. As discussed previously, initial attack of the NHC-based catalyst on the aliphatic aldehyde, followed by the interaction between the Breslow intermediate and the aromatic aldehyde, leads to the formation of the **D** acyloin product. In contrast, acyloin products of reversed chemoselectivity (*i.e.* **C** acyloin products) are formed when the NHC catalyst attacks the carbonyl moiety of the aromatic aldehyde followed by nucleophilic attack of the corresponding Breslow intermediate on the aliphatic aldehyde (Scheme 5.3).



Scheme 5.3 Formation of the **C** acyloin product arises from initial attack of the NHC-based catalyst on the aromatic aldehyde

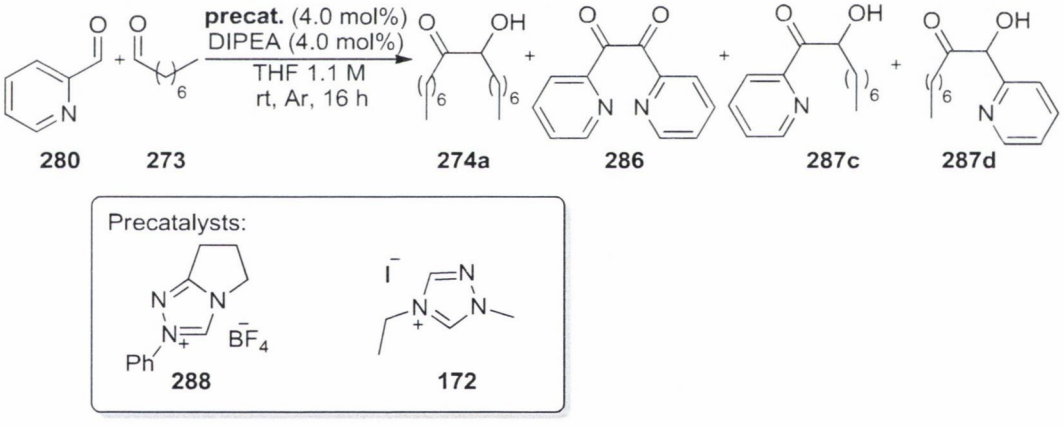
We speculated that if dimerisation of the aliphatic aldehyde **107** was occurring in the presence of precatalyst **100**, there would consequently be a lack of aliphatic aldehyde with which the Breslow intermediate (formed from interaction of the NHC and the aromatic aldehyde) can react. Hence in order to produce a more efficient model system, it was essential to employ an aliphatic aldehyde that was less capable of dimerising in the presence of precatalyst **100**. Hence we replaced hydrocinnamaldehyde (**107**) with the long chained aliphatic aldehyde octanal (**273**). To our delight the coupling of **273** and **280**, in the presence of triazolium salt **100**, furnished **287c** in 96% isolated yield, as shown in Scheme 5.4. This process was highly chemoselective and potential by-products were observed in little or no yield.



Scheme 5.4 Coupling of **280** with octanal (**273**) in the presence of triazolium precatalyst **100**

With an efficient model system in hand, we decided to evaluate the performance of other triazolium ion-based precatalysts in this reaction, hence we employed the phenyl substituted triazolium salt **288** and the aliphatic-substituted triazolium salt **172** as illustrated in Table 5.4. In the presence of **288** extremely high levels of pyridil product **286** were observed whilst **287c** was formed in extremely poor yields (entry 1). When precatalyst **172** was employed in this reaction, little or no crossed acyloin products were generated and large amounts of starting material were observed on ^{1}H NMR spectroscopic analysis (entry 2). These results were not entirely surprising as the electron-rich NHCs, generated upon deprotonation of precatalysts **288** and **172**, have been reported to be inefficient catalysts of the crossed acyloin condensation due to either facile reprotonation of the carbene centre by the alcohol moiety of the acyloin products or the amine conjugate base or because it not generated *in situ* in large amounts, as discussed previously in Section 4.1.

Table 5.4 Evaluation of triazolium salts in the coupling reaction between **280** and **273**



Entry	Precat.	Yield 274a (%)	Yield 286 (%)	Yield 287c (%)	Yield 287d (%)
1	**288**	6	42	<2	0
2	**172**	0	6	0	0

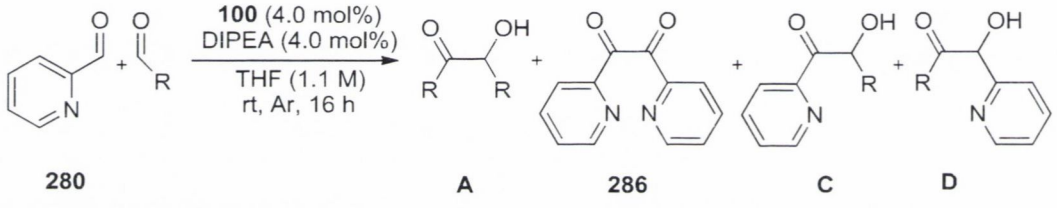
5.4 Evaluation of substrate scope:

5.4.1 The aliphatic aldehyde

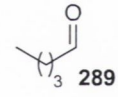
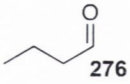
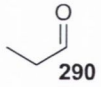
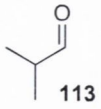
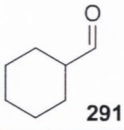
Encouraged by the high yields of acyloin product obtained in the presence of octanal (**273**), we set out to explore the substrate scope with regards to other aliphatic aldehydes in the

presence of 2-pyridinecarboxaldehyde (**280**) and precatalyst **100**. The results of this study are outlined in Table 5.5. We initiated this study by evaluating the effect of smaller straight-chained aldehydes on this NHC-mediated coupling reaction. We were pleased to observe a highly chemoselective process when valeraldehyde (**289**) was employed, as the corresponding product **292c** was obtained in 92% yield (entry 1). The catalyst also accepted butyraldehyde (**276**) and acyloin product **293c** was furnished in 97% yield (entry 2). Uniformly high levels of chemoselectivity were also observed when the smaller aliphatic aldehyde, propionaldehyde (**290**), was employed and **294c** was generated in 96% yield (entry 3).

Table 5.5 Coupling of 2-pyridinecarboxaldehyde (**280**) with various aliphatic aldehydes in the presence of triazolium salt **100**



280 A 286 C D

Entry	Aldehyde	Product	Yield A (%)[a]	Yield 286 (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	 289	**292**	4	4	92	0
2	 276	**293**	0	<2	97	0
3	 290	**294**	0	4	96	0
4	 113	**295**	0	12	49	27
5[b]		**295**	0	0	51	49
6	 291	**296**	5	6	62	26
7[b]		**296**	0	10	47	43

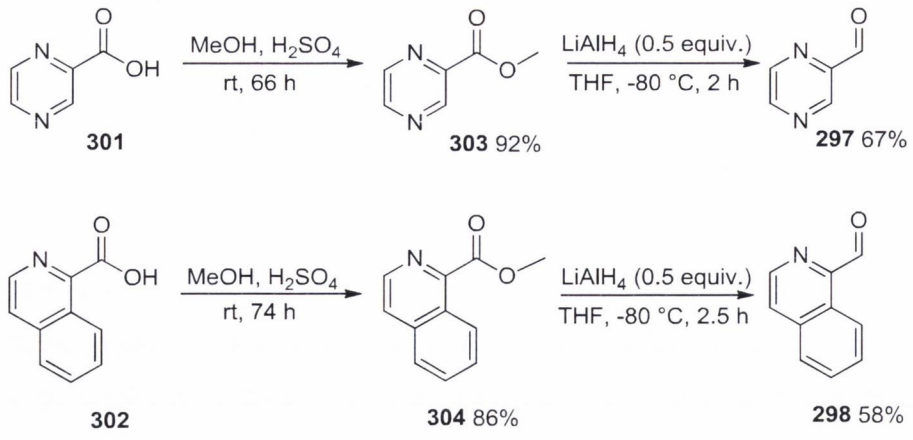
[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard. [b]Reaction carried out at 55°C.

Encouraged by the results obtained when unbranched aldehydes were employed in this reaction, we set out to explore the effect of branched aliphatic aldehydes on this process. Hence, we selected *iso*-butyraldehyde (**113**) and in the presence of **280** and precatalyst **100** we were surprised to observe the formation of the acyloin product **295d**, *i.e.* the crossed acyloin product of opposite chemoselectivity to the products synthesised thus far (entry 4). This product was observed by ^{1}H NMR spectroscopic methods however, it could not be isolated due to its rapid oxidation in air to generate its corresponding diketone. Upon observation of this **D** acyloin product we were curious to examine the effect of temperature on the ratio of crossed product formation *i.e.* **295c**:**295d**. We repeated the reaction at 55 °C and discovered that the two crossed products **295c** and **295d** were generated in a 1:1 ratio (entry 5). We thought it prudent to examine whether other branched aliphatic aldehydes behaved similarly, hence we employed cyclohexane carbaldehyde (**291**) in this process. The results we obtained were consistent with those from the previous experiments using the branched aldehyde **113**; the acyloin product **296d** was observed along with **296c**, when the reaction was performed at ambient temperature (entry 6) and the yield of **296d** increased when elevated temperatures were employed (entry 7).

5.4.2 The heteroaromatic aldehyde

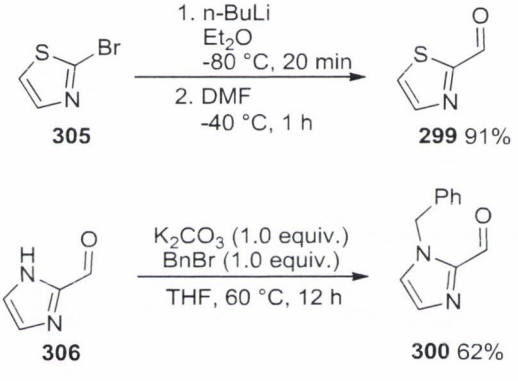
With an unusually chemoselective protocol in hand, we decided to evaluate the performance of various heteroaromatic aldehydes in the crossed acyloin condensation in the presence of the straight-chained aldehyde **273** and precatalyst **100**. We wished to determine if our proposed strategy of using pyridine-based aromatic aldehydes, bearing the nitrogen atom in the 2-position of the aryl ring, could also allow access to uniformly high levels of chemoselectivity in the crossed acyloin condensation.

In order to evaluate these aldehydes, bearing a nitrogen atom in the 2-position of the aryl ring, it was necessary to synthesise a range of aldehydes that were not commercially available (*i.e.* **297**, **298**, **299** and **300**). Using the inexpensive acids **301** and **302**, the corresponding esters **303** and **304** were synthesised in good to moderate yields. These esters were subsequently allowed to react in the presence of $LiAlH_4$ at –80 °C to furnish the corresponding aldehydes **297** and **298**. We followed the synthetic route employed in literature procedures as illustrated in Scheme 5.5.[155]



Scheme 5.5 Synthesis of aldehydes **297** and **298** from the corresponding carboxylic acids

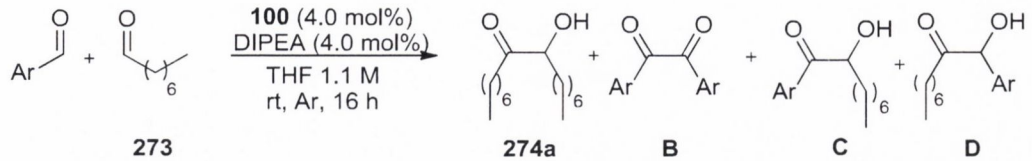
We also employed literature procedures to synthesise 5-membered heteroaromatic aldehydes **299**[156] and **300**[157] as shown in Scheme 5.6.



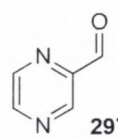
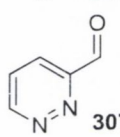
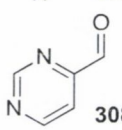
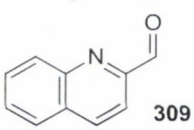
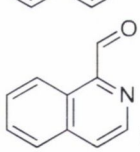
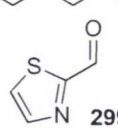
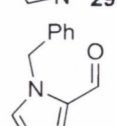
Scheme 5.6 Synthesis of aldehydes **299** and **300**

We subsequently focused our efforts on examining the performance of these synthesised substrates, amongst various other nitrogen-bearing heteroaromatic substrates, in the crossed acyloin condensation (Table 5.6). We observed that when aldehyde **297** was employed, a chemoselective process was observed and the acyloin product **310c** was furnished in a high yield of 96% (entry 1). Encouraged by this result we decided it prudent to examine the performance of the commercially available isomers of **297** (*i.e.* **307** and **308**). However, in the presence of these aldehydes, large amounts of the corresponding pyridil products **311b** and **312b** were formed (entries 2 and 3).

Table 5.6 Evaluation of heteroaromatic aldehydes bearing nitrogen in the 2-position of the aryl ring



273 274a B C D

Entry	Heteroaromatic Aldehyde	Product	Yield 274a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	 297	**310**	<2	<2	96	0
2	 307	**311**	36	40	14	0
3	 308	**312**	38	42	8	0
4	 309	**313**	<2	4	95	0
5	 298	**314**	21	19	55	0
6[b]		**314**	7	11	82	0
7	 299	**315**	30	31	29	0
8	 300	**316**	34	39	21	0

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard. [b]Reaction carried out at 40 °C.

We also wished to evaluate the performance of bulky heteroaromatic aldehydes in this process hence we employed commercially available quinoline-2-carbaldehyde (**309**) and its newly synthesised isoquinoline analogue **298**. The use of aldehyde **309** led to the observation of a highly chemoselective process and **313c** was formed in a satisfying 95% yield (entry 4). However, in the presence of the more sterically hindered aldehyde **298**, the acyloin product

314c was obtained in a moderate yield of 55% (entry 5). Large amounts of starting material remained, intact hence we repeated the reaction at 40 °C and observed a significant improvement in product yield to 82% (entry 6).

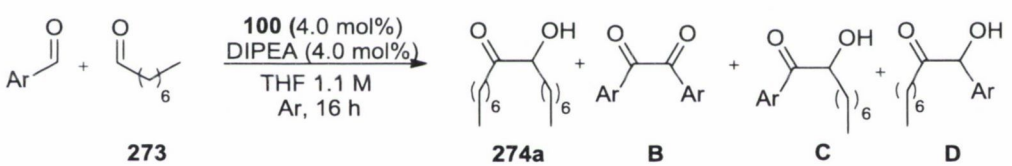
Furthermore, we explored the NHC-mediated coupling reaction between octanal (**273**) and the newly synthesised 5-membered heteroaromatic aldehydes **299** and **300**. We observed that these reactions favoured formation of crossed products **315c** and **316c** rather than those of opposite chemoselectivity (*i.e.* **315d** and **316d**). However, the yields of these products were hampered by the formation of the corresponding homodimers (entries 7 and 8). The results obtained from these studies imply that the presence of the nitrogen atom, adjacent to the aldehyde, allows for the formation of the corresponding **C** acyloin product in favour of the **D** acyloin product, however, the yield of crossed product is compromised by the formation of the corresponding pyridil products when π-excessive 5-membered heteroaromatic aldehydes are employed.

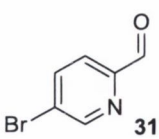
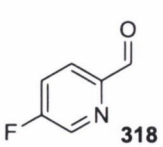
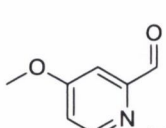
Intrigued by the different results obtained with regards to electronically diverse heteroaromatic aldehydes, we were curious to observe the effect of various substituted 2-pyridinecarboxaldehydes on this process (Table 5.7). We speculated that the addition of an electron-withdrawing substituent would impede the formation of the corresponding pyridil product and therefore lead to higher yields of the corresponding **C** acyloin product being obtained. Hence, we initiated this investigation by employing a 2-pyridinecarboxyaldehyde bearing an electron-withdrawing bromo-substituent in the 4-position of the aromatic ring (*i.e.* **317**). Whilst homodimer product **320b** was not observed, we did obtain small quantities of the crossed product **320d** along with 86% of product **320c** (entry 1). We decided to perform the experiment at 55 °C to observe the effect of heat on this process and observed very interesting results; at elevated temperatures, the yield of **320d** increased to 33% whilst there was a marked reduction in yield for **320c** (entry 2). We postulated that increasing the temperature further would allow for the sole formation of **320d**. It was essential to employ a suitable solvent that would allow the reaction to be carried out at 100 °C, hence we selected anhydrous dioxane. However, under these conditions, only starting material was observed and it is reasonable to assume that the carbene catalyst was destroyed at such a high temperature (entry 3). The reaction was also performed at -20 °C however, under these conditions octanal (**273**) reacted at a very slow rate and as a result pyridil formation dominated this process (entry 4).

We speculated that formation of acyloin product **320d** was due to reduction in basicity of the pyridine nitrogen atom and not due to the steric bulk of the bromine atom. To confirm this, we decided to employ a 2-pyridinecarboxaldehyde bearing a less sterically demanding electron-poor substituent. We discovered that in the presence of aldehyde **318**, at ambient temperature, **321d** was generated in 25% yield (entry 5). Complimentary to the results obtained in the presence of aldehyde **317**, the yield of **321d** increased to 35% when the reaction was performed at 55 °C (entry 6).

We thought it prudent to evaluate the effect of a 2-pyridinecarboxaldehyde, bearing a substituent that leads to an increase in basicity of the pyridine nitrogen atom. Hence we employed the commercially available aldehyde **319**, bearing the methoxy moiety in the 5-position. We observed that the use of this aldehyde led to large quantities of **322b** being observed (Table 5.7, entry 7). However, when heat was applied to this process the yield of **322b** diminished and higher quantities of **322c** were generated (entry 8).

Table 5.7 Evaluation of various substituted 2-pyridinecarboxaldehydes



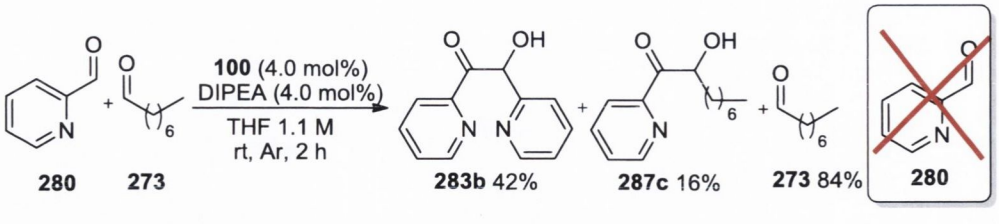
Entry	Temp. (°C)	Heteroaromatic aldehyde	Product	Yield 274a (%)[a]	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	18	 317	**320**	0	0	83	17
2	55		**320**	3	6	56	33
3	100		**320**	0	0	0	0
4	-20		**320**	0	43	14	0
5	18	 318	**321**	0	3	69	25
6	55		**321**	4	5	55	35
7	18	 319	**322**	0	34	32	0
8	55		**322**	0	22	53	0

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard.

5.5 A chemoselective crossed acyloin condensation: mechanistic studies

In this study we observed a highly chemoselective acyloin condensation between unbranched aliphatic aldehydes (either long or short chained) and various 2-pyridinecarboxaldehydes. We developed a protocol that allows access to **C**-type acyloin products in extremely high yields however, we were interested in determining the origins of the chemoselectivity observed as the archetypal crossed acyloin condensation in the presence of precatalyst **100** usually leads to the formation of **D** acyloin products, thus displaying a regioselectivity opposite to that observed in this study. We were also intrigued by the lack of chemoselectivity obtained from the reactions that employ branched aliphatic aldehydes and electron-poor 2-pyridinecarboxaldehydes.

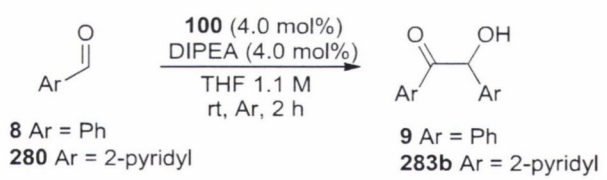
To gain some mechanistic insight into this process, the reaction between 2-pyridinecarboxyaldehyde (**280**) and octanal (**273**), in the presence of precatalyst **100**, was analysed carefully using ^{1}H NMR spectroscopic methods after a reaction time of 2 hours (Scheme 5.7). We speculated that after this relatively short reaction time, small quantities of acyloin product **287c** and starting material would be observed. However, we were surprised to notice only 16% of aldehyde **280** reacted with **273** and that most of **280** had in fact dimerised to form the homodimer **283b** which subsequently oxidised to generate **286**. This result seemed to be in disagreement with our analysis of the reaction after 24 hours, described earlier (Scheme 5.4), where **287c** was formed in extremely high yields (96%) whereas the amount of pyridil (**286**) was negligible. We considered that a plausible explanation for this occurrence was that the corresponding homodimer **283b** was generated initially at an extremely fast rate and that throughout the reaction (*i.e.* before being oxidised to **286** upon exposure to air), it underwent retroacyloin reactions to allow for the coupling reaction between the Breslow intermediate (formed from reaction between the NHC and either **280** or **283b**) and octanal to occur.



Scheme 5.7 Analysis of the coupling of **280** and **273** after 2 hours

To prove our hypothesis, we examined the rate of dimerisation of **280** in the presence of precatalyst **100**. We decided to compare the rate of this reaction against that of the dimerisation of benzaldehyde (**8**) to generate benzoin (**9**), to act as a control experiment. Initially we analysed both reactions by ^{1}H NMR spectroscopy after 1 hour. We discovered that aldehyde **8** reacted to form **9** in 84% yield (Table 5.8, Entry 1) while all of **280** reacted to form the corresponding homodimer **283b** (entry 2), which subsequently oxidised in air to form **286**. We consequently examined both reactions after 5 minutes and discovered that benzoin product **9** was only generated in 46% yield (entry 3) and quite remarkably all of the aldehyde **280** had dimerised to generate **283b** in this short amount of time (entry 4). In order to monitor whether this unexpected rapid reaction occurred spontaneously, we repeated it in the absence of precatalyst **100**; the fact that no product could be identified using ^{1}H NMR spectroscopic methods let us conclude that aldehyde **280** is highly reactive in the presence of the NHC catalyst (generated *in situ* upon deprotonation of precatalyst **100**) and forms homodimer **283b** at an extremely fast rate.

Table 5.8 Analysis of dimerisation of benzaldehyde (**8**) and 2-pyridinecarboxaldehyde (**280**) in the presence of precatalyst **100**



8 Ar = Ph
280 Ar = 2-pyridyl

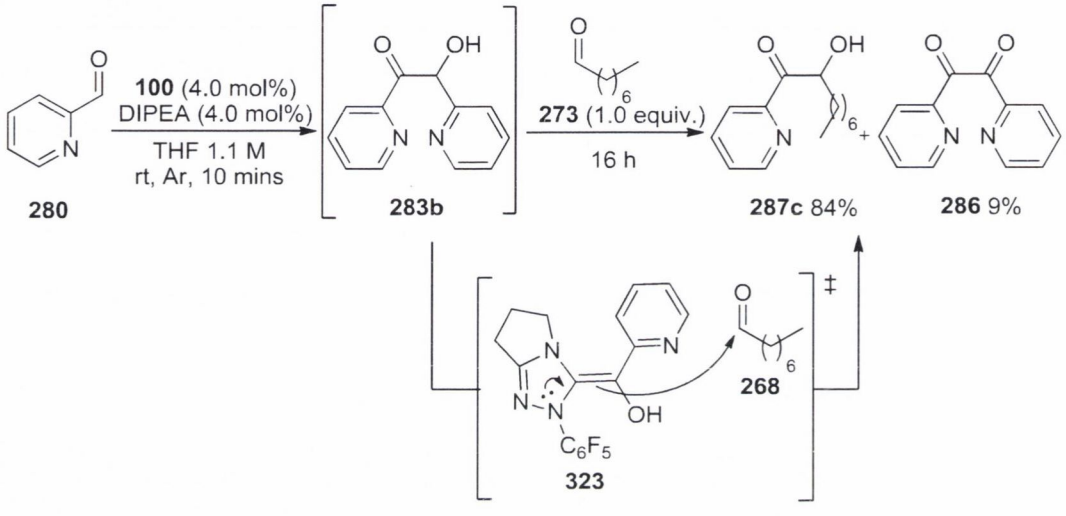
9 Ar = Ph
283b Ar = 2-pyridyl

Entry	Time (min)	Aldehyde	Product	Yield (%)[a]
1	60	**8**	**9**	84
2	60	**280**	**283b**	100
3	5	**8**	**9**	46
4	5	**280**	**283b**	100

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard.

We next turned our attention towards examination of the reversible formation of **283b**. Hence, aldehyde **280** was allowed to react in the presence of **100** for 10 minutes (to ensure quantitative formation of homodimer product **283b**) before aldehyde **273** was added and subsequently allowed to react for 16 h after which time the reaction mixture was analysed using ^{1}H NMR spectroscopy (Scheme 5.8). The fact that the crossed acyloin product **287c** could be detected in 84% yield clearly supported our hypothesis; reversible formation of

283b generated the Breslow intermediate **323** which subsequently reacted with aliphatic aldehyde **273** to generate the acyloin product **287c**. We postulate that the slight loss in product yield (in comparison to 96% yield of **287c** observed in an earlier study) was due to small amounts of air entering the reaction vessel during addition of octanal (**273**) *via* syringe and facilitating the oxidation of the homodimer **283b** to the corresponding diketone **286**.

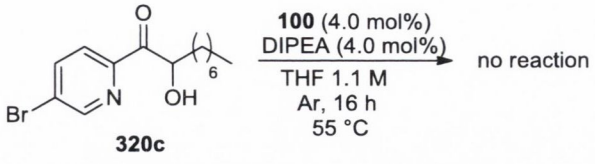


Scheme 5.8 Evidence for reversible formation of homodimer **283b**

We subsequently considered the possibility of reversible formation of the two different crossed products generated in the presence of various 2-pyridinecarboxaldehydes. We speculated that, in this particular study, the **C** acyloin product is stable and non-reversibly formed and that perhaps the **D** acyloin product is in fact being generated *in situ* but reversible formation of the **D** product is occurring hence allowing formation of the **C** product in high yields. However, we acknowledged that this is a theory difficult to prove as the **D** acyloin products are only observed in the reactions employing branched aliphatic aldehydes or 2-pyridinecarboxaldehydes bearing an electron-withdrawing substituent and are readily oxidised to diketones in the presence of air (similar to the reactivity observed for homodimer **283b**, *vide supra*).

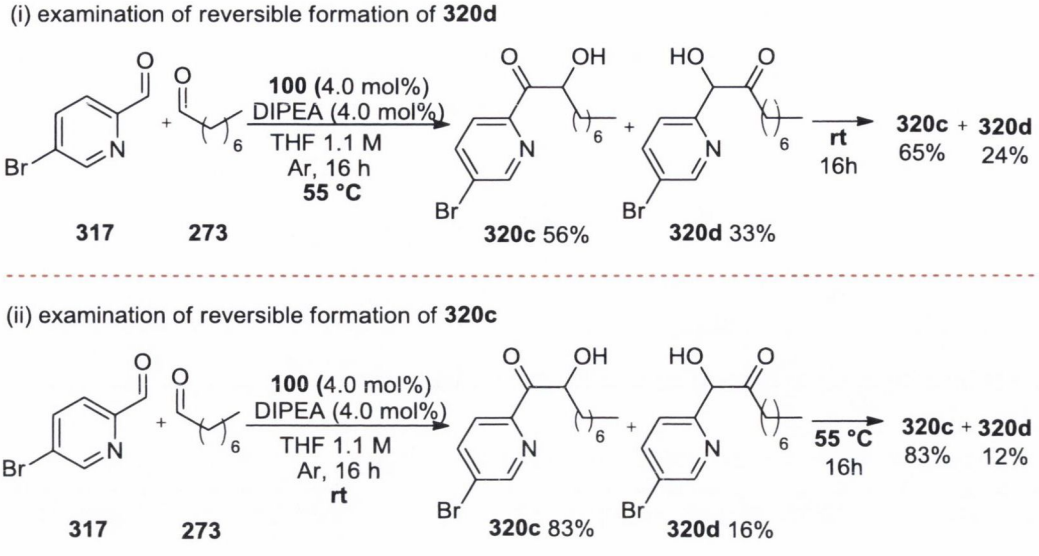
We decided to examine whether the **C** acyloin product (*i.e.* **320c**) is in fact stable and to establish that its formation is not reversible in the presence a NHC-based catalyst. Hence, we employed the bromo-substituted acyloin product **320c** which was reacted at 55 °C in the presence of precatalyst **100** and DIPEA, as the base used to form the NHC species *in situ* (Scheme 5.9). We were interested to observe whether the formation of potential by-products

such as **320d**, would occur under these reaction conditions, however, after 16 hours only starting material was observed by ^{1}H NMR spectroscopic analysis, thus suggesting that **320c** is not reversibly formed.



Scheme 5.9 Investigation to determine if **320c** can undergo detectable retroacyloin

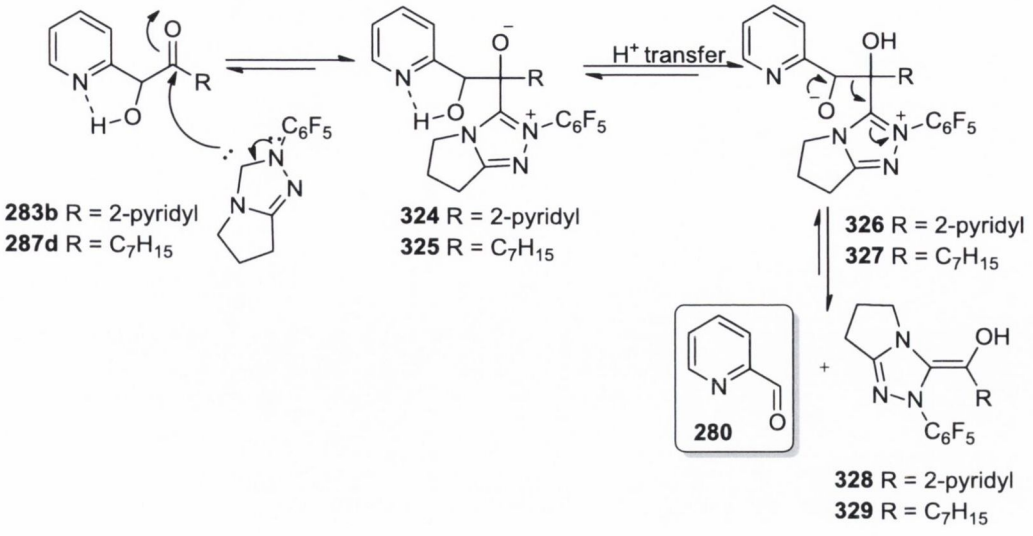
We then wished to examine the reversible formation of the crossed product of opposite chemoselectivity *i.e.* **320d**. It was necessary to generate **320d** *in situ* as, similarly to homodimer **283b**, this product is readily oxidised in air to form its corresponding diketone. Upon analysis of the experiments previously conducted, in which the bromo-substituted aldehyde **317** was employed, we noted that the formation of acyloin product **320c** was favoured at ambient temperature whereas yields of the acyloin product of opposite chemoselectivity (*i.e.* **320d**) increased at elevated temperatures. Based on this observation, we decided to design an experiment to test the reversible formation of **320d** and compared the outcome with the result obtained from the same reaction using **320c**. Hence we executed two experiments using aldehydes **317** and **273** in the presence of precatalyst **100**; the former reaction was carried out under the conditions that initially favoured the formation of **320d** (*i.e.* at 55 °C as shown in Scheme 5.10 (i)) whilst the latter was carried out under the conditions that favoured **320c** product formation (*i.e.* at ambient temperature as shown in Scheme 5.10 (ii)). These experiments allowed for the *in situ* generation of **320d** and **320c**, respectively. After 16 hours reaction time, the two experiments were continued under reaction conditions opposite to those employed for the first 16 hours *i.e.* the process that was being carried out at 55 °C was cooled to room temperature and *vice versa* for the other reaction (Scheme 5.10).



Scheme 5.10 Examination of reversible formation of **320d** and **320c**

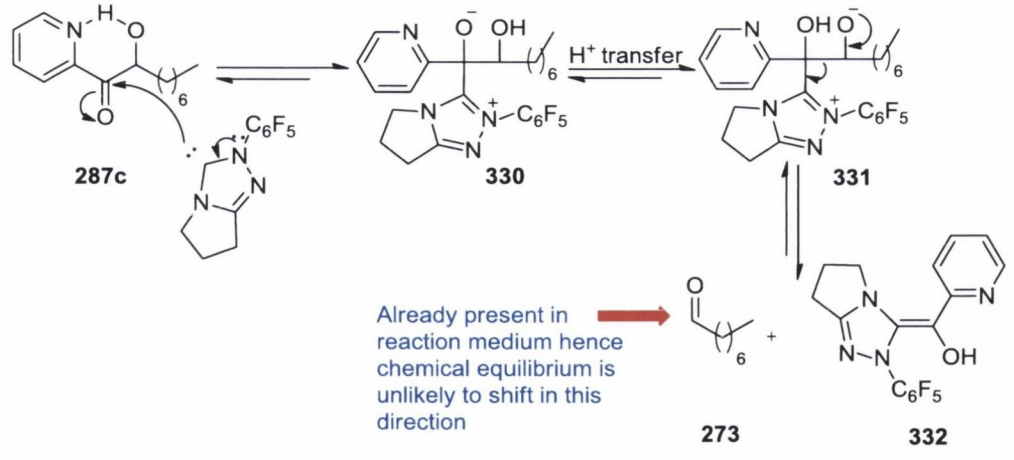
In case (i), we observed that the product yield of **320d** decreased over the course of the reaction by lowering the temperature and that the formation of product **320c** was favoured as yields increased, thereby implying that the crossed product **320d** was indeed reversibly formed. In contrast, in case (ii), there was no change in product yield of **320c** highlighting once more that this product cannot be reversibly formed.

Thus far, the experimental results seemed to point towards the confirmation that the homodimer of 2-pyridinecarboxaldehyde (*i.e.* **283b**) is reversibly formed. We were also able to confirm that the acyloin product **230d** is also reversibly formed and that **230c** is not. We have proved that 2-pyridinecarboxaldehyde (**280**) reacts rapidly to form its corresponding homodimer **283b** and as a result of this rapid reaction, there is an absence of aldehyde **280** from the reaction mixture. Therefore it is reasonable to assume that the overall equilibrium of the entire process shifts to form this free aldehyde. This shift in equilibria, to generate aldehyde **280**, may explain why the corresponding heteroaromatic homodimers and the **D** acyloin products are reversibly formed; the NHC catalyst (generated *in situ* upon deprotonation of **100**) attacks the carbonyl moiety of either of the α-hydroxyketones **283b** and **287d** to form intermediates **324** and **325**, respectively, which undergo proton transfer and lead to generation of the Breslow intermediates **328** and **329** and the free aldehyde **280** *via* reversible reactions (Scheme 5.11).



Scheme 5.11 Reversible formation of **B** and **D** acyloin products leads to generation of free aldehyde **280**

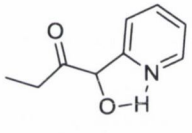
Similarly, when the **C** acyloin product (*e.g.* **287c**) is attacked by the NHC catalyst, reversible formation would lead to the generation of octanal (**273**). However, it is evident from our previous studies that this aldehyde dimerises at a very slow rate thus its constant presence in the reaction medium (until consumed to form the acyloin product **287c**) suppresses the destruction of acyloin product **287c** (Scheme 5.12).



Scheme 5.12 Reversible formation of **287c** would lead to generation of aldehyde **273**

While this theory tentatively explains why the **B** and **D** acyloin products, in this study, may be reversibly formed while the corresponding **C** acyloin product is not, it does not explain why high chemoselectivity is observed only in the presence of 2-pyridinecarboxaldehyde (**280**) and not, for example, when 4-pyridinecarboxaldehyde (**284**) is used. We can assume that both aldehydes possess similar electronic properties and react at an equally fast rate to

form the corresponding homodimers, therefore we speculated that the high levels of chemoselectivity observed in this study are due to the position of the nitrogen atom on the aromatic ring and its ability to interact *via* hydrogen bonding to the alcohol of the α-hydroxyketone product. In the case of homodimer **283b** and the various **D** acyloin products (e.g. **294d**), we can assume that there is a hydrogen bond interaction occurring between the alcohol moiety and the nitrogen atom to generate a 5-membered ring as shown in Figure 5.1. We postulate that, as a result of this hydrogen bond interaction, the hydroxyl group is not able to rotate freely which makes the carbonyl moiety alpha to the aliphatic side chain less sterically hindered and more prone to react with the NHC-based catalyst leading to the reversible process discussed above.



294d

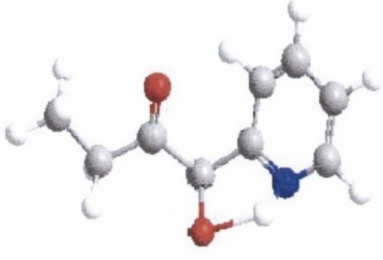
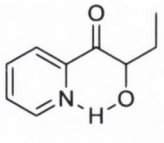


Figure 5.1 3D image of **D** acyloin product **294d** where hydrogen bond interaction between nitrogen of pyridine moiety and the alcohol group forms a 5-membered ring

In contrast, in the case of the **C** acyloin products (e.g. **294c**), the hydrogen bond formed between the nitrogen atom of the pyridine ring and the is generating a 6-membered ring as depicted in Figure 5.2, the carbonyl moiety is more hindered in this case and therefore less likely to be attacked by the NHC.



294c

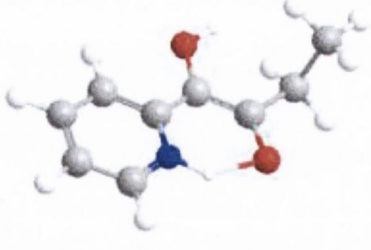
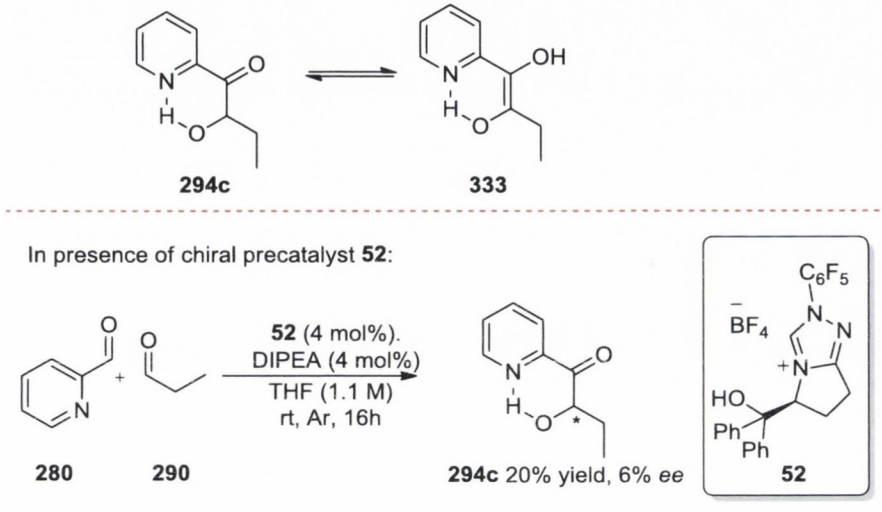


Figure 5.2 3D image of **C** acyloin product **294c** where hydrogen bond interaction between nitrogen of pyridine moiety and the alcohol group forms a 6-membered ring

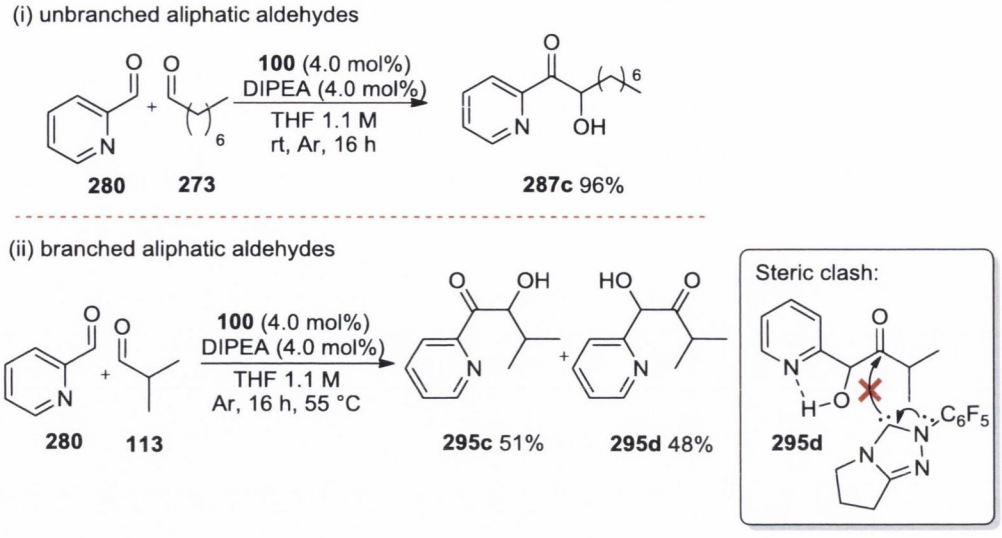
We also postulated that the rate of keto-enol tautomerisation occurring in acyloin products (formed from the coupling reaction between **280** and **290**) such as **294c** and that of opposite chemoselectivity (*i.e.* **294d**), would be significantly different, and that this interaction may

occur far more readily in a 6-membered ring than a 5-membered ring and hence block attack of the NHC on the carbonyl moiety as depicted in Scheme 5.13. Further evidence that supports the occurrence of this keto-enol tautomerisation is the extremely low *ee* value obtained when a chiral catalyst is applied to this process; in the presence of precatalsyt **52**, **294c** was obtained virtually as a racemic compound. We postulate that this extremely low value of enantioenrichment may be due to the racemisation occuring as a result of the constant interconversion of the two species **294c** and **333** in the basic media.



Scheme 5.13 Keto-enol tautomerisation of **294c**

We were also particularly intrigued by the difference in chemoselectivity observed when either unbranched or branched aliphatic aldehydes were employed. Indeed, when 2-pyridinecarboxaldehyde (**280**) was reacted with unbranched aliphatic aldehydes, a highly chemoselective process was observed, while the reaction with a branched aliphatic aldehyde (*i.e.* **113**) lacked chemoselectivity and gave rise to crossed products **295c** and **295d** (Scheme 5.14). We speculated that in the latter case the bulky aliphatic substituent of **295d** is blocking attack of the NHC on the carbonyl moiety and hence reversible formation cannot occur as illustrated in Scheme 5.14.



Scheme 5.14 Comparison of crossed acyloin condensations between aldehyde **280** and either (i) unbranched or (ii) branched aliphatic aldehydes

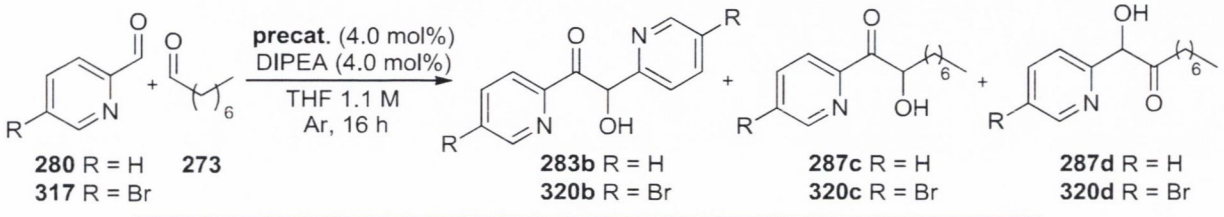
In order to tentatively provide a plausible explanation for the observed favoured formation of **295d** at elevated temperatures, we speculated that the higher temperatures are responsible for disrupting the hydrogen bond interaction between the nitrogen atom on the pyridine ring and the alcohol moiety. In the absence of this hydrogen bond interaction, the hydroxy group is not being 'held back' and therefore the attack of the NHC on the carbonyl group suffers from steric hindrance provided by both the hydroxy moiety and the branched substituent.

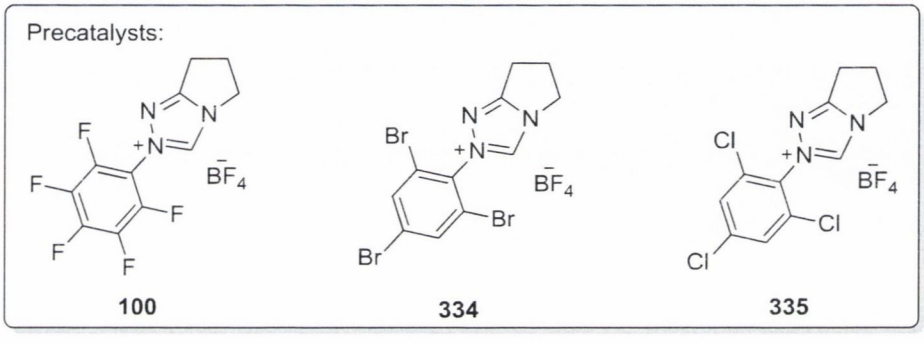
This disruption of the hydrogen bond described may also explain the observation of the **D** acyloin product (**320d**) when *para*-bromo-substituted pyridinecarboxaldehyde (**317**) is employed (Table 5.9, entry 2) in comparison to the reaction carried out under identical conditions in the presence of aldehyde **280** (entry 1). We speculate that the electron-withdrawing nature of the halogen atoms leads to a decrease of the pK_a of the pyridine nitrogen atom which results in a weakening of its hydrogen bonding interaction with the alcohol group and therefore the hampering of the reversible formation of **D** acyloin products (*i.e.* **320d**). This effect is further exaggerated when heat is applied and once again we speculate that hydrogen bonding is disrupted to a greater extent between the nitrogen atom and the alcohol moiety and steric hindrance between the attacking NHC and the hydroxy moiety occurs to prevent reversible formation of **320d** (entry 3).

To further investigate our theory of hydrogen-bond-dependent reversible formation of **D** acyloin products, we decided to use variants of precatalyst **100** bearing either bromo- or

chloro-substituents (**334** and **335,** respectively) for the crossed acyloin condensation between **317** and **273**. These triazolium salts were synthesised by my co-worker, Mr. E. Delaney. This set of experiments, using the novel electron-deficient precatalysts **334** and **335**, which share similar electronic properties to those of **100**, led to interesting results.

Table 5.9 Evaluation of precatalysts **334** and **335** in the cross coupling of **317** and **273**





Entry	Precat.	Temp. (°C)	Aldehyde	Yield B (%)[a]	Yield C (%)[a]	Yield D (%)[a]
1	**100**	18	**280**	<2	96	0
2	**100**	18	**317**	0	83	17
3	**100**	55	**317**	6	56	33
4	**334**	18	**317**	<2	88	8
5	**334**	55	**317**	<2	80	18
6	**335**	18	**317**	<2	92	4
7	**335**	55	**317**	<2	38	62

[a]Yield determined by ^{1}H NMR spectroscopic methods, using styrene (63 μL, 0.55 mmol, 0.5 equiv.) as an internal standard.

The use of precatalyst **334** led to the formation of products **320c** and **320d** in a similar ratio as obtained with precatalyst **110** either at room temperature or at 55 °C (Table 5.8, entry 3 and entry 4, respectively). Conversely, by employing the structurally similar triazolium precatalyst **335** rather unexpected results, in terms of chemoselective outcome of the reaction, were obtained. While the product yields ratio (**320c**:**320d**) obtained at 18 °C (entry 5) were in accordance with that formed in the presence of either **334** or **110**, the raise of temperature to 55 °C changed this ratio quite drastically and further exacerbated the loss of chemoselectivity

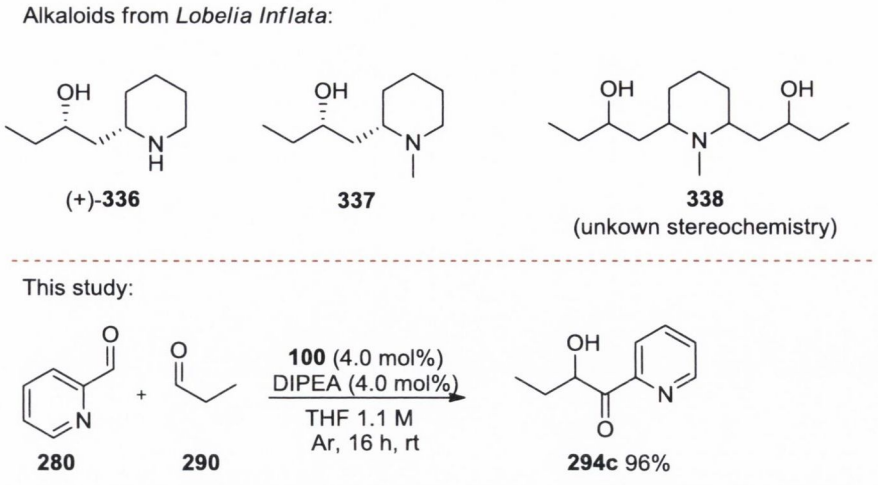
which led to product **320d** being formed in an unprecedented 62% yield (Table 5.8, Entry 6). This result seemed to imply that, despite the fact that the structural and electronic features of precatalyst **335** are similar to those of **334** and **110**, this precatalyst behaves distinctly when used in the crossed acyloin condensation using the reaction conditions described. The unusual behaviour of **335** has also recently been reported in different NHC-mediated transformations by fellow co-workers in our research group.

5.6 Synthesis of alkaloids from *Lobelia Inflata*

The piperidine strucutrual motif is observed in many natural alkaloids, such as those from the plant *Lobelia inflata*, medically, the most important of the *Lobelia* family. In the 19th century this plant was used for the treatment of asthma but there has been renewed interest in the alkaloids derived from this plant due to their biological profile and, specifically, their memory-enhancing properties.[158] These alkaloids have recently been the focus of considerable synthetic efforts so that they can be studied as potential therapeutics for the treatment of alzheimers.[159]

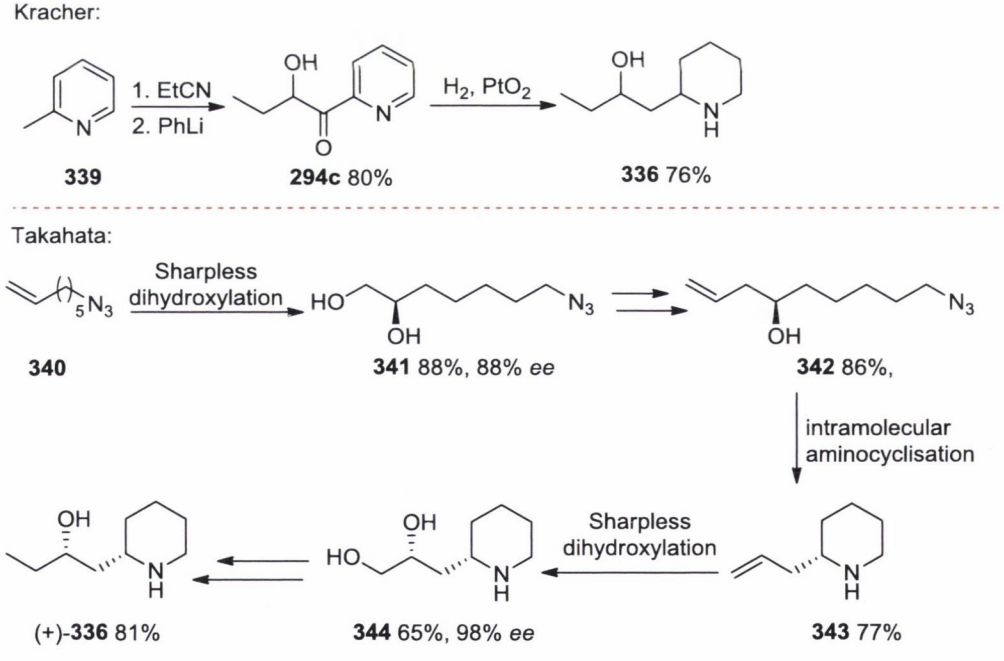
We observed that many of the alkaloids from the plant, *Lobelia inflata* possessed similar structural features to compounds synthesised during this study. These alkaloids include (+)-8-ethylnorbelol ((+)-**336**), (2RS)-1-[(2SR)-N-methyl-piperidin-2-yl]butan-2-ol (**337**) and 8-10-diethyllobelidiol (**338**) of which the stereochemistry remains unknown (Scheme 5.15). With a highly chemoselective protocol in hand that allows access to pyridine-based-α-hydroxyketones in unprecedented yields, we decided to apply the same synthetically useful process to the synthesis of these particular alkaloids.

In 1962, Kracher[160] reported the first racemic synthesis of **336** which involved reacting α-picoline (**339**) with propionitrile to generate **294c**. This compound **294c** was subsequently subjected to hydrogenation over platinum oxide to furnish the racemic product **336** in 76% yield (Scheme 5.16). However, limited experimental data was reported for this compound. Kracher also investigated the pharmacological profile of related analogues but no results were disclosed for **336**. A report by Takahata[161] still remains the only asymmetric synthesis of (+)-8-ethylnorbelol **336**. A Sharpless dihydroxylation of **340** followed by an intramolecular aminocyclisation and a second Sharpless dihydroxylation allowed access to (+)-**336** in >98% *ee* (Scheme 5.16).



Scheme 5.15 Comparison of alkaloids from the plant *Lobelia Inflata* and acyloin product **294c**, synthesised during this study

To date there is only one report of the synthesis of **337**. De Kimpe[159] and co-workers accessed the racemate (+)-**337** *via* a complex 6-step procedure which yielded the desired product in an overall yield of 69%. The biosynthetic pathway of **338** has been studied far less than other alkaloids from the *Lobelia* plant and its stereochemistry remains unknown.

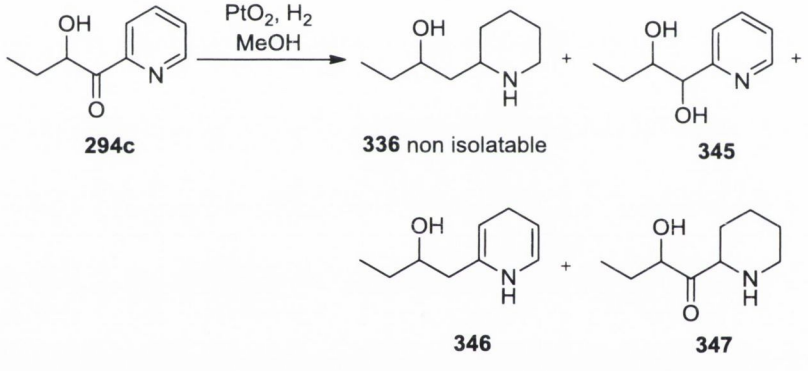


Scheme 5.16 Racemic and asymmetric synthesis of **336** reported by Kracher and Takahata, respectively

As the alkaloid **336** has been synthesised both racemically and asymmetrically, we decided to focus our efforts on the synthesis of **337** and subsequently apply the same synthetic route

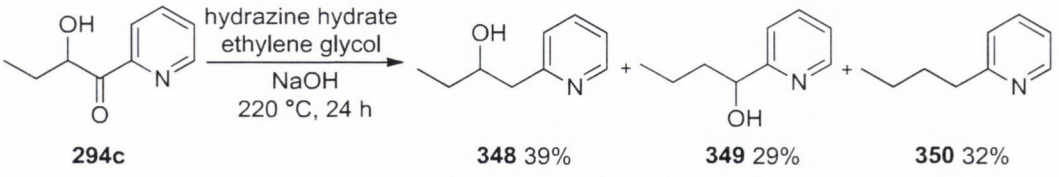
towards the synthesis of **338**. We envisaged obtaining the various diastereoisomers of **338** with the aim of assigning stereochemistry to this particular alkaloid.

Inspired by the synthetic route employed by Kracher, towards **336**, we envisaged reducing the both carbonyl *motif* and the pyridine ring of **294c** in the presence of hydrogen and platinum oxide followed by *N*-methylation of **336** to access **337**. However, we were disappointed to observe that adherence to the procedure reported by Kracher led to the reduction of the carbonyl group to an alcohol moiety and as a result, only the corresponding diol **345** was observed (Scheme 5.17). We attempted to improve reaction conditions by increasing the loading of platinum oxide and hydrogen pressure. We observed the formation of **336** by ^{1}H NMR spectroscopic methods along with considerable quantities of by-products **345**, **346** and **347**. Purification of **336** proved problematic, as this compound was extremely polar and could not be separated from the by-products by column chromatography.



Scheme 5.17 Attempted synthesis of **336** from **294c**

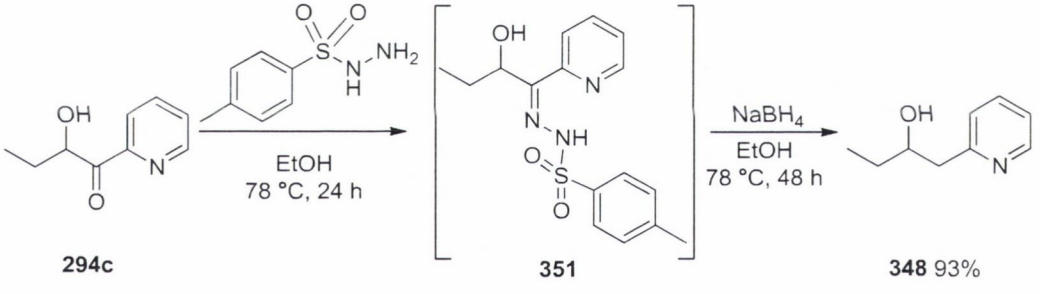
We decided to employ an alternative synthetic route to access **337** from **294c**. We postulated that complete reduction of the carbonyl moiety would generate the corresponding alkane **348**. *N*-alkylation of **348** would furnish a pyridinium salt which we speculated would be reduced rapidly in the presence of hydrogen and platinum oxide to generate **347**. In order to obtain **348** we performed a modified Wolff Kishner reduction,[162] however, under the harsh basic conditions, by-products **349** and **350** were also formed.



Scheme 5.18 Wolff Kishner reduction

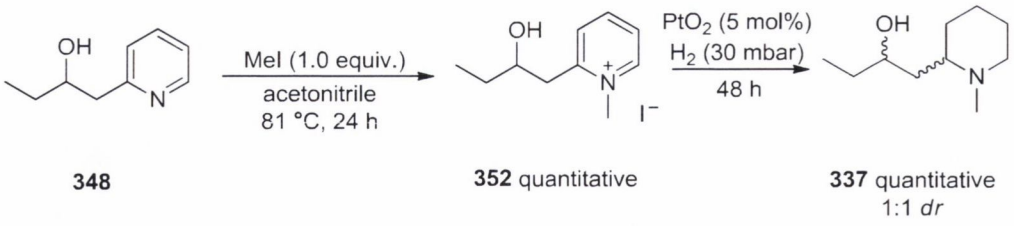
Whilst we were pleased to observe the formation of **348**, we wished to access **348** in synthetically useful yields and hence we opted to employ an alternative synthetic.

We were encouraged by a recent[163] study on the reduction of a carbonyl moiety to an alkane in a two step process that involved the use of *para*-toluene sulfonyl hydrazine and sodium borohydride. Hence, we subjected our acyloin product **294c** to similar reaction conditions and gratifyingly the corresponding alkane **348** was furnished in 93% yield from this two-step, one pot process (Scheme 5.19).



Scheme 5.19 Synthesis of **348** from **294c**

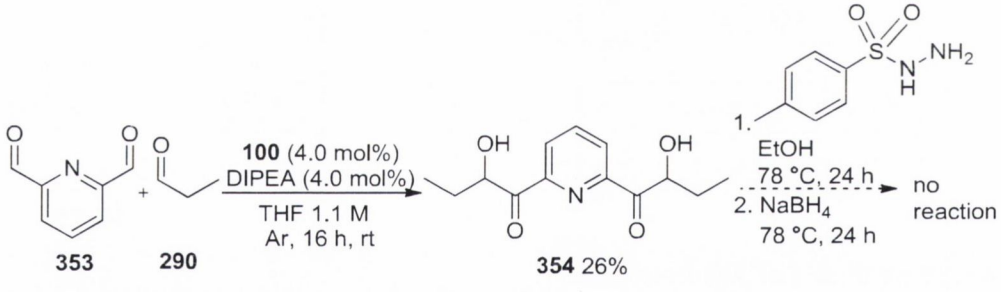
With **348** in hand, we envisaged carrying out an *N*-alkylation at the nitrogen of the pyridine ring to generate the corresponding pyridinium salt **352** and we postulated that this species would be reduced readily to the corresponding piperidine ring in the presence of hydrogen and platinum oxide. Gratifyingly, hydrogenation of **352** over platinum oxide allowed access to the racemic compound **337** in quantitative yield and a 1:1 ratio of diastereoisomers, which were separated by column chromatography (Scheme 5.20).



348 **352** quantitative **337** quantitative 1:1 *dr*

Scheme 5.20 Synthesis of alkaloid **337**

Inspired by this very short and successful synthesis we wished to apply the same protocol to the synthesis of the alkaloid **338**. Hence we employed the commercially available aldehyde **353** which we allowed to react with propionaldehyde (**290**) in the presence of precatalyst **100**. We obtained the desired crossed product **354** in a modest yield of 26% (Scheme 5.21). Before optimising reaction conditions for the coupling reaction between **353** and **290**, we decided it prudent to examine the reaction of this bulkier substrate **354** with *para*-toluene sulfonyl hydrazine and sodium borohydride. However, to our disappointment, **354** did not react with *para*-toluene sulfonyl hydrazine. We repeated the reaction at 70 °C, however, only starting material was observed by ^{1}H NMR spectroscopic methods; we postulated that **354** was too sterically hindered by be attacked by the bulky hydrazine.



353 **290** **354** 26%

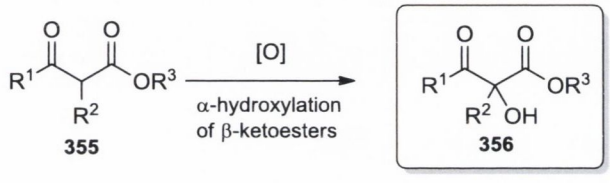
Scheme 5.21 Attempted synthesis of di-substituted alkaloid **338** from acyloin product **354**

We were disappointed to observe that the substrate **354** was not compatible with our synthetic procedure and did not allow access to the relatively unstudied alkaloid **338**. However, we did develop a simple protocol that allows access to the natural product **337** from **294c**, which was synthesised *via* a highly chemoselective NHC-mediated crossed acyloin condensation.

5.7 Crossed acyloin reaction between heteroaromatic aldehydes and α-ketoesters

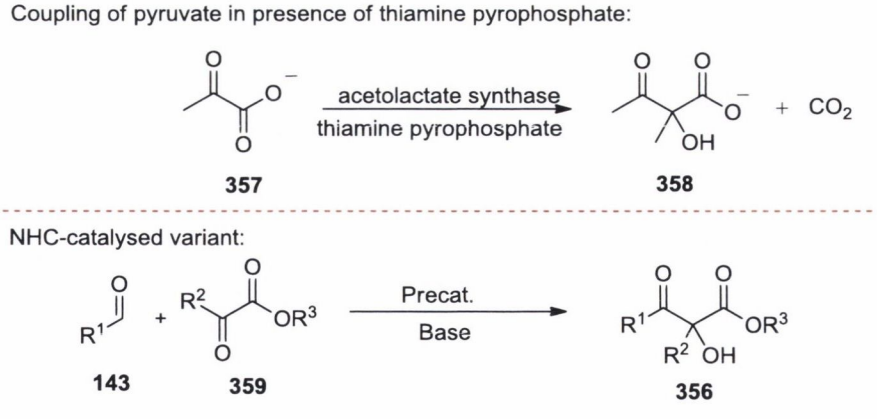
α-Hydroxy-β-ketoacid derivatives incorporating a quaternary stereogenic centre in the α–position (*i.e.* **356**) are structural features in a range of natural products.[164,165] In addition, they are densely functionalised, highly synthetically-pliable molecules which can serve as

useful precursors to the α-hydroxy acid/α-hydroxy ketone motifs remarkably common in naturally occurring biomolecules,[166] tetracycline/glycylcycline antibiotics,[167,168] artificial β-amino acids/alcohols and α,β-dihydroxylated acids (in addition to a plethora of other useful building blocks). However, the undoubted synthetic utility of these materials is curtailed by the synthetic routes to these compounds – which are based in the main on often functional-group sensitive α-oxidation methods (Scheme 5.22).[169–172]



Scheme 5.22 Current synthetic routes towards α-hydroxy-β-ketoacids **356**

Inspired by the mode of action of the thiamine pyrophosphate-dependent enzyme acetolactate synthase, which catalyses the coupling of two molecules of pyruvate to generate acetolactate (a precursor to valine, leucine and isoleucine, Scheme 5.23),[173,174] we envisaged the possibility of developing an analogous route to **356** from the direct *N*-heterocyclic carbene (NHC)-catalysed coupling of an aldehyde **143** and an α-ketoester **359** in a chemoselective crossed acyloin condensation (AC) reaction.

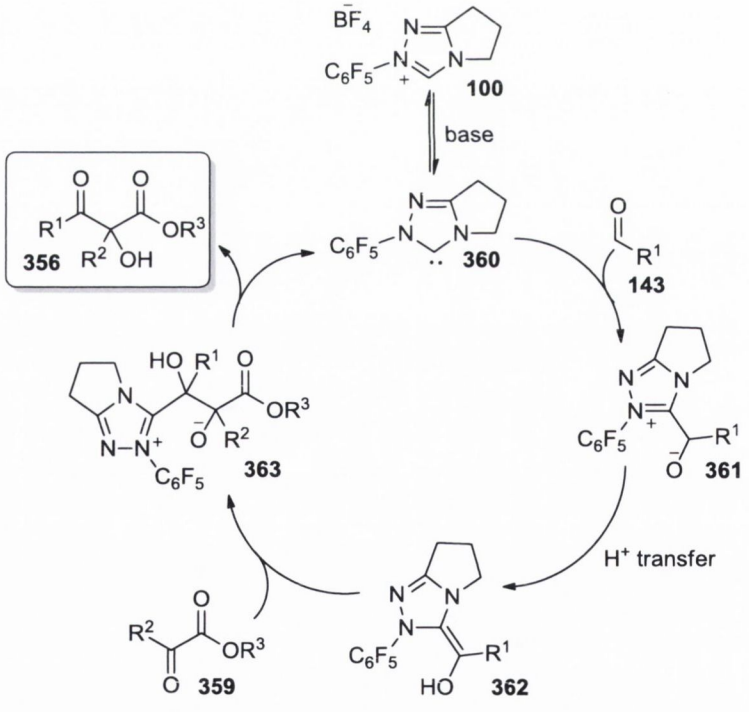


Scheme 5.23 Rationale for coupling of an aldehyde and an α-ketoester in presence of NHC-based catalyst

In order to access α-hydroxy-β-ketoacids **356** it is necessary that a chemoselective bias be established in the reaction; the NHC, derived from precatalyst **100**, must eschew reaction with the aldehyde substrate **143** to generate the corresponding Breslow intermediate **362** and

add preferentially to ketoester **359** to afford the cross-coupled product **356** *via* adduct **363** (Scheme 5.24). However, as previously discussed, examples of intermolecular chemoselective crossed-acyloin reactions involving two aldehydes are very rare, and at the outset of this project, the only ketone substrates that were shown to participate in a chemoselective cross coupling reaction were the highly activated heterocyclic trifluoromethylketones reported by Enders.[97]

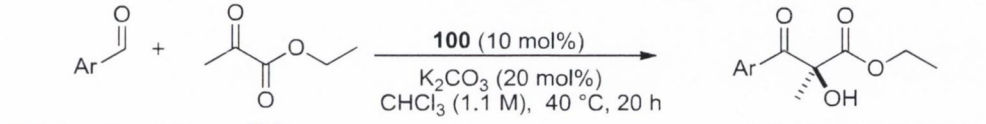
Initially, the efficiency of the coupling reactions involving aromatic aldehydes was disappointing and the coupling reaction between various aromatic aldehydes and commercially available ethyl pyruvate (**364**) proceeded in mediocre yields. This was not entirely surprising; as previously discussed, the NHC, derived from precatalyst **100**, has preference to attack less sterically demanding aldehydes and often reaction of the NHC with the aromatic aldehydes is slow. After considerable experimentation carried out by Dr. Christopher Rose and Dr. S. Gundala, it was found that the use of chloroform as the reaction solvent allowed the access to the desired α-hydroxy-β-ketoacids in improved yields.



Scheme 5.24 Pathway of the coupling reaction between aldehyde **143** and **359**, in presence of precatalyst **100**, to generate **356**

Concurrently, we were investigating the use of **280** in the crossed acyloin condensation as described above. Taking cue from the favourable interaction between the NHC, derived from

100, and the aromatic aldehyde **280**, we decided it prudent to also examine the performance of **280** in this particular protocol. To our delight when **280** was allowed to react with **364**, the product **365** was furnished in and extremely high isolated yield of 92% (Scheme 5.25). We were also curious to observe whether a chemoselective process occurred in the presence of **265** and to our delight, **265** coupled with the α-ketoester **364** to generate the corresponding product in uniformly high yields.



280 Ar = 2-pyridyl
265 Ar = 3-pyridyl

364

365 Ar = 2-pyridyl 92%
366 Ar = 3-pyridyl 91%

Scheme 5.25 Coupling of ethyl pyruvate (**364**) with aldehydes **280** and **265**, in presence of **100**, generates α-hydroxy-β-ketoacids **365** and **366** in extremely high yields

5.8 Conclusions

In conclusion, we have developed a highly chemoselective protocol that exploits the electronic properties of 2-pyridinecarboxaldehyde to allow access to a wide range of asymmetrical acyloin products in extremely high yields for the first time. We evaluated the substrate scope of this process and were extremely pleased to observe that both long and short chain aliphatic aldehydes afforded excellent yields of the corresponding **C** acyloin products. We have managed to exploit this highly chemoselective process to allow access to **337**, an alkaloid from *Lobelia inflata*, medically the most important plant of the *Lobelia* family.

We also examined a wide range of heteroaromatic aldehydes, bearing a nitrogen atom in the 2-position of the aryl ring, in the crossed acyloin condensation. We synthesised novel α-hydroxyketones in high yields, but perhaps more importantly we can now predict which products (of the four possible products) will be formed depending on the electronic properties of the particular aldehyde or what temperature the reaction is executed at. We have proven that the electronic density of the nitrogen atom, in the 2-position of the aryl ring of the aldehyde, are extremely important in establishing a chemoselective bias within the reaction and that alteration of the electronics of this nitrogen atom hamper the formation of a single major acyloin product. We have discovered that when the nitrogen atom, in the 2-position of

the aryl ring, is relatively basic, pyridil formation will dominate. However, when an electron-withdrawing substituent is placed on the ring, the **D** acyloin product will form, along with appreciable yields of the **C** acyloin product. Yields of the **D** acyloin product can be increased further when heat is applied to the reaction.

Whilst we obtained novel α-hydroxyketones in high yields, our ultimate goal is to gain an insight into the operations of both Breslow intermediate formation and subsequent Breslow intermediate interaction in order to determine the factors that promote a chemoselective crossed acyloin condensation. We have discovered that the NHC-based catalyst, derived from precatalyst **100**, reacts at an extremely fast rate with 2-pyridinecarboxaldehyde (in comparison to reaction of the NHC with the partner aliphatic aldehyde) to generate the corresponding homodimer product. However, reversible formation of this homodimer product, constantly generates the corresponding Breslow intermediate (bearing the pyridine moiety) which subsequently reacts with the aliphatic aldehyde to generate the **C** acyloin product; which we have proved is irreversibly formed. We also rationalised that the steric bulk provided by branched aliphatic aldehydes and disruption of the hydrogen bond between the nitrogen atom and the alcohol moiety prevents reversible formation of the **D** product.

We have also developed the first chemoselective, intermolecular crossed acyloin condensaion reaction between aromatic aldehydes and inexpensive α-ketoesters catalysed by an NHC catalyst. In this reaction the two partners can react to furnish densely functionalised products of high potential synthetic utility containing a quaternary stereocentre in good to excellent yields.

5.9 Future work

Having developed the first protocol, to our knowledge, that allows access to high yields of the **C** acyloin product when the two partner aldehydes are used in a 1:1 ratio, it is now our goal to understand the reason for this particular chemoselectivity. We have attempted a number of test reactions to gain insight into the role of the nitrogen atom when placed in the *ortho* position of one partner aldehyde in this particular reaction. We have postulated a theory to explain the reason for the observed chemoselectivity but it is important that we undergo computational studies to prove this theory. It is also our ultimate goal to design and synthesise both an achiral and chiral triazolium salt that also bears a nitrogen atom within the

catalytic scaffold that, upon deprotonation, would be capable of promoting the formation of α-hydroxyketones with chemoselectivity of type **C** in high yields.

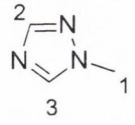
6. Experimental

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent $CDCl_3$, DMSO-d_6 or D_2O and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm) or H_2O (δ = 4.79 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz, respectively) with total proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. An arbitrary numbering system is employed to aid the assignment of the ^1H NMR signals. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT- time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical Ionization (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Acetonitrile, toluene, dichloromethane (CH_2Cl_2) and chloroform (CH_3Cl) were distilled over calcium hydride and stored under argon. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium-benzophenone and stored under argon. Methanol (MeOH) and isopropyl alcohol (*i*-PrOH) were dried over activated 3Å molecular sieves. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns. Elemental analysis was not performed as most compounds synthesised below were obtained as oils, not solids, and therefore elemental analysis would not be a viable option. In order to keep methods of characterisation consistent, we made the decision not to carry out elemental analysis on solid compounds. We also

decided that all methods of characterisation described below are evident enough proof that these compounds were formed as previously reported compounds that bear similar structures to those that we synthesised were published without data for elemental analysis.

6.1 Experimental procedures and data for Chapter 2

1-Methyl-1*H*-1,2,4-triazole (174)[175]

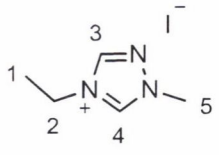


To a flame-dried 250 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged MeOH (80 mL) and sodium (3.40 g, 148.00 mmol). The solution was stirred for 5 mins before 1,2,4-triazole (10.00 g, 144.80 mmol, 1.0 equiv) was added and the mixture stirred at room temperature until the solid had dissolved. The vessel was then placed under a protective atmosphere of argon and cooled to 0 °C in a H_2O/ice bath. Iodomethane (9.0 mL, 144.80 mmol, 1.0 equiv) was added dropwise *via* syringe. Stirring was continued for 5 mins at 0 °C before warming to room temperature and stirring for a further 2 h under argon before refluxing at 60 °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 (4.69 g, 39%) that was dried under vacuum for several hours.

δ_H (400 MHz, $CDCl_3$): 3.80 (s, 3H, H-1), 7.78 (s, 1H, H-2), 7.93 (s, 1H, H-3).

HRMS (*m/z*-ESI): $[M+H]^+$ found 84.0564 ($C_3H_6N_3$ requires 84.0562).

4-Ethyl-1-methyl-1*H*-[1,2,4]triazol-1-ium iodide (172)



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 (4.20 g, 50.60 mmol, 1.0 equiv). The vessel was placed under a protective atmosphere of argon and ethyl iodide (8.9 mL, 106.27 mmol, 2.1 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 °C.

δ_H (400 MHz, DMSO-d_6): 1.42 (t, J 7.3, 3H, H-1), 4.03 (s, 3H, H-5), 4.20 (q, J 7.3, 2H, H-2), 9.18 (s, 1H, H-3), 10.03 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 15.0, 39.1, 43.4, 143.1, 144.7.

ν_{max} (neat)/cm^{-1}: 3423, 3028, 1773, 1583, 1164, 990, 730, 720, 653.

HRMS (*m/z*-ESI): $[M]^+$ found 112.0874 ($C_5H_{10}N_3$ requires 112.0875).

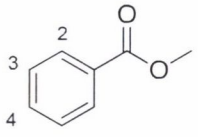
General Procedure A (Esterification of benzaldehyde in presence of triazolium salt 172 using various alcohols)

To a 10 mL vial equipped with a magnetic stirring bar was charged the triazolium precatalyst **172** (36.0 mg, 0.15 mmol, 15 mol%). Dry THF (2.5 mL) and the relevant alcohol were added. DBU (170 μL, 1.10 mmol, 110 mol%) was added and the solution stirred for 2 mins. Benzaldehyde (102 μL, 1.00 mmol) was then added. The vessel was sealed with a plastic lid perforated by 4 holes, 2 mm in diameter. The reaction mixture was stirred for the indicated time and temperature. The solvent was then removed *in vacuo* and the resulting residue subjected to flash chromatography eluting with a mixture of 10% Et_2O in hexanes to yield the ester product.

General Procedure B (Esterification of cyclic diketones in presence of triazolium salt 172 and using methyl iodide)

To a 25 mL vial equipped with a magnetic stirring bar was charged the triazolium precatalyst **172** (18.0 mg, 0.07 mmol, 15 mol%). Dry THF (1.25 mL) and deionised water (63 μL) were added. DBU (170 μL, 1.10 mmol, 220 mol%) was added and the solution was stirred for 2 mins. The 1,2-diketone (0.50 mmol) was then added. The vessel was sealed with a plastic lid perforated by 4 holes (2 mm in diameter). After stirring for 20 h at room temperature, $MgSO_4$ (1.40 mmol, 170.0 mg) and iodomethane (156 μL, 2.5 mmol) were added and stirred for 12 h at room temperature. The solvent was then removed *in vacuo* and the resulting residue subjected to flash chromatography eluting with a mixture of 10% EtOAc in hexanes to yield the ester product.

Methyl benzoate (171)[176]

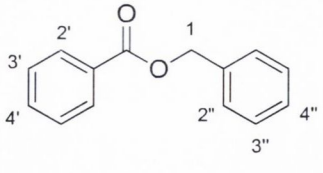


Prepared according to general procedure **A** with the addition of methanol (2.5mL). The reaction was stirred for 18 h at room temperature. Upon purification by column chromatography (R_{fTLC} = 0.28), **171** was obtained as a colourless oil (128.0 mg, 94%).

δ_H (400 MHz, $CDCl_3$): 3.89 (s, 3H, O-CH_3), 7.43 (app. t, 2H, H-3), 7.54 (t, J 7.7, 1H, H-4), 8.02 (d, J 7.4, 2H, H-2).

HRMS (*m/z*-ESI): $[M+H]^+$ found 137.0609 ($C_8H_9O_2$ requires 137.0603).

Benzyl benzoate (175)[177]

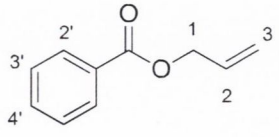


Prepared according to general procedure **A** with the addition of benzyl alcohol (311 μL, 3.00 mmol, 3.0 equiv). The reaction was stirred for 24 h at 45 °C. Upon purification by column chromatography (R_{fTLC} = 0.54), **175** was obtained as a pale yellow oil (153.2 mg, 72%).

δ_H (400 MHz, $CDCl_3$): 5.35 (app. d, 2H, H-1), 7.34-7.47 (m, 7H, H-2", H-3', H-3", H-4"), 7.52 (t, 1H, J 7.5, H-4'), 8.13 (d, 2H, J 7.5, H-2').

HRMS (*m/z*-EI): $[M]^+$ found 212.0845 ($C_{14}H_{12}O_2$ requires 212.0837).

Allyl benzoate (176)[178]

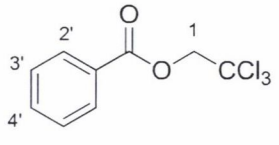


Prepared according to general procedure **A** with the addition of allyl alcohol (204 μL, 3.00 mmol, 3.0 equiv). The reaction was stirred for 24 h at 45 °C. Upon purification by column chromatography (R_{fTLC} = 0.43), **176** was obtained as a pale yellow oil (117.4 mg, 69%).

δ_H (400 MHz, $CDCl_3$): 4.81 (d, 2H, J 5.6, H-1), 5.25-5.30 (app. d, 1H, H-3), 5.27 (dd, 1H, J 1.2, 17.2, H-3), 5.98-6.07 (m, 1H, H-2), 7.42-7.48 (app. t, 2H, H-3'), 7.54 (t, 1H, J 7.4, H-4'), 8.05 (d, 2H, J 7.4, H-2').

HRMS (*m/z*-EI): $[M]^+$ found 162.0680 ($C_{10}H_{10}O_2$ requires 162.0681).

2,2,2-Trichloroethyl benzoate (177)[179]



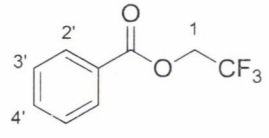
Prepared according to general procedure **A** with the addition of 2,2,2-trichloroethanol (288 μL, 3.00 mmol, 3.0 equiv). The reaction was stirred for 24 h at 45 °C. Upon purification by

column chromatography (R_{fTLC} = 0.39), **177** was obtained as a pale yellow oil (155.0 mg, 61%).

δ_H (400 MHz, $CDCl_3$): 4.95 (s, 2H, H-1), 7.46-7.51 (app. t, 2H, H-3'), 7.59 (t, 1H, J 7.6, H-4'), 8.11 (d, 2H, J 7.6, H-2').

HRMS (*m/z*-EI): $[M]^+$ found 251.9520 ($C_9H_7O_2Cl_3$ requires 251.9512).

2,2,2-Trifluoroethyl benzoate (178)[180]

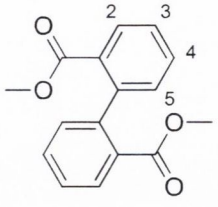


Prepared according to general procedure **A** with the addition of benzyl alcohol (311 μL, 3.00 mmol, 3.0 equiv). The reaction was stirred for 24 h at 45 °C. Upon purification by column chromatography (R_{fTLC} = 0.32), **178** was obtained as a pale yellow oil (153.2 mg, 72%).

δ_H (400 MHz, $CDCl_3$): 4.71 (q, 2H, J_{FH} 8.4, H-1), 7.44-7.49 (app.t, 2H, H-3'), 7.61 (t, 1H, J 7.5, H-4'), 8.06 (d, 2H, J 7.5, H-2').

HRMS (*m/z*-EI): $[M]^+$ found 204.0397 ($C_9H_7F_3O_2$ requires 204.0398).

Dimethyl biphenyl-2,2'-dicarboxylate (198)[181]

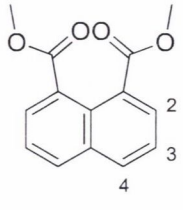


Prepared according to general procedure **B** using phenanthrene-9,10-dione (104.1 mg, 0.50 mmol). Upon purification by column chromatography (R_{fTLC} = 0.35), **198** was obtained as a pale yellow solid (110.2 mg, 82%). Mp 73-75 °C (lit.[181] 74-75 °C).

δ_H (400 MHz, $CDCl_3$): 3.59 (s, 6H, O-CH_3), 7.18 (d, 2H, J 7.6, H-2), 7.40 (app. t, 2H, H-4), 7.51 (app. t, 2H, H-3), 7.98 (d, 2H, J 7.6, H-5).

HRMS (*m/z*-ESI): $[M+H]^+$ found 271.0984 ($C_{16}H_{15}O_4$ requires 271.0970).

Dimethyl biphenyl-2,2'-dicarboxylate (200)[182]

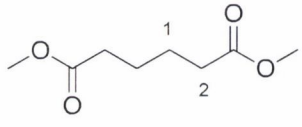


Prepared according to general procedure **B** using acenaphthenequinone (91.0 mg 0.50 mmol). Upon purification by column chromatography (R_{fTLC} = 0.30), **200** was obtained as a pale yellow solid (80.4 mg, 66%). M.p 100-104 °C (lit.[182] 102-103 °C).

δ_H (400 MHz, $CDCl_3$): 3.90 (s, 6H, O-CH_3), 7.53 (app. t, 2H, H-3), 7.97-8.00 (m, 4H H-2 and H-4).

HRMS (*m/z*-ESI): $[M+H]^+$ found 245.0817 ($C_{14}H_{13}O_4$ requires 245.0814).

Adipic acid dimethyl ester (204)[183]

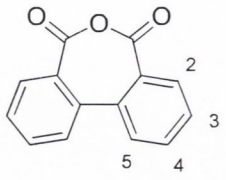


Prepared according to general procedure **B** using 1,2-cyclohexanedione (50.1 mg, 0.50 mmol). Upon purification by column chromatography (R_{fTLC} = 0.51), **204** was obtained as a colourless oil (32.0 mg, 18%).

δ_H (400 MHz, $CDCl_3$): 1.65-1.72 (m, 4H, H-1), 2.33-2.40 (m, 4H, H-2), 3.69 (s, 6H, O-CH_3).

HRMS (*m/z*-ESI): $[M+H]^+$ found 175.0971 ($C_{14}H_{13}O_4$ requires 175.0973).

dibenzo[c,e]oxepin-5,7-dione (205)[184]



To a 25 mL vial equipped with a magnetic stirring bar was charged the triazolium precatalyst **172** (18.0 mg, 0.07 mmol, 15 mol%). Dry THF (1.25 mL) and deionised water (63 μL) were added. DBU (170 μL, 1.10 mmol, 220 mol%) was added and the solution stirred for 2 min. Phenanthrene-9,10-dione (104.1 mg, 0.50 mmol) was then added. The vessel was sealed with a plastic lid perforated by 4 holes (2 mm in diameter). After stirring for 20 h at room temperature, $MgSO_4$ (1.40 mmol, 170.0 mg) and TFAA (353 μL, 2.50 mmol) were added and stirred for 12 h. The solvent was then removed *in vacuo* and the resulting residue was subjected to flash chromatography (hexanes:EtOAC, 1:1) to yield **205** as a white solid; 164.0 mg (73%). M.p 215-217 °C (lit.[184] 217 °C).

δ_H (400 MHz, $CDCl_3$): 7.49-7.54 (app. t, 2H, H-3), 7.61 (d, 2H, J 7.9, H-2), 7.65-7.71 (app. t, 2H, H-4), 7.80 (d, 2H, J 7.9, H-5).

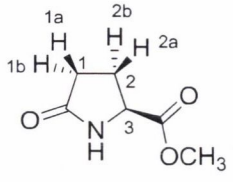
δ_C (100 MHz, $CDCl_3$): 128.9, 129.1, 130.5, 130.9, 133.4, 135.2 (q) 162.9 (C=O).

ν_{max} (neat)/cm^{-1}: 1731, 1597, 1440, 1214, 1065, 1032, 727, 649.

HRMS (*m/z*-ESI): [M-H] found 223.0395 ($C_{14}H_8O_3$ requires 223.0395).

6.2 Experimental procedures and data for Chapter 3

(*S*)-Methyl 5-oxopyrrolidine-2-carboxylate (210)[186]

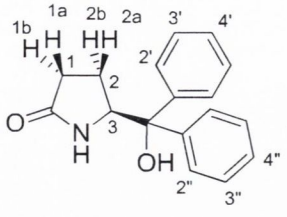


An oven dried 250 mL round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, was charged with (*S*)-pyroglutamic acid (10.00 g, 77.52 mmol) and Dowex-50W (X8-200, 5.00 g). Methanol (93 mL, 0.83 M) was added and the reaction mixture was placed under an atmosphere of argon (balloon). The reaction was heated at reflux for 36 h. The solution was cooled to room temperature and filtered under gravity to remove the solid. The solution was concentrated *in vacuo* affording the crude mixture which was purified by flash chromatography (9:1 EtOAc-hexanes, R_{fTLC} = 0.10) to afford **210** as a colourless oil (10.64 g, 96 %). $[\alpha]_D^{20}$ = –6.3 (*c* 1.00 in CH_2Cl_2), lit.,[185] $[\alpha]_D^{20}$ = –7.0 (*c* 1.00 in CH_2Cl_2), for *S* enantiomer.

δ_H (400 MHz, $CDCl_3$): 1.78-1.80 (m, 1H, H-2a), 1.96-2.00 (m, 2H, H-1a, H-1b), 2.08-2.13 (m, 1H, H-2b), 3.38 (s, 3H, O-CH_3), 3.93 (dd, 1H, J 8.8, 5.0, H-3), 7.35 (bs, 1H, N-H)

HRMS (*m/z*-ESI): $[M+Na]^+$ found 166.0477 ($C_6H_9N_2NO_3Na$ requires 166.0480).

(*S*)-5-(Hydroxydiphenylmethyl)pyrrolidin-2-one (211)[187]

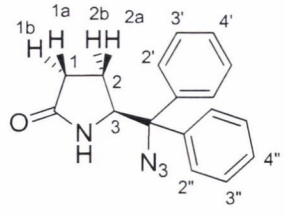


An oven dried 250 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with **210** (7.49 g, 52.33 mmol). The flask was fitted with a septum and placed under an argon atmosphere (balloon). THF (41 mL) was added *via* syringe and the resulting solution cooled to –78 °C. The solution was allowed to equilibrate at this temperature (*ca.* 15 minutes). Phenylmagnesium bromide (3.0 M solution in diethyl ether, 60 mL, 180.00 mmol) was slowly added *via* syringe over a 20 minute period and the resulting solution stirred for an additional 60 minutes at –78 °C. The solution was allowed to warm to room temperature then stirred for an additional 12 h. The reaction was cooled to 0 °C and quenched with aqueous HCl (5% (*v/v*), 60 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 200 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. Recrystallisation from CH_2Cl_2/Et_2O 9:1 afforded **211** (9.93 g, 71%) as a white solid, m.p. 194-195 °C, lit.,[186] 193-194 °C; $[\alpha]_D^{20}$ = –78.4 (c 1.30 in $CHCl_3$), lit.,[186] $[\alpha]_D^{20}$ = –80.8 (*c* 1.30 in $CHCl_3$), for *S* enantiomer with 100% *ee*.

δ_H (400 MHz, $CDCl_3$): 1.93-2.00 (m, 1H, H-2a), 2.09-2.12 (m, 1H, H-2b), 2.20-2.31 (m, 1H, H-1a), 2.32-2.42 (m, 1H, H-1b) 3.23 (bs, 1H, OH) 4.73 (dd, 1H, J 8.3, 5.0, H-3), 5.44 (bs, 1H, OH), 7.23-7.27 (m, 2H, H-4'and H-4"), 7.29-7.39 (m, 4H, H-3'and H-3"), 7.45-7.53 (app. dd, 4H, H-2', H-2").

HRMS (*m/z*-ESI): $[M+Na]^+$ found 290.1145 ($C_{17}H_{17}NO_2Na$ requires 290.1157).

(*S*)-5-(Azidodiphenylmethyl)pyrrolidin-2-one (212)



To an oven dried 250 mL round bottomed flask, equipped with a magnetic stirring bar was added sodium azide (6.00 g, 9.35 mmol) and $CHCl_3$ (170 mL). The solution was cooled to 0 °C and sulfuric acid (70% (*v/v*), 3.3 mL) was added to generate a solution of hydrazoic acid. While at this temperature, **211** (5.00 g, 18.70 mmol) was added. The solution was allowed to warm to room temperature and the reaction was stirred for 4 h. Ice-cold water (90 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (5% (*w/v*), 90 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (6:4 EtOAc-hexane, $R_{f\,TLC}$ = 0.24) to give **212** (4.85 g, 89%) as a white solid, m.p. 118 °C; $[\alpha]_D^{20}$ = –53.9 (*c* 0.22 in $CHCl_3$).

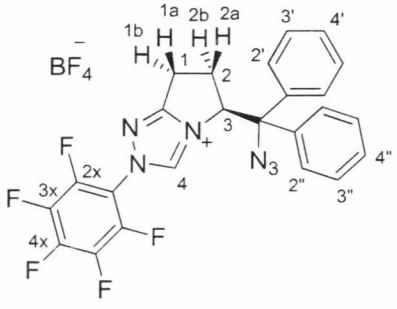
δ_H (400 MHz, $CDCl_3$): 1.71-1.75 (m, 1H, H-2a), 2.06-2.18 (m, 2H, H-2b and H-1a), 2.19-2.30 (m, 1H, H-1b) 4.73 (dd, 1H, J 8.3, 3.4, H-3), 5.81 (s, 1H, NH), 7.29-7.34 (m, 2H, H-4'and H-4") 7.35-7.48 (m, 8H, H-2', H-2" H-3'and H-3").

δ_C (100 MHz, $CDCl_3$): 22.3, 28.6, 59.3, 76.2 (q), 127.2, 127.3, 127.9 128.0, 128.2, 128.5, 138.7 (q) 138.7 (q), 177.8 (C=O).

ν_{max} (film)/cm^{-1}: 2937, 2114 (azide), 1601 (C=O), 1497, 1260, 1115, 924, 698, 674.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 315.1216 ($C_{17}H_{16}N_4ONa$ requires 315.1222).

(*S*)-5-(Azidodiphenylmethyl)-2-(perfluorophenyl)-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium (206)



To a 100 mL oven dried round-bottomed flask, equipped with a stirring bar, was added **212** (1.00 g, 3.43 mmol) and trimethyloxonium tetrafluoroborate (507.0 mg, 3.43 mmol). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (16 mL) was added *via* syringe and the solution was stirred at room temperature for 2 h. To the flask was added pentafluorophenyl hydrazine (679.0 mg, 3.43 mmol) and the solution was stirred at room temperature for a further 12 h. The solvent was removed *in vacuo*. The crude reaction was equipped with a reflux condenser and placed under an atmosphere of argon (balloon). To the flask was added freshly distilled chlorobenzene (32 mL), followed by triethylorthoformate (1.4 mL, 8.58 mmol) *via* syringe. The resulting solution was allowed to react at 130 °C for 12 h. The solution was allowed to cool to room temperature and the solvent was removed in *vacuo* resulting in a brown residue. Recrystallisation from 2-propanol afforded **206** (1.06 g, 53%) as a pale brown solid, m.p. 231-234 °C; $[\alpha]_D^{20} = -50.9$ (*c* 0.49 in $CHCl_3$).

δ_H (400 MHz, DMSO-d_6): 2.24-2.47 (m, 1H, H-2a), 2.76-2.91 (m, 1H, H-2b), 2.99-3.13 (m, 1H, H-1a), 3.46-3.62 (m, 1H, H-1b), 6.15 (app. d, 1H, H-3), 7.19-7.25 (app. d, 2H, H-4' and H-4"), 7.33-7.38 (m, 2H, H-

3'), 7.40-7.47 (m, 4H, H-2' and H-3"), 7.47-7.53 (m, 2H, H-2"), 9.39 (s, 1H, H-4).

δ_C (100 MHz, DMSO-d_6): 22.9, 30.1, 71.1 (q), 72.3, 102.4 (qC, t, J 12.9), 126.3, 127.0, 128.1, 128.3, 128.5, 128.7, 136.4 (qC, d, J 254.5), 138.1 (qC, d, J 255.6), 138.2 (qC, d, J 251.0) 143.3 (q), 147.2 (q) 148.6, 165.4 (q).

δ_F (376 MHz, DMSO-d_6): –158.9 (t, J 18.3, 1F F-4x) -153.7 (s, 4F, BF_4), –146.3 (t, 2F, J 18.3, F-3x), -145.07 (d, 2F, 'J 18.3, F-2x).

ν_{max} (film)/cm^{-1}: 3135, 2112, 1529, 1511, 1492, 1452, 1427, 1286, 1241, 1069, 1036, 1015,936, 873, 773, 715, 669.

HRMS (*m/z*-ESI): $[M]^+$ found 484.1432 ($C_{24}H_{17}F_5N_7$ requires 484.1429).

Procedure C: General procedure for the synthesis of triazole-based substrates *via* a 'click' reaction on a tertiary azide

An oven dried round-bottomed flask, equipped with a magnetic stirring bar, was charged with the relevant azide (6.87 mmol), copper sulfate (1.72 g, 6.87 mmol), and sodium ascorbate (4.08 g, 20.61 mmol). CH_2Cl_2/H_2O (1:1, 7.0 mL) was added followed by phenylacetylene (2.3 mL, 20.61 mmol). The reaction was allowed to stir at room temperature for 12 h. The solution was partitioned between CH_2Cl_2 (5.0 mL) and H_2O (5.0 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 3.0 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified using column chromatography.

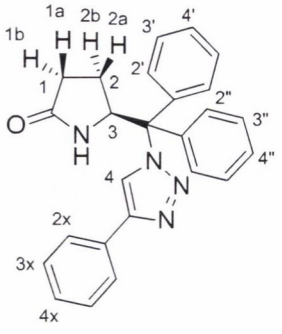
Procedure D: General procedure for the alkylation of pyrrolidin-2-ones using Meerwein's salt

To an oven dried round bottomed flask, equipped with a stirring bar, was added the relevant pyrrolidin-2-one (3.43 mmol) and trimethyloxonium tetrafluoroborate (507.0 mg, 3.43 mmol). The flask was fitted with a septum and placed under an argon atmosphere (balloon). CH_2Cl_2 (16 mL) was added *via* syringe and the solution was stirred at room temperature for 12 h. The mixture was cooled to 0 °C and the reaction was quenched by the slow addition of a saturated aqueous $NaHCO_3$ solution (14 mL). The solution was partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the crude product.

Procedure E: General procedure for (S)-5-(aminodiphenylmethyl)pyrrolidin-2-one amidation

In an oven dried round bottomed flask, equipped with a magnetic stirring bar was placed **235** (1.83 g, 6.87 mmol). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). To the flask was added freshly distilled pyridine (10 mL) and freshly distilled CH_2Cl_2 (20 mL). The solution was cooled to 0 °C and allowed to equilibrate at this temperature for 10 min before the appropriately substituted benzoyl chloride was added. The resulting solution was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with HCl (1 N, 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solution was concentrated *in vacuo* to obtain the crude mixture.

(*S*)-5-(Diphenyl(4-phenyl-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-2-one (219)



Prepared according to general procedure **C** using **212** (2.00 g, 6.87 mmol. The crude residue was purified by flash chromatography (8:2 EtOAc-hexanes, R_{fTLC} = 0.31) to give **219** (2.30 g, 83%) as a cream solid, m.p. 109-110 °C; $[\alpha]_D^{20}$ = +11.6 (*c* 0.34 in $CHCl_3$).

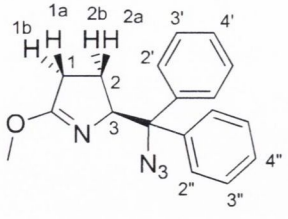
δ_H (400 MHz, $CDCl_3$): 1.30-1.39 (m, 1H, H-2a) 1.99-2.10 (m, 1H, H-1a) 2.12-2.19 (m, 1H, H-2b), 2.61-2.75 (m, 1H, H-1b), 5.74 (app. d, 1H, H-3), 6.14 (bs, 1H, NH), 7.18-7.27 (m, 4H, H-3' and H-3") 7.34 (t, 1H, J 7.4, H-4x), 7.38-7.49 (m, 8H, H-3x, H-2', H-2", H-4' and H-4"), 7.48-7.52 (s, 1H, H-4), 7.78 (d, 2H, J 7.0, H-2x).

δ_C (100 MHz, $CDCl_3$): 23.7, 28.5, 59.0, 81.3 (q), 120.7, 125.3, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 128.9, 129.6, 130.5 (q), 137.6 (q), 138.0 (q), 141.2 (q), 183.5 (C=O).

ν_{max} (film)/cm^{-1}: 3059, 2100, 1688, 1494, 1447, 1282, 1254, 1073, 1028, 907, 808, 763, 748, 617, 518.

HRMS (*m/z*-ESI): $[M + Na]^+$ found 417.1675 ($C_{25}H_{22}N_4ONa$ requires 417.1681).

(2S)-2-(Azidodiphenylmethyl)-5-methoxypyrrolidine (230)



Prepared according to general procedure **D** with the addition of **212** (1.00 g, 3.43 mmol). The crude residue was purified by flash chromatography (1:1 EtOAc-hexanes, R_{fTLC} = 0.36) to give **230** (882.7 mg, 84%) as a pale yellow oil, $[\alpha]_D^{20}$ = +15.9 (*c* 0.42 in $CHCl_3$).

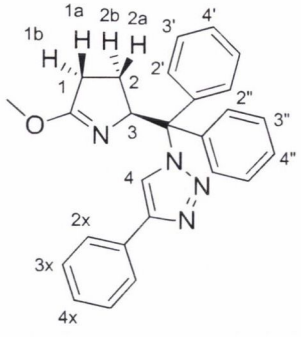
δ_H (400 MHz, $CDCl_3$): 1.64-1.78 (m, 1H, H-1a), 1.79-1.92 (m, 1H, H-2a) 2.13-2.56 (m, 1H, H-2b), 2.25-2.37 (m, 1H, H-2b), 3.80 (s, 3H, O-CH_3), 4.99-5.05 (m, 1H, H-3), 7.19-7.42 (m, 8H, H-2', H-2", H-3' and H-3") 7.54-7.60 (m, 2H, H-4'and H-4").

δ_C (100 MHz, $CDCl_3$): 29.1, 33.2, 55.4, 75.1 (q), 81.6, 127.9, 128.1, 128.3 128.6, 128.8, 129.0, 134.6 (q), 134.8 (q), 175.6 (C=N).

ν_{max} (film)/cm^{-1}: 3060, 2100, 1655, 1447, 1250, 1058, 1021, 733, 630, 556, 505, 428, 364, 290.

HRMS (*m/z*-ESI): $[M+CH_3OH+H]^+$ found 339.1828 ($C_{19}H_{23}N_4O_2$ requires 339.1816).

1-(((2S)-5-Methoxypyrrolidin-2-yl)diphenylmethyl)-4-phenyl-1H-1,2,3-triazole (231)



Prepared according to general procedure **C** using **230** (2.12 g, 6.87 mmol). The crude residue was purified by flash chromatography (8:2 hexanes-EtOAc, R_{fTLC} = 0.32) to give **231** (2.14 g, 76 %) as a white solid, m.p. 215-217 °C; $[\alpha]_D^{20}$ = –53.2 (*c* 0.24 in $CHCl_3$).

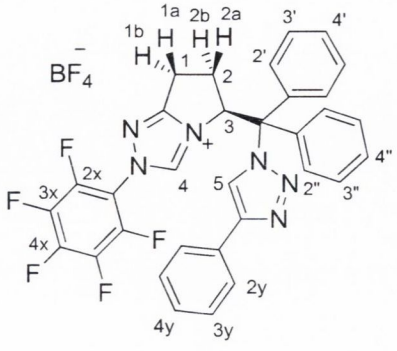
δ_H (400 MHz, $CDCl_3$): 2.19-2.38 (m, 4H, H-1a, H-1b, H-2a and H-2b), 3.61 (s, 3H, O-CH_3), 5.56-5.73 (m, 1H, H-3), 7.21-7.39 (m, 11H, H-2', H-2", H-3', H-3", H-3x and H-4x), 7.39-7.55 (m, 3H, H-4, H-4' and H-4"), 7.75 (d, 2H, J 7.0, H-2x).

δ_C (100 MHz, $CDCl_3$): 27.0, 30.4, 55.3, 60.3 (q), 72.6, 122.2, 125.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.6, 129.5, 130.7 (q), 141.3 (q), 142.0 (q), 145.4 (q), 174.8 (C=N).

ν_{max} (film)/cm^{-1}: 3058, 1648, 1482, 1353, 1224, 694, 588, 447, 352, 242.

HRMS (*m/z*-ESI): $[M + H]^+$ found 409.2026 ($C_{26}H_{25}N_4O$ requires 409.2023).

(S)-5-(Diphenyl(4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2-(perfluorophenyl)-2,5,6,7-tetrahydropyrrolo[2,1-c][1,2,4]triazol-4-ium (207)



To a 25 mL Erlenmeyer flask was added pentafluorophenyl hydrazine (4.95 g, 50 mmol) and diethyl ether (8.0 mL). To this was slowly added tetrafluoroboric acid diethyl ether complex until a brown solid precipitated, which was immediately filtered through a Büchner funnel and stored under vacuum. To an oven dried 100 mL round-bottomed flask, equipped with a stirring bar, was added **231** (1.40 g, 3.43 mmol) and the freshly made hydrazonium salt (981.0 mg, 3.43 mmol, 1.0 equiv.). The flask was fitted with a septum and placed under an argon atmosphere (balloon). CH_2Cl_2 (16 mL) was added *via* syringe and the solution was stirred at room temperature for 12 h. The solvent was removed *in vacuo*. The crude reaction mixture was equipped with a reflux condenser and placed under an argon atmosphere (balloon). To the flask was added freshly distilled chlorobenzene (32 mL) *via* syringe, followed by triethylorthoformate (1.4 mL, 8.58 mmol) *via* syringe. The resulting solution was allowed to react at 130 °C for 12 h. The solution was allowed to cool to room temperature and the solvent was removed in *vacuo* resulting in a brown residue. Recrystallisation from 2-propanol afforded **207** (824.1 mg, 41%) as a pale brown solid, m.p. 231-234 °C; $[\alpha]_D^{20} = -50.9$ (*c* 0.46 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6): 2.12-2.19 (m, 1H, H-2a), 2.24-2.30 (m, 1H, H-2b), 2.89-3.10 (m, 1H, H-1a), 3.41-3.52 (m, 1H, H-1b), 6.11 (app. d, 1H, H-3), 7.23-7.29 (app. d, 2H, H-4' and H-4"), 7.35-7.39 (m, 4H, H-3'

and H-3"), 7.43-7.6 (m, 3H, H-3y and H-4y), 7.47-7.53 (m, 4H, H-2' and H-2"), 7.60-7.64 (m, 3H, H-5 and H-2y) 9.21 (s, 1H, H-4).

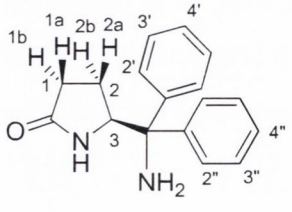
δ_C (100 MHz, DMSO-d_6): 30.9, 32.1, 72.3, 73.5 (q), 101.7 (t, q, J 12.1), 125.1, 125.2, 126.3, 127.1, 127.3, 127.5, 128.1, 128.4, 128.7, 130.4, 133.4 (q), 135.4 (qC, d, J 254.5), 138.2 (qC, d, J 255.6), 138.7 (qC, d, J 251.0), 143.3 (q), 145.9 (q), 147.2 (q) 148.6, 168.2 (q).

δ_F (376 MHz, DMSO-d_6): –156.9 (t, 1F, J 18.1, F-4x) -152.8 (s, 4F, BF_4), -146.0 (t, 2F, J 18.1, F-3x), -142.7 (d, 2F, J 18.1, F-2x).

ν_{max} (film)/cm^{-1}: 1694, 1687, 1654, 1001, 549, 501, 467, 430, 312, 267, 218.

HRMS (*m/z*-ESI): $[M]^+$ found 585.1826 ($C_{32}H_{22}F_5N_6$ requires 585.1822).

(S)-5-(Aminodiphenylmethyl)pyrrolidin-2-one (235)



To an oven dried 50 mL round bottomed flask, equipped with a magnetic stirring bar, was added **212** (2.00 g, 6.87 mmol). The flask was fitted with a rubber septum and placed under an Ar atmosphere (balloon). Freshly distilled methanol (35 mL) was added *via* syringe. The

suspension was charged with powdered zinc (2.25 g, 34.35 mmol) and ammonium formate (2.17 g, 34.35 mmol) and again placed under an atmosphere of argon (balloon). The reaction mixture was allowed to stir for 15 h at room temperature. The reaction mixture was diluted with EtOAc and filtered through a pad of celite (4.00 g). The resulting filtrate was washed with EDTA.8Na (0.1 N, 40 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and then concentrated *in vacuo* to afford the crude amine **235** in quantitative yield as a colourless oil; $[\alpha]_D^{20} = -72.9$ (*c* 0.28 in $CHCl_3$).

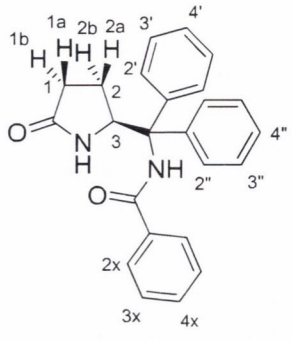
δ_H (400 MHz, $CDCl_3$): 1.56 (bs, 2H, NH_2), 2.00-2.28 (m, 4H, H-1a, H-1b and H-2a and H-2b), 4.64-4.71 (m, 1H, H-3), 5.51 (s, 1H, NH), 7.13-7.47 (m, 10H, H-2', H-2", H-3', H-3", H-4'and H-4").

δ_C (100 MHz, $CDCl_3$): 21.2, 30.4, 60.6, 71.2 (q), 127.5, 127.9, 128.1, 128.3, 129.4, 129.7, 140.2, 141.1, 178.2 (C=O).

ν_{max} (film)/cm^{-1}: 3424, 2960, 1676, 1204, 750, 583, 491, 427, 315, 293, 170.

HRMS (*m/z* - ESI): $[M+Na]^+$ found 289.1324 ($C_{17}H_{18}N_2ONa$ requires 289.1311).

(*S*)-*N*-((5-Oxopyrrolidin-2-yl)diphenylmethyl)benzamide (236)



General procedure **E** was followed using benzoyl chloride (2.4 mL, 20.61 mmol). The crude mixture was purified by column chromatography (6:4 EtOAc-hexanes, R_{fTLC} = 0.26) to afford **236** (806.0 mg, 54 %) as a cream solid, m.p. 196 °C; $[\alpha]_D^{20}$ = –35.29 (*c* 0.41 in $CHCl_3$).

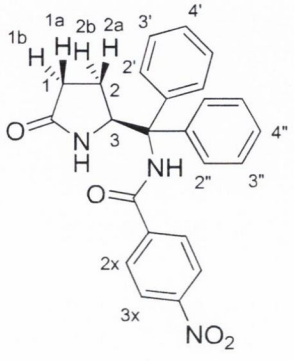
δ_H (400 MHz, $CDCl_3$): 1.63-1.79 (m, 1H, H-2b), 1.85-1.91 (app. t, 1H, H-2a), 1.96-1.99 (m, 1H, H-1b), 2.37-2.51 (m, 1H, H-1a), 5.77 (app. d, 1H, J 8.7, H-3), 6.36 (bs, 1H, NH), 7.09 (bs, 1H, NH), 7.24-7.32 (m, 4H, H-2' and H-2"), 7.33-7.04 (m, 4H, H-3' and H-3"), 4.41-7.43 (m, 2H, H-4' and H-4"), 7.43-7.5 (t, 2H, J 7.2, H-3x), 7.55 (t, 1H, J 7.2, H-4x), 7.77 (d, 2H, J 7.2, H-2x).

δ_C (100 MHz, $CDCl_3$): 23.7, 28.3, 56.2, 70.0 (q), 126.4, 127.2, 127.4, 127.6, 128.0, 128.1, 128.3, 128.4, 131.6, 133.8 (q), 140.3 (q), 141.8 (q), 166.4 (C=O), 179.1 (C=O).

ν_{max} (film)/cm^{-1}: 3378, 3187, 3059, 1681, 1670, 1663, 1500, 1475, 1445, 1289, 1254, 1031, 799, 697, 605.

HRMS (*m/z*-ESI): $[M + Na]^+$ found 393.1574 ($C_{24}H_{22}N_2O_2Na$ requires 393.1579).

(*S*)-4-Nitro-*N*-((5-oxopyrrolidin-2-yl)diphenylmethyl)benzamide (240)



General procedure **E** was followed using *p*-nitrobenzoyl chloride (6.37 g, 34.35 mmol). Purification *via* column chromatography (6:4 EtOAc-hexanes, R_{fTLC} = 0.27) afforded **240** (1.64 g, 54 %) as a cream solid, m.p. 228-229 °C; $[\alpha]_D^{20}$ = –42.9 (*c* 0.33 in $CHCl_3$).

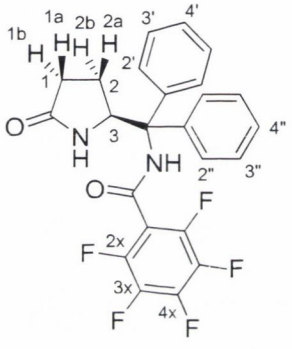
δ_H (400 MHz, $CDCl_3$): 1.68-1.81 (m, 1H, H-2b), 1.82-1.92 (m, 1H, H-2a), 1.92-2.02 (app. t, 1H, H-1b), 2.38-2.51 (m, 1H, H-1a), 5.71 (app. d, 1H, H-3), 6.43 (bs, 1H, NH), 7.11 (bs, 1H, NH), 7.29-7.33 (m, 2H, H-4' and H4"), 7.35-7.48 (m, 8H, H-2', H-2", H-3' and H-3"), 7.92 (d, 2H, J 8.5, H-2x), 8.29 (d, 2H, J 8.5, H-3x).

δ_C (100 MHz, $CDCl_3$): 23.9, 28.8, 56.7, 68.9 (q), 123.7, 123.9, 127.8, 128.0, 128.3, 128.4, 128.5, 128.6, 140.1 (q), 140.3 (q), 141.9 (q), 149.6 (q), 165.2 (C=O), 179.1 (C=O).

ν_{max} (film)/cm^{-1}: 3374, 3203, 3066, 1670, 1682, 1513, 1463, 1343, 1284, 1107, 1032, 933, 721, 709, 693, 647.

HRMS (*m/z*-ESI): $[M + Na]^+$ found 438.1421 ($C_{24}H_{21}N_3O_4Na$ requires 438.1430).

(*S*)-2,3,4,5,6-Pentafluoro-N-((5-oxopyrrolidin-2-yl)diphenylmethyl)benzamide (241)



General procedure **E** was followed using pentafluorobenzoyl chloride (4.9 mL, 34.35 mmol). The crude mixture was purified by column chromatography (5:5 EtOAc-hexanes, R_{fTLC} = 0.22) to afford **241** (1.64 g, 49 %) as a cream solid, m.p. 119 °C; $[\alpha]_D^{20}$ = –18.67 (*c* 0.45 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 1.60-1.74 (m, 1H, H-2b), 1.83-1.94 (m, 1H, H-2a), 1.95-2.04 (app. t, 1H, H-1b), 2.37-2.50 (m, 1H, H-1a), 5.59 (app. d, 1H, H-3), 6.19 (bs, 1H, NH), 6.94 (bs, 1H, NH), 7.20-7.25 (m, 2H, H-4' and H4"), 7.34-7.48 (m, 8H, H-2', H-2", H-3' and H-3").

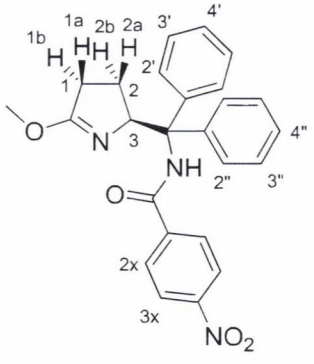
δ_C (100 MHz, $CDCl_3$): 23.3, 28.2, 56.3, 69.0 (q), 121.1 (q), 127.4, 127.6, 128.0, 128.0, 128.1, 128.2, 136.0 (qC, t, J 250.0), 138.9 (qC, d, J 258.9), 140.6 (qC, d, J 259.3), 144.2 (q), 146.1 (q) 156.5 (C=O), 178.3 (C=O).

δ_F (376 MHz, $CDCl_3$): –159.0 (t, J 18.0, 1F F-4), –147.1 (t, J 18.0, 2F, F-3), –145.05 (d, J 18.0, 2F, F-2).

ν_{max} (film)/cm^{-1}: 3236, 3060, 1685, 1542, 1494, 1447, 1254, 1043, 988, 789, 747, 699, 659, 640, 513.

HRMS (*m/z*-ESI): $[M + Na]^+$ 483.1098 ($C_{24}H_{17}F_5N_2O_2Na$ requires 483.1108).

N-(((2S)-5-Methoxypyrrolidin-2-yl)diphenylmethyl)-4-nitrobenzamide (244)



Prepared according to general procedure **D** with the addition of **240** (1.42 g, 3.43 mmol). Purification *via* column chromatography (7:3 hexanes-EtOAc, R_{fTLC} = 0.33) afforded **244** (618.7 mg, 56 %) as a pale yellow solid, m.p. 74-76 °C; $[\alpha]_D^{20}$ = -63.8 (*c* 0.51 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 1.76-1.85 (m, 1H, H-1a), 1.86-1.93 (m, 1H, H-2a), 1.96-2.04 (m, 1H, H-2b), 2.23-2.31 (m, 1H, H-1b), 3.89 (s, 3H, O-CH_3) 5.09-5.17 (m, 1H, H-3), 7.26-7.40 (m, 8H, H-2', H-2", H-3', H-4"), 7.66-7.73 (app. d, 2H, H-4' and H-4"), 7.77 (bs, 1H, NH), 7.96 (d, 2H, J 8.7, H-2x), 8.27 (d, 2H, J 8.7, H-3x).

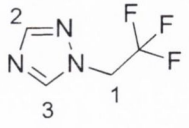
δ_C (100 MHz, $CDCl_3$): 26.1, 30.8, 55.7, 68.4 (q), 72.8, 123.7, 127.2, 127.4, 127.5, 127.7, 128.1, 128.8, 129.1, 139.8 (q), 142.1 (q), 149.5 (q), 163.9 (C=O), 175.2 (C=N).

ν_{max} (film)/cm^{-1}: 3058, 1648, 1521, 1245, 990, 699, 514, 457, 375, 244.

HRMS (*m/z* - ESI): $[M + Na]^+$ found 452.1582 ($C_{25}H_{23}N_3O_4Na$ requires 452.1581).

6.3 General procedures and data for Chapter 4

1-(2,2,2-Trifluoroethyl)-1H-1,2,4-triazole (249)



To a flame-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged 1,2,4-triazole (6.00 g, 86.87 mmol, 1.0 equiv.) followed by DMF (60 mL) and the mixture was stirred at room temperature until the solid had dissolved. The vessel was then placed under a protective atmosphere of argon and cooled to 0 °C in a H_2O/ice bath. K_2CO_3 (14.42 g, 104.36 mmol, 1.2 equiv.) was then added and the reaction was allowed to stir at room temperature for 30 min. The vessel was again cooled to 0 °C and 2,2,2-trifluoroethyl trifluoromethanesulfonate (15 mL, 104.36 mmol, 1.2 equiv.) was added dropwise *via* syringe. Stirring was continued for 5 min at 0 °C before the flask was then fitted with a condenser, ensuring to maintain the reaction vessel under an atmosphere of argon. The reaction was stirred at 50 °C for 24 h. Upon cooling, the solvent was removed *in vacuo* and H_2O (60 mL) was added. The product was washed with H_2O (3 x 60 mL), the organic layer dried over $MgSO_4$ and concentrated *in vacuo* to yield the title product as a yellow liquid (8.40 g, 64%) that was dried under vacuum for 6 h.

δ_H (400 MHz, $CDCl_3$): 4.72 (q, 2H, J_{FH} 8.3, H-1), 7.83 (s, 1H, H-2), 8.15 (s, 1H, H-3).

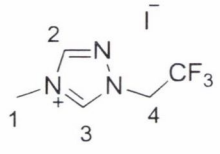
δ_C (100 MHz, $CDCl_3$): 36.4, 50.2 (qC, q, J 35.8), 144.7, 152.5.

δ_F (376 MHz, $CDCl_3$): –69.4 (t, 3F, J 8.6, CF_3).

ν_{max} (film)/cm^{-1}: 3032, 1021, 766, 721, 693, 648, 555, 512, 213, 194.

HRMS (*m/z*-EI): $[M]^+$ found 151.0360. ($C_4H_4F_3N_3$ requires 151.0357).

4-Ethyl-1-methyl-4*H*-[1,2,4]triazol-1-ium iodide (247)



To a flame-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged **249** (4.00 g, 26.50 mmol, 1.0 equiv). The vessel was placed under a protective atmosphere of argon and methyl iodide (3.3 mL, 53.00 mmol, 2.0 equiv.) was added *via* syringe. The flask was covered with aluminium foil and the reaction mixture stirred for 96 h at room temperature. The resulting precipitate was filtered, washed with cold Et_2O (3 x 20 mL) to yield **247** as a white crystalline solid (3.34 g, 43%).

δ_H (400 MHz, DMSO): 4.08 (s, 3H, H-1), 5.45 (q, 2H, J_{FH} 8.7, H-4), 9.31 (s, 1H, H-2), 10.2 (s, 1H, H-3).

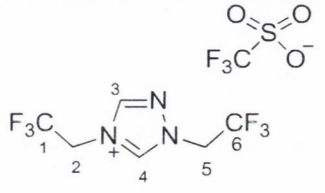
δ_C (100 MHz, DMSO): 35.1, 40.3, 51.3 (qC, q, J 36.1), 146.1, 147.0.

δ_F (376 MHz, DMSO): –71.3 (t, 3F, J 8.2, CF_3).

ν_{max} (film)/cm^{-1}: 2956, 928, 795, 648, 532, 502, 489, 215, 179, 152.

HRMS (*m/z*-ESI): $[M]^+$ found 166.0587 ($C_5H_7F_3N_3$ requires 166.0587).

4-Ethyl-1-methyl-4*H*-[1,2,4]triazol-1-ium iodide (255)



To a flame-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged **249** (4.00 g, 26.50 mmol, 1.0 equiv). The vessel was placed under a protective atmosphere of argon and 2,2,2-trifluoroethyl trifluoromethanesulfonate (12 mL, 79.50 mmol, 3.0 equiv) was added *via* syringe. The flask was then fitted with a condenser ensuring to maintain the reaction vessel under an atmosphere of argon. The reaction was stirred at 60 °C for 96 h. The resulting precipitate was filtered, washed with cold Et_2O (3 x 20 mL) to yield the title product as a white crystalline solid (3.25g, 32%).

δ_H (400 MHz, DMSO-d_6): 5.52 (q, 2H, J_{FH} 8.6, H-5), 5.67 (q, 2H, J_{FH} 8.6, H-2), 9.53 (s, 1H, H-3), 10.51 (s, 1H, H-4).

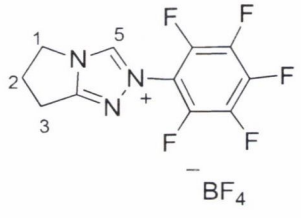
δ_C (100 MHz, DMSO-d_6): 34.9, 35.8, 47.8 (qC, q, J 35.7), 51.8 (qC, q, 35.7), 146.6, 147.2.

δ_F (376 MHz, DMSO-d_6): –77.8, –70.0 (t, 3F, J 8.8, F-1), –69.1 (t, 3F, J 8.8, F-6).

ν_{max} (film)/cm^{-1}: 3131, 1255, 1172, 843, 762, 636, 613, 515, 509, 455, 392, 226, 180.

HRMS (*m/z*-ESI): $[M]^+$ found 234.0470. ($C_6H_6F_6N_3$ requires 234.0460).

2-Pentafluorophenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (100)[62]



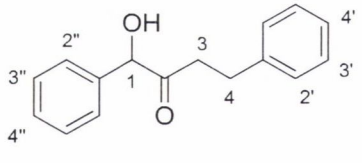
An oven-dried 500 mL round bottomed flask was equipped with a magnetic stirrer and placed under an atmosphere of argon. To the reaction vessel was added with 2-pyrrolidinone (2.00 g, 26.30 mmol) and CH_2Cl_2 (130 mL). Trimethyloxonium tetrafluoroborate (3.90 g, 26.30 mmol) was added and the reaction stirred under an atmosphere of argon for 12 h. Pentafluorophenyl hydrazine (5.20 g, 26.30 mmol) was added to the reaction mixture and stirred for 2 h. Concentration *in vacuo* produced a pale orange solid. The crude mixture was heated under vacuum at 110 °C for 2 h. Triethylorthoformate (21.90 mL, 131.61 mmol) was added to the reaction and heated at 110 °C for 1 h (under argon). Upon cooling to room temperature the crude solid precipitated. The crude mixture was filtered and washed with toluene (60 mL) to give a white solid, **100** (4.68 g, 49%); m.p.: 248-250 °C (lit.,[62] 248-253 °C).

δ_H (600 MHz, DMSO-d_6): 2.70-2.76 (m, 2H, H-2), 3.20-3.31 (m, 2H, H-1), 4.45-4.47 (m, 2H, H-3), 10.51 (s, 1H, H-5).

General Procedure F: for the NHC-mediated crossed acyloin condensation

To a 5 mL oven dried, round-bottomed flask equipped with a magnetic stirring bar was charged the relevant triazolium ion-based precatalyst. The flask was fitted with a septum seal and placed under an atmosphere of argon. Dry THF (1.0 M) was charged to the reaction, followed by consecutive addition of each freshly distilled aldehyde (2.00 mmol) and DIPEA (35 μL, 0.20 mmol, 10 mol%). The flask was then fitted with a condenser ensuring to maintain the reaction vessel under an atmosphere of argon. The reaction was stirred at 40 °C for 24 h. The reaction was then allowed to cool to room temperature. CH_2Cl_2 (3.0 mL) and deionised H_2O (3.0 mL) were added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 x 3.0 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The product was purified using flash chromatography. Note: The internal standard styrene (114 μL, 1.00 mmol) was added to the reaction prior to the work up.

1-Hydroxy-1,4-diphenylbutan-2-one (109d)[93]



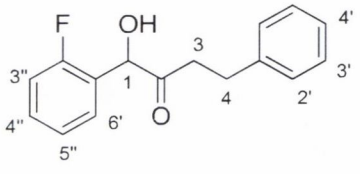
General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and benzaldehyde (204 μL, 2.00 mmol, 1.0 equiv). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.31) to afford **109d** (461.4 mg, 96%) as a white solid. M.p.: 62-63 °C (lit.,[93] 63-65 °C).

δ_H (400 MHz, $CDCl_3$): 2.56-2.70 (m, 2H, H-3), 2.71-2.81 (m, 1H, H-4), 2.82-2.92 (m, 1H, H4) 4.27 (d, 1H, J 4.3, OH), 5.02 (d, 1H, J 4.29, H-1), 7.02

(d, 2H, J 7.2, H-2'), 7.12-7.18 (m, 1H, H-4'), 7.26-7.28 (m, 2H, H-3'), 7.23-7.30 (m, 2H, H-2"), 7.36-7.43 (m, 3H, H-3" and H-4").

HRMS (*m/z*-ESI): $[M+Na]^+$ found 263.1044 ($C_{16}H_{16}O_2Na$ requires 263.1043).

1-(2-Fluorophenyl)-1-hydroxy-4-phenylbutan-2-one (253d)[93]

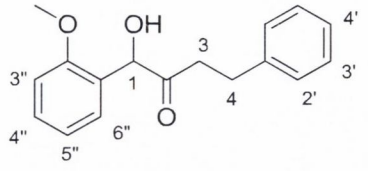


General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 2-fluorobenzaldehyde (211 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.32) to afford **253d** (475.3 mg, 92%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.59-2.96 (m, 4H, H-3 and H-4), 4.26 (d, 1H, J 4.4, OH), 5.36 (d, 1H, J 4.4, H-1), 7.02-7.26 (m, 8H, H-2', H-3', H-4', H-4", H-5" and H-6"), 7.26-7.34 (m, 1H, H-3").

HRMS (*m/z*-ESI): $[M+Na]^+$ found 281.0944 ($C_{16}H_{15}FO_2Na$ requires 281.0948).

1-Hydroxy-1-(2-methoxyphenyl)-4-phenylbutan-2-one (254d)[93]

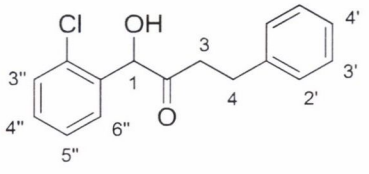


General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and *ortho*-anisaldehyde (241 μL, 2.00 mmol, 1.0 equiv). The reaction was carried out at 60 °C. The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.23) to afford **254d** (508.2 mg, 94%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.55-2.99 (m, 4H, H-3 and H-4), 3.78 (s, 3H, O-CH_3), 4.20 (bs, 1H, OH), 5.32 (s, 1H, H-1), 6.88 (d, 1H, J 8.1, H-3") 6.91-6.97 (app t., 1H, H-5"), 7.05 (d, 2H, J 3.6, H-2'), 7.12-7.26 (m, 4H, H3', H4" and H-6"), 7.29 (t, 1H, J 8.1, H-4').

HRMS (*m/z*-ESI): $[M+Na]^+$ found 293.1152 ($C_{17}H_{18}O_3Na$ requires 293.1148).

1-(2-Chloro-phenyl)-1-hydroxy-4-phenyl-butan-2-one (257d)[93]

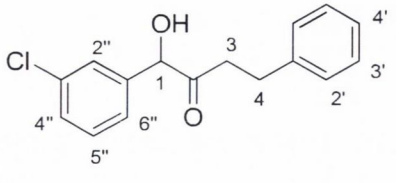


General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 2-chlorobenzaldehyde (225 μL, 2.00 mmol, 1.0 equiv). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.34) to afford **257d** (526.1 mg, 96%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.56-2.71 (m, 1H, H-3), 2.72-2.99 (m, 3H, H-3 and H-4), 4.51 (bs, 1H, OH), 5.54 (s, 1H, H-1), 7.05 (d, 2H, J 7.4, H-2"), 7.13-7.29 (m, 6H, H-3", H-4", H-4', H-5' and H-6'), 7.43 (d, 1H, J 7.5, H-3').

HRMS (*m/z*-ESI): $[M+Na]^+$ found 297.0657 ($C_{16}H_{15}ClO_2Na$ requires 297.0653).

1-(3-Chlorophenyl)-1-hydroxy-4-phenylbutan-2-one (258d)[93]



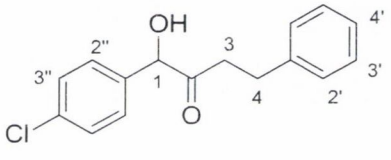
General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 3-chlorobenzaldehyde

(226 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.26) to afford **258d** (522.0 mg, 95%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.57-2.74 (m, 2H, H-3), 2.76-2.92 (m, 1H, H-4), 4.29 (bs, 1H, OH), 4.98 (s, 1H, H-1), 7.03 (d, 2H, J 7.3, H-2'), 7.11-7.32 (m, 7H, H-3', H-4' H-2", H-4", H-5", H-6").

HRMS (*m/z*-ESI): $[M+Na]^+$ found 297.0654 ($C_{16}H_{15}ClO_2Na$ requires 297.0653).

1-(4-Chlorophenyl)-1-hydroxy-4-phenylbutan-2-one (259d)[93]

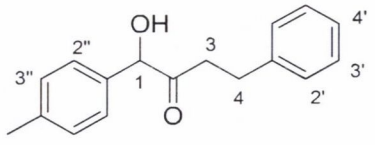


General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 4-chlorobenzaldehyde (281.1 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.26) to afford **259d** (527.5 mg, 96%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.59-2.72 (m, 2H, H-3), 2.76-2.92 (m, 1H, H-4), 4.85 (bs, 1H, OH), 5.00 (s, 1H, H-1), 7.03 (d, 2H, J 7.3, H-2'), 7.14-7.26 (m, 5H, H-2", H-3' and H-4'), 7.30 (d, 2H, J 8.4, H-3").

HRMS (*m/z* - ESI): $[M-H]^-$ found 273.0688 ($C_{16}H_{14}ClO_2$ requires 273.0687).

1-Hydroxy-4-phenyl-1-*p*-tolylbutan-2-one (260d)[95]

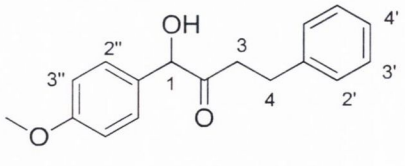


General procedure **F** was employed using precatalyst **255** (77.00 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and *p*-tolualdehyde (236 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.33) to afford **260d** (468.0 mg, 92%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.35 (s, 3H, CH_3), 2.59-2.71 (m, 2H, H-3), 2.74-2.83 (m, 1H, H-4), 2.84-2.94 (m, 1H, H-4), 4.27 (bs, 1H, OH), 5.00 (s, 1H, H-1), 7.05 (d, J 7.3, 2H, H-2'), 7.11-7.19 (m, 4H, H-2" and H-3"), 7.20-7.64 (m, 3H, H-3' and H-4').

HRMS (*m/z* - ESI): $[M+Na]^+$ found 277.1203. ($C_{17}H_{18}O_2Na$ requires 277.1199).

2-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-1-one (261d)[95]



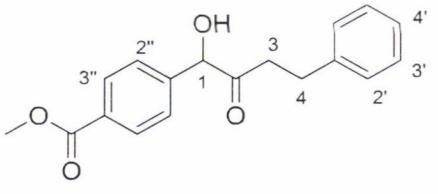
General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and *para*-anisaldehyde

(243 μL, 2.00 mmol, 1.0 equiv.). The reaction was carried out at 60 °C for 40 hours. The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.16) to afford **261d** (454.2 mg, 84%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.59-2.67 (m, 1H, H-3), 2.72-2.92 (m, 2H, H-4), 3.78 (s, 3H, O-CH_3), 4.23 (d, 1H, J 3.9, OH), 4.97 (d, 1H, J 3.9, H-1), 6.85 (d, 2H, J 8.5, H-3"), 7.03 (d, 2H, J 7.4, H-2'), 7.12-7.25 (m, 5H, H-2", H-3', H-4')

HRMS (*m/z*-ESI): $[M+Na]^+$ found 293.1155 ($C_{17}H_{18}O_3Na$ requires 293.1148).

Methyl 4-(1-hydroxy-2-oxo-4-phenylbutyl)benzoate (262d)[95]

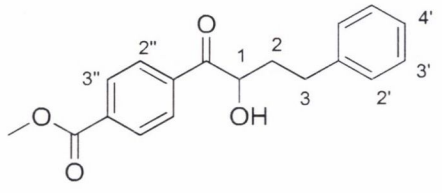


General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and methyl 4-formylbenzoate (328.3 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.22) to afford **262d** (537.0 mg, 90%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.54-2.91 (m, 4H, H-3 and H-4), 3.90 (s, 1H, O-CH_3) 4.37 (bs, 1H, OH), 5.07 (s, 1H, H-1), 7.00 (d, 2H, J 7.4, H-2"), 7.12-7.23 (m, 3H, H-3' and H-4"), 7.33 (d, 2H, J 8.2, H-2') 7.99 (d, 2H, J 8.2, H-3").

HRMS (*m/z*-ESI): $[M+Na]^+$ found 321.1099 ($C_{18}H_{18}O_4Na$ requires 321.1097).

Methyl 4-(1-oxo-2-hydroxy-4-phenylbutyl)benzoate (262c)



General procedure **F** was employed using precatalyst **100** (72.6 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and methyl 4-formylbenzoate (328.3 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.25) to afford **262c** (59.7 mg, 10%) as a pale yellow solid. M.p: 49-51 °C.

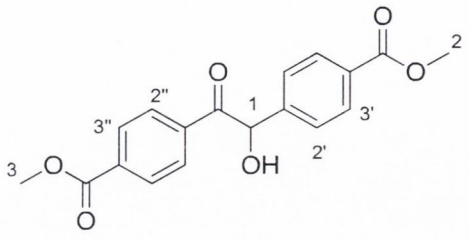
δ_H (400 MHz, $CDCl_3$): 1.74-1.87 (m, 1H, H-2), 2.05-2.18 (m, 1H, H-2), 2.72-2.90 (m, 2H, H-3) 3.64 (bs, 1H, OH), 3.94 (s, 3H, O-CH_3) 4.97-5.05 (m, 1H, H-1), 7.11-7.30 (m, 5H, H-2', H-3' and H-4'), 7.77 (d, 2H, J 8.6, H-3"), 8.08 (d, 2H, J 8.6, H-2")

δ_C (100 MHz, $CDCl_3$): 31.4, 37.5, 52.6, 72.4, 126.3, 128.4, 128.5, 128.7, 129.8, 134.6 (q), 136.7 (q), 140.8 (q), 165.9 (C=O), 201.8 (C=O).

ν_{max} (film)/cm^{-1}: 3060, 1699, 1675, 1266, 110, 875, 783, 749, 629, 538, 455, 421, 207, 163.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 321.1095 ($C_{18}H_{18}O_4Na$ requires 321.1097).

1,2-bis(4-methylbenzoate)-2-hydroxyethanone (262b)



General procedure **F** was employed using precatalyst **100** (72.6 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and methyl 4-formylbenzoate (328.3 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexane-EtOAc, R_{fTLC} = 0.18) to afford **262b** (91.9 mg, 14%) as a white solid. M.p.: 124-126 °C.

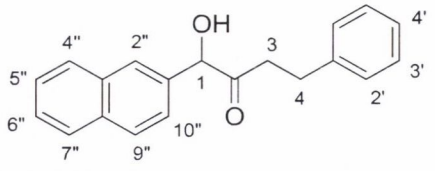
δ_H (600 MHz, $CDCl_3$): 3.86 (s, 3H, H-2), 3.89 (s, 3H, H-3), 4.50 (d, 1H, J 5.9, OH) 5.99 (d, 1H, J 5.9, H-1), 7.38 (d, 2H, J 7.9, H-2'), 7.91 (d, 2H, J 8.1, H-3"), 7.97 (d, 2H, J 7.9, H-3'), 8.04 (d, 2H, J 8.1, H-2").

δ_C (100 MHz, $CDCl_3$): 52.2, 52.5, 76.2, 127.7, 128.8, 129.8, 130.4, 134.7 (q), 136.5 (q), 142.9 (q), 143.0 (q), 165.7 (C=O), 166.4 (C=O), 198.2 (C=O).

ν_{max} (film)/cm^{-1}: 3462, 1712, 1672, 1276, 1105, 635, 525, 486, 424, 273, 167.

HRMS (*m/z* - ESI): $[M+Na]^+$ found 351.0844 ($C_{18}H_{16}O_6Na$ requires 351.0839).

1-Hydroxy-1-(naphthalen-2-yl)-4-phenylbutan-2-oneone (263d)



General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 2-napthaldehyde (312.4 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexane-EtOAc, R_{fTLC} = 0.24) to afford **263d** (534.3 mg, 92%) as a yellow oil.

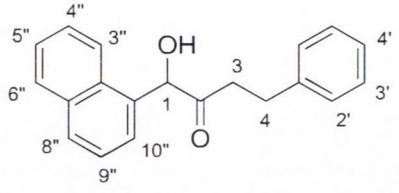
δ_H (400 MHz, $CDCl_3$): 2.57-2.99 (m, 4H, H-3 and H-4) 4.41 (bs, 1H, OH), 5.19 (s, 1H, H-1), 6.99 (d, 1H, J 7.2, H-2'), 7.09-7.22 (m, 3H, H-3' and H-4'), 7.30 (d, 1H, J 8.2, H-10"), 7.47-7.53 (m, 2H, H-5" and H-6"), 7.71 (s, 1H, H-2"), 7.78-7.86 (m, 3H, H-4", H-7" and H-9").

δ_C (100 MHz, $CDCl_3$): 29.6, 39.6, 80.0, 124.3, 126.3, 126.5, 126.6, 127.2, 127.8, 128.0, 128.2, 128.5, 129.0, 133.3 (q), 133.4 (q), 135.1 (q), 140.1 (q), 208.7 (C=O).

ν_{max} (film)/cm^{-1}: 3442, 1711, 746, 567, 518, 464, 437, 332, 295, 227, 155.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 313.1205 ($C_{20}H_{18}O_2Na$ requires 313.1199).

1-Hydroxy-1-(naphthalen-1-yl)-4-phenylbutan-2-one (264d)



General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 1-napthaldehyde (272 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.24) to afford **264d** (534.3 mg, 92%) as a yellow oil.

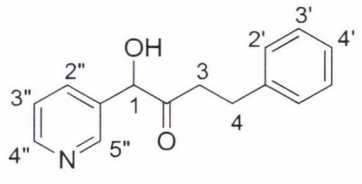
δ_H (400 MHz, $CDCl_3$): 2.42-2.53 (m, 1H, H-3), 2.62-2.81 (m, 2H, H-4), 2.84-2.93 (m, 1H, H-3), 4.37 (bs, 1H, OH), 5.54 (s, 1H, H-1), 6.96 (d, 1H, J 7.2, H-2'), 7.10-7.21 (m, 3H, H-3' and H-4'), 7.36-7.46 (m, 2H, H-4" and H-10"), 7.47-7.53 (m, 2H, H-5" and H-8"), 7.82-7.91 (m, 2H, H-3" and H-6"), 7.93-7.99 (m, 1H, H-9").

δ_C (100 MHz, $CDCl_3$): 29.7, 39.6, 79.1, 123.6, 125.4, 126.1, 126.3, 127.0, 127.9, 128.3, 128.5, 129.0, 129.7, 131.2 (q), 133.4 (q), 134.3 (q), 140.2 (q), 209.9 (C=O).

ν_{max} (film)/cm^{-1}: 3460, 1712, 1697, 862, 775, 474, 462, 424, 368, 314, 225, 202.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 313.1196 ($C_{20}H_{18}O_2Na$ requires 313.1199).

1-Hydroxy-4-phenyl-1-(pyridin-3-yl)butan-2-one (269d)



General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 3-pyridinecarboxaldehyde (188 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (3:2 hexanes-EtOAc, R_{fTLC} = 0.28) to afford **269d** (434.2 mg, 90%) as a yellow oil.

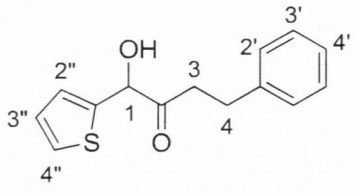
δ_H (400 MHz, $CDCl_3$): 2.65-2.80 (m, 2H, H-4), 2.78-2.94 (m, 2H, H-3), 4.39 (bs, 1H, OH), 5.08 (s, 1H, H-1), 7.05-7.09 (d, 2H, J 6.8, H-2'), 7.20-7.54 (m, 4H, H-3', H-3" and H-4'), 7.53 (d, 1H, J 7.8, H-2"), 8.61 (app. s, 2H, H-4" and H-5").

δ_C (100 MHz, $CDCl_3$): 29.1, 39.1, 77.2, 123.5, 126.0, 127.7, 128.2, 133.8 (q), 134.1, 139.3 (q), 148.6, 149.6, 207.2 (C=O).

ν_{max} (film)/cm^{-1}: 3360, 2998, 1706, 1681, 1619, 1585, 1513, 1363, 1244, 1178, 1068, 1027, 985, 914, 851, 729, 757.

HRMS (*m/z*-ESI): $[M+H]^+$ found 242.1182 ($C_{15}H_{16}NO_2$ requires 242.1181).

1-Hydroxy-4-phenyl-1-(thiophen-2-yl)butan-2-one (270d)



General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 2-thiophenecarboxaldehye (187 μL, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.25) to afford **270d** (408.9 mg, 83%) as a yellow oil.

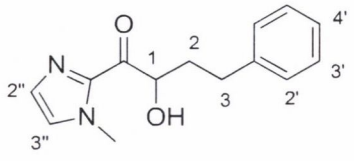
δ_H (400 MHz, $CDCl_3$): 2.73-2.97 (m, 4H, H-3 and H-4), 4.33 (d, 1H, J 3.8 OH), 5.30 (d, 1H, J 3.8, H-1), 6.96-7.00, (m, 1H, H-3"), 7.02 (m, 1H, H-2"), 7.09 (d, 2H, J 7.6, H-2'), 7.14-7.32 (m, 4H, H-3', H-4' and H-4").

δ_C (100 MHz, $CDCl_3$): 29.7, 39.3, 75.1, 126.4, 126.5, 126.6, 127.2, 128.2, 128.6, 140.1, 140.8, 207.3.

ν_{max} (film)/cm^{-1}: 3451, 1714, 1649, 1077, 696, 618, 510, 464, 326, 233, 192.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 269.0602 ($C_{14}H_{14}O_2SNa$ requires 269.0607).

2-Hydroxy-1-(1-methyl-1H-imidazol-2-yl)-4-phenylbutan-1-one (272d)



General procedure **F** was employed using precatalyst **100** (72.6 mg, 0.20 mmol) with the addition of hydrocinnamaldyhde (263 μL, 2.00 mmol, 1.0 equiv.) and 1-methyl-2-imidazolecarboxaldehyde (220.2 mg, 2.00 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (3:2 hexanes-EtOAc, R_{fTLC} = 0.24) to afford **272d** (142.8 mg, 29%) as a pale yellow oil.

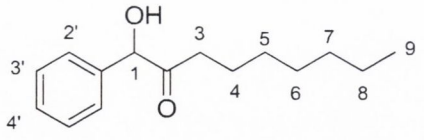
δ_H (400 MHz, $CDCl_3$): 2.00-2.14 (m, 1H, H-2b), 2.28-2.40 (m, 1H, H-2a), 2.77-2.87 (app. t, 2H, H-3a and H-3b), 3.93 (s, 3H, N-CH_3), 4.41 (bs, 1H, OH), 4.92-4.99 (m, 1H, H-1), 7.02 (s, 1H, H-2") 7.09-7.28 (m, 6H, H-2', H-3', H-3" and H-4').

δ_C (100 MHz, $CDCl_3$): 29.73, 39.3, 75.2, 126.3, 126.5, 126.6, 127.2, 128.2, 128.5, 140.1 (q), 140.7 (q), 207.2 (C=O).

ν_{max} (film)/cm^{-1}: 3315, 2972, 1046, 668, 552, 494, 468, 425, 397, 364, 311, 298, 180.

HRMS (*m/z*-ESI): $[M+H]^+$ found 245.1283 ($C_{14}H_{17}N_2O_2$ requires 245.1285).

1-Hydroxy-1-phenylnonan-2-one (274d)[95]



General procedure **F** was employed using precatalyst **255** (77.0 mg, 0.20 mmol) with the addition of octanal (312 μL, 2.00 mmol, 1.0 equiv.) and benzaldehyde (204. μL, 2.00 mmol, 1.0 equiv.). The reaction was carried out at 60 °C. The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.38) to afford **274d** (426.5 mg, 91%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 0.79-.90 (m, 3H, H-9), 1.08-1.34 (m, 8H, H-5, H-6, H-7 and H-8), 1.40-1.56 (m, 2H, H-4), 2.26-2.47 (m, 2H, H-3), 4.34 (d, 1H, J 4.4, OH), 5.06 (d, 1H, J 4.4, H-1), 7.25-7.40 (m, 5H, H-2', H-3', H-4').

HRMS (*m/z*-ESI): $[M+Na]^+$ found 257.1507 ($C_{15}H_{22}O_2Na$ requires 257.1512).

6.4 General procedures and data for Chapter 5

General Procedure G: for the NHC-mediated crossed acyloin condensation between aromatic aldehydes and hydrocinnamaldehyde (preliminary conditions)

To a 5 mL oven-dried round-bottomed flask, equipped with a magnetic stirring bar, was added K_2CO_3 (6.0 mg, 0.04 mmol) that had been finely ground using a mortar and pestle. The reaction vessel was evacuated and heated with a heat gun for 4 one-min intervals. When cooled to ambient temperature precatalyst **100** (15.9 mg, 0.04 mmol) was added and the flask was fitted with a septum. The reaction was evacuated for 4 min and then placed under an atmosphere of argon (balloon). The required aldehydes were distilled under vacuum and used directly. The reaction flask was charged with distilled THF (1.0 M), followed by hydrocinnamaldehyde (115 µl, 1.10 mmol, 1.0 equiv.) and the relevant aldehyde (1.10 mmol, 1.0 equiv.). Styrene (63 µL, 0.55 mmol) was added as an internal standard to allow assessment of the reaction progress by ^{1}H NMR spectroscopy. The reaction was stirred at room temperature for 40 h. CH_2Cl_2 (3.0 mL) and deionised H_2O (3.0 mL) were added. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (4 x 3.0 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvents were removed under reduced pressure. The product was purified using column chromatography.

General Procedure H: for the NHC-mediated crossed acyloin condensation between heteroaromatic aldehydes and aliphatic aldehydes (optimised conditions)

To a 5 mL oven-dried round-bottomed flask, equipped with a magnetic stirring bar and placed under an atmosphere of argon (balloon), was added precatalyst **100** (15.9 mg, 0.04 mmol). The reaction flask was charged with distilled THF (1.0 M) and DIPEA (8 µl, 0.04 mmol). The two freshly-distilled aldehydes were subsequently added. The reaction was stirred at room temperature for 16 h. CH_2Cl_2 (3.0 mL) and deionised H_2O (3.0 mL) were added, the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (4 x 3.0 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The product was purified using column chromatography.

Note: Styrene (63 μL, 0.55 mmol) was added (before work-up) as an internal standard to allow assessment of the reaction progress by ^{1}H NMR spectroscopy.

General Procedure I: the esterification of heteroaromatic carboxylic acids

To a 250 mL oven-dried round-bottomed flask, equipped with a magnetic stirring bar, was placed the carboxylic acid (72.90 mmol) and methanol (56 mL). To this was slowly added sulfuric acid (98%, 16 mL, 300.00 mmol). The reaction was stirred at room temperature for 72 h before $NaHCO_3$ (33.00 g, 400.00 mmol) in H_2O (140 mL) was added. The crude mixture was filtered and concentrated *in vacuo*. The organic phase was extracted with CH_2Cl_2 (3 x 60 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure.

General Procedure J: reduction of heteroaromatic esters to corresponding aldehydes

A 50 mL oven dried round bottomed flask was equipped with a magnetic stirring bar, placed under an atmosphere of argon (balloon) and charged with the relevant ester (7.25 mmol) and THF (20 mL). The contents of the flask were cooled to –83 °C. A THF solution of $LiAlH_4$ (2.5 M, 11 mL, 3.69 mmol) was slowly added over a 1 h period and the mixture was stirred for 1 h at this temperature. Acetic acid (99%, 1.0 mL, 16.40 mmol) was added slowly. The mixture was warmed to room temperature and HCl (0.5 M, 13 mL, 234.00 mmol) was added. The organic layer was extracted with chloroform (8 x 8.0 mL), washed with $NaHCO_3$ (10 mL), dried over $MgSO_4$ and the solvents were removed under reduced pressure.

General Procedure K: Reduction of pyridine ring using methyl iodide followed by hydrogenation over PtO_2

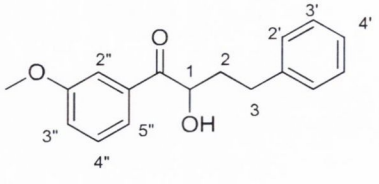
To a 10 mL oven-dried round bottomed flask, fitted with a magnetic stirring bar, was placed **348** (302.4 mg, 2.00 mmol, 1.0 equiv.), methyl iodide (125 μL. 2.00 mmol, 1.0 equiv.) and acetonitrile (8.0 mL). The flask was fitted with a condenser and placed under an atmosphere of argon (balloon). The mixture was heated under reflux for 24 h. Upon cooling, the solvent was removed under reduced pressure. To the crude mixture was added PtO_2 (23.0 mg, 0.05

mmol) and EtOH (8.0 mL). Hydrogenation was carried out by allowing the reaction to stir, at room temperature and at a hydrogen pressure of 30 mbar, for 48 h. The mixture was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude product was partitioned between EtOAc (2.0 mL) and water (2.0 mL) and extracted with EtOAc (3 x 2.0 mL), washed with brine (2.0 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*.

General procedure L: The cross coupling of aromatic aldehydes and ethyl pyruvate

A flame-dried screw-capped Schlenk tube equipped with a magnetic stirring bar was charged with K_2CO_3 (14.0 mg, 0.10 mmol) and evacuated. The base was then heated to 65 °C for 30 sec and subsequently cooled to room temperature under argon. After this procedure had been performed twice precatalyst **100** (18.0 mg, 0.05 mmol) was added. The solids were dried for an additional 1 h under high vacuum at room temperature. Dry $CHCl_3$ (500 μL) was added and the resulting mixture was stirred for 10 min at room temperature. To the orange suspension was added ethyl pyruvate (97 μL, 0.85 mmol, 1.7 equiv.) followed by the aromatic aldehyde (0.50 mmol, 1.0 equiv.). The Schlenk tube was sealed with a cap and the reaction mixture was stirred at 40 °C under argon. After 20 h, the solvent was removed under reduced pressure. The resulting mixture was subjected to column chromatography yielding the corresponding α-hydroxy-β-ketoester.

2-Hydroxy-1-(3-methoxyphenyl)-4-phenylbutan-1-one (281c)[93]



General procedure **G** was employed using 3-anisaldehyde (133 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexane-EtOAc, R_{fTLC} = 0.31) to afford **281c** (62.4 mg, 21%) as a colourless liquid.

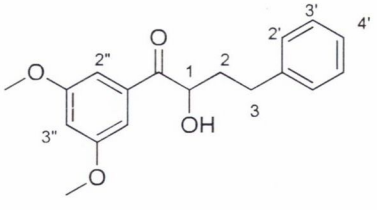
δ_H (400 MHz, $CDCl_3$): 1.79-1.90 (m, 1H, H-2b), 2.13-2.25 (m, 1H, H-2a), 2.76-2.97 (m, 2H, H-3) 3.73 (bs, 1H, OH), 3.85 (s, 3H, O-CH_3) 5.00-5.07 (m, 1H, H-1), 7.06-7.67 (m, 9H, H-2', H-2", H-3', H-3", H-4', H-4" and H-5").

δ_C (100 MHz, $CDCl_3$): 30.8, 37.3, 55.0, 71.8, 112.2, 120.5, 125.7, 127.8, 128.1, 129.0, 129.4, 134.2 (q), 140.5 (q), 159.5 (q), 201.4 (C=O).

ν_{max} (film)/cm^{-1}: 3027, 2937, 2937, 1702, 1685, 1488, 1432, 1260, 1110, 875, 783, 749, 697, 528.

HRMS (*m/z*-ESI): $[M-H]^-$ found 269.1169 ($C_{17}H_{17}O_3$ requires 269.1178).

1-(3,5-Dimethoxyphenyl)-2-hydroxy-4-phenylbutan-1-one (282c)



General procedure **G** was employed using 3,5-dimethoxybenzaldehyde (186.5 mg, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.25) to afford **282c** (174.9 mg, 53%) as a colourless liquid.

δ_H (400 MHz, $CDCl_3$): 1.81-1.87 (m, 1H, H-2b), 2.15-2.20 (m, 1H, H-2a), 2.81-2.89 (m, 2H, H-3) 3.73 (bs, 1H, OH), 3.80 (s, 6H, O-CH_3) 4.97 (m,

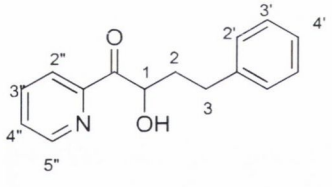
1H, H-1), 6.68 (app. t, 1H, H-3"), 6.91 (app. d, 2H, H-2"), 7.09-7.24 (m, 3H, H-2' and H-4'), 7.29-7.33 (m, 2H, H-3').

δ_C (100 MHz, $CDCl_3$): 30.8, 37.3, 55.1, 71.7, 105.9, 107.1, 125.7, 128.0, 128.3, 134.7 (q), 140.6 (q), 160.5 (q), 201.4 (C=O).

ν_{max} (film)/cm^{-1}: 3474, 3062, 3003, 2988, 2839, 1679, 1591, 1454, 1428, 1299, 1154, 1064, 1010, 924, 846, 749, 698, 673, 518.

HRMS (*m/z*-ESI): $[M-H]^-$ found 299.1286 ($C_{18}H_{19}O_4$ requires 299.1283).

2-Hydroxy-4-phenyl-1-(pyridin-2-yl)butan-1-one (283c)



General procedure **G** was employed using 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol). The crude mixture was purified by column chromatography (6:4 hexanes-EtOAc, R_{fTLC} = 0.28) to afford **283c** (108.7 mg, 41%) as a yellow liquid.

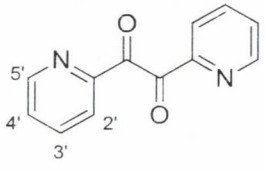
δ_H (400 MHz, $CDCl_3$): 1.96-2.09 (m, 1H, H-2b), 2.33-2.44 (m, 1H, H-2a), 2.08-2.96 (m, 2H, H-3, 4.16 (bs, 1H, OH), 5.32 (dd, 1H, J 7.8, J 3.3, H-1), 7.15-7.23 (m, 3H, H-3' and H-4'), 7.26 (d, 2H, J 7.4, H-2'), 7.50-7.55 (m, 1H, H-3"), 7.88 (app. t, 1H, H-4"), 8.05 (d, 1H, J 7.6, H-2"), 8.71 (d, 1H, J 4.8, H-5").

δ_C (100 MHz, $CDCl_3$): 31.1, 34.3, 80.2, 125.2, 126.7, 128.0, 129.1, 136.3, 138.1, 142.3 (q), 149.2, 152.4 (q), 200.5 (C=O).

ν_{max} (film)/cm^{-1}: 3469, 3062, 2862, 1708, 1603, 1517, 1496, 1262, 1178, 1076, 746, 697, 518.

HRMS (*m/z*-ESI): $[M + H]^+$ found 242.1184 ($C_{15}H_{16}NO_2$ requires 242.1181).

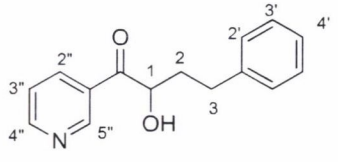
1,2-Di(pyridin-2-yl)ethane-1,2-dione (286)[187]



General procedure **G** was employed using 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol). The crude mixture was purified by column chromatography (5:1 hexanes-EtOAc, R_{fTLC} = 0.28) to afford **286** (28.0 mg, 12%) as an orange solid; m.p.: 155-156 °C (lit.,[187] 155-157 °C).

δ_H (400 MHz, $CDCl_3$): 7.11-7.18 (m, 1H, H-3'), 7.76-7.82 (m, 1H, H-4'), 7.84-7.88 (m, 1H, H-2'), 8.40-8.45 (m, 1H, H-5').

2-Hydroxy-4-phenyl-1-(pyridin-3-yl)butan-1-one (269c)



General procedure **G** was employed using 3-pyridinecarboxaldehyde (105 μL, 1.10 mmol). The crude mixture was purified by column chromatography (3:2 hexane-EtOAc, R_{fTLC} = 0.27) to afford **269c** (24.5 mg, 9%) as a yellow liquid.

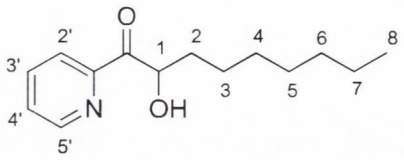
δ_H (400 MHz, $CDCl_3$): 1.86-1.93 (m, 1H, H-2b), 2.17-2.22 (m, 1H, H-2a), 2.72-2.93 (m, 2H, H-3), 3.72 (bs, 1H, OH), 5.02 (dd, 1H, J 1.9, 8.6, H-1), 7.19-7.34 (m, 5H, H-2', H-3' and H-4'), 7.43 (dd, 1H, J 4.8, 7.7, H-3"), 8.06 (d, 1H, J 7.7, H-2"), 8.83 (app. s, 1H, H-4"), 8.98 (s, 1H, H-5").

δ_C (100 MHz, $CDCl_3$): 30.1, 38.2, 72.0, 123.5, 125.9, 127.9, 128.2, 135.4 (q), 137.0, 139.5 (q), 149.2, 153.7, 200.5 (C=O).

ν_{max} (film)/cm^{-1}: 3358, 2928, 1708, 1681, 1623, 1585, 1513, 1363, 1244, 1178, 1073, 1027, 980, 911, 851, 729, 755, 699.

HRMS (*m/z*-ESI) : $[M + Na]^+$ found 264.1004 ($C_{15}H_{15}NO_2Na$ requires 264.1000).

2-Hydroxy-1-(pyridin-2-yl)nonan-1-one (287c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and octanal (172 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.25) to afford **287c** (248.5 mg, 96%) as a yellow oil.

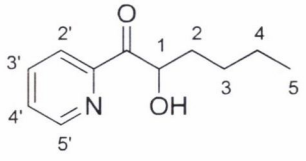
δ_H (400 MHz, $CDCl_3$): 0.79-0.87 (m, 3H, H-8), 1.15-1.31 (m, 8H, H-4, H-5, H-6 and H-7), 1.34-1.55 (m, 2H, H-3), 1.58-1.69 (m, 1H, H-2a), 1.89-2.00 (m, 1H, H-2b), 3.94 (bs, 1H, OH), 5.24 (dd, 1H, J 3.7, 7.9, H-1), 7.46-7.51 (m, 1H, H-4'), 7.82-7.88 (m, 1H, H-3'), 8.04 (d, 1H, J 7.7, H2'), 8.65 (d, 1H, J 4.7, H-5').

δ_C (100 MHz, $CDCl_3$): 14.1, 22.6, 25.1, 29.1, 29.4, 31.7, 34.8, 74.5, 123.0, 127.6, 137.1, 149.2, 151.6 (q), 202.2 (C=O).

ν_{max} (film)/cm^{-1}: 3058, 2925, 1702, 1697, 1488, 1432, 1260, 998, 875, 794, 643, 588, 528, 452, 224.

HRMS (*m/z*-ESI): $[M+H]^+$ found 236.1650 ($C_{14}H_{22}NO_2$ requires 236.1645).

2-Hydroxy-1-(pyridin-2-yl)hexan-1-one (292c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and pentanal (117 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.16) to afford **292c** (189.2 mg, 89%) as a yellow oil.

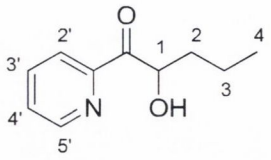
δ_H (600 MHz, $CDCl_3$): 0.83-0.94 (m, 3H, H-5), 1.13-1.58 (m, 4H, H-3 and H-4), 1.59-1.74 (m, 1H, H-2a), 1.92-2.06 (m, 1H, H-2b), 5.23 (m, 1H, H-1), 7.46-7.55 (m, 1H, H-4'), 7.83-7.93 (m, 1H, H-3'), 8.04 (d, 1H, J 7.8, H2'), 8.65 (d, 1H, J 4.1, H-5').

δ_C (100 MHz, $CDCl_3$): 13.5, 22.0, 26.8, 34.2, 74.1, 122.6, 127.2, 136.8, 148.4, 151.1 (q), 201.7 (C=O).

ν_{max} (film)/cm^{-1}: 3457, 3058, 2957, 1689, 1217, 669, 504, 445, 402, 333, 293, 158.

HRMS (*m/z*-ESI): $[M+H]^+$ found 194.1185 ($C_{11}H_{16}NO_2$ requires 194.1176).

2-Hydroxy-1-(pyridin-2-yl)pentan-1-one (293c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and butyraldehyde (100 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.21) to afford **293c** (185.3 mg, 94%) as a yellow oil.

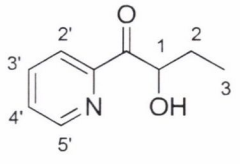
δ_H (400 MHz, $CDCl_3$): 0.79-0.87 (t, 3H, J 7.3, H-4), 1.36-1.68 (m, 3H, H-2a and H-3), 1.87-1.97 (m, 1H, H-2b), 3.90 (bs, 1H, OH), 5.24 (dd, 1H, J 3.7, 7.9, H-1), 7.46-7.52 (m, 1H, H-4'), 7.82-7.89 (m, 1H, H-3'), 8.04 (d, 1H, J 7.7, H2'), 8.65 (d, 1H, J 4.7, H-5').

δ_C (100 MHz, $CDCl_3$): 14.0, 18.5, 37.1, 74.5, 123.1, 127.7, 137.2, 148.9, 151.6 (q), 202.3 (C=O).

ν_{max} (film)/cm^{-1}: 3016, 1728, 1305, 1217, 608, 598, 532, 472, 423, 379, 337, 289, 208.

HRMS (*m/z*-ESI): $[M+Na]^+$ found 202.0828 ($C_{10}H_{13}NO_2Na$ requires 202.0838).

2-Hydroxy-1-(pyridin-2-yl)butan-1-one (294c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and propionaldehyde (80 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.24) to afford **294c** (167.2 mg, 92%) as a yellow oil.

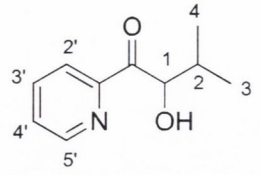
δ_H (400 MHz, $CDCl_3$): 0.92 (t, 3H, J 7.2, H-3), 1.64-1.76 (m, 1H, H-2a), 1.93-2.05 (m, 1H, H-2b), 3.90 (bs, 1H, OH), 5.16-5.20 (m, 1H, H-1), 7.43-7.49 (app. t, 1H, H-4'), 7.80-7.86 (app. t, 1H, H-3'), 8.02 (d, 1H, J 7.7, H2'), 8.63 (d, 1H, J 4.7, H-5').

δ_C (100 MHz, $CDCl_3$): 8.8, 27.5, 75.0, 122.6, 127.2, 136.8, 148.4, 151.1 (q), 201.7 (C=O).

ν_{max} (film)/cm^{-1}: 3059, 1704, 1351, 1089, 912, 794, 647, 557, 464, 408, 332, 291.

HRMS (*m/z*-ESI): $[M+H]^+$ found 166.0856 ($C_9H_{12}NO_2$ requires 166.0862).

2-Hydroxy-3-methyl-1-(pyridin-2-yl)butan-1-one (295c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and *iso*-butyraldehyde (100 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.26) to afford **295c** (90.7 mg, 46%) as a yellow oil.

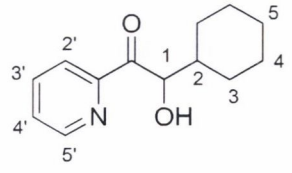
δ_H (600 MHz, $CDCl_3$): 0.78 (d, 3H, J 6.9, H-3), 1.10 (d, 3H, J 6.9, H-4), 2.32-2.41 (m, 1H, H-2), 3.80 (bs, 1H, OH), 5.14 (d, 1H, J 3.3, H-1), 7.46-7.51 (m, 1H, H-4'), 7.82-7.88 (m, 1H, H-3'), 8.04 (d, 1H, J 7.7, H-2'), 8.65 (d, 1H, J 4.7, H-5').

δ_C (100 MHz, $CDCl_3$): 15.2, 19.9, 31.9, 78.7, 122.9, 127.6, 137.2, 148.9, 151.8 (q), 202.3 (C=O).

ν_{max} (film)/cm^{-1}: 3340, 2928, 1692, 1464, 1023, 775, 742, 665, 566, 536, 522, 408, 364, 219.

HRMS (*m/z*-ESI): $[M+H]^+$ found 180.1030 ($C_{10}H_{14}NO_2$ requires 180.1019).

2-Cyclohexyl-2-hydroxy-1-(pyridin-2-yl)ethanone (296c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-pyridinecarboxaldehyde (105 μL, 1.10 mmol, 1.0 equiv.) and cyclohexanecarboxaldehyde (133 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.35) to afford **296c** (139.9 mg, 58%) as a yellow oil.

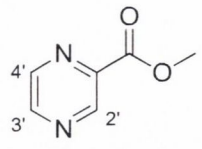
δ_H (600 MHz, $CDCl_3$): 0.98-1.53 (m, 6H, H-4, H-5), 1.55-1.83 (m, 4H, H-3), 1.93-2.04 (m, 1H, H-2), 3.82 (bs, 1H, OH), 5.09 (d, 1H, J 3.7, H-1), 7.46-7.51 (m, 1H, H-4'), 7.82-7.88 (m, 1H, H-3'), 8.04 (d, 1H, J 7.7, H2'), 8.65 (d, 1H, J 4.7, H-5').

δ_C (100 MHz, $CDCl_3$): 25.8, 25.9, 26.0, 26.4, 30.0, 41.8, 78.0, 122.9, 127.6, 137.2, 148.8, 151.9 (q), 202.2 (C=O).

ν_{max} (film)/cm^{-1}: 3498, 2925, 1693, 1583, 1300, 987, 744, 618, 526, 484, 364, 252, 211.

HRMS (*m/z*-ESI): $[M+H]^+$ found 220.1321 ($C_{13}H_{18}NO_2$ requires 220.1332).

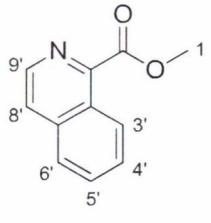
Methyl pyrazine-2-carboxylate (303)[155]



General procedure **I** was employed using pyrazinecarboxylic acid (10.10 g, 72.90 mmol). The crude mixture was purified by column chromatography (1:1 hexanes-EtOAc, R_{fTLC} = 0.41) to afford **303** (8.66 g, 86%) as a white solid; m.p.: 59-60 °C (lit. 57-58 °C).

δ_H (400 MHz, $CDCl_3$): 3.93 (s, 3H, O-CH_3), 8.62 (d, 1H, J 1.9, H-4'), 8.67 (d, 1H, J 1.9, H-3'), 9.20 (s, 1H, H-2').

Methyl isoquinoline-1-carboxylate (304)[188]

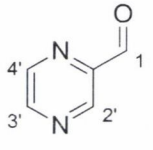


General procedure **I** was employed using *iso*quinoline-1-carboxylic acid (12.62 g, 72.90 mmol). The crude mixture was purified by column chromatography (1:1 hexane-EtOAc, R_{fTLC} = 0.38) to afford **304** (8.46 g, 62%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 4.09 (s, 3H, H-1), 7.65-7.76 (m, 2H, H-4' and H-5'), 7.82 (d, 1H, J 5.6, H-8'), 7.87 (d, 1H, J 8.2, H-6'), 8.63 (d, 1H, J 5.6, H-9'), 8.84 (d, 1H, J 8.2, H-3').

HRMS (*m/z*-ESI): $[M+Na]^+$ found 210.0523 ($C_{11}H_9NO_2Na$ requires 210.0525).

Pyrazine-2-carbaldehyde (297)[155]

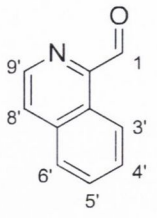


General procedure **J** was employed using **303** (1.00 g, 7.25 mmol). The crude mixture was purified by column chromatography (100% hexanes, R_{fTLC} = 0.24) to afford **297** (572.1 mg, 73%) as a yellow liquid.

δ_H (400 MHz, $CDCl_3$): 8.71 (d, 1H, J 1.8, H-4'), 8.75 (d, 1H, J 1.8, H-3'), 9.11 (s, 1H, H-2'), 10.09 (s, 1H, H-1).

HRMS (*m/z*-ESI): $[M+H]^+$ found 109.0393 ($C_5H_5N_2O$ requires 109.0396).

Isoquinoline-1-carbaldehyde (298)[189]

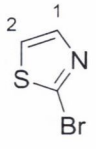


General procedure **J** was employed using **304** (1.36 g, 7.25 mmol). The crude mixture was purified by column chromatography (100% hexanes, R_{fTLC} = 0.58) to afford **298** (831.9 mg, 73%) as a yellow liquid.

δ_H (400 MHz, $CDCl_3$): 7.70-7.76 (m, 1H, H-5'), 7.83-7.90 (m, 1H, 4'), 7.95 (d, 1H, J 8.4, H-6'), 8.10 (d, 1H, H 8.6, H-8'), 8.30 (d, 1H, J 8.6, H-9'), 8.36 (d, 1H, J 8.4, H-3').

HRMS (*m/z*-ESI): $[M+H]^+$ found 158.0597 ($C_{10}H_8NO$ requires 158.0600).

2-Bromothiazole (305)[156]



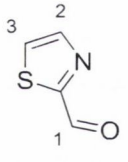
To a 25 mL oven dried round bottomed flask, equipped with a magnetic stirring bar and placed under an atmosphere of argon (balloon), was added thiazole (425.7 mg, 5.00 mmol) and distilled THF (10 mL). The contents of the flask were cooled to –70 °C. n-BuLi (4.0 mL,

10.00 mmol, 2.5 M in hexanes) was added slowly over a period of 30 min. The reaction was stirred at this temperature for 1 h. Carbon tetrabromide (485 μL, 5.00 mmol) in THF (10 mL) was added and the mixture was stirred at this temperature for 20 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl (4.0 mL), diluted with diethyl ether (10 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.22) to afford **305** (782.5 mg, 96%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.28 (d, 1H, J 3.6, H-1), 7.58 (d, 1H, J 3.6, H-2).

HRMS (*m/z*-ESI): $[M+H]^+$ found 163.9178 (C_3H_3BrNS requires163.9171).

Thiazole-2-carbaldehyde (299)[156]



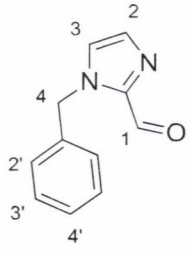
To a 25 mL oven dried round bottomed flask, equipped with a magnetic stirring bar and placed under an atmosphere of argon (balloon), was added n-BuLi (2.5 mL, 4.90 mmol, 2 M in hexanes) and ether (8.0 mL). The reaction was allowed to cool to –78 °C and **305** (780.0 mg, 4.75 mmol) was added dropwise over a period of 1 h. The mixture was stirred at this temperature for 1 h, and then a solution of DMF (348.2 mg, 4.75 mmol) in ether (5.0 mL) was added. The mixture was stirred for 1 h at –78 °C temperature and then warmed to –15° C and allowed to stir for 18 h. The reaction mixture was then extracted with 4 M HCl (4 x 2.0

mL), the aqueous layers were combined, cooled in an ice-bath, and neutralized with sodium bicarbonate. The aqueous layer was extracted with CH_2Cl_2 (4 x 35 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (system) afforded **299** (489.1 mg, 91%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.75 (d, 1H, J 3.1, H-2), 8.10 (d, 1H, J 3.1, H-3), 10.00 (s, 1H, H-1).

HRMS (*m/z*-ESI): $[M+H]^+$ found 114.0009 (C_4H_4NOS requires 114.0014).

1-Benzyl-1H-imidazole-2-carbaldehyde (300)[157]



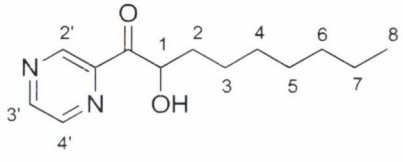
A 25 mL oven dried round bottomed flask was charged with lH-imidazole-2-carbaldehyde (240.0 mg, 2.40 mmol) and THF (5.0 mL). The contents of the flask were cooled to 0 °C and potassium carbonate (662.0 mg, 4.80 mmol) was added. At this temperature benzyl bromide (342 μL, 2.88 mmol) was added dropwise. The reaction was stirred at 60 °C for 12 h. Then the mixture was filtered and the solvent was evaporated under reduced pressure. The organic layer was extracted with EtOAc (3 x 2.0 mL), washed with water (2.0 mL) and brine (2.0 mL) and dried over anhydrous$MgSO_4$. The solvent was removed *in vacuo* and purification by

column chromatography (hexanes:EtOAc = 9:1) afforded **300** (276.4 mg, 62%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 5.56 (s, 2H, H-4), 7.09 (app. s, 1H, H-2), 7.15 (d, 2H, J 7.4, H-2'), 7.22-7.33 (m, 4H, H-3, H-3' and H-4').

HRMS (*m/z*-ESI): $[M+H]^+$ found 187.0875 ($C_{11}H_{11}N_2O$ requires 187.0871).

2-Hydroxy-1-(pyrazin-2-yl)nonan-1-one (310c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of **297** (118.9 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 µL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.20) to afford **310c** (244.3 mg, 94%) as an orange oil.

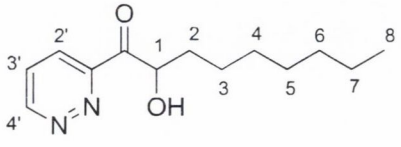
δ_H (400 MHz, $CDCl_3$): 0.88-0.89 (m, 3H, H-8), 1.21-1.31 (m, 8H, H-4, H-5, H-6, H-7), 1.36-1.56 (m, 2H, H-3), 1.58-1.68 (m, 1H, H-2a), 1.90-2.00 (m, 1H, H-2b), 5.24 (dd, 1H, J 3.6, 7.9, H-1), 8.65-8.67 (app. t, 1H, H3'), 8.80 (d, 1H, J 2.6, H-4'), 9.26 (s, 1H, H-2').

δ_C (100 MHz, $CDCl_3$): 14.1, 22.6, 25.1, 29.1, 29.3, 31.7, 34.8, 74.0, 143.5, 144.5, 145.8 (q), 148.4, 202.1 (C=O).

ν_{max} (film)/cm^{-1}: 3458, 2952, 2954, 1735, 1697, 1413, 1167, 939, 889, 725, 598, 546, 486, 352, 297, 238, 167.

HRMS (*m/z*-ESI): $[M+H]^+$ found 237.1601 ($C_{13}H_{21}N_2O_4$ requires 237.1603).

2-Hydroxy-1-(pyridazin-3-yl)nonan-1-one (311c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of pyridazine-3-carbaldehyde (115 μL, 1.10 mmol, 1.0 equiv.) and octanal (172 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.22) to afford **311c** (31.2 mg, 12%) as an orange oil.

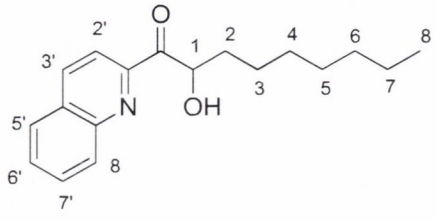
δ_H (400 MHz, $CDCl_3$): 0.81-0.90 (m, 3H, H-8), 1.18-1.34 (m, 8H, H-4, H-5, H-6, H-7), 1.35-1.61 (m, 2H, H-3), 1.67-1.79 (m, 1H, H-2a), 1.99-2.10 (m, 1H, H-2b), 2.29 (s, 1H, OH), 5.48 (dd, 1H, J 3.7, 7.8, H-1), 7.68-7.73 (m, 1H, H-3'), 8.18 (dd, 1H, J 1.8, 8.5, H-2'), 8.46 (dd, 1H, J 1.8, 5.3, H-4').

δ_C (100 MHz, $CDCl_3$): 14.1, 22.6, 25.2, 29.1, 29.4, 31.7, 35.0, 74.7, 125.8, 127.6, 153.5, 154.5 (q), 201.4 (C=O).

ν_{max} (film)/cm^{-1}: 3001, 1748, 1693, 899, 514, 499, 456, 382, 321, 276, 208, 164, 129.

HRMS (*m/z*-ESI): $[M+H]^+$ found 237.1604 ($C_{13}H_{21}N_2O_4$ requires 237.1598).

2-Hydroxy-1-(quinolin-2-yl)nonan-1-one (313c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 2-quinolinecarboxaldehyde (157.2 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.23) to afford **313c** (288.8 mg, 92%) as a yellow solid; m.p.: 39-41 °C.

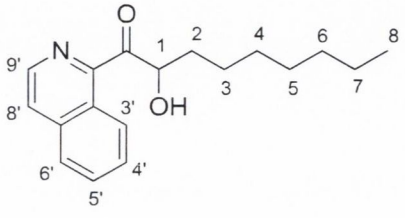
δ_H (400 MHz, $CDCl_3$): 0.82-0.94 (m, 3H, H-8), 1.21-1.40 (m, 10H, H-3, H-4, H-5, H-6 and H-7), 1.53-1.69 (m, 1H, H-2a), 1.73-1.86 (m, 1H, H-2b), 4.30 (bs, 1H, OH), 5.48 (dd, 1H, J 3.5, 8.1, H-1), 7.66-7.37 (m, 1H, H-6'), 7.78-7.86 (m, 1H, H-7'), 7.90 (d, 1H, J 8.4, H2'), 8.12-8.23 (m, 2H, H-5' and H-8'), 8.33 (d, 1H, J 8.4, H-3').

δ_C (100 MHz, $CDCl_3$): 13.6, 22.2, 24.7, 28.6, 28.8, 31.3, 34.7, 74.2, 118.5, 127.3, 128.6, 129.3 (q), 129.9, 130.0, 136.9, 146.3 (q), 150.6 (q), 201.9 (C=O).

ν_{max} (film)/cm^{-1}: 3303, 2919, 1703, 1281, 968, 899, 789, 721, 691, 623, 597, 488, 422, 356, 291, 142.

HRMS (*m/z*-ESI): $[M+H]^+$ found 286.1804 ($C_{18}H_{24}NO_2$ requires 286.1802).

2-Hydroxy-1-(isoquinolin-1-yl)nonan-1-one (314c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of **298** (157.2 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.25) to afford **313c** (248.0 mg, 79%) as a yellow solid; m.p.: 31-33 °C.

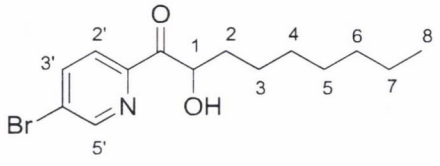
δ_H (400 MHz, $CDCl_3$): 0.81-0.88 (m, 3H, H-8), 1.19-1.34 (m, 8H, H-4, H-5, H-6, H-7), 1.39-1.63 (m, 2H, H-3), 1.72-1.84 (m, 1H, H-2a), 2.02-2.13 (m, 1H, H-2b), 4.15 (bs, 1H, OH), 5.45 (dd, 1H, J 3.9, 7.9, H-1), 7.62-7.70 (app. t, 1H, H-5'), 7.80-7.84 (app. t, 1H, H-3'), 7.89 (d, 1H, J 8.0, H6'), 8.11-8.20 (m, 2H, H-3' and H-8') 8.32 (d, 1H, J 8.6, H-9').

δ_C (100 MHz, $CDCl_3$): 14.1, 22.6, 25.1, 29.1, 29.3, 31.7, 35.1, 74.7, 118.9, 127.7, 129.0, 129.7 (q), 130.3, 130.5, 137.3, 146.8 (q), 151.1 (q), 202.5 (C=O).

ν_{max} (film)/cm^{-1}: 3305, 2915, 1703, 1261, 820, 500, 424, 398, 337, 292, 234, 154, 121.

HRMS (*m/z* - ESI): $[M+H]^+$ found 286.1806 ($C_{18}H_{24}NO_2$ requires 286.1802).

1-(5-Bromopyridin-2-yl)-2-hydroxynonan-1-one (320c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 5-bromopyridine-2-carboxaldehyde (204.6 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 μL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.45) to afford **320c** (276.5 mg, 80%) as a yellow solid; m.p.: 140-142 °C.

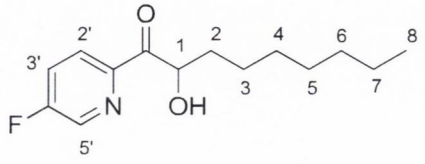
δ_H (400 MHz, $CDCl_3$): 0.81-0.91 (m, 3H, H-8), 1.18-1.33 (m, 8H, H-4, H-5, H-6, H-7), 1.33-1.55 (m, 2H, H-3), 1.57-1.67 (m, 1H, H-2a), 1.89-1.98 (m, 1H, H-2b), 3.58 (bs, 1H, OH), 5.25 (dd, 1H, J 3.7, 7.8, H-1), 7.93-7.8.03 (m, 2H, H-2' and H-3'), 8.73 (s, 1H, H-5').

δ_C (100 MHz, $CDCl_3$): 13.6, 22.2, 24.7, 28.5, 28.6, 28.7, 31.2, 73.7, 123.8, 139.5, 149.8, 177.9 (q), 201.3 (C=O).

ν_{max} (film)/cm^{-1}: 3058, 2851, 1635, 1278, 1197, 804, 703, 457, 432, 398, 331, 284, 172.

HRMS (*m/z*-ESI): $[M+H]^+$ found 314.0738 ($C_{14}H_{21}BrNO_2$ requires 314.0750).

1-(5-Fluoropyridin-2-yl)-2-hydroxynonan-1-one (321c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 5-fluoropyridine-2-carboxaldehyde (137.6 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 µL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.55) to afford **321c** (186.7 mg, 67%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 0.80-0.87 (m, 3H, H-8), 1.18-1.30 (m, 8H, H-4, H-5, H-6, H-7), 1.33-1.55 (m, 2H, H-3), 1.56-1.66 (m, 1H, H-2), 1.89-1.98 (m, 1H, H-2), 3.61 (bs, 1H, OH), 5.25 (dd, 1H, J 3.7, 7.8, H-1), 7.51-7.58 (m, 1H, H-3'), 8.14 (dd, 1H, J_{FH} 4.6, J 8.6, H-2'), 8.04 (d, 1H, J_{FH} 2.8, H-5').

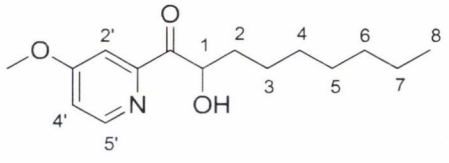
δ_C (100 MHz, $CDCl_3$): 14.1, 22.6, 25.1, 29.1, 29.3, 31.7, 35.0, 74.1, 123.8 (d, J_{FC} 18.4), 125.2 (d, J_{FC} 5.9), 137.6 (d, J_{FC} 24.4), 147.9 (q, d, J_{FC} 4.5), 160.25 (q), 162.9 (q), 202.93 (C=O).

δ_F (376 MHz, $CDCl_3$): -118.0 (m, 1F, F-4').

ν_{max} (film)/cm^{-1}: 3009, 1758, 1691, 1431, 1205, 733, 684, 601, 572, 511, 451, 398, 254, 196.

HRMS (*m/z*-ESI): $[M+H]^+$ found 254.1552 ($C_{14}H_{21}FNO_2$ requires 254.1551).

2-Hydroxy-1-(4-methoxypyridin-2-yl)nonan-1-one (322c)



General procedure **H** was employed using precatalyst **100** (14.5 mg, 0.04 mmol) with the addition of 4-methoxypyridine-2-carboxaldehyde (150.9 mg, 1.10 mmol, 1.0 equiv.) and octanal (172 µL, 1.10 mmol, 1.0 equiv.). The crude mixture was purified by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.32) to afford **322c** (148.9 mg, 51%) as a yellow oil.

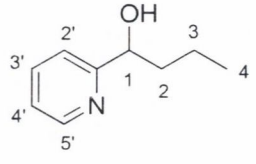
δ_H (400 MHz, $CDCl_3$): 0.81-0.90 (m, 3H, H-8), 1.22-1.31 (m, 8H, H-4, H-5, H-6, H-7), 1.35-1.56 (m, 2H, H-3), 1.61-1.76 (m, 1H, H-2a), 1.90-2.00 (m, 1H, H-2b), 3.92 (s, 3H, O-CH_3), 5.17 (dd, 1H, J 3.7, 7.8, H-1), 6.98-7.02 (m, 1H, H-4'), 7.58 (s, 1H, H-2'), 8.46 (d, 1H, J 6.3, H-5').

δ_C (100 MHz, $CDCl_3$): 14.0, 22.5, 24.6, 28.9, 31.6, 33.8, 34.8, 55.4, 75.0, 108.3, 114.1, 149.9, 153.7 (q), 166.7 (q), 201.9 (C=O).

ν_{max} (film)/cm^{-1}: 2925, 1737, 1592, 1036, 747, 577, 424, 418, 397, 342, 294, 222, 186, 161.

HRMS (*m/z*-ESI): $[M+H]^+$ found 266.1753 ($C_{15}H_{24}NO_3$ requires 266.1751).

1-(Pyridin-2-yl)butan-1-ol (349)[190]

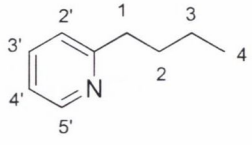


A 50 mL oven-dried round-bottomed flask, equipped with a magnetic stirring bar, was charged with **294c** (825.0 mg, 5.00 mmol, 1.0 equiv.), hydrazine hydrate (740 μL, 20.00 mmol, 4.0 equiv., 85% solution) and ethylene glycol (25 mL). The flask was fitted with a condenser and heated to 140 °C for 2 h. NaOH (800.0 mg, 20.00 mmol, 4.0 equiv.) was added and the flask was fitted with a Dean Stark apparatus. The reaction was heated to 220 °C and allowed to react for 24 h. The reaction was cooled to room temperature and diluted with H_2O (20 mL). The organic layer was extracted with CH_2Cl_2 (2 x 10 mL), washed with brine (10 mL) and H_2O (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. Purification by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.21) afforded the by-product **349** (219.3 mg, 29%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 0.92 (t, 3H, J 7.6, H-4), 1.37-1.49 (m, 2H, H-3), 1.63-1.83 (m, 2H, H-2), 4.70-4.77 (m, 1H, H-1), 7.16-7.22 (app. t, 1H, H-3'), 7.22-7.25 (m, 1H, H-2'), 7.64-7.71 (m, 1H, H-2'), 8.53 (d, 1H, J 4.9, H-5').

HRMS (*m/z*-ESI): $[M+H]^+$ found 152.1069 ($C_9H_{14}NO$ requires 152.1070).

2-Butylpyridine (350)[191]

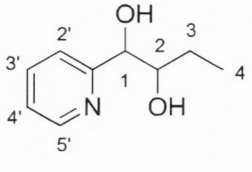


350 was synthesised and isolated as a by-product under the reaction conditions discussed above *i.e.* for the synthesis of **349**. Purification by column chromatography (4:1 hexanes-EtOAc, R_{fTLC} = 0.39) afforded the by-product **350** (216.2 mg, 32%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 0.92 (t, 3H, J 7.3, H-4), 1.31-1.42 (m, 2H, H-3), 1.64-1.74 (m, 2H, H-2), 2.77 (t, 2H, J 7.6, H-1) 7.07 (dd, 1H, J 5.0, 7.8, H-4'), 7.12 (d, 1H, H-2'), 7.53-7.59 (m, 1H, H-3'), 8.50 (d, 1H, J 5.2, H-5').

HRMS (*m/z* - ESI): $[M+Na]^+$ found 158.0950 ($C_9H_{13}NNa$ requires 158.0946).

1-(Pyridin-2-yl)butane-1,2-diol (345)



A 5 mL oven dried round bottom flask, fitted with a magnetic stirring bar, was charged with **294c** (165.0 mg, 1.00 mmol), PtO_2 (11.5 mg, 0.05 mmol) and EtOH (2.0 mL). The contents of the flask were placed under an atmosphere of hydrogen (balloon) and allowed to react for 18 h. The mixture was filtered through a pad of celite and the solvent reduced in vacuo. EtOAc (2.0 mL) and H_2O (2.0 mL) were added and the organic layer was extracted was extracted with EtOAc (3 x 1.0 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (9:1 hexanes-EtOAc, R_{fTLC} = 0.12) afforded **345** (162.2 mg, 97%) as a yellow oil.

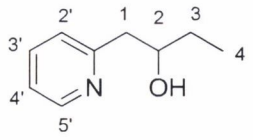
δ_H (400 MHz, $CDCl_3$): 0.93 (t, 3H, J 7.2, H-3), 1.32-1.41 (m, 1H, H-3), 1.54-1.66 (m, 1H, H-3), 3.70-3.80 (m, 1H, H-2), 4.73 (d, 1H, J 4.5, H-1), 5.16-55.2 (m, 1H, H-1), 7.19-7.26 (m, 1H, H-4'), 7.32 (d, 1H, J 7.8, H-2'), 7.65-7.72 (m, 1H, H-3'), 8.53 (d, 1H, J 4.4, H-5').

δ_C (100 MHz, $CDCl_3$): 10.1, 25.6, 75.0, 76.1, 121.9 122.6, 122.8, 137.0, 148.1, 159.6 (q).

ν_{max} (film)/cm^{-1}: 3208, 3104, 1459, 867, 721, 609, 555, 494, 413, 382, 366, 303, 275, 197.

HRMS (*m/z*-ESI): $[M+H]^+$ found 168.1027 ($C_9H_{14}NO_2$ requires 168.1019).

1-(Pyridin-2-yl)butan-2-ol (348)



A 100 mL oven dried round bottom flask was fitted with a magnetic stirring bar and placed under an atmosphere of argon (balloon). To the flask was added **294c** (825.0 mg, 5.00 mmol, 1.0 equiv.), *para*-toluenesulfonyl hydrazide (931.2 mg, 5.00 mmol, 1.0 equiv.) and EtOH (50 mL). The flask was fitted with a condenser and the reaction was heated at reflux for 24 h. The contents of the flask were cooled to 0 °C and $NaBH_4$ (2.84g, 15.0 equiv.) was added. The reaction was heated at reflux for 48 h. Upon being cooled to room temperature, the mixture was filtered and the solvent was removed under reduced pressure. EtOAc (10 mL) and water (10 mL) were added and the crude mixture was extracted with EtOAc (3 x 5.0 mL), washed with brine (5.0 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography afforded **348** (703.0 mg, 93%) as yellow oil.

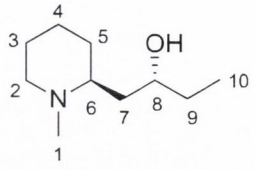
δ_H (600 MHz, $CDCl_3$): 0.98 (t, 3H, J 7.7, H-4), 1.47-1.64 (m, 2H, H-3), 2.78-2.85 (m, 1H, H-1), 2.88-2.95 (m, 1H, H-1), 3.90-3.99 (m, 1H, H-2), 4.92 (bs, 1H, OH), 7.09-7.16 (m, 2H, H-2' and H-4'), 7.57-7.62 (app. t, 1H, H-3'), 8.45 (app. s, 1H, H-5').

δ_C (100 MHz, $CDCl_3$): 9.9, 29.8, 42.9, 72.5, 121.3, 123.6, 136.6, 148.4, 160.3 (q).

ν_{max} (film)/cm^{-1}: 3338, 2964, 1436, 1160, 1035, 743, 550, 489, 421, 387, 303, 255, 196.

HRMS (*m/z*-ESI): $[M]^+$ found 152.1069 ($C_9H_{14}NO$ requires 152.1070).

1-(1-Methylpiperidin-2-yl)butan-2-ol (337a)[159]

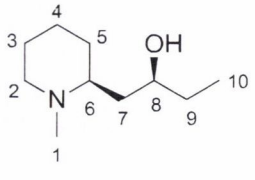


General procedure **K** was employed. The crude mixture was purified by column chromatography (1:1 hexanes-EtOAc, R_{fTLC} = 0.14) to afford **337a** (166.2 mg, 48%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 0.96 (t, 3H, J 6.8, H-10), 1.18-1.50 (m, 5H, H-3a, H-4a, H-5a and H-7), 1.52-1.54 (m, 2H, H-9), 1.55-1.57 (m, 3H, H-3b, H-4b and H-5b), 2.45 (s, 3H, H-1), 2.48-2.53 (m, 2H, H-2), 3.01-3.08 (m, 1H, H-6), 3.71-3.76 (m, 1H, H-8).

HRMS (*m/z*-ESI): $[M+H]^+$ found 172.1704 ($C_{10}H_{22}NO$ requires 172.1700).

1-(1-Methylpiperidin-2-yl)butan-2-ol (337b)[159]

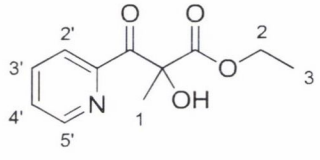


General procedure **K** was employed. The crude mixture was purified by column chromatography (1:1 hexanes-EtOAc, R_{fTLC} = 0.10) to afford **337a** (164.5 mg, 47% as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 0.94 (t, 3H, J 7.2, H-10), 1.31-1.52 (m, 9H, H-3, H-4, H-5a, H-7 and H-9), 1.67-1.70 (m, 1H, H-5b), 2.42 (s, 3H, H-1), 2.53-2.72 (m, 2H, H-2), 2.81-2.95 (m, 1H, H-6), 3.76-3.79 (m, 1H, H-8).

HRMS (*m/z*-ESI): $[M+H]^+$ found 172.1703 ($C_{10}H_{22}NO$ requires 172.1701).

Ethyl 2-hydroxy-2-methyl-3-oxo-3-(pyridin-2-yl)propanoate (365)



Prepared according to the general procedure **L**, using 2-pyridinecarboxaldehyde (48 μL, 0.50 mmol). Purificiation by column chromatography (hexanes-Et_2O, 9:1. R_{fTLC} = 0.18) afforded **365** (102.2 mg, 92%) as a yellow oil.

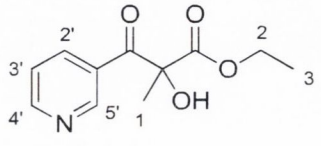
δ_H (600 MHz, $CDCl_3$): 1.10 (t, 3H, J 7.0, H-3), 1.70 (s, 3H, H-1), 4.17 (q, 2H, J 7.0, H-2), 5.31 (bs, 1H, OH), 7.49-7.56 (m, 1H, H-4'), 7.89-7.98 (m, 1H, H-3'), 8.13 (d, 1H, J 8.0, H-2'), 8.61 (d, 1H, J 4.6, H-5').

δ_C (100 MHz, $CDCl_3$): 13.4, 20.6, 61.1, 78.6 (q), 123.2, 127.2, 137.4, 147.7, 150.6 (q), 172.1 (C=O), 193.5 (C=O).

ν_{max} (film)/cm^{-1}: 3462, 2985, 1752, 1710, 1570, 1585, 1441, 1301, 1275, 1237, 1133, 1095, 941, 705, 684.

HRMS (*m/z* - ESI): $[M+Na]^+$ found 246.0741 ($C_{11}H_{13}NO_4Na$ requires 246.0742).

Ethyl 2-hydroxy-2-methyl-3-oxo-3-(pyridin-3-yl)propanoate (366)



Prepared according to the general procedure **L**, using 3-pyridinecarboxaldehyde (48 μL, 0.50 mmol). Purificiation by column chromatography (hexanes-Et_2O, 1:1. R_{fTLC} = 0.38) afforded **366** (101.0 mg, 91%) as an orange oil.

δ_H (600 MHz, $CDCl_3$): 1.19 (t, 3H, J 7.0, H-3), 1.76 (s, 3H, H-1), 4.27 (q, 2H, J 7.0, H-2), 4.81 (bs, 1H, OH), 7.39 (dd, 1H, J 8.2, 4.8, H-3'), 8.32 (d, 1H, J 8.2, H-2'), 8.80 (app. s, 1H, H-4'), 9.23 (s, 1H, H-5').

δ_C (100 MHz, $CDCl_3$): 13.4, 22.9, 62.4, 79.5 (q), 123.0, 129.1, 136.6, 150.1, 152.8 (q), 171.9 (C=O), 194.3 (C=O).

ν_{max} (film)/cm^{-1}: 3092, 2986, 2939, 1698, 1587, 1420, 1370, 1267, 1232, 1160, 1107, 1028, 1014, 983, 859, 701.

HRMS (*m/z* - ESI): $[M+H]^+$ found 224.0930 ($C_{11}H_{14}NO_4$ requires 224.0923).

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