An Exploration of Novel Intermediates in N-Heterocyclic Carbene (NHC) Catalysis

A thesis submitted for the degree of Doctor of Philosophy

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This thesis is dedicated to my parents George & Adele.

For fostering my curiosity,

And teaching me to never give up.

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me, unless otherwise acknowledged, during the period of 2015-2019 and has not been presented for examination for any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publication from which they are derived.

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Acknowledgements

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To Rachel, we got thrown in the deep end together at the beginning of this journey and somehow managed to keep each other afloat – something I will always be thankful to you for. I know I can always come to you for advice with chemistry (or life) and you'll help me in any way that you can. I also know that without you, this thesis would not be as good. I, too, will miss our ideas sessions and lab banter, even if I eventually drove you to move labs. We've been through a lot together, and even though we'll go our separate ways, I'm sure I've made a life-long friend.

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Publications and Presentations

Publications

5. Enantioselective N-heterocyclic Carbene Catalysis Exploiting Imine Umpolung

Jared E. M. Fernando, Yuji Nakano, Changhe Zhang and David W. Lupton

Angew. Chem. Int. Ed. **2019**, *58*, 4007.

4. Quantification of the Michael-Acceptor Reactivity of α,β-Unsaturated Acyl Azolium Ions

Alison Levens, Feng An, Jared E. M. Fernando, Armin R. Ofial, David W. Lupton and Herbert Mayr

Top. Catal. **2018**, *61*, 585.

3. Enantioselective N-heterocyclic Carbene Catalysis via the Dienyl Acyl Azolium

Rachel M. Gillard, Jared E. M. Fernando and David W. Lupton

Angew. Chem. Int. Ed. **2018**, *57*, 4712.

2. N-Heterocyclic Carbene Catalyzed Transformylation

Jared E. M. Fernando, Alison Levens, Daniel Moock and David W. Lupton

Synthesis **2017**, *49*, 3505.

1. All-carbon N-heterocyclic Carbene-catalyzed (3+2) Annulation using Donor-Acceptor Cyclopropanes

Lisa Candish, Rachel M. Gillard, Jared E. M. Fernando, Alison Levens and David W. Lupton

Isr. J. Chem. **2016**, *56*, 522.

Presentations

Oral Presentation: Investigations into NHC catalyzed Imine Umpolung.

RACI 43rd Annual Synthesis Symposium, Melbourne, Victoria, Australia. **2018**

Poster Presentation: NHC catalyzed imine umpolung: Enantioselective intermolecular aza-Stetter reaction.

The 16th Belgian Organic Synthesis Symposium (BOSS XVI), Brussels, Belgium. **2018**

Poster Presentation: Kinetic Analysis of the α,β-Unsaturated Acyl Azolium and Related Intermediates

RACI Centenary Congress, Melbourne, Victoria, Australia. **2017**

Poster Presentation: An N-Heterocyclic Carbene Catalyzed Transformylation

RACI 41st Annual Synthesis Symposium, Melbourne, Victoria, Australia. **2016**

Poster Presentation: An N-Heterocyclic Carbene Catalyzed Transformylation

MonCat Symposium, Melbourne, Victoria, Australia. **2016**

Abstract

Central to the discovery of new methodologies is the elucidation and exploration of novel reactive intermediates. Two novel intermediates in N-heterocyclic Carbene (NHC) catalysis that have been discovered in the past 5 years are the aza-Breslow intermediate and the dienyl acyl azolium. The aza-Breslow intermediate is an iminyl equivalent of the Breslow intermediate, where umpolung of an imine has occurred, allowing bond formation with electrophiles at the formerly electrophilic carbon. At the time that this thesis was presented, only 3 examples of the aza-Breslow intermediate's use in synthesis existed, and none of them were enantioselective or intermolecular. The dienyl acyl azolium is a higher unsaturated homologue of the α,β-unsaturated acyl azolium that shows enhanced electrophilicity at the acyl-, β- and δ-positions. Prior to the studies presented herein, only one use of the dienyl acyl azolium with activation of the δ-position had been previously reported.

The first chapter of this thesis provides an overview of the discovery of the Breslow intermediate and its use in synthesis. Following this, a number of other commonly used NHC intermediates that have been discovered more recently are discussed. Both umpolung intermediates and normal polarity intermediates as well as their uses in synthesis are reviewed. Chapter one also discloses a brief introduction into both the aza-Breslow intermediate and the dienyl acyl azolium.

The second chapter details the discovery of an enantioselective intermolecular aza-Stetter reaction. The reaction proceeds between benzoyl protected imines and chromanones via imine umpolung. The optimization and generality of the reaction are explored as well as the utility of the aza-Stetter products. The discovery of an aza-benzoin reaction is also briefly discussed.

The third chapter presents a mechanistic investigation into the aza-Stetter reaction that is discussed in chapter two. Evidence for an aza-Stetter pathway is presented along with a kinetic study into the order of the reaction. The turnover limiting step of the reaction mechanism is also examined through the use of competition studies.

The fourth chapter involves an investigation into an NHC catalyzed (4+3) annulation for the synthesis of cycloheptenes via the dienyl acyl azolium. This reaction was originally attempted with cyclopropanes, however, the trimethylsilyl enol ethers of β-ketoesters proved to be the successful

nucleophile. Whilst a (4+3) reaction was discovered, it was marred by poor yields and enantioselectivity. However, during the course of these investigations, a (4+2) annulation was discovered that eventually led to the first enantioselective use of the dienyl acyl azolium.

Chapter five details experimental procedures and spectroscopic data of all the compounds utilized in chapters 2-4.

Abbreviations

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
Cat.	Catalyst
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(dimethylamino)sulfur trifluoride
DBU	1,8-diazabicy clo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DIBAL-H	Diisobutyl aluminium hydride
DIPEA	Diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
E	Electrophile
EWG	Electron withdrawing group
ee	Enantiomeric excess
e.r.	Enantiomeric ratio
eq.	Equation
equiv.	Equivalent

ESI	Electrospray ionization
Et	Ethyl
h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass-spectrometry
IMes	1,3-bis(trimethylphenyl)imidazole-2-ylidene
iPr	*iso*-propyl
IR	Infrared
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
KO^{t}Bu	Potassium *tert*-butoxide
LRMS	Low resolution mass spectroscopy
Me	Methyl
Mes	Mesityl (2,4,6-trimethylphenyl)
min	Minutes
M.P.	Melting point
MS	Molecular sieves
N	Nucleophilicity parameter
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PG	Protecting group

Ph	Phenyl
PivOH	Pivalic acid
PMP	*para*-methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
*p*TSA	*para*-toluenesulfonic acid
R_f	Retention factor
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
^{t}Bu	*tert*-butyl
^{t}BuOH	*tert*-butanol
temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TMSF	Trimethylsilyl fluoride
Tol	Tolyl
Ts	Tosyl

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Chapter 1: Common Reactive Intermediates in N-Heterocyclic Carbene Catalysis

1.1 Background

1.1.1 Introduction to N-Heterocyclic Carbenes

In recent years, the chemistry of N-heterocyclic carbenes (NHCs) has expanded significantly, evident by the growing number of unique transformations possible through their use.[1-2] NHCs have not only become versatile ligands for transition metals[1], but have also emerged as powerful organic catalysts.[2]

Carbenes are a structurally diverse family of carbon containing neutral compounds that possess a divalent carbon atom with six valence electrons.[1] They can exist in two possible states, the triplet or singlet state which are characterised by the distribution of the two non-bonding electrons at the sp^2-hybridised carbene centre. NHCs exist in the singlet state with a formally sp^2-hybridised lone pair and an unoccupied p-orbital at the carbene centre.[1, 3] The presence of at least one nitrogen atom flanking the carbene center provides π-electron donation into the vacant p-orbital as well as inductive withdrawal of electron density by virtue of the more electronegative nitrogen atoms. This is known as the "push-pull" effect which leads to an increase in the singlet-triplet energy gap, serving to stabilise NHCs in the singlet state (Figure 1).

Within the area of organocatalysis, some of the most commonly utilised NHC scaffolds are the imidazolylidene, triazolylidene, and thiazolylidene (Figure 1).[2] Whilst this is not an exhaustive list, these different scaffolds allow NHCs to be tailored to a number of different reactions by varying the heteroatoms, substitution pattern, ring size, and the *N*-substituents. This makes NHCs highly useful catalysts for reaction discovery and subsequent use in the synthesis of complex natural products.[4]

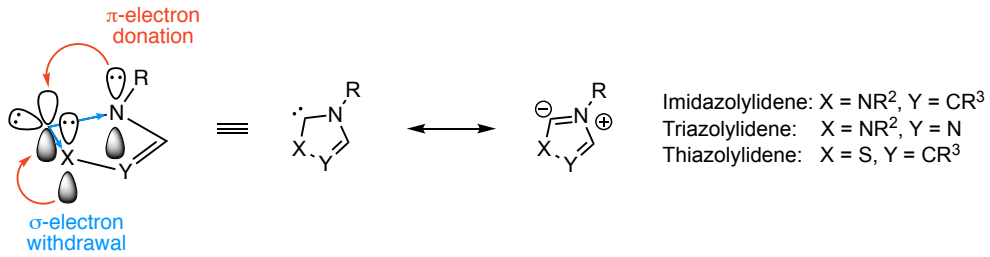
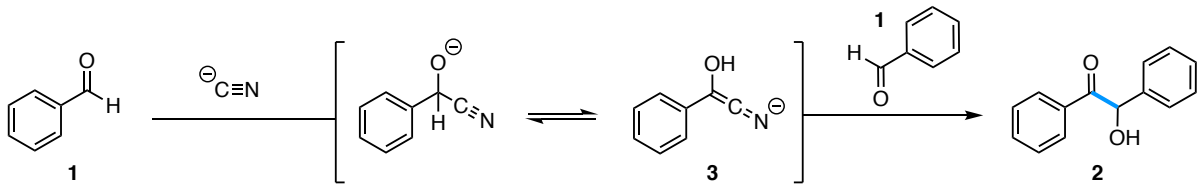


Figure 1: Common NHC motifs

1.2 The Breslow Intermediate

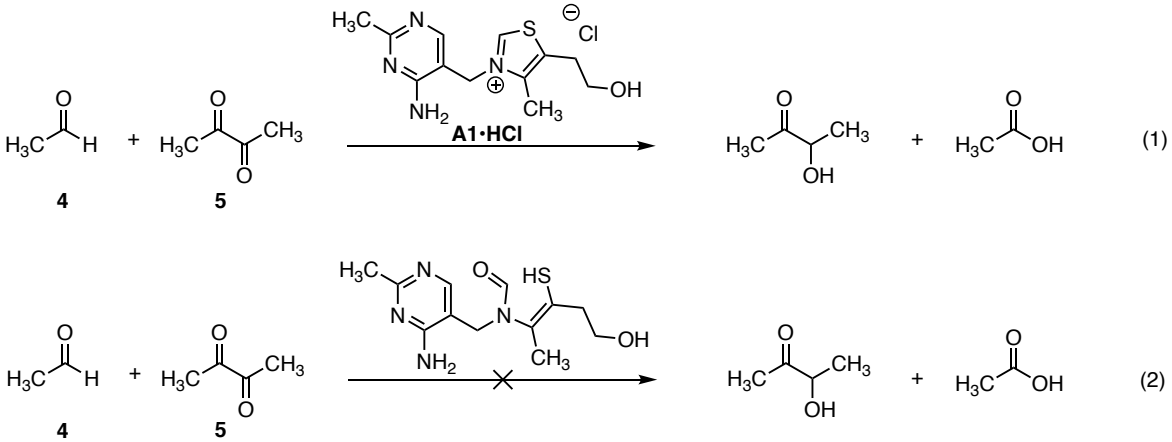
1.2.1 The elucidation of the benzoin condensation mechanism

The benzoin condensation was first disclosed in 1832 by Wöhler and Liebig,[5] this report described the dimerization of aldehydes (i.e. **1**) to give α-hydroxyketones **2** using cyanide anions (Scheme 1). The mechanism of this reaction was not determined for another 70 years, when Lapworth proposed intermediate **3**, in which the cyanide anion enables reversal of the innate polarity of the carbonyl. This allows addition to another equivalent of aldehyde to render the benzoin product **2**.[6]



Scheme 1: Cyanide anion catalysed benzoin reaction

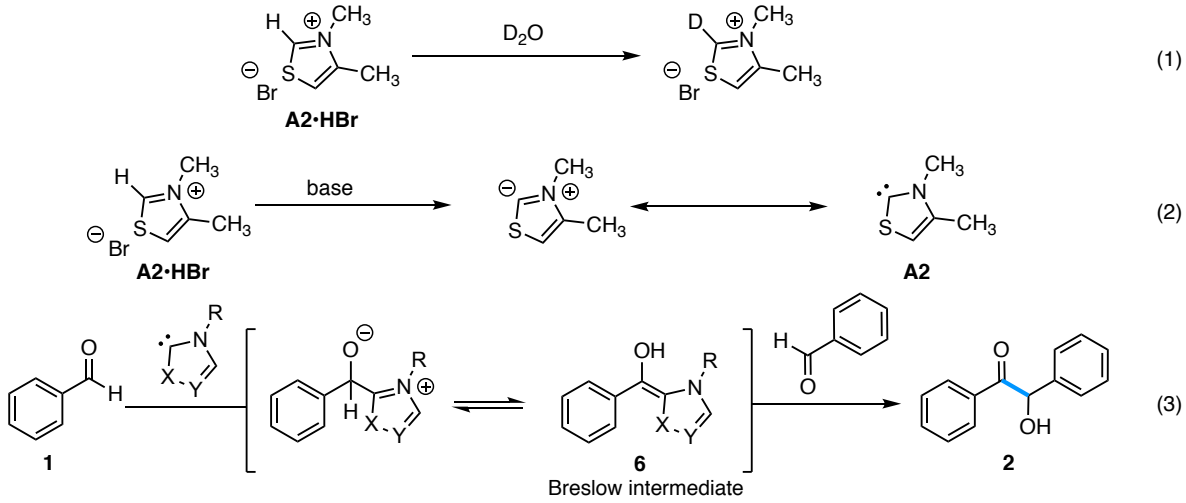
It was not until 1943 that Ukai and co-workers discovered that cyanide anions could be replaced with thiazolium salts, giving the same products in a catalytic fashion.[7] This led to the realisation that the catalytic activity of thiamine **A1•HCl**[i] was due to the thiazolium moiety. In 1954, Mizuhara demonstrated that thiamine could catalyse a number of reactions that had been observed in biological systems such as the benzoin condensation between acetaldehyde **4** and butandione **5** (Scheme 2, eq. 1), and that thiamine **A1•HCl** showed no activity when the thiazolium ring component had been opened (Scheme 2, eq. 2).[8]



Scheme 2: Thiazolium catalysed benzoin reaction

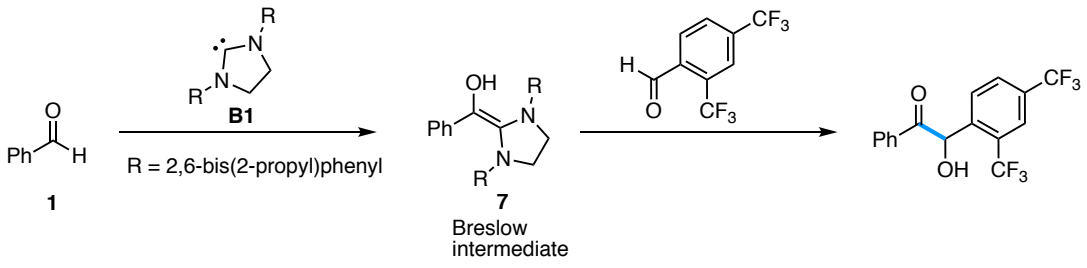
[i] Herein, naming of NHC catalysts follows this notation where the letter denotes the scaffold and the number denotes the *N*-substituent, done chronologically by order of appearance, which is followed by the counter ion.

These studies paved the way for the elucidation of the mechanism of the benzoin condensation. After showing that the C2 proton of thiazoliums (i.e. **A2•HBr**) rapidly exchanged with deuterium (Scheme 3, eq. 1), Breslow proposed a mechanism that involved initial carbene formation (Scheme 3, eq. 2). The carbene **A2** could then invert the polarity of the previously electrophilic carbon to yield a nucleophilic centre, in a similar fashion to the cyanide anion mechanism proposed by Lapworth (Scheme 3, eq. 3).[9] The enamine-like intermediate, now known as the Breslow intermediate (i.e. **6**), has since been invoked in numerous NHC catalysed transformations in the years since its initial discovery.



Scheme 3: Mechanistic insights into the benzoin reaction and discovery of the Breslow intermediate

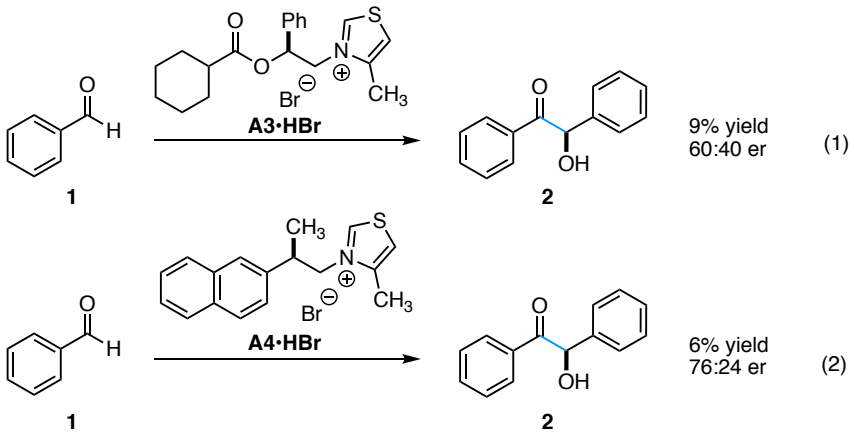
It was not until 2012 that the mechanism presented by Breslow was conclusively proven. Using carbenes with a saturated backbone (i.e. **B1**), Berkessel and co-workers were able to isolate and unambiguously characterise the Breslow intermediate (i.e. **7**) for the first time (Scheme 4).[10] Subsequently, they were able to demonstrate that these isolated intermediates react as acyl anion equivalents and participate in benzoin reactions, as predicted by Breslow.



Scheme 4: Isolation of the Breslow intermediate

1.2.2 The enantioselective benzoin reaction

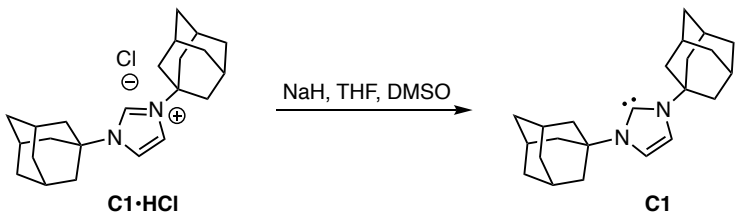
The use of NHC catalysts, in place of cyanide anions, enabled the development of enantioselective variants of the benzoin condensation. In 1966, Sheehan and co-workers reported the first enantioselective variant using chiral thiazolium salt **A3•HBr** (Scheme 5, eq. 1), albeit with modest e.r. (60:40).[11] The reaction was hindered by poor yields and only modest levels of enantioselectivity, however the authors later reported improved, albeit still modest, enantioselectivity using a modified thiazolium salt **A4•HBr** bearing a naphthyl moiety (Scheme 5, eq. 2).[12]



Scheme 5: The first enantioselective benzoin reactions

1.2.3 The first isolatable NHCs

After Breslow's mechanistic insights, NHCs were considered highly reactive intermediates that were impossible to isolate. Pioneering work by the groups of Wanzlick[13] and Öfele[14] demonstrated the synthesis and isolation of the first ligated NHC species. However, the area of NHC catalysis remained relatively inactive until the early 1990's when Arduengo and co-workers isolated the first crystalline carbene.[15] They achieved this via synthesis of a bisadamantyl imidazolium chloride **C1•HCl** followed by deprotonation to provide the carbene species **C1** (Scheme 6). This structure was then verified unequivocally by single crystal X-ray diffraction and showed thermal stability in the absence of oxygen and water.



Scheme 6: Generation of the crystalline NHC

Arduengo's synthesis triggered a renewed interest in the area of N-heterocyclic carbenes. After the initial report, many other groups reported the successful synthesis of stable carbenes. Most notably, perhaps, were the syntheses of the mesityl substituted imidazole **C2** (IMes) by Arduengo in 1992[16] and the triphenyl triazole **D1** (TPT) by Enders in 1996 (Figure 2).[17] These catalysts remain amongst the most commonly used and successful NHC catalysts today.

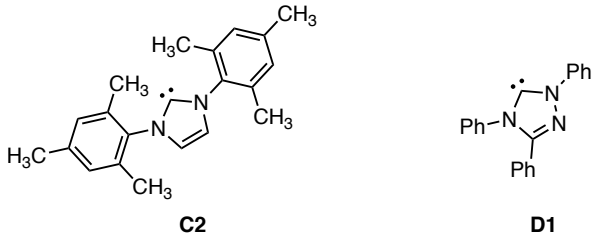


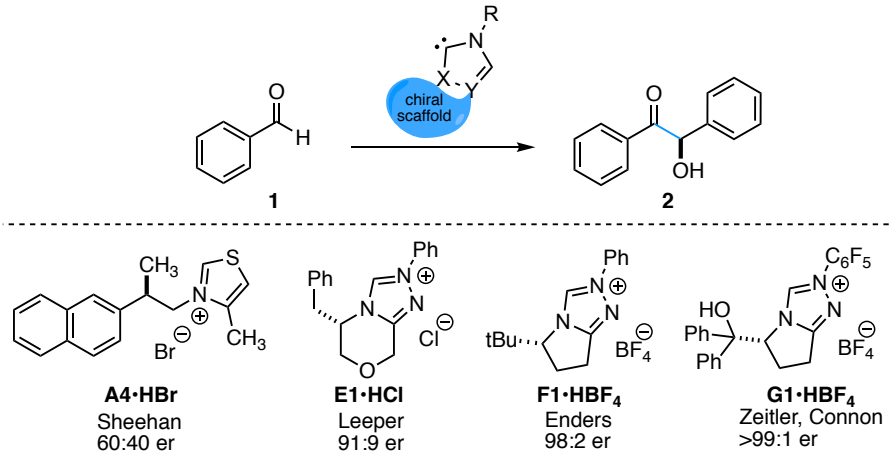
Figure 2: IMes **C2** and TPT **D1** catalysts synthesised by Arduengo and Enders respectively

With this sudden surge in the synthesis and characterisation of stable NHCs,[15, 16, 17] the challenges of highly enantioselective reactions could be addressed through modifications to the catalyst that were previously thought to be unfeasible.

1.2.4 Improvements to the enantioselective benzoin reaction

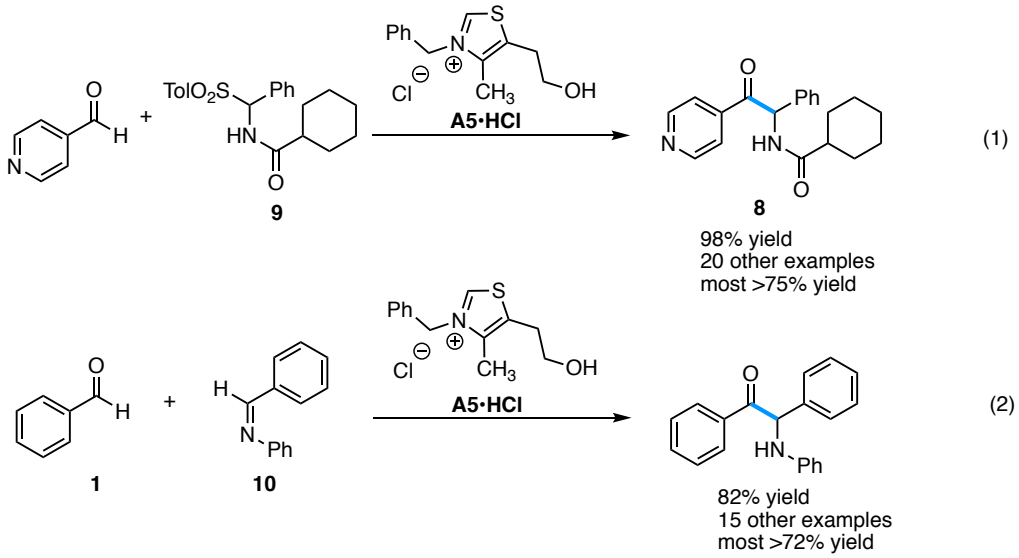
The next major advances came after Arduengo's isolation of bench stable carbenes. A variety of homochiral NHCs were then synthesised by several groups, leading to vast improvements in the enantioselectivity of carbene catalysed benzoin reactions (Scheme 7). The groups of Leeper[18] and Enders[19] greatly improved the enantioselectivity through use of chiral triazoliums **E1•HCl** and **F1•HBF$_4$**, allowing e.r. values of up to 91:9 and 98:2 respectively. Bicyclic triazoliums were key to the success of these reactions. Using nitrogen in place of sulphur allows for an additional bulky substituent that helps to block the approach of the electrophile from one direction in the bond forming transition state.[18] The annulation not only prevents competitive deprotonation at the C3 position[19], but also provides a rigid structure for the transfer of stereochemical information by blocking attack from one face of the Breslow intermediate. The additional nitrogen atom in the heterocycle also provides extra charge stabilisation, resulting in triazolium ylides being more stable than thiazolium ylides.[20] Scheidt also highlighted the sensitivity of acyl anion chemistry to slight changes in the sterics and electronics of the heteroazolium core (*vide infra*).[21-22] More recently, the use of a hydrogen bonding atom on the chiral portion of the catalyst, along with an electron deficient *N*-substituent such as pentafluorophenyl

(i.e. **G1•HBF$_4$**), has allowed the synthesis of essentially one enantiomer of the α-hydroxy ketone product **2**.[23]



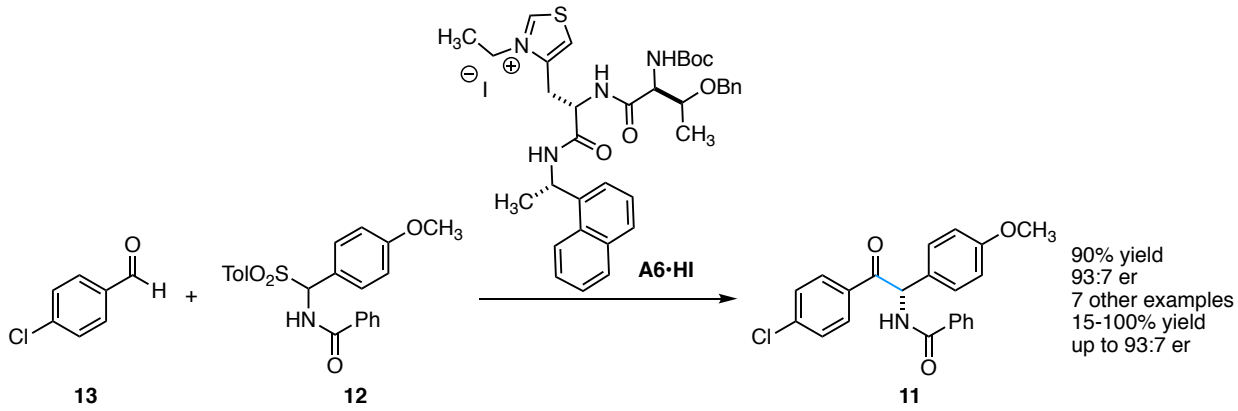
Scheme 7: Improvements to chiral catalysts in the enantioselective benzoin reaction

Benzoin reactions can also be achieved using imines as a secondary electrophile to afford α-amino ketones (i.e. **8**). The first report on this subject was by Murry, Frantz *et al.* in 2001 (Scheme 8, eq. 1) using imines generated in situ from α-amido sulfones (i.e. **9**).[24] Generation of α-amino ketone **8** was achieved in excellent yield using thaizolium catalyst **A5•HCl**. This work has since been extended to include less activated imines such as *N*-phenyl imines (i.e. **10**), reported by You and co-workers (Scheme 8, eq. 2).[25]



Scheme 8: NHC catalysed cross benzoin reactions utilising imines

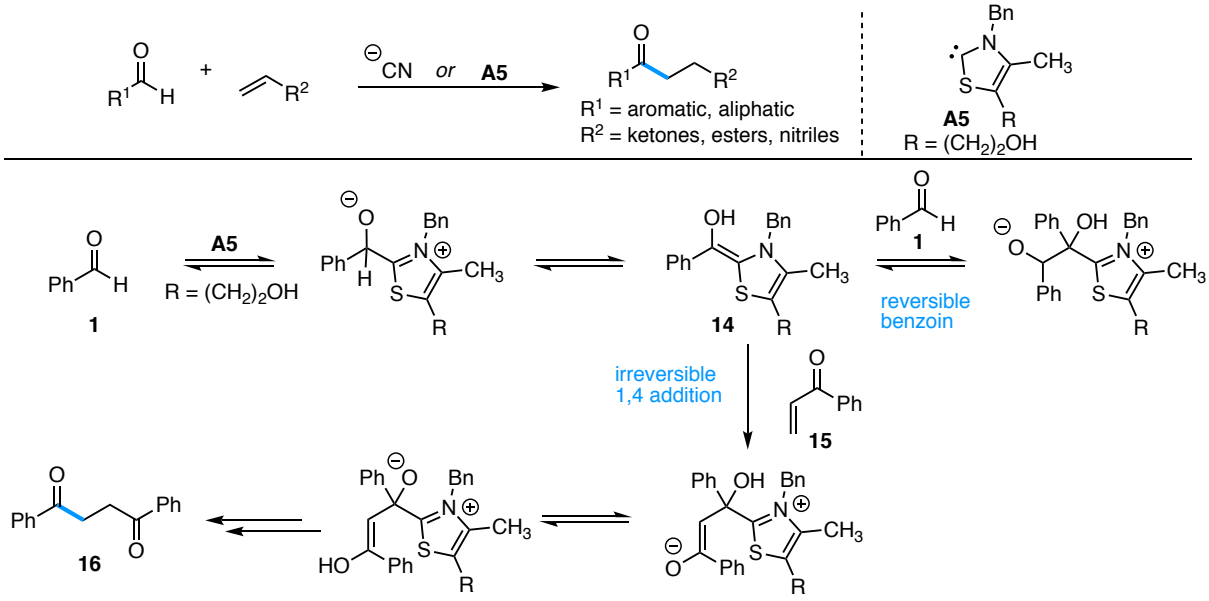
Miller and co-workers used thiazolium **A6•HI** bearing a peptide derivative to synthesise similar α-amino ketones (i.e. **11**) from α-amido sulfones (i.e. **12**) and benzaldehyde derivatives (i.e. **13**) with good enantiocontrol (Scheme 9).[26] However, in some cases racemisation of the products was observed, leading to a trade-off between yield and enantioselectivity.



Scheme 9: Enantioselective cross benzoin reaction utilising imines

1.2.5 The Stetter reaction

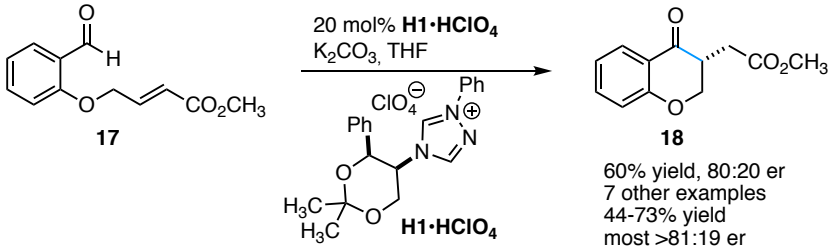
The reversible nature of the benzoin reaction[27] allows irreversible 1,4-addition of the Breslow intermediate (i.e. **14**) to Michael acceptors (i.e. **15**, Scheme 10). In 1976, Stetter and co-workers reported the first example of such a reaction, allowing the synthesis of a range of 1,4-dicarbonyl compounds (i.e. **16**).[27-28] Both aromatic and aliphatic aldehydes were compatible in the reaction, and could be coupled with a variety of different Michael acceptors including α,β-unsaturated ketones, esters and nitriles.



Scheme 10: The Stetter reaction allowed by the reversible nature of the benzoin reaction

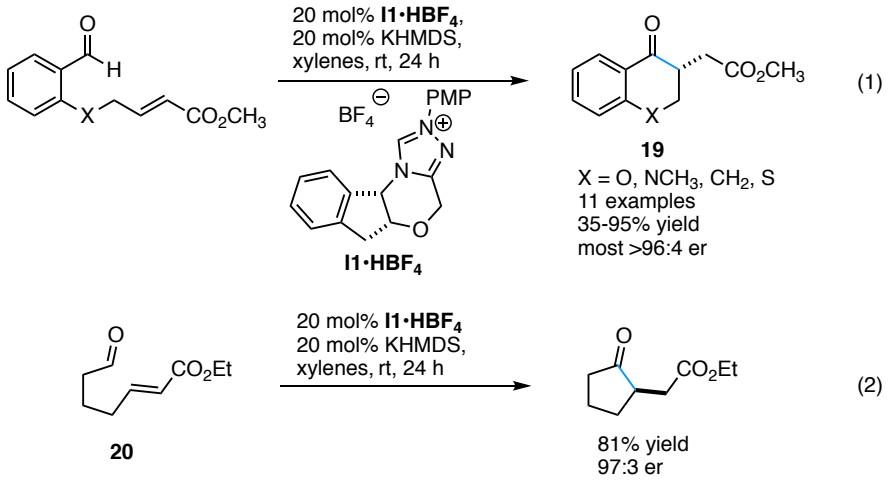
1.2.6 The intramolecular enantioselective Stetter reaction

As β-substituted Michael acceptors often resulted in diminished yields, early attempts at an asymmetric intermolecular Stetter reaction were met with limited success.[22, 27] Consequently, the first enantioselective variants of the Stetter reaction were intramolecular. The first intramolecular Stetter reaction was reported by Ciganek in 1995,[29] and following this, Enders developed the first asymmetric variant (Scheme 11).[30] The cyclisation of salicylaldehyde derivatives bearing tethered α,β-unsaturated esters (i.e. **17**) afforded chromanones (i.e. **18**) with good yields and enantiocontrol (up to 85:15 er).



Scheme 11: The first enantioselective intramolecular Stetter reaction by Enders

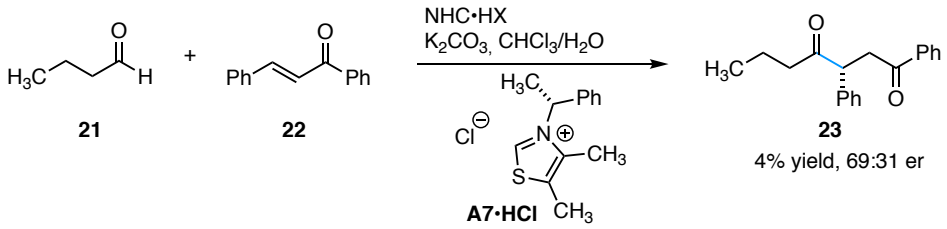
Following this first report, Rovis and co-workers were able to improve upon these results through the use of chiral triazolium **I1•HBF$_4$**, with enantioselectivities up to 97:3 e.r. achieved (Scheme 12, eq. 1).[31] They found the large, rigid indanol based ring system to be highly efficient in the transfer of stereochemistry. Interestingly, this transformation could also be achieved using a range of different tethers to synthesis heterocycles containing oxygen, nitrogen and sulphur (i.e. **19**).[31] In subsequent studies, Rovis was able to broaden the scope of this transformation with aliphatic aldehydes (i.e. **20**) with a variety of different tethered acceptors (Scheme 12, eq. 2) including various esters, amides, and ketones,[32-33] various tether lengths,[34] substrates with pre-existing stereocentres,[35] substrates that result in quaternary centres[36] and substrates that require control of diastereoselectivity.[22, 37] The groups of Bach,[38] Miller,[39] and Tomioka[40] all reported asymmetric intramolecular Stetter reactions, however, none were able to match the enantioselectivities of the examples reported by Rovis.



Scheme 12: Improvements to the enantioselective intramolecular Stetter reaction

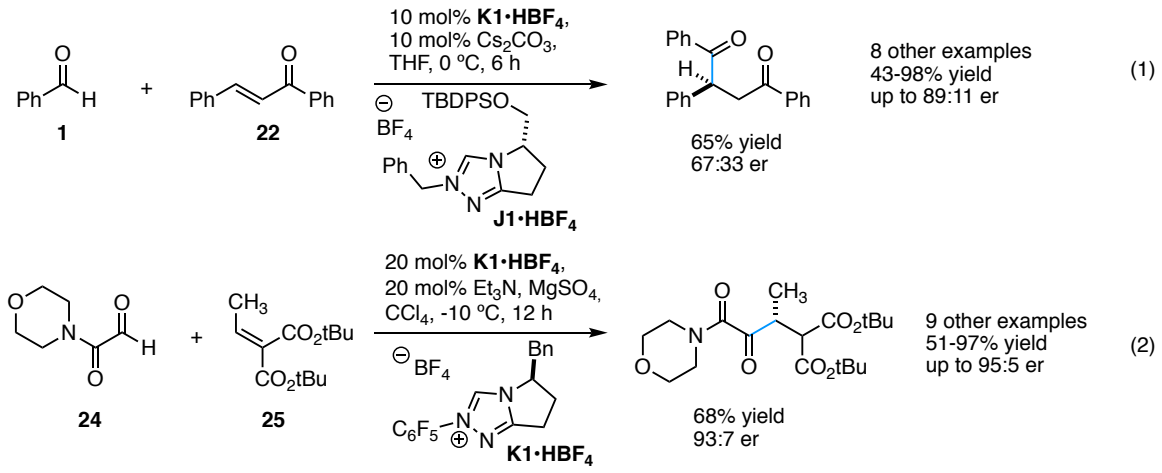
1.2.7 The intermolecular enantioselective Stetter reaction

The enantioselective intermolecular Stetter reaction was first reported by Enders in 1999 (Scheme 13).[41-42] Using a chiral thiazolium catalyst **A7•HCl**, Enders was able to couple aliphatic aldehyde **21** with chalcone **22** to give 1,4-diketone **23** with modest enantioselectivty (69:31 er) and only 4% yield.



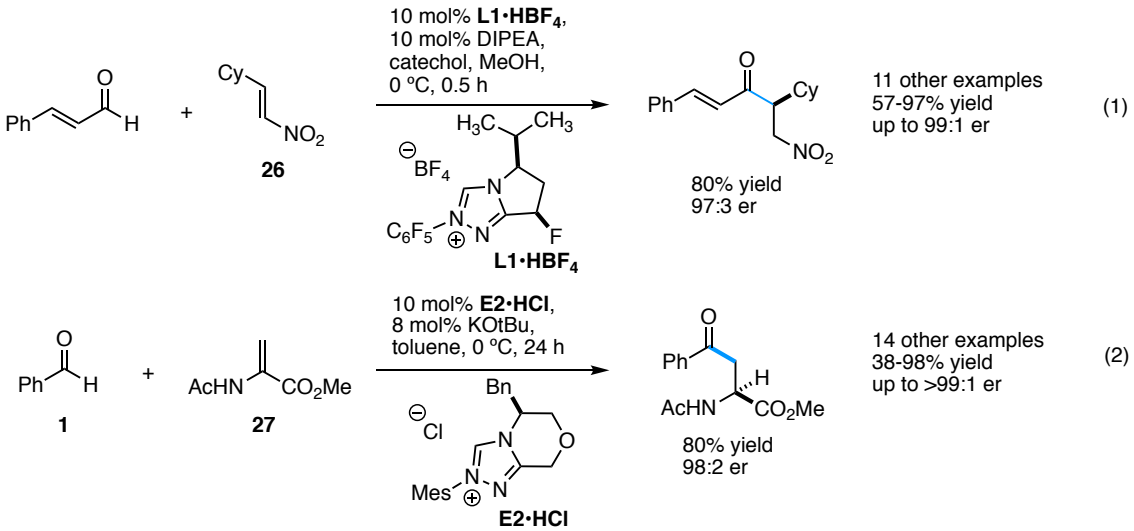
Scheme 13: The first enantioselective intermolecular Stetter reaction by Enders

It was not until 2008, however, that the groups of Enders[43] and Rovis[44] produced the first highly enantioselective examples of intermolecular Stetter reactions. As discussed in section 1.2.4, Bicyclic triazoliums were key to the improvement. Enders and colleagues described the coupling of aromatic aldehydes (i.e. **1**) with chalcones (i.e. **22**) in good yields with promising enantioselectivity of up to 89:11 er (Scheme 14, eq. 1). Concurrently with Enders' work, the Rovis group demonstrated the Stetter reaction between glyoxamides (i.e. **24**) and α,β-unsaturated malonates (i.e. **25**) with good yields and excellent levels of stereocontrol (Scheme 14, eq. 2).



Scheme 14: The first highly enantioselective intermolecular Stetter reactions

In 2011, Rovis discovered the coupling of nitroalkenes (i.e. **26**) with various aldehydes (Scheme 15, eq. 1).[45-46] Electron poor NHC **K1•HBF$_4$** bearing a fluorine atom was found to increase yields and selectivity by increasing interactions between the developing positive charge on the Breslow intermediate and the developing negative charge on the nitroalkene.[47] Interestingly, Rovis found that using catechol as an additive dramatically increased the reactivity of the system.[45] This likely accelerates the proton transfer that is necessary to form the Breslow intermediate, which has previously been demonstrated to be the rate determining step in the intramolecular reaction.[48] Glorius and colleagues discovered an intermolecular Stetter reaction with aryl aldehydes (i.e. **1**) and acrylates bearing an α-acetamide group **27** (Scheme 15, eq. 2).[49] Contrary to previous approaches, this transformation relies on an asymmetric protonation event, rather than enantioselective addition of the acyl anion to an electrophile, to generate chiral products.



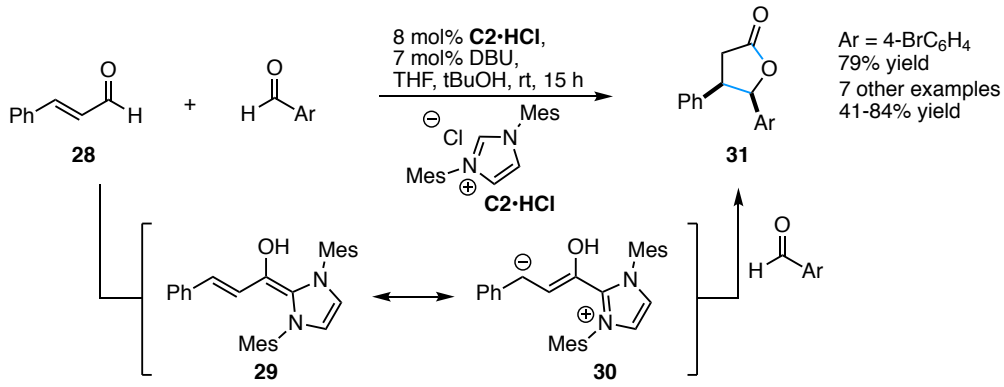
Scheme 15: Enantioselective NHC catalysed Stetter reactions with activated coupling partners

The benzoin and Stetter reactions have been extensively studied since they were first discovered, and a multitude of synthetically useful variations are now achieved through the use of NHC catalysts.[50-51] These reactions are possible by the polarity inversion of aldehydes and the generation of the Breslow intermediate. However, there are a number of other umpolung intermediates that have been discovered in NHC catalysis more recently.

1. 3 Common Umpolung Intermediates in NHC Catalysis

1.3.1 Discovery of the homoenolate

In 2004, the groups of Bode and Glorius concurrently disclosed reactions that proceed via the NHC homoenolate (i.e. 30, Scheme 16).[52-53] NHC addition to α,β-unsaturated aldehydes (i.e. **28**) provides the Breslow intermediate **29**, which can tautomerise to the NHC homoenolate **30**. Thus, the formerly electrophilic β-carbon has undergone an umpolung event, enabling reactions with electrophiles at this position. Bode and Glorius were both able to exploit this novel intermediate in the synthesis of substituted γ-butyrolactones **31** in good yields. The homoenolate has since been invoked in numerous NHC catalysed reactions.[54-56]

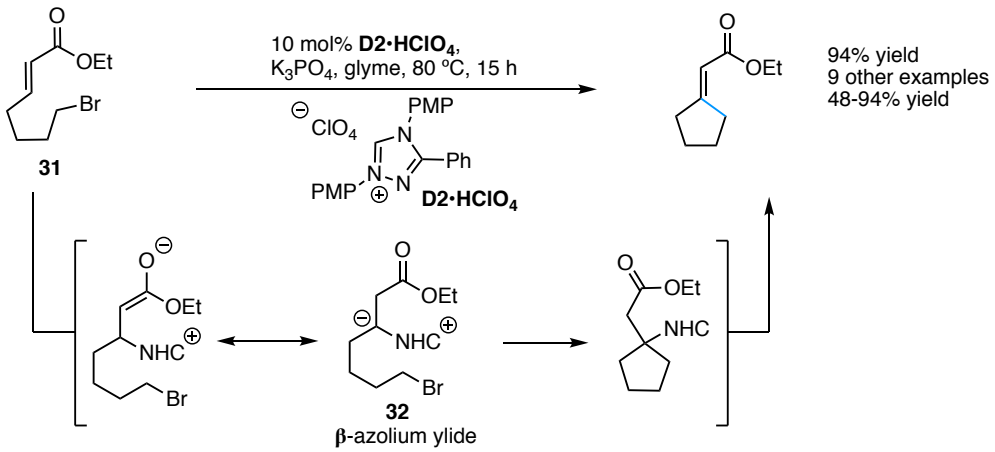


Scheme 16: Discovery and use of the homoenolate in the synthesis of γ-lactones

1.3.2 Discovery of the β-azolium ylide

Whilst NHCs usually add to carbonyls, in 2006 Greg Fu reported the conjugate addition of an NHC to α,β-unsturated ester **31** to form an intermediate now known as the β-azolium ylide (i.e. **32**).[57] Much like the homoenolate, this intermediate has undergone an umpolung event at the β-position, allowing for functionalisation with electrophiles. Fu and co-workers were able to affect the cyclisation of unsaturated esters **31** with tethered halides or other leaving groups. Preliminary mechanistic studies

suggest that the reaction occurs via umpolung of the Michael acceptor, rather than initial displacement of the alkyl halide. Since its initial discovery, enantioselective reactions utilising the β-azolium ylide have also been realised.[58-59]

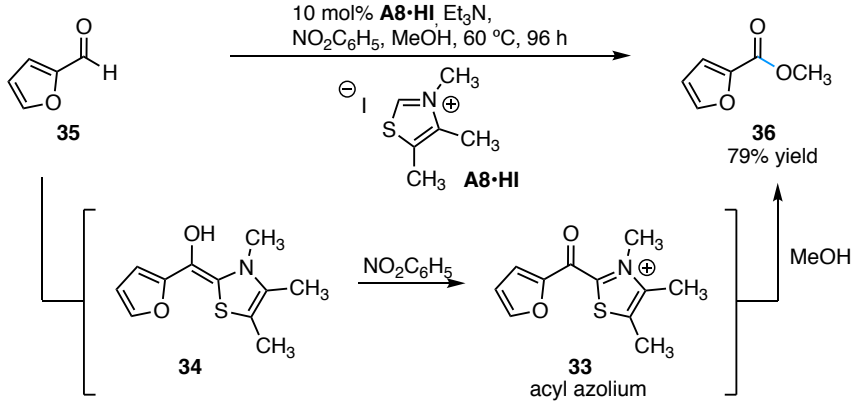


Scheme 17: First use of the β-azolium ylide by Fu

1.4 Normal Polarity Intermediates in NHC Catalysis

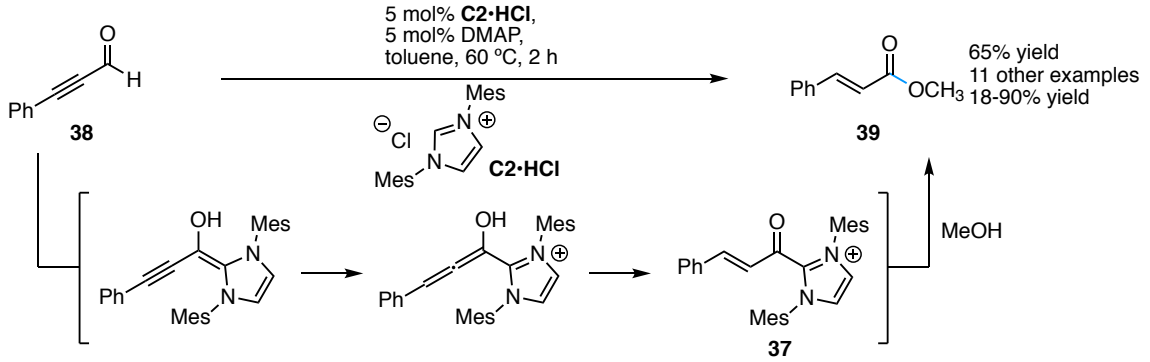
1.4.1 The acyl azolium and α,β-unsaturated acyl azolium

The ability of NHCs to reverse the innate polarity of carbonyl containing compounds has been known for years. However, the chemistry of normal polarity intermediates has received significantly less attention. One such intermediate is the acyl azolium (i.e. **33**), which displays enhanced electrophilicity at the acyl position, relative to the parent carbonyl compound. First postulated by Castells in 1977, the acyl azolium **33** is formed via oxidation of the Breslow intermediate **34**, enabling conversion of furfural **35** to the corresponding methyl ester **36**.[60]



Scheme 18: First use of the acyl azolium intermediate

It was not until 1999 that the α,β-unsaturated acyl azolium **37** was proposed by Townsend in the biosynthesis of Clavulaninic acid.[61-62] Despite its significance, catalytic use of the α,β-unsaturated variant of the acyl azolium didn't develop until the mid 2000s. In 2006, Zeitler showed that ynals (i.e. **38**) could be used to generate the α,β-unsaturated acyl azolium **37**, which then underwent esterification reactions,[63] generating a variety of esters (i.e. **39**) with *E*-selectivity up to 95:5 (Scheme 19).



Scheme 19: First use of the α,β-unsaturated acyl azolium intermediate

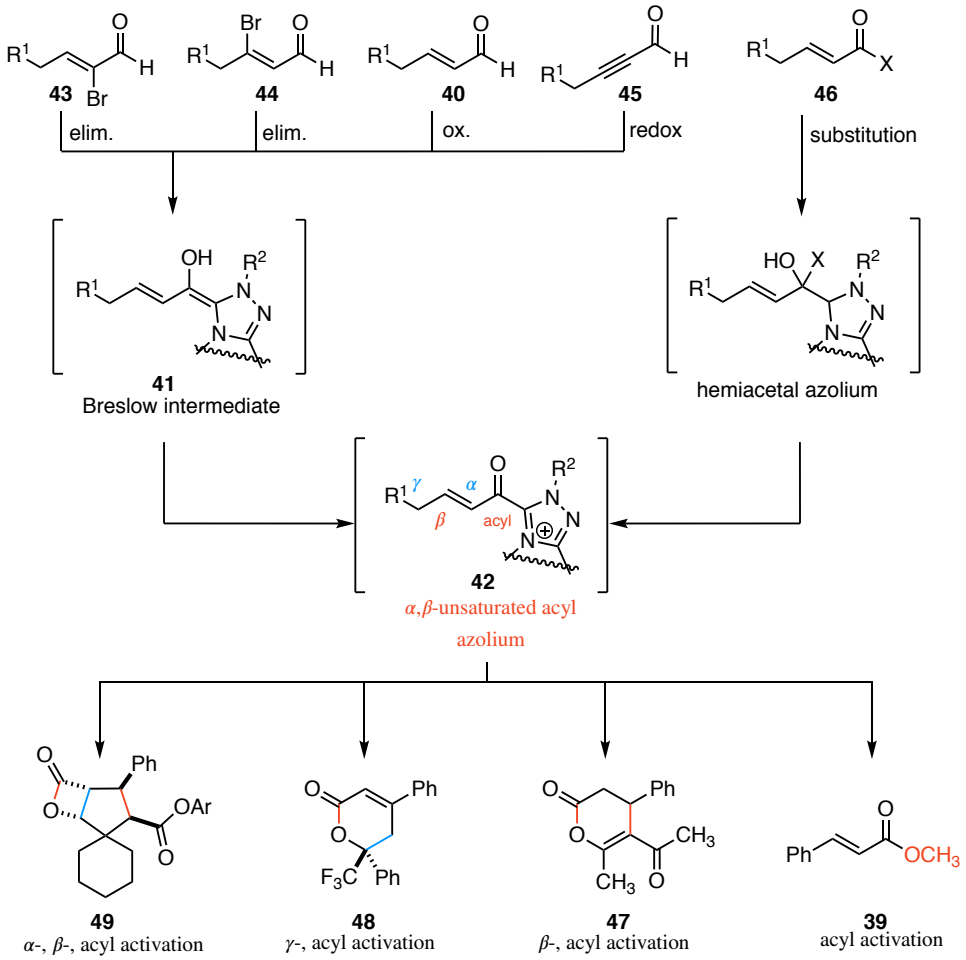
Whilst commonly accessed from enals (i.e. **40**) via oxidation of the Breslow intermediate **41**, the α,β-unsaturated acyl azolium **42** can be accessed in a variety of alternate ways. For example, it can be accessed via elimination reactions of bromo enals (i.e. **43** or **44**), redox isomerisation of ynals **45**, or more recently via direct NHC addition to substrates in the ester oxidation state **46** (Scheme 20).[64] Initially, simple esterification reactions were examined, such as the example by Zeitler described above.[63] However, once formed, the α,β-unsaturated acyl azolium **42** allows for a diverse range of complex reaction cascades to occur, with bond forming events at the α- , β- , γ- , and acyl positions.

In 2009, the Lupton group demonstrated the first annulation reaction of the α,β-unsaturated acyl azolium **42** with the formation of dihydropyranones (i.e. **47**) through NHC-induced fragmentation of enol esters.[65] This report also demonstrates use of acyl fluorides as a method for accessing the α,β-unsaturated acyl azolium **42** via direct substitution. In the years following this study, activation of the β-position of the α,β-unsaturated acyl azolium **42** has become common.[64]

In 2012, Chi demonstrated γ-deprotonation of the α,β-unsaturated acyl azolium **42**, allowing for annulation at the γ- and acyl carbons.[66] In this example, the α,β-unsaturated acyl azolium **42** is accessed via oxidation of the Breslow intermediate **41**. Chi and co-workers were able to suppress

homoenolate, enolate and acyl anion chemistry to successfully couple enals **40** with trifluoromethyl ketones in an enantioselective annulation to produce δ-lactones **48** with a Lewis acid co-catalyst.

In 2013, the Lupton group was able to exploit the α,β-unsaturated acyl azolium **42** in the formation of functionalised cyclopentyl fused β-lactones (i.e. **49**).[67-68] This cascade is achieved through reaction with a nucleophile at the β-position, followed by reaction between the transient azolium enolate and an electrophile, and concludes with β-lactonisation at the acyl position. This reactivity pattern has been demonstrated by many others in a diverse range of NHC catalysed cascades.[64]

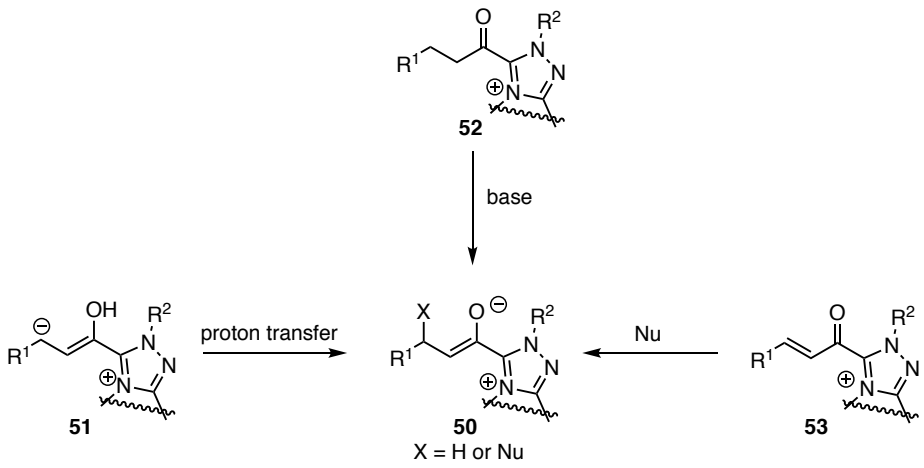


Scheme 20: Methods of accessing the α,β-unsaturated acyl azolium and some common reactivity patterns in complex reaction cascades

Whilst this is not an exhaustive list of reactions possible via the α,β-unsaturated acyl azolium **42**, it demonstrates its importance within the field. Umpolung intermediates dominated early NHC chemistry, however, in the last 15 years, normal polarity intermediates have been utilised far more.

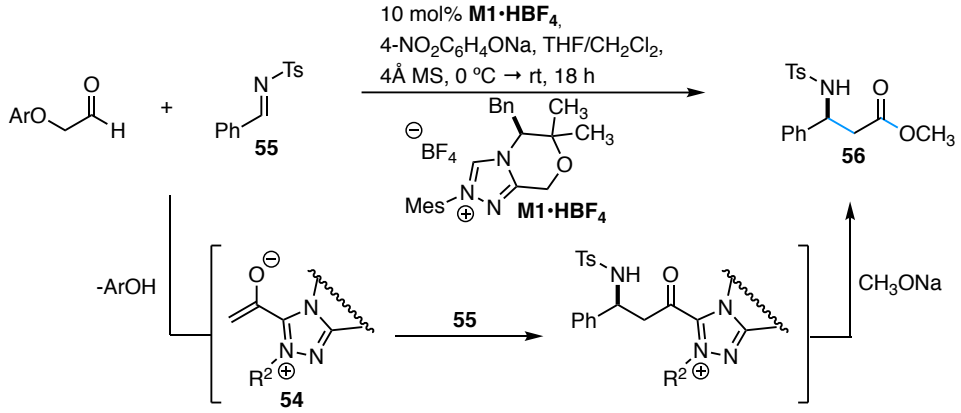
1.4.2 The azolium enolate

Another common normal polarity intermediate in NHC catalysed cascades is the azolium enolate **50** (Scheme 21). This intermediate is commonly accessed through a number of different routes including a proton transfer from the homoenolate **51**, deprotonation of the acyl azolium **52**, or is a secondary intermediate after a nucleophile has added to the β-position of the α,β-unsaturated acyl azolium **53**. This normal polarity intermediate allows for reaction with electrophiles at the α-position, often in a stereoselective manner.



Scheme 21: Common methods of generating the azolium enolate

In 2009, Scheidt and co-workers utilised the azolium enolate **54** in an enantioselective Mannich reaction (Scheme 22).[69] Formation of the azolium enolate **54** was achieved through elimination of a phenol, and reaction with imines (i.e. **55**) provides a range of β-amino carbonyl compounds (i.e. **56**). Depending on the trapping agent used, Scheidt was able to synthesise a variety of acids, esters, amides, alcohols and peptides.

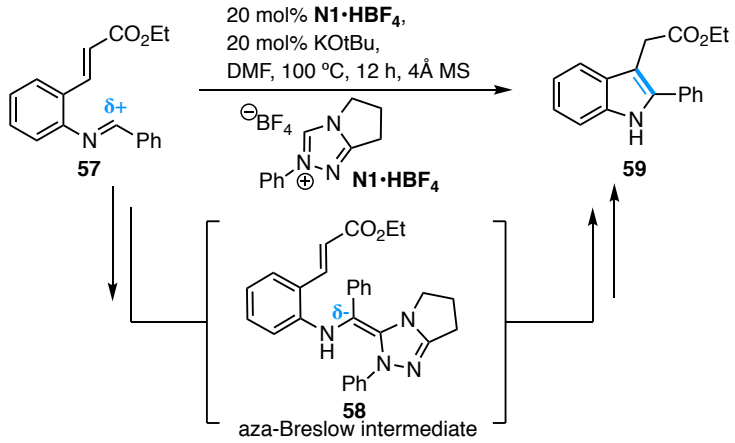


Scheme 22: Scheidt's use of the azolium enolate in synthesis of γ-amino esters

1.5 Novel Intermediates in NHC Catalysis

1.5.1 The aza-Breslow intermediate

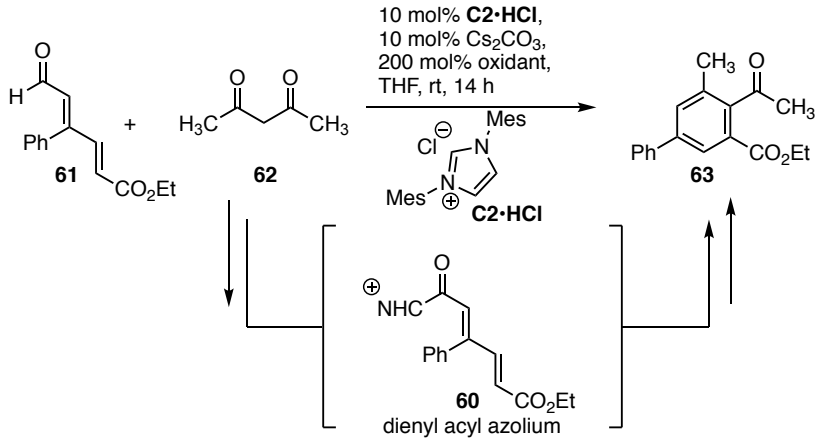
In the last 5 years, there have been some exciting new reactive intermediates discovered in NHC catalysis. Whilst the polarity inversion of aldehydes by NHCs has been known for decades (*vide supra*), the polarity inversion of imines (i.e. **57**) has proved far more difficult.[70] Whilst the iminyl equivalent of the Breslow intermediate had been theorised, it was not until 2017 that Biju reported the first use of the aza-Breslow intermediate **58** in the synthesis of indoles **59** (Scheme 23). The use of this intermediate in enantioselective reactions is of great interest to the Lupton group.



Scheme 23: First use of the aza-Breslow intermediate in Biju's synthesis of indoles

1.5.2 The α,β-γ,δ-diunsaturated acyl azolium

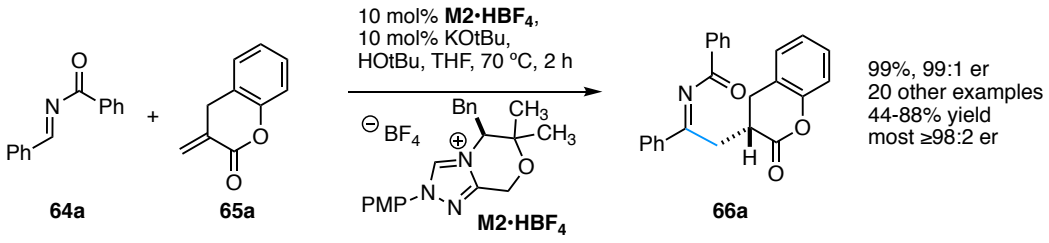
The α,β-γ,δ-diunsaturated acyl azolium or dienyl acyl azolium (i.e. **60**) is a vinylogous extension of the α,β-unsaturated acyl azolium. Until our work in the area, there had only been one successful use of the dienyl acyl azolium in synthesis. In 2015, Chi and co-workers were able to access the dienyl acyl azolium **60** from α,β-γ,δ-diunsaturated aldehydes (i.e. **61**) and an external oxidant, which allowed synthesis of cyclohexyl β-lactones through reaction with 1,3 diketones (i.e. **62**, Scheme 24). However, due to spontaneous decarboxylation and oxidation, they were unable to access any chiral materials, resulting in functionalised arene products (i.e. **63**). The use of the dienyl acyl azolium **60** in the synthesis of six and seven membered rings in an enantioselective fashion is an ongoing area of research in the Lupton group.



Scheme 24: First example of δ-activation of the dienyl acyl azolium

1.6 Objectives

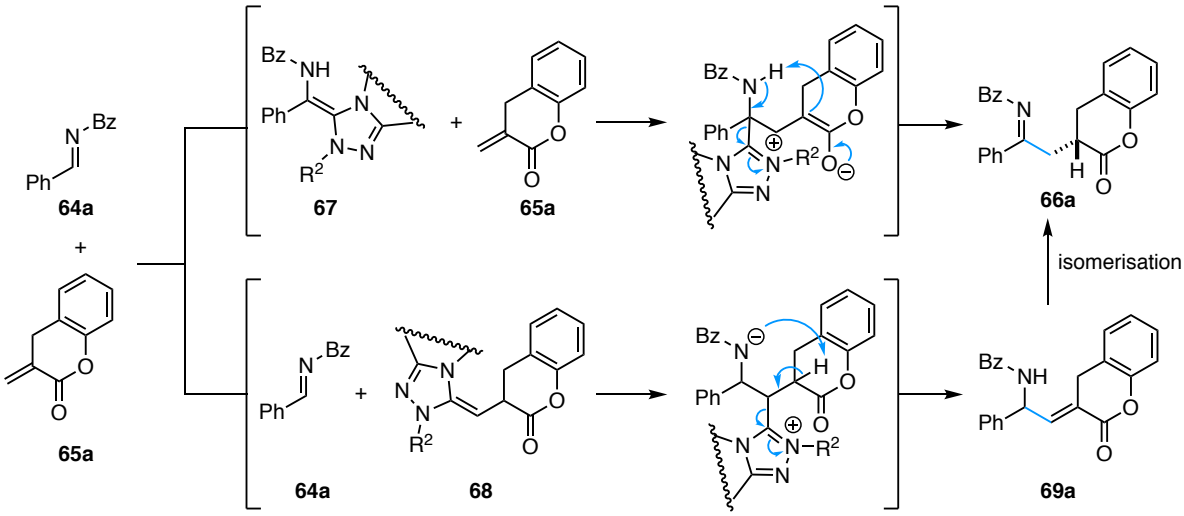
This thesis focuses on the use of novel intermediates in NHC catalysis. At the time that these doctoral studies commenced, there were no examples of the aza-Breslow intermediate being utilised in synthesis. However, during the course of our own investigations, three transformations exploiting the aza-Breslow intermediate were released.[70, 71, 72] Of those transformations, only two form new carbon-carbon bonds, and both examples are intramolecular and result in aromatic and achiral products. The challenges of an enantioselective, intermolecular reaction utilising the aza-Breslow intermediate remained unresolved. Chapter 2 explores the ultimately successful efforts undertaken to discover the first enantioselective aza-Stetter reaction (Scheme 25) between benzoyl imines (i.e. **64a**) and chromanones (i.e. **65a**) giving γ-imino lactones (i.e. **66a**). Reaction discovery and optimisation are described, along with the scope of the reaction and an investigation into the utility of the products. A related aza-benzoin reaction is also discussed.



Scheme 25: The aza-Stetter reaction presented in Chapter 2

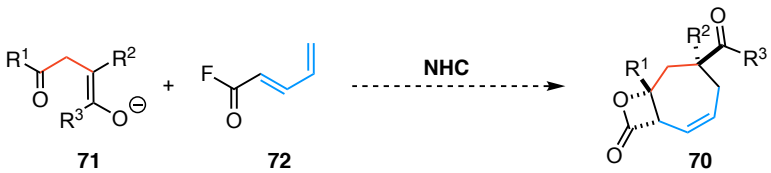
In Chapter 3, studies are undertaken to elicit the mechanism of the aza-Stetter reaction presented in Chapter 2. Two plausible mechanisms exist for the coupling of benzoyl imines **64a** and chromanones

65a (Scheme 26). One involves formation of the aza-Breslow intermediate **67**, which couples with chromanones **65a** to produce γ-imino esters **66a**. The other involves NHC addition to the chromanone **65a** to provide the β-azolium ylide **68** to provide enone **69a** which can then isomerise to give the same γ-imino esters **66a**. Experiments detailing isomerisation studies, deuterium labelling and kinetic analyses are all discussed along with the proposed mechanism.



Scheme 26: The possible mechanistic pathways of the aza-Stetter reaction

In Chapter 4, an investigation into the use of the α,β-γ,δ-diunsaturated acyl azolium or dienyl acyl azolium in the synthesis of cycloheptenes **70** from 1,3-dipoles (e.g. **71**) and dienyl acyl fluorides **72** is undertaken (Scheme 27). At the time that these doctoral studies commenced, there was only one successful use of this intermediate with bond forming occurring at the δ-position. This reaction, reported by Chi (see chapter 4 for details), demonstrates the synthesis of achiral aromatic compounds via the dienyl acyl azolium. We were interested in the use of the dienyl acyl azolium in an enantioselective annulation reaction.



Scheme 27: General outline for (4+3) annulation presented in Chapter 4

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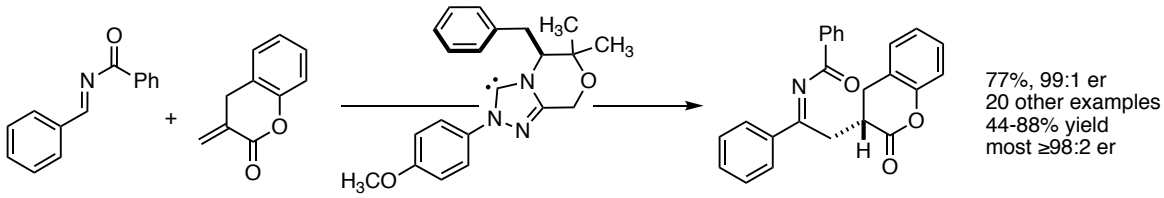
Chapter 2: An Enantioselective, Intermolecular Aza-Stetter Reaction via the Aza-Breslow Intermediate

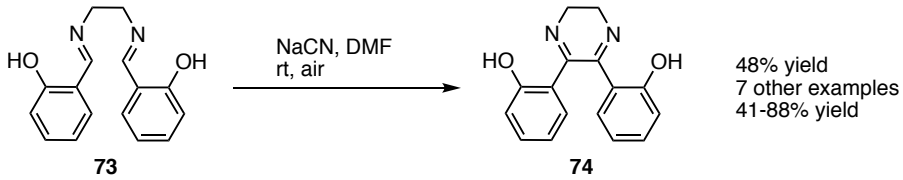


The work presented in this chapter involves the discovery of the first intermolecular and enantioselective reaction that proceeds via the aza-Breslow intermediate. A total of 21 examples of this aza-Stetter reaction are presented with good to excellent yields and exceptional enantioselectivity (most ≥98:2). The synthetic utility of the imine products was also investigated. In addition, a related aza-benzoin reaction, which represents the first NHC catalysed imine-imine coupling, is discussed.

2.1 Background

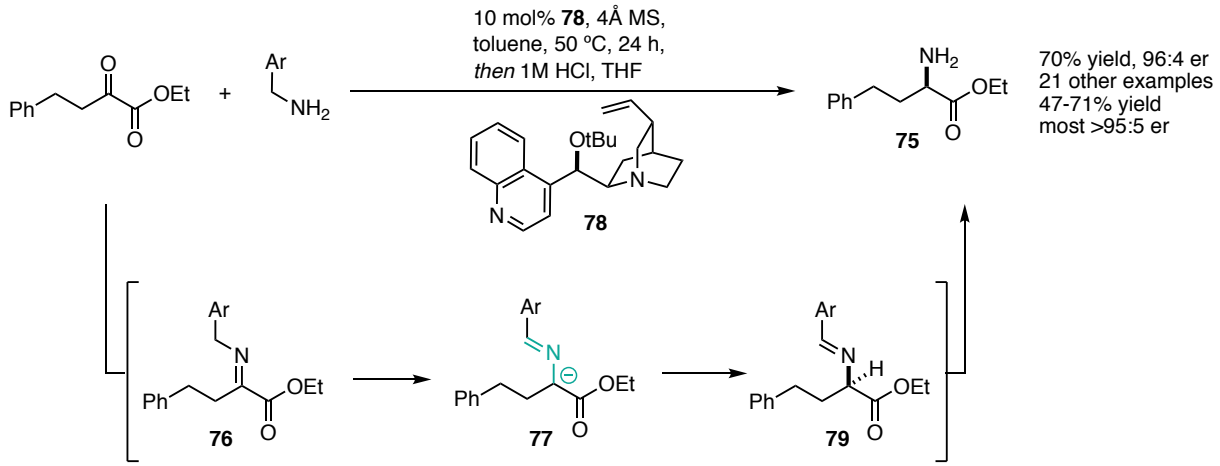
2.1.1 Umpolung of imines

Although the umpolung of carbonyl containing compounds has been studied extensively (see Chapter 1), polarity inversion of imines has received less attention. In the modern era, Miller and colleagues achieved coupling of aldimines (i.e. **73**) by using cyanide anions to generate iminyl anion equivalents (Scheme 1).[1] The use of aerobic conditions leads to ring closed diimines (i.e. **74**) in reasonable yields. This methodology was later used in the synthesis of imidazolylidenes.[2]



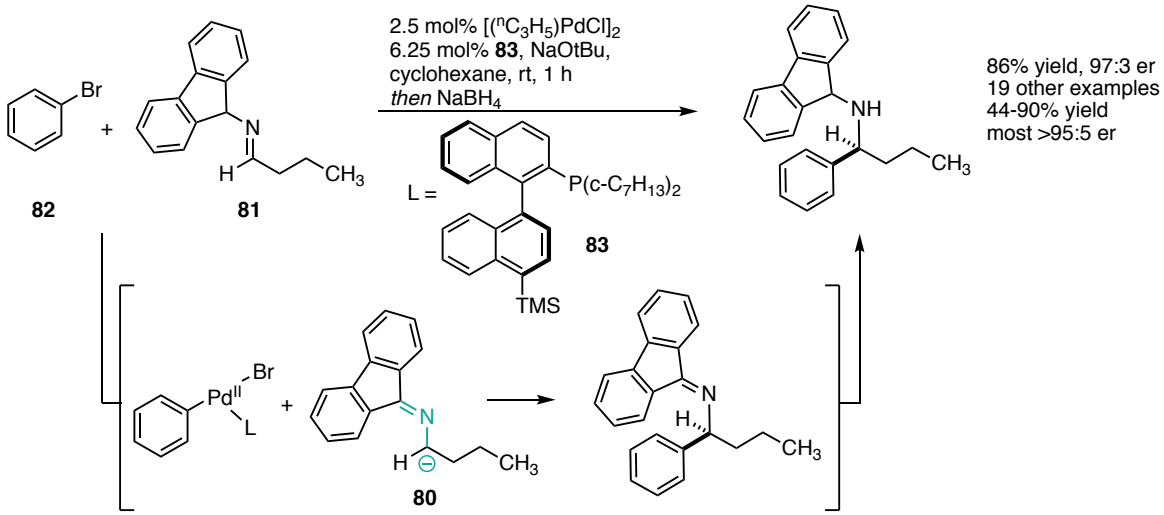
Scheme 1: Aldimine cyclisation utilising cyanide anions

The chemistry of 2-azaallyl anions presents a distinct approach to the polarity inversion of imines, and has been studied extensively over the last decade.[3] Early efforts in the area focussed on the synthesis of chiral amines via biomimetic transamination reactions. For example, the group of Shi was able to synthesise chiral α-aminoacid derivatives (i.e. **75**) by first generating imine **76** in situ, followed by generation of aza-allyl anion **77** (Scheme 2). Stereoselective protonation, mediated by cinchonadine derived catalyst **78** then gives imine **79** which is hydrolysed to give aminoester **75** in good yields and with high enantiopurity.[4]



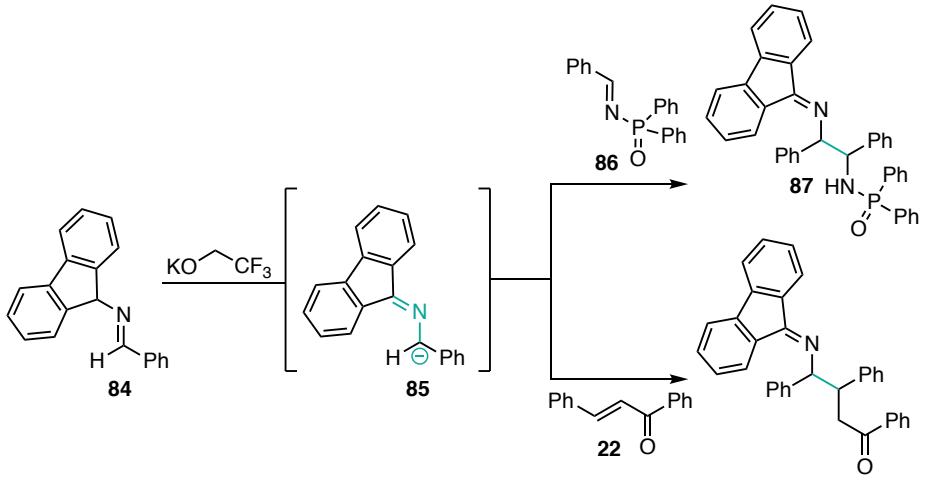
Scheme 2: Generation of α-aminoacid derivatives via aza-allyl anions

The extension of this work to the use of aza-allyl anions as nucleophiles in carbon-carbon bond forming reactions proved somewhat more challenging. The first highly enantioselective and catalytic reactions were only reported very recently. Specifically, the Buchwald group discovered a palladium catalysed arylation reaction (Scheme 3) that exploits aza-allyl anions (i.e. **80**) derived from 9-aminofluorene-derived imines (i.e. **81**) as the nucleophilic partner to couple with various aryl halides (i.e. **82**).[5] High levels of enantioselectivity were achieved using the phosphine based biaryl ligand **83**.



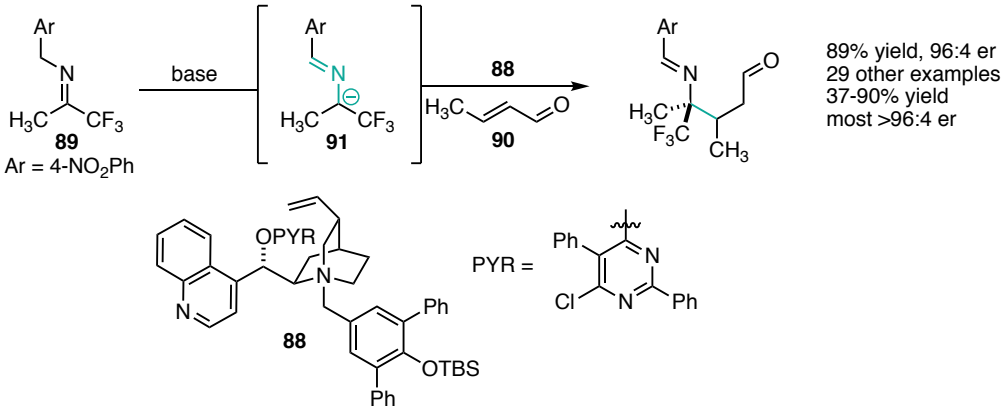
Scheme 3: Palladium catalysed arylation utilising aza-allyl anions

In 2014, Kobayashi and co-workers showed that catalytic imine-imine cross coupling could be achieved via the aza-allyl anion (Scheme 4).[6] Deprotonation of 9-fluorenyl imines **84** gave allyl anion **85** which coupled with *N*-phosphinoyl imines **86** to give amino imine **87**. In addition, chalcone **22** could also be used as an electrophile, demonstrating the viability of Michael acceptors in these transformations.



Scheme 4: Aza-allyl anions coupled with imines and chalcone

In 2017, Deng and co-workers achieved the first stereoselective addition of azaallyl anions to Michael acceptors using a chiral organocatalyst (Scheme 5).[7] Through careful optimisation of the cinchona alkaloid catalysts (i.e. **88**), they were able to achieve the highly enantioselective coupling of trifluoromethyl imines **89** with enals (i.e. **90**) via 2-azaallyl anions **91**. The reaction shows remarkable regioselectivity, with alkylation occurring exclusively at the carbon furthest from the 4-nitrophenyl group. The reaction also showed wide functional group tolerance and excellent stereocontrol.

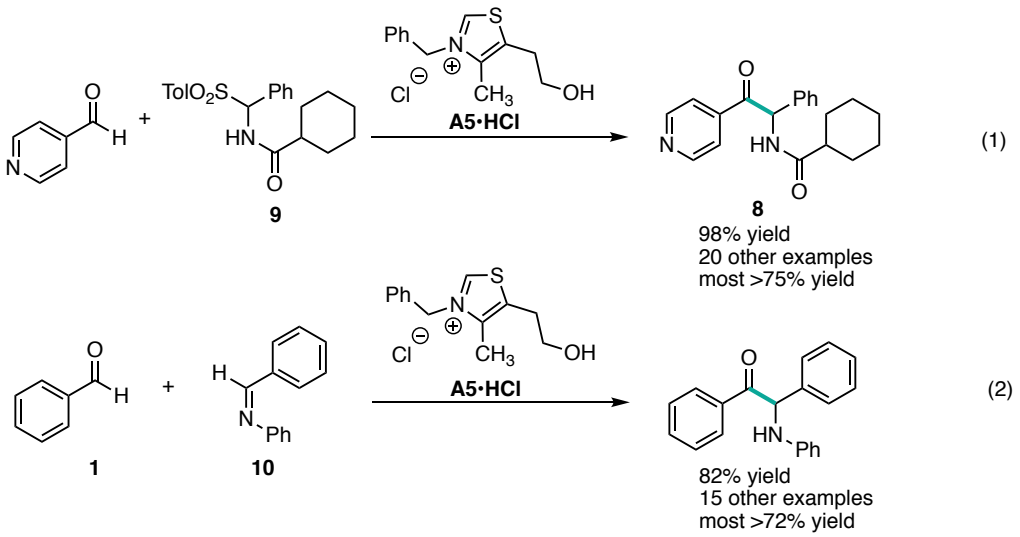


Scheme 5: Stereoselective aza-allyl anion addition to Michael acceptors

Although this represents a significant advancement in the area, generalized approaches to the catalytic generation of iminyl anion equivalents are still underdeveloped.

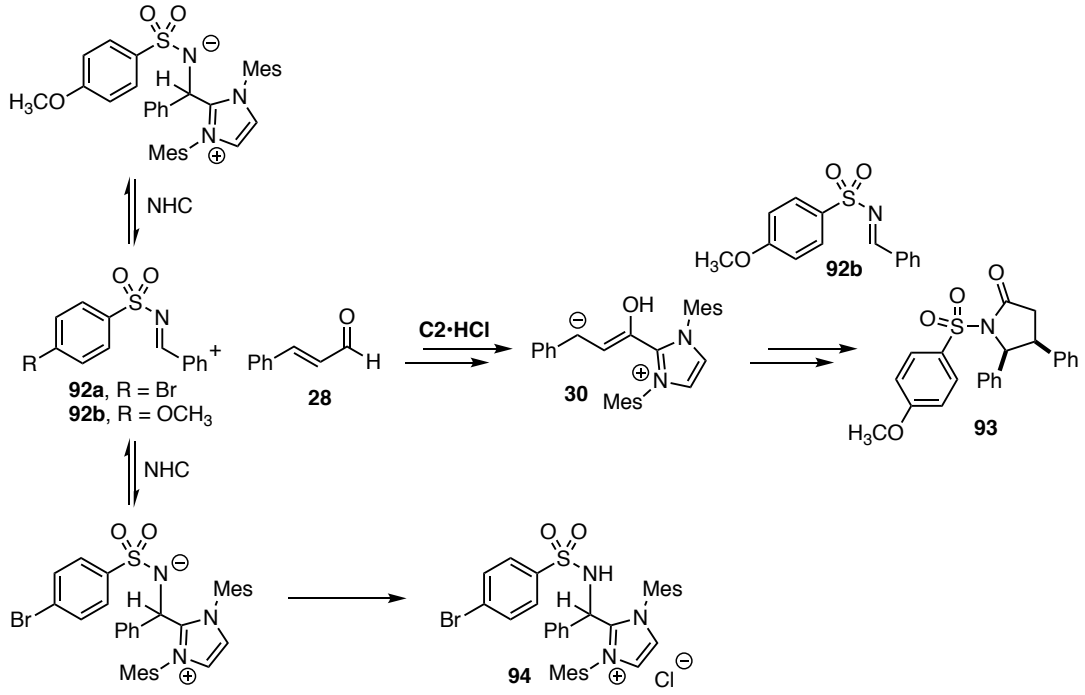
2.1.2 Imines as electrophiles in NHC catalysis

Whilst NHCs play a major role in the umpolung of carbonyl compounds, their use in imine umpolung is underdeveloped. This is surprising considering that the use of imines as electrophilic partners in NHC catalysed reactions is well established. One of the earliest reactions utilising imines as electrophiles involved benzoin reactions coupling imines with benzaldehydes. In 2001, Murray and Frantz exploited imines, generated in situ from α-amido sulfones **9**,[8] to produce α-amino ketones **8** in excellent yields using thaizolium catalyst **A5•HCl** (Scheme 6, eq. 1). This work has since been extended to include less activated imines such as *N*-phenyl imines (i.e. **10**), as reported by You and co-workers (Scheme 6, eq. 2).[9] In addition, Miller and co-workers have since developed an enantioselective variant using a thiazolium derived from a modified peptide.[10]



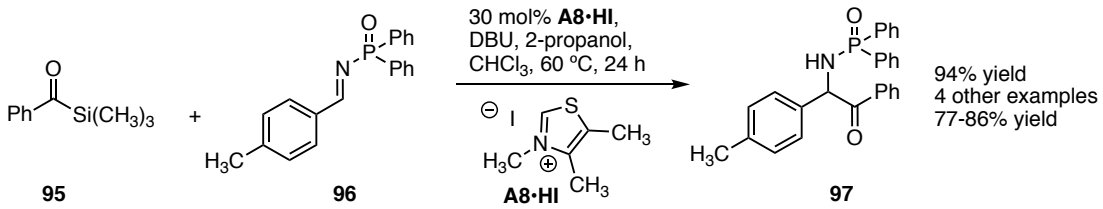
Scheme 6: Imines as electrophiles in NHC catalysed benzoin reactions

In 2005, Bode showed that tosyl protected imines (i.e. **92**) could react with the homoenolate **30** generated from enals (i.e. **28**) to give γ-lactams **93.** Central to the success of this reaction was the realisation that electron poor sulfonyl protected imines (i.e. **92a**) resulted in irreversible catalyst addition (i.e. **94**). In contrast, electron rich sulfonyl protected imines (i.e. **92b**) rendered NHC addition reversible, and allowed the desired lactam formation, via the homoenolate **30**, to occur (Scheme 7).[11]



Scheme 7: *N*-Protecting group affecting reversibility of carbene addition to imines

Scheidt and co-workers were able to demonstrate that acyl anion equivalents generated from acyl silanes (i.e. **95**) can also couple with imines (i.e. **96**) to form α-aminoketones **97** (Scheme 8).[12] Again, careful choice of protecting group was key to the reactions success, as benzoyl, sulfonyl and sulfinyl protected imines all reacted irreversibly with the NHC catalyst, whereas *N*-phosphinoyl imines (i.e. **96**) allowed the desired reaction to occur. Interestingly, thiazoliums (i.e. **A8•HI**) were shown to catalyse the transformation most efficiently, despite the almost exclusive use of triazoliums in more recent acyl anion chemistry. This highlights the effect that subtle changes in sterics and electronics in the heteroazoliums can have on reaction outcomes.

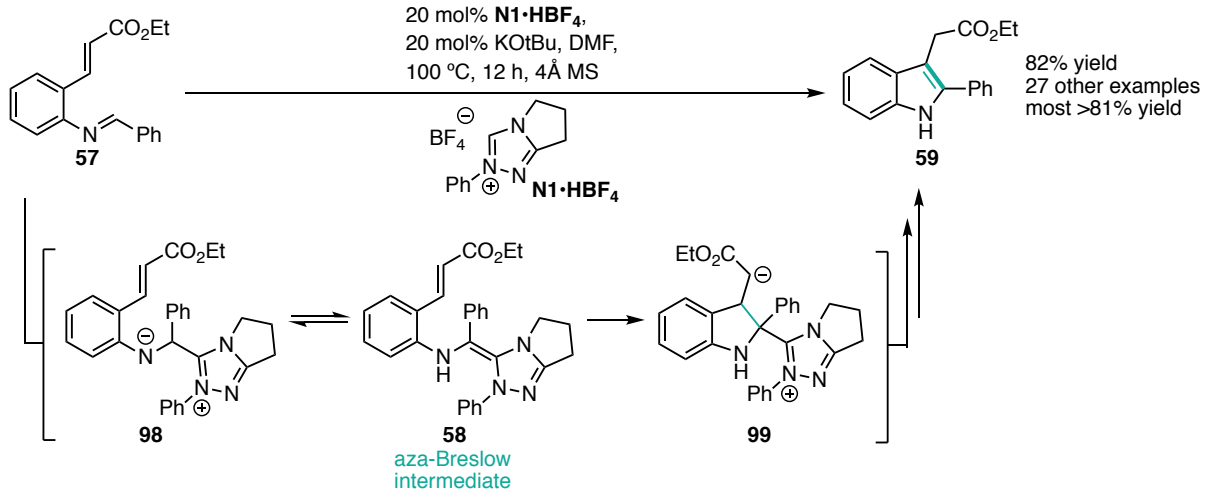


Scheme 8: Scheidt's synthesis of α-aminoketones **97**

There have been several other studies that employ imines as electrophiles in NHC catalysed reactions.[13-17] These all demonstrate the compatibility of imines as electrophilic coupling partners in umpolung chemistry. They also highlight the need for careful choice of the *N*-protecting group and catalyst, due to the tendency for the NHC to be rendered inert by irreversible addition to some imines. While a number of these studies implicate a transient aza-Breslow intermediate,[11, 12] none of them were able to isolate, or utilise, the aza-Breslow intermediate itself in catalytic imine umpolung.

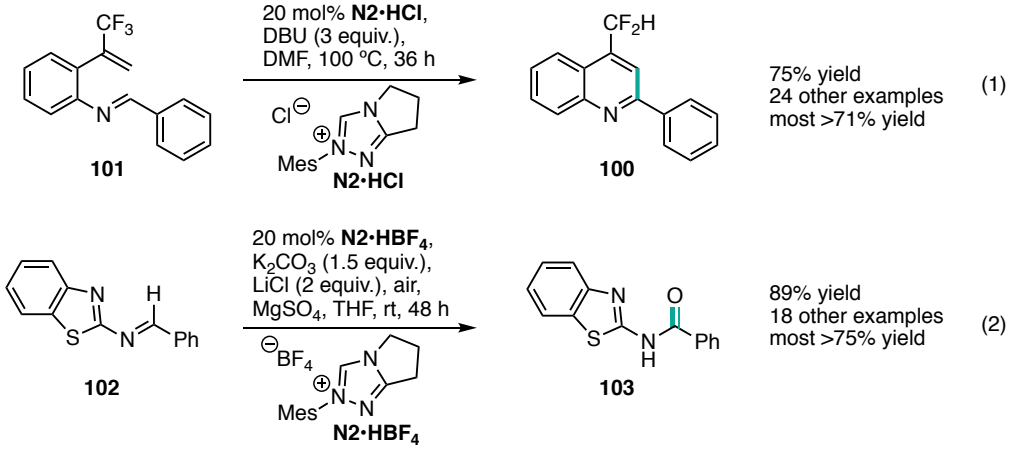
2.1.3 The use of the aza-Breslow intermediate in synthesis

It was not until 2017 that the first catalytic reaction utilising the aza-Breslow intermediate was realised. Biju and co-workers discovered the cycloisomerisation of imine **57** to afford indoles (i.e. **59**) in good to excellent yields (Scheme 9).[18] The postulated mechanism involves NHC addition to the imine, to provide aza-anion **98** followed by tautomerisation to the aza-Breslow intermediate **58**. Cyclisation into the tethered α,β-unsaturated ester provides intermediate **99**, which is followed by elimination of the catalyst to give indoles **59** in excellent yields. This study provided proof of principle that the aza-Breslow intermediate could be used in catalytic carbon-carbon bond formation and paved the way for future studies in the area. Mechanistic studies in this work are discussed in Chapter 3.



Scheme 9: Biju's synthesis of indoles via the aza-Breslow intermediate

Following their initial report, Biju and co-workers reported similar reactions for the synthesis of 4-difluormethyl quinolone derivatives (i.e. **100**), again utilising the aza-Breslow intermediate (scheme 10, eq. 1).[19] In this case cyclisation into the trifluoromethyl styrene **101** followed by catalyst elimination and base mediated 1,3-proton shift provides the aromatic products (i.e. **100**) in good yields. In the same year, the Huang group published an oxidative amidation of aldimine **102** that proceeds via the aza-Breslow intermediate (scheme 10, eq. 2). The transformation occurs under aerobic conditions utilising LiCl as a co-catalyst to provide a range of functionalised amides (i.e. **103**).[20]

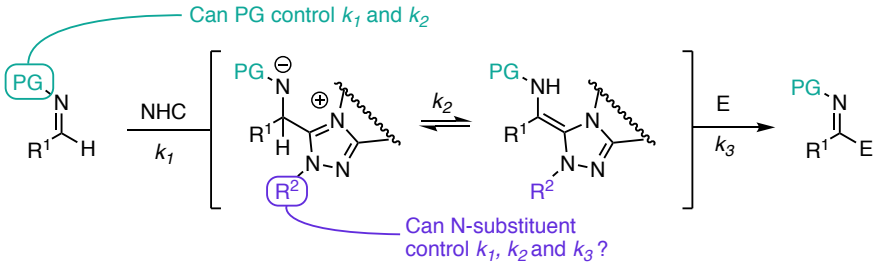


Scheme 10: Biju's synthesis of quinolones (1) and Huang's synthesis of amides (2)

Whilst these studies demonstrate the viability of the aza-Breslow intermediate in catalysis, the challenges of an enantioselective and intermolecular reaction remain unsolved.

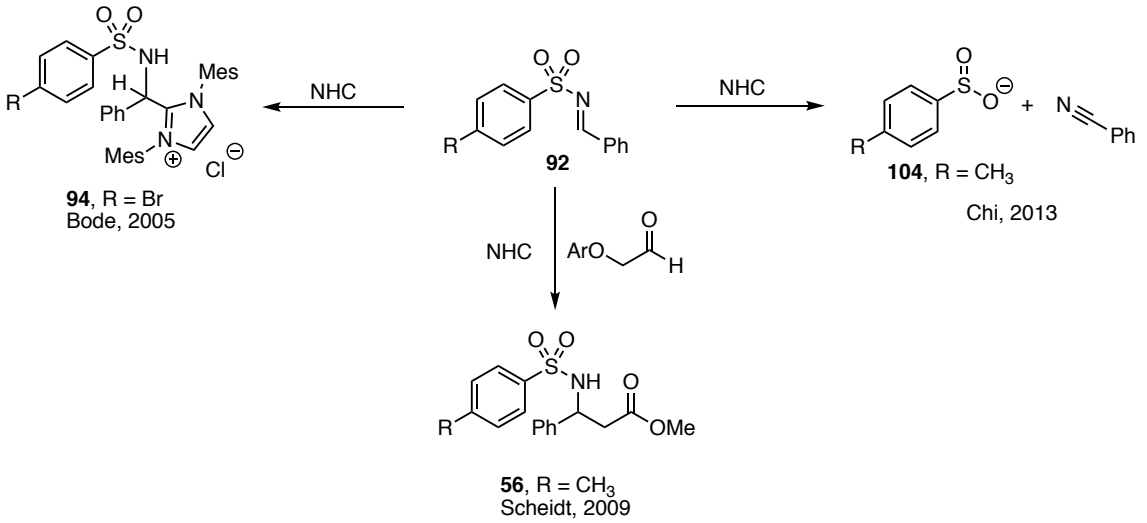
2.1.4 Synthetic strategy for reactions via the aza-Breslow intermediate

It is with these challenges in mind that we set about our investigation into the NHC catalysed aza-benzoin and aza-Stetter reactions. In order for these reactions to be successful, it would be imperative to control the relative rates of a number of important transformations. Firstly, carbene addition to the imine (i.e. k_1). Next, aza-Breslow intermediate formation (i.e. k_2). And lastly, reaction with the chosen electrophile (i.e. k_3). Careful choice of protecting group and catalyst would be crucial in controlling these rates k_1, k_2, and k_3 (Scheme 11).



Scheme 11: Controlling the formation of the aza-Breslow intermediate through catalyst and protecting group selection

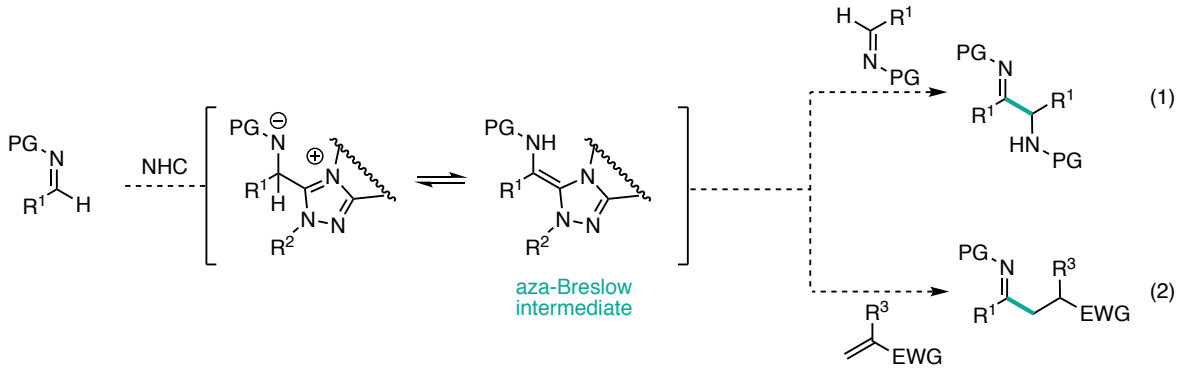
Likely to play the greatest role on the success of our reaction design was the nature of the protecting group on the imine. A number of studies involving imines as electrophiles in NHC catalysed reactions have shown that carbenes add irreversibly with certain protecting groups. For example, Bode found that sulfonyl protected imines (i.e. **92**) resulted in stable carbene-imine adducts (i.e. **94**) that prevented catalyst turnover (Scheme 12).[11-12] In contrast, other studies with tosyl protected imines, such as Scheidt's synthesis of β-amino esters **56**, resulted in good catalytic activity.[13-14] Finally, studies by Chi revealed that NHCs can liberate sulfinic anions (i.e. **104**) from tosyl protected imines.[21] The variability of these outcomes highlights the highly sensitive nature of these transformations to the *N*-protecting group, catalyst, and reaction conditions. What is common to most studies that use imines as electrophiles in NHC-catalyzed reactions is the use of electron withdrawing *N*-protecting groups.[22] Consequently, we believe that electron withdrawing groups on the nitrogen will help facilitate the desired reactions. Specifically, this should render the imine suitably electrophilic, while stabilising the negative charge on the nitrogen prior to tautomerisation to the aza-Breslow intermediate.



Scheme 12: Differing reaction outcomes from changes to *N*-protecting group

A second factor that we considered to be pivotal to this reaction design was the nucleophilcity of the catalyst. In previous studies, it was determined that the nucleophilicity of NHC catalysts can vary by several orders of magnitude with different *N*-substituents.[23] So by considering the selection of the NHC catalyst, and the protecting group of the imine the rate of their union should be controlled. Additionally, studies into *N*-substituent effects in related acyl anion chemistry demonstrate that both the sterics and electronics of the *N*-substituents affect the kinetics (both k_1 and k_2, see Scheme 11) of the reaction.[24-25] Bode demonstrated that the mesityl *N*-substituent enhances the rate of Breslow intermediate formation and ascribe this effect to irreversible addition to aldehydes, whereas electron poor *N*-substituents add reversibly.[24] However, studies into the related Stetter reaction from the Smith group attribute differences in reactivity to differences in the rate of proton transfer necessary to form the Breslow intermediate.[25] Whilst this proton transfer has been shown to be the rate determining step in intramolecular Stetter reactions,[26] it is unknown as to whether the same would be the case in an intermolecular aza-benzoin or aza-Stetter reaction.

This chapter describes the discovery of two novel NHC catalysed reactions exploiting imine umpolung. The first is an aza-benzoin reaction that represents the first NHC catalysed imine-imine coupling (Scheme 13, eq. 1). The second is an aza-Stetter reaction that proceeds with high levels of enantioselectivity (Scheme 13, eq. 2). To the best of our knowledge, this represents the first enantioselective NHC catalysed reaction that utilises the aza-Breslow intermediate.

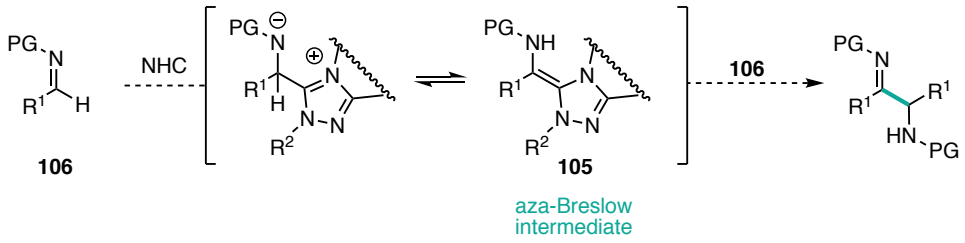


Scheme 13: Proposed aza-benzoin and aza-Stetter reactions

2.2. Aza-Benzoin Reaction

2.2.1 Synthetic strategy

Investigations into the utilisation of the aza-Breslow intermediate (i.e. **105**) began with an aza-analogue of the benzoin reaction (Scheme 14). As reactions that involve Michael acceptors involve mechanistic ambiguities as to whether they proceed via imine umpolung or umpolung of the Michael acceptors, an aza-benzoin reaction was a logical starting point in our studies. If the dimerization of imines (i.e. **106**) could be achieved, there would be no doubt as to the intermediacy of the aza-Breslow intermediate (i.e. **105**) within our reaction design.

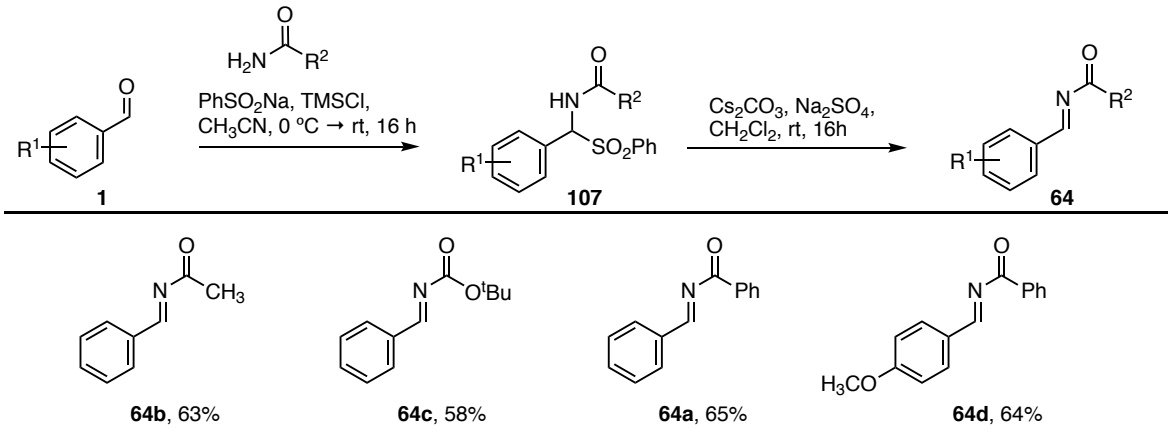


Scheme 14: Proposed aza-benzoin reaction

2.2.2 Synthesis of imine substrates

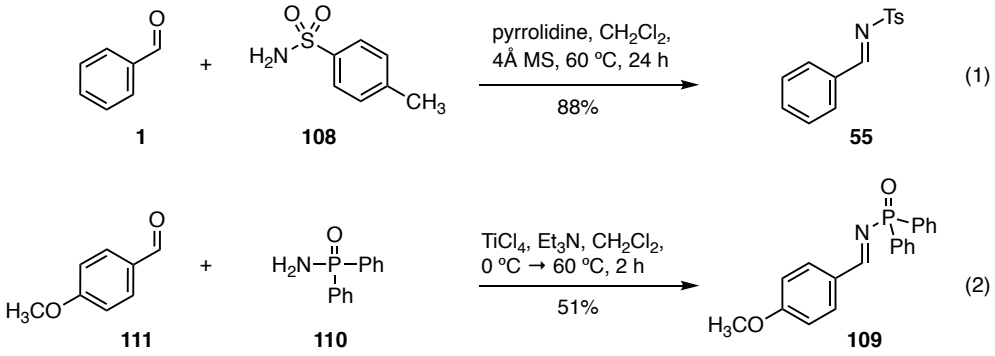
As discussed above, the protecting group on the nitrogen was considered to be an important factor in the successful outcome of the reaction. Thus, we set about synthesising a range of differentially protected imines (i.e. **64a-f**) derived from benzaldehydes. Three approaches were exploited to access the three distinct families of imines. A modified procedure by Miller[27] (Scheme 15) was used to access benzoyl and carbamoyl protected imines (i.e. **64a-d**). Firstly, benzaldehyde **1** was converted to the corresponding α-amido sulfones **107** using an appropriate amide, or carbamate, and the sodium salt

of benzene sulfinic acid in the presence of chlorotrimethylsilane (TMSCl). These sulfones **107** were transformed, without purification, into the corresponding imines **64a-d** by elimination of sulfinic acid using caesium carbonate. In this manner, benzoyl **64a** and **64d**, acetyl **64b** and boc **64c** protected imines were successfully synthesised in good yields.



Scheme 15: Synthesis of imines **64a-d**

The tosyl protected imine **55** was prepared from benzaldehyde **1** and tosyl amine **108** in the presence of molecular sieves and pyrrolidine in one step using the approach of Frias and co-workers (Scheme 16).[28] Lastly, by following the procedure of Crampton et al.[29] the phosphonate protected imine **109** was prepared by the reaction of phosphinic amide **110** with 4-methoxybenzaldehyde **111** in the presence of $TiCl_4$ in reasonable yield. With these imines in hand, the benzoin reaction could be trialled.

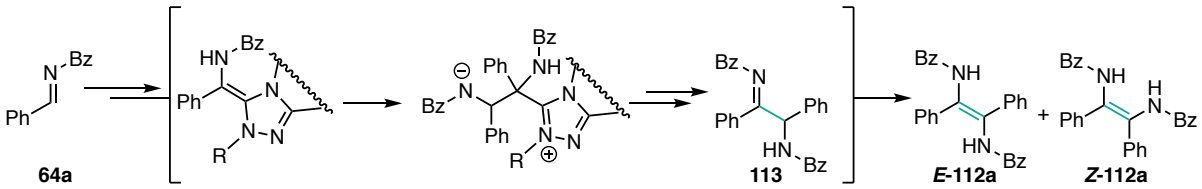


Scheme 16: Synthesis of imines **55** and **109**

2.2.3 Reaction discovery and optimisation

It was postulated that the proton transfer necessary to form the aza-Breslow could be rate determining as shown by Rovis in a related intramolecular Stetter reaction.[26] The same group also discovered that addition of a protic additive increased the rate and yield of the Stetter reaction.[30] Computational studies by Sunoj also demonstrate that the activation barriers for the Breslow intermediate formation are much lower in the presence of a Brønsted acid.[31] Infact, protic additives have been shown to benefit a range of organocatalytic reactions.[32-33] With these studies in mind, we began our reaction discovery using tertiary butyl alcohol (^{t}BuOH) as an additive. Furthermore, as we were uncertain regarding what type of catalyst would favour the aza-benzoin reaction, a wide range of catalysts were tested.

When trialled in the aza-benzoin reaction, the acetyl **64b**, boc **64c**, tosyl **55** and phosphonate **109** protected imines all failed to give any reaction using achiral triazolium **N3•HBF$_4$** (Table 1, entries 1 & 2). Pleasingly, however, the benzoyl protected imine in refluxing THF gave enediamine product **112a** in a 39% yield as a 1:1 ratio of *E*- and *Z*-isomers (Table 1, entry 3). We propose that this product is formed by isomerisation of the amino imine product **113** after a successful aza-benzoin reaction (Scheme 17). This is similar to the isomerisation observed by Becker in related compounds.[34]

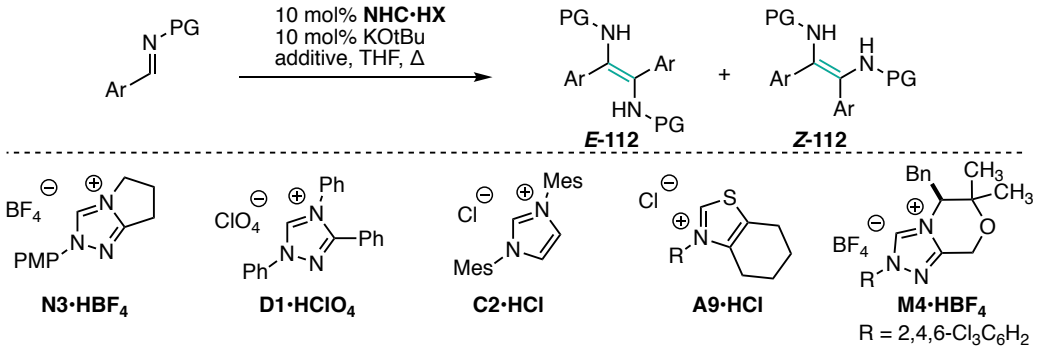


Scheme 17: Proposed formation of enediame **112**

Switching to the more electron rich 4-methoxyphenyl imine **64d** only slightly improved the yield of **112b** (Table 1, entry 4). Using the less nucleophilic TPT catalyst **D1•HClO$_4$** still afforded the coupled diamine **112b**, however, with no improvement in yield (Table 1, entry 5). Removal of ^{t}BuOH from the reaction mixture caused the reaction to fail (Table 1, entry 6), while IMes **C2•HCl**, thiazolium **A9•HCl** and chiral triazolium **M4•HBF$_4$** all proved unsuitable for the reaction (Table 1, entry 7). It is likely that a fine balance exists between a catalyst that enables the formation of the aza-Breslow intermediate, and the ability of the resultant aza-Breslow intermediate to act as a nucleophile in the reaction. Unfortunately, as isomerisation of the amino imine intermediate **113** to achiral enediamine

112 was observed in all cases, the development of an enantioselective variant of this reaction was not possible.

Table 1: Discovery of the aza-benzoin reaction



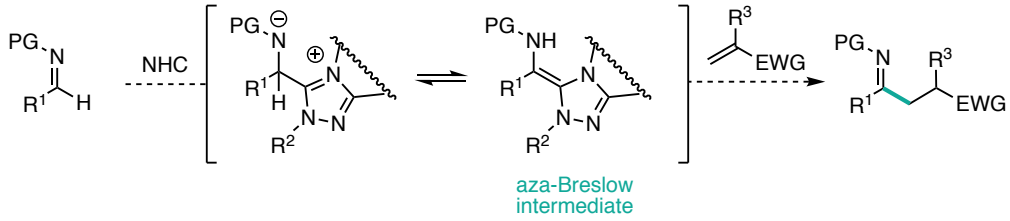
Entry	PG	NHC	Additive	Ar	Yield
1	Ac, Boc, Ts	**N3**	^{t}BuOH	Ph	N/R
2	P(O)Ph$_2$	**N3**	^{t}BuOH	4-OCH$_3$Ph	N/R
3	Bz	**N3**	^{t}BuOH	Ph	39%
4	Bz	**N3**	^{t}BuOH	4-OCH$_3$Ph	40%
5	Bz	**D1**	^{t}BuOH	4-OCH$_3$Ph	38%
6	Bz	**D1**	-	4-OCH$_3$Ph	N/R
7	Bz	**C2, A9, M4**	^{t}BuOH	4-OCH$_3$Ph	N/R

This discovery represents the first imine-imine benzoin reaction to be catalysed by NHCs, and only the fourth example of the successful use of the aza-Breslow intermediate in synthesis. Although the desired amino imine product was never observed, we were encouraged to continue our investigations into the chemistry of the aza-Breslow intermediate.

2.3 Aza-Stetter Reaction[i]

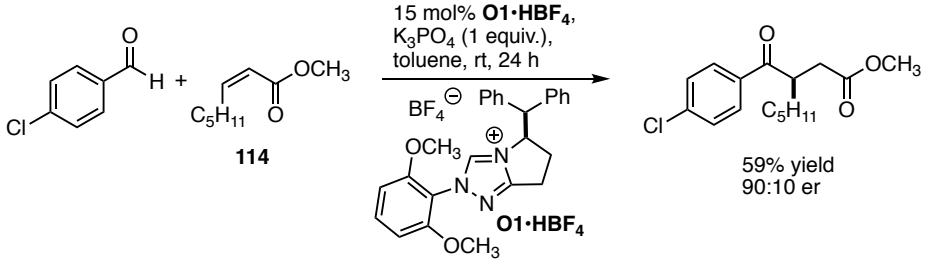
2.3.1 Synthetic strategy

Attention was now directed to the use of the aza-Breslow intermediate in an intermolecular aza-Stetter reaction (Scheme 18). In order to study this reaction, it was first necessary to synthesise a suitable Michael acceptor.



Scheme 18: Proposed aza-Stetter reaction

Many previous approaches to the Stetter reaction have been made possible by highly activated alkenes.[22, 30, 35-38] However, work by the Glorious group has shown that simple acrylates can be used in intermolecular enantioselective Stetter reactions.[39] Although this report demonstrated the possibility of simple substrates in enantioselective reactions, only one example of an acrylate with a β-substituent (i.e. **114**) was reported (Scheme 19), and with diminished enantiomeric ratio (90:10 er).



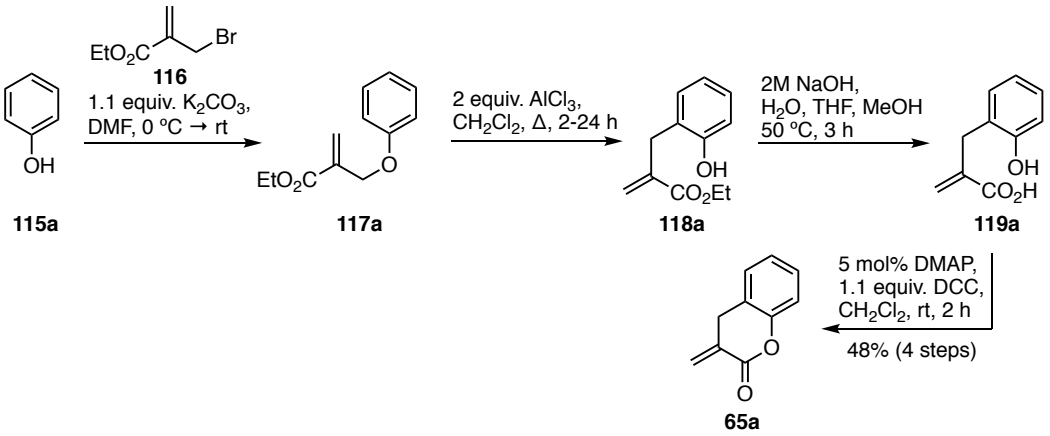
Scheme 19: Glorius' example of a β-substituted acrylate in an enantioselective Stetter reaction

2.3.2 Synthesis of Michael acceptor

With these limitations in mind, we identified a 1,1-disubstituted olefin, such as chromanone **65a**, as a suitable substrate to investigate the 1,4-addition of the aza-Breslow intermediate (Scheme 20). Whilst the electrophilicity of this exact species has not been measured, the electrophilicity of related α,β-unsaturated esters have been shown to have E-values of between -18 and -23.[40] This is less electrophilic

[i] Optimisation of the aza-Stetter reaction was performed in conjunction with Yuji Nakano (60/40)

than the measured values of imines bearing electron withdrawing protecting groups (−11 to −16),[41] which should allow selective carbene addition to benzoyl imines (i.e. **64a**) in the presence of the Michael acceptor **65a**. Following a modified procedure by Sunitha et al.[42] starting from phenol **115a** and ethyl 2-(bromomethyl)acrylate **116**, etherification provided ether **117a** (Scheme 20). Next, $AlCl_3$ was used to promote the Claisen rearrangement to give ester **118a**. Exposure to aqueous sodium hydroxide then provided acid **119a** which was cyclised in the presence of DMAP and DCC to give the desired chromanone **65a** in 48% yield over four steps. With a suitable Michael acceptor in hand, the aza-Stetter reaction could be investigated.



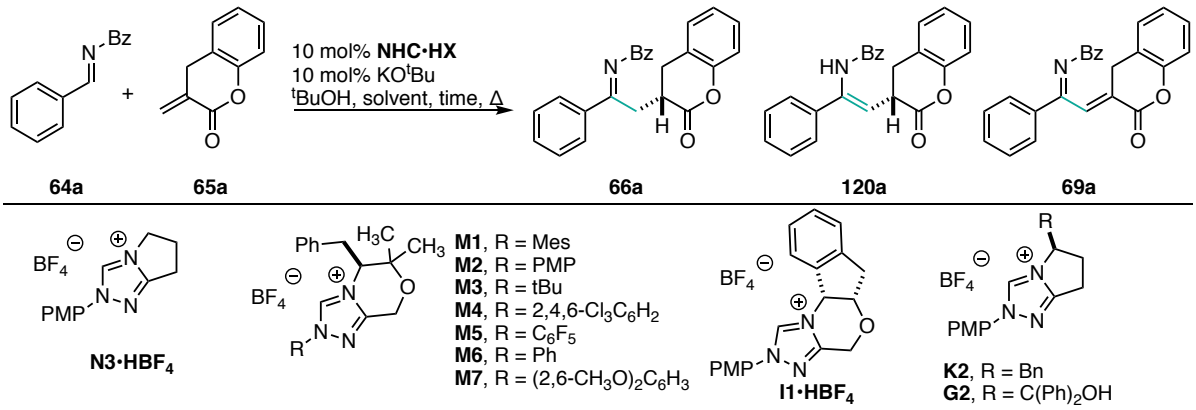
Scheme 20: Synthesis of chromanone **65a**

2.3.3 Initial reaction discovery and optimisation

With the knowledge gained from our study into the aza-benzoin reaction, we knew that ^{t}BuOH was critical for the formation of the Breslow intermediate (see Table 1, entry 6). However, due to the observed isomerisation of the aza-benzoin products, we were also wary of the role that ^{t}BuOH may play in a similar isomerisation to enamine (i.e. **120a**) and enone (i.e. **69a**) products in the related aza-Stetter reaction. Therefore, we began investigations using 10 mol% ^{t}BuOH, rather than the equivalent used previously. Optimisation of the aza-Stetter reaction began with a catalyst screen. Unfortunately, achiral catalyst **N3•HBF$_4$**, the optimal catalyst for the benzoin reaction, failed to provide the desired product, instead giving isomeric enone **69a** (Table 2, entry 1). Whilst this product is consistent with β-umpolung of the Michael acceptor, we propose that both the enamine and enone isomers form via isomerisation of imine **66a**. Mechanistic studies support this hypothesis and are presented in Chapter three. Moving to the chiral morpholinone family, catalysts with mesityl, tertiary butyl, 2,4,6-trichlorophenyl, C_6F_5 and phenyl *N*-substituents (catalysts **M1**, **3-6•HBF$_4$**) all failed to

provide the aza-Stetter product **66a**. (Table 2, entry 2). However, the more nucleophilic PMP substituted catalyst **M2•HBF$_4$** gave the enamine product **120a** in a 49% yield in a 5:2 ratio with the enone product (Table 2, entry 3). The more electron rich 2,6-$(CH_3O)_2C_6H_3$ catalyst also gave coupled material, providing enone product **69a** in a 46% yield (Table 2, entry 4). Interestingly, these observations show that electron rich catalysts are ideal for the aza-Stetter reaction. This is contrast to the observations with the standard Stetter reaction where C_6F_5, 2,4,6-trichlorophenyl *N*-substituted catalysts provide superior results.[25, 43] Returning to catalysts with the PMP *N*-substituent, alternate chiral scaffolds were examined. When the indanol derived catalyst **I1•HBF$_4$** was trialled in dioxane, the desired imine **66a** was isolated in a 43% yield and an excellent 98:2 er (Table 2, entry 5). Pyrrolidine derived catalyst **K2•HBF$_4$** gave only enone isomer **69a** (Table 2, entry 6) and catalyst **G2•HBF$_4$** that bears a hydrogen bonding donor produced no conversion at all (Table 2, entry 7). Lastly, switching back to the PMP substituted morpholinone catalyst **M2•HBF$_4$** in dioxane, the desired imine **66a** was isolated in a 50% yield and an er of 98:2 (Table 2, entry 8).

Table 2: Initial reaction discovery and optimisation



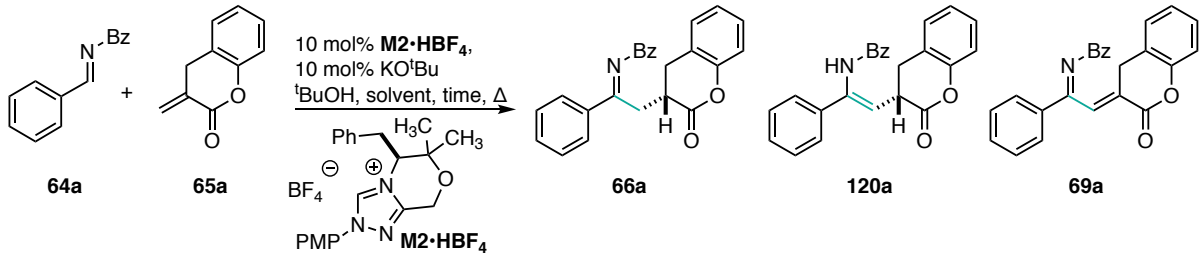
Entry	NHC	Solvent	Time	**66**:**120**:**69**, yield	er
1	**N3**	THF	4 h	0:0:1, 82% **69**	-
2	**M1**, **3-6**	THF	4 h	-	-
3	**M2**	THF	4 h	0:5:2, 49% **120**	-
4	**M7**	THF	4 h	0:0:1, 46% **69**	-
5	**I1**	Dioxane	2 h	2:1:0, 43% **66**	98:2
6	**K2**	Dioxane	2 h	0:0:1, 80% **69**	-
7	**G2**	Dioxane	2 h	-	-
8	**M2**	Dioxane	2 h	5:0:3, 50% **66**	98:2

2.3.4 Impact of solvent and time

With the optimal catalyst in hand, a solvent screen was then conducted. Polar solvents can stabilise charged intermediates, such as the cationic acyl azolium intermediate, while neutral species such as the Breslow intermediate are less affected by changes in solvent.[44] However, we reasoned that formation of the Breslow intermediate proceeds through a charged species (see scheme 18), which may be stabilised by polar co-ordinating solvents such as THF. In addition, the undesired imine **66** to enamine **120** tautomerisation may also be affected by solvent selection.[45]

The conditions previously found to be best are shown in Table 3, entry 1. Switching the solvent to the less co-ordinating DCE resulted in lower conversion, and a greater proportion of the isomerised enamine product **120a** (Table 3, entry 2). The more polar solvents, glyme and DMF, both failed to give any product, instead leading to decomposition of imine **64a** (Table 3, entries 3 & 4). In order to test whether lower polarity solvents prevent conversion to the undesired enamine tautomer **120a**, benzene and toluene were tested in the reaction. Benzene was found to provide the desired imine **66a**, however, showed a significant amount of enamine **120a** and enone **69a** tautomers (Table 3, entry 5). Toluene was also promising, providing the imine **66a** in a 49% yield and a 98:2 er (Table 3, entry 6). However, when the solvent was switched back to THF and the reaction time was reduced, the imine **66a** was isolated in a 65% yield, improved over both dioxane and toluene, with minimal isomerisation and an excellent er of 99:1 (Table 3, entry 7). This suggests, perhaps, that the imine isomer **66a** forms in the reaction first. Isomerisation studies are presented in detail in Chapter 3.

Table 3: Solvent screen



Entry	Solvent	Time	**66**:**120**:**69** yield	er
1	dioxane	2 h	5:0:3, 50% **66**	98:2
2	DCE	24 h	3:7:0, 24% conv.	-
3	glyme	24 h	-	-
4	DMF	20 h	-	-
5	benzene	20 h	2:4:5, 83% conv.	-
6	toluene	20 h	5:2:0, 49% **66**	98:2
7	THF	2 h	7:1:0, 65% **66**	99:1

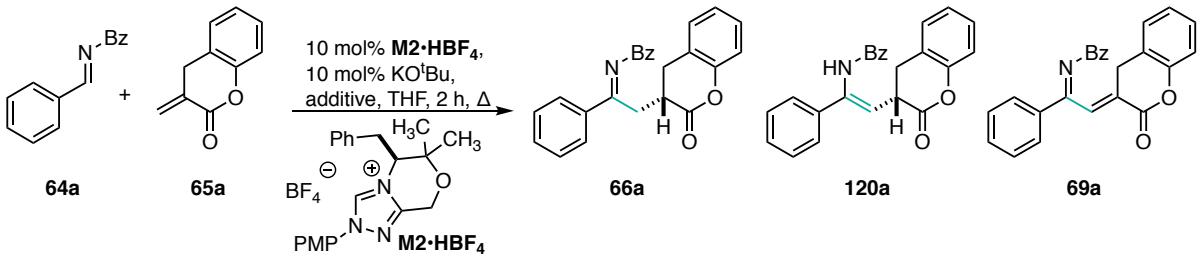
2.3.5 Impact of additives

As previously discussed, the nature of the additive has a significant impact on a number of reactions of the Breslow intermediate.[30-31] This is consistent with our preliminary studies on the aza-benzoin reaction, as it was noted that the addition of ^{t}BuOH was essential to the reactions success. Thus, to further improve the yield and selectivity of the reaction studies now focused on a more thorough examination of the role of the protic additive in this reaction.

Firstly, the ^{t}BuOH was removed. This resulted in a diminished yield of 57% of imine **66a**, and surprisingly, also resulted in more of the isomerised enamine product **120a** (Table 4, entry 1). This suggests that ^{t}BuOH has an important role in the formation of the aza-Breslow intermediate, but may not affect isomerisation of imine **66a** to enamine **120a** and enone **69a** as previously thought. In contrast, increasing the amount of ^{t}BuOH used from 10 mol% (Table 4, entry 2) to 100 mol% (Table 4, entry 3) pleasingly gave an increased yield of 77% of the desired imine **66a** with an improved ratio of imine **66a** to enamine **120a**. When phenol and catechol were tested as alternate proton shuttle, no reaction was observed (Table 4, entries 4 & 5). Lastly, hexafluoroisopropanol (HFIP) and pivalic acid gave low yields with significantly higher levels of isomerisation observed (Table 4, entries 6 & 7). We reasoned that it is possible that the lower steric bulk of phenol and catechol may allow them to

protonate and quench one of the reactive intermediates – either the aza-Breslow intermediate or the transient enolate present after 1,4-addition (see Chapter 3 for detailed mechanism). Protonation of either of these intermediates would prevent the reaction occurring.

Table 4: Additive screen



Entry	Additive (%)	**66**:**120**:**69** yield	er
1	-	3:1:0, 57% **66**	99:1
2	^{t}BuOH (10 %)	7:1:0, 65% **66**	99:1
3	^{t}BuOH (100%)	8:1:0, 77% **66**	99:1
4	Phenol (100%)	-	-
5	Catechol (100%)	-	-
6	HFIP (100%)	2:0:5, 24% **66**	96:4
7	PivOH (100%)	3:0:2, 29% **66**	80:20

The optimised conditions for the aza-Stetter reaction were found to be 10 mol% of PMP *N*-substituted morpholinone catalyst **M2•BF$_4$** generated with 10 mol% of KO^{t}Bu. The reaction is performed in THF at reflux for two hours with one equivalent of ^{t}BuOH used as an additive.

2.4 *In Situ* Derivatisations

Throughout the optimisation studies, it became apparent that during the reaction and chromatographic purification, isomerisation of imine **66a** to enamine **120a** and enone **69a** occurs. In order to avoid this, *in situ* derivatisations were attempted using various organometallic reagents to generate a more stable amine product **121**.[46-48] While this approach can potentially address stability issues, due to the presence of multiple electrophilic functionality, namely imine, amide, and ester functionalities, chemoselectivity would be imperative for this approach to succeed.

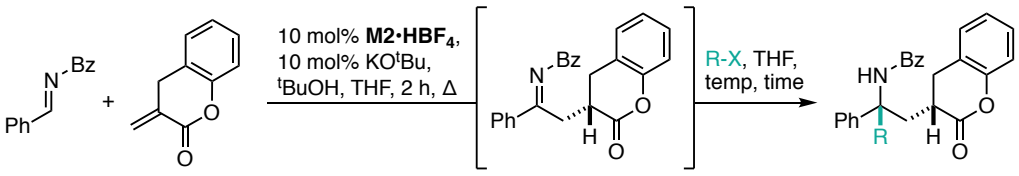
Our attempts at nucleophilic additions began with a range of Grignard reagents (Table 5, entries 1-4), as they have been shown to successfully perform 1,2-additions to imines bearing electron withdrawing *N*-substituents, in preference to isomerisation.[47, 49] Low temperatures were used to control chemoselectivity. Unfortunately, both the phenyl Grignard reagent and the bulky isopropyl Grignard did not react at this temperature (Table 5, entries 1 & 4). Vinyl magnesium bromide gave the undesired enamine isomer as the only product (Table 5 entry 3). Pleasingly, the methyl Grignard reagent gave the desired addition product **121a** in a 35% yield, albeit with poor diastereoselectivity (1:1 dr). Organolithium reagents have also been shown to add to imines,[50] so butyl lithium was tested in the reaction (Table 5, entry 5). Unfortunately, this resulted in complete conversion to the enamine isomer with only moderate yield (47%).

As competing addition to the ester moiety was postulated to be a problem with these derivatizations, diethyl zinc was tested as a nucleophile due to its reduced nuclephilicity (Table 5, entries 6). Unfortunately, this resulted in no reaction. Tomioka showed that diethyl zinc can be used in conjunction with copper triflate and a phosphine co-catalyst to affect the ethylation of imines.[51] Unfortunately, when these conditions were trialled no reaction was observed (Table 5, entry 7).

As low conversion was observed using methyl magnesium bromide, higher temperatures and longer reaction times, as well as increasing the equivalents of nucleophile, were tested. Unfortunately, at higher temperatures, methyl magnesium bromide affected the isomerisation of imine **66a** to enamine **120a** (Table 5, entry 8). Returning to phenyl magnesium bromide at higher temperatures resulted in a 25% yield of the amine product **121b** (Table 5, entry 9). Lastly, increasing the equivalents of phenyl Grignard reagent resulted in an increased yield of 32% (Table 5, entry 10). However, significant

amounts of decomposition were observed in this reaction, likely due to reaction at the various electrophilic functionalities possible at higher temperatures.

Table 5: Nucleophilic derivitisations



64a **65a** **66a** **121**

Entry	Nucleophile (equiv.)	temp	time	Product (yield, dr)
1	PhMgBr (1.5)	–78 °C	1.5 h	-
2	MeMgBr (1.5)	–78 °C	1.5 h	**121a**, R = Me, 35%, 1:1 dr
3	Vinyl-MgBr (1.5)	–78 °C	1.5 h	**120a**, 28%
4	iPrMgBr (3)	–78 °C	2 h	-
5	nBuLi (1.5)	–78 °C	1.5 h	**120a**, 47%
6	Et_2Zn (3)	0 °C	16 h	-
7*	Et_2Zn(3)	0 °C	16 h	-
8	MeMgBr (3)	–78 °C → rt	4 h	**120a**, 29%
9	PhMgBr (1.5)	–78 °C → rt	4 h	**121b**, R = Ph, 25%
10	PhMgBr (3)	–78 °C → rt	4 h	**121b**, R = Ph, 32%

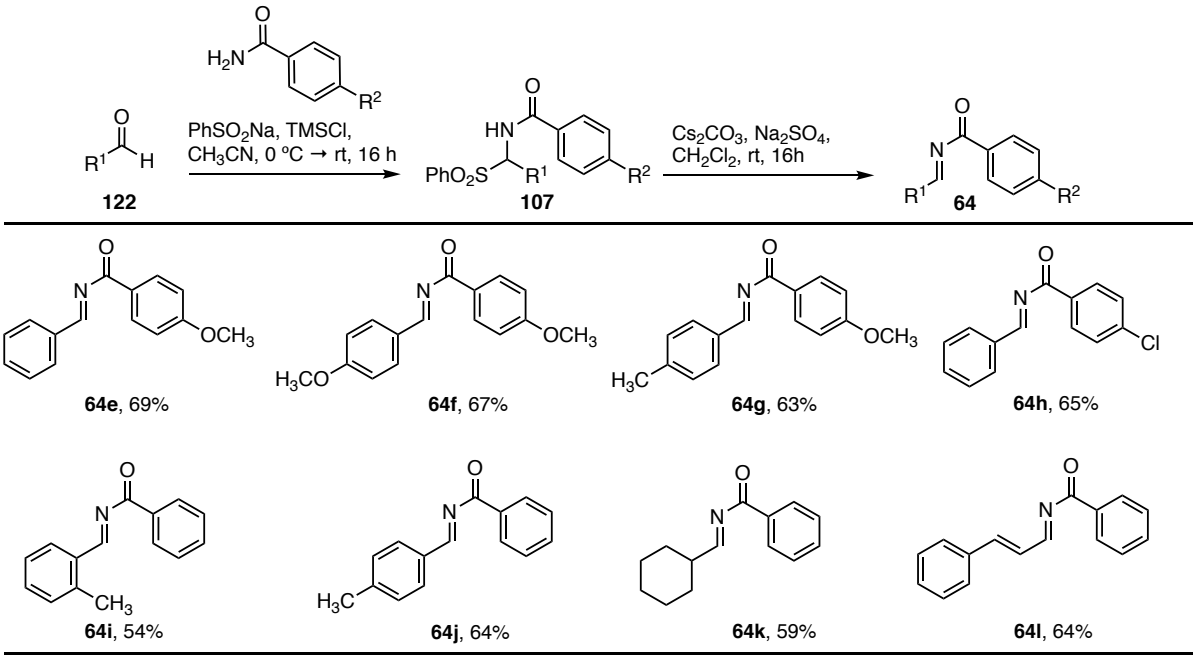
*Reaction performed with 3 mol% copper triflate and *tert*-butyl (*S*)-(1-(diphenylphosphaneyl)-3-methylbutan-2-yl)carbamate

Unfortunately, while reactions at the imine functionality of γ-imino ester **66a** were observed, this route proved to be less efficient at producing the desired product than conventional methods for isolation. An investigation into *in situ* reductions by another group member was similarly unsuccessful. As such, *in situ* derivitisations were abandoned. Instead, when isolating the products after a reaction, the column chromatography step was performed very quickly in order to minimise the time the imines spent on silica. This helped reduce unwanted isomerisation and allow for increased yields of the isolated imine products.

2.5 Aza-Stetter Scope

2.5.1 Synthesis of benzoyl imines

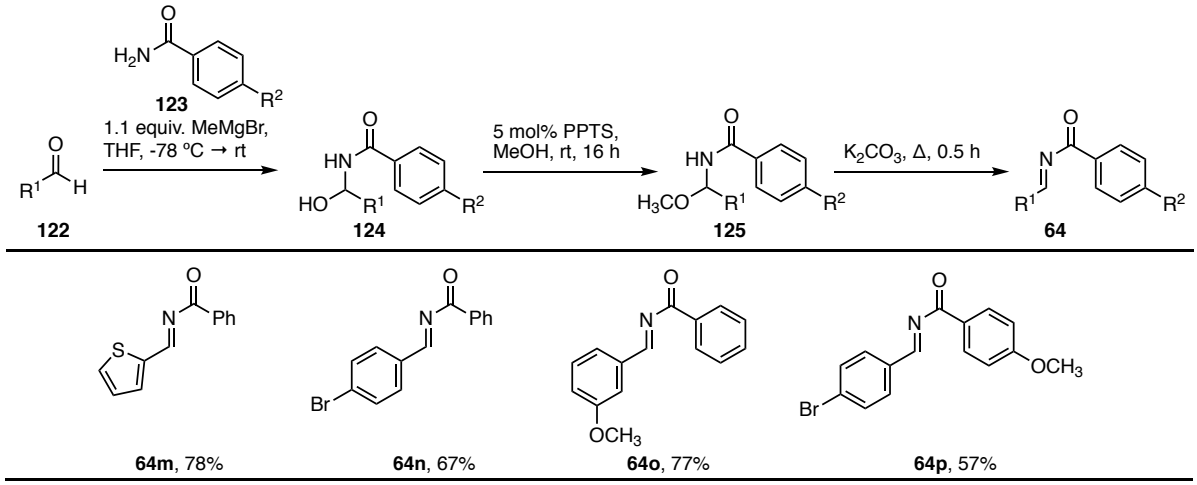
In order to investigate the generality of the reaction, a number of different imines and Michael acceptors were synthesised. Starting with imines, various benzoyl protected imines were synthesised using two general procedures from the literature. The first is the same as described previously (Scheme 15). Firstly, the appropriate aldehyde **122** was converted to the corresponding α-amido sulfones **107** using a suitable benzamide **123** and the sodium salt of benzene sulfinic acid in the presence of TMSCl (Scheme 21). The α-amido sulfones **107** were then transformed to the desired imines using caesium carbonate and sodium sulphate. A range substituted aldimines **64e-l** were synthesized in good yields over the two steps (54-69%) including electron rich (**64e-g**), electron poor (**64h**) and electron neutral (**64i-j**). In addition to imines derived from benzaldehydes, an aliphatic example **64k** and an imine derived from cinnamaldehyde **64l** were synthesised in a 59% yield and 64% yield respectively.



Scheme 21: Synthesis of benzoyl imines

The second method used to prepare benzoyl imines **64** involved the synthesis of hemiaminals **124** using methyl magnesium bromide following the procedure of Halli et al. (Scheme 22).[52] Etherification the presence of pyridinium *p*-toluenesulfonate (PPTS) then gave the corresponding methyl ethers **125** which were converted to the desired imines **64** (57-78% yield) upon elimination under high

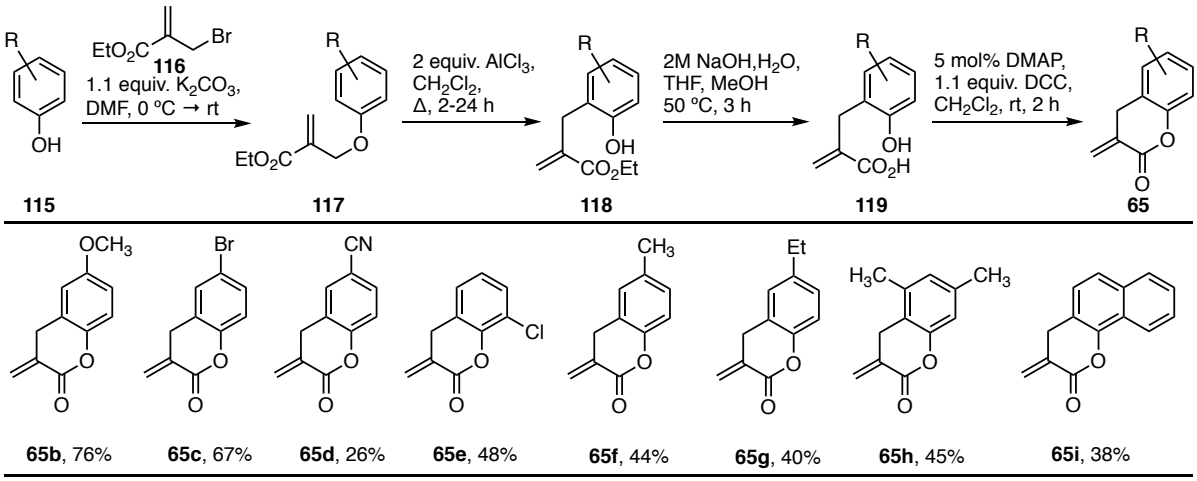
vacuum at elevated temperatures. A range of different aryl imines bearing electron donating (**64o** & **64p**), withdrawing (**64n** & **64p**), and heteroaromatic groups i.e. **64m**.



Scheme 22: Synthesis of benzoyl imines

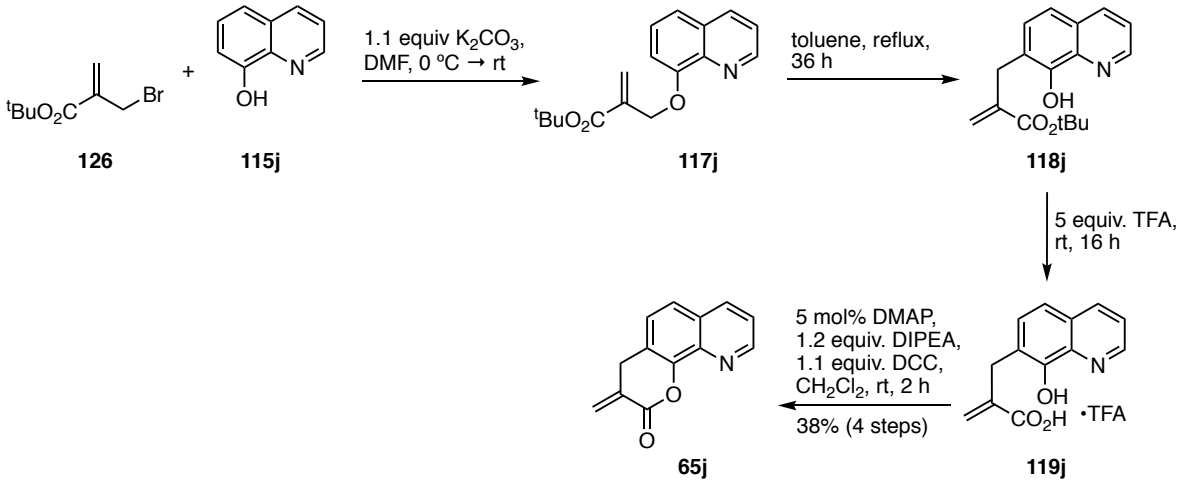
2.5.2 Synthesis of Michael acceptors

Attention then turned to the synthesis of different Michael acceptors. This began with the same synthetic route developed to prepare chromanone **65a**. Using the same sequence as described above (Scheme 20), a range substituted chromanones were prepared in good yields over the 4 steps (26-76%) including electron rich (**65b**), electron poor (**65c-e**), and electron neutral (**65f-i**) species (Scheme 23).



Scheme 23: Synthesis of chromanones

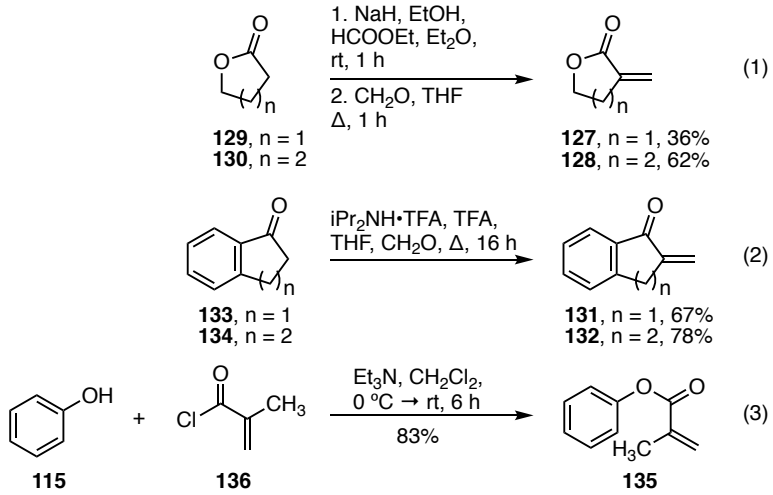
With a slight modification to the procedure, quinoline derived lactone **65j** could be synthesised (Scheme 24). Specifically, after alkylation with tertiary butyl ester **126**, ether **117j** was obtained which was converted to phenol **118j** by Claisen rearrangement. Deprotection of the ester functionality with trifluoroacetic acid (TFA) gave the corresponding acid **119j** which was lactonised using DMAP and DCC to give the quinolone derived lactone **65j** in a 38% yield across four steps.



Scheme 24: Synthesis of quinoline derived chromanone

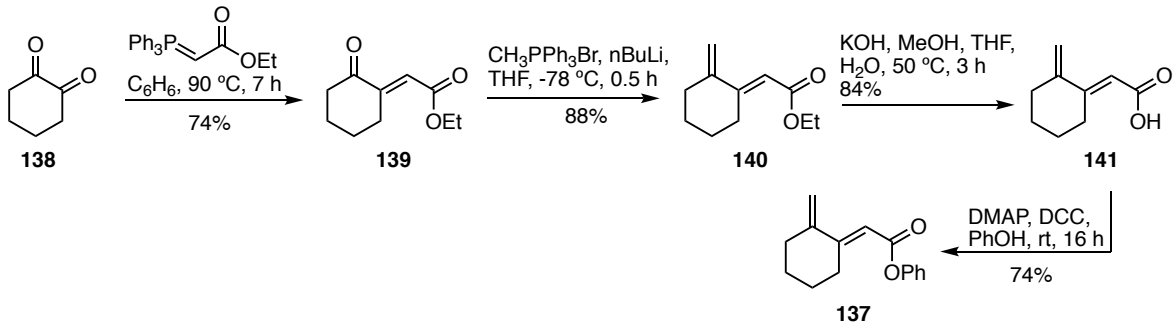
Next, attention turned to substrates that differed from the chromanone based materials described previously (Scheme 25). First, utilising a procedure by Fernandes et al.[53] the non-aromatic five- and six-membered Michael acceptors **127** and **128** were synthesised upon exposure of the corresponding lactones **129** and **130** to sodium hydride and ethyl formate, followed by paraformaldehyde.

In addition, ketone derived Michael acceptors **131** and **132** were prepared starting with indanone **133** and tetralone **134** using the procedure of Bugarin et al.[54] using paraformaldehyde and isopropyl amine trifluoroacetic acid salt as a catalyst in good yields. Lastly, the non-annulated variant **135** was synthesised in one step from phenol **115a** and methacroloyl chloride **136** following the procedure of Kakuchi et al.[55]



Scheme 25: Synthesis of Michael acceptors

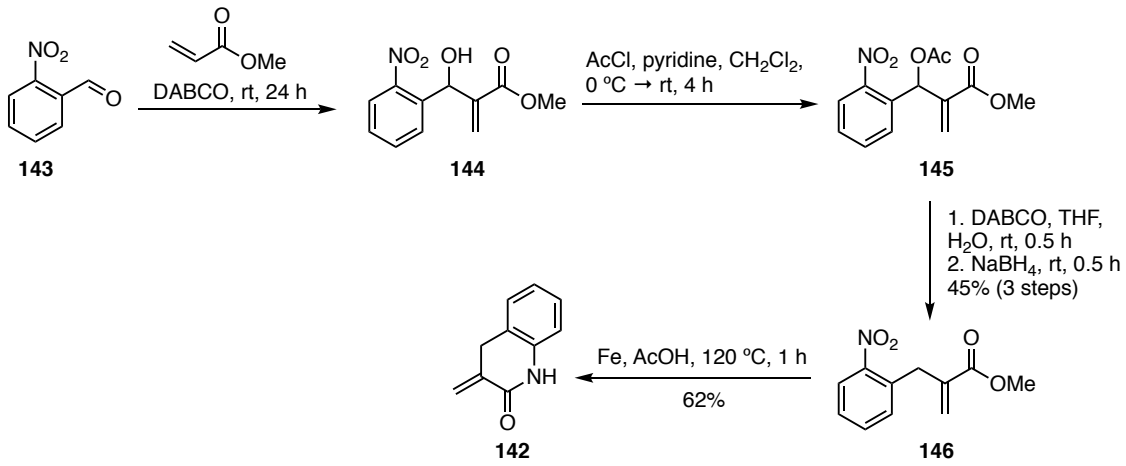
Extended Michael acceptors are of great interest to the Lupton group due to their potential use in annulation reactions, however, could also see use in the discovered aza-Stetter reaction. Synthesis of an α,β-γ,δ-vinyligous Michael acceptor **137** was achieved to examine a vinylogous aza-Stetter reaction (Scheme 26). Starting with 1,2-cyclohexadione **138**, and following the procedure of Taylor, a Wittig reaction provides ester **139** in a 74% yield.[56] A second Wittig reaction, utilising a procedure by Blanchett et al., provides α,β-γ,δ-diunsaturated ester **140** which can itself be used as a substrate in the aza-Stetter reaction.[57] Hydrolysis to the acid **141** followed by esterification with phenol using a procedure by Olsen et al.[58] then provides the α,β-γ,δ-diunsaturated phenolic ester **137** as it became clear that the aromatic portion of the electrophile appears to be important to its reactivity (see scheme 36).



Scheme 26: Synthesis of α,β-γ,δ-diunsaturated esters **137** & **140**

Lastly, lactam **142** was synthesised in 4-steps from *o*-nitro benzaldehyde **143** (Scheme 27). Starting with a Morita-Bayliss-Hillman reaction, using the procedure of Saikia et al.,[59] alcohol **144** formed and

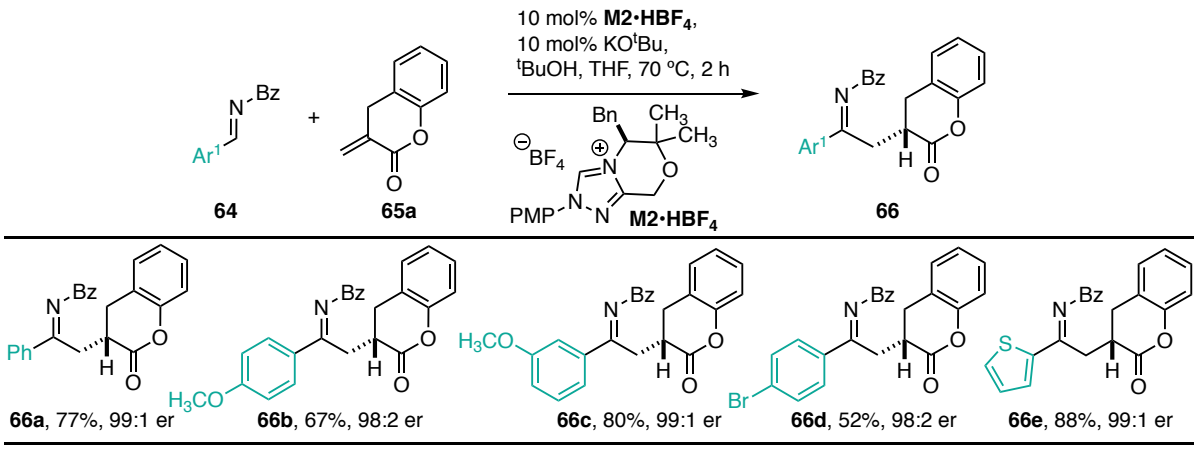
was then acetylated using standard conditions to give ester **145**.[60] The acetyl group can then reductively cleaved in a two-step process following a procedure by Felpin et al.[61] using DABCO and sodium borohydride to give ester **146** in 45% yield across 3 steps. Using a procedure by Ramachary et al.[62] reductive lactamisation then gave lactam **142** in 62% yield.



Scheme 27: Synthesis of lactam **142**

2.5.3 Variation of imine aryl group in the aza-Stetter reaction

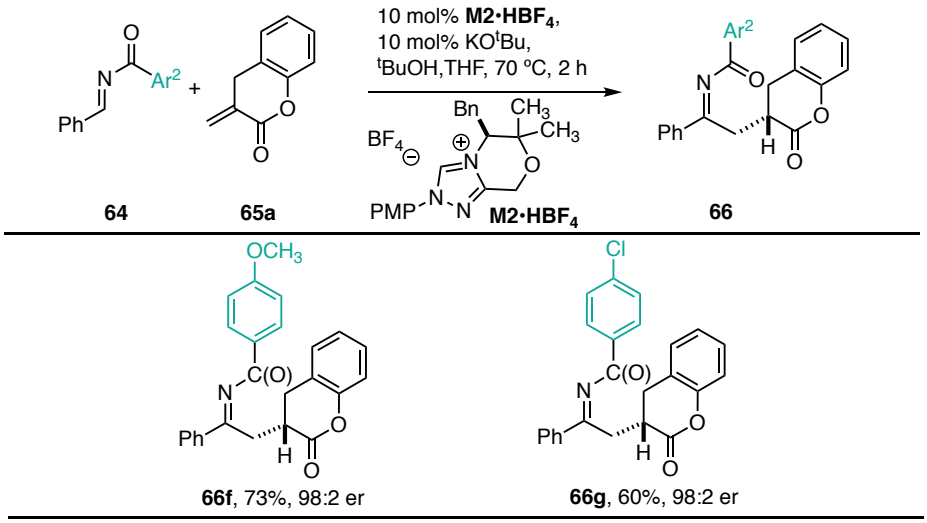
With 14 different benzoyl protected imines **64a, 64d-p** in hand, the scope of the aza-Stetter reaction with respect to the imine coupling partner was undertaken. We were interested in investigating the electronics of the aryl group of the imine starting material (i.e. **64**). When trialled in the reaction with chromanone **65a**, imine **64d** with an electron rich aryl group gave the desired γ-imino lactone **66b** in a reduced yield of 67% (Scheme 28). Conversely, electron rich imine **64o** gave an increased yield (80%) of lactone **66c**. Both occurred with high levels of enantioselectivity. Electron poor imine **64n** resulted in a reduced yield of 52% of the γ-imino lactone **66d**. Thiophene derived imine **64m** performed exceptionally in the reaction, providing the γ-iminoester **66e** in an 88% yield and 99:1 er. In general, more electron rich imines (e.g. **66c**) gave increased yields in the reaction, perhaps due to an aza-Breslow intermediate with increased nucleophilicity.



Scheme 28: Scope of the aza-Stetter reaction with relation to imine aryl group

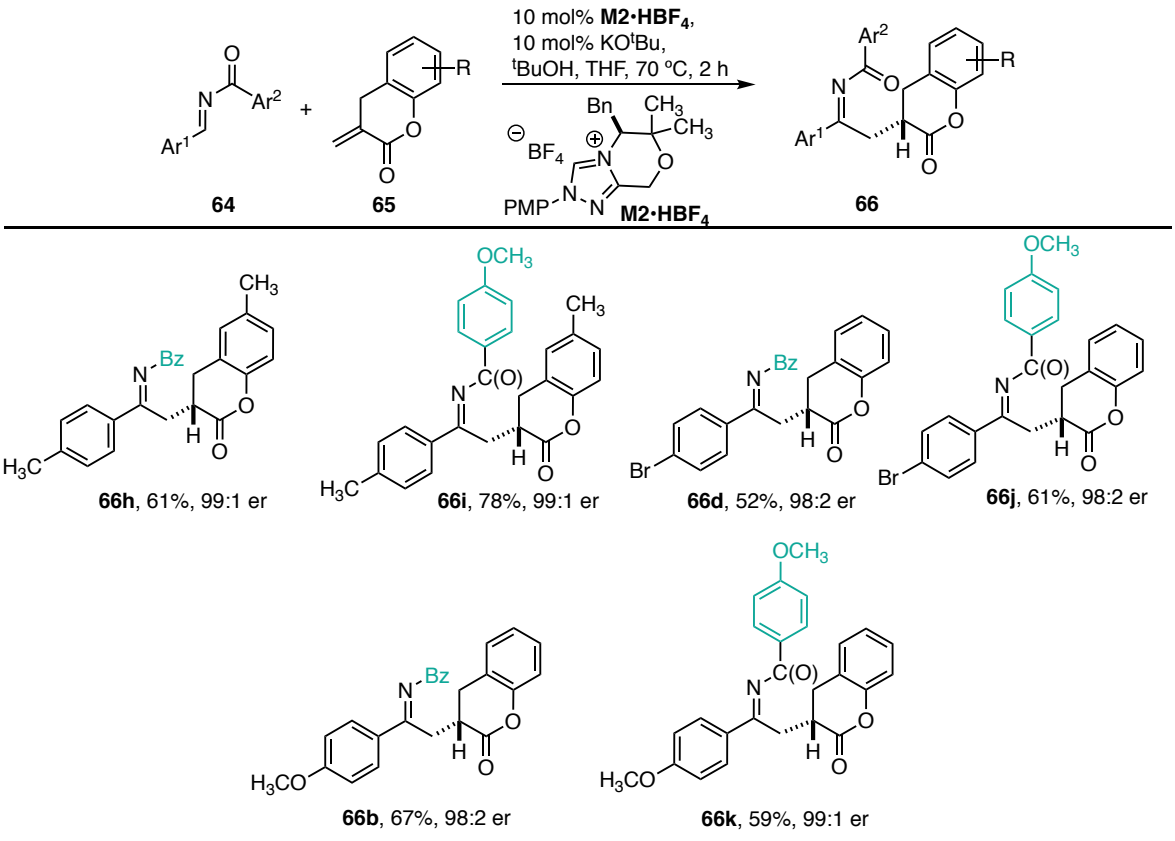
2.5.4 Variation of imine protecting group in the aza-Stetter reaction

Next, the electronics of the protecting group were examined. While throughout the optimisation it was demonstrated that the protecting group was integral to the reactions success, the subtle impact of the benzoyl groups electronics had not been examined. Pleasingly, when using electron rich benzoyl protected imine **64e** the product **66f** was obtained in a 73% yield with minimal isomerisation observed. This improved outcome may be due to increased nucleophilicity of the aza-Breslow intermediate. In contrast, electron poor benzoyl imine **64h** gave γ-iminoester **66g** in a reduced yield of 60%. Purification of this product proved difficult due to an observed increase in enamine product during column chromatography.



Scheme 29: Scope of the aza-Stetter reaction with relation to protecting group

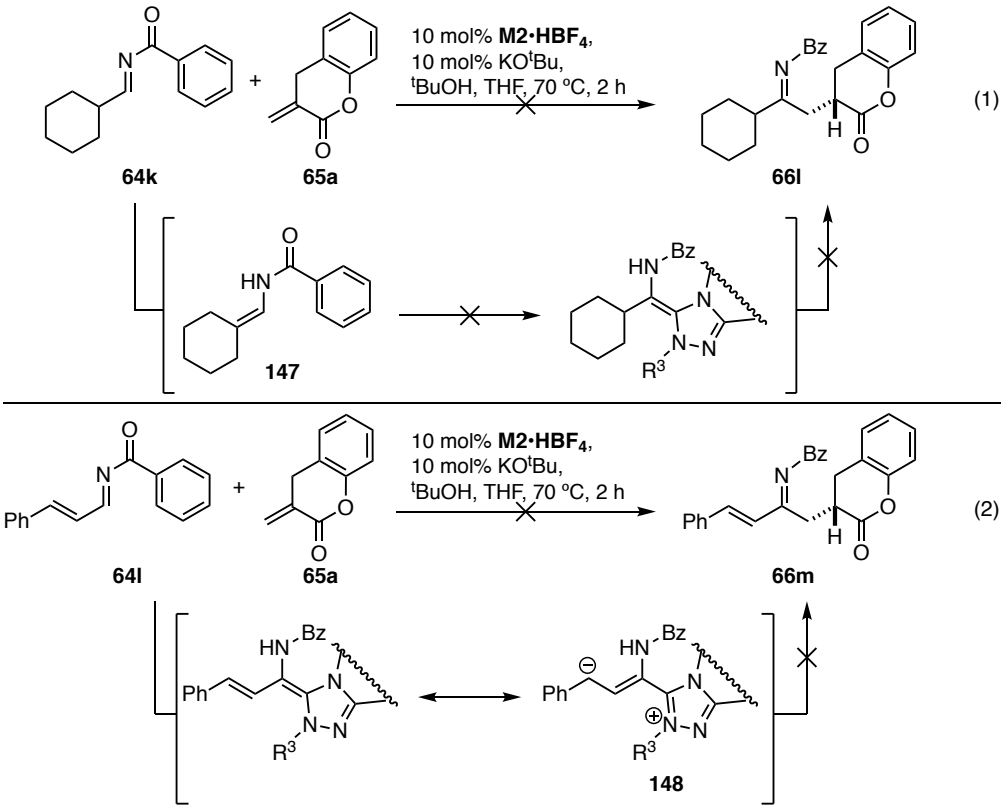
The success of the electron rich benzoyl group in the formation of imine **66f** was found to translate to other substrates that showed poor efficacy in the reaction (Scheme 30). For example, imine **64j** could be used to synthesise γ-imino ester **66h** in a 61% yield with high levels of enantioselectivity. However, when the imine was exchanged for the electron rich benzoyl protected imine **64g**, the yield of iminoester **66i** increased to 78% whilst enantiocontrol was maintained. Similar results were achieved with electron poor 4-bromo substrate **64n**, which resulted in an increase to 61% yield of iminoester **66j** from 52% of iminoester **66d**. However, utilising electron rich benzoyl imine **64f** resulted in a decreased yield of 59% of iminoester **66k** when compared to the benzoyl protected variant **66b**. It is likely that the observed increase in yields of some γ-iminoesters is due to the electron rich benzoyl group reducing the amount of isomerisation by reducing acidity of the α-protons of the imine. The reduced yield of iminoester **66k** observed could be caused by the very electron rich nature of imine **64f** causing a reduction in rate of NHC addition, resulting in lower conversions and increased reaction times, allowing greater amounts of isomerisation.



Scheme 30: Effect of the electron rich benzoyl group on yield

2.5.5 Incompatible imines in the aza-Stetter reaction

Unfortunately, imines derived from aliphatic aldehydes (i.e. **64k**) showed no reactivity in the aza-Stetter reaction (Scheme 31). This is most likely due to their reduced electrophilicity when compared to their aromatic counterparts. It is also likely that facile isomerisation to the enamine isomer **147** prevents NHC addition to aliphatic imines (i.e. **64k**) as decomposition of the imine was observed in the reaction, whilst the chromanone **65a** was recovered unreacted. In a similar manner, the imine derived from cinamaldehyde **64l** gave no reaction under our conditions. We reasoned that the bulky catalyst used could allow for formation of an aza-homoenolate **148**, which may be less reactive towards a 1,4-addition with the chromanone **65a**, and could be more easily quenched.[63]

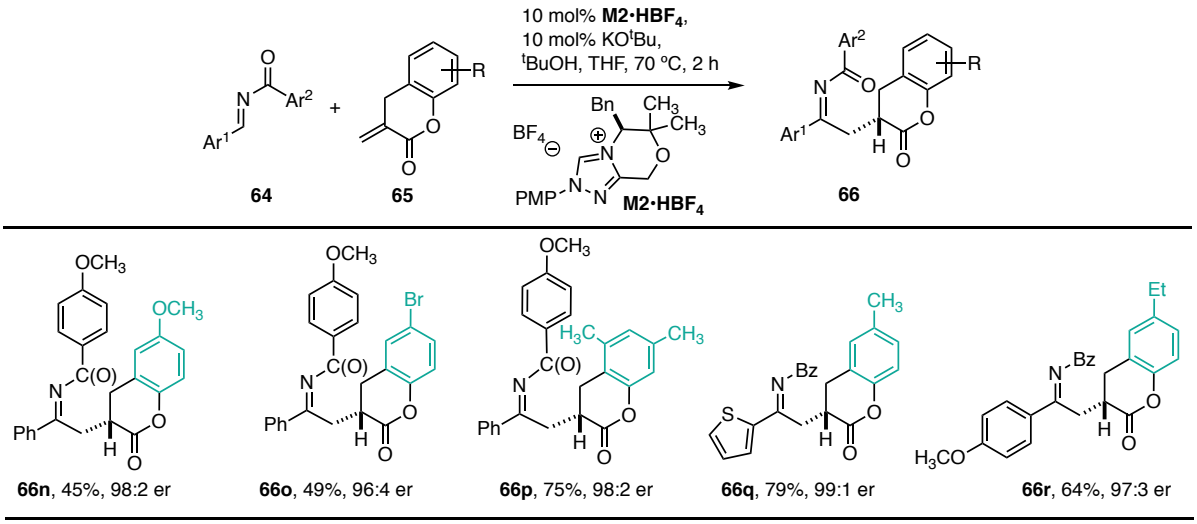


Scheme 31: Incompatible imines in the aza-Stetter reaction

2.5.6 Variation of Michael acceptors in the aza-Stetter reaction

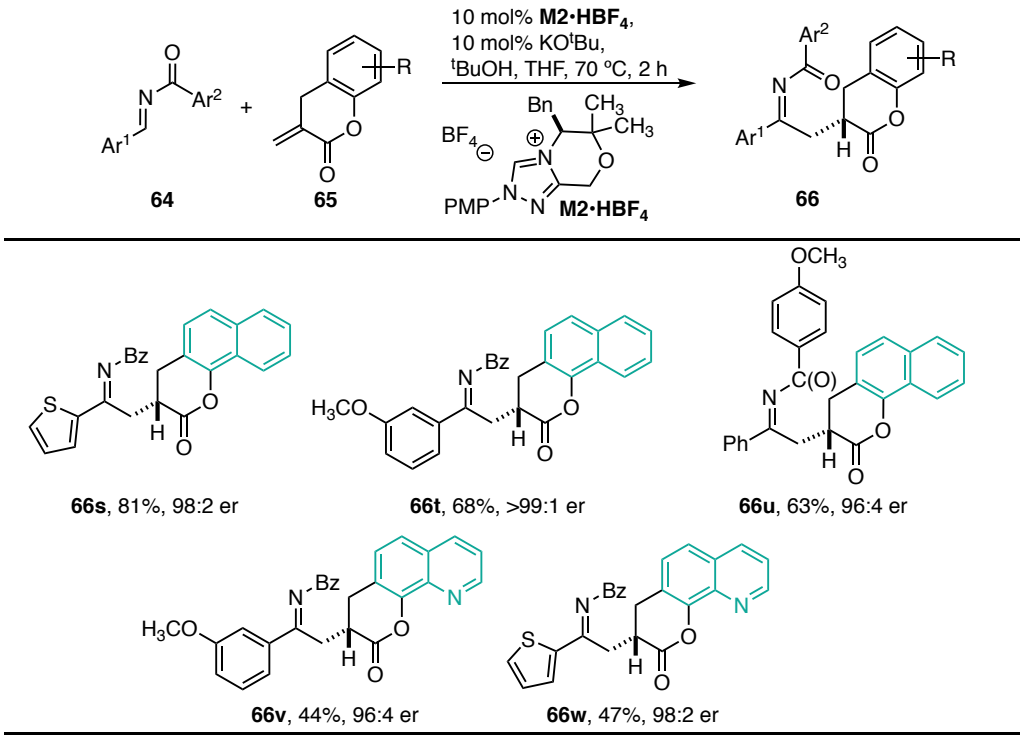
With 17 Michael acceptors prepared, along with the benzoyl imines introduced previously, the generality of the aza-Stetter reaction was now examined with respect to the Michael acceptor (Scheme 32). First, the effect of electronics of the chromanone coupling partner were examined. It was reasoned that electron withdrawing groups on the chromanone should increase the electrophilicity of this species, resulting in increased yields. When electron rich chromanone **65b** was subjected to the

reaction conditions, a reduced yield of 45% of iminoester **66n** was observed, consistent with this hypothesis. However, when electron poor chromanone **65c** was used, it also resulted in a reduced yield of iminoester **66o**. This may be because the increased electrophilicity of this species could result in the carbene adding to the Michael acceptor rather than the imine, thereby sequestering the carbene and consuming the Michael acceptor.[64] Although no tail to tail dimer was ever isolated, the reactions with electron poor species did result in decomposition which could possibly be attributed to β-anion chemistry. Bulky substituents were tolerated well in the reaction with dimethyl iminolactone **66p** isolated in a 75% yield, with good levels of enantiocontrol. Methyl and Ethyl substituents were also tolerated in the reaction with iminolactones **66q** and **66r** isolated in 79% and 64% respectively.



Scheme 32: Scope of the aza-Stetter reaction with relation to chromanone

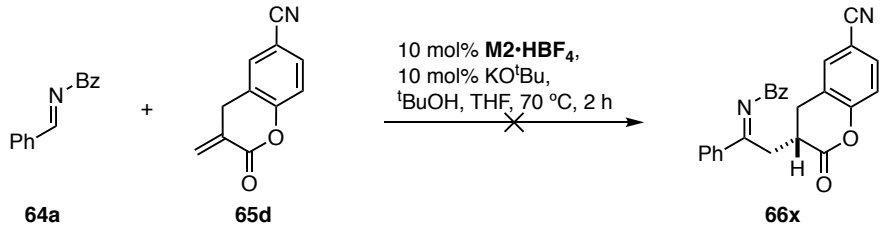
The range of chromanone partners could also be extended to tricyclic aromatic species such as naphthyl and quinoline derived chromanones **65i** and **65j** (Scheme 33). Unsurprisingly, the naphthyl chromanone performed similarly to the parent chromanone **65a**, giving imines **66s-u** in good yield and excellent enantioselectivity. Unfortunately, using quinoline derived chromanone **65j** a significant reduction in yield was observed with iminoesters **66v-w**, although the enantioselectivity remained high. This low yield, we believe, is due to difficulties in purification. The increased polarity of the quinolone products led to extended time for chromatographic separation, which may have led to increased decomposition, and hence, reduced yields.



Scheme 33: Scope of the aza-Stetter reaction with extended aromatic substrates

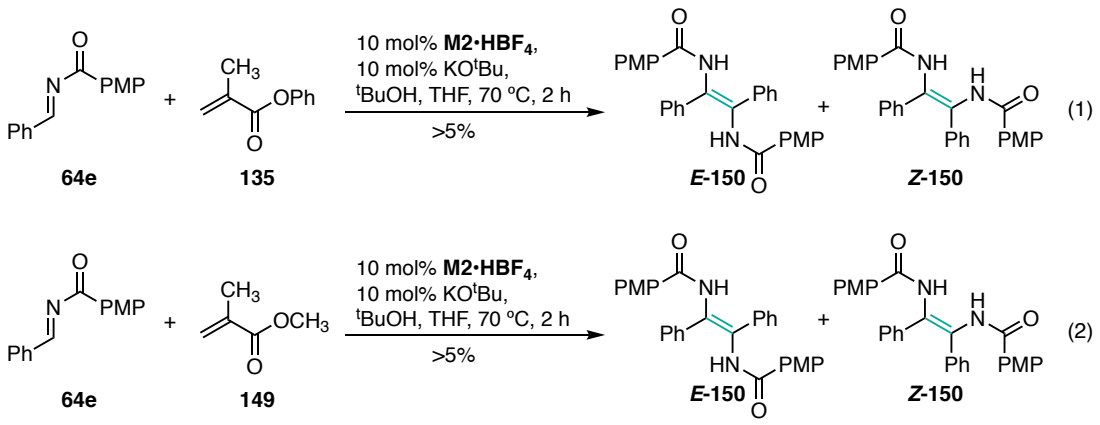
2.5.7 Incompatible Michael acceptors in the aza-Stetter reaction

Unfortunately, a number of Michael acceptors that were not compatible with the reaction conditions. Chromanones containing strongly electron withdrawing groups, such as a nitrile (i.e. **65d**), failed to give any coupled materials (i.e. **66x**, Scheme 34). As discussed above, this may be because the increased electrophilicity of this species could result in the carbene adding to the Michael acceptor.



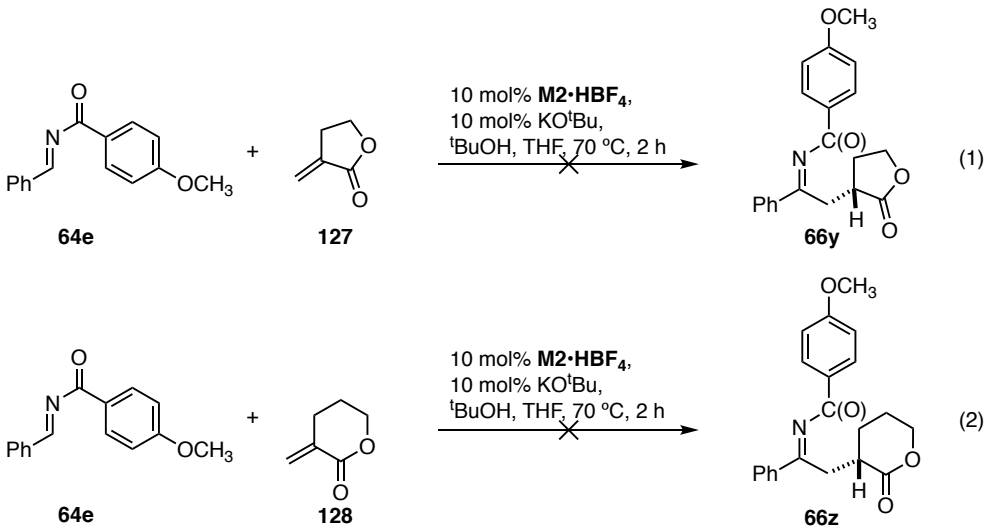
Scheme 34: Incompatible electron poor chromanones

When acrylates (i.e. **135** & **149**) were used as the Michael acceptors, none of the desired imine was observed (Scheme 35). Instead, trace amounts of the benzoin products ***E*-150** and ***Z*-150** were the only isolated materials. This was true with both the phenyl ester and methyl ester, using a number of different imines. We reasoned that the lack of annulation in these substrates may allow the olefin to reside in conformations that reduce conjugation, and hence, the reactivity necessary for 1,4- addition.



Scheme 35: Incompatible acrylates in the aza-Stetter reaction

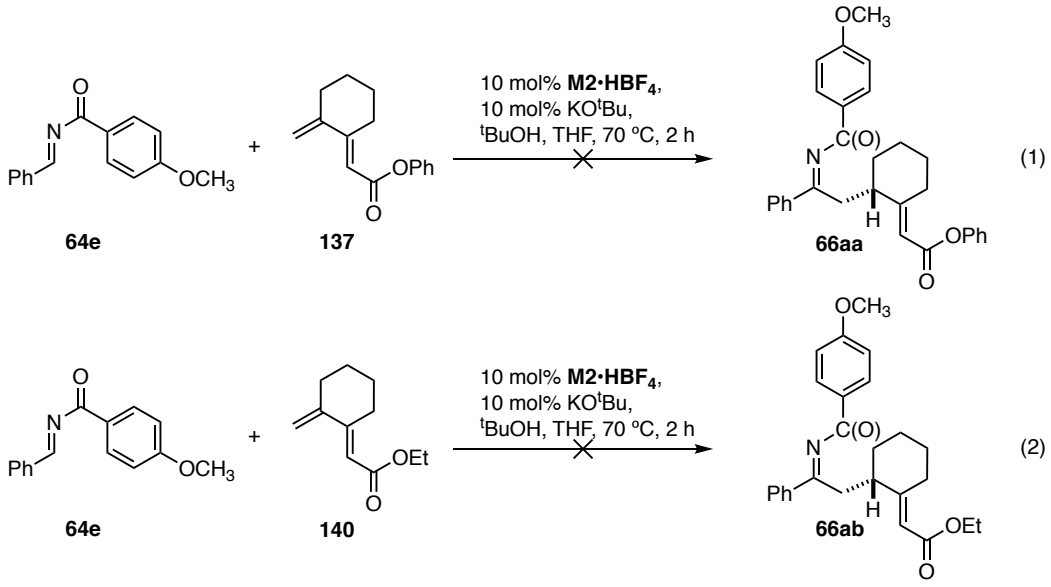
Lactones that did not contain an aromatic ring (i.e. **127** & **128**) were also tested in the aza-Stetter reaction (Scheme 36). Unexpectedly, in all cases and using multiple imines substrates, no aza-Stetter products (i.e. **66y-z**) were observed. Most of the starting materials were recovered from these reactions, with decomposition of the benzoyl imine also observed. This result suggests that the aromatic ring plays an important role in the viability of the reaction. Considering its lack of proximity to the Michael acceptor and the modest impact on alkene electrophilicity expected from this change, this result is surprising.



Scheme 36: Other incompatible Michael acceptors

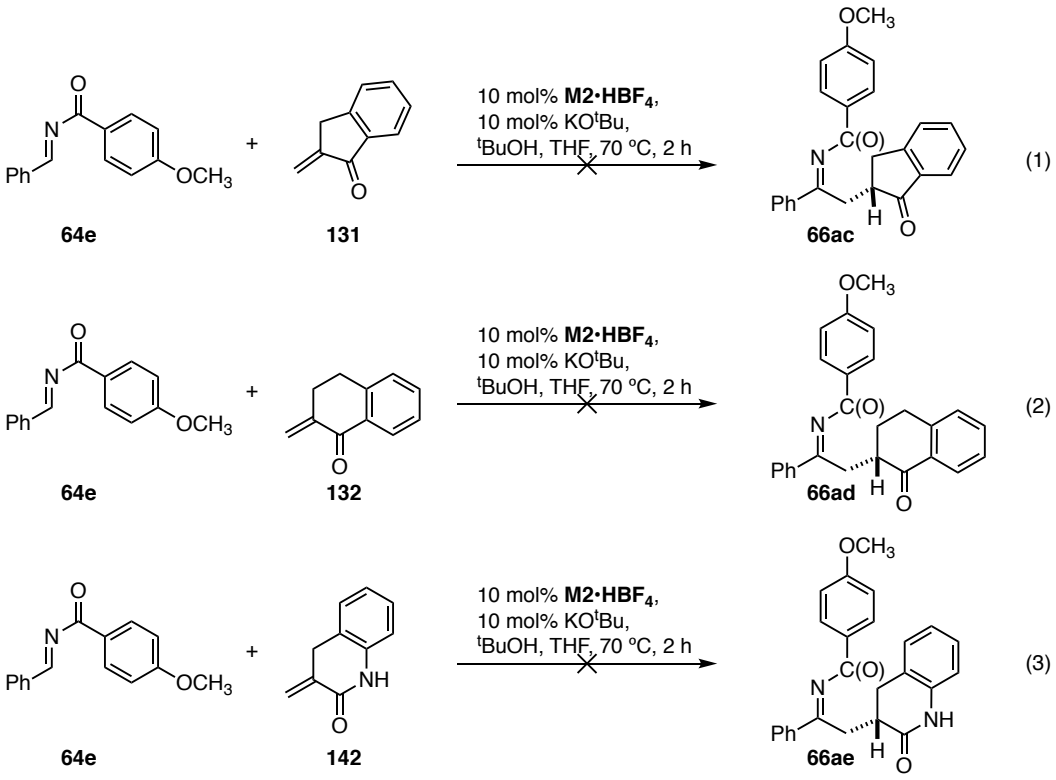
Extended Michael acceptors (i.e. **137** and **140**) showed no reactivity at either the 6- or 4-position (Scheme 37). Again, only the benzoin product **150** was isolated in trace amounts with none of the iminolactones **66aa-ab** observed. Both the ethyl ester and phenyl ester were incompatible. Substrates of this kind have shown reactivity at the 6-position with alternate nucleophiles, such as enolates of β-

ketoesters, within the group.[65] It is likely that the reduced electrophilicity of these species results in lack of reaction.



Scheme 37: Incompatible dienyl Michael acceptors

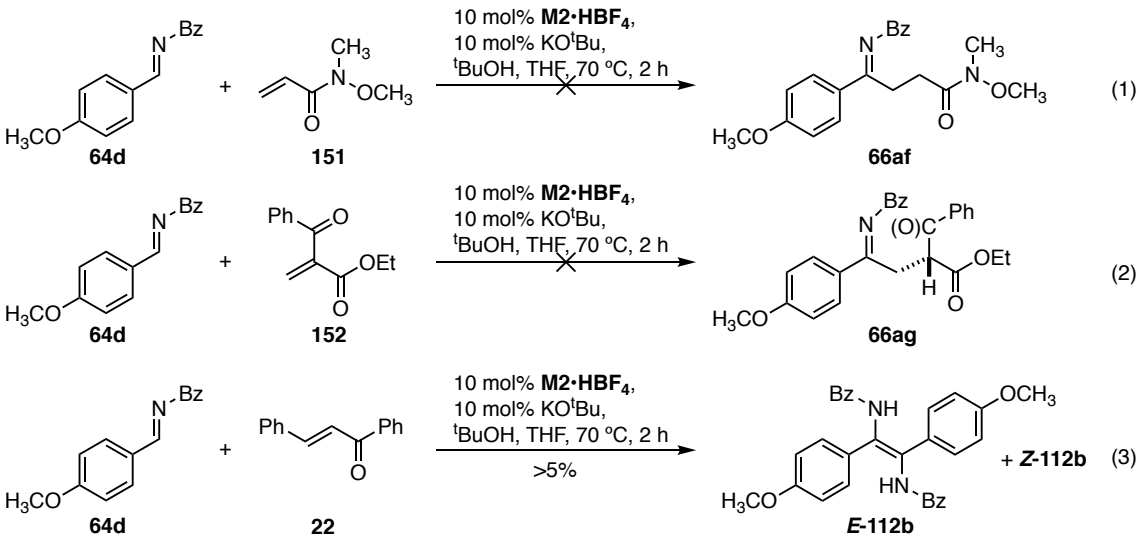
We were interested in Michael acceptors derived from ketones and amides (Scheme 38). To this end, ketones **131** and **132** and amide **142** were tested in the aza-Stetter reaction. Unfortunately, in the case of ketones **131** and **132**, only significant decomposition and polymerisation was observed rather than γ-iminoesters **66ac-ad**. This is likely due to the increased electrophilicity of the ketone facilitating NHC addition to the Michael acceptor, leading to oligomerisation and polymerisation in the reaction. The amide Michael acceptor **142** also produced none of the desired product **66ae**. We believe this may be due to the acidic proton on the nitrogen quenching the reaction. So far, attempts to protect that nitrogen have resulted in a mixture of olefin-isomers.



Scheme 38: Non-ester substrates in the aza-Stetter reaction

A range of more exotic Michael acceptors[ii] were also tested in the aza-Stetter reaction (Scheme 39). In the case of the acrylamide **151** significant polymerisation of the substrate was observed, with none of the desired imine product **66af** (Scheme 39, eq. 1). The methylene malonate **152** also decomposed in the reaction conditions, giving none of iminoester **66ag** (Scheme 39, eq. 2).[66] Finally, chalcone **22** gave no reaction and a small amount of the benzoin product **112** was observed (Scheme 39, eq. 3). This is likely due to the β-substituent hindering nucleophilic addition of the aza-Breslow intermediate.

[ii] Michael acceptors were donated by Jhi Ametovski, Adam Ametovski and Changhe Zhange respectively

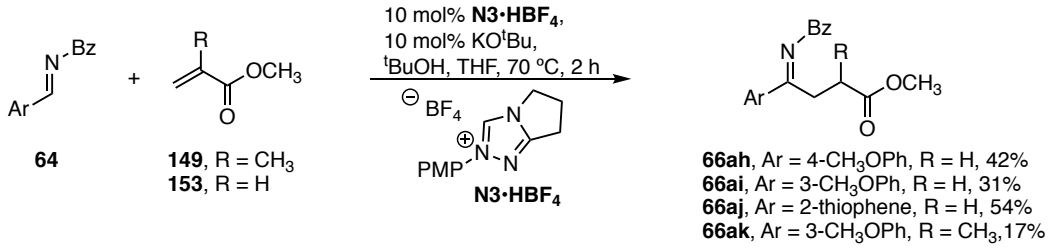


Scheme 39: Non-ester substrates in the aza-Stetter reaction

These studies indicate that the aza-Breslow intermediate is likely to be only a moderately nucleophilic species, as slight variations in the electrophilicity of the Michael acceptor result in no reaction or decomposition. Whilst there was limited variability in the tolerated Michael acceptors, a total of 21 examples of γ-iminoesters **66a-k** and **66n-w** were isolated in moderate to excellent yields (44-88%) and excellent enantioselectivity (most ≥98:2 er).

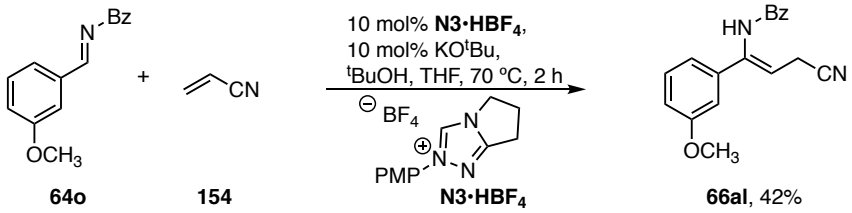
2.6 An Achiral Variant of the Aza-Stetter Reaction

The aza-Stetter reaction appears to have a somewhat limited scope, due to a fine balance between a number of different reaction pathways (*vide supra*). The critical role of the chromanone derived Michael acceptors (i.e. **65**) in facilitating the reaction remains unknown. However, whilst some substrates were incompatible using the standard conditions, some success was achieved with acrylate substrates using achiral catalyst **N3•HBF$_4$** bearing a PMP *N*-substituent. A total of four new achiral γ-iminoesters **66ah-ak** could be synthesised from simple acrylates (Scheme 40). Using methyl acrylate **153** and imines with electron rich (**64d** and **64o**) and heteroaromatic aryl groups (**64m**), iminoesters **66ah-aj** were formed in 31-54% yields. Unfortunately, when methyl methacrylate **149** was used the yield was significantly reduced, with iminoester **66ak** formed in 17% yield.



Scheme 40: Acrylates in an achiral aza-Stetter reaction

The achiral version of the aza-Stetter reaction also tolerates non-ester substrates. When acrylonitrile **154** is used with electron rich imine **64o** the reaction proceeds to give enamine **66al** (Scheme 41). Shortening reaction time gave the same results, with only enamine **66al** isolated with no imine ever observed. Even though the imine isomer was unable to be produced, this represents the first example of a non-ester substrate in the aza-Stetter reaction.

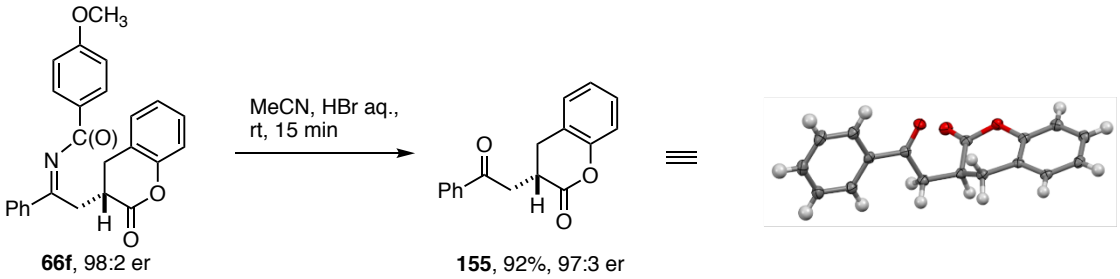


Scheme 41: Acrylonitrile in an achiral aza-Stetter reaction

2.7 Derivatisations[iii]

Derivatisations of the aza-Stetter products were undertaken to probe their utility, and to determine absolute stereochemistry. Due to the general instability of the imine products X-ray analysis was challenging. Consequently, it was reasoned that hydrolysis of the imine to a ketone would result in an adduct better suited to analysis. As such, hydrolysis of iminoester **66f** using hydrobromic acid in acetonitrile gave γ-ketoester **155** in a 92% yield with only slight erosion of the enantiomeric ratio (Scheme 42). Single crystals were grown and X-ray analysis performed and the absolute stereochemistry of the compounds was determined to be *(S)* as shown.

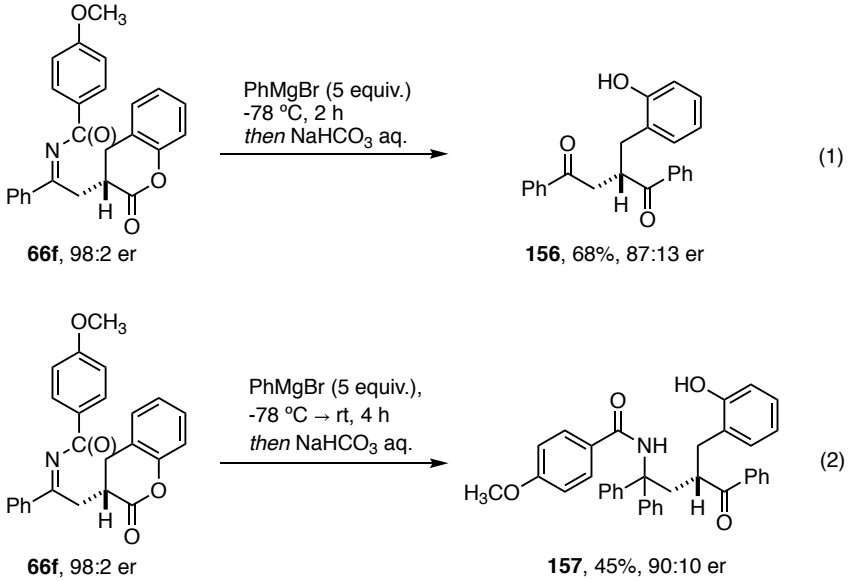
[iii] Derivatisations were performed in conjunction with Changhe Zhang



Scheme 42: Hydrolysis of iminoester **66f** to grow crystals

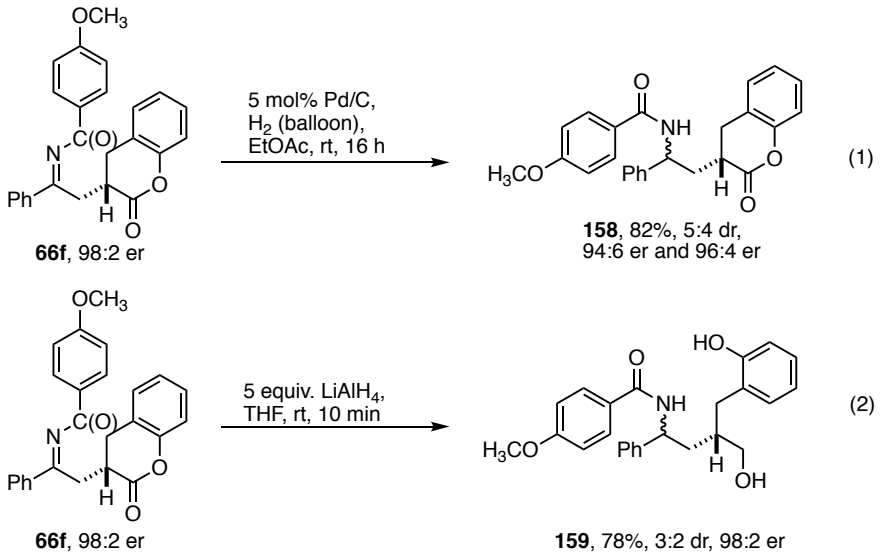
Next, we believed that we could perform a chemoselective Grignard addition to the imine functionality present in the γ-iminoesters. Starting with a reaction of phenyl magnesium bromide with imine **66f** at low temperatures, the reaction was slow and required multiple equivalents of Grignard reagent to facilitate the reaction (Scheme 43, eq. 1). Pleasingly a chemoselective addition was possible, but reaction occurred at the lactone in preference to the imine, and ketone **156** was isolated upon hydrolysis of the imine during aqueous work up in a 68% yield with slight erosion of the enantiomeric ratio.

Following this, we believed an exhaustive addition of phenyl magnesium bromide at higher temperatures would result in an amine product, rather than a ketone (Scheme 43, eq. 2). When the Grignard reaction was allowed to warm to room temperature in order to facilitate complete addition to both the lactone and the imine, gives triphenyl benzamide **157** was isolated in a 45% yield with slightly lowered enantiomeric ratio.



Scheme 43: Grignard addition to γ-iminolactones

Next, reductions of the imine functionality in γ-iminoester **66f** was examined. A hydrogenation utilising palladium on carbon results in a reduction of the imine that occurs in high yield but with modest diastereoselectivity to give amine **158** (Scheme 44, eq. 1). This modest selectivity is perhaps caused simply by the chiral centre being too remote to direct the reduction. Next, we attempted reduction with lithium aluminium hydride (Scheme 44, eq. 1). This reduces both the imine and the lactone to provide amino diol **159** in good yield but again with modest diastereoselectivity.



Scheme 44: Derivatisations of imine products

2.8 Conclusions

The work presented herein represents the first enantioselective reaction of the aza-Breslow intermediate. A total of 21 examples of the aza-Stetter reaction are reported with good yields (44-88%) and excellent enantioselectivity (most ≥98:2 er). An aza-benzoin reaction was also discovered which represents the first imine-imine coupling catalysed by NHCs. Given the large array of reactions that exploit the Breslow intermediate (accessed from aldehydes), it is likely that discovery of the aza-Breslow variants of these reactions could open a new field of NHC catalysis. This exploration will lead to a diverse range of methodologies involving imines in both umpolung and normal polarity reactions. These reactions would involve novel imine based NHC intermediates and allow access to important nitrogen-containing compounds. Work on this topic is on-going within the Lupton group.

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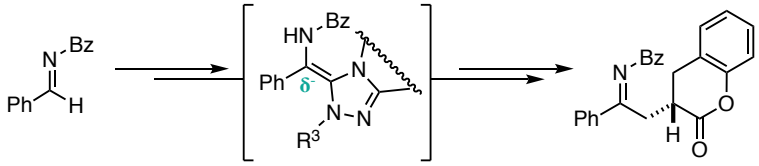
Chapter 3: Mechanistic Insight into the NHC Catalysed Synthesis of γ-iminoesters



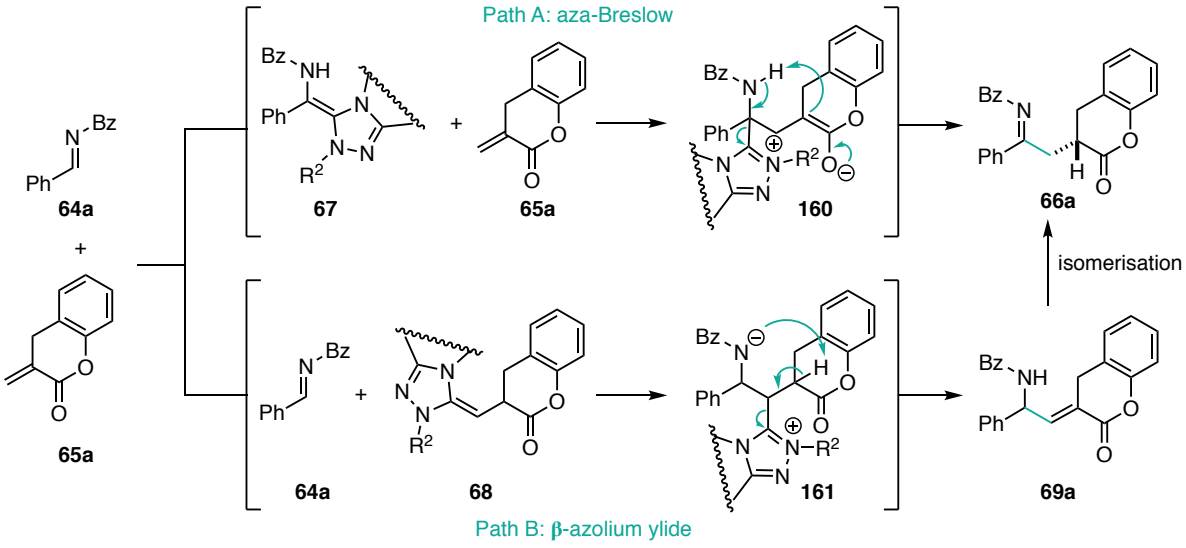
The work presented in this chapter involves an investigation into the mechanism of the NHC catalysed synthesis of γ-iminoesters detailed in Chapter two. Mechanistic studies into the isomerisation between imine, enamine and enone support imine umpolung rather than umpolung of the Michael acceptor. A preliminary kinetic analysis shows that the reaction is first order in relation to catalyst and imine, and zero order with respect to lactone. This, along with competition studies, suggest that the turnover limiting step is NHC addition to the imine. Deuterium labelling studies also support the proposed mechanism.

3.1 Background

3.1.1 Overview and context

There have been extensive studies undertaken on the mechanism of the benzoin and Stetter reactions as well as a number of investigations into the Breslow intermediate itself (*vide supra*).[1-11] However, due to the limited number of examples of reaction discovery with the aza-Breslow intermediate,[12-14] there have been far fewer mechanistic studies of this intermediate.

The NHC catalysed synthesis of γ-iminoesters described in chapter two could proceed via two conceivable mechanisms (Scheme 1). The first possibility involves NHC addition to the imine **64a** and subsequent formation of the aza-Breslow intermediate **67**. The 1,4-addition of the aza-Breslow intermediate **67** to the Michael acceptor **65a** provides intermediate **160**. An intramolecular proton transfer and catalyst elimination then provides the γ-imino lactone **66a**. The second possibility begins with catalyst addition to the Michael acceptor **65a** and formation of the β-azolium ylide **68**.[15-16] This β-umpolung intermediate can then undergo addition to imine **64a** to give intermediate **161** followed by a similar intramolecular proton transfer and catalyst elimination to provide enone **69a**. This species can then undergo olefin isomerisation to provide the γ-imino lactone product **66a**.

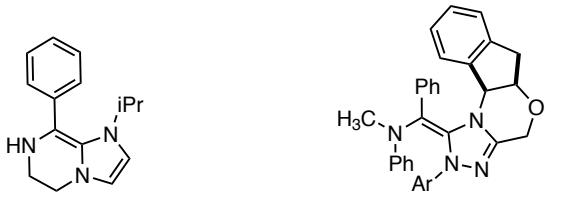


Scheme 1: Possible mechanistic pathways to γ-imino lactone **66a**

The work presented in this chapter outlines mechanistic studies into the NHC catalysed reaction previously described in Chapter two. Firstly, an investigation is undertaken to determine which of the mechanistic pathways is more likely. This is followed by studies to determine the turnover limiting step. A kinetic study is also undertaken to determine reaction order with relation to each of the starting materials.

3.1.2 Isolation of the aza-Breslow intermediate

In 2009, the Douthwaite group were the first to isolate an aza-Breslow intermediate through use of an NHC with a tethered aldimine to promote formation of the cyclic aza-Breslow intermediate **162** (Figure 1).[17] This pioneering work was the first to confirm the aza-Breslow intermediate's existence. Following this, Rovis *et. al.* isolated and fully characterised the aza-Breslow intermediate **163** by addition of the indanol NHC to iminium salts.[18] These studies also demonstrated the reversible nature of carbene addition to imines. They were, however, unable to demonstrate that these isolated intermediates could react as iminyl anion equivalents in the same way that Berkessel showed for the Breslow intermediate (see Chapter 1).[4] Therefore, whether the aza-Breslow intermediate could be used to facilitate catalytic imine umpolung reactions remained unknown.



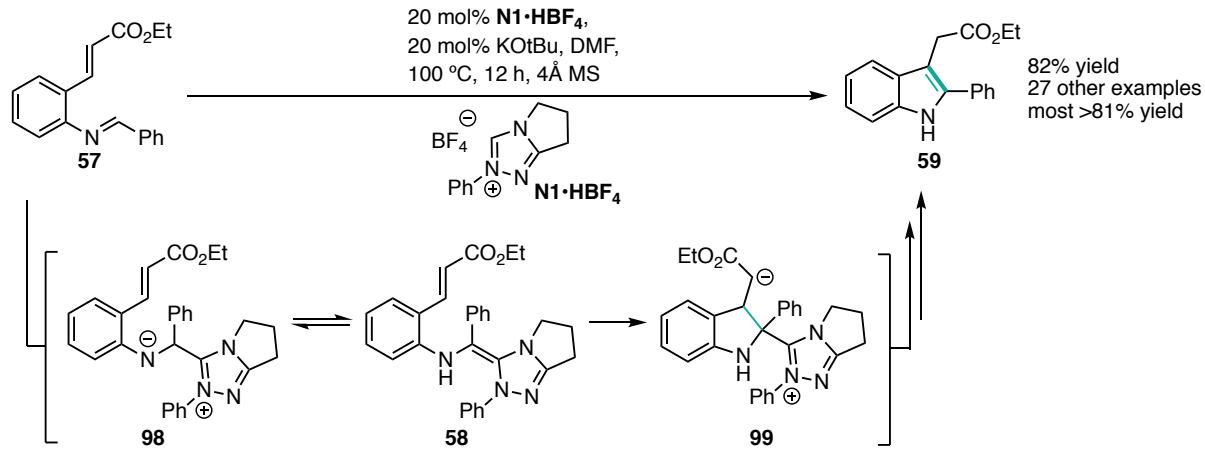
162
Douthwaite 2009

163, Ar = 2,4,6-$Br_3C_6H_2$
Rovis 2012

Figure 1: Isolated aza-Breslow intermediates

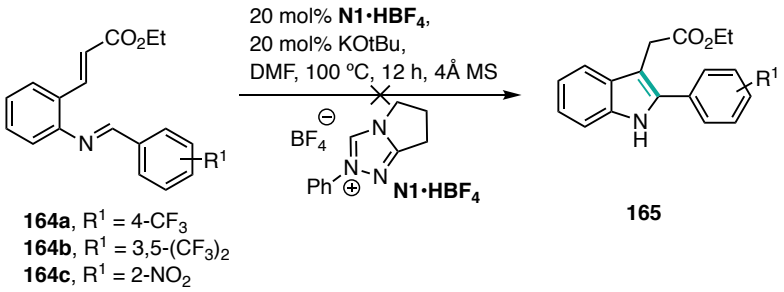
3.1.3 Use of the aza-Breslow intermediate in synthesis

It wasn't until 2017 that the first catalytic reaction utilising the aza-Breslow intermediate was realised (Scheme 2). Biju and co-workers discovered an annulation reaction of imines with tethered Michael acceptors (i.e. **57**) to afford indoles (i.e. **59**) in good to excellent yields.[12] Biju proposed that this occurs via umpolung of the imine functionality by NHC addition to give intermediate **98** before formation of the aza-Breslow intermediate **58**. Cyclisation provides enolate **99** before catalyst elimination and proton transfer yields indole **59**.



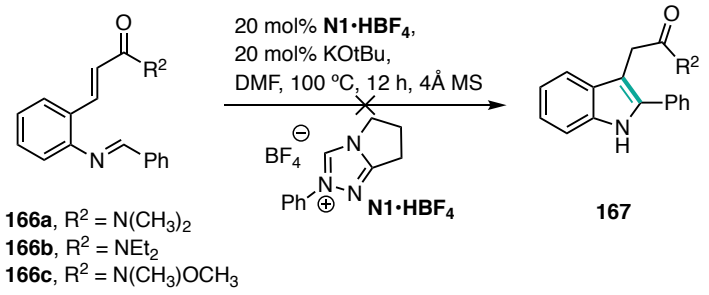
Scheme 2: Biju's synthesis of indoles via NHC catalysis

Whilst they were unable to isolate the aza-Breslow intermediate **58**, some important preliminary mechanistic studies were undertaken (Scheme 3). Firstly, when imines with electron withdrawing groups (i.e. **164a-c**) were used, no reaction was observed. Biju suggests this is because the resultant aza-Breslow intermediate is not nucleophilic enough to perform the required Michael addition. If umpolung of the Michael acceptor was the prevailing mechanism, one might expect electron poor imines to act as better electrophiles in this reaction.



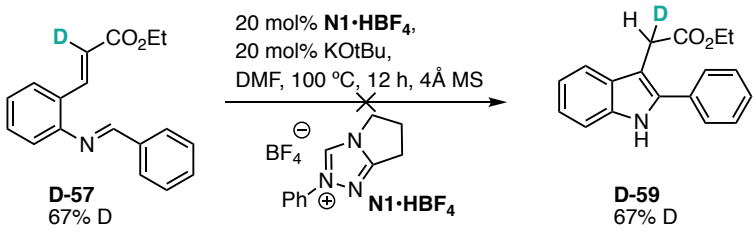
Scheme 3: Biju's mechanistic studies through varied electronics of the imine

Next, when the ester moiety is replaced with a less electrophilic amide (i.e. **166a-c**), indole formation is again prevented (Scheme 4). If umpolung of the Michael acceptor was the prevailing mechanism, it would be expected that a more electron rich Michael acceptor would still facilitate formation of indole **167**. These results are both consistent with the aza-Breslow mechanism, however they also highlight that the aza-Breslow intermediate is only moderately nucleophilic, with modest changes to substrate causing the reaction to fail – a result mirrored by our own work in the area (see Chapter two).



Scheme 4: Biju's mechanistic studies through varied electronics of the Michael acceptor

Biju and co-workers also undertook deuterium labelling studies in an attempt to confirm their mechanistic hypothesis (Scheme 5). After labelling the α-position of the ester (i.e. **D-57**) the reaction resulted in 100% retention of deuterium in the same position within the product (i.e. **D-59**). If the NHC were to add to the Michael acceptor, one might expect to see some scrambling/erosion of the deuterium at the α-position due to the reversibility of β-azolium ylide formation. Again, this suggests a pathway that proceeds via imine umpolung.



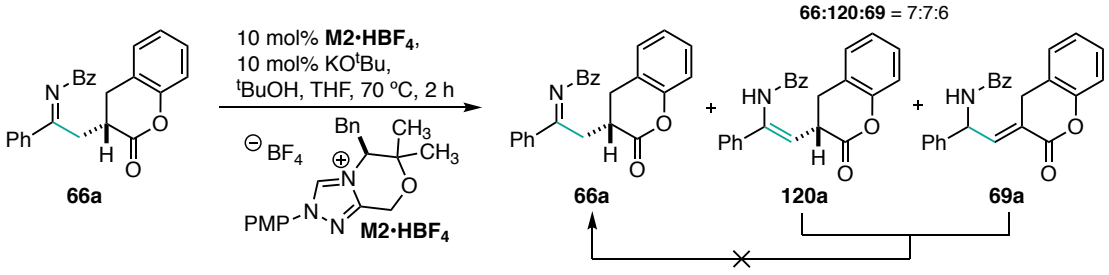
Scheme 5: Biju's mechanistic insights via deuterium labelling

3.2 Elucidation of the Reaction Mechanism

3.2.1 Isomerisation Studies

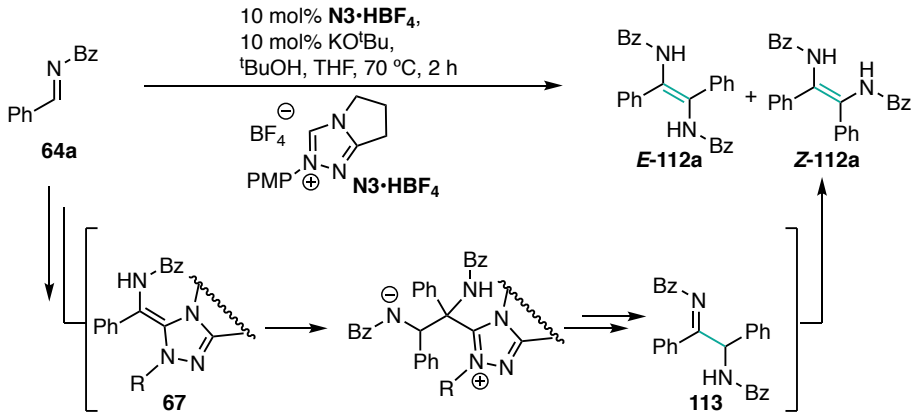
During our optimisation and scope studies (see Chapter 2) we often observed the formation of enamine **120** and enone **69** along with the desired imine **66**. We postulated that these isomers are produced after initial formation of the imine **66**, followed by an isomerisation event, and not the other way around. In order to investigate this, we set about designing an isomerisation study (Scheme 6). After isolating imine **66a**, it was resubjected to the reaction conditions. This gave a mixture of imine **66a**, enamine **120a** and enone **69a** in a 7:7:6 ratio. However, when the enamine **120a** and enone **69a** isomers were resubjected to the reaction conditions, none of the imine product **66a** was observed. This indicates that the imine **66a** forms first and isomerises to the enamine **120a** and enone **69a** over time. If the β-azolium ylide (i.e. **68**, Scheme 1) is formed, then elimination of the NHC would provide

enone **69a** or enamine **120a**. Since these are unable to isomerise to the major product, imine **66a**, these studies are not consistent with β-azolium ylide formation, and suggest an aza-Breslow pathway.



Scheme 6: Imine, enamine and enone isomerisation studies

The aza-benzoin reaction (discussed in detail in Chapter 2) also provides evidence for the viability of aza-Breslow formation (Scheme 7). As there is no secondary electrophile, the only way that the enediamine **112** can form is via the aza-Breslow intermediate **67**. Whilst this is not direct evidence for its formation in the presence of conjugate acceptor **65**, it does prove the aza-Breslow intermediate **67** is able to form with our substrates under our reaction conditions.

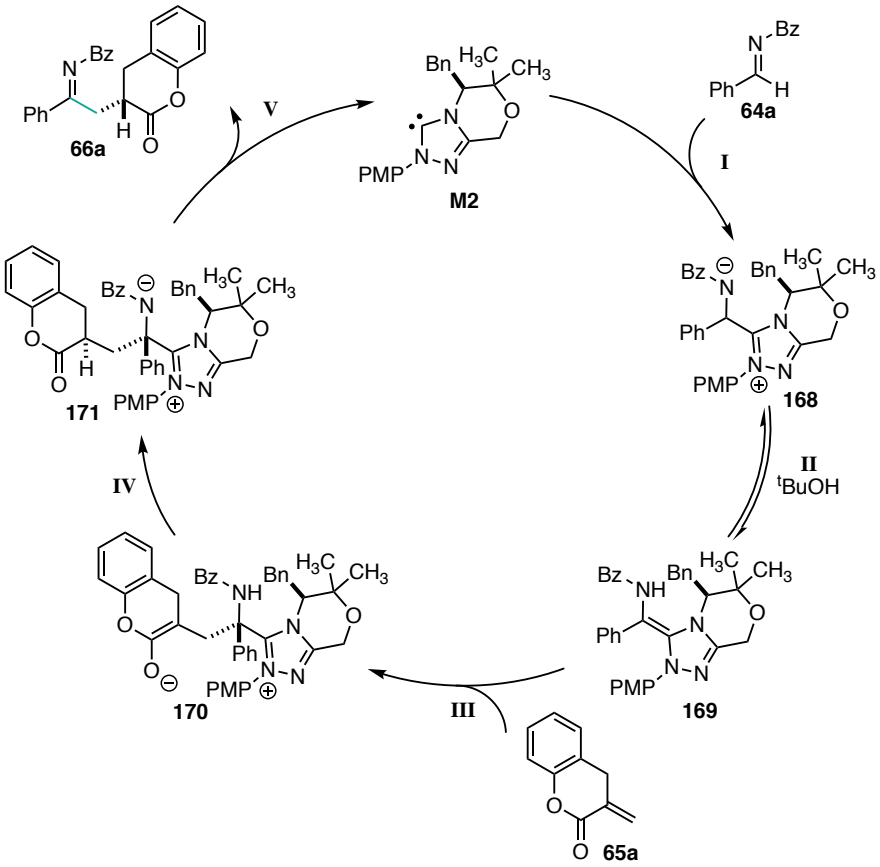


Scheme 7: Proposed formation of enediame **112**

3.2.2 Proposed mechanism

Taking these results into consideration, a likely mechanism for the reaction is as follows. The reaction begins with addition of the NHC **M2** to the benzoyl protected imine **64a** (Scheme 8, step **I**) to give intermediate **168**, which undergoes tautomerisation mediated by ^{t}BuOH (Scheme 8, step **II**) to give the aza-Breslow intermediate **169**. The aza-Breslow intermediate **169** then undergoes 1,4-addition to chromanone **65a** (Scheme 8, step **III**) to afford enolate **170**. This enolate can then undergo a

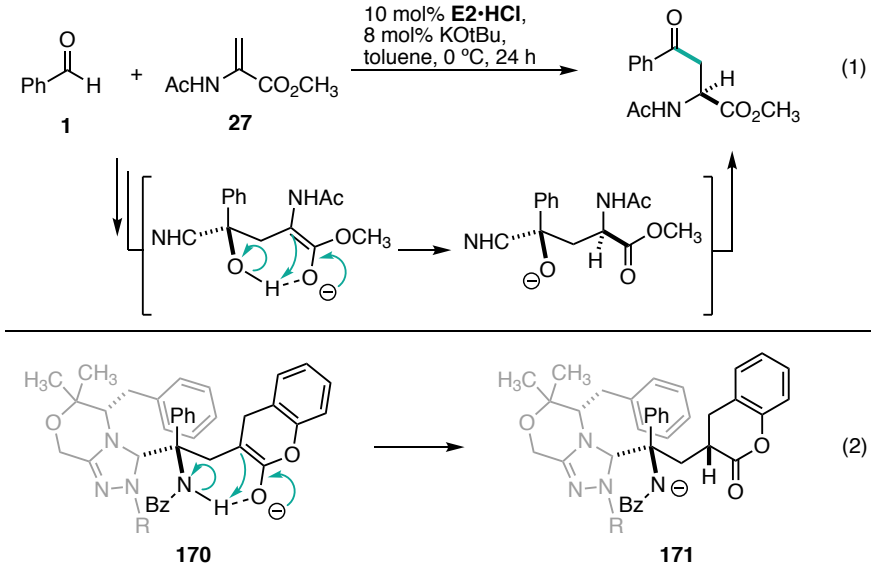
diastereoselective protonation (Scheme 8, step **IV**) which is likely to occur in an intramolecular fashion to give aza-anion **171**. Elimination of the catalyst then provides the product **66a** and completes the cycle (Scheme 8, step **V**).



Scheme 8: Proposed mechanism of the aza-Stetter reaction

3.2.3 Proposed enantiodetermining event

The proposed mechanism closely resembles the mechanism proposed by Glorius in a related Stetter reaction where the enantiodetermining event is an intramolecular proton transfer (Scheme 9, eq. 1).[19] The enantioselective 1,4-addition of the aza-Breslow intermediate creates a transient stereocentre in intermediate **170** (Scheme 8, Step **III**). This enolate **170** can undergo an intramolecular proton transfer that is likely stabilised by hydrogen bonding between the enolate oxygen and the hydrogen of the amine (Scheme 9, eq. 2). This transfers the chiral information, resulting in a new stereocentre in intermediate **171**. The original stereocentre is then destroyed upon catalyst elimination, as the imine functionality is regenerated (Scheme 8, step **V**).

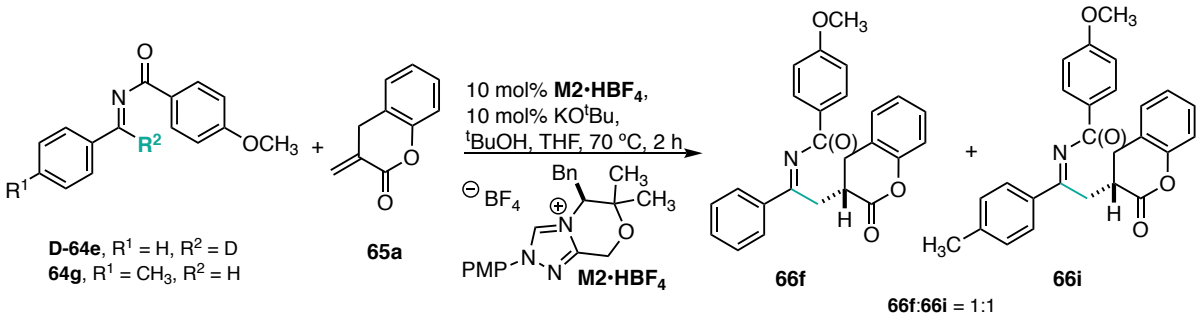


Scheme 9: Diastereoselective proton transfer as the enantiodetermining step

3.3 Examination of the Turnover Limiting Step

3.3.1 Investigation of kinetic isotope effects

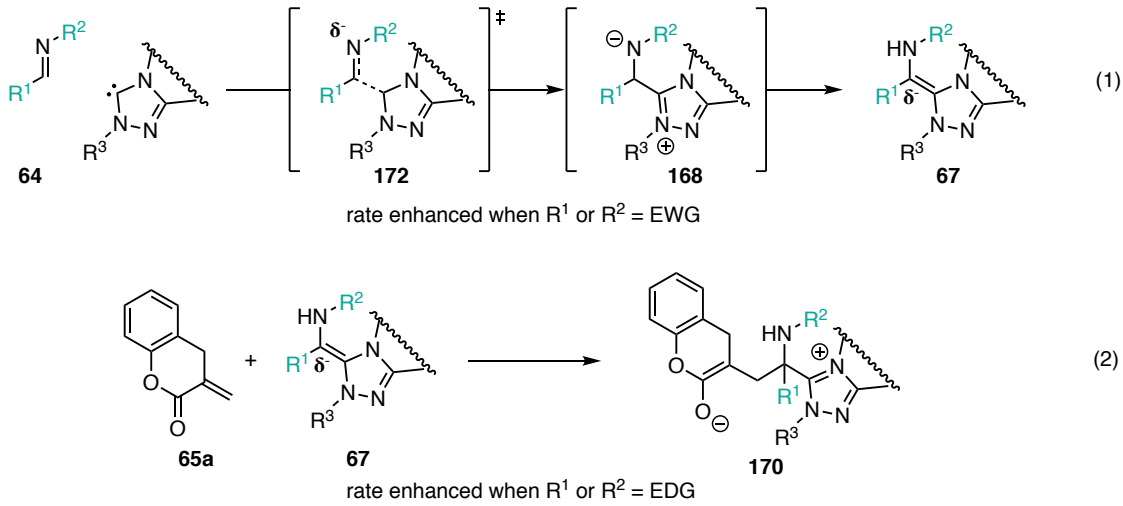
Next a number of experiments were conducted to determine the turnover limiting step. We initially believed the proton transfer required to form the aza-Breslow intermediate (Scheme 8, step **II**) would be rate determining step. In order to investigate this, deuterated imine **D-64e** was synthesised. A competition study was then conducted between deuterated imine **D-64e** and non-deuterated imine **64g** (Scheme 10). If the turnover limiting step was this proton transfer, the reaction should display a kinetic isotope effect (KIE) and the rate of the reaction should reduce when the deuterated imine **D-64e** is used. In this competition study, this would result in more of product **66i** forming in comparison to product **66f** as the reaction would be faster with the non-deuterated imine **64g**. The competition gave a 1:1 mixture of the products of each of the imines, indicating that there is no primary kinetic isotope effect and the proton transfer is unlikely to be the turnover limiting step.



Scheme 10: Investigation into KIE in the formation of the aza-Breslow intermediate

3.3.2 Competition studies

As the proton transfer leading to the aza-Breslow intermediate is unlikely to be turnover-limiting, it was postulated that this step could either be NHC addition to the imine (Scheme 8, step **I**) or 1,4-addition of the aza-Breslow intermediate into the chromanone (Scheme 8, step **III**). In the case that NHC addition to the imine was rate limiting, a more electrophilic imine should enhance the rate of addition as they are better able to stabilise the negative charge in transition state **172** and intermediate **168** (Scheme 11, eq. 1). In the case that 1,4-addition was turnover limiting, a more nucleophilic aza-Breslow intermediate **67** derived from a more electron rich imine should enhance the rate of formation of enolate **170** and hence the reaction (Scheme 11, eq. 2).

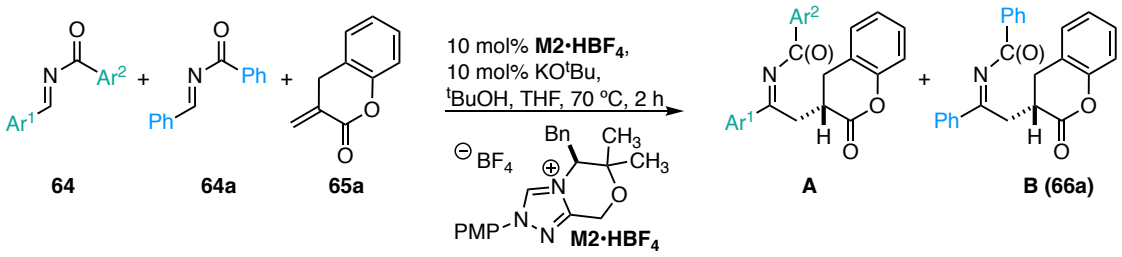


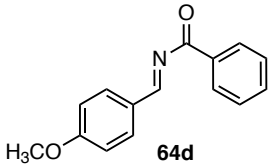
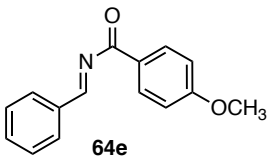
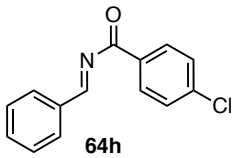
Scheme 11: Possible rate determining steps: NHC addition to imine (1) or 1,4-addition of the aza-Breslow intermediate (2)

To examine the reactions sensitivity to electronic changes at Ar^1 and Ar^2 a series of competition experiments were conducted (Table 1). When equimolar amounts of electron rich imine **64d** and electron neutral imine **64a** were subjected to the reaction conditions, the two products **66b** and **66a** formed in a 0.34:1 ratio (Table 1, entry 1) indicating a reduction in rate due to the presence of electron donating groups. In a similar experiment, electron rich imine **64e** was used and also resulted in a product ratio consistent with a rate reduction caused by the more electron rich imine **64e** (Table 1, entry 2). Lastly, when electron poor imine **64h** was used in place of the electron rich imines **64d** & **64e**, a ratio of products of 2.5:1 was observed, indicating rate enhancement with the electron poor imine **64h** (Table 1, entry 3). In all cases a rate enhancement was observed with the less electron rich

imine of the pair, which is consistent with the turn over limiting event being NHC addition to the imine, rather than 1,4-addition of the aza-Breslow intermediate to the chromanone **65**.

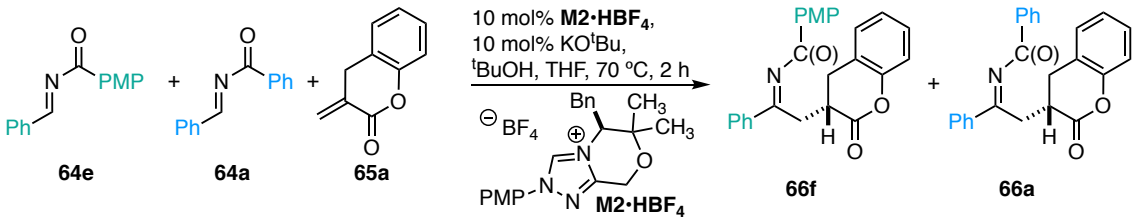
Table 1: Competition studies of electronically different imines



Entry	Imine 1	Imine 2	Ratio (A: B)
1	 **64d**	**64a**	0.34 : 1
2	 **64e**	**64a**	0.45 : 1
3	 **64h**	**64a**	2.5 : 1

3.3.3 Monitored competition study

To ensure that the product outcomes are a result of a difference in kinetics, rather than potential differences in stability of the products, a monitored competition study was undertaken (Scheme 12). Utilising deuterated benzene as the solvent, the reaction in Table 1, entry 2 was repeated in a Youngs tap NMR tube and the concentration of the products measured using integration against an internal standard (Figure 2). As can be seen, the formation of γ-iminoester **66a** occurs at a much faster rate than γ-iminoester **66f** (Figure 1). Furthermore, almost no decomposition was observed in the hour after the reaction had reached 100% conversion. This confirms that the observed ratios are indeed due to enhanced rate of product formation, rather than selective decomposition of one product. This monitoring study also failed to identify any NHC adducts in the reaction mixture, which is consistent with a slow initial step in the reaction mechanism.



Scheme 12: Monitored competition study

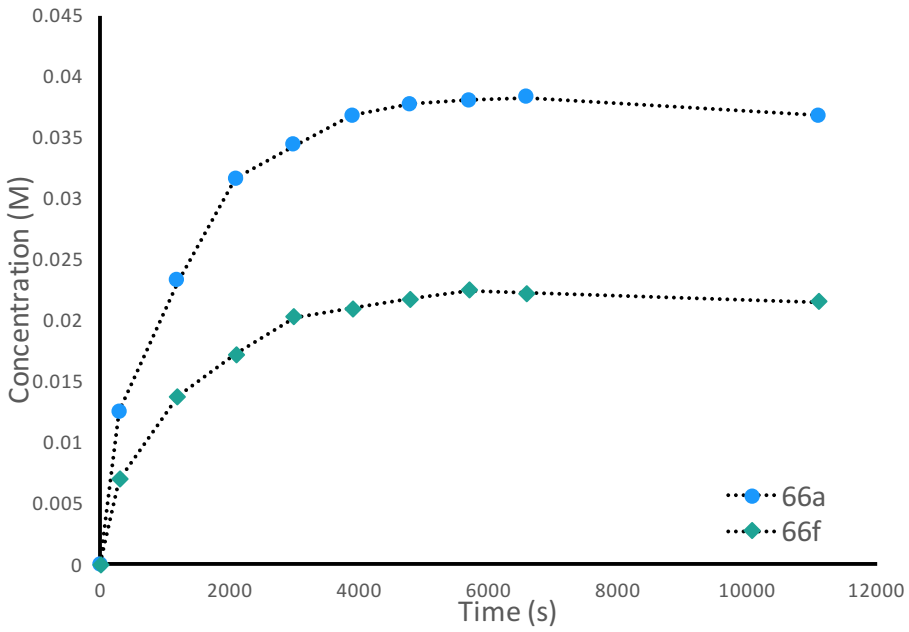


Figure 2: Concentration of imine **66** over time

3.4 Determination of Reaction Order

Having determined that the likely turnover limiting step in the reaction is NHC addition to the imine, we wished to investigate the reaction order with relation to each of the starting materials as well as the catalyst. We hypothesized that if this is the turnover limiting step then the reaction would be first order in relation to both imine and catalyst and zero order with respect to the lactone.

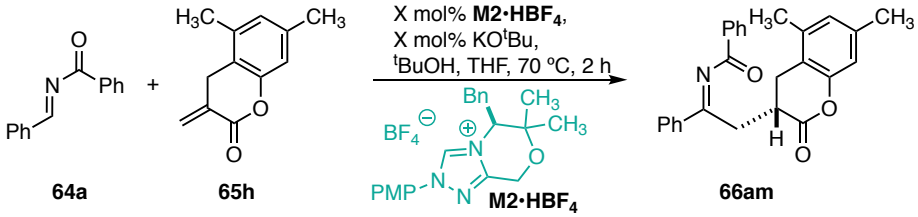
In order to measure the rate of reaction, the formation of aza-Stetter product **66**, and the consumption of imine **64** and lactone **65** (which were essentially the same) were measured using NMR. The reaction was conducted in deuterated benzene in a Youngs tap NMR tube. The consumption of starting materials and formation of product were then determined by integration and normalized against an internal standard. The concentration of each of the reactants were then varied one by one, and the kinetics compared. The slopes of the natural log of the decay curve can then be compared in

order to determine reaction order. Each experiment was performed in duplicate, and the rate order determined according to the equation shown below where y = order.[20]

$$\ln\left(\frac{(\text{slope})_A}{(\text{slope})_B}\right) = y \ln\left(\frac{(\text{conc.})_A}{(\text{conc.})_B}\right)$$

3.4.1 Determination of reaction order with respect to catalyst

Determination of reaction order began with an investigation into the effect of the concentration of catalyst **M2** on the reaction kinetics utilising imine **64a** and lactone **65h** (Scheme 13).



Scheme 13: Reaction order determination by varying catalyst concentration

The reaction was conducted at two different concentrations of catalyst **M2**, one at 0.005 M (10 mol% catalyst loading) and one at 0.010 M (20 mol% catalyst loading) and the decay curves measured with respect to the consumption of lactone **65h** (Figure 3). The reaction shows the expected exponential decay, and when the natural log of the decay is taken the result is a linear relationship with very good R^2 values (both >0.98). By using the trendline data (Table 2) and the equation above, the order of the reaction was calculated to be 0.74 with respect to catalyst. This indicates that the order is positive and approximately first order.

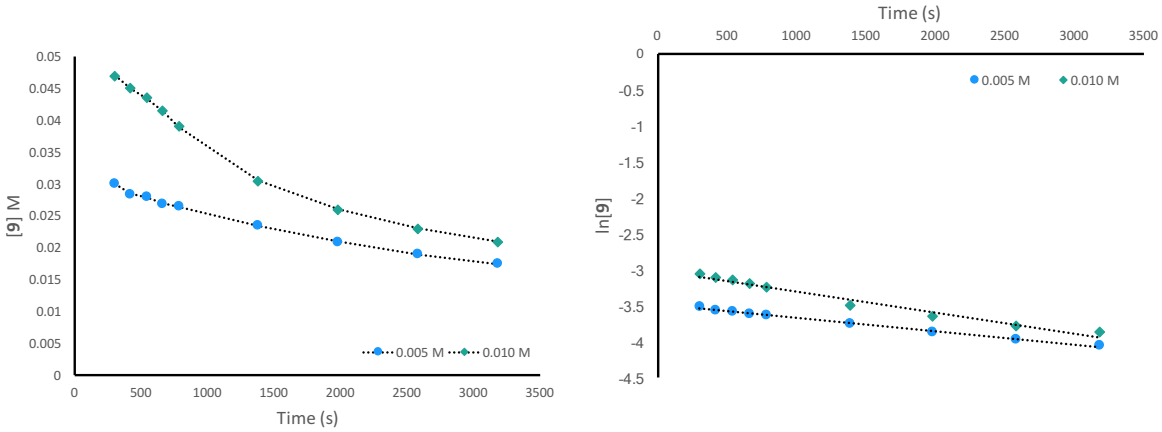


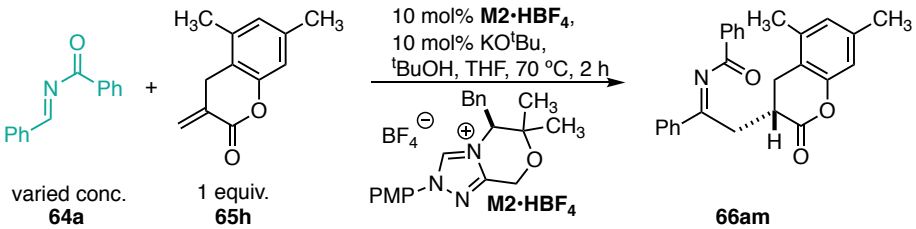
Figure 3: Reaction decay curve (left) and Ln[**65h**]with respect to time (right)

Table 2: Trendline data for ln[**65h**] vs time for effect of **M2**

	0.005 M **M2**	0.010 M **M2**
Slope	-0.000195	-0.000327
Y-intercept	-3.471832	-2.975393
R square	0.9944	0.9848

3.4.2 Determination of reaction order with respect to imine

With the order of the reaction with respect to catalyst **M2** determined, attention could then turn to the order with respect to imine **64a** (Scheme 14). If, as proposed, the imine **64a** is a part of the turnover limiting step (*vide supra*), then the order of the reaction should be first order as well.



Scheme 14: Reaction order determination by varying imine concentration

In the same manner as above, the reaction was conducted at two different concentrations of imine **64a**, one at 0.025 M (50 mol% imine) and one at 0.050 M (100 mol% imine) and the decay curves measured with respect to the disappearance of lactone **65h** (Figure 4). The expected linear

relationship when the natural log of the decay is taken is observed with very good R^2 values (both >0.96). Using the trendline data (Table 3), and the equation above, the order of the reaction was calculated to be 1.12 with respect to imine, indicating that the order is positive and approximately first order, as expected.

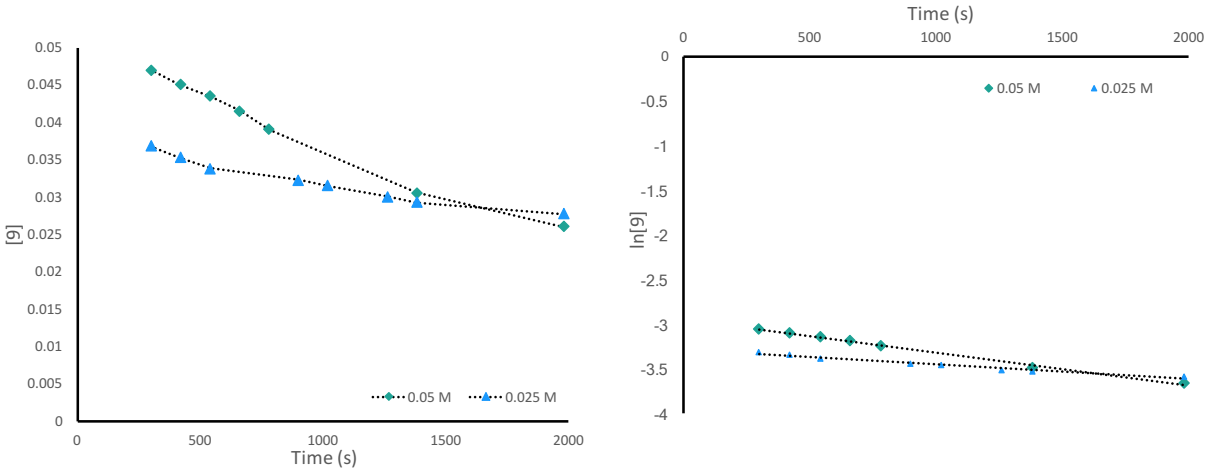


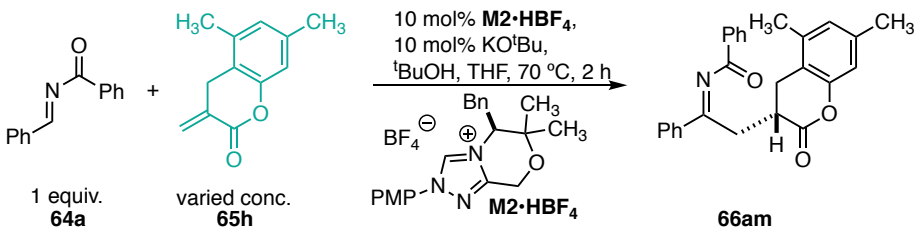
Figure 4: Reaction decay curve (left) and Ln[**65h**]with respect to time (right)

Table 3: Trendline data for ln[**65h**] vs time for effect of **64a**

	0.050 M **64a**	0.025 M **64a**
Slope	-0.000365	-0.000167
Y-intercept	-2.949673	-3.281466
R square	0.9926	0.9606

3.4.3 Determination of reaction order with respect to lactone

Lastly, the order of the reaction with respect to lactone **65h** was determined (Scheme 15). Given that lactone **65h** is not a part of the proposed turnover limiting step, the order of the reaction with respect to lactone **65h** should be zero order.



1 equiv. **64a** varied conc. **65h** **66am**

Scheme 15: Reaction order determination by varying lactone concentration

In the same manner as above, the reaction was conducted at two different concentrations of lactone **65h**, one at 0.050 M (100 mol% lactone) and one at 0.100 M (200 mol% lactone) and the decay curves measured with respect to the disappearance of imine **64a** (Figure 5). The exponential decay and the natural log of the decay are both of the expected shape with very good R^2 values (both >0.99). Using the trendline data (Table 4) and the equation above, the order of the reaction was calculated to be 0.30 with respect to lactone, indicating that the order is approximately zero order.

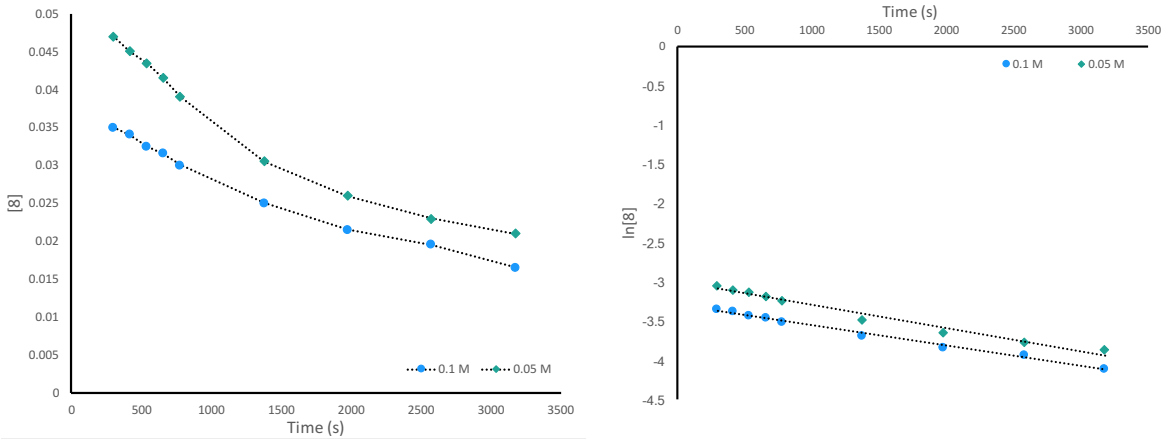


Figure 5: Reaction decay curve (left) and Ln[**64a**]with respect to time (right)

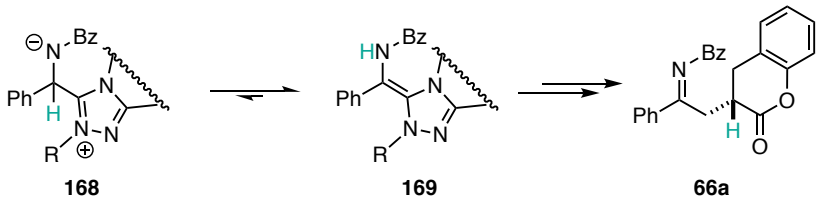
Table 4: Trendline data for ln[**64a**] vs time for effect of **65h**

	0.05 M **65h**	0.025 M **65h**
Slope	-0.000365	-0.000295
Y-intercept	-2.949673	-3.266180
R square	0.9926	0.9971

These preliminary mechanistic studies show the reaction is close to 0 order in relation to chromanone (0.30) and first order in relation to NHC (0.74) and imine (1.12). This is consistent with a turnover limiting step being NHC addition to the imine.

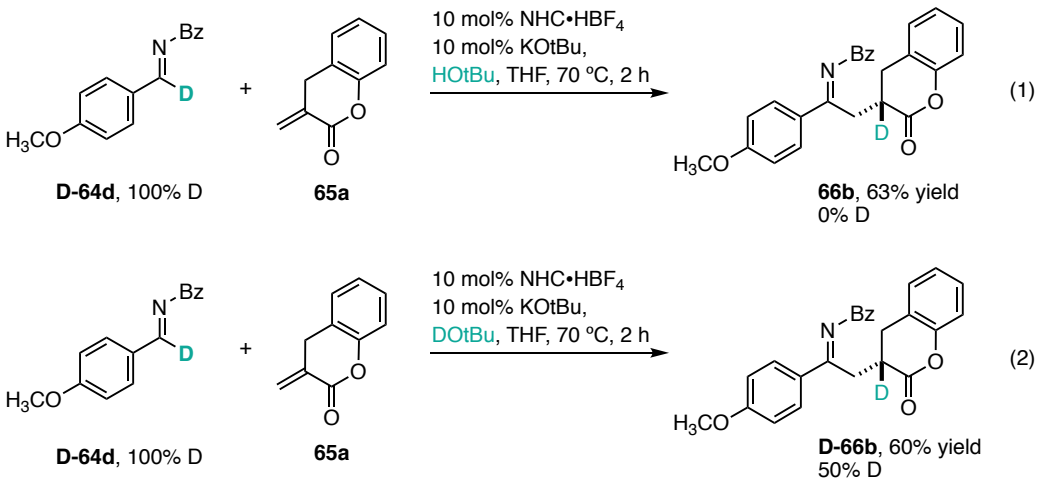
3.5 Deuterium Labelling Studies

Deuterium labelling studies were also conducted to examine the mechanism. In the formation of the aza-Breslow intermediate **169**, a proton transfer occurs from aza-anion **168** (Scheme 16). This proton would end up in the α-position of the ester after the intramolecular proton transfer in our proposed mechanism (Scheme 8, step **IV**).



Scheme 16: Proton transfers during the formation of γ-imino ester **66a**

In order to confirm this, deuterated imine **D-64d** was subjected to the optimised reaction conditions (Scheme 17, eq. 1). However, after isolation of the γ-imino lactone **66b**, no deuterium incorporation was observed. We believed this is due to the ^{t}BuOH in the reaction eroding the deuterium incorporation. The ^{t}BuOH has already been shown to play an important role in the formation of the aza-Breslow intermediate (see Chapter 2). We believed that if we switched to the deuterated variant, ^{t}BuOD, then the deuterium labelling study could yield a deuterated product. Pleasingly, the reaction yielded the expected product **D-66b** with 50% deuterium incorporation. It is possible that protons from various sources eroded the level of deuterium incorporation, including the ^{t}BuOH that is liberated from deprotonation of the NHC by ^{t}BuOK and potentially some residual water in the THF.

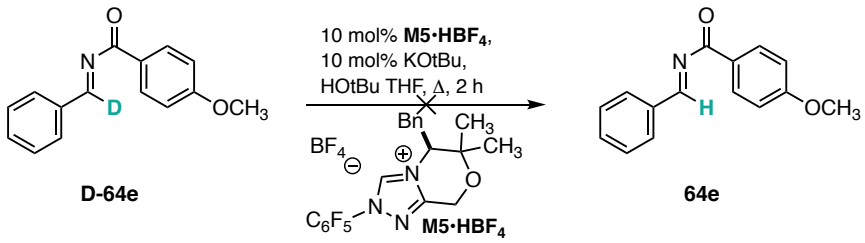


Scheme 17: Deuterium labelling studies to determine mechanism

3.6 Investigation into Electron Poor NHCs

Lastly, during our optimisation studies (see Chapter 2), it was noted that electron poor *N*-substituents failed to give the aza-Stetter product. As electron poor NHCs have been the catalysts of choice in the related field of acyl anion chemistry, we were interested in why they failed to yield results in the similar aza-Breslow chemistry. We proposed two possible explanations: firstly, the electron poor catalysts were not nucleophilic enough to add to the imine, or secondly, the aza-Breslow intermediate that forms with electron poor catalysts is not nucleophilic enough to perform the required 1,4-addition.

In order to investigate this, a simple scrambling study was proposed (Scheme 18). When deuterated imine **D-64e** was subjected to less nucleophilic NHC catalyst **M5** in the presence of ^{t}BuOH, imine **D-64e** was reisolated without loss of deuterium. If the aza-Breslow intermediate had formed, some proton incorporation in the imine from ^{t}BuOH would be expected, resulting in erosion of the deuterium content. As this was not observed, this means that electron-poor NHCs are unsuitable in aza-Breslow chemistry because of failure to form the aza-Breslow intermediate, rather than formation of a species that is not nucleophilic enough to perform the 1,4-addition to an electrophile.



Scheme 18: Investigation on aza-Breslow intermediate formation with electron poor NHCs

3.7 Conclusions

This chapter details the mechanistic investigations into the aza-Stetter reaction described in Chapter 2. The turnover limiting step was found to be NHC addition to the imine. Supporting this, was the reaction order which was measured and found to be first order in catalyst and imine, and zero order with respect to the lactone. Deuterium labelling studies were undertaken that also support this. Further to this, monitoring the reaction by ^{1}H NMR failed to identify any intermediates, an observation consistent with a slow initial step. Somewhat surprisingly, more nucleophilic catalysts are required to generate the aza-Breslow intermediate in comparison to the Breslow intermediate. All of the mechanistic studies are consistent with imine umpolung rather than umpolung of the Michael acceptor. This insight will allow future reactions involving the aza-Breslow intermediate to be designed, with appropriate coupling partners and catalysts. In a similar fashion to the Breslow intermediate, understanding its formation, as well as kinetics and turnover is paramount to designing novel methodologies in this area.

3.8 References

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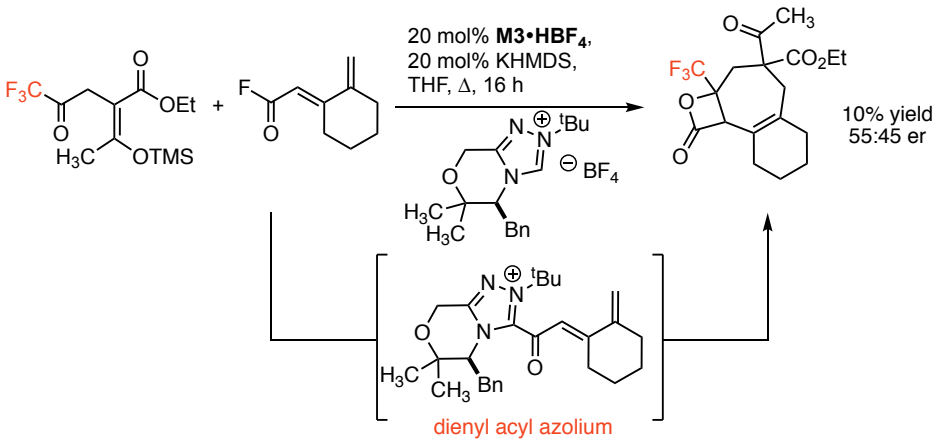
Chapter 4: All-Carbon (4+3) Annulation via the α,β-γ,δ-Dienyl Acyl Azolium



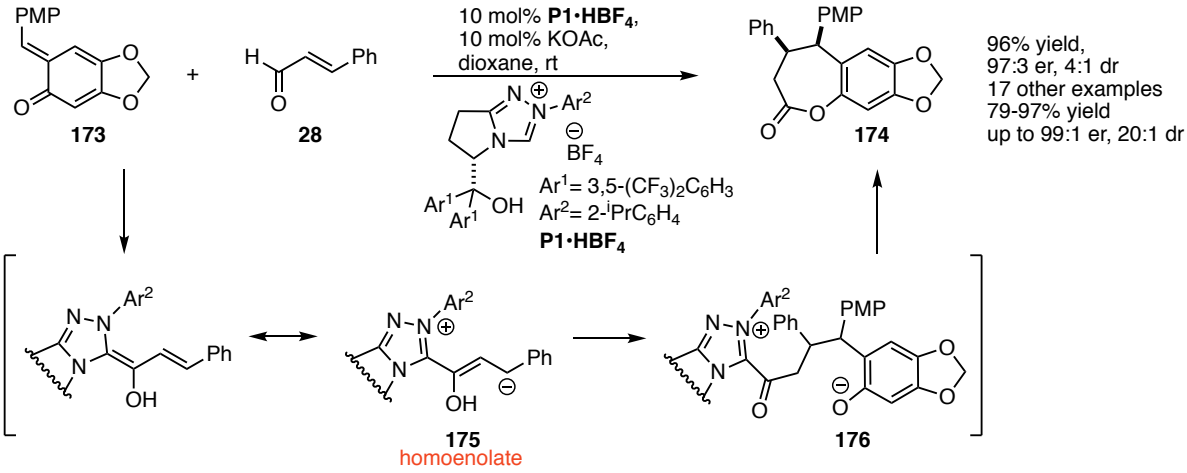
The work presented in this chapter comprises of studies into an all carbon (4+3) annulation of the α,β-γ,δ-dienyl acyl azolium with keto enolates. Reactions of the δ-position in diunsaturated species are challenging as the β- and acyl positions are often more reactive. It was found that trifluoromethyl ketones could promote the desired transformation, however, this proceeded with low yield and enantioselectively. In the course of these studies, a related (4+2) annulation was discovered which represents the first enantioselective reaction to proceed via the α,β-γ,δ-dienyl acyl azolium.

4.1 Introduction to NHC Catalysed (4+3) Annulations

NHCs have emerged as versatile organocatalysts for a number of different annulation cascades. By exploiting the various intermediates available through NHC catalysis, a plethora of annulation reactions to synthesize four-, five-, and six-membered rings have been realised.[1-6] However, the synthesis of seven-membered rings via NHC catalysis has received significantly less attention. This is particularly striking when considering all carbon variants.

4.1.1 (4+3) annulations via the homoenolate

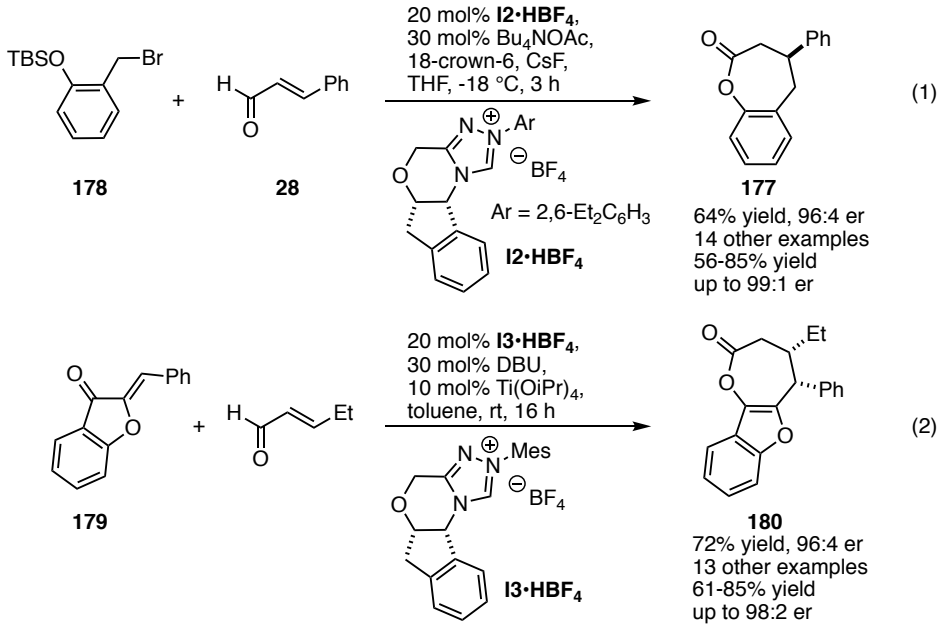
To the best of our knowledge, the first NHC catalyzed (4+3) annulation was reported by Ye and co-workers in 2013 (Scheme 1).[7] Their reaction utilises α,β-unsaturated enals **28** and *o*-quinone methides **173** to afford functionalized ε-lactones (i.e **174**) in good yields and with high enantioselectivity (98:2 er). This reaction proceeds via the NHC homoenolate **175**, which undergos Michael addition with the *o*-quinone methide **173** to provide phenoxide **176**. Lactonisation closes the seven-membered ring to provide the lactone product **174** and regenerates the catalyst.



Scheme 1: Ye's (4+3) annulation via the homoenolate

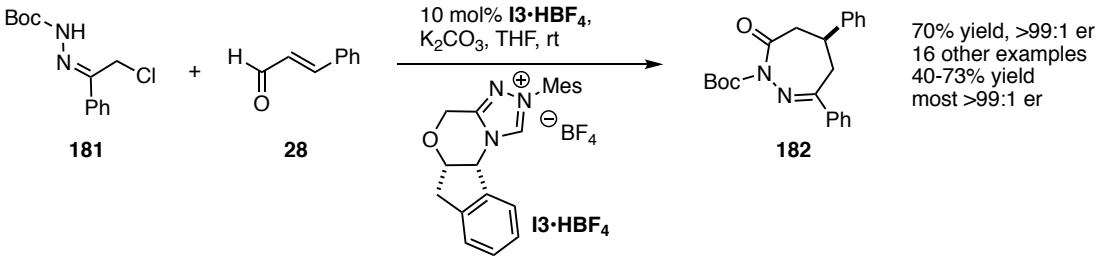
In the same year, Scheidt reported a similar strategy for the formation of ε-lactones (i.e. **177**) using a dual Lewis base activation approach (Scheme 2, eq. 1).[8] Similar to Ye's report, an NHC catalyst was used to access the homoenolate from α,β-unsaturated enals (i.e **28**), whilst a fluoride source was used to generate *o*-quinone methides *in situ* from silicon protected phenols (i.e **178**). *In situ* generation of a reactive intermediate such as this allowed for a broader range of substrates in comparison to the (4+3) annulation achieved by Ye. The following year, Zhou and co-workers showed that similar

transformations were possible with heterocyclic enones (i.e **179**) in place of *o*-quinone methides in their synthesis of ε-lactones (i.e. **180**, Scheme 2, eq. 2) .[9]



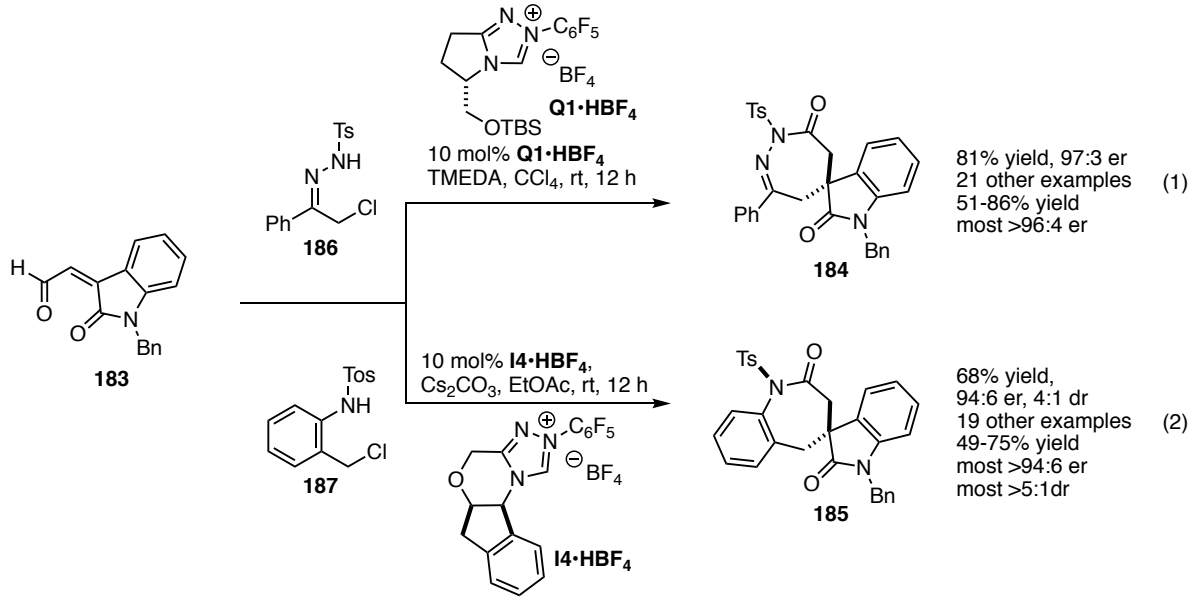
Scheme 2: Scheidt and Zhou's (4+3) reactions

The synthesis of nitrogen containing seven membered rings by NHC catalysis is also possible. In 2014, Glorius and co-workers reported the cyclisation of enals **28** and hydrozones (i.e. **181**) that proceeds via the NHC homoenolate (Scheme 3).[10] They were able to synthesise a number of 1,2-diazapines (i.e. **182**) in good yields and with excellent levels of stereocontrol.



***Scheme 3*:** Glorius' (4+3) for the synthesis of 1,2-diazapines **182**

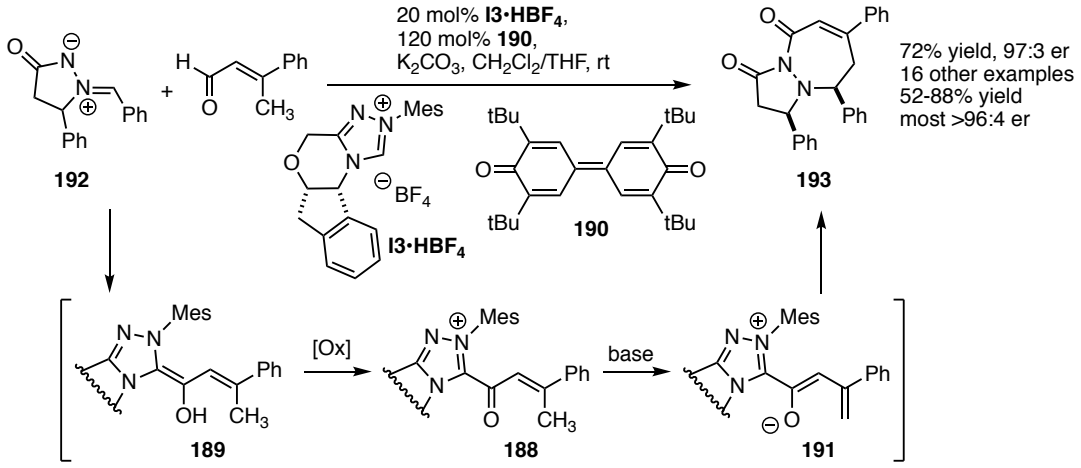
Following this, Enders and co-workers reported a similar transformation using an isatin derived enal **183** (Scheme 4).[11] Again, the homoenolate is formed en route to 1,2-diazapines **184** (Scheme 4, eq. 1) and benzazepines **185** (Scheme 4, eq. 2) using α-chlorohydrazones (i.e. **186**) or *N*-tosylanilines (i.e. **187**). Both transformations were achieved with high levels of enantioselectivity albeit with limited disatereoselectivity for the benzazepines (i.e. **185**).



Scheme 4: Enders' synthesis of diazapines and benzazepines

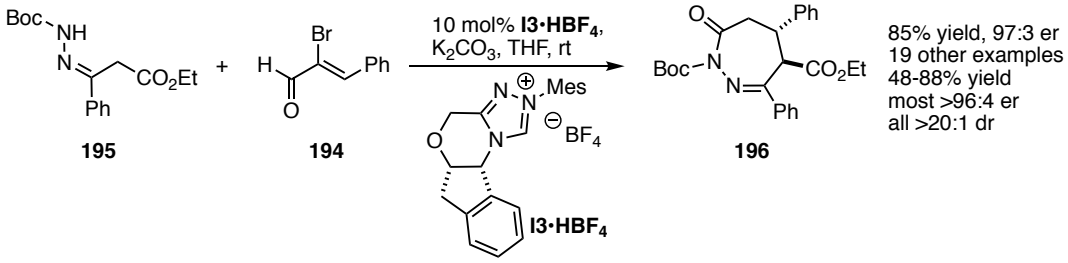
4.1.2 (4+3) annulations via the α,β-unsaturated acyl azolium

While these pioneering studies utilized the NHC homoenolate, recent advances have shown that stereoselective (4+3) annulations can also be accomplished through the α,β-unsaturated acyl azolium. Chi and co-workers were able to access the α,β-unsaturated acyl azolium **188** via the Breslow intermediate **189** and an external oxidant **190** (Scheme 5).[12] Upon exposure to base, this intermediate then forms the extended acyl azolium dienolate **191** and cyclises with 1,3-dipolar azomethine imines (i.e **192**) to afford highly enantioenriched dinitrogen fused seven-membered cyclic products (i.e. **193**).



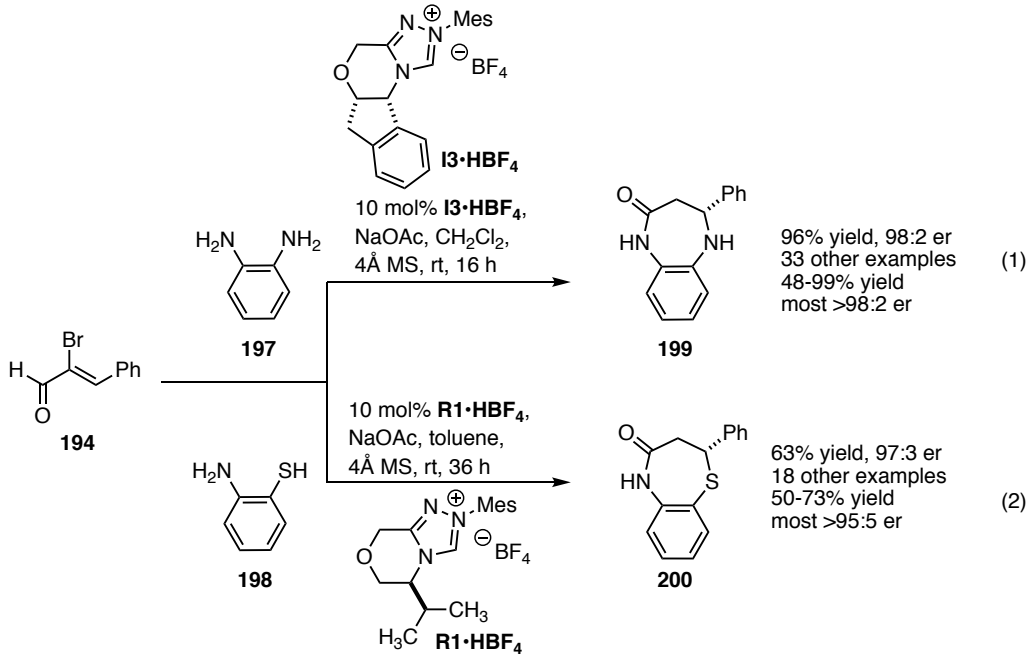
Scheme 5: Chi's (4+3) via the α,β-unsaturated acyl azolium

The group of Xin-Ping Hui reported another approach to seven membered rings in 2017. Once again exploiting α,β-unsaturated acyl azoliums accessed from α-bromoenals (i.e. **194**), they found that base mediated annulation with *N*-tosyl hydrazones (i.e. **195**) gave 1,2-diazapines **196** with excellent enantio- and diastereoselectivity (Scheme 6).[13]



Scheme 6: Hui's synthesis of diazapines via the α,β-unsaturated acyl azolium

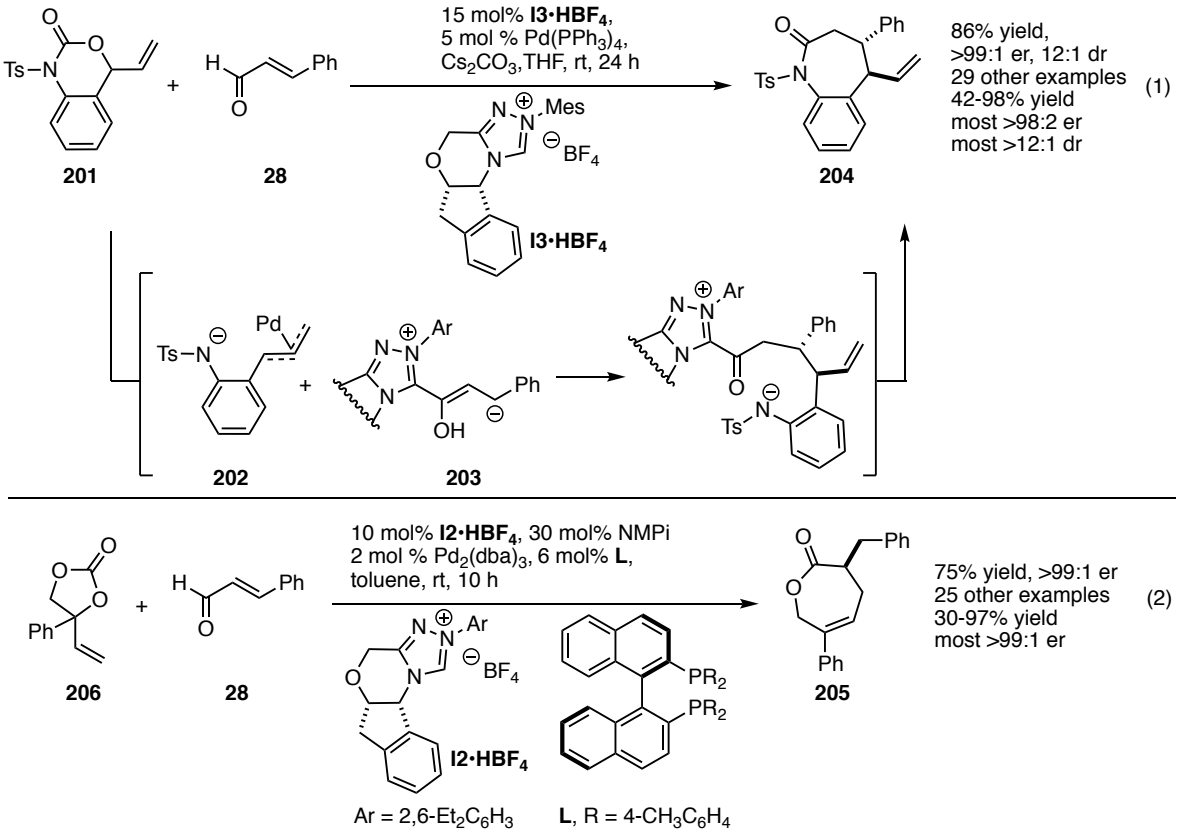
The α,β-unsaturated acyl azolium can also be utilised in the synthesis of seven-membered rings bearing heteroatoms in the 1- and 5- positions (Scheme 7). The group of Du was able to promote a stereoselective (4+3) annulation of the α,β-unsaturated acyl azolium with *bis*-nucleophiles (i.e. **197** or **198**) in order to synthesise 1,5-benzodiazepines **199** and 1,5-benzothiazepines **200** with excellent levels of stereocontrol.[14, 15]



Scheme 7: Du's (4+3) via the α,β-unsaturated acyl azolium

4.1.3 (4+3) annulations via co-operative catalysis

Recently, Glorius reported the use of co-operative catalysis for the synthesis of oxygen and nitrogen containing seven-membered rings (Scheme 8). In 2016, they described the regio- and enantioselective annulation of α,β-unsaturated enals **28** and vinyl benzoxazinanones **201** (Scheme 8, eq. 1).[16] By utilizing palladium catalysis to generate an allyl cation (i.e. **202**) and NHC catalysis to generate the homoenolate (i.e. **203**), they were able to promote cyclisation to provide benzazepines **204** in good yields and with exceptional enantiocontrol (>99:1 er). Two years later, Glorius and co-workers were able to expand the scope of their co-operative catalysis methodology to the synthesis of challenging ε-caprolactones **205**, utilizing vinyl carbonates (i.e. **206**) and enals (i.e. **28**) to access a palladium allyl cation and the azolium enolate respectively (Scheme 8, eq. 2).[17]



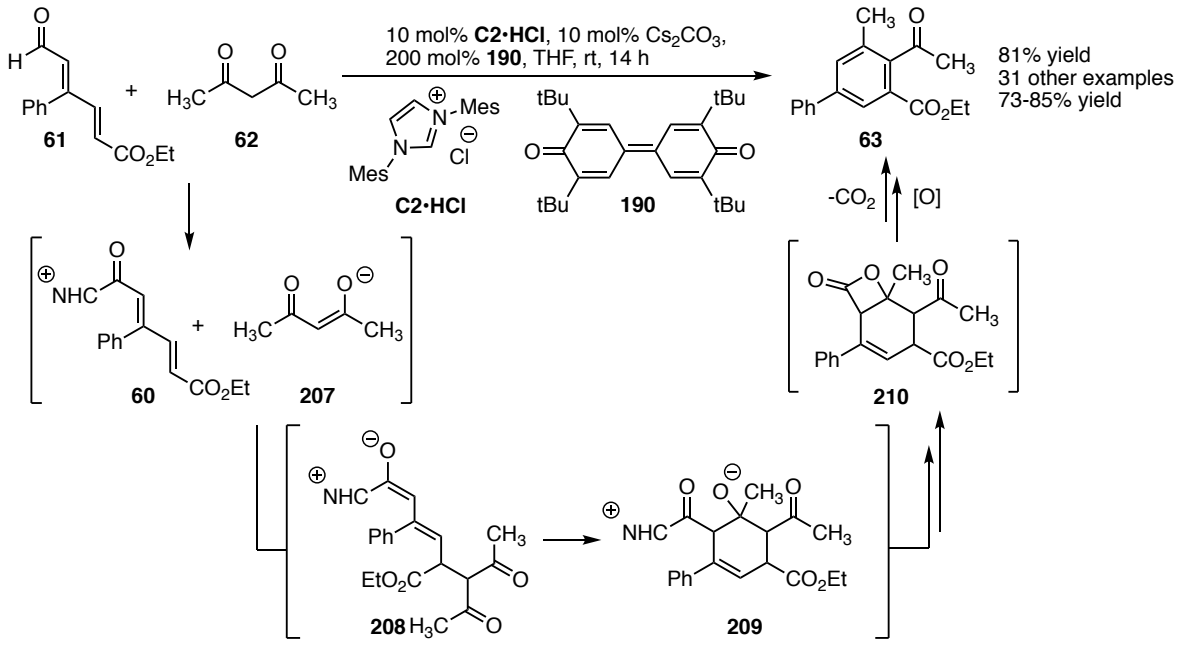
Scheme 8: Glorius' (4+3) reactions utilizing co-operative catalysis

Whilst these studies all represent significant advancements in the synthesis of seven-membered rings by NHC catalysis, there are currently no examples of an all-carbon (4+3) annulation. The majority of the strategies discussed involve the use of α,β-unsaturated aldehydes as 3-carbon donors (homoenolates or α,β-unsaturated acyl azoliums) with reactions at the β- and acyl-position. We

reasoned that we could utilize a dienyl acyl azolium as a 4-carbon donor in an NHC catalyzed (4+3) reaction with C-C bond formation at the δ- and acyl- positions.

4.1.4 Activation of the delta carbon in α,β-γ,δ-diunsaturated systems

In 2015, Chi reported the cyclisation of dienals **61** with 1,3 dicarbonyl species (i.e. **62**) affording substituted benzenes (i.e. **63**). Whilst there are a few examples of the α,β-γ,δ-dienyl acyl azolium **60** being used earlier,[18-20] this is the first and only example with bond formation occurring at the δ-carbon.[21] The proposed reaction mechanism begins with 1,6-addition of an enolate **207** generated from a 1,3 diketone **62** into the α,β-γ,δ-dienyl acyl azolium **60**, generated from dieal **61** and external oxidant **190**, to give intermediate **208** (Scheme 9). An aldol reaction provides intermediate **209** which is followed by lactonisation to give β-lactone **210** and regenerate the catalyst. Decarboxylation of β-lactone **210** occurs *in situ* which is followed by oxidation of the resultant diene to furnish aromatic compounds **63**. Of particular note is the use of increased sterics at the β-position of dienyl acyl azolium **60** in order to facilitate 1,6-addition in preference to 1,4-addition.



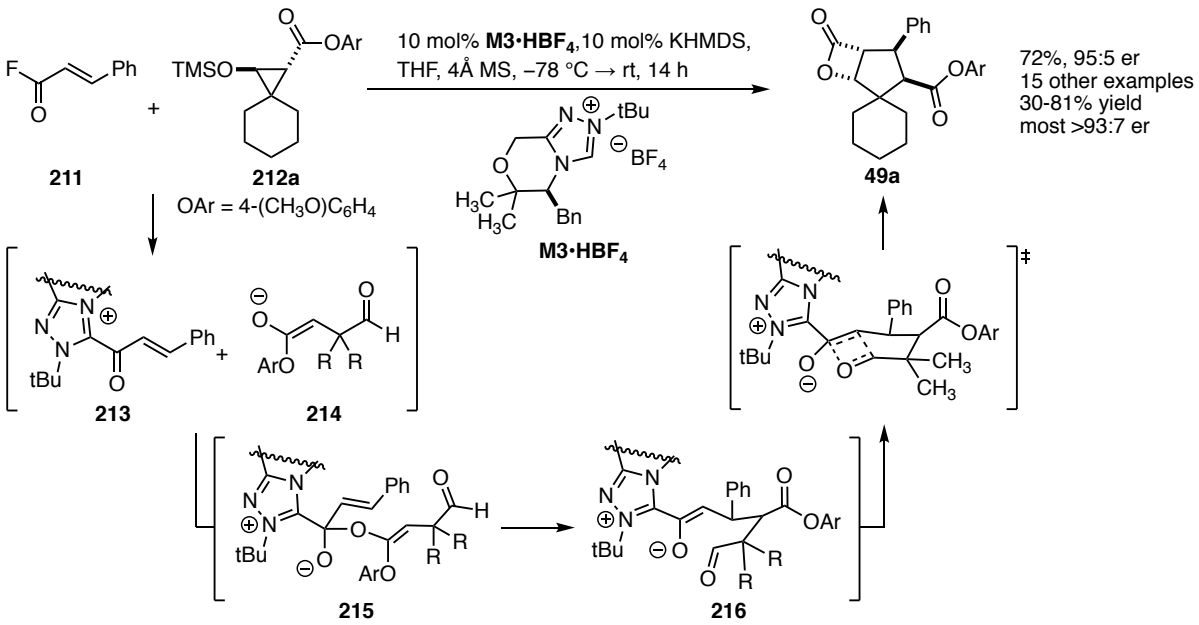
Scheme 9: Proposed mechanism of (4+2) annulation by Chi

Increasing the steric demand at the β-position relative to the δ-position in order to promote 1,6-addition in favour of 1,4-addition appears to be imperative for the success of this strategy. Having

identified the viability of the δ- and acyl bond formation with dienyl acyl azoliums, attention then turned to finding a suitable 3-carbon donor for the proposed (4+3) annulation.

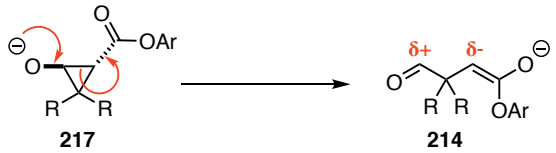
4.1.5 Lupton's NHC catalysed (3+2) annulation

In 2013 the Lupton group reported an NHC catalyzed (3+2) annulation of α,β-unsaturated acyl fluorides (i.e. **211**) and donor-acceptor cyclopropanes (i.e. **212a**). The reaction provides heavily functionalised β-lactone fused cyclopentanes (i.e. **49a**) with excellent stereocontrol.[20, 22] The reaction is initiated by addition of the NHC to the acyl fluoride **211** resulting in formation of the α,β-unsaturated acyl azolium **213**. This triggers desilylation and *retro*-aldol reaction of the cyclopropane **212a** to give the bifunctional enolate **214**. Direct *O*-acylation provides the intermediate hemiacetal **215** which undergoes an Ireland–Coates Claisen rearrangement providing intermediate **216**. The reaction is then completed by a semi-concerted (2+2) aldol/lactonization process to afford β-lactone fused cyclopentane **49a** and regenerate the catalyst.



Scheme 10: Proposed mechanism of (3+2) annulation by Lupton

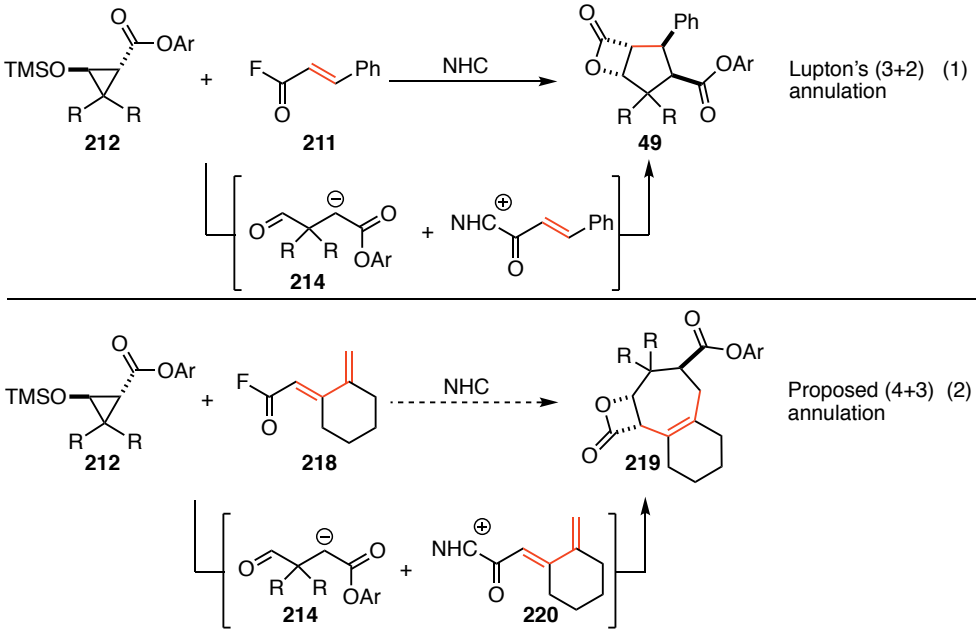
One of the key aspects in this reaction is the use of cyclopropanes as a 3-carbon donor. Upon deprotection, the cyclopropyl alkoxide (i.e. **217**) opens to provides a 1,3-dipole (i.e. **214**) that acts as both a nucleophile and electrophile in the reaction. This type of substrate design allows complex and novel reaction cascades that use these highly reactive intermediates in annulations such as the (3+2) annulation described above.



Scheme 11: Opening of cyclopropane to provide dipole **214**

4.1.6 Proposed all carbon (4+3) annulation via the α,β-γ,δ-dienyl acyl azolium

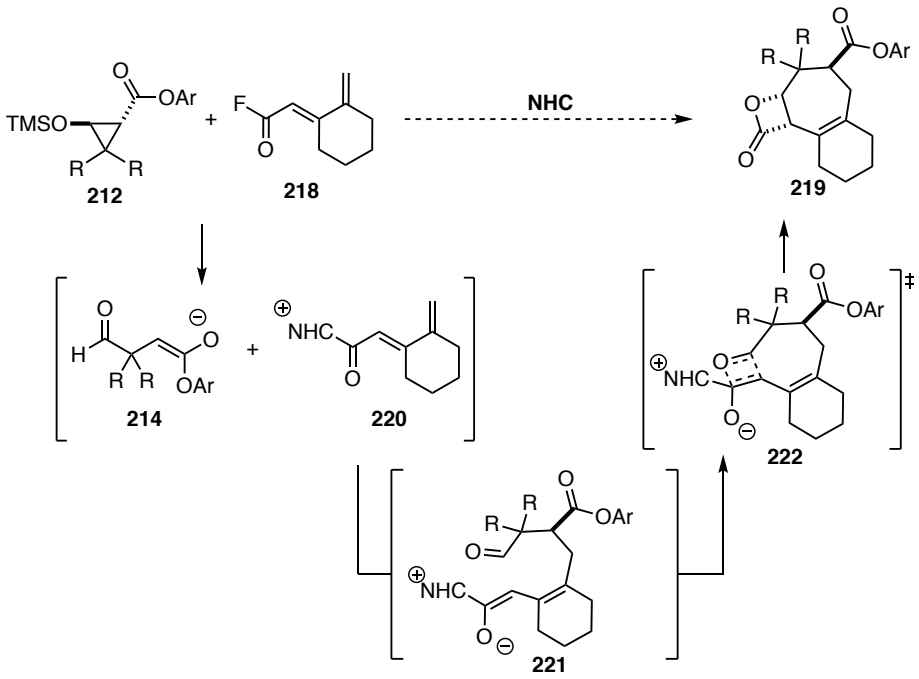
We believed that the use of the dienyl acyl fluorides (i.e. **218**) in conjunction with the cyclopropanes **212** from the previously reported (3+2) annulation (Scheme 12, eq. 1) would allow discovery of a novel (4+3) annulation (Scheme 12, eq. 2), providing funtionalised cycloheptenes (i.e. **219**). If realized, this would represent the first enantioselective annulation reaction utilising the dienyl acyl azolium (i.e. **220**). We believed an element of annulation in acyl fluoride **218** to be imperative to the reactions success. The use of annulation will ensure good conjugation necessary for the 1,6-addition of the enolate **214** in preference to 1,4-addition which will be impeded by β-substitution. Activation of acyl fluoride **218** through a Lewis base, such as an NHC, has already been shown to increase the electrophilicity of unsaturated systems by several orders of magnitude.[23] We postulated that these strategies could overcome some of the challenges of 7-membered ring synthesis.



Scheme 12: Proposed (4+3) cycloaddition

The proposed mechanism of this (4+3) annulation begins with NHC addition to the dienyl acyl fluoride **218** to form the dienyl acyl azolium **220** which triggers *retro*-aldol fragmentation of the

cyclopropane **212** to give bifunctional enolate **214** (Scheme 13). Next, 1,6-addition of enolate **214** to the dienyl acyl azolium **220** provides intermediate **221**. Finally, a semi-concerted aldol/lactonisation via transition state **222** affords the desired cycloheptene **219** and regenerates the catalyst. The work presented in this chapter focuses on our investigations into an all-carbon (4+3) annulation utilizing the α,β-γ,δ-dienyl acyl azolium (i.e. **220**).



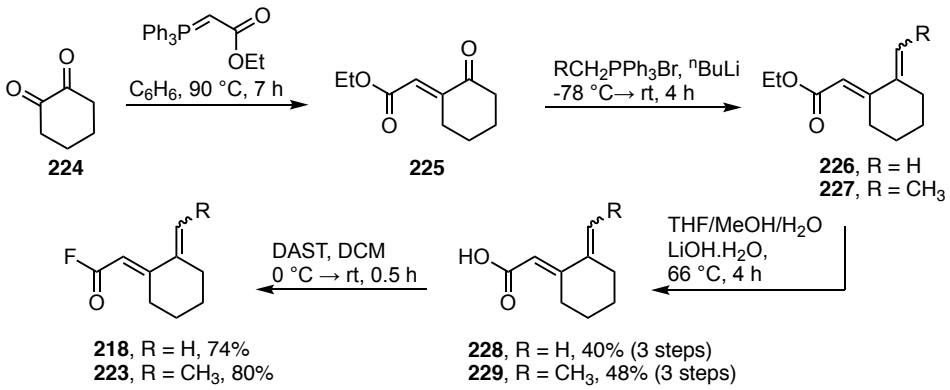
Scheme 13: Proposed mechanism of (4+3) annulation

4.2 (4+3) Annulations Utilising Cyclopropanes

4.2.1 Synthesis of key substrates

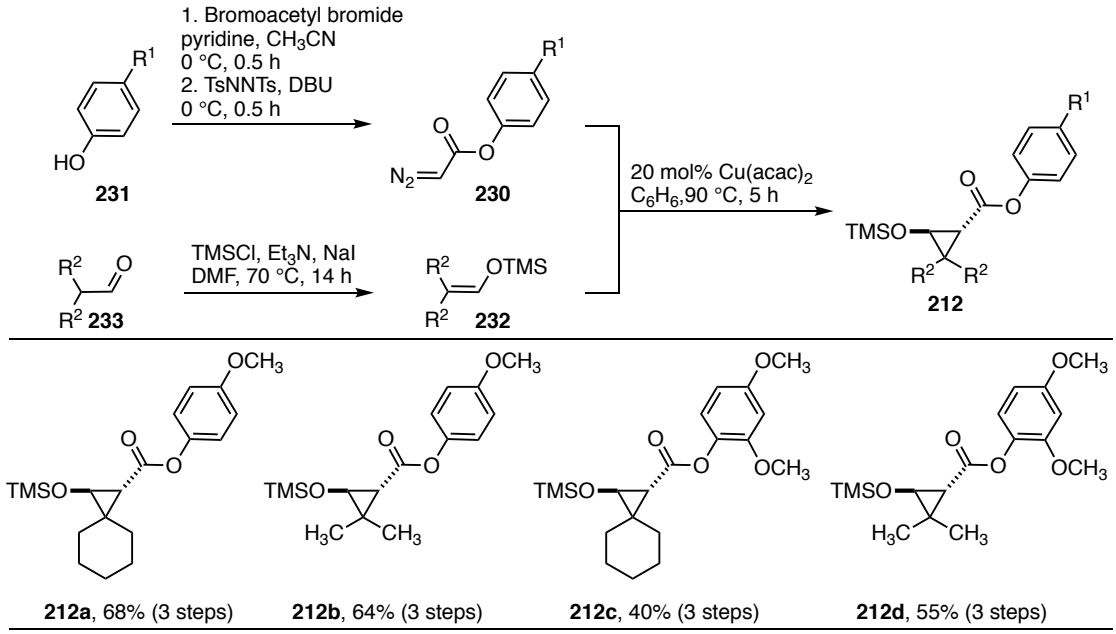
In order to assess whether the proposed (4+3) annulation could be achieved, an appropriate dienyl acyl fluoride substrate was required. As previously mentioned, we anticipated the need for a 1,1-disubstituted olefin with annulation to block the β-position and maintain the reactive s-cis geometry. With this in mind, studies commenced with the synthesis of acyl fluorides **218** and **223** (Scheme 14).[24] Starting from 1,2-cyclohexadione **224**, a Wittig reaction[25] provided ketoester **225**, which was followed by a second Wittig with either methyl or ethyl triphenylphosphonium bromide to provide dienyl esters **226** and **227**. Ester hydrolysis with lithium hydroxide[26] provided conjugated acids **228** and **229** in good yield over 3 total steps. These acids were then converted to the corresponding acyl fluorides **218** and **223** using diethylamino sulfurtrifluoride (DAST).[27] Unfortunately, these acyl fluorides are prone to decomposition so storage at –20 °C and timely use of

these substrates was imperative. Acyl fluoride **218** with no δ-substitution was the preferred substrate for the reaction, however, it also decomposed far more quickly than acyl fluoride **223**.



Scheme 14: Synthesis of acyl fluoride substrates **218** and **223**

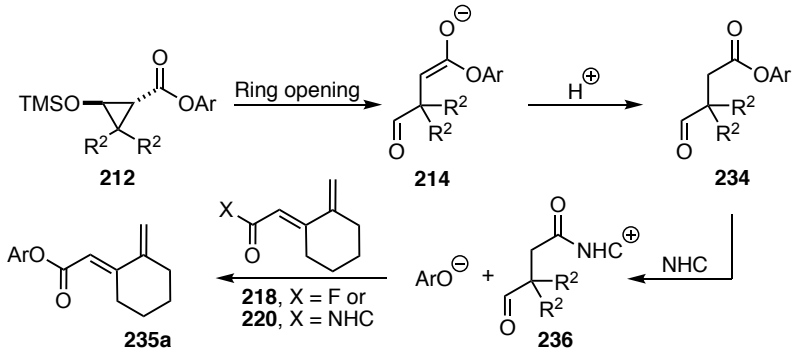
With appropriate acyl fluorides in hand, attention turned to the synthesis of cyclopropanes. We envisaged the use of a copper catalyzed carbene insertion into an appropriate TMS enol ether, a method developed by Reissig,[28] as a convenient route to accessing these substrates (Scheme 15). Following a procedure by Fukuyama et al,[29] phenyl diazoacetates (i.e. **230**) were synthesized by reaction of an appropriate phenol (i.e. **231**) with bromoacetyl bromide followed by *N,N′*-ditosylhydrazine.[30] The synthesis of TMS enol ethers (i.e. **232**) was performed using known procedures, starting from the appropriate aldehyde (i.e. **233**).[31] The combination of the TMS enol ethers **232** and phenyl diazoacetates **230** in the presence of copper acetylacetone provided the desired cyclopropanes **212** in good yields across three total steps. Electron rich aryl esters were selected as they gave optimal results in Lupton's (3+2) annulation.[20, 22]



Scheme 15: Synthesis of cyclopropanes **212**

4.2.2 Initial attempts at NHC catalyzed (4+3) annulation

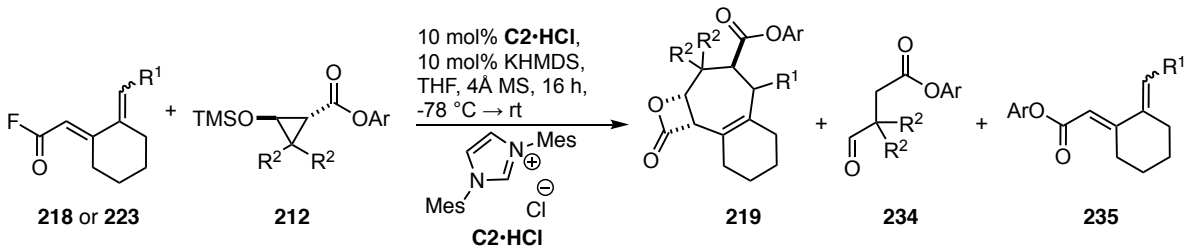
With the required substrates in hand, their viability in the proposed (4+3) annulation was examined (Table 1). Acyl fluoride **223** and cyclopropanes **212b** were initially subjected to conditions optimised for the analogous (3+2) annulation. Namely, IMes (**C2**) was used as the catalyst with a 10 mol% loading in THF at -78 °C (Table 1, entry 1). Unfortunately, this failed to provide the desired product **219**, with 43% of the quenched product **234** and 20% of the transesterified product **235** isolated. The formation of the quenched enolate **234** is postulated to occur from protons on the HMDS byproduct of carbene deprotonation or from protons on the acyl fluoride (Scheme 16). The NHC can then add to the ester fragment of this quenched product, or indeed, the cyclopropane to release a phenoxide and provide acyl azolium **236**. This phenoxide can then attack either an acyl fluoride (e.g. **218**) or dienyl acyl azolium (e.g. **220**) to give the ester byproduct **235**.

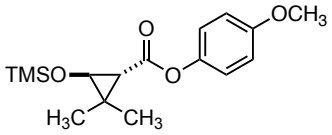
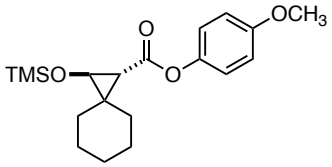
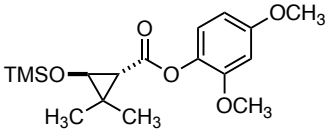
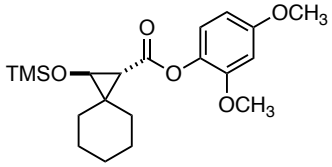


Scheme 16: Proposed formation of side products **234** and **235**

Reaction with acyl fluoride **218** lacking δ-substituents produced near identical results (Table 1, entry 2). It was thought that bulkier and more electron rich cyclopropanes may reduce enolate quenching, as observed by Lupton et al.[22] To this end, cyclopropanes **212a** and **212c-d** were tested (Table 1, entries 3-8). Unfortunately, similar results were observed across all substrates tested. However, the mass spectrum of the crude reaction mixtures of between cyclopropane **212c** and acyl fluoride **218** (Table 1, entry 8) demonstrated the presence of a molecular ion peak corresponding to the desired product **219c**. This suggested that trace quantities of the desired cycloheptene may have been forming.

Table 1: Attempts at NHC catalysed (4+3) annulation



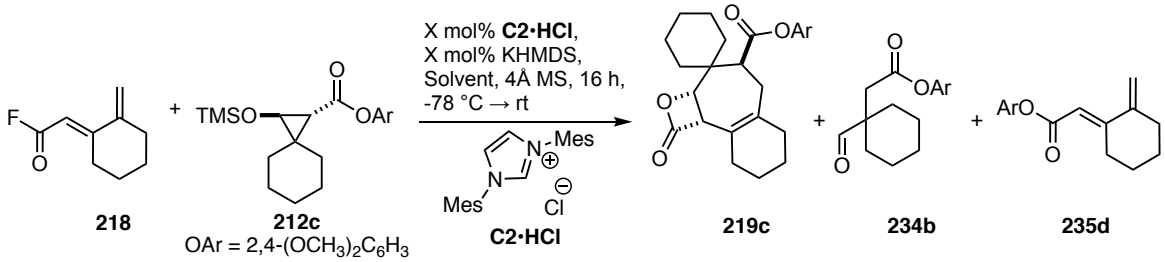
Entry	Cyclopropane	Acyl fluoride	Result
1		**223**, $R^1 = CH_3$	0% **219**, 43% **234a**, 20% **235a**
2		**218**, $R^1 = H$	0% **219**, 40% **234a**, 20% **235b**
3		**223**, $R^1 = CH_3$	0% **219**, 45% **234b**, 21% **235a**
4		**218**, $R^1 = H$	0% **219**, 49% **234b**, 19% **235b**
5		**223**, $R^1 = CH_3$	0% **219**, 44% **234a**, 22% **235c**
6		**218**, $R^1 = H$	0% **219**, 40% **234a**, 25% **235d**
7		**223**, $R^1 = CH_3$	0% **219**, 41% **234b**, 25% **235c**
8		**218**, $R^1 = H$	0% **219**, 40% **234b**, 26% **235d**

4.2.3 Effect of solvents on NHC catalyzed (4+3) annulation

To try and exploit the trace formation of **219c** observed in the reaction of cyclopropane **212c** with dienyl acyl fluoride **218**, conditions were varied in an attempt to increase the yield of cycloheptene **219c**. To this end, a range of different solvents were examined, along with increasing the catalyst loading (Table 2). As the reaction suffered from unwanted side products, it was thought that increasing the catalyst loading may help increase the rate of the desired reaction in relation to the quenching of the cyclopropane and transesterification side reaction.

When the reaction was conducted in THF with 10% IMes (**C2**) (Table 2, entry 1) significant amounts of aldehyde **234b** was isolated along with the ester **235d**. A similar result was seen when 20% IMes was used, however, an increased amount of decomposition was also observed (Table 2, entry 2). Almost identical results were observed when the reaction was conducted in toluene with either 10% or 20% IMes (Table 2, entries 3 & 4). Lastly, ether was trialled as the solvent, again giving similar results with most of the recovered material consisting of aldehyde **234b**, along with ester **235d** (Table 2, entries 5 & 6).

Table 2: Solvent variation in attempted (4 + 3) annulations



Entry	Solvent	X (%)	Result
1	THF	10	0% **219c**, 51% **234b**, 20% **235d**
2	THF	20	Trace **219c**, 49% **234b**, 24% **235d**
3	Toluene	10	0% **219c**, 45% **234b**, 25% **235d**
4	Toluene	20	Trace **219c**, 45% **234b**, 22% **235d**
5	Ether	10	0% **219c**, 65% **234b**, 13% **235d**
6	Ether	20	Trace **219c**, 52% **234b**, 11% **235d**

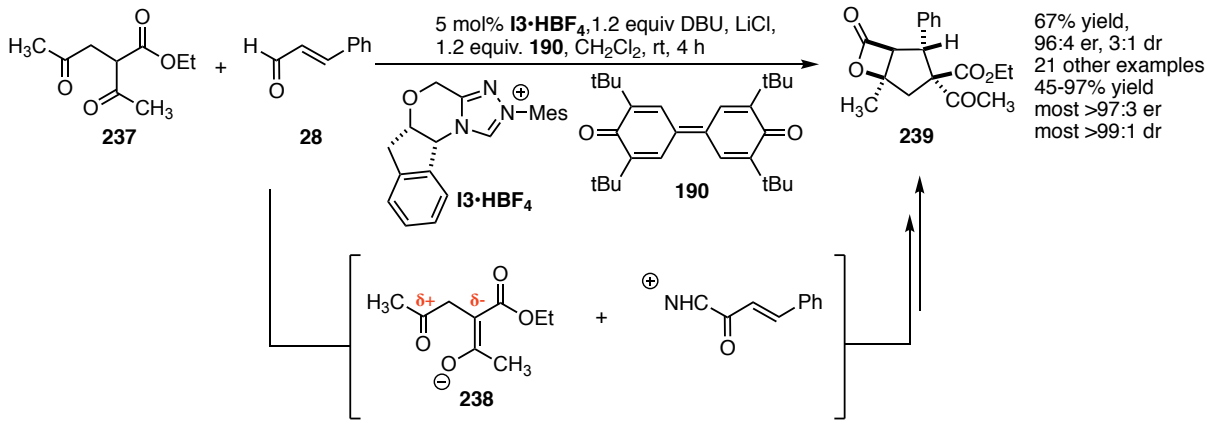
It was clear that the viability reaction was being hampered by undesired side reactions leading to quenched enolate **234** and ester **235**. Unfortunately, all attempts at varying the acyl fluoride coupling

partner, as well as the reaction conditions to suppress these side reactions were ineffective. We believed that these issues stemmed from the highly reactive bifunctional enolate **214** that is formed via cyclopropane opening. Therefore, we decided to investigate less reactive dipoles which aren't as prone to quenching.

4.3 (4+3) Annulations Utilising Alternate Bifuntional 3-Carbon Dipoles

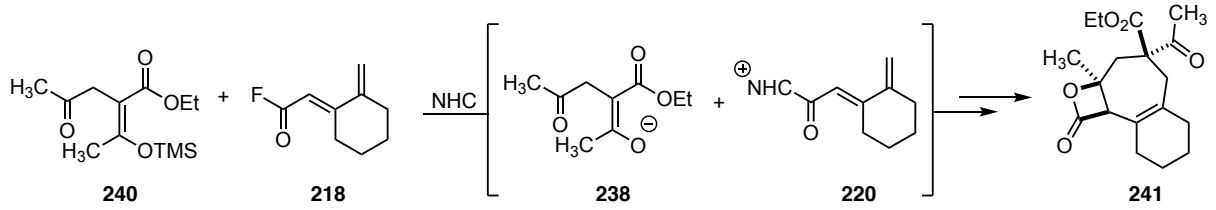
4.3.1 Studer's bifunctional 3-carbon dipole

Due to the incompatibility of cyclopropanes with the dienyl acyl azolium (i.e. **218**), it was necessary to find a viable bifuntional 3-carbon dipole. Studer and co-workers previously introduced γ-keto ester **237** as a 3-carbon dipole (i.e. **238**) in their synthesis of cyclopentanes **239** (Scheme 17).[32] This dipole **238** reacts in a similar manner to the cyclopropane derived dipole (i.e. **214**), however, due to the two electron withdrawing groups displays a lower nucleophilicity value which we believed would suppress the rapid quenching observed previously.



Scheme 17: Studer's cyclopentane synthesis using β-ketoester nucleophiles

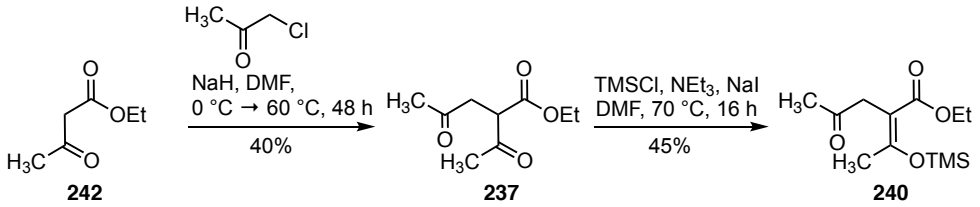
We believed we could modify Studer's nucleophile (i.e. **237**) through formation of the corresponding TMS-enol ether (i.e. **240**) which would be unmasked by NHC mediated defluorination desilylation as previously foreshadowed (Scheme 18). The newly proposed reaction mechanism is similar to the previously proposed (4+3) annulation with desilylation of the TMS-enol ether **240** generating the dipole **238** which can react in an analogous fashion with dienyl acyl azolium **220** generated from acyl fluoride **218** to eventually provide cyloheptene **241** (Scheme 18).



Scheme 18: Proposed (4+3) annulation with alternate nucleophile

4.3.2 Synthesis of TMS enol ether 240

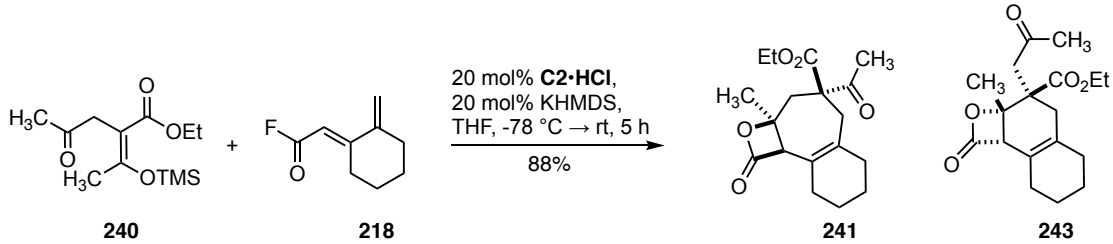
To examine this approach, TMS enol ether **240** was required. Its synthesis commenced with commercially available ethyl acetoacetate **242** which was alkylated with chloroacetone to give γ-ketoester **237** in modest yield (Scheme 19). Conversion to the corresponding TMS-enol ether **240** was achieved by treatment with trimethylsilyl chloride(TMSCl) in the presence of trimethylamine. With the desired pro-nucleophile **239** in hand, it's viability in the (4+3) annulation was examined.



Scheme 19: Synthesis of modified 3-carbon dipole **240**

4.3.3 Attempted (4+3) annulation with TMS enol ether 240

Acyl fluoride **218** was used in the initial attempts at this modified (4+3) annulation (Scheme 20). The reaction was carried out using the conditions reported for the (3+2) annulation reaction however, with 20 mol% catalyst loading. Pleasingly, after just 5 hours, complete consumption of the starting materials was observed and a single product was isolated from the reaction mixture. Mass spectrometry confirmed the required mass of the cycloheptene **241**, however, we recognized the possibility of a cyclohexene product **243**.



Scheme 20: Attempted (4 + 3) annulation using TMS enol ether **240**

4.3.4 Characterisation of annulated product 241 or 243

Utilising NMR techniques, the structure of the cyclized product was confirmed as either the cycloheptene **241** or the cyclohexene **243** as the observed spectra are consistent with both structures (Figure 1). Comparison of the ^{1}H NMR spectrum of the product to the starting acyl fluoride **218** showed a loss of all olefinic protons, while comparison to the TMS enol ether **240** revealed a distinct lack of the resonance at 0.14 ppm which corresponds to the trimethylsilyl moiety.

Most significantly, the ^{1}H NMR spectrum of the product displayed five signals between 2.2 and 3.6 ppm. The most downfield signal is a singlet at 3.53 ppm which integrates to 1 proton and displays no coupling, and as such, is assigned as H^{a}. Four of these signals correspond to diastereotopic methylene groups as the doublets at 3.15 and 2.78 ppm correspond to only one carbon in the HSQC, as do the broad doublets at 2.35 and 2.26 ppm. HMBC correlations were used to assign these methylene groups. The broad doublets at approximately 2.3 ppm show an HMBC correlation to both of the olefinic carbons, allowing them to be assigned as H^{c} and $H^{c'}$. This leaves the doublets at 3.15 and 2.78 ppm to be assigned as H^{b} and $H^{b'}$. The singlets at 2.14 and 1.63 ppm can be assigned as H^{d} and H^{e} respectively, as the protons adjacent to the carbonyl are more deshielded than those in the other methyl group.

The downfield region of the ^{13}C NMR spectrum showed a peak characteristic of a β-lactone carbonyl at 205.4 ppm as well as two other carbonyl peaks that correspond to the methyl ketone and the ester moiety. It also contained two olefinic peaks and a peak at 81.4 ppm corresponding to the carbon adjacent to the β-lactone oxygen atom. Confirmation of the β-lactone functionality was taken from the IR spectrum which displayed an absorption at 1814 cm^{-1}.

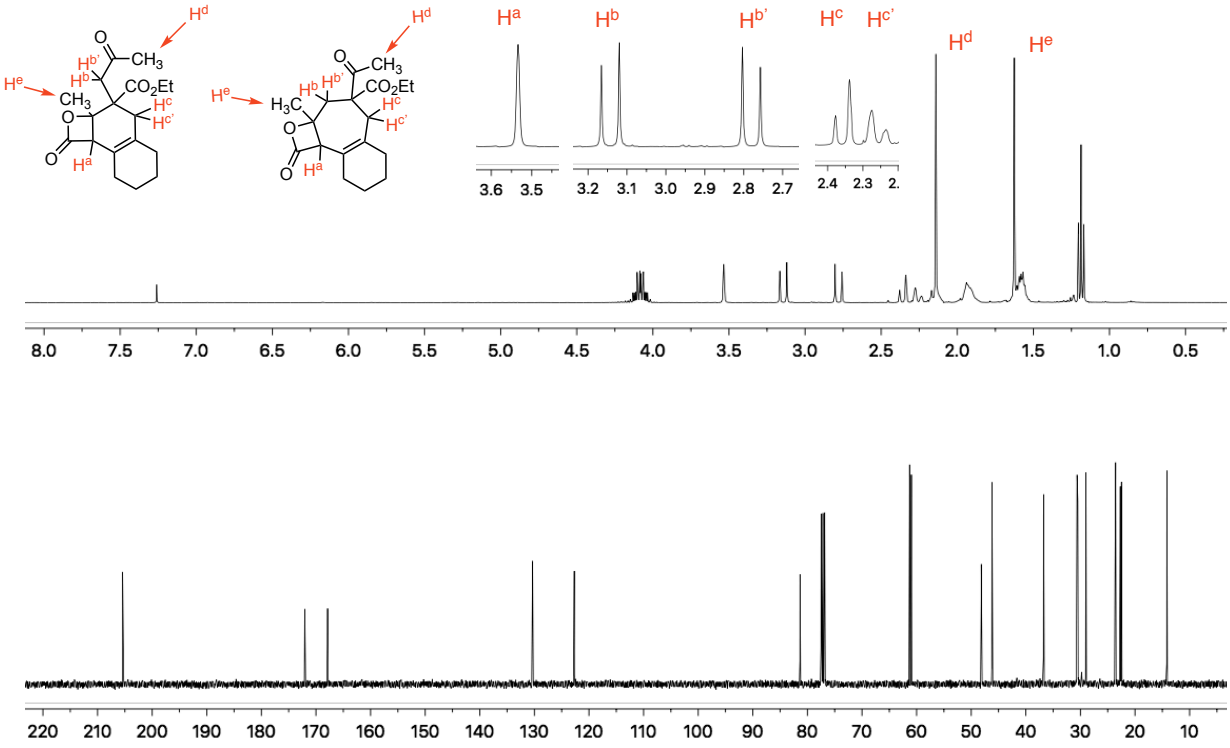


Figure 1: Characterisation of cyclized product

Unambiguous assignment of the product as either cycloheptene **241** or cyclohexene **243** proved very difficult, as each proton or cabon environments has an analogous environment in the other possible structure. However, there are a few HMBC correlations that are unique to each structure (Figure 2). In the cycloheptene **241**, a correlation between C^{e} and $H^{b/b'}$ should be observed as this is between 3 bonds. This should not be observed in the cyclohexene **243** structure, as these atoms are 4 bonds away. Similarly, a correlation between C^{b} and H^{d} should be observed in cyclohexene **243** and not in cycloheptene **241**. As there is an observed correlation between C^{b} and H^{d} and no observed correlation between C^{e} and $H^{b/b'}$ protons, the structure was tentatively assigned as cyclohexene **241**.

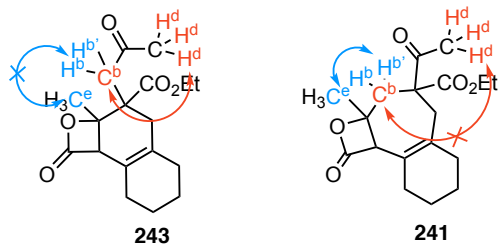
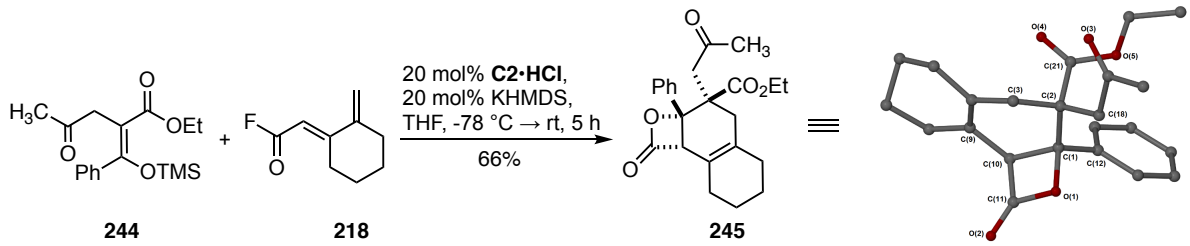


Figure 2: Observed HMBC correlations (orange) and not observed correlations (blue) in cycloheptene **241** and cyclohexene **243**

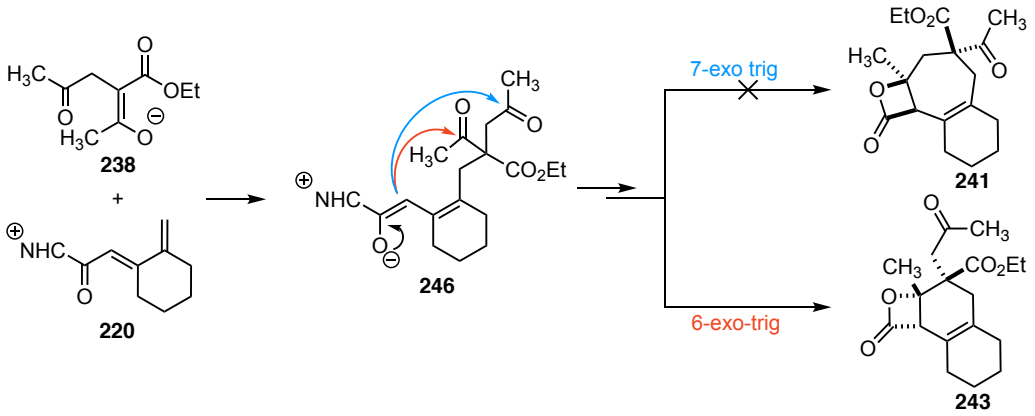
As the 2D NMR assignment was not definitive, attempts were undertaken to grow single crystals of the product for unambiguous structural assignment. Unfortunately, despite the solid nature of the product, recrystallization did not provide crystals of sufficient quality for X-ray analysis. It was reasoned that if the reaction could be repeated with a phenyl ketone rather than a methyl ketone, the extra rigidity in the system may promote crystal growth. Pleasingly, when the reaction was conducted using TMS enol ether **244** the corresponding product was isolated in 66% yield. Gratifyingly, crystals of sufficient quality could be grown and X-ray analysis provided unambiguous proof that the structure was in fact the cyclohexene **245**. This retrospectively gives confirmation of cyclohexene **243** as well.



Scheme 21: (4+3) annulation for product determination and crystal structure of **245**

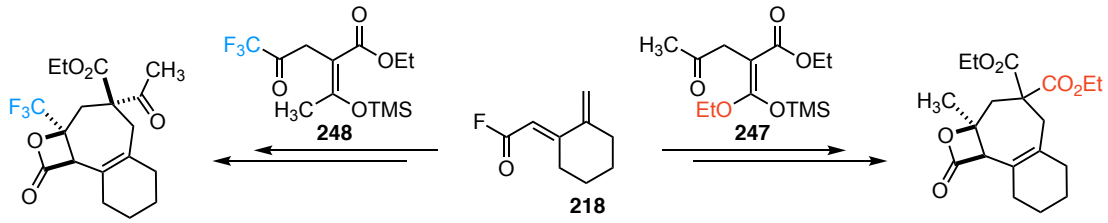
4.3.5 Proposed mechanism for formation of cyclohexene

Formation of cyclohexene **243** or **245** is due to the intermediate **246** having two possible routes of aldol cyclisation, a 6-*exo*-trig cyclisation and a 7-*exo*-trig cyclisation (Scheme 22). The six-membered ring is formed due to kinetic favourability of the cyclohexene compared to a cycloheptene.[33-35] Although this was not our intended reaction design, we were still encouraged by the formation of this six-membered ring. This serendipitous discovery represents the first example of an annulation utilizing the dienyl acyl azolium that generates products with stereocentres. Furthermore, this product validates our reaction design as C-C bond formation at the δ-carbon was observed. Moreover, as the β-lactone motif remained intact, so there is opportunity for this reaction to be rendered enantioselective. Development of this newly discovered (4+2) annulation was carried out by a colleague, Rachel Gillard, whilst the exploration of a possible (4+3) continued herein.



Scheme 22: Pathway to six and seven membered ring products

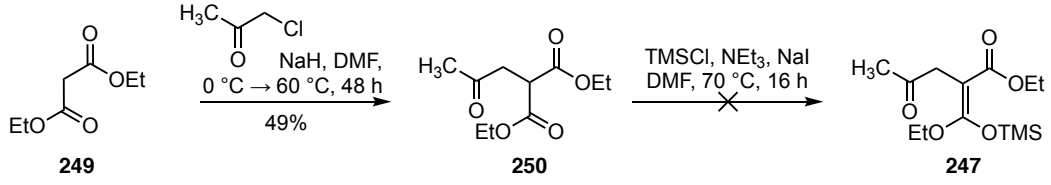
We envisaged a number of strategies to suppress the undesired cyclohexene forming. Specifically, this could be achieved by either lowering the electrophilicity of the functional group at the position of 6-exo trig cyclisation, or increasing the electrophilicity of the functional group at the position of 7-exo trig cyclisation. To this end, two new nucleophiles were proposed, silyl ketene acetal **247** would, upon deprotection, reveal an ester moiety, lowering the favourability of 6-exo trig cyclisation pathway. Trifluoromethyl ketone **248** would increase the electrophilicity at the desired point of cyclisation, increasing the favourability of the 7-exo trig cyclisation pathway.



Scheme 23: New 3-carbon dipoles to favour seven membered ring formation

4.3.6 Synthesis of substrates to promote (4+3) annulation

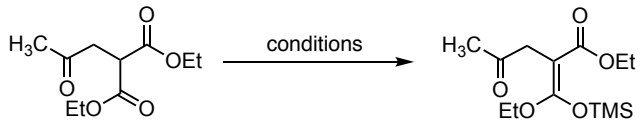
Studies commenced with the synthesis of diester substrate **247** (Scheme 24). Following conditions reported by Studer et al., diethyl malonate **249** was alkylated with chloroacetone to provide γ-ketoester **250** in moderate yield. Unfortunately, when subjected to the same conditions as previously used for TMS enol ether formation, none of the desired silyl ketene acetal **247** could be isolated.



Scheme 24: Attempted synthesis of diester 3-carbon dipole **247**

The synthesis of dipole **247** was then repeated using a number of different conditions (Table 3). As silyl ketene acetals are known to be sensitive to air and moisture, great care was taken to maintain the reaction mixture, and possible products, under inert atmosphere. Firstly, it was thought that triethyl amine may not be a strong enough base for the reaction, so LDA and ^{n}BuLi were examined following the procedure of Saalfrank et al.[36] (Table 3, entries 1 & 2). Unfortunately, this did not yield the desired product. Next, it was thought that a TBS group may increase the stability of the resultant silyl ketene acetal and allow for its isolation. However, when trialled, only starting materials were reisolated (Table 3, entry 3). Next, a modified procedure of Collins et al. was tested (Table 3, entries 4-6) as it was utilized in the synthesis of similar compounds.[37] Unfortunately, at room temperature (Table 3, entry 4), elevated temperature (Table 3, entry 5) and with TBSCl (Table 3, entry 6), none of the desired product was isolated. Finally, it was thought that bromination, followed by lithium halogen exchange may be more facile than direct deprotonation. To this end, bromination of **250** was conducted following the procedure of Wolfe et al.[38] Unfortunately, despite successful formation of the corresponding bromide, none of the desired product was formed after treatment with ^{n}BuLi and TMSCl (Table 3, entry 7).

Table 3: Attempted synthesis of silyl ketene acetal **247**

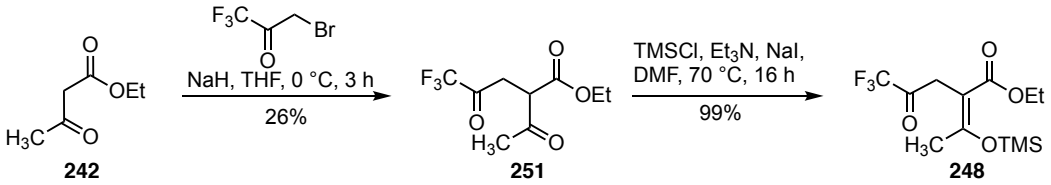


250 **247**

Entry	Conditions	Result
1	LDA, THF, TMSCl, -78 °C → rt, 2 h	0% yield
2	^{n}BuLi, THF, TMSCl, -78 °C → rt, 2 h	0% yield
3	LDA, THF, TBSCl, -78 °C → rt, 2 h	0% yield
4	NaH, DME, TMSCl, 0 °C → rt, 2 h	0% yield
5	NaH, DME, TMSCl, 0 °C → 50 °C, 2 h	0% yield
6	NaH, DME, TBSCl, 0 °C → 50 °C, 2 h	0% yield
7	Br_2, CH_2Cl_2, 0 °C, 0.5 h *then* ^{n}BuLi, THF, TMSCl, -78 °C, 1 h	0% yield

After many subsequent unsuccessful attempts at preparing the silyl ketene acetal **247**, our attention turned to the preparation of trifluoromethyl ketone **248** (Scheme 25). Starting from ethylacetoacetate

242, alkylation with α-bromo trifluoropropanone gave trifluoromethyl ketone **251** in a 26% yield.[39] Conversion to TMS enol ether **248** using standard conditions was then performed, giving the desired substrate in 99% yield.

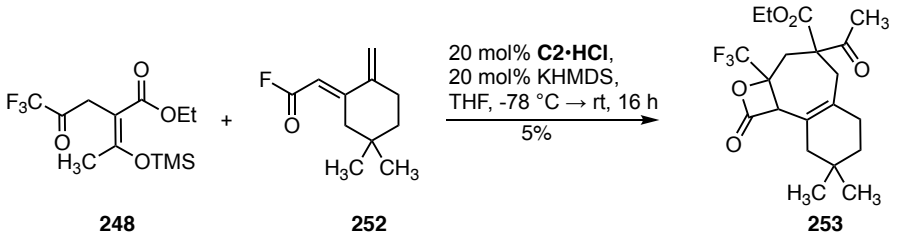


242 **251** **248**

Scheme 25: Synthesis of TMS enol ether **248**

4.3.7 Attempted (4+3) annulation with trifluoromethyl ketone 248

With trifluoromethyl ketone substrate **248** in hand, the (4+3) annulation was re-examined, this time with dimethyl acyl fluoride **252** (Scheme 26).[i] Gratifyingly, when treated with the conditions that previously gave the six-membered ring, the desired cycloheptene **253** was isolated albeit in 5% yield (Scheme 26).



248 **252** **253**

Scheme 26: (4+3) annulation with trifluoromethyl ketone **248**

4.3.8 Characterisation of cycloheptene 253

The structure was confirmed by 1D and 2D NMR experiments as well as mass spectrometry and comparison to the previously confirmed cyclohexene **243** (Figure 3). Comparison of the ^{1}H NMR spectrum of the product to the starting acyl fluoride **252** showed a loss of all olefinic protons, while comparison to the TMS enol ether **248** revealed a distinct lack of the resonance at 0.14 ppm which corresponds to the trimethylsilyl moiety. In contrast to the cyclohexene **243**, this cycloheptene **253** structure shows five signals between 4.5 and 5.6 ppm. The furthest downfield is assigned as H^{a}, the β-lactone proton. This has been shifted further downfield from its cyclohexene counterpart due to the presence of the CF_3 group. The two sets of doublets at 4.6 and 3.2 were assigned due to HMBC

[i]Acyl fluoride donated by Rachel Gillard

interactions with the olefinic carbons, with the resonances further downfield assigned as H^{c} and $H^{c'}$ due to their proximity to the electron withdrawing ketone and ester moieties. This leaves the two broad singlets at 4.8 to be H^{b} and $H^{b'}$ which do not strongly couple to each other, perhaps due to a strange ring geometry brought about by the β-lactone. Most notably, however, is the presence of the methyl ketone H^{e} and lack of methyl group at around 1.6 ppm. If the cyclisation had occurred at the methyl ketone, it would be expected that the methyl group would be at approximately 1.6 ppm, similar to H^{e} in cyclohexene **243** (Figure 1). The downfield region of the ^{13}C NMR spectrum showed the correct number of peaks in both the downfield and upfield regions. The β-lactone functionality was again confirmed by IR, with an absorption at 1810cm^{-1}.

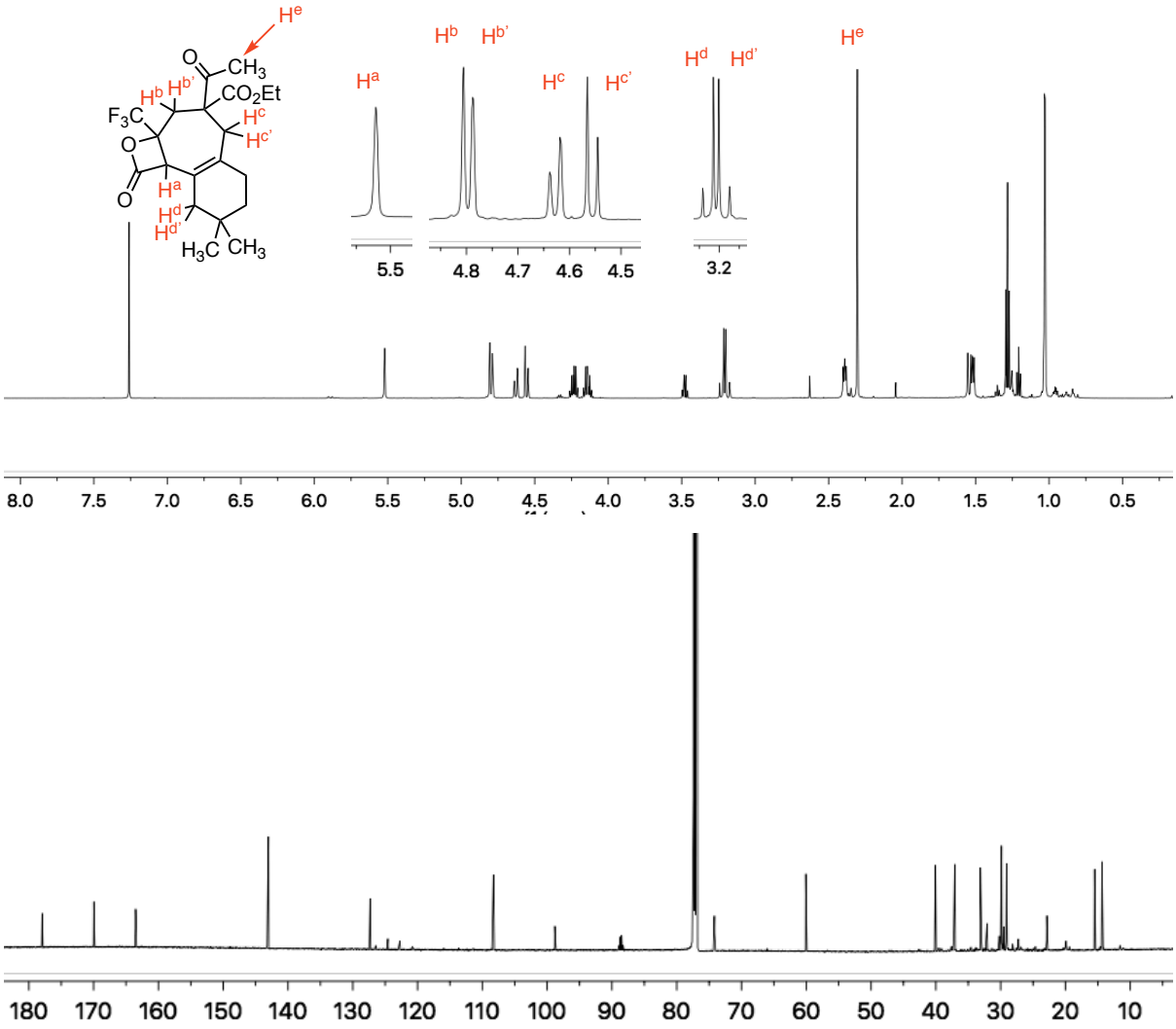


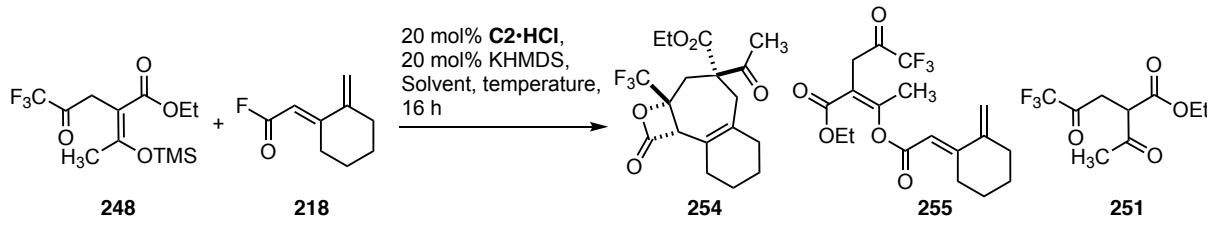
Figure 3: Characterisation of cycloheptene **253**

4.4 Optimisation of (4+3) Annulation

4.4.1 Effect of temperature and solvent

Returning to the original acyl fluoride **218**, studies commenced with variation of the reaction temperature. At lower temperatures, the reaction did not go to completion, with the side products resulting from *O*-acylation **255** and enolate quenching **255** also isolated along with cycloheptene **254** (Table 4, entry 1). When the mixture was heated to reflux (Table 4, entry 2) the yield of enol ester **255** increased and only a trace of cycloheptene **254** was observed. The optimal outcome was achieved at room temperature, with a slightly increased yield of cycloheptene **254** observed although the major materials isolated remained the enol ester **255** and quenched enolate **251** (Table 4, entry 3). Conducting the reaction in toluene provided only trace amounts of the cycloheptene **254** (Table 4, entry 4). The reaction was slowed in dioxane with reduced conversions leading to lower yields of all products (Table 4, entry 5). DCE showed none of the desired product, with significant enolate quenching observed. THF was found to be the best solvent, perhaps due to its ability to solvate enolates such as the nucleophile in this reaction.

Table 4: Optimisation of NHC catalyzed (4+3) annulation



248 **218** **254** **255** **251**

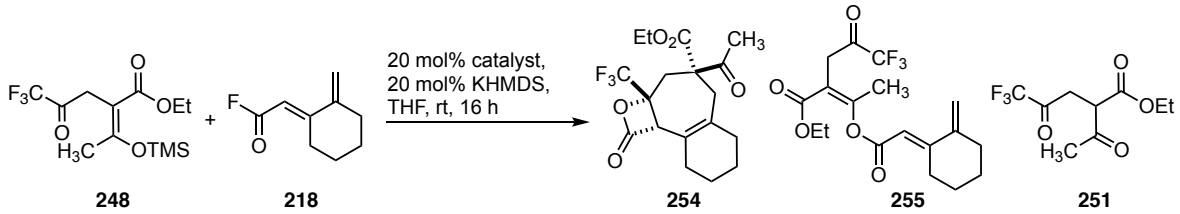
Entry	Temperature	Solvent	Result
1	-78	THF	3% **254**, 12 % **255**, 40% **251**
2	reflux	THF	Trace **254**, 19% **255**, 45% **251**
3	rt	THF	5% **254** 15% **255**, 35% **251**
4	rt	toluene	Trace **254**, 22% **255**, 40% **251**
5	rt	dioxane	Trace **254**, 17% **255**, 34% **251**
6	rt	DCE	0% **254**, 14% **255**, 49% **251**

4.4.2 Catalyst screen

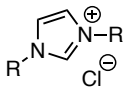
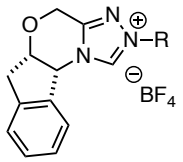
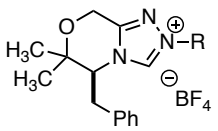
With variation of the temperature and solvent giving only marginally improved results, a catalyst screen was undertaken. Both achiral and chiral catalysts were examined to allow a broad range of steric and electronic variation to be achieved. Switching from IMes, **C2** (Table 5, entry1) to the bulkier IAd

C1 was expected to suppress *O*-acylation. Whilst this proved to be the case, it also prevented formation of the desired cycloheptene **254** (Table 5, entry2). When testing the indanol derived homochiral catalysts, mesityl **I3** and pentafluorophenyl **I4** *N*-substituted catalysts failed to provide the desired product (Table 5, entries 3 & 4). In contrast, the electron rich tertiary butyl *N*-substituted catalyst **I5** gave a 3% yield of the desired product **254** (Table 5, entry 5). The enantiomeric ratio was not determined as an insufficient quantity of the cycloheptene **254** was isolated. Switching to the morpholinone scaffold, electron poor and electron neutral *N*-substituted catalysts (**M5** & **M6**) gave none of the cycloheptene product **254** (Table 5, entries 6 & 7). However, switching to the mesityl *N*-substituted catalyst **M1** gave a modest 3% yield of cycloheptene **254** (Table 5, entry 8). Again, the tertiary butyl *N*-substituted catalyst **M3** produced the best yield on the morpholinone scaffold with 5% cycloheptene isolated (Table 5, entry 9). Given that the electron rich catalysts gave the best result, we were somewhat surprised when the electron rich catalysts **M2** and **M7** produced none of the desired cycloheptene **254** (Table 5, entries 10 & 11).

Table 5: Catalyst screen of (4+3) annulation



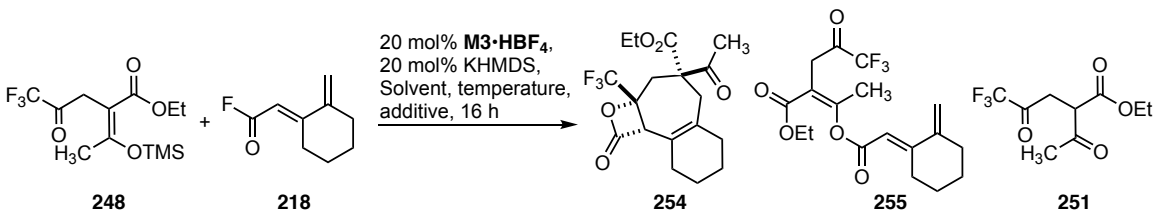
248 **218** **254** **255** **251**

Entry	Catalyst		Result
1		**C2**, R = Mes	5% **254**, 15% **255**, 35% **251**
2		**C1**, R = Adamantyl	0% **254**, 0% **255**, 55% **251**
3		**I3**, R = Mes	0% **254**, 10% **255**, 49% **251**
4		**I4**, R = C_6F_5	0% **254**, 0% **255**, 55% **251**
5		**I5**, R = ^{t}Bu	3% **254**, 9% **255**, 41% **251**
6		**M5**, R = C_6F_5	0% **254**, 0% **255**, 52% **251**
7		**M6**, R = Ph	0% **254**, 13% **255**, 36% **251**
8		**M1**, R = Mes	3% **254**, 11% **255**, 42% **251**
9		**M3**, R = ^{t}Bu	5% **254**, 12% **255**, 39% **251**
10		**M2**, R = 4-$OCH_3C_6H_4$	0% **254**, 18% **255**, 55% **251**
11		**M7**, R = 2,6-$(OCH_3)_2C_6H_3$	0% **254**, 15% **255**, 45% **251**

4.4.3 Re-optimisation with chiral catalyst

With a new lead catalyst **M3**, the impact of temperature and solvent, as well as additives were examined. As the catalyst is a homochiral NHC, the enantioselectivity of the reaction was also assessed. In other studies, the tertiary butyl morpholinone NHC **M3** has been found to give the highest and high enantioselectivity at elevated temperatures.[40] Pleasingly, when the reaction was conducted in THF heated to reflux (Table 6, entry 1) this gave an increased yield of 10% of cycloheptene **254** albeit with poor enantioselectivity (55:45 er). Repeating the reaction in higher boiling solvents including toluene, dioxane and DMF resulted in no product formation (Table 6, entries 2-4). Addition of LiCl has been used by Studer in related reactions,[32] however, the reaction failed under these conditions (Table 6, entry 5). Molecular sieves were added in an attempt to prevent quenching of the enolate by adventitious water,[22] however, in the presence of the molecular sieves the reaction failed (Table 6, entry 6). Finally, given that ionic additives such as LiCl were detrimental to the outcome, the reaction was performed under salt free conditions. However, this showed no improvement in yield or enantioselectivity (Table 6, entry 7). Given the low yields observed across all conditions trialled, we believed modification of the substrates was required. Specifically, we suspected that issues associated with the reaction stemmed from the decomposition of the acyl fluoride **218**. Thus, we rationalised that an acyl fluoride less prone to decomposition may allow increased yields.

Table 6: Optimisation of enantioselective (4+3) annulation

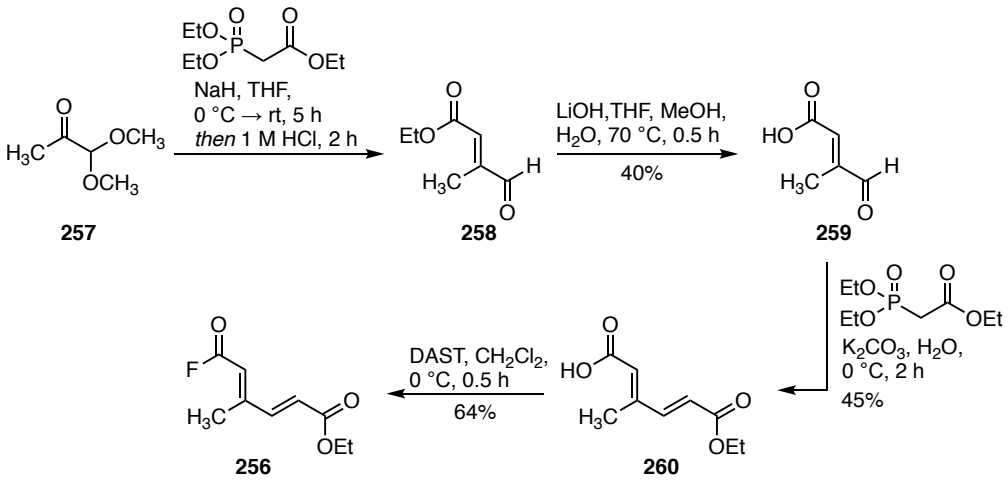


248 **218** **254** **255** **251**

Entry	Solvent	Temperature	Additive	Yield	er
1	THF	66	-	10%	55:45
2	toluene	110	-	trace	-
3	dioxane	100	-	trace	-
4	DMF	110	-	0%	-
5	THF	66	LiCl	0%	-
6	THF	66	4Å mol. sieves	0%	-
7	THF	66	salt free	10%	55:45

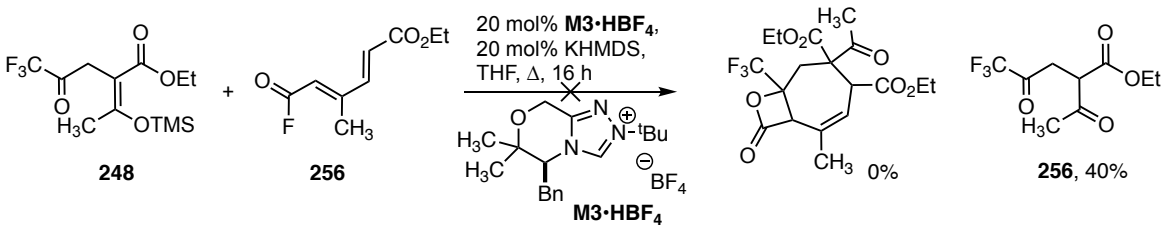
4.4.4 Synthesis and use of alternate acyl fluoride 256

To this end, we targeted acyl fluoride **256**, as it closely resembles the diunsaturated aldehyde that Chi and coworkers used in their (4+2) reaction of the dienyl acyl azolium (Scheme 27).[21] Furthermore, activating the δ-position by adding an electron withdrawing group may further promote the desired 1,6-addition. Starting from commercially available methyl glyoxal dimethyl acetal **257**, a one pot HWE reaction followed by acetal hydrolysis gave aldehyde **258** in excellent yield (scheme 25).[41] Hydrolysis then provided acid **259** in moderate yields. A HWE reaction is used to convert the aldehyde **259** to α,β-unsaturated ester **260**. Finally, conversion to the acyl fluoride **256** was achieved using DAST in 64% yield.[27]



Scheme 27: Synthesis of acyl fluoride **256**

With acyl fluoride **256** in hand, it's viability in the reaction was examined (Scheme 28). Unfortunately, when subjected to the reaction conditions, the only product isolated was the quenched enolate **251**. This result suggests that substituents at the δ-position may not be tolerated. Alternately, the keeping the acyl fluoride in the reactive s-cis conformation may be essential to the reactions success.

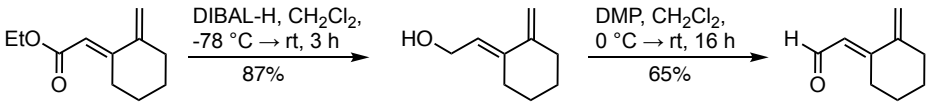


Scheme 28: Attempted (4+3) using acyl fluoride **256**

4.5 Oxidative NHC Catalysis

4.5.1 Synthesis of dienal substrate

Given that little success had been seen to this point with acyl fluorides, studies that focused on the use of oxidative access to the dienyl acyl azolium, similar to that of Chi,[12] were examined. To this end, using a modified synthesis to that of acyl fluoride **218**, we set about preparing α,β-γ,δ-diunsaturated aldehyde **261** (Scheme 29). Reduction of the previously synthesized ester **226** with diisobutyl aluminium hydride (DIBAL-H) gave alcohol **262**, which was subsequently oxidized using Dess-Martin periodinane to give the desired aldehyde **261**. This substrate was extremely volatile, and displayed an even greater affinity to decomposition than the analogous acyl fluoride **218**.



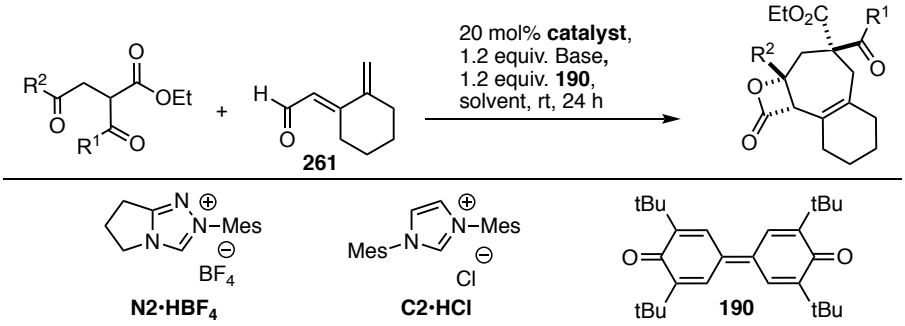
226 **262** **261**

Scheme 29: Synthesis of aldehyde **261**

4.5.2 Attempted oxidative (4+3) annulation

Nevertheless, a number of reactions were trialled with the aldehyde **261**, using established conditions for oxidative NHC catalysis.[21, 32] A range of different nucleophiles were also trialled. Since these conditions do not require the use of TMS protection of the enol this allowed previously inaccessible substrates to be examined. Firstly, using conditions reported by Studer,[32] trifluoromethyl ketone **251** was used as the nucleophile in dichloromethane and mesityl catalyst **N2**, none of the desired product was observed (Table 7, entry 1). Switching to the phenyl ketone derived nucleophile **263** gave no better outcome in the reaction (Table 7, entry 2). Utilising the malonate derived nucleophile **250**, which was unable to be used previously, was unfortunately unsuccessful at both room temperature and refluxing temperature (Table 7, entries 3 & 4). Next, utilizing conditions presented by Chi,[21] namely IMes (**C2**) as the catalyst in THF, the outcome remained the same using both the malonate derived nucleophile **250** and trifluoromethyl ketone nucleophile **251** (Table 7, entry 5 & 6).

Table 7: Attempted oxidative (4+3) annulation

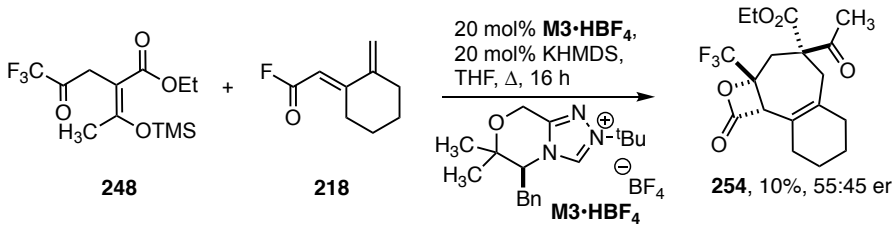


Entry	Solvent	Nucleophile	Cat.	Base	Result
1	DCM	**251**, R^1 = Me, R^2 = CF_3	**N2**	DBU	0%
2	DCM	263, R^1 = Ph, R^2 = CF_3	**N2**	DBU	0%
3	DCM	**250**, R^1 = EtO, R^2 = Me	**N2**	DBU	0%
4	DCM (45 °C)	**250**, R^1 = EtO, R^2 = Me	**N2**	DBU	0%
5	THF	**250**, R^1 = EtO, R^2 = Me	**C2**	$CsCO_3$	0%
6	THF	**251**, R^1 = Me, R^2 = CF_3	**C2**	$CsCO_3$	0%

After varying the 3-carbon dipole, the acyl fluoride, and the reaction conditions, the best results achieved in a (4+3) annulation were a 10% yield and 55:45 er (Table 6, entry 7). As such, efforts towards a highly enantioselective all-carbon (4+3) annulation via the dienyl acyl azolium were abandoned at this point.

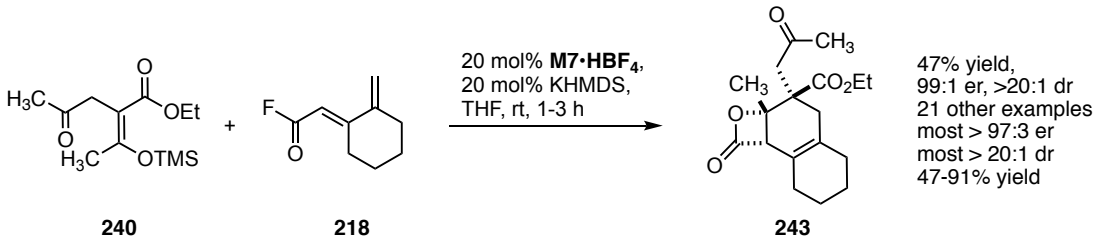
4.6 Conclusions

An NHC catalysed (4+3) annulation involving the α,β-γ,δ-dienyl acyl azolium was discovered (Scheme 30). The use of TMS enol ethers (i.e. **248**) derived from γ-ketoesters, instead of the originally designed cyclopropanes, was crucial to this discovery. Importantly, the use of a trifluoromethyl ketone was required to promote attack at the desired position to give a cycloheptene (i.e. **254**) rather than the analogous cyclohexene. Unfortunately, despite extensive efforts the desired cycloheptene **254** could only be prepared in a 10% yield and with low enantiopurity (55:45 er).



Scheme 30: (4+3) reaction discovered

While the outcome of studies towards the (4+3) annulation were disappointing, during the course of the study a serendipitous (4+2) reaction was discovered with high yields and excellent diastereoselectivity. Further exploration of this reaction completed in the group has rendered this reaction enantioselective and has since been published (Scheme 31).[42] This represents the first enantioselective reaction that proceeds via the dienyl acyl azolium.



Scheme 31: (4+2) reaction discovered

4.7 References

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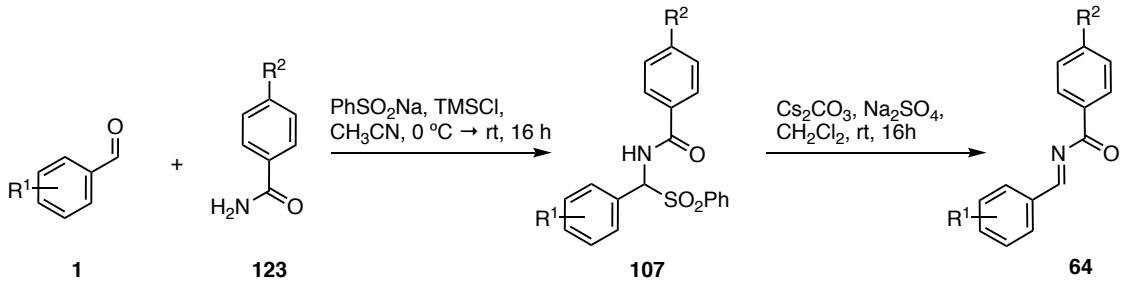
Chapter 5: Experimental Section

5.1 General experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX600 spectrometer operating at 600 MHz for proton and 150 MHz for carbon nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei, and a Bruker DRX300 spectrometer operating at 300 MHz for proton nuclei. 2D correlation spectra were recorded on a Bruker DRX400 spectrometer. Infrared spectra (ν_{max}) were recorded on an Agilent Cary 630 FTIR Spectrometer. High resolution mass spectra (HRMS) (ESI) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration. Analytical chiral HPLC was performed with a Perkin Elmer Series 200 HPLC using either a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. or using RegisCell™ 5μm (4.6 mm x 25 cm) obtained from Regis Technologies, Inc. with visualization at 210, 254, 260 or 280 nm. Optical rotations were measured with a PolAAr 3005 polarimeter at 589 nm. Flash column chromatography was performed on silica gel (Davisil LC60A, 40-63 μm silica media) using compressed air. Thin layer chromatography (TLC) was performed using aluminum-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F254 plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with vanillin stain followed by heating. Starting materials and reagents were purchased from Sigma-Aldrich or Oakwood and were used as supplied. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passing over activated alumina. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an atmosphere of nitrogen. Triazolium salts **N3**•BF_4,[1] M**1-7**•BF_4,[2] **I1**•BF_4,[3] K2•BF_4,[4] and G2•BF_4,[4] were all made according to literature procedures.

5.2 Experimental Section for Chapter Two

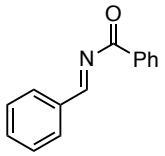
5.2.1 Synthesis of benzoyl imines: general procedure A



1 **123** **107** **64**

Following a modified procedure of Reider,[5] benzenesulfinic acid sodium salt (25 mmol, 1.5 eq) followed by the appropriate amide **123** (25 mmol, 1.5 eq) was added to a RBF and the flask charged with acetonitrile (250 mL) and the contents stirred under a positive pressure of nitrogen. To the resulting slurry was added the appropriate aldehyde **1** (16.7 mmol, 1.0 eq) in one portion. The mixture was cooled to 0 °C and chlorotrimethylsilane (33.3 mmol, 2.0 eq) slowly added. The reaction was allowed to warm to room temperature and stirred for 16 hours. To the heterogeneous mixture was added water (250mL) and the resulting suspension stirred for 30 minutes. The α-amido sulfones **107** were isolated by filtration as a fine white solid and used without further purification. Next, following a modified procedure of Schaus,[6] Cs_2CO_3 (3.3 g, 10 mmol) and Na_2SO_4 (1.4 g, 10 mmol) were added to a RBF. The solids were flame-dried under high vacuum and then allowed to cool. The α-amido sulfone **107** (730 mg, 2 mmol) from the previous step was added in one portion followed by CH_2Cl_2 (30 mL). After stirring at room temperature for 16 hours, hexanes (~40 mL) was added and the mixture filtered through Celite. The Celite was rinsed with hexanes (2 x 50 mL) and the combined fractions concentrated under reduced pressure to give imines **64** as white to yellow solids.

(*E*)-*N*-benzylidenebenzamide (64a)



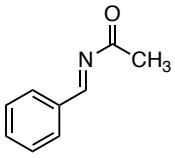
Following general procedure A, the title compound was prepared in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.23-8.12 (m, 2H), 8.02-7.94 (m, 2H), 7.62-7.57 (m, 2H), 7.55-7.45 (m 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 164.6, 134.6, 133.6, 133.4, 133.3, 130.2, 130.0, 129.0, 128.5.

Spectroscopic data was consistent with the literature.[7]

(*(E)*-*N*-benzylideneacetamide (64b)

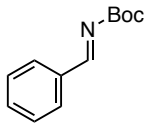


Following general procedure A, the title compound was prepared in 58% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.97-7.70 (m, 2H), 7.62-7.33 (m, 3H), 2.33 (s, 3H) ppm

Spectroscopic data was consistent with the literature.[8]

***tert*-butyl (*E*)-benzylidenecarbamate (64c)**



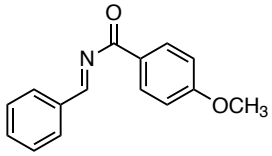
Following general procedure A, the title compound was prepared in 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 1.59 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.5, 134.1, 133.5, 130.0, 128.8, 82.2, 27.6 ppm

Spectroscopic data was consistent with the literature.[9]

(*E*)-*N*-benzylidene-4-methoxybenzamide (64e)



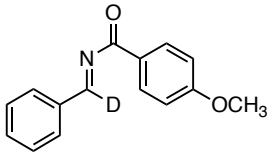
Following general procedure A, the title compound was prepared in 67% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, 1H), 8.17-8.12 (m, 2H), 8.01-7.96 (m, 2H), 7.59-7.49 (3H, m), 6.99-6.94 (m, 2H), 3.88 (s, 3H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.2, 164.4, 163.9, 134.7, 133.1, 132.4, 129.9, 128.9, 126.1, 113.8, 55.5 ppm

Spectroscopic data was consistent with the literature.[10]

(*E*)-4-Methoxy-*N*-(phenylmethylene-*d*)benzamide (D-64e)



Following general procedure A, the title compound was prepared in 56% yield.

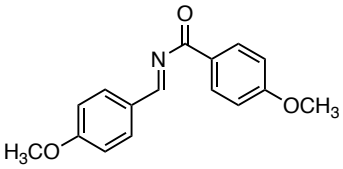
IR ν_{max} 1653, 1594, 1574, 1257, 1051, 1015, 771 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42-8.34 (m, 2H), 7.70-7.63 (m, 2H), 7.10-7.06 (m, 1H), 7.05-7.02 (m, 2H), 6.76-6.68 (m, 2H), 3.17 (s, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.3, 163.6 (t, J = 19 Hz), 162.9, 134.2, 131.7, 131.6, 129.0, 127.7, 126.1, 112.9, 53.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{15}H_{12}DNO_2$, 241.1096, requires 241.1082.

(*E*)-4-Methoxy-*N*-(phenylmethylene-*d*)benzamide (64f)



Following general procedure A, the title compound was prepared in 67% yield.

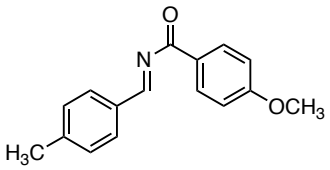
IR ν_{max} 1639, 1594, 1504, 1249, 1156, 1013, 793 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.21-8.10 (m, 2H), 7.99-7.87 (m, 2H), 7.02-6.97 (m, 2H), 6.97-6.92 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 164.4, 163.9, 163.9, 132.5, 132.3, 127.8, 126.7, 114.5, 113.8, 55.6, 55.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{15}NO_3$, 270.1130, requires 270.1125.

(*E*)-4-Methoxy-*N*-(phenylmethylene-*d*)benzamide (64g)



Following general procedure A, the title compound was prepared in 63% yield.

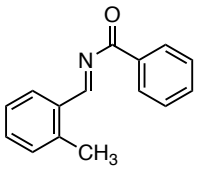
IR ν_{max} 1654, 1599, 1570, 1503, 1160, 1017, 991, 808 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.48-8.34 (m, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.77-6.67 (m, 2H), 3.19 (s, 3H), 1.99 (s, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 179.58, 165.23, 164.11, 143.74, 133.02, 132.84, 130.39, 129.76, 129.72, 114.09, 54.90, 21.53 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{15}NO_2$, 254.1186, requires 254.1176.

(*E*)-*N*-(2-methylbenzylidene)benzamide (64i)



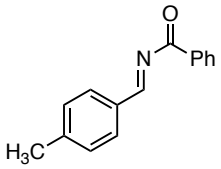
Following general procedure A, the title compound was prepared in 54% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (s, 1H), 8.10 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.96 dt, *J* = 6.8, 1.6 Hz, 2H), 7.62-7.41 (m, 4H), 7.24-7.31 (m, 2H), 2.70 (s, 3H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 125.7, 128.9, 129.9, 132.0, 132.1, 132.3, 132.5, 133.1, 134.7, 140.8, 163.3, 182.5;

Spectroscopic data was consistent with the literature.[6]

(*E*)-*N*-(4-methylbenzylidene)benzamide (64j)



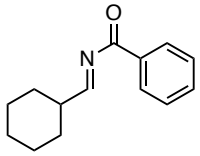
Following general procedure A, the title compound was prepared in 64% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (s, 1H,), 8.05 (d, J = 8.4 Hz, 2H), 7.98 (dt, J = 6.2, 1.6 Hz, 2H), 7.62-7.48 (m, 3H), 7.28 (d, J = 8.4 Hz, 2H), 2.43 (s, 3H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.9, 164.3, 144.4, 134.7, 133.2, 133.2, 130.7, 130.2, 130.0, 129.2, 128.9, 21.8 ppm

Spectroscopic data was consistent with the literature.[6]

(*E*)-*N*-(cyclohexylmethylene)benzamide (64k)



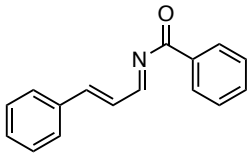
Following general procedure A, the title compound was prepared in 59% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 2.36 (m, 1H), 1.96 (m, 2H), 1.79 (m, 2H), 1.69 (m, 1H), 1.35 (m, 4H), 1.25 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 172.6, 133.2, 129.7, 128.3, 44.2, 28.7, 25.8, 25.2.

Spectroscopic data was consistent with the literature.[6]

N-((1*E*,2*E*)-3-phenylallylidene)benzamide (64l)



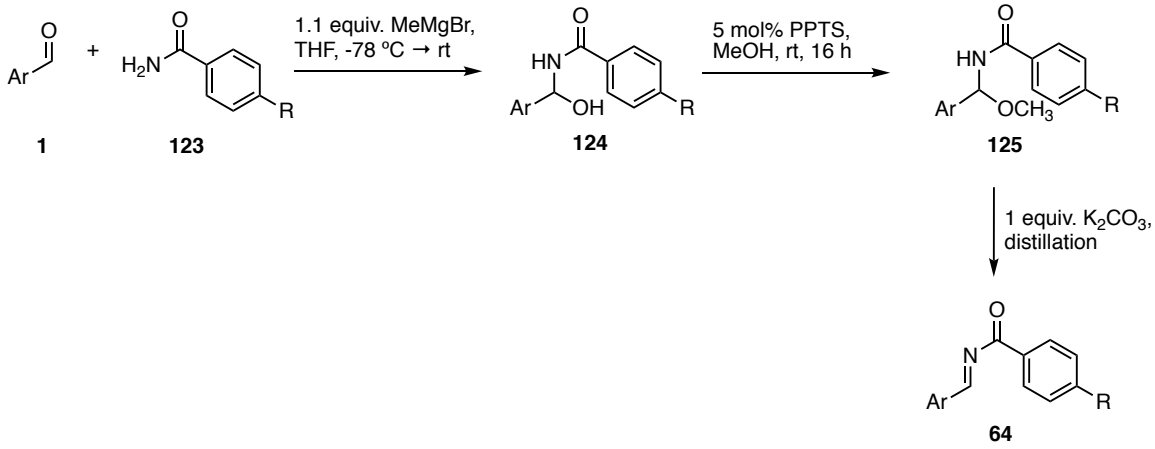
Following general procedure A, the title compound was prepared in 64% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (d, *J* = 9.2 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.52-7.31 (m, 4H), 6.98 (dd, *J* = 16, 9.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 166.3, 149.9, 134.9, 133.6, 130.8, 130.3, 129.2, 128.6, 128.3, 126.9.

Spectroscopic data was consistent with the literature.[6]

5.2.2 Synthesis of benzoyl imines: general procedure B

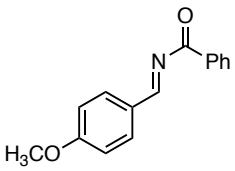


Following a modified procedure of Manolikakes and coworkers,[11] the hemiaminals **124** are prepared in two steps. A flame-dried RBF was charged with the appropriate amide (1.1 eq, 5.5 mmol) and dry THF (20 mL). The resulting mixture was cooled to -78 °C and MeMgCl (1.8 mL, 5.5 mmol, 3 M in ether) was added slowly via a syringe with vigorous stirring. During the addition, a white solid precipitates. The resulting mixture was warmed to room temperature and stirred for 30 minutes. The reaction mixture was cooled to 0 °C and the aldehyde (5 mmol) added rapidly. The reaction mixture was allowed to warm to room temperature and stirred until TLC analysis showed complete consumption of the aldehyde (5-16 hours). After completion saturated aqueous $NaHCO_3$ (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4). **Note:** The crude hemiaminals are unstable towards prolonged contact with water. Therefore, a rapid workup is recommended. After evaporation of the solvents the crude hemiaminal **124** was dried at room temperature over 2-3 h under high vacuum. The hemiacetal **124** was used for the next step without further purification.

The crude hemiaminal **124** was dissolved in methanol (20 mL) and pyridinium *p*-toluenesulfonate (5 mol%) added. The reaction was stirred for 16 hours before saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After evaporation of the solvents, the crude product was purified via flash chromatography with neutralized silica (2% Et_3N in solvent).

Following a modified procedure reported by Aggarwal and co-worker,[12] the hemiaminal ether **125** (3 mmol) and dried K_2CO_3 powder were heated slowly until the hemiaminal ether melts (K_2CO_3 remains solid) under reduced pressure (0.1 mBar) during which time MeOH evolved. Following distillation, the desired imines **64** were obtained as a clear yellow oil which solidified slowly as pale yellow solids.

(*E*)-*N*-(4-methoxybenzylidene)benzamide (64d)



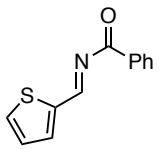
Following general procedure B, the title compound was prepared in 76% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, 1H), 8.20 (dd, *J* = 1.0, 8.2 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.67-7.53 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 164.4, 163.9, 133.9, 133.3, 132.2, 130.2, 128.4, 127.6, 114.4, 55.5 ppm

Spectroscopic data was consistent with the literature.[7]

(*E*)-*N*-(Thiophen-2-ylmethylene)benzamide (64m)



Following general procedure B, the title compound was prepared in 78% yield.

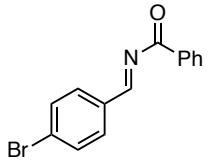
IR ν_{max} 1648, 1519, 1265, 1011, 717, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 1.0 Hz, 1H), 8.29-8.17 (m, 2H), 7.80-7.66 (m, 2H), 7.63-7.54 (m, 1H), 7.53-7.41 (m, 2H), 7.23-7.19 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 159.1, 141.6, 136.9, 134.2, 134.1, 133.9, 130.7, 128.8 (one peak overlapped) ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{12}H_{10}NOS$ 216.0445, requires 216.0478.

(*E*)-*N*-(4-bromobenzylidene)benzamide (64n)



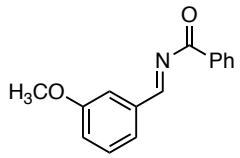
Following general procedure B, the title compound was prepared in 67% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (s, 1H), 8.16-8.13 (m, 2H), 7.86-7.82 (m, 2H), 7.67-7.65 (m, 2H), 7.60 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.50-7.46 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.7, 163.4, 133.7, 133.4, 133.1, 132.3, 131.2, 130.1, 128.5, 128.3 ppm

Spectroscopic data was consistent with the literature.[7]

(*E*)-*N*-(3-Methoxybenzylidene)benzamide (64o)



Following general procedure B, the title compound was prepared in 77% yield.

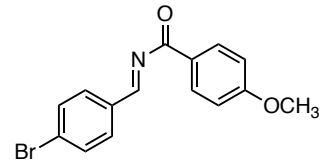
IR ν_{max} 1669, 1606, 1577, 1239, 1050, 1038 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.20-8.12 (m, 2H), 7.67-7.58 (m, 1H), 7.57-7.55 (m, 1H), 7.53-7.46 (m, 3H), 7.45-7.40 (m, 1H), 7.14 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 3.90 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 181.3, 164.6, 160.4, 136.3, 133.9, 133.6, 130.5, 130.3, 128.9, 124.0, 120.4, 113.2, 55.8 ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{15}H_{14}NO_2^+$ 241.1009, requires 241.1019.

(*E*)-*N*-(4-Bromobenzylidene)-4-methoxybenzamide (64p)



Following general procedure B, the title compound was prepared in 57% yield (544 mg) from the corresponding hemiaminal ether (distillation at 200 °C, 0.1 mBar) as yellow solid.

IR ν_{max} 1600, 1254, 1163, 1014, 821 cm^{-1}.

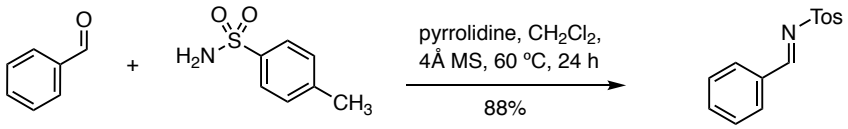
^{1}H NMR (400 MHz, C_6D_6) δ 8.43 (s, 1H), 8.34 (AA'BB', *J* = 8.9 Hz, 2H), 7.26 (AA'BB', *J* = 8.5 Hz, 1H), 7.16 (AA'BB', *J* = 8.5 Hz, 2H), 6.72 (AA'BB', *J* = 8.9 Hz, 1H), 3.17 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ 179.5, 164.6, 164.4, 134.4, 133.2, 132.6, 131.8, 129.0, 127.4, 114.5, 55.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{15}H_{13}{}^{79}BrNO_2$, 318.0094, 320.0089 requires 318.0124, 320.0104.

5.2.3 Synthesis of imines 55 & 109

(*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (55)



1 **108** **55**

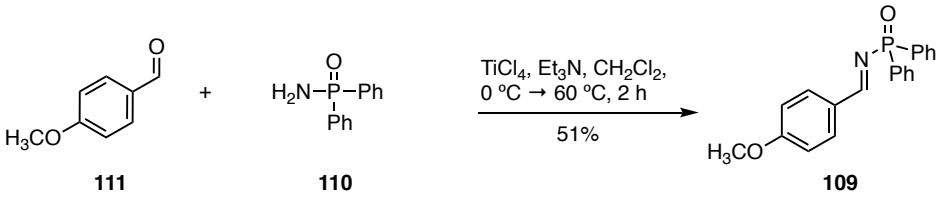
Following a procedure by Morales,[13] to a solution of *p*-toluenesulfonamide **108** (1.71 g, 10 mmol) in dichloromethane (30 ml) and 4Å molecular sieves (1g/mmol), benzaldehyde **1** (1.27 g, 12 mmol) and pyrrolidine (71 mg, 1 mmol) were added. The mixture was stirred in a sealed vial at 60 °C for 24 hours. The reaction was filtered through Celite® to give the desired imine **55** as a pale yellow solid (2.27 g, 88%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.92–7.87 (m, 4H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.45 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 145.7, 139.8, 133.2, 131.9, 131.1, 130.2, 129.1, 127.4, 23.3

Spectroscopic data was consistent with the literature.[14]

(*E*)-*N*-(4-methoxybenzylidene)-*P*,*P*-diphenylphosphinic amide (109)



111 **110** **109**

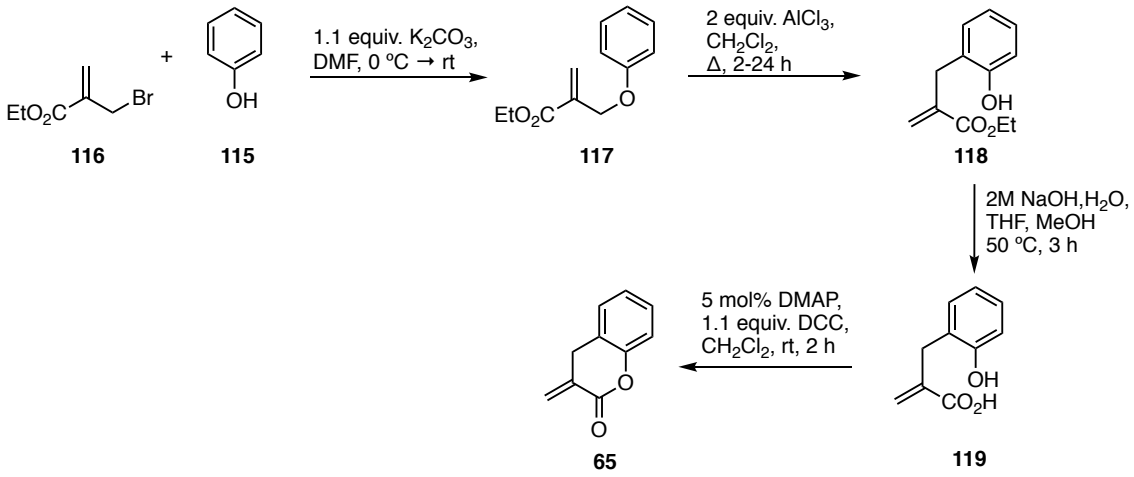
Following a procedure by Campton,[15] titanium tetrachloride (0.5 equiv, 0.55 mL, 5.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the aldehyde **111** (1 equiv, 1.36 g, 10.0 mmol), diphenylphosphinic amide **110** (1 equiv, 2.21 g, 10.0 mmol) and triethylamine (3.5 equiv, 3.54 g, 35.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and room temperature for 1 h. The suspension was filtered through a silica pad, washed with 1:1 CH_2Cl_2/EtOAc. The filtrate was concentrated to a cream solid and purified by fast flash

chromatography (1:1 CH_2Cl_2 /EtOAc). The desired imine **109** was isolated as pale yellow solid (1.67 g, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, *J* = 32 Hz, 1H), 7.99-7.95 (m, 2H), 7.95-7.90 (m, 4H), 7.49-7.42 (m, 6H), 7.01-6.97 (m, 2H), 3.88 (s, 3 H) ppm

Spectroscopic data was consistent with the literature.[16]

5.2.4 General procedure for the synthesis of chromanones



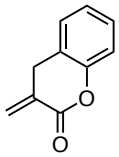
To a mixture of phenol **115** (12 mmol) and K_2CO_3 (1.38 g, 12 mmol) in DMF (30 mL) was added ethyl 2-(bromomethyl)acrylate **116** (1.93 g, 10 mmol) at 0 °C. After stirring for 15 minutes the reaction was allowed to warm to room temperature and stirred until the bromide was consumed by TLC (16–24 hours). The reaction was diluted with water, extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with NaOH (20 mL of a 2M solution), water (3 x 20 mL) and brine (30 mL), dried ($MgSO_4$) and filtered. The solvent was then evaporated and the resultant ether **117** was used in the next step without further purification.

The oily residue **117** was dissolved in dry CH_2Cl_2 (30 mL) and $AlCl_3$ (2 equiv.) added. The mixture was refluxed until the starting material was consumed (1–3 h). The reaction was cooled to 0 °C and water (20 mL) added carefully followed by HCl (20 mL of a 1M solution). After stirring for 15 minutes, the biphasic mixture was separated and aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (30 mL) followed by brine (30 mL). After being dried ($MgSO_4$) and filtered, the solvent was evaporated giving phenol **118** which was used in the next step without further purification.

Ester **118** was dissolved in MeOH (15 mL) and NaOH (15 mL of a 2M solution) added. The mixture was either heated to reflux for 2 h or stirred at room temperature for 16 hours. The mixture was diluted with water (20 mL), extracted with ether (2 x 20mL), separated, and the aqueous layer acidified to pH <2 with HCl. After extraction with CH_2Cl_2 (3 x 20 mL), the combined organic extracts were dried (MgSO4), filtered and the solvent evaporated. The resultant acid **119** was used in the next step without further purification.

Acid **119** was dissolved in CH_2Cl_2 (30 mL) and a solution of DMAP (5 mol%) and DCC (1.1 equiv.) in CH_2Cl_2 (10mL) was added. The reaction was stirred at room temperature for 2 hours before being quenched with water (20 mL). The mixture was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (20mL) and dried ($MgSO_4$) followed by filtration and evaporation of the solvent. The residue was purified via flash column chromatography. To fully remove the urea byproduct, the lactone obtained after column chromatography was dissolved in ether and filtered through HPLC syringe filters (hydrophobic, 25mm × 0.2 μm, Merk), to give pure chromanones **65**.

3-methylenechroman-2-one (65a)



Following the general procedure, the title compound was prepared in 48% yield over four steps.

R_f 0.4 (80:20 *v*/*v* hexanes : ethyl acetate).

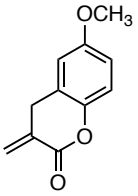
IR ν_{max}, 2988, 1749, 1637, 1557, 1490, 1459, 1227, 1193, 1170, 1139, 1080, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8 Hz, 1H), 6.44 (s, 1H), 5.80 (s, 1H), 3.83 (s, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.8, 131.7, 128.6, 128.2, 127.7, 124.5, 121.1, 117.0, 32.0

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{10}H_8O_2$ 161.0604, requires 161.0603.

6-methoxy-3-methylenechroman-2-one (65b)



Following the general procedure, the title compound was prepared in 76% yield (722 mg) over four steps.

R_f 0.25 (90:10 *v/v* hexanes : ethyl acetate).

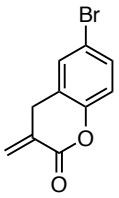
IR ν_{max} 3105, 2932, 2835, 1723, 1493, 1433, 1203, 1120, 962, 872, 802 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.9 Hz, 1H), 6.80-6.74 (m, 1H), 6.70-6.65 (m, 1H), 6.43-6.38 (m, 1H), 5.79-5.72 (m, 1H), 3.79 (s, 3H), 3.78-3.76 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.3, 144.8, 131.8, 128.5, 122.11, 117.7, 113.4, 112.7, 55.7, 32.3 ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{11}H_{10}O_3$ 191.0703 requires 191.0703.

6-Bromo-3-methylenechroman-2-one (65c)



Following the general procedure, the title compound was prepared in 67% (800 mg) over four steps.

R_f 0.34 (2:8, v/v EtOAc : hexanes)

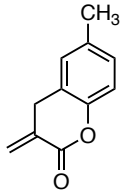
IR ν_{max} 1744, 1637, 1474, 1224, 972, 877, 817 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) 7.41-7.27 (m, 2H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.44 (br s, 1H), 5.80 (br s, 1H), 3.78 (br s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 150.1, 131.4, 130.9, 130.7, 129.5, 123.4, 118.9, 117.2, 31.9 ppm.

LRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{10}H_7{}^{79}BrO_2$ 238.9, requires 239.0.

6-Methyl-3-methylenechroman-2-one (65f)



Following the general procedure, the title compound was prepared in 44% yield (765 mg) over four steps.

R_f 0.25 (90:10 *v*/*v* hexanes : ethyl acetate).

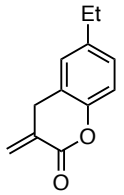
IR ν_{max} 2922, 1749, 1720, 1468, 1189, 1140, 1080, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.00 (m, 1H), 6.99-6.91 (m, 2H), 6.57-6.19 (m, 1H), 6.15-5.56 (m, 1H), 3.76 (brs, 2H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.2, 134.5, 132.4, 129.1, 128.7, 128.5, 121.2, 117.1, 32.4, 21.0.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{11}H_{11}O_2$ 175.0740, requires 175.0754.

6-Ethyl-3-methylenechroman-2-one (65g)



Following the general procedure, the title compound was prepared in 40% yield (753 mg) over four steps (the compound was preserved in freezer as it polymerized readily).

R_f 0.27 (90:10 *v*/*v* hexanes : ethyl acetate).

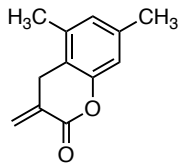
IR ν_{max} 2963, 2928, 2852, 1748, 1717, 1494, 1251, 1207, 1134, 1112, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.04 (m, 1H), 7.00-6.95 (m, 2H), 6.40 (td, *J* = 2.0, 1.0 Hz, 1H), 5.75 (td, *J* = 2.1, 1.0 Hz, 1H), 3.79-3.76 (m, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 149.3, 141.0, 132.4, 128.7, 127.9, 127.3, 121.2, 117.2, 32.5, 28.5, 16.0 ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{12}H_{12}O_2$ 189.0907, requires 189.0910.

5,7-Dimethyl-3-methylenechroman-2-one (65h)



Following the general procedure, the title compound was prepared in 45% yield (840 mg) over four steps.

R_f 0.26 (90:10 *v*/*v* hexanes : ethyl acetate).

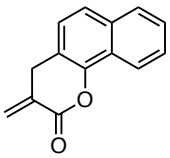
IR ν_{max} 3025, 2915, 2857, 1736, 1619, 1293, 1225, 1131, 960, 850, 795, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.73 (s, 1H), 6.46-6.42 (m, 1H), 5.81-5.75 (m, 1H), 3.71-3.65 (m, 2H), 2.29 (s, 3H), 2.25 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 151.1, 138.3, 136.2, 132.1, 129.1, 127.2, 116.6, 115.5, 29.5, 21.3, 19.3 ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{12}H_{13}O_2$ 189.0908, requires 189.0910.

3-Methylene-3,4-dihydro-2*H*-benzo[*h*]chromen-2-one (65i)



Following the general procedure, the title compound was prepared in 38% yield (800 mg) over four steps.

R_f 0.30 (80:20 *v*/*v* hexanes : ethyl acetate).

IR ν_{max} 3057, 2929, 1729, 1596, 1377, 1261, 1126, 1091, 801, 754 cm^{-1}.

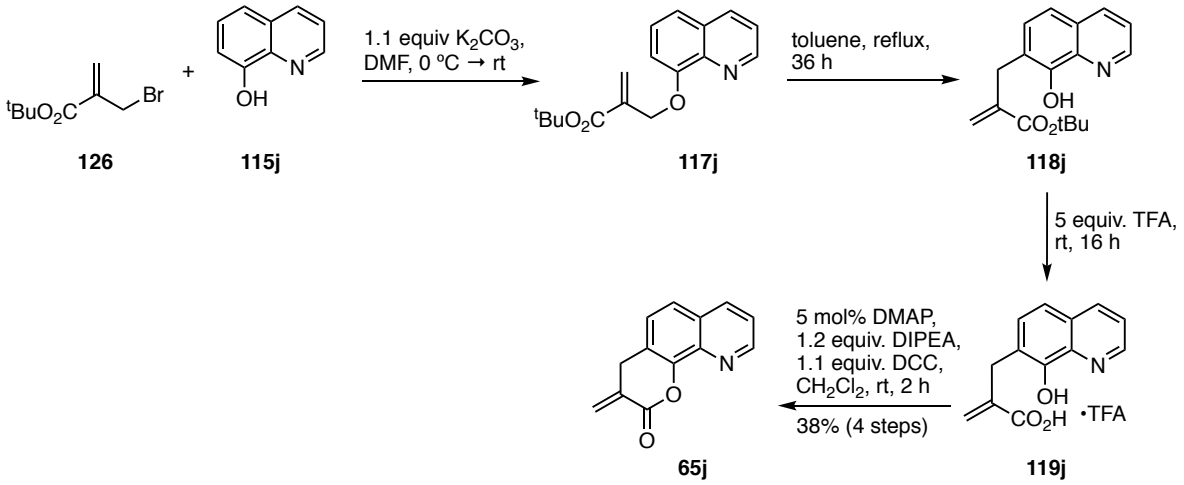
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.68-7.44 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.68-6.31 (m, 1H), 5.85-5.82 (m, 1H), 3.96-3.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 145.8, 133.7, 132.0, 129.2, 127.8, 127.0, 126.8, 125.3, 124.6, 124.1, 121.4, 115.9, 32.4.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{14}H_{11}O_2$ 211.0732, requires 211.0754.

5.2.5 Synthesis of quinoline derived lactone 65j

3-Methylene-3,4-dihydro-2*H*-pyrano[3,2-*h*]quinolin-2-one (65j)



Following the general procedure, after alkylation to give ether **117j**, phenol **118j** was obtained through the thermal Claisen rearrangement by heating to reflux in toluene for 36 hours. Ester **118j** was deprotected with TFA (5 equiv.) in CH_2Cl_2 (20 mL) to give acid **119j**. Lactonisation was performed using DMAP and DCC to give the quinolone derived lactone **65j** in a 38% yield (800 mg) over four steps.

R_f 0.27 (20:80 *v*/*v* hexanes : ethyl acetate).

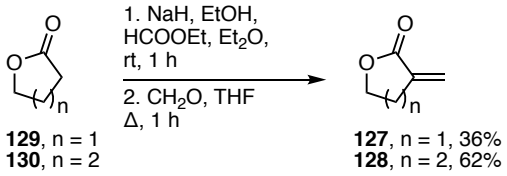
IR ν_{max} 3047, 2988, 1730, 1468, 1292, 1149, 1128, 941, 843, 788, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.38-7.29 (m, 1H), 6.53 (td, *J* = 2.1, 0.9 Hz, 1H), 5.85 (td, *J* = 2.2, 0.9 Hz, 1H), 4.04-3.98 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 151.2, 146.0, 138.6, 136.1, 131.5, 129.5, 128.6, 126.1, 124.0, 122.0, 120.2, 32.7 ppm.

HRMS (ESI) *m/z* Found: $(M+H)^+$ $C_{13}H_{10}NO_2$ 212.0703, requires 212.0706.

5.2.6 General procedure for the synthesis of α,β-unsaturated lactones



129, n = 1
130, n = 2

127, n = 1, 36%
128, n = 2, 62%

Following the procedure of Fernandes,[17] to a suspension of NaH (0.352 g, 8.8 mmol, 1.1 equiv, 60% dispersion in mineral oil) in dry Et_2O (15 mL) under nitrogen, absolute EtOH (0.05 mL, 0.88 mmol, 0.11 equiv) was added drop wise. A mixture of the appropriate lactone **129** or **130** (8.0 mmol, 1.0 equiv) and ethyl formate (0.8 mL, 9.6 mmol, 1.2 equiv) were added drop wise to give a steady reflux with H_2 gas evolution. After completion of the addition, the reaction mixture was stirred for 1 h. The white solid was then washed with Et_2O and dried under vacuum. To the white solid, THF (20 mL) and paraformaldehyde (1.2 g, 40.0 mmol, 5.0 equiv) were added under nitrogen atmosphere. The suspension was heated to reflux immediately for 1 h. Then the reaction mixture was ice cooled and quenched with sat. aq. K_2CO_3 (5.0 mL). THF was removed under vacuum and the aq. mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give the lactones as colorless oils.

3-methylenedihydrofuran-2(3*H*)-one (127)

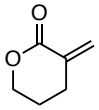
Following the general procedure, the title compound was prepared in 36% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (t, *J* = 3.0 Hz, 1H), 5.63 (t, *J* = 3.0 Hz, 1H), 4.30 (t, *J* = 7.2 Hz, 2H) 2.97 (tt, *J* = 7.2, 3.1 Hz, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 134.8, 121.5, 65.8, 27.4.

Spectroscopic data was consistent with the literature.[18]

3-methylenetetrahydro-2*H*-pyran-2-one (128)



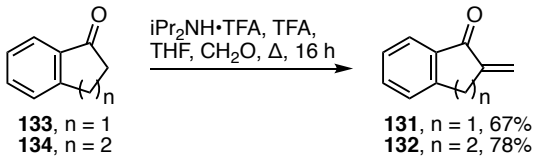
Following the general procedure, the title compound was prepared in 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 1.6 Hz, 1H), 5.56 (d, *J* = 1.6 Hz, 1H), 4.37 (t, *J* = 5.3 Hz, 2H), 2.68 (tt, *J* = 6.3, 1.6 Hz, 2H), 1.99-1.90 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 133.9, 127.8, 68.6, 28.4, 22.9 ppm

Spectroscopic data was consistent with the literature.[19]

5.2.7 General procedure for the synthesis of α,β-unsaturated ketones

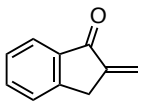


133, n = 1
134, n = 2

131, n = 1, 67%
132, n = 2, 78%

Following a procedure by Bugarin,[20] to a mixture of a carbonyl compound **133** or **134** (1.0 mmol) and paraformaldehyde (2.0 mmol, 200 mol%) in dry THF (10 mL) is added the catalyst (1.0 mmol, 100 mol%) and trifluoroacetic acid (0.1 mmol, 10 mol %). The reaction mixture is stirred, open to the atmosphere, at reflux for 2 h. The reaction mixture is cooled down to room temperature and a second addition of paraformaldehyde (2.0 mmol, 200 mol %) is performed. Next, the reaction mixture is stirred at reflux for an additional 6 h. The reaction mixture is cooled down and the solvent is removed under reduced pressure, dissolved in Et_2O and washed with HCl (1 x 30 mL of a 1M solution), NaOH (1 x 30 mL of a 1M solution), and brine (1 x 30 mL). The solution mixture is dried (Na_2SO_4) and concentrated under vacuum. The crude product is purified by silica gel column chromatography.

2-methylene-2,3-dihydro-1*H*-inden-1-one (131)



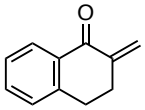
Following the general procedure, the title compound was prepared in 67% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 1H), 6.20 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 6.38 (s, 1H), 5.65 (s, 1H), 3.77 (s, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 149.9, 143.3, 138.3, 134.9, 127.6, 126.4, 124.3, 119.3, 31.8 ppm

Spectroscopic data was consistent with the literature.[21]

2-methylene-3,4-dihydronaphthalen-1(2*H*)-one (132)



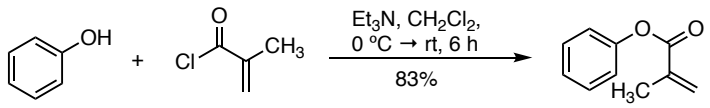
Following the general procedure, the title compound was prepared in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd *J* = 7.6, 1.2 Hz, 1H) 7.50-7.25 (m, 3H), 6.23 (s, 1H), 5.44 (s, 1H), 2.99 (t, *J* = 6.8 Hz, 2H), 2.80-2.88 (m, 2H, CH2) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 133.9, 127.8, 68.6, 28.4, 22.9 ppm

Spectroscopic data was consistent with the literature.[20]

5.2.8 Synthesis of Michael acceptors 135 & 142



115 **136** **135**

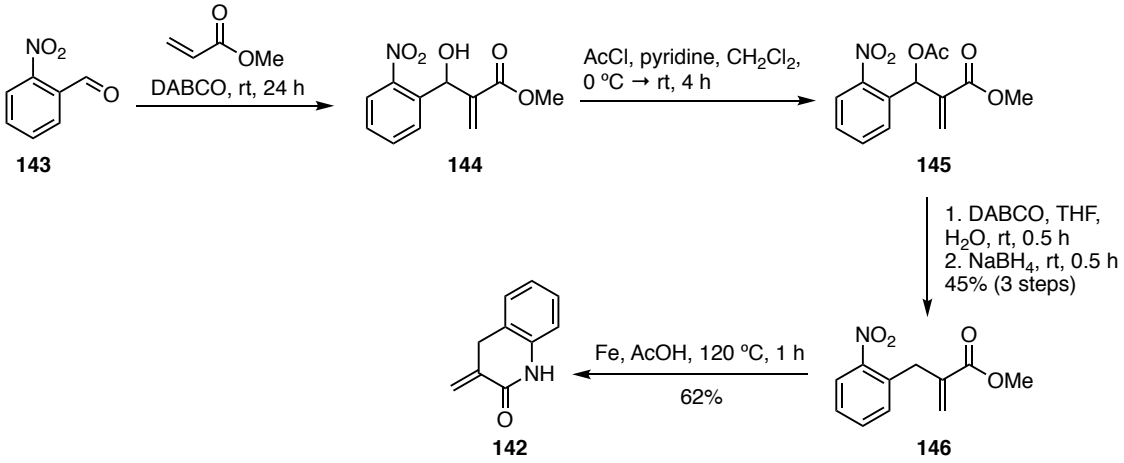
Following a procedure by kakuchi,[22] to a solution of phenol **115** (1.00 g, 11 mmol) in CH_2Cl_2 (10 mL) and triethylamine (1.24 g, 12 mmol), a solution of methacryloyl chloride **136** (1.34 g, 13 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C dropwise. The reaction mixture was stirred at room temperature overnight. After the reaction was complete, the reaction mixture was filtered to remove a generated precipitate. The filtrate was rinsed with HCl (1 x 30 mL of a 1M solution), K_2CO_3 (1 x 30 mL of a 1M solution), and water (1 x 30 mL). The organic phase was dried over $MgSO_4$. The obtained crude product was further purified by column chromatography to give phenyl methacrylate **135** as transparent liquid (1.34 g, 83%).

R_f 0.3 (98:2 v/v hexanes : ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.01 (m, 5H), 6.39 (s, 1H), 5.78 (s, 1H), 2.10 (s, 3H).

Spectroscopic data was consistent with the literature.[22]

3-methylene-3,4-dihydroquinolin-2(1*H*)-one (142)



Following a procedure by Saikia,[23] *o*-nitrobenzaldehyde **143** (1 equiv.) was stirred with an methancrylate (1 equiv.) with 20 mol% of DABCO at room temperature for 24 h. On completion, the reaction was poured into water (10 mL/mmol) and extracted with ethyl acetate (3 x 10 mL/mmol). The solution mixture is dried (Na_2SO_4) and concentrated under vacuum to give alcohol **144** which was used without further purification.

Following a procedure by Batchu,[24] alcohol **144** was combined with Acetly chloride (1.05 equiv.) and pyridine (1.05 equiv.) in CH_2Cl_2 (20 mL/mmol) at 0 °C and the mixture was stirred for 3 h. Upon completion, the mixture was diluted with water (20 mL/mmol) and the organic layer separated and washed with HCl (1 x 30 mL of a 1M solution) and brine (1 x 30 mL). The combined organic fractions were concentrated under vacuum to give acetate **145** which was used without further purification.

Following a procedure by Felpin,[25] acetate **145** (1 equiv.) was added to a stirred solution of DABCO (I equiv.) in THF (5 mL/mmol) and water (2 mL/mmol) at room temperature. After 15 min of stirring, $NaBH_4$ (1 equiv.) was added portionwise to the reaction mixture. After being stirred for 15 min, water (5 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give ester **146** which was used without further purification.

Following a procedure by Ramachary,[26] in a glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the methyl 2-(2- nitrobenzyl)acrylate **146** was added 3 mL of acetic acid, and then the 3

mmol of Fe powder was added and the reaction mixture was stirred at 120 °C for 1h. The crude S-2 reaction mixture was treated with saturated aqueous $NaHCO_3$ solution; then the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure product **142** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

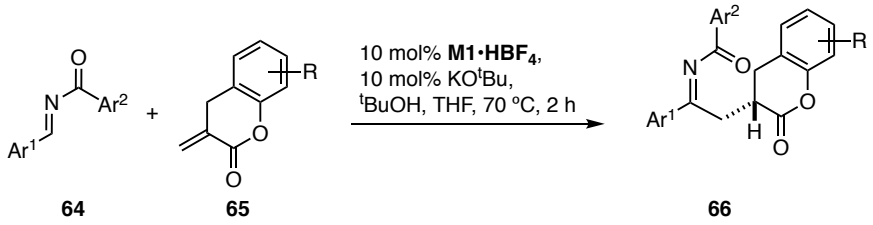
R_f 0.3 (70:30 v/v hexanes : ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (br s, 1H), 7.19-7.12 (m, 2H), 6.98 (t, *J* = 8 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 6.31 (s, 1H), 5.58 (s, 1H), 3.84 (s, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 136.6, 135.6, 127.6, 127.5, 123.7, 123.0, 122.2, 115.7, 33.8

Spectroscopic data was consistent with the literature.[26]

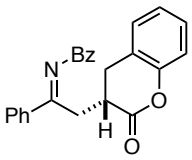
5.2.9 General procedure for the NHC catalysed aza-Stetter reaction



64 65 66

To a flame-dried reaction vial containing **M2•BF$_4$** (4.3 mg, 0.01 mmol) was added tert-butanol (0.20 mL of a 0.5 M solution in THF, 0.10 mmol) and potassium tert-butoxide (0.20 mL of a 0.05 M solution in THF, 0.01 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. The appropriate imine **64** (0.12 mmol) and lactone **65** (0.10 mmol) were then added as a solution in THF (1.5 mL) and the vial sealed and the reaction mixture stirred at 70 °C for 2 hours. Concentration under reduced pressure and purification *via* column chromatography then gave the aza-Stetter products **66**.

(*S,E*)-*N*-(2-(2-Oxochroman-3-yl)-1-phenylethylidene)benzamide (66a)



Following the general procedure the title compound was prepared using imine **64a** and chromanone **65a** in a 77% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 95:5, 1 ml/min, λ = 254 nm, fraction t_r = 14.47 (major enantiomer) and 21.62 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 13.7 (c = 0.10, $CHCl_3$)

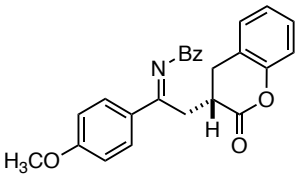
IR ν_{max} 1761, 1657, 1235, 1141, 759 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.18-8.03 (m, 2H), 7.71-7.59 (m, 2H), 7.09-7.03 (m, 3H), 7.00-6.93 (m, 3H), 6.85-6.76 (m, 2H), 6.68 (td, *J* = 7.1, 1.7 Hz, 1H), 6.60 (br d, *J* = 7.1 Hz, 1H), 3.40 (dd, *J* = 15.9, 5.5 Hz, 1H), 2.99-2.85 (m, 1H), 2.57-2.33 (m, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 170.2, 167.3, 151.6, 135.9, 133.4, 132.0, 131.8, 129.5, 129.1, 128.8, 128.5, 128.3, 127.8, 124.6, 122.5, 116.8, 37.3, 36.3, 29.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{19}NO_3$, 370.1436, requires 370.1438.

(*S,E*)-*N*-(1-(4-Methoxyphenyl)-2-(2-oxochroman-3-yl)ethylidene)benzamide (66b)



Following the general procedure the title compound was prepared using imine **65d** and chromanone **65a** in a 67% yield.

R*f* 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 30.99 (major enantiomer) and 35.49 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 18.0 (c = 0.07, $CHCl_3$)

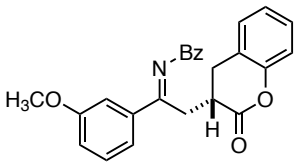
IR ν_{max} 1757, 1655, 1600, 1458, 1258, 1143, 1090, 1020, 794 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.18-8.11 (m, 2H), 7.74-7.67 (m, 2H), 7.12-7.05 (m, 3H), 6.84-6.77 (m, 2H), 6.67 (td, *J* = 7.2, 1.7 Hz, 1H), 6.63-6.60 (m, 1H), 6.59-6.54 (m, 2H), 3.51 (dd, *J* = 15.5, 5.0 Hz, 1H), 3.15 (s, 3H), 3.01-2.94 (m, 1H), 2.66 (dd, *J* = 15.8, 6.2 Hz, 1H), 2.55 (dd, *J* = 15.5, 7.9 Hz, 1H), 2.48-2.42 (m, 1H) ppm

^{13}C NMR (150 MHz, C_6D6) δ 178.9, 169.5, 166.2, 162.6, 152.1, 134.2, 133.0, 130.2, 129.7, 129.0, 128.8, 128.41, 128.35, 124.2, 123.1, 116.7, 114.4, 54.9, 37.7, 36.0, 29.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{21}NO_4$, 400.1546, requires 400.1543.

(*S,E*)-*N*-(1-(3-Methoxyphenyl)-2-(2-oxochroman-3-yl)ethylidene)benzamide (66c)



Following the general procedure the title compound was prepared using imine **64o** and chromanone **65a** in an 80% yield.

R*f* 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 56.37 (major enantiomer) and 69.00 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 18.5 (c = 0.12, $CHCl_3$)

IR ν_{max} 1758, 1648, 1578, 1487, 1260, 1137, 1036, 784, cm^{-1}

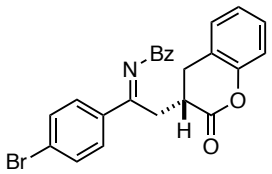
^{1}H NMR (600 MHz, C_6D_6) δ 8.15-8.10 (m, 2H), 7.47-7.43 (m, 1H), 7.26-7.22 (m, 1H), 7.08-7.04 (m, 3H), 6.92 (t, *J* = 8.0 Hz, 1H), 6.84-6.77 (m, 2H), 6.73-6.66 (m, 2H), 6.64-6.60 (m, 1H), 3.44 (dd,

J = 17.9, 4.6 Hz, 1H), 3.22 (s, 3H), 3.00-2.92 (m, 1H), 2.56 (dd, *J* = 15.8, 6.3 Hz, 1H), 2.49 (dd, *J* = 15.8, 6.3 Hz, 1H), 2.44-2.37 (m, 1H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.6, 169.1, 167.0, 160.0, 151.7, 137.9, 133.5, 132.7, 129.7, 129.3, 128.5, 128.0, 123.8, 122.6, 119.9, 117.4, 116.3, 112.6, 54.4, 36.9, 36.5, 29.0 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{21}NO_4$, 400.1522, requires 400.1543.

(*S,E*)-*N*-(1-(4-Bromophenyl)-2-(2-oxochroman-3-yl)ethylidene)benzamide (66d)



Following the general procedure the title compound was prepared using imine **64n** and chromanone **65a** in a 52% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 85:15, 1 ml/min, λ = 254 nm, fraction t_r = 32.03 (major enantiomer) and 40.77 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 65.0 (c = 0.06, $CHCl_3$)

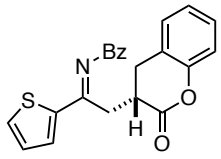
IR ν_{max} 1762, 1664, 1487, 1233, 1141, 757 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.11-8.03 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.12-7.03 (m, 5H), 6.84-6.77 (m, 2H), 6.75-6.58 (m, 2H), 3.24 (dd, *J* = 15.9, 5.6 Hz, 1H), 2.89-2.75 (m, 1H), 2.51 (dd, *J* = 15.9, 6.3 Hz, 1H), 2.44-2.30 (m, 2H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.34, 168.90, 166.17, 151.67, 135.06, 133.27, 132.89, 131.84, 131.63, 129.45, 129.28, 129.11, 128.51, 125.82, 123.93, 122.49, 116.38, 36.83, 35.98, 28.95 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{18}{}^{79}BrNO_3$, 448.0524, requires 448.0543.

(*S,E*)-*N*-(2-(2-Oxochroman-3-yl)-1-(thiophen-2-yl)ethylidene)benzamide (66e)



Following the general procedure the title compound was prepared using iming **64m** and chromanone **65a** in an 88% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 95:5, 1 ml/min, λ = 254 nm, fraction t_r = 73.71 (minor enantiomer) and 87.74 (major enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 11.0 (c = 0.25, $CHCl_3$)

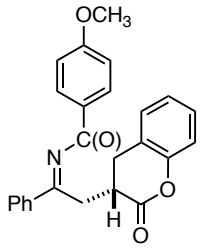
IR ν_{max} 1758, 1648, 1488, 1457, 1231, 1136, 1136, 755 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.17-8.11 (m, 2H), 7.22-7.18 (m, 1H), 7.11-7.03 (m, 3H), 6.84-6.76 (m, 3H), 6.66 (td, *J* = 7.6, 1.5 Hz, 1H), 6.55 (br d, *J* = 7.6 Hz, 1H), 6.47 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.44 (dd, *J* = 15.1, 5.0 Hz, 1H), 2.97-2.89 (m, 1H), 2.64 (dd, *J* = 15.7, 6.2 Hz, 1H), 2.57 (dd, *J* = 15.1, 8.0 Hz, 1H), 2.41-2.32 (m, 1H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.3, 169.2, 160.5, 152.0, 141.6, 133.8, 133.2, 131.9, 131.8, 129.8, 128.8, 128.4, 128.3, 124.2, 122.9, 116.6, 38.0, 35.9, 29.4 (1 missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{22}H_{17}NO_3S$, 376.0986, requires 376.1002.

(*S,E*)-4-Methoxy-*N*-(2-(2-oxochroman-3-yl)-1-phenylethylidene)benzamide (66f)



Following the general procedure the title compound was prepared using imine **64e** and chromanone **65a** in a 73% yield.

R_f 0.3 (70:30 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 92:8, 1 ml/min, λ = 254 nm, fraction t_r = 18.57 (major enantiomer) and 27.18 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 26.1 (c = 0.23, $CHCl_3$)

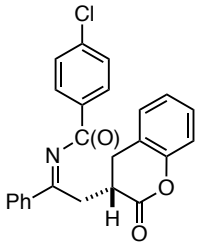
IR ν_{max} 1757, 1680, 1600, 1489, 1239, 1134, 1025, 753 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.84 (m, 2H), 7.81-7.74 (m, 2H), 7.49-7.37 (m, 3H), 7.25-1.20 (m, 1H), 7.15-7.10 (m, 1H), 7.06 (td, *J* = 7.4, 1.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.95-6.88 (m, 2H), 3.85 (s, 3H), 3.69 (dd, *J* = 15.8, 5.1 Hz, 1H), 3.28-3.18 (m, 1H), 3.07-2.93 (m, 2H), 2.93-2.82 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 170.3, 167.0, 163.8, 151.6, 136.2, 131.7, 131.6, 129.0, 128.5, 128.3, 127.8, 125.6, 124.6, 122.6, 116.8, 114.0, 55.6, 37.3, 36.2, 29.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{21}NO_4$, 400.1520, requires 400.1543.

(*S,E*)-4-Chloro-*N*-(2-(2-oxochroman-3-yl)-1-phenylethylidene)benzamide (66g)



Following the general procedure the title compound was prepared using imine **64h** and chromanone **65a** in a 60% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 92:8, 1 ml/min, λ = 254 nm, fraction t_r = 14.29 (major enantiomer) and 22.81 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 3.4 (c = 0.23, $CHCl_3$)

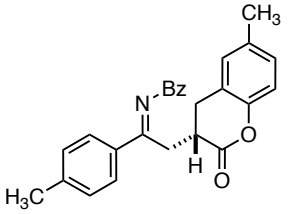
IR ν_{max} 1762, 1663, 1488, 1459, 1233, 1142, 1092, 757 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 7.88-7.82 (m, 2H), 7.62-7.57 (m, 2H), 7.02-6.94 (m, 5H), 6.83-6.80 (m, 2H), 6.74-6.67 (m, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 3.31 (dd, *J* = 16.1, 6.1 Hz, 1H), 2.97-2.86 (m, 1H), 2.49-2.33 (m, 3H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 177.8, 169.5, 168.1, 152.1, 139.6, 136.9, 132.1, 131.4, 131.1, 129.2, 129.0, 128.4, 124.3, 122.9, 116.8, 37.1, 37.0, 29.3 ppm (2 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{18}{}^{35}ClNO_3$, 404.1022 , requires 404.1048.

(*S,E*)-*N*-(2-(6-Methyl-2-oxochroman-3-yl)-1-(*p*-tolyl)ethylidene)benzamide (66h)



Following the general procedure the title compound was prepared using imine **64j** and chromanone **65f** in a 61% yield.

R$_f$ 0.3 (85:15 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 33.71 (major enantiomer) and 49.15 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 21.5 (c = 0.16, $CHCl_3$)

IR ν_{max} 1757, 1655, 1604, 1257, 1140, 1087, 1025, 793 cm^{-1}

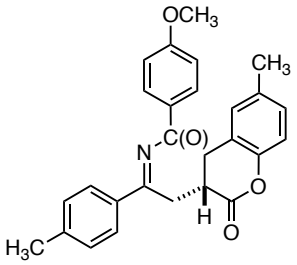
^{1}H NMR (400 MHz, C_6D_6) δ 8.17-8.09 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.10-7.04 (m, 3H), 6.81 (d, *J* = 7.9 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.36 (s, 1H), 3.54 (dd, *J* =

15.6, 5.1 Hz, 1H), 3.06-2.93 (m, 1H), 2.67-2.53 (m, 2H), 2.51-2.40 (m, 1H), 1.94 (s, 3H), 1.93 (s, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 179.0, 169.7, 167.2, 150.1, 141.8, 134.1, 134.0, 133.5, 133.0, 129.7, 128.9, 128.82, 128.78, 122.7, 116.4, 37.7, 36.4, 29.4, 21.2, 20.6 (2 missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{23}NO_3$, 398.1755 , requires 398.1751.

(*S,E*)-4-Methoxy-*N*-(2-(6-methyl-2-oxochroman-3-yl)-1-(*p*-tolyl)ethylidene)benzamide (66i)



Following the general procedure the title compound was prepared using imine **64g** and chromanone **65f** in a 78% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 ml/min, λ = 254 nm, fraction t_r = 33.20 (major enantiomer) and 46.46 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 51.6 (c = 0.08, $CHCl_3$)

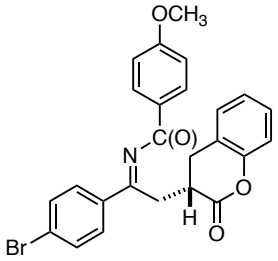
IR ν_{max} 2954, 2921, 1758, 1638 1598, 1508, 1493, 1314, 1244, 1137, 1082, 1021, 995, 811, 790, 779, 749 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.17-8.08 (m, 2H), 7.75-7.67 (m, 2H), 6.88-6.82 (m, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.67-6.60 (m, 3H), 6.40-6.36 (m, 1H), 3.56 (dd, *J* = 15.7, 5.3 Hz, 1H), 3.12 (s, 3H), 3.10-3.01 (m, 1H), 2.67-2.61 (m, 2H), 2.50 (dd, *J* = 15.8, 13.4 Hz, 1H), 1.95 (s, 3H), 1.94 (s, 3H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.7, 169.8, 166.9, 163.8, 150.1, 141.7, 134.4, 133.5, 131.9, 129.7, 128.9, 128.8, 126.6, 122.8, 116.4, 114.2, 54.8, 37.6, 36.4, 29.4, 21.2, 20.6 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{25}NO_4$, 428.1838, requires 428.1856.

(*S,E*)-*N*-(1-(4-Bromophenyl)-2-(2-oxochroman-3-yl)ethylidene)-4-methoxybenzamide (66j)



Following the general procedure the title compound was prepared using imine **64p** and chromanone **65a** in a 61% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 92:8, 1 ml/min, λ = 280 nm, fraction t_r = 20.27 (major enantiomer) and 25.89 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 8.1 (c = 0.15, $CHCl_3$)

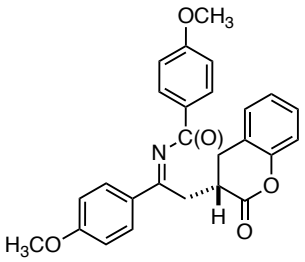
IR ν_{max} 1762, 1605, 1489, 1458, 1255, 1010, 756 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.12-8.02 (m, 2H), 7.41-7.31 (m, 2H), 7.14-7.08 (m, 2H), 6.85-6.78 (m, 2H), 6.73-6.67 (m, 1H), 6.68-6.62 (m, 3H), 3.26 (dd, *J* = 15.9, 5.8 Hz, 1H), 3.13 (s, 3H), 2.96-2.85 (m, 1H), 2.57-2.37 (m, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.4, 169.5, 166.2, 164.0, 152.1, 135.8, 132.2, 131.9, 129.5, 126.2, 126.0, 124.3, 123.0, 116.8, 114.3, 54.9, 37.2, 36.4, 29.4 (2 missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{20}{}^{79}BrNO_3$, 478.0647 , requires 478.0648.

(*S,E*)-4-Methoxy-*N*-(1-(4-methoxyphenyl)-2-(2-oxochroman-3-yl)ethylidene)benzamide (66k)



Following the general procedure the title compound was prepared using imine **64f** and chromanone **65a** in a 59% yield.

R_f 0.3 (70:30 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 95:5, 1 ml/min, λ = 280 nm, fraction t_r = 36.18 (major enantiomer) and 41.51 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 67.7 (c = 0.40, $CHCl_3$)

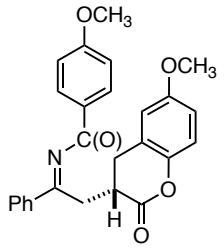
IR ν_{max} 1757, 1646, 1600, 1488, 1458, 1247, 1143, 1022, 755 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 6.84-6.78 (m, 2H), 6.71-6.61 (m, 4H), 6.59 (d, *J* = 8.4 Hz, 2H), 3.53 (dd, *J* = 15.6, 5.2 Hz, 1H), 3.15 (s, 3H), 3.13 (s, 3H), 3.07-2.99 (m, 1H), 2.68 (dd, *J* = 15.5, 6.2 Hz, 1H), 2.61 (dd, *J* = 15.6, 7.8 Hz, 1H), 2.50 (t, *J* = 15.5 Hz, 1H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.6, 169.7, 165.8, 163.8, 162.5, 152.1, 131.9, 130.1, 129.3, 128.4, 128.3, 126.8, 124.2, 123.2, 116.7, 114.4, 114.2, 54.9, 37.6, 36.0, 29.4 (1 missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{23}NO_5$, 430.1639, requires 430.1649.

(*S,E*)-4-Methoxy-*N*-(2-(6-methoxy-2-oxochroman-3-yl)-1-phenylethylidene)benzamide (66n)



Following the general procedure the title compound was prepared using imine **64e** and chromanone **65b** in a 45% yield.

R_f 0.3 (70:30 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 260 nm, fraction t_r = 22.27 (major enantiomer) and 30.74 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 18.0 (c = 0.08, $CHCl_3$)

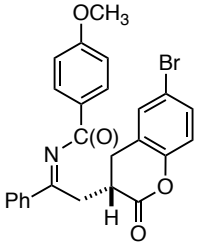
IR ν_{max} 1758, 1640, 1596, 1459, 1244, 1142, 1092, 757 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.13-8.06 (m, 2H), 7.77-7.70 (m, 2H), 7.05-6.98 (m, 3H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.67-6.58 (m, 2H), 6.49-6.43 (m, 1H), 6.31 (d, *J* = 2.9 Hz, 1H), 3.49 (dd, *J* = 15.8, 5.6 Hz, 1H), 3.22 (s, 3H), 3.13 (s, 3H), 3.10-2.96 (m, 1H), 2.68-2.43 (m, 3H). ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 169.8, 167.2, 163.9, 156.4, 146.0, 137.1, 131.9, 131.2, 128.9, 126.5, 124.0, 117.5, 114.2, 113.8, 113.2, 55.2, 54.9, 37.3, 36.6, 29.7 ppm (1 overlapping or missing)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{23}NO_5$, 430.1645 , requires 430.1649.

(*S,E*)-*N*-(2-(6-Bromo-2-oxochroman-3-yl)-1-phenylethylidene)-4-methoxybenzamide (66o)



Following the general procedure the title compound was prepared using imine **64e** and chromanone **65c** in a 49% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 70:30, 1 ml/min, λ = 280 nm, fraction t$_r$ = 39.29 (major enantiomer) and 78.16 (minor enantiomer); er = 96:4 $[\alpha]_D^{25}$ = 64.1 (c = 0.13, $CHCl_3$)

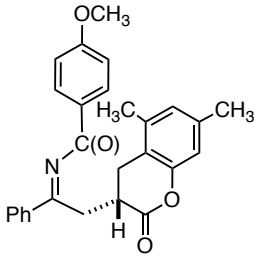
IR ν_{max} 1763, 1638, 1598, 1476, 1247, 1067, 1023, 785 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.17-8.00 (m, 2H), 7.77-7.64 (m, 2H), 7.08-6.98 (m, 3H), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.70-6.58 (m, 3H), 6.39 (d, *J* = 8.7 Hz, 1H), 3.37 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.12 (s, 3H), 2.94-2.78 (m, 1H), 2.51 (dd, *J* = 15.9, 7.5 Hz, 1H), 2.40-2.21 (m, 2H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.5, 168.9, 166.8, 163.9, 150.9, 137.0, 131.9, 131.3, 131.2, 131.2, 129.0, 128.7, 126.3, 125.0, 118.3, 116.8, 114.3, 54.9, 36.8, 36.3, 28.9 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{20}{}^{79}BrNO_4$, 478.0637, requires 478.0648.

(*S,E*)-*N*-(2-(5,7-Dimethyl-2-oxochroman-3-yl)-1-phenylethylidene)-4-methoxybenzamide (66p)



Following the general procedure the title compound was prepared using imine **64e** and chromanone **65h** in a 75% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 92:8, 1 ml/min, λ = 280 nm, fraction t$_r$ = 16.41 (major enantiomer) and 24.76 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 29.1 (c = 0.79, $CHCl_3$)

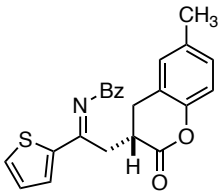
IR ν_{max} 1759, 1677, 1606, 1254, 1132, 757 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.16-8.09 (m, 2H), 7.77-7.68 (m, 2H), 7.03-6.97 (m, 3H), 6.67-6.61 (m, 2H), 6.60 (br s, 1H), 6.45 (br s, 1H), 3.51 (dd, *J* = 15.9, 5.6 Hz, 1H), 3.12 (s, 3H), 3.05-2.92 (m, 1H), 2.69 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.61 (dd, *J* = 16.0, 7.3 Hz, 1H), 2.25-2.11 (m, 1H), 1.97 (s, 3H), 1.89 (s, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.5, 169.8, 167.3, 163.8, 152.2, 137.7, 137.2, 136.1, 131.9, 131.1, 129.7, 126.7, 126.6, 118.6, 115.1, 114.2, 54.9, 37.0, 36.7, 26.4, 20.8, 18.9 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{25}NO_4$, 428.1853, requires 428.1856.

(*S,E*)-*N*-(2-(6-Methyl-2-oxochroman-3-yl)-1-(thiophen-2-yl)ethylidene)benzamide (10o)



Following the general procedure the title compound was prepared using imine **64m** and chromanone **65f** in a 79% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 46.08 (major enantiomer) and 50.36 (minor enantiomer); er = 99:1 $[\alpha]_D^{25}$ = 25.5 (c = 0.33, $CHCl_3$)

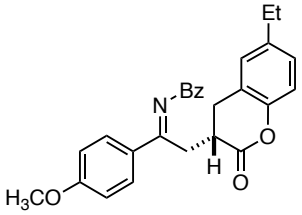
IR ν_{max} 1757, 1649, 1493, 1410, 1255, 1142, 823, 740 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.16-8.10 (m, 2H), 7.18 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.12-7.03 (m, 3H), 6.78 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.67-6.61 (m, 1H), 6.48 (dd, *J* = 5.1, 3.8 Hz, 1H), 6.33-6.28 (m, 1H), 3.49 (dd, *J* = 14.9, 4.8 Hz, 1H), 3.02-2.93 (m, 1H), 2.69 (dd, *J* = 15.7, 6.2 Hz, 1H), 2.61 (dd, *J* = 14.9, 8.5 Hz, 1H), 2.47-2.35 (m, 1H), 1.94 (s, 3H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.0, 169.1, 160.4, 149.6, 141.5, 133.5, 133.2, 132.8, 131.6, 131.4, 129.4, 128.6, 128.5, 128.4, 128.0, 122.2, 115.9, 37.9, 35.5, 29.0, 20.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{23}H_{19}NO_3S$, 390.1139, requires 390.1158.

(*S,E*)-*N*-(2-(6-Ethyl-2-oxochroman-3-yl)-1-(4-methoxyphenyl)ethylidene)benzamide (66r)



Following the general procedure the title compound was prepared using imine **64d** and chromanone **65g** in a 64% yield.

R*f* 0.3 (80:20 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 85:15, 1 ml/min, λ = 280 nm, fraction t_r = 31.09 (major enantiomer) and 53.39 (minor enantiomer); er = 97:3 $[\alpha]_D^{25}$ = 36.4 (c = 0.38, $CHCl_3$)

IR ν_{max} 1758, 1664, 1599, 1251, 1137, 1026, 799 cm^{-1}

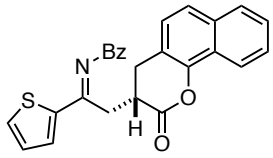
HPLC Daicel AD-H, hexane : *i*PrOH 85:15, 1 ml/min, λ = 280 nm, fraction t_r = 31.09 (major enantiomer) and 53.39 (minor enantiomer); er = 97:3 $[\alpha]_D^{25}$ = 36.4 (c = 0.38, $CHCl_3$)

^{1}H NMR (600 MHz, C_6D_6) δ 8.20-8.10 (m, 2H), 7.77-7.70 (m, 2H), 7.11-7.05 (m, 3H), 6.79 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.71-6.66 (m, 1H), 6.59-6.53 (m, 2H), 6.48 (s, 1H), 3.58 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.15 (s, 3H), 3.04-2.95 (m, 1H), 2.75 (dd, *J* = 15.8, 6.2 Hz, 1H), 2.58 (dd, *J* = 15.8, 8.3 Hz, 1H), 2.51 (t, *J* = 15.4 Hz, 1H), 2.28 (q, *J* = 7.6 Hz, 2H), 0.99 (t, *J* = 7.6, 3H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 179.0, 169.7, 166.2, 162.6, 150.2, 140.2, 134.1, 133.0, 130.7, 130.2, 129.7, 128.8, 128.3, 122.8, 116.5, 114.4, 114.0, 54.9, 37.9, 36.0, 29.5, 28.4, 15.9 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{25}NO_4$, 428.1863, requires 428.1856.

(*S,E*)-*N*-(2-(2-Oxo-3,4-dihydro-2*H*-benzo[*h*]chromen-3-yl)-1-(thiophen-2-yl)ethylidene)benzamide (66s)



Following the general procedure the title compound was prepared using imine **64m** and chromanone **65i** in an 81% yield.

R*f* 0.3 (85:15 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 230 nm, fraction t_r = 25.65 (major enantiomer) and 31.27 (minor enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 51.9 (c = 0.05, $CHCl_3$)

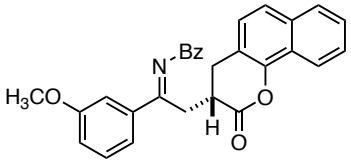
IR ν_{max} 1754, 1665, 1380, 1261, 1133, 1087, 806 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.08-8.02 (m, 1H), 8.00-7.90 (m, 2H), 7.35-7.27 (m, 1H), 7.10-6.96 (m, 4H), 6.91-6.81 (m, 3H), 6.57 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 6.27 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.29 (dd, *J* = 15.0, 4.9 Hz, 1H), 2.87-2.75 (m, 1H), 2.54 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.42 (dd, *J* = 15.0, 8.1 Hz, 1H), 2.29 (dd, *J* = 16.0, 13.2 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 168.8, 160.2, 146.4, 141.4, 133.5, 133.5, 132.8, 131.6, 131.4, 129.4, 128.5, 128.3, 126.4, 126.2, 125.4, 123.7, 123.5, 121.0, 117.1, 37.5, 35.6, 29.2 (1 missing or overlapping) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{19}NO_3S$, 426.1159, requires 426.1158.

(*S,E*)-*N*-(1-(3-Methoxyphenyl)-2-(2-oxo-3,4-dihydro-2*H*-benzo[*h*]chromen-3-yl)ethylidene)benzamide (66t)



Following the general procedure the title compound was prepared using imine **64o** and chromanone **65i** in a 68% yield.

R_f 0.3 (85:15 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 52.79 (major enantiomer) and 70.66 (minor enantiomer); er = >99:1 $[\alpha]_D^{25}$ = 32.1 (c = 0.12, $CHCl_3$)

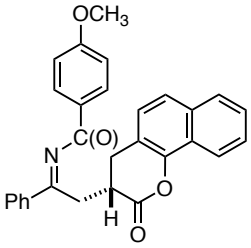
IR ν_{max} 1758, 1655, 1578, 1241, 1127, 1084, 807, 695 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ δ 8.07-7.99 (m, 1H), 7.98-7.89 (m, 2H), 7.36-7.26 (m, 2H), 7.13-6.97 (m, 4H), 6.88-6.84 (m, 3H), 6.75-6.70 (m, 1H), 6.55-6.46 (m, 2H), 3.29 (dd, *J* = 16.0, 5.4 Hz, 1H), 3.02 (s, 3H), 2.88-2.75 (m, 1H), 2.47 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.41-2.29 (m, 2H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 179.0, 169.4, 167.4, 160.4, 146.9, 138.2, 133.9, 133.1, 130.12, 129.7, 128.9, 127.4, 126.7, 126.6, 125.7, 124.1, 123.9, 121.4, 120.3, 117.8, 117.5, 113.0, 54.8, 37.2, 36.8, 29.6 ppm (1 overlapping or missing)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{29}H_{23}NO_4$, 450.1690, requires 450.1700.

(*S,E*)-4-Methoxy-*N*-(2-(2-oxo-3,4-dihydro-2*H*-benzo[*h*]chromen-3-yl)-1-phenylethylidene)benzamide (66u)



Following the general procedure the title compound was prepared using imine **64e** and chromanone **65i** in 63% yield.

R*f* 0.3 (85:15 v/v hexanes : ethyl acetate)

HPLC Daicel OD-H, hexane : *i*PrOH 92:8, 1 ml/min, λ = 254 nm, fraction t_r = 23.35 (major enantiomer) and 35.95 (minor enantiomer); er = 96:4 $[\alpha]_D^{25}$ = 66.4 (c = 0.14, $CHCl_3$)

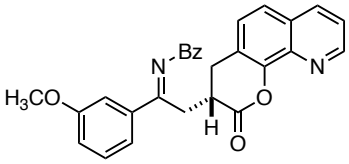
IR ν_{max} 1753, 1648, 1602, 1378, 1250, 1126, 1024, 754 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.29-8.22 (m, 1H), 8.18-8.10 (m, 2H), 7.77-7.71 (m, 2H), 7.56-7.50 (m, 1H), 7.25-7.18 (m, 3H), 7.04-6.98 (m, 3H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.68-6.62 (m, 2H), 3.49 (dd, *J* = 15.9, 5.6 Hz, 1H), 3.11 (s, 3H), 3.10-3.02 (m, 1H), 2.71-2.54 (m, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 178.5, 169.5, 167.1, 163.9, 146.9, 137.2, 133.9, 132.5, 131.9, 131.2, 128.9, 126.7, 126.6, 126.5, 125.8, 124.1, 123.9, 121.4, 117.6, 114.3, 113.5, 54.8, 37.1, 36.7, 29.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{29}H_{23}NO_4$, 450.1687, requires 450.1700.

(*S,E*)-*N*-(1-(3-Methoxyphenyl)-2-(2-oxo-3,4-dihydro-2*H*-pyrano[3,2-*h*]quinolin-3-yl)ethylidene)benzamide (66v)



Following the general procedure the title compound was prepared using imine **64o** and chromanone **65j** in 44% yield.

R*f* 0.3 (50:50 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 ml/min, λ = 254 nm, fraction t_r = 57.91 (minor enantiomer) and 74.30 (major enantiomer); er = 96:4 $[\alpha]_D^{25}$ = 76.0 (c = 0.10, $CHCl_3$)

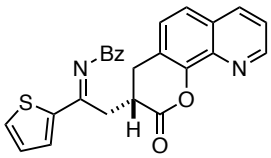
IR ν_{max} 1758, 1663, 1578, 1464, 1370, 1258, 1129, 1090, 832 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.75 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.15-8.07 (m, 2H), 7.60-7.57 (m, 1H), 7.49 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.31-7.25 (m, 1H), 7.10-7.03 (m, 3H), 7.02-6.96 (m, 1H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.76-6.71 (m, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 3.51 (dd, *J* = 16.1, 5.0 Hz, 1H), 3.24 (s, 3H), 3.03-2.95 (m, 1H), 2.72 (dd, *J* = 16.1, 6.6 Hz, 1H), 2.61-2.51 (m, 2H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 168.8, 167.7, 166.9, 160.0, 150.2, 146.9, 138.5, 137.6, 134.7, 133.9, 133.4, 132.7, 131.1, 129.8, 129.3, 126.0, 122.7, 121.1, 120.0, 117.6, 112.5, 54.5, 36.5, 36.3, 29.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{28}H_{22}N_2O_4$, 451.1652, requires 451.1652.

(*S,E*)-*N*-(2-(2-Oxo-3,4-dihydro-2*H*-pyrano[3,2-*h*]quinolin-3-yl)-1-(thiophen-2-yl)ethylidene)benzamide (66w)



Following the general procedure the title compound was prepared using imine 64m and chromanone **65j** in a 47% yield.

R_f 0.3 (50:50 v/v hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 ml/min, λ = 210 nm, fraction t_r = 40.41 (minor enantiomer) and 75.80 (major enantiomer); er = 98:2 $[\alpha]_D^{25}$ = 54.8 (c = 0.12, $CHCl_3$)

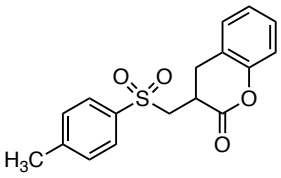
IR ν_{max} 1758, 1663, 1577, 1467, 1260, 1096, 1028, 799 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.76 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.14-8.11 (m, 1H), 7.61-7.54 (m, 1H), 7.43 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.22 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.10-7.03 (m, 2H), 7.02-6.98 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.78 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.74 (dd, *J* = 8.3, 4.1 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.48 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.51 (dd, *J* = 14.9, 4.5 Hz, 1H), 3.03-2.92 (m, 1H), 2.81 (dd, *J* = 16.1, 6.5 Hz, 1H), 2.65-2.49 (m, 2H) ppm

^{13}C NMR (150 MHz, C_6D_6) δ 178.0, 168.6, 167.6, 160.3, 150.2, 146.9, 141.3, 138.5, 134.7, 133.4, 132.8, 131.6, 131.6, 131.1, 129.4, 128.5, 126.1, 122.7, 121.3, 121.1, 37.3, 35.5, 29.4 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{25}H_{18}N_2O_3S$, 449.0937, requires 449.0930.

3-(Tosylmethyl)chroman-2-one (66an)



Following the general procedure the title compound was prepared using imine **55** and chromanone **65a** in 70% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

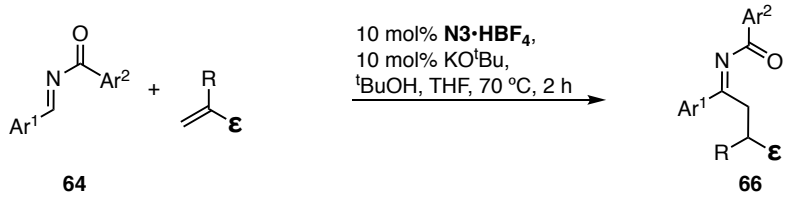
IR ν_{max} 1758, 1490, 1460, 1310, 1290, 1231, 1151, 1085, 769 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.79 (m, 2H), 7.42-7.35 (m, 2H), 7.31-7.26 (m, 1H), 7.25-7.21 (m, 1H), 7.14 (td, *J* = 7.5, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.00 (dd, *J* = 14.0, 2.2 Hz, 1H), 3.56 (dd, *J* = 15.6, 5.9 Hz, 1H), 3.35-3.18 (m, 2H), 3.09-2.97 (m, 1H), 2.46 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 151.3, 145.5, 136.4, 130.3, 128.9, 128.5, 128.1, 125.0, 122.0, 116.8, 55.9, 35.1, 29.6, 21.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{17}H_{16}O_4S$, 317.0830, requires 317.0842.

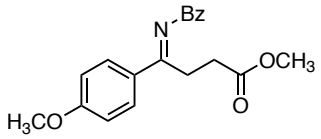
5.2.10 General procedure for the NHC catalysed achiral aza-Stetter reaction



64 66

To a flame-dried reaction vial containing **N3•HBF$_4$** (3.0 mg, 0.01 mmol) was added tert-butanol (0.20 mL of a 0.5 M solution in THF, 0.10 mmol) and potassium tert-butoxide (0.20 mL of a 0.05 M solution in THF, 0.01 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. The appropriate imine **64** (0.12 mmol) and Michael acceptor (0.10 mmol) were then added as a solution in THF (1.5 mL) and the vial sealed and the reaction mixture stirred at 70 °C for 2 hours. Concentration under reduced pressure and purification *via* column chromatography then gave the aza-Stetter products **66**.

Methyl (*E*)-4-(benzoylimino)-4-(4-methoxyphenyl)butanoate (66ah)



Following the general procedure the title compound was prepared using imine **64d** and methyl acrylate **153** in a 42% yield.

R$_f$ 0.3 (80:20 v/v hexanes : ethyl acetate)

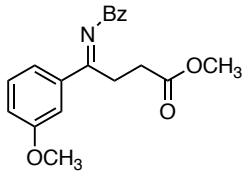
IR ν_{max} 1735, 1674, 1599, 1510, 1249, 1221, 1166, 1027, 830 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.22-8.07 (m, 2H), 7.75-7.61 (m, 2H), 7.13-7.03 (m, 3H), 6.65-6.47 (m, 2H), 3.23 (s, 3H), 3.16 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 172.0, 167.3, 162.1, 134.0, 132.4, 129.7, 129.3, 128.4, 113.9, 54.5, 50.9, 31.2, 30.2 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{19}NO_4$, 326.1388, requires 326.1387.

Methyl (*E*)-4-(benzoylimino)-4-(3-methoxyphenyl)butanoate (66ai)



Following the general procedure the title compound was prepared using imine **64o** and methacrylate **153** in a 31% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

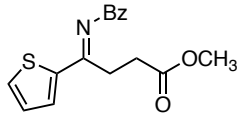
IR ν_{max} 1734, 1674, 1599, 1509, 1248, 1220, 1164, 1029, 830 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.18-8.06 (m, 2H), 7.43-7.39 (m, 1H), 7.21 (d, 1H), 7.10-7.01 (m, 3H), 6.96-6.91 (m, 1H), 6.75-6.71 (m, 1H), 3.25 (s, 3H), 3.22 (s, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.58 (t, *J* = 7.4 Hz, 2H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.8, 175.9, 168.6, 160.4, 138.9, 134.5, 133.1, 130.3, 129.6, 128.9, 120.5, 117.6, 113.2, 54.5, 50.9, 31.2, 30.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{19}NO_4$, 326.1387, requires 326.1387.

Methyl (*E*)-4-(benzoylimino)-4-(thiophen-2-yl)butanoate (66aj)



Following the general procedure the title compound was prepared using imine **64m** and methyl acrylate **153** in a 54% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

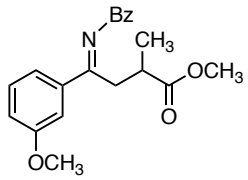
IR ν_{max} 1740, 1688, 1598, 1510, 1250, 1220, 1166, 1096, 1028, 799 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.22-8.07 (m, 2H), 7.12 (d, *J* = 3.8 Hz, 1H), 7.10-7.02 (m, 3H), 6.78 (d, *J* = 4.5 Hz, 1H), 6.48 (t, *J* = 4.5 Hz, 1H), 3.19 (s, 3H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 172.1, 162.3, 142.0, 134.1, 133.0, 131.8, 131.4, 129.8, 128.8, 51.3, 31.9, 30.6 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{25}NO_3S$, 302.0850, requires 302.0845.

Methyl (*E*)-4-(benzoylimino)-4-(3-methoxyphenyl)-2-methylbutanoate (66ak)



Following the general procedure the title compound was prepared using imine **64o** and methyl methacrylate **149** in a 17% yield.

R_f 0.3 (85:15 v/v hexanes : ethyl acetate)

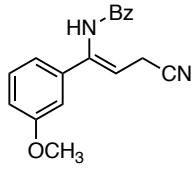
IR ν_{max} 1734, 1674, 1599, 1509, 1248, 1221, 1160, 1030, 830 cm^{-1}

^{1}H NMR (600 MHz, C_6D_6) δ 8.18-8.06 (m, 2H), 7.43-7.39 (m, 1H), 7.21 (d, 1H), 7.10-7.01 (m, 3H), 6.96-6.91 (m, 1H), 6.75-6.71 (m, 1H), 3.25 (s, 3H), 3.22 (s, 3H), 3.18 (dd, *J* = 15.7, 8.2 Hz, 1H), 3.01-2.94 (m, 1H), 2.56 (dd, *J* = 15.7, 6.3 Hz, 1H), 1.05 (d, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 175.6, 168.7, 160.4, 138.9, 134.4, 133.0, 130.0, 129.8, 128.9, 120.5, 117.7, 113.2, 55.0, 51.6, 39.8, 37.8, 17.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{21}NO_4$, 340.1533 , requires 340.1543.

(*Z*)-*N*-(3-Cyano-1-(3-methoxyphenyl)prop-1-en-1-yl)benzamide (66al)



Following the general procedure the title compound was prepared using imine **64o** and acrylonitrile **154** in a 43% yield.

R_f 0.3 (80:20 v/v hexanes : ethyl acetate)

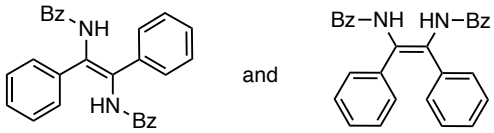
IR ν_{max} 1637, 1601, 1511, 1483, 1257, 1026, 799 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 7.62-7.56 (m, 2H), 7.13-7.08 (m, 1H), 7.05-6.95 (m, 3H), 6.91-6.87 (m, 1H), 6.76-6.69 (m, 2H), 6.68 (br s, 1H), 5.38 (t, *J* = 6.5 Hz, 1H), 3.23 (s, 3H), 2.78 (d, *J* = 6.5 Hz, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 160.4, 139.1, 137.1, 134.0, 132.0, 130.0, 128.8, 119.08, 117.8, 114.8, 113.2, 112.4, 54.8, 17.1 ppm (1 missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{18}H_{16}N_2O_2$, 293.1254 , requires 293.1285.

(*E*)-*N,N'*-(1,2-Diphenylethene-1,2-diyl)dibenzamide and (*Z*)-*N,N'*-(1,2-Diphenylethene-1,2-diyl)dibenzamide (112a)



To a flame-dried reaction vial containing **N3•BF$_4$** (4.3 mg, 0.01 mmol) was added tert-butanol (0.20 mL of a 0.5 M solution in THF, 0.10 mmol) and potassium tert-butoxide (0.20 mL of a 0.05M solution in THF, 0.01 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Imine **64a** (0.10 mmol) was then added in THF (1.5 mL) and the reaction mixture was stirred at 70 °C for 2 hours before being concentrated *in vacuo* and purified *via* column chromatography. The title compound was prepared in a 39% yield.

MP: 268-273 °C, Literature: 270-272 °C.[27]

R$_f$ 0.3 (70:30 v/v hexanes : ethyl acetate)

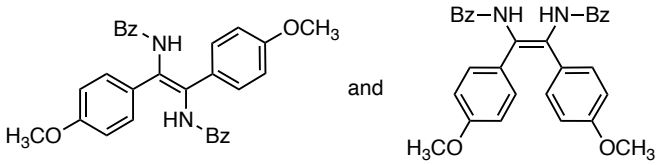
IR ν_{max} 1638, 1599, 1478, 1447, 1227, 687 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6) δ 8.21-8.11 (m, 4H), 7.80-7.71 (m, 2H), 7.70-7.60 (m, 2H), 7.27-7.04 (m, 14H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 179.2, 167.4, 165.6, 136.81, 135.8, 133.1, 132.8, 132.3, 131.2, 131.0, 129.1, 129.0, 128.9, 128.5, 128.4, 128.4, 128.3, 125.0 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{28}H_{22}N_2O_2$, 419.1751 , requires 419.1754.

(*E*)-*N,N'*-(1,2-Bis(4-methoxyphenyl)ethene-1,2-diyl)dibenzamide and (*Z*)-*N,N'*-(1,2-Bis(4-methoxyphenyl)ethene-1,2-diyl)dibenzamide (112b)



Following the general procedure the title compound was prepared using imine **64o** in a 40% yield.

R$_f$ 0.3 (70:30 v/v hexanes : ethyl acetate)

IR ν_{max} 1638, 1599, 1509, 1478, 1228, 1170, 1024, 832, 702, cm^{-1}

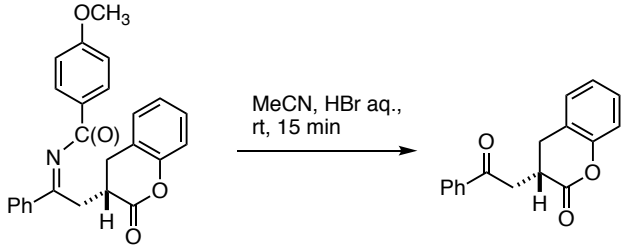
^{1}H NMR (400 MHz, C_6D_6) δ 8.17-8.09 (m, 4H), 7.71-7.63 (m, 2H), 7.63-7.56 (m, 2H), 7.26-7.23 (m, 1 H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.12-7.06 (m, 1H), 7.03-6.94 (m, 5H), 6.77-6.70 (m, 2H), 6.68-6.62 (m, 2H), 3.25 (s, 3H), 3.20 (s, 3H) ppm

^{13}C NMR (100 MHz, C_6D_6) δ 179.7, 166.7, 166.0, 162.7, 160.2, 133.6, 133.5, 132.5, 131.3, 131.0, 130.7, 129.52, 129.5, 127.36, 114.9, 114.4, 54.8, 54.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{30}H_{26}N_2O_4$, 479.1955, requires 479.1965.

5.2.11 Derivatizations

(*R*)-3-(2-Oxo-2-phenylethyl)chroman-2-one (155)



A solution of imine **66f** (20 mg, 0.05 mmol) in MeCN (1 mL) was added HBr (0.5 mL of a 48% solution) and the reaction stirred for 15 minutes. The mixture was diluted with water (10 mL) and ethyl acetate (10 mL). The biphasic mixture was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). After filtration, the organic solvent was removed under reduced pressure and residue purified *via* flash column chromatography over silica. To give ketone **16j** (12 mg, 92% yield)

R_f 0.25 (80:20 *v*/*v* hexanes : ethyl acetate).

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 ml/min, λ = 254 nm, fraction t_r = 23.33 (major enantiomer) and 21.17 (minor enantiomer); er = 97:3 $[\alpha]_D^{25}$ = –49.4 (c = 0.008, $CHCl_3$).

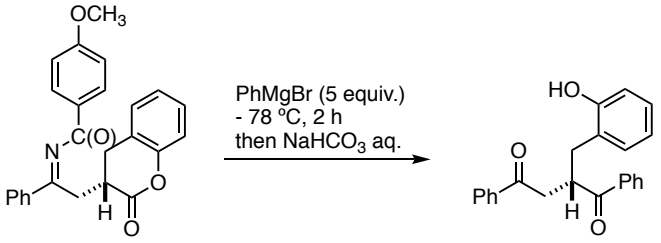
IR ν_{max} 2921, 1756, 1681, 1134, 768, 753, 690 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05-7.98 (m, 2H), 7.63-7.58 (m, 1H), 7.54-7.45 (m, 2H), 7.31-7.26 (m, 1H), 7.22-7.16 (m, 1H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.86 (dd, *J* = 18.0, 4.4 Hz, 1H), 3.48 (dddd, *J* = 13.8, 7.6, 6.3, 4.4 Hz, 1H), 3.21 (dd, *J* = 18.0, 7.6 Hz, 1H), 3.11 (dd, *J* = 15.4, 6.3 Hz, 1H), 2.94 (dd, *J* = 15.4, 13.8 Hz, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 171.0, 152.0, 136.8, 133.9, 129.1, 128.7, 128.5, 128.4, 124.8, 123.1, 117.1, 39.0, 35.5, 29.9.

HRMS (ESI) *m/z* found: $(M+H)^+$ $C_{17}H_{14}O_3$ 267.1003, requires 267.1016.

(*R*)-2-(2-Hydroxybenzyl)-1,4-diphenylbutane-1,4-dione (156)



To a solution of imine **66f** (20 mg, 0.05 mmol) in THF (1 mL) at –78 °C was added a diluted solution of PhMgBr (0.8 mL of a 3M solution in ether, in 1 mL THF). The reaction was stirred at –78 °C for 1 hour and then quenched with aq. $NaHCO_3$ (2 mL) slowly. After warming to room temperature, the mixture was diluted with HCl (10 mL of a 1M solution) and ethyl acetate (10 mL). After stirring for 15 minutes, the biphasic mixture was separated and the aqueous layer extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure and residue was purified via flash column chromatography over silica to give the title compound **15j** (12 mg, 68% yield).

R_f 0.21 (80:30 *v*/*v* hexanes : ethyl acetate).

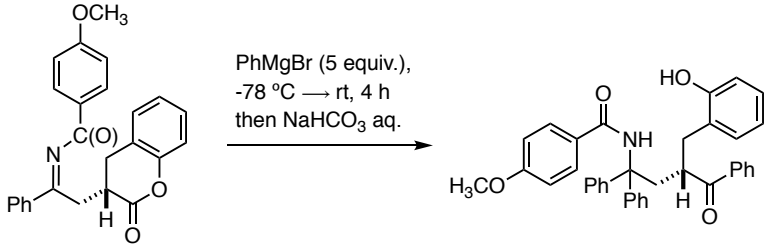
HPLC Daicel AD-H, hexane : *i*PrOH 85:15, 1 ml/min, λ = 254 nm, fraction t_r = 18.59 (major enantiomer) and 20.11 (minor enantiomer); er = 87:13. $[\alpha]_D^{25}$ = +6 (c = 0.006, $CHCl_3$). **IR ν_{max}** 3391, 3064, 2921, 1671, 1595, 1448, 1218, 1002, 755, 688 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.89 (m, 4H), 7.63-7.50 (m, 2H), 7.49-7.35 (m, 4H), 7.15-7.04 (m, 2H), 6.93 (brs, 1H), 6.88-6.83 (m, 1H), 6.78-6.72 (m, 1H), 4.52-4.42 (m, 1H), 3.51 (dd, *J* = 18.5, 5.4 Hz, 1H), 3.34-3.10 (m, 2H), 2.79 (dd, *J* = 13.9, 5.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 199.3, 154.8, 136.6, 136.3, 134.0, 133.7, 131.6, 129.0(2), 128.9(9), 128.5(8), 128.5(6), 125.3, 120.8, 116.6, 42.5, 41.1, 32.7 ppm (one peak overlaps).

HRMS (ESI) *m/z* found: $(M+H)^+$ $C_{23}H_{20}O_3$ 345.1466, requires 345.1485.

(*R*)-*N*-(3-(2-Hydroxybenzyl)-4-oxo-1,1,4-triphenylbutyl)-4-methoxybenzamide (157)



To a solution of imine **66f** (20 mg, 0.05 mmol) in THF (1 mL) at –78 °C was added a diluted solution of PhMgBr (0.8 mL of a 3M solution in ether, in 1 mL THF). The reaction was stirred at –78 °C for 2 hours, warmed to room temperature before being quenched with aq. $NaHCO_3$ (2 mL). The mixture was further diluted with water (10 mL) and ethyl acetate (10 mL). The biphasic mixture was separated and the aqueous layer extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure and the residue purified *via* flash column chromatography over silica, to give **14j** (13 mg, 45% yield).

R_f 0.18 (60:40 *v*/*v* hexanes : ethyl acetate).

HPLC Daicel AD-H, hexane : *i*PrOH 25:75, 1 ml/min, λ = 260 nm, fraction t_r = 4.51 (major enantiomer) and 8.24 (minor enantiomer); er = 90:10 $[\alpha]_D^{25}$ = –4.3 (c = 0.022, $CHCl_3$)

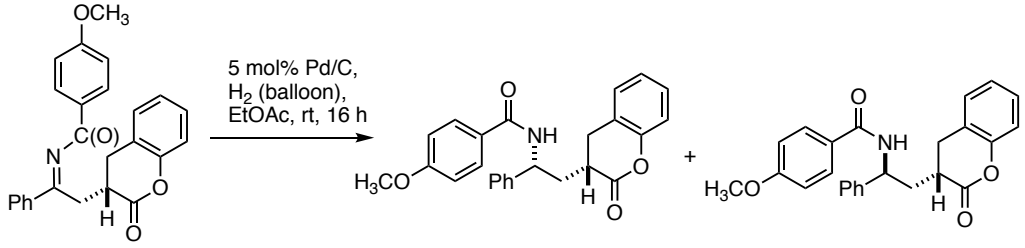
IR ν_{max} 3200, 3063, 2900, 1656, 1607, 1485, 1256, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.59 (m, 4H), 7.50-7.41 (m, 1H), 7.40-7.34 (m, 2H), 7.29-7.21 (m, 2H), 7.21-7.12 (m, 6H), 7.11-6.96 (m, 4H), 6.92-6.82 (m, 3H), 6.74-6.68 (m, 1H), 6.63-6.54 (m, 1H), 5.44 (brs, 1H), 3.82 (s, 3H), 3.86-3.75 (m, 1H), 3.44 (dd, *J* = 14.6, 9.3 Hz, 1H), 3.00 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.63-2.53 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 165.9, 162.5, 154.2, 144.9, 142.7, 136.6, 133.5, 131.9, 129.2, 128.9, 128.6, 128.3(3), 128.3(1), 128.0(4), 127.9(9), 127.9(0), 127.3, 127.2, 127.0, 125.0, 121.0, 116.2, 114.0, 65.9, 55.8, 43.0, 42.7, 36.1 ppm.

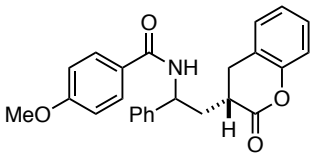
HRMS (ESI) *m/z* found: $(M+H)^+$ $C_{37}H_{33}NO_4$ 556.2447, requires 556.2482.

4-Methoxy-*N*-(2-((*R*)-2-oxochroman-3-yl)-1-phenylethyl)benzamide (158)



To a mixture of imine **66f** (20 mg, 0.05 mmol) and Pd/C (3 mg) in a RBF plugged with a septum was added dry ethyl acetate (2 mL). A balloon charged with H_2 gas with a long needle outlet was inserted through the septum and the tip of the needle immersed in the solution. The reaction was stirred for 16 hours at room temperature before removal of the solvent. The residue was purified via flash chromatography over silica to provide **(*R,S*-16j)** and **(*S,S*-16j)** in a 5:4 ratio (16 mg, 82% yield, 5:4 dr).

4-Methoxy-*N*-((*R or S*)-2-((*R*)-2-oxochroman-3-yl)-1-phenylethyl)benzamide (*R,S*-158) or (*S,S*-158)



R_f 0.27 (60:40 *v*/*v* hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 70:30, 1 ml/min, λ = 254 nm, fraction t_r = 12.40 (major enantiomer) and 16.59 (minor enantiomer); er = 94:6. $[\alpha]_D^{25}$ = –41.0 (c = 0.011, $CHCl_3$)

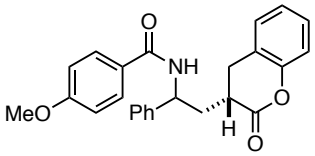
IR ν_{max} 3346, 2933, 1747, 1624, 1503, 1260, 11142, 758 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (AA'BB', *J* = 8.8 Hz, 2H), 7.43-7.39 (m, 2H), 7.38-7.32 (m, 2H), 7.29-7.20 (m, 3H), 7.10 (td, *J* = 7.5, 1.2 Hz, 1H), 7.02 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.90 (AA'BB', *J* = 8.8 Hz, 2H), 5.35 (ddd, *J* = 12.0, 8.1, 4.1 Hz, 1H), 3.83 (s, 3H), 3.21 (dd, *J* = 15.4, 6.0 Hz, 1H), 2.96 (ddt, *J* = 15.4, 12.9, 1.0 Hz, 1H), 2.85 (dq, *J* = 12.0, 6.0 Hz, 1H), 2.72 (ddd, *J* = 14.6, 12.0, 6.0 Hz, 1H), 2.00 (ddd, *J* = 14.6, 6.0, 4.1 Hz, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 166.8, 162.6, 151.7, 142.7, 129.2(1), 129.1(8), 128.7, 128.5, 128.0, 126.7, 126.5, 125.0, 122.8, 116.9, 114.1, 55.7, 52.5, 37.9, 37.1, 30.4 ppm.

HRMS (ESI) *m/z* found: $(M+Na)^+$ $C_{25}H_{23}NO_4$ 424.1473, requires 424.1519.

4-Methoxy-*N*-((*R or S*)-2-((*R*)-2-oxochroman-3-yl)-1-phenylethyl)benzamide (*R,S*-158) or (*S,S*-158)



R_f 0.33 (60:40 *v*/*v* hexanes : ethyl acetate)

HPLC Daicel AD-H, hexane : *i*PrOH 70:30, 1 ml/min, λ = 254 nm, fraction t_r = 12.33 (major enantiomer) and 16.46 (minor enantiomer); er = 97:3. $[\alpha]_D^{25}$ = +15.2 (c = 0.004, $CHCl_3$)

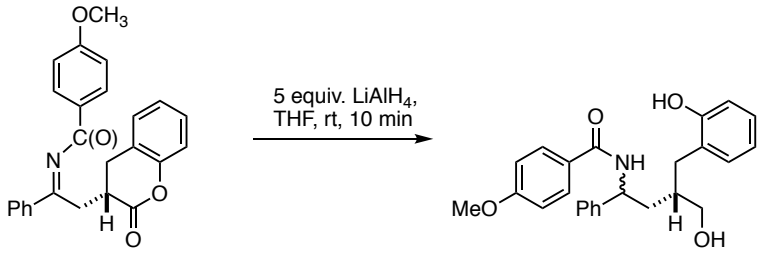
IR ν_{max} 3346, 2933, 1747, 1624, 1503, 1260, 11142, 758 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (AA'BB', *J* = 8.8 Hz, 1H), 7.42-7.37 (m, 2H), 7.36-7.32 (m, 2H), 7.29-7.21 (m, 3H), 7.16 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.08 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.92 (AA'BB', *J* = 8.8 Hz, 2H), 5.42 (td, *J* = 7.8, 6.2 Hz, 1H), 3.84 (s, 3H), 3.11-2.92 (m, 2H), 2.65 (dtd, *J* = 13.1, 6.4, 5.1 Hz, 1H), 2.55 (dt, *J* = 14.5, 6.4 Hz, 1H), 2.43 (ddd, *J* = 14.5, 7.8, 5.1 Hz, 1H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 166.4, 162.6, 151.6, 141.3, 129.3, 129.2, 128.7, 128.3, 128.1, 126.8, 126.6, 124.9, 122.9, 116.9, 114.1, 55.7, 51.7, 36.8, 35.6, 29.4 ppm.

HRMS (ESI) *m/z* found: $(M+H)^+$ $C_{25}H_{23}NO_4$ 402.1705, requires 402.1700.

***N*-((*1R and S,3S*)-4-hydroxy-3-(2-hydroxybenzyl)-1-phenylbutyl)-4-methoxybenzamide (159)**



Following a procedure reported by Toste and coworkers,[28] a stirred solution of imine **66f** (20 mg, 0.05 mmol) in THF (2 ml) was added powdered $LiAlH_4$ (9.5 mg, 0.25 mmol) and the reaction was stirred at room temperature for 10 min. After this time, the reaction was carefully quenched with water (2 mL) and extracted with ethyl acetate (2 x 10 mL). The combined extracts were dried ($MgSO_4$), evaporated, and purified by flash column chromatography over silica to give **17j** as a 3:2 mixture of diastereomers (16 mg, 78% yield, 3:2 dr).

R_f 0.20 (40:60 *v/v* hexanes : ethyl acetate).

HPLC Daicel Regis, hexane : *i*PrOH 90:10, 1 ml/min, λ = 210 nm, diastereoisomer 1: fraction t_r = 39.53 (major enantiomer) and 45.60 (minor enantiomer); er = 97:3; diastereoisomer 2: fraction t_r = 24.45 (minor enantiomer) and 31.52 (major enantiomer); er = 98:2 $[\alpha]_D^{25}$ = –49.4 (c = 0.008, $CHCl_3$). $[\alpha]_D^{25}$ = +9.2 (c = 0.003, $CHCl_3$)

IR ν_{max} 3300, 2931, 1702, 1605, 1501, 1252, 1176, 1028, 754, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (AA'BB', *J* = 8.6 Hz, 2H), 7.69 (AA'BB', *J* = 8.5 Hz, 1.3H), 7.56 (brs, 1.7H), 7.39-7.34 (m, 4H), 7.34-7.27 (m, 4H), 7.12-7.04 (m, 1.8H), 7.04-6.97 (m, 1.7H), 6.93-6.86 (m, 3.4H), 6.86-6.73 (m, 3.1H), 6.58 (d, *J* = 7.7 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 0.7H), 5.38-5.26 (m, 1.7H), 3.82 (s, 5.1H), 3.67 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.54 (d, *J* = 4.7 Hz, 1.3H), 3.45 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.20 (brs, 1.5H), 2.89 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.80 (dd, *J* = 13.9, 8.0 Hz, 0.7H), 2.73-2.61 (m, 1.8H), 2.21-2.10 (m, 1H), 2.08-1.91 (m, 2.6H), 1.90-1.75 (m, 1.8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.0, 162.8, 162.7, 155.5, 155.3, 142.5, 142.2, 131.8, 131.7, 129.3(1), 129.2(5), 129.1(6), 128.1, 128.0, 127.9, 127.1, 126.9, 126.8, 126.5, 126.3, 125.9, 120.8, 120.6, 117.0, 116.8, 114.1(8), 114.1(5), 66.2, 64.0, 63.7, 55.8, 52.5, 52.2, 38.9(2), 38.9(0), 38.6(4), 38.5(5), 32.2, 31.7 ppm two peaks missing or overlapping.

HRMS (ESI) *m/z* found: $(M+H)^+$ $C_{25}H_{27}NO_4$ 406.2015, requires 406.2013.

5.3 Experimental Section for Chapter Three

5.3.1 Determination of reaction order with respect to catalyst

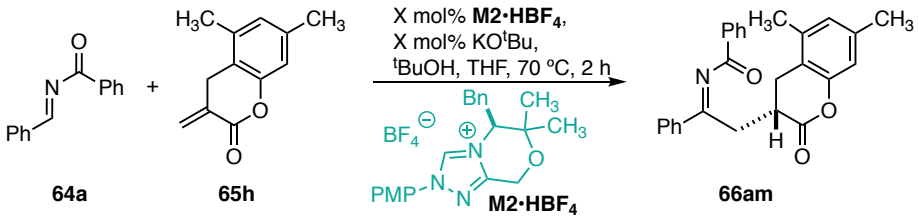
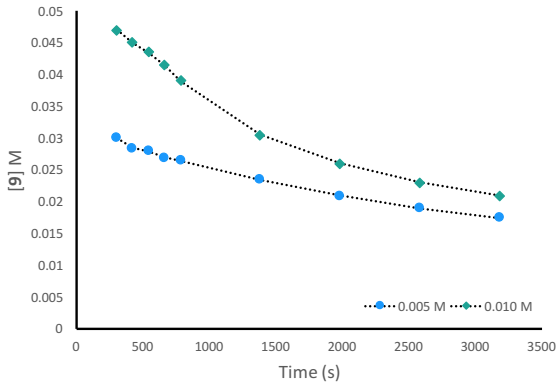
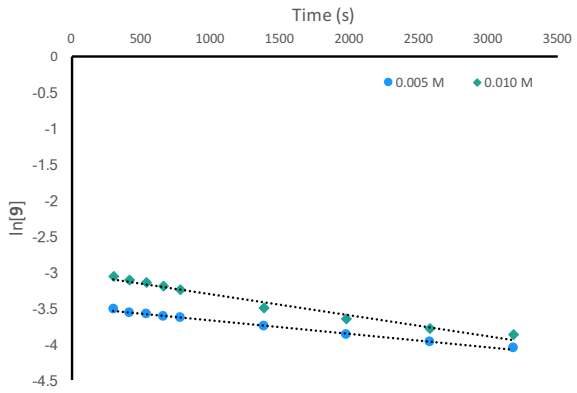


Table SI-1. Raw data for impact of [**M2**] on rate of reaction

0.005 M **M2**			0.010 M **M2**		
Time (s)	[65h] (M)	ln[65h]	Time (s)	[65h] (M)	ln[65h]
300	0.0300	-3.50655	300	0.0470	-3.05760
420	0.0285	-3.55785	420	0.0450	-3.10109
540	0.0280	-3.57555	540	0.0435	-3.13499
660	0.0270	-3.61191	660	0.0415	-3.18206
780	0.0265	-3.63061	780	0.0390	-3.24419
1380	0.0235	-3.75075	1380	0.0305	-3.49002
1980	0.0210	-3.86323	1980	0.0260	-3.64965
2580	0.0190	-3.96331	2580	0.0230	-3.77226
3180	0.0175	-4.04555	3180	0.0210	-3.86323





Trendline data for ln[65h] vs time for effect of **M2**

	0.005 M **M2**	0.010 M **M2**
Slope	-0.000195	-0.000327
Y-intercept	-3.471832	-2.975393
R square	0.9944	0.9848

$$\ln\left(\frac{(\text{slope})_A}{(\text{slope})_B}\right) = y \ln\left(\frac{(\text{conc.})_A}{(\text{conc.})_B}\right)$$

$$\ln\left(\frac{-0.000195}{-0.000327}\right) = y \ln\left(\frac{0.005}{0.010}\right)$$

$$-0.5169 = -0.6931y$$

$$y = \frac{-0.5169}{-0.6931}$$

$$y = 0.74$$

Equation 1: Determination of reaction order with respect to catalyst

5.3.2 Determination of reaction order with respect to imine

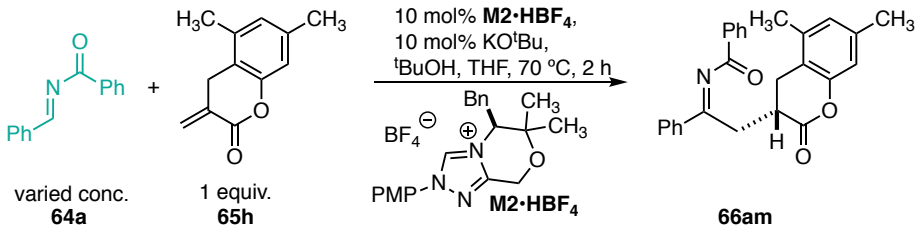
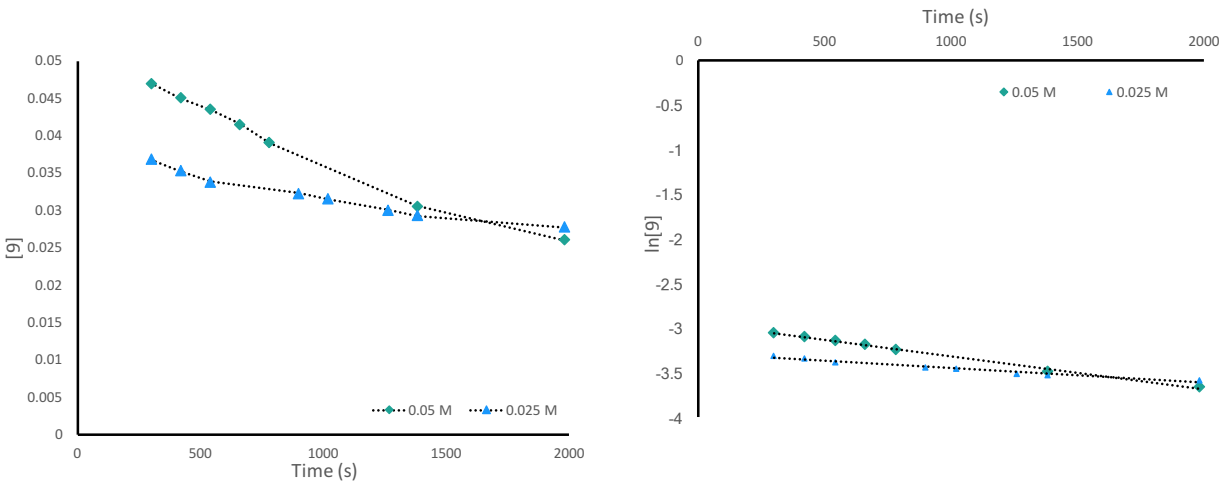


Table SI-2. Raw data for impact of [**64a**] on rate of reaction

0.050 M **64a**			0.025 M **64a**		
Time (s)	[**65h**] (M)	ln[**65h**]	Time (s)	[**65h**] (M)	ln[**65h**]
300	0.0470	-3.05760	300	0.03675	-3.30361
420	0.0450	-3.10109	420	0.03525	-3.34528
540	0.0435	-3.13499	540	0.03375	-3.38877
660	0.0415	-3.18206	900	0.03225	-3.43423
780	0.0390	-3.24419	1020	0.03150	-3.45776
1380	0.0305	-3.49002	1380	0.02925	-3.53187
1980	0.0260	-3.64965	1980	0.02775	-3.58451



Trendline data for ln[**65h**] vs time for effect of **64a**

	0.050 M **64a**	0.025 M **64a**
Slope	-0.000365	-0.000167
Y-intercept	-2.949673	-3.281466
R square	0.9926	0.9606

$$\ln\left(\frac{(\text{slope})_A}{(\text{slope})_B}\right) = y \ln\left(\frac{(\text{conc.})_A}{(\text{conc.})_B}\right)$$

$$\ln\left(\frac{-0.000365}{-0.000167}\right) = y \ln\left(\frac{0.050}{0.025}\right)$$

$$0.7819 = 0.6931y$$

$$y = \frac{0.7819}{0.6931}$$

$$y = 1.12$$

Equation 2: Determination of reaction order with respect to imine

5.3.3 Determination of reaction order with respect to lactone

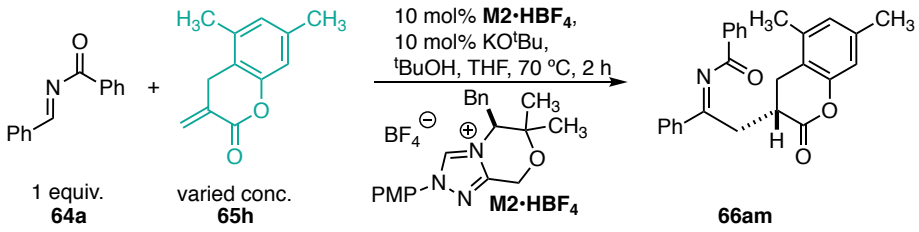
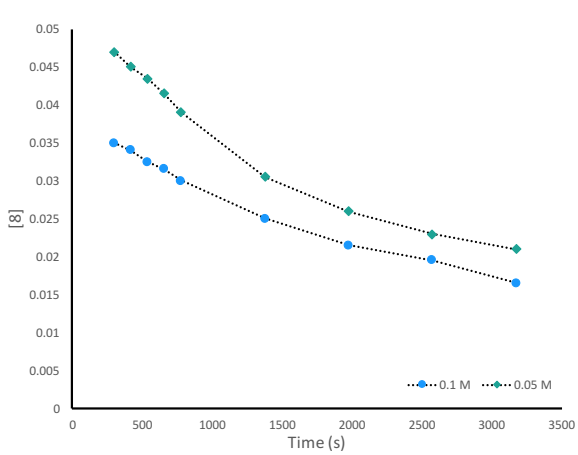
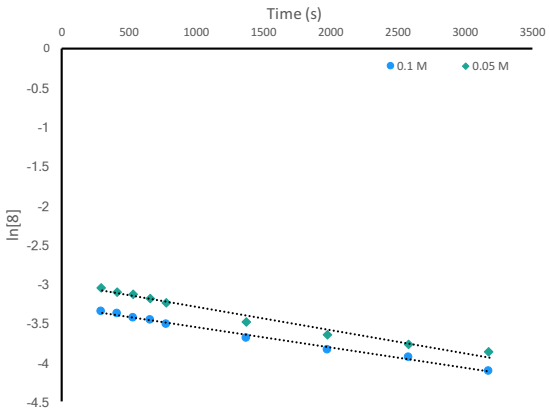


Table SI-3. Raw data for impact of [**65h**] on rate of reaction

0.05 M **65h**			0.10 M **65h**		
Time (s)	[**64a**] (M)	ln[**64a**]	Time (s)	[**64a**] (M)	ln[**64a**]
300	0.0350	-3.35240	300	0.0470	-3.05760
420	0.0340	-3.38139	420	0.0450	-3.10109
540	0.0325	-3.42651	540	0.0435	-3.13499
660	0.0315	-3.45776	660	0.0415	-3.18206
780	0.0300	-3.50655	780	0.0390	-3.24419
1380	0.0250	-3.68887	1380	0.0305	-3.49002
1980	0.0215	-3.83970	1980	0.0260	-3.64965
2580	0.0195	-3.93734	2580	0.0230	-3.77226
3180	0.0165	-4.10439	3180	0.0210	-3.86323





Trendline data for ln[**64a**] vs time for effect of **65h**

	0.05 M **65h**	0.10 M **65h**
Slope	-0.000365	-0.000295
Y-intercept	-2.949673	-3.266180
R square	0.9926	0.9971

$$\ln\left(\frac{(\text{slope})_A}{(\text{slope})_B}\right) = y \ln\left(\frac{(\text{conc.})_A}{(\text{conc.})_B}\right)$$

$$\ln\left(\frac{-0.000365}{-0.000295}\right) = y \ln\left(\frac{0.050}{0.100}\right)$$

$$-0.2129 = -0.6931y$$

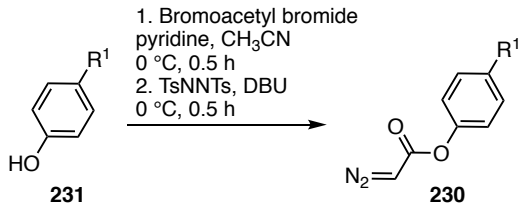
$$y = \frac{-0.2129}{-0.6931}$$

$$y = 0.30$$

Equation 1: Determination of reaction order with respect to chromanone

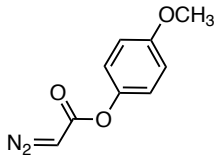
5.4 Experimental Section for Chapter Four

5.4.1 General procedure for the synthesis of phenyldiazoacetates



Following the procedure of Fukuyama bromoacetyl bromide (1.31 ml, 15 mmol) was added to a stirred solution of the appropriate phenol (10 mmol) and pyridine (1.61 ml, 20 mmol) in acetonitrile (50 ml) at 0 °C over 10 minutes. The mixture was stirred at this temperature for a further 5 minutes and then quenched with water (30 ml). The reaction mixture was extracted with methylene chloride (3 x 30 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated, and the crude residue purified via flash column chromatography. *N,N'*-Ditosylhydrazine (5.46 g, 16 mmol) was added to a solution of the phenyl bromoacetate (8 mmol) in tetrahydrofuran (40 ml) and the mixture was cooled to 0 o C. 1,8-Diazabicycloundec-7-ene (5.98 ml 40 mmol) was added dropwise over 20 minutes at this temperature. Upon completion of the addition the reaction was quenched by the addition Na_2CO_3 (30 ml of a saturated aqueous solution). The reaction mixture was extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated, and the crude residue purified via flash column chromatography.

4-Methoxyphenyl 2-diazoacetate (230a)



Following the general procedure the title compound was prepared in 78% yield.

R_f 0.3 (1:3, v/v EtOAc : hexanes)

IR ν_{max} 3105, 2111, 1698, 1500, 1332, 1178 cm^{-1}

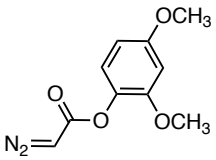
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (AA'BB', J = 9.0 Hz, 2H), 6.89 (AA'BB', J = 9.0 Hz, 2H), 4.97 (brs, 1H), 3.80 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 157.3, 138.7, 122.4, 114.4, 55.6, 46.3

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_9H_8N_2O_3$, 215.0426, requires 215.0427

Spectroscopic data was consistent with the literature.[29]

2,4-Dimethoxyphenyl 2-diazoacetate (230b)



Following the general procedure the title compound was prepared in 72% yield.

R_f 0.3 (1:1, v/v EtOAc : hexanes)

IR ν_{max} 3113, 2110, 1701, 1504, 1364, 1139 cm^{-1}

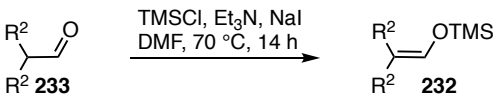
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 9.0 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.43 (dd, J = 9.0, 2.5 Hz, 1H), 4.98 (brs, 1H), 3.80 (s, 3H), 3.79 (s, 3H)

^{13}C NMR (100 MHz, CDCl3) δ 173.1, 158.4, 151.9, 133.0, 123.0, 103.8, 100.0, 55.7, 55.5, 48.7

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{10}H_{10}N_2O_4$, 245.0536, requires 245.0533

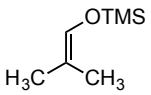
Spectroscopic data was consistent with the literature.[29]

5.4.2 General procedure for the synthesis of TMS enol ethers



Following a modified procedure described by Tamaru[30] to a solution of the appropriate aldehyde **233** (10 mmol), in hexanes (30 mL) was added triethylamine (2.09 mL, 15 mmol) and chlorotrimethylsilane (1.90 mL, 15 mmol) and the reaction mixture was heated to 50 °C and stirred for 16 hours. The resulting white suspension was filtered through Celite®, washed with n-hexanes (3 x 20 mL), and concentrated to afford a crude liquid that was purified via distillation under high vacuum.

Trimethyl((2-methylprop-1-en-1-yl)oxy)silane (232a)



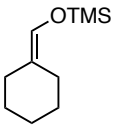
Following the general procedure the title compound was prepared in 62% yield.

IR ν_{max} 1685 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (m, 1H), 1.58 (m, 3H), 1.54 (m, 3H).

Spectroscopic data was consistent with the literature.[31]

(cyclohexylidenemethoxy)trimethylsilane (232b)



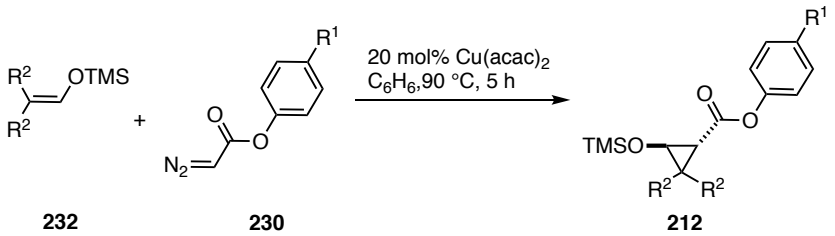
Following the general procedure the title compound was prepared in 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 2.18 - 2.15 (m, 2H), 1.95 - 1.92 (m, 2H), 1.52 - 1.46 (m, 6H), 0.16 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 130.4, 122.9, 30.9, 28.8, 27.4, 27.35, 25.7, 0.20.

Spectroscopic data was consistent with the literature.[32]

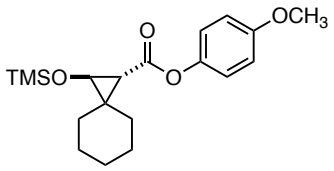
5.4.3 General procedure for the synthesis of donor-acceptor cyclopropanes



232 **230** **212**

Following the procedure of Reissig, to a stirring solution of copper(II)acetylacetone (20 mol%, 105 mg, 0.4 mmol) and the appropriate silyl enol ether **232** (4 mmol) at 90 °C was added the phenyl diazoacetate **230** (2 mmol) in benzene (4 ml) dropwise over 3 hours. Upon completion of the addition the reaction mixture was heated for a further 1 hour and then cooled to room temperature. The mixture was then concentrated and alumina (700 mg) and pentane (4 ml) added to the crude residue. The mixture was again concentrated and the resulting solid loaded onto a short (2 cm) column of Celite® and the column eluted with pentane (50 ml). The eluent is dried ($MgSO_4$), filtered, concentrated and the resultant residue purified via distillation.

(±)-4-Methoxyphenyl 2-((trimethylsilyl)oxy)spiro[2.5]octane-1-carboxylate (212a)



Following the general procedure the title compound was prepared in 68% yield as a mixture of cis and trans isomers (2:3).

IR ν_{max} 2925, 2851, 1736, 1505, 1248, 1194 1036 cm^{-1}

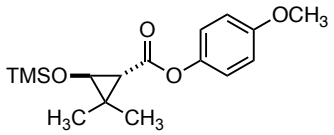
^{1}H NMR (600 MHz, $CDCl_3$) δ *trans* 6.87 (AA'BB', J = 9.5 Hz, 2H), 6.77 (AA'BB', J = 9.5 Hz, 2H), 3.79 (s, 3H), 3.76 (d, J = 3.0 Hz, 1H), 1.70-1.26 (m, 11H), 0.19 (s, 9H) *cis* 6.88 (AA'BB', J = 9.5 Hz, 2H), 6.76 (AA'BB', J = 9.5 Hz, 2H), 3.79 (s, 3H), 3.59 (d, J = 6.5 Hz, 1H), 1.70-1.26 (m, 11H), 0.17 (s, 9H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 167.9, 157.1, 156.9, 144.4(3), 144.3(6), 128.3, 122.6, 122.4, 114.4, 114.3, 64.3, 62.4, 55.5(8), 55.5(6), 38.0, 36.5, 33.6, 30.3, 29.7, 27.9, 26.4, 25.4, 25.3, 25.2, 24.6, 23.1, -0.29, -0.38 (one signal overlapping)

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{19}H_{28}O_4Si$, 371.1654, requires 371.1649

Spectroscopic data was consistent with the literature.[29]

(±)-4-Methoxyphenyl 2,2-dimethyl-3-((trimethylsilyl)oxy)cyclopropanecarboxylate (212b)



Following the general procedure the title compound was prepared in 81% yield as a mixture of cis and trans isomers (3:7).

IR ν_{max} 2954, 2851, 1738, 1503, 1379, 1193, 1105, 1063 cm^{-1}

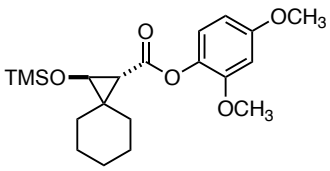
^{1}H NMR (600 MHz, $CDCl_3$) δ *trans* 6.98 (AA'BB', J = 9.0 Hz, 2H), 6.87 (AA'BB', J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.76 (d, J = 3.0 Hz, 1H), 1.67 (d, J = 3.0 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.19 (s, 9H) cis 6.99 (AA'BB', J = 9.0 Hz, 2H), 6.86 (AA'BB', J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.58 (d, J = 7.0 Hz, 1H), 1.60 (d, J = 7.0 Hz, 1H), 1.36 (s, 3H), 1.14 (s, 3H), 0.16 (s, 9H)

^{13}C NMR (150 MHz, $CDCl_3$) δ trans 170.5, 157.1, 144.3, 122.4, 114.4, 65.7, 55.6, 34.2, 30.4, 19.8, 18.2, -0.35

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{16}H_{24}O_4Si$, 331.0, requires 331.1

Spectroscopic data was consistent with the literature.[29]

(±)-2,4-Dimethoxyphenyl 2-((trimethylsilyl)oxy)spiro[2.5]octane-1-carboxylate (212c)



Following the general procedure the title compound was prepared in 41% yield as a mixture of cis and trans isomers (3:7).

IR ν_{max} 2925, 2851, 1740, 1508, 1236, 1118, 1032 cm^{-1}

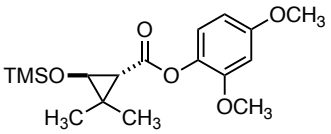
^{1}H NMR (600 MHz, $CDCl_3$) δ *trans* 6.92 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 6.42 (dd, J = 8.5, 3.0 Hz, 1H), 3.79 (s, 6H), 3.77 (d, J = 2.5 Hz, 1H), 1.69-1.28 (m, 11H), 0.20 (s, 9H) c*is* 6.92 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 6.42 (dd, J = 8.5, 3.0 Hz, 1H), 3.78 (s, 6H), 3.58 (d, J = 6.0 Hz, 1H), 1.69-1.28 (m, 11H), 0.16 (s, 9H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 158.2, 151.9, 133.7, 122.9, 103.8, 100.2, 64.4, 55.6(4), 55.5(8), 37.8, 33.4, 30.4, 27.9, 26.4, 25.4, 24.9, -0.34

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{20}H_{30}O_5Si$, 401.1, requires 401.2

Spectroscopic data was consistent with the literature.[29]

(±)-2,4-Dimethoxyphenyl 2,2-dimethyl-3-((trimethylsilyl)oxy)cyclopropanecarboxylate (212d)



Following the general procedure the title compound was prepared in 67% yield as a mixture of cis and trans isomers (1:4).

IR ν_{max} 2954, 2851, 1737, 1504, 1247, 1194, 1106, 1063 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ *trans* 6.93 (d, J = 8.5 Hz, 1H), 6.52 (s, 1H), 6.43 (d, J = 8.5 Hz, 1H), 3.76 (s, 6H), 3.76 (d, J = 3.0 Hz, 1H), 1.70 (d, J = 3.0 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.20 (s, 9H) *cis* 6.93 (d, J = 8.5 Hz, 1H), 6.52 (s, 1H), 6.43 (d, J = 8.5 Hz, 1H), 3.76 (s, 6H), 3.06 (d, 6.5 Hz, 1H), 1.66 (d, J = 6.5 Hz, 1H), 1.34 (s, 3H), 1.15 (s, 3H), 0.16 (s, 9H)

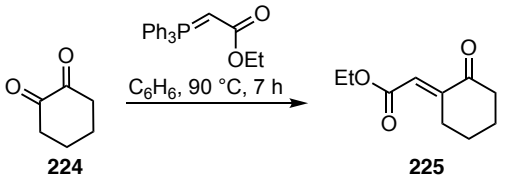
^{13}C NMR (100 MHz, $CDCl_3$) δ170.0, 158.2, 151.8, 133.8, 123.2, 103.8, 100.2, 64.7, 55.7, 55.6, 34.0, 30.1, 19.7, 18.2, -0.47

LRMS (ESI) m/z Found: (M+Na)+ , $C_{17}H_{26}O_5Si$, 361.0, requires 361.1

Spectroscopic data was consistent with the literature.[29]

5.4.4 Synthesis of α,β-unsaturated ester 225

Ethyl 2-(2-oxocyclohexylidene)acetate (225)



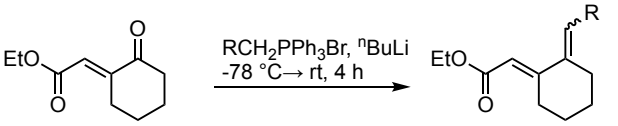
224 **225**

Following a procedure by Taylor,[33] to a solution of 1,2-cyclohexadione (3.36 g, 30 mmol) in dry benzene (120 mL) was added (carbethoxymethylene)triphenylphosphorane (15.7 g, 45 mmol), and the mixture heated to reflux for 7 h. At this time the mixture was cooled to room temperature and concentrated *in vacuo* and the resultant residue triturated in hexane to remove the triphenylphosphine oxide. The hexane extracts were combined and concentrated *in vacuo* and purified via column chromatography. All data agreed with literature values.[33]

R_f (3:7 ethyl acetate:hexanes) 0.30

IR ν_{max} 2933, 1714, 1635, 1441, 1368, 1294, 1182, 1038, 900 cm^{-1} **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.09 (td, J = 6.4 Hz, 2.0 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.92 - 1.89 (m, 2H), 1.83 - 1.77 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.6, 166.5, 151.6, 122.5, 60.9, 41.4, 29.1, 23.8, 14.5.

5.4.5 General procedure for the synthesis of dienyl esters

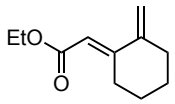


225

226, R = H
227, R = CH_3

Following a procedure by Blanchett,[34] to a suspension of methyl or ethyl triphenylphosphonium bromide (10.7 g, 30.0 mmol) in dry THF (90 mL) was added n-BuLi (18.8 mL, 30.0 mmol, 1.6 M in hexanes) at -78 °C and the mixture was stirred and allowed to warm to room temperature. After 45 minutes the homogenous mixture was cooled back down to -78 °C and the appropriate ketone or aldehyde (30.0 mmol) in THF (30 mL) was added dropwise over 10 minutes. The mixture was stirred at this temperature for a further 30 minutes before being warmed to 0 °C, quenched with water (90 mL), extracted with n-hexanes (3 x 100 mL), dried (Na2SO4), filtered and concentrated under vacuum and purified via column chromatography.

Ethyl 2-(2-methylenecyclohexylidene)acetate (226)



The title compound was prepared using a the general procedure using Ethyl triphenylphosphonium bromide in a 64% yield.

R_f 0.23 (1:19 ethyl acetate:hexanes)

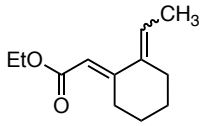
IR ν_{max} 2933, 1714, 1635, 1441, 1368, 1294, 1182, 1038, 900 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 4.99 (s, 1H), 4.76 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.92 (m, 2H) 2.33 (m, 2H) 1.69 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.04, 113.34, 111.03, 60.02, 35.70, 30.11, 26.86, 26.29, 14.67

HRMS found $(M + H)^+$ 181.1220, found $(M + Na)^+$ 203.1044, $C_{11}H_{17}O_2^+$ requires 181.1229, $C_{11}H_{17}O_2Na^+$ requires 203.1048.

Ethyl 2-(2-ethylidenecyclohexylidene)acetate (227)



The title compound was prepared using a the general procedure using Ethyl triphenylphosphonium bromide in a 49% yield as a mixture of *cis* and *trans* isomers (1:1).

R_f0.4 (1:19 ethyl acetate:hexanes)

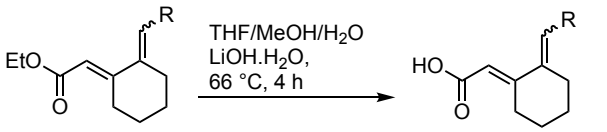
IR ν_{max} 2930, 1714, 1624, 1444, 1369, 1173, 1036 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ *A:* 5.73 (m, 1H), 5.62 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.19-2.86 (m, 2H), 2.31-2.28 (m, 2H), 1.68-1.64 (m, 7H), 1.29 (t, J = 6.8 Hz, 3H). *B:* 5.56 (m, 1H), 5.35 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.19 - 2.86 (m, 2H), 2.26 -2.23 (m, 2H), 1.68-1.64 (m, 7H), 1.28 (t, J = 6.8, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.3, 163.4, 159.5, 141.6, 141.4, 121.3, 120.2, 115.7, 112.5, 60.0, 59.9, 38.6, 31.0, 30.1, 28.5, 28.0, 27.9, 26.3, 25.9, 14.7, 13.7.

LRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{12}H_{18}O_2$, 194.2, requires 194.1.

5.4.6 General procedure for the synthesis of dienyl acids

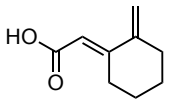


226, R = H
227, R = CH_3

228, R = H, 80%
229, R = CH_3, 88%

Following a procedure by Doering,[35] to a solution of the dienyl ester (1 equivalent, 16 mmol) in 1:1:1 MeOH:H_2O:THF (24 mL) was added LiOH.H_2O (3 equivalents, 48 mmol) and mixture heated to refluxing temperatures for 4 h. The solution was then cooled to room temperature before concentrating removing all solvents except H_2O *in vacuo*. The mixture was then extracted into CH_2Cl_2 (50 mL) before acidifying the aqueous phase with concentrated HCl. The aqueous phase was then extracted with CH_2Cl_2 (5 x 40 mL) and these organic fractions combined, dried and concentrated *in vacuo* to yield the crude product which was then purified via flash chromatography

2-(2-methylenecyclohexylidene)acetic acid (228)



Following the general procedure the title compound was prepared in 68% yield.

R_f (3:7 v/v EtOAc:hexanes) 0.3.

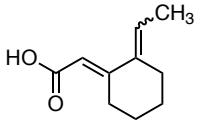
IR ν_{max} 2932, 1668, 1610, 1408, 4597, 1230, 896 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.02 (s, 1H), 4.80 (s, 1H), 2.94 (m, 2H), 2.34 (m, 2H), 1.69 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.9, 112.5, 111.7, 98.8, 35.6, 30.3, 26.8, 26.2.

HRMS (ESI) m/z Found: $(M-H)^-$, $C_9H_{12}O_2$ 151.0763, requires, 151.0756.

2-(2-ethylidenecyclohexylidene)acetic acid (229)



Following the general procedure the title compound was prepared in 88% yield as a mixture of *cis* and *trans* isomers (1:1).

R_f 0.3 (3:7 v/v hexanes : ethyl acetate).

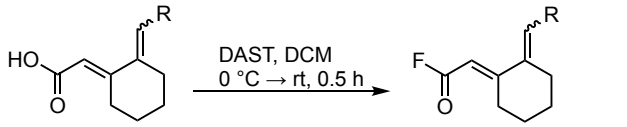
IR ν_{max} 2928, 2856, 1677, 1615, 1409, 1285, 1207 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ *A:* 5.77 (m, 1H), 5.68 (m, 1H), 2.91-2.87 (m, 2H), 2.33-2.30 (m, 2H), 1.73-1.65 (m, 7H). *B:* 5.60 (m, 1H), 5.39 (m, 1H), 2.91-2.87 (m, 4H), 2.28-2.24 (m, 2H), 1.73-1.65 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 141.5, 141.3, 134.2, 134.0, 132.5, 132.4, 128.9, 128.8, 38.6, 31.3, 30.3, 28.4, 27.9, 26.2, 25.8, 14.7, 13.8.

HRMS (ESI) m/z found: $(M-H)^-$ 165.0911. $C_{10}H_{14}O_2^-$ requires 165.0921.

5.4.7 General procedure for the synthesis of dienyl acyl fluorides

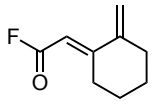


228, R = H
229, R = CH_3

218, R = H, 74%
223, R = CH_3, 80%

To a stirring solution of the appropriate dienyl acid (0.620 g, 5.00 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added diethylaminosulfur trifluoride (0.73 mL, 5.50 mmol, 1.1 eq.). The resulting solution was stirred for 45 minutes before quenching with saturated aqueous $NaHCO_3$. The organic layer separated and the aqueous layer extracted with DCM (2 x 10 mL). The organic layers were combined and dried over sodium sulphate and concentrated on a rotary evaporator at 50 °C at atmospheric pressure. The crude residue was purified via distillation under high vacuum to give the desired acyl fluoride

2-(2-methylenecyclohexylidene)acetyl fluoride (218)



Following the general procedure the title compound was prepared in a 91% yield and stored in a plastic vial at -20 °C to help prevent decomposition.

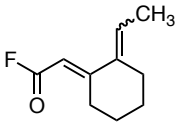
IR ν_{max} 2937, 2863, 1798, 1608, 1439, 1089, 905, 869 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.80 (m, 1H), 5.11-5.08 (m, 1H), 4.91-4.88 (m, 1H), 2.95–2.87 (m, 2H), 2.42-2.34 (m, 2H), 1.80-1.66 (m, 4H) ppm

^{13}C NMR (101 MHz, CDCl3) δ 170.1 (d, J = 12.1 Hz), 156.3 (d, J = 224.2 Hz), 148.7 (d, J = 3.0 Hz), 113.0, 107.4 (d, J = 52.5 Hz), 35.2, 30.6, 26.2, 25.8 ppm

LRMS (EI) m/z Found: $(M)^+$, $C_9H_{11}FO$, 154.1, requires 154.1.

2-(2-ethylidenecyclohexylidene)acetyl fluoride (223)



Following the general procedure the title compound was prepared in a 48% yield as a mixture of *cis* and *trans* isomers (1:1).

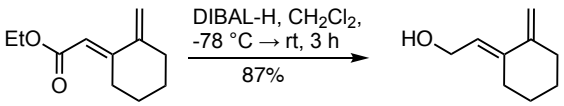
IR ν_{max} 2959, 1801, 1611, 1259, 1091, 1016, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ *A:* 5.78 (m, 1H), 5.71 (m, 1H), 2.90-2.84 (m, 2H), 2.35-2.28 (m, 2H), 1.78-1.65 (m, 7H). *B:* 5.55 (m, 1H), 5.47 (m, 1H), 2.90-2.84 (m, 4H), 2.35-2.28 (m, 2H), 1.78-1.65 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.03, 157.78, 155.43, 155.10, 124.37, 122.28, 110.32, 109.74, 106.81, 106.22, 38.36, 31.81, 30.78, 28.15, 27.49, 25.73, 25.27, 14.76, 13.92.

5.4.8 Synthesis of dienal 261

(*E*)-2-(2-methylenecyclohexylidene)ethan-1-ol (262)

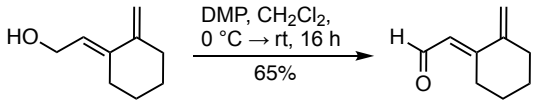


226 **262**

To a solution of ester # (0.585 g, 3.25 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added DIBAL-H (8.13 mL of a 1.0 M in toluene, 8.125 mmol, 2.5 equivalents) dropwise. This mixture was stirred for 3 hours and allowed to slowly warm to room temperature. After completion, the reaction was diluted with ether (20 mL) and 1 mL of NaOH (15 % solution) was added slowly followed by 2 mL of water and the resulting slurry was stirred for 15 mins. This mixture was then filtered through a bed of celite, dried over sodium sulfate, and concentrated under reduced pressure to give the title compound which was essentially pure and used without purification (0.400 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72-5.59 (m, 1H), 4.93-4.83 (m, 1H), 4.63 (dd, J = 2.5, 1.4 Hz, 1H), 4.20 (dd, J = 6.8, 5.8 Hz, 2H), 3.44-3.37 (m, 1H), 2.31-2.20 (m, 4H), 1.69-1.58 (m, 4H) ppm

(*E*)-2-(2-methylenecyclohexylidene)acetaldehyde (261)

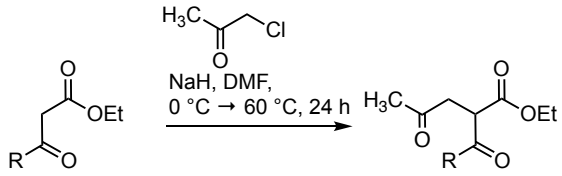


262 **261**

To a solution of the alcohol # (0.400 g, 2.77 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Dess-Martin Periodinane (1.27 g, 3.00 mmol, 1.1 equiv) in one portion. The suspension was slowly warmed to room temperature and stirred for 16 h. The mixture was filtered through a plug of silica over a pad of celite (washed through with 3 x 20 mL of CH_2Cl_2), then quenched with saturated sodium bicarbonate (6 mL). The phases were separated and the organic layer was washed with sodium bicarbonate (2 x 10 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, filtered through celite, and concentrated under reduced pressure. Flash chromatography (CH_2Cl_2) provided the volatile dienal (0.244 g, 65%). This dienal is prone to very fast decomposition when concentrated and as such was used fresh and stored as a solution in DCM if needed.

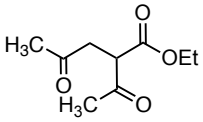
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (d, *J* = 8.2 Hz, 1H), 6.02 (dt, *J* = 8.2, 1.5 Hz, 1H), 5.16-5.02 (m, 1H), 4.97-4.84 (m, 1H), 2.91-2.71 (m, 2H), 2.48-2.30 (m, 2H), 1.88-1.64 (m, 4H).

5.4.9 General procedure for the synthesis of β-ketoesters and malonates



Following a modified procedure by Romo,[36] Sodium Hydride (0.51g of 60% NaH in mineral oil, 12.8 mmol) was added to a flame dried RBF followed by anhydrous DMF (24 mL) and the mixture was stirred and cooled to 0 °C. Ethyl acetoacetate (1.53 mL, 12.0 mmol) was added dropwise and allowed to stir for 15 minutes. Chloroacetone (2.88 mL, 35.8 mmol, 3.0 eq.) and the reaction was heated to 50 °C for 24 hours. After this time, the reaction was cooled to ambient temperature and quenched with saturated ammonium chloride. The mixture was extracted with ethyl acetate (4 x 20 mL) and then washed with water (20 mL) and brine (20 mL). The organic layers were combined and dried over sodium sulphate, filtered, concentrated and purified by flash column chromatography 1:4 EtOAc : hexanes) to give the desired product.

Ethyl 2-acetyl-4-oxopentanoate (237)



Following the general procedure the title compound was prepared in 40% yield as a colourless oil.

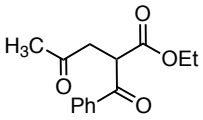
R_f 0.2 (80:20 v/v hexanes : ethyl acetate).

IR ν_{max} 2984, 1739, 1711, 1359, 1259, 1157, 1019, 866, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.99 (dd, *J* = 5.7, 8.2, 1H), 3.12 (dd, *J* = 6.9, 18.5, 1H), 2.93 (dd, *J* = 6.9, 18.5, 1H), 2.33 (s, 3H), 1.26 (1, *J* = 7.1, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 202.3, 168.9, 61.8, 53.9, 41.6, 30.2, 29.8, 14.1.

Ethyl 2-benzoyl-4-oxopentanoate (237a)



Following the general procedure the title compound was prepared in 55% yield as a colourless oil.

R_f 0.3 (80:20 v/v hexanes : EtOAc)

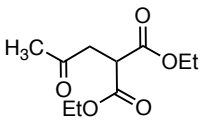
IR ν_{max} 2983, 2939, 1735, 1717, 1683, 1267, 1237, 1156, 689 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.93 (m, 2H), 7.61–7.51 (m, 1H), 7.46-7.41 (m, *J* = 7.3, 1.4 Hz, 2H), 4.87 (t, *J* = 6.3 Hz, 1H), 4.09 (qt, *J* = 7.1, 1.2 Hz, 2H), 3.26–3.04 (m, 2H), 2.1 (s, 3H), 1.11 (tt, *J* = 7.1, 1.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 194.6, 169.2, 136.0, 133.6, 128.7 (2), 128.7 (0), 61.7, 48.9, 42.3, 29.8, 13.9 ppm (1 peak missing or overlapping)

HRMS (ESI) m/z Found: (M+H)+, C14H16O4, 249.1121, requires 249.1117.

Diethyl 2-(2-oxopropyl)malonate (250)



Following the general procedure the title compound was prepared in 59% yield as a colourless oil.

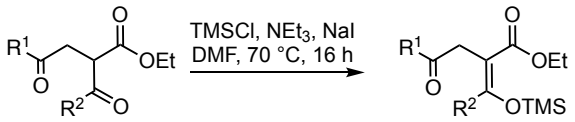
R_f 0.2 (80:20 v/v hexanes : ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (dq, *J* = 7.2, 2.4 Hz, 4H), 3.79 (t, *J* = 7.2 Hz, 1H), 2.98 (d, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 169.4, 61.5, 47.2, 42.1, 29.6, 14.1 ppm

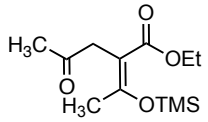
Spectroscopic data was consistent with the literature.[37]

5.4.10 General procedure for the synthesis of TMS enol ethers



Following a modified procedure described by Tamaru,18 to a solution of the appropriate β-ketoester (10 mmol), in *n*-hexanes or benzene (30 mL) was added triethylamine (2.09 mL, 15 mmol) and chlorotrimethylsilane (1.90 mL, 15 mmol) and the reaction mixture was heated to 50 °C and stirred for 16 hours. The resulting white suspension was filtered through Celite®, washed with *n*-hexanes (3 x 20 mL), and concentrated to afford a crude liquid that was purified *via* distillation under high vacuum.

Ethyl 4-oxo-2-(1-((trimethylsilyl)oxy)ethylidene)pentanoate (240)



Following the general procedure the title compound was prepared in 45% yield as a colourless oil.

IR νmax 2960, 1700, 1651, 1249, 1106, 1018, 838 cm-1

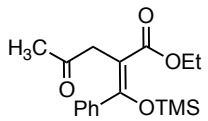
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.2 Hz, 2H), 2.84 (m, 2H), 2.20 (t, *J* = 1.6 Hz, 3H), 1.56 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.14 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.6, 108.1, 100.3, 58.0, 43.0, 27.6, 13.0, 12.9, 0.02.

HRMS (ESI) *m/z* Found: (M+H)+, C12H22O4Si, 259.1348, requires 259.1360.

Spectroscopic data was consistent with the literature.[38]

Ethyl (*Z*)-4-oxo-2-(phenyl((trimethylsilyl)oxy)methylene)pentanoate (244)



Following the general procedure the title compound was prepared in 78% yield as a colourless oil.

IR νmax 2958, 1703, 1624, 1245, 1107, 1011, 841 cm-1

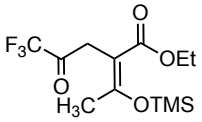
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.42-7.37 (m, 3H) 4.14 (q, *J* = 7,1 Hz, 2H) 3.10 (s, 3H), 1.67 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.16 (s, 9H) ppm

^{13}C NMR (100 MHz, CDCl3) δ 165.3, 162.3, 129.4, 127.8, 109.0, 102.3, 59.9, 46.4, 29.2, 14.4, 1.7 ppm (2 peaks missing or overlapping)

HRMS (ESI) *m/z* Found: (M+H)+, C17H24O4Si, 321.15.14, requires 321.1517.

Spectroscopic data was consistent with the literature.[38]

Ethyl (E)-5,5,5-trifluoro-4-oxo-2-(1-((trimethylsilyl)oxy)ethylidene)pentanoate (248)



Following the general procedure the title compound was isolated in a 74% yield as a colourless liquid

R_f 0.6 (80:20 v/v hexanes : ethyl acetate)

IR ν_{max} 2963, 1703, 1627, 1389, 1327, 1254, 1198, 1153, 1110, 1090, 1060, 1021, 960, 900, 841, 756, 690 cm^{-1}

^{1}H NMR (400 MHz, CDCl3) δ 4.54 (d, J = 11.6 Hz, 1H), 4.31-4.23 (m, 2H), 4.18- 4.10 (m, 1H), 2.30 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.11 (s, 9H) ppm

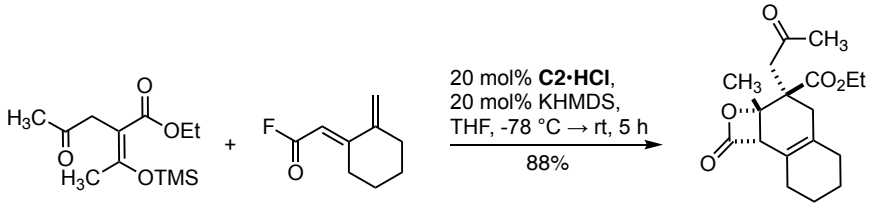
^{13}C NMR (151 MHz, CDCl3) δ 176.0, 164.2, 124.4 (q, J = 282 Hz), 104.2, 85.4 (q, J = 32 Hz), 75.0 (q, J = 2 Hz), 60.0, 15.5, 14.2, 1.25 ppm

HRMS (ESI) m/z Found: (M+Na)+ , $C_{12}H_{19}F_3NaO_4Si$, 335.0906, requires 335.0902.

Spectroscopic data was consistent with the literature.[38]

5.4.11 Synthesis of cyclohexene β-lactone 243

Ethyl 2a-methyl-1-oxo-3-(2-oxopropyl)-2a,3,4,5,6,7,8,8b-octahydro-1*H*-naphtho[2,1-*b*]oxete-3-carboxylate (243)



Following a modified procedure by Lupton,[38] IMes.HCl (6.8 mg, 0.02 mmol) was added to a flame dried flask under a flow of nitrogen. To this, tetrahydrofuran (2 mL) was added followed by potassium hexamethyldisilazide (0.04 mL of a 0.5M solution in toluene, 0.02 mmol) and the solution was left to stir for 15 minutes. In a second flask, a solution of the silyl enol-ether **#** (26 mg, 0.1 mmol) and the acyl fluoride **#** (15.4 mg, 0.1 mmol) in tetrahydrofuran (2 mL) was stirred over activated 4Å molecular sieves for 30 minutes. This mixture was then cooled to -78 °C before adding the catalyst solution dropwise. The cooling bath was allowed to warm slowly to room temperature as the reaction stirred for 5 hours. The reaction mixture was concentrated and purified by flash column chromatography (1:4 v/v EtOAc : hexanes) to give the product in a 88% yield (31 mg, 0.098 mmol) as a single diastereomer as observed by ^{1}H NMR (>20:1 dr).

R_f 0.3 (80:20 v/v hexanes : ethyl acetate).

IR ν_{max} 2932, 2853, 1814, 1720, 1444, 1363, 1298, 1194, 1096, 1030 cm^{-1}.

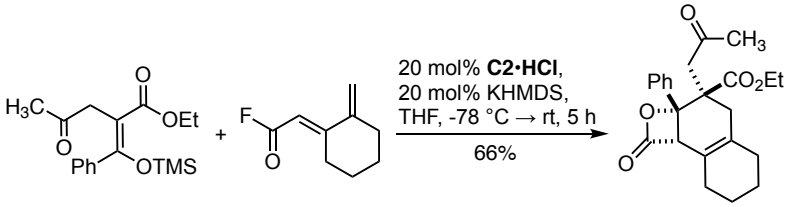
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10-4.05 (m, 2H), 3.53 (s, 1H), 3.14 (d, *J* = 18.4 Hz, 1H), 2.38-2.23 (m, 2H), 2.17-2.10 (m, 1H), 2.14 (s, 3H), 1.97-1.85 (m, 3H), 1.63 (s, 3H), 1.62-1.52 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 172.1, 167.9, 130.3, 122.7, 81.4, 61.2, 61.0, 48.2, 46.2, 36.7, 30.6, 30.5, 29.0, 23.5, 22.7, 22.5, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{18}H_{24}O_5$, 321.1688, requires 321.1697.

5.4.12 Synthesis of cyclohexene β-lactone 245

Ethyl (2a*R*,3*R*,8b*S*)-1-oxo-3-(2-oxopropyl)-2a-phenyl-2a,3,4,5,6,7,8,8b-octahydro-1*H*-naphtho[2,1-*b*]oxete-3-carboxylate (245)



Following a modified procedure by Lupton,[38] IMes.HCl (6.8 mg, 0.02 mmol) was added to a flame dried flask under a flow of nitrogen. To this, tetrahydrofuran (2 mL) was added followed by potassium hexamethyldisilazide (0.04 mL of a 0.5M solution in toluene, 0.02 mmol) and the solution was left to stir for 15 minutes. In a second flask, a solution of the silyl enol-ether **#** (32 mg, 0.1 mmol) and the acyl fluoride **#** (15.4 mg, 0.1 mmol) in tetrahydrofuran (2 mL) was stirred over activated 4Å molecular sieves for 30 minutes. This mixture was then cooled to -78 °C before adding the catalyst solution dropwise. The cooling bath was allowed to warm slowly to room temperature as the reaction stirred for 5 hours. The reaction mixture was concentrated and purified by flash column chromatography (1:4 v/v EtOAc : hexanes) to give the product in a 66% yield (25 mg, 0.066 mmol) as a single diastereomer as observed by ^{1}H NMR (>20:1 dr).

R_f 0.35 (80:20 v/v hexanes : EtOAc)

MP 89-91 °C

IR ν_{max} 2929, 1828, 1720, 1362, 1206, 900, 729, 702 cm^{-1}

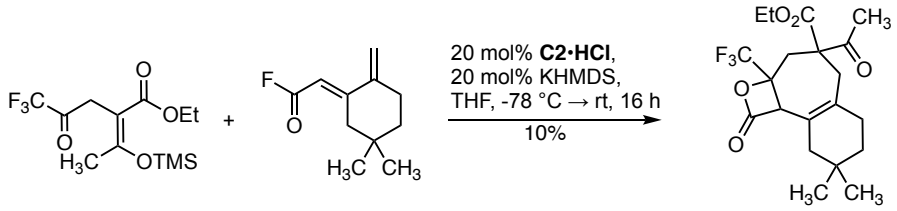
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 3H), 7.25-7.22 (m, 2H), 3.98 (s, 1H), 3.79 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.67 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.33 (ABq, *J* = 18.2 Hz, 1H), 2.90-2.85 (m, 1H), 2.83 (ABq, *J* = 18.2 Hz, 1H), 2.30-2.11 (m, 3H), 2.09 (s, 3H), 2.07-1.96 (m, 2H), 1.79-1.64 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 170.2, 166.5, 137.7, 131.5, 127.4, 127.0, 125.5, 119.6, 81.9, 61.3, 59.8, 50.0, 42.0, 33.1, 29.9, 29.7, 27.5, 21.8, 21.7, 12.7 ppm

HRMS (ESI) *m/z* Found: (M+H)+, $C_{23}H_{26}O_5$, 383.1852, requires 383.1852.

5.4.13 Synthesis of cycloheptene β-lactone 253

Ethyl 4-acetyl-8,8-dimethyl-1-oxo-2a-(trifluoromethyl)-1,2a,3,4,5,6,7,8,9,9b-decahydrobenzo[3,4]cyclohepta[1,2-*b*]oxete-4-carboxylate (253)



248 **252** **253**

To a flame-dried reaction vial containing ##•HBF_4 (7.7 mg, 0.02 mmol) in THF (1 mL) was added potassium bis(trimethylsilyl)amide (0.04 mL, 0.02 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. To this was added a solution of the appropriate TMS enol ether (31 mg, 0.1 mmol) and acyl fluoride (15.4 mg, 0.1 mmol) in THF (1 mL). The reaction mixture was stirred at reflux overnight. The mixture was concentrated in vacuo and the crude residue was purified via column chromatography. The title compound was prepared in a 10% yield (3.7 mg, 0.01 mmol) as a single diastereoisomer (>20:1) as observed by ^{1}H NMR.

R_f 0.3 (95:5 v/v hexanes : ethyl acetate)

HPLC Daicel OJ-H, hexane : *i*PrOH 99:1, 1 ml/min, λ = 254 nm, fraction t_r = 5.56 (major enantiomer) and 7.15 (minor enantiomer); er = 55:45

IR ν_{max} 2927, 2856, 1810, 1708, 1449, 1367, 1259, 1217, 1151, 1078, 1037, 1015, 705, 725 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.52 (br s, 1H), 4.85-4.75 (m, 2H), 4.63 (d, J = 12.0, Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.28-4.08 (m, 2H), 3.23 (ABq, J = 18.0 Hz, 1H), 3.19 (ABq, J = 18.0 Hz, 1H), 2.42-2.36 (m, 2H), 2.31 (s, 3H), 1.59-1.49 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.032 (s, 3H), 1.027 (s, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 169.9, 163.4, 142.9, 127.2, 123.5 (q, J = 282 Hz) , 108.2, 98.7, 88.5 (q, J = 33 Hz), 74.1, 60.0, 40.0, 37.0, 33.0, 29.0, 28.99, 28.95, 15.4, 14.3, 14.2 ppm

HRMS (ESI) m/z Found: (M+H)+ , $C_{20}H_{25}F_3O_5$, 403.1729, requires 403.1727.

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Appendix 1
X-Ray Crystal Structures

Ethyl (2aR,3R,8bS)-1-oxo-3-(2-oxopropyl)-2a-phenyl-2a,3,4,5,6,7,8,8b-octahydro-1H-naphtho[2,1-b]oxete-3-carboxylate

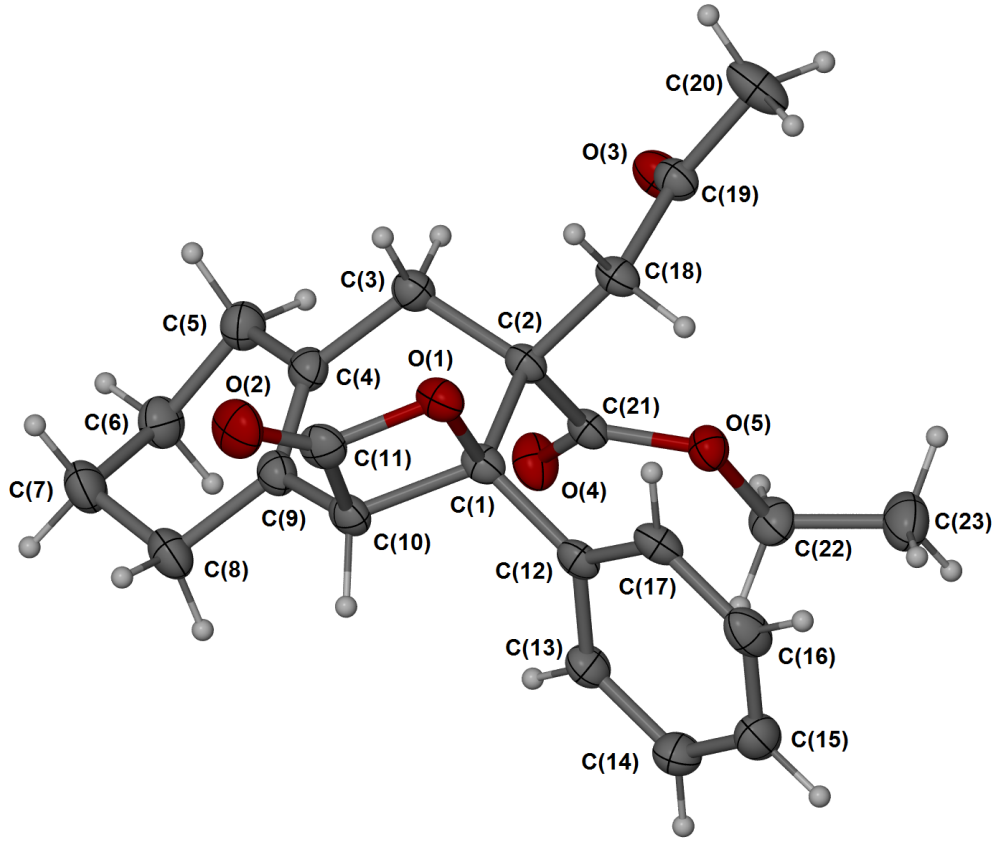

Figure A1 | *Molecular diagram of x*

Table A1 Crystal data and structure refinement for **x**

Identification code	shelx
Empirical formula	C23 H26 O5
Formula weight	382.44
Temperature	123(2) K
Wavelength	1.54184 A
Crystal system,	Triclinic
Space group	P-1
a/Å	8.7327(3)
b/Å	10.5796(4)
c/Å	12.7344(4)
α/°	114.007(4)
β/°	92.435(3)
γ/°	109.582(4)
Volume/Å^3	990.47(7)
Z	2
P_{calc}g/cm^3	1.282
μ/mm^{-1}	0.728
F(000)	408
Crystal size/mm^3	0.25 x 0.13 x 0.08
2Θ range for data collection/°	3.885 to 66.890
Limiting indices	-10<=h<=10, -12<=k<=12, -14<=l<=15
Reflections collected	14172
Independent reflections	3513 [R_{int} = 0.0209]
Data / restraints / parameters	3513 / 0 / 274
Goodness-of-fit on F^2	1.043
Final R indices [I >2σ (I)]	R_1 = 0.0360, wR_2 = 0.0917
Final R indices [all data]	R_1 = 0.0382, wR_2 = 0.0940
Largest diff. peak/hole/ e Å^{-3}	0.266 and -0.180

Table A2 Bond lengths (Å) for **x**

O(1)-C(11)	1.3733(16)
O(1)-C(1)	1.4994(14)
O(2)-C(11)	1.1906(16)
O(3)-C(19)	1.2102(15)
O(4)-C(21)	1.2008(15)
O(5)-C(21)	1.3369(15)
O(5)-C(22)	1.4551(15)
C(1)-C(12)	1.5024(17)
C(1)-C(10)	1.5599(16)
C(1)-C(2)	1.5612(16)
C(2)-C(21)	1.5337(16)
C(2)-C(18)	1.5380(16)
C(2)-C(3)	1.5398(17)
C(3)-C(4)	1.5088(17)
C(4)-C(9)	1.3345(18)
C(4)-C(5')	1.5030(18)
C(4)-C(5)	1.5030(18)
C(5)-C(6)	1.510(2)
C(5')-C(6')	1.656(13)
C(6)-C(7)	1.526(4)
C(6')-C(7')	1.49(2)
C(7)-C(8)	1.540(3)
C(7')-C(8')	1.402(11)
C(8)-C(9)	1.5072(17)
C(8')-C(9)	1.5072(17)
C(9)-C(10)	1.4991(18)
C(10)-C(11)	1.5199(18)
C(12)-C(13)	1.3940(17)
C(12)-C(17)	1.3943(17)
C(13)-C(14)	1.3834(19)
C(14)-C(15)	1.3851(19)
C(15)-C(16)	1.384(2)
C(16)-C(17)	1.3862(19)
C(18)-C(19)	1.5167(16)
C(19)-C(20)	1.5029(18)
C(22)-C(23)	1.492(2)

Table A3 Bond angles (°) for **x**

C(11)-O(1)-C(1)	91.40(9)
C(21)-O(5)-C(22)	115.80(9)
O(1)-C(1)-C(12)	109.88(9)
O(1)-C(1)-C(10)	89.09(8)
C(12)-C(1)-C(10)	114.83(10)
O(1)-C(1)-C(2)	108.23(9)
C(12)-C(1)-C(2)	115.35(10)
C(10)-C(1)-C(2)	115.94(10)
C(21)-C(2)-C(18)	110.45(9)
C(21)-C(2)-C(3)	109.43(10)
C(18)-C(2)-C(3)	110.35(10)
C(21)-C(2)-C(1)	108.17(9)
C(18)-C(2)-C(1)	108.65(9)
C(3)-C(2)-C(1)	109.75(9)
C(4)-C(3)-C(2)	114.68(10)
C(9)-C(4)-C(5')	122.45(11)
C(9)-C(4)-C(5)	122.45(11)
C(9)-C(4)-C(3)	120.77(11)
C(5')-C(4)-C(3)	116.78(11)
C(5)-C(4)-C(3)	116.78(11)
C(4)-C(5)-C(6)	113.74(12)
C(4)-C(5')-C(6')	106.9(4)
C(5)-C(6)-C(7)	109.7(2)
C(7')-C(6')-C(5')	114.6(12)
C(6)-C(7)-C(8)	110.81(18)
C(8')-C(7')-C(6')	106.6(12)
C(9)-C(8)-C(7)	111.49(12)
C(7')-C(8')-C(9)	117.1(5)
C(4)-C(9)-C(10)	119.90(11)
C(4)-C(9)-C(8)	123.40(12)
C(10)-C(9)-C(8)	116.70(11)
C(4)-C(9)-C(8')	123.40(12)
C(10)-C(9)-C(8')	116.70(11)
C(9)-C(10)-C(11)	115.40(10)
C(9)-C(10)-C(1)	118.91(10)
C(11)-C(10)-C(1)	83.84(9)
O(2)-C(11)-O(1)	125.97(12)
O(2)-C(11)-C(10)	138.37(13)
O(1)-C(11)-C(10)	95.65(9)
C(13)-C(12)-C(17)	118.96(12)
C(13)-C(12)-C(1)	119.64(11)
C(17)-C(12)-C(1)	121.40(11)
C(14)-C(13)-C(12)	120.59(12)

C(13)-C(14)-C(15)	119.87(12)
C(16)-C(15)-C(14)	120.21(13)
C(15)-C(16)-C(17)	119.97(12)
C(16)-C(17)-C(12)	120.38(12)
C(19)-C(18)-C(2)	115.33(10)
O(3)-C(19)-C(20)	121.63(11)
O(3)-C(19)-C(18)	123.07(11)
C(20)-C(19)-C(18)	115.30(11)
O(4)-C(21)-O(5)	123.73(11)
O(4)-C(21)-C(2)	124.27(11)
O(5)-C(21)-C(2)	111.97(10)
O(5)-C(22)-C(23)	107.47(11)

Appendix 2
Publications from Doctoral Studies

Review

Israel Journal of Chemistry

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All-carbon N-heterocyclic Carbene-catalyzed (3+2) Annulation using Donor-Acceptor Cyclopropanes

Lisa Candish, Rachel M. Gillard, Jared E. M. Fernando, Alison Levens, and David W. Lupton*[a]

To Professors Martin G. Banwell and Dennis K. Taylor for their Introduction to the Chemistry of Cyclopropanes

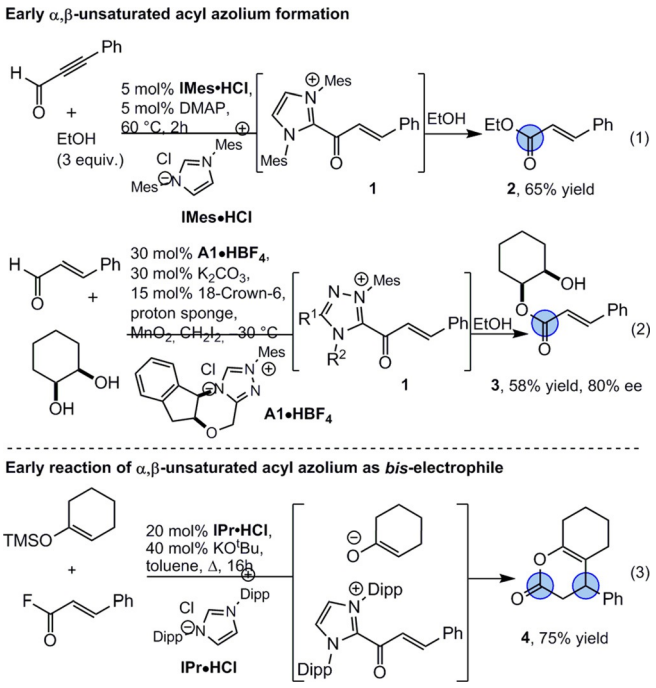
Abstract: Donor-acceptor cyclopropanes are known to serve as dipole precursors capable of engaging in (3+2) annulations with electron-deficient π-systems. In 2013, the reaction of donor-acceptor cyclopropanes with α,β-unsaturated acyl fluorides in an all-carbon (3+2) annulation was discovered. The reaction proceeds in good yields using the IMes NHC to provide diastereomerically pure β-lactone-fused cyclopentanes bearing four contiguous stereocentres. Subsequent studies demonstrated that N-*t*-butyl substituted homochiral morpholinone NHCs allowed the reaction to be achieved in up to 98% *ee*. In this account, a background to this reaction is introduced, along with a complete account of the strengths, limitations and challenges encountered while developing this chemistry.

Keywords: annulation · cyclopentane · donor-acceptor cyclopropanes · enantioselectivity · N-heterocyclic carbene

1. Introduction

The α,β-unsaturated acyl azolium intermediate (i.e., **1**) has emerged as an important intermediate in modern N-heterocyclic carbene (NHC) organocatalysis.[1] In the mid-2000s, Zeitler and Scheidt independently reported the preparation of this intermediate (Scheme 1, Eqs. 1 and 2) and its conversion to the corresponding esters (i.e., **2** and **3**).[2,3] However, it was not until 2009 that studies from our group allowed the development of reactions that involve C–C bond formation β- to the carbonyl group (Eq. 3) to provide pyranone products (i.e., **4**).[4] The reaction shown can be considered as proceeding via either a Claisen-type mechanism, or a Michael addition, with the specifics likely determined by the substrate. Following these studies, a host of reactions that formally involve the introduction of a nucleophile to the β-carbon and a second nucleophile to the acyl group have been communicated, with early studies from Bode,[5] Studer[6] and Xiao.[7]

Evident in all initial studies on the α,β-unsaturated acyl azolium was the underutilised nature of the acyl azolium enolate (i.e., **5**). This intermediate is known to engage in C–C bond-forming reactions, but was simply being protonated to yield the second nucleophilic motif and acyl azolium **6** (Scheme 2). Our first attempts to exploit acyl azolium enolate **5** in C–C bond-forming chemistry culminated in an all-carbon (4+2) annulation[8] (*vide infra*), while more recently, we have exploited this intermediate in an enantioselective (3+2) annulation.[9] Pivotal to the success of this later reaction was the use of donor-acceptor cyclopropanes.



Scheme 1. Early studies with α,β-unsaturated acyl azoliums.

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In this personal account, an introduction to NHC-catalyzed cascades that exploit the α,β-unsaturated acyl azolium and the acyl azolium enolate are reported.

Fluoride-mediated ring opening of donor-acceptor cyclopropanes, and the application of donor-acceptor cyclopropanes in annulations are described. In addition, the discovery of the enantioselective NHC-catalyzed synthesis of cyclopentanes via a (3+2) annulation with donor-acceptor cyclopropanes is discussed, as are related reaction discoveries that use donor-acceptor cyclopropane surrogates.

2. Reactions Exploiting the Acyl Azolium and Acyl Azolium Enolate

2.1 (4+2) Annulation by Vinylogous Michael/Aldol/Lactonisation/Decarboxylation

In 2011, studies from our group demonstrated that the α,β-unsaturated acyl azolium could engage in reaction cascades exploiting acyl azolium enolate **5a** (Scheme 3).[8] Specifically, this was possible with TMS dienol ether **7** and α,β-unsaturated acyl fluoride **8**. Upon exposure to suitable NHCs, loss of TMS-F gave the α,β-unsaturated acyl azolium **1a** and dienolate **9**. Vinylogous Michael addition then provided acyl azolium enolate **5a**, which cyclises with the unmasked ketone functionality to avail β-lactone intermediates, which undergo decarboxylation to yield diene **10** (Scheme 3). The discovery of this reaction was fraught with challenges with chemoselectivity;[10] however, it also demonstrated NHC-triggered fluoride-mediated desilylation as a powerful approach to unmasking latent functionality.[11] While we had used this type of strategy in related transformations,[4] its realisation in this context would provide significant inspiration for the development of the (3+2) annulation.

Lisa Candish graduated with a B.Sc. (Honours, 1st class) in 2009, majoring in chemistry, before completing a Ph.D. at Monash University under the supervision of Assoc. Professor Lupton in 2014. Her studies focused on acyl anion-free reactions using NHC catalysis and the synthesis of natural products. In 2014, she commenced postdoctoral studies in the group of Professor Dr. Frank Glorius, Westfälische Wilhelms-Universität Münster, as a von Humboldt fellow.

Rachel M. Gillard completed a Bachelor of Science at the University of Auckland before graduating with Honours (1st class) in medicinal chemistry in 2014, under the supervision of Dr. Jonathan Sperry. In 2015, she commenced studies towards a Doctorate of Philosophy under the supervision of Assoc. Professor David W. Lupton. Her studies are focused on natural product synthesis utilizing NHC catalysis.

Jared E. M. Fernando completed a B.Sc. at Monash University, majoring in chemistry and astrophysics, then Honours (1st class) in chemistry in 2014, under the supervision of Professor Andrea Robinson. In 2015, he commenced studies towards a Doctorate of Philosophy under the supervision of Assoc. Professor David W. Lupton. His studies focus on reaction discovery using NHC catalysis and natural product synthesis.

Alison Levens completed a B.Sc. (Honours, 1st class) with a major in chemistry in 2012 at Monash University. She then commenced studies towards a Doctorate of Philosophy in 2013 under the supervision of Assoc. Professor David W. Lupton. During her Ph.D. studies, she has worked in collaboration with Professor Herbert Mayr (Ludwig Maximilians Universität München) on the properties of NHCs, although most of her research has been focused on the development of NHC-catalyzed all-carbon annulations.

David W. Lupton graduated with a B.Sc. (Honours, 1st class) in 2001 (University of Adelaide, supervised by Professor Dennis K. Taylor) and a Ph.D. in 2005 (Australian National University, supervised by Professor Martin G. Banwell). Between 2005 and 2007, Dr. Lupton performed postdoctoral studies with Professor Barry M. Trost (Stanford University) as a fellow of the American Australian Association. In 2007, he took an academic appointment at Monash University, receiving an Australian Research Council Future Fellowship in 2011 and promotion to Assoc. Professor in 2014. His studies focus on the use of catalysis to uncover novel reactivity and enable chemical synthesis.

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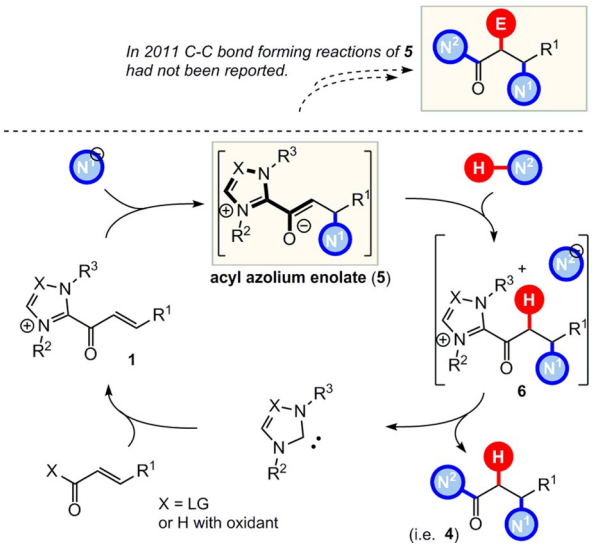
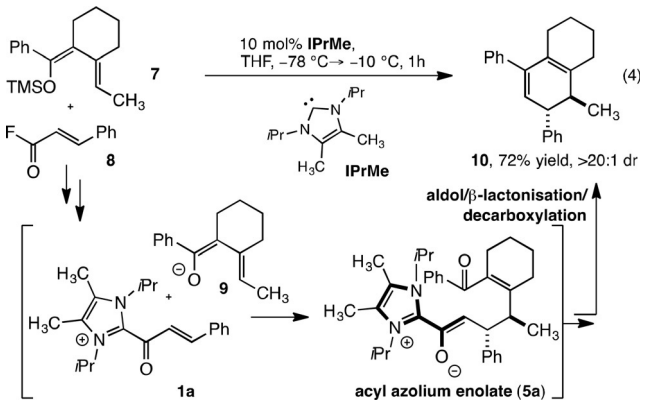


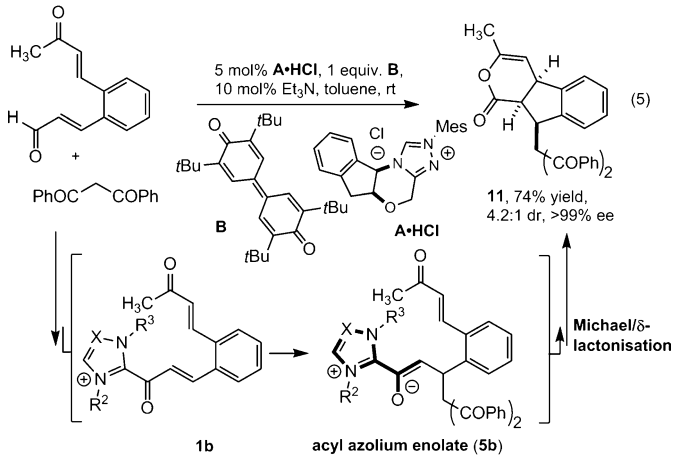
Scheme 2. Overview of the reactivity of α,β-unsaturated acyl azoliums (**1**).



Scheme 3. NHC-catalyzed (4+2) annulation of TMS dienol ethers and α,β-unsaturated acyl fluorides.

2.2 Michael/Michael/Lactonisation

Around the same time as the (4+2) annulation studies were reported, Studer demonstrated that α,β-unsaturated acyl azoliums could react with a nucleophile in the β-position, followed by an electrophile with the resultant acyl azolium enolate, to give cyclopentane **11** (Scheme 4).[12] This was achieved by addition of a doubly activated methylene to α,β-unsaturated acyl azolium **1b** to give acyl azolium enolate **5b**, which engaged in intramolecular Michael addition to assemble a cyclopentyl intermediate. Finally, the NHC was liberated through lactonisation to provide tricycles such as **11** (Eq. 5).



Scheme 4. NHC-catalyzed intermolecular Michael, intramolecular Michael, lactonisation cascade.

3 NHC-catalyzed (3+2) Annulation with Donor-Acceptor Cyclopropanes

Our interest in donor-acceptor cyclopropanes to enable (3+2) annulations arose due to a number of features well suited to our reaction design.[13] Firstly, donor-acceptor cyclopropanes can serve as masked aldehyde equivalents. In the context of an NHC-catalyzed acyl azolium reaction, this was considered desirable, as this should impede undesired acyl anion chemistry. Secondly, donor-acceptor cyclopropanes are known to open through the action of fluoride ions, thereby potentially being compatible with our acyl fluoride chemistry (Scheme 3). Finally, donor-acceptor cyclopropanes are known to undergo annulation with electron-poor π-systems.

3.1 (3+2) Annulations with Donor-Acceptor Cyclopropanes

In work from Graziano, it was found that donor-acceptor cyclopropanes undergo fragmentation and subsequent annulation with various all-carbon π-systems to give cyclopentanes (Scheme 5).[14,15] Related studies have been reported by Reissig, with the annulation of 2-siloxycyclopropylcarboxylates (*vide infra*) with tetracyanoethylene.[14a] In the case of reactions between tetracyanoethylene (**12**) and unsubstituted (**13a**) or mono-substituted donor-acceptor cyclopropanes (**13b**), the expected cyclopentanes **14a** and **14b** formed in 80% yield after less than 1 hour (Eq. 5). The reaction was significantly hindered by the introduction of dimethyl functionality, requiring 24 hours to reach the same yield of cyclopentane **14c**.[14b] In reactions with dimethyl acetylenedicarboxylate (**15**), the related reaction required more forcing conditions and gave inseparable mixtures of cyclopentene **16** and diene **17** (Eq. 7).[15] The formation of the uncyclized by-product provides support for the presence of intermediate **18** *en route* to both observed products. Presumably the α,β-unsaturated acyl azolium (i.e., **1**) can be considered

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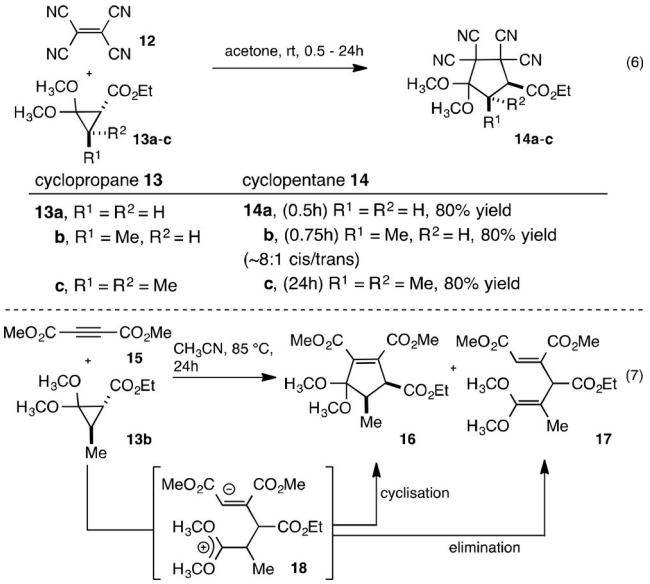


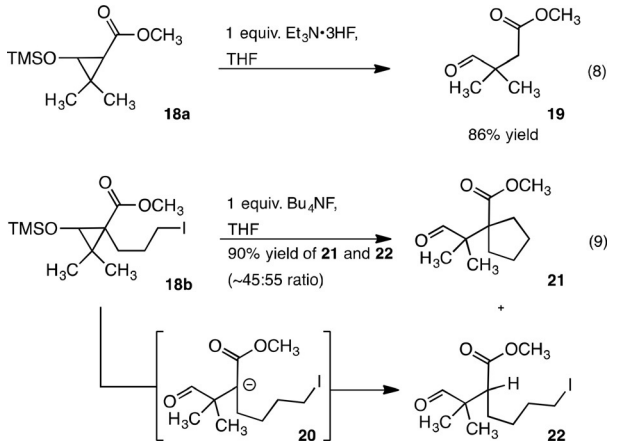
Scheme 5. (3+2) annulations with donor-acceptor cyclopropanes and electron-poor all-carbon π-systems.

a LUMO-lowered π-system (relative to the acyl fluoride), potentially allowing reaction in a fashion analogous to that described in Eqs. 6 and 7.

3.2 Fluoride-mediated Ring Opening

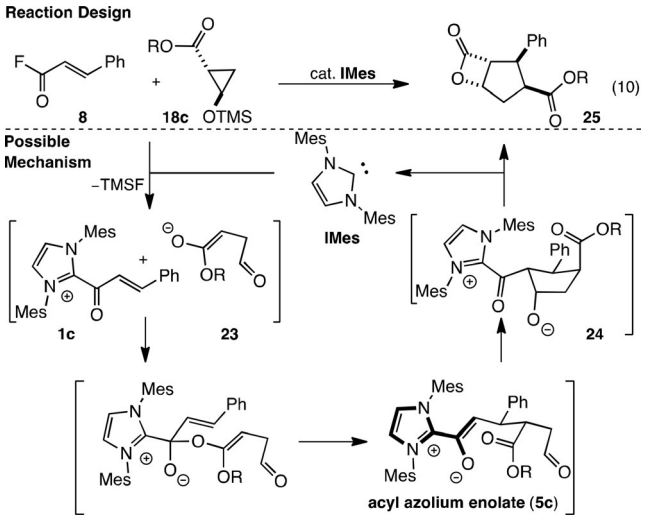
Equally important to our synthetic design were studies reported by Reissig.[16,17] In work reported in the mid-1980s, it was found that donor-acceptor cyclopropanes undergo facile fragmentation in the presence of fluoride sources to provide β-formyl esters. For example, exposure of donor-acceptor cyclopropane **18a** to $Et_3N{\cdot}3HF$ in THF allowed formation of β-formyl ester **19** in 86% isolated yield (Eq. 8). In some cases, the ester enolate intermediate (i.e., **20**) could be trapped with electrophilic functionality to yield more complex molecules, such as cyclopentane **21** (Eq. 9). Unfortunately, the yield was often modest due to competitive protonation to yield formyl ester by-products (i.e., **22**). While *in situ* trapping of these species in reactions such as those of Graziano was not demonstrated, it seemed likely that these two approaches could be merged effectively (Scheme 6).

Thus, taking the observations of Reissig and Graziano together, we envisaged a reaction cascade in which NHC-mediated defluorination of an α,β-unsaturated acyl fluoride **8** would lead to concomitant fragmentation of a donor-acceptor cyclopropane (i.e., **18c**) to yield ester enolate aldehyde **23** and α,β-unsaturated acyl azolium **1c**. Their union in either a direct Michael addition, or C–O bond formation, followed by Claisen rearrangement, would then provide acyl azolium enolate **5c**. In contrast to previous studies in which proton transfer at this point led to lactone products, the presence of the pendant alde-



Scheme 6. Fluoride-mediated ring opening of donor-acceptor cyclopropanes.

hyde would promote cyclisation to give cyclopentyl alkoxide **24**, which following β-lactonisation would give the cyclopentyl-fused β-lactone **25** and liberate the NHC catalyst (Scheme 7).



Scheme 7. Reaction design for the NHC-catalyzed all-carbon (3+2) annulation.

3.3 Discovery

Studies commenced with the preparation of donor-acceptor cyclopropane **18d** using procedures communicated by Reissig.[18] Upon exposure to the IMes NHC in the presence of acyl fluoride **8** in toluene, reaction occurred to provide cyclopentane **25d** (Eq. 11); however, undesired protonation afforded aldehyde **26d** as the major product (result not shown). Introduction of 4Å molecular sieves decreased formation of this aldehyde, which was further retarded by switching from toluene to THF; however, only 41% of the expected product was formed, along with the same amount of aldehyde **26d**. Quenching of the

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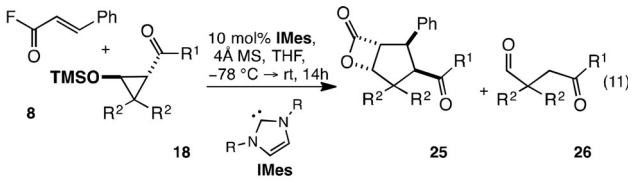
ester enolate is a common challenge encountered in studies focused on reaction discovery via the ester enolate intermediate (*vide supra*). Unfortunately, a screen of other NHC catalysts failed to improve the outcome of the reaction. It was reasoned that modification of the donor-acceptor cyclopropane could hinder the background protonation reaction. The most obvious entry to such a strategy would be through modification of the ester functionality to give ester enolates with different reactivity profiles. While the donor-acceptor cyclopropane bearing an electron-poor aryl ester (i.e., **18e**) gave a 1:1 mixture of **25e** and **26e** in similar yield to the reaction with **18d**, phenyl ester **18f** and electron-rich aryl ester **18g** both gave the desired product as the major material. In the latter case, this was achieved in 89% isolated yield with only 4% of the β-formyl ester **26g**. The reaction's significant sensitivity to the carbanion stabilising group in the donor-acceptor cyclopropane was observed when the reaction was attempted with phenyl ketone-containing donor-acceptor cyclopropane **18h**. In this case, the expected product **25h** formed in only 11% isolated yield with 55% isolated yield of the β-formyl phenyl ketone **26h** (Scheme 8).



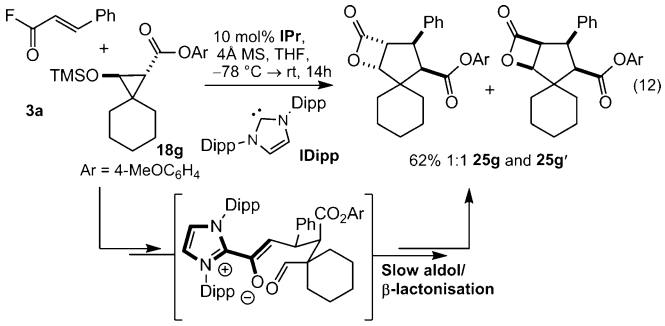
cyclopropane **18**	cyclopentane **25**	aldehyde **26**
18d, R^1 = OEt; R^2 = -$(CH_2)_5$-	41%	41%
e, R^1 = O(4-BrC_6H_4); R^2 = -$(CH_2)_5$-	43%	43%
f, R^1 = OPh; R^2 = -$(CH_2)_5$-	78%	16%
g, R^1 = O(4-$MeOC_6H_4$); R^2 = -$(CH_2)_5$-	89%	4%
h, R^1 = Ph; R^2 = CH_3	11%	55%

Scheme 8. Reaction discovery and optimization through modification of the acceptor group.

Interestingly, increasing the bulk of the NHC catalyst using the optimised conditions led to a loss of diastereoselectivity. Presumably, this arose due to a slower rate of aldol/β-lactonisation, allowing rotation of the acyl azolium enolate, thereby leading to a mixture of β-lactone **25g** and **25g′** (Scheme 9).

3.4 Scope and Limitations

Much of the generality of this reaction was discussed in detail previously;[9] however, some additional comments are warranted (Figure 1). In general, the reaction was sensitive to the nature of the phenolic ester about the cyclopropane. Thus, with 4-methoxy phenolic esters, good generality could be achieved to produce cyclopentanes bearing aromatic substituents derived from the β-position of the α,β-unsaturated acyl fluoride (e.g., **25i**–**25k**). The



Scheme 9. Loss of diastereoselectivity using the **IPr** NHC catalyst.

yield was decreased slightly when aliphatic groups were installed in this position (i.e., **25l**). Switching to alternate disubstituted cyclopropanes, it was found that the yield was modest, or the reaction failed, with the 4-methoxy phenolic esters; however, the desired reactivity could be regained though the use of a more electron-rich 2,4-dimethoxy phenolic ester group. For example, cyclopentane **25m** formed in 47% yield, while the more electron-rich ester allowed **25o** to form in 79% isolated yield. Finally, the reaction is viable when a single R^3 group is present; however, the diastereoselectivity is modest with cyclopentanes **25q** and **25r** formed in 30% and 41% yields, with 6:1 and 5:1 dr, respectively.

A number of limitations have been observed since our earlier report. Firstly, the reaction using α,β-unsaturated acyl fluorides bearing an α-substituent, while viable, is not high yielding. This is unsurprising, as the reaction now gives rise to materials bearing a challenging quaternary centre (i.e., **25s**). Furthermore, this mirrors some of our earlier observations with related substrates in Claisen reactions.[19] An additional limitation relates to the use of unsubstituted cyclopropane **18t**. When reacted, the expected cyclopentane **25t** is not formed. Instead, the product of Claisen condensation and esterification of the resultant lactol forms **27**. This pathway is not possible, or is impeded by, substituents α- to the aldehyde functionality. Potentially, the modest yields observed with the formation of **25q** and **25r** relate to complications due to this type of side reaction.

3.5 Enantioselectivity

A number of studies from our group have focused on the chemistry of ester oxidation state substrates (such as acid fluoride and enol esters) in NHC catalysis. While novel reactivity has often been observed, as is the case with the (3+2) annulation with donor-acceptor cyclopropanes, this has only been possible by employing imidazolium-derived NHCs (i.e., IMes). We postulated that enol esters and acyl fluorides, as we most routinely study, are less electrophilic than the more commonly used aldehyde-containing substrates; hence, highly nucleophilic and Lewis basic car-

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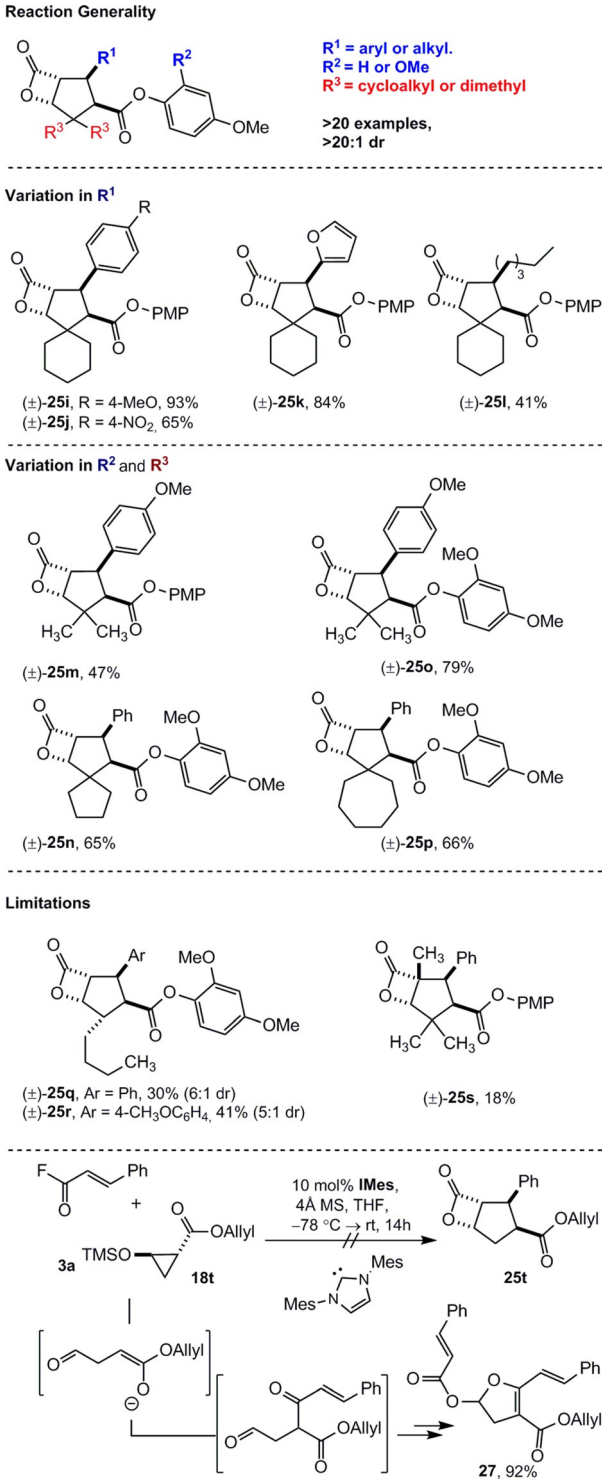
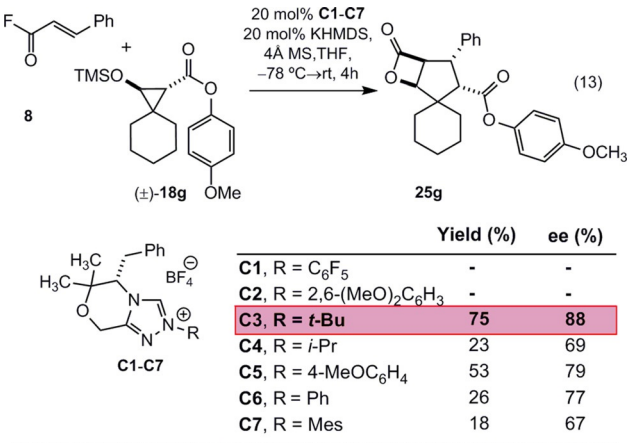
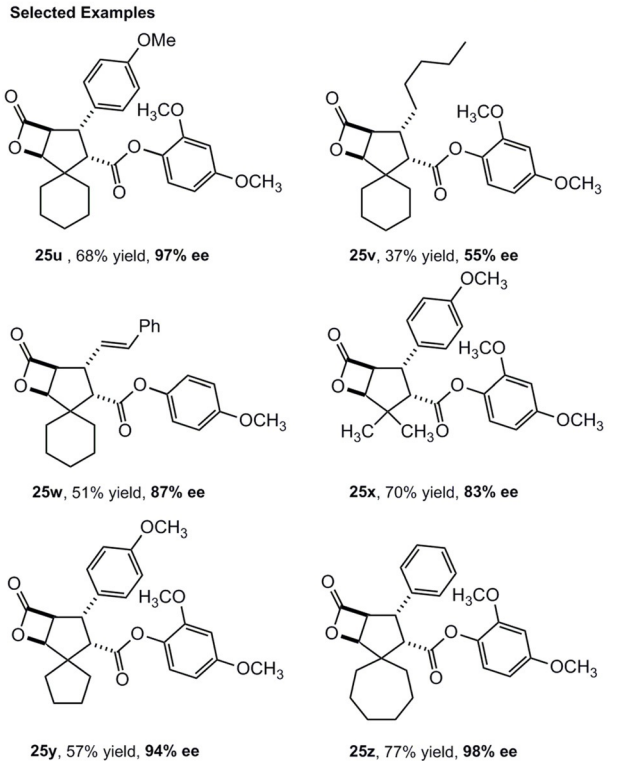


Figure 1. Reaction scope and limitations.

benes are required. While this does not impede development of non-enantioselective processes, it has proved more difficult to develop enantioselective reactions, primarily due to the relative scarcity of homochiral imidazolium NHCs. A solution to this situation was possible by examining the impact of N-substitution on common triazolium NHC precatalysts, specifically hoping to deliver NHCs with enhanced nucleophilicity over the more commonly studied N-C_6F_5 or N-Mes triazolium catalysts. Within the context of the (3+2) annulation discussed here, systematic modification of the N-substituent of a number of chiral triazolium precatalysts was undertaken.[9b] While the (3+2) annulation could be achieved with many chiral scaffolds, we found that the Leeper/Scheidt morpholinone[20] family of NHCs (i.e., **C**) gave the most promising results (Eq. 13). Specifically, while C_6F_5 (**C1**) and 2,6-$(MeO)_2C_6H_3$ (**C2**) NHCs were not suitable for the reaction, *t*-Bu (**C3**), *i*-Pr (**C4**), 4-MeOPh (**C5**), Ph (**C6**) and Mes (**C7**) substituted NHCs all gave



	Yield (%)	ee (%)
C1, R = C_6F_5	-	-
C2, R = 2,6-$(MeO)_2C_6H_3$	-	-
C3, R = ***t*-Bu**	75	88
C4, R = *i*-Pr	23	69
C5, R = 4-$MeOC_6H_4$	53	79
C6, R = Ph	26	77
C7, R = Mes	18	67



Scheme 10. Catalyst development for the enantioselective (3+2) annulation and selected examples.

the expected product in serviceable yields, and with enantioselectivity ranging from 67–88% *ee*. Gratifyingly, the highest enantioselectivity, achieved with *t*-butyl catalyst **C3**, was associated with good yield after modest optimisation (Scheme 10).

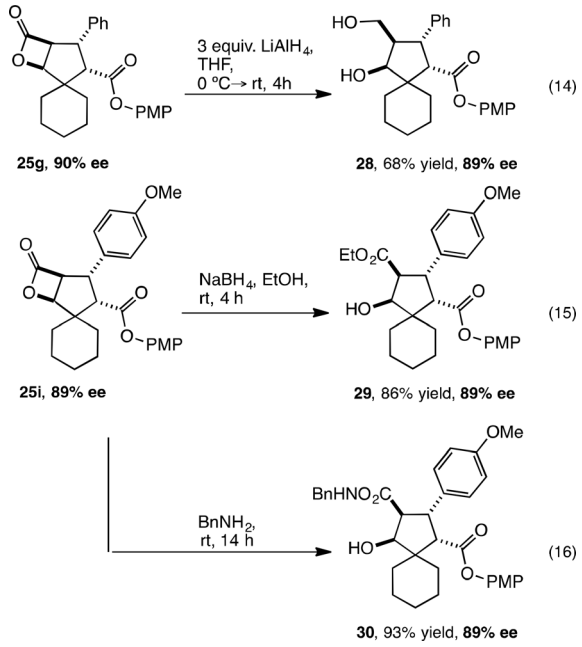
Exploiting these conditions with a range of donor-acceptor cyclopropanes and α,β-unsaturated acyl fluorides allowed the synthesis of various cyclopentyl β-lactones with similar generality to the non-enantioselective variant of the reaction. In terms of the degree of enantioselectivity, a number of comments can be made. In most cases, the use of more electron-rich aryl esters than the 4-$MeOC_6H_4$, namely the 2,4-$(MeO)_2C_6H_3$, increased the enantioselectivity. For example, the synthesis of **25g** was achieved in 90% *ee*, while **25u** was formed with 97% *ee*. Variation of the cinnamoyl fluoride was possible, although β-aliphatic examples led to modest enantioselectivity; for example, **25v** formed with 55% *ee*. Unsaturated cyclopentanes derived from α,β,γ,δ-unsaturated acyl fluorides, i.e., **25w**, formed with acceptable enantiopurity. Similarly, modification from the cyclohexyl-fused compounds (i.e., **25g**) to the dimethyl (i.e., **25x**) or cyclopentyl (i.e., **25y**) decreased the enantioselectivity slightly, while the cycloheptyl-fused β-lactone **25z** was formed with an improved 98% *ee*.

3.6 Derivatization of the β-Lactone Products

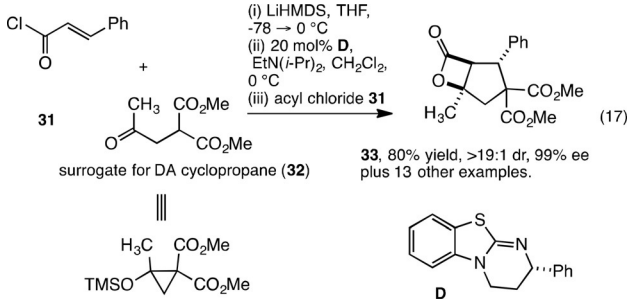
As a prelude to studies focused on the application of cyclopentyl β-lactones, such as **25**, in complex target synthesis, a number of simple derivatizations were examined. Specifically, it was observed that under reductive conditions it was possible to convert β-lactone **25g** to 1,3-diol **28** without any concomitant reduction of the phenolic ester functionality or less enantiopurity. Similarly, the opening of β-lactone **25i** with either alcoholic nucleophiles, to form **29**, or amines, to form **30** was possible without affecting the phenolic ester functionality (Scheme 11).

3.7 Related (3+2) Annulations

Concurrent to our work, a related study was reported by Romo *et al.*,[21] allowing annulation of α,β-unsaturated acyl chlorides **31** with keto malonate **32** using isothiourea catalyst **D** (Eq. 17). This reaction was achieved by initially exposing malonate **32** to one equivalent of LiHMDS, then introducing the catalyst, in the presence of an equivalent of $EtN(i\text{-}Pr)_2$, before introducing the acyl chloride **31**. This led to the generation of a range of cyclopentyl-fused β-lactones **33** (Scheme 12). In contrast to our studies, all reactions required malonate functionality and gave ketone-derived β-lactone products, thereby providing an orthogonal approach to functionalised enantioenriched cyclopentane products.



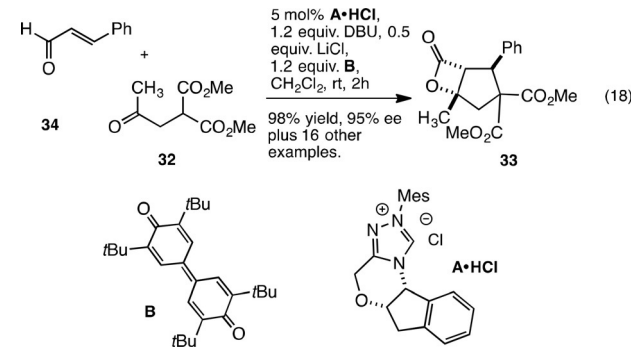
Scheme 11. Derivatisation of cyclopentyl β-lactones **25g** and **i**.



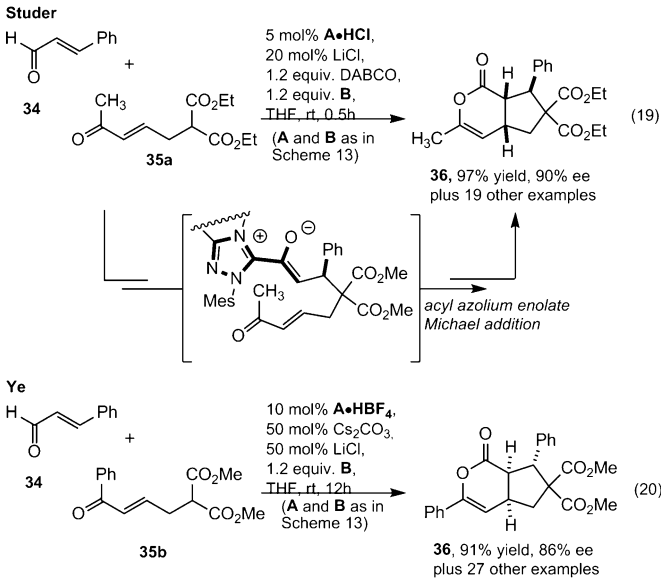
Scheme 12. Isothiourea-catalyzed approach to a related (3+2) annulation.

More recently, Studer reported a NHC-catalyzed (3+2) annulation which exploited α,β-unsaturated acyl azoliums generated under oxidative conditions from the corresponding aldehyde (i.e., **34**), which are annulated with the donor-acceptor cyclopropane surrogate **32** (Eq. 18).[22] Once more, this approach provided an excellent entry to a range of enantioenriched cyclopentyl β-lactones **33** (17-examples) with high selectivity and yield (Scheme 13).

Very recently, a new application of the acyl azolium enolate has been communicated concurrently by Studer[23] and Ye.[24] In these reactions, conjugate addition to the α,β-unsaturated acyl azolium leads to the formation of the acyl azolium enolate, which rather than undergoing β-lactonisation, undergoes a Michael addition followed by lactonisation to give δ-lactone **36** (Eqs. 19 and 20). In contrast to Studer's 2011 study (Scheme 4), the pro-nucleophile and Michael acceptor are tethered within malonate **35** (Scheme 14).



Scheme 13. Oxidative NHC-catalyzed approach to a related (3+2) annulation.



Scheme 14. NHC-catalyzed intermolecular Michael, intramolecular Michael, lactonisation cascade.

4. Summary

Donor-acceptor cyclopropanes have proven to be well suited to NHC-based reaction discovery with acyl fluoride substrates. This has allowed functionality poorly suited to NHC catalysis to be exploited, hence allowing a (3+2) annulation that would not be possible without the use of donor-acceptor cyclopropanes. Pivotal to the development of the reaction was the capacity to modify the behaviour of the ester enolate intermediate to allow undesired protonation to be suppressed.

The discovery of this reaction constitutes an early example of a growing family of NHC-catalyzed reactions with α,β-unsaturated acyl azoliums that results in C–C bond formation both α- and β- to the carbonyl group. Based on the interest in α,β-unsaturated acyl azolium chemistry which involves C–C bond formation β- to the carbonyl, it is likely that a range of related, and potentially enantioselective, reactions exploiting this type of reactivity pattern will be communicated in the coming years.

Acknowledgements

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Synthesis J. E. M. Fernando et al. Paper

N-Heterocyclic Carbene Catalyzed Transformylation

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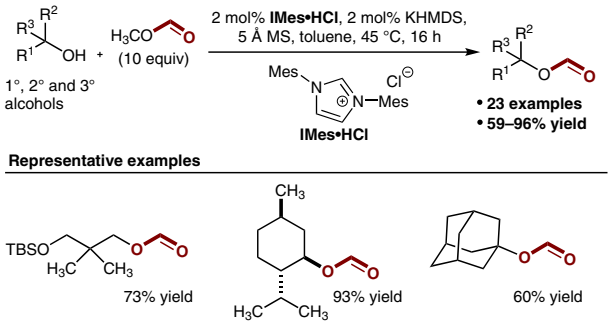
Dedicated to Prof. Herbert Mayr in celebration of his 70th birthday.



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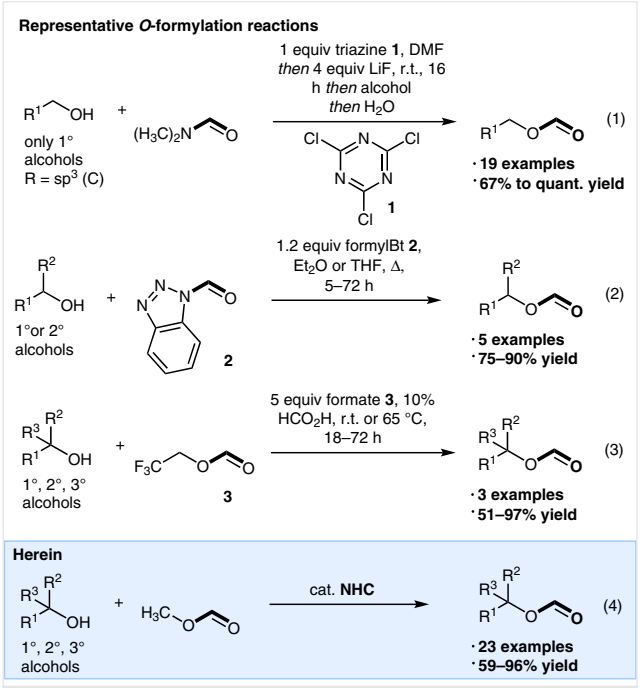
Abstract The N-heterocyclic carbene (NHC) catalyzed transformylation has been developed for the conversion of 1°, 2°, and 3° alcohols to the corresponding formates. The reaction employs low catalyst loadings and methyl formate as the formyl transfer reagent. The scope of the reaction is broad with 23 examples reported with good yields (59–96%). The reaction is insensitive to common nitrogen and oxygen protecting groups and can be achieved in the presence of a number of heterocycles.

Key words N-heterocyclic carbene catalysis, transformylation, formate synthesis

The formylation of alcohols defines a useful protecting group strategy. Formates display acid stability, while being labile under mildly basic conditions to which common esters are often stable.[1] In addition to enabling protection strategies, formates can be exploited in subsequent functional group interconversions. For example, the Oppenauer oxidation directly provides the corresponding carbonyl compounds,[2] reductive cleavage allows deoxygenation,[3] while condensation gives vinylogous carbonates.[4] Physically the formate is sterically undemanding, while often imparting a depressed boiling point in the product. Despite these features the application of formates is limited.[1] In part this may be due to challenges in their synthesis. The most common approaches to their preparation involve in situ generation of formylating species,[5] use of stoichiometric formylating agents,[6] or acid-catalyzed transformylation.[7] Specifically, Vilsmeier–Haack strategies are common[5a] with, for example, recent studies demonstrating that triazine **1** is suited to the chemoselective formylation of primary alcohols [Scheme 1 (1)].[5b] Alternately, Katritzky and Wittenburger independently developed the formylating agents formyl benzotriazole **2** and fluoro ester **3** [Scheme 1 (2) and (3)].[6a,c] While many conditions have been developed for the synthesis of formate esters, limitations remain relating to chemoselectivity, cost of reagents, and in some cases toxicity.

Exploiting our experience in NHC-organocatalysis[8] with esters,[9,10] and building on studies of related transesterifications,[11] we envisioned a transformylation strategy to prepare formate esters [Scheme 1 (4)]. Such a strategy could address a number of limitations in existing methods. Specifically it would be catalytic and exploit simple, cheap, and



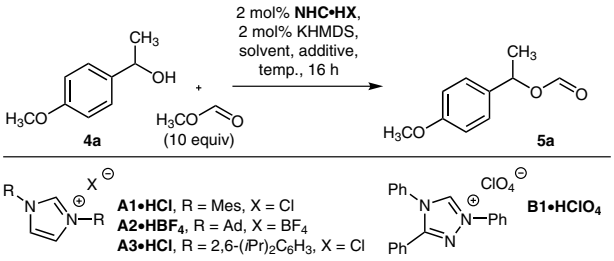
Scheme 1 Background and overview

non-toxic starting materials, and it would also have mild reaction conditions. Herein, we report studies on this chemistry that have delivered simple and mild conditions for the conversion of 1°, 2°, and 3° alcohols into the corresponding formate esters. Key to the success of this approach has been the introduction of 5Å molecular sieves, presumably to suppress reversibility. The reaction displays good generality with 23 examples reported.

Studies commenced by examining the transformylation of secondary alcohol **4a** with 10 equivalents of methyl formate in THF heated to 45 °C in the presence of common bases. While no conversion was observed with triethylamine (Table 1, entry 1), KHMDS provided a 15% yield of benzyl formate **5a** (Table 1, entry 2).[12] While the yield was modest, this result highlights the viability of Brønsted base mediated transformylation reactions. When 2 mol% IMes·HCl precatalyst (**A1**·HCl) was introduced, the yield of benzyl formate **5a** more than doubled (Table 1, entry 3), while changing to toluene, and maintaining the temperature at 45 °C, increased the yield further (Table 1, entry 4). Alternate imidazolium-derived NHCs **A2** and **A3** decreased the yield of **5a** (Table 1, entries 5 and 6), while the less basic Enders triazolium derived NHC **B1**[13] gave none of the expected product (Table 1, entry 7). The outcome of the reaction was slightly poorer when performed at increased temperatures (Table 1, entries 8 and 9), an observation attributed to the volatility of formate **5a**. Similar reaction outcomes were observed in DMF (Table 1, entry 10) while introduction of 5Å molecular sieves to sequester liberated methanol and suppress the reverse reaction increased the yield of **5a** from 65 to 82% (Table 1, entry 4 cf. entry 11). Similar, increases in yield were achieved using 5Å MS in either DMF or THF (Table 1, entries 12 and 13). Having identified conditions that exploit low catalyst loading (2 mol%) and cheap and readily available reagents, the reaction scope was examined.

Having optimized conditions for the formylation of 2° alcohols (i.e., **4a**), we next examined the generality across a range of 1°, 2°, and 3° alcohols. In general, all reactions gave good isolated yields of the expected formates with an order of reactivity in which 1° is faster than 2°, and 2° faster than 3°. In some cases yields were modest, which was often associated with challenges in isolation due to the volatility of lower molecular weight products. Specifically studies started with a range of simple aliphatic 1° alcohols, the corresponding formates **5b–e** were prepared in 80–90% isolated yield (Scheme 2). In addition the reaction tolerated electron-poor aromatic groups, giving **5f** in 65% isolated yield, and electron-rich aromatic groups, providing **5g** and **5h** in 78 and 86% isolated yield respectively. The excellent reactivity of the later substrate was further examined with formate **5h** prepared using 1.1 equivalents of methyl formate (cf. 10 equiv) in 78% yield, furthermore 1.1 equivalents of methyl formate and 1 mol% **A1** gave formate **5h** in 75% yield. Returning to the optimized conditions, the presence

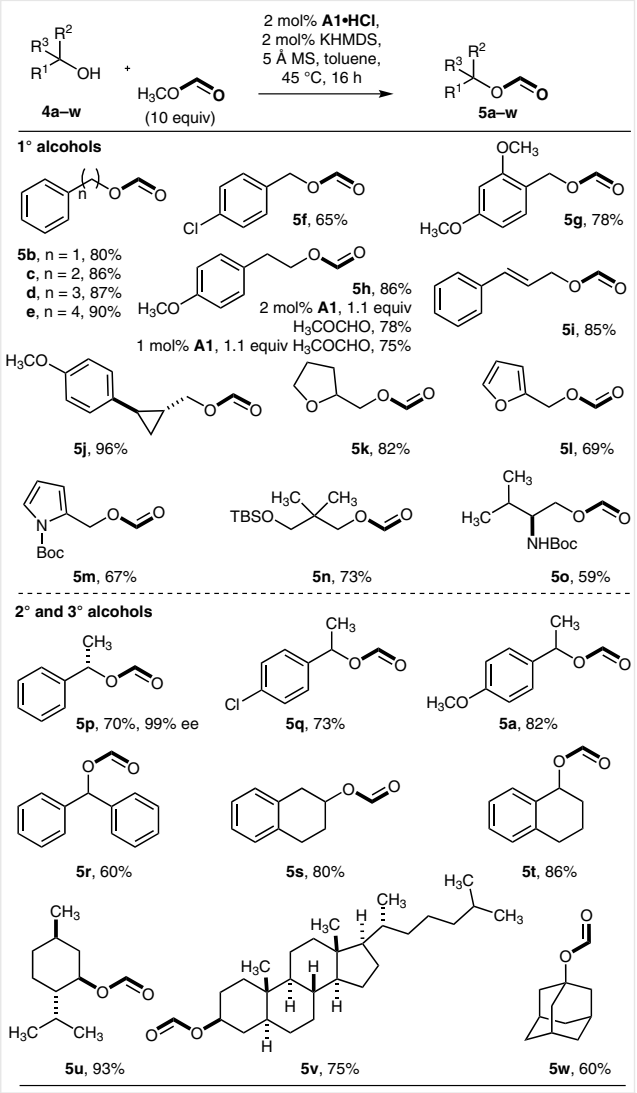
Table 1 Optimization of the NHC-Catalyzed Transformylation



Entry	NHC·HX	Solvent	Additive	Temp (°C)	Yield (%) of **5a**[a]
1	–[b]	THF	–	45	0
2	–	THF	–	45	15
3	**A1**·HCl	THF	–	45	37
4	**A1**·HCl	toluene	–	45	65
5	**A2**·HBF_4	toluene	–	45	54
6	**A3**·HCl	toluene	–	45	42
7	**B1**·$HClO_4$	toluene	–	45	0
8	**A1**·HCl	toluene	–	75	60
9	**A1**·HCl	toluene	–	95	40
10	**A1**·HCl	DMF	–	45	53
11	**A1**·HCl	toluene	5 Å MS	45	82
12	**A1**·HCl	DMF	5 Å MS	45	67
13	**A1**·HCl	THF	5 Å MS	45	68

[a] Isolated yield following chromatography.
[b] Et_3N was used instead of KHMDS.

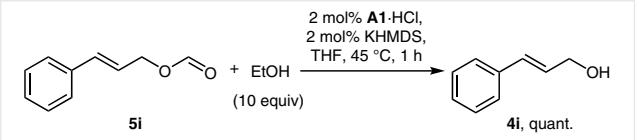
of unsaturation (**4i**), strained rings (**4j**), or aliphatic/aromatic heterocycles (**4k**,**l**) were examined, giving the expected esters **5** with 69–96% isolated yield. The sensitivity of the reaction to common protecting groups such as Boc or TBS was examined with Boc-pyrrole **4m**, TBS ether **4n**, and Boc-valine derivative **4o**, all formylated in acceptable yields. A thorough examination of 2° alcohols commenced with homochiral (*S*)-α-methylbenzyl alcohol (**4p**). This was converted into the corresponding formate **5p** without loss of enantiopurity (**4p**, 99% ee → **5p**, 99% ee). Unsurprisingly, and as observed with 1° alcohols, electron-rich and -poor substrates were equally suited to the reaction conditions giving benzyl formates **5q** and **5a** in good yield. Similarly benzophenone, β-tetralone, and α-tetralone derived alcohols **4r–t** were formylated to give formates **5r–t** in good to excellent isolated yield. Aliphatic alcohols present in more complex bioactive substrates such as menthol (**4u**) and steroid **4v** were converted into formates **5u** and **5v** in 93% and 75% isolated yield, respectively. Finally, adamantanol **4w** was smoothly converted into the corresponding formate **5w** in 60% isolated yield.



Scheme 2 Scope of the NHC-catalyzed transformylation; isolated yields following column chromatography are given

The reversibility of this reaction can be exploited for the deprotection of formate esters. Thus, in the absence of molecular sieves, exposure of cinnamyl formate (**5i**) to 10 equivalents of ethanol and 2 mol% NHC **A1**, provided cinnamyl alcohol **4i** in quantitative yield after 1 hour (Scheme 3).

The NHC-catalyzed formylation of 1°, 2°, and 3° alcohols has been achieved using mild reaction conditions. The presence of common oxygen and nitrogen protecting groups are tolerated, as are various heterocycles. The reaction may occur via either a Lewis or Brønsted base mediated pathway.[14,15] Based on the observation of partial reactivity using simple bases, it is likely that the reaction is occurring via Brønsted base catalysis. Finally, the complementary deprotection has also been demonstrated.



Scheme 3 Deformylation

The formylation presented herein highlights the versatility of NHCs as powerful organocatalysts, which enable various activation modes. Particularly pleasing is the observation that one of the simplest catalysts (IMes) is ideally suited to the reaction, and that good activity can be observed with only 1 mol% catalyst and a slight excess of the formylating reagent.

For details of equipment, sources of chemicals etc., see the Supporting Information. PE = petroleum ether.

Formates 5; General Procedure

To a flame-dried flask containing a stirrer bar and activated 5 Å molecular sieves was added IMes·HCl (**A1**·HCl, 6.8 mg, 0.02 mmol) and toluene (2 mL) under an inert atmosphere. To this stirred suspension 0.5 M KHMDS in toluene (0.04 mL) was added and the mixture stirred for 15 min. An appropriate alcohol (1 mmol) and methyl formate (600 mg, 10 mmol) were then added as a solution in toluene (2 mL) and the flask sealed and heated to 45 °C for 16 h. The crude mixture was loaded directly onto a chromatography column (silica gel) to give the formates.

1-(4-Methoxyphenyl)ethyl Formate (5a)

Yield: 148 mg (82%). ^{1}H and ^{13}C NMR data were identical with the literature.[12]

Benzyl Formate (5b)

Yield: 109 mg (80%). ^{1}H and ^{13}C NMR data were identical with the literature.[5a]

Phenethyl Formate (5c)

Yield: 129 mg (86%). ^{1}H and ^{13}C NMR data were identical with the literature.[16]

3-Phenylpropyl Formate (5d)

Yield: 143 mg (87%). ^{1}H and ^{13}C NMR data were identical with the literature.[17]

4-Phenylbutyl Formate (5e)

Colourless oil; yield: 160 mg (90%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2931w, 1727s, 1496w, 1453m, 1159s, 1030w, 908w, 745m, 698s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.31–7.17 (m, 5 H), 4.19 (m, 2 H), 2.66 (m, 2 H), 1.71 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 141.8, 128.3, 125.8, 63.7, 35.3, 28.0, 27.5 (one signal overlapping).

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{14}O_2$: 178.1; found: 178.2.

4-Chlorobenzyl Formate (5f)

Yield: 111 mg (65%). ^{1}H and ^{13}C NMR data were identical with the literature.[16]

2,4-Dimethoxybenzyl Formate (5g)

Colourless oil; yield: 153 mg (78%); R_f = 0.3 (EtOAc/PE, 1:4).

IR (ATR): 2938m, 1715s, 1613s, 1588m, 1509s, 1458m, 1438m, 1366m, 1291m, 1269m, 1207s, 1153s, 1130s, 1031s, 922m, 735m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.27–7.24 (m, 1 H), 6.49–6.46 (m, 2 H), 5.19 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 161.1, 159.0, 131.7, 115.9, 104.0, 98.5, 61.3, 55.5, 55.4.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}O_4$: 196.1; found: 196.1.

4-Methoxyphenethyl Formate (5h)

Colourless oil; yield: 153 mg (86%); R_f = 0.5 (EtOAc/PE, 1:4).

IR (ATR): 2937w, 1717s, 1613m, 1584w, 1512s, 1465m, 1442m, 1375w, 1245s, 1155s, 1112s, 1031s, 979m, 921m, 830s, 748w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.15 (m, 2 H), 6.86 (m, 2 H), 4.35 (dt, *J* = 7.0, 0.7 Hz, 2 H), 3.79 (s, 3 H), 2.92 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 158.4, 129.8, 129.3, 113.9, 64.6, 55.2, 34.0.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}O_3$: 180.1; found: 180.2.

Cinnamyl Formate (5i)

Pale yellow oil; yield: 140 mg (85%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2932w, 1717s, 1494m, 1449m, 1148s, 965s, 899m, 741s, 732m, 691s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.41–7.39 (m, 2 H), 7.36–7.32 (m, 2 H), 7.30–7.26 (m, 1 H), 6.70 (d, *J* = 16 Hz, 1 H), 6.29 (dt, *J* = 16, 6.8 Hz, 1 H), 4.85–4.82 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 136.1, 134.9, 128.7, 128.3, 126.7, 122.48, 64.5.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}O_2$: 162.1; found: 162.1.

[2-(4-Methoxyphenyl)cyclopropyl]methyl Formate (5j)

Colourless oil; yield: 198 mg (96%); R_f = 0.6 (EtOAc/PE, 1:4).

IR (ATR): 2937w, 1717s, 1612w, 1514s, 1459m, 1244s, 1174s, 1149s, 1114m, 1032s, 948m, 899m, 873m, 826s, 802m, 753w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.02 (m, 2 H), 6.82 (m, 2 H), 4.16 (m, 2 H), 3.78 (s, 3 H), 1.89 (m, 1 H), 1.43 (m, 1 H), 0.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 158.1, 133.7, 127.3, 114.0, 67.7, 55.4, 21.4, 20.8, 13.4.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{14}O_3$: 206.1; found: 206.1.

(Tetrahydrofuran-2-yl)methyl Formate (5k)

Colourless oil; yield: 107 mg (82%); R_f = 0.5 (EtOAc/PE, 1:4).

IR (ATR): 2951w, 2874w, 1717s, 1450w, 1163s, 1083s, 1018m, 914m, 879w, 843w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 4.27–4.21 (m, 1 H), 4.18–4.06 (m, 2 H), 3.93–3.77 (m, 2 H), 2.07–1.85 (m, 3 H), 1.68–1.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 76.4, 68.6, 66.0, 28.1, 25.8.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_6H_{10}O_3$: 153.1; found: 153.0.

Furan-2-ylmethyl Formate (5l)

Colourless oil; yield: 87 mg (69%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2938w, 1717s, 1502w, 1448w, 1361w, 1153s, 1135s, 1016m, 922m, 884m, 818w, 741s, 699w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.43 (s, 1 H), 6.44–6.37 (m, 2 H), 5.15 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 148.9, 143.6, 111.2, 110.8, 57.5.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_6H_6O_3$: 126.0; found: 126.0.

***tert*-Butyl 2-[(Formyloxy)methyl]-1*H*-pyrrole-1-carboxylate (5m)**

Pale yellow oil; yield: 151 mg (67%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2980w, 1718s, 1479w, 1458w, 1370m, 1315s, 1254m, 1152s, 1124s, 1064m, 976m, 843m, 771m, 734m, 694m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.29 (dd, *J* = 4.0, 4.0 Hz, 1 H), 6.33–6.29 (m, 1 H), 6.14 (t, *J* = 4.0 Hz, 1 H), 5.37 (s, 2 H), 1.59 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 148.9, 128.1, 123.1, 116.2, 110.3, 84.4, 58.9, 28.0.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}NO_4$: 226.1; found: 226.0.

3-(*tert*-Butyldimethylsiloxy)-2,2-dimethylpropyl Formate (5n)

Colourless oil; yield: 180 mg (73%); R_f = 0.7 (EtOAc/PE, 1:9).

IR (ATR): 2956m, 1730s, 1473w, 1251m, 1162s, 1094s, 1006w, 940w, 834s, 774s, 668w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 0.8 Hz, 1 H), 3.97 (d, *J* = 0.8 Hz, 2 H), 3.34 (s, 2 H), 0.90 (s, 6 H), 0.88 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 69.2, 68.5, 36.2, 26.0, 21.6, 18.4, 5.5.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{26}O_3Si$: 269.2; found: 269.1.

2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl Formate (5o)

Colourless oil; yield: 136 mg (59%); R_f = 0.6 (EtOAc/PE, 1:4).

IR (ATR): 3300br, 2967w, 1691s, 1509m, 1459w, 1391w, 1366m, 1243m, 1154s, 1023m, 865w, 780w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 4.61–4.48 (m, 1 H), 4.26–4.14 (m, 2 H), 3.73–3.63 (m, 1 H), 1.81 (oct, *J* = 8.0 Hz, 1 H), 1.44 (s, 9 H), 0.95 (dd, *J* = 8.0, 4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 155.7, 79.5, 64.2, 54.5, 28.4, 19.4, 18.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{21}NO_4$: 254.1; found: 254.1.

(*S*)-1-Phenylethyl Formate (5p)

Yield: 105 mg (70%). ^{1}H and ^{13}C NMR data were identical with the literature.[16] HPLC (AD-H 5μm, λ = 238 nm, hexane/*i*-PrOH = 98:2, 1.0 mL/min): t_R = 4.797 (minor), 5.140 min (major); er 99.5:0.5.

1-(4-Chlorophenyl)ethyl Formate (5q)

Yield: 135 mg (73%). ^{1}H and ^{13}C NMR data were identical with the literature.[18]

Benzhydryl Formate (5r)

Yield: 105 mg (60%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

1,2,3,4-Tetrahydronaphthalen-2-yl Formate (5s)

Yield: 141 mg (80%). ^{1}H and ^{13}C NMR data were identical with the literature.[19]

1,2,3,4-Tetrahydronaphthalen-1-yl Formate (5t)

Yield: 152 mg (86%). ^{1}H and ^{13}C NMR data were identical with the literature.[6a]

(–)-Menthyl Formate (5u)

Yield: 171 mg (93%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

Dihydrocholesterol-Derived Formate 5v

White solid; yield: 313 mg (75%); R_f = 0.7 (EtOAc/PE, 1:9).

IR (ATR): 2932s, 2849s, 1727s, 1466m, 1445m, 1373w, 1177s, 1131m, 995w, 922m, 867w, 803w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 4.86–4.77 (m, 1 H), 1.99–1.94 (m, 1 H), 1.87–0.95 (m, 30 H), 0.90–0.85 (m, 9 H), 0.82 (s, 3 H), 0.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 73.9, 56.6, 56.42, 56.36, 44.8, 44.7, 40.1, 39.7, 36.9, 36.3, 36.0, 35.61, 35.59, 34.1, 32.1, 28.7, 28.4, 28.2, 27.6, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.4, 12.2.

MS (EI): m/z $[M]^+$ calcd for $C_{28}H_{48}O_2$: 416.4; found: 416.3.

Adamantan-1-yl Formate (5w)

Yield: 108 mg (60%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588449. Included are experimental procedures, characterization of all new compounds and copies of 1H and 13C NMR spectra.

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NHC Catalysis

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Enantioselective N-Heterocyclic Carbene Catalysis via the Dienyl Acyl Azolium

*Rachel M. Gillard, Jared E. M. Fernando, and David W. Lupton**

Abstract: *Herein we report the enantioselective N-heterocyclic carbene catalyzed (4+2) annulation of the dienyl acyl azolium with enolates. The reaction exploits readily accessible acyl fluorides and TMS enol ethers to give a range of highly enantio- and diastereo-enriched cyclohexenes (most > 97:3 er and > 20:1 dr). The reaction was found to require high nucleophilicity NHC catalysts with mechanistic studies supporting a stepwise 1,6-addition/β-lactonization.*

N-Heterocyclic carbenes (NHC) enable diverse transformations via normal and reverse polarity intermediates.[1] In 2006, formation and esterification of the α,β-unsaturated acyl azolium (**1**) was discovered.[2] Subsequent studies demonstrating its use in a broad range of transformations[11,2–5] generally involving (3+*n*)[3] or (2+*n*)[4] annulations to provide sp^3-rich materials in excellent yield and with high enantiopurity.

While acyl azolium **1** has received significant attention, very little has been directed to the chemistry of higher unsaturated homologs,[6a] such as the dienyl acyl azolium (i.e. **2**) (Figure 1). The paucity of chemistry involving dienyl acyl azolium **2** is striking and contrasts, for example, iminium organocatalysis which exploits both the α,β-unsaturated iminium and the dienyl iminium (**3**) in many enantioselective tranformations.[6b–f] To the best of our knowledge, the dienyl acyl azolium has only been successfully exploited once, in Chi's synthesis of substituted benzene derivatives **4** [Eq. (1)].[7] In addition we attempted to access the dienyl acyl azolium from ester **5**, however we found fragmentation was not possible and an olefin isomerization Diels–Alder reaction gave [2.2.2]-bicyclic compounds such as **6** [Eq. (2)].[8] Herein, we report a new strategy for dienyl acyl azolium formation that has enabled the discovery of an enantioselective (4+2) annulation [Eq. (3)]. The reaction allows the highly diastereo- and enantioselective (most > 97:3 er and > 20:1 dr) synthesis of polycyclic β-lactones (i.e. **7**). In addition to providing a novel approach to β-lactones[9] this is the first example of enantioselective catalysis via the dienyl acyl azolium.

To avoid the olefin isomerization observed with ester **5** we envisioned using acyl fluorides (i.e. **8**), substrates suited to the generation of unsaturated Lewis base adducts.[10] In addition,

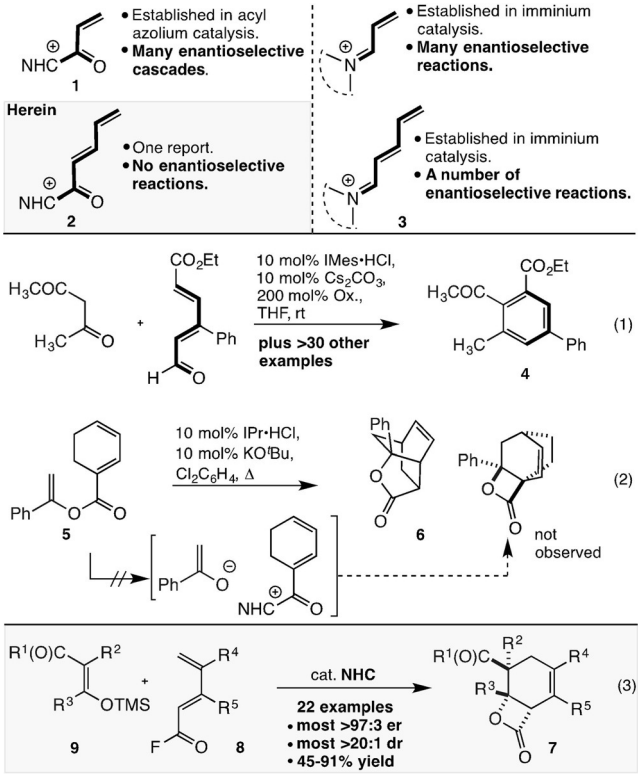

Figure 1.

deletion of the δ-substituent to favor 1,6-addition, and eliminate olefin isomerization, was deemed desirable. Thus, reaction discovery commenced with dienyl acyl fluoride **8a**, prepared from cyclohexanone in four-steps,[11] and TMS enol ether **9a**, prepared from benzyl acetoacetate in one. Their coupling was expected to provide products bearing three contiguous stereocentres including a quaternary carbon thereby reducing the likelihood of aromatization. When attempted with triazolylidene **A** in THF, β-lactone **7a** formed with modest yield, while the more nucleophilic IMes NHC **B1** gave the same product as a single diasteroisomer (> 20:1 dr) and in 74 % yield (Table 1, entries 1 and 2). Using IPr (**B2**) a 15 % yield of lactone **7a** with little diastereoselectivity was observed (Table 1, entry 3). The outcome with IMes **B1** was not improved using alternate solvents (Table 1, entries 4–6). Development of the enantioselective variant commenced by examining the impact of the N-substituent on reaction outcome (Table 1, entries 7–9). These studies demonstrated that more nucleophilic NHCs, which additionally bear *ortho*-disubstitution, were necessary (i.e. **C4** and **5**).[12,13] Of these catalyst **C5**[14] was preferred giving β-lactone **7c** in a > 99:1 enantiomeric ratio, albeit with poor diastereoselec-

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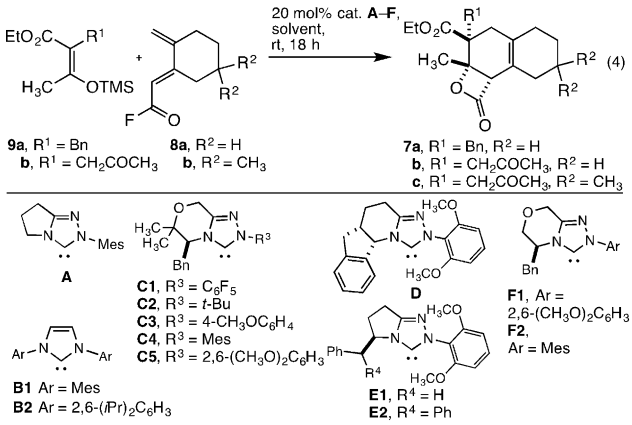
Table 1: Selected Optimizations.



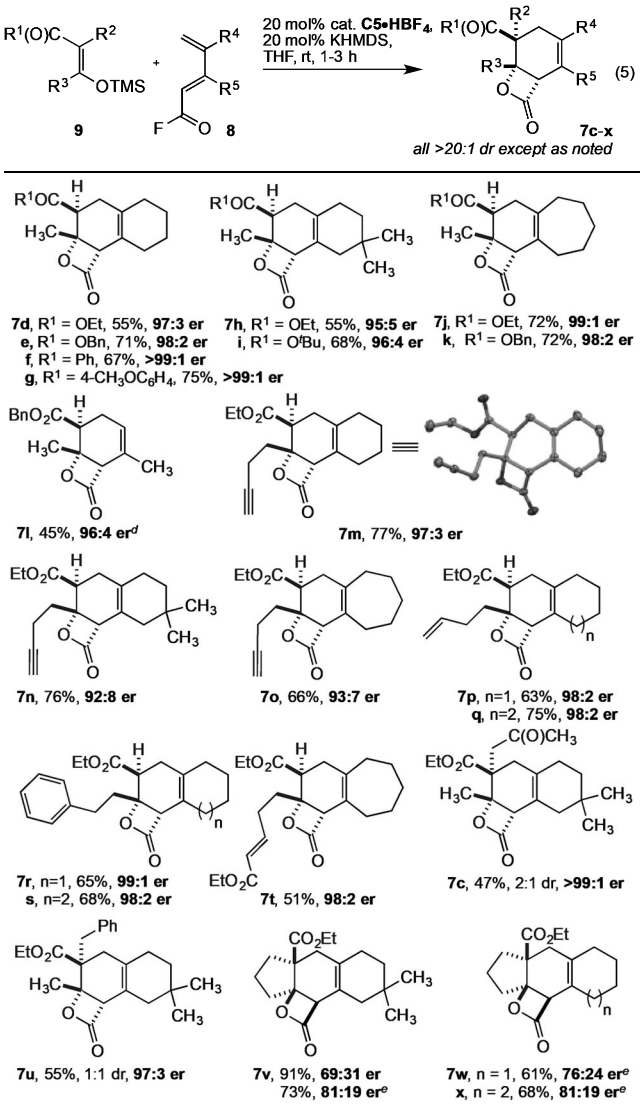
Entry	Cat.[a]	9/8	Solvent	Yield[b]	dr[c]	er[d]
1[c]	**A**	**a/a**	THF	48	3:1	–
2	**B1**	**a/a**	THF	74	>20:1	–
3	**B2**	**a/a**	THF	15	2:1	–
4	**B1**	**a/a**	DMF	11	2:1	–
5	**B1**	**a/a**	$C_6H_5CH_3$	60	19:1	–
6	**B1**	**a/a**	dioxane	54	19:1	–
7	**C1–3**	**b/a**	THF	–	–	–
8	**C4**	**b/a**	THF	32	3:1	88:12
9	**C5**	**b/b**	**THF**	**47**	**2:1**	**>99:1**
10	**D**	**b/b**	THF	20	97:3	98:2
11	**E1**	**b/b**	THF	32	7:3	81:19
12	**E2**	**b/b**	THF	35	6:1	63:37
13	**F1**	**b/b**	THF	35	3:1	91:9
14	**F2**	**b/b**	**THF**	**30**	**6:1**	**96:4**

[a] NHCs generated with KHMDS. [b] Isolated yield of **7**. [c] Diastereomeric ratio by ^{1}H-NMR analysis [d] er determined by HPLC over chiral stationary phases.

tivity and yield (Table 1, entry 9). Examining the 2,6-$(CH_3O)_2C_6H_3$ substituent on indanol (**D**) and pyrrolidine scaffolds (**E1** and **2**) failed to improve the outcome, while desmethyl morpholinone catalysts bearing either a 2,6-$(CH_3O)_2C_6H_3$ (**F1**) or Mes (**F2**) N-substituent gave similar outcomes (Table 1, entries 10–14). Although the optimal conditions (Table 1, entries 9 and 14) retain limitations in preparing **7c** this proved to be an outlier with all other β-lactones formed in this study isolated in good yield with excellent enantio-, and diasteropurity (see below).

Reaction generality was examined with fourteen TMS enol ethers of 1,3-diketones or β-ketoesters **9** and four dienyl acyl fluorides **8** (Table 2). TMS enol ethers of ethyl, benzyl and *t*-butyl β-ketoesters when $R^2 = H$ produced six cyclohexyl, dimethylcyclohexyl and cycloheptyl fused β-lactones (**7d**, **e** and **h–k**) in good yields. TMS enol ethers of 1,3-diketones were also viable giving ketone containing β-lactones **7f** and **g** both in >99:1 er and good yield. In all eight examples high enantiopurity (≥95:5 enantiomeric ratio) with complete diastereoselectivity was observed (>20:1 dr). Indeed, whilst studying generality 20 of the 22 examples formed as single diastereoisomers. The enforced s-*cis* conformation (i.e. annulation across R^4 and R^5) has been essential in related NHC catalyzed annulations.[4a] Pleasingly in this study acylic dienyl acyl fluoride **8d** ($R^4 = H$; $R^5 = CH_3$) could be employed to

Table 2: Scope of the (4+2) annulation.[a–c]

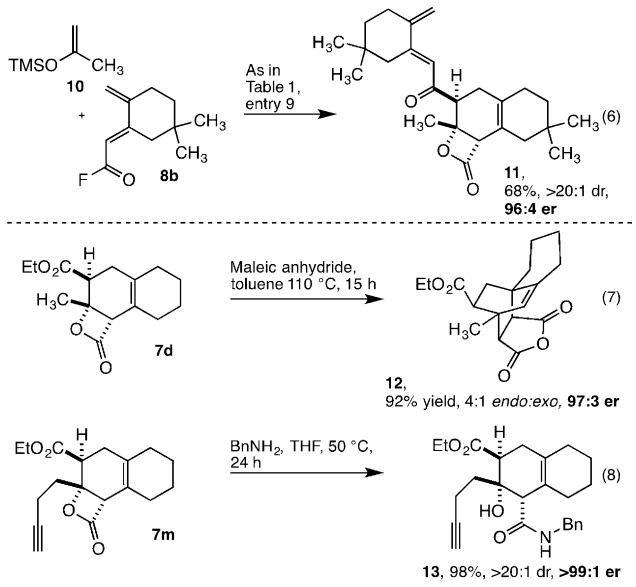


[a] Isolated yield. [b] Diastereomeric ratio by ^{1}H-NMR analysis. [c] er determined by HPLC over chiral stationary phases. [d] reaction heated to reflux. [e] 20 mol% **F2** at 0°C.

give cyclohexene **7l** in 96:4 er and with acceptable yield. Next, changes to the R^3-group were examined to produce tricyclic β-lactones bearing alkyne (**7m–o**), alkene (**7p** and **q**), aromatic (**7r** and **s**), and α,β-unsaturated ester (**7t**) functionality. In all cases the enantioselectivity remained high with most products obtained in ≥98:2 enantiomeric ratio. In the case of alkyne **7m** X-ray crystalographic analysis was performed to determine absolute stereochemistry.[15a] As highlighted in the optimization, substrates in which $R^2 = H$ allow construction of a challenging quaternary carbon with high enantioselectivity (>99:1 er), although poor diastereoselectivity and yield (Table 1, entry 9). This was further demonstrated with benzyl β-lactone **7u** prepared in 97:3 er, but as a 1:1 mixture of diastereoisomers. In contrast, cyclic TMS enol ethers gave quaternary carbon containing compounds, that is, tetracycle **7v**, with excellent yield (91%) and diastereoselectivity (>20:1), although modest enantioselec-

tivity (69:31 er). This could be improved using catalyst **F2** at 0 °C, with β-lactone **7v** formed in 81:19 er. These conditions were suitable for the synthesis of **7w** and ***x*** which formed with similar enantioselectivity and yield. The later product contains a tetracyclic ring system reminiscent of the yonarolide and scabrolide natural products[16] and is assembled in a concise 4-step sequence from commercial materials.

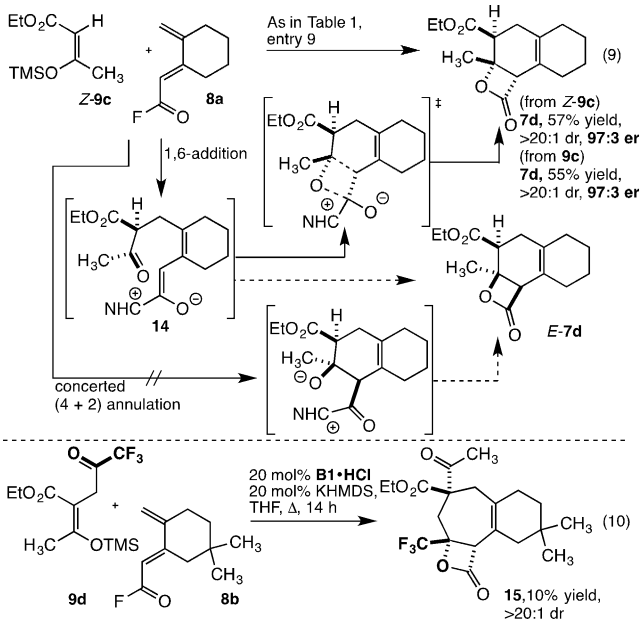
Simple enolates have been sparingly exploited in NHC catalyzed reactions of acyl azolium.[3a] When the (4+2) annulation was examined with the TMS enol ether of acetone (i.e. **10**) and dienyl acyl fluoride **8b** a Claisen-condensation/(4+2) annulation provided **11** in 96:4 er [Scheme 1, Eq. (6)]. This result suggests that the δ-position of the dienyl acyl azolium is less electrophilic than the β-position of the related α,β-unsaturated acyl azolium, thus Claisen condensation is kinetically favored over 1,6-addition.



Scheme 1. Reaction of TMS enol ether of acetone (**10**) and β-lactone stability.

The β-lactone products in this study were expected to have moderate stability due to the presence of unsaturated functionality likely to stabilise the biradicaloid transition state of decarboxylation.[17] Consistent with this prediction, it was found that decarboxylation occurred when the β-lactones were heated at reflux in dimethylformamide. While quaternary carbon containing compounds (i.e. **7a**) gave the expected diene (see the Supporting Information, SI) substrates lacking this functionality (i.e. **7d**) gave mixtures of olefin containing products. However, when the decarboxylation was performed in the presence of maleic anhydride a 92% yield of [2.2.2]-bicycle **12**[15b] was obtained, as a 4:1 mixture of the separable *endo* and *exo* isomers, indicating that the Diels–Alder reaction is more facile than olefin isomerization. As a consequence of the relatively high stability of the β-lactone β-hydroxy amide **13** could be prepared in 98% yield and > 99:1 enantiomeric ratio by simple ring-opening with benzylamine.

Mechanistically a stepwise or concerted annulation is potentially viable. To probe these scenarios *Z*-**9c** was prepared and reacted with acyl fluoride **8a** under the standard conditions [Scheme 2, Eq. (9)]. In a concerted reaction *Z*-**9c** should give *E*-**7d**. In the event the product of this reaction was **7d**, with similar yield, and identical stereoselectivity to its



Scheme 2. Mechanistic studies and (4+3) annulation.

formation from **9c**. Thus, the reaction likely proceeds via 1,6-addition to give acyl azolium enolate **14** which undergoes rotation prior to a pseudo-concerted aldol β-lactonization.[17] The likelihood of a stepwise mechanism introduces the possibility for alternate (4+*n*) reactions. For example β-lactone **7c** contains a pendant methyl ketone, that could have delivered a (4+3) adduct. Failure to observe this product is likely due to a more rapid 6-*exo*-trig cyclization (cf. 7-*exo*-trig) of the acyl azolium enolate intermediate analogous to **14**. To overcome this kinetic bias, and expand the scope of chemistry accessible via dienyl acyl azolium **2**, trifluoro methyl ketone **9d** was prepared. Pleasingly this produced cycloheptene **15** however, despite significant optimization, the yield remained poor [Eq. (10)].

Studies reported herein exploit the dienyl acyl azolium in an enantioselective (4+2) annulations with enolates. As with the lower homolog (the α,β-unsaturated acyl azolium) good outcomes can be achieved with enolates of β-ketoesters and 1,3-diketones.[3] Pleasingly these are highly abundant materials. The transformation gives rise to a diverse range of bi-, tri-, and tetracyclic β-lactones with high stereochemical purity and yield. In addition to the significant potential of this reaction to deliver enantioenriched building blocks for synthesis these studies demonstrate the first enantioselective reaction of the dienyl acyl azolium. Preliminary studies have demonstrated the viability of a (4+3) annulation, however the dienyl acyl azolium could be exploited in a host of alternate reactions by appropriate selection of the coupling partner.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,6-addition · dienyl acyl azolium · enantioselective catalysis · N-heterocyclic carbene · β-lactonization

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ORIGINAL PAPER

Quantification of the Michael-Acceptor Reactivity of α,β-Unsaturated Acyl Azolium Ions

Alison Levens[1] · Feng An[2] · Jared E. M. Fernando[1] · Armin R. Ofial[2] · David W. Lupton[1] · Herbert Mayr[2]

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Abstract
2-Cinnamoylimidazolium ions **4** have been synthesized by treatment of 2-cinnamoylimidazoles **8** with methyl triflate. They were characterised by NMR and mass spectroscopy, in one case (**4f**) also by X-ray analysis. The kinetics of their reactions [and also those of cinnamoyl fluoride (**1**)] with stabilised carbanions **9a–e** and silyl ketene acetal **9f** (reference nucleophiles) were measured photometrically. The correlation log $k(20\ °C) = s_N\,(E + N)$ was used to calculate the electrophilicity parameters E of the cinnamoyl azolium ions **4** from the resulting second-order rate constants k and the previously reported N and s_N parameters of the reference nucleophiles **9**. All 2-cinnamoylimidazolium ions **4** were found to be 2–4 orders of magnitude more electrophilic than cinnamoyl fluoride (**1**) showing that the direct attack of nucleophiles at **1** can be avoided if sufficient concentrations of **4** are produced in the NHC-catalysed reactions of **1** with nucleophiles. From the range of electrophilicity($-12 < E < -10$) for the cinnamoylimidazolium ions **4** one can derive that only nucleophiles stronger than $N \approx 7$ will react with **4** at 20 °C in reasonable time, suggesting that in NHC-catalysed reactions of cinnamoyl fluoride (**1**) with silyl enol ethers (typically $4 < N < 7$), enolate ions, produced by fluoride-induced desilylation of silyl enol ethers, are the active nucleophiles.

Keywords Kinetics · Organocatalysis · Nucleophilic carbenes · Reactivity · Electrophilicity

1 Introduction

N-Heterocyclic carbenes (NHCs) have been used as catalysts for numerous C–C bond forming reactions [1–17]. Several of these transformations proceed via intermediate acyl azolium ions, a field of great current interest [13, 14, 18–45]. In 2009, Lupton et al. reported the N-heterocyclic carbene (NHC) catalysed annulation of α,β-unsaturated acyl fluorides (**1**) with trialkylsilyl enol ethers (**2**) to afford dihydropyranones (**3**) (Scheme 1) [18].

In addition to defining a new approach to α,β-unsaturated acyl azoliums (**4**), these studies allowed the first β-additions to these intermediates [18–24]. Subsequent studies by the Monash group and others have uncovered annulations of the α,β-unsaturated acyl azolium with alternate *di*-nucleophiles or bifunctional partners ([18–24]; for selected annulations with bifunctional partners, [25–32]).

A plausible mechanism for this reaction is depicted in Scheme 1. The reaction of the NHC with the acyl fluoride **1** yields the acyl azolium ion **4** and fluoride ion (*Step 1*), which desilylates the silyl enol ether **2**. The resulting enolate ion **5** combines with the acyl azolium ion **4** to generate **6** (*Step 2*) [19, 33–36]. Subsequent tautomerisation yields the acyl azolium ion **6′** (*Step 3*), which cyclises with formation of the dihydropyranone **3** and regeneration of the NHC catalyst (*Step 4*). While this mechanism is reasonable, alternate scenarios can be envisioned that give rise to the same outcome (for selected mechanistic contributions to the field of

Dedicated to the memory of George A. Olah, creator of a new access to organic reactivity.

Alison Levens and Feng An contributed equally to this work.

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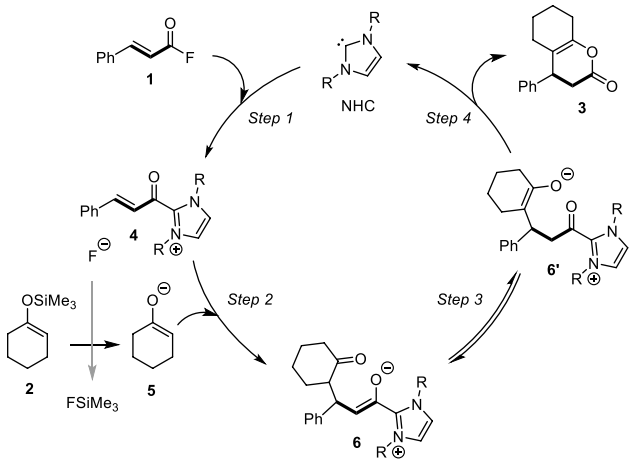


Scheme 1 Plausible catalytic cycle for the NHC-catalysed reaction of acyl fluoride **1** with 1-(trimethylsiloxy)-cyclohexene (**2**)

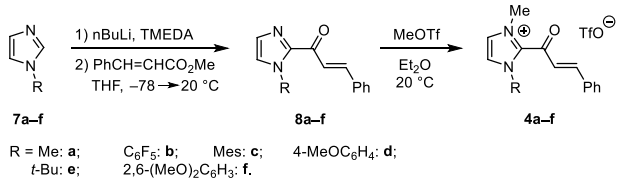
NHC catalysis [36–45]). To test the viability of the proposed mechanism and to explore the scope of this reaction principle we have addressed the following questions:

(1) Which NHCs are nucleophilic enough to react with acyl fluorides?
(2) Are α,β-unsaturated acyl azolium ions generally more electrophilic than the corresponding α,β-unsaturated acyl fluoride, i.e., can background reactions be suppressed?
(3) Which types of nucleophiles are able to attack at the unsaturated acyl azoliums? Specifically, is the silyl enol ether **2** or the desilylated enolate **5** the nucleophile in this reaction?

In previous work, we had already reported the influence of the substituents R on the nucleophilic reactivities of the NHCs ([46, 47]; for studies on the impact of the N-substituent in NHC organocatalysis see [48–51]). Furthermore, the electrophilicity of the α,β-unsaturated acyl azolium ion **4a** (R = Me) has been determined in collaboration with Studer et al. [36]. Building upon these studies, we now report a kinetic analysis of the electrophilicities of a series of α,β-unsaturated acyl azolium ions (**4b–f**) and of acyl fluoride **1** which allows the above questions to be answered.

2 Synthesis of the Acyl Imidazolium Triflates

Cinnamoylimidazolium triflates **4b–f** were prepared in analogy to the previously reported synthesis of **4a** [36]: Treatment of the imidazoles **7b–f** with n-butyl lithium and methyl cinnamate gave the cinnamoyl-imdazoles **8b–f**, which were methylated with methyl triflate in diethyl ether at ambient



Scheme 2 Synthesis of the cinnamoylimidazolium triflates **4b–f** (for **4a**, see [36])

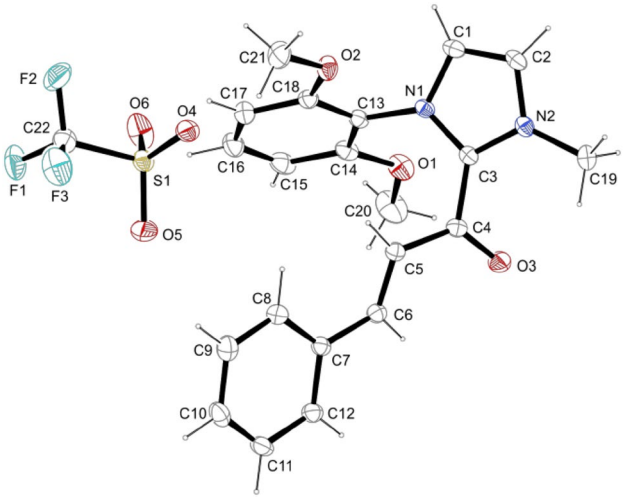
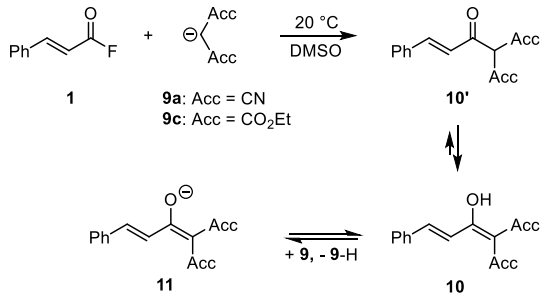


Fig. 1 ORTEP plot of the single crystal X-ray structure of **4f** (represented by 50% thermal ellipsoids) [see Footnote 1]

temperature to give the acyl imidazolium triflates **4b–f** (Scheme 2).

Cinnamoylimidazolium triflate **4f** was crystallised at room temperature by vapour diffusion of pentane into a saturated solution of **4f** in dichloromethane and subsequently analysed by single crystal X-ray crystallography (Fig. 1).[1] The dihedral angle of 11° (O3–C4–C5–C6) in the X-ray structure of **4f** in Fig. 1 shows that the coplanarity of the CC double bond and the carbonyl group is not significantly disturbed by the bulky 2,6-dimethoxy-substituted phenyl ring attached to N1 of the imidazolium ring. In this conformation, the carbonyl group can activate the conjugated CC double bond for 1,4-additions almost as efficiently as in the previously investigated acyl imidazolium electrophile **4a** [36], which showed a dihedral angle of 6° for the Michael-acceptor unit. The plane of the imidazolium group in crystals

[1] CCDC 1532919 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre (for details on the isolation and characterisation of **4f** see Supporting Information).



Scheme 3 Reactions of cinnamoyl fluoride (**1**) with the carbanions **9a** and **9c**

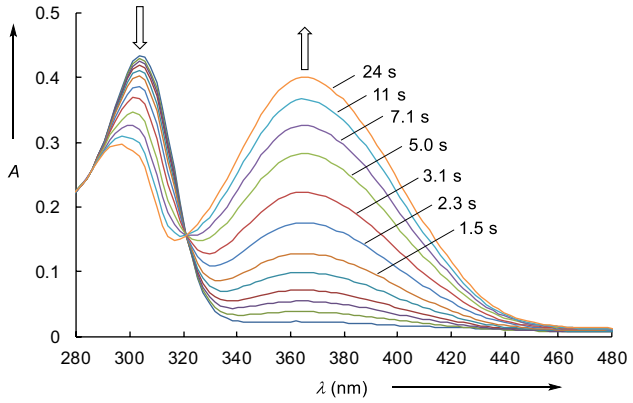


Fig. 2 UV–Vis spectra (stopped-flow method) during the reaction of **1** (5.08×10^{-5} M) with **9c** (3.11×10^{-3} M) in DMSO at 20 °C

of **4f** is twisted by 40° relative to the adjacent carbonyl group, similar to the corresponding twist in **4a** (35°) [36].

3 Determination of the Electrophilicity of the Acyl Fluoride 1

The reactions of the acyl fluoride **1** with the carbanions **9a** and **9c** initially gave the unsaturated ketone **10′**. It is not clear whether this substitution proceeds through tetrahedral intermediates or whether fluoride departs before the new C–C bond is fully established. Tautomerisation of **10′** gave the enols **10**, which were characterised by NMR spectroscopy (Scheme 3). Under the conditions of the kinetic experiments (**9a** and **9c** were used in high excess over **1** to achieve pseudo-first-order conditions) subsequent deprotonation yielded the highly delocalised weakly basic enolate ions **11**.

An isosbestic point was observed when **1** was combined with 61 equivalents of **9c** indicating that **10** does not accumulate in the course of the reaction (Fig. 2). The fact that the absorbance at λ = 312 nm (reactant **1**) decreases 24% more slowly than the λ = 364 nm absorbance increases (product **11**) is due to the fact that the absorption band of **1** overlaps

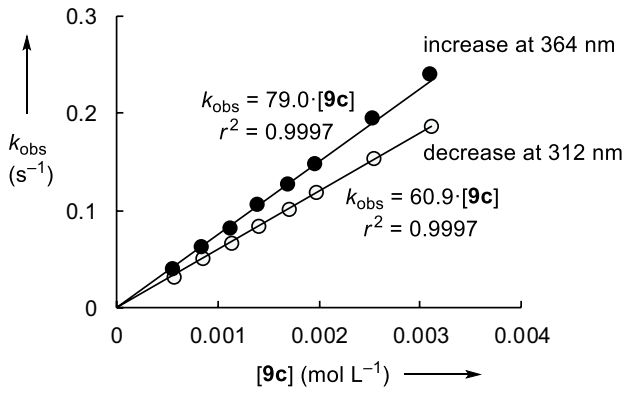
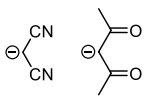
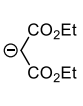
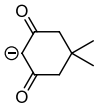
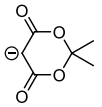
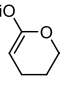


Fig. 3 Plot of the first-order rate constants k_{obs} versus the concentration of **9c** for the reaction of **1** with **9c** in DMSO at 20 °C

Table 1 Reference nucleophiles and their *N* and s_N parameters in DMSO (data from Footnote 2)

	9a	9b	9c	9d	9e	9f
						
N (s_N)	19.36 (0.67)	17.64 (0.73)	20.22 (0.65)	16.27 (0.77)	13.91 (0.86)	10.52 (0.78) in MeCN

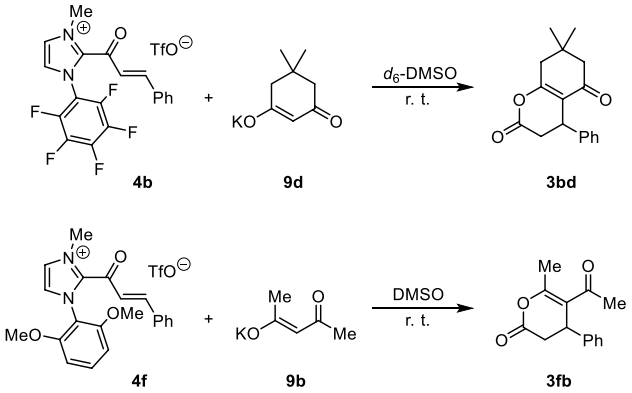
with the signal of the developing product, in line with the hypsochromic shift of the 312 nm maximum during the reaction. The monoexponential increase of the concentration of **11** indicates the first-order dependence of the rate on the concentration of **1**, and the linear increase of the first-order rate constants with the concentration of the carbanion **9** (Fig. 3) shows that CC-bond formation and not the subsequent proton transfer to give **11** is rate-determining. The reaction thus follows second-order kinetics, first order in **1** and first order in **9**.

4 Determination of the Electrophilicities of the Acyl Azolium Ions 4b–f

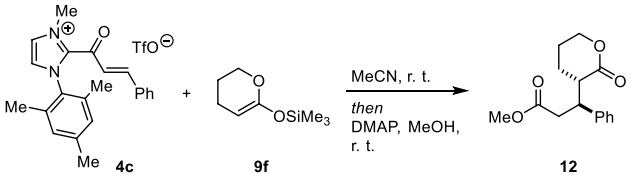
In order to quantify the electrophilicities of the acyl azolium ions we have studied the kinetics of their reactions with the carbanions **9a–e** and the ketene acetal **9f** (reference nucleophiles, Table 1).[2]

As representative examples for the course of the reactions of the acyl azolium ions with carbanions, we have investigated the reactions of **4b** and **4f** with different potassium

[2] Access to all reactivity parameters at http://www.cup.lmu.de/oc/mayr/DBintro.html.



Scheme 4 Formation of dihydropyranones **3** by the reactions of cinnamoyl azolium ions with carbanions



Scheme 5 Conjugate addition of the ketene acetal **9f** to the acyl azolium ion **4c**

give the lactone analogue of intermediate **6**. As this reaction was not carried out under basic conditions as the reactions in Scheme 4, deprotonation of the lactone fragment does not occur. As a consequence, cyclisation does not take place and the reaction stops at the stage of **6**. Methanolic workup converts the corresponding acyl azolium ion into the methyl ester **12** (Scheme 5).

As the acyl azolium ions **4b–f** (the analogous reaction of **4a** has previously been reported [36]) have UV-maxima between 320 and 355 nm, the kinetics of their reactions with the nucleophiles **9a–f** could be followed photometrically in DMSO solution (**9a–e**) or acetonitrile (**9f**, Fig 4a) using conventional UV–Vis spectrometers with fiber optics or stopped-flow instruments as described previously [36]. By using more than 10 equivalents of the nucleophiles, pseudo-first order conditions were achieved as shown by the monoexponential decays of the absorbances of **4**, which is illustrated for the reaction of **4f** with **9f** in Fig. 4b. Figure 4c furthermore shows exemplarily that k_{obs} increases linearly with the concentration of the nucleophiles **9**, and the slopes of these correlations correspond to the second-order rate constants k_2 listed in Table 2.

In numerous kinetic investigations we have shown that the rate constants for the reactions of nucleophiles with carbenium ions and electron-deficient π-systems can be expressed by Eq. (1), where nucleophiles are characterised by two solvent-

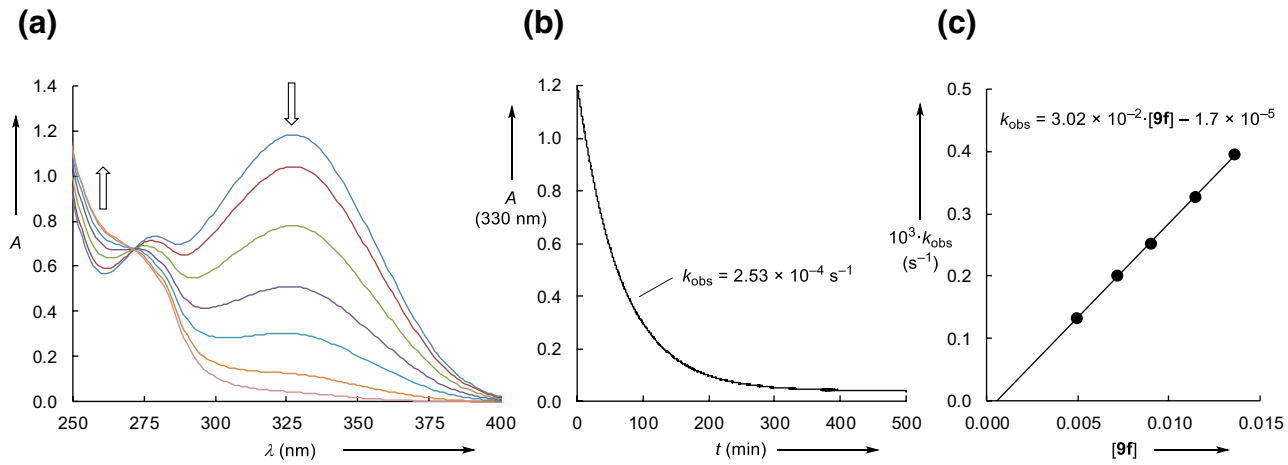


Fig. 4 **a** UV–Vis spectra during the reaction of **4f** (1.24×10^{-4} mol L^{-1}) with **9f** (9.04×10^{-3} mol L^{-1}) in acetonitrile at 20 °C; **b** determination of the first-order rate constant k_{obs} from the decay of the absorbance *A* at 330 nm with time; **c** determination of the second-order rate constant k_2 from the linear correlation of k_{obs} with [**9f**]

salts as shown in Scheme 4. The mechanism of these reactions corresponds to Steps 2–4 of Scheme 1.

A different type of product was observed in the reaction of **4c**-OTf with the ketene acetal **9f** (Scheme 5). Since fluoride ions are absent when a pregenerated acyl azolium triflate **4**-OTf is used, we can assume that **9f**, which is considerably more nucleophilic ($N = 10.52$, Table 1) than the enol ether **2** ($N = 5.21$ [52]), directly attacks the acyl azolium ion **4c** to

dependent parameters, N and s_N, and electrophiles are characterised by the electrophilicity parameter E (for development of this relationship see [52–54] and Footnote 2).

$$\log k(20\ ^\circ\mathrm{C}) = s_N(E + N) \quad (1)$$

As shown in Fig. 5 for the reactions of **4b, 4c**, and **4f** (and for all other acyl azolium ions in the Supporting

Table 2 Second-order rate constants for the reactions of acyl fluoride **1** and acyl azolium ions **4a–f** with nucleophiles **9a–f** in DMSO at 20 °C and the resulting electrophilicity parameters *E*

Electrophiles	Nuc	k_2 (L mol^{-1} s^{-1})	*E*
1	**9a**	4.25×10^{2}	(−15.4)[a]
	9c	7.90×10^{1}	(−17.3)[a]
4a (R = Me)[b]	**9a**	2.29×10^{5} [b]	−11.52[b]
	9b	5.84×10^{4} [b]	
	9d	9.03×10^{3} [b]	
	9e	2.75×10^{2} [b]	
	9f[c]	6.19×10^{-2} [b,c]	
4b (R = C_6F_5)	**9d**	1.50×10^{5}	−10.09
	9e	2.44×10^{3}	
	9f[c]	6.34×10^{-1} [c]	
4c (R = Mes)	**9a**	2.12×10^{5}	−11.48
	9b	3.15×10^{4}	
	9d	7.78×10^{3}	
	9e	1.61×10^{2}	
	9f[c]	7.39×10^{-2} [c]	
4d (R = 4-MeOC_6H_4)	**9a**	8.97×10^{4}	−11.79
	9b	1.78×10^{4}	
	9d	5.87×10^{3}	
	9e	1.22×10^{2}	
	9f[c]	3.47×10^{-2} [c]	
4e (R = *t*-Bu)	**9a**	8.23×10^{4}	−11.80
	9b	1.64×10^{4}	
	9d	5.60×10^{3}	
	9e	1.74×10^{2}	
	9f[c]	2.56×10^{-2} [c]	
4f (R = 2,6-$(MeO)_2C_6H_3$)	**9a**	8.28×10^{4}	−12.02
	9b	1.12×10^{4}	
	9d	3.70×10^{3}	
	9e	5.25×10^{1}	
	9f[c]	3.02×10^{-2} [c]	

[a]Eq. (1) unreliable, see text

[b]Data for **4a** from [36]

[c]In acetonitrile

Information) all plots of (log *k*)/s_N versus *N* are linear with slopes close to 1.0. The fact, that the deviations from the correlation lines in Fig. 5, where the slope of 1.0 was enforced, are negligible, indicates that all reactions follow Eq. (1), i.e., the negative intercepts on the abscissa (log *k* = 0) correspond to the electrophilicity parameters *E* for the acyl azolium ions **4**, which are listed in the last column of Table 2.

In accordance with unpublished work of the München group, Eq. (1) does not work well for the reactions of nucleophiles with acyl halides. The different electrophilicity parameters *E* of **1**, derived from its reactions with **9a** and **9c** (first two entries in Table 2) also illustrate the limitations of Eq. (1). Nevertheless, these numbers give an estimate for

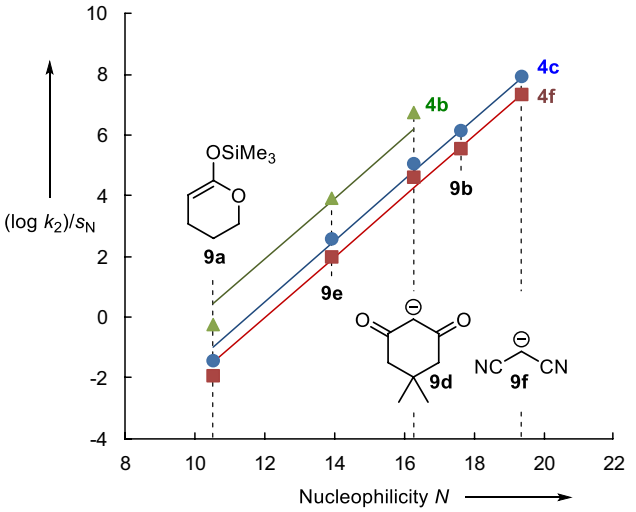


Fig. 5 Plot of (log *k*)/s_N versus *N* for the reactions of **4b, 4c**, and **4f** with the reference nuceophiles **9**; slopes of the correlations are fixed to 1.0, as required by Eq. (1)

the electrophilic reactivity of cinnamoyl fluoride **1** and allow us to answer the key questions raised above.

5 Conclusions

(1) Though Eq. (1) is not suitable for accurately predicting rate constants for the reactions of acyl halides with nucleophiles, the estimated *E* value for **1** in Table 2 suggests that **1** will react with all common imidazole- and triazole-derived NHCs ($14 < N < 23$) (see Footnote 2), though the reactions with triazole-derived carbenes are expected to be slow.

(2) Comparison of the electrophilicities of **4a–f** ($-12 < E < -10$) with the approximate reactivity parameter of **1** ($E \approx -16$) shows that acyl azolium ions **4a–f** are considerably more reactive than **1**, which can also be derived from the directly measured rate constants for their reactions with the malononitrile anion **9a** (Table 2). As a consequence, background reactions, i.e., the direct attack of nucleophiles at **1** will not take place as long as sufficient concentrations of **4** are produced.

(3) From the electrophilicity parameters *E* of **4a–f** one can derive that direct reactions of ordinary silyl enol ethers, such as **2**, with the acyl azolium ions **4a–f** are unlikely to occur at ambient temperature. From $N = 5.21$ (and $s_N = 1.0$) for enol ether **2** [52] and $-12 < E < -10$ for the acyl imidazolium ions **4a–f** (Table 2) one can calculate (Eq. 1) that the direct attack of **2** at **4a–f** would lead to 50% conversion within 1–70 days in 1 M solutions

of the reactants at 20 °C. This calculation supports the previously suggested mechanism for the NHC-catalysed reaction of **1** with siloxycyclohexene **2** through the enolate **5** (Scheme 1). As shown in Scheme 5, the 10^5 times more nucleophilic ketene acetal **9f** ($N = 10.52$) (see Footnote 2) can directly attack at acyl azolium ions, however, and does not require a prior fluoride-induced desilylation. Thus, nucleophiles with $N \approx 10$, including suitably substituted enamines and methylated pyrroles (see Footnote 2), can be expected to be reactive enough to rapidly attack at acyl azolium ions but too sluggish to undergo fast reactions with acyl fluorides and are, therefore, considered promising candidates for further NHC-catalysed reactions with acyl fluorides.

Acknowledgements The authors thank the Australian Research Council (Discovery Program DP120101315) and the Deutsche Forschungsgemeinschaft (SFB 749, Project B1) for financial support and Dr. Peter Mayer for the X-ray analysis of **4f**. DWL is grateful to the Alexander von Humboldt Foundation for the Ludwig-Leichardt Award.

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NHC Catalysis Hot Paper

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Enantioselective N-Heterocyclic Carbene Catalysis that Exploits Imine Umpolung

*Jared E. M. Fernando, Yuji Nakano, Changhe Zhang, and David W. Lupton**

Abstract: *The catalytic umpolung of imines remains an underdeveloped approach to reaction discovery. Herein we report an enantioselective aza-Stetter reaction that proceeds via imine umpolung using N-heterocyclic carbene catalysis. The reaction proceeds with high levels of enantioselectivity (all ≥96:4 er) and good generality (21 examples). Mechanistic studies are reported and are consistent with turnover-limiting addition of the NHC to the imine.*

N-Heterocyclic carbenes (NHCs, **1**) provide access to normal and reversed-polarity intermediates that are integral to many reactions.[1] While a wide range of reactive intermediates are accessible, they are almost invariably formed via the Breslow intermediate (**2**), itself derived from aldehyde substrates (**3**). Alternate substrates for NHC catalysis are known, such as esters,[2] ketones,[3] and conjugate acceptors,[4] however these remain less commonly examined, and a number of functional groups have been largely overlooked.

Imines are easily prepared electrophiles that would appear well suited to polarity-inversion catalysis. Surprisingly enantioselective reactions of such substrates, under any type of catalysis, have only recently been reported, with access to 2-aza-anion intermediates enabling various alkylations.[5,6] NHC catalysis with imines has been known since the early 2000s, however, these studies demonstrate that while they are viable as electrophilic coupling partners, they do not undergo polarity inversion.[7,8] For example, in 2005, the Bode group reported the coupling of cinnamaldehydes with sulfonate-imine **4** to give pyrolidinones **5** [Figure 1, Eq. (1)] in a reaction that proceeds via the homoenolate intermediate, not the imine umpolung (aza-Breslow) intermediate.[8b] Independent work by the groups of Hou[9a] and Chi[9b] has demonstrated that related Ts-imines can serve as precursors to the sulfinate anion, presumably through fragmentation of the aza-Breslow intermediate. However, it wasn't until 2017 that Biju and Suresh independently reported cycloisomerization of imine **6** to indole **7** [Figure 1, Eq. (2)] in the first NHC catalyzed reaction involving imine umpolung.[10a,d] Subsequently, the aza-Breslow intermediate has been invoked in the oxidation of imines to amides,[10b] and a quinolone synthesis.[10c] While these reports demonstrate the viability of the aza-Breslow intermediate in reaction discovery, key challenges remain, perhaps most notably regarding enantioselective catalysis. As part of our interest in NHC catalysis with unconventional substrates, we commenced studies on this topic. In addition to providing a new enantioselective transformation, we felt that such studies could facilitate access to nitrogenous secondary intermediates analogous to the Breslow intermediate (Figure 1). Herein, we report an enantioselective intermolecular aza-Stetter reaction [Figure 1, Eq. (3)].[11] The reaction proceeds with excellent enantioselectivity, allowing a range of imines (**8**) to couple with 3-methylene-chroman-2-ones (**9**) to provide highly enantioenriched γ-imino lactones (**10**). While the enantioselective reaction requires 3-methylene-chroman-2-ones, achiral catalysts allow use of simple acrylates.

We postulated that the imine protecting group would be most influential on aza-Breslow intermediate formation, and hence reaction viability. Thus, studies commenced by screening a number of protected aldimines (**8a–e**) using achiral catalyst **A1** (Table 1, entries 1 and 2). When heated in THF at reflux, imines **8a–d** gave no coupled products, with **8a**, **b**, and **d** isolated unchanged, while **8c** gave the product of sulfinate addition.[9c] In contrast, benzoyl imine **8e** gave enone **12e** in 82% yield of isolated product. We believe that the unique viability of this protecting group is due to a combination of its electron-withdrawing capacity and enhanced stability compared to **8c**. Formation of **12e** is consistent with a reaction of

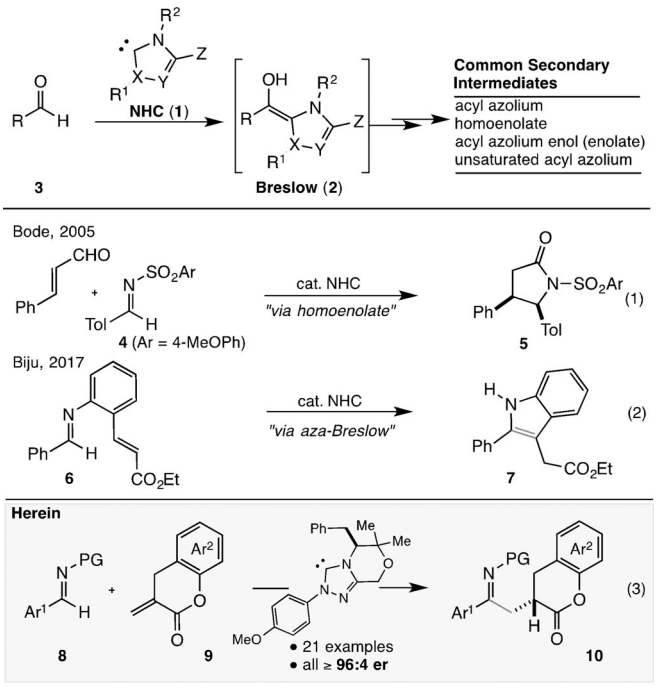

Figure 1. Previously and this work.

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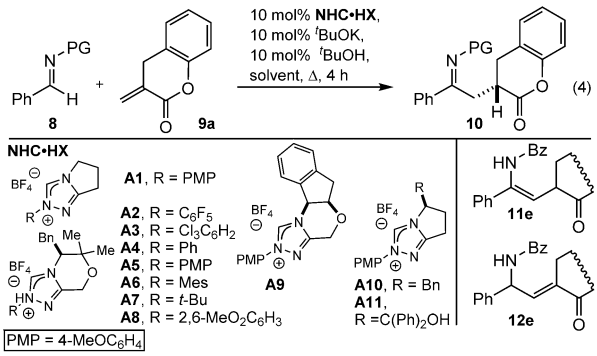
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201812585.

Table 1: Discovery of the enantioselective aza-Stetter.



Entry	NHC	Imine	solvent	**10**/**11**/**12**[a]	Yield[b]	er[c]
1	**A1**	**8a** (Boc)	THF	–	0	–
		8b (Ac)				
		8c (Ts)				
		8d ($P(O)Ph_2$)				
2	**A1**	**8e** (Bz)	THF	–	82 (**12e**)	–
3	**A2–4**, **A7**	**8e** (Bz)	THF	–	0	–
4	**A5**	**8e** (Bz)	THF	0:5:2	49 (**11e**)	–
5	**A6**	**8e** (Bz)	THF	–	*trace*	–
6	**A8**	**8e** (Bz)	THF	0:0:1	46 (**12e**)	–
7[d]	**A5**	**8e** (Bz)	Dioxane	5:0:3	50	98:2
8[d]	**A9**	**8e** (Bz)	Dioxane	2:1:0	43	98:2
9[d]	**A10**	**8e** (Bz)	Dioxane	0:0:1	80 (**12e**)	ND[e]
10[d]	**A11**	**8e** (Bz)	Dioxane	–	0	–
11[d]	**A5**	**8e** (Bz)	THF	7:1:0	65	98:2
12[d,f]	**A5**	**8e** (Bz)	THF	8:1:0	77	99:1

[a] Ratio by ^{1}H NMR analysis. [b] Yield of isolated product. [c] By HPLC with a chiral stationary phase. [d] 2 h. [e] ND = not determined. [f] 100 mol% ^{t}BuOH.

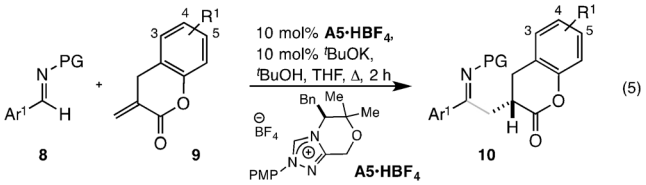
either the polarity-inverted conjugate acceptor[4] or the imine, followed by isomerization of **10e** to enone **12e**, with subsequent mechanistic studies supporting the later (see below). Attention was now directed to identification of catalysts for the enantioselective variant of the reaction. While catalysts **A2–4** and **A7** gave no coupled material (Table 1, entry 3), the more nucleophilic[12] **A5** (R = 4-$MeOC_6H_4$)[13] and **A8** (R = 2,6-$MeO_2C_6H_3$)[14] gave enamine **11e** and isomeric enone **12e** in comparable yields (Table 1, entries 4 and 6). By exploiting shorter reaction times, in higher-boiling dioxane, isomerization was somewhat suppressed, which allowed γ-imino ester **10e** to be isolated in 50% yield with excellent enantiopurity (98:2 er) (Table 1, entry 7). A similar outcome was achieved with indanol **A9**, while pyrrolidine **A10** exclusively gave enone **12e**, and catalyst **A11** gave no coupled products (Table 1, entries 8–10). With catalyst **A5**, the outcome was improved by returning to the lower-boiling THF (Table 1, entry 11), while use of an equivalent of ^{t}BuOH[15a] gave **10e** in 77% yield and in a 99:1 enantiomeric ratio (Table 2, entry 12).

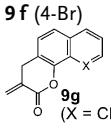
Having achieved a highly enantioselective reaction, the generality was examined by coupling twelve aryl and heteroaryl aldimines to seven chromanones (Table 2). Aldimines bearing electron-donating, electron-withdrawing, and heteroaromatic Ar^1 substituents all coupled to lactone **9a** to give aza-Stetter products **10e–i** with high enantiopurity (all ≥98:2 er), with the highest yields obtained when using electron rich imines (Table 2, entries 1–5). Unfortunately, aliphatic imines bearing acidic α-protons, such as the benzoyl imine of *iso*-butyraldehyde, underwent facile isomerization to the corresponding enamine, a common limitation in imine based catalysis.[16] Next, the imine protection was modified, with 4-MeOBz- and 4-ClBz-protected aldimines reacting to give the four products **10j–m** with 59–73% yield and ≥98:2 er (Table 2, entries 6–9).

Next, we examined a series of chromanone derivatives bearing alkyl (**9b**, **d** and **e**), electron-releasing (**9c**), or electron-withdrawing (**9f**) groups at the 3-, 4-, and 5-positions. All gave the expected aza-Stetter products (**10n–t**) with excellent enantioselectivity (≥96:4 er). The yields suggest a sensitivity to electronic effects, with the electron-rich and electron-poor products **10q** and **10t** formed in modest yields of 45 and 49% (Table 2, entries 10–16). Finally naphthalene- and quinoline-derived chromanones (**9g** and **9h**) coupled with various imines to give the expected products **10u–y** with excellent enantioselectivity (all ≥96:4 er), although the heterocyclic products formed with modest yields (Table 2, entries 17–21).

Attempts to expand the range of conjugate acceptors met with limited success. For example, chalcone, cyclohexan-2-one, 2-amino acrylates, and methylmethacrylate all failed to couple with various imines using catalyst **A5**. In these cases,

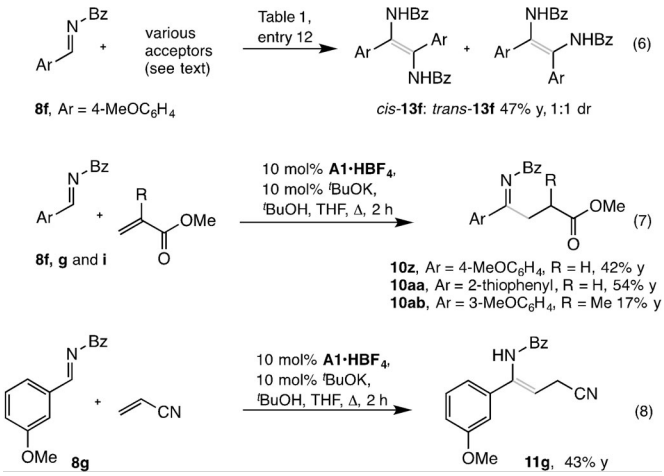
Table 2: Scope of the enantioselective aza-Stetter.



entry	Ar^1	PG	**9** (R^1)	Product **10**	Yield **10**[a]	er[b]
1	Ph	Bz	**9a** (H)	**e**	77	99:1
2	4-$MeOC_6H_4$	Bz	**9a** (H)	**f**	67	98:2
3	3-$MeOC_6H_4$	Bz	**9a** (H)	**g**	80	99:1
4	4-BrC_6H_4	Bz	**9a** (H)	**h**	52	98:2
5	2-thiophenyl	Bz	**9a** (H)	**i**	88	99:1
6	Ph	(4-MeO)Bz	**9a** (H)	**j**	73	98:2
7	4-BrC_6H_4	(4-MeO)Bz	**9a** (H)	**k**	61	98:2
8	4-$MeOC_6H_4$	(4-MeO)Bz	**9a** (H)	**l**	59	99:1
9	Ph	(4-Cl)Bz	**9a** (H)	**m**[c]	60	98:2
10	4-MeC_6H_4	(4-MeO)Bz	**9b** (4-Me)	**n**	78	99:1
11	2-thiophenyl	Bz	**9b** (4-Me)	**o**	79	99:1
12	4-MeC_6H_4	Bz	**9b** (4-Me)	**p**	61	99:1
13	Ph	(4-MeO)Bz	**9c** (4-MeO)	**q**	45	98:2
14	4-$MeOC_6H_4$	Bz	**9d** (4-Et)	**r**	64	97:3
15	Ph	(4-MeO)Bz	**9e** (3,5-Me_2)	**s**	75	98:2
16	"	(4-MeO)Bz	**9f** (4-Br)	**t**	49	96:4
17	"	(4-MeO)Bz	 **9g** (X = CH)	**u**	63	96:4
18	2-thiophenyl	Bz		**v**	81	98:2
19	3-$MeOC_6H_4$	Bz		**w**	68	>99:1
20	2-thiophenyl	Bz	**9h** (X = N)	**x**	47	98:2
21	3-$MeOC_6H_4$	Bz		**y**	44	96:4

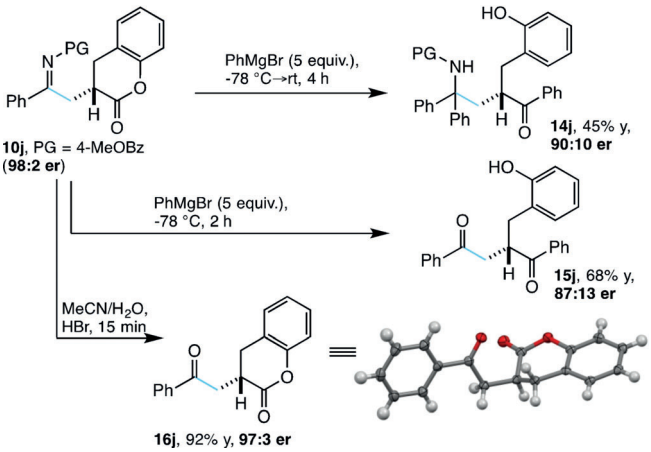
[a] Yield of isolated **10**. [b] By HPLC with chiral stationary phases. [c] Compound **10m** contaminated by ≈10% of inseparable byproduct, likely **11m** and **12m**.

the acceptor was often isolated while the imine dimerized to give aza-benzoin products **13** [Eq. (6)]. In contrast to the benzoin condensation of aldehydes, which is considered to be reversible,[15b] aza-benzoin **13** did not serve as an aza-Breslow precursor,[17] and hence formation of **13** impacts the generality of the aza-Stetter reaction. In contrast, when the achiral catalyst **A1** was used, methylacrylate and methylmethacrylate gave the aza-Stetter products **10z–ab** [Eq. (7)], while acrylonitrile gave the related enamine **11g** [Eq. (8)]. These reactions suggest that alternate variants of the enantioselective aza-Stetter reactions may well be viable, although the current reaction shows significant sensitivity to substitution, with methylmethacrylate-derived **10ab** forming in low yield.

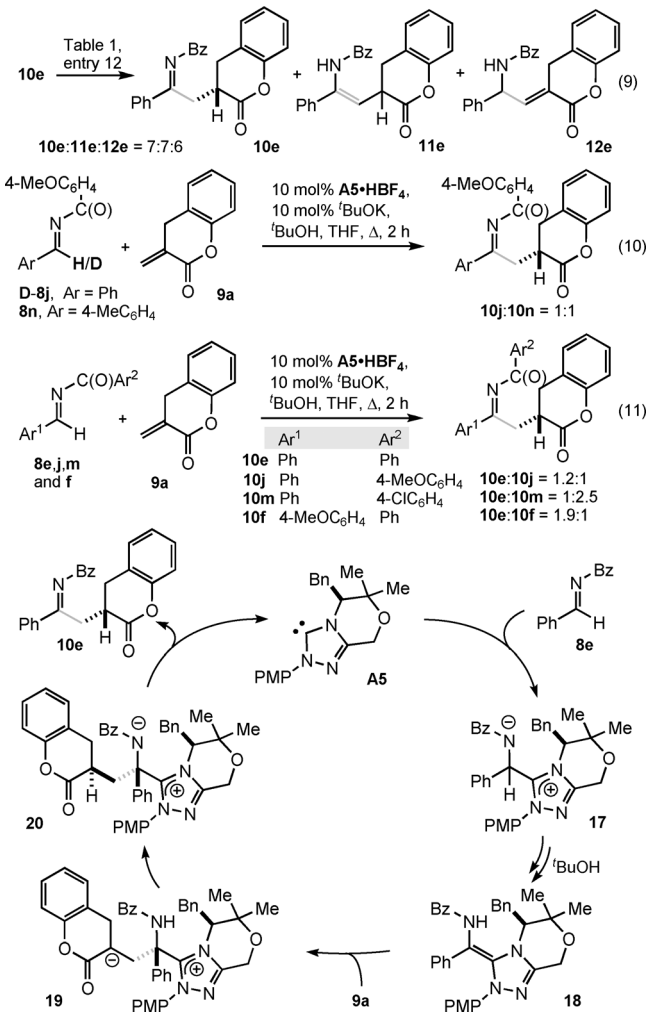


Derivatization was undertaken to examine the reactivity of the products and allow the absolute configuration to be determined (Scheme 1). Exhaustive addition of PhMgBr to **10j** gave triphenyl benzamide **14j**, while at lower temperature, chemoselective addition of PhMgBr gave diketone **15j**. Some erosion of enantiopurity was observed in both cases. Finally hydrolysis gave γ-keto ester **16j**, from which single-crystal X-ray analysis was performed to allow absolute configuration to be determined.[18]

From our optimization and scope studies, it appears that the aza-Breslow intermediate is less reactive than the Breslow intermediate, and that catalysis requires highly nucleophilic NHCs. To gain more detailed mechanistic information, studies commenced by examining the significance of enamine and enone formation observed during optimization. When imine **10e** was re-subjected to the reaction conditions a 7:7:6 mixture of **10e**, **11e**, and **12e** was obtained [Scheme 2, Eq. (9)]. In contrast, re-subjection of enamine **11e** or enone **12e** to the reaction conditions failed to produce **10e**, with **11e** and **12e** returned, along with unidentified decomposition products. These results are consistent with imine umpolung leading to **10e**, rather than homoenolate formation providing **11e** or **12e**, which isomerizes to imine **10e**. Next, experiments were performed to examine the turnover-limiting step. Competition between **D-8j** and **8n**, with associated controls,[19a] showed an absence of a primary KIE [Scheme 2, Eq. (10)], thus deprotonation is unlikely to be turnover-limiting. When competition studies with electronically differentiated protecting groups (i.e. **8e** vs. **8j** and **8e** vs. **8m**) were undertaken, the results demonstrated that the reaction is



Scheme 1. Derivatization studies with aza-Stetter product **10j** and ORTEP of ketone **16j**.



Scheme 2. Mechanistic studies.

enhanced by electron-withdrawing imine protection [Scheme 2, Eq. (11)].[19b] This trend was also observed with competition experiments involving manipulation of the electronic properties of the imine Ar^1 group (**8e** vs. **8f**). Taken together, these results are consistent with turnover-limiting addition of the NHC to the imine to afford **17**. Further support for this interpretation can be derived from kinetic studies into the order of the reaction.[20] Preliminary studies show the reaction to be close to zero order with respect to the chromanone (0.30), and first order with respect to the NHC (0.74) and imine (1.12). Unfortunately, while related aza-Breslow intermediates have been isolated,[7,8] this was not possible with benzoyl imine **8**, with all attempts leading to the formation of dimeric aza-Benzoin products **13**. In summary, we conclude that turnover-limiting addition to the imine is followed by ^{t}BuOH mediated tautomerization to afford aza-Breslow **18**, which undergoes 1,4-addition to chromanone **9** to provide enolate **19**. Diastereoselective protonation provides **20**[21] with elimination of the catalyst to complete the cycle.

Herein, we report the first enantioselective NHC-catalyzed reaction involving imine umpolung. Key to its success is the use of catalysts more nucleophilic than those used in acyl anion reactions. Good generality with respect to the imine was observed, while the conjugate acceptor is more limited. Mechanistic studies implicate turnover-limiting addition of the NHC to the imine.

A wealth of reactions exploit the Breslow intermediate en route to diverse secondary intermediates (Scheme 1). While our studies show the aza-Breslow intermediate to be less reactive, we expect related, as well as unique, enantioselective reaction designs to be possible via related secondary intermediates. Studies on this topic are ongoing.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enantioselective catalysis · imine umpolung · N-heterocyclic carbenes · Stetter reaction

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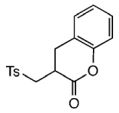

10c

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[17] Subjection of **13f** to the reaction conditions with acceptor **9a** failed to provide imine **10f**.

[18] Single crystal X-ray analysis of γ-ketoester **18j** using CuK radiation for absolute stereochemistry. CCDC 1862310 (**18j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] a) Competition between **8j** and **n** was performed and the **10j**/**10n** ratio determined as a baseline for the competition defined in Eq. (9); b) To assess whether the ratio of products in the competition relates to kinetics of the reaction or stability of the product, the competition between **8n** and **8j** was monitored by ^{1}H-NMR (see the Supporting Information). The ratio of products is constant over the entire reaction, which is consistent with a kinetic interpretation.

[20] The order of the reaction with respect to imine **8e**, chromanone **9a**, and catalyst **A5** was determined (see the Supporting Information for details). While these studies are consistent with our mechanism, ongoing work is being performed to enhance the accuracy.

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Communications

NHC Catalysis

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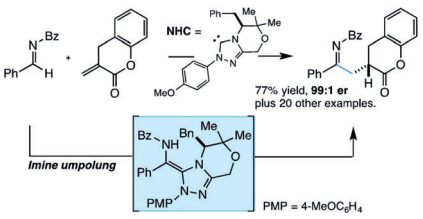
Enantioselective N-Heterocyclic Carbene Catalysis that Exploits Imine Umpolung



Poles apart: Imine umpolung is an underdeveloped area of enantioselective catalysis. N-Heterocyclic carbenes (NHCs) were used to catalyze an enantioselective aza-Stetter reaction. In contrast to acyl umpolung with NHCs, this reaction requires highly nucleophilic catalysts. The reaction is highly enantioselective (all $\geq$96:4 er) and accepts various imines and 3-methylenechroman-2-ones.