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TUTORIAL REVIEW

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Organocatalytic Lewis base functionalisation of carboxylic acids, esters and anhydrides *via* C1-ammonium or azolium enolates

Louis C. Morrill and Andrew D. Smith*

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This *tutorial review* highlights the organocatalytic Lewis base functionalisation of carboxylic acids, esters and anhydrides *via* C1-ammonium/azolium enolates. The generation and synthetic utility of these powerful intermediates is highlighted through their application in various methodologies including aldol-lactonisations, Michael-lactonisations/lactamisations and [2,3]-rearrangements.

Key learning points

This tutorial review will:

(1) Define C1-ammonium and azolium enolates and place them in context with other related methodologies.

(2) Outline how these enolates can be accessed from carboxylic acids, esters and anhydrides and why this is desirable.

(3) Showcase the utility of these enolates in organic synthesis.

(4) Provide clear explanations of the mechanisms of reactions and insights into the origin of stereocontrol.

(5) Show the current scope and limitations of this area and define challenges for the future.

1. Introduction

The development of new synthetic methods that allow rapid access to valuable chemical motifs from readily accessible starting materials is an enduring goal of organic synthesis. Organocatalysis is now a thoroughly established member of the organic chemists' toolbox, with a range of reaction modes defined and applied to diverse synthetic transformations.[1] Lewis bases,[2] most simply defined by their ability to donate a lone pair of electrons, have found widespread utility in organocatalysis, particularly *via* enamine,[3] iminium[4] and SOMO[5] activation. Lewis base organocatalysis also encompasses both ammonium[6] and azolium[7] enolate reaction modes that utilise tertiary amine or N-heterocyclic carbene (NHC) catalysts respectively. Both have become powerful synthetic methods for challenging catalytic and asymmetric bond forming reactions and useful synthetic transformations. Ammonium and azolium enolates are commonly classified into three subtypes, C1-, C2- and C3-ammonium/azolium enolates based upon the number of atoms between the corresponding Lewis basic catalyst (LB, Fig. 1) and the oxygen atom of the enolate.[6]

C1-ammonium enolates have traditionally been accessed *via* the nucleophilic attack of a tertiary amine catalyst on either a pre-formed or *in situ* generated ketene formed from an acid chloride (Fig. 2).[6,8] C1-azolium enolates can be formed in a similar manner using NHCs and ketenes. Alternatively, α-functionalised aldehydes or enals can be employed as precursors in redox catalysed transformations,[7] while aliphatic aldehydes are useful C1-azolium enolate precursors in the presence of a stoichiometric oxidant.[9] However, the development of alternative routes to C1-ammonium or azolium intermediates that do not employ unstable ketenes, their precursors or a redox transformation is an active field of research. To this end, this review exclusively concentrates on strategies for the generation of C1-ammonium or azolium intermediates from alternative, bench-stable starting materials at the carboxylic acid oxidation level, namely carboxylic acids, esters or anhydrides.

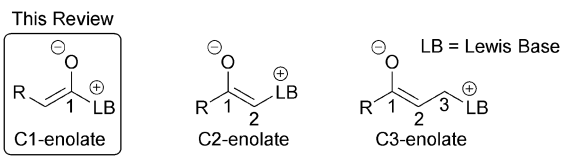

Fig. 1 Classification of ammonium/azolium enolates.

These strategies all rely upon the initial acylation of a tertiary amine or NHC Lewis base catalyst to form a transient

EastCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, UK KY16 9ST. E-mail: ads10@st-andrews.ac.uk

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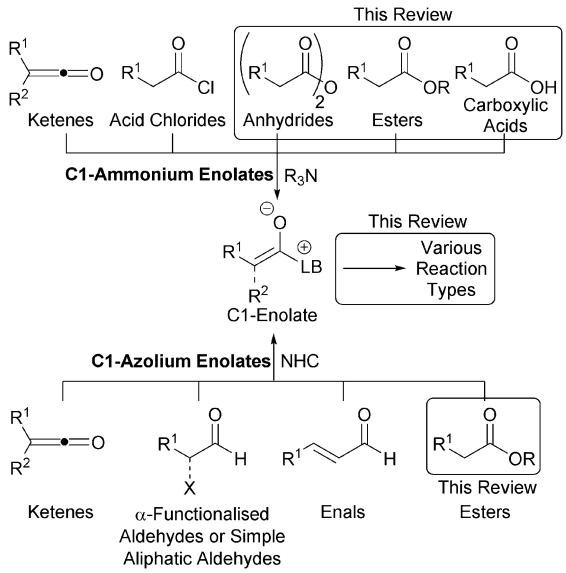

Fig. 2 Overview of organocatalytic C1-enolate generation.

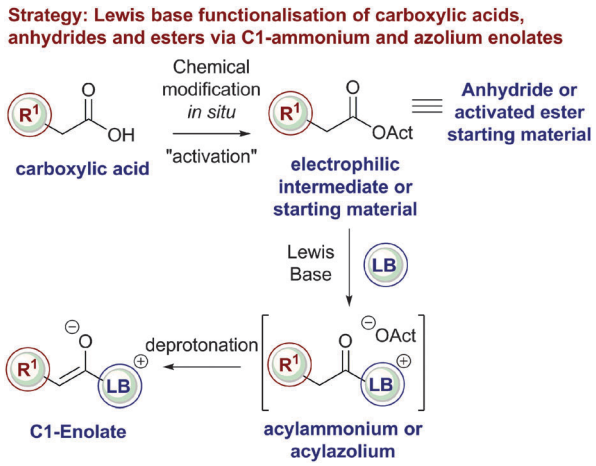

Fig. 3 Overview of strategy of C1-enolate generation from carboxylic acids, anhydrides and esters.

acylammonium or acylazolium intermediate from a carboxylic acid, anhydride or ester starting material that can subsequently undergo deprotonation to afford the corresponding C(1)-enolate (Fig. 3). Despite the commercial availability, high stability and low cost of a variety of carboxylic acids, they have been sparsely used as starting materials in Lewis base organocatalysis. Direct reaction of an acid with a Lewis base results in non-productive salt formation, so acid substrates must firstly be derivatised *in situ* to generate an "activated" electrophilic species (such as a mixed anhydride) that can be readily intercepted by the Lewis basic tertiary amine or NHC, generating an acylammonium or acylazolium intermediate *en route* to the corresponding enolate. Alternatively, bench stable acid anhydrides or "activated" phenolic esters are directly susceptible to nucleophilic attack by a Lewis base to generate the desired acylammonium or acylazolium intermediate.

In this context, this review will describe the generation of C1-ammonium enolates from carboxylic acid, ester and anhydride starting materials. The use of various tertiary amine Lewis basic catalysts will be demonstrated, including Cinchona alkaloids, pyridine-derived nucleophiles and isothioureas. The subsequent utility of these enolates towards both intra- and intermolecular processes will be discussed and placed in context with their utility in natural product synthesis. The generation of C1-azolium enolates from carboxylic ester starting materials using NHC catalysts will also be described; to date the use of carboxylic acids and anhydrides to prepare azolium anolates has not been described but this clearly offers new opportunities for exploitation.

Louis C. Morrill

Louis was born in Wick (UK) and obtained his MChem degree from the University of St Andrews, including a one-year placement at Astrazeneca in Loughborough (UK). He recently completed his PhD under the supervision of Prof. Andrew Smith at the University of St Andrews, funded by The Carnegie Trust for the Universities of Scotland. His research focused on the organocatalytic functionalisation of carboxylic acids using isothioureas.

Andrew D. Smith

Andy was born in Middlesbrough (UK) and gained a DPhil (supervised by Prof. Steve Davies) in 2000 from Jesus College, University of Oxford. Awarded the cross-disciplinary Weston Junior Research Fellowship for post-doctoral studies (New College, Oxford, 2000) a further research collaboration with Prof. Davies was established. In October 2005, ADS was appointed as a Royal Society URF within the School of Chemistry at the University of St Andrews, was promoted to Reader in 2010, and Professor in 2012. Research within the ADS group is currently directed towards the development of novel catalytic methods, with a particular interest in the development of Lewis base promoted catalytic processes, including the use of NHCs and isothioureas in organocatalysis.

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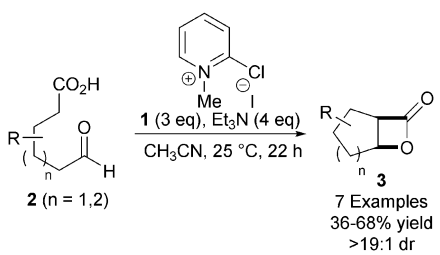
2. Carboxylic acids as C1-ammonium enolate precursors

2.1. Intramolecular processes

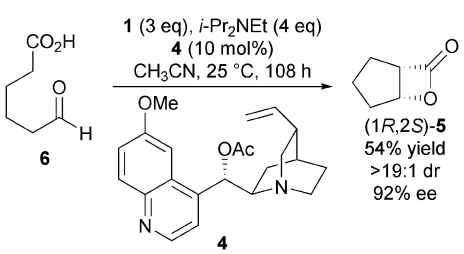
Taking inspiration from the early work of Wynberg in generating β-lactones in a catalytic and asymmetric fashion,[10] Romo and co-workers developed the first example of a catalytic and asymmetric nucleophile-catalysed aldol-lactonisation (NCAL) reaction using a carboxylic acid starting material.[11] While the Wynberg methodology generates enantiomerically enriched β-lactones, the Romo methodology addressed limitations of this approach – such as the use of pre-generated ketene and the necessity for using highly reactive aldehyde substrates such as chloral. Treatment of a range of aldehyde-acids **2** with Mukaiyama reagent **1**[12] and Et_3N promotes the intramolecular NCAL reaction, generating a variety of *cis*-bicyclic β-lactones **3** in good yields (Scheme 1). Syringe pump addition of substrate over 10 h and using CH_3CN as solvent were identified as important factors for obtaining high yields.

This process was rendered asymmetric through use of chiral tertiary amines. For example, using *O*-acetyl quinidine **4** as the Lewis base generates bicyclic β-lactone (1*R*,2*S*)-**5** from **6** in high ee, providing evidence for a NCAL reaction pathway over a possible thermal [2+2] cycloaddition (Scheme 2).

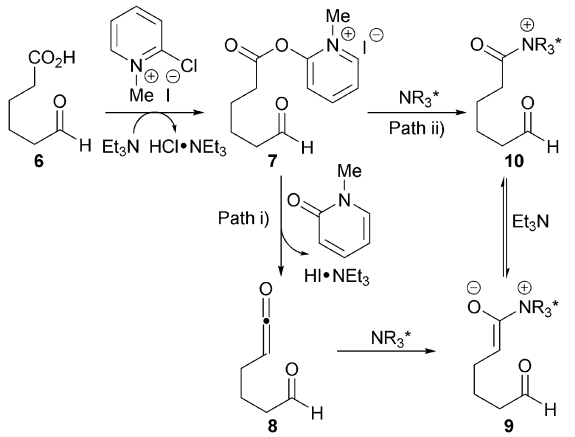
The proposed mechanism involves initial derivatisation of carboxylic acid **6** with Mukaiyama's reagent and base to form activated ester **7** *in situ* (Scheme 3). Two possible pathways are then proposed: (i) ketene **8** may form *via* elimination, which can be intercepted by the cinchona catalyst to generate ammonium enolate **9**; or (ii) the catalyst may undergo acylation with the activated ester to form acyl ammonium **10** that gives ammonium enolate **9** upon deprotonation. It is likely that the acyl ammonium pathway (path ii) is more prevalent due to ketene **8** being present at very low concentrations at room temperature.



Scheme 1 Nucleophile-catalysed aldol-lactonisation (NCAL) reaction.



Scheme 2 Chiral amine catalysed asymmetric NCAL reaction.



Scheme 3 Generation of ammonium enolate **9** from aldehyde-acids.

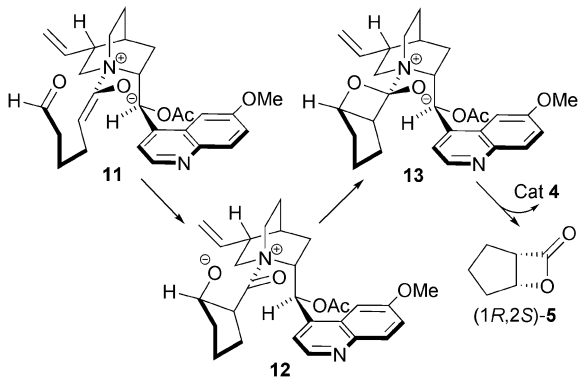


Fig. 4 Stereochemical rationale for the asymmetric NCAL reaction.

The origin of the stereoselectivity in this process can be explained by the aldehyde approaching the *Re* face of ammonium enolate **11**, opposite to the steric bulk of the quinoline ring, generating **12**. Nucleophilic attack on the *Si* face of the aldehyde gives *cis*-aldolate **13**, which undergoes lactonisation to generate the *cis*-β-lactone **5** (Fig. 4).

Various quinidine derivatives were tested as catalysts in this NCAL protocol, with changing the nature of the functional group at C9 (a variety of esters, a carbamate and a carbonate) having minimal influence upon observed enantioselectivities (Scheme 4).[13] Significantly, through the use of either pseudo enantiomeric *O*-acetyl quinine **14**, or rigidified catalyst **15**, the enantiomeric β-lactone (1*S*,2*R*)-**5** can be prepared in high ee.

The ability of modified Mukaiyama reagents **16–18** to increase reaction yields for the catalytic asymmetric NCAL reaction whilst maintaining high levels of enantioselectivity have also been investigated (Fig. 5).[14,15] This was primarily attributed to: (i) improved reagent solubility, allowing reactions to be carried out in less polar solvents such as THF and CH_2Cl_2 and minimising potential ring-opening reactions promoted by polar media; (ii) less nucleophilic counterions – triflate and tetrafluoroborate – reducing β-lactone decomposition.

In 2011, the Dikshit group demonstrated a catalytic asymmetric aza variant of the NCAL reaction (Scheme 5).[16] Using modified

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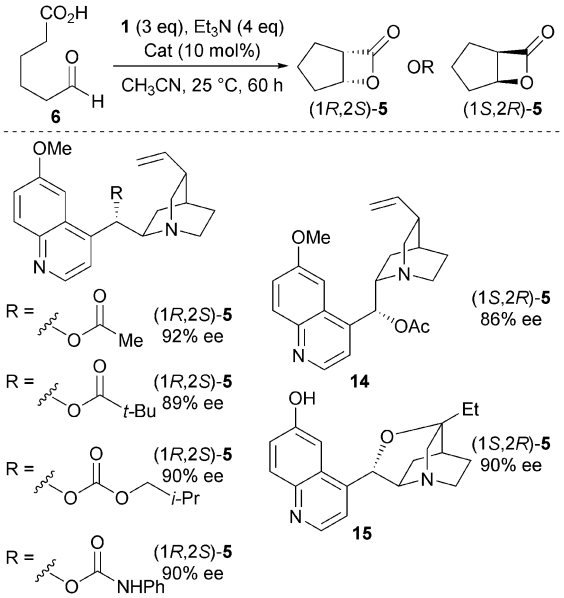


Scheme 4 Various chiral amine catalysts for the NCAL reaction.

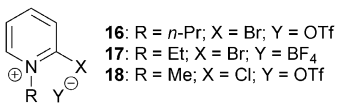
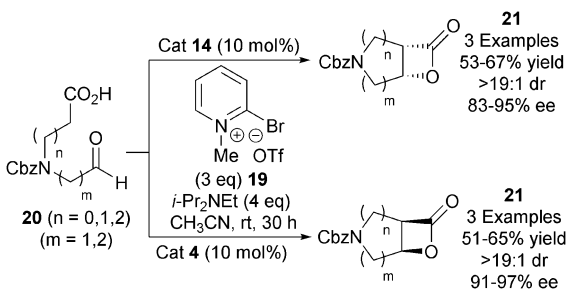


Fig. 5 Modified Mukaiyama reagents for the NCAL reaction.

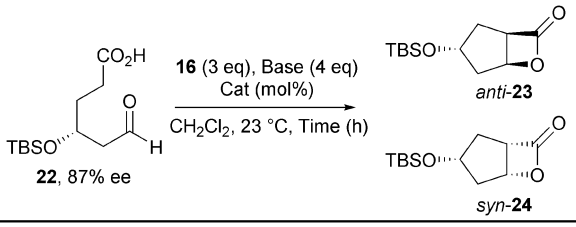


Scheme 5 Aza variant of the intramolecular NCAL reaction.

Mukaiyama's reagent **19**, amino acid derived aldehyde-acids **20** could be converted into either enantiomer of the corresponding bicyclic β-lactone **21** through use of either *O*-acetyl quinine **14** or *O*-acetyl quinidine **4**, in good yields (51–67%) and high enantioselectivities (83–97% ee). This strategy provides evidence for the wider application of Romo's NCAL strategy towards alternative heterocyclic systems.

Building upon this work, Romo developed a diastereoselective NCAL reaction that allowed the conversion of enantiomerically enriched aldehyde-acid substrates bearing γ- and δ-substituents into bicyclic β-lactones in high diastereoselectivity.[17] Amongst several examples, treatment of aldehyde-acid **22** (87% ee) under the standard NCAL conditions using Et_3N as the nucleophilic promoter, gives a substrate controlled 2 : 1 mixture of diastereomeric *anti*- and *syn*-β-lactones **23** and **24** respectively (Table 1). Chiral catalysts were next examined to test if catalyst control could override the inherent substrate bias. Use of *O*-TMSQD results in a reversal of diastereoselectivity (1 : 7 *anti* : *syn*) representative of the mismatched case, while employing *O*-TMSQN gives exclusively the *anti*-β-lactone (>19 : 1 *anti* : *syn*) indicative of a matched situation.

Table 1 Doubly diastereoselective β-lactone formation



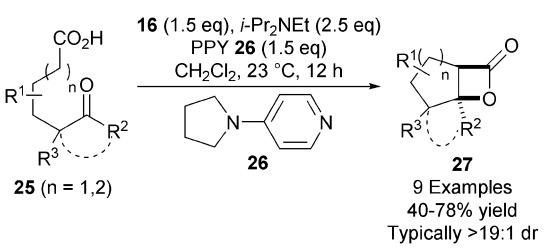
Entry	Catalyst (mol%)	Base	Time (h)	Yield (%)	dr (**23** : **24**)
1	Et_3N (100)	Et_3N	48	58	2 : 1
2	*O*-TMSQD (10)	i-Pr_2EtN	72	73	1 : 7
3	*O*-TMSQN (10)	i-Pr_2EtN	72	60	>19 : 1

The potential to access both tetrahydrofuran- and tetrahydropyran-fused β-lactones *via* the same NCAL process was also investigated, however this generally resulted in both poor diastereoselectivities and isolated yields.

In a significant advance, the NCAL methodology was extended towards less reactive keto-acid substrates **25**.[18] Using superstoichiometric quantities of 4-pyrrolidino pyridine (PPY) **26**, the ammonium enolate formed is sufficiently reactive to undergo bis-cyclisation, affording a variety of bicyclic and tricyclic β-lactones **27** in high yield and diastereoselectivity (Scheme 6).

To showcase the utility of this methodology, it was used as the key step in an enantioselective synthesis of (+)-dihydroplakevulin A **28**, known to be a precursor to DNA polymerase inhibitor plakeuvulin A **29** (Scheme 7). Under optimised conditions, enantioenriched keto-acid **30** undergoes bis-cyclisation to give bicyclic β-lactone **31** in moderate yield and excellent dr, which is easily converted over two steps into (+)-dihydroplakevulin A **28** through ring-opening with MeOH followed by silyl deprotection.

Further applications of this methodology were disclosed in the synthesis of both (±)-cinnabaramide A and (±)-salinosporamide A **32** (Scheme 8).[19] For example, bis-cyclisation of keto-acid **33** (1 : 1 dr), catalysed by PPY, gives β-lactone **34** in 34% yield and 2 : 1 dr with the major diastereoisomer subsequently elaborated to **32**. The moderate yield of the key bis-cyclisation step is likely due to the difficult functionalisation of a sterically congested α,α-disubstituted carboxylic acid group and again highlights some of the current limitations of this methodology.



Scheme 6 Bis-cyclisation of keto-acids.

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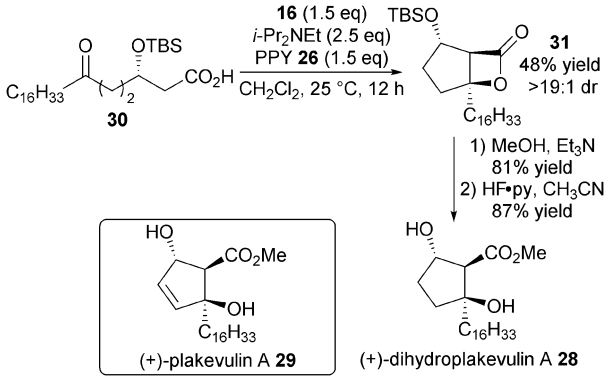
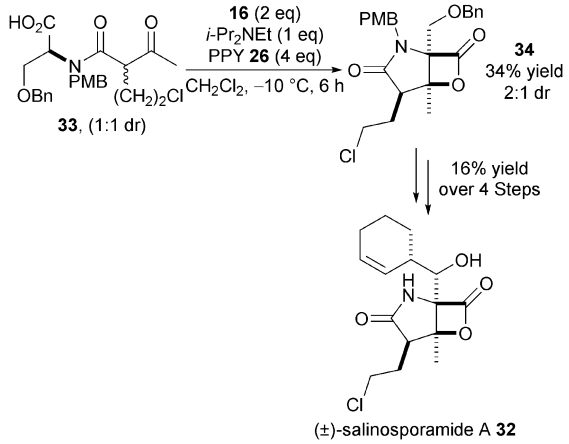
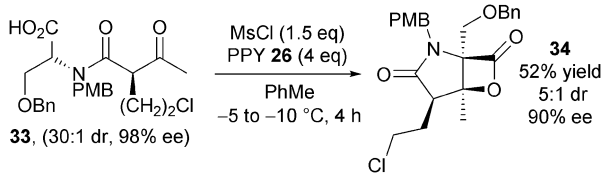


Scheme 7 Synthesis of (+)-dihydroplakevulin A.



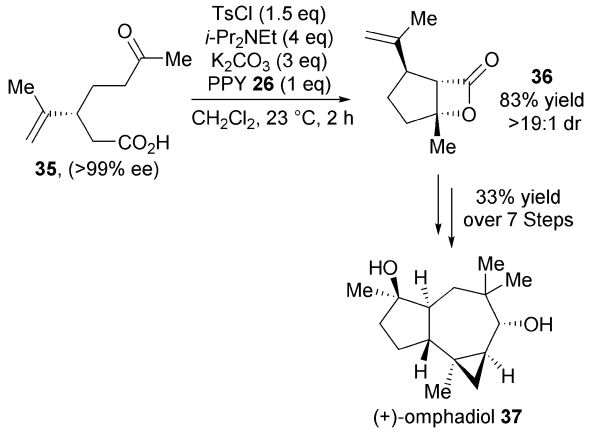
Scheme 8 Synthesis of (±)-salinosporamide A.



Scheme 9 Modified route towards (−)-salinosporamide A.

Romo subsequently demonstrated that (−)-salinosporamide A **32** could be obtained in enantiomerically enriched form (Scheme 9).[20,21] This was achieved by synthesising enantio- and diastereomerically pure keto-acid **33** and utilising modified bis-cyclisation conditions that minimise racemisation of the starting material. Employing mesyl chloride as activating agent at −5 to −10 °C in toluene gave bicyclic β-lactone **35** in 53% yield, 5:1 dr and 90% ee on gram scale. Elaboration of **35** into (−)-salinosporamide A **33** was analogous to the previous synthesis.

In 2011, Romo and co-workers again demonstrated the utility of the NCAL reaction towards natural product synthesis. Bis-cyclisation of (*R*)-carvone derived keto-acid **35**, using TsCl as activating agent and 4-PPY as the nucleophilic Lewis base catalyst, gave the desired β-lactone product **36** in 83% yield and >19:1 dr (Scheme 10).[22] Importantly, in the context of natural product



Scheme 10 Application of NCAL towards synthesis of (+)-omphadiol.

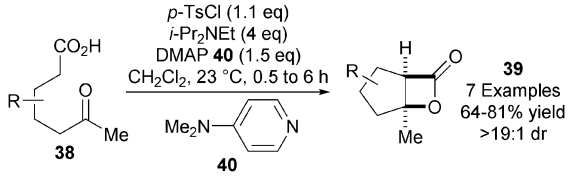
synthesis, this NCAL reaction can be carried out on greater than 10 g scale. β-Lactone **36** was elegantly elaborated into molecularly complex (+)-omphadiol **37** over 7 steps in an impressive 33% overall yield, representing the first total synthesis of this product.

In the key bis-cyclisation step towards the synthesis of (+)-omphadiol, Romo and co-workers noted that K_2CO_3 as base in combination with i-Pr_2NEt as ''shuttle base'' was optimal for achieving a high yield of **36** in a significantly reduced reaction time of 2 h (typically 24 h). This led to the development of a more practical and scalable general procedure for the highly diastereoselective NCAL reaction of keto-acids **38** into bicyclic β-lactones **39** using commercially available *p*-TsCl as activating agent and DMAP **40** as nucleophilic catalyst (Scheme 11).[23]

In 2008, Romo and co-workers utilised the NCAL reaction to access a range of tricyclic β-lactones **41** from keto-acids **42** using their standard reaction conditions (Scheme 12).[24] Interestingly, these products undergo an unusual dyotropic rearrangement *via* 1,2-acyl migration upon treatment with Lewis acidic $Zn(OTf)_2$, giving bridged γ-lactones **43** with high stereospecificity.

As a proof of principle, Romo reported the first asymmetric bis-cyclisation of keto-acid **44** using stoichiometric quantities of commercially available (*S*)-tetramisole hydrochloride **45**, forming **46** in 97% ee (Scheme 13). This experiment provided both the first direct evidence for nucleophile involvement in the stereodefining step of biscyclisations with keto-acid substrates and the first demonstration of isothioureas in ammonium enolate chemistry.

In a significant breakthrough, Romo extended this approach to the first catalytic asymmetric NCAL reaction of keto-acids.[25] Isothiourea (*S*)-HBTM **47**, developed by Birman as a highly efficient *O*-acyl transfer agent,[26] catalyses the transformation of a range of



Scheme 11 Improved procedure for NCAL of keto-acids.

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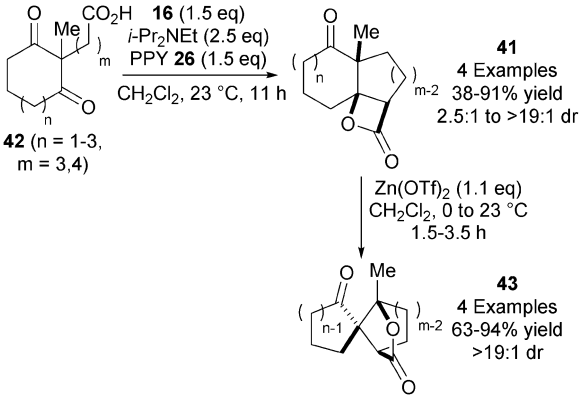
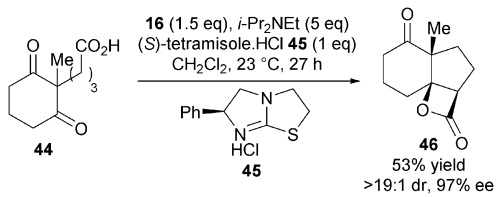
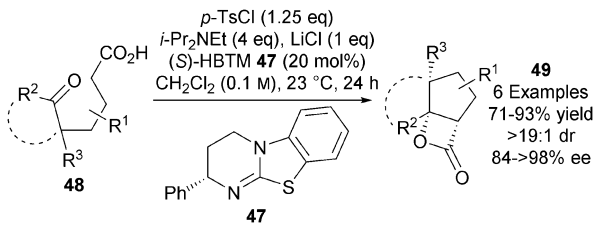


Scheme 12 Tricyclic β-lactone synthesis and dyotropic rearrangements.



Scheme 13 Stoichiometric asymmetric synthesis of tricyclic β-lactone.



Scheme 14 Catalytic asymmetric synthesis of bi- and tricyclic β-lactones.

keto-acids **48** into bi- and tricyclic β-lactones **49** (Scheme 14). Careful optimisation showed that that *p*-TsCl was the optimal carboxylic acid activating agent and that use of both 0.1 M concentrations and 1 eq. of LiCl Lewis acid co-catalyst were optimal for obtaining **49** in high isolated yields (71–93%) and in excellent enantioselectivities (84 to >98% ee).

A model is provided that explains the observed relative and absolute configuration (Fig. 6). Formation of the (*Z*)-ammonium enolate, with Li–S chelation results in a bicyclic chair-like transition state **50** that includes ketone activation by Li, rationalising the observed increase in yield.

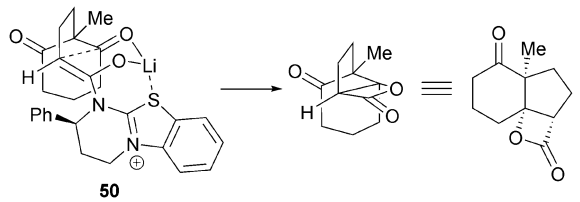
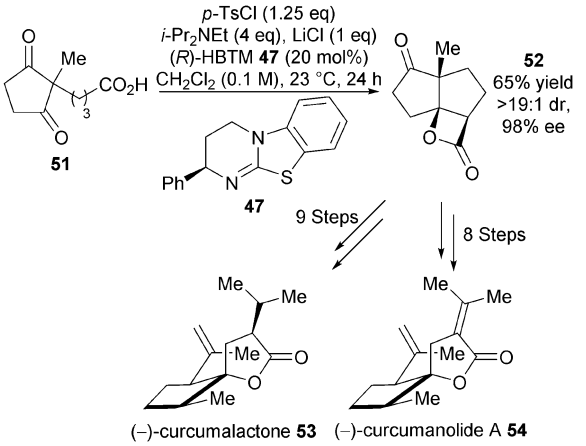


Fig. 6 Stereochemical rationale for the asymmetric NCAL reaction.

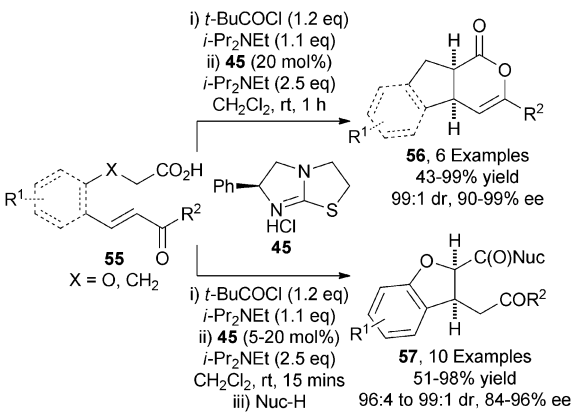


Scheme 15 Application of the catalytic asymmetric NCAL reaction.

In a powerful demonstration of utility, this catalytic asymmetric NCAL reaction was later used by the Romo group as a key step towards their asymmetric synthesis of (−)-curcumanolide A and (−)-curcumalactone.[27] Desymmetrisation of dione **51** using (*R*)-HBTM **47** (20 mol%), *p*-TsCl as activating agent and LiCl as Lewis acid additive gave the desired enantiomer of tricyclic β-lactone **52** in 65% yield, >19 : 1 dr and 98% ee on gram scale (Scheme 15). This key building block was further elaborated into (−)-curcumalactone **53** and (−)-curcumanolide A **54** in 9 and 8 steps, respectively.

Building upon these precedents, the first application of carboxylic acid derived ammonium enolates in Michael addition processes was demonstrated by the Smith group.[28] Using commercially available pivaloyl chloride as activating agent and (*S*)-tetramisole hydrochloride **45** as nucleophilic precatalyst, a range of enone-acids **55** undergo intramolecular Michael addition-lactonisation to give functionalised indenes **56** or dihydrofuran carboxylates **57** (after *in situ* ring-opening) with excellent diastereo- and enantiocontrol (up to 99 : 1 dr, up to 99% ee) (Scheme 16).

This approach was later applied to the synthesis of disubstituted pyrrolidines.[29] Enone-acids **58**, made *in situ via* either ozonolysis/Wittig olefination or cross metathesis from **59**,



Scheme 16 Intramolecular Michael addition-lactonisation.

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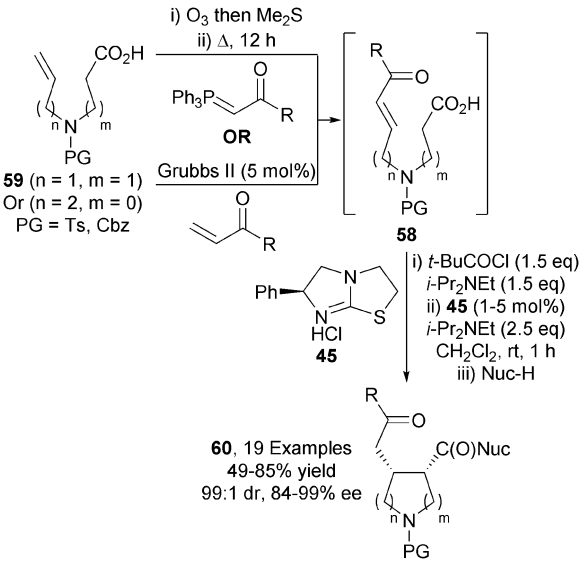
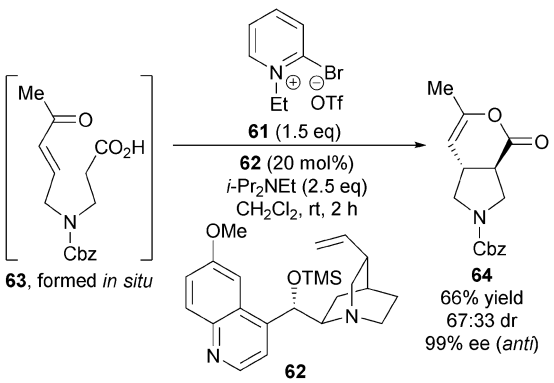


Scheme 17 Telescoped synthesis of stereodefined pyrrolidines.

were transformed into 2,3- or 3,4-*syn*-disubstituted pyrrolidines **60** under similar catalytic conditions in excellent diastereo- and enantiocontrol (up to 99 : 1 dr, up to 99% ee) (Scheme 17).

Notably, the diastereoselectivity of this transformation can be reversed through judicious choice of nucleophilic catalyst. Using modified Mukaiyama's reagent **61** as activating agent and OTMS-quinidine **62** as catalyst, enone-acid **63** gives 3,4-*anti*-disubstituted pyrrolidine **64** preferentially in modest diastereoselectivity (67 : 33 dr) with the major diastereoisomer formed in excellent enantioselectivity (99% ee) (Scheme 18).

In the tetramisole promoted cyclisations, the observed stereoselectivity can be explained *via* pre-transition state assembly **65** in which the enolate oxygen is orientated *syn* to the sulfur atom of the catalyst, allowing for a stabilising n_o to σ^*_{C-S} interaction (or electrostatic stabilisation). Michael addition then proceeds *anti* to the stereodirecting phenyl substituent *via* the enolate *Si*-face generating the *syn*-product (Fig. 7). For the OTMS-quinidine catalysed reaction, cyclisation proceeds preferentially *via* the enolate *Re*-face (pre-transition state assembly **66**), which minimises steric clashes with the ethylene bridge within the quinidine skeleton, giving the *anti*-diastereoisomer as the major product in high ee.



Scheme 18 Accessing the 3,4-*anti* diastereoisomer.

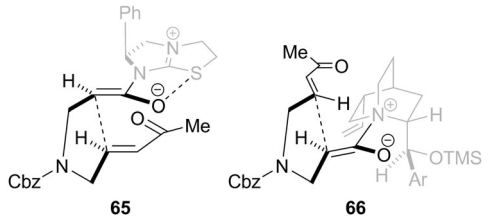


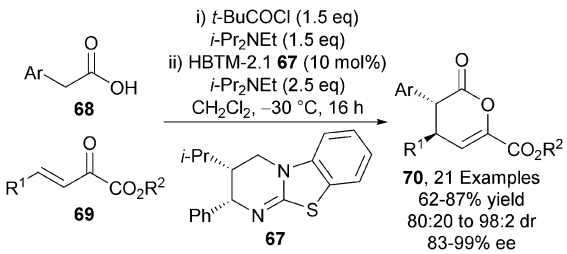
Fig. 7 Stereochemical rationale for Lewis base promoted intramolecular Michael addition-lactonisations.

2.2. Intermolecular processes

The intramolecular NCAL and related Michael addition-lactonisation methodologies showcase the power of this carboxylic acid functionalisation strategy. Reviewing Romo's *intramolecular* NCAL strategy employing aldehyde-acid starting materials and cinchona alkaloid Lewis bases, Gaunt and Johansson remarked "*The moderate reactivity of the zwitterionic ammonium enolates is bypassed in the intramolecular reaction because of the proximity of the aldehyde, but it cannot be avoided in the intermolecular process*".[6] To extend this protocol to intermolecular processes remained elusive until 2011 when the Smith group extended their methodology towards the first application of carboxylic acid derived ammonium enolates in intermolecular processes.[28] HBTM-2.1 **67** effectively catalyses the intermolecular Michael addition-lactonisation of arylacetic acids **68** and α-keto-β,γ-unsaturated esters **69** in the presence pivaloyl chloride, giving *anti*-dihydropyranones **70** with excellent diastereo- and enantiocontrol (up to 98 : 2 dr, up to 99% ee) (Scheme 19). The isothiourea derived ammonium enolate formed by employing HBTM-2.1 **67** is seemingly sufficiently nucleophilic to promote the challenging *intermolecular* bond forming process.

This intermolecular protocol was extended towards alternative electron deficient Michael acceptors. Employing trifluoromethyl enones **71** under closely related reaction conditions generates trifluoromethyl bearing *anti*-dihydropyranones **72** with high stereocontrol (up to 95 : 5 dr, up to >99% ee) (Scheme 20).[30] Notably, these heterocyclic products could be readily derivatised into those containing CF_3-stereogenicity *via* highly diastereoselective methods including hydrogenation of **73** to form saturated lactone **74** or reduction with $LiAlH_4$ to give lactol **75** with no erosion in enantiopurity.

Kinetic investigations indicated this process to be *first order* in mixed anhydride **76** and HBTM-2.1 **67**, whilst being *zero order* in trifluoromethyl enone **77** (Scheme 21). Increasing the



Scheme 19 Isothiourea-catalysed intermolecular Michael addition-lactonisation.

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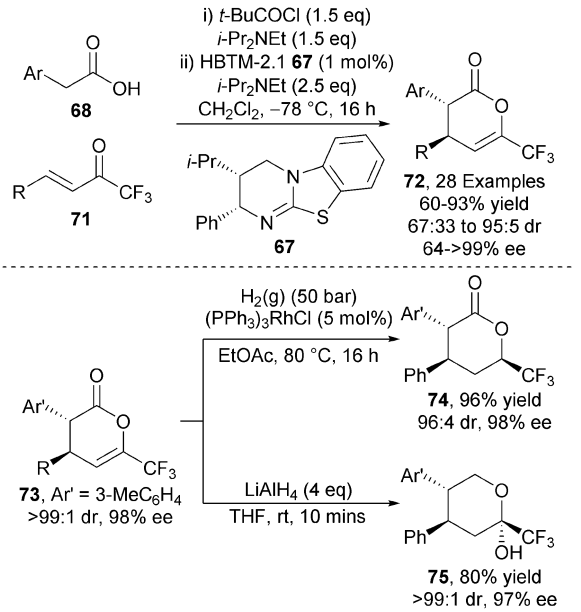
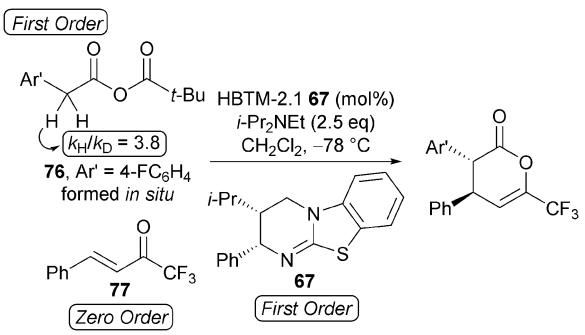
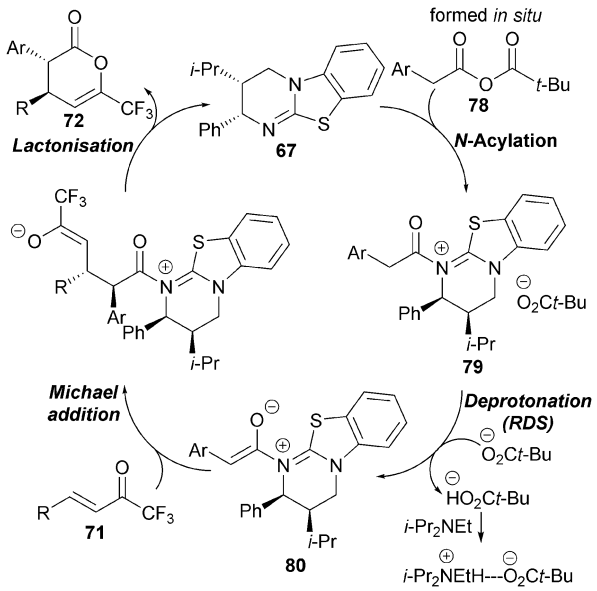


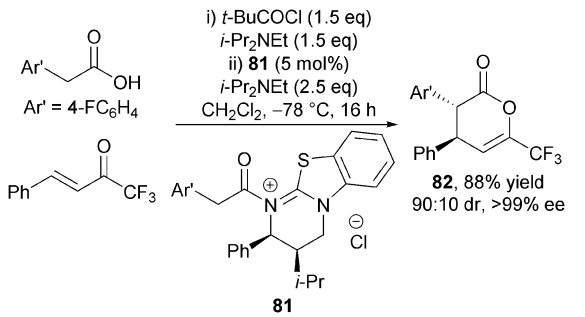
Scheme 20 CF_3-containing heterocycle formation.



Scheme 21 Kinetic investigations.



Scheme 22 Proposed catalytic cycle.



Scheme 23 Validation of isothiouronium ion as a plausible intermediate.

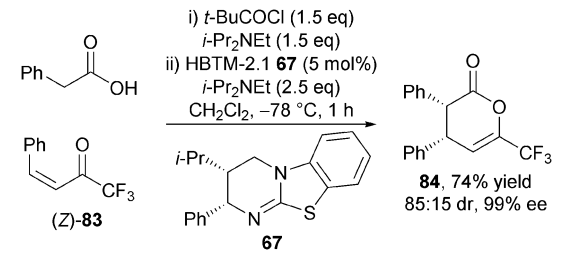
stoichiometry of i-Pr_2NEt (up to 8 equivalents) had a negligible effect upon reaction rate, consistent with the rate-determining transition structure being constructed from the catalyst and the mixed anhydride. Importantly, a primary kinetic isotope effect k_{obsH}/k_{obsD} = 3.8 is observed when the reaction is performed using α,α-di-deuterio 4-fluorophenylacetic acid, consistent with deprotonation being rate determining.

Based upon these kinetic observations, a catalytic cycle for the reaction has been proposed that proceeds *via* initial *in situ* formation of mixed anhydride **78**, which is intercepted by HBTM-2.1 **67** to form the corresponding acyl ammonium ion **79** (Scheme 22). Rate-determining deprotonation by pivalate generates the (*Z*)-ammonium enolate **80** which undergoes stereoselective Michael addition with trifluoromethyl enone **71**, followed by intramolecular cyclisation to afford *anti*-dihydropyranone **72** with regeneration of the catalyst.

Evidence for the presence of an acyl isothiouronium ion such as **79** in the catalytic cycle was provided through its use as a precatalyst. **81** was prepared and isolated by reaction of HBTM 2.1 with the corresponding acid chloride, and used as precatalyst, giving *anti*-dihydropyranone **82** in identical diastereo- and enantiocontrol (90 : 10 dr and 99% ee) to that employing HBTM-2.1 **67** directly in this protocol (Scheme 23).

Furthermore, the organocatalytic reaction was shown to be stereospecific, with the (*Z*)-enone **83** affording *syn*-dihydropyranone **84** in high diastereoselectivity (85 : 15 dr) with the major diastereoisomer formed in excellent enantioselectivity (99% ee) (Scheme 24). This useful experiment revealed that the either diastereoisomer of the product can be obtained *via* judicious choice of starting material configuration.

Models explaining the observed stereoselectivity involve the isothiouronium heterocycle adopting a half-chair type conformation



Scheme 24 Reaction stereospecificity.

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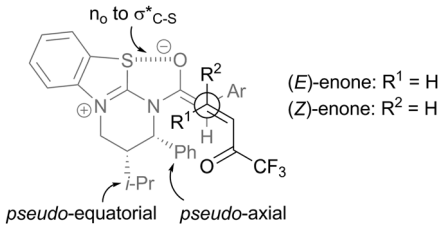
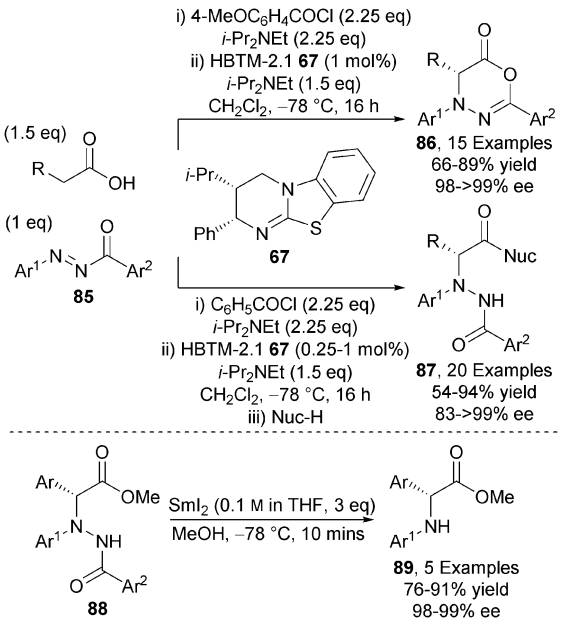


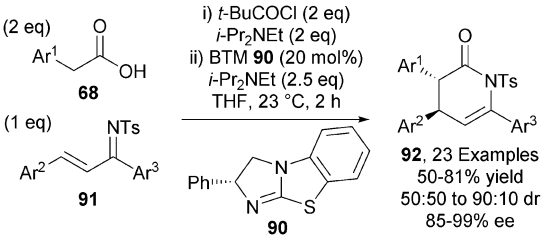
Fig. 8 Stereochemical rationale.

with the C(2)-phenyl substituent pseudoaxial to minimise 1,2 steric interactions and the C(3)-i-Pr unit pseudoequatorial (Fig. 8).[31] Within the (*Z*)-ammonium enolate, the oxygen atom preferentially lies *syn* to the sulfur atom within the isothiouronium ion, allowing a stabilising n_o to σ^*_{C-S} interaction. The reaction proceeds though the diastereomeric transition states shown, giving the observed *anti*-diastereoisomer (from (*E*)-enone) or *syn*-diastereoisomer (from (*Z*)-enone) in high enantiomeric excess.

In addition to carbon-carbon bond forming reactions, the catalytic asymmetric α-amination of carboxylic acids using isothioureas has been demonstrated.[32] HBTM-2.1 **67** efficiently catalyses the α-functionalisation of a range of carboxylic acids with *N*-aryl-*N*-aroyl diazenes **85** at low catalyst loadings (as low as 0.25 mol%), giving either 1,3,4-oxadiazin-6-ones **86** or *N*-protected α-amino acid derivatives **87** upon ring-opening with excellent enantiocontrol (up to >99% ee) (Scheme 25). Importantly, non-arylacetic acids could be incorporated in this protocol through the use of a highly electron deficient Michael acceptor and PS-BEMP as base. The N–N bond within the hydrazide products **88** could be readily cleaved using SmI_2 to afford bespoke *N*-aryl-α-aryl glycine building blocks **89** in excellent enantioselectivity.



Scheme 25 Isothiourea-catalysed α-amination of carboxylic acids.

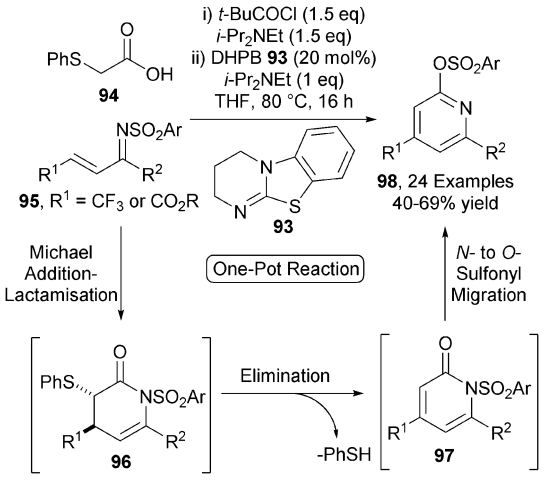


Scheme 26 Intermolecular Michael addition-lactamisation.

Carboxylic acid derived ammonium enolates have also been used in Michael addition-lactamisation processes.[33] BTM **90** efficiently catalysed the asymmetric formal [4+2] cycloaddition between arylacetic acids **68** and ketimines **91**, giving a range of *anti*-dihydropyridones **92** with good diastereocontrol (typically 85 : 15 dr) and excellent enantiocontrol (up to 99% ee) (Scheme 26).

Building upon this work, this Michael addition-lactamisation protocol was applied to the synthesis of functionalised pyridines.[34] Achiral isothiourea DHPB **93** efficiently catalyses the Michael addition-lactamisation process between (phenylthio)acetic acid **94** and ketimines **95**, initially giving dihydropyridones **96** (Scheme 27). These products undergo rapid elimination of thiophenol to give pyridones **97**, followed by intramolecular *N*- to *O*-sulfonyl transfer upon heating, affording a range of 2,4,6-substituted pyridines **98** in acceptable yields (40–69%) over 3 steps in one-pot. A closely related one-pot protocol was later developed to access a range of trifluoromethyl substituted 2-pyrones.[35]

Of particular note in this chemistry is that the activating sulfonyl group on the ketimine is transformed into the synthetically useful functional handle (the 2-sulfonate group) in the resulting pyridines. A number of derivatisations showcasing the versatility of this group were demonstrated, including a host of cross-coupling methodologies. This methodology was also applied to the synthesis of **99** – a pyridine with known biological activity as a COX-2 inhibitor (Scheme 28). Pyridine **100** was accessed from ketimine **101** in 53% yield using the



Scheme 27 One-pot organocatalytic pyridine synthesis.

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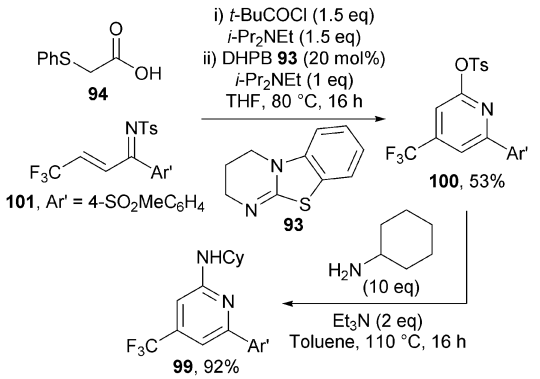
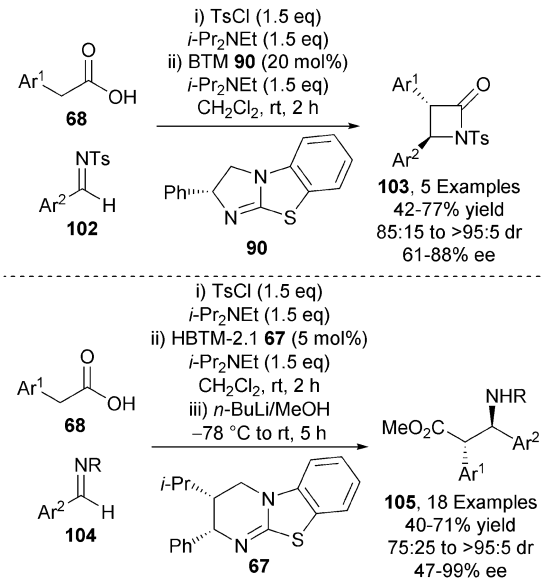


Scheme 28 Rapid assembly of biologically active pyridine.

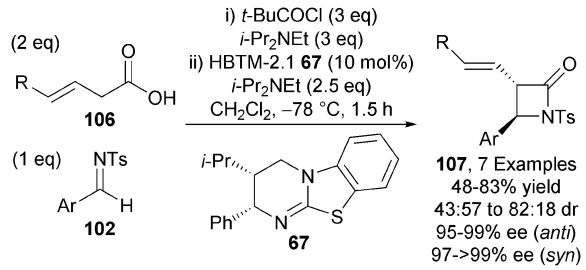
optimised reaction conditions and subsequent S_NAr with cyclohexylamine afforded **99** in 92% yield.

In 2014, the first intermolecular formal [2+2] cycloaddition involving a carboxylic acid derived ammonium enolate was demonstrated.[36] BTM **90** effectively catalyses the annulation of arylacetic acids **68** and *N*-sulfonyl imines **102**, in the presence of tosyl chloride, giving β-lactams **103** with excellent diastereocontrol and high enantiocontrol (up to >95 : 5 dr, up to 88% ee) (Scheme 29). Alternatively, using HBTM-2.1 **67** as catalyst, a range of β-amino esters **105** could be accessed after *in situ* ring-opening with *n*-BuLi/MeOH in excellent diastereo- and enantiocontrol (up to >95 : 5 dr, up to 99% ee).

The isothiourea-mediated functionalisation of 3-alkenoic acids proceeding *via* an ammonium dienolate has also been disclosed by Smith and co-workers.[37] α-Functionalisation of the intermediate dienolate derived from 3-alkenoic acids **106** and HBTM-2.1 **67** with *N*-tosyl aldimines **102** gives a range of β-lactams **107** with modest diastereocontrol (up to 82 : 18 dr), although each diastereoisomer is formed with excellent enantioselectivity (typically >95% ee) (Scheme 30).



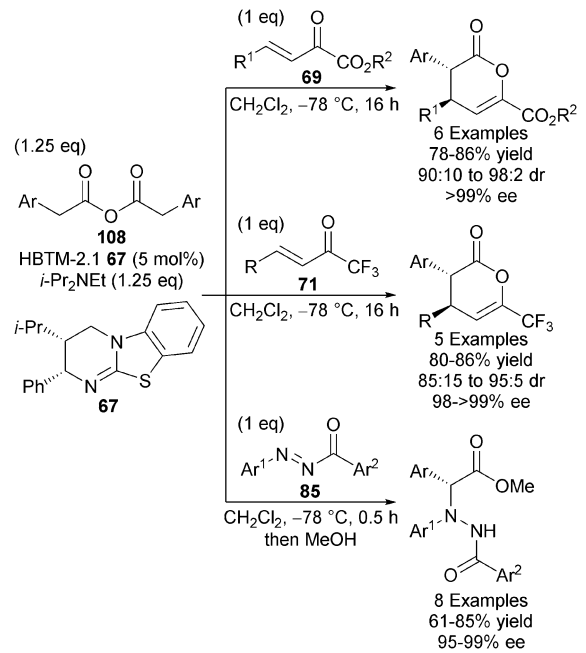
Scheme 29 Formal [2+2] cycloadditions using *N*-sulfonyl imines.



Scheme 30 α-Functionalisation of 3-alkenoic acids.

3. Anhydrides as C1-ammonium enolate precursors

One notable disadvantage of the *in situ* acid activation strategy is the formation of by-products such as pyridones (from Mukaiyama-type reagents) and pivalic anhydride (from pivaloyl chloride) which can in some cases be difficult to separate from the desired products. Anhydrides are already pre-disposed towards nucleophilic attack by a Lewis base and so do not need to be pre-activated in the same manner as carboxylic acids. Upon addition of a Lewis base, the only by-product is one equivalent of parent carboxylic acid, which is easily removed from the product *via* basic work-up. With this advantage in mind, the Smith group demonstrated that HBTM-2.1 **67** effectively catalyses the intermolecular Michael addition-lactonisation of 2-arylacetic anhydrides **108** and a range of Michael acceptors, namely α-keto-β,γ-unsaturated esters **69**, trifluoromethyl enones **71** and *N*-aryl-*N*-aroyl diazenes **85**, giving diverse synthetic building blocks with high diastereo- and enantiocontrol (up to 98 : 2 dr, up to >99% ee) (Scheme 31).[38] C1-ammonium enolates derived from 2-arylacetic anhydrides were also applied towards formal [2+2]



Scheme 31 2-Arylacetic anhydrides as C1-ammonium enolate precursors.

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cycloadditions with *N*-sulfonyl imines, giving β-lactams with high diastereo- and enantiocontrol (up to >95:5 dr, up to 99% ee).[36]

4. Carboxylic esters as C1-ammonium and C1-azolium enolate precursors

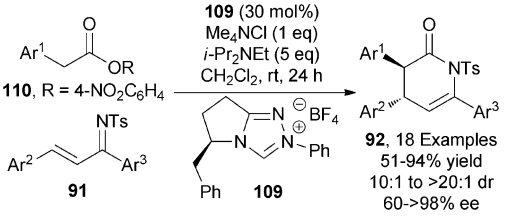
Activated esters are susceptible towards nucleophilic attack by a Lewis base tertiary amine or NHC and so have found utility as C1-ammonium and azolium enolate precursors.

4.1. C1-azolium enolates from carboxylic esters

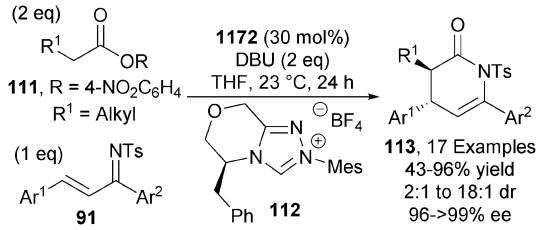
This section will focus on the generation and utility of C1-azolium enolates from carboxylic ester starting materials using NHC catalysts. C1-azolium enolates are commonly accessed from aldehyde, enal and ketene starting materials. Despite the potential practical advantages of accessing these enolates from bench stable esters or alternative carboxylic ester derivatives, this area has received little attention.[39] In 2012, Chi reported the first NHC mediated activation of stable carboxylic esters to generate C1-azolium enolates.[40] After initial optimisation, triazolium-based chiral precatalyst **109** (30 mol%) promoted the asymmetric formal [4+2] cycloaddition of activated arylacetic esters **110** and ketimines **91** giving a range of *anti*-dihydropyridones **92** in high diastereoselectivity (10:1 to >20:1 dr), with the major diastereoisomer formed in moderate to excellent enantioselectivity (60 to >98% ee) (Scheme 32). Notably, the use of both Me_4NCl (1 eq.) and excess i-Pr_2NEt (5 eq.) were necessary for achieving high stereoselectivity. The use of high catalyst loadings (30 mol%) and the formation of toxic *p*-nitrophenol by-product are notable drawbacks of this entry to C1-azolium enolates.

The Chi group later expanded the scope of this reaction to include simple activated alkylacetic esters **111** through the use triazolium precatalyst **112** (30 mol%). In the presence of DBU, *anti*-dihydropyridines **113** are obtained in excellent yields and stereoselectivities (up to 18:1 dr, up to >99% ee) (Scheme 33).[41] Further work by the same group highlighted the ability to organocatalytically functionalise the simplest activated acetic ester (R^1 = H in Scheme 33) using similar reaction conditions.[42]

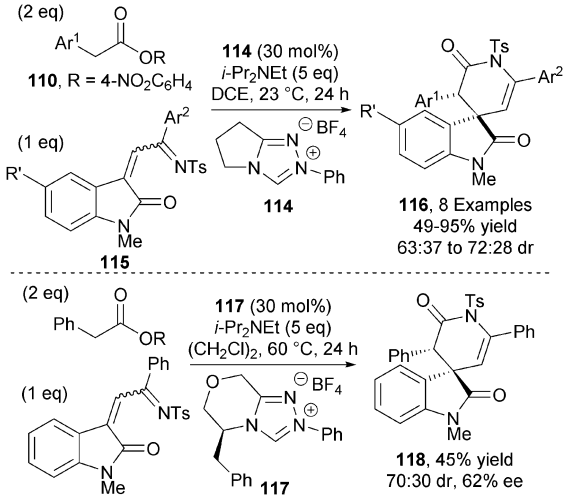
Chi and co-workers also applied ester-derived C1-azolium enolates towards the synthesis of spyrocyclic oxindoles.[43] Achiral NHC precatalyst **114** (30 mol%), in the presence of base, promotes the reaction between activated arylacetic esters **110** and isatin-derived azadienes **115** giving a range of spyrocyclic oxindoles **116** in modest diastereoselectivities (63:37 to 72:28 dr) (Scheme 34). Attempts to render the process asymmetric were thwarted by the low reactivity of the azadienes. The best result was obtained using



Scheme 32 NHC-catalysed functionalisation of activated arylacetic esters.



Scheme 33 Activated alkylacetic esters as C1-azolium enolate precursors.

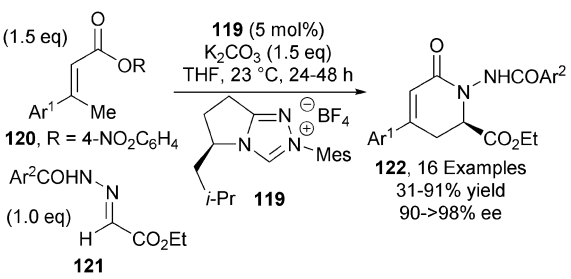


Scheme 34 NHC-catalysed spirocyclic oxindole formation.

L-phenylalanine-derived triazolium salt **117**, affording δ-lactam **118** in 45% yield with modest diastereo- and enantiocontrol (70:30 dr and 62% ee).

In 2013, Chi reported the first NHC-catalysed asymmetric γ-functionalisation of α,β-unsaturated esters *via* an azolium dienolate intermediate.[44] Triazolium NHC precatalyst **119**, in the presence of K_2CO_3, effectively promotes the γ-activation of α,β-unsaturated esters **120** that undergo addition to hydrazones **121** to give δ-lactam products **122** in high yield and with excellent levels of enantioselectivity (up to >98% ee) (Scheme 35). Using slightly modified reaction conditions, γ-substituted and β,β′-dialkyl substituted α,β-unsaturated esters could also be used in this protocol, giving the corresponding δ-lactams in moderate to good yields and enantioselectivity.

A proposed catalytic cycle for this process involves initial formation of acyl azolium **123**, which undergoes γ-deprotonation



Scheme 35 NHC-catalysed γ-activation of activated esters.

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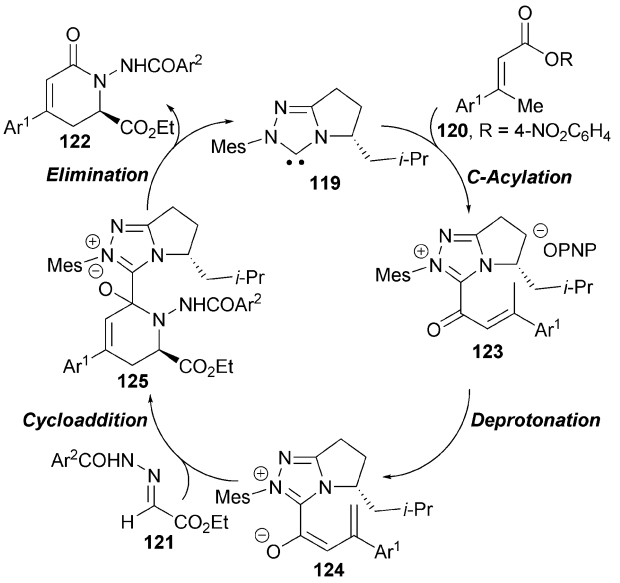


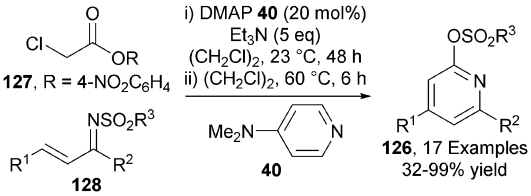
Scheme 36 Proposed catalytic cycle.

to form the key C1-azolium dienolate **124** (Scheme 36). Subsequent stereoselective nucleophilic attack towards hydrazone **121** gives NHC-bound adduct **125** that rapidly collapses to give δ-lactam **122** with regeneration of the catalyst.

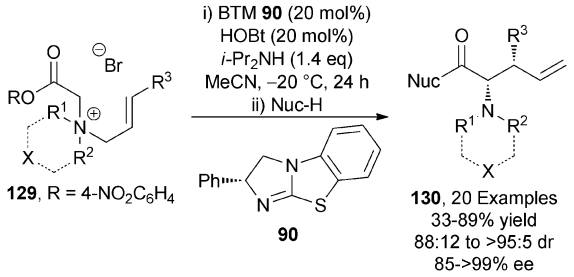
4.2. C1-ammonium enolates from carboxylic esters

C(1)-ammonium enolates can also be generated from a tertiary amine and a 4-nitrophenol ester. In a closely related process to that outlined previously,[34] the Chi group demonstrated that DMAP **40** catalyses the one-pot formation of pyridines **126** from activated α-chloro acetic esters **127** and chalcone-derived imines **128** in moderate to excellent yields (32–99%) (Scheme 37).[45] The use of α-chloro acetic esters avoids the formation of thiophenol (in Smith's system) but this advantage is offset by the formation of the toxic *p*-nitrophenol by-product and the need to prepare the ester from the acid in a separate synthetic step.

The only asymmetric use of C(1)-ammonium enolates from activated esters has been through the demonstration of an isothiourea-catalysed asymmetric [2,3]-rearrangement of allylic ammonium ylides.[46] A range of allylic quaternary ammonium salts **129** (either isolated or made *in situ*), undergo BTM **90**-catalysed [2,3]-rearrangement in the presence of i-Pr$_2$NH as base and HOBt additive to afford a range of *syn*-α-amino acid derivatives **130** in excellent diastereo- and enantiocontrol (up to >95:5 dr, up to >99% ee) (Scheme 38).



Scheme 37 Pyridines from activated α-chloro acetic esters.



Scheme 38 [2,3]-Rearrangement of allylic ammonium ylides.

5. Future challenges

This tutorial review has summarised a number of Lewis base strategies employing tertiary amine and NHC catalysts and carboxylic acid, anhydride or ester starting materials. Despite the range of innovative strategies that have been developed in this area, challenges and opportunities remain. The drive to maximise reaction effectiveness and catalyst efficiency will demand catalytic procedures that proceed routinely at low catalyst loadings and that are amenable to large-scale product formation. The application of these strategies to natural product targets and other relevant biologically active materials will continue to inspire new strategies and disconnections. Other key fundamental questions also remain within this research area. In the relentless drive for efficiency and atom economy can a catalytic activating agent be used to promote the functionalisation of carboxylic acids rather than a stoichiometric reagent? In the use of carboxylic esters can other less toxic starting materials be used as alternatives to electron deficient phenols? Can we use renewable feedstocks as convenient starting materials for this chemistry and prepare value-added products? Can the repertoire of catalysts that promote these reaction processes be extended to other Lewis base families? In this context, the generation of C1-ammonium and azolium enolates from carboxylic acids, anhydrides or esters offers many opportunities for future reaction development as well as the invention of new modes of chemical reactivity and discovery.

6. Conclusions

The use of carboxylic acids, esters and anhydrides as bench stable C1-ammonium/azolium enolate precursors is a rapidly expanding area of research. The potential advantages of using these precursors over traditional starting materials such as ketenes strengthens the potential appeal of this chemistry towards industry. Due to the diverse nature of reactions discovered from these nucleophilic intermediates, it is clear that many new applications remain to be discovered in the coming years.

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