Recent Developments in the Use of Catalytic Asymmetric Ammonium Enolates in Chemical Synthesis

Matthew J. Gaunt* and Carin C. C. Johansson

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

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1. Introduction

Catalytic enantioselective transformations of carbonyl compounds via enolates that comprise the enolization and bond-forming step have received considerable attention within the synthetic organic chemistry community. Many of these methods have exploited the versatile properties of asymmetric Lewis acid complexes that display basic and/or acidic properties and have successfully lead to the development of a range of useful enantioselective processes.[1] In the last 6 years, the resurgence of interest in small organic molecules as catalysts has strongly impacted on the area of direct catalytic asymmetric enolate transformations. In particular, the use of nonracemic secondary amines as catalysts for the generation and reaction of enamines has resulted in a plethora of asymmetric processes that directly transform aldehydes and ketones into useful α-functionalized molecules.[3] However, in this case, the reaction manifold cannot accommodate the use of carbonyl functional groups such as esters, amides, nitriles, or other electron-withdrawing motifs. Therefore, the development of alternative methods for the direct formation of asymmetric enolate equivalents using other types of organic catalysts represents an important avenue of research in enantioselective catalysis.

This review details the recent development of methods that use chiral tertiary amine catalysts as a source to generate asymmetric ammonium enolates. Historically, the cinchona alkaloids (Figure 1) have provided the most common source

of these catalysts because they possess a catalytically active nucleophilic quinuclidine nitrogen atom that is embedded within a chiral environment, hence providing a well-defined molecular architecture that is a prerequisite for asymmetric induction.[4] In addition to the naturally occurring cinchona alkaloids, planar chiral DMAP (4-N,N-dimethylaminopyridne) derivatives (Figure 1) can also be used as nucleophilic catalysts. Although these catalysts often require more complex synthesis, the corresponding "pyridinium" enolates often display enhanced reactivity compared to their cinchona alkaloid counterparts.[5]

2. Types of Ammonium Enolates

For the purpose of this review, ammonium enolates are defined as nucleophilic species that are generated by the action of a chiral tertiary amine catalyst and contain a covalent bond between substrate and catalyst. The ammonium enolates can be generated via a number of different pathways (I, II, and III), as illustrated in Scheme 1. The nucleophilic properties of the tertiary amine catalyst (R_3N) can be exploited through the reaction with electrophiles such as ketenes (path I) or α-bromocarbonyl compounds and a base (path II) to form C1 and C2 ammonium enolates, respectively. Finally, 1,4-addition of the nucleophilic amine catalyst to an α,β-unsaturated carbonyl compound results in a C3 ammonium enolate (III).

3. Catalytic Asymmetric C1 Ammonium Enolates

3.1. Background

The formation of C1 ammonium enolates is most readily realized from the treatment of a ketene or activated carboxylate function with a nucleophilic tertiary amine catalyst (and a base in the latter case). The following sections describe the reactions of catalytically generated C1 asymmetric ammonium enolates and their use in chemical synthesis.

The reaction of a chiral tertiary amine catalyst and a ketene or ketene equivalent represents the most widely employed class of this type of asymmetric enolate intermediate. The area has been extensively reviewed in recent years, and to avoid duplication of these excellent overviews, only processes, in the main part, that have been reported since 2003 will be covered here.[6]

The early work with ammonium enolates was mainly carried out by Pracejus and Sauer and exploited ketene dimerization reactions.[7,8] Inspired by this work, many groups have used this reaction as a route into the synthesis of β-lactones and, subsequently, polyketide-type natural prod-

* To whom correspondence should be addressed. E-mail: mjg32@cam.ac.uk.

Matthew Gaunt received his degree in Chemistry from the University of Birmingham in 1995. He moved to the University of Cambridge to carry out his graduate studies as a Wellcome Trust Scholar with Dr. Jonathan B. Spencer, finishing in 1999. Following this, he completed postdoctoral studies as a GlaxoWellcome Postdoctoral Fellow at the University of Pennsylvania, where he worked with Professor Amos B. Smith. He returned to the U.K. to work with Professor Steven Ley as a Junior Research Fellow at Magdalene College and as a Ramsay Memorial Fellow. In 2004 he was awarded a Royal Society University Research Fellow and began his independent research group at the University of Cambridge. In October 2006 he was appointed Lecturer in Organic Chemistry at Cambridge. The group's research was recognized through the award of the DowPharma Prize for Creativity in Chiral Chemistry in 2005. His research interests involve the development of new catalytic strategies for chemical synthesis and focus on enantioselective organocatalysis and metal-catalyzed C–H bond functionalization and their application in complex molecule synthesis.

Carin Johansson received her degree in Chemistry from UMIST in 2003. She moved to the University of Cambridge to carry out her graduate studies with Dr Matthew Gaunt. During her Ph.D., she developed an enantioselective organocatalytic intramolecular cyclopropanation reaction catalyzed by modified cinchona alkaloid catalysts. After completion of her Ph.D. in 2006, she remained at the University of Cambridge with Dr. Matthew Gaunt, as a postdoctoral research associate, but switched fields and is currently investigating new Pd(II) catalyzed C–H functionalization processes. Her research interests center on the development of new catalytic methodologies and their use in natural product synthesis.

Figure 1. Chiral tertiary amine catalysts.

Scheme 1. Ammonium Enolates

Scheme 2. Proposed Mechanism for Ketene Dimerization

Scheme 3. Enantioselective Ketene Dimerization

ucts.[9] The mechanism of dimerization is echoed in many other related processes and involves initial attack of the nucleophilic amine catalyst to the ketene electrophile (Scheme 2). The resulting zwitterionic ammonium enolate, while only moderately reactive, contains sufficient nucleophilicity to attack another molecule of the reactive ketene. From the newly formed acyl ammonium intermediate, intramolecular *O*-acylation displaces the amine catalyst and forms the ketene dimer.

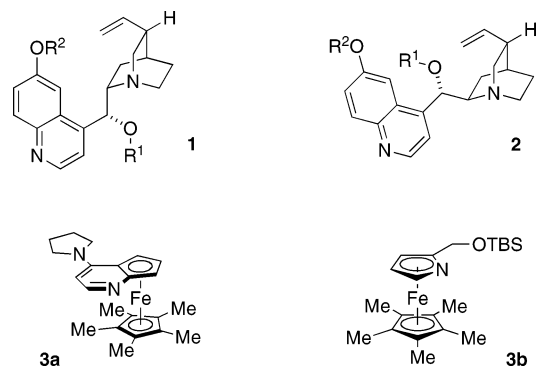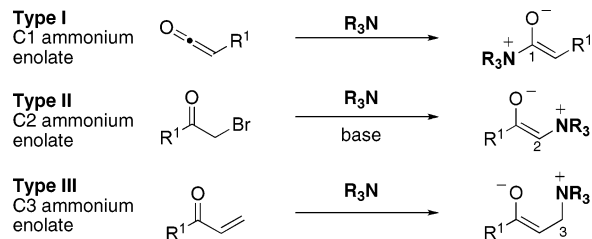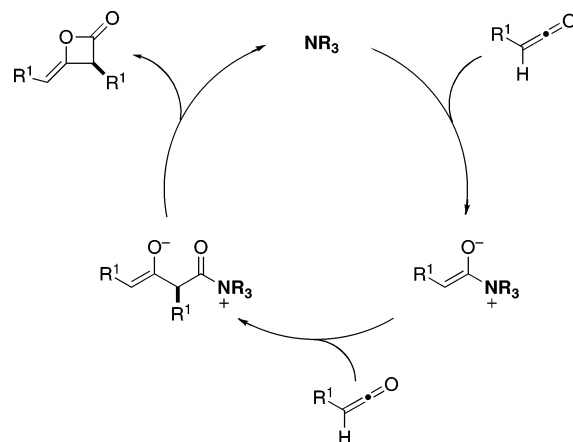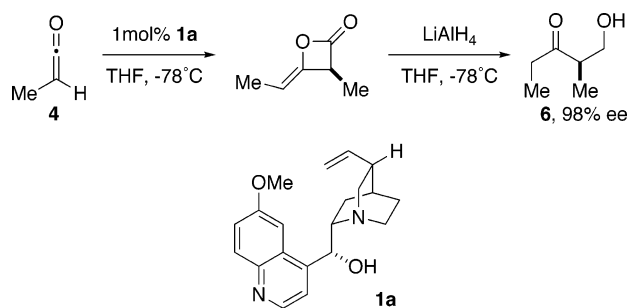Cinchona alkaloids have been the most prominent catalyst for this transformation, and in particular, Calter reported a catalytic asymmetric dimerization of methylketene, **4** (Scheme 3).[10] This simple transformation forms highly versatile polyketide building blocks (**6**) in moderate yield but excellent ee and has been integral in a number of syntheses relating to polyketide natural product assembly.

While Samtleben and Pracejus[7] and Sauer[8] developed the early work in the ketene area, it was the pioneering studies of Wynberg that provided the basis for much of the current studies into this type of organocatalysis. In one of the early contributions to "modern enantioselective organocatalysis", Wynberg and co-workers reported the formation of β-lac-

Scheme 4. Wynberg's β-Lactone Synthesis
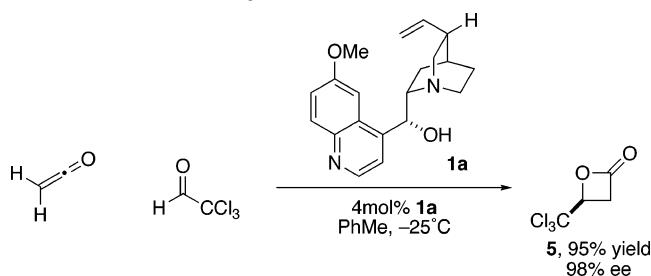
Scheme 5. Mechanism of β-Lactone Formation
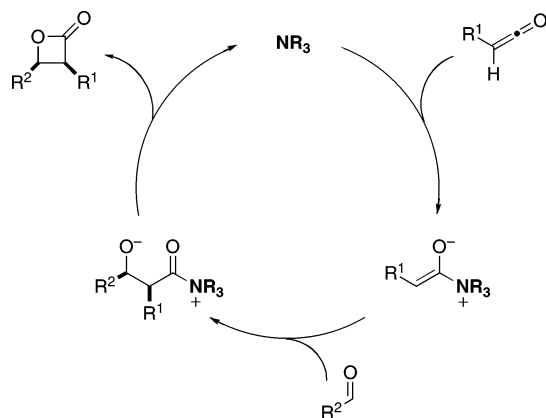
tones (**5**) via a cinchona alkaloid catalyzed aldol lactonization tactic (Scheme 4).[11]

The mechanism is similar to that of ketene dimerization in that the zwitterionic ammonium enolate provides the carbon nucleophile (Scheme 5). In this case, aldol reaction followed by cyclization of the newly formed alkoxide onto the acyl ammonium species forms the β-lactone. One drawback associated with Wynberg and co-workers' original process was the requirement that the aldehydes were highly reactive, presumably to compete with ketene dimerization. As a result of this, only aldehydes containing electron-withdrawing groups adjacent to the carbonyl were suitable coupling partners, and although the reaction often returned good results, it was restricted in scope.
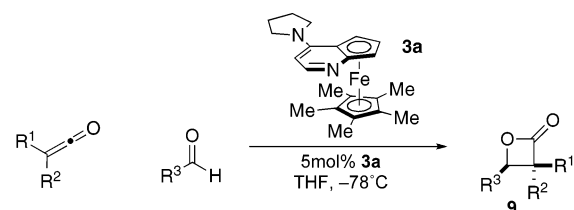
3.2. Recent Developments in the Synthesis of β-Lactone Formation

In recent years, there has been a significant effort toward the development of a more general process. Romo and co-workers have shown that an intramolecular version of the Wynberg β-lactone synthesis reaction produces a range of bicyclic lactones (**8**) from the reaction of the ammonium enolate with the tethered aldehyde function.[12] The mechanism involves formation of the activated carboxyl function (Scheme 6) from the carboxylic acid, **6** (using the Mukaiyama salt, **7**), that can be subsequently intercepted with the nucleophilic catalyst, *O*-acetylquinidine, **2b**. The acyl ammonium intermediate forms the C1 ammonium enolate, and an intramolecular aldol reaction proceeds through a similar pathway to that outlined in Scheme 2 to form bicyclic β-lactones (**8**) in high ee and moderate-to-good yields using 10 mol % of the catalyst. Both enantiomers are accessible using either the Ac-QD or Ac-Q catalysts. In a modification to their original process, Romo and co-workers showed that an analogue of the Mukaiyama salt (TfO⁻ or BF₄⁻ counterion instead of I⁻) can be used to improve the output from the reaction.

Scheme 6. Catalytic Intramolecular β-Lactone Synthesis
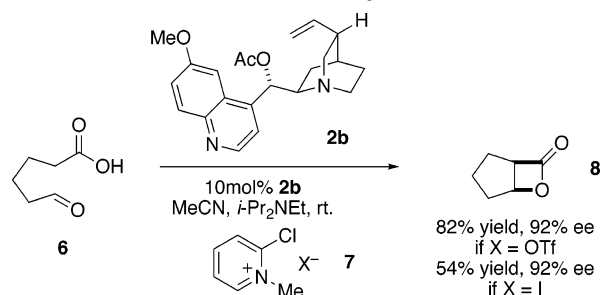

The new salts are more soluble as well as preventing side reactions associated with the I⁻ attacking the electrophilic pyridinium leading to a deactivated system.[13]

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. To overcome the apparent low reactivity of the cinchona alkaloid derived ammonium enolates, Wilson and Fu showed that planar chiral DMAP derived nucleophiles **3** react directly with a range of aldehydes forming the β-lactones **9** in excellent yield and ee (Scheme 7).[14] Furthermore, disubstituted ketenes could also be exploited to form highly functionalized lactones, which is notable because the more-substituted ammonium enolates should be inherently less reactive on steric grounds. Interestingly, they note that the reaction temperature must be lowered to −78 °C in order to isolate the desired β-lactone, suggesting that the ammonium enolates derived from the planar chiral DMAP derivatives are highly reactive intermediates.

Scheme 7. β-Lactone Synthesis with Planar Chiral DMAP Catalysts

entry	R¹	R²	R³	ee %	yield %
1	Et	Et	Ph	91	92
2	Et	Et	2-naphthyl	89	77
3	Et	Et	4-(CF₃)C₆H₄	80	74
4	Et	Et	4-(MeCO)C₆H₄	81	76
5	Et	Et	4-MeC₆H₄	89	67
6	Me	Me	Ph	76	68
7	–(CH₂)₆–		Ph	82	71
8	iPr	Me	Ph	91	48
9	c-C₅H₉	Me	Ph	88	53

Nelson and co-workers also addressed the scope and reactivity problems associated with Wynberg's early findings by employing a metal Lewis acid cocatalyst to assist the reaction between the ammonium enolate and the aldehyde.[15] In addition to using *O*-TMS quinidine **1c** as the source of ammonium enolate, they found that LiClO₄ was optimal for the templating role. As a result, a wide range of aldehydes and simple acid chlorides (precursors to ketenes) were converted to β-lactones in high yield, dr (diastereomeric ratio), and enantiomeric excess (ee) (Scheme 8). The proposed mechanism involves capture of the zwitterionic ammonium enolate with the LiClO₄ forming the lithioam-

Scheme 8. Lewis Acid Assisted β-Lactone Synthesis
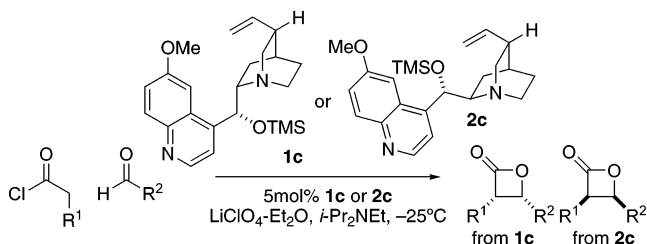
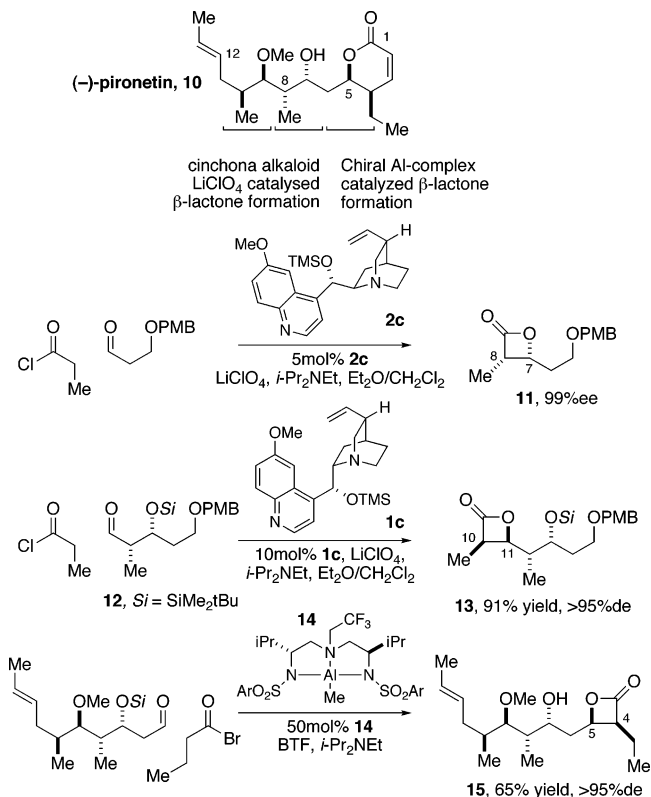| entry	catalyst	R^1	R^2	ee %	de %	yield %
1	**1a**	H	c-C$_6$H$_{11}$	94	–	85
2	**1a**	H	CMe$_3$	96	–	71
3	**1a**	H	CH$_2$CH$_2$Ph	92	–	80
4	**2c**	H	CH$_2$OBn	84	–	70
5	**2c**	Me	CH$_2$CH$_2$Ph	>99	96	84
6	**2c**	Me	(CH$_2$)$_8$CHCH$_2$	99	90	74
7	**2c**	Me	CH$_2$OBn	99	76	68
8	**2c**	Me	CH$_2$CH(CH$_3$)$_2$	99	90	72
9	**1c**	Me	c-C$_6$H$_{11}$	97	>96	74
10	**2c**	Me	C$_6$H$_5$	>99	96	78
11	**2c**	Me	4-F-C$_6$H$_4$	>99	>96	85
12	**1c**	Me	2-Cl-C$_6$H$_4$	>99	96	80
13	**2c**	Me	2-CH$_3$-C$_6$H$_4$	>99	>96	76

Scheme 9. Proposed Mechanism for Lewis Acid Assisted β-Lactone Synthesis

Scheme 10. Lewis Acid Assisted β-Lactone Synthesis

Scheme 11. Proposed Catalytic Cycle

monium enolate. The Li-enolate can now mediate aldehyde addition via a closed Zimmerman−Traxler transition state (Scheme 9), presumably improving the efficiency and stereoselectivity in the reaction and forming the *syn*-aldol product prior to cyclization.

An elegant application of the cinchona alkaloid−Lewis acid catalyzed β-lactone formation was reported by Nelson and co-workers as part of their synthesis of the polyketide natural product (−)-pironetin.[16] In their synthesis of (−)-pironetin, they utilize three β-lactone constructions en route to their target (Scheme 10). A diastereoselective and enantioselective β-lactone formation (to **11**) catalyzed by quinidine derivative **2c** is used to form the key chiral aldehyde **12**. This aldehyde is then the substrate for a second lactone forming reaction. In this case, the quinine derived catalyst **1c** mediates a matched reaction between propionyl chloride and chiral aldehyde **12** to form the β-lactone **13** in 91% yield and >95% de (diastereomeric excess). Finally, a late-stage Lewis acid (**14**) catalyzed β-lactone synthesis (to **15**),[16] again

in good yield and excellent de, completes the core structure, and this product (**15**) is readily elaborated to the (−)-pironetin structure. The overall iterative use of catalytic asymmetric β-lactone formation provides a powerful strategy for the rapid stereoselective synthesis of polypropionate natural products.

3.3. Recent Developments in β-Lactam Formation

The Staudinger reaction combines ketenes with imines to form β-lactams via an overall [2+2]-cycloaddition process (see Scheme 11).[17] Many auxiliary based methods successfully form these important motifs, but the corresponding catalytic asymmetric variations have not been so forthcoming.[18] Lectka and co-workers first demonstrated that cinchona alkaloid catalysts would form ammonium enolates from acid chlorides and that their reaction with imines lead to the β-lactam products (see Scheme 12).[19] The enantio- and diastereoselectivities in these reactions were high although the yields were moderate. The scope of the ketene component

Scheme 12. Catalytic Enantioselective Staudinger Reaction
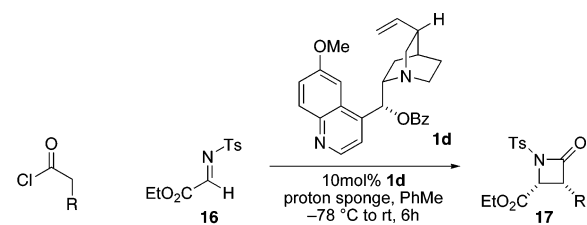
entry	R	ee %	dr	yield %
1	Ph	96	99:1	65
2	Et	99	99:1	57
3	OPh	99	99:1	45
4	OAc	98	>99:1	61
5	OBn	95	99:1	56

Scheme 13. Lewis Acid Assisted Catalytic Enantioselective Staudinger Reaction
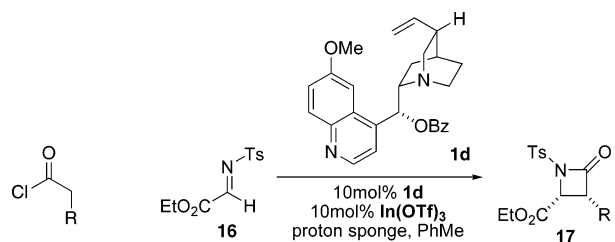
entry	R	ee %	dr	yield %
1	Ph	99	99:1	65
2	Et	99	99:1	57
3	Bn	96	33:1	60
4	CH$_2$OPh	>95	50:7	53
5	OAc	98	99:1	61
6	OPh	99	99:1	45
7	OBn	95	99:1	56
8	CHCH$_2$	98	99:1	58
9	N$_3$	97.5	25:1	47
10	Br	96	98:2	61

Scheme 14. Fu's Catalytic Enantioselective Staudinger Reaction

entry	R^1	R^2	R^3	dr	ee %	yield %
1	–(CH$_2$)$_6$–		Ph	–	81	84
2	–(CH$_2$)$_6$–		2-furyl	–	92	90
3	–(CH$_2$)$_6$–		1-styryl	–	91	82
4	–(CH$_2$)$_6$–		c-C$_3$H$_5$	–	94	89
5	–(CH$_2$)$_6$–		c-C$_6$H$_{11}$	–	94	76
6	Et	Et	2-furyl	–	92	93
7	Et	Et	1-styryl	–	92	83
8	Ph	i-Bu	Ph	8:1	98	88
9	Ph	i-Bu	2-furyl	11:1	98	97
10	Ph	i-Bu	1-styryl	10:1	98	95
11	Ph	i-Bu	c-C$_3$H$_5$	15:1	89	88
12	Ph	Et	2-furyl	9:1	95	97
13	Ph	Et	c-C$_3$H$_5$	10:1	98	98

Scheme 15. Fu's Reversal of Diasteroselectivity in a Catalytic Enantioselective Staudinger Reaction
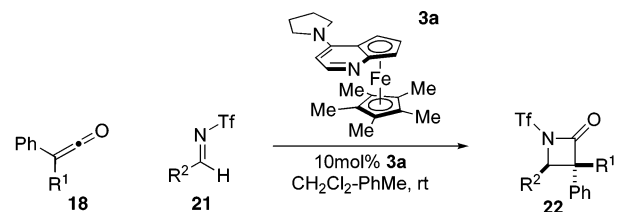
entry	R^1	R^2	dr	ee %	yield %
1	Et	Ph	86:14	63	60
2	Me	Ph	98:2	81	83
3	i-Bu	Ph	97:3	63	72
4	Me	4-FC$_6$H$_4$	96:4	85	84
5	Me	4-(CF$_3$)-C$_6$H$_4$	97:3	69	80
6	Me	4-(OMe)-C$_6$H$_4$	81:19	82	76
7	Me	2-Me-C$_6$H$_4$	81:19	99	89
8	Me	2-Br-C$_6$H$_4$	80:20	84	79
9	Me	2-naphthyl	98:2	94	76
10	Ph	Ph	–	98	62

was good; however, the reaction only worked with a single, highly reactive imine.

In a subsequent finding, the use of metal triflate cocatalysts dramatically improved the output from the reaction.[20] A screen of metals revealed that indium(III) triflate afforded the desired β-lactam **17** in routinely high yield for most substrates (Scheme 13). The rationale behind the effect of the In(III) source could be manifested in many ways. Leckta and co-workers propose that, with a specifically tailored cinchona alkaloid catalyst, the metal activates the imine, not the ammonium enolate, via intermediate **16·In(OTf)$_3$**. Despite these impressive results, the same group continued to improve the process by developing base systems and additives that further increased yields toward a highly effective β-lactam synthesis protocol.[21]

Although the overall efficiency of the β-lactam process is greatly improved by the addition of Lewis acids, the dependence of highly reactive imines persisted. Hodous and Fu identified that the enhanced reactivity of their ammonium enolates derived from planar chiral DMAP derivative **3a** also affected the Staudinger reaction of disubstituted ketenes **18**,

but now with a range of imine electrophiles to form highly substituted β-lactams **20** (Scheme 14).[22] With unsymmetrical ketenes and Ts-imines **19**, they found the reaction was highly enantio- and diastereoselective, producing the β-lactams **20** in good yield.

An interesting reversal in diastereoselectivity can be achieved by employing Tf-imines **21** in the reaction (Scheme 15).[23] The switch in selectivity is attributed to an alternative mechanistic pathway (Scheme 16) and is explained by initial attack of the nucleophilic catalyst **3a** at the highly electrophilic imine carbon of **21** forming a tetrahedral triflimide anion **23**. The new anion, itself asymmetric by virtue of the chiral catalyst now covalently attached, attacks the ketene **18** and forms a new ammonium enolate **24**. Displacement of the catalyst by the enolate forms the β-lactam **22**, and the reversal in diastereoselectivity is presumably due to the intramolecular nature of the C−C bond formation, as opposed to the intermolecular union in the conventional Staudinger reaction. Notably, a range of imines **21** and

Scheme 16. Proposed Catalytic Cycle
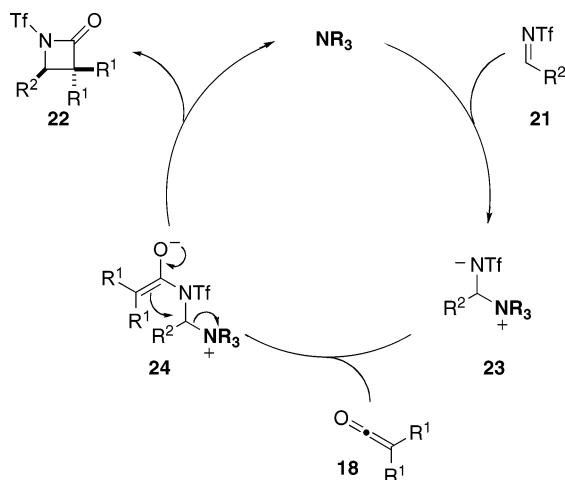
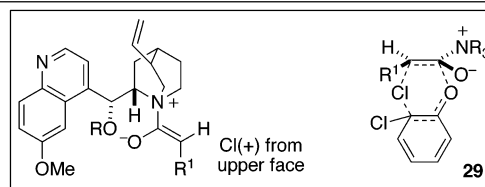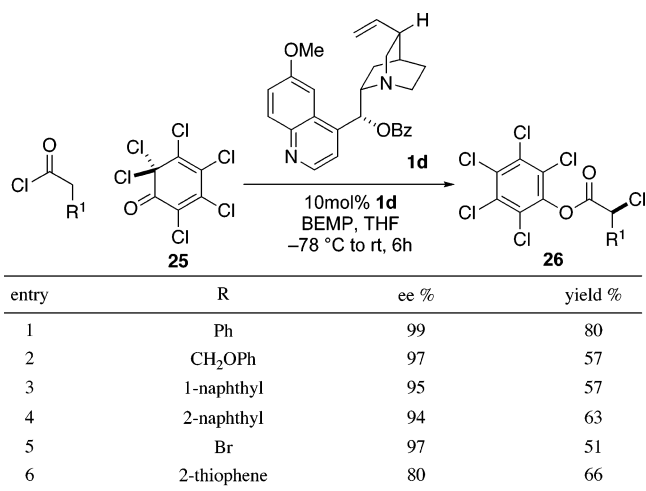**Scheme 17. Catalytic Enantioselective Halogenation**
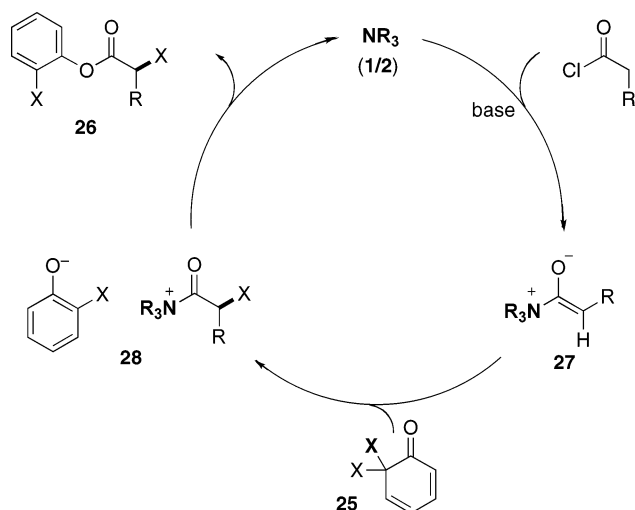
ketenes **18** react in both these series, providing access to a variety of substituted β-lactams **22** in high yields and excellent selectivities.
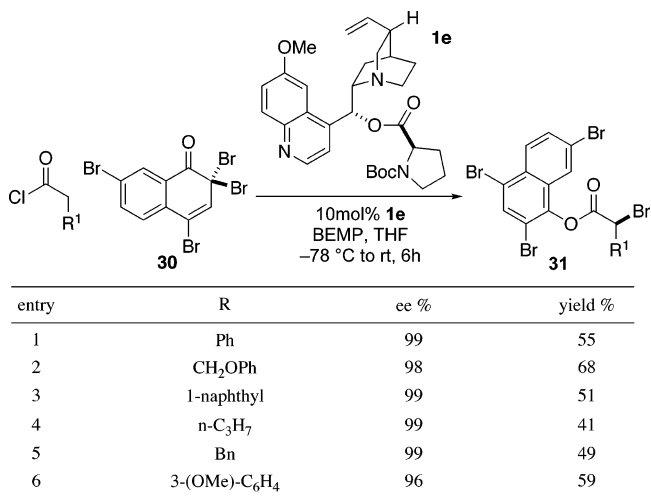
3.4. α-Halogenation Reactions

Ammonium enolates derived from cinchona alkaloid catalysts can also be intercepted with electrophilic halogen sources to form versatile enantioenriched α-chloro- and α-bromoesters **26** from acid chlorides (Schemes 17 and 18). A number of common electrophilic chlorine sources failed to produce the desired products on reaction with ammonium enolates; however, the polychloroquinone derived reagents **25** underwent smooth halogenation of the ammonium enolates (produced by the action of the cinchona alkaloid catalyst (**1/2**) and a stoichiometric base on the corresponding acid chloride) to form the desired products **26** in excellent ee (Scheme 18).[24] The proposed mechanism involves attack of the ammonium enolate **27** onto the polychloroquinone **25**, generating the chlorinated acyl ammonium species and phenolate ion pair **28**. The electrophilic chlorine atom is located next to the carbonyl group in the polychloroquinone **25**. On the basis of molecular mechanics calculations, Lectka and co-workers proposed that the mechanism of the chlorination proceeds through the transition state **29** shown in Scheme 18.[25] Therefore, following attack of the enolate, the proximal nature of the phenolate to the acyl ammonium group initiates

Scheme 18. Catalytic Enantioselective Chlorination

entry	R	ee %	yield %
1	Ph	99	80
2	CH$_2$OPh	97	57
3	1-naphthyl	95	57
4	2-naphthyl	94	63
5	Br	97	51
6	2-thiophene	80	66

Scheme 19. Catalytic Enantioselective Bromination

entry	R	ee %	yield %
1	Ph	99	55
2	CH$_2$OPh	98	68
3	1-naphthyl	99	51
4	n-C$_3$H$_7$	99	41
5	Bn	99	49
6	3-(OMe)-C$_6$H$_4$	96	59

a rapid displacement of the amine catalyst. This step is important in suppressing any racemization of the product, as a prolonged lifetime of the acyl ammonium intermediate would expose the sensitive stereogenic center to potential racemization.

A range of bases can be used, including polymer supported BEMP and proton sponge; however, the most effective system for a high yielding, stereoselective, and efficient reaction was the use of NaH/15−C−5 or NaHCO$_3$, making the process more amenable to larger-scale and continuous-flow systems while maintaining yield and ee's.[26]

The corresponding bromination reaction proceeds under similar conditions with an appropriate brominating agent (Scheme 19). Again, polybromoquinones provided the electrophilic source of bromine, although in this case a *p*-bromoquinone was used initially.[27a] The reaction generally proceeded with high yield and ee; however, on a larger scale, problems with racemization occurred.[27b] On the basis of mechanistic observations in the chlorination reaction, it was proposed that the racemization came about because of the

prolonged lifetime of the acyl ammonium species prior to its eventual interception with the phenolate.[27b,c] To facilitate this trapping process, an *o*-bromoquinone electrophile would locate the phenolate next to the acyl ammonium center, thus promoting the ester formation and reducing the lifetime of the optically sensitive intermediate. With a modified cinchona alkaloid catalyst **1e**, a carefully designed *o*-bromoquinone electrophile **30**, and Hünig's base or NaH, a highly efficient bromination process was realized that readily performs on gram scale with high yield and ee to yield the desired chiral bromoesters **31**.[27]

The importance of these nonracemic halocarbon products as chemical intermediates in organic synthesis is well-established, and they can be easily transformed into numerous other functional groups. This catalytic method is certainly competitive with other asymmetric halogenation processes.
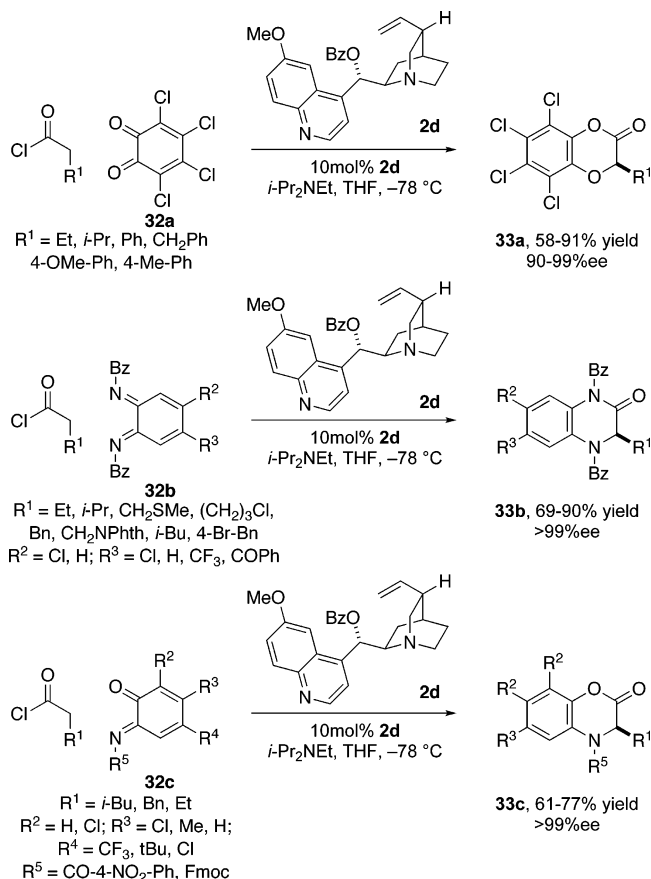
3.5. [4+2]-Cycloaddition Type Reactions

The reactivity of ammonium enolates **27** was further exploited by Lectka and co-workers, who showed that the enolates participated in [4+2]-cycloaddition-type reactions with *o*-quinones **32** to form the cyclic lactone products **33** in very high ee and good yield (Scheme 20).[28] The chemoselectivity for the [4+2]-pathway is surprising given that the competing [2+2]-pathway to the β-lactone was proposed to be the kinetic product. However, Lectka and co-workers reasoned that the re-aromatization of the quinone provided a driving force for the [4+2]-product.

Scheme 20. Postulated Catalytic Cycle for [4+2]-Cycloaddition
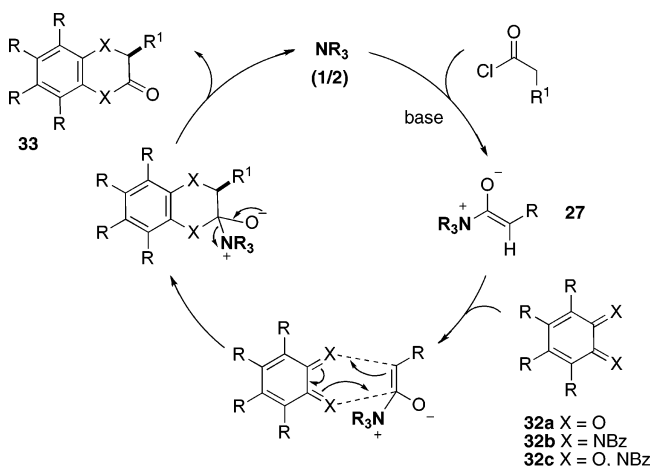
A range of *o*-quinones, of type **32a**, work well in this cycloaddition reaction catalyzed by **2d**, and the products **33a** contain a carbinol function in the α-position to the carboxy group, with selectivities often realized in 99% ee and good yield.[28] Moreover, reaction with the aza-analogues of *o*-quinones (**32b**) effectively forms the α-amino acid motif, again in excellent yield and ee.[29] In addition, both of these reactions generate active ester **33a** and amide groups **33b** that are easily displaced, providing a versatile platform for further elaboration. Finally, the reaction of mixed *N,O-o*-diquinones, of type **32c**, are selective with C−N bond formation preferred over C−O bond formation at the asymmetric center.[30] It is notable that the ee's for all substrates reported in this series of papers are routinely high, emphasizing the reliable asymmetric induction afforded by the catalytic ammonium enolate system (see Scheme 21).

Scheme 21. Inverse Electron Demand Diels−Alder Reaction

33a, 58–91% yield
90–99%ee

32a
R^1 = Et, *i*-Pr, Ph, CH₂Ph
4-OMe-Ph, 4-Me-Ph

32b
R^1 = Et, *i*-Pr, CH₂SMe, (CH₂)₃Cl,
Bn, CH₂NPhth, *i*-Bu, 4-Br-Bn
R^2 = Cl, H; R^3 = Cl, H, CF₃, COPh

33b, 69–90% yield
>99%ee

32c
R^1 = *i*-Bu, Bn, Et
R^2 = H, Cl; R^3 = Cl, Me, H;
R^4 = CF₃, tBu, Cl
R^5 = CO-4-NO₂-Ph, Fmoc

33c, 61–77% yield
>99%ee

4. Type B Ammonium Enolates: Catalytic Asymmetric Ammonium Ylides

Nucleophilic amine catalysts can also be used to form ammonium ylides in combination with the use of a base.[31] In contrast to sulfur ylides,[32] ammonium ylides have received scant attention, and there are only limited reports of the use of simple trialkyl amines and pyridines being used as stoichiometric reagents in cyclopropanation, epoxidation, and olefination reactions.[31] However, exploitation of catalytic asymmetric ammonium ylides was not realized until Gaunt and co-workers reported that asymmetric ammonium ylides (Scheme 22) could function as cyclopropanation agents (Scheme 23).[33]

Scheme 22. Asymmetric Ammonium Ylides
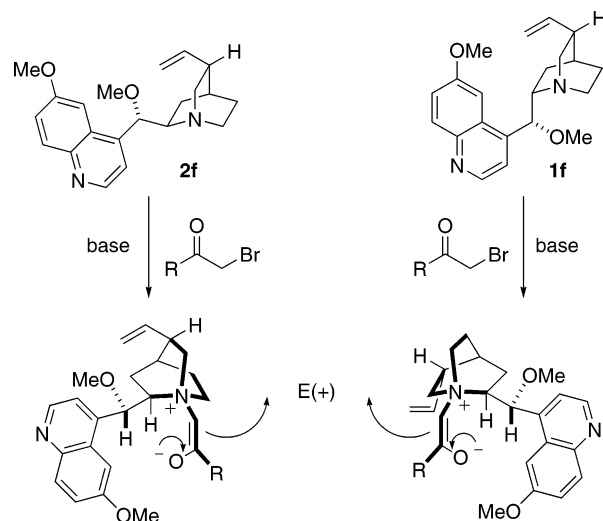
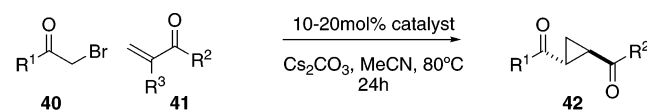**Scheme 23. Proposed Catalytic Cycle for Cyclopropanation**

Scheme 25. Catalytic Enantioselective Cyclopropanation

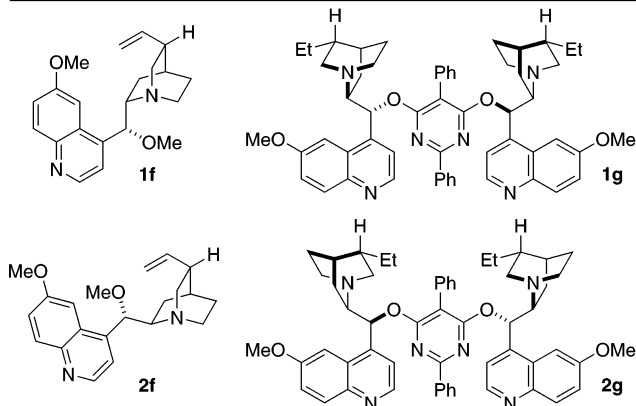| entry	catalyst	R^1	X	ee %	yield %
1	**1h**	CH$_2$CH$_2$Ph	CH$_2$	97	84
2	**1h**	Me	CH$_2$	98	68
3	**1h**	c-C$_6$H$_{11}$	CH$_2$	95	79
4	**1h**	Ph	CH$_2$	98	78
5	**1h**	4-Br-C$_6$H$_4$	CH$_2$	96	83
6	**1h**	3-OMe-C$_6$H$_4$	CH$_2$	99(+)	77
7	**2h**	3-OMe-C$_6$H$_4$	CH$_2$	99(−)	83
8	**1h**	3-(N-Me-indole)	CH$_2$	98(+)	95
9	**2h**	3-(N-Me-indole)	CH$_2$	99(−)	85
10	**1h**	Et	NBn	97	27
11	**1h**	1-(2-pyrrolidone)	CH$_2$	99	77

They demonstrated the potential of this approach via the development of a highly selective process that formed 1,2-disubstituted cyclopropanes **42** in high yield, dr, and ee from reaction between α-bromocarbonyls **40** and electron-deficient alkenes **41** (Scheme 24). Simple cinchona alkaloid derivatives **1f/2f** can be used as catalysts to provide either enantiomer of the cyclopropane. The mechanism involves an initial S$_N$2 reaction between the amine catalyst and the bromocarbonyl to form a quaternary ammonium salt **43**
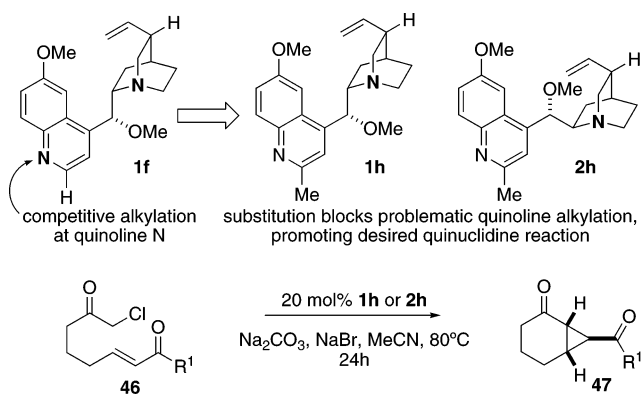
Scheme 24. Catalytic Enantioselective Cyclopropanation

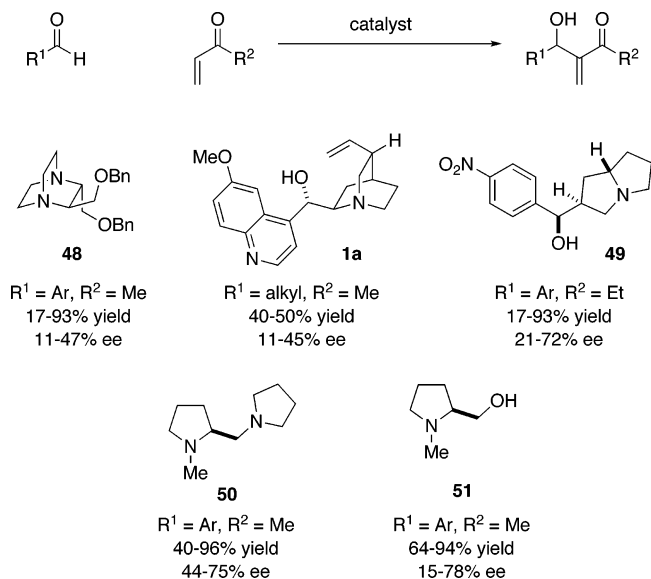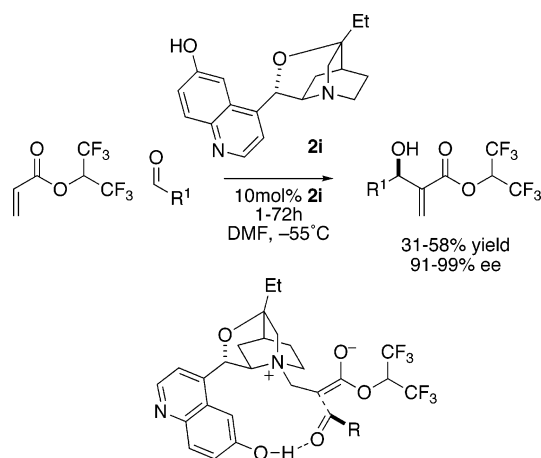| entry	catalyst	R^1	R^2	R^3	ee %	yield %
1	**1f**	Ot-Bu	Ph	H	86	96
2	**1f**	Ot-Bu	4-(NEt$_2$)-C$_6$H$_4$	H	84	73
3	**1f**	Ot-Bu	4-(Br)-C$_6$H$_4$	H	85	83
4	**1f**	NEt$_2$	Ph	H	97	94
5	**1g**	NMe(OMe)	4-(Br)-C$_6$H$_4$	H	96	67
6	**1g**	NMe(OMe)	3-(Br)-C$_6$H$_4$	H	96	60
7	**1f**	Ot-Bu	Ph	Me	92	63
8	**1f**	Ot-Bu	OBn	H	80	75
9	**1f**	Ot-Bu	OMe	NBoc$_2$	97(+)	90
10	**2g**	Ot-Bu	OMe	NBoc$_2$	90(−)	83
11	**1f**	NMe(OMe)	C$_5$H$_{11}$	H	96(+)	65
12	**2g**	NMe(OMe)	C$_5$H$_{11}$	H	92(−)	77
13	**1f**	NMe(OMe)	3-(N-Me-indole)	H	95(+)	74
14	**2g**	NMe(OMe)	3-(N-Me-indole)	H	94(−)	84

(Scheme 23). The presence of the positively charged ammonium ion lowers the pK_a of the adjacent protons such that they can be removed through the action of a weak carbonate base to form the ammonium ylide **44**. Michael addition of the ylide onto the electron-deficient alkene forms a new enolate **45** that, in turn, can undergo an internal displacement of the C−NR$_3$ bond, closing the cyclopropane ring and releasing the catalyst.[34]

The intermolecular cyclopropanation process is successful for a range of substrates, providing a broad range of functionality in the products. Simple cinchona alkaloid catalysts (**1f/2f**) can be used, but more complex **1g** and **2g** amines routinely offered a higher ee for either enantiomer (Scheme 24).[34]

The corresponding intramolecular reaction can also be affected, although a new catalyst system **1h/2h** had to be designed in order to develop a truly efficient process (Scheme 25). While early results identified a highly enantioselective reaction, the yields of the reaction were moderate.[35] Mechanistic investigations revealed that the quinoline nitrogen atom was not an innocent bystander in these reactions and participated in nonproductive salt-forming side reactions. However, Gaunt and co-workers found that substituting the adjacent C−H bond for C−Me blocked alkylation on the quinoline N-atom (**1h/2h**), promoting the reaction to follow the desired ylide pathway to the [4.1.0]-bicycloalkanones **47**. The catalytic cyclopropanation tactic worked in excellent yield and ee over a range of substrates, forming products containing a useful [4.1.0]-bicycloalkanone ring system that can be further transformed through strain-releasing reactions.[36]

5. Type C Ammonium Enolates: Catalytic Asymmetric C3 Substituted Ammonium Enolates

The reactivity of type C ammonium enolates, classified as having the ammonium group at C3, is exemplified by

Scheme 26. Early Attempts toward Catalytic Asymmetric Morita−Baylis−Hillman Reactions

48
R[1] = Ar, R[2] = Me
17-93% yield
11-47% ee

1a
R[1] = alkyl, R[2] = Me
40-50% yield
11-45% ee

49
R[1] = Ar, R[2] = Et
17-93% yield
21-72% ee

50
R[1] = Ar, R[2] = Me
40-96% yield
44-75% ee

51
R[1] = Ar, R[2] = Me
64-94% yield
15-78% ee

Scheme 27. Catalytic Asymmetric Morita−Baylis−Hillman Reactions

2i
10mol% **2i**
1-72h
DMF, −55°C

31-58% yield
91-99% ee

application of tertiary amine catalysts in the Morita−Baylis−Hillman reaction and its aza-counterpart. Traditionally, the MBH-type reactions have been notoriously difficult to successfully catalyze with high enantioselectivity and acceptable rates.[37] Many catalysts have been tested on this reaction and a number of catalysts have recently (**1a**, **48**−**51**) provided moderate enantioselectivity in variable yield (Scheme 26).[38] It is notable that many of these catalysts contain an element of "bifunctionality", wherein the role of the nucleophilic amine is coupled with a potential H-bond donor. This observation has been critical in designing more selective catalysts for this process. There have been many studies toward the development of a catalytic asymmetric Morita−Baylis−Hillman (MBH) reaction, and extensive overviews of this area have been recently reported; therefore, only new and relevant advances are detailed here.[39,40]

A major breakthrough in the MBH reaction was made when Hatakeyama and co-workers discovered that β-isocupreidine **2i** was a good catalyst for this reaction (Scheme 27).[40] The role of the hydroxyl group was extremely important toward a selective outcome of this reaction, as it was proposed that a hydrogen bond to the aldehyde organizes the transition structure toward a stereoselective reaction. Although the yields ranged from moderate to very good, the

Scheme 28. Catalytic Asymmetric Aza-Morita−Baylis−Hillman Reactions

2i
10mol% **2i**
24-36h
DMF-PhMe, −55°C

up to 80% yield
73-97% ee
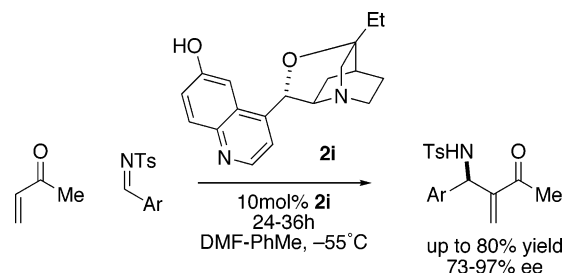
Scheme 29. Catalytic Asymmetric Morita−Baylis−Hillman Reactions with Bifunctional Catalysts

10mol% **52**
PhMe-CPME
−15°C

88-100% yield
97-95% ee

52
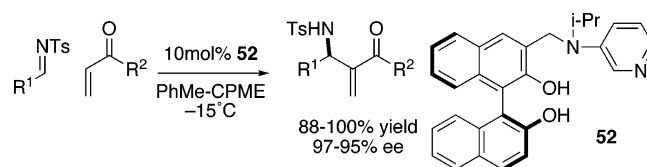
enantioselectivity observed in the reaction was excellent and represented the first consistent results in excess of 90%.

The corresponding aza-MBH reaction could also be catalyzed with high enantioselectivity using the β-isocupreidine catalyst **2i**. While methyl acrylate and acrylonitrile afforded lower ee's, the reaction using methyl vinyl ketone and Ts-imines afforded the aza-MBH products in good yields and excellent ee's (Scheme 28).[41]

Finally, a recent example of bifunctional asymmetric catalysis has led to a new solution for this difficult process (Scheme 29). Sasai and co-workers reported that a binol catalyst **52** containing a pendant DMAP derivative could effectively catalyze the MBH reaction of enones and acrolein to Ts-imines in excellent yield and ee.[42] The enone ketone function is presumably activated by the binol through a hydrogen bond, catalyzing the addition of the pyridine to an activated alkene initiating the coupling and forming the products on elimination of the nucleophilic catalyst group.

6. Conclusion

In line with many aspects of enantioselective organocatalysis, the use of catalytically generated ammonium enolates in asymmetric catalysis is a reemerging area in organic synthesis. Many powerful transformations can be accomplished using a nucleophilic chiral amine catalyst, such as β-lactam and β-lactone formation, [4+2]-cycloadditions, carboxylic acid derivative synthesis, and ketene dimerization, cyclopropanation, and MBH reactions. The catalysts used for these types of transformations are most often derived from the cinchona alkaloids or planar-chiral DMAP complexes. In many cases, the products are obtained in good yields and with very high enantioselectivities. The increasing number of publications within this field strongly reflects the high potential of catalytic asymmetric ammonium enolate mediated transformations and their usefulness in organic synthesis.

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