Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis

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Received April 4, 2003

Contents

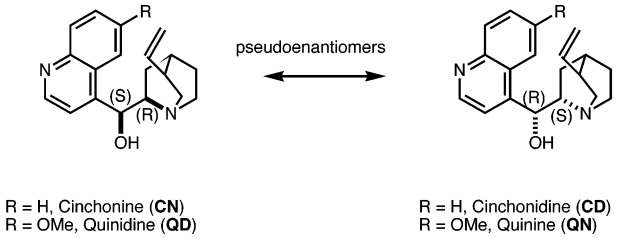
1. Introduction and Historical Perspective

Catalytic asymmetric synthesis is providing chemists with new and powerful tools for the efficient synthesis of complex molecules. While many of the most notable catalytic systems are metal-based[1] and rely on chiral Lewis acid and organometallic redox-based catalysis, increasing numbers of asymmetric reactions are catalyzed by chiral nucleophiles, building on the vast assortment of reactions in nature in which nucleophiles play pivotal roles.[2] Chiral amines play a central role in this expanding area of asymmetric catalysis and provide the primary theme of this review. Other classes of nucleophiles, such as chiral phosphoramides[3] and amine oxides,[4] complement catalysis by chiral amines, but their chemistry is comprehensively covered elsewhere in this issue. Although chiral amines have been utilized extensively as chiral ligands,[5] they have also shown great promise in catalyzing a broad range of asymmetric transformations, yielding optically enriched products in high selectivity and yield that may not be accessible through alternative asymmetric technology. Mechanistically speaking, chiral amines can also serve as bases; they can give rise to intermediate nucleophiles such as enamines and to intermediate electrophiles such as iminium ions. From our point of view, reactions involving enamines and iminium ions are considered to be separate classes. On the other hand, it is often difficult to distinguish between mechanisms involving base and nucleophilic catalysis, and consequently we have included examples of both, especially when ambiguity exists.

Historically, the cinchona alkaloids were the first chiral amines to be used in asymmetric catalysis, most notably in the pioneering work of Pracejus from the 1960s on disubstituted ketene alcoholysis. Cinchona alkaloids also possess a rich and colorful history that is rooted in natural products and pharmaceutical chemistry.[6] They are isolated en masse by extracting the bark of the cinchona tree, which is native to tropical regions. Outside of organic chemistry, the cinchona alkaloids have found wide use as food flavorings (for example as the bitter principle of tonic water[7]) and in the treatment of malaria.[8] Additionally, their roles as ligands, chromatographic selectors,[9] and NMR discriminating agents[10] have been examined extensively over the past thirty years. Pracejus,[11] Morrison and Mosher,[12] Wynberg,[13] and Gawronski[14] have all published reviews on the catalytic chemistry of cinchona alkaloids over the past four decades.

The cinchona alkaloid family consists of two pairs of diastereomers, namely, cinchonine/cinchonidine and quinine/quinidine (Scheme 1). Due to the wide-

Scheme 1



R = H, Cinchonine (**CN**)
R = OMe, Quinidine (**QD**)

R = H, Cinchonidine (**CD**)
R = OMe, Quinine (**QN**)

spread use of cinchona alkaloids, all four members are readily available in large quantities from most chemical suppliers.[15] They can be easily anchored covalently to a solid support for ready separation and reuse of the catalyst. The β-hydroxyamine portions of the molecules, which are responsible for imparting selectivity, are often termed "pseudoenantiomeric". Practically speaking, if quinine affords one enanti-

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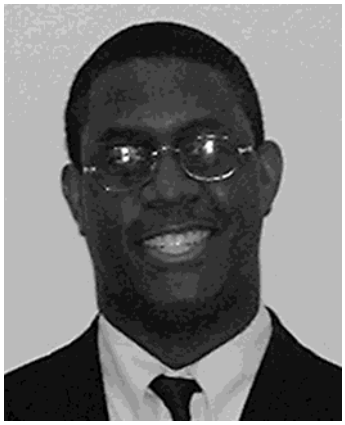
10.1021/cr020061a CCC: $44.00
Published on Web 08/13/2003



Stefan France obtained his bachelors degree in chemistry in 2000 from Duke University, where he studied physical organic chemistry with Professor Eric Toone. His graduate career began in the fall of 2000 when he joined the research group of Professor Tom Lectka. Stefan's Ph.D. research centers around the development of new methodology for the catalytic, asymmetric halogenation of alkenes and ketones. Stefan currently holds graduate fellowships sponsored by UNCF, Merck, and Pfizer.

David Guerin received his bachelors degree in pharmacy with a minor in chemistry from the University of Rhode Island in 1998. He then began his graduate work investigating the use of peptidic catalysts under the direction of Professor Scott Miller at Boston College, receiving his Ph.D. in 2003. He is currently a process chemist with Vertex Pharmaceuticals in Cambridge, Massachusetts.

omer in excess through a catalytic process, quinidine will usually give the opposite enantiomer in comparable enantioselectivity. Quinuclidine, forming the core of the cinchona alkaloids, is a competent nucleophile, whose nucleophilicity is comparable to piperidine, pyridine, and morpholine toward carbonyl containing organic molecules (Table 1).[16]

Although the cinchona alkaloids occupy a central position in the field from a historical standpoint, the past few years have witnessed an explosion of interest in the development of other classes of amine-based catalysts. For example, heterocyclic amines such as imidazole[17] and guanidine[18] have long been known to serve as nucleophilic catalysts, and recent work has centered around their incorporation into chiral scaffolds, both nonnatural and peptide-based, to serve as catalysts for a wide variety of asymmetric transformations (vide infra). Furthermore, chiral versions of common amines, such as DMAP derivatives (**1**) and noncinchona derivatives of quinuclidine (**2**),[19] have been successfully developed for use in asymmetric synthesis (Figure 1). Other amine catalysts, both simple and complex, have been synthesized and screened in asymmetric reactions, such as DABCO derivatives (**3**), pyrrolidines (**4**), as well as a library of chiral bicyclic amines (**5**).[20] All of these different catalysts will be discussed in the following sections in the context of different reaction classes.

Scott J. Miller was born in Buffalo, New York, in 1966. He received his B.A. and Ph.D. degrees from Harvard University under the guidance of David A. Evans. Following postdoctoral studies with Robert H. Grubbs at Caltech, he joined the faculty at Boston College in 1996, where he is currently a Professor of Chemistry. His research interests are in the areas of synthesis, catalysis, and chemical biology.

Tom Lectka is a native of Detroit, Michigan, who attended graduate school at Cornell University in John McMurry's laboratory, obtaining his Ph.D. in 1990. After a Humboldt Fellowship to study at Heidelberg in 1991, he joined Dave Evans's laboratory at Harvard University with an NIH Postdoctoral Fellowship. In 1994 he began his tenure at Johns Hopkins University, where he was promoted to full Professor in 2002. His research interests include catalytic, asymmetric reactions of imines, amides, and ketenes, asymmetric halogenation reactions, "switchable" mechanisms in synthesis, solid-phase synthesis, and synthetic rotamase catalysts.

Table 1. Nucleophilicity Parameters of Common Amines in Reaction with α-Ketenylbenzocyclobutenone

amine	N_+[a]
diethylamine	3.21
quinuclidine	2.98
piperidine	2.70
pyridine	2.67
morpholine	2.50
triethylamine	1.57

[a] $\log(k/k_o)$ where k is the second-order rate constant for the reaction of a cation−nucleophile pair in a specific solvent and k_o is the rate constant for the reference nucleophile, usually water.

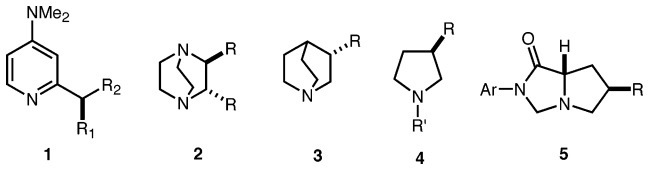


Figure 1. Examples of nucleophilic amines.

2. Reactions Catalyzed by Chiral Nucleophilic Amines

2.1. Kinetic Resolution of Alcohols and Amines

4-(Dimethylamino)pyridine (DMAP) is one of the most frequently used nucleophilic catalysts.[21] DMAP provides rate acceleration in numerous reactions,[22] especially in acylation reactions that use anhydrides as the acyl donor. In fact, acylation reactions of alcohols with anhydrides typically take place with rates that are several orders of magnitude greater in the presence of a nucleophilic catalyst. However, attempts to make chiral variants of DMAP for efforts in asymmetric catalysis have been notably rare, in most cases due to difficulties in synthesis. A pioneering contribution involving a chiral DMAP reagent **6** for asymmetric acyl transfer[23] was introduced by Vedejs and Chen (Figure 2). This DMAP derivative

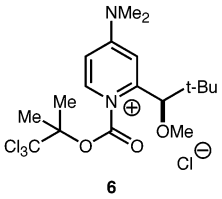


Figure 2. Vedejs' stoichiometric reagent for kinetic resolution.

6 was used in the kinetic resolution of various secondary alcohols.[24,25] Selectivity factors (*s*) of 11−53 were obtained for several of the alcohols screened. However, a significant drawback is that this reagent is apparently not effective catalytically.

Fu and co-workers then introduced "planar-chiral" DMAP derivatives as enantioselective catalysts.[26] DMAP itself is not chiral and possesses two mirror planes, the first being in the plane of the pyridine ring, with the second passing perpendicularly through the two nitrogens. One can effectively eliminate these two mirror planes, the first through π-complexation and the second by introduction of a substituent on the 2-position of the pyridine ring. This design allowed Fu and co-workers to develop effective enantioselective catalysts for several reaction classes.

At the outset of this work, several chiral and achiral heterocyclic metal complexes based on ferrocene were developed and screened for nucleophilic rate enhancement in acyl transfer reactions, cyanosilylation of aldehydes, and alcohol additions to ketenes (Figure 3). These complexes exhibited differing reactivities in the aforementioned reactions (catalyst **8** being the most reactive in each process), with each exhibiting rate acceleration as compared to reactions in the absence of catalyst.

With the benchmark reactivity of planar chiral DMAP complexes established, asymmetric catalysis was investigated using chiral complex **7**. Using

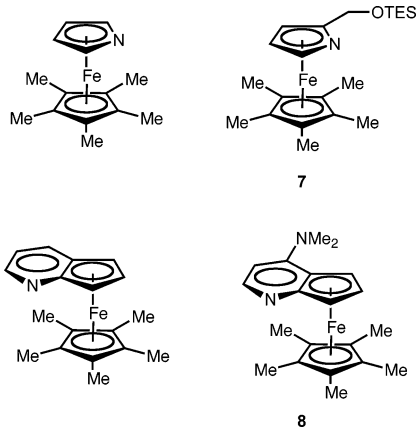
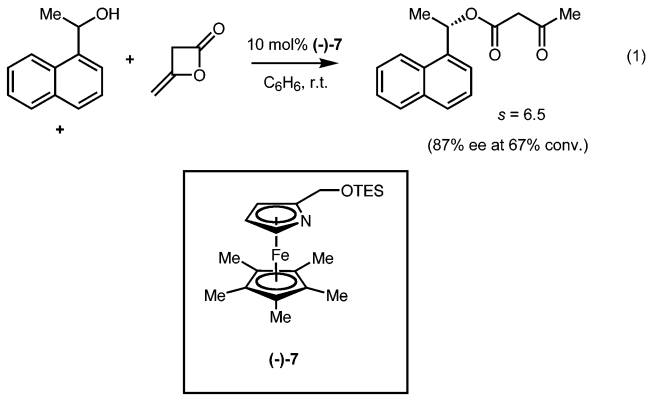


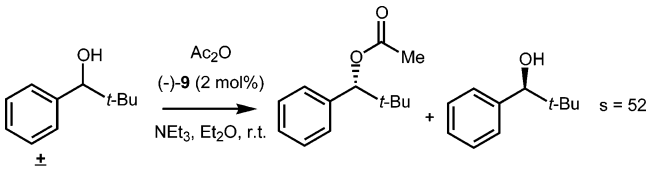
Figure 3. Chiral and achiral heterocyclic metal complexes.

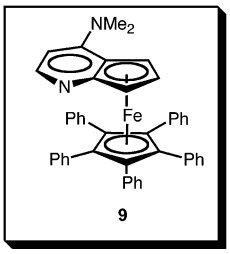
optically pure complex (−)-**7**, racemic α-methyl naphthylcarbinol was resolved using diketene[27] as the acyl donor, exhibiting an *s* value of 6.5 (87% ee at 67% conversion, eq 1).



Further catalyst development involved examining the effect of increasing the steric bulk of the cyclopentadienyl unit, by making derivatives incorporating an Fe(C_5Ph_5) complex.[28] Because complex **8** exhibited higher reactivity than other complexes that were developed, it was screened for its potential in asymmetric catalysis as well. However, it was found that in the kinetic resolution of racemic *sec*-phenylethanol, catalyst **8** afforded minimal selectivity (s = 1.7). By switching the cyclopentadienyl group from a C_5Me_5 group to a C_5Ph_5, a more selective complex was developed. An improved kinetic resolution of *sec*-phenylethanol was realized using catalyst (−)-**9** (2 mol %), leading to a more selective reaction with an s = 14. A variety of aryl−alkyl and alkenyl−alkyl carbinols are good substrates for this reaction, and in one case, a highly selective resolution is performed exhibiting an s = 52 (eq 2).

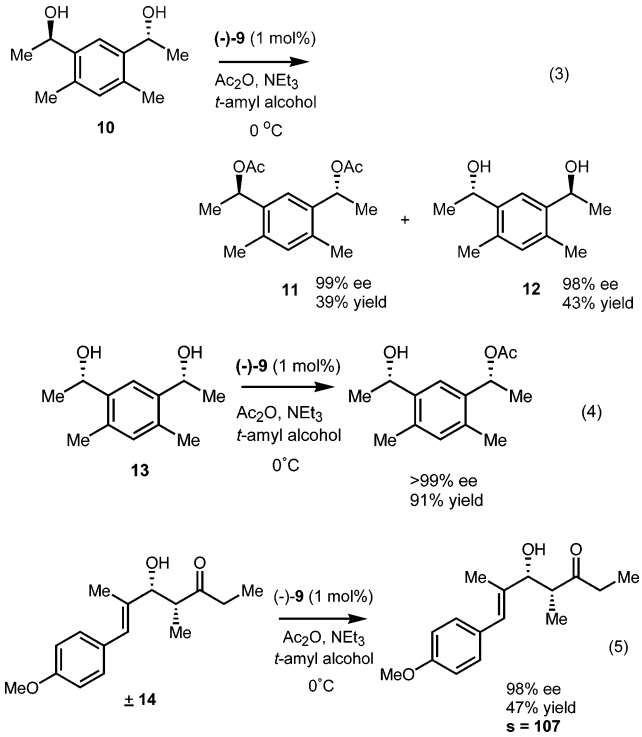
Through further reaction development, it was found that solvent played a critical role in enantioselectivity.[29] *t*-Amyl alcohol was found to be the optimal solvent in terms of reactivity as well as selectivity. With reactivity enhancement, reactions were performed at 0 °C to further increase enantioselectivity, to where *s* values ranging from 32 to 95 were obtained for various aryl-alkyl carbinol substrates. Having identified optimal reaction conditions, other alcohol substrate classes were resolved using complex **9**, including diols, allylic alcohols,[30]



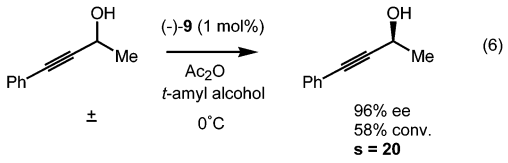


(2)

and propargylic alcohols.[31] Interestingly, when racemic diol **10** is subjected to a kinetic resolution reaction, a sequential enantioselective process occurs to provide diol **12** and diacetate **11** in excellent enantioselectivity (>98% ee); very little of the monoacetate is produced (eq 3). In a related experiment, *meso*-diol **13** undergoes an efficient desymmetrization[32] process to afford the monoacetate in high enantioselectivity and yield (>99% ee and 91% yield, eq 4). An application of this methodology in target-oriented synthesis is highlighted by the effective resolution of racemic **14**, which is a key intermediate in a recent total synthesis of epothilone A by Lerner and co-workers (eq 5).[33] Finally, propargylic alcohols are resolved with good enantioselectivities (*s* values up to 20), adding to the growing class of alcohol subtypes that may be efficiently resolved with this catalyst (eq 6).



Despite the various nonenzymatic methods that have been developed for the kinetic resolution of racemic alcohols, there has been less success in the development of nonenzymatic protocols to resolve racemic amines.[34] Presumably this is the result of the



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increased reactivity of amine nucleophiles in comparison to alcohol nucleophiles, with reactivity often occurring in the absence of a catalyst. As a starting point, a stoichiometric reagent **15** (Figure 4) was

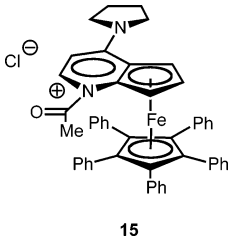


Figure 4. Fu's stoichiometric reagent for amine resolution.

developed for the resolution of amines, and provided good enantioselectivities (up to 91% ee).[35] After these efforts, a catalytic variant was developed using an *O*-acylated azlactone as the acyl donor (Figure 5).[36]

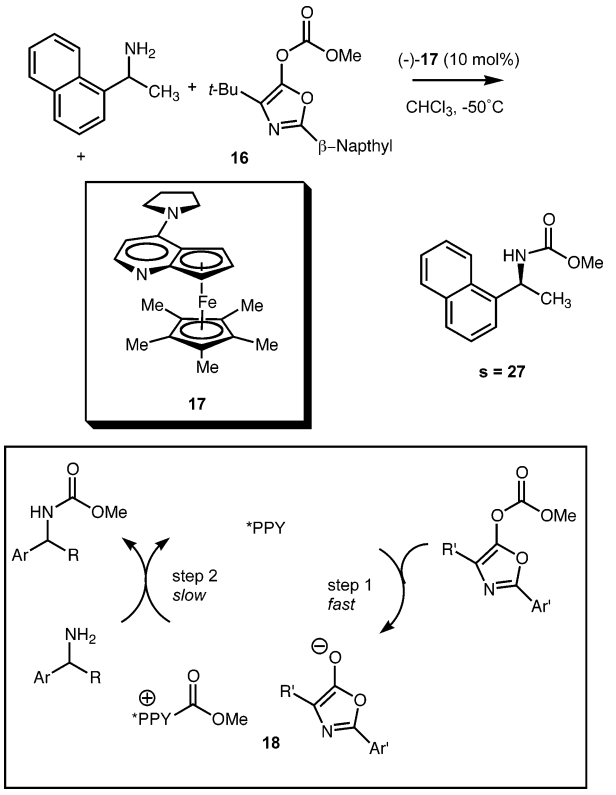
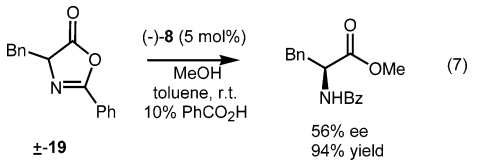


Figure 5. Kinetic resolution of racemic amines.

Critical to the success of a kinetic resolution of an amine substrate is the use of an acyl donor that will not react with the amine in the absence of catalyst, which would lead to a nonselective reaction. After screening several acylating agents, it was found that *O*-acylazlactone **16** reacts more readily with catalyst **17** than it does with amine substrate. With this acylating agent, racemic 1-phenylethylamine was resolved with an appreciable level of enantioselectivity ($s = 2.8$) using a 10 mol % catalyst loading.

Subsequent reaction optimization led to a highly selective resolution of 1-phenylethylamine to give an *s* factor of 27. Mechanistically, it is believed that the first step of the reaction is catalyst acylation to afford an ion pair **18**, which is the resting state of the catalyst. Acylation of the amine followed by regeneration of the catalyst is rate, as well as, stereochemistry determining.

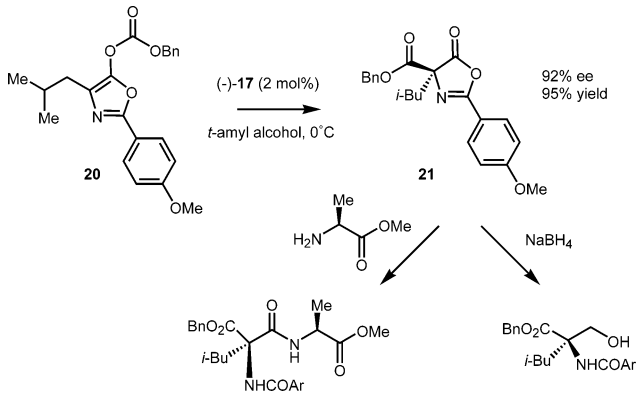
While kinetic resolution reactions are effective in delivering optically enriched starting materials and products, they are inherently inefficient, in that an ideal reaction can only maximally afford a 50% yield. A powerful catalytic process would be to couple the kinetic resolution event to a racemization event, thereby creating a dynamic kinetic resolution (DKR).[37] Using complex **8**, an enantioselective DKR of azlactones was developed to furnish optically enriched α-amino esters in moderate ee.[38] Azlactone **19** was subjected to DKR conditions using catalyst (−)-**8** to afford the corresponding α-amino ester in 94% yield and 56% ee (eq 7). Interestingly, enantioselectivities could be improved by using sterically bulky alcohols (up to 78% ee using *i*-PrOH); however, reaction times were prohibitively slow.[39]



(7)

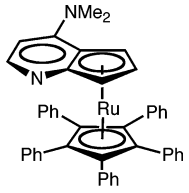
Complex (−)-**17** was shown to catalyze the rearrangement of *O*-acylated azlactones to afford the corresponding azlactone with a new quaternary carbon stereocenter.[40,41,42] *O*-Acylazlactone **20** was treated with 2 mol % of catalyst (−)-**17** at 0 °C in *t*-amyl alcohol solvent to afford the rearranged product **21** in 92% ee and 95% yield (Scheme 2). These

Scheme 2



products are versatile synthons, in that they can be converted to dipeptides through treatment with an amino ester, and to α-alkyl serine derivatives by treatment with $NaBH_4$. Mechanistically, this reaction is somewhat similar to the kinetic resolution of racemic amines described above. Fast reaction of the catalyst with substrate forms an intermediate ion pair, with subsequent C-acylation as the rate and stereochemistry-determining step.

The above are examples of various planar-chiral DMAP derivatives that are highly effective catalysts for numerous reaction types and are all based on ferrocenyl systems. It is possible that changing the metal of these complexes could have a marked impact in terms of both reactivity as well as selectivity. In this regard, Fu has investigated ruthenium-based systems in kinetic resolution reactions of secondary alcohols, as well as the DKR of azlactones.[43] Ruthenium catalyst **22** (Figure 6) was synthesized and



22

Figure 6. Fu's ruthenium-based complex.

compared with its iron analogue in the kinetic resolution of *sec*-phenylethanol with acetic anhydride. Under identical conditions, ruthenium-based **22** is slightly more reactive but was shown to be less selective than its iron analogue, providing an *s* value of 10 (compared to 43 with the iron-complex). In the case of the DKR of azlactones, the ruthenium-based catalyst showed a modest increase in selectivity when compared to the iron complex. While this study did not afford marked improvements in the efficiencies of these catalytic processes, it nevertheless provides valuable mechanistic information with regard to how these catalysts function and what parameters are necessary for high activity and selectivity.

In 1997, Fuji developed a catalyst for enantioselective acyl transfer based on the well-known nucleophile 4-pyrrolidinopyridine (PPY).[44] Catalyst **23** was found to be an effective catalyst (5 mol %) for the kinetic resolution of racemic alcohol **24** (X=O) using $(i\text{-PrCO})_2O$ as the acylating agent, affording k_{rel} values of up to 12.3 (Figure 7). Further reaction development led to the discovery that amide substrates (X = NH) are resolved with greater selectivities (up to k_{rel} >18).[45] In general, substrates that possess electron donating groups on the aromatic ester/amide moiety exhibit higher enantioselectivities. Through rigorous ^1H NMR studies, it was determined that catalyst **23** adopts what is referred to as an open conformation, where the naphthalene ring and the pyridine ring are positioned away from each other. In addition, it appears that in this conformation the pyridine is free to rotate about the C−N bond, exemplified by the fact that the two protons ortho to the pyridine nitrogen are indistinguishable on the NMR time scale. However, when acylated, the catalyst adopts a closed conformation **25**, where the naphthalene and acylpyridinium moiety are involved in a significant $\pi-\pi$ interaction, sufficiently blocking the si face of the carbonyl to attack. The authors refer to this conformational change as an "induced-fit" process, much like the conformational change that enzymes undergo upon binding with ligand. It is proposed that the aromatic ring of the substrate is involved in another aromatic

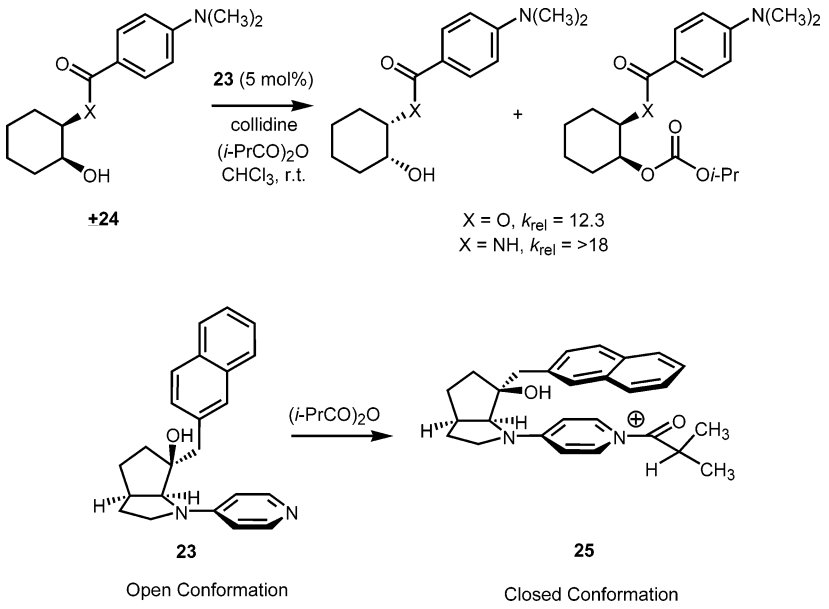
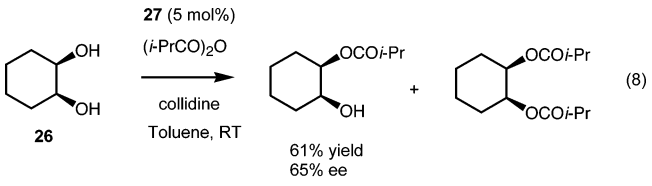
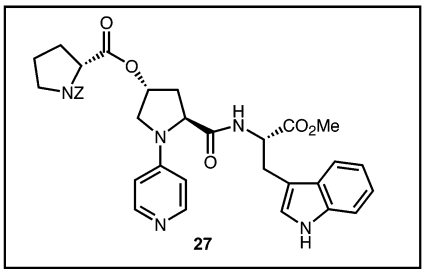


Figure 7. Fuji's PPY catalyst for kinetic resolution.

$\pi-\pi$ interaction with the catalyst, to form a well organized transition state that can account for the high stereoselectivity. This is consistent with the observation that electron-rich aromatic substrates afford higher selectivities, possibly through a better $\pi-\pi$ interaction with the electron-poor acylpyridinium ion.

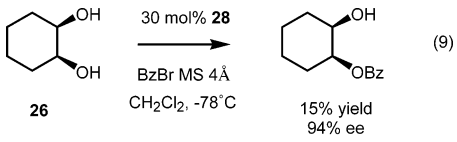
More recently Kawabata and Fuji have tried to develop other PPY analogues for enantioselective acylation.[46] Chiral PPY analogues possessing two distinct functional side chains on the pyrrolidine ring were prepared from 4-hydroxy-l-proline and screened in the desymmetrization of *meso*-diols. *Meso*-diol **26** was treated with $(i\text{-PrCO})_2O$ in the presence of **27** (5 mol %) to afford the mono-acetate in 65% ee (eq 8).The minor product of this reaction is the diacetate,

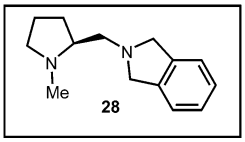




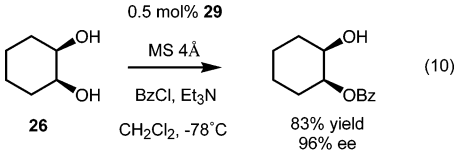
which is a result of a subsequent kinetic resolution process that actually slightly improves enantioselectivity. While the selectivities of this process are moderate, the modularity of these systems should allow for further catalyst development.

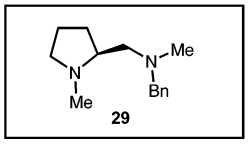
Oriyama and co-workers have developed a highly enantioselective desymmetrization of meso-diols, catalyzed by a chiral diamine derived from proline.[47,48] *meso*-Diol **26** was treated with benzoyl bromide in the presence of diamine **28** (30 mol %) to afford the corresponding monoacetate in 94% ee, but with low yield (15%, eq 9). In order for the reaction to proceed





to greater conversion, stoichiometric quantities of diamine were required. Upon further investigation, diamine **29** was found to be active in loadings as low as 0.5 mol % when coupled with the addition of Et_3N to afford products in high yield and enantioselectivity (eq 10).[49] Catalysts **28** and **29** were subsequently

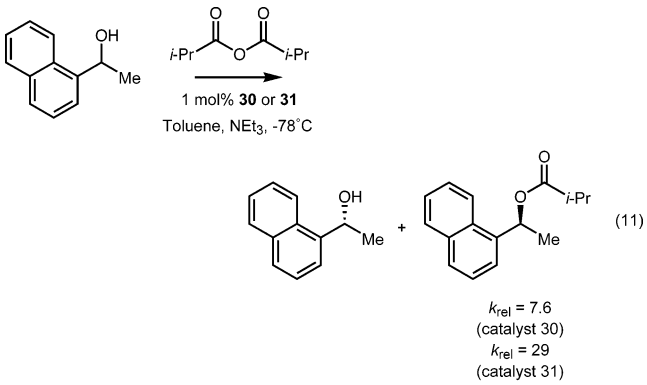


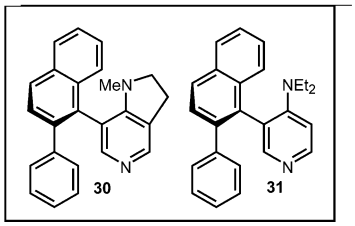


found to be highly efficient catalysts for the kinetic resolution of various racemic secondary alcohols (*s* values from 4 to 200), with *trans*-2-phenylcyclohexanol providing the highest selectivities up to $s = 200$ with **29**.[50] While the exact reaction mechanism is not clear, the authors propose that the diamine coordinates in a bidentate fashion to the carbonyl carbon of the acid halide, which in turn leads to sufficient catalyst rigidity to account for the high enantio-

selectivities. The Oriyama method is one of the early examples of efficient catalysis by chiral organic catalysts. Its impact is demonstrated by its easy application to the asymmetrization of numerous cyclic and acyclic diols and secondary alcohols. It remains very useful today for the production of chiral building blocks for various medicinally important compounds.

Spivey and co-workers have developed axially chiral analogues of DMAP that have been shown to be selective in the kinetic resolution of various arylalkyl carbinols.[51−53] Catalyst **30**, whose chirality is the result of restricted rotation about the biaryl bond, was synthesized in racemic form, the enantiomers of which were separated by chiral HPLC. Catalyst **30** afforded moderate enantioselectivity in the kinetic resolution of racemic α-methylnaphthylcarbinol, providing a $k_{rel} = 7.6$ (eq 11). It was thought that

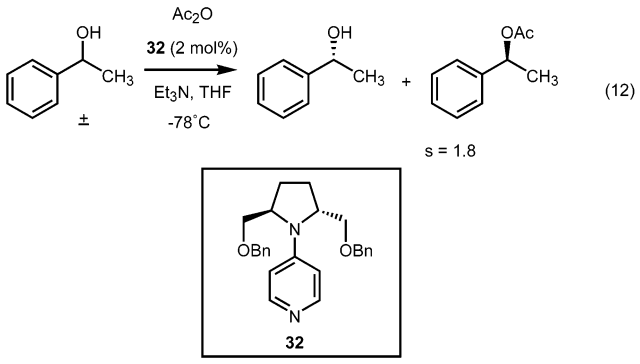




selectivities could be improved by making derivatives of **30** that were more differentiated in the plane of DMAP which passes perpendicularly through the two pyridine nitrogens (left to right differentiation). The 3 and 5 positions of the pyridine ring in catalyst **30** are both substituted with a carbon substituent, while in catalyst **31**, these two positions are differentiated in that now one position is substituted with a hydrogen, leading to a potentially more asymmetric environment. In fact, when **31** is used in the same kinetic resolution reaction, a much higher k_{rel} value of 29 is obtained.[54]

With continuing interest in the development of novel acyl-transfer catalysts, Spivey has developed a C_2-symmetric analogue of PPY that shows slight enantioselectivity in the kinetic resolution of *sec*-phenylethanol.[55] Catalyst **32** affords a k_{rel} value of 1.8 in the resolution of *sec*-phenylethanol with Ac_2O, but nevertheless establishes that derivatives of this type may prove useful in asymmetric acylation upon further development (eq 12).

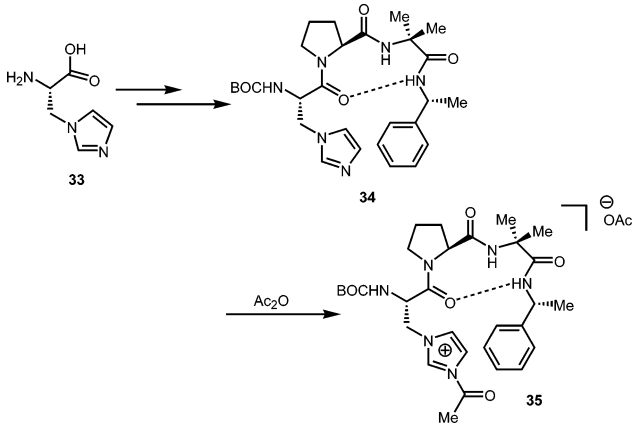
Miller has developed protocols for the kinetic resolution of alcohols using nucleophilic peptides. The search for low-molecular weight peptides[56,57] that may function as enantioselective catalysts derives



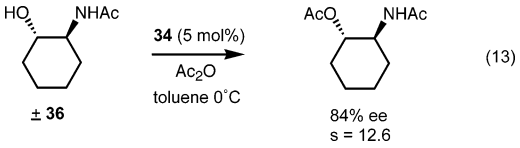
from the "biomimetic" principles of enzymatic catalysis. Peptide−substrate interactions are the hallmark of the fidelity which enzymes exhibit for their ligand. Inspired by this principle, Miller and co-workers have developed peptide-based catalysts[58] for a range of reactions, including acyl transfer, conjugate addition,[59] and phosphorylation, very often proceeding in high enantioselectivity. The modularity of peptide-based systems allows for the rapid synthesis and screening of many analogues, if necessary, to achieve the desired stereoselectivity. In addition, since these are "metal-free" organocatalytic[60] systems, these reactions can be carried out under mild conditions without rigorous exclusion of moisture and oxygen and are quite tolerant of substrate functionality.

Early work focused on peptides that had a propensity to form stable secondary structures in solution.[61] In addition, peptides were armed with an appropriately positioned functional group to carry out the catalysis. The first generation catalyst design drew heavily from the peptide design literature.[62] It was thought that by incorporating an amino acid residue that was an analogue of the known nucleophilic catalyst *N*-methylimidazole (NMI) into a peptide scaffold that was predicted to adopt a stable β-turn type structure in solution, a viable enantioselective catalyst for asymmetric acyl transfer could be designed. In this manner, imidazoyl alanine **33**[63] was incorporated into a peptide backbone containing the β-turn nucleating framework of proline-α-aminoisobutyric acid[64] to give peptide catalyst **34** (Scheme 3). In a given catalytic acylation reaction, treatment of **34** with acetic anhydride could generate acyl imidazolium ion **35**, now a potent acylating reagent.[65] Generation of an acyl imidazolium intermediate in

Scheme 3



proximity to the chirality inherent in the peptide backbone should confer asymmetry. To increase the possibility of a kinetically significant peptide−substrate interaction in the transition state (much like an enzyme−substrate complex), which could lead to improved stereoselection, racemic substrate **36** was chosen as the substrate for kinetic resolution. The presence of amide functionality increases the likelihood of a hydrogen bonding interaction with the peptide backbone. In this regard, racemic substrate **36** was treated with Ac_2O in the presence of **34** (5 mol %) in toluene at 0 °C to afford the corresponding acetate in 84% ee ($s = 12.6$, eq 13). Through solvent



(13)

screening, it was found that the reaction was highly solvent-dependent. Reactions carried out in nonpolar solvents afford higher enantioselectivities than those carried out in polar solvents ($s = 12.6$ in toluene compared to $s = 1.3$ in acetonitrile). This is the result of the fact that nonpolar solvents tend to favor the formation of intramolecular hydrogen bonds that serve to rigidify the catalyst, while polar solvents tend to disrupt these interactions leading to a more conformationally flexible system.

Expansion of this methodology led to marked improvements in enantioselectivity for the above reaction, and mechanistic studies were performed to shed light on the factors essential for efficient catalysis.[66] Further catalyst development led to the discovery that divergence in enantioselectivity[67] could be achieved by simply changing one critical stereogenic center, the result being a reversal in absolute stereoinduction. Catalyst **37**, possessing an L-Pro residue at the $i + 1$ position affords modest enantioselectivity for the above kinetic resolution reaction of racemic **36**, preferentially acylating the (*S*,*S*) enantiomer. However, by simply substituting the L-Pro residue for D-Pro, catalyst **38** now preferentially acylates the (*R*,*R*) enantiomer and also exhibits an increase in enantioselection ($s = 28$, Figure 8). This

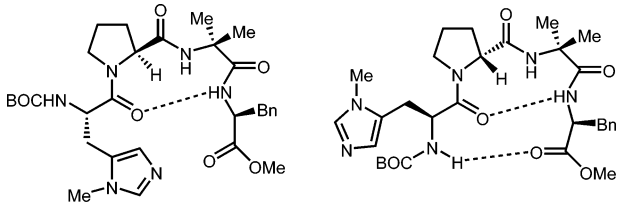


Figure 8. Diastereomeric peptide catalysts that exhibit enantiodivergence.

indicates that a single stereogenic center serves to orchestrate the stereochemical course of the kinetic resolution reaction. Of note is the increase in overall enantioselectivity, which can be attributed to increased conformational rigidity of the peptide catalyst. ^{1}H NMR solvent titration studies[68] indicate that peptide **37** adopts a β-turn type structure possessing one intramolecular hydrogen bond, while catalyst **38** adopts a conformation that has two intramolecular hydrogen bonds. This increased conformational rigidity results in higher enantioselectivities for kinetic resolution.

The above studies indicate a significant correlation between conformational rigidity and degree of enantioselection. To probe this discovery further, a series of octapeptide catalysts were synthesized and screened for activity in the kinetic resolution of racemic **36**. Octapeptides of this type had been previously shown to possess four intramolecular hydrogen bonds[69] and should exhibit increased conformational rigidity. Octapeptide **39** affords excellent enantioselectivity in the kinetic resolution of **36**, affording a $k_{rel} = 51$ (Figure 9). Interestingly, the L-Pro analogue of pep-

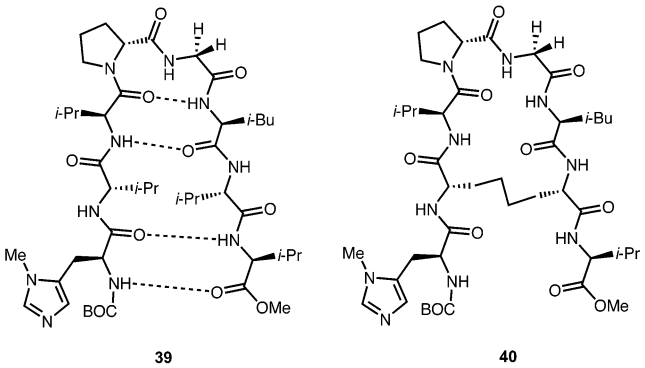


Figure 9. Octapeptide catalysts for kinetic resolution.

tide **39** exhibits markedly lower enantioselectivity ($k_{rel} = 7$), reinforcing the findings in the tetrapeptide cases above. A comparison of the two octapeptides by ^{1}H NMR indicated that while **39** exhibits a sharp spectrum, the L-Pro variant was extremely broad, possibly indicating increased conformational flexibility or peptide aggregation. Attempts were made to further rigidify octapeptide **39** through covalent tethering of the two "arms" of the peptide.[70] Peptide **40** was made via a ring-closing metathesis/hydrogenation protocol involving a peptide with appropriately positioned allyl glycine residues. Interestingly, this rigidified peptide affords a less selective resolution ($k_{rel} = 12$, for substrate **36**). This result indicates that a degree of conformational flexibility is required for high enantioselection.

To gain further mechanistic insight, rigorous kinetic studies were performed to elucidate the order of both catalyst and substrate, to garner information on whether the catalyst acts as a monomeric or higher order species in the stereochemistry-determing step. Kinetic studies indicate that this reaction is first-order in both substrate and catalyst, indicating that the catalyst is acting as a monomeric species under the reaction conditions. It was also determined that the enantioselectivities are the result of an enantiomer-specific accelerative process, indicating the possibility of a transition-state hydrogen-bonding interaction with substrate. In fact, octapeptide **39** was shown to be even more catalytically active than DMAP, which is interesting in that the nucleophilic residue is based on NMI, which is not as active of an

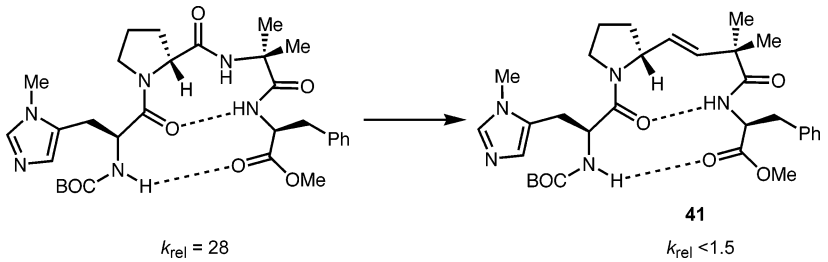


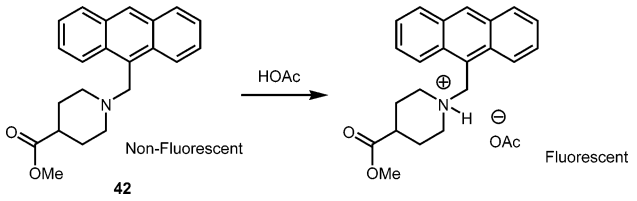
Figure 10.

acylation catalyst. The synthesis of peptide **41**, which incorporates a trans-alkene isosteric[71] replacement for the Pro−Aib amide, further lends support for the role of this amide in the stereochemistry-determining step.[72] Peptide **41** processes substrate **36** with minimal enantioselectivity, giving a k_{rel} value of <1.5 (Figure 10).

In the development of enantioselective catalytic reactions, very often the rate-limiting step is the assay of reaction products for selectivity. Often this involves some form of chiral HPLC or GC assay, which, depending on assay time, can be prohibitive if applied to the assay of hundreds or even thousands of catalysts that libraries may afford.[73] Due to the fact that reactivity is coupled to enantioselectivity in the above kinetic resolution reactions, it was possible to develop a simple fluorescence-based assay for catalyst discovery.[74,75] During the kinetic resolution reaction, each turnover event results in the formation of acetic acid as a byproduct. Fluorophore **42** was found to be highly fluorescent in the presence of acetic acid, with fluorescence intensity being a function of acetic acid concentration (Scheme 4). Because reactivity is coupled to selectivity, it was possible to screen more catalysts at a given time, due to the facility of a simple visual assay (by eye or fluorescence micrograph). Using this technique, a fluorescently labeled split-pool library (solid-support bound) of octapeptide catalysts was screened for activity in the kinetic resolution of *sec*-phenylethanol, an unfunctionalized alcohol which had not been resolved selectively with previously described peptides. This technique allowed for the development of a highly selective octapeptide **43**, which was an efficient catalyst for the kinetic resolution of several unfunctionalized secondary alcohols. *sec*-Phenylethanol is effectively resolved with peptide **43**, affording a k_{rel} = 20 (Figure 11). Substrates **44** and **45** were both processed in even higher enantioselectivity (k_{rel} = >50). This fluorescence-based assay was then extended to develop a screening method based on parallel enantiomer analysis.[76,77] Peptide catalysts were evaluated in parallel for reactivity with each enantiomer, and peptides that exhibited significant reactivity differences for each enantiomer were selected for further study in kinetic resolution reactions. Through this method, peptide **46** was identified as a catalyst that effectively resolved tertiary alcohol substrates, a substrate class that had not been previously studied with nonenzymatic catalysts. Tertiary alcohol substrates **47** and **48** are resolved with k_{rel} values of >50 and 40, respectively (Figure 12). Other substrates are processed efficiently, although with somewhat lower selectivities (k_{rel} = 19−40).

The secondary alcohol is a common retron in natural product total synthesis. In this regard, peptide-catalyzed kinetic resolution was investigated in

Scheme 4



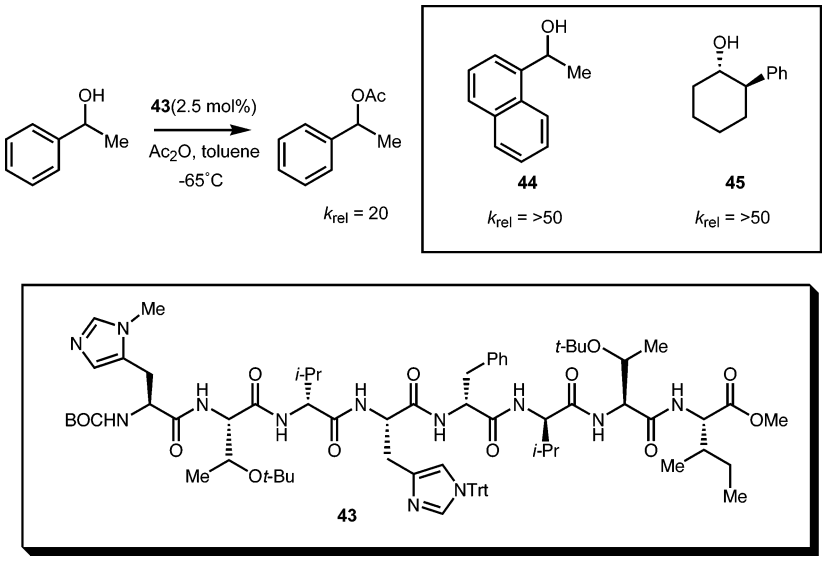


Figure 11. Highly selective octapeptide for unfunctionalized alcohols.

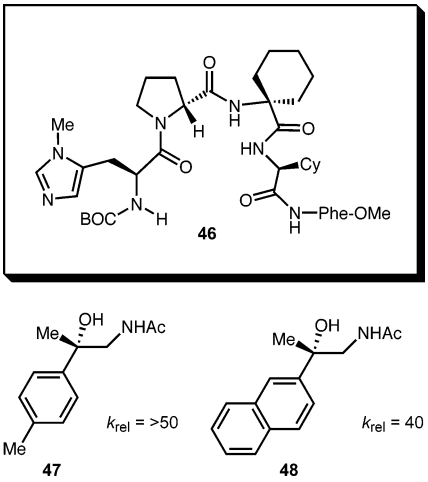
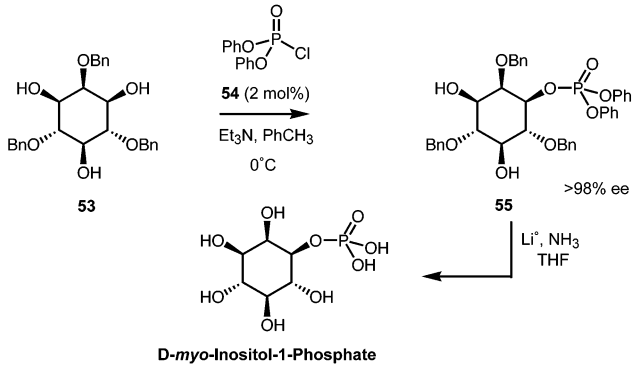


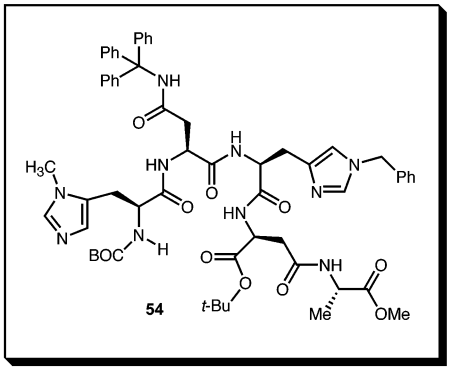
Figure 12. Selective pentapeptide for tertiary alcohol resolution.

the context of a total synthesis of a mitosane core, in hopes of developing an enantioselective total synthesis of mitomycin C (Scheme 5).[78,79] Racemic allylic alcohol **49**, accessed in an efficient manner from commercially available isatin, is resolved by catalyst **50** (2 mol %), affording recovered optically enriched allylic alcohol with a $k_{rel} = 27$. Catalyst **50** was discovered in rapid fashion by screening a small library of 152 pentapeptide catalysts. Optically pure alcohol **51** could be obtained after one recrystallization, and could be subsequently converted to mitosane core **52** in seven steps.

Owing to the critical importance of phosphorylated natural products (i.e., D-*myo*-inositol-1-phosphate, D-**I-1P**) in signal transduction pathways, it would be beneficial to develop catalysts that can perform enantioselective phosphoryl transfer. Mechanistically, phosphoryl transfer is similar to acyl transfer in that it can be promoted by nucleophiles such as DMAP. In preliminary studies, it was essential to find an appropriate phosphorylating agent that could be subjected to catalysis by NMI. Once catalytic conditions were established (several secondary alcohols were phosphorylated efficiently with diphenylchlorophosphate, 2.5 mol % NMI, and Et_3N), a library of 39 peptide catalysts was screened in the desymmetrization reaction of inositol substrate **53**.[80] Several catalysts were found to exhibit appreciable enantioselectivity, most notably peptide **54**, which delivers product **55** in > 98% ee (Scheme 6).

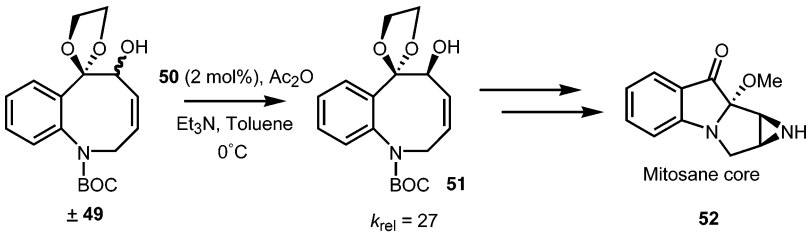
Scheme 6

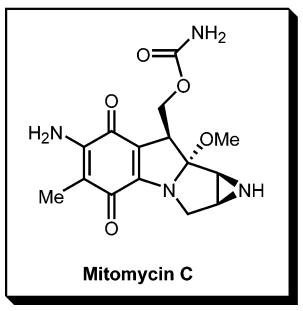


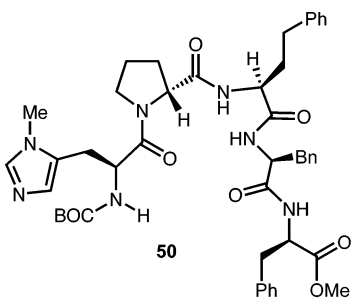


Conversion to D-*myo*-inositol-1-phosphate commenced in short order by global deprotection of **55** using Li^o/NH_3 conditions to afford the natural product.[81] Interestingly, in peptide screens that resulted in the discovery of peptide **54**, several peptides were found to selectively phosphorylate the enantiotopic 3-position of substrate **53**, albeit with lower selectivities. Further catalyst screening (both random and

Scheme 5

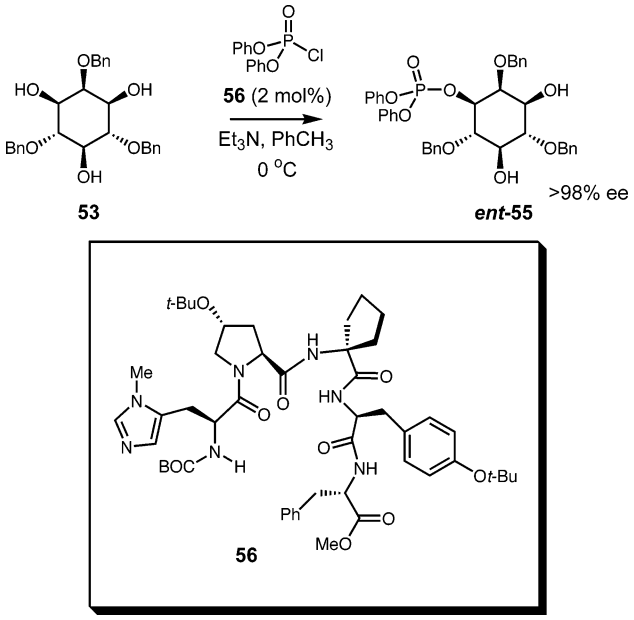






focused libraries) led to the development of peptide **56**, which delivers enantiomeric ***ent*-55** in excellent enantioselectivity (>98%, Scheme 7).[82] **D-I-3P** could be similarly obtained via global deprotection using dissolving metal conditions.

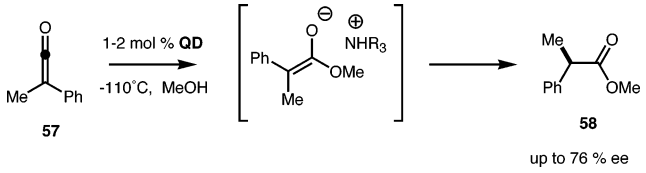
Scheme 7



2.2. Ketene Acylation

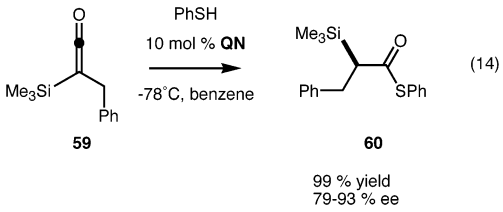
The development of stereoselective methods to access optically pure arylpropionic acids is an important area of research, due to the prevalence of this scaffold in numerous pharmacologically active compounds.[83] One of the earliest uses of chiral amines in asymmetric catalysis was demonstrated by Pracejus in the 1960s. He employed quinidine (QD) to catalyze the asymmetric alcoholysis of simple disubstituted ketenes **57** (Scheme 8).[84]

Scheme 8



The proposed mechanism is that the alcohol is activated via a hydrogen bond with the tertiary amine of quinidine. Alcoholysis of the ketene is followed by quenching of the resulting enolate by the chiral ammonium salt. Optically active esters **58** are isolated in up to 76% enantiomeric excess (ee). A high background rate accounts for the modest selectivities.

Recently, Whitehead modified Pracejus's methodology to achieve the cinchona alkaloid catalyzed reaction of silylketenes **59** with thiophenol to generate enantiopure α-silylthioesters **60** (eq 14).[85] The proposed mechanism involves the attack of the alkaloid on the ketene and formation of a zwitterionic



(14)

enolate. The enolate abstracts a proton from the thiophenol, and the thiolate subsequently displaces the catalyst (Figure 13).

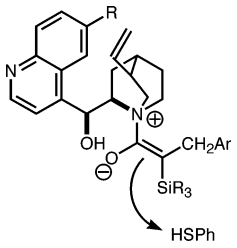


Figure 13. Whitehead's zwitterionic enolate.

Fu and co-workers have also developed a method to access aryl propionic acids through an enantioselective addition of methanol to ketene substrates.[86] Ketene **61** is treated with MeOH in the presence of 10 mol % of catalyst **7** in toluene at −78 °C to afford the desired arylpropionic acid in 97% yield and 80% ee. It was found that the addition of 2,6-di-*tert*-butylpyridinium triflate[87] as an alternative proton source to MeOH was beneficial, leading to higher enantioselectivities. This reaction is believed to proceed via nucleophilic catalysis, whereby the catalyst reacts with the ketene to form a zwitterionic intermediate **62**, which then is protonated stereoselectively to afford ion pair **63**. Alkoxide addition leads to the product and regenerates the catalyst for subsequent reactions. Preliminary mechanistic studies indicate that product ee varies linearly with respect to catalyst ee. This absence of a nonlinear effect[88] suggests that the catalyst is operating in a monomeric fashion in the stereochemistry-determining step (Figure 14).

Fu has also shown that pyrrole-type substrates add stereoselectively to ketenes in the presence of chiral-planar DMAP catalysts.[89] It was established at the outset that pyrrole substrates were not sufficiently nucleophilic to add to ketenes in the absence of catalyst. After screening several pyrrole derivatives, it was found that 2-cyanopyrrole was the most effective nucleophile in terms of enantioselectivity. 2-Cyanopyrrole adds to ketene substrate **64** in the presence of 2 mol % of catalyst (+)-**17** at room temperature to afford adduct **65** in 98% ee and 95% yield. Adduct **65** is a versatile synthon and can be converted to the corresponding acids, esters, amides, aldehydes, or alcohols, with little erosion of enantiomeric excess (≤2% racemization). In contrast to the previous examples, this reaction is not thought to proceed via nucleophilic catalysis. A mechanistic analysis led the authors to propose involvement of chiral Bronsted-acid catalysis in asymmetric induction. The proposed mechanism involves deprotonation of 2-cyanopyrrole by catalyst to give ion pair **66**,

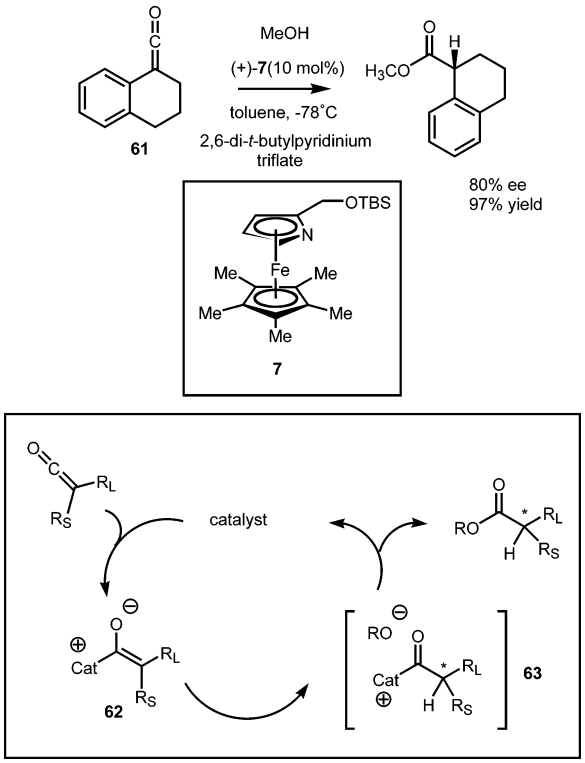
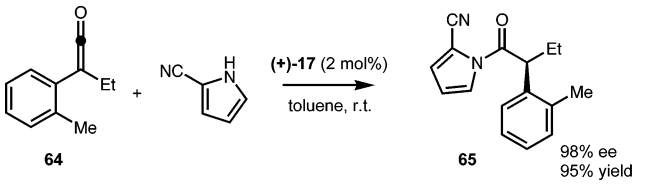


Figure 14. Enantioselective alcohol addition to ketenes.

the anion of which can react with the ketene substrate to afford a new ion pair **67**. Proton transfer from the protonated catalyst to the achiral enolate generates the chiral *N*-acyl pyrrole with subsequent catalyst turnover (Figure 15).



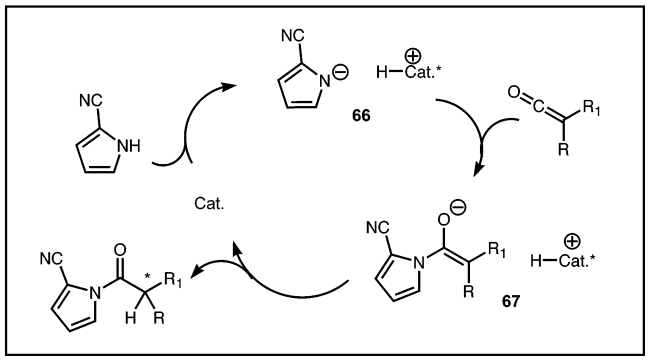
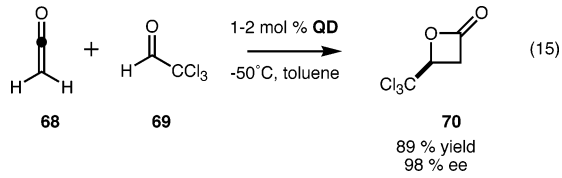


Figure 15. Enantioselective amine addition to ketenes.

2.3. Cycloadditions

2.3.1. β-Lactone Formation

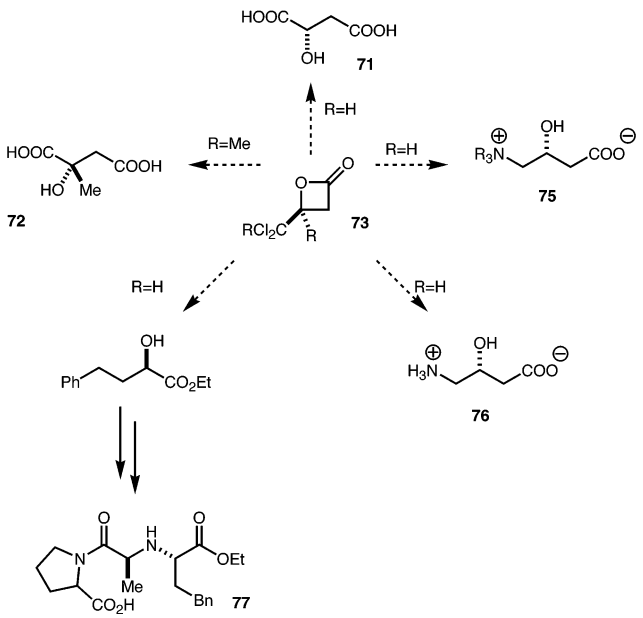
Building upon the initial acylation studies, Wynberg successfully reported the first [2+2] addition of ketene **68** to polychlorinated aldehydes **69** in the presence of cinchona alkaloids to yield *β*-lactones **70** in high yield (89%) and enantioselectivity (98% ee) (eq 15).[90] The proposed mechanism involves the



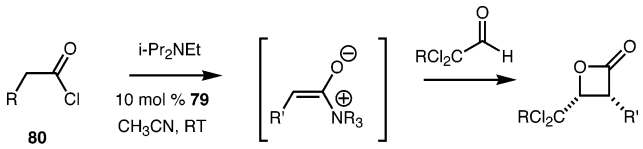
formation of a zwitterionic intermediate, arising from the nucleophilic attack of the quinuclidine ring of the catalyst on the ketene, followed by a stepwise addition to the aldehyde. Unprotected QD is used, although it rapidly catalyzes its own acylation. Supporting this hypothesis, reactions using preacylated alkaloid gave similar enantioselectivities.

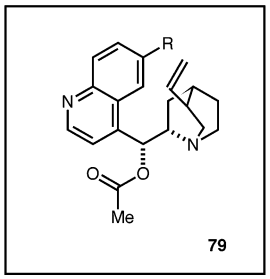
β-Lactones are highly useful intermediates in the synthesis of chiral products.[91,92] Wynberg successfully synthesized enantiopure malic acid[93] (**71**) and citramalic acid[94] (**72**, from lactone **73**, Scheme 9). Similarly, Song converted lactone **73** to (*R*)-carnitine[95] (**75**) and (*R*)-GABOB[96] (**76**) by selective reduction. The key step in the synthesis of enalapril (**77**), an ACE inhibitor, involves the ring opening of a *β*-lactone ring to yield a *β*-hydroxyketone.[97] Furthermore, this cycloaddition has been commercialized for large-scale production.

Scheme 9

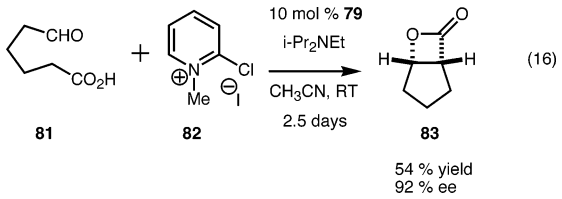


Scheme 10



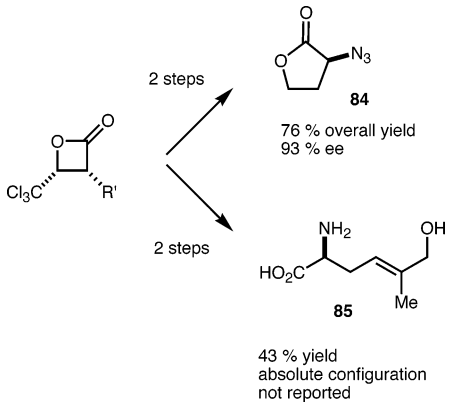


Romo expanded Wynberg's method using *O*-acetyl quinidine (**79**) to cyclize a wide variety of aldehydes and ketenes. He also simplified Wynberg's procedure by using ketenes generated in situ by two separate methods: (A) dehydrohalogenation of acid chlorides **80** with Hunig's base (Scheme 10)[98] and (B) carboxylic acid activation of **81** using Mukaiyama's reagent (**82**) followed by generation of the presumed ammonium enolate intermediate with Hunig's base (eq 16).[99]



Using method B, Romo afforded bicyclic β-lactones **83** via an intramolecular [2+2] cycloaddition in good yield, moderate diastereoselectivity and high enantioselectivity. He reported the synthesis of (*S*)-α-azidobutyro lactone **84** and a natural amino acid (**85**) isolated from the seeds of the tropical plant *Blighia unijugata* (Scheme 11).[100]

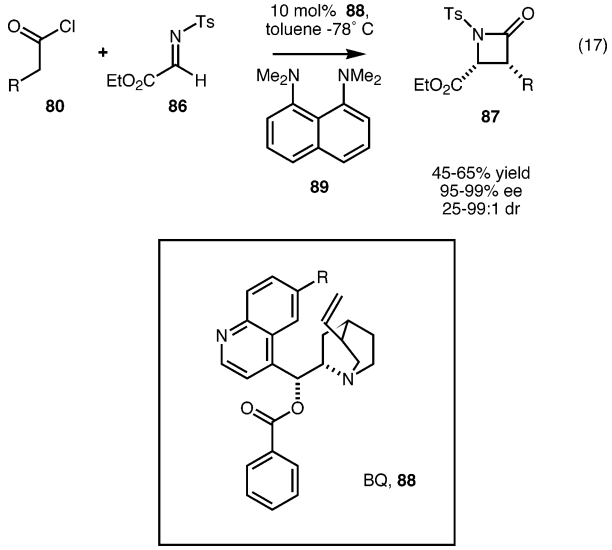
Scheme 11



2.3.2. β-Lactam Formation

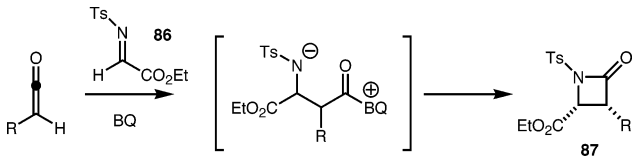
The medicinal importance of β-lactams continues to expand at a surprising rate.[101] However, the use of natural β-lactam antibiotics is being compromised by bacterial resistance, making the synthesis of nonnatural analogues a pressing concern.[102] Even more important, β-lactams (especially nonnatural ones) have been applied to several nonantibiotic uses in recent years, particularly concerning the development of mechanism-based serine protease inhibitors[103] of elastase,[104] cytomegalovirus protease,[105] thrombin,[106] prostate specific antigen,[107] β-lactamase,[108] and cell metastasis.[109]

Recently, Lectka reported the first catalytic, asymmetric [2+2] cycloaddition of ketenes and imines **86** to form β-lactams **87** using cinchona alkaloid derivatives including *O*-benzoylquinine (BQ, **88**) (eq 17).[110] The use of stoichiometric tertiary amines for dehydrohalogenations of acid chlorides to form ketenes is complicated by the fact that they are usually too nucleophilic. The use of a stoichiometric base that is thermodynamically strong, but kinetically non-



nucleophilic, serves to overcome this problem. This strategy, which Lectka terms "shuttle deprotonation," utilizes a catalytic, chiral nucleophile (BQ, **88**), that is kinetically active, to dehydrohalogenate the acid chloride in the first step. Exploiting the premise that proton transfers between heteroatoms are inherently fast, the kinetically favored base (BQ) then rapidly transfers its proton to proton sponge (PS, **89**), the thermodynamically active, but kinetically restricted base, to regenerate itself for another catalytic cycle. Lectka has also expanded this strategy to include inexpensive bases such as K_2CO_3 and NaH as replacements for proton sponge (**89**).[110b] BQ then attacks the ketene, forming the zwitterionic enolate, which subsequently attacks the electrophilic iminoester **86** to afford β-lactams **87** (Scheme 12).

Scheme 12



Molecular mechanics calculations aimed at predicting both the sense and the degree of optical induction were also reported.[111] Figure 16 shows the complex derived from the reaction of benzoylquinine (**88**) with phenylketene. This calculation shows the re face of the ketene enolate open to approach of the iminoester electrophile, while si-face approach is almost 7 kcal/mol higher in energy.

Similar calculations were performed on various cinchona derivatives to identify the source of induction and were compared against experimental results (Table 2). The fact that the predicted energetic differences correlate in a general sense with the magnitude of the enantioselectivity makes this a viable method for the design of new nucleophilic catalysts. An interesting result of the study is the importance of the methoxy group of the catalyst in maintaining the chiral environment around the ketene. When the methoxy group was removed, enantioselectivity was reduced tremendously. This

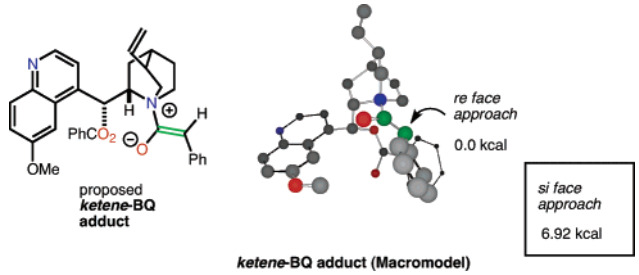


Figure 16. Stereochemical model of the putative zwitterionic intermediate of BQ with phenylketene.

Table 2. Correlation between Theoretical Calculations and Experimental Results for β-Lactam Formation

catalyst	ΔE^a	% ee
benzoylquinine	6.92	99
benzoyl-epi-quinine	6.69	99
benzamidoquinine	3.84	89
deoxyquinine	2.09	72
benzoylcinchonidine	0.13	5

[a] Difference in kcal/mol between the re and si faces of the ketene−catalyst adduct.

seems to be due to the free rotation of the quinoline ring that is normally blocked by the methoxy group.

The mechanism of the reaction of phenylacetyl chloride (**90**) with imino ester **86** catalyzed by BQ (and PS (**89**) as stoichiometric base) was further investigated through kinetics experiments. One of the most interesting aspects of the kinetic study is the fact that free ketenes need not be involved in enantioselective reactions when employing proton sponge as base (Figure 17). This result is in contrast to the use of other bases for ketene formation in the reaction, such as potassium carbonate and sodium hydride. In these cases, the optimal reaction conditions mandate that ketene formation precede enantioselective cycloaddition.

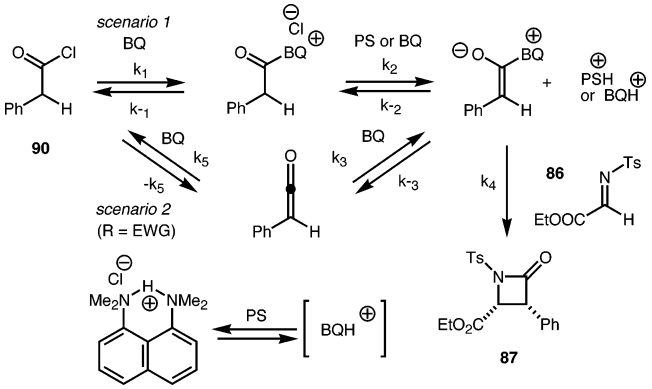
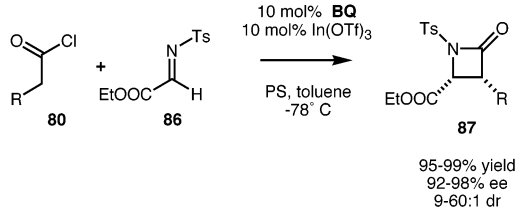


Figure 17. Mechanism of β-lactam formation with proton sponge.

Although β-lactams are formed with high selectivities in this reaction, their chemical yields were moderate. Presumably, a portion of the ketene-derived zwitterionic enolate was being diverted before reaction with the imine. On the basis of previous work utilizing a chiral Lewis acid to make iminoester **86** more electrophilic through chelation and highly reactive to nucleophilic activated alkenes,[112] Lectka envisaged that imine activation by a Lewis acid would favor the desired reaction pathway while suppressing any side reactions. He reported a tandem, Lewis acid/nucleophile bifunctional system using 10 mol % $In(OTf)_3$ to chelate the imine **86** and 10 mol % BQ (eq 18).[113] Kinetics experiments showed



(18)

that the metal catalyst increases the rate of product formation but not consumption of starting material, thus improving chemoselectivity. In each case, this novel system significantly increased the chemical yields while maintaining high enantioselectivities.

To expand this bifunctional method, homogeneous complexes in which the chiral nucleophile and Lewis acid were both present in the same entity were synthesized (Figure 18). Putative bis(salicylate) metal

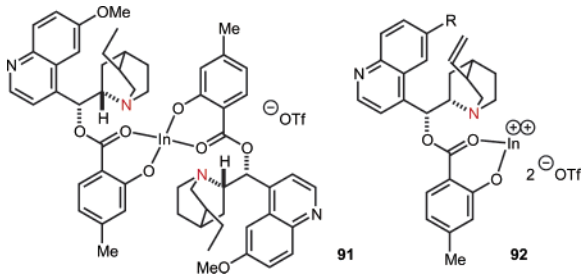


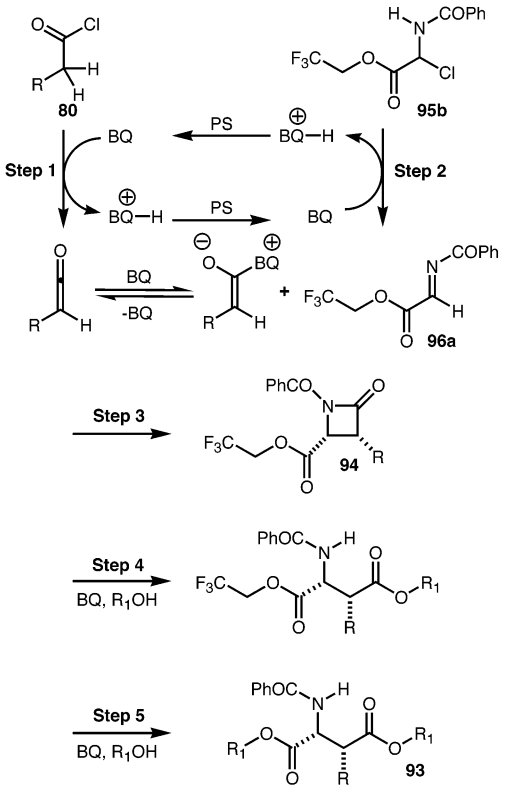
Figure 18. Bifunctional quinine derivatives.

complex **91** containing two catalytically active quinuclidine moieties does not show an increase in yield of the desired β-lactam **87**. This is possibly due to congestion in the coordination sphere of the metal that prevents appreciable chelation to the α-imino ester (**86**) and/or a reduction in Lewis acidity of the metal center. However, when the less congested complex **92** was used, it afforded products in 80% yield (99% ee and 8:1 dr).

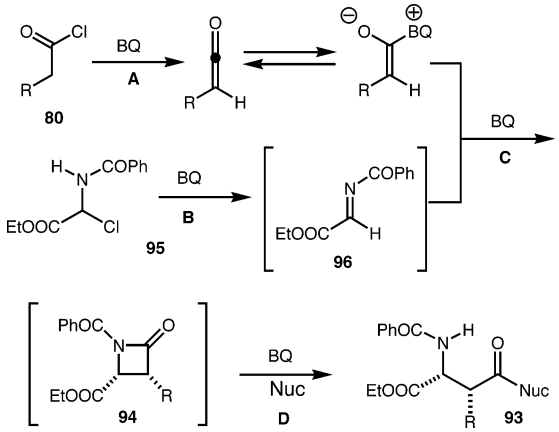
N-Acyl-β-lactams **94** were easily converted to β-amino acids **93** through the use of BQ as a multifunctional catalyst (Scheme 13).[114,115] Here, the chiral nucleophilic catalyst serves up to five distinct roles in one reaction flask. To date, approaches based on the use of one specific catalyst capable of performing multiple tasks in a reaction sequence remain limited.[116] In this reaction scenario, BQ acts as a dehydrohalogenating agent for the synthesis of both ketene (role 1, step 1) and *N*-acylimine **96** (role 2, step 2), from the acid chloride **80** and *N*-acyl-α-chloroamine **95**, respectively, an asymmetric catalyst for the [2+2] cycloaddition between the ketene and imine (role 3, step 3), a nucleophilic catalyst for ring-opening (role 4, step 4), and a transesterification catalyst for ester exchange (role 5, step 5).

BQ was also found to greatly enhance the rate of β-lactam ring opening (Scheme 14). Even at elevated temperatures, a large rate difference was observed

Scheme 13



Scheme 14

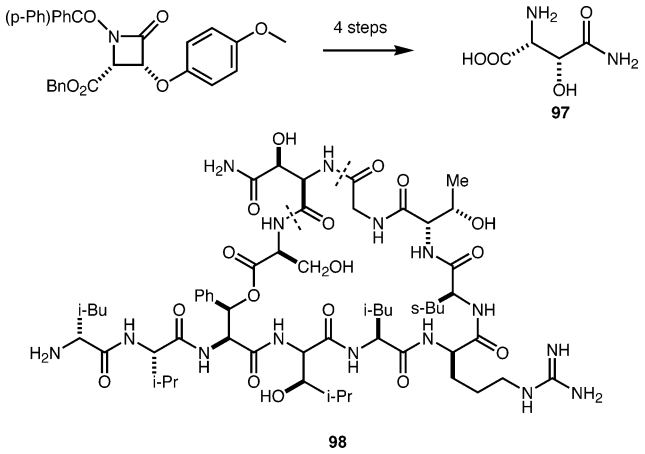


between the BQ-catalyzed and uncatalyzed methanolysis reactions. To ensure that the catalyst BQ facilitated the ring opening and transesterification steps of this reaction, a control experiment was conducted using preformed β-lactam **94a** (R = Ph). The results of this experiment confirmed that BQ was indeed an active catalyst for this process based on the notable rate depression in its absence even at elevated temperatures (14 h with BQ vs 48 h with no catalyst).

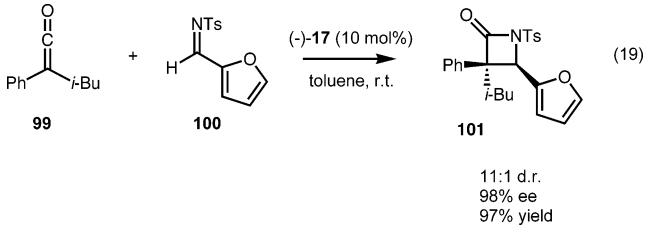
This method was applied to the enantioselective synthesis of the unnatural amino acid L-threo-β-hydroxyasparagine, a key subunit (**97**) of the antibiotic lysobactin (**98**) (Scheme 15).[115]

The asymmetric synthesis of β-lactams is another reaction that lends itself to enantioselective catalysis with planar-chiral DMAP derivatives.[117] Unsymmetrical ketene **99** reacts with tosylimine **100** in the

Scheme 15



presence of catalyst (−)-**17** (10 mol %) to afford the corresponding β-lactam **101** as an 11:1 mixture of diastereomers in 97% yield and 98% ee (eq 19).



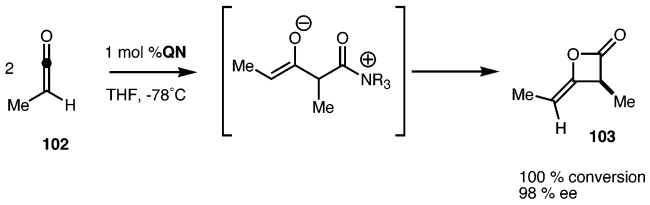
(19)

Various symmetrical and unsymmetrical ketenes react with a host of imine substrates to afford products in good to excellent ee (81−98%). In addition, the product β-lactams **101** can be further functionalized through treatment with amines to access amides and through reduction to afford γ-amino alcohols. Again this reaction is believed to proceed through a nucleophilic mechanism, whereby catalyst adds to ketene to generate a zwitterionic enolate that can react with the imine in a Mannich-type addition pathway. Subsequent β-lactam formation then liberates the catalyst to complete the cycle.

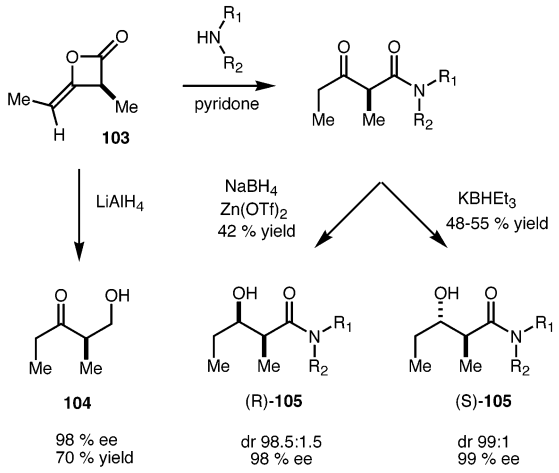
2.3.3. Ketene Dimerization

Calter has reported that cinchona alkaloids catalyze the [2+2] dimerization of methylketene (**102**) in high enantioselectivity (98% ee) (Scheme 16).[118] Formation of the ammonium enolate followed by acylation of the ketene and then lactone formation seems to be the most plausible mechanism. Methyl ketene dimer (**103**) can be easily derivatized by lithium aluminum hydride reduction to yield alcohol **104** or by ring opening with amines in the presence of pyridone, followed by aldol reactions of the resulting enolates to polypropionates (**105**), useful polyketide precursors (Scheme 17).[119] This methodology was applied to the catalytic asymmetric synthesis of a key segment of the following: pamamycin 621A[120] (**106**), a potent antibiotic; siphonarienal (**107**),[121] a marine natural product with interesting biological activity; and a key segment of the C21−C34 chain (**108**) of the aplyronines, a stereochemically complex family of polyketide natural products (Figure 19).[122]

Scheme 16



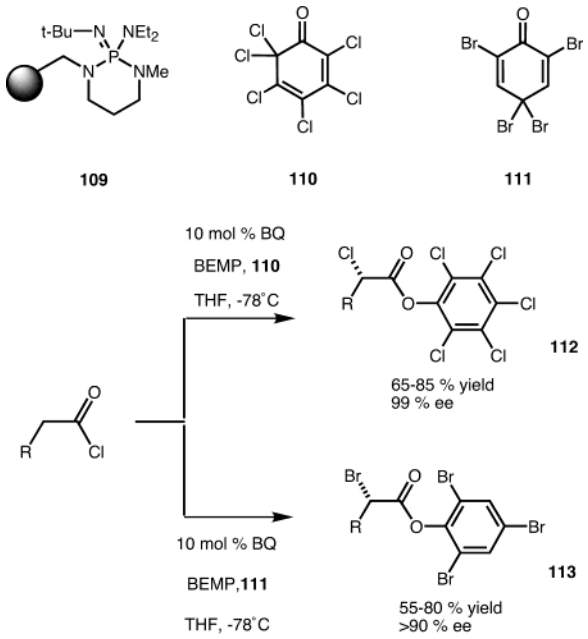
Scheme 17



2.4. Halogenation

It is well known in synthetic organic chemistry that oxidative halogenations of organic molecules constitute an extremely important class of reactions. Halocarbon products are useful chemical intermediates, serving as branch points in the synthesis of numerous functionalized molecules.[123] Within this context, α-halogenations of carbonyl compounds have played a particularly notable role.[124] The full utility of chiral, optically active α-carbonyl halides could be extended by suitable catalytic, asymmetric halogenation reactions.[125] A recent example is Lectka's catalytic asymmetric α-halogenation/esterification of acid chlorides. Initially, ketene is formed through the shuttle deprotonation strategy (Scheme 12), using BQ as the shuttle base and the phosphazine basic resin, BEMP (**109**),[126] K_2CO_3,[127] or NaH,[128] as the thermodynamic base. Ketene reacts with BQ to generate the zwitterionic enolate, which attacks a quinone based electrophilic halogenating reagent such as **110** or **111**. Phenolate (released after the quinone gives up a halogen) displaces and regenerates the catalyst to afford activated α-halogenated esters **112** and **113** in 55−85% yield and with >90% ee (Scheme 18).

Scheme 18



The optically pure α-haloesters can be further derivatized by displacement of the ester by amines, thiols and alcohols without racemization. This system could be applied to the extremely important problem of catalytic asymmetric fluorination, where cinchona derivatives have already been used, though only stoichiometrically.[129]

2.5. Baylis–Hillman Reactions

The Baylis−Hillman reaction allows the direct preparation of α-methylene-*β*-hydroxycarbonyl compounds by the base-catalyzed reaction of α,*β*-unsaturated carbonyl compounds with aldehydes. Baylis−Hillman products can be transformed into numerous useful compounds, such as aziridines, epoxides, triols, and aldol products.[130] Furthermore, these α-methylene-*β*-hydroxy carbonyl compounds are key precursors to a host of natural and nonnatural target molecules. While the Baylis−Hillman reaction of chiral aldehydes or chiral Michael acceptors has been shown to proceed in some cases, with high diastereoselectivities, the field of chiral catalysts for the Baylis−Hillman reaction is less well-developed. Examples of the Lewis acid-catalyzed reaction have been reported with moderate success.[131]

The tertiary amine-catalyzed reaction involves generation of the enolate **114** by conjugate addition of the amine. Attack on the aldehyde by the enolate, followed by elimination of the amine, affords the Baylis−Hillman product **115** (Scheme 19).

Early work involved enantiopure DABCO derivative **116** to catalyze the reaction of methyl vinyl

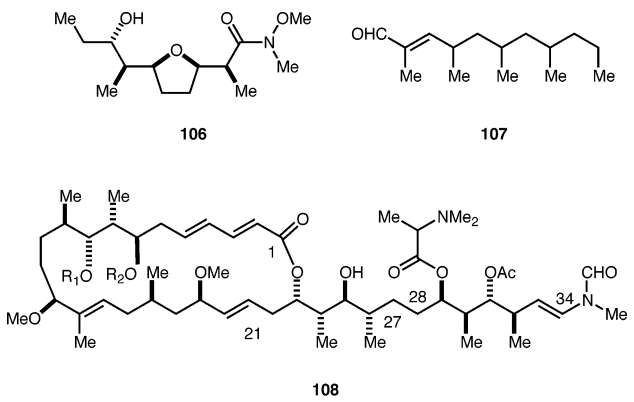
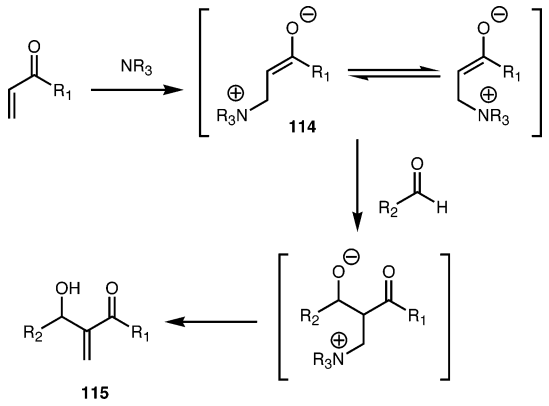
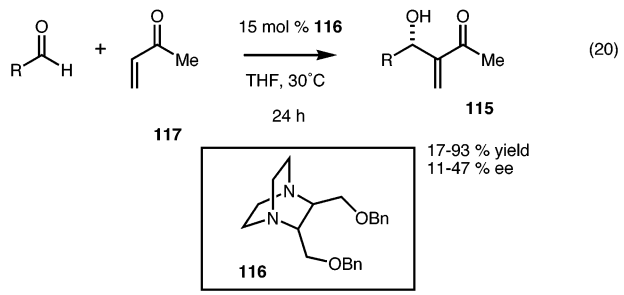


Figure 19. Targets synthesized from *β*-lactone ring opening.

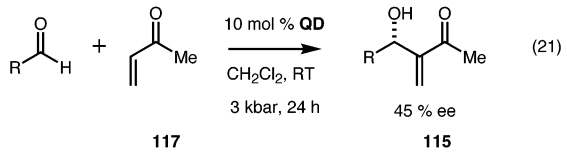
Scheme 19



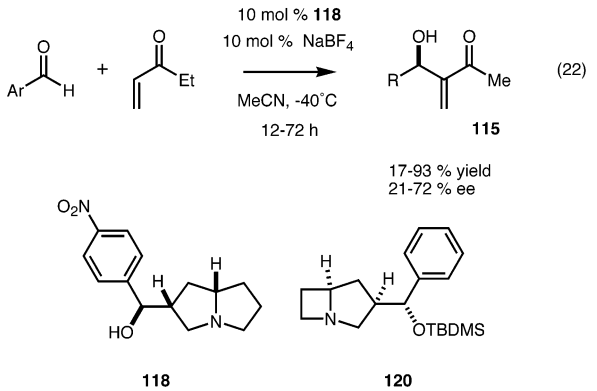
ketone (**117**) with various aldehydes (eq 20) yielding **115** in up to 47% ee.[132]



Similarly, high-pressure mediated Baylis−Hillman reactions between aliphatic aldehydes and methyl vinyl ketone (**117**) using QD as a catalyst were reported (eq 21), obtaining a modest 45% ee at 3 Kbar.[133]



Chiral pyrrolizidine base **118** derived from L-proline was synthesized for the reaction of ethyl and methyl vinyl ketones with electron-deficient aromatic aldehydes (eq 22).[134] Products were formed in moder-



ate to good yield (17−93%) and moderate enantioselectivities (21−72% ee). The proposed mechanism involves the key intermediate **119** (Figure 20). Enantioselectivity is enhanced when the chelating metal ion is sodium. The hydroxy group is crucial to the

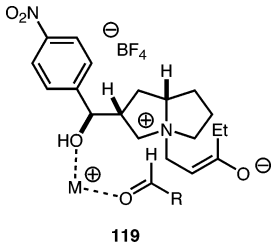
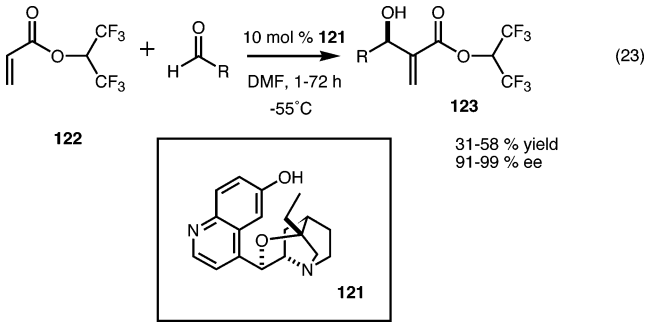


Figure 20. Key intermediate in Barrett's proposed mechanism.

formation of this intermediate and is well noted for enhancing the rate of the reaction.[135] Recently, bicyclic azetidine derivative **120** was employed under similar conditions, noting a substantive rate increase although the product selectivities were low (26% ee).[136]

Hatakeyama developed the first efficient, catalytic asymmetric Baylis−Hillman reaction using easily attainable quinidine derivative **121** (eq 23).[137] In the



presence of 10 mol % catalyst **121**, various aromatic and aliphatic aldehydes were reacted with enone **122** to give α-methylene-β-hydroxy esters **123** in low to moderate yields, but with enantioselectivities as high as 99%. The reaction times are highly substrate dependent, varying between 1 and 72 h.

While this report is a very promising lead in the development of a highly efficient asymmetric version, there are a few disadvantages. Foremost, Hatakeyama's method suffers from the formation of dioxanones as byproducts, ultimately lowering the yields. Also, the ability to synthesize the opposite enantiomers of the products is not noted. Crucial to the activity of the catalyst is the deprotection of the methoxy group of the quinoline ring to yield a free hydroxyl. A kinetic study would shed light on the proposed model for selectivity, which relies on a 13-membered ring (Figure 21). Another plausible mechanism would be second order in catalyst, having additional chiral direction and a hydrogen bond donated by a second molecule of catalyst. Nevertheless, Hatakeyama's procedure still remains the most ef-

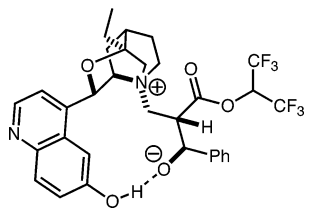
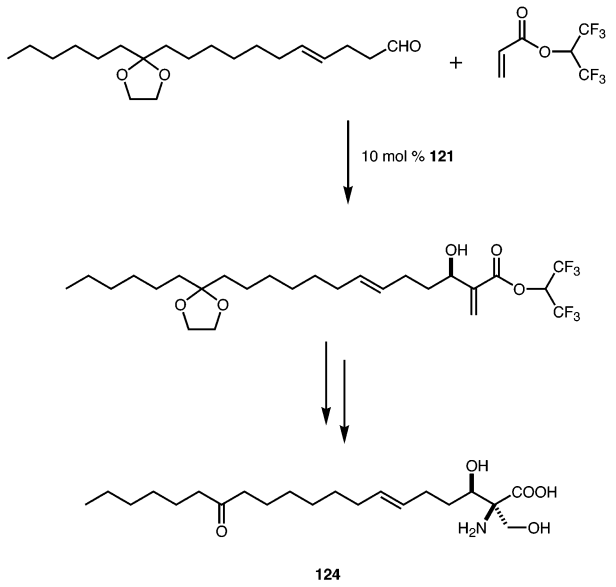


Figure 21. Hatakeyama's proposed 13-member ring intermediate.

Scheme 20

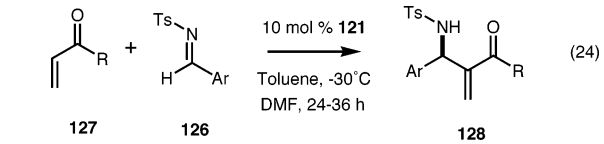


ficient catalytic Baylis−Hillman reaction documented and also one of the most successful examples of catalysis by chiral amines in the literature.

This methodology was applied toward the enantioselective syntheses of the potent immuno-suppressant (−)-mycestericin E[138] (**124,** Scheme 20) and biologically active epopromycin B[139] (**125**, Scheme 21).

Recently, the asymmetric Baylis−Hillman reaction of imines **126** with activated alkenes **127** was developed (eq 24).[140] Using 10 mol % of **121**, α-methylene-*β*-amino acid derivatives **128** were afforded after 24 h in moderate yield with enantioselectivities ranging from 68 to 99% ee, depending on the active alkene used. Similar to Hatakeyama's model, an amine−alkaloid hydrogen-bonded intermediate is proposed as the origin of stereoselectivity.

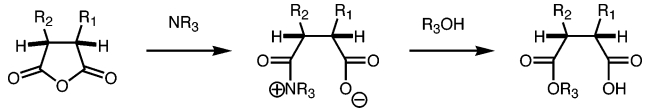
A bifunctional asymmetric system for the three-component Baylis−Hillman reaction with sulfonamides, arylaldehydes and various Michael acceptors was subsequently introduced (eq 25).[141] Utilizing 2 mol % $Ti(O^iPr)_4$ in the presence of 4 Å molecular sieves to catalyze the rapid in situ formation of a *N*-sulfonylimine, combined with 15 mol % **121** to catalyze the Baylis-Hillman reaction, α-methylene-*β*-amino acid derivatives **128** were formed in good yields (up to 80%) and in good enantioselectivities (up to 68% ee). Attempts to optimize these conditions have afforded products in up to 95% yield and up to 74% ee.[142]



2.6. Desymmetrization of Cyclic Anhydrides

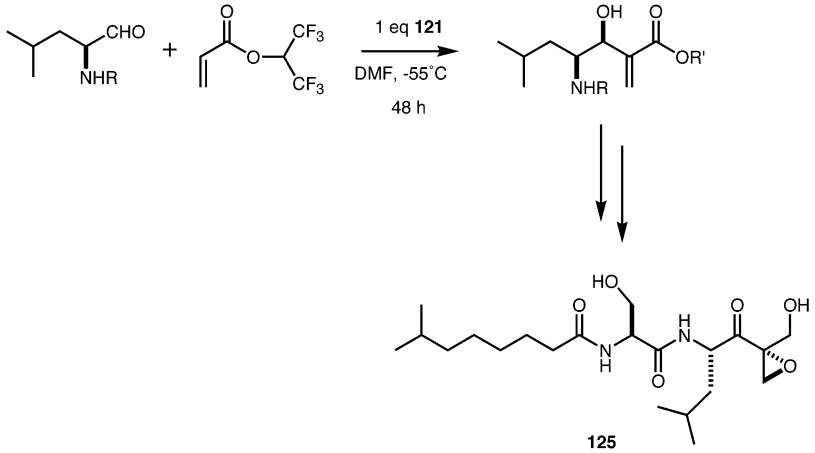
Asymmetric induction based on the desymmetrization of cyclic meso anhydrides has become recognized as an efficient strategy for the synthesis of dicarboxylic acid monoesters and nonracemic lactones.[143] Tertiary amines have been demonstrated to catalyze the opening of anhydrides by attack on the least hindered carbonyl, generating an acylammonium salt, followed by displacement of the amine by an alcohol to afford hemi-esters (Scheme 22).

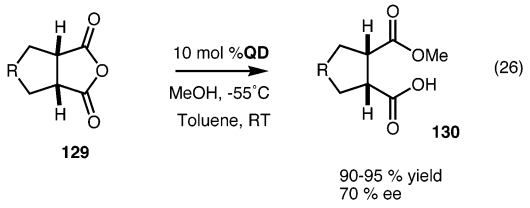
Scheme 22



The first efficient cinchona-alkaloid-catalyzed asymmetric ring-opening of prochiral anhydrides **129** was reported in the 1980s (eq 26).[144] Using 10 mol % of QD, the resulting monoesters **130** were obtained in high yields (up to 95%) and in good enantioselectivities (up to 70% ee). The reaction proceeds via general base catalysis by the quinuclidine moiety of the alkaloid; the relative configuration of the C-9 hydroxyl group with respect to the C-8 quinuclidine amino functionality determines the selectivity of the

Scheme 21

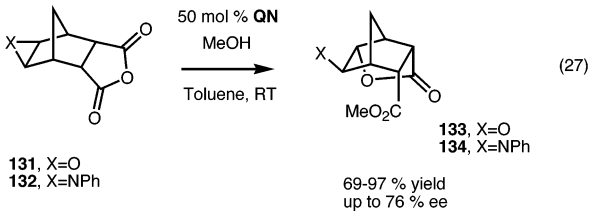




(26)

reaction. An interesting note is that the natural alkaloid configuration showed high activity for all substrates, whereas the *epi*-alkaloids were fairly inactive.

An approach to enantiomeric lactono-esters **133** or **134** resulting from the desymmetrization of meso epoxy anhydrides **131** or *N*-phenylimino anhydrides **132** was reported with moderate asymmetric induction (up to 76% ee) and good yield (69−97%) (eq 27).[145] The disadvantage of this method lies in the

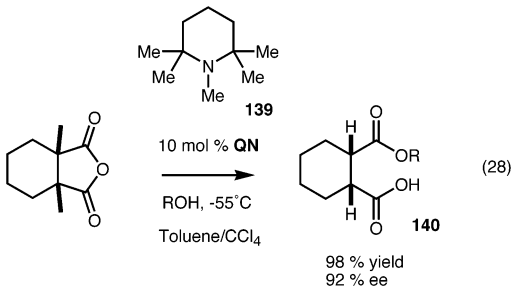


(27)

use of 0.5 equiv of the catalyst in order to induce selectivity. On the basis of studies with polymer-supported alkaloids, Aitken argues there is a competition between enantioselective catalysis by the quinuclidine nitrogen and nonselective catalysis by the quinoline nitrogen.

Another important entry into the efficient synthesis of chiral β-lactones involves the ring opening of 3-methylglutaric anhydride (**135**) promoted by hydroquinine (**136**) (Scheme 23).[146] The resulting β-carboxymethyl-β-methyl-β-lactones **137**, formed in moderate yield (70%) with high enantioselectivity (>90% ee), were converted to optically pure 3-hydroxy-3-methylglutaric amides **138**.

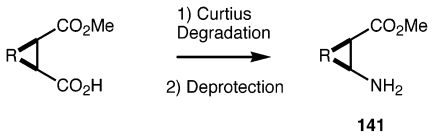
Recently, an efficient enantioselective desymmetrization of anhydrides was published.[147,148] Utilizing a stoichiometric amount of a sterically hindered tertiary amine base **139** and 10 mol % quinine, hemiesters **140** were afforded in high yields (up to 98%) and high enantioselectivities (up to 92% ee) (eq 28).



(28)

This methodology was applied to the asymmetric synthesis of unnatural β-amino acids **141** (Scheme 24).[149] The overall reaction sequence involves the

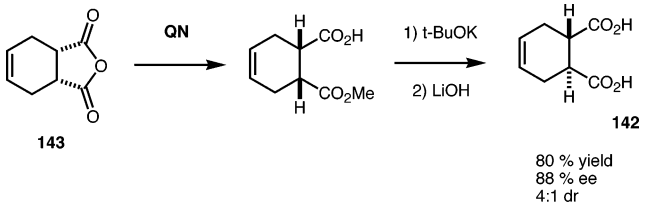
Scheme 24



asymmetric desymmetrization of meso anhydrides followed by subsequent Curtius degradation of a suitable acyl azide. The reaction is highly flexible and permits the introduction of various removable N-protecting groups.

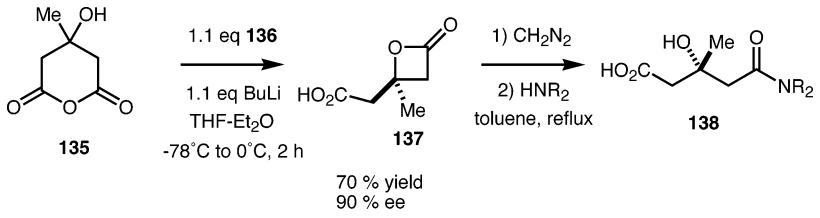
This procedure was adapted for large-scale synthesis of both enantiomers of *trans*-4-cyclohexene-1,2-dicarboxylic acid (**142**) from the cis anhydride **143** (Scheme 25).[150]

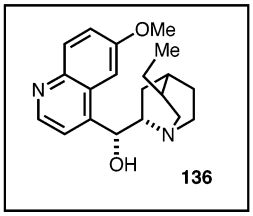
Scheme 25



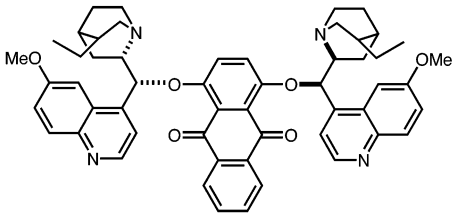
A catalytic, asymmetric procedure for the ring-opening of anhydrides[151] using a dimeric anthraquinone-based alkaloid **144**, previously used as a ligand in asymmetric dihydroxylations and aminohydroxylations, was reported. The half-esters were formed in high enantioselectivity (up to 96% ee) with 100% conversion from the anhydride (Scheme 26).

Scheme 23

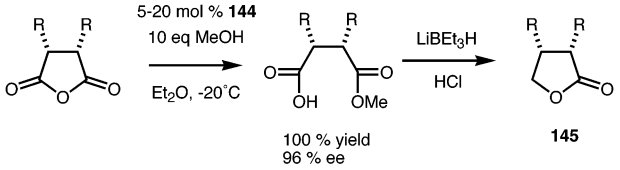




Scheme 26

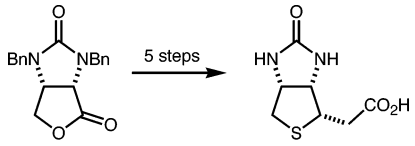


144

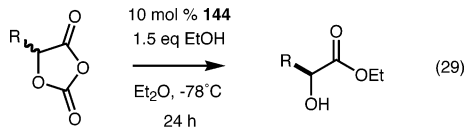


They were subsequently converted to β-aryl-γ-lactones **145** by reduction with $LiBEt_3H$. A formal catalytic asymmetric synthesis of (+)-biotin (**146**) was also achieved (Scheme 27).[152]

Scheme 27



The asymmetric synthesis of α-hydroxy esters **147** through an alkaloid catalyzed dynamic kinetic resolution of 1,3-dioxolane-2,4-diones **148** (eq 29) was recently discussed.[153] The cyclic anhydrides are re-



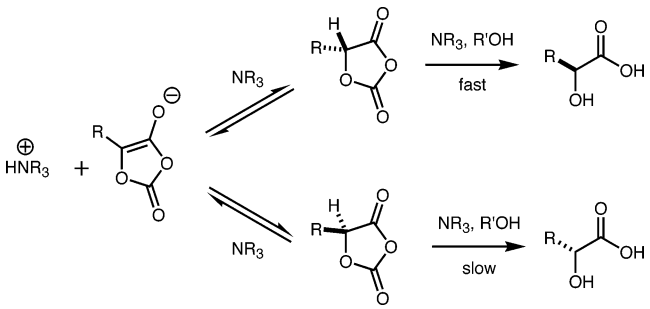
(29)

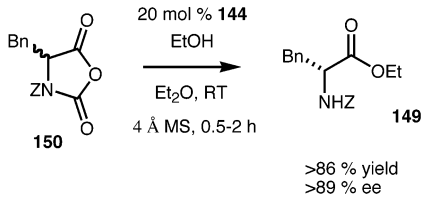
solved in high yield into optically pure α−hydroxy esters through alkaloid-catalyzed racemization and ring-opening of the anhydride (Scheme 28).

Similarly, an asymmetric synthesis of α-amino acids **149** through the dynamic kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (**150**) was developed (eq 30).[154]

The first paper describing the use of noncinchona-based catalysts for the enantioselective desymmetrization of cyclic anhydrides has recently been pub-

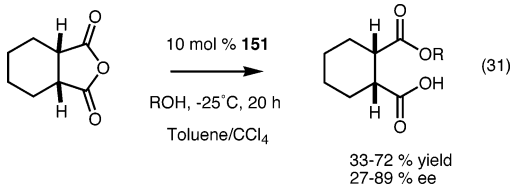
Scheme 28





(30)

lished.[155] Asymmetric methanolysis of meso cyclic anhydrides proceeded in toluene in the presence of (6*R*,7A*S*)-(2−6-hydroxy)hexahydro-1H-pyrrolo[1,2-C]-imidazol-1-one (**151**) to give the corresponding mono esters with enantioselectivities up to 89% ee (eq 31).



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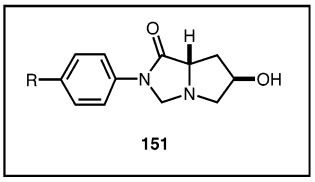


151

2.7. C-Acylation

Another protocol has been developed to access quaternary carbon centers through an enantioselective *C*-acylation of silyl ketene acetals.[156] Various enolsilanes react with acetic anhydride in the presence of catalyst **152** (5 mol %) to afford the corresponding products in high yields and excellent enantioselectivities (up to 99% ee, Figure 22). Mechanistically, it is believed that this reaction is governed by a dual activation process of both the electrophile and the nucleophile. In this manner, acetic anhydride reacts with the catalyst to afford acylpyridinium ion **153** (electrophile activation). The enolsilane reacts with **153** to generate a new ion pair **154**, the enolate anion now being more nucleophilic. Subsequent reaction generates the newly formed quaternary carbon center, with catalyst turnover. Experimental evidence lends support to this mechanistic hypothesis. First, no reaction takes place in the absence of catalyst (no reaction after 60 h at room temperature). However, upon addition of 5 mol % catalyst, a rapid reaction occurs ($t_{1/2} = 0.3$ h). It was found that the silyl ketene acetal does not react in the presence of a preformed acylpyridinium reagent where the counterion is SbF_6^-, indicating the need for generation of the silicon-free enolate. Furthermore, $Me_4N[OAc]_4$ is an effective nonenantioselective catalyst for this reaction.

2.8. Cyanation

Cyanohydrins occupy an important interface between chemistry and biology.[157] They have a well-documented enzymatic history but have considerable synthetic potential as chiral building blocks in or-

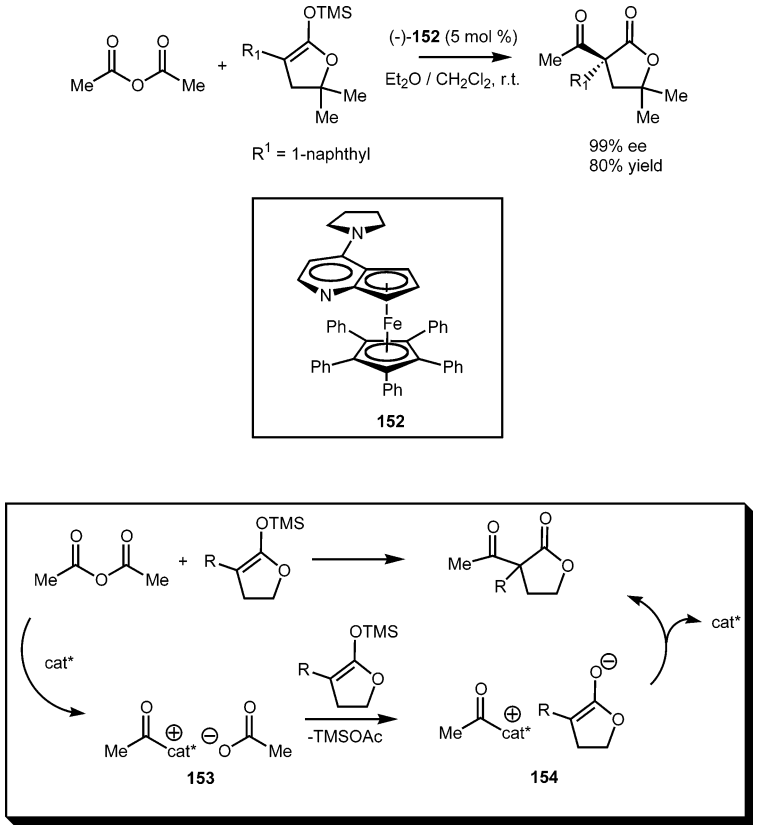
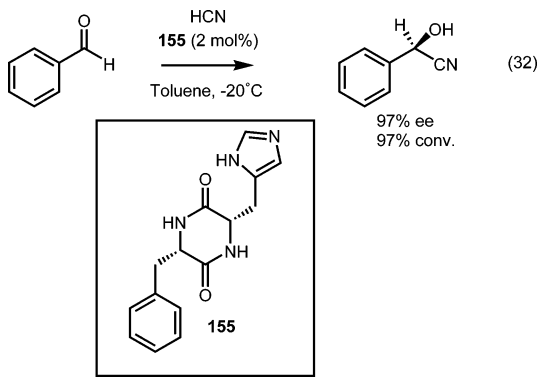


Figure 22. Enantioselective acylation of enolsilanes.

ganic synthesis. Inspired by the ability of the enzyme oxynitrilase[158] to catalyze enantioselective hydrogen cyanide addition to aldehydes,[159] Inoue and co-workers set out to develop a nonenzymatic approach to this reaction. The diketopiperazine derived from the cyclocondensation of phenylalanine and histidine **155** was found to catalyze the addition of hydrogen cyanide to benzaldehyde to afford the corresponding cyanohydrin in up to 90% ee.[160] It was found that enantioselectivities are a function of reaction time, in that if the reaction was allowed to proceed to greater conversions, the ee begins to erode, indicating that under the reaction conditions racemization takes place. Subsequent optimization of this reaction led to the development of a highly efficient synthesis of optically enriched mandelonitrile derivatives.[161] Benzaldehyde reacts with hydrogen cyanide in the presence of **155** (2 mol %) in toluene at −20 °C to deliver (*R*)-mandelonitrile in 97% ee and 97% conversion (eq 32).



(32)

A stereochemical model was proposed to account for the observed stereoinduction (Figure 23). The authors invoke a model in which the aldehyde is activated via hydrogen bonding to catalyst, which serves to orient the aldehyde in a fashion where the re face of the carbonyl is shielded by the phenyl group. The imidazolium ion then delivers cyanide to the si face of the carbonyl. It was found that this reaction is quite sensitive to subtle effects, and the best enantioselectivities were obtained with catalyst that is prepared in a completely amorphous form, so that the reaction mixture obtained is a clear gel.[162,163] In addition, the reaction mixture has "thixotropy," where the highest enantioselectivities are obtained as the viscosity of the mixture is lowered. Interestingly, Danda[164] and co-workers and later Lipton[165] have shown that this reaction exhibits asymmetric autocatalysis, which significantly improves the degree of enantioselectivity.[166] In fact, Danda has shown that by using an essentially racemic catalyst (2% ee), product of 82% ee is obtained when the reaction is doped with a small amount of optically enriched (92% ee) product at the outset of the reaction. This catalyst has been successfully immobilized on various solid

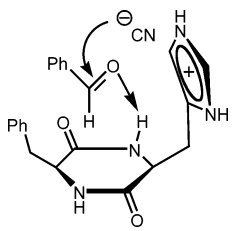


Figure 23. Proposed model for stereoselective cyanide addition.

supports, including incorporation into sol−gel glass[167] and various polystyrene and polysiloxane based resins,[168] allowing for the recovery and reuse of these catalysts.

To garner more mechanistic information, this reaction has been subjected to numerous mechanistic studies. Solution[169] and solid-state[170] NMR spectroscopic studies, as well as molecular modeling,[171] have been carried out, although these studies primarily involved monomeric diketopiperazines and may not be directly applicable due to this reaction's heterogeneity. An alternative mechanism to the above reaction proposed by Inoue was developed by North and co-workers,[172] after finding that **155** catalyzes the oxidation of benzaldehyde to benzoic acid, presumably through a hemiaminal intermediate. If applied to this hydrocyanation reaction, it is possible that the imidazole may activate the aldehyde through this hemiaminal intermediate, and subsequent attack by cyanide gives product (Figure 24). Shvo and

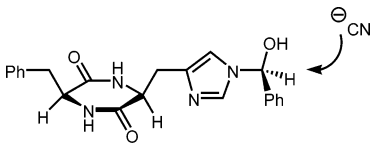
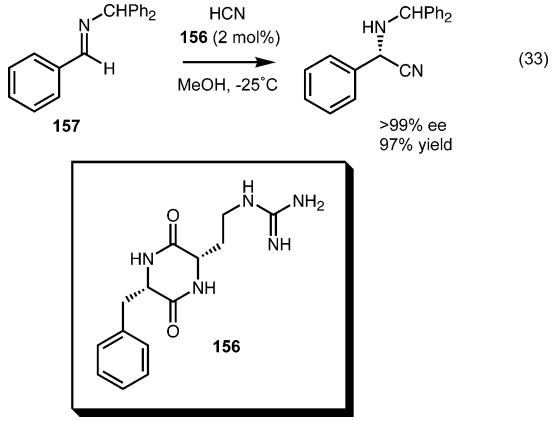


Figure 24. Alternate mechanism via hemiaminal intermediate.

co-workers[173] determined through kinetic studies that this reaction is second-order in catalyst, supporting a mechanism where there is simultaneous activation of the aldehyde and cyanide by two different histidine side chains. This can either be accomplished by hydrogen bonding of a protonated imidazolium ion to aldehyde with HCN activation by neutral histidine or by invoking a hemiaminal intermediate with concomitant HCN activation.

An enantioselective addition of HCN to imines (Strecker-type addition) represents a useful method to access compounds that can be readily converted to optically pure α-amino acids.[174,175] In analogy to the hydrocyanation of aldehydes in their pioneering work, Lipton and co-workers sought to use diketopiperazine **155** as a catalyst for HCN addition to various aldimine substrates to access optically enriched α-amino nitrile synthons.[176] However, it was found that with catalyst **155**, no asymmetric induction is observed in the addition of HCN to benzaldimine substrates. It was speculated that the imine nitrogen of the substrate was sufficiently basic enough to undergo protonation and subsequent addition of cyanide without the intervention of catalyst. Catalyst **156**,[177] derived from (*S*)-norarginine, was found to be an effective asymmetric catalyst for this addition, presumably due to the increased basicity afforded by the guanidine moiety. In this manner, *N*-benzhydryl imine **157** is treated with HCN in the presence of 2 mol % **156** to afford the desired α-aminonitrile in >99% ee and 97% yield (eq 33). Concomitant hydrolysis and *N*-deprotection is carried out under acidic conditions (6N HCl, 60 °C), to afford (*S*)-phenylglycine without loss of enantiomeric excess.



(33)

After Lipton's studies, Corey and Grogan developed a bicyclic guanidine catalyst for enantioselective cyanide addition to aldimines.[178] C_2-symmetric guanidine catalyst **158** provides several optically enriched α-amino nitriles in good ee (up to 88%, Figure 25). Mechanistically, it is believed that **158** forms a hydrogen bond to HCN to form complex **159**, which then activates this aldimine substrate (via hydrogen-bonding) to form a termolecular ion pair **160**. Finally, addition of cyanide within **160** affords α-aminonitrile product, with catalyst turnover. It was found that the protecting group on nitrogen was critical for selectivity, with the authors speculating that π-stacking interactions between substrate and catalyst help to rigidify the transition-state assembly.

Deng reported the first catalyzed asymmetric cyanation of ketones in the presence of cinchona alkaloids in high yields (up to 99%) and in high enantioselectivity (up to 97% ee) (eq 34).[179] The proposed mechanism involves the displacement of cyanide on cyanoester **161** by catalyst **144** to generate an ammonium salt. Next, attack on the ketone by cyanide generates a tertiary alkoxide, which displaces the alkaloid catalyst to form tertiary cyanocarbonates **162**.

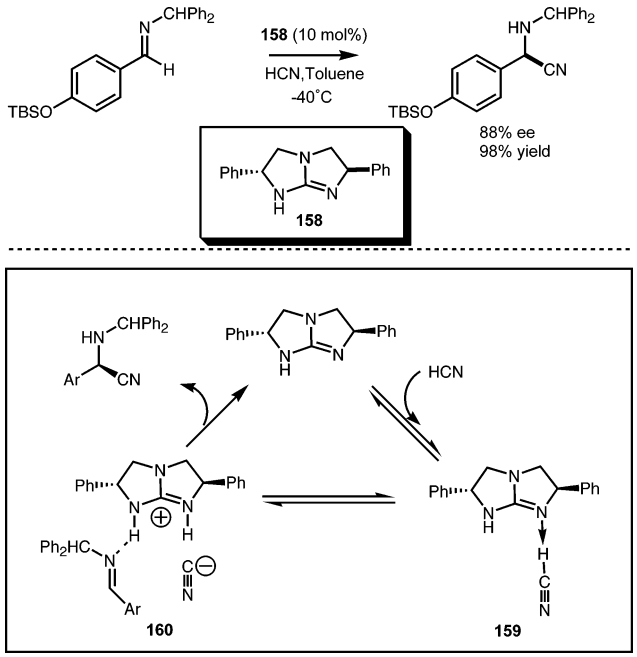
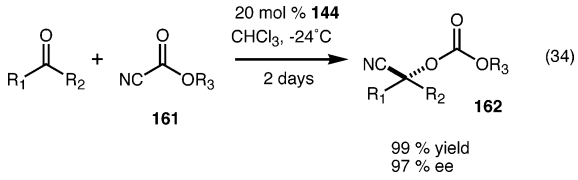


Figure 25. Chiral guanidine-based catalyst for Strecker addition.



3.Solid Phase Chemistry

3.1. Solution Catalysis

Polymer-supported catalysts, reagents, and substrates have found numerous applications in synthetic organic chemistry.[180,181] The ease of recovery and recycling of polymeric reactants makes their use attractive in asymmetric catalysis. Polymers often provide unique microenvironments, that, in many cases, result in enhanced enantioselectivity.[182]

Cinchona alkaloids have also become highly useful in solid-phase chemistry (Figure 26). The ability to

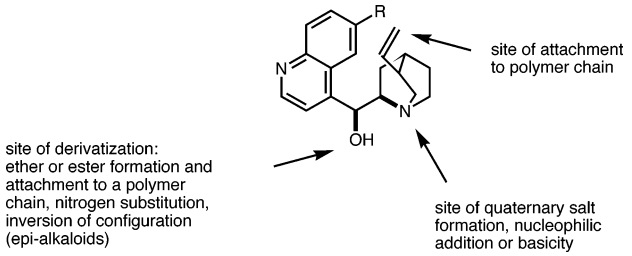
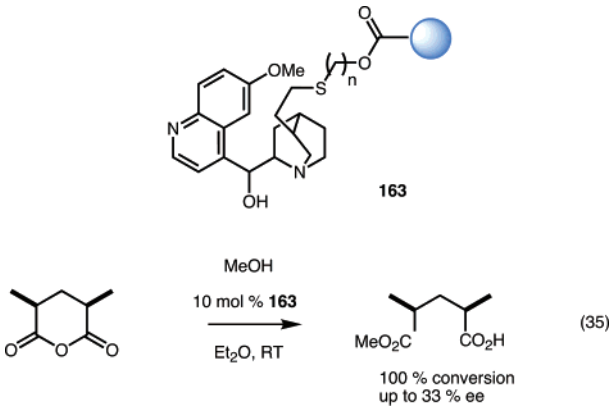


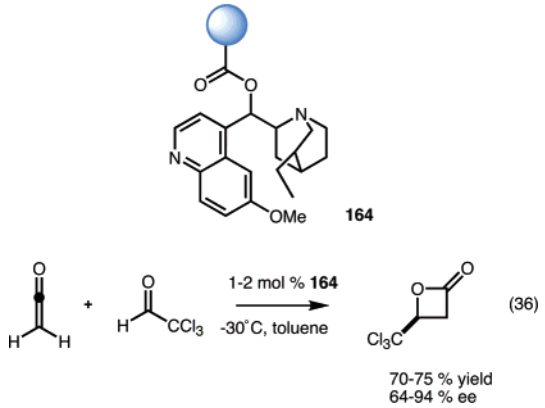
Figure 26. Sites of cinchona alkaloid derivatization.

synthesize a number of polymers attached at different points on the alkaloid make it possible to change the properties of the catalyst without greatly affecting the reactivity. The use of polymer-bound cinchona alkaloids as asymmetric catalysts has been extensively studied ever since the pioneering work by Sharpless for the asymmetric dihydroxylation of olefins.[183,184] Initially, the hydroxy group and the quinuclidine nitrogen were used as sites for anchoring to the polymeric backbone. Success with these catalysts was limited due to diminished interactions (steric or inductive) or modified conformations caused by the polymeric anchor. Accordingly, polymers were synthesized using the C-10, C-11 double bond of the alkaloid as the attachment site. Strategies for the preparation of polymer-supported cinchona alkaloids include utilizing an insoluble polymeric matrix for support, immobilization on an inorganic support, such as silica gel, and utilizing a soluble polymer support that can be readily separated after precipitation.



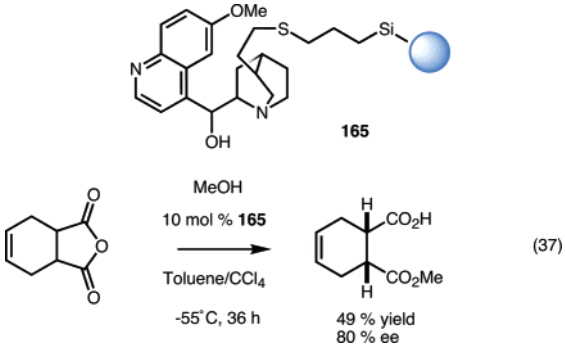
Polymer-supported quinines **163** having spacer groups between the polymeric matrix and the catalytic center have been developed. These polymers catalyzed the desymmetrization of a cyclic anhydride in up to 33% ee (eq 35).[185]

Homo-acrylate polymers of cinchona alkaloids **164** catalyze the enantioselective cycloaddition of ketene to chloral to yield the β-lactone in moderate to high selectivity (64−94% ee) (eq 36).[186] The result is



comparable to those obtained with monomeric alkaloids as catalysts. Interestingly, enantioselectivity increased when the temperature was raised from −50°C to −30°C, due to what is known as the "polymeric" effect. In various solvents, polymers coil and are nearly contiguous in motion and at low temperature, the polymer coils can be to some degree tightly contracted, lowering catalytic activity as a result of the steric hindrance.

A comparison of the catalytic ability of polymer-bound to non-polymer-bound quinidine for the catalytic desymmetrization of meso-anhydrides (eq 37),[187] using quinidine that was supported to siliceous materials through a thioether linker (**165**), was recently reported. Supported catalysts afforded product in similar yield (49%) and enantioselectivity (80% ee) with respect to the parent alkaloid (45% yield, 85% ee).



The asymmetric addition of hydrogen cyanide to 3-phenoxybenzaldehyde catalyzed by a quinidine-acrylonitrile copolymer **166** was shown to give cyanohydrins in high yield (98%) with moderate selectivity (46% ee) (eq 38).[188] The selectivities achieved were

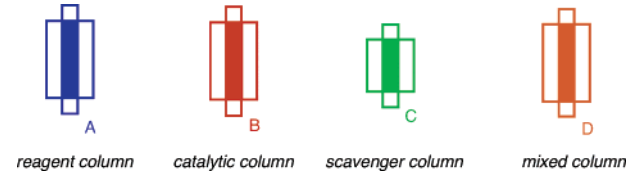
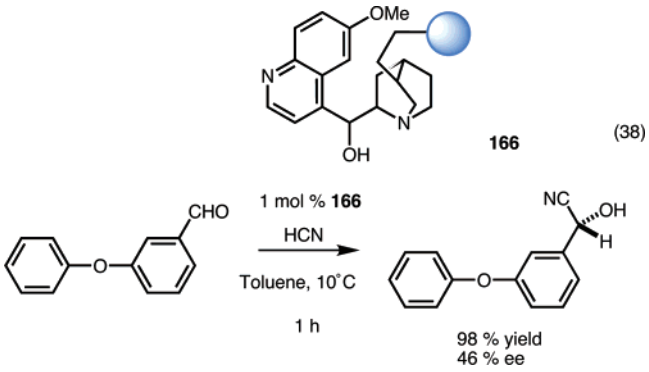


Figure 27. The different column types for column asymmetric catalysis.

substantially higher than those from the monomeric alkaloid (22% ee).



3.2. Catalysis on Sequentially-Linked Columns

The concept of employing solid-phase reagents packed into columns has been extensively explored in academic chemistry. A recent paper details the use of HPLC columns for catalytic, asymmetric hydrolysis reactions. In industry, reaction columns have been used for large-scale synthesis for quite some time; however, much of the technology is proprietary. Lectka has reported a catalytic asymmetric reaction process that involves the use of solid-phase reagents and catalysts that constitute the packing of a series of reaction columns.[189]

The different types of columns that constitute an assembly are shown in Figure 27. Columns labeled A contain stoichiometric reagents that convert precursors into substrates suitable for the catalytic, asymmetric reaction. They must eventually be replaced or regenerated after the reagent is spent. Column type B is packed with the asymmetric catalyst, loaded onto a suitable polymeric support. Columns labeled C contain scavenger resins to remove byproducts and effect purification. A mixed column D is represented also containing both catalysts and reagents packed together. Each column represents stages in normal synthetic sequences such as substrate preparation, stoichiometric, and catalytic reactions and finally purification steps. Lectka terms this strategy sequential column asymmetric catalysis, or sequential CAC, when at least one of the steps involves a catalytic, asymmetric transformation. This strategy can be applied to the synthesis of β-lactams from α-chloroglycines and ketenes (Scheme 29). [190]

The sequential CAC assembly consists of three fritted, jacketed columns (each 2 cm wide), including two top columns (type A) for reagent synthesis, a catalytic column (type B) into which the reagent columns feed, and a scavenger resin column (type C) below the catalytic column. One of the top columns

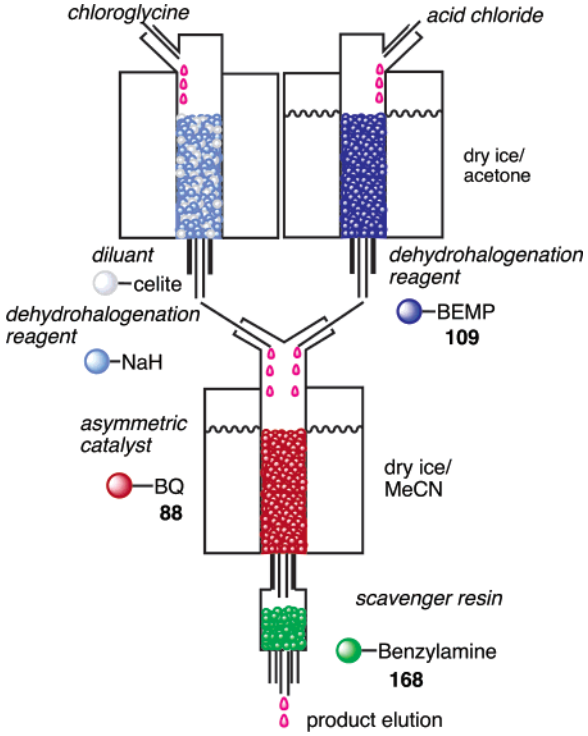
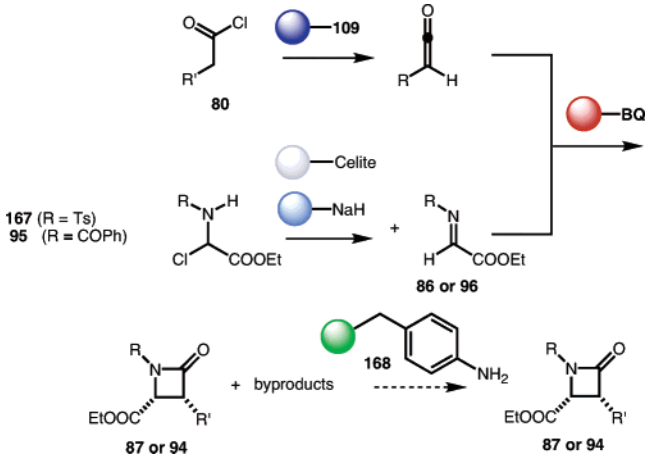


Figure 28. Column asymmetric catalysis assembly.

Scheme 29



was packed with solid-phase dehydrohalogenating agents such as the phosphazene base BEMP resin **109**, the other top column with a mixture of NaH and Celite (the Celite proved to be a convenient diluant for formation of imines **96** from stable α-chloroglycines **95**). The catalytic column was loaded with catalyst beads. The NaH/Celite column was kept at room temperature, and the catalyst loaded column was cooled to −43° C with a dry ice/acetonitrile mixture. A solution of acid chloride **80** was added to the top of the column and allowed to percolate by gravity through the BEMP resin and onto the catalyst-loaded resin of the middle column. Concurrently, a solution of α-chloroamine **95** was added to the NaH/Celite column and allowed to drip by gravity through solid bases onto the catalyst-loaded resin of the middle column. The reaction was initiated by allowing a slow drip of solvent from the bottom of the column to allow complete elution of the column contents over the course of 2 h. After passing through

the scavenger resin column, the eluted reaction mixture was concentrated to afford β-lactam **94** in 90% ee and 10:1 dr (cis:trans). Simple crystallization of the residue affords optically and analytically pure **94** (>99% ee, 98/2 cis−trans dr) in 62% yield. A whole range of ketenes and acyl-substituted chloroglycines can be used in this procedure to produce a spectrum of β-lactam products.

4. Conclusion

The role that chiral nucleophilic catalysts play in asymmetric synthesis has grown tremendously over the last 30 years. Chiral amines represent a powerful and useful means of accomplishing chemical transformations. Their diverse range of activity allows them to function as acids/bases, nucleophiles, and chiral promoters. From natural products such as the alkaloids and simple amino acids to more complex compounds such as peptides and heterocyclic amines, these catalysts are offering promising results in numerous areas of organic synthesis.

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CR020061A