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Bifunctional Asymmetric Catalysis: Cooperative Lewis Acid/Base Systems

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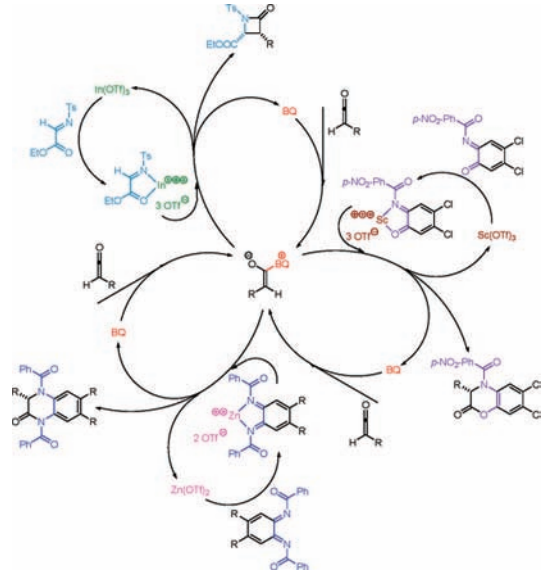
CONSPECTUS

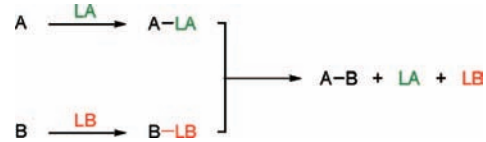
In the field of catalytic, asymmetric synthesis, there is a growing emphasis on multifunctional systems, in which multiple parts of a catalyst or multiple catalysts work together to promote a specific reaction. These efforts, in part, are result-driven, and they are also part of a movement toward emulating the efficiency and selectivity of nature's catalysts, enzymes. In this Account, we illustrate the importance of bifunctional catalytic methods, focusing on the cooperative action of Lewis acidic and Lewis basic catalysts by the simultaneous activation of both electrophilic and nucleophilic reaction partners. For our part, we have contributed three separate bifunctional methods that combine achiral Lewis acids with chiral cinchona alkaloid nucleophiles, for example, benzoylquinine (BQ), to catalyze highly enantioselective cycloaddition reactions between ketene enolates and various electrophiles. Each method requires a distinct Lewis acid to coordinate and activate the electrophile, which in turn increases the reaction rates and yields, without any detectable influence on the outstanding enantioselectivities inherent to these reactions. To place our results in perspective, many important contributions to this emerging field are highlighted and our own reports are chronicled.



1. Introduction

A timely debate underway in the organic chemistry community involves the relative merits of Lewis acid catalysis versus organocatalysis for asymmetric synthesis. Very often, the two approaches are complementary, such that, in some cases, they may even be employed together, working in tandem in a single reaction. These bifunctional systems may result in a *termolecular* complex, in which two substrates are concurrently activated and their reaction directed by the catalysts (Scheme 1).[1] In this Account, we discuss bifunctional systems consisting of Lewis acidic and Lewis basic (especially nucleophilic) cocatalysts that work in concert to promote electrophilicity and nucleophilicity in reactive partners while providing high optical induction. Although the bifunctional concept looks good "on paper", many things can go wrong upon execution. Part of the difficulty is the large potential for quenching reactions; for instance, the Lewis acid may react with the Lewis base or with the nucleophilic

SCHEME 1. Bifunctional Lewis Acid/Base (LA/LB) Catalysis



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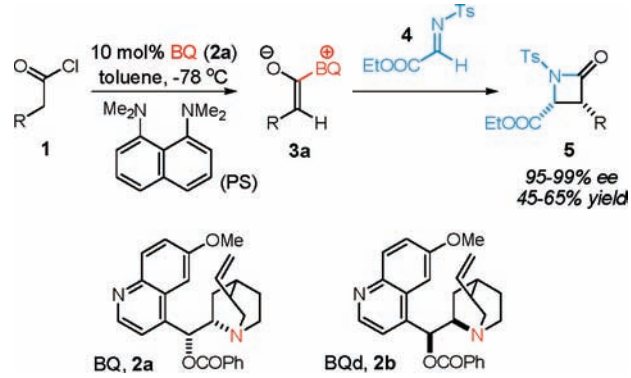
reagent (B, Scheme 1, before or after activation by the Lewis base) and so on. The key, therefore, is to fine-tune the reaction conditions and catalysts, so that only the desired reaction occurs. For example, the use of a "hard" Lewis acid and a "soft" Lewis base (using Pearson's terminology) may alleviate the problem of catalyst quenching.[2] As we will see, finding the right catalyst pair and reaction conditions may give rise to a powerful bifunctional system.

Few bifunctional systems of this sort have been well-defined and mechanistically explored, partly because of their inherent complexity. Of note, Shi has reported a lithium-assisted Baylis–Hillman reaction catalyzed by cinchona alkaloid derivatives.[3] An asymmetric cyanosilylation of ketones was proposed by Shibasaki et al. to occur via a tethered Lewis acid/phosphine oxide system based on glucose.[4] These authors have also developed a series of tethered catalysts based on a BINOL template, which have been applied to a variety of reactions.[1] Nájera and Saá have designed a similar system for the cyanophosphorylation of aldehydes.[5] Yamamoto has used cooperative catalysis to promote both the Sakurai–Hosomi allylation and the Mukaiyama aldol reaction by combining chiral Ag–phosphine complexes with a catalytic amount of fluoride ion.[6] More recently, Fujimoto and Yamamoto accomplished the enantioselective allylation of aldehydes via a bisoxazoline–Lewis acid complex bearing a remote phosphine oxide.[7] Calter et al. have applied a Lewis acid/cinchona alkaloid system to the synthesis of disubstituted β-lactones[8] and β-lactams.[9] Peters used a similar system for the reaction of sulfenes and aldehydes; the β-sultone products were only obtained in good yield and enantiomeric excess (ee) in the presence of a Lewis acid.[10] Additionally, Snapper and Hoveyda have achieved imine chelation by a small peptide-bound Lewis acid to effect an asymmetric Strecker reaction.[11] These examples, especially the representative cases highlighted below, complement our own bifunctional systems.

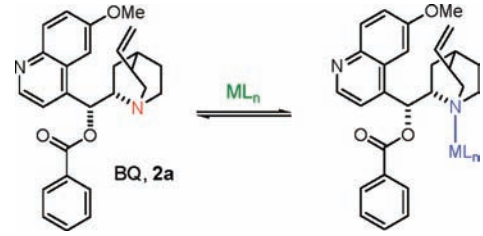
2. β-Lactams via [2 + 2] Cycloaddition of Imino Esters and Ketenes

Our interest in the field of bifunctional catalysis arose out of long-standing frustration with the generally low to moderate yields that we obtained in our method for the catalytic, asymmetric synthesis of β-lactams (Scheme 2).[12] Although the yields were often unsatisfactory, the enantioselectivity of the reaction was uniformly outstanding. Our catalyst choice, benzoylquinine (BQ, **2a**), has been shown to promote highly enantioselective reactions in a variety of substrates.[13] We believed

SCHEME 2. Original β-Lactam Method



SCHEME 3. Cocatalyst Quenching



that the desired reaction of the ketene enolate (**3**)[12a] and the imine was slow enough to allow for the formation of polymeric byproducts. On the basis of our previous successes with activated imine alkylations,[14] we reasoned that the addition of a Lewis acid cocatalyst would render the imine more electrophilic, thereby increasing the rate of the desired [2 + 2] cycloaddition pathway and suppressing the unwanted secondary reactions.

Bifunctional System. We began our bifunctional studies[15] by adding 10 mol % of the metal complexes that worked best for our imine alkylations (and that were conveniently on our laboratory shelves), including $Rh(PPh_3)_3OTf$ and $Cu(PPh_3)_2ClO_4$, to the standard reaction conditions to form β-lactams. To our surprise, the overall yield *decreased* in the presence of the respective metal. We monitored the the Cu^{I} reaction by UV–vis spectroscopy and found evidence of metal–amine (of the cinchona alkaloid catalyst) binding; this is an example of the long-feared cocatalyst quenching (Scheme 3).

On the other hand, Aggarwal et al. found that group III and lanthanide triflates significantly enhanced their DABCO-catalyzed Baylis–Hillman reaction, whereas "traditional" Lewis acids lead to diminished yields.[16] Coupled with our own initial results, these findings suggested that harder, less azaphilic metals would minimize the catalyst quenching that we previously observed. A full spectrum of metal salts were screened with this in mind, and we found that triflates of Al^{III}, Sc^{III}, Zn^{II}, and In^{III} resulted in increased reaction rates and significantly enhanced chemical yields. We determined indium(III) triflate

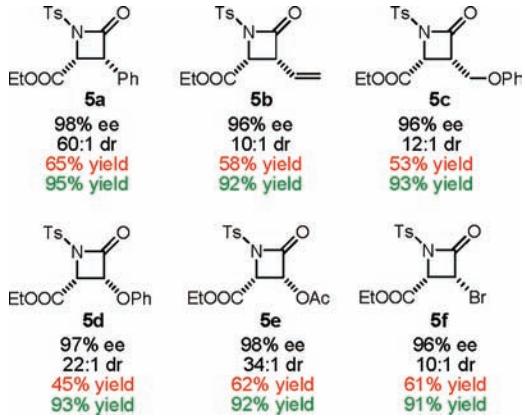


FIGURE 1. Sample of β-lactams synthesized, employing cocatalysts BQ and $In(OTf)_3$ (yields in red without metal).

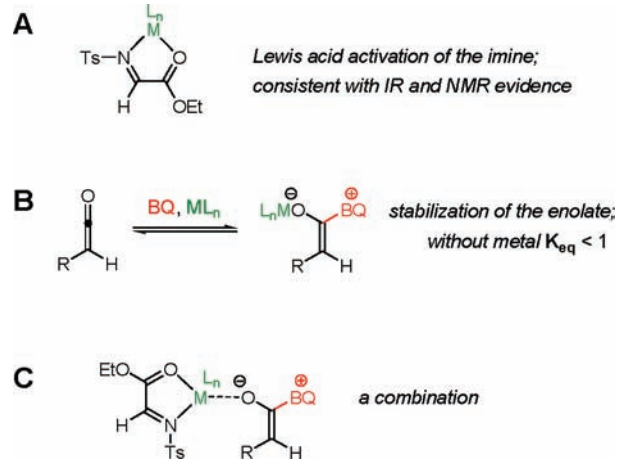
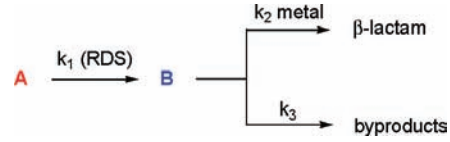


FIGURE 2. Possible roles of the Lewis acid.

to be the best cocatalyst across the board; ironically, indium-based Lewis acids have infrequently been used in organic synthesis, and their coordination chemistry is not well-explored.[17] One reason may be that In^{III} binds to many ligands reversibly and with comparatively low affinity.[18] The most striking aspect of In^{III} coordination chemistry is characteristically fast ligand on/off rates; even bidentate ligands are generally highly labile.[19] This fact may hold one reason why In^{III} works efficiently in our system, and in contrast to Cu^{I}, any In^{III} binding to the cinchona alkaloid catalyst is highly reversible and perhaps of low affinity. This argument raises the question of how to account for the increased yields observed for Sc^{III}, Al^{III}, and Zn^{II} when each is known to have slower ligand exchange rates. A plausible explanation is that the ligand exchange between the quinuclidine nitrogen and the imino ester must favor the bidentate binding afforded by the imino ester. Having firmly established $In(OTf)_3$ as the best overall Lewis acid cocatalyst for our reaction, we applied this system to various substrates to determine the scope of its influence (Figure 1). Generally, the yields increase by 1.5–2-fold with the In^{III} cocatalyst, and enantioselectivity is excellent and virtually unaffected by the metal.

Role of the Lewis Acid. There are three plausible mechanistic alternatives that could account for the observed effect of the Lewis acid. We originally postulated that In^{III} binds to the imino ester and increases its reactivity toward the nucleophilic ketene enolate (Figure 2A). Another possibility is that the metal binds to the zwitterionic enolate, making it more thermodynamically stable (Figure 2B). This would have a two-pronged effect: (1) the more stable ketene enolate would be more chemoselective, eliminating undesired side reactions, and (2) assuming equilibrium between the ketene and the enolate, metal binding is expected to increase the relative concentration of the enolate, thereby accounting for the increased

SCHEME 4. Metal-Mediated Chemoselectivity of the Bifunctional Pathway

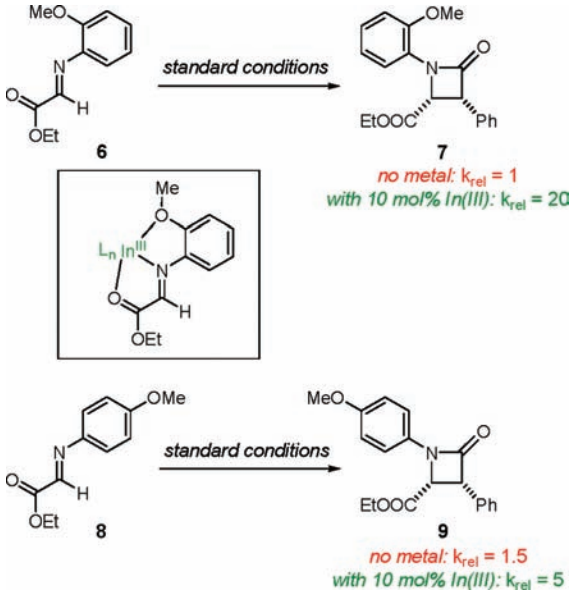


rate of the reaction. A third possibility involves the simultaneous operation of both alternatives, with the metal organizing a termolecular-activated complex (Figure 2C). On the basis of substantial mechanistic evidence, we were able to eliminate the metal–enolate binding scenarios (parts B and C of Figure 2).[15b] Notably, Calter and Huang have reported a similar bifunctional system, in which the Lewis acid acts by binding and organizing a chelating version of the ketene enolate instead of activating the imine.[9] They use a cinchona alkaloid nucleophile in conjunction with a Lewis acid to form β-lactams from aryl imines and phenoxyacetyl chloride. In this system, bidentate metal–enolate binding is preferred to monodentate metal–imine binding for hard Lewis acids.

We had previously determined that the rate-determining step (RDS) of the metal-free reaction involves acylation of the catalyst by the acid chloride and/or ketene formation.[12b] In our bifunctional system, we found that the metal cocatalyst does not participate in the RDS but has a substantial effect on the chemoselectivity of a process after the RDS (Scheme 4), an observation consistent with the established RDS of the metal-free reaction. Using a "knock-out" strategy where we avoid the original RDS by preformation of the ketene,[20] we determined that In^{III} enhances the rate of the C–C bond-forming step.[15b]

We have also established that metal binding to the imino ester plays a pivotal role in the bifunctional reaction. Coordination and complexation of metals with imino esters are well-precedented,[21] and we found IR and NMR evidence that In^{III} does bind to the imino ester in our system. However, we

SCHEME 5. PMP− Versus OMP−Imine Reaction Rates



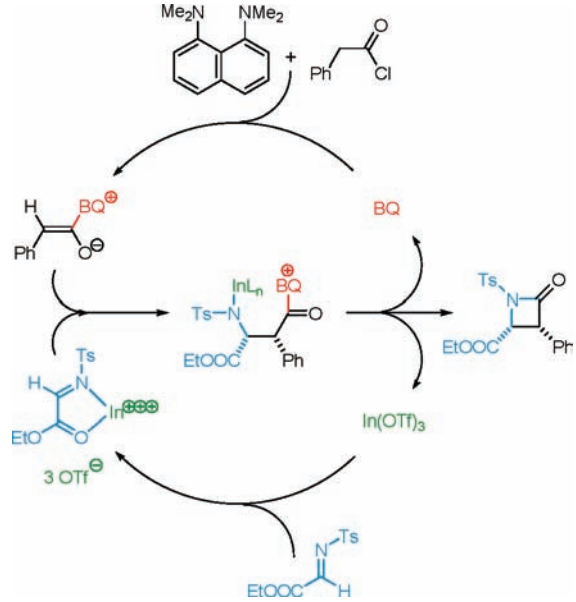
designed what we believe is a more direct (and more elegant) test for productive metal binding. We modified the N substituent of the imino ester to contain an additional metal-binding moiety (**6**, Scheme 5). In the absence of the metal cocatalyst, **8** reacts slightly faster (1.5×) than **6**. However, when $In(OTf)_3$ is added as a cocatalyst, the reactivity is reversed: imino ester **6** reacts 4 times faster than substrate **8**. Both substrates react faster with the metal than without; while imino ester **8** receives only a 3-fold rate increase from the metal cocatalyst, **6** experiences a tremendous 20-fold rate increase. The difference is clearly due to the tridentate nature of **6**. The *o*-methoxy group helps hold the metal in place, so that it spends relatively more time activating the imine.

Mechanistic Hypothesis for the Bifunctional Reaction. Combining all of these data allows us to formulate a mechanism for the bifunctional reaction of ketenes with imino esters (Scheme 6). Acylation of BQ forms the nonmetal-coordinated zwitterionic enolate; activation of the imino ester by the In^{III} cocatalyst facilitates the C−C bond-forming addition reaction; and a transacylation then forms the β-lactam and regenerates the catalyst.

3. Other Seminal Examples

Lewis Acid−BINOL−Phosphine Oxide Catalysts. A useful class of bifunctional catalysts was developed by Shibasaki et al. in 1999 for the asymmetric Strecker reaction.[22] Using BINOL as a scaffold, they envisioned a catalyst-organized transition-state complex, where Al^{III} activates the carbonyl oxygen, while the tethered phosphine oxide interacts with TMS−CN. On the basis of IR and other control experiments,

SCHEME 6. Proposed Mechanism of Bifunctional [2 + 2] Cycloaddition



the authors proposed a transition-state model for the enantioselective reaction (Figure 3).

These Al^{III}−BINOL−P(O) bifunctional catalysts are particularly useful because, with minor modifications, a variety of asymmetric reactions can be effected. For example, Shibasaki applied this catalyst system to the Reissert reaction, which forms quaternary products in high yield and excellent enantioselectivity (Figure 4), simply by increasing the Lewis acidity of Al^{III}.[23]

In a similar use of a bisphosphoryl BINOL system, Ishihara employed a conjugate Lewis acid−Lewis base system to perform highly enantioselective (up to >99% ee) alkylations of aldehydes with dialkylzinc to produce a series of chiral sec-

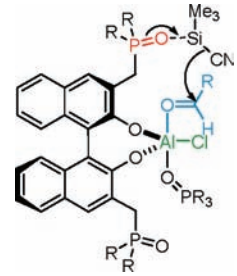


FIGURE 3. Dual activation in Shibasaki's Strecker reaction.

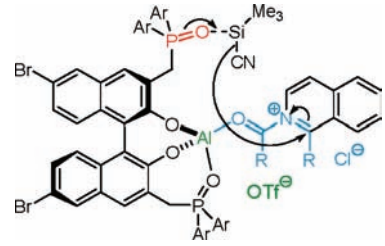


FIGURE 4. Shibasaki's bifunctional Reissert reaction.

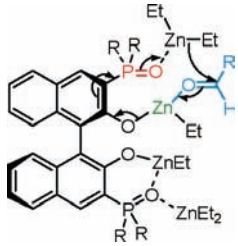


FIGURE 5. Ishihara's asymmetric alkylation reaction.

FIGURE 6. Kozlowski's proposed intermediate.

ondary alcohols.[24] It was noted that the phosphoryl group was essential for high catalytic activity. Lewis acidic Zn^{II} activation of the aldehyde was complemented with Lewis basic phosphoryl activation of the dialkylzinc, leading to substrate alkylation (Figure 5).

Lewis Acid–Salen Catalysts. Several interesting bifunctional systems based on the combination of metal–salen complexes with Lewis bases have recently been developed. Chen et al. used a chiral titanium–salen complex in conjunction with an achiral *N*-oxide Lewis base to catalyze the cyanosilylation of aldehydes.[25] Moberg performed the enantioselective cyanation of aldehydes to produce optically active cyanohydrin esters in high yield and ee, employing a catalytic system derived from a dimeric Ti^{IV}–salen complex and triethylamine.[26] Kozlowski has used a novel titanium–salen complex containing a remote nucleophile to catalyze dialkylzinc additions to various substrates, including α-ketoesters[27] and α-iminoesters,[28] with high yield and moderate enantioselectivity. The Lewis acid complex activates the electrophile, and the nucleophile enhances the reactivity of dialkylzinc (Figure 6).

In 2007, a stereochemically complex bifunctional catalytic system was developed by Lin et al. that promotes a [2 + 2] cycloaddition between ethenone and benzyloxyacetaldehyde to produce the corresponding β-lactone in high yield (91%) and ee (>99%).[29] The configuration of the diaminopropanoic acid linker (Figure 7, one diastereomer shown) proved to be inconsequential; the chiral induction is provided solely by the Lewis base. This is notable because the quinuclidine-bound enolate is presumed to attack the metal-activated aldehyde

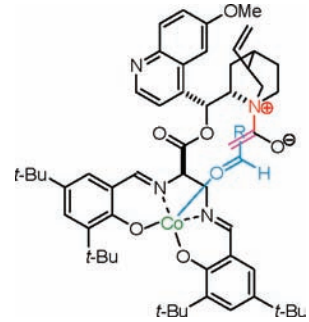


FIGURE 7. Lin's proposed activated complex.

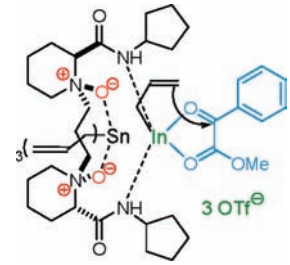


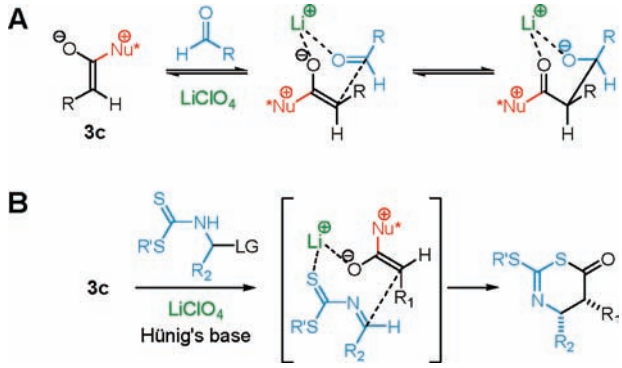
FIGURE 8. Feng's proposed transition-state complex.

intramolecularly. The researchers propose a bifunctional manifold based on several control experiments, including one test where no product was formed in a catalytic system composed of a discrete Co^{II}–salen complex and a quinine derivative.

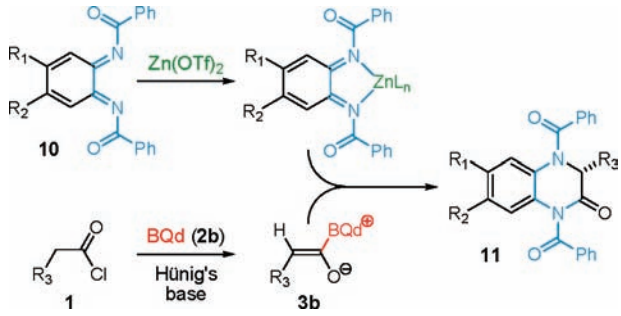
Other Noteworthy Systems. A recent report by Feng et al. highlights the cooperative catalytic action of indium(III) and a chiral bis-*N*-oxide additive, which together effect the enantioselective allylation of α-ketoesters.[30] Remarkably, the bis-*N*-oxide catalyst alone promoted the reaction of tetraallylstannane with the substrate in low yield with no optical induction; the presence of $In(OTf)_3$ was necessary to produce chiral products in good yield and ee. Their proposed transition state involves In^{III} coordination to the substrate and the chiral additive, while the *N*-oxide initiates the In^{III}-assisted transfer of the allyl group (Figure 8).

Nelson et al. have reported several remarkable lithium-assisted reactions of cinchona alkaloid ketene enolates. In 2004, the authors enhanced their [2 + 2] cycloaddition reaction of aldehydes and ketenes with $LiClO_4$ to activate otherwise unreactive, sterically hindered aldehydes. This bifunctional system expands the scope of these cycloaddition reactions, providing access to disubstituted β-lactones, through a putative metal-organized six-member transition-state complex (Scheme 7A).[31] More recently, Nelson proposed a similar transition-state argument for the lithium/cinchona alkaloid cocatalyzed reaction of ketenes and *N*-thioacyl imines (Scheme 7B). This system affords the [4 + 2] cycloadducts in high yield with excellent stereochemical control.[32]

SCHEME 7. Nelson's Lithium-Organized Activated Complex



SCHEME 8. Bifunctional *o*-Benzoquinone Diimide Reaction



4. [4 + 2] Cycloaddition of *o*-Benzoquinone Derivatives and Ketenes

Everyone knows that catalytic, enantioselective Diels–Alder reactions have become powerful tools for the construction of six-membered rings, with extensive synthetic applications to natural and unnatural products with a wide range of biological activity.[33] Typically, they are catalyzed by a chiral Lewis acid (or Lewis base) through dienophile activation. There are few well-documented cases for activation of both diene and dienophile in tandem.[34] Here, we present two examples of the bifunctional catalysis of hetero-Diels–Alder reactions, developed in our laboratory, that exploit the obvious metal-chelating abilities of *o*-benzoquinone derivatives.

***o*-Benzoquinone Diimides.** In the first stages of our investigation, we discovered that the reaction between ketene enolates and *o*-benzoquinone diimides (QDIs, **10**, Scheme 8) forms the [4 + 2] cycloadduct quinoxalinones (**11**) in outstanding enantioselectivity (>99% ee) but low yields.[34a] In the initial screen (no metal cocatalyst), the reaction also proceeded slowly with the formation of unidentified byproducts in addition to the desired quinoxalinone. Drawing an analogy to our bifunctional β-lactam system,[15b] we believed that activation of the potentially chelating benzoquinone diimide by a Lewis acid cocatalyst may increase the rate of the desired reaction. We tested our hypothesis by screening the metal salts that

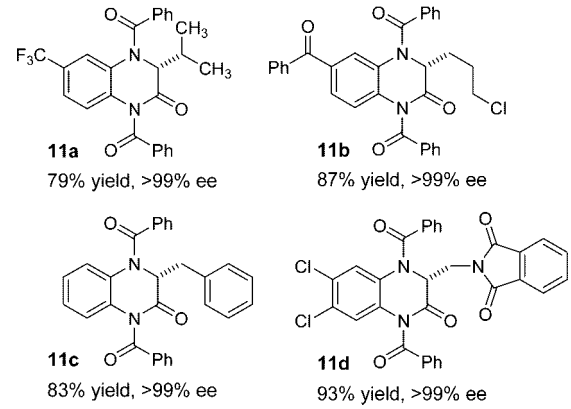


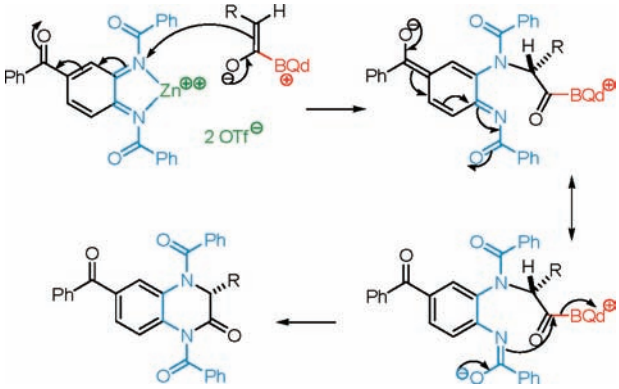
FIGURE 9. Sample quinoxalinones from the standard bifunctional reaction.

were most successful in our bifunctional β-lactam method, namely, $Al(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $Zn(OTf)_2$. Our results demonstrated an increase in yield for all four cocatalysts, although $Zn(OTf)_2$ proved to be the best and most cost-effective of the group. It was used for all subsequent reactions, which produced products in generally high yield and phenomenal enantioselectivity (Figure 9).

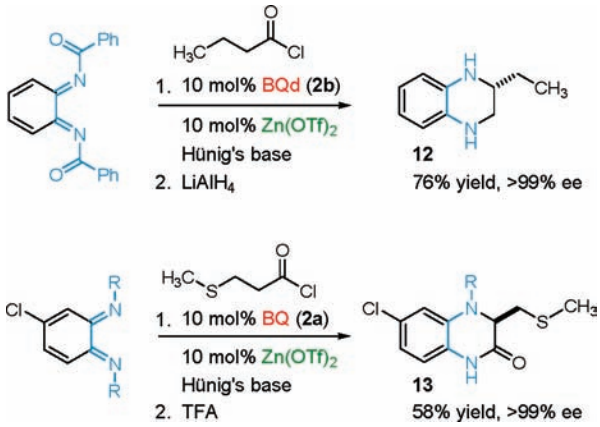
Although a detailed mechanistic study has yet to be undertaken, we believe that the Lewis acid activates the diimide through chelation without affecting the nucleophilic enolate. We explored this possibility by observing the interaction of the metal triflate with the QDI by IR. The imine and carbonyl stretches of QDI shift to lower frequency in the presence of 1 equiv of $Zn(OTf)_2$. Scandium(III) triflate, the second best performer in our screen, causes similar bathochromic shifts; these results were consistent with PM3 vibrational analysis, indicating that the Zn^{II} and Sc^{III} coordinate to the diimide. In an initial rate study, we observed a 20-fold rate increase when 10 mol % $Zn(OTf)_2$ cocatalyst was added to a standard reaction, without erosion of enantioselectivity.

We also investigated the regioselectivity of this method when using unsymmetrical QDIs. In each case, only one regioisomer was produced and, again, only one enantiomer was detected (Figure 9). A proposed mechanism for the regioselective cycloaddition, which can be rationalized by resonance considerations, is shown in Scheme 9. We believe the reaction proceeds in a stepwise fashion, initiated by nucleophilic attack of the ketene enolate to the most electrophilic nitrogen. The products of these reactions may have significant biological applications. Quinoxalinones have structural similarities to benzodiazepines[35] but have not been investigated as thoroughly. To demonstrate the utility of this method, we synthesized two biologically active compounds: compound **12**, an inhibitor of cholesterol ester transfer protein,[36] and

SCHEME 9. Proposed Mechanism of Regioselective Bifunctional Cycloaddition



SCHEME 10. Synthesis of Drug Targets, R = CO_2−*i*-Pr



compound **13**, which exhibits strong antiviral activity against HIV[37] (Scheme 10).

***o*-Benzoquinone Imides.** Having successfully employed Lewis acid cocatalysts to improve the rate and yield of ketene enolate reactions with both imino esters and QDIs, we sought to improve upon the [4 + 2] cycloaddition reaction of *o*-benzoquinone imides (QIs, **14**, Scheme 11) and acid-chloride-derived ketene enolates.[34b] These asymmetric reactions produce dihydro-1,4-benzoxazinones, which can lead to α-amino acid derivatives. The standard reaction in the absence of metal forms the benzoxazinone (**15**) in modest yield and >99% ee.[38] We discovered that after forming the cycloadduct **15**, we can directly transform the product to an α-amino acid derivative (**16**) by quenching the reaction with MeOH; subsequent oxidative cleavage of the aryl group gives the free amine **17** (Scheme 11).

Using this method, we can obtain a broad spectrum of natural and non-natural α-amino acids in >99% ee. As in the earlier cases, we wanted to make our method more useful by optimizing the yields through the use of a Lewis acid cocatalyst. A number of metal triflates were screened for this purpose, and we found that $In(OTf)_3$, $Zn(OTf)_2$, and $Sc(OTf)_3$

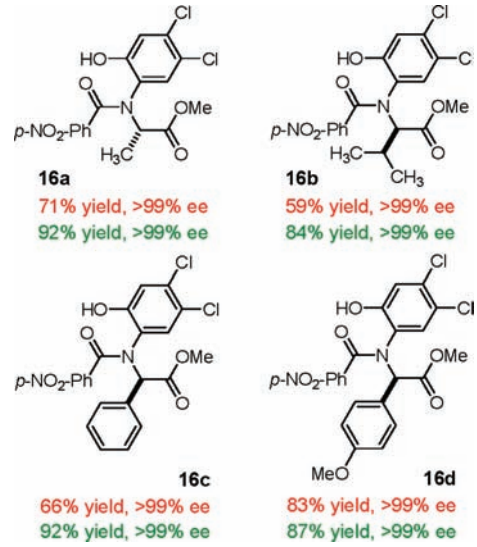
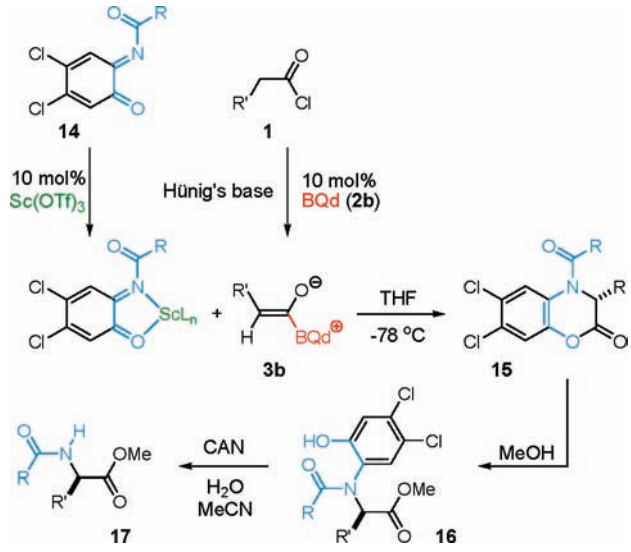


FIGURE 10. Amino acid derivatives from the standard bifunctional reaction (red indicates the absence of metal).

SCHEME 11. Bifunctional QI Reaction To Form α-Amino Acid Derivatives, R = *p*-NO_2−Ph



provided increased yields. We believe the Lewis acid coordinates to the quinone imide to enhance its electrophilicity, thereby increasing the reaction rate and ultimately the yield. We compared several substrates in the $Sc(OTf)_3$ cocatalyzed bifunctional system and found considerably increased yields (up to a 42% increase), and once again, all products were nearly enantiopure (Figure 10).

5. Conclusion

As these examples demonstrate, chiral organic catalysts and Lewis acids may combine to form systems of great power and potential. Most remarkable is the range of metal complexes that can be employed, virtually spanning the Periodic Table

from lithium to indium. For our own part, we have contributed to this rapidly growing field with three separate methods that combine cinchona alkaloid nucleophiles with Lewis acids, to increase the reaction rates and yields with no loss in selectivity, through simultaneous activation of both nucleophilic and electrophilic reagents.

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FOOTNOTES

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