Advances in the Catalytic, Asymmetric Synthesis of β-Lactams

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ABSTRACT
In this Account, we illustrate our contribution to the catalytic, asymmetric synthesis of β-lactams through a flexible [2 + 2] cycloaddition strategy. We also explore the scope of our methodology and comment on future directions.

Introduction

First synthesized in 1907 by Staudinger,[1] the four-membered cyclic amide derivatives of 3-aminopropionic acids known as β-lactams did not come to the fore in organic chemistry until Fleming's landmark 1929 discovery of penicillin.[2] The resulting recognition of the β-lactam moiety as the key pharmacophoric component of the penam antibiotics initiated a flurry of synthetic activity. Today, thousands of chiral compounds containing β-lactam rings are known. Whether isolated from natural sources or chemically synthesized, they are marked by high efficacy and safe toxicological profiles, so more than 70 years after its initial discovery, penicillin and its derivatives are still the most commonly used antibiotics.[3] Unfortunately, the war with microorganisms is relentless and has led to significant bacterial resistance to the most commonly used members of this class of antibiotics.[4] In turn, researchers have responded with investigations into novel β-lactams, ones stable to β-lactamases, for example, which retain high potency and broad activity both in vivo and in vitro.[5] So the battles continue.

Outpacing and overshadowing the growing difficulties in using β-lactams as antibiotics are the many important nonantibiotic uses developed in recent years.[6] Some of the most notable recent discoveries concern the development of potential quality-of-life applications such as mechanism-based serine protease inhibitors (Figure 1)[7] of elastase,[8] cytomegalovirus protease,[9] thrombin,[10] prostate-specific antigen,[11] β-lactamase,[12] and cell metastasis[13] and as inhibitors of acyl-CoA cholesterol acyl transferase.[14] Clearly, β-lactams remain a worthwhile goal for the synthetic organic chemist, and in this Account, we illustrate our contribution to the catalytic, asymmetric synthesis of nonnatural, pharmaceutically active β-lactams, by employing a flexible and inexpensive [2 + 2] cycloaddition strategy.

Intensive research has generated numerous methods of synthesizing the β-lactam skeleton.[15] Commonly, the lactam ring is formed through either ketene−imine cyclizations[16] (the Staudinger reaction) or ester enolate−imine condensations[17] (the Gilman−Speeter reaction). However, other notable methods are sometimes employed, including photoinduced rearrangements,[18] and radical cyclizations.[19] Despite all of these synthetic methods for obtaining achiral or racemic β-lactams, until recently asymmetric methodology has remained scarce, largely limited to chiral auxiliary based systems.[20] While effective, these methods require additional steps to add and then remove the chiral auxiliary, which usually cannot be reused without significant recovery and purification efforts. It occurred to us that a more general methodology based on asymmetric catalysis would be extremely useful in the development of chiral β-lactam chemistry. We chose to focus our efforts on a catalytic modification of the highly effective Staudinger method, due to the ready availability of substituted imines and the relative ease of generating ketenes and ketene equivalents from commercially available acid halides. In fact, "highly effective" is insufficient to convey the potential speed of the standard Staudinger reaction.[21] Background rates are often so high using this process that it was necessary for us to first *break* the reaction before we could *fix* it to render it catalytic, not to mention asymmetric.

Predating our work on a more general catalytic, asymmetric β-lactam synthesis, a number of other researchers contributed very significantly to developments in the field. Doyle's rhodium-catalyzed C−H insertion into diazoacetamides,[22] Alper's rhodium-catalyzed ring expansion−carbonylation of aziridines,[23] Tomioka's amine-catalyzed condensation of ester enolates and imines,[24] and Miura's pioneering catalytic, asymmetric variations on the Kinugasa reaction[25] have all provided us with novel access to the β-lactam skeleton. Following our work, Fu has published his interesting findings on the cycloaddition of disubstituted ketenes and imines catalyzed by a planar

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Anthony Weatherwax has been awarded several baccalaureate degrees from State University of New York (SUNY), Albany, Arizona, and Maryland. He joined the Lectka group in 2001 and is currently investigating methods for the asymmetric synthesis of β-lactams.

Andrew E. Taggi obtained his B.S. from Cornell University in 1998. His graduate research with Tom Lectka concerned the development of new methodology for the use of ketenes in catalytic, asymmetric synthesis for which he received an ACS DOC Fellowship, sponsored by Organic Reactions, Inc. A.T. is currently a postdoctoral associate with Professor Jerrold Meinwald (Cornell).

Tom Lectka is a native of Detroit who was graduated from Oberlin College in 1986. He obtained his Ph.D from Cornell University, where he worked in John McMurry's laboratory. After a Humboldt Fellowship to study at Heidelberg, he joined Dave Evans's laboratory at Harvard University as a postdoc. In 1994, he began at Johns Hopkins University, where he was promoted to Professor in 2002. His research interests broadly span problems in catalysis and mechanistic organic chemistry.

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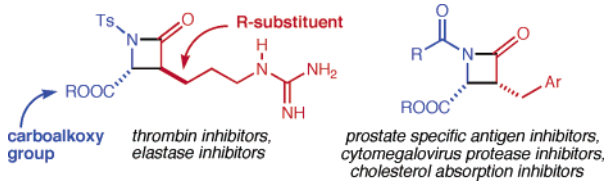


FIGURE 1. General structures for serine-protease β-lactam inhibitors.

chiral nucleophile to form optically active trisubstituted β-lactams.[26] He has further expanded upon the scope of the asymmetric Kinugasa reaction by using diverse nitrones and acetylenes in conjunction with a chiral copper complex.[27]

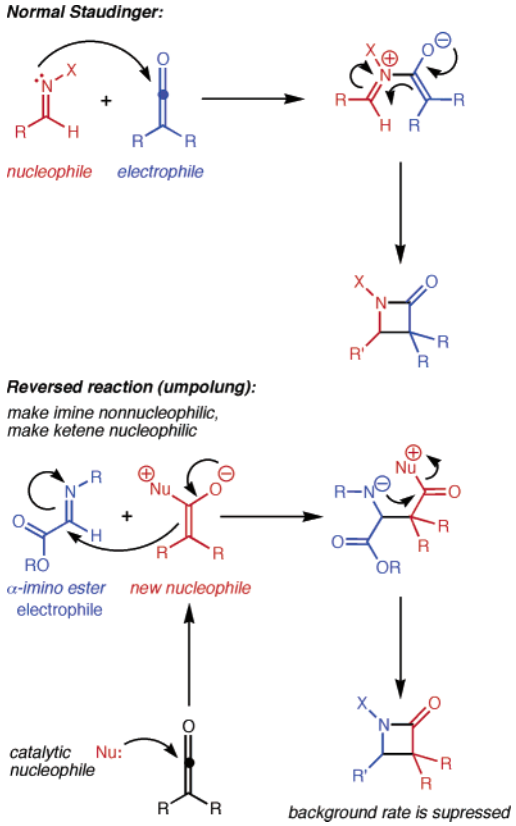
What follows is an account of our research into the chiral nucleophile-catalyzed cycloaddition of ketenes (and derived enolates) and imines. It is by no means intended as a comprehensive review of the emerging field, but a more personalized story of our experiences and results. It has been divided according to both the synthetic methodology employed and potential applications: catalytic, asymmetric cyclization of ketenes/zwitterionic enolates and imines, bifunctional systems, the synthesis of β-aspartic acid derivatives from β-lactams, and asymmetric catalysis on sequentially linked columns. While our own work, combined with that of others, shows that significant strides have been made in the field of enantioselective β-lactam synthesis, ultimately the development of novel, catalytic, asymmetric reactions has just begun, and further advances are forthcoming.

Catalytic, Asymmetric [2 + 2] Cyclization of Ketenes/Zwitterionic Enolates and Imines

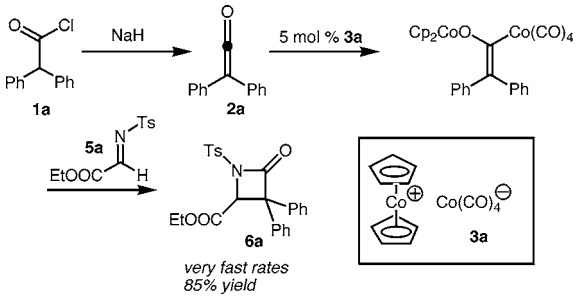
Our interest in catalytic β-lactam chemistry arose several years ago in a roundabout way. We noticed at that time that many of the new clinically active β-lactam serine protease inhibitors contained a carboalkoxy-substituent at the β-carbon and could be described as nonnatural derivatives of aspartic acid. We recognized immediately that such β-lactams could be imagined to arise from a Staudinger-type cyclization of ketenes and α-imino esters[28] (which we had very fruitfully used in the asymmetric synthesis of amino acid derivatives catalyzed by chiral Lewis acids).[29]

The Staudinger reaction is known as a high background rate process; normally no catalyst is needed to initiate smooth reaction at low temperatures. Therefore, for the catalytic, asymmetric reaction to work, we had to "break" the classical Staudinger pathway (in which the imine nitrogen acts as a nucleophile toward the ketene) and restart it with a reaction of reversed polarity (umpolung) in which the ketene and imine switch roles; namely, the imine becomes an electrophile and the ketene a nucleophile. The alteration of the imine polarity was accomplished through the addition of an electron-withdrawing group to the normally nucleophilic nitrogen and a carboalkoxy substituent to the imine carbon. Conversion of the ketene to a nucleophile lies at the heart of our catalytic methodology. Reversal of ketene polarity was accomplished through the use of a nucleophilic catalyst that could reversibly combine with the ketene through attack at the reactive carbon center to form a zwitterionic enolate.[30] Such a species would be capable of subsequent nucleophilic attack on the electrophilic α-carbon of the imine to yield, after displacement of the nucleophile to regenerate the catalyst, the desired lactam product (Scheme 1).

Scheme 1. Staudinger Reaction "Umpolung"

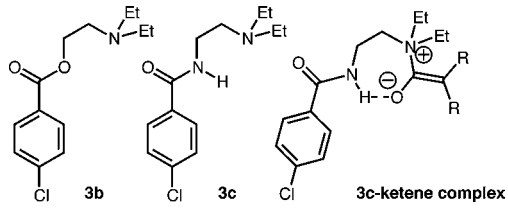


Scheme 2. Cobalt Complex Catalyzed Bifunctional β-Lactam Formation



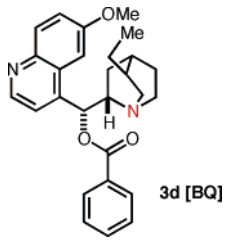
At the genesis of the project, we had investigated low-valent cobalt carbonyl anions as active acylation catalysts. We found that the unusual bifunctional organometallic complex cobalticenium tetracarbonyl cobaltate (**3a**) contains both a nucleophilic anion (Lewis base) and cation (Lewis acid) that could act in concert with each other (Scheme 2).[31] Applying this methodology to the scenario described above, we found that complex **3a** was a superior catalyst for the cyclization of disubstituted ketenes and imino esters, giving β-lactams in good yield (up to 85%) with fast rates.

However, questions of practicality arose when we screened chiral, low-valent cobalt complexes, a fact that encouraged us to explore other easy-to-prepare chiral nucleophiles with catalytic activity. We discovered that a diverse array of catalysts, including other metal-based nucleophiles, phosphites, and amines promoted the reaction of ketenes with α-imino ester **5a** in moderate to good yields (45−65%). As a first step toward an asymmetric β-lactam synthesis, we attempted to catalyze the reaction diastereoselectively, using disubstituted ketenes as our substrates. Our theory was that a catalyst containing a nucleophilic center in tandem with an electrophilic center (e.g. a hydrogen bond donor) could potentially rigidify the expected intermediate activated complex and thus potentially afford products in higher diastereomeric ratio (dr).[32] Experiments with the catalysts **3b** and **3c** supported



this theory. The catalyst capable of hydrogen bonding (**3c**) consistently outperformed the catalyst with only a nucleophilic center (**3b**) and provided β-lactam products with high diastereoselectivities (3:97 cis/trans ratio for **3c** vs 33/66 for **3b**). We believe that this difference is attributable to the rigid **3c**−ketene complex made possible by the adjacent amide hydrogen bond donating site, which is unavailable in the corresponding ester linkage.

Given the successful development of the diastereoselective amine catalysts, we were prompted to screen optically active cinchona alkaloid derivatives as potential enantioselective and diastereoselective catalysts as well.[33] We were pleased to discover that when we tried an acyl derivative of quinine, namely, benzoylquinine **3d**, with diphen-



ylketene **2a**, β-lactam **6a** was obtained in high enantioselectivity (99% ee) albeit in only modest (36%) yield.[34]

One of the most challenging aspects to this new chemistry, aside from the design of the catalytic system, was the development of methodology for using highly reactive monosubstituted ketenes.[35] These intermediates must be usually formed in situ and at reduced temperatures to prevent unwanted side reactions, most commonly dimerization and polymerization. While we found hindered amine bases such as Hünig's base inadequate, the combination of a cinchona alkaloid derivative such as benzoylquinine (BQ) and the nonnucleophilic amine base, proton sponge **4** (PS), as a proton sink worked handily,

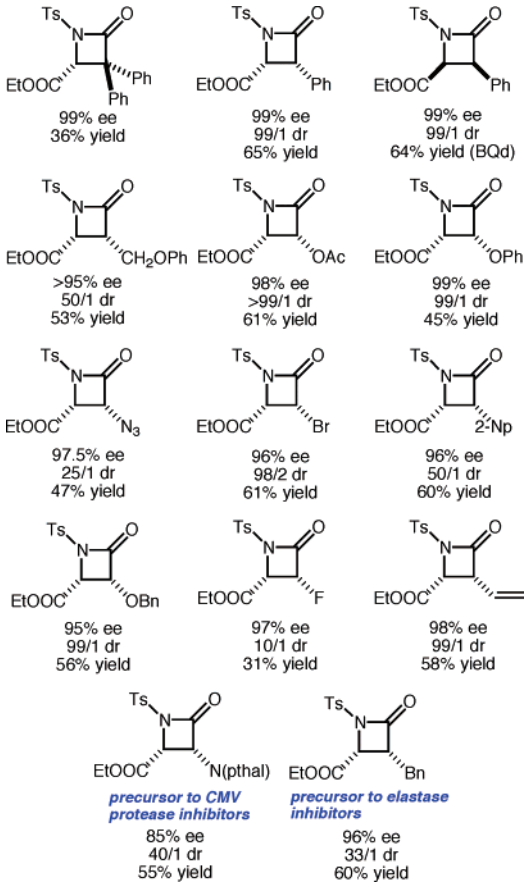
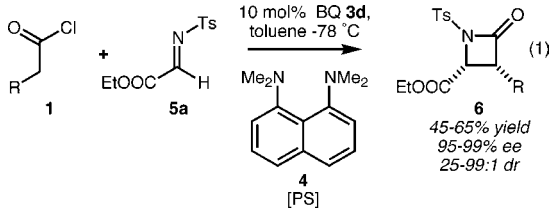


FIGURE 2. Diverse β-lactams synthesized through the catalytic, asymmetric cycloaddition reaction.

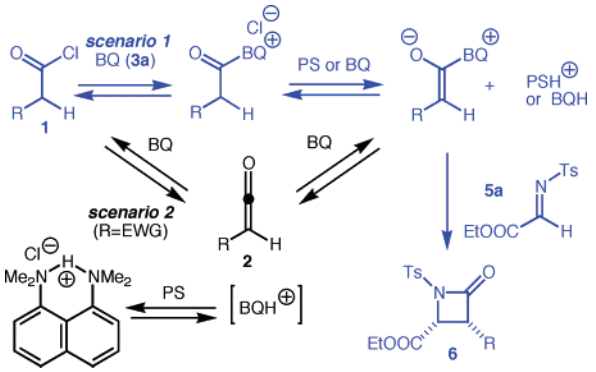
forming the β-lactam products **6** in very high ee and dr from a variety of acid chloride substrates (eq 1).[36] This



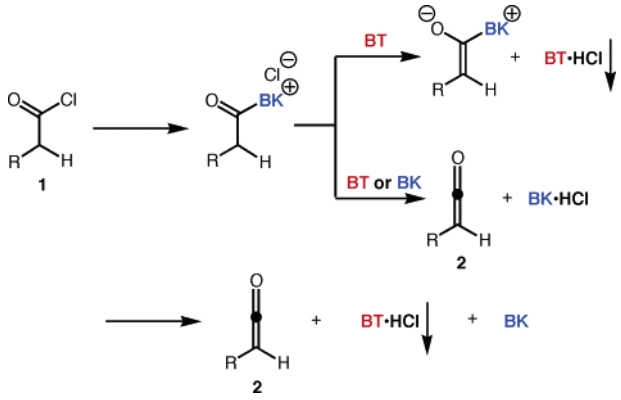
methodology is compatible with aryl-, alkyl, alkenyl-, halo-, azo-, and oxy-substituted ketenes (Figure 2). Of note, we were successful in synthesizing both a phthalimido- and a benzyl-substituted β-lactam, which have been identified as precursors to cytomegalovirus protease inhibitors and human leukocyte elastase inhibitors.[8,9]

We examined the mechanism of the reaction through a series of kinetics studies (Scheme 3). For the reaction of an acid chloride **1** with imino ester **5a** catalyzed by BQ and using PS as the stoichiometric base, we determined that the acylation of BQ by the acid chloride/ketene is the rate-determining step, followed by a series of fast cyclization steps with the imino ester. In some cases, the rate of product formation exceeds that of ketene formation when measured independently. This surprising discovery requires that enolate generation in these cases *occurs directly* from the acid chloride. Discrete ketene formation is consequently circumvented!

Scheme 3. Mechanism of β-Lactam Formation with Proton Sponge



Scheme 4. Ketene/Enolate Formation via Shuttle Deprotonation



The "ketene-free" mechanistic path is pictured in blue in Scheme 3. The mechanism described would also be dependent to some degree on the acid chloride substrate chosen. For acid chlorides with electron-withdrawing substituents, dehydrohalogenation to form the ketene prior to reaction with the catalyst predominates with proton sponge base. When using other stoichiometric bases for lactam formation (phosphazene bases, NaH, etc.), discrete ketenes are synthesized in a "preformation" step.

This mechanism also leads to a semantic question posed by a referee to our original communication: in light of what we have discovered, is this process still to be considered a Staudinger reaction? Even though the starting materials are the same, the mechanism is radically different.

PS does not directly act as a base in the dehydrohalogenation of the acid chloride substrate. Instead, through a mechanism we refer to as "shuttle deprotonation" (Scheme 4), the catalyst takes on the additional role of the kinetic base (BK) in the reaction. PS then plays the role of the thermodynamic base (BT), either by abstracting an α-proton from the acylammonium intermediate or by deprotonating the BQ and regenerating the catalyst. In this way, BQ acts not only as the chiral catalyst in the ketene/imine cyclization but also as a catalytic "shuttle" between the acid chloride proton source and the PS proton sink.

Examining the shuttle base principle further, we found that we could employ other less expensive thermodynamic bases in place of PS and still achieve the same results. However, the occurrence of "clean" ketene formation

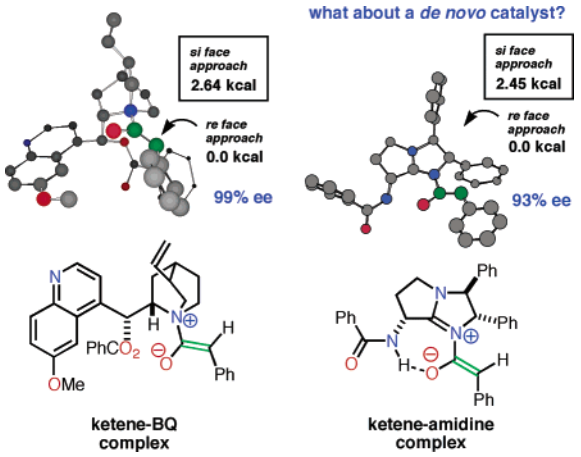
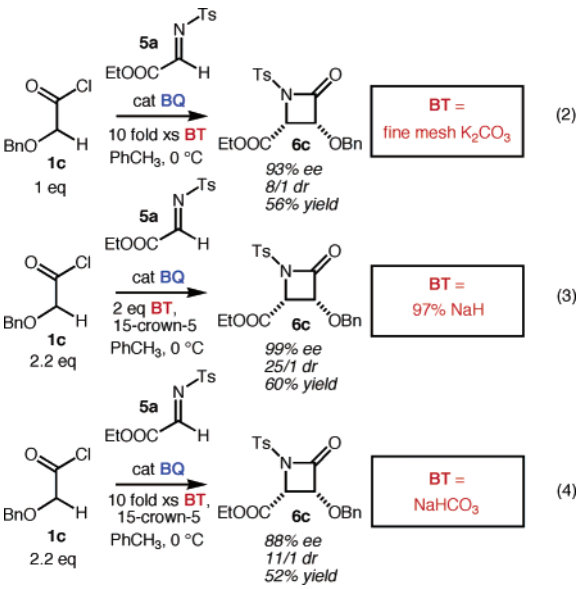


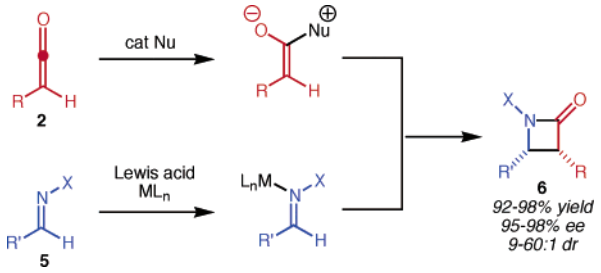
FIGURE 3. Stereochemical models of the putative zwitterionic intermediate of phenylketene with natural and designed reaction catalysts.

differs among the methods. With either, potassium carbonate (eq 2) or sodium hydride (eq 3) as the stoichiometric base, a ketene preformation step is required for the reaction to proceed satisfactorily, whereas with PS or sodium bicarbonate[37] (eq 4), ketene preformation is not a prescribed requirement, and in some instances, as we have demonstrated, ketenes may play little or no role.



In addition to our kinetics study, molecular mechanics calculations using the Macromodel program proved to be useful for further illumination of the factors affecting the β-lactam forming reaction. The results predicted both the sense and degree of optical induction.[38] For example, in the case of the model of the ketene−BQ complex derived from the reaction of benzoylquinine (BQ) with phenylketene (Figure 3), the calculation was performed using a modified AMBER force field and demonstrated that the *re*-face of the ketene enolate was open to approach of the imino ester electrophile, whereas *si*-face approach is much more hindered, over 2.5 kcal/mol higher in energy. In our experience with this force field, an energy difference on

Scheme 5. Bifunctional Lewis Acid/Nucleophile Catalysis



this scale is a good predictor of high enantioselectivity (>90%).

The predictive power of these calculations also inspired us to design a de novo catalyst. Combining molecular modeling calculations with our earlier observations on the positive influence of a stabilizing hydrogen bond to the enolate, we synthesized a chiral, nucleophilic amidine. The catalyst worked exactly as predicted, giving the β-lactam product in up to 93% ee. This success has impelled us to develop these catalysts (which in some cases are more nucleophilic than BQ) further, and reports will be published in due course.

A Bifunctional Catalyst System Using a Tandem Lewis Acid/Nucleophile Pair

Inspired by our previous work using Lewis acids to catalyze reactions of imino esters with enol silanes, allyl silanes, silyl ketene acetals, and alkenes,[39] we sought to combine these two methodological approaches into a single bifunctional system (Scheme 5). Our impetus for this was simple—although cinchona alkaloid derivatives afforded excellent ee and dr in β-lactam products, the yields were often moderate due to byproduct formation. Our hope was that, by enhancing the reactivity of the imine, we could improve the chances of a successful reaction with the weakly nucleophilic zwitterionic enolate/catalyst complex. A major concern in this work was the possibility of self-quenching reactions between the nucleophile and the Lewis acid, which would lead to a catalyst that was "dead all around". One promising precedent had recently been reported by Aggarwal, which illustrated that tertiary amines could be successfully combined with metal salts as effective catalysts for the notoriously sluggish Baylis–Hilman reaction.[40]

Our initial attempts at a bifunctional system using metal salts "off the shelf" were disappointing. As an initial screen, we employed 10 mol % of metal salts such as Mg(OTf)$_2$, $CuClO_4$·(MeCN)$_4$ (which works very well for amino acid synthesis), and La(III) salts (Aggarwal's precedent) in a solution of BQ (10 mol %), 1 equiv of PS as a stoichiometric base, imino ester **5a**, and an acid chloride, **1**, in a standard reaction in toluene at −78 °C to form β-lactam **6** (eq 5).[41] The observed yields were decreased,

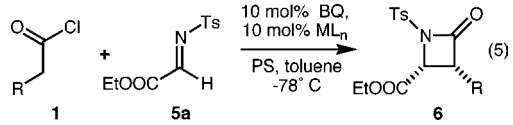
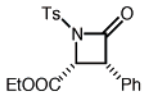
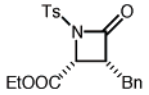
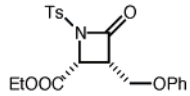
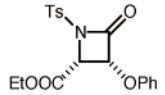
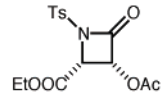
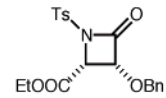


Table 1. Comparative Yields of β-Lactam through the Use of a Tandem Bifunctional Lewis Acid/Nucleophile System

entry	product	yield before	yield after	ee	dr (cis/trans)
1		65%	95%	98%	60/1
2		60%	94%	98%	9/1
3		53%	93%	96%	12/1
4		45%	93%	97%	22/1
5		61%	92%	98%	34/1
6		56%	98%	96%	11/1

in some instances due to apparent binding of BQ to the metal. It seemed that our fears of self-quenching were justified. Indeed, in the case of the combination of BQ and $CuClO_4$·(MeCN)$_4$, the solution turned blue-green in color, indicating the formation of a BQ·Cu(II) complex in which Cu(I) had been oxidized, in hindsight an expected outcome.

We continued with our screening and were pleased to find that the use of the triflates of Sc(III), Al(III), Zn(II), and In(III) (10 mol %) along with BQ (10 mol %) resulted in significantly increased chemical yields in the asymmetric synthesis of β-lactams (Table 1). Of this series of metals, In(OTf)$_3$ (95% yield) was the best performer, followed by Zn(OTf)$_2$ (85% yield), while Al(OTf)$_3$ and Sc(OTf)$_3$ were found to be only slightly less effective (78% and 80% yield, respectively). In terms of practical use, one's choice of cocatalyst might be dictated by cost as much as effectiveness, Zn(OTf)$_2$ salts being cheapest while In(OTf)$_3$ salts are more moderately priced.

Next, we began to address the intriguing mechanistic reasons for increased yields. At this time, we are entertaining three possible scenarios. The first, and the one we had originally envisioned, is that the metal binds to the imine, activating it to subsequent attack by the nucleophilic enolate/catalyst complex (Figure 4, structure **A**) and enhancing the rate of product formation. This scheme is consistent with the mechanistic model we had developed in our previous work on Lewis acid-catalyzed reactions of imino esters.[36] Our second scenario is a postulated stabilization of the zwitterionic enolate by the metal, leading to greater chemoselectivity and making the enolate more thermodynamically favored, supposing an equilibrium between ketene and enolate (Figure 4, structure **B**).[42] The third scenario is a blending of the first two. It supposes that structures **A** and **B** occur in concert with

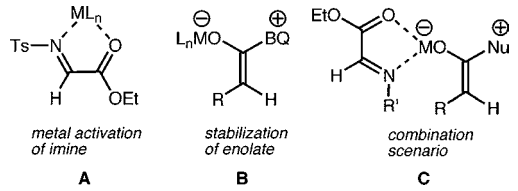


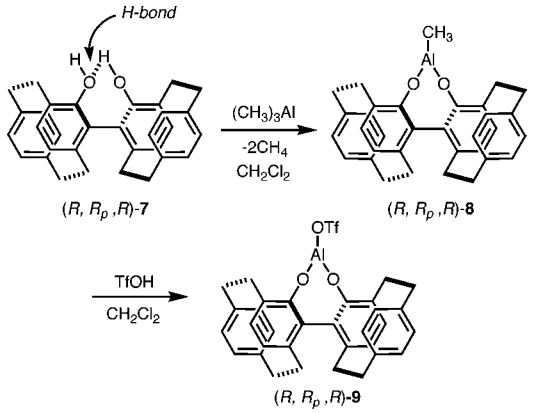
FIGURE 4. The three proposed reactive assemblies for the bifunctional Lewis acid/nucleophile catalysis.

the metal organizing both enolate and imine into a termolecular activated complex (Figure 4, structure **C**). Subsequent kinetics studies showed that the addition of metals had no affect on the rate of acid chloride consumption, an observation consistent with all three models. They also showed an increase of 30−40% in the rate of product formation, demonstrating a significant improvement in the chemoselectivity of the reaction and again consistent with all three models. However, when the results of our research into catalytic asymmetric α-halogenation[43] are taken into account, all three scenarios no longer appear equal. In these studies, no comparable yield increase was observed upon addition of Lewis acids (the halogenating agent is not anticipated to bind effectively to a metal) leading us to postulate that chelation to the imine (Figure 4, structures **A** or **C**) is the most probable scenario. With these initial observations in hand, the mechanism becomes somewhat clearer, but a precise mechanistic picture requires further investigation.

Note that while in some cases the bifunctional system gives reaction yields of more than double the non-metal-catalyzed reactions, occasionally a side effect is reduced diastereoselectivity. Whereas the normal BQ-catalyzed reaction offers up to 99:1 dr, the maximum dr for the metal-catalyzed reaction is 60:1. While in some cases, the greatly increased yields compensate for this, in others it is a distinct disadvantage. As a possible remedy, we considered employing various ligand−metal complexes to increase the dr. We examined a number of candidates, but each time met with limited success. We did, however, note that the steric bulk of the ligand (and ultimately, the metal complex) can have a positive effect on reaction dr. Serendipitously, for an unrelated project, we had synthesized a new sterically encumbered biaryl ligand system (Scheme 6). The chiral bulk in ligand (R,R_p,R)-**7** not only projects "horizontally" back from the metal center but also projects "vertically" up and down from the catalytic center, in contrast to binol, which projects much less steric bulk in the vicinity of the metal. We hoped that such a bulky ligand would have a pronounced effect on the diastereoselectivity (and enantioselectivity) of the bifunctionally catalyzed reactions. Our ligand, (R,R_p,R)-**7**, constitutes the first C_2-symmetric bis(cyclophane) diol, a system incorporating both axial ("horizontal") and planar ("vertical") chiral elements.[44]

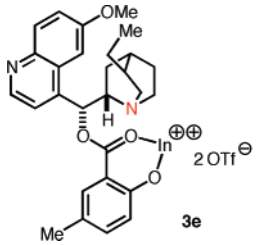
Complex (R,R_p,R)-**9** was generated through one of two methods, either the procedure outlined in Scheme 6 (treatment of (R,R_p,R)-**7** with trimethylaluminum followed by triflic acid) or in situ generation through treatment of

Scheme 6. Synthesis of the First C_2-Symmetric Bis(cyclophane) Diol Ligand Complex



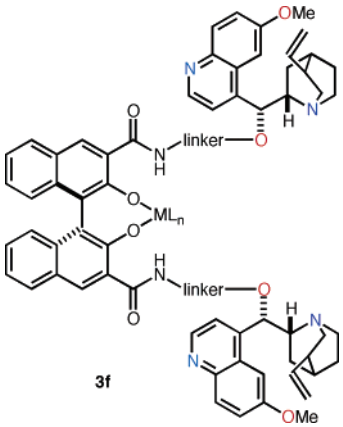
(R,R_p,R)-**7** with $Al(OTf)_3$ and PS. We screened complex (R,R_p,R)-**9** (10 mol % BQ, PS as base) in the formation of β-lactam under standard conditions (toluene solvent, −78 °C), and found that the diastereoselectivity of the reaction improved dramatically, to greater than 99:1. The enantioselectivity was excellent at 99%, as was the yield (85%). Unfortunately, the utility of the cyclophane ligand (R,R_p,R)-**7** was limited to some extent by apparently poor binding to the "hot" metals (scandium, zinc, and indium) normally employed in our bifunctional system. Future studies with this catalyst system would logically pair the chiral complex with an achiral nucleophile. It is our hope that such a system could lead to the elusive *trans*-substituted β-lactams, a goal that has proved difficult to achieve when simply using a chiral nucleophilic catalyst.

As a logical extension of the bifunctional system described above, we have also designed homogeneous complexes in which the chiral nucleophile and the Lewis acid are combined in a single unit. Such catalysts are interesting not only for their potential to enhance this particular reaction but also for their analogy to enzymes, which often contain multiple catalytic centers. For example, we synthesized the chelating cinchona alkaloid derivative **3e** in



two steps from quinine. The salicylate metal complex, containing a catalytically active quinuclidine moiety, afforded products in 85% yield, 99% ee, and 11:1 dr, results that approach our findings with bare metal salts and facilitate mechanistic studies that prove difficult with partially soluble metal salts.

Given the reduced dr obtained with the salicylate complex, we designed the novel homogeneous catalyst **3f**, which, while still incorporating the BQ moiety, offers more



steric bulk as a chiral ligand. Preliminary tests have shown improved dr (20:1) with similar yields and ee's; further intensive study of the system is forthcoming.

β-Substituted Amino Acids from β-Lactams

While in some cases the Ts group may be conserved in the β-lactam product, we are aware that it is not an ideal solution to many chemical problems. Initially, we had developed a new method using SmI_2 that cleanly deprotected the β-lactam without eroding its enantiopurity.[36] Later we sought to explore the use of imines with different electron-withdrawing protecting groups on nitrogen. For example, *N*-acyl-β-lactam products would be much more useful for a number of applications. In addition, *N*-acyl-β-lactams are also very susceptible to nucleophilic ring opening by amines and alcohols, providing potential entry into classes of β-amino acid products.[45] We recently reported a new method for the catalytic, asymmetric synthesis of β-substituted aspartic acid derivatives in which the chiral nucleophilic catalyst serves up to *five* distinct roles in a one-pot procedure: catalytic dehydrohalogenation of acid chlorides **1** to form ketenes **2** (step 1, Scheme 7); catalytic dehydrohalogenation of α-chloroglycines **10** to form the corresponding imines **5b** (step 2); catalyzed [2 + 2]-cycloaddition to produce intermediate acyl β-lactams **11** (step 3); nucleophilic ring opening to afford optically enriched β-substituted aspartic acids **12c**, in high enantioselectivity and diastereoselectivity (step 4); and finally, nucleophile-catalyzed transesterification (step 5).[46] When desired, the β-lactam products can be directly isolated before addition of the ring-opening nucleophile at the end of the reaction. We have expanded this methodology to the synthesis of both simple β-amino acids and more complex polypeptides.[47]

Asymmetric Catalysis on Sequentially Linked Columns

In the course of our work on β-lactam synthesis, we had occasionally turned to the use of solid-phase bases as dehydrohalogenating agents to produce ketene solutions free from contaminants. The utility of this solid-phase approach sparked our interest sufficiently to entice us to attempt the entire β-lactam synthesis using such methodology. We named this new strategy sequential column

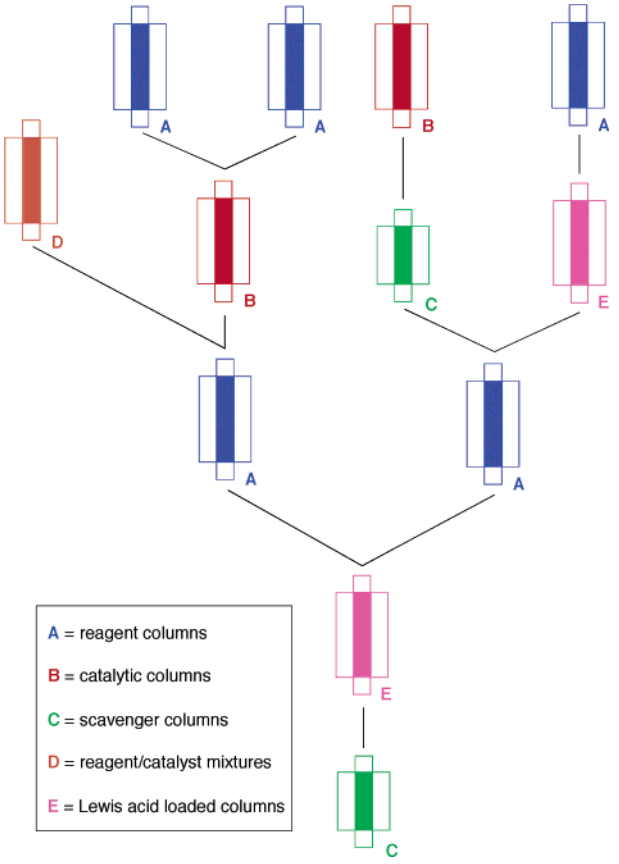
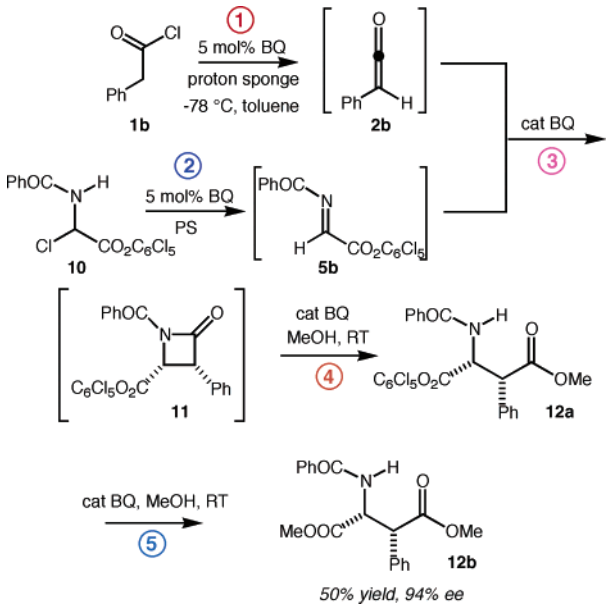


FIGURE 5. Working concept for a "synthesis machine."

Scheme 7. A Catalyst That Promotes Ketene (Enolate) Formation, Imine Formation, Cycloaddition, Ring-Opening Alcoholysis, and Transesterification



asymmetric catalysis, or sequential CAC.[48] Our trials with the CAC system proved fruitful, and these successes opened our eyes to its potential for broad application. We envision the development of a system such as the one pictured in Figure 5, wherein columns loaded with reagents and catalysts affixed to solid supports are used

to systematically modify and combine multiple substrates. The reaction sequence is orchestrated via a regulated flow system, eventually yielding pure product without the need for intermediate isolation or purification steps; in essence, a "synthesis machine." We are actively pursuing this as the ultimate goal of our sequentially linked column assembly methodology.

Conclusion

It is clear that with the recent discovery of broad classes of new biologically active β-lactams, the field remains vigorous. Future research directions include the development of methodology for the catalytic asymmetric synthesis of *trans*-β-lactams, β-lactam-containing (and -derived) natural products, and inhibitors of interest.

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