α-Imino Esters: Versatile Substrates for the Catalytic, Asymmetric Synthesis of α- and β-Amino Acids and β-Lactams

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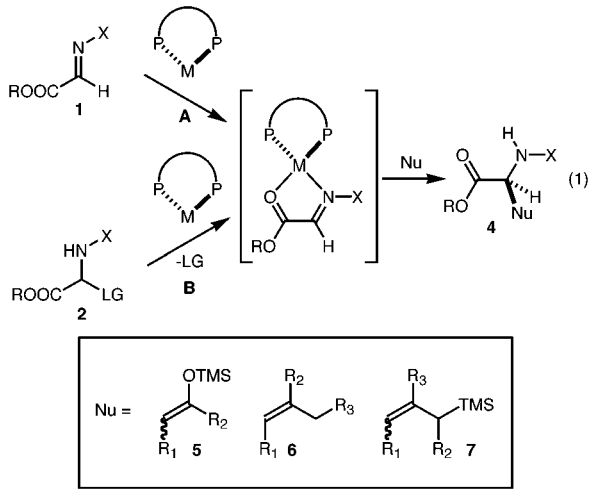
ABSTRACT

The catalytic asymmetric addition of organic nucleophiles to α-imino esters has emerged as one of the most promising and intensely investigated routes to optically enriched α- and β-amino acid derivatives and β-lactams. The importance of α-imino esters stems not only from the vast appeal of the potential product classes,[1] but also from their remarkable reactivity as highly electrophilic imines. With each passing year, the number of publications concerning the asymmetric alkylation of imino esters grows significantly. The asymmetric alkylation of imines[2] and N,O-acetals has been in itself a subject of intense interest.[3] In this Account, we wish to illustrate our contribution to this timely field, as well as to highlight the seminal contributions of others.

1. Introduction

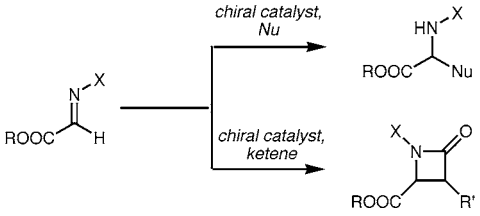
α-Imino esters have been known in synthetic organic chemistry for many years, having been used in imino ene reactions as precursors to amino acids in notable work by Weinreb and Tschaen in 1982.[4,5] In the meantime, strides were made in asymmetric reactions of these substrates, especially those involving chiral auxiliaries.[6]

It occurred to us in the mid 1990s that α-imino esters would make excellent electrophilic substrates for catalytic, asymmetric reactions. We envisaged a Lewis acid coordinating both the imine N and the ester O atoms simultaneously in a chelate interaction that could enhance selectivity:



Since that time, a profusion of attractive new procedures has been developed to exploit the electrophilic nature of α-imino esters for catalytic, asymmetric synthesis. For purposes of clarity, we subdivide this account into three parts: α-imino ester synthesis, α-amino acid synthesis, and the synthesis of β-lactams and β-amino acids (Scheme 1). A mechanistically interesting set of asymmetric catalysts has been employed to effect these new transformations, ranging from chiral Lewis acids and catalytic metal enolates to all-organic catalysts (including alkaloid derivatives and amino acids). It is clear that the exploitation of α-imino esters for catalytic, asymmetric reactions has just begun, and further advances are on the horizon.

Scheme 1. General Route to Amino Acids and β-Lactams



2. The Synthesis of α-Imino Esters

α-Imino esters can either be synthesized prior to use or in situ, with the stability of the imine often acting as the deciding factor. For example, imine **1a**, which is stable for extended periods of time, is synthesized by refluxing ethyl glyoxylate with *p*-toluenesulfonyl isocyanate in toluene for 5 days (Scheme 2).[7] The reaction time can be decreased by addition of a catalytic amount of $AlCl_3$.[8] In the case of imine **1b** where the *N*-protecting group is more electron rich, such as in the case of *p*-methoxyphenyl (PMP), the imine can be synthesized through condensa-

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Ahmed M. Hafez received his B.S. (1997) and M.A. (1998) in chemistry from the College of William and Mary in Virginia, where he studied host−guest and carbohydrate chemistry with Professor Chris Abelt. He joined Professor Tom Lectka's research group in 1998, and his Ph.D. research focuses on catalytic asymmetric synthesis with ketenes, including innovative work on the first catalytic, asymmetric α-halogenation, and the development of asymmetric catalysis on sequentially linked columns and continuous flow reaction systems.

Tom Lectka is a native of Michigan who was graduated from Oberlin College in 1985. He attended graduate school at Cornell University in John McMurry's laboratory. 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, and "switchable" mechanisms in synthesis.

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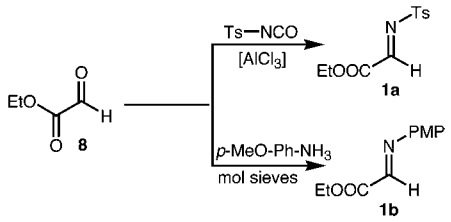
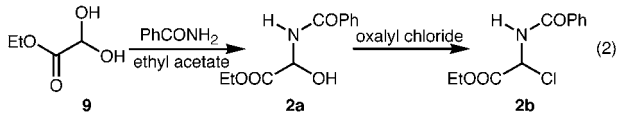
Scheme 2. Synthesis of α-Imino Esters



tion of the aldehyde **8** with the free amine in the presence of a dehydrating agent.[9]

Due to the high reactivity of *N*-acyl imino esters, they are not easily purified and thus are often made in situ from the corresponding α-haloglycine.[10] For example, the hydrate of ethyl glyoxylate **9** is refluxed in ethyl acetate with benzamide to yield *N*,*O*-acetal **2a**, which is then chlorinated with oxalyl chloride to form α-haloglycine **2b**:

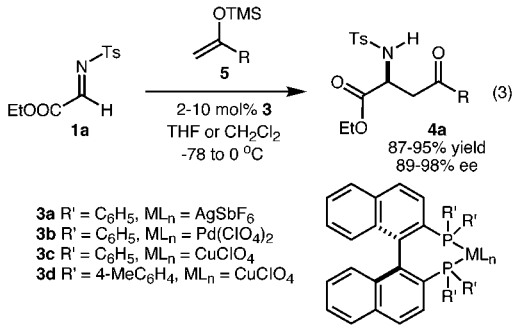


(2)

The addition of a base converts **2b** to the N-acyl imine.[11] *N*-Tosyl imines can also be made according to similar procedures from the appropriate α-haloglycine or even the *N*,*O*-acetal.

3. Catalytic, Asymmetric α-Amino Acid Synthesis

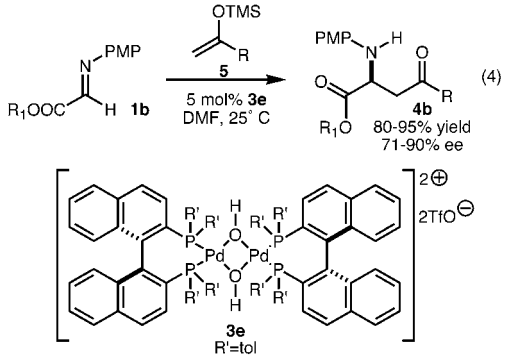
Initially, we decided to investigate the Lewis acid-catalyzed alkylation of α-imino esters with enol silane nucleophiles. The first and most enduring lesson we learned upon initiating our investigations into catalytic, enantioselective alkylations of α-imino esters was the importance of the substituent on nitrogen. We first chose to investigate *N*-silyl α-imino esters with the view that the silyl group would be easily removed in a subsequent deprotection step. However, the reaction of the *N*-silyl α-imino esters with enol silane **5** catalyzed by a number of phosphine-based metal complexes **3** at −78 °C led exclusively to racemic products, a fact that we attributed primarily to high background rate. The situation was transformed when we investigated tosyl imino ester **1a** and found that chiral bis(phosphine) copper complexes could catalyze its alkylation by enol silanes in high enantioselectivity for a variety of substrates:



(3)

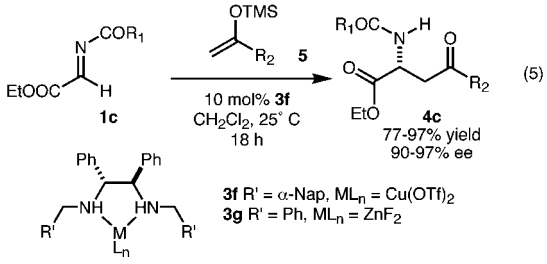
The complexes **3a**, **3c**, and **3d** were screened, determining that **3d** performed exceptionally well, giving high yields (95%) and selectivities (98% ee) even when this reaction was conducted at 0 °C in the presence of only 2 mol % catalyst.[12]

As our initial submission was under review, Sodeoka et al. reported a system that provided an interesting and remarkable contrast to ours.[13] In this case, the authors employed a hydrated Pd(II)-based chiral Lewis acid system that operates through the catalytic generation of enolates:



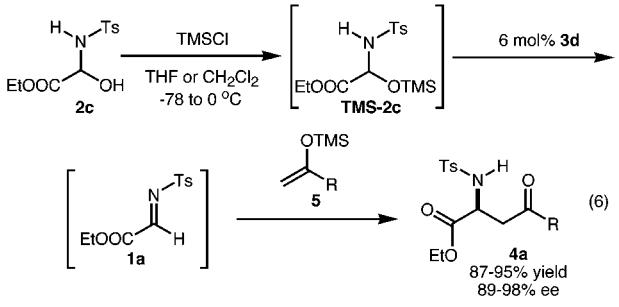
(4)

Kobayashi et al. have reported a useful extension of this methodology to the alkylation of *N*-acyl imino esters by enol silanes to produce *N*-acylated amino acids (eq 5).[14] This new asymmetric methodology was showcased by the synthesis of HPA-12, a ceramide trafficking inhibitor. Kobayashi et al. have recently developed an aqueous variant of this reaction using *N*-hydrazino imino esters and Zn-based catalyst **3g** in a water/THF mixture.[15]



(5)

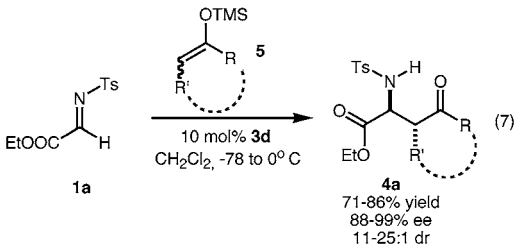
Alternatively, we have also developed a practical, preparative scale synthesis of α-amino acid derivatives by replacing imine **1a** with hydrolytically stable *N*,*O*-acetal **2c** with minimal loss of selectivity or yield:[16]



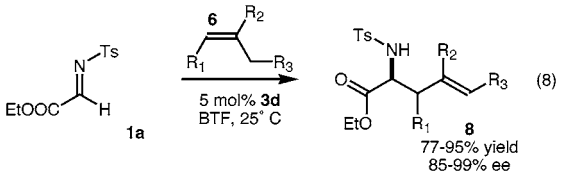
(6)

Enantio- and Diastereoselective Imine Alkylation. It was noted that excellent anti diastereoselectivity (up to 25:1) as well as enantioselectivity (up to 99% ee) can be

obtained in the reaction in eq 7 regardless of the geometry of the enol silane **5**.[17,18] The diastereoselectivity of the reaction was found to be strongly influenced by the nature of the phosphine ligands we employed (PPh_3, BINAP, and Tol-BINAP):

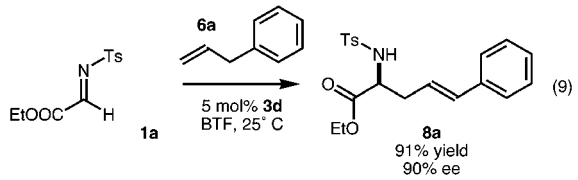


The Catalytic, Enantioselective Imino Ene Reaction. Building on the precedents of Weinreb,[5] we have also developed the first effective example of a catalytic, enantioselective imino ene reaction:[19]

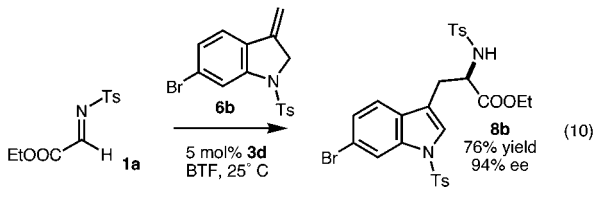


Optimization established that benzotrifluoride (BTF) is the best solvent for the reaction. BTF combines ideal solubilizing power with an aromatic nature that appears to be beneficial to selectivity. The olefins we investigated were subjected to the standard reaction conditions (BTF solvent, room temperature, 5 mol % catalyst, and a 2:1 olefin: imino ester stoichiometry) affording products in excellent yield and enantioselectivity (eq 8).

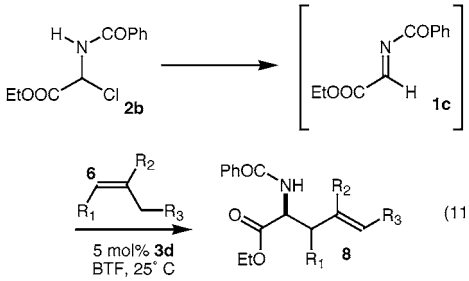
This reaction was used to produce quantities of a protected styrylalanine **8a**, a valuable pharmaceutical intermediate in excellent yield and 90% ee:



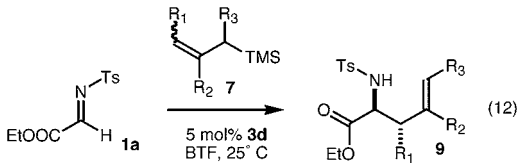
Rich et al. have also used our enantioselective imino ene protocol to synthesize an enantioenriched substituted tryptophan destined for use in the total synthesis of complestatin:[20]



In unpublished work that we believe will prove to be practical, we are employing α-chloroglycines as precursors to N-acyl-α-imino esters for the catalytic imino ene reaction, to produce simple, optically enriched N-acylated α-amino acid products (eq 11), with the intention of extending this methodology to the synthesis of more complex polypeptide chains:

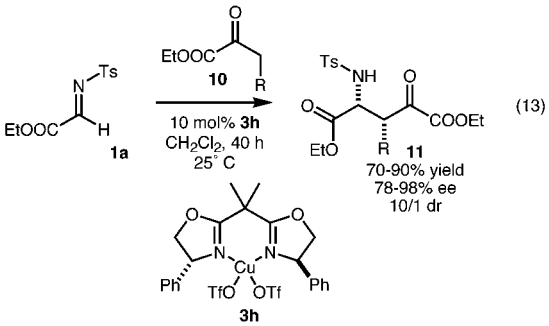


Catalytic, Enantioselective Allylations of α-Imino Esters. As a complement to our work with enol silane and alkene nucleophiles, we have developed a catalytic, enantio- and diastereoselective procedure for the addition of allylsilanes **7** to α-imino ester **1a** catalyzed by complex **3d**, demonstrating the utility of this reaction as an alternative means to homoallylic α-amino acid derivatives **9**:[13b,21]



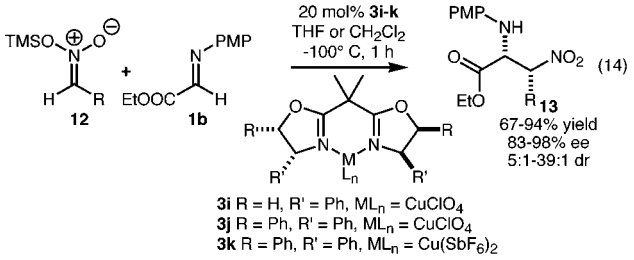
It was found that the presence of aromatic moieties in the allylsilane nucleophile significantly enhances selectivity (raising ee's from 65% to >90% for a number of substrates). Jørgensen has also reported an allylation method using catalyst **3d** affording products in moderate to good ee's.[22]

Other Nucleophiles. With the viability of copper-based catalysts for alkylations of α-imino esters by enol silanes and alkenes established, Jørgensen has expanded the number of nucleophiles that could react with α-imino esters.[23] One different class of nucleophiles included ketones with highly enolizable α-protons. For example, α-protio glyoxyl ketones gave products in high yield and enantioselectivity (70−90% yield, 78−98% ee) when condensed with α-imino ester **1a**:[24]



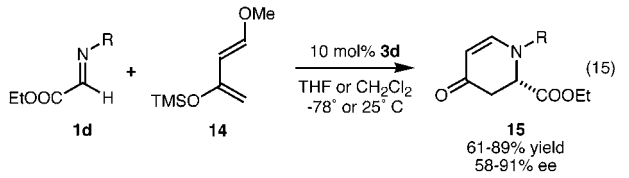
Whether the reaction proceeds in part through the generation of metal enolates was not established, but the enol content of ketones **10** is expected to be significant.

Jørgensen et al. have also reported the catalytic, enantioselective cycloaddition of TMS-nitronates with α-imino esters catalyzed by **3i**−**k**:[25]



High yields and ee's were obtained in the reaction for a variety of substrates, but the appropriate catalyst had to be determined on a case-by-case basis. This principle was extended to develop an enantioselective nitro-Mannich reaction through the use of nitroalkanes, with acidic α-protons, as enolizable nucleophiles.[26]

A catalytic, enantioselective hetero Diels-Alder reaction employing imino ester **1d** with suitable dienes was also reported by Jørgensen:[27]



Enantioselectivities ranged from fair to very good. A number of catalyst systems were screened, and it was concluded once again that this issue should be addressed on a case-by-case basis.

Structure of Catalytic Complex of 3d with 1a. Interesting reports on the intermediacy of Pd(II)- and Cu(II)-based enolates in catalytic asymmetric imine additions and aldol reactions appeared at the time of our first submissions in this area and prompted us to examine whether they might be involved in our system. As postulated above, we believe that chiral Lewis acid complexes **3** chelate imino esters **1a** and activate them for enantioselective addition (structure **A**, Figure 1). We also investigated a Pd(II)-based bis(phosphine) complex as a catalyst for the reaction which led to racemic products.[28] Unlike Sodeoka's system, ours in all probability does not operate through an "enolate" mechanism. What, then, causes the difference between ours and Sodeoka's? In Sodeoka's system, water plays a crucial role in modifying the catalyst and facilitating enolate formation. A little bit of water in this case makes a big difference in the mechanism!

Metal Binding. We have proposed that imino ester **1a** is activated by metals through a five membered chelate structure (structure **A**).[12b] Jørgensen et al., in contrast, have proposed two structures where imino ester **1a** binds to copper in a bidentate fashion through a sulfonyl oxygen and the glyoxylate oxygen (structure **B**) or a tridentate fashion through a sulfonyl oxygen, the imine nitrogen, and the glyoxylate oxygen (structure **C**), thus accounting for the reversal in sense of induction that is observed as compared to the use of *N*-acyl imino esters.[27] IR evidence is consistent with chelate structure **A**, although the alternative forms **B** and **C** cannot be conclusively ruled out on this basis. To shed light on the discussion, we

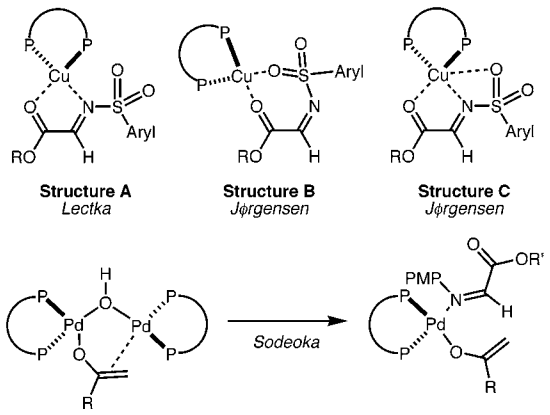
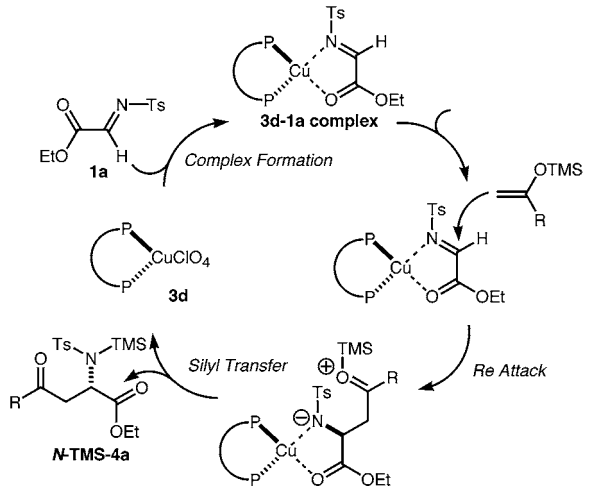


FIGURE 1. Proposed catalyst structure and metal binding modes.

recently turned our attention to density functional calculations (DFT). In place of a binap ligand, we employed triphenylphosphine groups. The tolyl methyl was also not included, being far removed from the sites of reactivity. At the B3LYP/3-21G* level, structure **C** is not computationally stable (i.e., a simultaneous interaction between two oxygen atoms and the imine nitrogen cannot be maintained). Alternative structure **B**, proposed in a similar form by Jørgensen, is computationally stable, although it is much higher in energy than chelate **A**. Combined with the unfavorable entropy term to be expected for a formation of a seven membered chelate and the cis disposition of the substituents about the C=N bond, **B** would seem to be highly disfavored as a viable intermediate complex, although one could argue that it is of course the reactivity of the complex that determines its contribution as a reaction manifold. Here again, coordination of the sulfonyl oxygen, rather than the imine nitrogen, would certainly make the imine carbon atom (the site of nucleophilic attack) less electrophilic and hence less reactive.

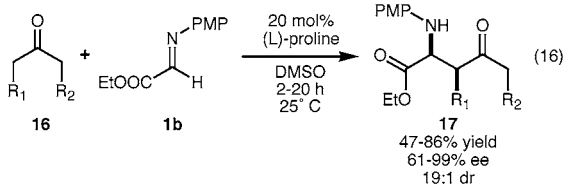
Mechanism of Catalytic Enol Silane Imino Alkylation. On the basis of our mechanistic insights, a proposed catalytic cycle for our reaction is depicted in Scheme 3. The first step is the formation of an activated imine/Cu-(I) complex **3d**−**1a** which rigidifies the system, minimizing the degrees of freedom that the imine can possess. The

Scheme 3. Proposed Catalytic Cycle for the Catalytic Enantioselective α-Imino Ester Alkylation



enol silane then attacks the activated catalyst-imine complex. Transilation occurs to yield *N*-TMS−**4a**, which is hydrolyzed during workup.

Extension of the Hajos-Wiechert Reaction. In a notable recent development in α-imino ester chemistry, Barbas et al. have reported the alkylation of a PMP substituted α-imino ester (**1b**) by ketones with proline catalysis through a Hajos-type aldol reaction.[29] Advantages of this procedure include the use of inexpensive, all-organic catalysts:



16 1b 17

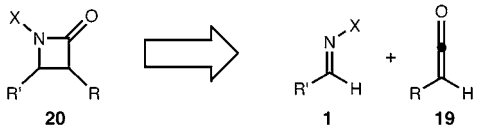
In some cases, however, 20 mol % catalyst must be used, along with 6 equivalents of ketone.

4. Catalytic, Enantioselective β-Lactam and β-Amino Acid Synthesis

Several years ago we became interested in the problem of catalytic, asymmetric β-lactam synthesis.[30] At that time, there were a few pioneering enantioselective processes known;[31] however, none represented a general solution to what from our standpoint was a very significant problem. While the medicinal importance of β-lactams continues to expand, the use of natural β-lactam antibiotics is being compromised by bacterial resistance, making the synthesis of nonnatural analogues a priority. Even more importantly, β-lactams (especially nonnatural ones) have achieved many important nonantibiotic uses in recent years, especially concerning the development of mechanism-based serine protease inhibitors.[32]

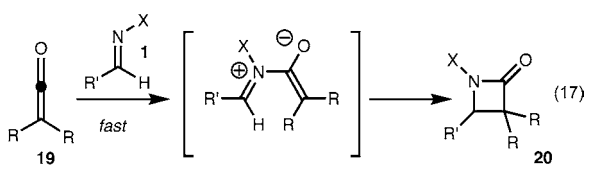
One of the most popular methods for the construction of the β-lactam skeleton is the Staudinger condensation of ketenes and imines (Scheme 4). In this reaction, the

Scheme 4. General β-Lactam Disconnection



20 1 19

imine acts as a nucleophile by attacking the electrophilic ketene to generate an intermediate that then cyclizes:



19 20

This reaction proceeds quite rapidly at low temperature in the absence of a catalyst. Ironically, this reaction in fact worked *too* well and we had to first "break" it before we could design a catalytic asymmetric methodology.

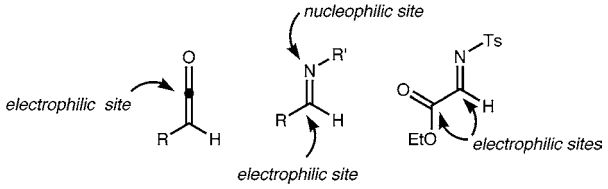
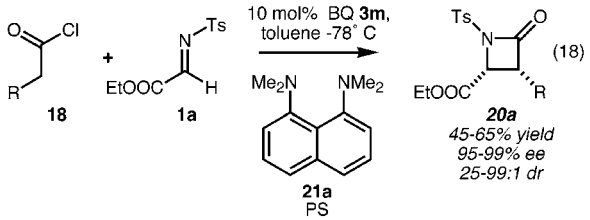


FIGURE 2. Electrophilicity of imines and ketenes.

Strategy for the Catalytic Asymmetric Synthesis of β-Lactams. We envisaged that if the lone pair of electrons on the imine could be restrained (delocalized into an electron withdrawing group), the background rate would be greatly suppressed. If the ketene were converted to an organic enolate by reaction with a catalytic nucleophile, it could now attack the electron deficient imine; effectively reversing the polarity of the reaction (Figure 2). α-Imino esters are perfect candidates for this type of reaction because they are highly electrophilic. When we mixed a solution of α-imino ester **1a** together with diphenylketene, no β-lactam product was detected.

Results. We found that the catalytic nucleophile for this reaction can be anything from a tertiary amine base to a low-valent, metal centered complex.[33,34] Chiral nucleophiles that we investigated included cinchona alkaloid derivatives, which catalyzed the reaction in good chemical yields and outstanding enantioselectivities and diastereoselectivities (dr, cis/trans ratio). These "all-organic" catalysts complement the use of Lewis acids and metals in other asymmetric transformations.

One of the most challenging aspects of this reaction chemistry proved to be the use of reactive monosubstituted ketenes. These intermediates can only be practically made in situ, usually from tertiary amine bases. Unfortunately, standard tertiary amines catalyzed our reaction, resulting in eroded selectivities. However, when we employed benzoylquinine (**3m**, BQ) and proton sponge (**21a**, PS) as a nonnucleophilic proton sink, desired β-lactams were formed in very high ee and dr for a variety of ketenes:[30]



18 1a 21a PS

Molecular mechanics calculations using the Macromodel program proved to be fruitful at predicting both the sense and the degree of optical induction. For example, model phenylketene-**3m** shows the complex derived from reaction of benzoylquinine (BQ) with phenylketene (Figure 3). This calculation (performed using a modified AMBER force field) shows the *re*-face of the ketene enolate open to approach of the imino ester electrophile, while *si*-face approach is several kcal/mole higher in energy.

The mechanism of the reaction of phenylacetyl chloride (**18a**) with imino ester **1a** catalyzed by BQ (and PS as stoichiometric base) was investigated through kinetics

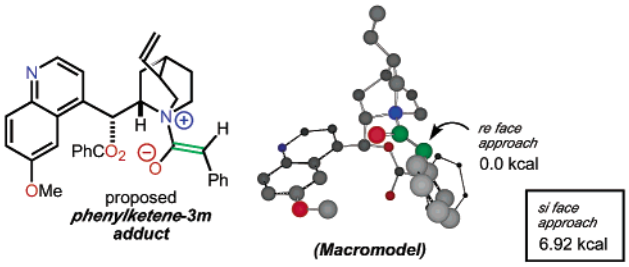
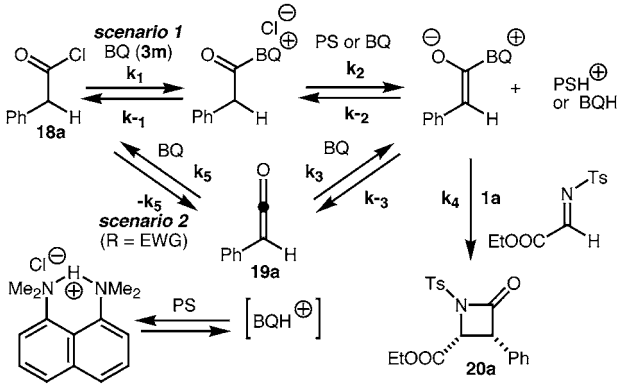


FIGURE 3. Stereochemical model of the putative zwitterionic intermediate of BQ with phenylketene.

experiments. Rate-determining acylation of the catalyst was established, followed by fast reaction with imino ester **1a**. 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 (Scheme 5). This result is in contrast to the use of other bases for ketene formation in the reaction, such as potassium carbonate and sodium hydride.[35] In these cases, the optimal reaction conditions mandate that ketene formation precede enantioselective cycloaddition.

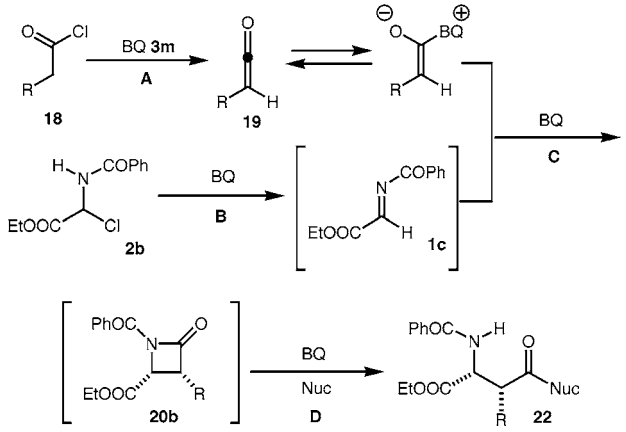
Scheme 5. Mechanism of β-Lactam Formation with Proton Sponge



***β*-Substituted Amino Acids from *β*-Lactams.** Since the tosyl group on imino ester **1a** is not an ideal solution for many chemical problems,[36] *N*-acyl-*β*-lactam products would be much more useful for a number of applications. *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. We reported a new method for the catalytic, asymmetric synthesis of *β*-substituted aspartic acid derivatives in which the chiral nucleophilic catalyst serves up to *four* distinct roles in a one-pot procedure: catalytic dehydrohalogenation of acid chlorides to form ketenes (step A); catalytic dehydrohalogenation of α-chloroglycines to form the corresponding imines (step B); catalyzed [2+2]-cycloaddition to produce intermediate acyl *β*-lactams (step C); and finally, nucleophilic ring opening to afford optically enriched *β*-substituted aspartic acids in high enantioselectivity and diastereoselectivity (step D).[37] In this work, it was found that BQ catalyzed ring opening by alcohols, while amines and amino acids reacted without a catalyst (Scheme 6).

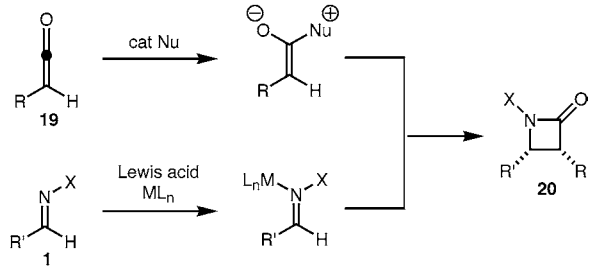
A Bifunctional Catalyst System Using a Tandem Lewis Acid/Nucleophile Pair. Having established enantioselec-

Scheme 6. A Catalyst that Plays Four Roles

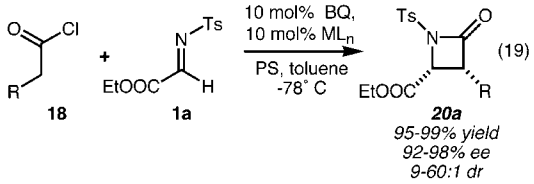


tive Lewis acid and nucleophile catalyzed reactions of imino esters, we sought to determine whether we could combine the best of both catalyst systems, resulting in a Lewis acid/nucleophile bifunctional system (Scheme 7).[38] However, simply mixing together a potent nucleophile with a strong Lewis acid can lead to self-quenching reactions that preclude catalysis. Recently Aggarwal showed that tertiary amines could be combined with metal salts to accelerate the Baylis-Hilman reaction, a process long noted for its sluggish rates of product formation.[39]

Scheme 7. Bifunctional Lewis Acid/Lewis Basic Catalysis



In an initial screen, we employed 10 mol % of metal salts such as $Mg(OTf)_2$, $CuClO_4{\cdot}(MeCN)_4$ and $YbCl_3$ in a solution of BQ (10 mol %), 1 equiv proton sponge as a stoichiometric base, imino ester **1a**, and acid chloride in a standard reaction in toluene at −78 °C, to form *β*-lactam **20**:



In each case, the overall yield of the reaction decreased in the presence of metal, perhaps due to self-quenching. However, it was gratifying to discover that using the metal 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. Overall, $Zn(OTf)_2$ (85%) and $In(OTf)_3$ (95%) had the most salutary effect on chemical yield. Ultimately, it may be that economic considerations (Zn(II) salts are the

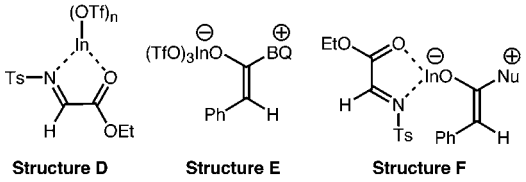


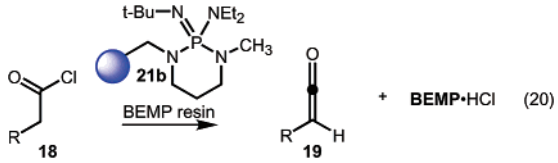
FIGURE 4. The three mechanistic proposals for the bifunctional Lewis acid/Lewis basic catalysts.

cheapest, whereas In(III) is moderately priced) will dictate the choice of cocatalyst.

Several possible mechanistic steps for the dramatic effect of the metal cocatalyst come to mind. The first is that the metal binds the imine and activates it toward nucleophilic attack by the zwitterionic enolate, thus enhancing the rate of product formation (Figure 4, structure **D**). This is consistent with our mechanistic model for the Lewis acid-catalyzed reactions of enol silanes and alkenes with imino ester **1a** (structure **A**, Figure 1). It is also possible that the metal stabilizes the zwitterionic enolate, making it more chemoselective in its reactivity and thermodynamically favoring its formation, assuming an equilibrium between ketene and enolate (structure **E**).[40] The third scenario is that the interactions represented by structures **D** and **E** are operating in concert, with the metal organizing both enolate and imine in a termolecular activated complex (structure **F**).

Kinetics experiments confirmed that the metal is having its effect after the rate-determining step of the reaction. For example, we found that the addition of the metal salt does not increase the rate of acid chloride consumption—an observation consistent with the established rate-determining step of the reaction involving the acylation of the catalyst by the acid chloride. However, the rate of product formation is increased by about 30−40%, demonstrating a significant improvement in the chemoselectivity of the reaction. Additionally, the fact that no comparable yield increase was observed when we applied this procedure to our catalytic, asymmetric α-halogenation reaction (the halogenation reagent is not anticipated to bind effectively to a metal)[41] led us to believe that metal chelation to the imine **1a** (structure **D** or **F)** is the most probable scenario for catalytic enhancement. Given these initial observations, a more precise mechanistic picture awaits further investigation.

Asymmetric Catalysis on Serially Linked Columns. On several occasions, we have employed solid-phase dehydrohalogenating agents such as the phosphazene base BEMP packed into chilled addition funnels to produce clean solutions of ketenes, free from amine base, and ammonium salt contaminants (eq 20).[42] This suggested a strategy whereby the entire asymmetric process of β-lactam synthesis is performed on sequentially linked columns. Reagents and catalysts are attached to a solid phase support and loaded onto the appropriate columns. The substrates are present in the liquid phase that flows through the column. As a substrate encounters each successive column, it grows in complexity and is finally purified by flowing through a scavenger column. Consequently, one can imagine a number of columns attached in series and/or in parallel, so that in the end a synthesis of a fairly complex molecule can be conducted through the flow system. We term this strategy sequential column asymmetric catalysis, or sequential CAC, when at least one of the steps involves a catalytic, asymmetric transformation. We found several advantages in conducting this reaction on columns, including obviating the need to isolate and/or manipulate highly reactive ketenes, separating and recycling the different solid-phase catalysts and reagents for additional reactions with ease, and finally, avoiding strong agitation that can degrade resin beads when they are spinning in solution.



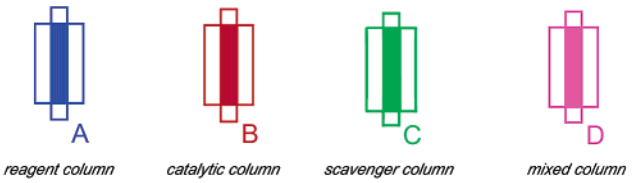


FIGURE 5. The different column types for asymmetric catalysis on sequentially linked columns.

The different types of columns that constitute an assembly are shown in Figure 5. 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, containing both catalysts and reagents packed together, can also be employed. Each column represents stages in normal synthetic sequences such as substrate preparation, stoichiometric and catalytic reactions, and finally, purification steps.

Sequential CAC is illustrated with an assembly consisting 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 (Figure 6). One of the top columns was packed with BEMP resin **21b**, the other top column with a mixture of NaH and Celite. The catalytic column was loaded with catalyst beads **3m**. A solution of phenylacetyl chloride **18a** in THF 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, the α-chloroamine **2d**, in a solution of THF, 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 THF from

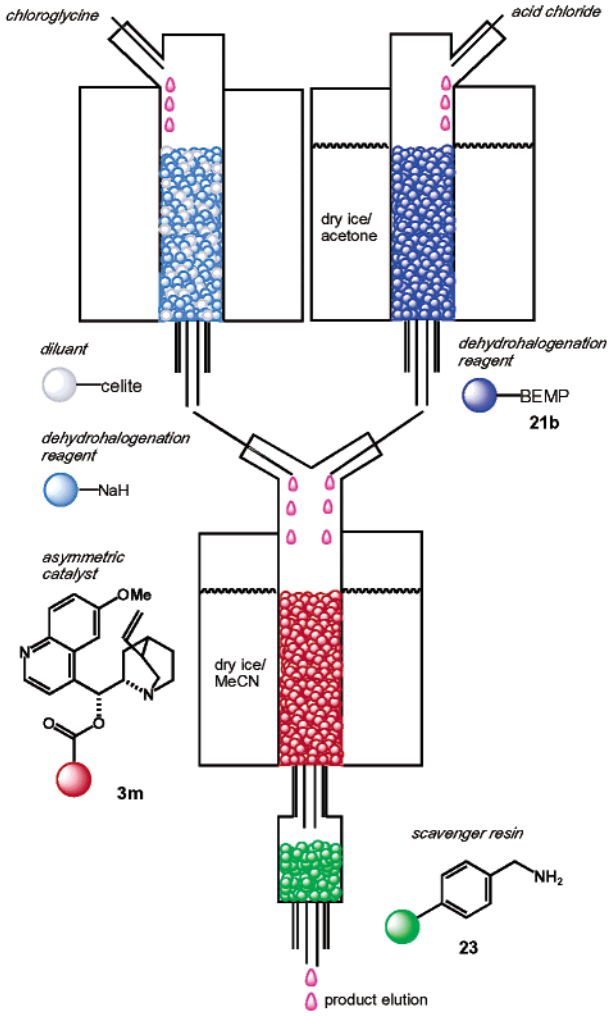
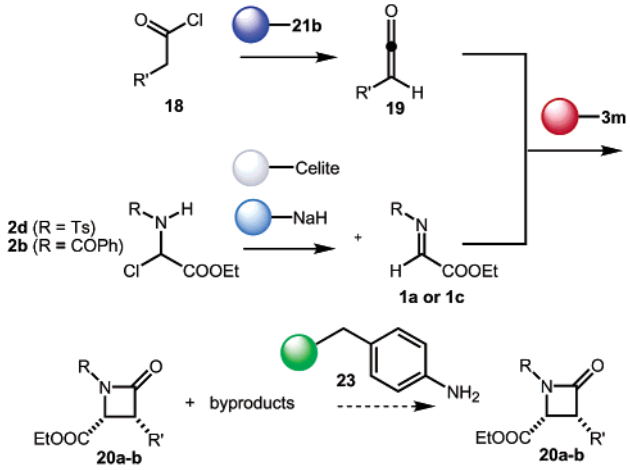


FIGURE 6. Column asymmetric catalysis assembly.

Scheme 8. Column Asymmetric Catalysis



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 fairly pure β-lactam **20a** in 90% ee and 10:1 dr (cis:trans) (Scheme 8). Simple crystallization of the residue affords optically and analytically pure material (>99% ee, 98/2 cis−trans dr) in 62% yield. We believe that a whole range of ketenes and acyl-substituted chloroglycines can be used in this procedure to produce a spectrum of β-lactam products.

Conclusion

Through the design of a series of novel reactions, we and others have found α-imino esters to be excellent reagents for the catalytic asymmetric synthesis of α- and β-amino acids, as well as β-lactams. Their strong electrophilicity, in conjunction with their ability to chelate metal-based catalysts, are integral to successful catalytic asymmetric reactions. With their track record, α-imino esters will surely find even more uses in the years to come.

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