Bifunctional Lewis Acid-Nucleophile-Based Asymmetric Catalysis: Mechanistic Evidence for Imine Activation Working in Tandem with Chiral Enolate Formation in the Synthesis of β-Lactams

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Abstract: We report a mechanistically based study of bifunctional catalyst systems in which chiral nucleophiles work in conjunction with Lewis acids to produce β-lactams in high chemical yield, diastereoselectivity, and enantioselectivity. Chiral cinchona alkaloid derivatives work best when paired with Lewis acids based on Al(III), Zn(II), Sc(III), and, most notably, In(III). Homogeneous bifunctional catalysts, in which the catalyst contains both Lewis acidic and Lewis basic sites, were also studied in detail. Mechanistic evidence allows us to conclude that the chiral nucleophiles form zwitterionic enolates that react with metal-coordinated imines. Alternative scenarios, which postulated metal-bound enolates, were disfavored on the basis of our observations.

Introduction

As prime examples of polyfunctional catalyst systems, enzymes provide precisely arrayed functional groups operating in concert on a substrate within an active site.[1] Metalloenzymes are an interesting subset of polyfunctional catalysts that utilize metal ions as Lewis acids and/or redox centers in conjunction with "organic" functional groups to enhance reaction rates. Zinc proteases are especially notable examples;[2] these enzymes efficiently chelate zinc hydrates and facilitate nucleophilic attack on the substrate. Synthetic chemists have long sought to employ the principles of polyfunctional catalysts (especially bifunctional catalysts) in designed systems as well.[3] It has only been in recent years that substantial progress has been made in the use of well-defined bifunctional systems as applied to asymmetric catalysis.[4] Several of these systems combine a metal ion (usually as part of a chiral Lewis acid complex) with a Lewis base in the form of an organic functional group.[5] The precise mechanism by which synthetic bifunctional systems act is often unknown, due in part to their inherent complexity. For our part, we made the

Scheme 1. Tandem Lewis Acid/Nucleophile Catalyzed Synthesis of β-Lactams
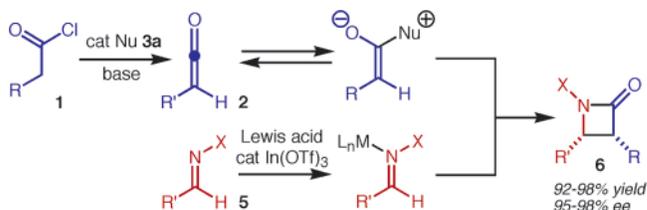
recent discovery that a chiral nucleophile working in tandem with an achiral Lewis acid (a metal salt or derived complex) could dramatically enhance the rates and yields of the catalytic, asymmetric β-lactam-forming cycloaddition developed in our laboratories (Scheme 1).[6]

We now present a full, mechanistically based account of our findings, buttressed by substantial kinetic and stereochemical evidence that allows us to propose a detailed mechanism by which the reactions occur and to confirm our original design hypothesis involving imine activation. Our aim is to provide one of the few instances in which an asymmetric, bifunctionally catalyzed system has been identified and defined in detail. The underlying principle of our system is the belief that by combining an organic catalyst with a metal, one can enhance reaction rates and yields, particularly in the case of traditionally slow reactions. Theoretically, the use of a Lewis acid and a

(1) (a) Murray, G. I. *J. Pathol.* **2001**, *195*, 135−137. (b) Huang, X.; Holden, H. M.; Raushel, F. M. *Annu. Rev. Biochem.* **2001**, *70*, 149−180.

(2) (a) Kim, D. H.; Mobashery, S. *Curr. Med. Chem.* **2001**, *8*, 959−965. (b) Auld, D. S. *Astacins* **1997**, 119−131. (c) Monetcucco, C.; Schiavo, G. *Trends Biochem. Sci.* **1993**, *18*, 324−327.

(3) Bifunctional catalysis has often been defined as involving a mechanism in which two functional catalysts (in this case a Lewis base and Lewis acid) are involved in the rate-determining step, such that rate enhancement is observed. The term concerted catalysis has also been proposed to describe the simultaneous action of two catalysts and could be applied to a variant of our system reported herein. (a) Swain, C. G.; Brown, J. F., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2538−2543. (b) DiMauro, E. F.; Mamai, A.; Kozlowski, M. C. *Organometallics* **2003**, *22*, 850−855.

(4) (a) Groger, H. *Chem.−Eur. J.* **2001**, *7*, 5247−5257. (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882. (c) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339−2342. (d) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190−1197.

(5) (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (b) Woolley, P. *J. Chem. Soc., Chem. Commun.* **1975**, *14*, 579−580. (c) Dong, S. D.; Breslow, R. *Tetrahedron Lett.* **1998**, *39*, 9343−9346. (d) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931−7944.

(6) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603−1605.

Lewis base in concert could also lead to a self-quenching reaction, but when the right pair is combined, for example a hard metal ion with a soft base (using Pearson's terminology), reaction rates may increase significantly.[7] The most important precedent for this is found in the work of Aggarwal on catalysis of the Baylis–Hillman reaction through the use of an achiral Lewis base, such as dabco, together with a lanthanide metal triflate salt, to yield the desired products with enhanced rates.[8]

Background. The use of "rationally designed" bifunctional Lewis acid/Lewis base systems in asymmetric catalysis has only recently come of age. This new methodology can be divided into two main classes: two-component systems, in which Lewis acids and Lewis bases work in tandem; and homogeneous bifunctional catalysts. However, there are relatively few examples of the combination of achiral Lewis acids and chiral Lewis bases. Of note, Shi has reported an efficient aza-Baylis–Hillman reaction in which Ti(Oi-Pr)$_4$ is used to catalyze imine formation while a cinchona alkaloid derivative attacks the enone substrate.[9] Similarly, a chiral Lewis acid and an achiral Lewis base can be utilized for the cyanosilylation of aldehydes,[10] as Chen et al. have shown. In this case the authors employed an achiral N-oxide in conjunction with a chiral titanium complex to achieve catalysis. Similarly, Yamamoto has successfully applied a tandem Lewis acid/Lewis base system to both the Sakurai–Hosomi allylation and the Mukaiyama aldol reaction.[11] His system involves the use of a chiral Ag–phosphine complex and a catalytic amount of fluoride ion. On the other hand, use of chiral Lewis acids in tandem with chiral Lewis bases has been relatively unexplored in organic synthesis.

Bifunctional catalysts, ones that contain both Lewis acidic and basic sites, can play two possible roles. They can either activate both reagents and substrates or one reactive center can bind the substrate while another center performs the transformation. Shibasaki has designed a series of bifunctional catalysts that incorporate Lewis basic sites onto a binol template.[12] His catalyst system has been applied to asymmetric hydrophosphonylation, as well as the cyanosilylation of aldehydes and related Michael reactions. Baeza et al. have designed a similar system for the cyanophosphorylation of aldehydes.[13] Hoveyda has employed a small peptide with a Lewis acidic site for imine chelation to effect an asymmetric Strecker reaction.[14] Kozlowski's dialkylzinc addition to keto esters utilizes a titanium–salen complex containing nucleophilic appendages to effect the transformation.[15] Additionally, Annunziata et al.[16] have reported a related bifunctional system in which a Lewis acid and nucleophile act in sequential reactions but not in tandem. These examples offered us some background for the design of an efficient bifunctional system for the asymmetric synthesis of β-lactams.

Results and Discussion

Metal Screening. A while ago we discovered that benzoylquinine (BQ), in the presence of a stoichiometric base, could catalyze the formation of β-lactams with high enantioselectivity and moderate to good chemical yields, employing acid chlorides as ketene precursors or "equivalents" and α-imino esters as reaction partners. The mechanistic hypothesis we favor for β-lactam cycloaddition reactions involves the formation of zwitterionic enolates that add to the imino ester nucleophilically to form reactive intermediates leading to the desired β-lactam products (eq 1).[17] Much of the remaining mass balance of the reaction is attributable to polymerized acid chloride and imino ester. It occurred to us that an additional mode of activation may enhance chemical yields; for example, if a Lewis acid cocatalyst were also present in the reaction to activate the imino ester further, an enhancement in the yield of desired products by alteration of the reaction manifold could be expected.


$$\text{(1)}$$
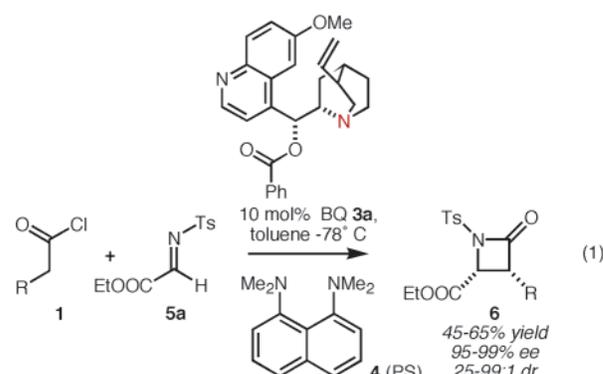
We drew upon our extensive experience with the activation of α-imino esters by chiral Lewis acids for guidance. Our previous work in this area detailed the catalytic, asymmetric alkylation of α-imino esters and N,O-acetals with enol silanes, silyl ketene acetals, alkenes, and allylsilanes to form a wide variety of α- and β-amino acid derivatives in high chemical yield, high anti-diastereoselectivity, and uniformly high enantioselectivity using chiral late transition metal bis(phosphine) complexes as catalysts (Scheme 2).[18]

Our catalyst of choice, easily prepared from Cu(I) salts and (R)- or (S)-tol-binap, has also been exploited by other groups, demonstrating the wide scope, flexibility, and utility of this chiral Lewis acid system.[19] We began our studies by adding substoichiometric amounts of metal cocatalysts. We chose the late transition metal based salts and complexes that worked well in our Lewis acid-catalyzed imino ester chemistry, including

(7) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539.
(8) (a) Aggarwal, V. *J. Org. Chem.* **1998**, *63*, 7183−7189. (b) Aggarwal, V. *J. Org. Chem.* **2002**, *67*, 510−514.
(9) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941−1947.
(10) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949−952.
(11) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593−5601.
(12) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Nogami, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2003**, *51*, 702−709.
(13) Baeza, A.; Casas, J.; Najera, C.; Sansano, J. M.; Saa, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143−3146.
(14) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599.
(15) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781−3784.
(16) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A. *Eur. J. Org. Chem.* **2003**, *8*, 1428−1432.

(17) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.
(18) (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090−6091. (c) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006−11007. (d) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168−2169.
(19) (a) Yao, S.; Fang, X.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1998**, 2547−2548. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844−4849. (c) Saaby, A.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114−4115. (d) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem.−Eur. J.* **2000**, *6*, 2435−2448.

Scheme 2. Catalytic, Asymmetric Alkylation of α-Imino Esters and N,O-Acetals
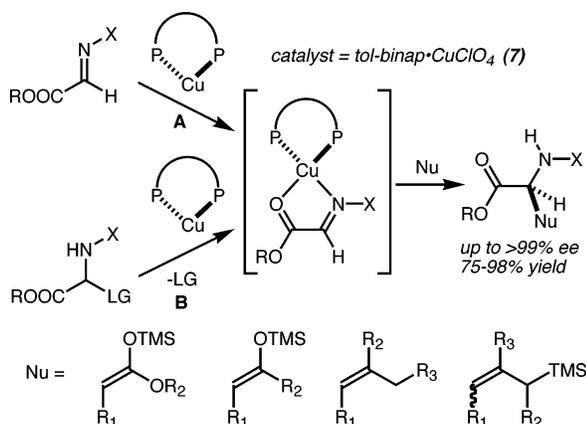
Table 1. Initial Metal Screen To Form β-Lactam **6a** with Phenylacetyl Chloride and Imino Ester **5a**, Catalyzed by BQ **3a** in Toluene

entry	Lewis acid[a]	% yield[b]
1	none	65
2	(Ph₃P)₃RhOTf	27
3	(Ph₃P)₂PdCl₂	30
4	Ni(dppe)Cl₂	32
5	Cu(OTf)₂	35
6	Mg(OTf)₂	36
7	Sn(OTf)₂	44
8	Sm(OTf)₃	45
9	Cu(Ph₃P)₂ClO₄	49
10	Yb(OTf)₃	50
11	YbCl₃	52
12	Eu(fod)₃	55
13	Al(OiPr)₃	56
14	La(OTf)₃	63
15	TBDMSOTf	64
16	AgOTf	67
17	Al(OTf)₃	78
18	Sc(OTf)₃	80
19	Zn(OTf)₂	85
20	In(OTf)₃	95

[a] 10 mol % of the Lewis acid was added to the standard reaction (entry 1). [b] Isolated yield after column chromatography.

phosphine–Rh(I) complexes and the precursor salt Cu(PPh₃)₂-ClO₄. Our rationale was based on the fact that these catalysts were established to work well at imino ester activation. However, to our surprise, when we added 10 mol % of these metal complexes to the standard reaction conditions to form β-lactam **6a**, the overall yield of the reaction *decreased* in the presence of the respective metal (Table 1, entries 2 and 9).[20] This result is almost certainly due to the preferential binding of late transition metals such as Cu(I) and Rh(I) to the tertiary amine catalyst; Cu(I) is known to have a high affinity for amines, and when we monitored the reaction by UV, a characteristic shift indicative of metal binding took place, as well as a gradual shift to characteristic bands of Cu(II), indicating metal oxidation. The binding of the metal to the quinuclidine nitrogen of benzoyl-quinine (BQ) naturally reduces its efficacy as a nucleophilic catalyst and results in low yields. This is an example of the "self-quenching" conundrum that we had mentioned earlier (eq 2) and an example of why correlations between Lewis acidity and imino ester binding, for example, cannot easily be drawn.

Additionally, when Cu(PPh₃)₂ClO₄ was added to a solution of BQ in toluene, the color rapidly changed from clear to blue, again implying that the BQ is acting as a ligand and possibly promoting the oxidation of the metal. We also tried Mg(II), Sn(II), and Cu(II) salts; however, each afforded poor yield of desired product (Table 1, entries 3–7). Similarly disappointing results were observed when Pd(II) and Ni(II) were screened as cocatalysts. With these other Lewis acids, the poor solubility of the catalysts may also be at least partially to blame as well.

quenched catalyst
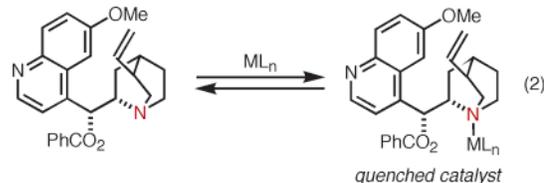
Screening of Triflate Salts and Other Metal Complexes. In his studies of metals for the Baylis–Hillman reaction, Aggarwal screened a large number of metal salts and found that both group III and lanthanide metals gave the best results in his reactions. These facts, coupled with our own results, suggested to us that less azaphilic metal salts and complexes would be desirable to diminish potential binding to the quinu-clidine nitrogen of the BQ. Although the lanthanides did not work well for us (Table 1, entries 8 and 10–12), to our satisfaction, we found that using the metal triflates of Sc(III), Al(III), Zn(II), and In(III) (10 mol %) resulted in increased rates of product formation and significantly enhanced chemical yields (Table 1, entries 16–20). Overall the use of Zn(OTf)₂ (85%) and In(OTf)₃ (95%) resulted in the greatest increase in chemical yield, while Al(OTf)₃ (78%) and Sc(OTf)₃ (80%) were slightly less effective but still very promising.

Results with Indium(III). Having established that In(OTf)₃ was the best overall Lewis acid cocatalyst for promoting our reaction,[21] we applied this system to various substrates to determine its applicability and effect on the reaction enantio-selectivity (ee) and diastereoselectivity (dr) (Figure 1). Generally speaking, reaction ee's are maintained in the high 90's and chemical yields increased by a factor of 1.5–2. For example, **6a** was obtained in 95% yield and 98% ee (dr = 60:1), which represents a 1.5-fold yield increase (Figure 1). In the case of **6d** we were even able to double the yield without noticeable decrease in selectivity. An area of minor concern was the diastereoselectivity of a few of our β-lactam products; in many cases the dr was clearly maintained with the use of In(III) as a cocatalyst, but in a minority of cases it eroded somewhat (for example lactams **6b** and **6f**) from 50:1 to around 10:1. Nevertheless, we thought it was a problem worth addressing to ensure high levels of selectivity for all the reactions.[22]

The coordination chemistry of In(III) is a scantily explored topic.[24] One reason for this may be the fact that In(III) seemingly binds to many ligands with comparatively low affinity and is

(20) Standard reaction conditions consisted of 10 mol % BQ **3a**, 1 equiv of proton sponge as a stoichiometric base, 1 equiv of imino ester **5a**, and 1 equiv of acid chloride in toluene at −78 °C.

(21) For a recent review on indium-catalyzed reactions, see the following: Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015–3019.

(22) We recently reported the synthesis of a *C₂*-symmetric bis(cyclophane diol) ligand and its application toward improving the diastereoselectivity of our bifunctional system: Wack, H.; France, S.; Hafez, A. M.; Drury, W. J., III; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, *69*, 4531–4533.

(23) Yields in red represent isolated yields from original reaction without the added Lewis acid. Yields in blue represent isolated yields employing In(OTf)₃ as a cocatalyst.

(24) Carty, A. J.; Tuck, D. G. *Prog. Inorg. Chem.* **1975**, *19*, 243–337.
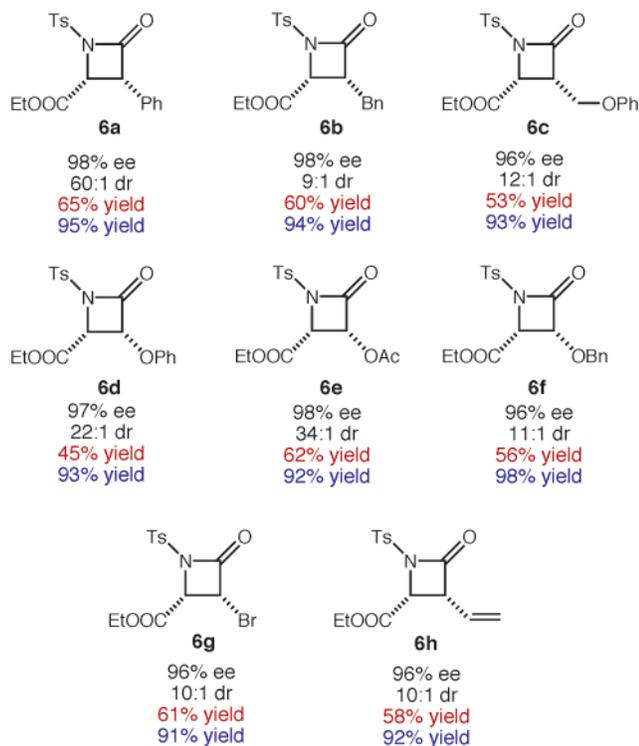
Figure 1. β-Lactams synthesized by employing BQ and In(OTf)$_3$ co-catalyst.[23]

characterized by fast "on/off" rates.[25] However, it binds halide ions with relatively high affinity. Although its trihalide salts have been employed as catalysts in numerous reactions,[26] few reports of catalytic systems using In(III) with an organic ligand have been published, and no effective chiral In(III)-based Lewis acid catalytic systems are known as of this writing. Ligand exchange is slow when InX$_3$ is combined with oxo- or aza-based ligands, such that mixed-ligand species are formed (InX$_n$L$_n$). Furthermore, In(III) can bind phosphines to form four-coordinate species and nitrogen- and oxygen-derived ligands to produce five- and six-coordinate species.[27] When bound to bidentate ligands, In(III) is known to form trigonal bipyramidal chelates of the type InL$_3$ (where L = a bidentate ligand). Whereas most Lewis acids would be deactivated or degraded in aqueous solutions, In(III) (most often InCl$_3$) binds water highly reversibly, and/or with low affinity, thus maintaining its activity. Consequently, we were concerned about the possible effects of the free chloride ions that are generated during the course of our reactions. Because of its poor solubility in our solvent, *in situ* generation of InCl$_3$ could be detrimental in that we might not observe the expected increase in yield. Fortunately, with proton sponge as our base, most chloride ions are presumably "soaked up" and precipitate as the proton sponge–hydrochloride salt. Additionally, this alleviates the issue of coordination of chloride ions to indium.[28]

Most studies have found that the exchange rate is often so rapid between the free ligand and InL$_3$ that it has been hypothesized that the intermediate complex is comprised of two

(25) Chung, H. L.; Tuck, D. G. *Can. J. Chem.* **1974**, *52*, 3944−3949.
(26) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347−2356.
(27) Paver, M. A.; Russell, C. A.; Wright, D. S. In *Comprehensive Organo-metallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: New York, 1995; Vol. 1, Chapter 11.
(28) No change in the UV spectrum of proton sponge was observed upon addition of In(OTf)$_3$ in THF (a solvent in which it is fully soluble).

bidentate ligands and one monodentate ligand.[29] This fact may provide the key to understanding why In(III) works so efficiently as compared to our other "active" metals (Al, Sc, and Zn). Ultimately, these fast on/off rates translate into a lower thermodynamic barrier to ligand exchange. In the Cu(I)-catalyzed system, the quinuclidine nitrogen of BQ acts in a deleterious manner by tightly binding the metal ion, while, with In(III), the binding to the amine is highly reversible and of perhaps lower affinity. Therefore, regardless of how well the ligand is activated, it will dissociate from the metal rapidly. However, this argument raises the question: how does one account for the increased yields with the other "active" metals when each is known to have slower on/off exchange rates? The answer may be fairly straightforward for scandium and aluminum. Both are highly oxophilic Lewis acids and therefore are less likely to bind the quinuclidine nitrogen. Zinc, however, is a bit more problematic, being an inherently softer Lewis acid than Sc(III) or Al(III) and is yet somewhat azaphilic. It should, therefore, bind preferentially to the quinuclidine nitrogen and thus lower the chemical yield. Since we are conversely observing an increased yield, a plausible explanation would be that ligand exchange between the monodentate quinuclidine nitrogen and the bidentate imino ester favors the latter (see below).

Lowering Metal Catalyst Loading. Although 10 mol % of the In(OTf)$_3$ was added to the reaction in our standard screening, we observed that most (if not all) of the salt did not dissolve completely in the toluene solvent—a seemingly "homeopathic" chemical system! Even when reagents and catalysts were added (such as BQ), the indium was not well solubilized (in a way, this was good news, indicating that tight binding of BQ to the metal was not occurring). This result implies that less cocatalyst is actually required. A titration experiment indicated that at any one time only about 10% of the added metal catalyst was dissolved in the reaction mixture (1 mol % cocatalyst), but it was enough to enhance the results of the reaction dramatically. In an attempt to rectify the problem, we employed THF, in which In(OTf)$_3$ is soluble. However, it led to eroded enantio-selectivities (85−90% ee's on average).
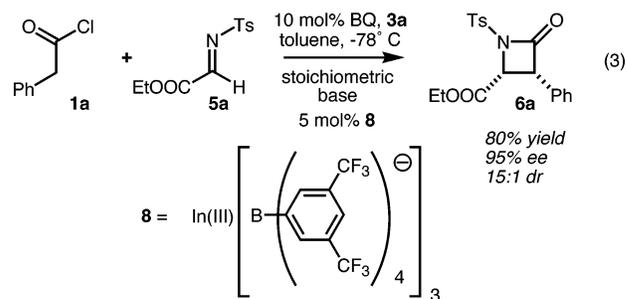
Considering that the quantity of fully soluble metal salt actually needed in the reaction would be considerably less than 10 mol %, we attempted to make the indium salt more soluble by changing the counterion to something "greasier" and bulkier than the triflate. Both tetraphenylborate[30] and "BArF"[31] were found to be suitable counterions to solubilize the metal, although

(29) Tuck, D. G. *Coord. Chem. Rev.* **1966**, *1*, 286−291. (b) Tuck, D. G. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 3, Chapter 25.2. (c) Pedrosa de Jesus, J. D. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 2, Chapter 15.7.
(30) Gillard, R. D.; Vaughan, D. H. *Transition Met. Chem.* **1978**, *3*, 44−48.

we suspect that in some cases the tetraphenylborate ion decomposes over the course of the reaction, a common occurrence.[32] Although the salts could be generated *in situ* through a phase transfer process, we found that isolating them led to higher yield and ee (eq 3). We achieved greater success with the In(BArF)$_3$ salt **8**, which, when loaded at 5 mol % gave β-lactam **6a** in 80% yield and 95% ee.

Alternatively, an interesting, soluble indium salt could be made in which the quinine unit was incorporated as part of the negatively charged counterion. For example, reaction of the sodium salt of quinine followed by treatment with triphenylborane and metal metathesis with In(OTf)$_3$ produces the mixed In(III) quinine salt **3b** (eq 4). Use of **3b** in a standard reaction results in product with high ee (98%), but only slightly enhanced yields (ca. 70%).


(4)

3b
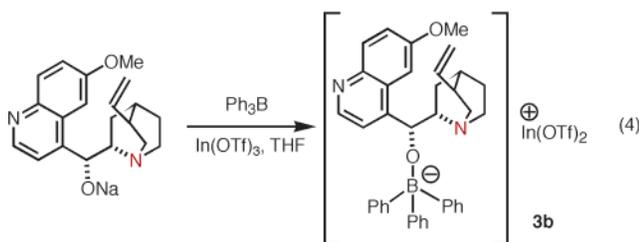
Bifunctional Catalysts. Unfortunately, the fact that most of the metal catalyst did not dissolve in the reaction vessel made potential mechanistic studies of the system difficult. What we needed was a completely soluble catalyst to ensure reproducibility. Therefore, we chose to investigate homogeneous complexes wherein the chiral nucleophile and Lewis acid were both present in the same entity. Consequently, we prepared the metal chelating alkaloid derivatives **3c** and **3d** in two steps from quinine. Complexation of the sodium alkoxide salt of **3d** and 0.5 equiv of the desired metal salt affords a putative bis-(salicylato)metal complex containing two catalytically active quinuclidine moieties.[33] Complex **3e**, derived from In(OTf)$_3$, yielded β-lactam product in 58% yield (95% ee, dr 1:1) in a standard reaction involving phenylacetyl chloride, proton sponge **4**, and imino ester **5a**. The 2:1 ligand:metal stoichiometry may have attenuated the Lewis acidity of the metal to a large extent and led to the disappointing result. However, when the complex derived from a 1:1 metal:ligand stoichiometry was used, it afforded products in 90% yield, 99% ee, and 10:1 dr. Most importantly, we now had a homogeneous system in hand with which we could undertake mechanistic studies.

3c, R=H
3d, R=Me

3e

3f
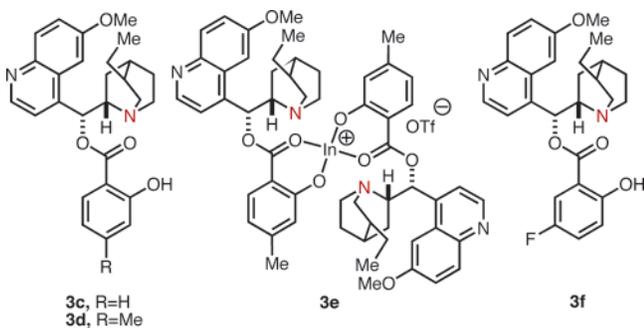
To validate the binding characteristics of our salicylate catalysts, we conducted a series of ^{19}F NMR experiments with

Scheme 3. Metal-Mediated Bifurcated Pathway for the Formation of β-Lactams
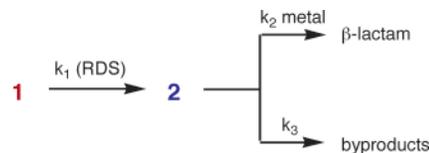
fluoro-substituted salicylate derivative **3f**. As compared to the spectrum of the metal-free catalyst, studies revealed a slight shift upfield from 6.0 to 5.7 ppm when 1 equiv of In(OTf)$_3$ was added incrementally.[34] We can assume that the appearance of only one peak in this metal experiment is the result of a very rapid exchange rate between the free Lewis acid and the In(III)−salicylate complex, a scenario consistent with the known coordinating properties of indium. A similar study was performed with zinc as the binding metal. Diethylzinc was heated with the fluorinated quinine−salicylate to yield Zn−**3f**, an uncharged complex. A ^{19}F shift was seen from 6.0 to 4.8 ppm. Addition of excess ligand **3e** produced a separate set of NMR resonances, indicating a slower metal exchange process, a marked contrast to the In(III) complex.

Mechanistic Studies on In(III)-Based Catalysis. In our initial studies, we discovered that the addition of a metal salt does not increase the rate of acid chloride consumption in the reaction of **1a** and **5a** (10 mol % **3a** as co-catalyst) with proton sponge as the stoichiometric base—an observation consistent with the established rate-determining step of the metal free reaction with proton sponge involving acylation of the catalyst by the acid chloride and/or ketene formation.[35] These experiments also confirmed that the metal is having its effect *after* the rate-determining step of the reaction (Scheme 3). However, the rate of product formation in the very initial stages of the reaction is increased by a factor of 3 or more, resulting in a substantial improvement in reaction chemoselectivity. The fact that the metal cocatalyst does not participate in the rate-determining steps (RDS) of the reaction pathway complicates a potential kinetic analysis. Additionally, we found that the reproducibility of our kinetic runs was called into question by the relative insolubility of the In(III)-based salts in the reaction medium. One way around this problem is to employ a preemptive strategy—to "knock out" the original RDS from the picture by preformation of the ketene. The best way to do this is to employ NaH[36] as the stoichiometric base. We must also solubilize the catalyst fully; for this purpose we chose to add 10 vol % propionitrile as a cosolvent. Under these conditions, we found that the initial rate of reaction (product formation) in the presence of 10 mol % In(III) was doubled over the rate of the reaction in the absence of metal.[37] The rate of reaction was found to be dependent on the metal cocatalyst, the ketene, the

(31) (a) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920−3922. (b) Chavez, I.; Alvarez-Carena, A.; Molins, E.; Roig, A.; Maniukiewicz, W.; Arancibia, A.; Arancibia, V.; Brand, H.; Manuel Manriquez, J. *J. Organomet. Chem.* **2000**, *601*, 126−132.
(32) Nishida, H.; Takada, N.; Yoshimura, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600−2604.
(33) See Supporting Information for details.
(34) NMR shifts are reported with respect to a CFCl$_3$ standard.
(35) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.
(36) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627−629.
(37) Conversions as close to 20% as possible were measured to negate the effect of product inhibition and catalyst degradation (which may occur through acylation of the phenolic oxygen).

Scheme 4. Kinetic Isotope Study To Identify the Rate-Determining Step
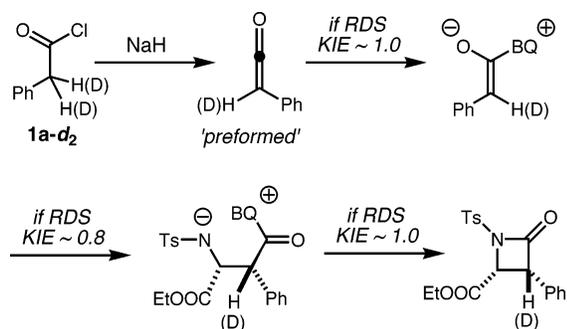
imine, and the cinchona alkaloid (all on a first-order basis). Complicating any analysis is the fact that the rate equation must have a term for the base (metal-free) reaction, which proceeds in parallel with the catalyzed reaction (eq 5). Additionally, we note that the propionitrile cosolvent (1) erodes the reaction diastereoselectivity, (2) increases the initial rate of the base reaction, and (3) lowers the rate of the metal catalyzed process (presumably by reducing the Lewis acidity of the metal salt). Thus, its use is not ideal from either a synthetic or a mechanistic standpoint.

$$\text{rate of reaction} = k_1[\text{imine}][\text{enolate}] + k_2[\text{imine}][\text{enolate}][\text{In(III)}] \quad (5)$$

Naturally the potential solution involves the use of the quinine−salicylate ligand **3c** (10 mol %) as a basis for mechanistic studies. Ligand **3c** also serves as the "shuttle" base in the preliminary ketene synthesis. In a standard experiment, we "preform" phenylketene in a reaction vessel from phenyl-acetyl chloride over enough time to ensure complete acid chloride consumption. In the control experiment, imino ester **5a** is added to the reaction mixture containing **3c** and the "preformed" ketene. The rate of product formation is then measured over the course of time. Concurrently, imino ester **5a** is added to a ketene solution containing the metal complex In(III)−**3c**. Under these conditions, the data show that the rate of product formation is linearly dependent on both the concentration of metal complex and the imino ester **5a**.

Which step is now rate determining? Is it the C−C lactam bond formation or a "downstream" transacylation step leading to ring formation? A kinetic isotope study addresses this question (Scheme 4). Once again, preformation of phenylketene removes acylation of catalyst as the RDS, whereas carbon−carbon bond formation and transacylation remain as potential RDS's. Phe-nylketene-d_1 is expected to give rise to a negligible KIE if the latter is the RDS, but an inverse secondary effect would be observed if C−C bond formation is the RDS, as a change in hybridization from sp^2 to sp^3 takes place. In the actual experiment, we found a KIE of 0.8, indicating that C−C bond formation is likely the RDS.[38]

Role of the Lewis Acid. In our original communication on this topic, we postulated that one of three plausible mechanistic alternatives could account for the observed effect of the Lewis acid in this bifunctional system. The one that we had conceived

from the outset (our "paper concept") is the idea that the metal activates the imine toward nucleophilic attack by the organic zwitterionic enolate, thereby enhancing the rate of product formation (structure **A**), which is also consistent with the kinetic data that we have amassed.[39]
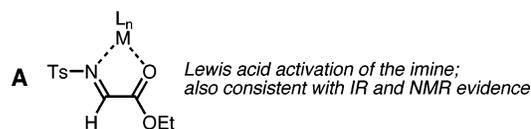
The second possibility is that the metal binds to the zwitterionic enolate, making it more chemoselective in its reactivity. The problem with this scenario is that the enolate reactivity should be lowered by metal binding, with concomitant increase in its thermodynamic stability. The formation of this chelated intermediate should be favored from a thermodynamic standpoint, assuming an equilibrium between the ketene and the enolate (structure **B**).[40] Metal binding is thus expected to increase the concentration of enolate relative to ketene or acid chloride, paradoxically accounting for an increase in the rate of reaction (eq 6)
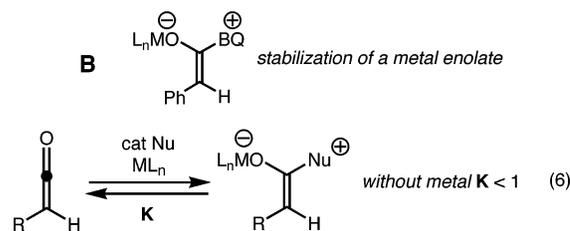
The third possibility is that both alternatives could be operating, with the metal organizing both enolate and imine in a termolecular activated complex (structure **C**).
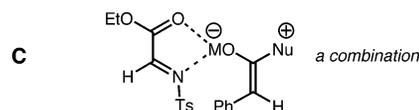
Addressing Scenario A. Metal Binding to the Imino Ester. In addition to kinetic data, we have amassed physical and chemical evidence that metal binding to the imino ester plays a pivotal role in the reaction. For example, as potentially chelating substrates, the coordination of metals and metal complexes to α-imino esters is well precedented in both our work and the work of others.[41] Given the fact that metals will bind the catalyst as well as the imine, it is often difficult to correlate metal-binding capacity with catalytic efficacy. Nevertheless, we sought to examine, through IR and NMR studies, the binding of catalytically active metals to imino ester substrate **5a**. For example, we found that In(III) induces a small shift of the imine proton in the ^{1}H NMR spectrum (8.28 to 8.04 ppm), along with a correspondingly small shift of the ester carbonyl

(38) Due to the number of potential manifolds in our reaction pathway, no one step can be defined as the *only* rate-determining step. The calculated KIE should be considered as an aggregate resulting from an ensemble of RDS's, which is in fact a common but underappreciated occurrence in complex chemical reactions.

(39) We have previously found that imine **5a** can be activated by late transition metal chiral bis(phosphine) complexes to catalyze the enantio- and diastereoselective addition of various nucleophiles: Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67−77.

(40) It is possible that the metal salt rather than catalyzing the formation of product *suppresses* the formation of undesired side products.
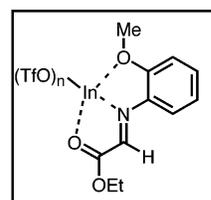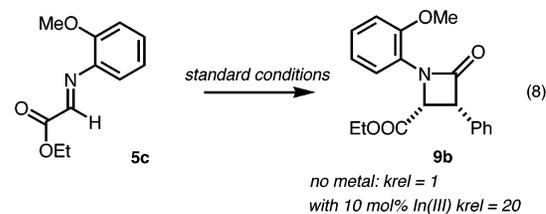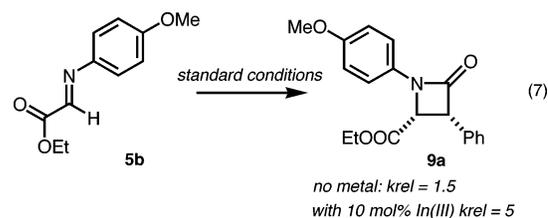
(41) (a) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415−5423. (b) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *16*, 2293−2297.

stretch (from 1751 to 1748 cm^{-1}), and a larger shift of the imine stretch (1630 to 1625 cm^{-1}) in the IR spectrum. Zn(II), another efficacious metal, produces stronger changes in ^{1}H chemical shifts (8.28 to 7.92 ppm) and IR frequencies (from 1751 to 1741 cm^{-1} and from 1630 to 1597 cm^{-1}, respectively). Thus, it looks like Zn(II) is a better Lewis acid than In(III) towards the imino ester, but it has lower on/off rates and perhaps a higher affinity for the quinuclidine nitrogen.
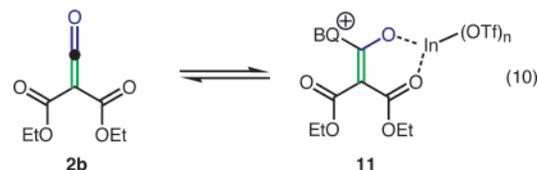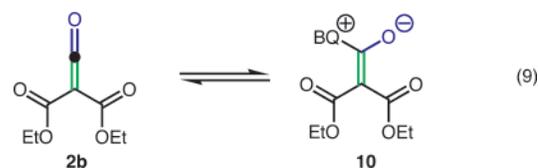
Another IR study was performed to understand the role of In(III) in our reaction. We had previously seen by NMR that ligand **3c** and In(III) form a complex when they are present in equimolar concentrations, but what happens when the imino ester is also present, as it is in our reaction? When the complex is in solution along with the imino ester in a 1:1 ratio, we observe a change in the IR spectra, more dramatic than with just the metal. The imino ester carbonyl stretch now shifts from 1751 to 1746 cm^{-1}, and the imine stretch now appears at 1621 cm^{-1} (from 1630 cm^{-1}). The carbonyl stretch for ligand **3c** also shifts in the presence of In(III) and the imine (from 1684 to 1694 cm^{-1}).

However, we have designed what we believe to be a more elegant test for productive metal binding to imino ester substrates. Imino esters **5b** and **c**, derived from ethyl glyoxylate and *p-* and *o-*methoxyaniline, respectively, are well-behaved substrates for the β-lactam forming reaction in the absence of metal cocatalysts. As expected, in the absence of metal, substrate **5b** reacts slightly faster than imino ester **5c**, which is more hindered due to the proximity of the methoxy group to the imine nitrogen (1.5:1 relative initial rate of formation of lactams **9a** to **9b**, eqs 7 and 8). On the other hand, in the presence of In-(OTf)$_3$ and Zn(OTf)$_2$ cocatalysts (10 mol %), the reactivity is reversed—substrate **5c** now reacts significantly faster (5:20 ratio for the relative rate of formation of **9a** to **9b** by NMR with In(OTf)$_3$). By virtue of its *o*-methoxy group, imino ester **5c** is tridentate in nature and, therefore, a better ligand for metals in general. Thus, if the metal activates the imine, all other things being equal, the better metal binder should be more reactive. Furthermore, since we have established that the metal cocatalyst increases the initial reaction rate, the chelated imine system should result in much faster product formation. (It should also be noted that imine **5c** can solubilize In(OTf)$_3$ fairly well in toluene conditions, whereas **5b** does not.)

Addressing Metal Binding to the Enolate and Metal Ion Catalysis of Ketene Dimerization. We also attempted to examine the interaction of metal ions (especially In(III) and Zn(II)) with ketenes and their zwitterionic enolates, thus coming at the problem from another angle. However, we were constrained by an unanticipated discovery; we found that when preformed ketene solutions are treated with 10 mol % In(OTf)$_3$ in toluene, a fast dimerization reaction ensues to afford high yields of the corresponding unsymmetrical ketene dimers in racemic form. Surprisingly enough, Lewis acid catalyzed ketene dimerization appears not to be a mechanistically well-studied reaction, although a few examples are known in the literature.[42] In our case, it seems that if free ketene is generated during our lactam-forming process, the corresponding reaction with the imino ester is much faster than dimerization, which does not appear to be a problem under our reaction conditions.

(42) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166−168.

(7)

no metal: *krel* = 1.5
with 10 mol% In(III) *krel* = 5

(8)

no metal: *krel* = 1
with 10 mol% In(III) *krel* = 20

Ultimately, we found that by moving to a more stable ketene, we were able to examine the interaction of this species with metal ions in the presence of BQ. In previous work, we characterized the zwitterionic enolate complex of ketene **2b** with BQ by IR and UV−Vis spectroscopy. We found that ketene **2b** is in equilibrium with complex **10** and that the equilibrium constant, even for such an electrophilic ketene, was still <1. An important question arises: how would a metal ion affect the equilibrium of eq 9? Although a metal-bound zwitterionic enolate should not be chemically more reactive than the corresponding unbound form, it may be more selective. Additionally, as discussed earlier, the presence of a metal such as In(III) may increase the amount of enolate that forms, thus increasing the rate of reaction through a perturbation of equilibrium (eq 10). We addressed this question by an examination of the effect that In(III) has on the relative concentrations of enolate and ketene. We discovered that the perturbation using ketene **2b**, BQ **3a**, and In(OTf)$_3$ is small (as measured by UV−Vis spectroscopy). Even with 1 equiv of In(III) in soluble form (THF solvent), the amount of ketene did not significantly diminish. As we would expect enolate **10**, substituted with carboethoxy groups, to be a good metal binder, the effect of metal on the equilibrium constant of simple ketenes in enolate formation may be negligible in comparison.


(9)

(10)

Reaction Mechanism: Addressing the Role of "Free" Metal. A plausible reaction mechanism involving catalyst **3c** must consider the possibility that both free and complexed indium takes part in the reaction. In an attempt to elucidate the roles of both ligand and metal, we performed standard UV−Vis experiments in which their proportions were varied. We determined that when the ligand to metal stoichiometry in THF was 1:1, substantial complexation occurred but that a small amount of free ligand remained. This fact implies that some "free" or very loosely bound metal is also in solution and plays a role in our overall reaction rate. Free metal is almost certainly in fast exchange with bound metal. In toluene, the quantity of free metal is considerably lower as the ligand binding constant increases, but the rate of reaction is approximately the same as it is in THF (namely, the initial rate is ~5 times the rate without metal)! We can conclude that in toluene, the metal complex plays a larger kinetic role than it does in THF.

Additionally, from the kinetic studies we performed in toluene with 10% propionitrile cosolvent (a system in which the activity of the metal is fairly attenuated due to solvation by the nitrile and the rate of the non-metal-catalyzed reaction increases as a result of increased polarity of the reaction medium) we estimate that ~20% of the product formation can be accounted for by the non-metal-catalyzed pathway. In toluene, using ligand **3c** and In(III) as catalysts, the non-metal pathway drops considerably, and therefore, the majority of the yield is attributed to the other two components. Therefore, our overall rate equation must be modified to include both the free metal and free ligand terms (eq 11). The rate constants (k_1−k_3) in this equation include the concentrations of all other substrates. An abbreviated proposed mechanism for the reaction involving free In(III) is shown in eq 12. Enolate formed from ligand (or complex In(III)−**3c**) reacts with In(III)-bound imino ester **5a** to produce the lactam product.

$$overall\ rate = k_1[\text{ligand}] + k_2[\text{ligand}][\text{In(III)}] + k_3[\text{ligand-metal complex}] \quad (11)$$

(12)
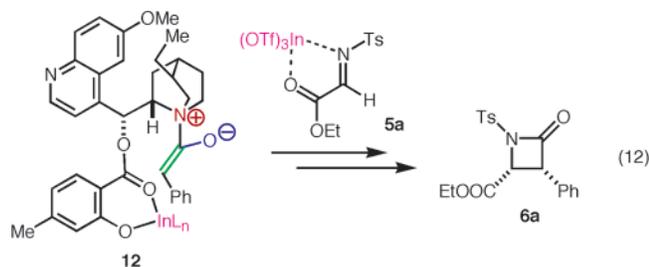
Reaction Mechanism: Addressing Scenarios B and C. An Alternative Test for Metal Binding to the Enolate. Upon further consideration we realized that we also had a potential test in hand for the diagnosis of intramolecular metal binding of In(III) to the enolate oxygen in complex **12**. Consider complex In(III)−**3d**, in which a metal binding unit is attached to quinine. If the metal does not bind to the oxygen atom of the enolate simultaneously, we would expect *re*-face selectivity (using our molecular mechanics calculations as a guide) as we have invariably seen in BQ-catalyzed reactions. On the other hand, if the metal binds to the oxygen atom of the enolate, for geometric reasons, the ketene faces should flip as the oxygen moves to bind the metal. This would lead to *si*-face exposure and a clear reversal of the observed stereoselectivity. To make
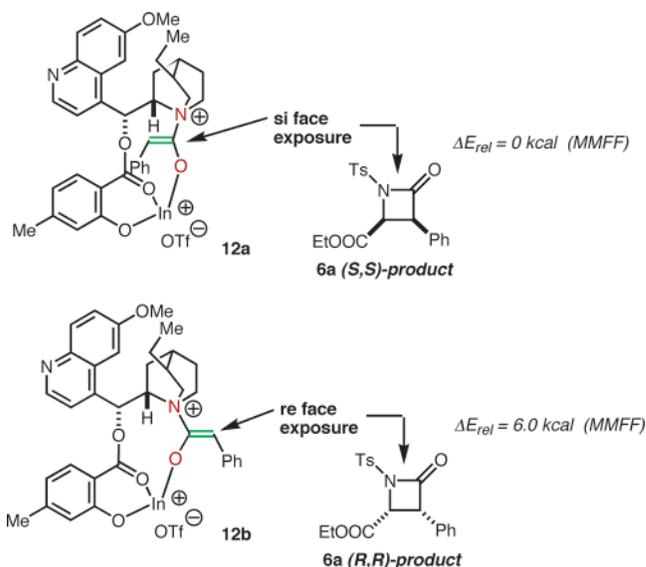
Figure 2. Expected facial discrimination of indium complex **12** for intramolecular bifunctional activation.
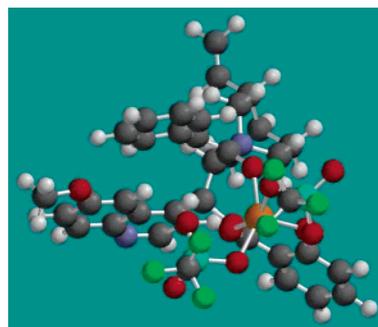
Figure 3. PM3-based model of metal enolate binding in complex **12a** showing expected *si*-face selectivity.

this prediction, we performed MMFF calculations on In(III)-based enolate complexes **12a** and **b** which should lead to *re*- and *si*-face selectivity, respectively (Figure 2). The *si*-face structure is almost 6 kcal/mol lower in energy, whereas the corresponding *re*-face structure is disadvantaged by virtue of a "flipped up" salicylate moiety, which seemingly adds strain to the complex. Thus, our prediction is that if the metal binds to the enolate oxygen, the opposite enantiomer should be formed preferentially.

Despite running the reaction under varied conditions, we have never observed this stereochemical reversal using complex **12** or even an attenuation of ee that would accompany such a pathway. We also know that the association constants of a variety of metals (including In(III)) with the salicylate group would preclude the presence of much free metal salt in solution—certainly too little would be present to account for the observed results. Thus, it appears as though intramolecular binding of the metal to the enolate oxygen can once again be disfavored at this point. This conclusion can also be rationalized by considering that a fair amount of strain energy is imparted in an activated complex such as **12a**. Figure 3 shows a model of a PM3 calculation that we performed on complex **12a**, showing how binding of the metal to the enolate oxygen would enforce *si*-face selectivity.

What then about *intermolecular* binding of the enolate oxygen through the metal center of another complex molecule? This is

where the labor involved in our kinetics experiments finally pays off. For example, we would anticipate that if another molecule of complex In(III)−**3d** were involved in the RDS, the rate dependence should vary as the square of the catalyst's concentration. That it does not argues against this enolate metal binding scenario.

We know from kinetics experiments that C−C bond formation occurs in the RDS, the stereochemistry-determining step in the cyclization reaction. The RDS must also involve the catalyst and the enolate. The same conclusions apply if we consider that the imino ester is activated by another complex molecule as well.

13
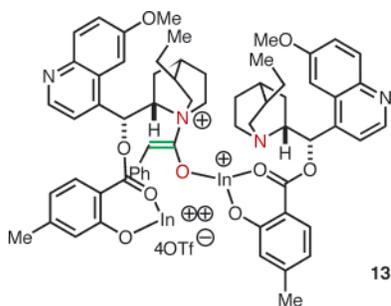
**Reaction Mechanism: An Alternative Way of Ruling Out Metal/Enolate Binding. Catalytic Halogenation Reactions.** A reaction that provides evidence to support our metal binding hypothesis is the catalytic, enantioselective chlorination of acid chlorides using benzoylquinine as the catalyst and the electrophilic, perchlorinated orthoquinone **14** as a halogenating agent (eq 13).[43] When we added a large variety of metal salts and complexes in an attempt to increase yields, no effect whatsoever was observed. If enolate stabilization were playing a role, we would, of course, expect the same effect as is observed in the β-lactam forming reactions.

Thus, we can conclude that the most plausible scenario for bifunctional activation involves a bifunctional complex that is consistent with scenario **A**, in which the metal binds to the imino ester following formation of the zwitterionic enolate.

(13)
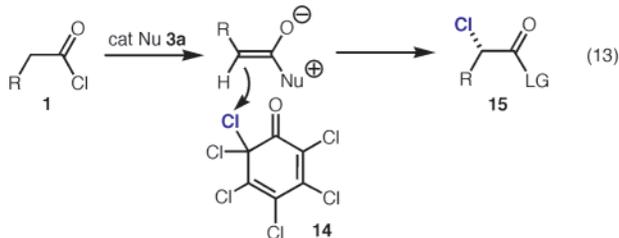
Mechanistic Hypothesis for Bound Metal. All of these data finally allow us to formulate a mechanism for the bifunctional reaction of catalyst system **3c** with ketenes and imino esters to produce β-lactams (Scheme 5). The first step involves the formation of a non-metal-coordinated zwitterionic enolate by the reaction of complex In(III)−**3d** with phenylketene. Imino ester **5a** then coordinates to the salicylate bound indium to form a ternary complex **16** in which C−C bond formation occurs as

(43) (a) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245−4255. (b) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532.

Scheme 5. Proposed Mechanism for the Synthesis of β-Lactams Catalyzed by Metal Complex In(III)−**3d**
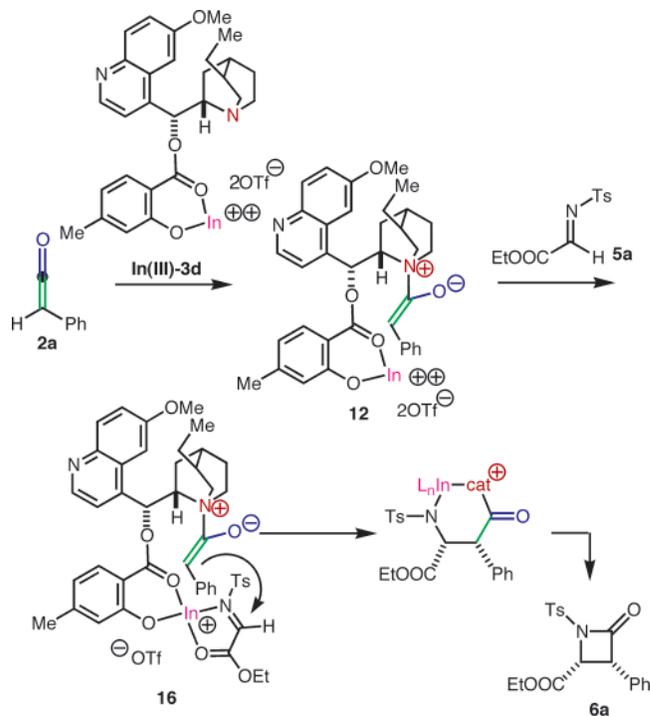
the RDS. Finally, transacylation followed by catalyst regeneration allow for additional catalytic cycles.

Conclusion

In summary, we have characterized an efficient bifunctionally catalyzed process for the synthesis of β-lactams that offers high yields as well as high diastereo- and enantioselectivities without deleterious byproduct formation by using metal salts in combination with chiral cinchona alkaloid nucleophiles. In(III) was found to be the most effective metal cocatalyst. A plausible mechanism for the activity of free metal and ligand-bound metal in our reaction is offered on the basis of the following mechanistic evidence: (1) Although In(III) solubilization experiments demonstrated activity at lower catalyst loadings, we were unable to overcome the deleterious solvent effects (lowered diastereoselectivity). (2) NMR and IR experiments offer substantive evidence for metal binding to the imino ester, strengthening our argument for the formation of an activated imine complex. (3) UV−Vis data disfavor the possibility of enolate−In(III) binding, as well as the formation of a ternary complex with catalyst **3a**. (4) Substantial binding and catalysis are observed when complex In(III)−**3c** is employed in our reaction, although there is a component of free metal catalysis in our rate equation. (5) Comparison of the rates of lactam formation with imines **5b** and **c** showed that In(III) can activate the imino ester and drastically change the relative rate of reaction. (6) Stereochemical evidence is supported by molecular modeling studies that disfavor intramolecular metal−enolate binding employing In(III)−**3c**. These results have led to an understanding of the role of In(III) as well as further clarifying our overall rate equation and providing an example of a clearly elucidated bifunctional catalyst system. Future expansion of this concept will include the effects of the combination of chiral nucleophiles

and chiral Lewis acids, the effects of Lewis acids on other imine substrates, and applications to bifunctional solid-phase synthesis procedures.

Experimental Section

General Procedure for the Tandem Nucleophile/Lewis Acid Promoted Synthesis of β-Lactams. To a suspension of In(OTf)$_3$ (3 mg, 0.013 mmol), benzoylquinine **3a** (5.6 mg, 0.013 mmol), and proton sponge (28 mg, 0.13 mmol) in toluene (7.5 mL) at −78 °C was added, dropwise, phenylacetyl chloride (**1a**) (20 mg, 0.13 mmol) in toluene (0.5 mL).[44] A solution of imine **5a** (32 mg, 0.13 mmol) in toluene (1 mL) was then added via syringe pump over 1 h. The reaction was allowed to warm to room temperature over 16 h before it was quenched with 1 M HCl (3 mL). The aqueous layer was then extracted twice with CH$_2$Cl$_2$, and the combined organic layers were dried over MgSO$_4$

and filtered through Celite. Absorption onto silica gel followed by column chromatography (10% EtOAc/hexanes) afforded product **6a** in 95% yield (46 mg) and 98% ee (dr 60:1).

Supporting Information Available: General procedures for the bifunctional, catalytic synthesis of β-lactams, synthesis of bifunctional catalysts and their complexes, and compound characterization, kinetic data, and UV−Vis data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA044179F

(44) For **6d,f**, the acid chloride was added to a solution of proton sponge and BQ in 7.5 mL of toluene and stirred at 0 °C for 30 min and then cooled to −78 °C. A suspension of In(OTf)$_3$ and the imine (1 mL of toluene) was added via syringe pump over 1 h.