Bifunctional Asymmetric Catalysis: A Tandem Nucleophile/Lewis Acid Promoted Synthesis of β-Lactams
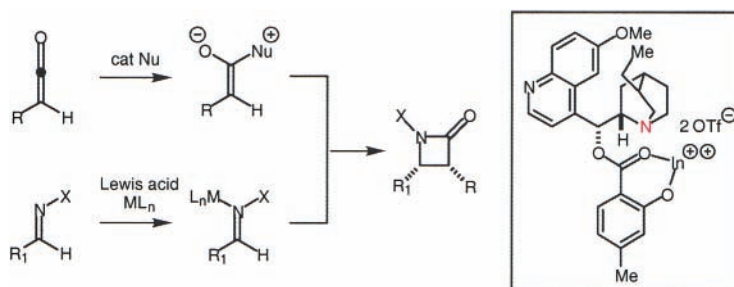
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ABSTRACT

We describe a superior procedure for the catalytic, asymmetric synthesis of β-lactams using a bifunctional catalyst system consisting of a chiral nucleophile and an achiral Lewis acid.

Bifunctional catalysis, in particular the combination of a Lewis acid working in tandem with a Lewis base or nucleophile, has been an appealing goal in organic chemistry for many years. Although bifunctional metal/organic systems always look good in theory, very often they do not function as intended. One of the most common reasons is the interference of a self-quenching reaction in which the Lewis base and Lewis acid combine to form a catalytically inactive adduct. In the past few years, however, considerable progress has been made in the development of bifunctional systems for organic synthesis wherein a weak Lewis base is used to work in concert with a Lewis acid.[1] Recently, a bifunctional system for the acceleration of the Baylis−Hillman reaction was reported wherein the authors combined a metal salt with a catalytic nucleophile, such as dabco.[2] Remarkably, the nucleophile and Lewis acid proved to be compatible with each other under the conditions of the reaction. In this contribution, we wish to report a system in which an *achiral* Lewis acid works in concert with a chiral nucleophile to effect a highly enantio- and diastereoselective catalytic reaction (Scheme 1). We hope that our results will point the way to the design of new systems for asymmetric catalysis with practical benefit for selectivity and yield.

We have published several studies on the catalytic, asymmetric synthesis of β-lactams, where we exploit a catalyzed reaction of nucleophilic ketenes and electrophilic imines[3] developed in our labs.[4] The enantioselectivity of this reaction is dependent on the use of a chiral nucleophile (in particular various synthetic cinchona alkaloid derivatives **5a,b**). The major limitation of this protocol has been the

(1) (a) Groger H. *Chem. Eur. J.* **2001**, *7*, 5247−5251. (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882. (c) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (d) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339−2342. For an example of Lewis acid/Brønsted acid bifunctional catalysis, see: (e) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599.

(2) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510−514.

(3) As a result of this role reversal, this process is mechanistically distinct from the classical Staudinger reaction.

chemical yield, generally ranging from 40% to 65%. Presumably, a portion of the ketene-derived zwitterionic enolate through which the reaction is believed to occur is being diverted before reaction with the imine **3** (X = Ts, R_1 = CO_2Et). We envisaged that the imine could be additionally activated by an adventitious Lewis acid, thereby favoring the desired reaction pathway while suppressing any side reactions (Scheme 1).

Scheme 1. Bifunctional Lewis Acid/Nucleophile Catalyzed Synthesis of β-Lactams
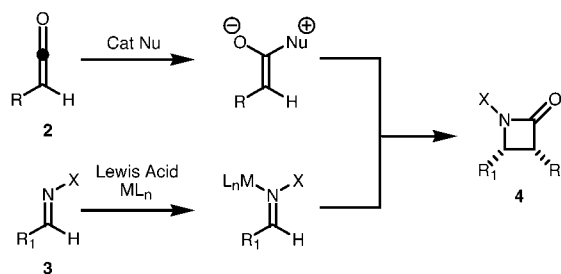
We began our studies by adding substoichiometric amounts of metal cocatalysts to our reaction mixtures. In our initial attempts, we employed 10 mol % of metal salts such as $Mg(OTf)_2$, $CuClO_4·(MeCN)_4$, and $YbCl_3$ to the standard reaction conditions to form β-lactam **4**.[5] In each case, the overall yield of the reaction *decreased* in the presence of the respective metal (Table 1, eq 1). This may be due to

Table 1. Initial Metal Screen to Form β-Lactams with Phenylacetyl Chloride and Imino Ester **3**, Catalyzed by BQ **5a** in Toluene

| entry	Lewis acid[a]	% yield[b]
1	none	65%
2	$Mg(OTf)_2$	36%
3	$Cu(MeCN)_4ClO_4$	49%
4	$YbCl_3$	55%
5	$La(OTf)_3$	63%
6	AgOTf	67%
7	$Al(OTf)_3$	78%
8	$Sc(OTf)_3$	80%
9	$Zn(OTf)_2$	85%
10	$In(OTf)_3$	95%

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

competitive binding of the metal to the quinuclidine nitrogen of benzoylquinine (BQ), thereby reducing its efficacy as a nucleophilic catalyst. For example, when $CuClO_4·(MeCN)_4$

(4) (a) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, 4, 627−629. (b) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387−390. (c) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853−10859. (d) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965. (e) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

was added to a solution of BQ in toluene, the color changed from clear to blue, implying that the BQ is acting as a ligand and possibly promoting the oxidation of the metal.

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). Overall the use of $Zn(OTf)_2$ (85%) and $In(OTf)_3$ (95%) resulted in the greatest increase in chemical yield, whereas $Al(OTf)_3$ (78%) and $Sc(OTf)_3$ (80%) were slightly less effective.
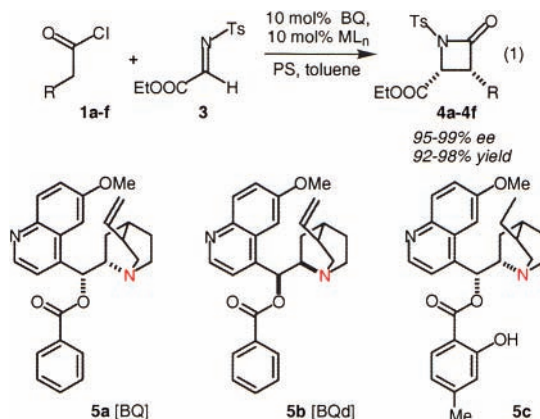
Three plausible mechanistic scenarios come to mind to explain the dramatic effect of the metal cocatalyst on the reaction. The first (and most obvious) is that the metal activates the imine toward nucleophilic attack by the organic zwitterionic enolate, thereby enhancing the rate of product formation (structure **A**).[6] One could also imagine that the metal modifies the zwitterionic enolate, making it more chemoselective in its reactivity. Its formation should be favored from a thermodynamic standpoint, assuming an equilibrium between the ketene and the enolate (structure **B**).[7] The third scenario is that both alternatives could be operating, with the metal organizing both enolate and imine in a *termolecular* activated complex (structure **C**). Kinetics experiments that we performed confirmed that the metal is having its effect *after* the rate-determining step of the reaction. For example, we discovered that the addition of 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.[8] However, the rate of product formation is increased by 30%, confirming a substantial improvement in reaction chemoselectivity. Although 10 mol % of the $In(OTf)_3$ was added to the reaction,

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

(6) We have previously found that imine **3** can be activated by late transition metal chiral bisphosphine 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.

(7) It is possible that the metal salt, rather than catalyzing the formation of product, *suppresses* the formation of undesired side products.

(8) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, in press.

we observed that some of the salt did not dissolve completely in the toluene solvent, implying that less cocatalyst is actually required.

$$\text{without metal } K < 1 \quad (2)$$
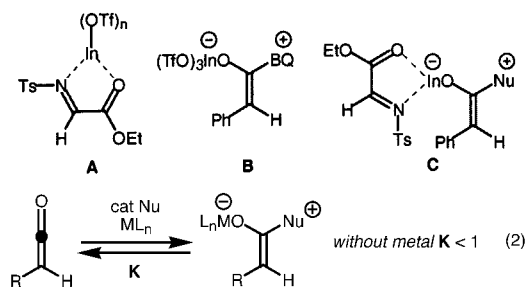
Having established that In(OTf)$_3$ was the best overall Lewis acid cocatalyst for promoting the reaction,[9] we applied this system to various substrates to determine the applicability and the effect on the reaction enantioselectivity (ee) and diastereoselectivity (dr). Generally speaking, the reaction ee's are maintained in the high 90's, and the chemical yields increased by a factor of 1.5−2. For example, **4a** was obtained in 95% yield and 98% ee (dr = 60/1), which represents a yield increase by a factor of 1.5. In the case of **4d** we were even able to double the yield without considerable decrease in selectivity (Table 2, entry 4).

Table 2. Catalytic, Asymmetric Synthesis of β-Lactams Employing BQ and In(OTf)$_3$ Cocatalyst

entry	product	yield[a]	yield[b]	ee[c]	dr (cis/trans)[d]
1	**4a**	65%	95%	98%	60/1
2	**4b**	60%	94%	98%	9/1
3	**4c**	53%	93%	96%	12/1
4	**4d**	45%	93%	97%	22/1
5	**4e**	61%	92%	98%	34/1
6	**4f**	56%	98%	96%	11/1

[a] Isolated yield from the original reaction without the added Lewis acid. [b] Isolated yield employing In(OTf)$_3$ as cocatalyst. [c] Enantioselectivity determined by chiral HPLC. [d] cis/trans ratio determined by ^{1}H NMR of the crude residue.

Next, we chose to investigate a homogeneous complex wherein the chiral nucleophile and Lewis acid were both present in the same entity. We prepared the chelating alkaloid derivative **5c** in two steps from quinine. Complexation of the sodium alkoxide salt of **5c** and 0.5 equiv of the desired metal salt affords a putative bis(salicylate) metal complex containing two catalytically active quinuclidine moieties.[10] Complex **6a**, 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, and imino ester. However, when complex **6b**, derived from 1:1 metal:ligand stoichiometry, was used, it afforded products in 80% yield, 99% ee and 8:1 dr. This observation and the fact that no comparable yield increase was observed when we applied this procedure to the catalytic, asymmetric α-halogenation reaction[11] led us to believe that metal chelation to the imine **3** (structures **A** or **C**) are the most probable scenarios for catalytic enhancement in this case.[12,13]
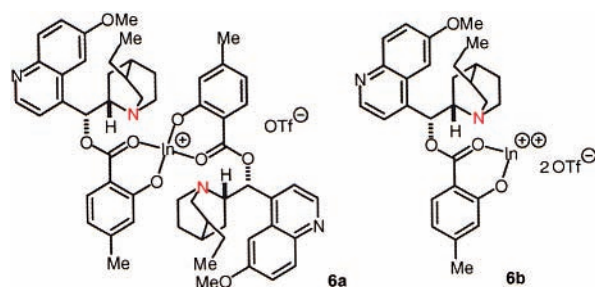
In conclusion, we have developed a bifunctional catalytic system in which a chiral nucleophile is paired with an achiral Lewis acidic metal salt to effect a high-yielding synthesis of optically enriched β-lactam products. Further studies will involve additional mechanistic and spectroscopic evidence as well as new bifunctional catalyst applications.

Supporting Information Available: General experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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

(10) See Supporting Information for details.

(11) We have successfully developed a catalytic, asymmetric α-halogenation procedure using monosubstituted ketenes as versatile substrates: (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532. (b) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.

(12) This would also suggest an equilibrium constant (K) of higher magnitude (eq 2).

(13) We have obtained IR evidence that supports metal chelation to the zwitterionic enolate intermediate formed by BQ and ketenes.