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A Multistage, One-Pot Procedure Mediated by a Single Catalyst: A New Approach to the Catalytic Asymmetric Synthesis of β-Amino Acids

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A catalytic asymmetric procedure for the preparation of β-amino acids (specifically β-substituted aspartic acid derivatives) is reported. The cinchona alkaloid catalyst benzoylquinine (BQ) mediates up to five distinct steps of a reaction pathway, all in one reaction vessel. The products of this reaction, highly optically enriched β-substituted aspartic acid derivatives, were prepared from *N*-acyl-α-chloroglycine esters and acid chlorides in the presence of the catalyst. This approach was also amenable to the synthesis of small polypeptides containing β-substituted aspartic acid units, including a non-natural fragment of the antibiotic lysobactin. The addition of Lewis acids to this system was found to accelerate the rate of specific steps in the reaction pathway. Mechanistic aspects of this reaction, such as imine formation and Lewis acid chelation to the β-lactam intermediate, were investigated through comparison of IR, NMR, and other physical data.

Introduction

Enzymes represent some of the most sophisticated and elegant machinery known for carrying out selective and highly specific chemical reactions. However, concurrent with this specificity comes the associated cost of complexity that can severely hamper their broader use as organic reagents. The use of small organic molecules as highly effective catalysts is being realized more frequently in organic synthesis.[1] However, a fundamental limitation prevalent with the use of small organic catalysts is that they usually perform only one chemical transformation in the overall reaction sequence. From a synthetic standpoint, it would be ideal if a single catalyst were capable of mediating a series of reactions in one reaction vessel. A biological analogy to such a process would be the use of a single enzyme (or enzyme complex) to carry out multiple steps in a biochemical pathway.

Substituted aspartic acid derivatives are currently of interest medicinally for use as inhibitors of L-asparagine synthetase,[2] key constituents of several proteins involved in the blood-clotting cascade,[3] and for their ability to act as nontransportable glutamate transporter blockers.[4] Additionally, β-amino acids are also used as α-amino acid surrogates for the construction of peptides possessing interesting folding patterns and conformational properties.[5] To date, there are several preparative methods for the catalytic asymmetric synthesis of β-amino acids.[6] Jacobsen[7] and Miller[8] have exploited the sequential azidation/reduction of α,β-unsaturated carbonyl compounds to this end. A different approach recently reported by Boger utilizes the Sharpless asymmetric amino hydroxylation of cinnamate esters.[9]

In this paper, we discuss results that have broadened the overall scope of our procedure for β-amino acid synthesis.[10] A noteworthy aspect of this approach includes the use of the organic catalyst benzoylquinine (BQ) that is capable of performing multiple catalytic roles in a single reaction flask. This catalyst carries out a series of chemical transformations, in essence a pathway of reactions. This method relies on the use of readily available and stable reagents to produce optically enriched β-lactams or β-substituted aspartic acid derivatives. We also examine mechanistic aspects of this reaction with the study of *N*-acylimine formation from α-chloroglycine derivatives and Lewis acid chelation to

(1) For a comprehensive review, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.

(2) Mokotoff, M.; Bagaglio, J. F.; Parikh, B. S. *J. Med. Chem.* **1975**, *18*, 354−358.

(3) (a) Hansson, T. G.; Kihlberg, J. O. *J. Org. Chem.* **1986**, *51*, 4490−4492. (b) Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289−6291. (c) Wagner, R.; Tilley, J. W.; Lovey, K. *Synthesis* **1990**, 785−786.

(4) Shimamoto, K.; Shigeri, Y.; Yasuda-Kamatani, Y.; Lebrun, B.; Yumoto, N.; Nakajima, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407−2410.

(5) North, M. *J. Peptide Sci.* **2000**, *6*, 301−313.

(6) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591−592. (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (d) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049−10053. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (f) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (g) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(7) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960.

(8) (a) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638. (b) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136.

(9) Boger, D. L.; Lee, R. J.; Bounaud, P.-Y.; Meier, P. *J. Org. Chem.* **2000**, *65*, 6770−6772.

(10) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387−390.

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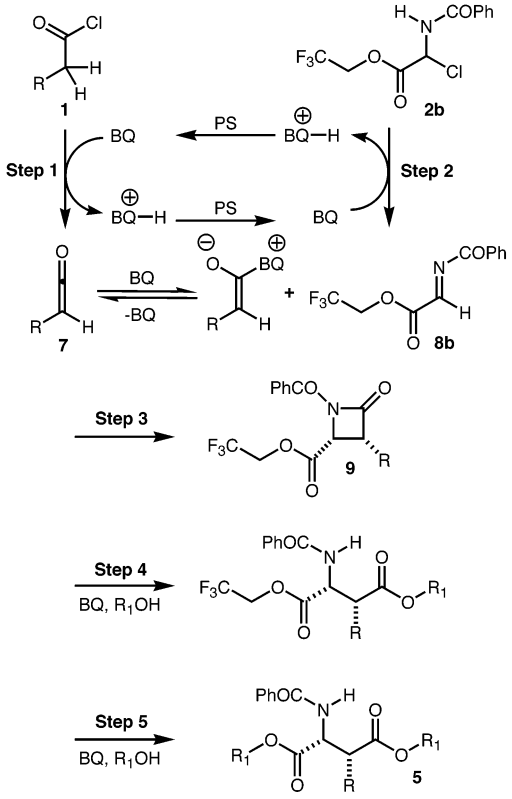
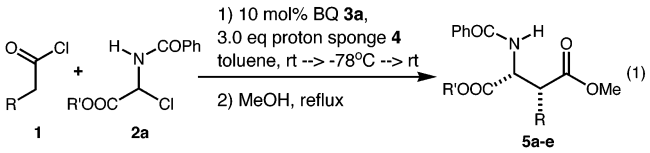
SCHEME 1. Reaction Pathway for β-Amino Acid Synthesis



β-lactams to facilitate ring opening. Furthermore, we utilize our methodology during the course of the synthesis of a fragment of the antibiotic lysobactin.

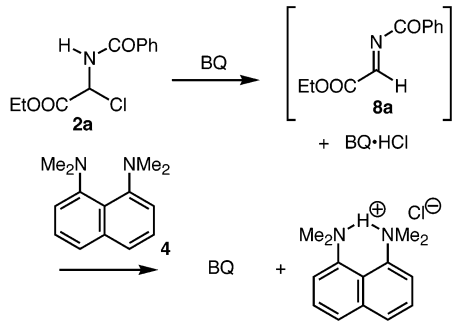
Results and Discussion

The Five Catalytic Roles of Benzoylquinine. Mechanistically, our synthesis of β-amino acids is unique in that the chiral cinchona alkaloid derivative BQ **3a** catalyzes up to five distinct sequential steps in one reaction flask (eq 1). To date, approaches based on the

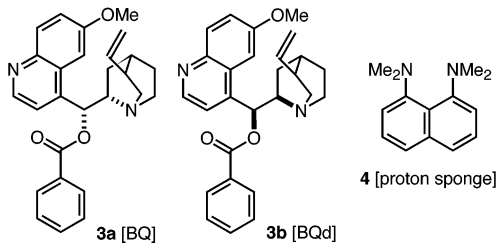


use of one specific catalyst capable of performing multiple tasks in a reaction sequence remain limited.[11] In this reaction scenario (Scheme 1), BQ acts as a dehydrohalogenating agent for the synthesis of ketene **7** (role 1, step 1) and *N*-acylimine **8** (role 2, step 2) from the acid chloride **1** and *N*-acyl-α-chloroamine **2**, respectively, an asymmetric catalyst for the [2 + 2] cycloaddition between the ketene and imine (role 3, step 3), a nucleophilic catalyst for ring opening (role 4, step 4), and a transesterification catalyst for ester exchange (role 5, step 5).

SCHEME 2. BQ-Catalyzed Dehydrohalogenation of α-Chloroglycine 2a



Initial experiments established that addition of α-chloroglycine **2a** to a solution of Proton Sponge **4** produces no reaction at room temperature. However, we found that in the presence of a catalytic amount of BQ (or other tertiary amines), **2a** underwent dehydrohalogenation to afford the intermediate imine **8a** at room temperature (Scheme 2). We believe that after dehydrohalogenation by BQ, the proton is relayed to the stoichiometric base, Proton Sponge. We have previously documented an analogous "shuttle" deprotonation system in the synthesis of reactive ketenes.[12] We also noted that simply mixing 1 equiv of Proton Sponge and acid chloride at low temperature does not produce detectable amounts of ketene. BQ serves as an excellent shuttle base when added to various solutions of acid chlorides in toluene at low temperature, allowing for ketene formation.[13]



In addition to the role of BQ in the stereoselective cycloaddition to form β-lactams, we found that in the presence of methanol, BQ greatly enhanced the rate of β-lactam ring opening (Scheme 3). Even at elevated temperatures, a large rate difference was observed between the BQ-catalyzed and uncatalyzed methanolysis reactions.[14]

To ensure that the catalyst BQ facilitated the ring opening and transesterification steps of this reaction, a control experiment was conducted using preformed β-lactam **9a** (R = Ph). The results of this experiment confirmed that BQ was indeed an active catalyst for this

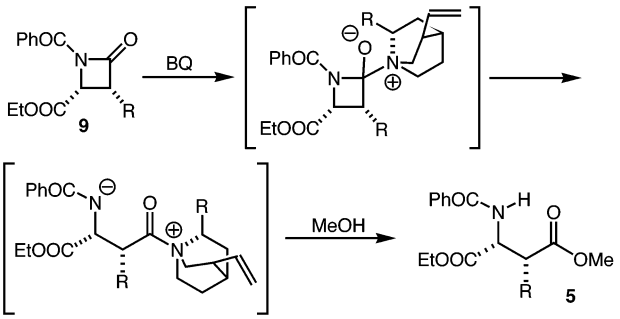
(11) Some examples of catalysts that perform at least two roles in a reaction sequence: (a) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045−1048. (b) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501. (c) Schenning, A. P. H. J.; Lutje Spelberg, J. H.; Hurbert, D. H. W.; Feiters, M. C.; Nolte, R. J. M. *Chem. Eur. J.* **1998**, *4*, 871−880. (d) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477−2480. (e) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (f) Bolm, C.; Dinter, C. L.; Seger, A.; Hocker, H.; Brozio, J. *J. Org. Chem.* **1999**, *64*, 5730−5731. (g) Shibasaki, M. *Chemtracts: Org. Chem.* **1999**, *12*, 979−998. (h) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

(12) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.

(13) The pK_a of Proton Sponge is 12, while that of BQ is not known, but probably similar to that of quinuclidine, which is 11.

(14) The uncatalyzed methanolysis took 48 h at reflux while the catalyzed reaction was complete in 14 h.

SCHEME 3. BQ-Catalyzed Ring-Opening Methanolysis



process based on the notable rate depression in its absence even at elevated temperatures (14 h with BQ versus 48 h with no catalyst). In a second control experiment, polymer-supported BQ **3c**[15] was utilized in the reaction to determine whether Proton Sponge or byproduct salts were responsible for the observed increased rate of methanolysis and transesterification. Removal of the polymer supported BQ prior to addition of methanol resulted in a reduced rate of ring opening and transesterification relative to when BQ was present. It was also noted that the rate of methanolysis (12 h) in the presence of polymer-supported BQ was comparable to that of the free, unbound BQ **3a**.

Catalytic, Asymmetric Synthesis of *β*-Amino Acids. We screened a number of acid chlorides with *N*-acyl-α-chloroglycine **2a** (Table 1) to furnish *β*-amino acids in a one-pot procedure. For example, a round-bottom flask was charged with α-chloroglycine **2a**, Proton Sponge **4**, and 10 mol % catalyst **3a** in toluene. The resulting suspension was stirred vigorously for 1 h and then diluted with toluene and cooled to −78 °C. A solution of phenylacetyl chloride **1a** in toluene was then added. The reaction was stirred for 6 h while gradually warming to room temperature. Methanol was added, and the mixture was heated at reflux for 14 h. Purification by column chromatography afforded **5a** in 62% yield (95% ee, 12/1 dr). Several different acid chlorides were used, including *β-O*-substituted acid chlorides such as **1b** and **1e**. Furthermore, with benzoylquinidine (BQd) **3b**, the pseudoenantiomer of **3a**, the opposite enantiomer is obtained in similar yields and selectivities (entry 2, Table 1).

We have also applied this procedure to the preparation of tripeptides. Using our methodology, *N*-acyl-α-chloroamine **2b** was allowed to react with phenylacetyl chloride **1a** and converted into the tripeptide **10** by the addition of 2 equiv of glycine methyl ester in 44% yield with 95% ee and 8/1 dr (eq 2). A control experiment established that, unlike methanolysis, the aminolysis reaction by glycine methyl ester showed no apparent rate dependence with respect to BQ. The stronger nucleophilic character of glycine is apparently the decisive factor in this particular case, allowing it to compete effectively with the BQ in the ring opening and transesterification steps of the reaction (Table 2).

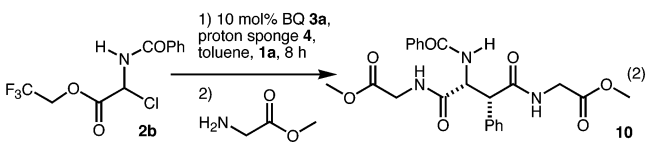
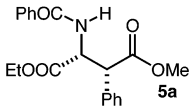
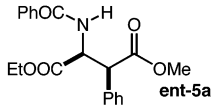
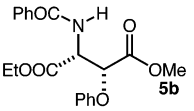
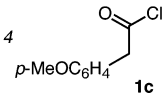
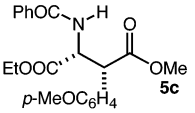
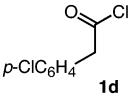
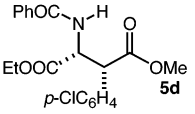
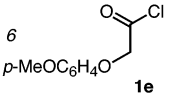
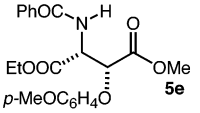


TABLE 1. One-Pot, Multicomponent α,*β*-Amino Acid Synthesis Using MeOH as the Ring-Opening Nucleophile

entry	acid chloride	product	yield (%)[a]	ee[b]	dr[c]
1	 **1a**	 **5a**	62	95	12/1
2[d]	 **1a**	 **ent-5a**	64	96	12/1
3	 **1b**	 **5b**	63	95	14/1
4	 **1c**	 **5c**	62	94	10/1
5	 **1d**	 **5d**	60	94	12/1
6	 **1e**	 **5e**	53	96	11/1

[a] Isolated yield of product after column chromatography. [b] Enantiomeric excess was determined by chiral HPLC. [c] Diastereomeric ratio was determined by crude ^{1}H NMR. [d] Opposite enantiomer was obtained by using benzoylquinidine (BQd) **3b**.

An Examination of Imine Formation from *N*-Acyl-α-chloroglycine Derivatives. To expand the general scope of this reaction, we have also carried out a systematic study of alternative bases and experimental methods for the preparation of *N*-acylimine **8a** from the parent α-chloroglycine **2a**.[16] Experimentally, *N*-acylimines represent useful precursors for the preparation of *N*-acylamino acids and *β*-lactams. Synthetic routes for the preparation of these products commonly involve the initial formation of a protected amine followed by subsequent deprotection and acylation to afford the desired *N*-acylated products. Although a more direct method would be the use of *N*-acylimines, procedures for their formation are rare due to their chemical instability.

We have found that the use of stoichiometric amounts of sodium hydride[17] offers a particularly attractive alternative for the formation of *N*-acylimine **8a** from α-chloroglycine **2a**.[18] The generation of the environmentally benign byproduct sodium chloride as opposed to potentially harmful ammonium salts, such as Proton Sponge hydrochloride, further highlights the value of this approach.[19] When sodium hydride was used as the stoichiometric base, comparable yields and selectivities (Table

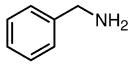
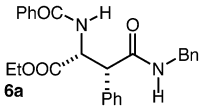
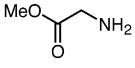
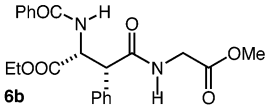
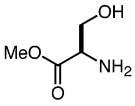
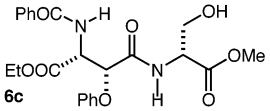
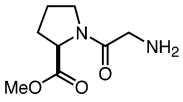
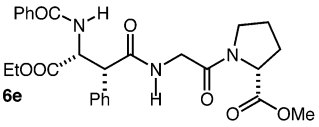
(15) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965.

(16) *N*-Benzoyl-α-chloroglycine derivative **2a** is easily prepared by the condensation of benzamide with ethyl glyoxlate followed by reaction with oxalyl chloride. See the Supporting Information.

(17) Dry NaH (95%) is utilized in the reaction.

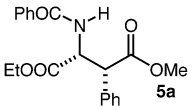
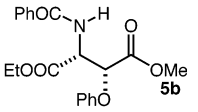
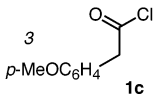
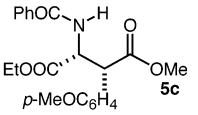
(18) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853−10859.

TABLE 2. One-Pot, Multicomponent α,β-Amino Acid Synthesis Using Amines as the Ring-Opening Nucleophile

entry	acid chloride	amine	product	yield (%)[a]	ee[b]	dr[c]
1	 **1a**		 **6a**	61	95	11/1
2	 **1a**		 **6b**	43	95	11/1
3	 **1b**		 **6c**	42	95	12/1
4	 **1a**		 **6e**	42	95	11/1

[a] Isolated yield of product after column chromatography. [b] Enantiomeric excess was determined by chiral HPLC. [c] Diastereomeric ratio was determined by crude ^{1}H NMR.

TABLE 3. α,β-Amino Acid Synthesis Using Sodium Hydride as a Base for *N*-Acylimine Formation

entry	acid chloride	product	yield (%)[a]	ee[b]	dr[c]
1	 **1a**	 **5a**	57	94	11/1
2	 **1b**	 **5b**	59	95	14/1
3	 **1c**	 **5c**	62	94	10/1

[a] Isolated yield of product after column chromatography. [b] Enantiomeric excess was determined by chiral HPLC. [c] Diastereomeric ratio was determined by crude ^{1}H NMR.

3) were obtained using the one-pot procedure. Drawing upon the work of Kobayashi,[20] we have also examined the use of polymer-bound bases as dehydrohalogenating reagents for *N*-acylimine formation. Kobayashi et al. have recently reported an asymmetric Mannich-type reaction utilizing a chiral copper catalyst for the preparation of *N*-acylated amino acids from *N*-acyl-α-chloroamines and enol silanes.[21]

The value of polymer-supported systems resides in the ease of product separation, a critical factor with respect to the chemistry and preparation of reactive *N*-acylimines. A survey of the commercially available resin-bound bases BEMP,[22] guanidine, and piperidine quickly established that the optimal base for dehydrohalogenation of the parent α-chloroglycine **2a** was a polymer-supported piperidine. Using this polymer resin for imine formation, followed by transfer of a filtered solution of the *N*-acylimine **8a** to a solution of preformed phenylketene **7a** and BQ **3a**, the desired β-amino acid **5a** was obtained in 52% yield with 94% ee and 12/1 dr. Previously, we have had success with the use of the highly basic polymer supported base BEMP as a dehydrohalogenating agent for the generation of ketenes from acid chlorides.[17] In contrast, none of the desired dehydrohalogenated *N*-acylimine product was formed upon exposure of the α-chloroglycine **2a** to BEMP resin. Instead, a series of degradation products were isolated from this generation method. Use of a less basic guanidine resin initially appeared more promising, but after repeated attempts to optimize the reaction conditions, isolated product yields remained low (13%).

Previously, we reported that carbonate salts, in the presence of a catalytic quantity of BQ, function as effective stoichiometric bases for the dehydrohalogenation of acid chlorides via a proton shuttle mechanism.[23] Extrapolation of this work to α-chloroglycine **2a** proved to be less rewarding. This method involved stirring a solution of α-chloroglycine **2a** in toluene for 8 h with an excess of K_2CO_3 and 10 mol % BQ. The carbonate salts were filtered off and the filtrate added to a solution of preformed phenylketene **7a** at −78 °C. Subsequent methanolysis, workup, and isolation of the desired product afforded insignificant quantities of the substituted β-amino acid product **5a**. The ineffectiveness of this last approach is likely due to decomposition of the *N*-acylimine intermediate during the extended reaction time with K_2CO_3.

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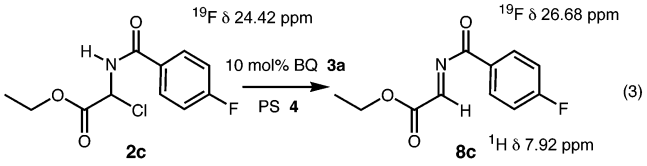
To elucidate the mechanistic role of BQ **3a** and Proton Sponge **4** as dehydrohalogenating agents of α-chloroglycine **2a** the reaction was monitored by ^{1}H NMR.[24] The formation of imine **8a** from α-chloroglycine **2a** was carried out and monitored by the periodic addition of aliquots of Proton Sponge and BQ to an NMR sample. Over the course of addition, a diagnostic singlet at 7.92 ppm corresponding to the imine CH proton was observed. This experiment verified that the formation of imine **8a** occurs under the reaction conditions. Unfortunately, the presence of byproduct salts and BQ made a more quantitative assessment of imine formation difficult. To address this issue, *N*-4-fluorobenzoyl-α-chloroglycine derivative **2c** was used in a ^{19}F NMR study to observe the relative rate of imine formation.[25] The starting *N*-4-fluorobenzoyl-α-chloroglycine **2c** gave one signal at 24.42 ppm (eq 3). The addition of Proton Sponge (2 equiv) did not result in any noticeable change in the ^{19}F NMR spectrum, thus ruling out the role of Proton Sponge as a dehydrohalogenating agent. However, upon addition of BQ (0.1 equiv) to the NMR sample, the peak at 24.42 ppm began to slowly diminish. Concurrent with the disappearance of the singlet at 24.42 ppm was the appearance of a new singlet at 26.68 ppm that we attribute to the formation of *N*-4-fluorobenzoylimine **8c** (eq 3).[26]

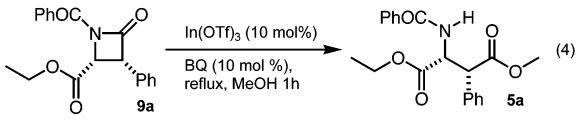


(3)

Under these experimental conditions, the *N*-4-fluorobenzoyl-α-chloroglycine **2c** had been totally consumed, and the formation of imine **8c** was complete within 0.5 h. Further study established that the reaction was not sensitive to the concentration of Proton Sponge and the overall rate of reaction was unaffected by the addition of excess Proton Sponge, thus supporting the role of BQ as the dehydrohalogenating agent.

Lewis Acid-Catalyzed Ring Opening of β-Lactams. The class B β-lactamase metalloenzymes, such as the zinc-dependent enzyme isolated from *Bacillus cereus*, are known to possess a broad substrate profile and to readily hydrolyze most classes of β-lactams.[27] Within these enzymatic systems, a metal center serves as an activator of the β-lactam carbonyl working in concert with a proximate water (or metal-bound hydroxide) molecule to facilitate ring cleavage.[28]

We have recently reported a bifunctional Lewis acid−Lewis base catalyst system for the synthesis of β-lactams.[29] Intrigued by the possibility of utilizing a bifunctional catalyst system for the enhancement of the BQ-mediated alcoholysis of β-lactams, we investigated the effect of adding metals to this reaction. As proposed, the addition of catalytic amounts of metals dramatically altered the rate of β-lactam ring opening. Our survey of Lewis acids revealed that metal triflate salts greatly enhanced the rate of ring opening. For example, addition of In(OTf)$_3$ (10 mol %) to a solution of β-lactam **9a** and 10 mol % BQ in MeOH, at reflux, resulted in the rapid conversion of β-lactam **9a** to the substituted β-amino acid **5a** in under 1 h (eq 4).



(4)

The comparable control reaction without the addition of a Lewis acid but in the presence of BQ took over 14 h to reach completion. Table 4 outlines a comparison of relative rates obtained for the methanolysis of β-lactam **9a** using different metal triflates. On the basis of these results, metal salts such as In(III) and the late transition metals Cu(II) and Zn(II) appear to be the Lewis acids of choice for facilitating β-lactam ring opening.

To garner further support for the catalytic role of the Lewis acid in this reaction, an IR experiment was conducted to determine the interaction between the β-lactam and Lewis acid (Figure 1). Upon addition of a stoichiometric amount of Cu(OTf)$_2$ to a solution of *N*-acyl-β-lactam **9a**, a shift in the β-lactam carbonyl stretching frequency from 1748 to 1746 cm^{-1} was observed. Additional shifts attributed to the *N*-acyl group carbonyl (1681 to 1684 cm^{-1}) and ester group (1797 to 1798 cm^{-1})

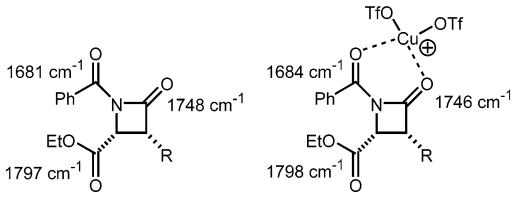


FIGURE 1. Carbonyl stretching frequencies in the presence of Cu(OTf)$_2$.

TABLE 4. Rates of β-Lactam 9a Ring Opening by MeOH in the Presence of BQ and Lewis Acids

catalyst	conversion time[a] (h)	relative rate
Cu(OTf)$_2$ + BQ	1	14.0
In(OTf)$_3$ + BQ	1	14.0
Zn(OTf)$_2$ + BQ	1.5	9.3
Sc(OTf)$_3$ + BQ	5	2.8
Cu(OTf)$_2$	8	1.7
Sc(OTf)$_3$	10	1.4
BQ	14	1.0
none	48	0.3

[a] Conversion times were monitored by TLC and confirmed by ^{1}H NMR.

(24) The ^{1}H NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in $CDCl_3$. The ^{1}H (400 MHz) chemical shifts are given in parts per million (δ) with respect to internal TMS standard.

(25) The ^{19}F NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in C_6D_6. The^{19}F (376 MHz) chemical shifts are given in parts per million (δ) with respect to internal $CFCl_3$ standard.

(26) We have also observed imine formation by ^{19}F NMR using the solid support base piperdine.

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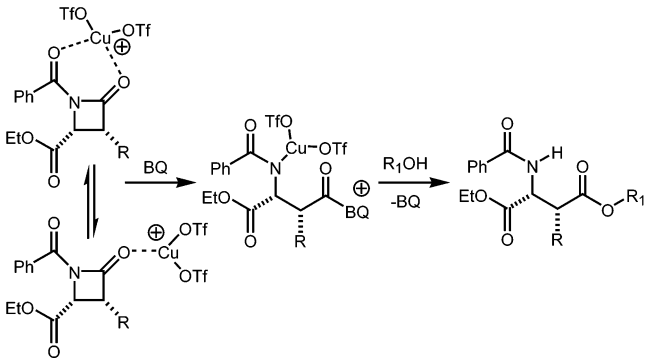
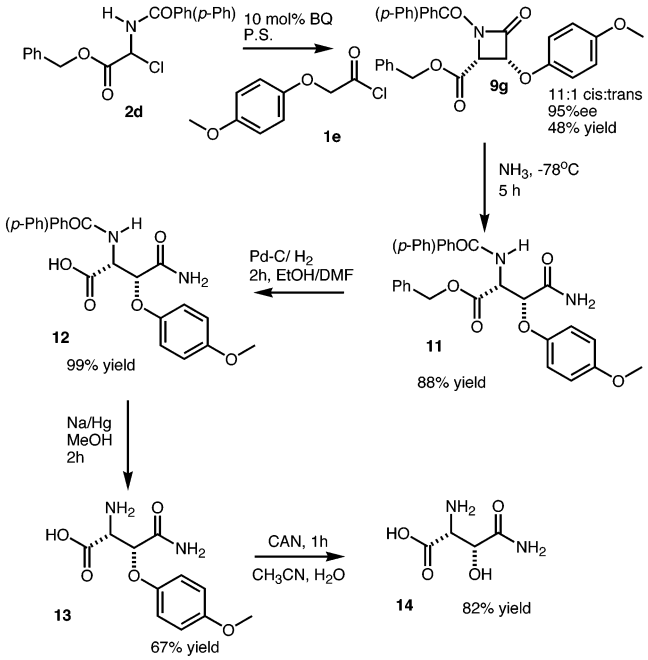
SCHEME 4. Lewis Acid Activation of β-Lactams for Alcoholysis

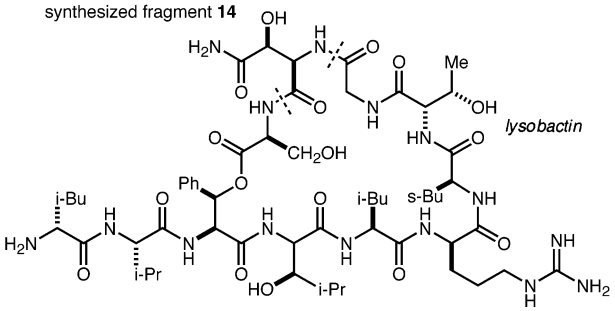


were also identified. The ring (C(O)−lactam) carbonyl stretch of a structurally similar *N*-acyl-*β*-lactam has been reported by Ojima et al. to occur at 1750 cm^{-1}, a number matching well with our observed figure of 1748 cm^{-1}.[30] The (C(O)N) acyl carbonyl shift of a similar *N*-benzoyl-*β*-lactam has been reported to occur at 1680 cm^{-1}.[31] It should be noted that the relatively small magnitude of the observed IR shifts in this experiment correlate with other reported findings. For example, a study by Lippard and colleagues found that the binding of a binuclear Zn complex to cephalothin resulted in a small, yet measurable, shift of the *β*-lactam carbonyl, 1773 to 1777 cm^{-1} (C(O)−lactam) and nitrogen acyl group, 1680 to 1683 cm^{-1} (C(O)N), respectively.[32] On the basis of our findings, it is highly plausible that Lewis acid activation involves the formation of a number of closely related chelation modes between the Lewis acid and the *N*-acyl-*β*-lactam **9a** (Scheme 4).

Synthesis of the L-*threo*-*β*-Hydroxyasparagine-Containing Subunit of Lysobactin. To highlight the scope of our methodology, we have prepared the unnatural amino acid L-*threo*-*β*-hydroxyasparagine as a key subunit in our proposed total synthesis of the antibiotic lysobactin.[33] Efforts directed toward the preparation of lysobactin and structurally related derivatives possessing improved therapeutic indices are of recent interest. Our approach to the synthesis of this key subunit rested on the disposition of the acid chloride and α-chloroglycine that we would use in our catalytic, asymmetric reaction to form the *β*-lactam intermediate. We determined that *p*-methoxyphenoxyacetyl chloride **1e** would provide an ideal protecting group for the *β*-hydroxy functionality in the final product. Our standard α-chloroglycine had to be modified in two ways in order to simplify the synthesis. First, the glycine nitrogen had to be protected by a biphenyl acyl group[34] that could be more easily removed than the benzoyl group on the original *N*-acyl-α-chloroglycine **2a**. Second, we switched from an ethyl ester to a benzyl ester that we envisaged would be easily hydrogenated before the final unmasking to produce L-*threo*-*β*-hydroxyasparagine **14**.

SCHEME 5. Synthesis of l-*threo*-*β*-Hydroxyasparagine Derivative





With these modifications made to our substrates, we set forth on our preparation of the *β*-hydroxyasparagine **14** by utilizing our standard PS/BQ protocol with (biphenyl-4-carbonyl)aminochloroacetic acid benzyl ester **2d** and *p*-methoxyphenoxyacetyl chloride **1e** to form the *cis*-*β*-lactam **9g** in 48% yield (11/1 dr, 95% ee). Aminolysis of the *β*-lactam gave the protected L-*threo*-*β*-hydroxyasparagine **11** in 88% yield. Hydrogenation of **11** removed the benzyl ester giving **12** in 99% yield. Deprotection of the biphenyl protecting group on the nitrogen by Na/Hg amalgam proceeded in 67% yield to give the free amine **13**. CAN oxidation unmasked the L-*threo*-*β*-hydroxyasparagine **14** in 82% yield (Scheme 5).

Similar to Boger and others, we observed that the unprotected carboxamide of an asparagine residue undergoes side reactions.[5] The L-*threo*-*β*-hydroxyasparagine **14** deteriorated into several byproducts upon standing after the CAN oxidative deprotection. Luckily, protection of the carboxamide prior to CAN oxidation eliminates these deleterious reactions and should provide for a straightforward solution in our proposed total synthesis of lysobactin that will be reported in due course.

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(34) The choice of a biphenyl amide protecting group afforded easy deprotection without interfering with other functional groups present in the molecule while maintaining the high yields and selectivities of the asparagine derivatives.

Conclusion. We have demonstrated that the organic catalyst BQ can serve as many as five distinct catalytic roles in the synthesis of β-substituted aspartic acid derivatives. This method involves the reaction of ketenes and *N*-acylimines formed in situ through dehydrohalogenation of the respective acyl halides and *N*-acyl-α-chloroglycines. In addition to its role as the dehydrohalogenating agent in this reaction, BQ also serves as a catalyst for the highly stereoselective formation of *N*-acyl-β-lactams with ee >90% and dr >10/1 in reasonable to good yields. Furthermore, the rates of β-lactam ring opening to the aspartic acid derivatives and subsequent transesterification were dramatically enhanced in the presence of BQ.

The use of alternative stoichiometric bases for imine generation was also examined. It was determined that the less costly base sodium hydride functioned as well as Proton Sponge to afford comparable yields of the desired products. This process was also amenable to the preparation of polypeptides by addition of individual amino acids or peptide fragments during the β-lactam ring opening stage of the reaction. Also, we established that the addition of Lewis acids during BQ-catalyzed alcoholysis further enhanced the overall rate of the reaction. The late transition metals $Cu(OTf)_2$ and $In(OTf)_3$ were found to be superior in the bifunctional Lewis acid−Lewis base-catalyzed methanolysis of *N*-acyl-β-lactams. Experimental evidence supports the existence of a cooperative interaction between the Lewis acid and Lewis base leading to the observed rate enhancement. Furthermore, utilization of this methodology allowed for the preparation of the L-threo-β-hydroxyaspararagine subunit of the antibiotic lysobactin whose total synthesis will be reported shortly.

Experimental Section

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used are commercially available. All solvents were dried and distilled by standard procedures. All acid chlorides were distilled by standard procedures. HPLC analysis was performed with a Waters Millipore Model 510 head unit, a Regis Technologies (*R*,*R*) Whelk-01 Chiral, a Waters Millipore Lambda-Max Model 481L spectrophotometer and a Hewlett-Packard integrator. Solution-phase IR data were recorded on a Bruker Vector 22 FTIR spectrometer.

General Procedure for β-Substituted Aspartic Acids 5a−e. A 25 mL round-bottom flask equipped with a stir bar was loaded under nitrogen with α-chloroamine **2a** (63 mg, 0.26 mmol), Proton Sponge **4** (83 mg, 0.39 mmol), and the benzoylquinine catalyst **3a** (6 mg, 0.013 mmol). Toluene (1 mL) was added to the mixture and stirred for 1 h. The solution was diluted with toluene (7 mL) and cooled to −78 °C in a dry ice/acetone bath. Phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in toluene (1 mL) was added to the reaction dropwise. The reaction was allowed to slowly warm to room temperature overnight. Excess methanol (6 mL) was added, and the solution was refluxed. The reaction was monitored by TLC and stopped when all of the β-lactam had reacted (∼14 h). The solvent was removed in vacuo, and the residue was taken up in chloroform (10 mL) and washed with 1 M HCl (3 × 10 mL). The organic layer was dried with $MgSO_4$ and filtered through Celite. The filtrate was concentrated, and the residue was submitted to flash column chromatography to yield **5a** in 62% yield (22 mg) and 95% ee.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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