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A Catalyst that Plays Multiple Roles: Asymmetric Synthesis of β-Substituted Aspartic Acid Derivatives through a Four-Stage, One-Pot Procedure

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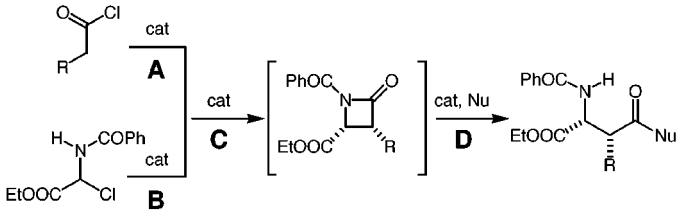
ABSTRACT



We report a new method for the catalytic, asymmetric synthesis of β-substituted aspartic acid derivatives in which the nucleophilic catalyst serves up to four discrete roles in a one-pot procedure: catalytic dehydrohalogenation of acid chlorides to form ketenes; catalytic dehydrohalogenation of α-chloroamines to form the corresponding imines; catalyzed [2 + 2]-cycloaddition to produce intermediate acyl β-lactams; and finally, nucleophilic ring opening to afford optically enriched β-substituted aspartic acids in high enantioselectivity and diastereoselectivity.

Extensive progress in the field of asymmetric catalysis over the past several years has led to the development of highly selective and efficient catalysts. Normally an asymmetric catalyst promotes one particular chemical transformation in a synthetic sequence.[1] One of the prime challenges of asymmetric synthesis would be to utilize catalysts to perform a number of tasks in a one-pot process.[2] We report herein a system for the synthesis of β-substituted amino acid derivatives (especially substituted aspartic acids)[3] that involves the use of inexpensive starting materials and an optically pure nucleophilic catalyst to produce highly optically enriched products in a one-pot procedure.[4] Our method involves up to four discrete stages, each catalyzed by the chiral nucleophilic catalyst benzoylquinine (**2a**, (BQ)):[5] catalytic dehydro-

(1) For example, see Jacobsen's synthesis of FR901464: Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974−9983.

(2) (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.

(3) For example, derivatives of β-hydroxyaspartic acid are known inhibitors of L-asparagine synthetase: (a) Mokotoff, M.; Bagaglio, J. F.; Parikh, B. S. *J. Med. Chem.* **1975**, *18*, 354−358. β-Hydroxyaspartic acids are present in many microorganisms: (b) Kornberg, H. L.; Morris, J. G. *J. Biochem.* **1965**, *95*, 577−586. (c) Ishiyama, T.; Furuta, T.; Takai, M.; Okimoto, Y.; Aizawa, S.; Shiman, A.; Yonehara, H. *J. Antibiot.* **1975**, *28*, 821−823. Various syntheses of L-erythro-β-hydroxyaspartic acid, a constituent of several proteins involved in the blood clotting cascade, have been reported: (d) Hansson, T. G.; Kihlberg, J. O. *J. Org. Chem.* **1986**, *51*, 4490−4492. (e) Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289−6291. (f) Wagner, R.; Tilley, J. W.; Lovey, K. *Synthesis* **1990**, 785−786. Derivatives of β-alkoxy and hydroxy aspartates are known nontransportable glutamate transporter blockers: (g) Shimamoto, K.; Shigeri, Y.; Yasuda-Kamatani, Y.; Lebrun, B.; Yumoto, N.; Nakajima, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407−2410.

(4) For a summary of recent asymmetric catalysis using nucleophiles, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.

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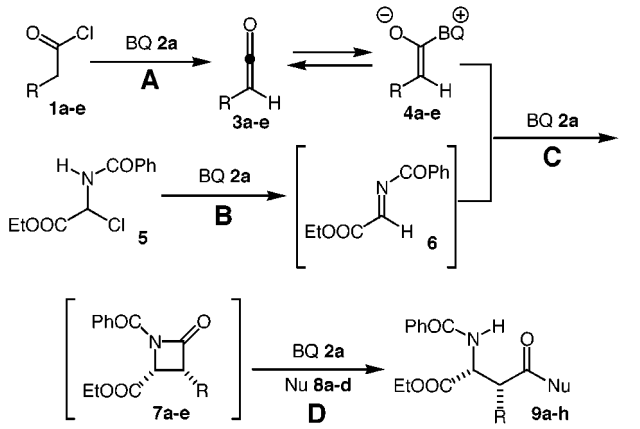
halogenation of acid chlorides **1** to form ketenes **3** (or derived zwitterionic intermediates **4**, (step A)), dehydrohalogenation of α-chloroamine **5** to form the corresponding imine **6** (step B),[6] catalyzed cycloaddition to produce intermediate β-lactams **7** (step C), and nucleophilic ring opening to form final products **9** (step D, Scheme 1).

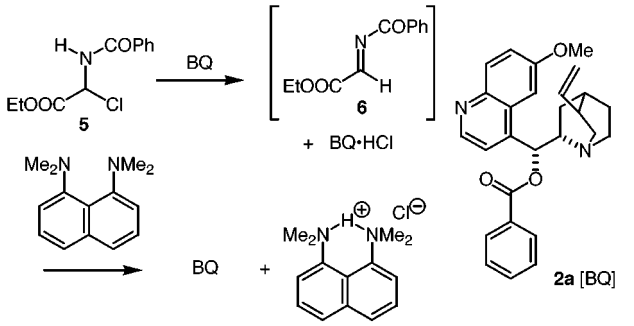
Scheme 1. A Four-Stage, One-Pot Procedure



The synthesis of optically enriched β-amino acid derivatives is a topic of intense interest in organic chemistry.[7] Catalytic, asymmetric methodology for this purpose has focused on the azidation of α,β-unsaturated carbonyl compounds and subsequent reduction of the products to the free amines.[8] Another approach would be to access β-lactam intermediates.[9] The success of our reaction is dependent on the intermediacy of chemically reactive *N*-acyl-β-lactams **7**, which are activated toward nucleophilic ring opening by alcohols and amines at the carbonyl carbon.

We performed a number of experiments to examine the role of catalyst **2a** in each step of the amino acid synthesis. Since the overall reaction involves intermediates that can be both isolated and characterized, we were able to perform each stage separately to assess the catalytic activity. Initial experiments established that addition of α-chloroamine **5** to a solution of highly basic proton sponge produces no reaction, even at elevated temperatures. However, we found that, in the presence of a catalytic amount of BQ (or other tertiary amine bases), **5** underwent dehydrohalogenation to afford intermediate imine **6** (Scheme 2). We believe that after

Scheme 2. BQ-Catalyzed Dehydrohalogenation of α-Chloroglycine



dehydrohalogenation by BQ, the proton is relayed to the stoichiometric base, proton sponge.[10] This is another example of shuttle deprotonation, which we have previously documented in the case of reactive ketene synthesis.[9c,11]

A second function BQ serves is ketene (or zwitterionic enolate) formation from acid chlorides using proton sponge as a nonnucleophilic, stoichiometric base. Aside from the role of BQ in the stereochemistry-determining cycloaddition,[9c] we found that in the presence of methanol, BQ greatly enhanced the rate of β-lactam ring opening.[12] Even at elevated temperatures, a large rate difference was observed between the BQ-catalyzed and uncatalyzed methanolysis reactions. To address whether proton sponge or byproduct salts were responsible for the increased rate of methanolysis, polymer-supported BQ **2b** was utilized in the reaction.[9b] Removal of **2b** prior to methanolysis resulted in a reduced rate of ring opening, relative to when BQ was present. These facts suggest that BQ acts as a nucleophilic catalyst in the β-lactam alcoholysis (Scheme 3). An additional control experiment confirmed that the enantioselectivity of the β-lactam intermediate and the final product were the same, discounting a potential chiral resolution by BQ in the ring-opening reaction.

(5) For other, excellent uses of cinchona alkaloids in asymmetric synthesis see the following. Ester synthesis from ketenes: (a) Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157−169. Lactone synthesis from ketenes: (b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. Ketene dimerization: (c) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006−8007. Baylis−Hillman reaction: (d) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219−10220. Osmylation reactions: (e) Kolb, H. C.; VanNieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. Phase-transfer catalysis: (f) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1999**, *120*, 13000−13001. (g) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355. Kacprzak, K.; Gawronski, J. *Synthesis-Stuttgart* **2001**, *7*, 961−998.

(6) α-Chloroamine **5** is easily made by the condensation of benzamide with ethyl glyoxylate followed by reaction with oxalyl chloride. See Supporting Information.

(7) (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.

(8) (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (b) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638.

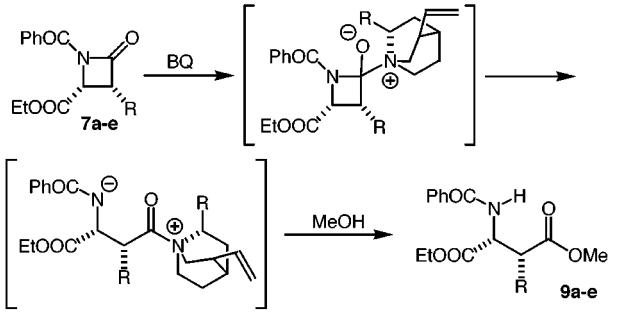
(9) We have recently reported a catalytic, asymmetric synthesis of β-lactams: (a) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem Soc.* **2001**, *123*, 10853−10859. (b) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965. (c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(10) For discussions concerning proton sponge basicity, see: (a) Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* **1990**, *26*, 255−279. (b) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215−1223.

(11) We have used powered carbonates as effective nonnucleophilic, stoichiometric bases for ketene generation: Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.

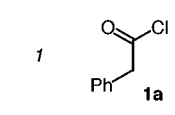
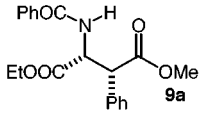
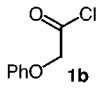
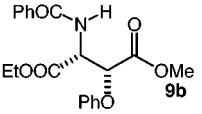
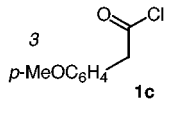
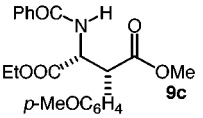
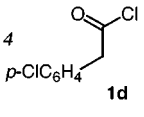
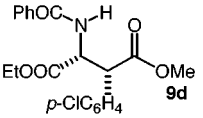
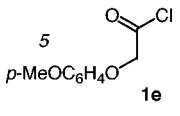
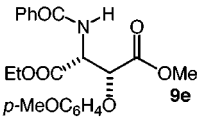
(12) The ring opening of β-lactams is known to be catalyzed by nucleophiles including azides: Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *J. Chem. Soc., Chem. Commun.* **1996**, 633−634.

Scheme 3. BQ-Catalyzed Ring-Opening Methanolysis



To establish the scope and practicality of the reaction, we screened a number of acid chlorides with α-chloroamine **5** (Table 1) to furnish the final products in a one-pot procedure.

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

entry	acid chloride	product	yield (%)[a]	er[b]	dr[c]
1			62	97.5/2.5	12/1
2			63	97.5/2.5	14/1
3			62	97/3	10/1
4			60	97/3	12/1
5			53	98/2	11/1

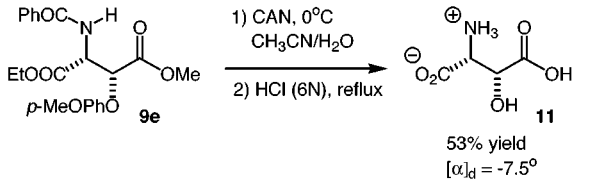
[a] Isolated yield of product after column chromatography. [b] Enantiomeric ratio was determined by chiral HPLC. [c] Diastereomeric ratio as determined by crude ^{1}H NMR.

For example, a 25-mL round-bottom flask was charged with α-chloroamine **5** (0.26 mmol), proton sponge (0.39 mmol), catalyst **2a** (0.013 mmol), and toluene (1 mL). The resulting suspension was stirred vigorously for 1 h, then further diluted with toluene (8 mL), and cooled to −78 °C. A solution of phenylacetyl chloride **1a** (0.13 mmol) in 1 mL of toluene was then added. The reaction was stirred for 6 h while gradually warming to room temperature. Methanol (4 mL) was added, and the mixture was heated at reflux for 4 h. The reaction was purified by column chromatography to afford **9a** (62%, 97.5/2.5 er, 12/1 dr, entry 1, Table 1).

Following the same procedure, α,β-amino acid derivatives **9b**−**e** were prepared (Table 1). The use of *p*-methoxyphenylacetyl chloride **1c** and *p*-chlorophenylacetyl chloride **1d** demonstrates that the reaction tolerates electron-donating and withdrawing groups on the aromatic ring without diminishing the yield or selectivity (entries 3 and 4, Table 1).

We anticipated that the use of *p*-methoxyphenoxyacetyl chloride **1e** would provide **9e** (entry 5, Table 1), which subsequently could be converted to β-hydroxyaspartic acid **11** (Scheme 4). Exemplifying this, **9e** was converted to the

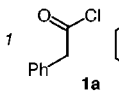
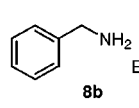
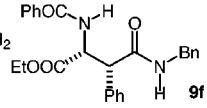
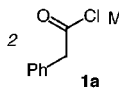
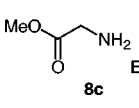
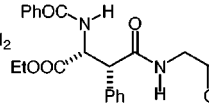
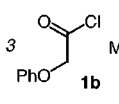
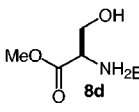
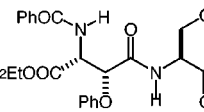
Scheme 4. Conversion of **9e** to β-Hydroxyaspartic Acid **11**



known glutamate uptake inhibitor (*R*,*R*)-2-amino-3-hydroxyaspartic acid (**11**) through a ceric ammonium nitrate (CAN) oxidation, followed by hydrolysis of the ester and amide groups, to afford **11** of known stereochemistry.

Additionally, the use of nucleophilic amines **8b**−**d** afforded ring-opened products **9f**−**h** (Table 2). For example,

Table 2. One-Pot Multicomponent α,β-Amino Acid Synthesis with α-Chloroglycine **5**

entry	acid chloride	amine	product	yield(%)[a]	er[b]	dr[c]
1				61	97.5/2.5	11/1
2				43	97.5/2.5	11/1
3				42	97.5/2.5	12/1

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

the addition of benzylamine (0.26 mmol) at room temperature afforded product **9f** (61%, 97.5/2.5 er, 11/1 dr, entry 1, Table 2). Likewise, ring opening by glycine methyl ester **8c** and (*S*)-serine methyl ester **8d**[13] afforded products **9g** and **9h** in similar selectivities and yield (entries 2 and 3, Table 2). Unlike methanolysis, ring opening of the intermediate β-lactams by amine nucleophiles proceeds rapidly in the absence of BQ.

(13) Epimerization of the hydroxymethyl group in **9h** was not observed under the reaction conditions.

In summary, we have developed a multistage, one-pot procedure for the synthesis of β-substituted aspartic acid derivatives. Hallmarks of the process involve the use of inexpensive starting materials and a chiral nucleophilic catalyst that performs up to four discrete roles. Further studies will center on the development of an iterative synthesis of polypeptides based on our β-substituted aspartic acid derivatives.

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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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