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Facile Synthesis of Bicyclic Amidines and Imidazolines from 1,2-Diamines

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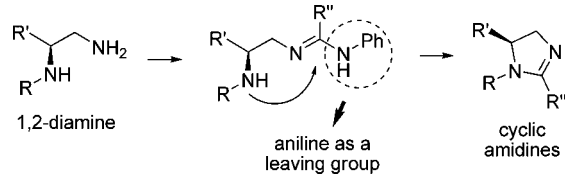
ABSTRACT



A facile synthesis of chiral bicyclic amidines and imidazolines from readily available 1,2-diamines has been developed. The reported synthetic strategy relies on an intramolecular cyclization which involves a carboxylic amide derived imidoyl chloride as a key intermediate and aniline serving as a leaving group.

Amidines are regarded as organic superbases and have been widely employed as key intermediates in the synthesis of heterocyclic compounds.[1] Amidines are also important in the pharmaceutical industry due to their unique biological properties.[2] Synthesis of chiral amidines has attracted much attention from synthetic organic chemists due to the widespread applications of amidines in asymmetric synthesis. Palladium−chiral amidine complexes were shown to catalyze enantioselective allylic substitution reactions[3] and allylic alkylations.[4] Oxazolines have been widely used as chiral ligands in asymmetric catalysis in the past few decades.[5] Imidazolines,[6] a class of structural analogues of oxazolines, have been intensively explored as chiral ligands in asymmetric synthesis in recent years. Various metal−chiral imidazoline complexes were applied to Diels−Alder reactions[7] and asymmetric hydrogenation reactions.[8] Besides their applications as chiral ligands, chiral imidazolines have also been utilized directly as organic catalysts in various reactions. Tsogoeva, Gobel, and co-workers utilized C_2-chiral bis(amidinium) catalysts for the asymmetric Diels−Alder reactions.[9] Tan et al. employed chiral imidazolines in asymmetric Baylis−Hillman reactions.[10] Using imidazolines as nucleophilic catalysts, Lectka and co-workers realized a diastereoselective synthesis of *trans*-β-lactams.[11] Recently, Kozlowski et al. applied bis(amidinium) to effect a Claisen rearrangement.[12] A C_3-symmetric chiral trisimidazoline was designed

(1) For the synthesis and conversion of amidine to useful compounds, see: (a) Granik, V. G. *Russ. Chem. Rev.* **1983**, *52*, 377. For recent selective references on synthesis of amidine, see: (b) Yamada, T.; Lukac, P. J.; George, M.; Weiss, R. G. *Chem. Mater.* **2007**, *19*, 96. (c) Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375. (d) Perrin, C. L.; Nuiiez, O. *J. Am. Chem. Soc.* **1986**, *108*, 5997. (e) Hills, M. S.; Hitchcock, P. B.; Mansell, S. M. *Dalton Trans.* **2006**, 1544. (f) Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677.

(2) (a) Guilford, W. J.; Shaw, K. J.; Dallas, J. L.; Koovakkat, S.; Lee, W.; Liang, A.; Light, D. R.; McCarrick, M. A.; Whitlow, M.; Ye, B.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 5415. (b) McCarthy, J. M.; Wright, D. L.; Schuster, A. J.; Abdullah, A. H.; Shea, P. J.; Eyster, R. *J. Med. Chem.* **1985**, *28*, 1721.

(3) Saitoh, A.; Achiwa, K.; Morimoto, T. *Tetrahedron: Asymmetry* **1998**, *9*, 741.

(4) Hu, X.-P.; Chen, H.; Dai, H.-C.; Hu, X.-Q.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 2073.

(5) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(6) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2009**, *351*, 489.

(7) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500.

(8) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.

(9) (a) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661. (b) Akalay, D.; Dürner, G.; Bats, J. W.; Bolte, M.; Göbel, M. W. *J. Org. Chem.* **2007**, *72*, 5618.

(10) Xu, J.; Guan, Y.; Yang, S.; Ng, Y.; Peh, G.; Tan, C.-H. *Chem. Asian J.* **2006**, *1*, 724.

(11) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461.

(12) Annamalai, V. R.; Linton, E. C.; Kozlowski, M. C. *Org. Lett.* **2009**, *11*, 621.

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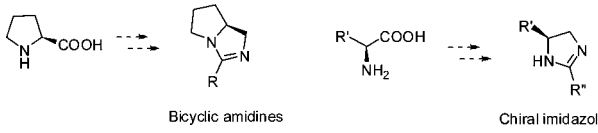
by the Fujioka group and used as catalyst in the asymmetric conjugate addition of β-ketoesters to nitroolefins.[13]

Our group has been actively investigating amino catalysis in the past few years, particularly those processes involving primary amino acid/primary amine based catalysts. We have applied a number of natural amino acids or their simple structural derivatives in a range of asymmetric organic reactions.[14] Very recently, we started an exploration of developing novel and efficient organic catalysts derived from amino acids. As a proof of concept study, a tryptophan-based bifunctional thiourea catalyst was designed and shown to be remarkably effective in promoting enantioselective Mannich reactions of α-fluoro-β-ketoesters.[15] Given the importance of chiral amidines in asymmetric synthesis and catalysis, we were intrigued by the possibility of deriving chiral cyclic amidines from natural amino acids. As shown in Scheme 1, starting from proline, bicyclic amidines may

Scheme 1. Preparation of Bicyclic Amidines or Chiral Imidazolines from Natural Amino Acids



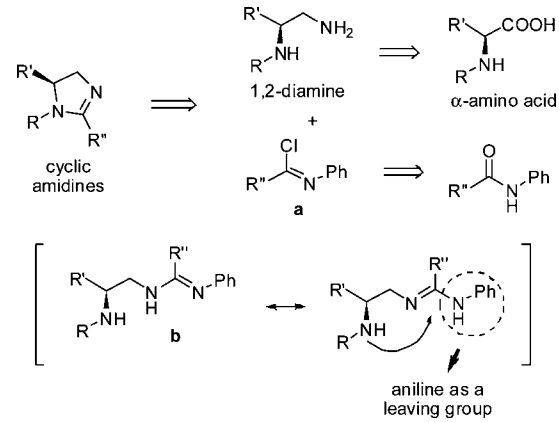
be synthesized, and utilization of primary amino acids could lead to the preparation of a range of chiral imidazolines. Herein, we wish to report a novel approach for the synthesis of chiral bicyclic amidines and imidazolines from readily available 1,2-diamines.

In general, there are three methods commonly used for the preparation of bicyclic amidines, which all employ an intramolecular reaction between a nitrogen nucleophile and properly activated lactam.Yamamoto and Maruoka reported an efficient synthesis of bicyclic amidines via an intramolecular nucleophilic attack of a free amino group on a lactam in the presence of $TiCl_4$. Alternatively, the corresponding iminoether could be used; however, its preparation involved strong acidic conditions.[16] Apparently, harsh reaction conditions posed severe disadvantages to this synthetic approach.

Hiemstra and co-workers developed a synthesis of bicyclic amidine, relying on the intramolecular reaction between a tethered amino group and a thiolactam function.[17] While this methodology was effective, the use of Lawesson's reagent and lengthy synthetic sequence required for the preparation of the key intermediate limited its applications. Shibasaki and co-workers recently disclosed an elegant approach which utilized an intramolecular cyclization of azido lactams. By employing the substrates with a properly installed azido group, facile cyclization occurred to yield a range of bicyclic amidines.[18] It was also reported that benzimidazoles can be prepared by the condensation between benzene-1,2-diamines and pivalaldehyde;[19] however, strong acidic conditions have to be employed and reactions typically proceeded in poor yields.

Our proposed synthetic strategy is illustrated in Scheme 2. We envisaged that cyclic amidines can be synthesized from

Scheme 2. Synthesis of Cyclic Amidines from Amino Acids/ Chiral Diamines



1,2-diamines and a properly designed condensation partner. α-Amino acids are abundant in nature, and they can offer easy access to various chiral 1,2-diamines with great structural diversity. *N*-Phenyl imidoyl chloride intermediate (**a**), which can be readily obtained from the corresponding *N*-phenyl carboxylic amide, seems to be a good choice for the condensation reaction.[20] Monoprotected diamine is expected to react with chloride **a** to yield amidine intermediate **b**, the subsequent intramolecular cyclization via a nucleophilic attack of the neighboring amino group is anticipated to afford cyclic amidine, expelling one molecule of aniline at the same time.

(13) Murai, K.; Fukushima, S.; Hayashi, S.; Takahara, Y.; Fujioka, H. *Org. Lett.* **2010**, *12*, 964.

(14) For reviews on primary amino acids and primary amines in asymmetric catalysis, see: (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (b) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (c) Peng, F.; Shao, Z. *J. Mol. Catal. A* **2008**, *285*, 1. (d) Chen, Y.-C. *Synlett* **2008**, 1919. (e) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759. For our work on primary amino acid/amine mediated organocatalysis, see: (f) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (g) Cheng, L.; Han, X.; Huang, H.; Wong, M. W.; Lu, Y. *Chem. Commun.* **2007**, 4143. (h) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018. (i) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812. (j) Zhu, Q.; Lu, Y. *Chem. Commun.* **2008**, 6315. (k) Zhu, Q.; Lu, Y. *Chem. Commun.* **2010**, *46*, 2235. (l) Jiang, Z.; Yang, H.; Han, X.; Luo, J.; Wong, M. W.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1368. (m) Jiang, Z.; Lu, Y. *Tetrahedron Lett.* **2010**, *51*, 1884. (n) Liu, C.; Lu, Y. *Org. Lett.* **2010**, *12*, 2278.

(15) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604.

(16) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.

(17) (a) Kotsuki, H.; Sugino, A.; Sakai, H.; Yasuoka, H. *Heterocycles* **2000**, *53*, 2561. (b) Ostendorf, M.; Dijkink, J.; Rutjes, F. P.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115. (c) Dijkink, J.; Eriksen, K.; Goubitz, K.; Van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron: Asymmetry* **1996**, *7*, 515.

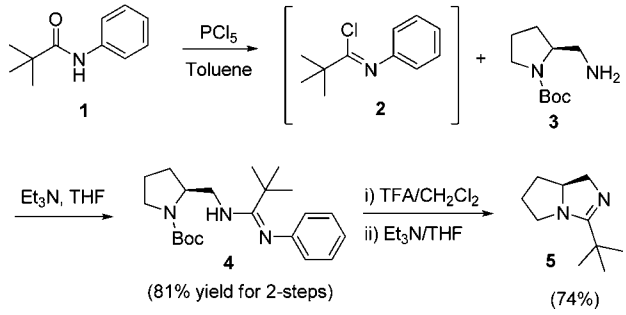
(18) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 478.

(19) Huang, H.-S.; Chen, T.-C.; Chen, R.-H.; Huang, K.-F.; Huang, F.-C.; Jhan, J.-R.; Chen, C.-L.; Lee, C.-C.; Lo, Y.; Lin, J.-J. *Bioorg. Med. Chem.* **2009**, *17*, 7418.

(20) *N*-Alkyl imidoyl chloride intermediates were too unstable to be employed in the synthesis.

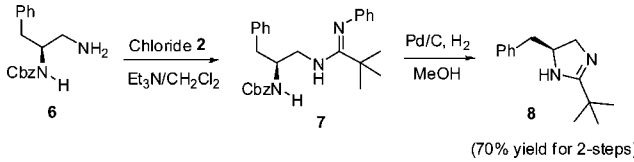
We next proceeded to test the feasibility of our proposed synthetic route, and a synthesis of a bicyclic amidine is illustrated in Scheme 3. *N*-Phenylpivalamide **1** was chosen as a starting material, and its reaction with phosphorus pentachloride[21] in toluene under refluxing conditions yielded imidoyl chloride **2**. Without purification, chloride **2** was subjected to the further reaction with proline derived diamine **3**, and advanced amidine intermediate **4** was isolated in 81% yield. The subsequent removal of the *N*-Boc protection then set the stage for the key cyclization step. A THF solution of deprotected amidine **4** with a neighboring free amino group at room temperature underwent a spontaneous intramolecular cyclization, affording the desired chiral bicyclic amidine **5** in good yield.[22] It should be noted that the reaction conditions employed in our synthesis are rather mild, and the reaction could be completed within 24 h at room temperature.

Scheme 3. Synthesis of Bicyclic Amidine from Proline



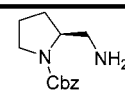
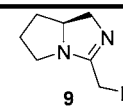
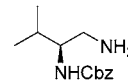
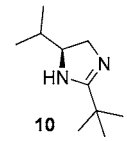
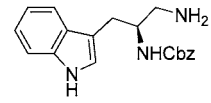
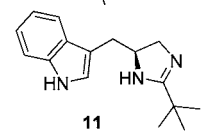
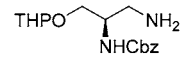
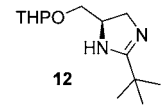
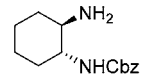
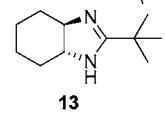
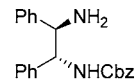
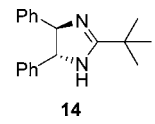
Alternatively, when a primary amino acid derived diamine was used, a chiral imidazoline was formed. As shown in Scheme 4, *N*-Cbz-protected diamine **6** derived from phenylalanine reacted smoothly with imidoyl chloride **2** to yield acyclic amidine **7**, which upon the cleavage of the Cbz group, spontaneously cyclized to yield imidazoline **8**. With the selection of Cbz as a protection instead of the Boc group, even weak acidic conditions could be avoided, and the intramolecular cyclization can proceed efficiently at essentially neutral conditions.

Scheme 4. Synthesis of Imidazoline **8** from Phenylalanine



Having proven the validity of our method and established efficient protocols for the preparation of bicyclic amidine/imidazoline from natural amino acid derived 1,2-diamines, we next proceeded to synthesize a number of other cyclic amidines from various chiral 1,2-diamines, and the results are summarized in Table 1. Substituents at the 2-position of the amidines can be varied: 2-benzyl-substituted bicyclic amidine **9** was synthesized when *N*-phenyl carboxylic amide derived from phenylacetic acid was used (entry 1). Diamines derived from valine, tryptophan, and protected serine led to the formation of imidazolines with different substituents at the 5-position (entries 2−4). Commercially available chiral 1,2-diamines could be used directly, and the corresponding imidazolines were obtained in high yields (entries 5 and 6). For synthetic convenience, the acyclic amidine intermediates generated from the reaction of diamines and crude imidoyl chloride did not need to be separated, and in situ cyclizations led to the final cyclic amidines in high overall yields. However, the limitation of the current method lies in that only amides derived from pivalic acid or phenylacetic acid worked effectively in the synthesis of cyclic amidines, as the imidoyl chloride intermediates derived from other amides were too unstable to be prepared.

Table 1. Preparation of Various Bicyclic Amidines from Readily Available Diamines[a]

entry	1,2-diamine	cyclic amidine	yield[b] (%)
1			70
2			88
3			80
4			78
5			81
6			84

[a] See Supporting Information for the full details of the synthesis. [b] Isolated yields.

In summary, we have developed a facile synthesis of chiral bicyclic amidines and imidazolines from readily available chiral 1,2-diamines. Our synthetic strategy relies on an

(21) Employing thionyl chloride or oxalyl chloride led to the formation of imidoyl chloride in very low yield.

(22) Aniline was observed during the reaction and could be isolated from the reaction mixture.

intramolecular cyclization which utilizes a carboxylic amide derived imidoyl chloride as a key intermediate and aniline serving as a leaving group. The reactions proceeded in high yields, and only one separation was required at the end of the synthesis. We anticipate the synthetic methods described will find wide applications in the synthesis of novel chiral amidines or amidine-containing molecules. Exploration of catalytic asymmetric reactions utilizing the chiral cyclic amidines generated in this report are currently ongoing in our laboratory.

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Supporting Information Available: Representative experimental procedures, analytical data, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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