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Modular Synthesis of Amine-Functionalized Oxazolines

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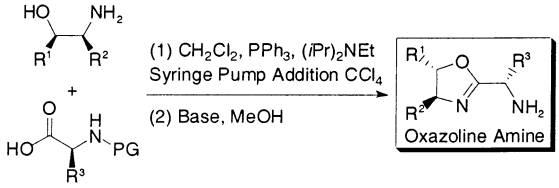
ABSTRACT



Substituted oxazoline amines have been prepared in high yield from β-amino alcohols and Fmoc-protected α-amino acids using CCl_4, PPh_3, and Hünig's base in a one-pot procedure followed by base-mediated deprotection.

The oxazoline scaffold is prevalent both in natural products[1] and ligands for asymmetric catalysis.[2,3] Consequently, the synthesis of oxazolines has generated intense interest among organic chemists.[4] In asymmetric catalysis, bis(oxazolines) have evolved as a "privileged" ligand structure, while other structurally divergent oxazolines have received considerably less attention.[5] In an effort to explore new oxazoline ligand templates for catalytic enantioselective reactions, we have targeted oxazoline amines (Figure 1). This oxazoline template contains three noteworthy features: (1) introduction of multiple chiral centers in which a variety of different substituents can be integrated, (2) the building blocks are commercially accessible with many available from the chiral pool, and (3) the pendant amine can be systematically elaborated. Markedly, this scaffold is also present in biologically relevant natural products.[1b−e] In this communication, we report a one-pot, modular synthesis of the oxazoline amine core from commercially available chiral building blocks.

The synthetic plan of the oxazoline amine[6] reveals that the oxazoline core can be synthesized by cyclic dehydration of a β-hydroxyamide (Figure 1). This is the most common method for oxazoline synthesis and is achieved by converting the hydroxyl group into a good nucleofuge.[4] The β-hydroxyamides can be accessed through amide bond formation using commercially available β-amino alcohols and suitably protected α-amino acids. A synthetically concise approach

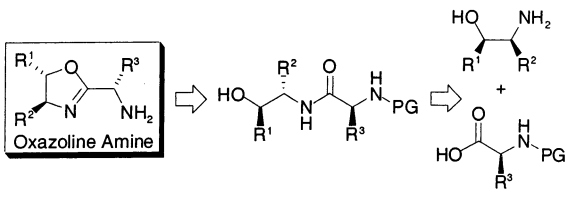


Figure 1. Oxazoline amine synthetic plan.

(1) Some examples include: (a) Agrobactin: Peterson, T.; Neilands, J. B. *Tetrahedron Lett.* **1979**, *20*, 4805. (b) Ascidiacyclamide: Hamamoto, Y.; Endo, M.; Nakagawa, M.; Nakanishi, T.; Mizukawa, K. *Chem. Commun.* **1983**, 323. (c) Lissoclinamides: Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; Brenk, A. L. v. d.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634. (d) Westiellamide: Prinsep, M. R.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L. *J. Nat. Prod.* **1992**, *55*, 140. (e) Bistratamide D: Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671. (f) Acinetobactin: Yamamoto, S.; Okujo, N.; Sakakibara, Y. *Arch. Microbiol.* **1994**, *162*, 249. (g) Ceratospongamide: Tan, L. T.; Williamson, R. T.; Gerwick, W. H.; Watts, K. S.; McGough, K.; Jacobs, R. *J. Org. Chem.* **2000**, *65*, 419.

(2) For a review of bis(oxazoline) ligands, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

(3) For an account of the use of Cu-bis(oxazoline) complexes in asymmetric catalysis, see: Johnson, J. S.; Evans, D. A. *Acc. Chem Res.* **2000**, *33*, 325.

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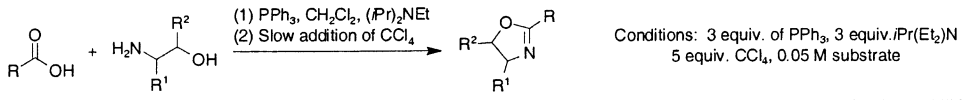
Table 1. One-Pot Synthesis of Protected Oxazoline Amines



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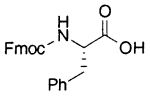
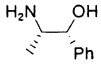
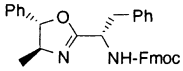
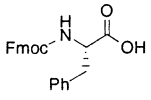
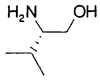
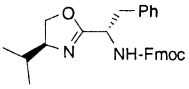
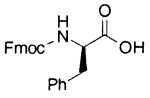
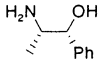
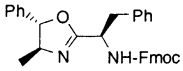
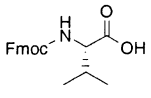
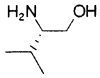
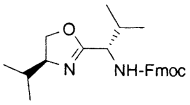
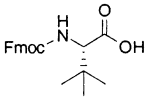
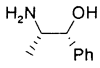
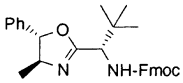
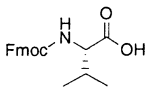
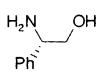
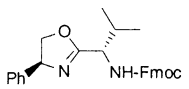
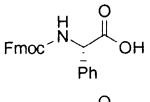
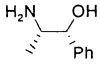
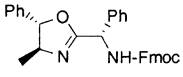
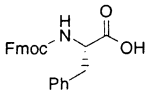
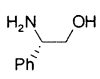
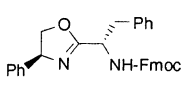
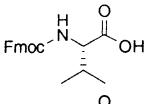
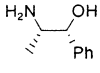
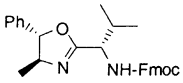
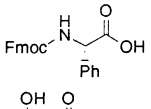
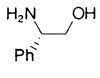
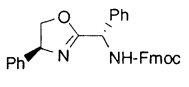
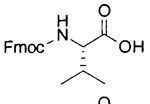
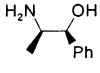
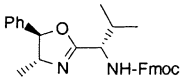
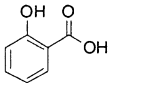
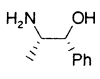
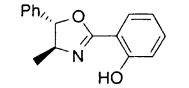
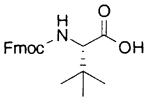
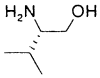
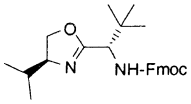
1				92	8				73
2				89	9				75
3				78	10				58
4				90	11				78
5				88	12				78
6				87	13				68
7				57	14				68

can be realized by combining the amide-bond formation and the cyclic dehydration in a single reaction pot. To effect this, precise control of the nucleophilicity of the various reactive groups has to be achieved.

A survey of the literature revealed that the largely underutilized procedure developed by Vorbrüggen and Krolikiewicz could be ideal.[7] In this procedure, the acid and β-amino alcohol are treated with CCl_4, PPh_3, and a base to generate the oxazoline in a single step. To prevent side reactions, either the CCl_4 or PPh_3 is added over 3 h to maintain low concentrations of the chlorophosphonium salt. At higher concentrations of the chlorophosphonium salt, the hydroxyl group of the β-amino alcohol competes with the carboxylate anion leading to the formation of acyl aziridines and isomeric oxazolines. Application of the Vorbrüggen procedure to the synthesis of oxazoline amines generates an additional level of complexity. The protecting group on the amino functionality of the α-amino acid must be stable to the basic conditions of the reaction and cannot be cleaved under acidic conditions since oxazolines are generally acid sensitive.

Preliminary experiments ruled out several protecting groups. The triflouroacetamide protecting group led to racemization of the α-amino acid under the reaction conditions.[8] In contrast, the Cbz-, Boc-, and Alloc-protected α-amino acids all cyclized cleanly, but removal of these protecting groups proved to be difficult.[9] Therefore, we redirected the effort toward a base-cleavable protecting group, which might be stable under oxazoline cyclization conditions. Fmoc offers the most convenient choice due to commercial availability of diverse Fmoc α-amino acids and a mild deprotection protocol. Modulating the basicity of the reaction conditions rendered Fmoc-protected α-amino acids

(4) Recent examples include the following. (a) PPh_3/DEAD: Roush, D. M.; Patel, M. M. *Synth. Commun.* **1985**, *15*, 675. (b) Burgess reagent: Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (c) $SOCl_2$: Gou, D.-M.; Liu, Y.-C.; Chen. C. S. *J. Org. Chem.* **1993**, *58*, 1287. (d) Polymer-supported Burgess reagent: Wipf, P.; Venkataraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659. (e) TsCl: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541. (f) DAST (diethylaminosulfur trifluoride): Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (g) Vilsmeir reagent: Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223. (h) Polymer-supported TsCl: Pirrung, M. C.; Tumey, L. N. *J. Comb. Chem.* **2000**, *2*, 675.

(5) For a recent review, see: Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680 and references therein.

(6) For the synthesis of oxazoline amines, see the following. (a) Ascidiacyclamide: Hamada, Y.; Kato, S.; Shiori, T. *Tetrahedron. Lett.* **1985**, *26*, 3223. (b) Westiellamide: Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (c) Lissoclinamide 7: Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *115*, 8449. (d) Bistratamide D: Downing, S. V.; Aguilar, E.; Myers, A. I. *J. Org. Chem.* **1999**, *64*, 826.

(7) (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353. (b) For a recent application, see: Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534.

(8) Benourgha, A.; Verducci, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1995**, *135*, 824.

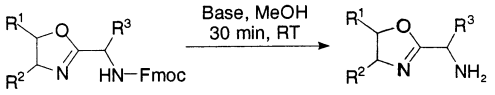
(9) Oxazolines with R^2 = Ph were destroyed during reductive removal of the Cbz. Removal of Boc under acidic conditions led to decomposition. Removal of Alloc with Pd(0) proceeded very slowly.

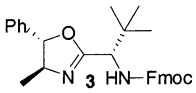
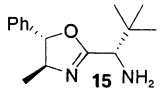
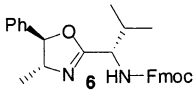
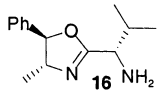
stable. The modifications include the following: (1) altering the solvent from CH_3CN/pyridine to dichloromethane, (2) substituting $(iPr)_2NEt$ for pyridine and NEt_3, and (3) holding the concentration <0.05 M.[10]

Using the modified conditions, we initially tested Fmoc-(*S*)-phenylalanine and (1*R*-2*S*)-norephedrine in the oxazoline-forming reaction. Gratifyingly, the corresponding oxazoline was isolated in 92% yield after flash chromatography (Table 1, entry 1). Encouraged by this initial result, the scope of the one-pot oxazoline synthesis was examined using various β-amino alcohols and Fmoc-protected α-amino acids (Table 1, entries 1−12). Using either enantiomer of the Fmoc-protected α-amino acids (entries 1−2) or the β-amino alcohol (entries 5−6), the desired diastereomers are formed in uniformly high yields. Large substituents are tolerated on the α-amino acid to the extent that *tert*-leucine cyclizes efficiently to the corresponding oxazoline in 78% yield (entry 3). Primary and secondary alcohols on the β-amino alcohol cyclize to provide the corresponding oxazolines in high yields (valinol, phenylglycinol, and norepheridine). Oxazoline formation using secondary alcohols gives a single diastereomer with inversion at the alcohol center, consistent with previously reported results.[7a] Other potentially useful oxazolines are prepared using this method, including pyridine-[11] and phenol-substituted[12] oxazolines (entries 13 and 14). Notably, the phenol does not need to be protected in the oxazoline formation.[7b]

A concern with this method is the possibility of racemization of the chiral center on the α-amino acid during activation for coupling. Racemization during coupling will be reflected in formation of epimeric products. Use of Fmoc-phenylglycine as a test substrate for this (entries 4 and 12)[13] afforded minimal epimeric product, as observed by ^{1}H NMR analysis (<10%). Importantly, no detectable racemization of the other α-amino acids is observed.

Table 2. Deprotection of Fmoc-oxazoline Amines



Entry	Base	Oxazoline	Product	Yield (%)
1	diethyl amine	 **3**	 **15**	99
2	piperidine	 **6**	 **16**	85

With the scope of this procedure examined, the stage was set for the crucial deprotection reaction. Trans-substituted oxazolines are known to be especially acid sensitive and therefore are difficult structures to access.[1a] To demonstrate the efficacy of this procedure in accessing these structures, oxazolines **3** and **6** were selected for deprotection (Table 2). Two common deprotection protocols for Fmoc were used in which oxazoline **3** was cleanly deprotected with 50% diethylamine in methanol in quantitative yield and oxazoline **6** was deprotected with 50% piperidine in methanol in slightly reduced yield (85%) after chromatography.[14]

In conclusion, we have developed a concise, one-pot procedure for the synthesis of protected oxazoline amines. The reaction proceeds in good to excellent yields and uses commercially available chiral building blocks. Significant diversity can be readily integrated into the scaffold by control of three stereocenters. The free oxazoline amine is prepared in excellent yields by removal of the Fmoc protecting group under mild conditions. Screening of oxazoline amines and derivatives for catalytic asymmetric reactions[15] and applications of this method in target-oriented synthesis are currently under investigation.

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Supporting Information Available: Experimental procedures, characterization, and ^{1}H NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Low concentrations were necessary to control Fmoc decomposition during the reaction.

(11) For the recent use of this ligand class, see: (a) Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, *66*, 7676. (b) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *Dalton* **2000**, *23*, 4432. (c) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (d) Perch, N. S.; Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2000**, *65*, 3836. (e) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499.

(12) For the use of these ligands, see: (a) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (b) Zondervan, C.; Feringa, B. L. *Tetrahedron: Asymmetry* **1996**, *7*, 1895. (c) Cozzi, P. G.; Gallo, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1995**, *14*, 4994. (d) Cozzi, P. G.; Gallo, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1995**, *34*, 2921. (e) Yang, H.; Khan, M. A.; Nicholas, K. M. *J. Mol. Catal.* **1994**, *91*, 319. (f) Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, *12*, 3485.

(13) Phenylglycine is often a test substrate for racemization in peptide couplings; see: Bodanszky, M. *Principles of Peptide Synthesis*, 2nd ed.; Springer-Verlag: Berlin, 1993.

(14) Using diethylamine to deprotect oxazoline **6** was unreliable.

(15) For recent examples of the use of oxazoline amine cores in asymmetric catalysis, see: (a) Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743. (b) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197.