Asymmetric Michael-Type Additions of Lithium Amides to Aromatic Systems Leading to Novel β-Amino Acids

Masanao Shimano and A. I. Meyers*

Department of Chemistry, Colorado State University Fort Collins, Colorado 80523

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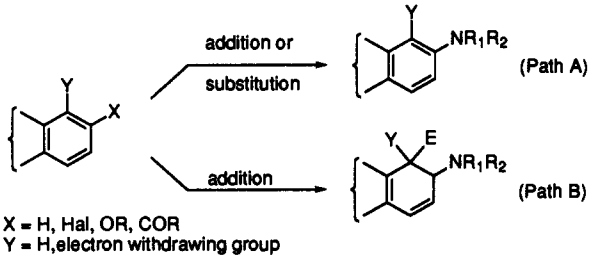
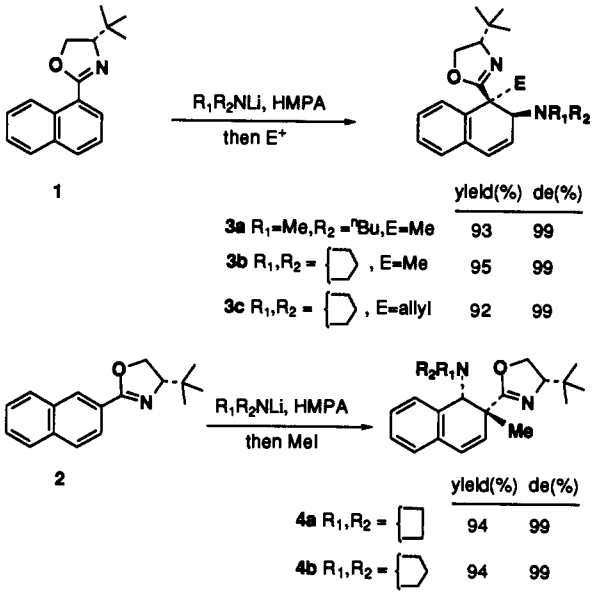
There are numerous methods to introduce an amino group into an aromatic ring system that retain the aromaticity of the nucleus (path A).[1,2] On the other hand, there appear to be no reported processes that directly introduce an amino group by interrupting the aromatic system, resulting in alicyclic amines (path B).



Furthermore, considerable effort[3,4] has been directed toward the synthesis of β-amino acids because of their occurrence in natural products,[5,6] as well as their utility as intermediates for preparing β-lactams,[7] therapeutically enhanced peptides,[8] chiral ligands, chiral building blocks, and chiral auxiliaries. Of these, the procedures involving a Michael addition of an amine to an α,β-unsaturated carbonyl compound[4] are the most versatile and simple. Although many Michael additions of amines have been described, there are no reports of the analogous direct amination of aromatic compounds.[9]

Scheme 1



In the course of our studies on oxazoline chemistry, we have developed several asymmetric carbon–carbon bond formation reactions[10,11] and also applied these to the synthesis of natural products.[11,12] Now we wish to describe a highly efficient regio- and stereoselective tandem addition of lithium amides–electrophiles to naphthalenes carrying the chiral oxazoline (**1**, **2**). The resulting doubly substituted products **3** and **4**, obtained in excellent yields and diastereoselectivity, were then transformed into the novel β-amino acids **7** and **8** of high enantiomeric purity.

1-[4′-(*S*)-*tert*-butyloxazolin-2′-yl]naphthalene, **1**,[13] and 2-[4′-(*S*)-*tert*-butyloxazolin-2′-yl]naphthalene, **2**,[13] served as suitable starting material for various lithium amide additions (Scheme 1). Both naphthyloxazolines reacted smoothly with lithium amides in the presence of HMPA (–78 and –50 °C), after which the addition of electrophiles afforded the desired products in excellent yields and with essentially complete diastereoselectivities.[14,15] However, in the absence of HMPA, poor yields were observed (**3a**, 30%, **3b**, 19%).[16]

In order to assess the stereochemical outcome, we subjected **4b** to single crystal X-ray analysis, which indicated a *trans* 1*S*,2*S*

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(3) (a) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. (b) Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M.-J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255. (c) Juaristi, E.; Escalante. *J. Org. Chem.* **1993**, *58*, 2282. (d) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758. (e) Mokhallalati, M. K.; Wu, M-J.; Pridgen, L. *Tetrahedron Lett.* **1993**, *34*, 47. (f) Jefford, C. W.; Wang, J. *Tetrahedron Lett.* **1993**, *34*, 1111. (g) Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307. (h) Jacobi, P. A.; Zheng, W. *Tetrahedron Lett.* **1993**, *34*, 2581. (i) Soloshonok, V. A.; Kirilenko, A. G.; Kukhar, V. P. *Tetrahedron Lett.* **1993**, *34*, 3621. (j) Bourzat, J. D.; Commerçon, A. *Tetrahedron Lett.* **1993**, *34*, 6049. (k) Palomo, C.; Aizpurua, J. M.; Miranda, J. I.; Mielgo, A.; Odriozola, J. M. *Tetrahedron Lett.* **1993**, *34*, 6325. (l) Hattori, K.; Yamamoto, H. *Synlett* **1993**, 239. (m) Murahashi, S.; Imada, Y. Kohno, M.; Kawakami, T. *Synlett* **1993**, 395. (n) Enders, D.; Klatt, M.; Funk, R. *Synlett* **1993**, 226. (o) Bates, R.; Gangwer, S. *Tetrahedron: Asymmetry* **1993**, *4*, 69 and references cited therein.

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(5) Recent reports about natural products including the β-amino acid moiety: (a) Rinehart, K. L.; Harada, K.-I.; Namikoshi, M.; Chen, C.; Harvis, C.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557. (b) Mynderse, J. S.; Hunt, A. H.; Moor, R. E. *J. Nat. Prod.* **1988**, *51*, 1299. (c) Helms, G. L.; Moor, R. E.; Niemczura, W. P.; Patterson, G. M.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298. (d) Kosemura, S.; Ogawa, T.; Totsuka, K. *Tetrahedron Lett.* **1993**, *34*, 1291. (e) Onuki, H.; Tachibana, K.; Fusetani, N. *Tetrahedron Lett.* **1993**, *34*, 5609. (f) Sone, H.; Nemoto, T.; Ishiwata, H.; Ojika, M.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8449.

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(9) There have been several reports of Michael-type *substitution reactions* of amines to the aromatic ring systems; see: (a) Meyers, A. I.; Gabel, R. *J. Org. Chem.* **1977**, *42*, 2653. (b) Tanaka, H.; Itoh, Y.; Ikushima, H.; Okamoto, M.; Kawai, Y.; Imanaka, H. *Tetrahedron Lett.* **1980**, *21*, 4359. (c) Meyers, A. I.; Reuman, M.; Gabel, R. J. *J. Org. Chem.* **1981**, *46*, 783.

(10) (a) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989. (b) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993. (c) Hulme, A. N.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 952.

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(13) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.

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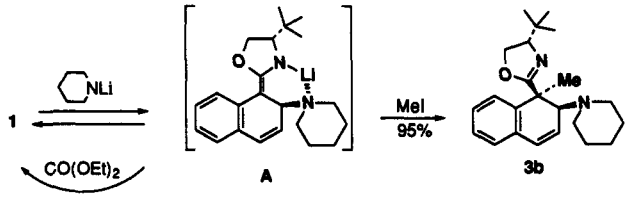
Scheme 2

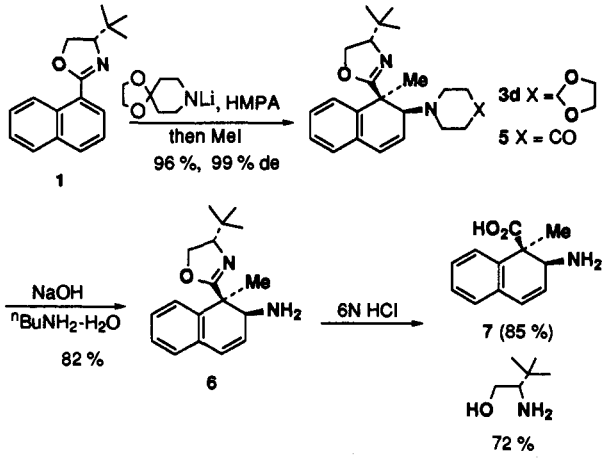


configuration for the piperidinyl and methyl groups, respectively. The stereochemical course of the addition was therefore consistent with previous organolithium additions to **1** and **2**.[13] The initial entry of the lithium amide to the naphthyloxazolines thus occurred from the β face and opposite the bulky *tert*-butyl group (Scheme 2, **A**). The subsequent alkylation of the intermediate azaenolate with the electrophile yielded the observed products, **3**. An unusual aspect of this process was observed when diethyl carbonate was used in the electrophilic step. As illustrated in Scheme 2, naphthyloxazoline **1**, when treated with lithium piperidide, gave **3b** after treatment with iodomethane, presumably via **A**. On the other hand, use of diethyl carbonate resulted in complete recovery of starting naphthyloxazoline **1**. This suggests that the adduct of naphthyloxazoline **1** and lithium piperidide is prone to reversal,[17] and only relatively reactive electrophiles (iodomethane, allyl bromide) lead to the desired products, whereas the relatively poor electrophile (diethyl carbonate) is ineffective. This unusual reversibility for **A** may simply be the result of the aromatic driving force. We also found that bulky amides (lithium diisopropylamide) gave only starting material, thus indicating that a significant steric effect was also operating.

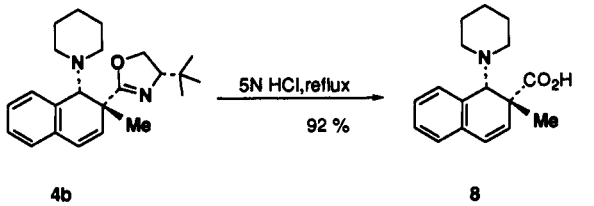
The present amide–naphthalene addition provided a stereospecific synthesis of novel β-amino acid **7** as shown in Scheme 3. In order to obtain the primary amino acid, we chose the piperidone ketal as a suitable ammonia equivalent. The reaction between naphthyloxazoline **1** and the lithium amide of the piperidone ketal went smoothly and afforded **3d** in 96% yield and 99% de.[15]

Hydrolysis of the acetal moiety in **3d** (concentrated HCl, 95%) was followed by the reverse Michael addition of carbon–nitrogen bonds in the piperidone ring to liberate the free primary amine. This was achieved by treatment of **5** with ^{n}BuNH$_2$ in aqueous NaOH. *n*-Butylamine played three important roles in this removal sequence: (1) to solubilize the substrate, (2) to trap the liberated divinyl ketone,[18] and (3) to protect the free amine **6** from oxidation. The removal of the oxazoline was carried out by hydrolysis (see

Scheme 3



the supplementary material), which gave the amino acid, **7** {$[\alpha]_D$ = 100.0° (c = 0.18, DMSO)} (85%, >99% ee[19]), along with the recovered 2-*tert*-butyl-2-aminoethanol (72%). It should be noted that the β-amino acid **7** is conformationally rigid due to the dihydronaphthalene ring system, thus making it a good candidate for use in peptidomimetics,[20] especially as β-turn mimetics. The piperidine adduct **4b** was also converted to the corresponding β-amino acid, **8** {$[\alpha]_D$ = 71.2° (c = 1.74, $CHCl_3$)} (92%, >99% ee[19]), by the same hydrolysis conditions (5 N HCl, reflux), which led to **7**.[21]



Further studies to reach a wide variety of novel, rigid β-amino acids and related 1,2-diamines in this series are underway and will be reported in due course.

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support of this work. A leave granted to M.S. by Kaken Pharmaceutical Co., Ltd. is also gratefully acknowledged.

Supplementary Material Available: Experimental procedures, compound characterization data, HPLC chromatograms for chiral amino acids assay, and the ^{1}H and ^{13}C NMR spectra for **3a-d, 4a,b, 7,** and **8** (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) All new materials were fully characterized. Copies of proton and carbon NMR spectra may be found in the supplementary material. All yields are isolated yields. The diastereoselectivities were determined by GC analysis or proton NMR of crude reaction mixtures.

(15) Following is a typical procedure: To a stirred, cooled (–5 °C) solution of 1,4-dioxa-8-azaspiro[4.5]decane (1.5 equiv) in THF was added ^{n}BuLi (1.4 equiv) dropwise. The reaction mixture was stirred at –5 °C for 45 min, then cooled to –78 °C, treated with HMPA (1.5 equiv), stirred for 5 min, and treated with 1-[4′-(*S*)-*tert*-butyloxazolin-2′-yl]naphthalene, **1** (1.0 equiv), in THF dropwise. The resulting yellow solution was stirred at –78 °C for 1 h, then warmed to –50 °C over 1 h, re-cooled down to –78 °C, and treated with iodomethane (1.6 equiv). After stirring at –78 °C for 20 min, the mixture was allowed to warm to –20 °C over 2 h. Extractive workup and flash chromatography (silica, EtOAc–hexane) gave pure product, **3d** (96%) {$[\alpha]_D$ = 513.0° (c = 2.80, $CHCl_3$)}.

(16) For analogous organolithium addition to naphthyloxazolines, HMPA was shown to have a deleterious effect; Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(17) To the best of our knowledge, this is the first example exhibiting the reversible addition of an lithium amide to an α,β-unsaturated system. However, the reversible addition of a simple amine under thermodynamic conditions has been reported: Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.

(18) Considerable amount of *N*-butylpiperidone was isolated after column chromatography.

(19) The enantiomeric excess of the amino acid **7** and **8** was determined as follows: **7** was converted into the corresponding amido ester and subjected to HPLC on a Chiralcel OD column eluting with 5% EtOH–hexane. **8** was also converted to the corresponding methoxymethyl ester and subjected to HPLC on a Chiralcel OD column eluting with 1% EtOH–hexane. The corresponding racemic derivatives of **7** and **8** were synthesized from 1-(4′,4′-dimethyloxazolin-2′-yl)naphthalene and analyzed under the same conditions.

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(21) It is of interest to note that the existence of a cosolvent (EtOH, MeOH, THF, etc.) completely prevented the hydrolysis of **4b** even when it was conducted at temperatures higher than 100 °C.