Diastereoselective 1,6-Additions of Lithium Amides to Naphthyloxazolines. A Route to Novel δ-Amino Acid Derivatives

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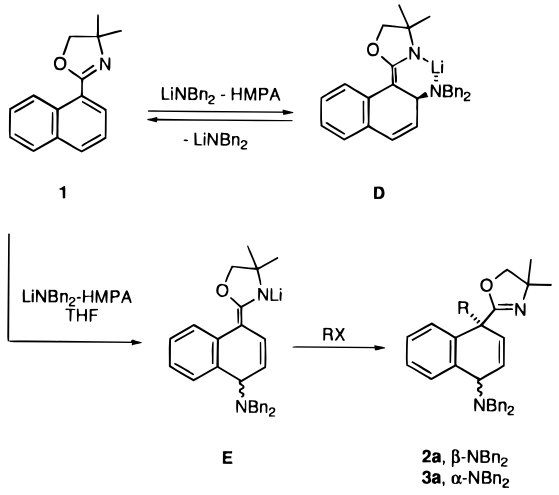
We recently described the efficient asymmetric addition of various lithium amides to the chiral naphthalene system, **A**, which gave the highly stereoselective tandem addition products **B** in good yield (Scheme 1).[1] It was also demonstrated that the latter could be transformed smoothly to a novel class of chiral, nonracemic β-amino acids (**C**). However, it was noted that severe limitations to the above process arose depending upon the nature of the lithium alkylamides. For example, when NR_2 was diethyl, diallyl, dibenzyl, etc., no addition product **B** was observed, and this was seen as a result of the bulky nature of the dialkylamines. It was also found that the addition of lithium dialkylamides to **A** was reversible and, in certain cases, can lose the adducts formed and return to starting material, **A**. This unusual behavior has now been further scrutinized, and we report, using a related, achiral naphthalene system **1**, an efficient and rare[2,3] diastereoselective 1,6-addition. Instead of obtaining the expected and related 1,4-addition as above for **A**−**B**−**C**, we have found that 1,6-addition products[4] (**2a**, **3a**) prevailed and were formed with a high degree of diastereoselectivity to ultimately form δ-amino acids.



The regiochemical study involved addition of lithium dibenzylamide to the simple naphthyl oxazoline **1** under varying amounts of HMPA added to the THF solvent In no case did any 1,4-addition product (from **D**) become visible. The isomeric adduct **4a** (Table 1) amounted to less than 10% of the total product, and the stereoselectivity initially observed in the 1,6-products **2a**:**3a** was approximately 5:1. Evaluation of the reaction conditions showed that 8−10 equiv of HMPA to lithium dialkylamides was actually the optimum quantity to effect very high yields of 1,6-addition with no 1,4-products observed. In order to assess the uniqueness of HMPA, an experiment substituting DMPU (*N*,*N*-dimethylpropyleneurea) was performed and led to no meaningful levels of 1,6-addition, giving mainly starting material.

With optimized conditions for conjugate 1,6-additions in hand, we proceeded to evaluate the scope of the process. It was found that lithium monoalkylamides and pyrrolidides[5] previously producing 1,4-adducts using 1.0 equiv of HMPA still gave mainly the same products.[1] However, the lithio dialkylamides (Table 1), which, in our previous report, all failed to produce any adducts, now gave satisfactory to excellent yields of only 1,6-adducts (Table 1, entries 1−7).[6]

Scheme 1

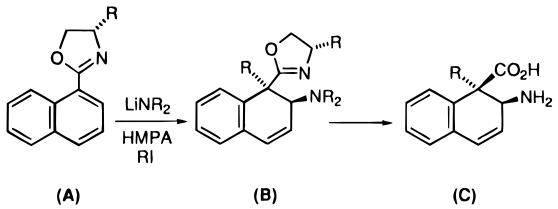
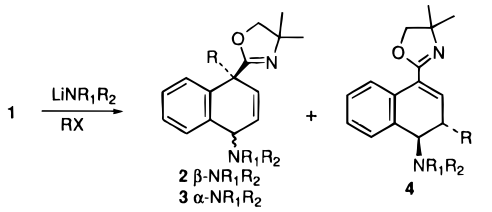


Table 1. Regioselective 1.6-Addition of Lithium Amides to 1



entry	R_1R_2NLi[a]	electrophile (RX)	product ratio[b] (**2** : **3** : **4**)	products(%)[c]
1	LiN(Ph)(Ph)	MeI	78 : 15 : 7	**2a**+**3a**(88),[d] **4a**(5)
2	LiN(Ph)(Ph)	BnBr	>98 : <1 : <1	**2b**(93)[f]
3	LiN(Ph)(Me)		89 : <2 : 9	**2c**(86), **4c**(6)
4	LiN(allyl)(allyl)	MeI	75 : 15 : 10	**2d**+**3d**(88),[e] **4d**(7)
5	LiN(allyl)(allyl)	MeOTf	83 : 17 : <1	**2d**+**3d**(92)
6	LiN(allyl)(allyl)		91 : <1 : 9	**2e**(85),[f] **4e**(4.5)
7	LiN(allyl)(allyl)	BnBr	>98 : <1 : <1	**2f**(92)

[a] The lithium amides were prepared in situ from corresponding amines and ^{n}BuLi, respectively. [b] Ratios determined by ^{1}H-NMR (270 MHz, $CDCl_3$) of the crude mixture. [c] Isolated yields. [d] Careful silica gel column chromatography could separate **2a** and **3a** from each other, but the yield was lowered. [e] Recrystallization could give nearly pure **2d** (>30:1). [f] **2b** and **2e** stereochemistry was confirmed by single-crystal X-ray determination.

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(1) (a) Shimano, M.; Meyers, A. I. *J. Am Chem. Soc.* **1994**, *116*, 6437. (b) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445.

(2) A report of 1,4-addition of amide cuprates also briefly described a 1,6-addition of benzylamine to an α,β,γ,δ-dienoate. Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am Chem. Soc.* **1992**, *114*, 5427.

(3) There have been several reports of 1,6-*substitution reactions* of amino functions to the aromatic ring systems; see: (a) Katrizky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039. (b) Bunce, N. J.; Cater, S. R.; Scaiano, J. C.; Johnston, L. J. *J. Org. Chem.* **1987**, *52*, 4214. (c) Makosza, M.; Bialecki, M. *J. Org. Chem.* **1992**, *57*, 4784. (d) Seko, S.; Kawamura, N. *J. Org. Chem.* **1996**, *61*, 442.

(4) Meyers, A. I.; Gant, T. G. *J. Org. Chem.* **1992**, *57*, 4225. We recently reported the highly diastereoselective 1,6-addition of lithioallylsilanes to 2-methoxy-1-naphthyloxazolines followed by quenching with alkyl halides. The products thus formed gave >98% *trans*-1-alkyl-4-(allylsilyl)-1,4-dihydronaphthalenes.

(5) The ratio of the 1,4-adduct to 1,6-adduct in the case of lithium piperidide was 98:2.

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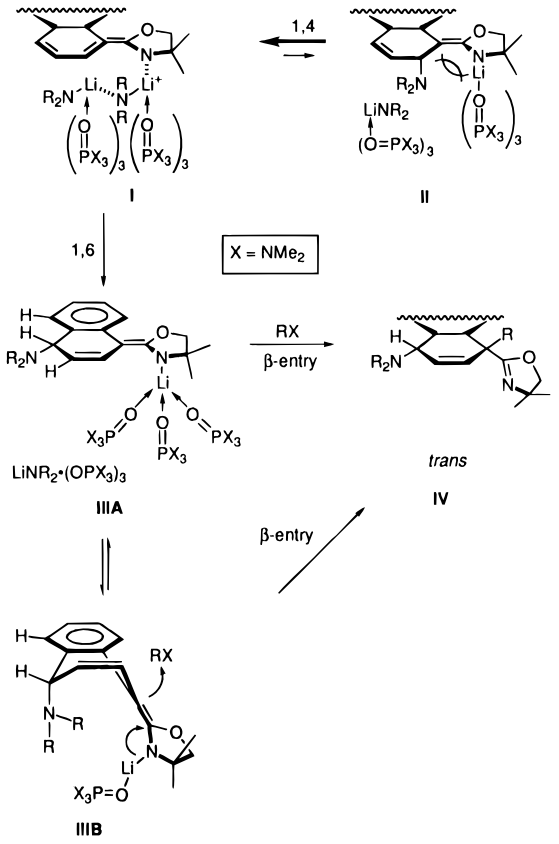
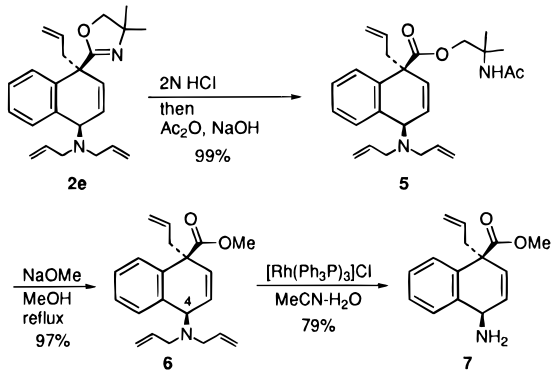
Scheme 2



As also seen from Table 1, the stereoselectivity of the tandem addition to **1** produced the β-disposed dialkylamino group in **2** and *trans* to the trapped alkyl halides. This was confirmed by a single-crystal X-ray determination. This remote stereochemical effect is somewhat reminiscent of our earlier study,[4] which also gave high levels of 1,6-*trans*-addition with allyl anions. Except for the two cases using methyl iodide or methyl triflate (Table 1, entries 1, 4, and 5) where 15−17% of the methyl product was *cis* to the dialkylamino (**3a**), the others were very highly selective for *trans* addition product (Table 1, entries 2, 3, 6, and 7). In view of the earlier observed reversibility of the amide additions to the naphthalenes (**1** to **D**), we may offer an early postulate for this process (Scheme 2). Since at least 6.0 equiv of HMPA was required to successfully effect the addition, we may envision a $LiNR_2$·HMPA dimer approaching the π-system of the naphthyloxazoline, **I**. If 1,4-addition is facile, as observed in our earlier study, then the adduct **II** may form. However, as we had seen earlier, the steric crowding in the amine adduct in **II** may simply force a reversal to the starting material, **I**. The other manifold open to this process is the 1,6-addition of **I** to afford the adduct, **III**. Here there is no visible steric crowding, so reversal back to **I** is no longer an issue. The second crucial step, the stereoselective alkylation to **IV**, can be considered to occur via **III**, which forms to avoid eclipsing the two adjacent (peri) hydrogens. Alkylation is then favored from the opposite face. This latter effect was offered by us in a recent report to account for *trans*-tandem addition in a 1,6-sense (see ref 4 above). These mechanistic proposals will, of course, require further study, but it is important to note that, as mentioned earlier, no 1,6 addition occurred unless there was at least 6.0 equiv of HMPA present (Table 1). The small amount of γ-alkyl products **4** observed (Table 1) could also be rationalized by anti-alkylation on **III**. However, we do not yet know the stereochemistry of the minor products, **4**, but we would expect it also to be *trans* to the dialkylamino group.[8]

Scheme 3



Because the primary amino group in amino acids may be utilized to form peptide and other amino functional groups, we felt that a demonstration of the synthesis of δ-amino acid methyl ester **7** would be both useful and appropriate (Scheme 3). To effect this transformation, the oxazoline group was first removed in a two-step sequence by the procedure described previously,[1b] furnishing the methyl ester **6** *via* the intermediate amido ester **5**. The desired cleavage of the diallyl groups to liberate the primary amine **7** was smoothly performed using the Wilkinson catalyst.[9]

It is of interest that the C_4 position in **6**, which is triply allylic and benzylic, still only produced the desired transformation to **7**.[10]

In conclusion, a novel and useful 1,6-addition of several secondary amine lithium salts to the 1-naphthyloxazoline provided an unusually remote-controlled stereoselective synthesis of an unusual δ-amino acid. Further studies of this process are underway and will be reported in due course.[11,12]

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support of this work. We are indebted to Miss M. Katori and Miss K. Shirafuji in the Kyoto laboratories of Kaken Pharm. Co., Ltd., for analytical and spectral data.

Supporting Information Available: Experimental procedures and compound characterization data, NMR (^{1}H and ^{13}C) spectra for **2a**−**f**, **3a**,**d**, **4a**,**c**−**e**, and **5**−**7**, and ORTEP structures for **2b** and **2e** (40 pages).

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(6) The lithium amides in Table 1 gave no 1,4-amino adducts in the presence of stoichiometric amounts of HMPA, and only starting oxazoline was recovered.

(7) The steric effects of allylic 1,3-strain have been discussed in several reviews: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(8) It is of interest that use of methyl triflate in place of methyl iodide completely suppressed the formation (<1%) of the 1,5-tandem methyl product, **4d** (Table 1).

(9) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.

(10) No double bond migration in the tetralin ring of **6** was observed during treatment with the Wilkinson catalyst.

(11) All new compounds were completely characterized, and these data are included in the supporting information.

(12) The author has deposited atomic coordinates for **2b** and **2e** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.