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# Consecutive Cyclization of Allylaminoalkene by Intramolecular Aminolithiation−Carbolithiation

**Susumu Tsuchida, Atsunori Kaneshige, Tokutaro Ogata, Hiromi Baba, Yasutomo Yamamoto, and Kiyoshi Tomioka***

*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*
*tomioka@pharm.kyoto-u.ac.jp*

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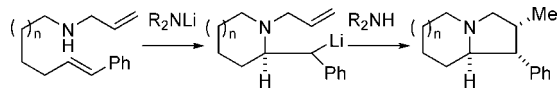
## ABSTRACT




**Consecutive cyclization of allylaminoalkenes by tandem aminolithiation−carbolithiation proceeded smoothly by using a lithium amide as a lithiating agent as well as protonating agent to give bicyclic amines, octahydroindolizine and hexahydro-1*H*-pyrrolizine, in reasonably high yield and diastereoselectivity.**

The prevalence of cyclic amines in natural products and biologically active compounds necessitates the development of novel methods for their syntheses.[1] Although brilliant syntheses of these compounds have been reported by using the methodologies of alkylation and hydrogenation of C−N double bonds,[2,3] approaches toward amination of C−C double bonds have begun only recently. Conjugate hydroamination of C−C double bonds activated by an electron-withdrawing group has met some successes through the reaction of lithium amide as a nitrogen nucleophile.[4,5] On the other hand, direct hydroamination[6,7] of simple C−C double bonds[8] has remained in a relatively undeveloped stage.

We have already reported the chiral ligand-controlled asymmetric conjugate amination reaction of enoates with lithium amides.[9] Quite recently, we also reported the lithium-catalyzed asymmetric intramolecular amination of aminoalkenes.[10] These reactions are characteristic of the involvement of lithiated intermediates. In the conjugate additionapproach, the alkylation of a lithium enolate intermediate provided N−C and C−C bonds in one pot.[9c,d] In the hydroamination approach, the aminolithiation intermediate is an organolithium **3** (Scheme 1). If this intermediate **3** is capable of being involved in carbolithiation with an intramolecular carbon−carbon double bond,[11,12] another organolithium **4** would be generated to give a bicyclic amine **5** upon protonation. We describe herein the realization of an aminolithiation−carbolithiation tandem process of **1** to provide a method of one-pot formation of bicyclic amine **5** (Scheme 1).

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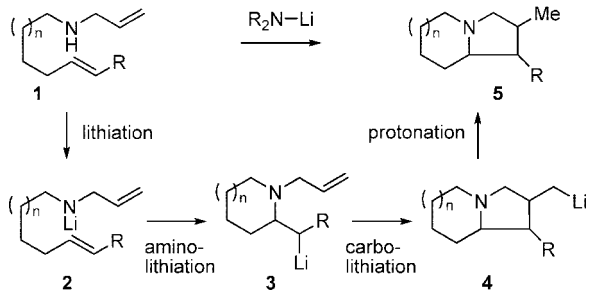
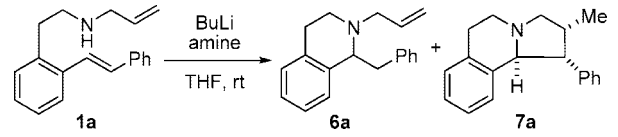
**Scheme 1.** Aminolithiation of **2** to Monocyclic Organolithium **3** and Its Carbolithiation to Bicyclic Amine **4**




In THF allylaminoalkene **1a** was treated with 0.1 equiv of butyllithium for 1 h at room temperature smoothly to give hydroamination product **6a** in 92% yield and **7a** was not detected (Table 1, entry 1). With 0.2 equiv of lithium diisopropylamide (LDA) for 2 h at room temperature, **6a** was isolated in 95% yield along with 1% yield of bicyclic amine **7a** (entry 2). Contrary to these disappointing results, the reaction with 1.5 equiv of butyllithium for 2 h at room temperature gave 33% yield of **7a** as a 1:4 mixture of two diastereomers and **6a** in 5% yield (entry 3). With 1.5 equiv of LDA, **7a** was isolated in 74% yield as a 6:1 mixture of two diastereomers along with **6a** in 15% yield (entry 4).

**Table 1.** Aminolithiation−Carbolithiation of **1a**




| entry | BuLi (equiv) | amine | equiv | time (h) | **6a**, yield (%) | **7a**, yield (%) | **7a** ratio[a] |
|---|---|---|---|---|---|---|---|
| 1 | 0.1 | none | 0 | 1 | 92 | 0 | nd |
| 2 | 0.2 | DIA | 0.2 | 2 | 95 | 1 | nd |
| 3 | 1.5 | none | 0 | 2 | 5 | 33 | 1:4:0 |
| 4 | 1.5 | DIA | 1.5 | 3 | 15 | 74 | 6:1:0 |
| 5 | 1.5 | pyrrolidine | 1.5 | 1 | 29/55[b] | 0 | nd |
| 6 | 1.5 | TMP | 1.5 | 2 | 9 | 53 | 30:10:1 |
| 7 | 1.5 | *t*-Bu(Tr)NH | 1.5 | 2 | 0 | 88 | 6:3:1 |
| 8[c] | 1.5 | *t*-Bu(Tr)NH | 1.5 | 14 | 0 | 85 | >30:1:0 |

[a] **7a**:*trans*,*trans*-isomer:*cis*,*trans*-isomer. [b] Yield of deallylated amine of **6a**. [c] The reaction was conducted in a 1:7 mixture of THF and toluene.

Consideration of competitive steps between protonation and carbolithiation of **3** led us to screening of amine as a proton source (entries 3−7). It was impressive to find that lithium pyrrolidide gave hydroamination product **6a** in 29% yield along with its deallylated amine in 55% yield without formation of carbolithiation product **7a** (entry 5). A bulkier lithium tetramethylpiperidide (TMP) gave **7a** in 53% yield and **6a** in 9% yield (entry 6). The most bulky *tert*-butyltritylamine[13] gave only **7a** in 88% yield without detective amount of **6a** (entry 7). These dependencies of formation of **7a** and **6a** on the bulkiness of amine rationalize the preferred carbolithiation of **3** and protonation of less crowded **4** with a bulky amine, and protonation of **3** with a less bulky amine.

Solvent effect is noteworthy to give an almost diastereomer free **7a** in 85% yield as a 30:1:0 diastereomer mixture in a 1:7 mixture of THF and toluene (entry 8). Major isomer was determined to be *trans*,*cis*-**7a** as shown by NOE.

The competition of carbolithiation and protonation of **3** was further experimentally evidenced by the lower temperature reaction. The reaction with 1.5 equiv of LDA at −20 °C for 6 h and further at rt for 3.5 h gave **6a** in 94% yield without production of **7a**. On the other hand, the reaction with 1.5 equiv of lithium *tert*-butyltritylamide at −20 °C for 21 h gave **7a** in 65% yield and **6a** in 10% yield.

The preferred production of **6a** and trace amount of **7a** by the treatment with a catalytic amount of butyllithium and

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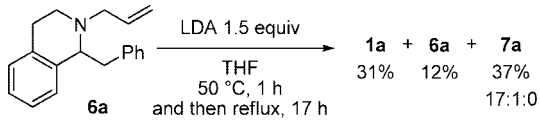
LDA is also rationalized by the protonation of **3** by **1a** itself that is considered to be a relatively less bulky amine (entries 1 and 2).

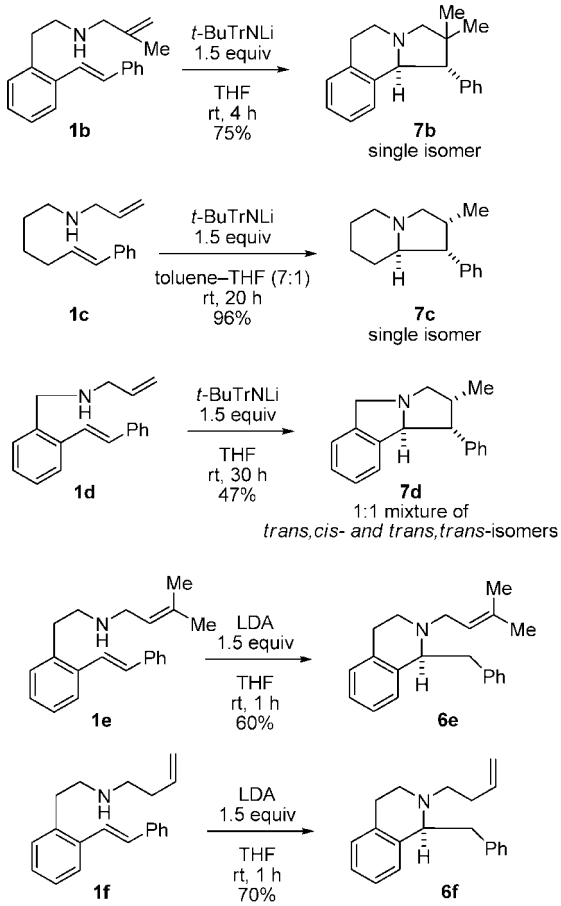
The intermediacy of **3** was evidenced by the production of **1a** and **7a** from **6a** (Scheme 2). Treatment of **6a** with 1.5 equiv of LDA in THF at reflux for 17 h gave **1a** in 31%, **6a** in 12%, and **7a** (17:1:0) in 37% yield. Lithiation at the benzylic position of **6a** in forming **3** seems to require a high refluxing temperature.

**Scheme 2.** Intermediacy of **3**




Having established the aminolithiation−carbolithiation tandem cyclization conditions, other allyl- and homoallylaminoalkenes **1b**−**f** were examined. As shown in Scheme 3, terminal primary alkyllithium producing tandem aminolithiation−carbolithiation proceeded smoothly to give bicyclic amines **7b**−**d** in reasonably high yield and diastereoselectivity.[14] Not only octahydroindolizines **7a**−**c** but also hexahydro-1*H*-pyrrolizine **7d** were produced.

**Scheme 3.** Successful Aminolithiation−Carbolithiation of **1b**−**d** and Unsuccessful Carbolithiation of **1e**,**f**



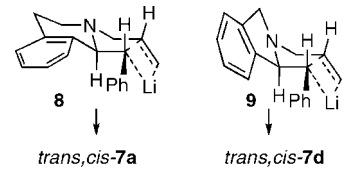




**Figure 1.** Stereochemical models **8** and **9**.

The structural limitation became apparent from the attempted cyclization of **1e** that produces Li−C bond at the tertiary carbon center through carbolithiation. The reaction stopped at the stage of aminolithiation to produce **6e**. Another limitation was 6-exo carbolithiation giving octahydro-1*H*-quinolizine. The reaction stopped at the aminolithiation stage to afford **6f**.

The model proposed by Bailey, and recently by Cohen and Jordan, rationalized stereochemistry in the intramolecular carbolithiation.[15] Thus, the model **8** fits for the preferencial production of *trans,cis*-**7a**−**c**. Although the model **9** predicts the formation of *trans,cis*-**7d**, involvement of lithiophilic THF in the transition state allows formation of *trans,trans*-**7d**.[15b,16]

A substoichiometric amount of lithium amide was found to give tandem aminolithiation−carbolithiation product **7a**. Portionwise addition of allylaminoalkene **1a** in THF to 0.36 equiv of *t*-BuTrNLi in THF during three 2 h intervals at room temperature gave **7a** in 64% yield along with **6a** in 17% yield.

In summary, we have demonstrated the double cyclization of allylaminoalkenes through tandem aminolithiation−carbolithiation providing ready access to bicyclic octahydroindolizine and hexahydro-1*H*-pyrrolizine skeletons. A catalytic amount of lithium amide was also shown to give tandem aminolithiation−carbolithiation product. Extension to other types of bicyclic amines and asymmetric reactions is the focus of future studies.

(14) It is obvious from Table 1 that the relative stereochemistry between azomethine carbon and benzyl methine carbon is highly controlled even with THF alone. Indeed, the reaction of **1b** gave a single diastereoisomer. The reaction of **1d** in toluene−THF mixed solvent system was not examined.

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**Note Added after ASAP Publication.** There was an error in the abstract/toc graphic, the corrected version was published on August 7, 2008.

**Supporting Information Available:** Experimental details and characterization of data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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