Novel [2,3]-Sigmatropic Rearrangement for Carbon−Nitrogen Bond Formation

Teruhiko Ishikawa,* Masatomo Kawakami, Miyuki Fukui, Ayako Yamashita, Jin Urano, and Seiki Saito*

Department of Bioscience and Biotechnology Faculty of Engineering, Okayama University Tsushima, Okayama, Japan 700-8530

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[2,3]-Sigmatropic rearrangement is a widespread method for regiospecific carbon−carbon or carbon−heteroatom bond formation in organic synthesis,[1] and enormous examples have been reported including their applications to asymmetric synthesis and natural product synthesis. For aza-versions,[2] a number of allylchalcogenide and allylamineimide derivatives have been demonstrated to be usable for transferring amino groups to allylic positions (Scheme 1). However, more simple and efficient methods for the construction of allylic amines from allylic alcohols are desirable.[3] And our recent studies on hydroxylamine-based chemistry[4] have led us to the discovery of novel [2,3]-sigmatropic rearrangement of *O*-allylic hydroxylamines in which a negatively charged nitrogen atom is a migration terminus (Scheme 1). In this paper we detail the features of such a [2,3]-sigmatropic rearrangement as a highly useful method for the synthesis of *N*-hydroxyallylamines, precursors for allylic amines, a biologically important class of compounds.

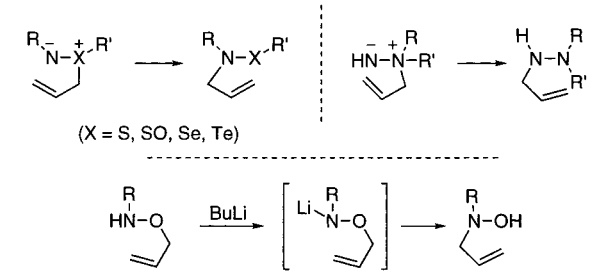
The substrates, *O*-(2-alkenyl)-*N*-(alkyl)hydroxylamine derivatives (**3**), can be obtained through a three-step conversion involving an S_N2 reaction between the corresponding allylic alcohols (**1**) and *N*-(hydroxy)phthalimide (**5**) under Mitsunobu conditions,[5] generation of an amino group (**2**), and final *N*-alkylation (Scheme 2). Serious problems encountered in this process were an S_N2'-type pathway taking place competitively in the case of secondary allylic alcohols and considerable dialkylation. However, Mitsunobu reaction employing the *N*-benzyl-*N*-(allyloxycarbonyl)hydroxylamine (**6**)[6] and 1,1-(azodicarbonyl)dipiperidine (ADDP)[5c] system followed by deprotection ($Pd(OAc)_2$, Et_3SiH, Et_3N)[7] provided an answer to those problems.

The results of the [2,3]-sigmatropic rearrangement for various *O*-(2-alkenyl)-*N*-(benzyl)-hydroxylamines (**3a**−**e**, **g**−**j**)[8] and *N*-butyl derivative (**3f**) leading to *N*-(hydroxy)allylamines (**7a**−**j**) are summarized in Table 1. Although the reactions were completed within 5 min at 0 °C in THF (1.2 equiv of BuLi) and no [1,2]-rearrangement was detected at all in any case, the reaction was categorized into one of two groups with regard to the yield of desired product, acceptable (>75%) or poor (<30%). The latter cases involved the breakup of conjugated systems (entries 2 and 8), the tertiary nature of the migration terminus (entry 3), and the endocyclic allylic double bond (entry 4). In these poor cases the rest of the product was recyclable allylic alcohols **1** stemming from N−O bond cleavage.[9] It is worth noting that when the oxygen atom links to the secondary carbon (entries 9 and 10), the reaction took place nicely in marked contrast to entry 8, even though it resulted in the breakup of the conjugated system, to give **7i**,**j** having exclusive *E* geometry in acceptable yields. This probably means that carbon−oxygen bond polarization developed at a transition state might be stabilized by the substituent at the oxygen-linking centers. It was also found that when such a substituent is a phenyl group like **8a**−**c**, we have only to heat a solution of **8** in DMF for 3 (**8a**) or 5 (**8b** and **8c**) h at 70 °C without a base, leading to the corresponding rearranged products (**9a**−**c**) in very high yields (Scheme 3).[10]

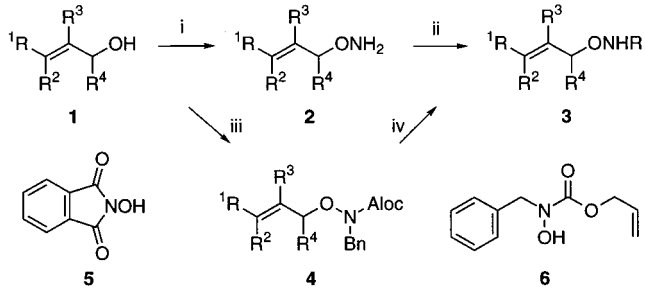
A convenient deprotecting procedure for the conversion of −NBn(OH) to $-NH_2$ has been developed which involves trifluoroacetic acid-promoted dehydration followed by basic hydrolysis ($NaHCO_3$) of the resulting imines.[11]

The present [2,3]-sigmatropic rearrangement proved fruitful when applied to 1,2- or 1,3-asymmetric induction.[12] Some

Scheme 1

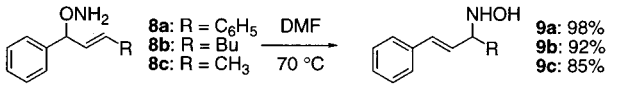


Scheme 2[a]



[a] Conditions: (i) 1. DEAD−Ph_3P, **5**/THF, 2. hydrazine; (ii) alkyl halide/Et_3N/DMF, (iii) **6**/ADDP−Bu_3P/benzene, (iv) $Pd(OAc)_2$/Et_3SiH/Et_3N,/DMF.

Scheme 3



(1) For reviews, see: (a) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.11. (b) Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 4, Chapter 4.6. (c) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885−902. (d) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 536−572.

(2) First example of carbon−nitrogen bond formation by means of [2,3]-sigmatropic rearrangement, see: Ash, A. S. F.; Challenger, F.; Greenwood, D. *J. Chem. Soc.* **1951**, 1877−1882. References for other entries are provided in the Supporting Information.

(3) For [3,3]-sigmatropic rearrangement leading to allylic amines, see: (a) Altenbach, H.-J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 4.5. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224.

(4) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 4607−4608.

(5) (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679−680. (b) Grochowski, E.; Jurczak, J. *Synthesis* **1976**, 682−684. (c) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

(6) Designed and prepared by ourselves (see the Supporting Information): to the best of our knowledge, no report for this compound has been published.

(7) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876.

(8) The effect of substituent on the nitrogen atom turned out to be crucial. For instance, *N*-acyl- or sulfonyl- versions were recovered unchanged after prolonged reaction time even at elevated temperature, and the nonsubstituted substrates (**2**) resulted in the formation of **1** through N−O bond cleavage under the same conditions.

(9) For instance, **3h** afforded a mixture of **7h** (30%) and cinnamyl alcohol (60%).

(10) It should be pointed out that no reaction took place when solutions of **3a**−**m** in toluene or DMF were heated even at 110 °C without any base.

(11) For instance, **7e** gave the corresponding free amine in 78% yield while the *O*-benzyl group of **7e** remained intact. Deprotection of **7h** under the conditions afforded not the free amine but the intermediary imine: see Supporting Information.

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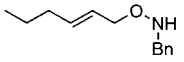
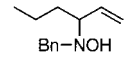
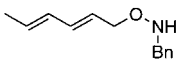
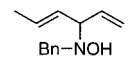
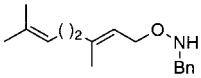
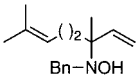
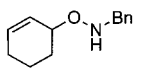
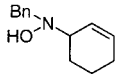
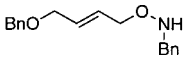
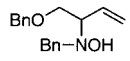
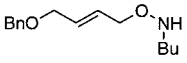
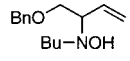
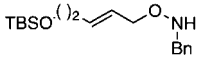
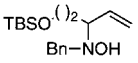
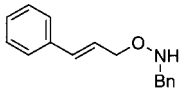
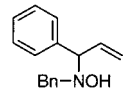
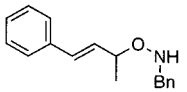
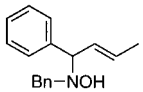
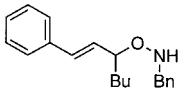
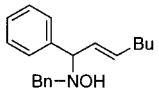
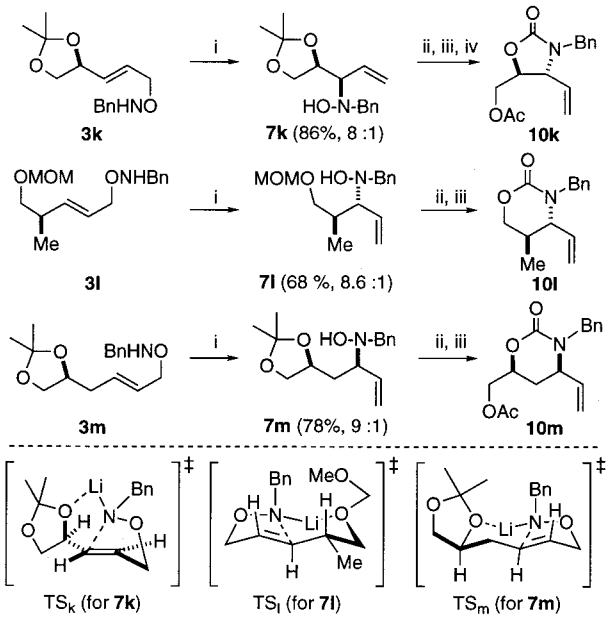
Table 1. [2,3]-Sigmatropic Rearrangement of *O*-Allylic-(*N*-benzyl)hydroxylamines[a]

Entry	Substrate		Product[b]		Yield/%[c]
1		**3a**		**7a**	82
2		**3b**		**7b**	25
3		**3c**		**7c**	20
4		**3d**		**7d**	30
5		**3e**		**7e**	81
6		**3f**		**7f**	86
7		**3g**		**7g**	81
8		**3h**		**7h**	30
9		**3i**		**7i**	75
10		**3j**		**7j**	76

[a] 1.1 equiv of BuLi/THF/0 °C, 5 min. *N*-Butyl derivative in entry 6. [b] All the products gave satisfactory spectroscopic data (NMR, IR, MS). [c] For products isolated by silica gel chromatography.

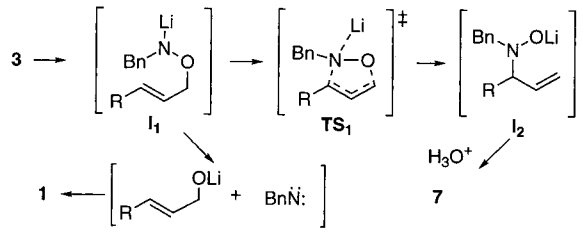
substrates **3k**−**m** with oxygen-bearing stereogenic centers gave **7k**−**m** (BuLi/toluene, 0 °C) with high diastereomeric ratios as shown (Scheme 4). Their absolute configurations were correlated to those of cyclic carbamate derivatives **10k**−**m**,[13] respectively, in which NOE was measured to determine the stereochemistry.[14] Transition states responsible for the observed stereoselectivity are illustrated as TS_k, TS_l, and TS_m, in which the chelation-controlled asymmetric induction may be operating (Scheme 4), suggesting the point of the rearrangement mechanism: the reaction should involve lithium amide (**I_1**) as the first intermediate, which leads to the second intermediate (**I_2**) through **TS_1** in a concerted manner (Scheme 5). The N−O bond cleavage possibly ensuing from **I_1** is a side reaction that gives **2** and, probably, the corresponding nitrenes as well.[15] No radical dissociation−recombination process is involved because no [1,2]-rearrangement product was detected at all in any case.

Scheme 4[a]



[a] Conditions: (i) BuLi/toluene/0 °C. (ii) 1. Zn, $Cu(OAc)_2$/AcOH−H_2O, 2. ClCOOMe, Et_3N/THF. (iii) 1. PTSA/EtOH, 2. NaH/THF. (iv) Ac_2O, Et_3N/THF. Overall yields from **7k**−**m** to **10k**−**m**, though not optimized, were 28, 59, and 31%, respectively.

Scheme 5



In conclusion, we have developed a novel [2,3]-sigmatropic rearrangement of *O*-allylic hydroxylamines as a simple and valuable method for the introduction of allylic amine functionality. Since it involves the lithium amide intermediate, the present rearrangement has the specific merit that it is capable of inducing a new stereogenic center relying on a preexisting stereogenic center in a 1,2- or 1,3-fashion through chelation control, which seems difficult to achieve by previous [2,3]- or [3,3]-sigmatropic pathways to an allylic amine.[2,3] Further advancements of this chemistry are currently under active investigation.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports, and Culture, Japan. We are also grateful to the SC-NMR Laboratory of Okayama University for high-field NMR experiments.

Supporting Information Available: Synthetic procedures for **3**, **7**, **8**, **9**, and **10**, their spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for **7** and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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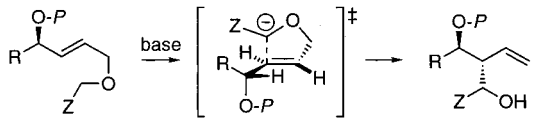
(12) In general, the high level of diastereoselection of [2,3]-Wittig rearrangement can be explained by the transition state shown below, which is stabilized through the antiperiplanar alignment of the allylic C*−O orbital to the approaching carbanion while the allylic conformation involving stereogenic center should be that by which the $A^{(1,3)}$ strain can be minimized: see ref 1a,b.



(*P* = protecting group)

(13) For the reductive N−O bond cleavage, see: Dondoni, A.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2551−2555.

(14) All products gave satisfactory spectroscopic data (NMR, IR, and MS). The stereochemistry of cyclic carbamates **10k**−**m** was determined by NOE measurements and the evaluation of J_{H-H} values: see the Supporting Information.

(15) When **3h** was treated with BuLi at −50 °C and the reaction was continued at that temperature, only the N−O bond cleavage took place. For nitrene formation from hydroxylamine derivatives, see: Appel, R.; Büchner, O. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 332−333.