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n-BuLi/$LiCH_2CN$-Mediated One-Carbon Homologation of Aryl Epoxides into Conjugated Allyl Alcohols

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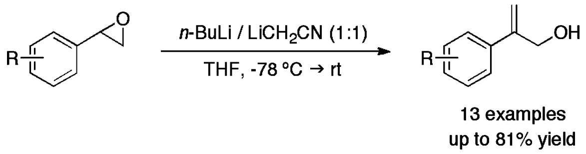
ABSTRACT



A series of styrene oxides in the presence of a 1:1 mixture of *n*-butyllithium (*n*-BuLi) and lithioacetonitrile ($LiCH_2CN$) in THF are converted into one-carbon homologated allyl alcohols in an unusual regioselective manner.

A lithiated acetonitrile ($LiCH_2CN$), first introduced by Kaiser[1] and Seebach[2] independently in 1968, is a readily available chemical species that can be prepared from acetonitrile (CH_3CN) and *n*-butyllithium (*n*-BuLi) in tetrahydrofuran. Due to the simplicity of use as well as functional versatility, the species has now been widely employed as a useful multipurpose reagent in the synthetic community.[3,4]

Recently, our group conducted a simple ring-opening addition of $LiCH_2CN$ to styrene oxide due to the need of 4-hydroxy-4-phenylbutanenitrile **1** as an authentic sample (Scheme 1). Based on a literature procedure (Scheme 1, eq 1),[5] we performed the reaction under essentially the same conditions, but at a lower temperature (−78 °C).[6] The reaction mixture was then gradually warmed up to room temperature (Scheme 1, eq 2). Strangely, the reaction proceeded poorly and a significant amount of starting material was recovered. Although desired alcohol **1** was obtained in modest yield (less than 10%), a non-negligible amount of allyl alcohol **2a** (13%) was also unexpectedly isolated. Another allyl alcohol **3a**, presumably an elimination product of **1**, was detected as well, but only in a trace amount. To confirm this curious observation, we then tested the exact literature condition (i.e., 0 °C). As anticipated, only product **1** was obtained nearly quantitatively and allyl alcohol **2a** was not observed at all. Therefore, our incidentally applied lower reaction temperature (i.e., −78 °C) seemed to be important to lead to **2a**.

Although it is known that the allylic alcohols **2a** and **3a** can be directly prepared from styrene oxide by using dimethylsulfonium methylide, $Me_2S{=}CH_2$ (Scheme 2),[7] the regioselectivity (**2a** vs **3a**) is opposite to ours. Also,

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(1) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.

(2) Crouse, D. N.; Seebach, D. *Chem. Ber.* **1968**, *101*, 3113.

(3) For recent selected examples ($LiCH_2CN$ in organic synthesis), see: (a) Taber, D. F.; Green, J. H.; Zhang, W.; Song, R. *J. Org. Chem.* **2000**, *65*, 5436. (b) Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423. (c) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 3668. (d) Pound, M. K.; Davies, D. L.; Pikington, M.; de Pina Vaz Sousa, M. M. *Tetrahedron Lett.* **2002**, *43*, 1915. (e) Bolshan, Y.; Chen, C.-Y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111. (f) Zenouz, A. M. *Tetrahedron Lett.* **2004**, *45*, 2967. (g) Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Quintavalla, A. *Tetrahedron* **2005**, *61*, 69. (h) Kawashima, T.; Kashima, H.; Wakasugi, D.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 3767. (i) Singh, K.; Arora, D.; Singh, S. *Tetrahedron Lett.* **2007**, *48*, 1349. (j) Robertson, J.; Tyrell, A. J.; Chovatia, P. T.; Skerratt, S. *Tetrahedron Lett.* **2009**, *50*, 7141. (k) Michon, C.; Sharma, A.; Bernardinelli, G.; Lacour, J. *Chem. Commun.* **2010**, *46*, 2206. (l) Saitoh, H.; Satoh, T. *Tetrahedron Lett.* **2010**, *51*, 3380. (m) Schwartz, B. D.; Banwell, M. G.; Cade, I. A. *Tetrahedron Lett.* **2011**, *52*, 4526. (n) Davis, M. C.; Groshens, T. J. *Synth. Commun.* **2012**, *42*, 2664.

(4) (a) Tomioka, T.; Takahashi, Y.; Vaughan, T. G.; Yanase, T. *Org. Lett.* **2010**, *12*, 2171. (b) Tomioka, T.; Sankranti, R.; Vaughan, T. G.; Maejima, T.; Yanase, T. *J. Org. Chem.* **2011**, *76*, 8053. (c) Tomioka, T.; Takahashi, Y.; Maejima, T. *Org. Biomol. Chem.* **2012**, *10*, 5113.

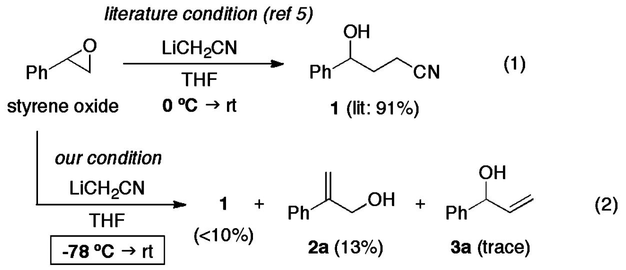
(5) Eagon, S.; Ball-Jones, N.; Haddenham, D.; Saavedra, J.; DeLieto, C.; Buckman, M.; Singaram, B. *Tetrahedron Lett.* **2010**, *51*, 6418.

(6) Since our group was accustomed to prepare/use $LiCH_2CN$ at −78 °C (see refs 4a−4c), we simply applied the temperature as usual, instead of 0 °C.

(7) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, I. P.; La Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.

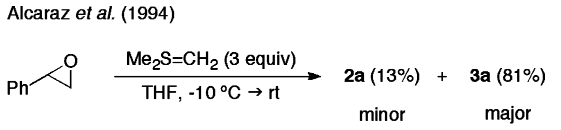
10.1021/ol402466y

Scheme 1. Ring-Opening Addition of $LiCH_2CN$ to Styrene Oxide



bis(trimethylstannyl)methane can alternatively lead to allylic alcohol **2a** as a major product (65%) from styrene oxide,[8,9] but no synthetic generality of this class of transformation has been studied/established yet. Herein, we report an unusual, regioselective transformation of styrene oxide into a one-carbon homologated conjugated allyl alcohol.

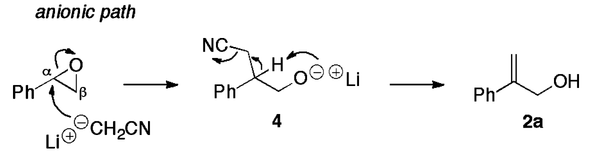
Scheme 2. $Me_2S{=}CH_2$ Mediated Transformation of Epoxide into One-Carbon Homologated Allyl Alcohol



As to the reaction mechanism, a simple anionic path (mechanism I) as illustrated in Scheme 3 was initially proposed. That is, a nucleophilic attack of $LiCH_2CN$ to the benzylic carbon of styrene oxide, followed by either intramolecular or intermolecular β-elimination from oxyanion intermediate **4**, seemed to be reasonable. Based on the mechanism, various reaction conditions were subsequently examined (i.e., reaction time, temperature, concentration, amount of $LiCH_2CN$ reagent, solvent, and additive); however, the yield of **2a** was hardly improved, and even worse, the reaction was poorly reproducible.

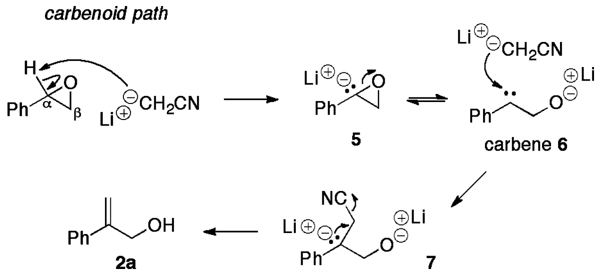
Prior to further optimization, we then proposed a carbenoid mediated mechanism (Scheme 4). The oxiranyl anion **5**, generated upon deprotonation of the acidic α-hydrogen of styrene oxide, often exhibits carbene-like reactivities via a presumed intermediate **6** (or a hybrid of **5** and **6**).[10] Subsequent nucleophilic addition of $LiCH_2CN$ to carbene **6**, followed by elimination of a cyanide ion from dianion **7**, should afford alcohol **2a**. It should be noted that anion **5** is typically formed at a very low temperature

Scheme 3. Plausible Mechanism I



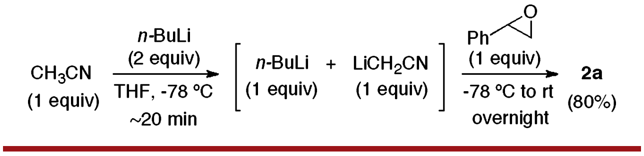
(below −78 °C) due to the thermal instability.[11] Thus, this alternative path seemed to be more reasonable to explain why alcohol **2a** was not produced at 0 °C, but −78 °C (see Scheme 1).

Scheme 4. Plausible Mechanism II



Based on these assumptions, we hypothesized that, if the carbenoid path (mechanism II) was mainly involved, the use of a stronger base than $LiCH_2CN$ (*e.g.*, *n*-BuLi) could more efficiently deprotonate the α-hydrogen and generate the key intermediates **5** and **6** for subsequent transformation. Hence, we treated styrene oxide with a 1:1 mixture of *n*-BuLi as a base and $LiCH_2CN$ as a nucleophile, which was simply prepared by exposing 1 equiv of CH_3CN to 2 equiv of *n*-BuLi in THF at −78 °C for 15−20 min.[12] To our delight, this attempt (Scheme 5) dramatically improved the yield of **2a** (13%→80%).[13] The protocol was also reproducible.

Scheme 5. Synthesis of Allyl Alcohol **2a** from Styrene Oxide



Accordingly, substrate generality of the protocol to various aryl epoxides was examined (Table 1). Styrene oxides that are *ortho*-, *meta*-, and *para*-alkylated (entries 1−3) as well as an arylated one (entry 4) were converted into the corresponding alcohols in fair to good yields (51−81%).

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(8) Maruyama, E.; Kikuchi, T.; Nishio, H.; Uematsu, M.; Sasaki, K.; Saotome, N.; Sato, T. *Nippon Kagaku Kaishi* **1985**, 350.

(9) Only two examples, styrene oxide (65%) and 1-phenylpropylene oxide (55%), are demonstrated.

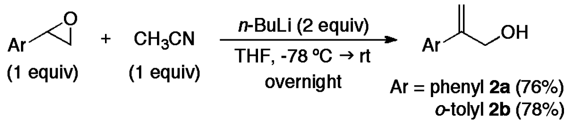
(10) (a) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700. (b) Morgan, K. M.; O'Connor, M. J.; Humphrey, J. L.; Buschman, K. E. *J. Org. Chem.* **2001**, *66*, 1600. (c) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. *Chem. Soc. Rev.* **2002**, *31*, 223.

(11) Nagaki, A.; Takizawa, E.; Yoshida, J. *Chem.—Eur. J.* **2010**, *16*, 14149.

(12) To confirm the existence of *n*-BuLi and $LiCH_2CN$, the 1:1 mixture was treated with benzaldehyde and both addition products were observed by NMR (~80% conversion).

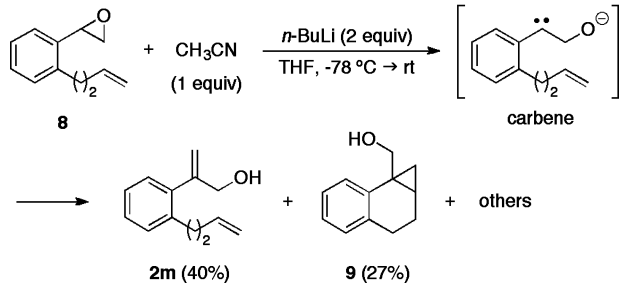
(13) Attempts to examine the effect of TMEDA led to inferior yields (~45%).

Scheme 6. Modified Addition Sequence



Scheme 7. Trapping Carbene Species

one-carbon homologation vs. cyclopropanation



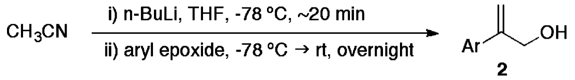
Naphthalene-based aromatic epoxides (entries 5 and 6) also smoothly underwent the transformation (71% and 77%, respectively). More substituted epoxides such as di- and trisubstituted epoxides (entries 7 and 8) provided desired products with similar efficiency (65%). Other than the simple styrene oxides, functionalized epoxides were further investigated. Chlorinated styrene oxide (entry 9) gave a slightly inferior result (44%) presumably due to the susceptibility of the halogen group to *n*-BuLi. A methoxy group (entry 10) and an acetal protecting group (entry 11) were compatible under the conditions (60% and 65%, respectively).

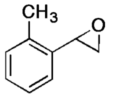
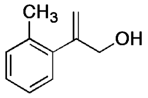
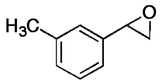
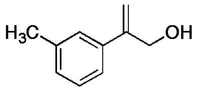
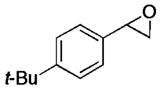
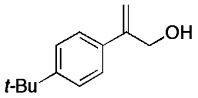
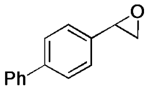
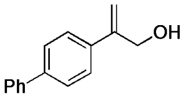
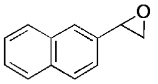
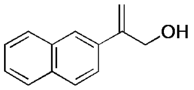
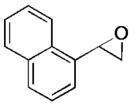
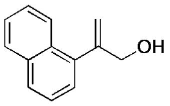
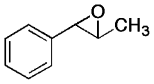
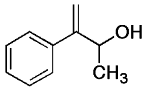
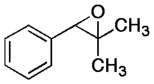
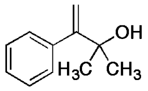
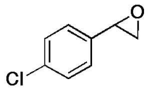
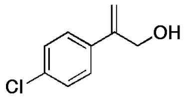
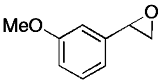
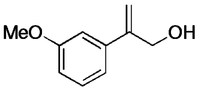
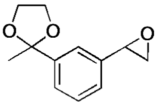
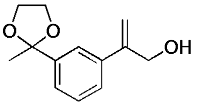
For operational simplicity, a modified condition without prior preparation of $LiCH_2CN$ was subsequently tested; viz., *n*-BuLi (2 equiv) was directly added into a solution of aryl epoxide (1 equiv) and CH_3CN (1 equiv) in THF at −78 °C (Scheme 6). This concise protocol yielded essentially identical results as our original stepwise procedure.

Lastly, to provide support for the presence of a proposed carbene intermediate in the reaction, an epoxide having an alkene moiety **8** was examined (Scheme 7). Along with allyl alcohol **2m** (40%), an intramolecular cyclopropanation adduct **9** (27%) was also isolated as a competitive side product. This observation implies that the carbene species is at least generated under the reaction conditions and possibly supports the carbenoid mechanism as well.

In summary, we reported our serendipitous discovery which involves a novel carbene-mediated transformation of styrene oxide into 2-phenyl-2-propen-1-ol. A 1:1 mixture of *n*-butyllithium and lithiated acetonitrile in tetrahydrofuran converted aryl epoxides into one-carbon homologated allyl alcohols in a highly regioselective manner. Further synthetic applications of this protocol are currently under study in our group.

Table 1. Synthesis of Allyl Alcohol **2** from Aryl Epoxide[a]



entry	aryl epoxide	allyl alcohol (2)		yield (%)
1			**2b**	80
2			**2c**	72
3			**2d**	51
4			**2e**	64
5			**2f**	71
6			**2g**	77
7			**2h**	65
8			**2i**	65
9			**2j**	44
10			**2k**	60
11			**2l**	65

[a] CH_3CN (2.1 mmol), *n*-BuLi (4.1 mmol), aryl epoxide (2.0 mmol), dry THF (3.0 mL).

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

The authors declare no competing financial interest.