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Reductive Spiroannulation of Nitriles with Secondary Electrophiles

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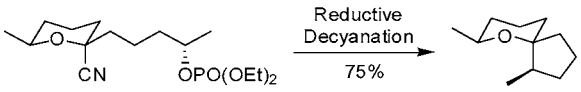
ABSTRACT



The scope of reductive decyanation and spiroannulation reactions has been expanded to include secondary electrophiles for potentially useful transformations. Secondary phosphates and chlorides, as well as terminal epoxides, cyclize in a stereospecific fashion. Both *endo* and *exo* modes of cyclization were observed with terminal epoxides.

The stereoselective formation of novel spirocycles provides an interesting challenge for organic chemists. Cyclization of alkyllithium reagents is an annulation strategy[1] that has potential in the formation of spirocycles. In exploration of the scope of reductive decyanation and cyclization reactions using Freeman's reagent (lithium-di-*tert*-butylbiphenylide, LiDBB),[2] recent efforts have shown that α-alkoxylithium intermediates cyclize onto tethered olefins and allylic methoxy ethers to give spirocyclic THP systems in a highly diastereoselective fashion.[3] Furthermore, spiroannulation with tethered primary chloride and phosphate electrophiles affords five-, six-, and, in some cases, seven-membered rings.[3] To further extend the utility of these transformations, spiroannulations with precursors bearing secondary electrophilic centers on the side chains were explored, and the results are reported herein.

Secondary electrophiles introduce a new stereocenter into the cyclization, which raises important stereochemical questions. Is the cyclization of a hindered tertiary organolithium onto a secondary electrophile possible under the reaction conditions? What is the stereochemistry of the two newly formed vicinal stereocenters? Will the lithium-bearing center react with retention or inversion of configuration? For cases of epimeric stereochemistry at the electrophilic center, will both diastereomers react? Will various electrophiles be compatible with conditions required for reductive decyanation?

To address these and other questions, optically pure cyclization precursors were constructed as shown in Table 1.[4] Cyclic nitriles such as **1** may be alkylated with use of an appropriate base to produce functionalized tertiary nitriles.[5] Such reactions are known to be highly stereoselective for six membered rings. Deprotonation of **1** with LDA in the presence of DMPU and the bis-electrophiles **2a**−**h** furnished the equatorial alkylated products **3a**−**h** as the only detectable stereoisomers (Table 1). For the chloride and diethyl phosphate side chains, this product serves as the cyclization precursor. For the epoxide substrates, further transformations were necessary. For example, dioxolane **3e** was deprotected with PPTS in methanol to give diol **4**,[6] which was then

(1) Alkenyllithium cyclizations: (a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C. *J. Org. Chem.* **1985**, *50*, 1999−2000. (b) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442−2448. (c) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336−1338. (d) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788−4796. (e) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981−2984.

(2) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *22*, 1924−1930.

(3) (a) Takaoka, L. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 818−820. (b) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* **2001**, *3*, 807−810. (c) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528−529.

(4) Procedures for the preparation of 2-cyano-THP **1** and iodides **2a**−**h** may be found in Supporting Information.

(5) Sinz, C. J.; Rychnovsky, S. D. *Top. Curr. Chem.* **2001**, *216*, 52−92. Alkylation of metalated cyanohydrin acetonides: Swenson, S. S.; Rychnovsky, S. D. *J. Org. Chem.* **1997**, *62*, 1333−1340.

(6) Mori, K.; Maemoto, S. *Liebigs Ann. Chem.* **1987**, 863. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 126.

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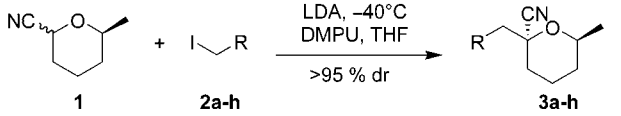
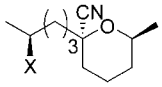
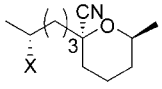
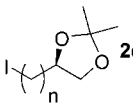
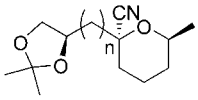
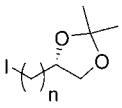
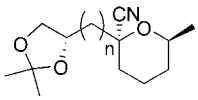
Table 1. Alkylation of 2-Cyano-THP with Bis-electrophiles

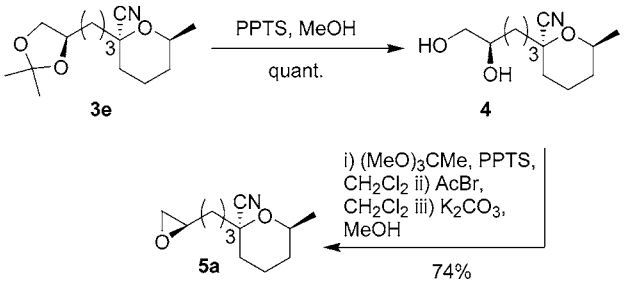


1 2a-h 3a-h

entry	iodide	product	yield
1	 2a,b		**3a** X = Cl, 77% **3b** X = diethyl phosphate, 66%
2	 2c,d		**3c** X = Cl, 63% **3d** X = diethyl phosphate, 64%
3	 2e,f		**3e** n = 3, 70% **3f** n = 4, 83%
4	 2g,h		**3g** n = 3, 76% **3h** n = 4, 76%

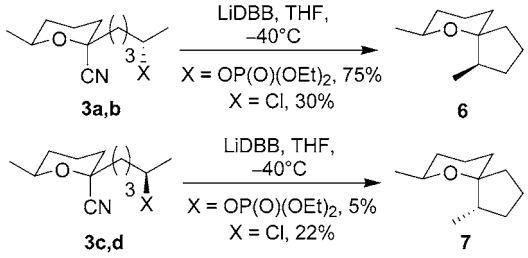
converted stereospecifically to the epoxide **5a** (Scheme 1).[7] The other epoxide substrates in Scheme 3 were prepared similarly.

Scheme 1. Preparation of Epoxide Precursor

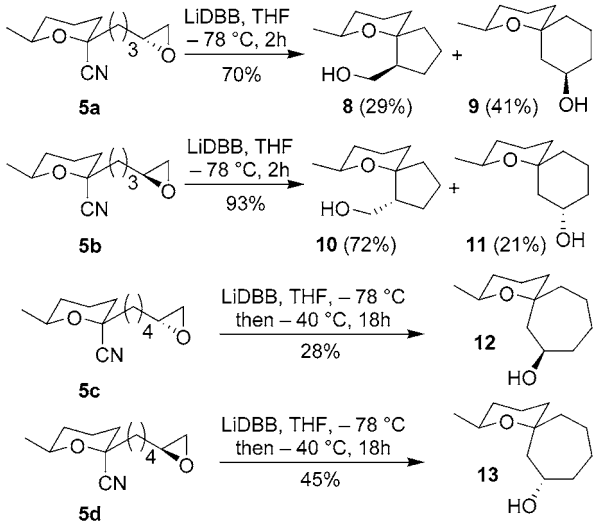


Reductive cyclizations of the secondary electrophile substrates are illustrated in Schemes 2 and 3. The diethyl phosphate precursors, whose primary homologue was found to be the optimal electrophile for 5-*exo* cyclizations,[3] exhibited a marked stereochemical bias in the cyclization.

Scheme 2. Spiroannulation of Secondary Chlorides and Phosphates



Scheme 3. Spiroannulation of Terminal Epoxides



Along with trace amounts of reduction and elimination byproducts, spirocycle **6** was isolated in 75% yield from the **3b** diastereomer. In contrast, **3d** produced very little (~5%) of the epimeric spirocycle **7**. Both chloride precursors **3a** and **3c** underwent spiroannulation to afford products in modest yields. These reactions are complicated by competitive reduction of the electrophile.[8] In all cases, however, the isolated spirocycles were single diastereomers, which strongly supports a stereospecific reaction. Indeed, correlation studies have shown that each reaction proceeds with inversion at the electrophilic center and with retention of configuration at the alkyllithium center (vide infra).[9]

Diastereomeric epoxide precursors **5a** and **5b** cyclize efficiently upon reductive decyanation (Scheme 3). The product distribution bifurcates between 5-*exo* and 6-*endo* modes of cyclization to a different extent for each diastereomer, with no reduction of the epoxide observed in either case.[10] Previous studies of the regioselectivity of alkyllithium–epoxide cyclizations indicate that 5-*exo* cyclization is strongly preferred in the absence of a Lewis acid (10:1 in favor of 5-*exo* for 4-oxiranyl-butyllithium); however, these studies employed only unhindered primary and aryllithium reagents.[11] The results in Scheme 3 are analogous to those reported by Coates et al. for cyclization of cyclopropyllithiums onto terminal epoxides.[12] For diastere-

(7) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.
(8) Grierson, D. S.; Sajus, H.; Zeller, E. *Synlett* **1991**, 44–46. Grierson, D. S.; Zeller, E. *Synlett* **1991**, 878–880.
(9) Related α-alkoxy alkyllithium reagents are configurationally stable under these reaction conditions: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202. Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H.; Skalitzky, D. J. *J. Org. Chem.* **1999**, *64*, 6849–6860. Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131. Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376–3377. Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842–853.
(10) Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976–8978. Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653–654.
(11) Cooke, M. P.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 3643–3646. Babler, J. H.; Bauta, W. E. *Tetrahedron Lett.* **1984**, *25*, 4323–4324. Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1978**, *43*, 3800–3802.

omer **5a**, 6-*endo* cyclization produces the major product. For **5b**, 5-*exo* cyclization is still preferred. As with the chloride and phosphate electrophiles, the epoxide cyclizations also yielded products as single diastereomers.

With these encouraging results in hand, homologated precursors **5c** and **5d** were prepared. Initial attempts to cyclize these precursors at −78 °C failed to give spirocyclic products, even in the presence of Lewis acids such as boron trifluoride etherate or magnesium bromide. Warming the organolithium intermediate to −40 °C resulted in the sluggish formation of 7-*endo* products **12** and **13** in modest yields. In no case was the expected 6-*exo* product isolated.

Assignment of the relative configuration for each of the eight spirocycles featured in Schemes 2 and 3 by NOE and NOESY methods proved to be difficult due to extensive overlap of methylene resonances. To address this issue, we prepared the *p*-nitrobenzoate derivatives of alcohols **8** and **10**, esters **14** and **15**, respectively. The X-ray crystal structures of esters **14** and **15** were obtained and are presented in Figure 1. These structures confirm that the axial alkoxy-

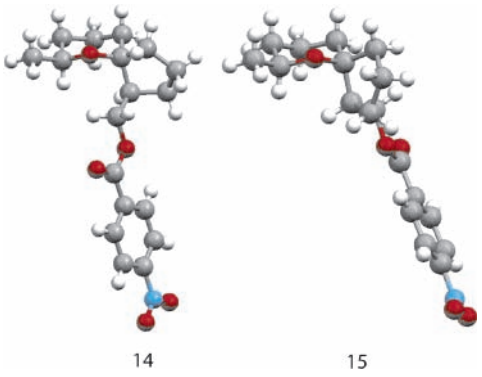


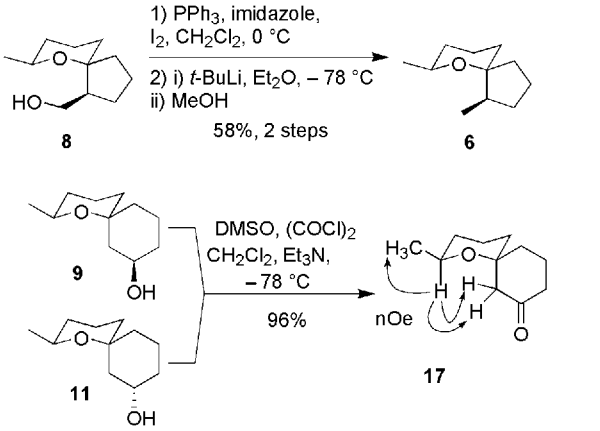
Figure 1. X-ray crystal structures of *p*-nitrobenzoates **14** and **15**.

lithium reacted with retention and the epoxides with inversion of configuration.

The structure of spirocycle **6** was confirmed by correlation with alcohol **8** as shown in Scheme 4. Similarly, spirocycle **7** was correlated with alcohol **10** (not shown). The GC, ^{1}H NMR, and ^{13}C NMR data indicated that the spirocycles obtained in this manner were identical to those obtained from chloride and phosphate cyclizations.[13] Alcohols **9** and **11** were independently oxidized to ketone **17**, and the regiochemistry of the cyclization was assigned by NOE analysis

(12) Last, L. A.; Fretz, E. R.; Coates, R. M. *J. Org. Chem.* **1982**, *47*, 3211−3219.

Scheme 4. Correlation of Spirocycles



of this compound.[14] The absolute configuration of the secondary alcohols in compounds **9** and **11**−**13** originates from the known configuration of the starting epoxides.

In summary, the scope of spiroannulation via reductive decyanation of tertiary nitriles has been expanded to include secondary electrophiles. Tethered secondary chlorides and dialkyl phosphates cyclized in modest to good yields, although stereochemical limitations exist. Terminal epoxides also serve as effective electrophiles for the reductive cyclization. Surprisingly, both *endo* and *exo* modes of cyclization were observed, with the *endo* mode dominating in most cases. Clean Walden inversion was observed in each of the cyclizations at secondary electrophilic centers. These reductive cyclization reactions are unusual and potentially useful stereoselective bond-forming processes in organic synthesis.

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Supporting Information Available: Detailed experimental procedures and analytical data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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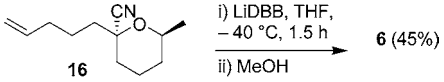
(13) To further correlate these secondary electrophile cyclizations with the previously reported terminal alkene spiroannulations (refs 1 and 3), alkene **16** was prepared and submitted to the standard conditions for reductive decyanation. Spirocycle **6** was isolated as a single diastereomer from the reaction mixture.



(14) Spirocycles **12** and **13** were oxidized, and their regiochemistry was assigned in the same manner. See Supporting Information.