Spiroannulation of THP Rings

Spiroannulation by Alkylation and Reductive Cyclization of Nitriles**

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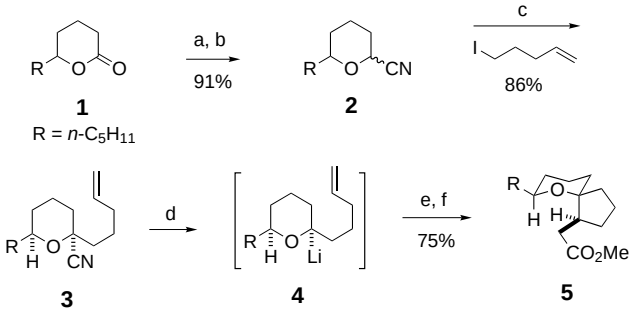
Annulation reactions occupy a central role in synthetic chemistry. Alkyllithium cyclizations onto alkenes or other electrophiles have been studied by a number of groups,[1] but have only rarely been applied to complex synthetic targets because of the limitations of the reaction.[2] In particular, unactivated alkene cyclizations work well only with terminal alkenes to form five-membered rings. A related S_N2' cyclization onto allylic alkoxy groups shows broader scope.[1b,3] Synthesis of the cyclization precursor also can be tedious. We report a new approach to alkyllithium cyclizations that takes advantage of the unique reactivity of nitriles. Nitriles can be alkylated efficiently to introduce functionalized alkyl chains. Tertiary nitriles can be reductively cleaved to form alkyllithium reagents[4] that cyclize in the presence of an internal electrophile. The combination of an alkylation and reductive cyclization results in a facile and unusual annulation reaction. Herein we describe the development of this strategy for the spiroannulation of tetrahydropyran rings, including an example in which two adjacent quaternary centers are formed with complete stereoselectivity.

Our interest in this spiroannulation strategy was piqued by a surprisingly facile alkyllithium cyclization onto a tethered alkene.[5] A diastereoselective version of this cyclization is outlined in Scheme 1. The 2-cyanotetrahydropyran **2** was prepared by reductive acetylation[6] of δ-decanolactone followed by treatment with trimethylsilyl cyanide (TMSCN) and a Lewis acid. Alkylation with 5-iodo-1-pentene produced the cyclization precursor **3**. In each of the alkylations of **2** reported herein, the selectivity was $>99{:}1$ in favor of the axial nitrile. Addition of **3** to excess lithium di-*tert*-butylbiphenylide (LiDBB)[7] in THF at $-78\,^{\circ}C$ and warming immediately to $-42\,^{\circ}C$ led to cyclization of the alkyllithium intermediate **4**. Trapping the alkyllithium product with CO_2 and working up the reaction with CH_2N_2 produced the spirocyclic ester **5** as a single diastereomer in 75% yield. The configuration of the quaternary center was assigned by NOE measurements. The configuration of the other new center was assigned by correlation with alkene **9** (vide infra). Reductive decyanation generated an axial lithium reagent,[4] that cyclized onto the alkene with retention of configuration.[8] The alkyllithium cyclized onto only one face of the alkene and led to a single diastereomer with the alkyllithium chain *cis* to the tetrahydropyran (THP) oxygen atom. This annulation reaction was carried out in two steps from cyanotetrahydropyran **2** and introduced two new stereogenic centers with high selectivity.



Scheme 1. Reagents and conditions: a) 1. DIBAL-H, $-78\,^{\circ}C$; 2. Ac_2O, DMAP, pyridine; b) TMSCN, $BF_3{\cdot}OEt_2$; c) LDA, $-40\,^{\circ}C$, THF, DMPU then iodide; d) add to excess LiDBB in THF, $-78\,^{\circ}C$, then warm to $-42\,^{\circ}C$; e) add CO_2 gas; f) CH_2N_2. DIBAL-H = diisobutylaluminum hydride.

We investigated the spirocyclization of a THP alkyllithium reagent with a TMS-alkyne and the results are shown in Scheme 2. Bailey and co-workers have shown that alkyllithium reagents cyclize efficiently onto alkynes with a net *cis* RLi addition across the alkyne.[9] The precursor for our study was prepared by alkylation of nitrile **2**. Reductive cyclization at $-40\,^{\circ}C$ delivered the spirocycle **7** in 58% yield, accompanied by reductive decyanation and alkyne reduction side products. The alkene geometry was determined by NOE measurements and was consistent with the precedent from Bailey and coworkers.

Allylic methoxyalkenes will participate as electrophiles in S_N2' alkyllithium cyclizations.[1b,3] They are more reactive than simple alkenes and have been used to form both five- and six-membered rings. The reductive cyclization of methoxyalkene substrates is illustrated in Scheme 3. The methoxyalkene side

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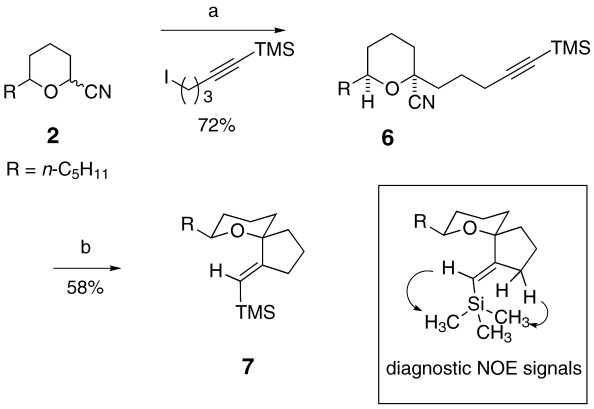
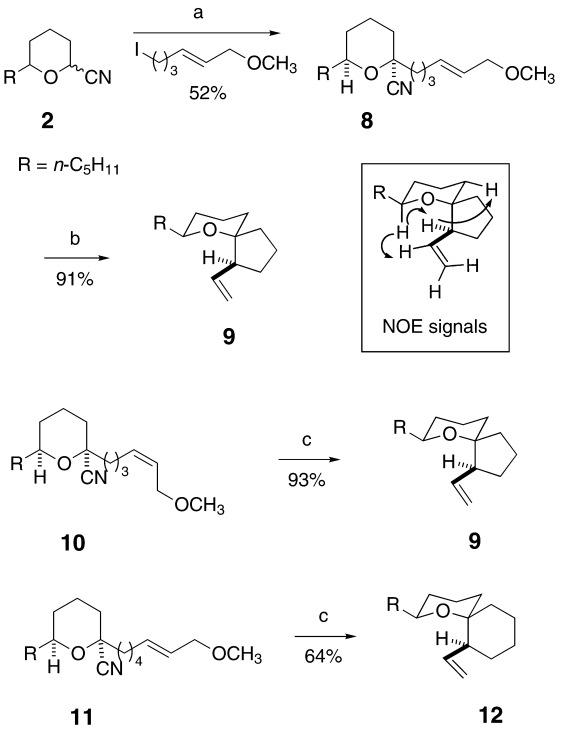


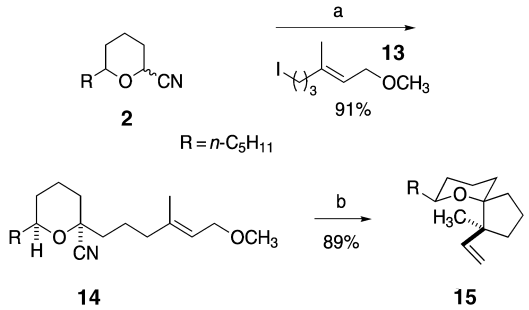
Scheme 2. Reagents and conditions: a) LDA, −40 °C, THF, DMPU then iodide; b) add to excess LiDBB in THF, −40 °C, 20 min, and then quench with MeOH. DMPU = *N*,*N*-dimethylpropyleneurea.



Scheme 3. Reagents and conditions: a) LDA, −40 °C, THF, DMPU then iodide; b) add to excess LiDBB in THF, −78 °C, 20 min, and then quench with MeOH; c) add to excess LiDBB in THF, −42 °C, 60 min, and then quench with MeOH.

chains were introduced by alkylation of cyanotetrahydropyran **2**. Cyclization of the *E* alkene **8** took place on addition to excess LiDBB at −78 °C. Spirocycle **9** was isolated in 91% yield as a single diastereomer. Its configuration was assigned by NOE experiments. The structure of ester **5** was confirmed by correlation with alkene **9**.[10] The *Z* alkene **10** was prepared by alkylation of **2** in 76% yield. Reductive cyclization gave moderate yields at −78 °C, but conducting the cyclization at −42 °C for 60 min led to an excellent yield of same spirocycle **9**. None of the diastereomeric product with the alkene *trans* to the oxygen atom was detected in the cyclization of either the *E* or *Z* alkene. The substrate for the six-membered ring cyclization, (*E*)-**11**, was prepared by alkylation of **2** in 77% yield. Reductive cyclization of **12** once again required the more forcing conditions to proceed efficiently. At −42 °C the cyclization gave **12** as a single isomer in 64% yield. The corresponding *Z* alkene (not shown) did not cyclize efficiently under these conditions. Cyclizations with methoxyalkenes produce both five- and six-membered rings efficiently and with excellent diastereoselectivity.

Reductive cyclization onto a trisubstituted alkene has the potential to form two adjacent quaternary centers, a challenging problem for synthetic chemists. We investigated this possibility with the methoxyalkene substrate **14** (Scheme 4).



Scheme 4. Reagents and conditions: a) LDA, −40 °C, THF, DMPU then iodide **13**; b) add to excess LiDBB in THF, −40 °C, 60 min, and then quench with MeOH.

Once again, the cyclization substrate was prepared by alkylation of nitrile **2** with iodide **13**. Addition of nitrile **14** to excess LiDBB at −40 °C in THF produced spirocycle **15** in 89% yield as a single diastereomer after workup. The configuration of **15** was assigned by NOE measurements.[11] The alkene ends up *cis* to the oxygen atom as was found with the methoxyalkene cyclizations in Scheme 3. This surprisingly efficient cyclization generates two new quaternary stereocenters with complete stereoselectivity.

Electrophiles that reduce more slowly than nitriles would be expected to cyclize in the reductive decyanation reaction. Grierson and co-workers reported the reductive cyclization of an aminonitrile phosphate using potassium and [18]crown-6.[12] Several cyclizations with halide and phosphate electrophiles are shown in Scheme 5. The cyclization substrates **16, 18**, and **19** were prepared by alkylation of nitrile **2** with alkyl iodides. Chloronitrile **16** cyclizes very efficiently on addition to excess LiDBB in THF at −78 °C. Formation of the spirocycle **17** demonstrates that the cyanohydrin functional group is reduced more rapidly than an alkyl chloride. Reductive cyclization of cyanophosphate **18** was even more efficient and led to a nearly quantitative yield of **17**. Formation of the six-membered ring **20** was problematic. Addition of **19** to excess LiDBB gave a mixture of spirocycle **20** and reduced product **21** in a 66:34 ratio. Spirocycle **20** was isolated in 41% yield. Attempts to improve the ratio by varying temperature, order of addition, and equivalents of LiDBB were unsuccessful. Cyclization of the phosphate corresponding to **19** led to reductive decyanation and

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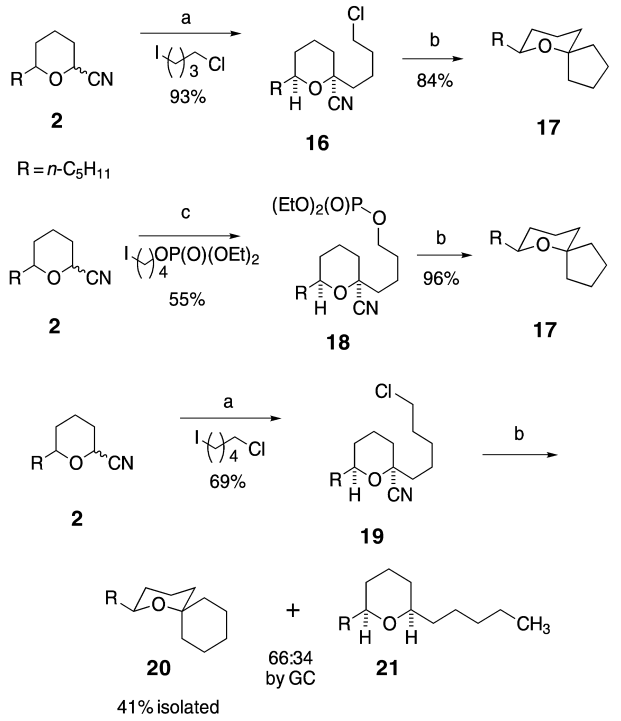
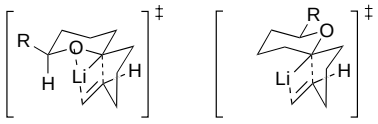


Scheme 5. Reagents and conditions: a) LDA, −40 °C, THF, DMPU then iodide; b) add to excess LiDBB in THF, −78 °C, 20–30 min, and then quench with MeOH; c) LDA, −40 °C, THF, then iodide.

essentially no cyclization. These spiroannulations are very efficient for the five-membered ring cases but produce six-membered rings with modest yields.

For each of the alkene cyclizations we found that the diastereomer with the alkyl chain *cis* to the THP oxygen atom was formed exclusively.[5] We have previously shown that these reductive decyanation cyclizations take place through an anionic cyclization rather than a radical cyclization.[5] Bailey, Wiberg, and co-workers proposed a model for the cyclization of alkyllithium reagents based on computational modeling.[1d] We have adapted their model to the cyclization of alkyllithium **4**; the competing cyclization transition states are **22**, with the alkene *cis* to the oxygen atom, and **24**, with the alkene *trans* to the oxygen atom. We propose that **22** should



22 **24**

be favored over **24** because it allows continuous coordination of the Li atom with the oxygen atom, whereas cyclization to the disfavored *trans* product requires that the strong Li–O dative bond be lost along the reaction coordinate. The same *cis* selectivity was observed with alkene cyclizations and methoxyalkene S_N2' cyclizations. The *cis* alkene–oxygen selectivity is a dependable feature of these cyclizations and the Li–O dative bond is a plausible rationale for this selectivity.

We have shown that spirocyclic rings are easily prepared from 2-cyanotetrahydropyrans. The key feature of this method is the use of a nitrile to facilitate alkylation and as a precursor to an alkyllithium reagent. The two-step sequence, alkylation and reductive cyclization, is successful with a variety of biselectrophiles, generates five- and six-membered rings, and is highly stereoselective. The axial alkyllithium reacts with retention of configuration, leading to axial attack of the internal electrophile. Alkene cyclizations strongly favor products with the alkene *cis* to the THP ring oxygen atom. This strategy even can be used to produce adjacent quaternary centers with excellent selectivity. We expect this reductive cyclization methodology to be a powerful new tool in organic synthesis.

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[1] a) D. G. Farnum, T. Monego, *Tetrahedron Lett.* **1983**, *24,* 1361–1364; b) W. F. Bailey, T. T. Nurmi, J. J. Patricia, W. Wang, *J. Am. Chem. Soc.* **1987**, *109,* 2442–2448; c) A. R. Chamberlin, S. H. Bloom, L. A. Cervini, C. H. Fotsch, *J. Am. Chem. Soc.* **1988**, *110,* 4788–4796; d) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113,* 5720–5727; e) W. F. Bailey, A. D. Khanolkar, K. V. Gavaskar, *J. Am. Chem. Soc.* **1992**, *114,* 8053–8060; f) W. F. Bailey, M. W. Carson, *J. Org. Chem.* **1998**, *63,* 361–365; g) A. Deiters, D. Hoppe, *J. Org. Chem.* **2001**, *66,* 2842–2849; h) W. F. Bailey, M. J. Mealy, *J. Am. Chem. Soc.* **2000**, *122,* 6787–6788; i) M. J. Mealy, W. F. Bailey, *J. Organomet. Chem.* **2002**, *646,* 59–67.

[2] a) W. F. Bailey, X.-L. Jiang, C. E. McLeod, *J. Org. Chem.* **1995**, *60,* 7791–7795; b) W. F. Bailey, X.-L. Jiang, *J. Org. Chem.* **1996**, *61,* 2596–2597; c) E. Coldham, R. Hufton, D. J. Snowden, *J. Am. Chem. Soc.* **1996**, *118,* 5322–5323; d) A. Deiters, D. Hoppe, *Angew. Chem.* **1999**, *111,* 529–532; *Angew. Chem. Int. Ed.* **1999**, *38,* 546–548.

[3] a) C. A. Broka, W. J. Lee, T. Shen, *J. Org. Chem.* **1988**, *53,* 1336–1338; b) C. A. Broka, T. Shen, *J. Am. Chem. Soc.* **1989**, *111,* 2981–2984; c) A. E. Harms, J. R. Stille, S. K. Taylor, *Organometallics* **1994**, *13,* 1456–1464.

[4] S. D. Rychnovsky, J. P. Powers, T. J. Lepage, *J. Am. Chem. Soc.* **1992**, *114,* 8375–8384.

[5] S. D. Rychnovsky, T. Hata, A. I. Kim, A. J. Buckmelter, *Org. Lett.* **2001**, *3,* 807–810.

[6] D. J. Kopecky, S. D. Rychnovsky, *J. Org. Chem.* **2000**, *65,* 191–198.

[7] P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45,* 1924–1930.

[8] K. Tomooka, N. Komine, T. Nakai, *Tetrahedron Lett.* **1997**, *38,* 8939–8942.

[9] a) W. F. Bailey, T. V. Ovaska, T. K. Leipert, *Tetrahedron Lett.* **1989**, *30,* 3901–3904; b) W. F. Bailey, T. V. Ovaska, *J. Am. Chem. Soc.* **1993**, *115,* 3080–3090; c) W. F. Bailey, N. M. Wachter-Jurcsak, M. R. Pineau, T. V. Ovaska, R. R. Warren, C. E. Lewis, *J. Org. Chem.* **1996**, *61,* 8216–8228.

[10] Alkene **9** was converted to ester **5** and shown to be identical by ^{1}H NMR, ^{13}C NMR, and HRMS. Conditions: a) 1. 9-borabicyclo[3.3.1]nonane (9-BBN); 2. NaOH, H_2O_2; b) 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), NaOCl, $NaClO_2$; c) CH_2N_2.

[11] See Supporting Information.

[12] a) E. Zeller, H. Sajus, D. S. Grierson, *Synlett* **1991**, 44–46; b) E. Zeller, D. S. Grierson, *Synlett* **1991**, 878–880.

  0044-8249/03/11507-0844 $ 20.00+.50/0