COMMUNICATION

ChemComm
www.rsc.org/chemcomm

# Intramolecular $S_N2'$ cyclization of an alkyllithium species onto a methoxy allyl ether is *syn* selective†

**Thomas E. La Cruz and Scott D. Rychnovsky***

*Department of Chemistry, 516 Rowland Hall, University of California Irvine, Irvine, California 92697-2025, USA. E-mail: srychnov@uci.edu; Fax: 949-824-6379; Tel: 949-824-8292*

***Received (in Corvallis, OR, USA) 10th November 2003, Accepted 19th November 2003***
***First published as an Advance Article on the web 4th December 2003***

**The preference for *syn*- or *anti*-addition of an intramolecular $S_N2'$ cyclization of an alkyllithium species onto a methoxy allyl ether has been proven unequivocally to take place by a *syn* $S_N2'$ mechanism.**

Alkyllithium cyclizations onto alkenes or alkoxy alkenes have interesting possibilities as ring-forming reactions.[1] The preference for *syn*- or *anti*-addition in the $S_N2'$ intramolecular cyclization of alkoxy alkenes has not been investigated. Examples by Farnum[2a] and Lautens[2b] support the view that *syn*-$S_N2'$ cyclization predominates, but their substrates prohibit *anti* cyclization. Stille,[2c] who showed that $S_N2'$ cyclization preferentially generates *E*-alkenes with 10–20 : 1 selectivity, assumes in his work that *anti*-$S_N2'$ cyclization of an organolithium species was favoured by analogy to cuprate additions.[3] Stille's substrate could only cyclize in an *anti* $S_N2'$ addition. Both *syn* and *anti* cyclizations are possible, but which mode is preferred?

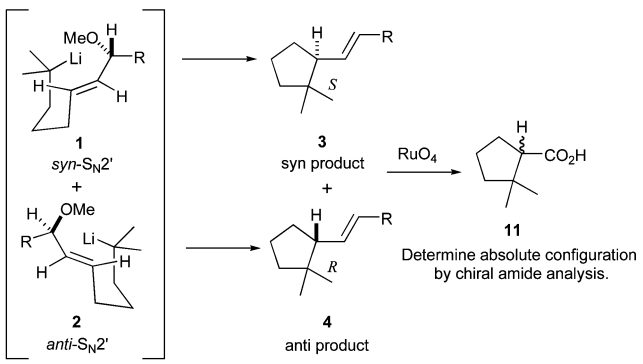
We envisioned an unbiased test of *syn*/*anti*-$S_N2'$ selectivity in alkyllithium cyclizations of a methoxy allyl ether, Scheme 1. Using the optically pure methoxy allyl ether substrate depicted, we predicted that the *syn*-$S_N2'$ cyclization would provide the *S* enantiomer **3**, whereas the *anti*-$S_N2'$ reaction would produce the *R* enantiomer **4** as illustrated in Scheme 1. In accordance with Stille's experimental results we expect the *E* olefin isomer to predominate regardless of *syn* or *anti* selectivity. Oxidation of the cyclization product to **11** followed by evaluation of the optical purity and absolute configuration of the stereocenter would determine the intrinsic bias for *syn*- or *anti*-$S_N2'$ cyclizations of alkyllithium reagents.

Synthesis of the enantiopure cyclization precursor is outlined in Scheme 2. Propargyl ketone **5** was synthesized by the nucleophilic addition of a lithium anion of the silyl ether of 4-pentyn-1-ol to a Weinreb amide, which was derived from commercially available 4-phenyl-butanoic acid.[4a] Enantioselective reduction of ketone **5** utilizing Noyori's asymmetric hydrogen-transfer catalyst gave the desired propargyl alcohol **6** in 81% yield, and 97% ee as determined by HPLC on a Chiracel-OD column.[4b,c] Propargyl alcohol **6** was subjected to a four step reaction sequence that included reduction of the alkyne to the *E* olefin (to give **7a**), formation of the allyl methyl ether (to **7b**), removal of the silyl protecting group (**7c**), and conversion of the primary alcohol to alkyl iodide **7d**.[4d,e] The quaternary center of the cyclization precursor **9** was installed by deprotonating commercially available isobutyronitrile, **8**, with lithium diisopropylamide, followed by alkylation with iodide **7d** to give the cyclization precursor **9** in 97% yield.[4f]

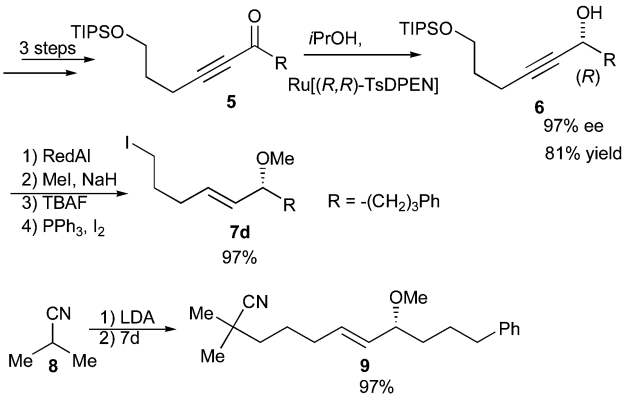
The enantiopure substrate **9** was subjected to reductive lithiation conditions utilizing LiDBB (lithium di-*tert*-butyl biphenylide) at −78 °C to generate a tertiary alkyllithium species.[5a–c] The product of the cyclization reaction, hydrocarbon **10**, was isolated in 37% yield with an *E*/*Z* selectivity of 97 : 3 as determined from the $^1$H NMR spectrum. The low yield associated with the cyclization reaction is a reflection of the difficulty in separating the cyclization product from the hydrocarbon side products.

Olefin **10** was oxidized with ruthenium tetraoxide to form carboxylic acid **11** (Scheme 3).[5d] A portion of acid **11** was treated with diazomethane and the enantiomeric ratio of the resulting methyl ester was determined by GC on a chiral column to be 95 : 5.[6,10] Thus the transfer of chirality from the methoxy center was *ca.* 96%.[7]

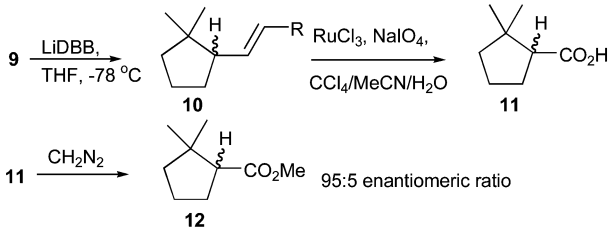
To determine the absolute configuration of the product, acid **11** was coupled to (*R*)-PGME (phenyl glycine methyl ester) to form diastereomeric amides **13** and **14** as illustrated in Scheme 4.[7,8] The $^1$H NMR spectrum of the amides formed from the oxidized cyclization product was compared to the spectrum of a standard mixture, which was derived from the racemic counterpart of acid **11**.[9,10] The major product was found to have chemical shifts of the two methyl singlets at 1.20 and 0.93 ppm. The chemical shifts of the




**Scheme 1** $S_N2'$ cyclization of methoxy allyl ethers: *syn*-selective or *anti*-selective?



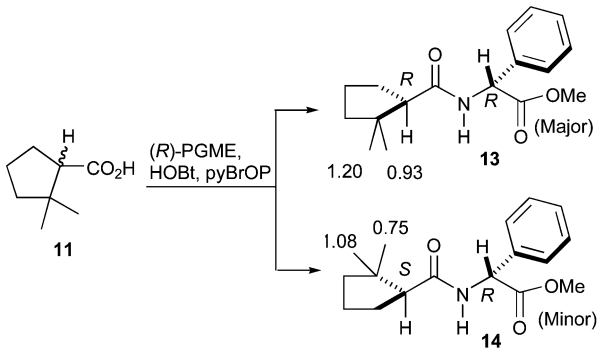

**Scheme 2** Synthesis of enantiopure cyclization precursor.




**Scheme 3** Reductive lithiation and cyclization.

† Electronic Supplementary Information (ESI) available: preparation and characterization of all compounds. See http://www.rsc.org/suppdata/cc/b3/b314358a/

DOI: 10.1039/b314358a




**Scheme 4** Chiral amide analysis.

two methyl singlets of the minor diastereomer were found further upfield at 1.08 and 0.75 ppm. The major product was identified as the (*R*,*R*)-diastereomer **13** based on these chemical shifts, and the minor was identified as the (*S*,*R*)-diastereomer **14**. The (*R*,*R*)-diastereomer **13** corresponds to the *S* enantiomer **3**. Thus the cyclization produced (*S*)-**3** through a *syn*-$S_N2'$ cyclization of alkene **9**. The *syn* pathway predominated over the *anti* pathway with at least a 20 : 1 preference.

The optically pure acyclic cyclization precursor was prepared and subjected to reductive lithiation mediated by LiDBB. The tertiary alkyllithium species thus formed cyclized onto a methoxy allyl ether moiety *via* an intramolecular $S_N2'$ mechanism. Oxidation of the alkene product to the carboxylic acid, and derivatization to a chiral phenyl glycine amide provided the absolute configuration and the *syn* preference of the cyclization reaction. In a conformationally unbiased system alkyllithium cyclizations onto methoxy alkenes prefer the *syn* $S_N2'$ cyclization pathway with approximately a 96% stereochemical preference.

This work was supported by the National Institutes of General Medicine (GM-65338).

## Notes and references

1 (*a*) Review: M. J. Mealy and W. F. Bailey, *J. Organomet. Chem.*, 2002, **646**, 59–67; (*b*) W. F. Bailey, J. J. Patricia, V. C. DelGobbo, R. M. Jarret and P. J. Okarma, *J. Org. Chem.*, 1985, **50**, 1999–2000; (*c*) A. R. Chamberlin, S. H. Bloom, L. A. Cervini and C. H. Fotsch, *J. Am. Chem. Soc.*, 1988, **110**, 4788–4796; (*d*) C. A. Broka, W. J. Lee and T. Shen, *J. Org. Chem.*, 1988, **53**, 1336–1338; (*e*) W. F. Bailey, A. D. Khanolkar and K. V. Gavaskar, *J. Am. Chem. Soc.*, 1992, **114**, 8053–8060; (*f*) M. J. Woltering, R. Frohlich and D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1764–1766; (*g*) K. Deng, A. Bensari and T. Cohen, *J. Am. Chem. Soc.*, 2002, **124**, 12106–12107; (*h*) M. Yus, R. Ortiz and F. F. Huerta, *Tetrahedron*, 2003, **59**, 8525–8542.

2 (*a*) D. G. Farnum and T. Monego, *Tetrahedron Lett.*, 1983, **24**, 1361–1364; (*b*) M. Lautens and S. Kumanovic, *J. Am. Chem. Soc.*, 1995, **117**, 1954–1964; (*c*) A. E. Harms, J. R. Stille and S. K. Taylor, *Organometallics*, 1994, **13**, 1456–1464.

3 (*a*) R. M. Magid, *Tetrahedron*, 1980, **36**, 1901–30; (*b*) Y. Gendreau and J. F. Normant, *Tetrahedron*, 1979, **35**, 1517–21; (*c*) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1984, **25**, 3059–62; (*d*) L. A. Paquette and C. J. M. Stirling, *Tetrahedron*, 1992, **48**, 7383–423.

4 (*a*) P. H. Dussault, C. T. Eary and K. R. Woller, *J. Org. Chem.*, 1999, **64**, 1789–1797; (*b*) K. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 285–290; (*c*) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738–8739; (*d*) H. Ishiyama, T. Takemura, M. Tsuda and J.-I. Kobayashi, *Tetrahedron*, 1999, **55**, 4583–4594; (*e*) L. R. G. Linde, M. Egbertson, R. S. Coleman, A. B. Jones and S. J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 2771–2776; (*f*) Y. Suzuki, A. Ohara, K. Sugaya, K. Takao and K. Tadano, *Tetrahedron*, 2001, **57**, 7291–7301.

5 (*a*) P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924–1930; (*b*) A. J. Buckmelter, J. P. Powers and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1998, **120**, 5589–5590; (*c*) S. D. Rychnovsky and L. Takaoka, *Angew. Chem., Int. Ed.*, 2003, **42**, 818–820; (*d*) P. J. Carlsen, T. Katsiki and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936–3938.

6 GC Retentions times: $R_t$ major-(*R*)-**12**: 17.12 min; $R_t$ minor-(*S*)-**12**: 19.05 min. GC analysis performed with a 30 m × 0.25 mm G-TA chiral column using a thermal gradient: 50 °C, 5 min, increase 5 °C $min^{-1}$ to 150 °C.

7 The *E*/*Z* selectivity was 97 : 3. If both the *E* and the *Z* isomer arose from stereoselective *syn*-$S_N2'$ processes (which would lead to opposite enantiomers of **11**) then the expected chirality transfer would be 97%.

8 Y. Nagai and T. Kusumi, *Tetrahedron Lett.*, 1995, **36**, 1853–1856.

9 Amides **13** and **14** were formed in an 86 : 14 ratio. We attribute the discrepancy between the **13** : **14** ratio and the enantiomeric ratio of ester **12** to partial racemization of the hindered acid on activation and coupling with the PGME amine.

10 An appropriate diastereomeric standard consisting of a 1 : 1 mixture of amides **13** and **14** was synthesized from the racemic counterpart of acid **11** and (*R*)-PGME. An appropriate enantiomeric standard for **12** was synthesized from racemic counterpart of acid **11**.