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Stereoselectivity of Intramolecular S_N' Cyclizations of Alkyllithium Reagents on Methoxy Alkenes

Thomas E. La Cruz and Scott D. Rychnovsky*

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, Irvine, California 92697-2025

srychnov@uci.edu

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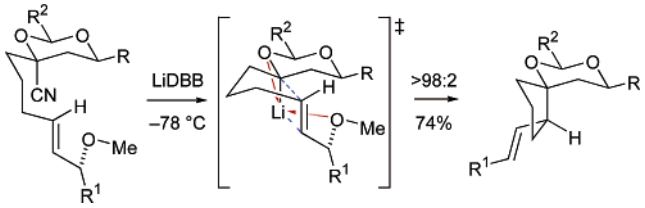

The cyclization of alkyllithium reagents onto methoxy alkenes has been investigated. The alkyllithium reagent was generated by reductive lithiation of an alkyl nitrile. In an unbiased substrate, a methoxy leaving group attached to a stereogenic secondary carbon atom led to the cyclization product with high optical purity. The configuration of the product demonstrated that the cyclization had proceeded with high syn-S_N' selectivity. Previously we have shown that 2-lithiotetrahydropyran reagents cyclize to form spirocycles with the alkene cis to the pyran oxygen. Substrates were prepared to evaluate the importance of the configuration of the secondary allyl methyl ether against the α-alkoxy alkyllithium configuration. In the matched case (cyano acetal **38**), a very selective cyclization ensued. In the mismatched case (cyano acetal **39**), the spiro ether selectivity dominated. The syn-S_N' selectivity overcame the normal *E* selectivity in the cyclization and accounted for the major product, *Z*-alkene **45**. Thus the stereochemical preference in these alkyllithium cyclizations is dominated by the spiroether effect, followed by the syn-S_N' selectivity and finally the preference for *E*-alkene formation.

Introduction

The S_N' carbon−carbon bond forming cyclization reaction of an alkyllithium species onto an allylic ether can be a valuable tool in synthetic organic chemistry.[1] Although the earliest example of an alkyllithium cyclization involved displacement of an alkoxy group,[2] the 5-exo-trig cyclization of a carbon−lithium bond into an unactivated alkene attracted more attention and has been investigated more often. Both the mechanism and the synthetic applications of the carbolithiation−cyclization reaction have been comprehensively investigated by Bailey.[3] However, the cyclization was found to be efficient only with unactivated terminal alkenes, or electron deficient alkenes. Alkyllithium cyclizations onto allyl ethers have a wider scope and more potential utility than cyclizations onto unactivated alkenes. These S_N' cyclizations of organolithium species were first studied systematically by the Broka and Chamberlin groups.[4] Since then other groups reported successful S_N' cyclization reactions using a variety of allyl ethers as the leaving group,[5] but fundamental questions about the preference for the syn or anti addition of the organolithium species still remained.

Cyclizations onto allylic acetates show syn-S_N' selectivity with soft nucleophiles such as malonates.[6] The selectivity with alkyllithium cyclizations is more confusing. Both the syn- and

(1) (a) Review: Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59−67. (b) Woltering, M. J.; Frohlich, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1764−1766. (c) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106−12107. (d) Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525−8542.

(2) Farnum, D. G.; Monego, T. *Tetrahedron Lett.* **1983**, *24*, 1361−1364.

(3) (a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999−2000. (b) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720−5727. (c) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053−8060.

(4) (a) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788−4796. (b) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336−1338. (c) Broka, C. A.; Shen, T *J. Am. Chem. Soc.* **1989**, *111*, 2981−2984.

(5) (a) Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621−7624. (b) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939−8942. (c) Bailey, W. F.; Tao, Y. *Tetrahedron Lett.* **1997**, *38*, 6157−6158.

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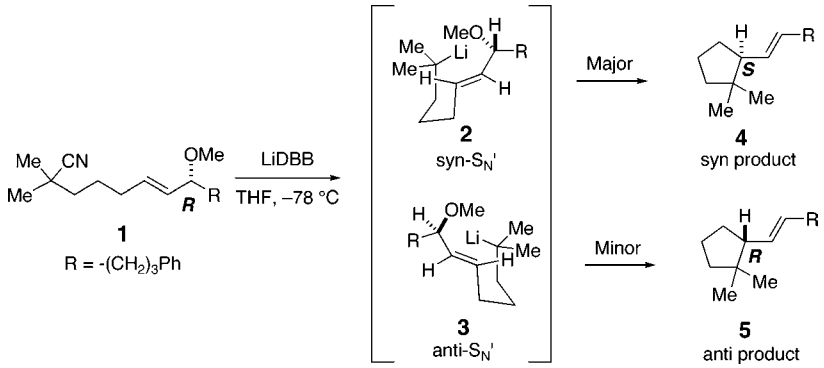
SCHEME 1. The S_N' Cyclization of Methyl Allyl Ethers Is Syn Selective

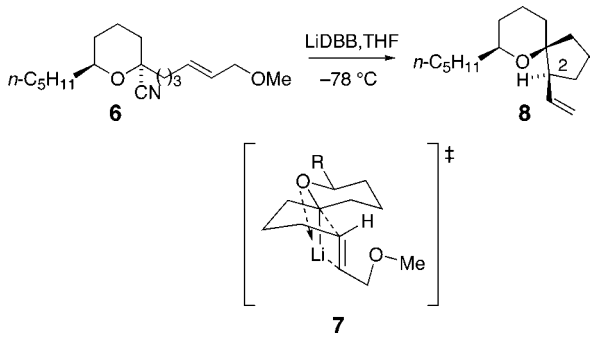


anti-S_N' cyclization reactions of alkoxy alkenes with organolithium reagents have been reported. However, the preference for syn or anti addition in an unbiased system has not been investigated. Examples by Farnum[2] and Lautens[7] support the view that syn-S_N' cyclization predominates, but their substrates were structurally biased to give solely the syn-S_N' product. Intermolecular S_N2' reactions have been investigated and in some cases found to prefer syn-S_N2' substitution, but the substrates are sterically biased and the conclusions may not be general.[8] Conversely, Stille showed that S_N' cyclization preferentially generates *E*-alkenes with 10:1 to 20:1 selectivity,[9] but he assumed in his work that anti-S_N' cyclization of an organolithium species was favored by analogy to cuprate additions.[10] Stille's substrate, which could only react in an anti-S_N' fashion, cyclized efficiently.[11] Both syn and anti cyclizations are possible depending on the structural constraints of the cyclization precursor, but which mode is preferred?

We have reported the cyclization of an unbiased substrate in an intramolecular S_N' alkyllithium cyclization reaction.[11] The optically pure acyclic cyclization precursor **1** was prepared and subjected to reductive lithiation by treatment with lithium di-*tert*-butylbiphenylide (LiDBB) (Scheme 1).[12] It was observed that the syn-S_N' pathway predominated over the anti pathway with a 20:1 preference.[11] In accordance with Stille's observation, the *E*-alkene was found to be the major product of the cyclization reaction. The experiment presented in Scheme 1 provided the first unbiased measure of syn- or anti-S_N' selectivity in alkyllithium cyclizations, and set the stage for the further development of this type of annulation reaction.

The α-alkoxy alkyllithium spiroannulation reaction of primary alkoxy alkenes has been investigated in our laboratories.[13] We found that for each S_N' spiroannulation reaction of primary allyl methyl ethers, the diastereomer with the alkene chain cis to the pyran oxygen atom was formed exclusively (Scheme 2).[13] In an unbiased case, the stereochemistry at the methoxy-substituted carbon controlled the configuration at the newly formed stereogenic center (Scheme 1), but in the spiro ether cyclizations, the configuration was dictated by the oxygen present in the ring. Scheme 2 illustrates our proposal for the transition state that leads to selective spiro ether formation, with strong lithium coordination to the ring oxygen dictating the approach of the alkene.[13] In a related observation, Cohen has shown that proximate alkoxylithium groups accelerate alkene cyclization reactions.[1c] If both selectivity elements, spiro ether selectivity and syn-S_N' selectivity, were combined in a single substrate, which would predominate? Setting these two directing effects against each other provides a criterion to measure the strength and reliability of these stereochemical interactions that will be useful in the design of new reactions.

SCHEME 2. Spiroannulation of Primary Allyl Methyl Ethers



We set out to investigate the dependability of the spiroether effect and the S_N' syn selectivity as outlined in Scheme 3. The S_N' cyclization of an organolithium species onto a stereogenic methoxy alkene derived from optically pure cyclic acetals was investigated both to study the stereoselectivity and to broaden the scope of S_N' alkyllithium cyclization reactions. Since the syn-S_N' pathway is intrinsically preferred,[11] substrate **9** is a matched case in which the interaction of the lithium and ring oxygen moieties and the parallel alignment of the carbon–lithium bond with the alkene favor diastereomer **11**. A proposed transition state geometry is illustrated with structure **10**. Cyclization of **9** is expected to take place with high diastereo-

(6) Bäckvall, J. E.; Vågberg, J. O.; Genêt, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 159–160.

(7) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954–64.

(8) (a) Arjona, O.; de Dios, A.; de la Pradilla, R. F.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906–3916. (b) Smith, A. B.; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516–14517.

(9) (a) Harms, A. E.; Stille, J. R.; Taylor, S. K. *Organometallics* **1994**, *13*, 1456–1464. (b) Bailey, W. F.; Zarcone, L. M. J. *Chirality* **2002**, *14*, 163–165.

(10) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1930. (b) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *35*, 1517–1521. (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059–3062. (d) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383–7423.

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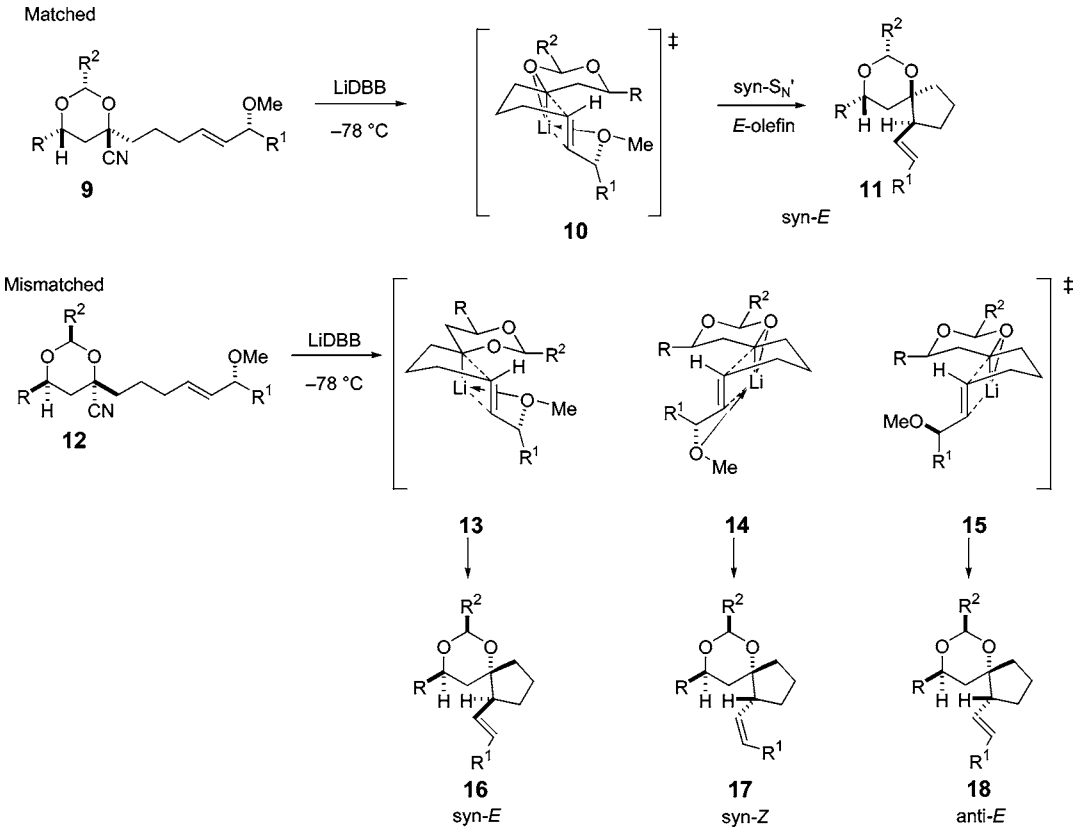
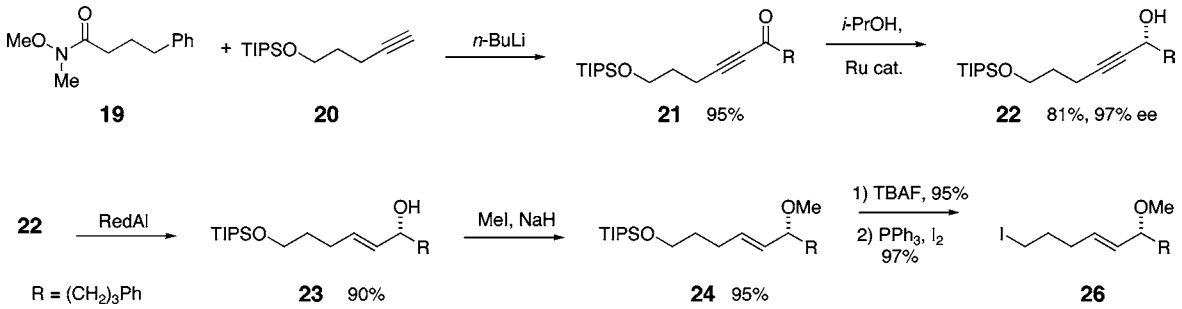
(12) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930. (b) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589–5590. (c) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* **2001**, *3*, 807–810.

(13) (a) Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 818–820. (b) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528–529.

SCHEME 3. S_N' Cyclization of Diastereomeric Allyl Methyl Ethers



SCHEME 4. Synthesis of Optically Active Alkyl Iodide 26



selectivity. Cyclic acetal **12** is a mismatched case, making the outcome of the cyclization reaction difficult to predict. If the syn-S_N' selectivity takes priority, then **16** or **17** would result depending on the importance of Li−O interaction versus *E*/*Z* selectivity. If syn to anti selectivity is modest and *E*-selectivity is important then **18** would be expected to predominate. Cyclization of these substrates will weigh the relative importance of syn-S_N' cyclizations, the spiroether effect, and *E*/*Z* selectivity against each other. The outcome of these experiments will answer fundamental questions about stereoselectivity in alkyllithium spiroannulation reactions.

Results

Synthesis of optically active allylic ether **26**, as outlined in Scheme 4, began with the addition of the lithium anion of TIPS ether **20** to Weinreb amide **19**, derived from commercially available 4-phenylbutanoic acid, to give the alkynyl ketone **21** in 95% yield.[14] Asymmetric reduction of ketone **21** with Noyori's hydrogen-transfer catalyst gave the desired propargyl alcohol **22** in 81% yield, and 97% ee.[15] Reduction of **22** with RedAl gave the *E*-alkene **23** in 90% yield, which was then methylated to give methyl allyl ether **24** in 95% yield.[16] Removal of the silyl group generated alcohol **25**, which was then converted to optically active alkyl iodide **26** in 97% yield.[17] The same optically active methyl allyl ether **26** was used for the initial studies of the S_N' cyclization and the more comprehensive alkyllithium cyclizations described herein.

Synthesis of the optically active acetals, as outlined in Scheme 5, began with β-keto ester **27** prepared by the method of

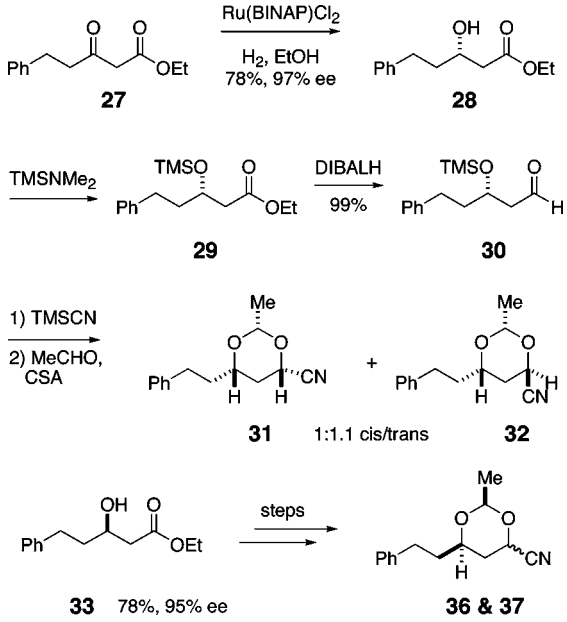
(14) Dussault, P. H.; Eary C. T.; Woller K. R. *J. Org. Chem.* **1999**, *64*, 1789−1797.

(15) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288. (b) Fujii, A.; Haack, K.-J.; Hashiguchi, S.; Ikariya, T.; Matsumura, K.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288−290.

(16) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (b) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J.-I. *Tetrahedron*, **1999**, *55*, 4583−4594.

(17) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978−980.

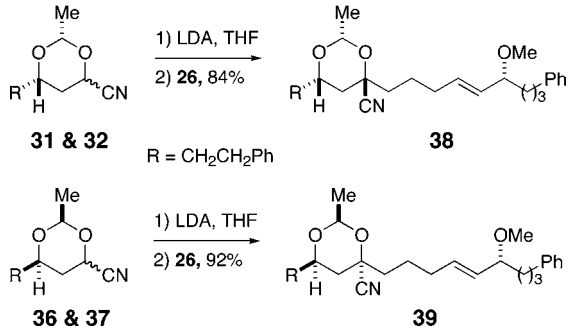
SCHEME 5. Synthesis of Optically Active Cyclic Acetals



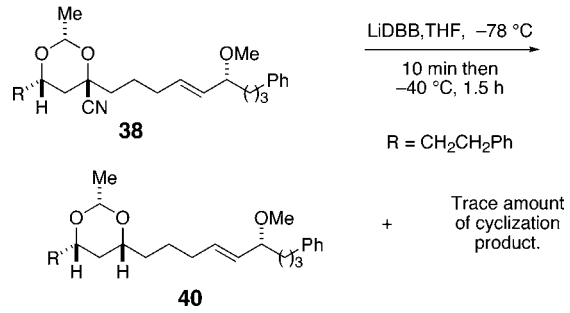
Roskamp.[18] Asymmetric hydrogenation of β-keto ester **27**, with Noyori's ruthenium BINAP catalyst, provided the desired (*S*)-β-hydroxy ester **28** in 78% yield and 97% ee.[19] The secondary alcohol was protected as the TMS ether and the resulting ester **29** was then reduced to aldehyde **30**. Aldehyde **30** was treated first with TMSCN, to generate a cyanohydrin, then acetylaldehyde and CSA to give a mixture of cis and trans acetals **31** and **32** (78% yield) in 1:1.1 ratio, respectively.[20] Minor diastereomers related to **31** and **32**, which have the methyl substituent in the axial position at C2, were present as 3−5% of the total diastereomeric mixture. Although acetals **31** and **32** could be separated by silica gel chromatography, it was found that the minor diastereomers bearing the methyl substituent in the axial position could not be separated from the major diastereomers. Fortunately, this minor impurity did not introduce any complications when the diastereomeric mixture was taken to the next step of the reaction sequence. The mixture comprised of acetals **31** and **32** was treated with lithium diisopropylamide and alkyl iodide **26** (Scheme 6) to afford the "matched" cyclization precursor **38** in 84% yield as a single diastereomer.[21] Repeating this route along with the substitution of (*S*)-BINAP by (*R*)-BINAP in the hydrogenation stage of the synthetic sequence led to the formation of acetals **36** and **37**. By using the same procedure, the "mismatched" cyclization precursor **39** was synthesized in 92% yield by alkylating the mixture of acetals **36** and **37** with iodide **26**.[21] With the successful synthesis of the desired optically active cyclization precursors, the reductive cyclizations could be investigated.

Initial attempts to cyclize nitrile **38** began with the procedure successfully used in other spiroacetal cyclizations.[13] Nitrile **38**

SCHEME 6. Alkylation of Acetals



SCHEME 7. Initial Attempts for the Reductive Cyclization of Cyano Acetal 38



was treated with 4 equiv of LiDBB at −78 °C and the reaction mixture was placed in a −40 °C bath for 1.5 h. The ^{1}H NMR spectrum of the crude reaction mixture revealed that the reduced acetal **40** was the major product of the reaction (Scheme 7). This experiment indicates that the S_N' cyclization of secondary methoxy alkenes to form a spiro compound takes place more slowly than that of primary methoxy alkenes. When the temperature of the reaction was maintained at −78 °C for an extended period of time (12 h), using THF as the solvent, the desired cyclized product **41** was isolated in 54% yield. However, a significant amount of acetal **40** was still detected. Evidently, proton abstraction from THF by the organolithium species is competitive with the cyclization pathway. The reaction was repeated with a 1:1 THF/hexanes solvent mixture to reduce the rate of THF deprotonation,[22] and these conditions afforded the best yield, 74%, of the cyclization product **41** (Scheme 8). Cyclization precursor **39** was subjected to the identical reaction conditions to produce the cyclization products in a combined 72% yield. The use of low temperatures, extended reaction times, and a THF/hexanes solvent system led to good yields in the reductive cyclization of nitriles **38** and **39** (Scheme 8).

The product distributions in the reductive cyclization reactions are presented in Scheme 8. Cyclization of the matched acetal **38** gave rise to spirocycle **41** with >98:2 *E*/*Z* selectivity. The coupling constant between the vinylic protons was found to be 15.4 Hz, consistent with an *E*-alkene geometry. The chemical shifts of the allylic proton and allylic carbon of acetal **41** were found to be δ 2.74 and 46.5 ppm, respectively. Furthermore, the configuration of the newly formed allylic stereocenter of **41** was determined by nOe measurements as illustrated in Figure 1. The olefin geometry, in conjunction with the configuration of the newly formed allylic center, leads to the conclusion that the cyclization of the matched acetal **38** occurs by a syn-S_N' mechanism with excellent selectivity.

(18) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260.

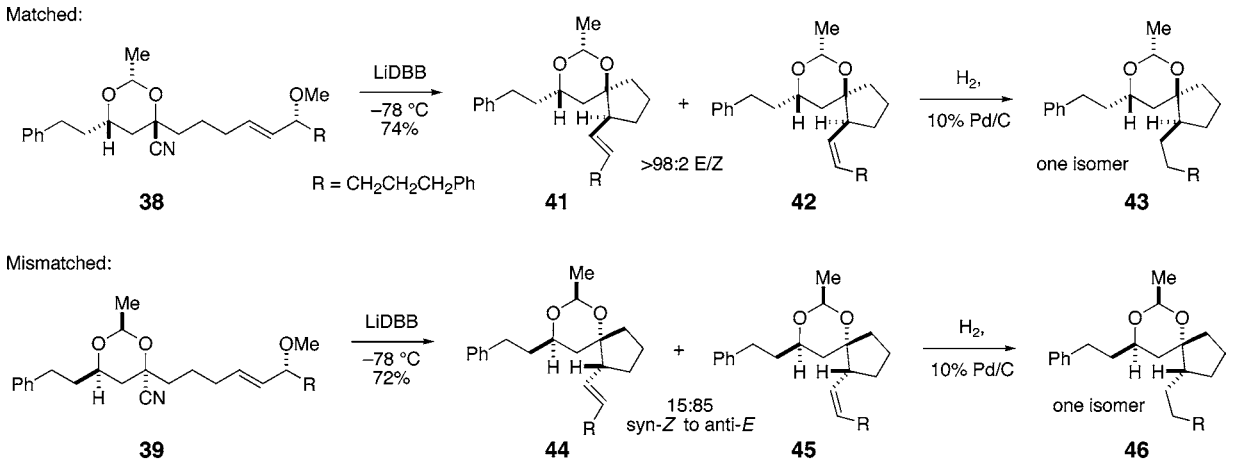
(19) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858.

(20) (a) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550−5551. (b) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559−1563. (c) Sinz, C. J.; Rychnovsky, S. D. *Top. Curr. Chem.* **2001**, *216*, 51−92.

(21) The minor axial methyl isomers apparently do not alkylate efficiently under these conditions, and were not observed in the alkylation products **38** or **39**.

(22) Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011−3014.

SCHEME 8. Olefin Geometry and Configuration of the Allylic Stereocenter



Cyclization of the mismatched acetal **39** gave an inseparable mixture of *E* and *Z* olefin isomers **44** and **45** in an 15:85 ratio. The coupling constants of the vinylic protons of the major isomer **45** were found to be ca. 10.5 Hz, consistent with a *Z*-alkene assignment. The chemical shifts of the allylic proton and carbon atoms of **45** were found to be δ 2.91 and 41.0 ppm, respectively. The configuration of the newly formed allylic center of **45** was determined to have the alkene cis to the ring oxygen by nOe measurements, as illustrated in Figure 1. Thus, the syn-S_N' cyclization predominates for the mismatched case in moderate selectivity.

The cyclizations were completely stereoselective with respect to the previously observed spiro ether preference. Cyclization of the matched acetal **38** gave rise to predominantly one product, acetal **41**, as determined by ^{1}H NMR and ^{13}C NMR analysis. Cyclization of the mismatched substrate **39**, however, gave a mixture of two inseparable geometric isomers that complicated the ^{1}H NMR spectrum of the product, making it difficult to unambiguously determine if the epimer at C7 was formed. The products of each cyclization reaction were hydrogenated to give *enantiomeric* acetals **43** and **46** as single diastereomers. The structures of these saturated products are illustrated in Scheme 8. These experiments confirm that the minor isomer for the mismatched cyclization, *E*-alkene **44**, has the same C7 configuration as the major isomer, *Z*-alkene **45**. The epimer at C7 was not a significant product in the cyclization of either nitrile **38** or **39**.

Discussion

Organolithium reagents derived from cyano acetals **38** and **39** cyclize onto secondary methoxy alkenes in an S_N' fashion and generate novel spiro compounds with two new stereogenic centers. The methyl ether is a robust functional group that can be installed at an early stage of a synthetic sequence.[9a] Primary allyl methyl ethers are more reactive than simple alkenes in the reductive cyclization reactions. Secondary allyl methyl ethers, however, react more slowly and proton abstraction from THF by the very basic α-alkoxy organolithium reagent appears to be a competing pathway. This decomposition pathway can be attenuated by generating the organolithium species in a THF−hexanes solvent mixture. The optimized S_N' cyclization of secondary methoxy alkenes is an efficient process.

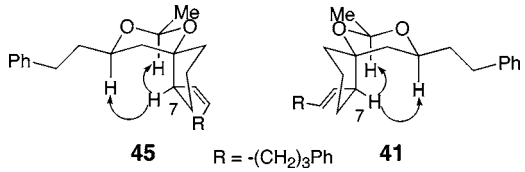


FIGURE 1. nOe measurements for major products **41** and **45**.

Cyclization of both matched and mismatched acetals gave exclusively products with the alkene chain cis to the ring oxygen, in good agreement with the stereochemical outcome of the S_N' cyclization of organolithiums derived from THP systems.[13] Cyclization of the matched cyano acetal **38** gave spiro product **41** with high diastereoselectivity, whereas cyclization of the mismatched cyano acetal **39** gave a mixture of two isomeric products, **44** and **45**, with identical C7 configurations. The spiro ether effect, resulting in an alkene cis to the ring oxygen, dominated the stereoselectivity.

A syn-S_N' addition takes priority over anti-S_N' addition in the cyclization of the mismatched substrate **39**. The preference for syn selectivity and the spiroether effect led to formation of the normally disfavored *Z*-alkene as the major isomer **45**, while the *E*-alkene **44** was formed as the minor isomer. The spiroether selectivity dominated in the formation of minor stereoisomer **44**, and an anti-S_N' transition state led to the *E*-alkene geometry. The dominant effect in these α-alkoxy alkyllithium cyclizations is the spiroether preference for an alkene cis to the ring oxygen (e.g., structure **7**, Scheme 2). The preference for the syn-S_N' cyclization (e.g., structure **2**, Scheme 1) is secondary, followed by the preference for *E*-alkene formation previously identified by Stille.[9]

Conclusion

The stereoselectivity of the intramolecular S_N' cyclization of an organolithium species derived from optically pure cyclic acetals was investigated. The cyclization event generated a spiro compound and simultaneously set two new stereogenic centers. Cyclization of the matched cyano acetal **38** followed the spiroether effect and the syn-S_N' mode to give one predominant product with excellent *E*-selectivity. Cyclization of the mismatched cyano acetal **39** gave a mixture of stereoisomers comprised of predominately the syn-S_N' product with the *Z*-alkene accompanied by the minor anti-S_N' cyclization product with an *E*-alkene geometry. In each case the spiroether effect, with strong lithium coordination to the ring oxygen dictating the approach of the alkene, dominated the selectivity and led

to the formation of a spiro ring with a single configuration at the spiro center and the adjacent allylic center. These experiments will be useful for predicting the stereochemical outcome of more complex alkyllithium cyclizations.

Experimental Section[23]

Mismatched Cyclization Precursor 39. To a 0 °C solution of diisopropylamine (0.0920 mL, 0.655 mmol) in THF (2.18 mL) was added *n*-butyllithium (1.6 M in hexanes, 0.405 mL, 0.648 mmol) dropwise over a 5 min period. The solution was stirred at 0 °C for 0.5 h and then cooled to −78 °C. A solution of acetals **36** and **37** (0.150 g, 0.649 mmol) in 1 mL of THF was added to the reaction mixture, and the resulting yellow solution was allowed to stir for 1 h at −78 °C. A solution of (*R*)-(9-iodo-4-methoxynon-5-enyl)-benzene (**26**) (0.116 g, 0.324 mmol) in THF (1.00 mL) was introduced into the reaction vessel and stirring was continued at −78 °C for 15 h. The excess anion was quenched with a saturated aqueous solution of NH_4Cl (1 mL), the mixture was washed with water (5 mL), and the aqueous layer was extracted with pentane (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (2 × 5 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (20% Et_2O/pentane) to give 0.138 g (92% yield) of the desired compound as a colorless oil: R_f 0.56 (20% Et_2O/pentane); $[\alpha]_D$ +43 (*c* 0.48, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.18 (m, 6H), 5.58 (dt, 1H, J = 15.2, 6.6 Hz), 5.29 (dd, 1H, J = 15.4, 8.1 Hz), 5.07 (q, 1H, J = 5.1 Hz), 3.89 (m, 1H), 3.48 (m, 1H), 3.23 (s, 3H), 2.82 (ddd, 1H, J = 14.1, 10.0, 5.4 Hz), 2.67 (m, 1H), 2.62 (t, 2H, J = 7.1 Hz), 2.12 (m, 2H), 1.92−1.60 (m, 10H), 1.54−1.48 (m, 2H), 1.38 (d, 3H, J = 5.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 141.3, 132.7, 131.6, 128.5, 128.4, 128.3, 128.2, 126.0, 125.7, 119.0, 96.5, 82.3, 74.1, 72.8, 55.9, 40.0, 39.3, 37.0, 35.9, 35.2, 31.7, 31.0, 27.3, 22.8, 20.7 ppm; IR (neat) 2930, 1603, 1495, 1453, 1333, 1140 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{30}H_{40}NO_3$ $[M]^+$ 461.2930, found 461.2916.

Matched Cyclization Precursor 38. Synthesis of acetal **38** was accomplished by following the same experimental protocol that was used for the preparation of acetal **39**. The diastereomeric mixture comprised of acetals **31** and **32** (0.278 g, 1.20 mmol) was alkylated with alkyl iodide **26** (0.216 g, 0.602 mmol), which gave the desired matched cyclization precursor **38** in 84% yield: R_f 0.56 (20% Et_2O/pentane); $[\alpha]_D$ −30 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.18 (m, 6H), 5.58 (dt, 1H, J = 15.3, 6.6 Hz), 5.29 (dd, 1H, J = 15.5, 8.1 Hz), 5.07 (q, 1H, J = 4.8 Hz), 3.88 (m, 1H), 3.47 (m, 1H), 3.23 (s, 3H), 2.81 (ddd, 1H, J = 14.2, 10.2, 5.5 Hz), 2.68 (m, 1H), 2.61 (t, 2H, J = 7.1 Hz), 2.12 (m, 2H), 1.91−1.60 (m, 10H), 1.54−1.48 (m, 2H), 1.38 (d, 3H, J = 5.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 141.3, 132.7, 131.6, 128.5, 128.4, 128.3, 128.2, 126.0, 125.7, 119.0, 96.5, 82.3, 74.1, 72.8, 55.9, 39.9, 39.3, 37.0, 35.9, 35.2, 31.7, 31.1, 27.4, 22.8, 20.7 ppm; IR (neat) 2928, 1603, 1496, 1454, 1378, 1143 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{30}H_{40}NO_3$ $[M]^+$ 461.2930, found 461.2919.

(23) The general experimental information may be found in the Supporting Information.

Spirocycle 41. Acetal **38** (40.0 mg, 0.087 mmol) was dissolved in 0.87 mL of 1:1 THF/hexanes. To this solution was added 0.1 mg of 1,10-phenanthroline, then the solution was cooled to −78 °C and titrated with *n*-BuLi (1.6 M in hexanes) to a brown-red endpoint to remove any trace of water. A solution of LiDBB (0.87 mL, 0.35 mmol), precooled to −78 °C, was introduced into the reaction vessel, and the resulting dark green mixture was allowed to stir at −78 °C for 12 h. The excess LiDBB was then quenched with 2 mL of MeOH, and the mixture was diluted with 5 mL of water. The aqueous phase was extracted with pentane (2 × 10 mL), then combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20% Et_2O/pentane) to give 26.0 mg of the cyclized product **41** (>98:2 *E*/*Z*, 74% yield) as a slightly yellow oil: R_f 0.50 (10% Et_2O/pentane); $[\alpha]_D$ −79 (*c* 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.20 (m, 6H), 5.51 (dd, 1H, J = 15.3, 9.3 Hz), 5.41 (dt, 1H, J = 15.2, 6.6 Hz), 4.82 (q, 1H, J = 5.0 Hz), 3.77 (m, 1H), 2.80 (ddd, 1H, J = 14.1, 9.8, 5.6 Hz), 2.72 (m, 2H), 2.62 (t, 2H, J = 7.6), 2.06 (q, 2H, J = 6.9 Hz), 1.99−1.83 (m, 3H), 1.75−1.63 (m, 4H), 1.62−1.48 (m, 3H), 1.46 (m, 2H), 1.26 (d, 3H, J = 5.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 142.0, 131.6, 129.8, 128.5, 128.4, 128.3, 128.2, 125.8, 125.7, 94.8, 83.3, 72.4, 46.5, 40.7, 39.5, 37.6, 35.4, 32.1, 31.4 (2C), 31.3, 21.3, 19.2 ppm; IR (neat) 2936, 1604, 1496, 1454, 1328, 1135 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{28}H_{36}O_2$ $[M]^+$ 404.2715, found 404.2718.

Spirocycle 45. Acetal **39** (30.0 mg, 0.065 mmol) was cyclized by using the same experimental protocol that was developed for the cyclization of acetal **38.** Cyclic acetals **44** and **45** were isolated as an inseparable mixture of geometric isomers (15:85 *E*/*Z*, respectively) (18.0 mg, 72% overall yield) as a slightly yellow oil: Major isomer 45: R_f 0.50 (10% Et_2O/pentane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.19 (m, 6H), 5.53 (app. t, 1H, J = 10.8 Hz), 5.35 (dt, 1H, J = 10.3, 6.8 Hz), 4.64 (q, 1H, J = 5.1), 3.65 (m, 1H), 2.91 (m, 1H), 2.78 (ddd, 1H, J = 13.8, 9.7, 5.6 Hz), 2.68 (ddd, 1H, J = 13.8, 9.3, 6.8 Hz), 2.62 (ddd, 2H, J = 7.5, 7.5, 3.2 Hz), 2.10−1.95 (m, 3H), 1.88 (m, 2H), 1.74−1.61 (m, 6H), 1.50 (m, 3H), 1.25 (d, 3H, J = 5.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 142.0, 131.4, 128.5, 128.4, 128.3, 128.2, 128.0, 125.8, 125.7, 95.2, 83.6, 72.4, 41.0, 40.9, 40.0, 37.6, 35.5, 32.1, 31.4, 31.3, 26.9, 21.3, 19.8 ppm; IR (neat) 2936, 1603, 1496, 1454, 1330, 1134 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{36}O_2Na$ $[M + Na]^+$ 427.2613, found 427.2618.

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Supporting Information Available: Experimental details for the preparation of the cyclization substrates and the characterization and correlation of the products as well as proton and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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