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An Improved Chiral Auxiliary for the Allene Ether Version of the Nazarov Cyclization

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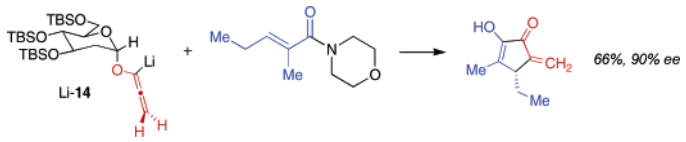
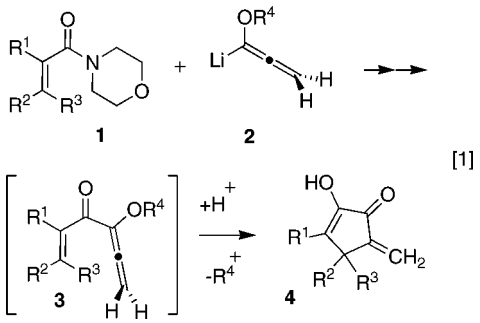
ABSTRACT



α-2-Deoxy-D-glucose derived ether 14 is a superior reagent for the allene ether version of the Nazarov cyclization. Enantiomeric excesses of products derived from trisubstituted morpholino enamides varied between 85% and 93% ee.

The Nazarov reaction has enjoyed a resurgence of interest by the organic synthesis community in recent years, due in part to the realization that the reaction offers a rapid means to simultaneously form a ring and control stereochemistry.[1] In this regard the Nazarov cyclization resembles the Diels−Alder cycloaddition. This similarity is much closer in the allene ether version of the Nazarov reaction, in which an enamide **1** and a lithioallenyl ether **2** are combined to produce cyclopentenone **4** in a *single* operation (eq 1).[2,3] The



intermediate allenyl vinyl ketone **3** cannot be isolated, but undergoes cyclization to **4** spontaneously upon workup.[4] The overall process is therefore effectively a cycloaddition.[5]

The highly reactive nature of **3** precludes the use of asymmetric catalysis for the enantioselective synthesis of **4**. Since the group R^4 on oxygen is lost (as a cation) during the cyclization, one option for the asymmetric synthesis of **4** is to use a homochiral R^4 group as a traceless chiral auxiliary.[3,6] In earlier work we described this approach for R^4 groups derived from β-D-glucose, α-D-glucose, α-2-deoxy-D-glucose, β-rhamnose, and camphor (**5**−**8** and **17**, Figure 1).[7−10] This work revealed several features of this

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(1) For reviews of the Nazarov reaction, see: (a) Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158. (b) Harmata, M. *Chemtracts* **2004**, *17*, 416−435. (c) Frontier, A.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606. (d) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479−6517. (e) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206.

(2) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

(3) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284−290.

(4) Relief of the strain associated with the allene, the small steric requirement for approach of the sp hybridized allenyl and β enone carbon atoms, and the polarization of the enol ether function all probably contribute to the ease of this cyclization.

(5) Allenes have been used for a variety of cyclizations. For recent examples, see: (a) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491−3494. (b) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615−618.

(6) The chiral auxiliary must impose a clockwise or counterclockwise bias on the sense of conrotation that controls the tetrahedral asymmetry of the ring carbon atom in **4**. There is also a structural restriction imposed on R^{4+}: it must be an α-oxo carbocation.

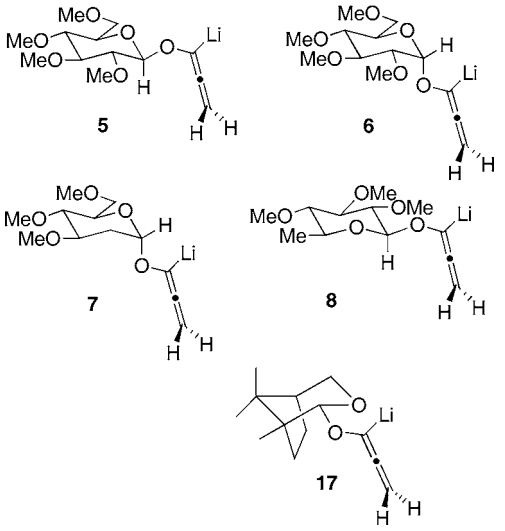
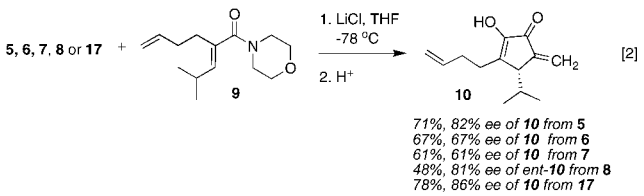


Figure 1. Allenyllithium reagents.

reaction. Perhaps the most important feature was that the absolute stereochemistry of the major cyclic product depends on the absolute stereochemistry of the anomeric carbon atom. For example, **5** and **6** lead to enantiomeric products. This is fortunate, as it allows cheap D-glucose to be used for both enantiomeric series of products. The second feature was that the optical purity of product was higher from the β-anomeric compounds **5** and **8** than from the α-anomers **6** and **7**. The third feature is puzzling, as it indicates that the methoxy substituents at C-2 and C-6, the ones that we expected to exert the greatest influence on the stereochemical course of the reaction, in fact have only a small effect on the optical purity of product. For example, allenyllithium **7**, derived from α-2-deoxy-D-glucose when combined with morpholino enamide **9**, leads to cyclopentenone **10** in 61% yield and 61% ee, whereas the reaction of **9** with **6** leads to **10** in 67% yield and 67% ee (eq 2). Therefore deleting the methoxy group at



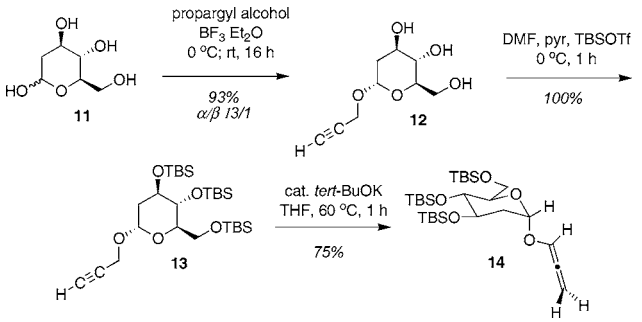
[2]

C-2 from **6** has a small effect on the optical purity of the product. The difference in the optical purity of product is insignificant for allenyllithiums **5** and **8** that lead to enantiomers of **10** in 82% ee and 81% ee, respectively. Allenyllithiums **5** and **8** are pseudoenantiomers, and differ with respect to the presence and absence of the primary methoxy group. Camphor derived allenyllithium **17** had been our most effective reagent, and led to **10** in 78% yield and 86% ee.

There is another aspect common to all the sugar-derived allenyllithiums, they are poorer nucleophiles than congeners with fewer oxygen substituents, and their addition reactions with enamides (cf. **9**) require the presence of several equivalents of LiCl for optimal yields.[11] The role of the LiCl is presumably to disrupt the aggregation of the allenyl anion. One of us (D.B.d.S.) hypothesized that replacing methoxy groups in **7** by *tert*-butyldimethylsilyloxy (OTBS) would suppress aggregation of the allenyllithium, leading to a more reactive nucleophile. What we did not anticipate was the improvement in the enantioselectivity of the Nazarov reaction that the change in oxygen protecting group would make.

Scheme 1 summarizes the synthesis of allene **14**. Commercially available 2-deoxy-D-glucose **11** was converted to

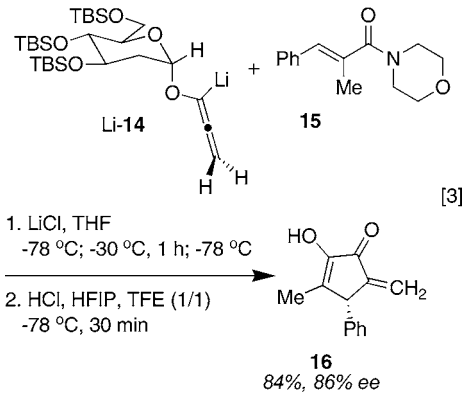
Scheme 1



propargyl glucoside **12** in 93% yield as a 13/1 ratio of α and β anomers.[12] Protection of the free hydroxyl groups as the *tert*-butyldimethylsilyl ethers gave **13** quantitatively. Isomerization of propargyl ether **13** to allenyl ether **14** was accomplished in the usual way, by warming in the presence of catalytic potassium *tert*-butoxide. Allene **14** was isolated in 75% yield following column chromatography. Prior to storage the allene was thoroughly dried by azeotropic distillation of toluene. Residual toluene was removed under high vacuum and the product stored at −5 °C under argon. Under these conditions **14** was stable for up to 2 months.

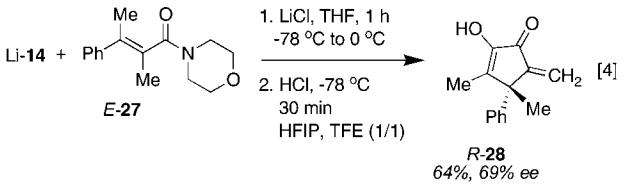
The cyclization reaction was optimized by using the readily available morpholino enamide **15** derived from α-methylcinnamic acid (eq 3). Even with noncoordinating OTBS groups it was necessary to add 7 equiv of LiCl relative to **14** to the reaction mixture in order for the addition of Li-**14** to enamide **15** to proceed in good yield. Warming the reaction mixture from −78 to −30 °C ensured that the addition would proceed to completion. Quenching the reaction mixture into a solution of HCl in 1/1 hexafluoro-2-propanol (HFIP) and trifluoroethanol (TFE) led to cyclopentenone **16** in 84% yield and 86% ee.

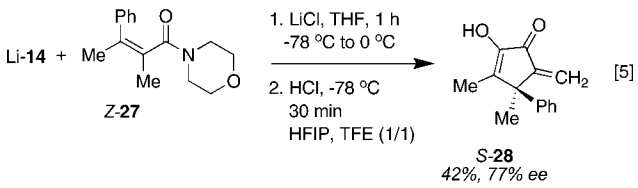
(7) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447−2450.
(8) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514.
(9) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.
(10) For related sugar derived allenyl ethers, see: (a) Rochet, P.; Vatèle, J.-M.; Goré, J. *Synthesis* **1994**, 795−799. (b) Meyerala, H. B.; Gurrada, S. R.; Mohan, S. K. *Tetrahedron* **1999**, *55*, 11331−11342. (c) Hausherr, A.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2001**, 1377−1385.
(11) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624−1654.
(12) Tronchet, J. M.; Zsély, M.; Geoffroy, M. *Carbohydr. Res.* **1995**, *275*, 245−258.



The LiCl may be playing more than one role in the reaction. For example, omitting it from the reaction of Li-**14** with **15**, but changing none of the other reaction parameters resulted in a sharply attenuated yield of highly optically enriched cyclopentenone **16** (38% yield and 99% ee). There were no other identifiable products from this reaction, and the high ee was not the result of accidental recrystallization of **16**. At the present time we do not have a satisfactory explanation for this intriguing result.

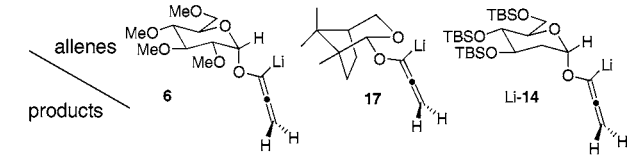
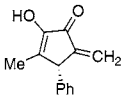
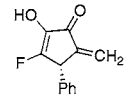
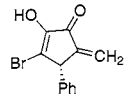
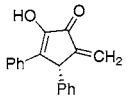
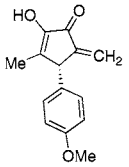
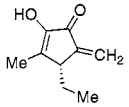
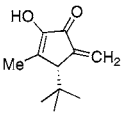
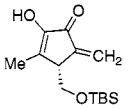
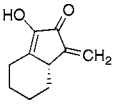
Our experimental results are compiled in Table 1, in which a comparison is made between Li-**14**, **6**, and camphor-derived allenyllithium **17**. Lithioallene Li-**14** leads to products of much higher optical purity than **6** in all cases, and in all but one case, that of cyclopentenone **23**, higher than **17**. The absolute stereochemistry of the major product from each of the three lithioallenes cited in Table 1 is the same, and has been assigned on the basis of our earlier work.[9] Optical purities listed in Table 1 for the reactions of Li-**14** are reported on the basis of at least two experiments, and were exactly reproducible (Chiralcel-OD column) and varied between 85% ee (92.5/7.5 er) for **24** and 93% ee (96.5/3.5 er) for **19**. There was more scatter in the reaction yields that varied from 53% to 85%, but the yields for individual reactions varied by no more than ±1% from run to run. On the basis of these data it is clear that Li-**14** represents a significant improvement over our earlier efforts.





The asymmetric Nazarov cyclization that generates a quaternary ring carbon atom is a greater challenge so we were curious to learn whether Li-**14** could be used successfully in this context. The reaction of Li-**14** with tetrasubstituted enamide *E*-**27** led to cyclopentenone *R*-**28** in 64% yield and 69% ee (eq 4).[13] Reaction of Li-**14** with *Z*-**27** led to the enantiomeric cyclopentenone *S*-**28** in 42% yield and 77% ee (eq 5). The lower yield of product for the *Z* enamide is likely due to steric inhibition of the reactive U-shaped conformer of the pentadienyl cation.[14] The results of eqs 4 and 5 demonstrate that both enantiomeric series of cyclo-

Table 1. A Comparison of Three Chiral Auxiliaries[a]

allenes / products	6	17	Li-14
			
	**16**	*58%, 67% ee*[b]	*71%, 77% ee*[c]	***84%, 86% ee***
	**18**		*55%, 58% ee*	***72%, 88% ee***
	**19**		*53%, 78% ee*	***78%, 93% ee***
	**20**	*84%, 65% ee*	*74%, 55% ee*	***60%, 89% ee***
	**21**	*69%, 63% ee*	*84%, 62% ee*	***53%, 87% ee***
	**22**		*69%, 74% ee*	***66%, 90% ee***
	**23**	*61%, 73% ee*	*84%, 87% ee*	***85%, 88% ee***
	**24**	*58%, 53% ee*	*81%, 65% ee*	***61%, 85% ee***
	**25**	*69%, 63% ee*	*62%, 69% ee*	***75%, 91% ee***

[a] The first number in each column refers to the yield of cyclopentenone. [b] See ref 7. [c] See ref 9.

(13) This same cyclopentenone had been prepared from *E*-**27** and **17** in 14% yield and 65% ee. The yield most likely could have been improved by allowing addition to take place at 0 °C, as was done with Li-**14**, rather than at −78 °C. The optical purity of *R*-**28** was slightly better from the reaction of Li-**14** than from the reaction with **17**.

pentenones are available from the *same* allene. The chiral auxiliary induces conrotation in the same absolute sense for both geometrical isomers of the enamide.

The reason Li-**14** is so much more effective than **6**, **7**, or **17** is not obvious at this time, but it seems unlikely that the C-6 OTBS group alone is responsible. Although the ground state conformation of pyran **14** is a chair with the *O*-allenyl group axial, this is not necessarily the case in the transition state for cyclization. Work by Woerpel has demonstrated that there are large differences in the conformational preferences of tetrahydropyran oxocarbenium ions relative to their uncharged precursors.[15] Specifically, alkoxy groups at C-3 and C-4 have a pseudoaxial preference in tetrahydropyran oxocarbenium ions. A late transition state for the stereochemistry determining cyclization step (cf. eq 3) can reasonably be assumed, therefore the interactions between auxiliary and pentadienyl cation that bias one conrotation in favor of the other may be modulated by conformational changes of the pyran. Work is in progress to probe this issue by systematically varying substituents and stereochemistry on the pyran. Regardless of the reason, the greatly improved enantioselectivity of cyclopentenones derived from **14** suggests that it will be useful in synthesis.

Acknowledgment. We thank the Department of Defense Breast Cancer Research Program (DAMD17-03-1-0685) and the National Institutes of Health (GM57873) for generous support.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR, HRMS, and IR data for **12**, **13**, and **14**; experimental procedure for **16**; reproductions of ^{1}H and ^{13}C NMR spectra for **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871−885.

(15) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528. See also: Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157−1160.