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Diastereoselective Radical Cyclization of Bromoacetals (Ueno-Stork Reaction) Controlled by the Acetal Center

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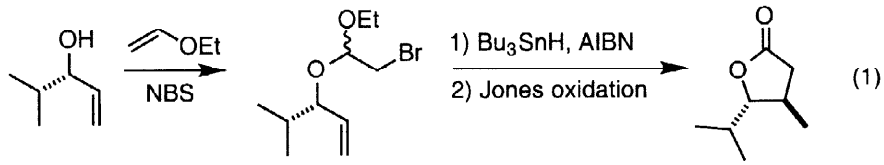
Abstract

The stereochemistry of the 5-*exo-trig* cyclization of bromoacetals (Ueno-Stork cyclization) can be controlled from the stereogenic acetal center. High stereoselectivities have been observed for the formation of 4-substituted tetrahydrofurans. Preparation of an optically pure β-substituted γ-butyrolactone by use of an easily removable chiral auxiliary is reported.

Keywords: radical cyclization; acetals; lactones; chiral auxiliary; asymmetric synthesis.

More than fifteen years ago, Ueno [1,2] and Stork [3] reported independently the very efficient 5-*exo* radical cyclization of bromoacetals. This reaction has been applied to several syntheses of natural products [4,5] and it belongs to the most efficient radical reactions described to date. The use of chiral allylic alcohols allows to synthesize polysubstituted lactones in enantiomerically pure form with good to excellent level of stereocontrol [6]. In these processes, the allylic chiral center controls completely the stereochemical outcome of the reaction (eq 1) [3]. The second stereogenic center at the acetal does not influence the stereochemical outcome.



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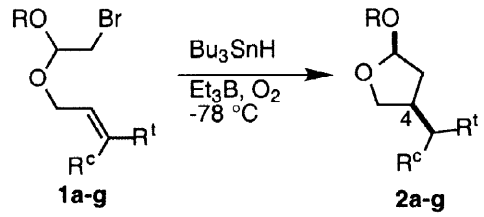
According to the above mentioned observations, it seems very hypothetical to control the stereochemical outcome of the Ueno-Stork cyclization from the acetal center. Therefore, this aspect of the reaction has been systematically neglected in the literature.[1] In this communication, we show that it is indeed possible to achieve very high levels of stereocontrol from the acetal center. Access to enantiomerically pure lactones by using an easily removable chiral auxiliary is also reported.

4-Substituted tetrahydrofurans. The bromoacetals **1a-1f** have been prepared by treatment with NBS of a mixture of the corresponding enol ethers and allylalcohols [2]. The cyclization reactions were conducted at -78 °C using tributyltin hydride and triethylborane-oxygen as initiator (eq 2),[2] results are summarized in the Table. In all cases, the major tetrahydrofuran product **2a-g** possesses a *cis* configuration.[3] The size of the alkoxy group has no influence on the stereochemical outcome as demonstrated by comparing entries 1, 3 and 5 (OR = OEt) with entries 2, 4 and 6 (OR = O*t*-Bu), respectively. However, the substitution of the alkene moiety has a marked influence. With terminal alkenes (R^t and R^c = H), the *cis* isomer was produced with an excellent stereoselectivity (entries 1 and 2, *cis/trans* >98:2). When the alkene moiety is monosubstituted at the terminal position (R^t = *n*-Bu, R^c = H), the stereoselectivity went down (*cis/trans* 92:8). With alkene disubstituted at the terminal position (R^t = R^c = Me), the *cis/trans* ratio dropped to 77:23 (entries 5 and 6). Finally, a good control of the stereochemistry was obtained with the allene **1g**. Cyclization of **1g** afforded 2-*tert*-butoxy-4-vinyl tetrahydrofuran **2g** as a *cis/trans* 92:8 mixture (entry 7).



1a-g **2a-g** (2)

1) The stereochemistry of Ueno-Stork cyclization products relative to the acetal center has been determined in some cases [7].

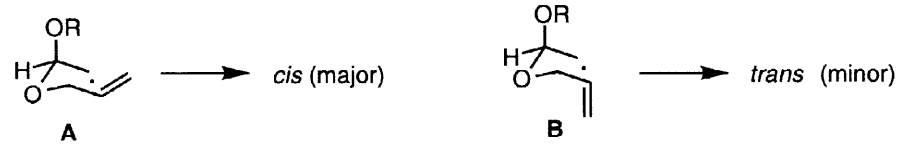
2) General procedure: A soln. of the bromoacetal **1a-g** (2.1 mmol) and Bu_3SnH (735 mg, 2.5 mmol) in toluene (52 ml) was cooled at -78 °C and a 1M soln of Et_3B in hexane (2.9 ml, 2.9 mmol) was added followed by air (2.0 ml). The soln. was kept at -78 °C for 3 h. A 1M NaOH soln. (30 ml) was added and the heterogenous mixture was stirred for 2 h at r.t. The organic layer was washed with H_2O, dryed over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash-chromatography (pentane/Et_2O) to afford the tedrahydofuran **2a-g**. The diastereomeric ratio were determined by ^{1}H-NMR before and after flash chromatography. Attempts to measure the diastereoselectivity by GC failed due to partial decomposition of the products.

3) The relative configuration have been assesssed by n.O.e. difference experiments.

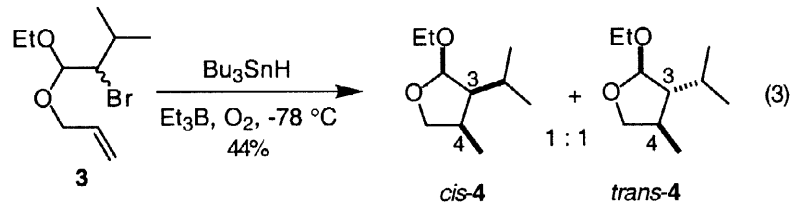
Table. Radical cyclization of **1a-1g** according to equation 1.[2]

Entry	Bromide	OR	R^t	R^c	Product	Yield	*cis/trans*
1	**1a**	OEt	H	H	**2a**	71%	>98 : 2
2	**1b**	O*t*-Bu	H	H	**2b**	68%	>98 : 2
3	**1c**	OEt	*n*-Pr	H	**2c**	75%	92 : 8
4	**1d**	O*t*-Bu	*n*-Pr	H	**2d**	71%	92 : 8
5	**1e**	OEt	Me	Me	**2e**	80%	77 : 23
6	**1f**	O*t*-Bu	Me	Me	**2f**	83%	77 : 23
7	**1g**	O*t*-Bu	CH_2		**2g**	71%	92 : 8

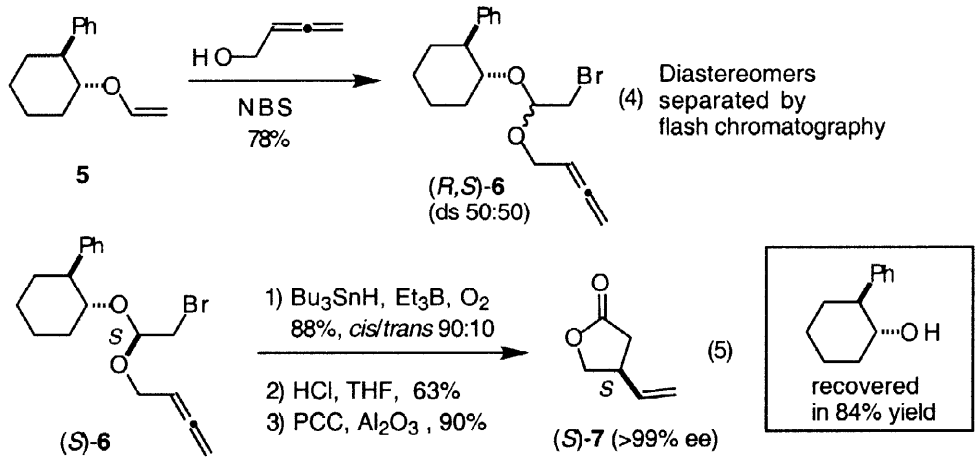
The stereochemical outcome to the cyclization can be rationalized with model **A** which is supported by *ab initio* calculations (6-31G*). This model differs from the Beckwith-Houk transition state model [8,9] by the preferential axial position occupied by the alkoxy group [10]. The minor diastereoisomer is formed via a boat-like transition state (model **B**) where the alkoxy group occupies also an axial position.



3,4-Disubstituted tetrahydrofurans. Based on model **A**, the stereochemistry at C(3) was expected to be difficult to control. Indeed, the Beckwith-Houk model predict a *cis* arrangement for the substituents at C(3) and C(4) and the axial alkoxy group is expected to favor the *trans* arrangement of the substituents at C(2) and C(3). The isopropyl substituted system **3** was examined first. Under our standard radical cyclization conditions, the tetrahydrofuran **4** was isolated as a 1:1 mixture of isomers (Eq 3), the stereochemistry at C(4) is fully controlled by the acetal center but as anticipated, the stereochemistry at C(3) is not controlled.



Preparation of an enantiomerically pure lactone. The acetal **6** has been prepared from the [(1*R*,2*S*)-2-phenylcyclohexyl]vinylether **5** [11] and 1,2-butadien-4-ol. The bromoacetalization furnished **6** as a 1:1 mixture of two diastereomers which were separated by flash chromatography (Eq 4). Reaction of the diastereomerically pure (*S*)-**6** with tributyltin hydride gave the 2-alkoxy-4-vinyl tetrahydrofuran in 88% yield as a *cis/trans* 90:10 mixture. After elimination of the minor diastereomer by flash chromatography, hydrolysis of the pure *cis* isomer followed by oxidation of the lactol gave the enantiomerically pure (>99% ee) lactone **7** (Eq 5). During the hydrolysis step, the chiral auxiliary was recovered in 84% yield.



Conclusions. We have shown that the acetal center can efficiently control the stereochemistry at C(4) of tetrahydrofurans during Ueno-Stork haloacetal cyclizations. Further investigations toward the control of the C(3) and C(5) centers as well as the improvement of the preparation of optically pure bromoacetals are currently underway.

Acknowledgments

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References

[1] Ueno Y, Chino K, Watanabe M, Moriya O, Okawara M J. Am. Chem. Soc. 1982;104:5564-5566.

[2] Ueno Y, Moriya O, Chino K, Watanabe M, Okawara M J. Chem. Soc. Perkin Trans 1 1986:1351-1356.

[3] Stork G, Mook R, Biller SA, Rychnovsky SD J. Am. Chem. Soc. 1983;105:3741-3742.

[4] Stork G, Sher PM, Chen H-L J. Am. Chem. Soc. 1986;108:6384-6385.

[5] Keck GE, Burnett DA J. Org. Chem. 1987;52:2958-2960.

[6] Itoh T, Sakabe K, Kudo K, Zagatti P, Renou M Tetrahedron Lett. 1998;39:4071-4074.

[7] Giese B, Erdman P, Göbel T, Springer R Tetrahedron Lett. 1992;33:4545-4548.

[8] Beckwith ALJ, Schiesser CH Tetrahedron 1985;41:3925-3941.

[9] Spellmeyer DC, Houk KN J. Org. Chem. 1987;52:959-974.

[10] Hackmann C, Schäfer HJ Tetrahedron 1993;49:4559-4574.

[11] Denmark SE, Schnute ME, Senanayake CBW J. Org. Chem. 1993;58:1859-1874.