Stereoselective Radical Reactions

Diastereoselective Radical-Mediated Hydrogen-Atom Abstraction**

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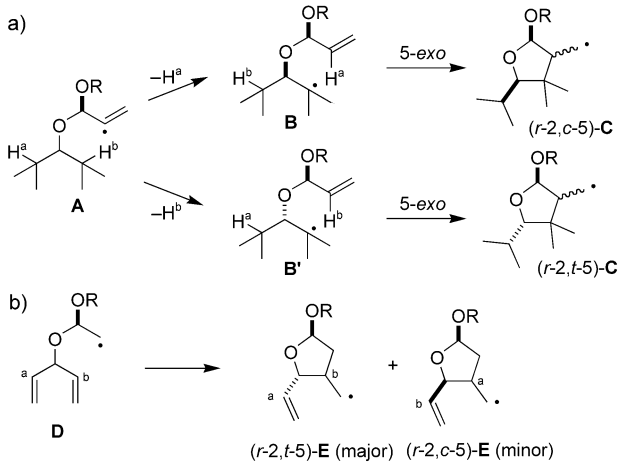
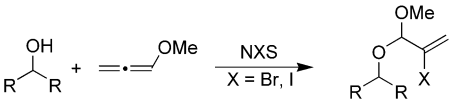
Radical reactions are becoming a very valuable tool for organic synthesis.[1] The mildness of the reaction conditions, their complementary nature to ionic processes, and the possibility of carrying out sequential reactions (cascade reactions) are some of the key factors of their success. Radical reactions can be used for highly stereoselective bond-forming reactions.[2] The stereochemistry of radical cyclizations has been studied extensively and reliable stereoselectivity rules (the Beckwith–Schiesser–Houk model) have been proposed.[3,4] Hydrogen-atom abstraction (also called radical translocation) is a bond-breaking–bond-forming process that is frequently encountered in radical reactions.[5] With proper design of substrates, radical translocation represents a unique mode for remote functionalization of unreactive C–H bonds. Until now, stereoselective hydrogen-atom abstractions have been considered as curiosities.[6–8] Herein we report examples of diastereoselective hydrogen-atom abstractions from chiral acetals and show that the stereochemical outcome is governed by rules similar to those developed for related cyclization processes.

We decided to investigate vinyl radicals of type **A** as model systems (Scheme 1 a).[9] The two hydrogen atoms H^a and H^b are diastereotopic, and hydrogen-atom abstraction can produce two diastereomeric radicals **B** and **B′** that cyclize to produce the tetrahydrofurans (*r*-2,*c*-5)-**C** and (*r*-2,*t*-5)-**C**, respectively.[10] The stereochemical outcome of these reactions will be then compared with that of the selective cyclization of the related systems **D** to **E**, which has been thoroughly investigated by us (Scheme 1 b).[11–13] The radical precursors were readily prepared from the corresponding alcohols, 1-methoxyallene, and *N*-bromo- or *N*-iodosuccinimide, according to Equation (1).[14]

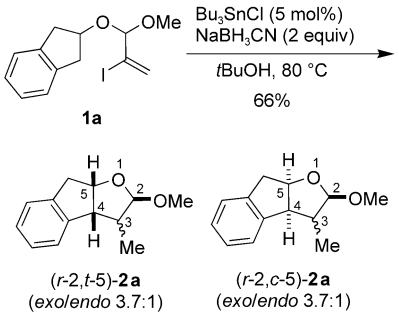


Scheme 1. a) Proposed radical 1,5-H abstraction and cyclization; b) stereoselective cyclization of a related system.



(1)

The reaction conditions for the hydrogen abstraction were optimized with substrate **1a** [Eq. (2)]. Attempts to carry out the reaction in benzene with the slow addition of tributyltin



(2)

hydride were unsuccessful, presumably because of the reaction of the intermediate alkenyl radical with benzene. Very reliable results were obtained by using the method of Stork et al. for the in situ generation of tin hydride in *tert*-butyl alcohol.[15] The best results were obtained by using Bu_3SnCl (5–10 mol%) in the presence of 2 equivalents of $NaBH_3CN$ in refluxing *tert*-butyl alcohol. A mixture of four diastereomers of **2a** was obtained. The two major diastereomers had the configuration *r*-2,*t*-5, and both result from the same diastereoselective hydrogen-atom abstraction. The stereoselectivity of the H-abstraction step (84:16) was determined from the ratio (*r*-2,*t*-5)-**2a**/(*r*-2,*c*-5)-**2a**. The cyclization step is stereoselective at C4 (*r*-2,*t*-4, *cis* ring junction) but not at C3 ((*r*-2,*c*-3)/(*r*-2,*t*-3) or *exo*/*endo* 3.7:1).

The stereochemistry of the hydrogen-atom abstraction is best explained by the chairlike model **F** depicted in Scheme 2. This model closely parallels model **G**, which has been

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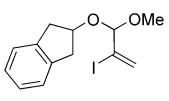
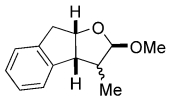
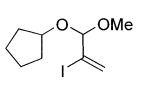
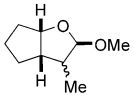
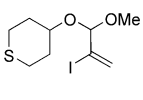
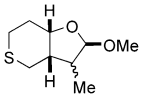
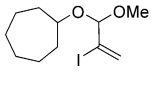
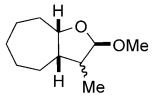
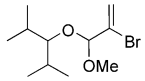
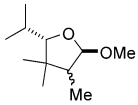
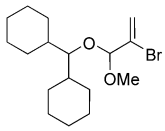
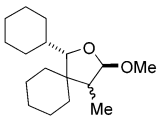
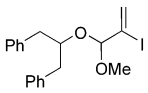
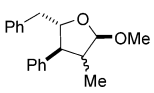
proposed based on experimental results and ab initio calculations for the Ueno–Stork cyclization reaction.[12] The 2-methoxy group occupies an axial position as a result of the anomeric effect, and the nonreacting group at C5 is in a pseudoequatorial position. The observed level of stereoselectivity at 80 °C is very similar for both processes (H-abstraction 84:16, cyclization 86:14).[9] The stereochemical outcome of the subsequent cyclization step can be rationalized by model **H**, whereby the major diastereomer results from a chairlike transition state and the minor from a boatlike transition state.

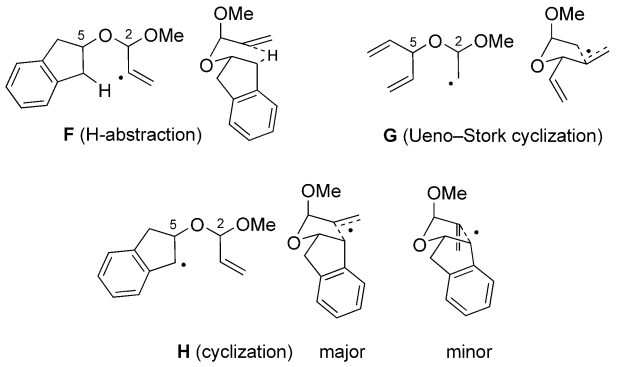
The reaction was then tested on several other haloacetals, and the results are described in Table 1. In the reactions of the cyclic alcohols **1b–d**, the stereoselectivity proved to be good for the five-, six- and seven-membered rings (**2b**: d.r. 89:11; **2c**: d.r. 94:6; **2d**: d.r. 86:14). The acyclic alcohols **1f–h** were also examined, and these underwent cyclization to the desired tetrahydrofurans **2f–h** with a similar level of stereoselectivity (d.r. 86:14) for the hydrogen-abstraction step.

This stereoselective hydrogen-atom-abstraction–cyclization is of synthetic interest and may find application in the preparation of diverse polysubstituted tetrahydrofurans. To demonstrate this point, we prepared the α-methylenelactone **5** with a tin-free hydrogen-atom-abstraction–cyclization as a key step (Scheme 3).[16,17] The propynal acetal **3**, which is readily available from the iodoacetal **1a**, was treated with thiophenol/AIBN to give the cyclic tetrasubstituted tetrahydrofuran (*r*-2,*t*-5)-**4** in 67% yield as a 2:1 mixture of *endo*/*exo* or (*r*-2,*t*-3)/(*r*-2,*c*-3) isomers.[18] Both products result from the same stereoselective hydrogen abstraction. The products of the minor H-abstraction were not isolated.[19] Oxidation of the cyclic acetal **4** with

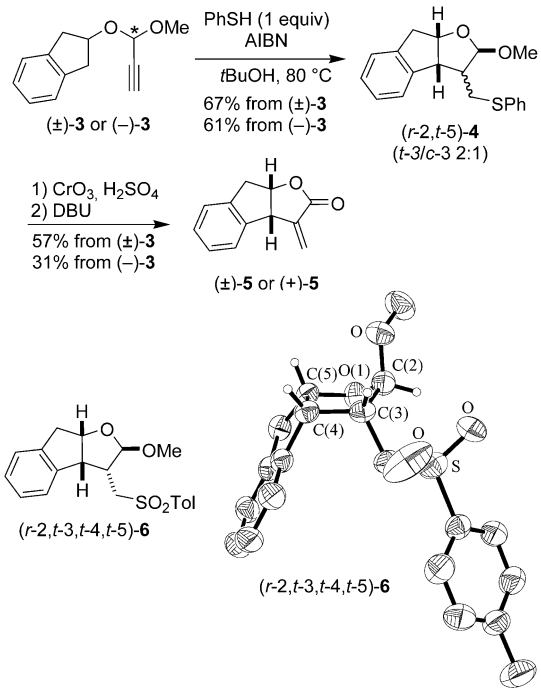
Table 1: Synthesis of polysubstituted tetrahydrofurans **2** through an initial stereoselective hydrogen abstraction and subsequent cyclization.[a]

	1	2[b]	(*r*-2,*t*-5)/(*r*-2,*c*-5)[c]	(*r*-2,*c*-3,*t*-5)/(*r*-2,*t*-3,*t*-5)[d]	Yield [%]
a			84:16	3.7:1	66
b			89:11	2.3:1	44
c			94:6	1.8:1	44
d			86:14	2.9:1	78
e			86:14	1.5:1	80
f			86:14	2.3:1	81
g			86:14	3.3:1	74

[a] See Equation (2) for reaction details. [b] Major isomer *r*-2,*t*-5 is shown. [c] d.r. for the hydrogen-atom abstraction. [d] d.r. for the cyclization of the radical intermediate resulting from the major H-abstraction product; stereochemistry at C4 is entirely controlled as indicated.



Scheme 2. Transition-state conformations for radical hydrogen-atom abstractions and radical cyclizations.



Scheme 3. Synthesis of racemic and nonracemic **5**, and X-ray crystal structure of **6**; AIBN = azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

an excess of CrO_3/H_2SO_4 followed by treatment of the crude oxidation product with DBU afforded the diastereomerically pure α-methylenelactone **5** in 57% yield. The relative configuration of the two stereoisomers of compound **4** were determined from NOE difference spectra. This result was confirmed by X-ray crystal-structure analysis of the sulfone **6**, prepared from **3** by reaction with thiocresol followed by oxidation of the major diastereomer with magnesium monoperphthalate.[20]

At this point, it was interesting to demonstrate that the transformation of **3** into **5** described above is applicable to the preparation of the nonracemic α-methylenelactone **5**. For this purpose, the racemic propynal acetal **3** was resolved by HPLC separation (Daicel Chiralcel OJ column; see Supporting Information). The α-methylenelactone (+)-**5** was obtained in 88% *ee* from enantiomerically enriched (−)-**3** (96% *ee*) according to the reaction sequence described above for (±)-**5**. As no separation of the diastereomers of the intermediate cyclized product **4** was attempted, the diastereoselectivity of the hydrogen-abstraction step can be estimated to be greater than 95:5. This is in agreement with the results obtained in the racemic series, for which only two diastereomers of **4** were detected resulting from a diastereoselective (>95:5) hydrogen abstraction.

In conclusion, we have demonstrated that hydrogen-atom abstraction can be highly stereoselective. The stereochemical outcome of the hydrogen abstractions can be explained by a model related to that developed for radical cyclizations. These results represent a step toward the development of stereoselective processes for the remote activation of centers that are usually unreactive under classical reaction conditions. For instance, by using acetals of type **1** and **3**, it is possible to activate alcohols at the β position. The chromatographic resolution of the starting acetals and the use of a chiral auxiliary to control the absolute stereochemistry at the acetal chiral center[11,13,21–23] should facilitate access to optically pure polysubstituted tetrahydrofurans and γ-lactones. Further work toward this goal is currently underway.

Experimental Section

Tin hydride mediated H-abstraction: Tributyltin chloride (13 μL, 0.05 mmol) and sodium cyanoborohydride (126 mg, 2.00 mmol) were added to a solution of the iodoacetal (1.00 mmol) in *t*BuOH (100 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at reflux for 5 h. After disappearance of the starting iodoacetal (monitored by TLC), the solution was cooled, and the *t*BuOH was evaporated under reduced pressure. The residue was filtered through silica gel, and the filtrate was evaporated under reduced pressure. Flash chromatography (AcOEt/hexane or Et_2O/pentane) of the residue afforded the desired cyclic compounds. The isomeric ratio was determined from ^{1}H NMR spectra of the crude product.

Thiophenol-mediated H-abstraction: A solution of AIBN (164 mg, 1.00 mmol) in benzene (2 mL) and a solution of thiophenol (110 mg, 1.00 mmol) in benzene (2 mL) were added by a syringe pump over 20 h to a solution of the dialkoxypropyne **3** (202 mg, 1.00 mmol) and AIBN (80 mg, 0.5 mmol) in refluxing *t*BuOH (100 mL). After disappearance of the starting acetal **3** (monitored by TLC), the solution was cooled, then concentrated under reduced pressure. The residue was filtered through silica gel, and the filtrate was concentrated under reduced pressure. Flash chromatography (AcOEt/hexane) of the residue afforded **4** (209 mg, 67% yield). The isomeric ratio was determined from ^{1}H NMR spectra of the crude product.

See Supporting Information for experimental procedures and characterization of compounds **1**–**6**.

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Keywords: acetals · asymmetric synthesis · hydrogen transfer · lactones · radical reactions

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[17] Preliminary investigations in our laboratory showed that this tin-free procedure is very general. This highly attractive method will be discussed elsewhere.
[18] The relative configurations at C3 of the major and minor products are reversed relative to **2a**. This is presumably a result of steric interactions between the OMe and the CH_2SPh groups that destabilize the chairlike transition state of the cyclization (see Scheme 2, model **H**).
[19] Several unidentified isomeric side products with a combined yield of less than 15% were removed during the chromatographic purification of **4**.
[20] The tolyl sulfone **6** is a colorless crystalline compound, whereas the corresponding phenyl sulfone is an oil. CCDC-209583 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cam-

bridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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