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Diastereoselective Intramolecular Hydride Transfer Triggered by Electrophilic Halogenation of Aryl Alkenes

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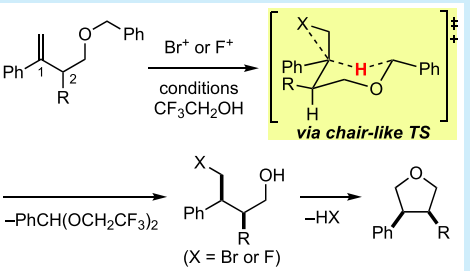
Supporting Information

ABSTRACT: Diastereoselective hydride transfer could be triggered by electrophilic halogenation (bromination or fluorination) of homoallylic alcohol O-Bn ethers. The resulting diastereomerically enriched haloalkyl alcohols underwent subsequent intramolecular nucleophilic substitution to afford the corresponding tetrahydrofurans.

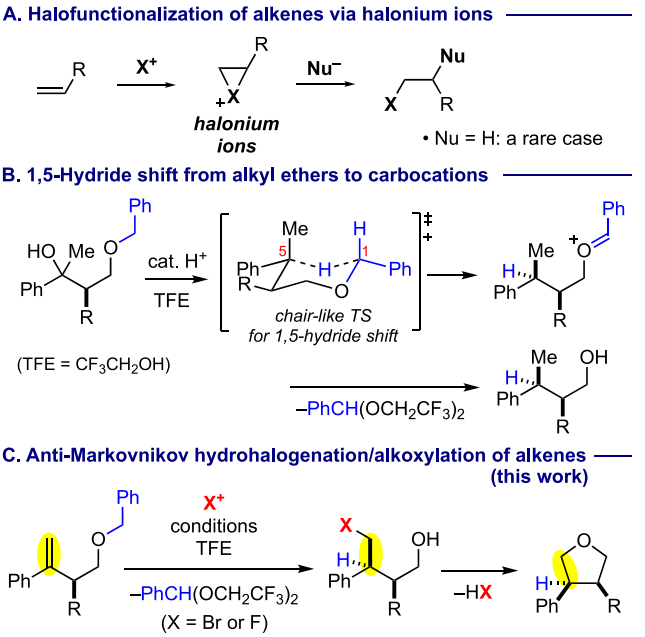


Electrophilic halo-functionalization of alkenes via halonium ion intermediates allows for facile installation of various functional groups onto alkenes.[1] In the presence of an appropriate internal or external nucleophile, the halonium ion intermediates can undergo ring opening at the carbon best able to stabilize the positive charge, thus enabling regioselective halo-functionalization of alkenes. In this regard, a variety of carbon and heteroatom-based nucleophiles have been utilized, whereas hydrides (H^-), which potentially enable *anti*-Markovnikov hydrohalogenation of alkenes, have rarely been employed for this purpose.

Our group[2] recently demonstrated that intramolecular 1,5-hydride transfer[3,4] from alkyl ethers to a carbocation generated from alcohols (via a protonation-elimination process) or alkenes (via a protonation event) could proceed through a six-membered ring chair-like transition state to construct stereogenic centers with a high level of diastereocontrol.[4,5] In this context, we hypothesized that 1,5-hydride transfer to halonium ions generated from homoallylic alcohol O-Bn ethers in the presence of an electrophilic halogen source might enable *anti*-Markovnikov hydrohalogenation (Scheme 1C). Herein, we demonstrate the execution of this concept with the development of diastereoselective electrophilic hydrobromination and fluorination of aryl alkenes. The resulting diastereomerically enriched haloalkyl alcohols undergo subsequent intramolecular nucleophilic substitution to afford substituted tetrahydrofurans under the optimized reaction conditions.

At the outset of the project, we examined the reactivity of homoallylic alcohol *O*-benzyl ether **1a** having a benzyl group at the allylic position (Scheme 2A). Extensive screening of various reaction parameters (see the SI for details) led to the two complementary optimized reaction conditions A and B.

Scheme 1. Halofunctionalization of Alkenes and 1,5-Hydride Transfer



Treatment of **1a** with 1.1 equiv of *N*-bromosuccinimide (NBS) in trifluoroethanol at 50 °C afforded 3,4-*cis*-disubstituted tetrahydrofuran **2a** in 74% yield with a diastereoselectivity of 91:9 (conditions A). 1-Chloromethyl-

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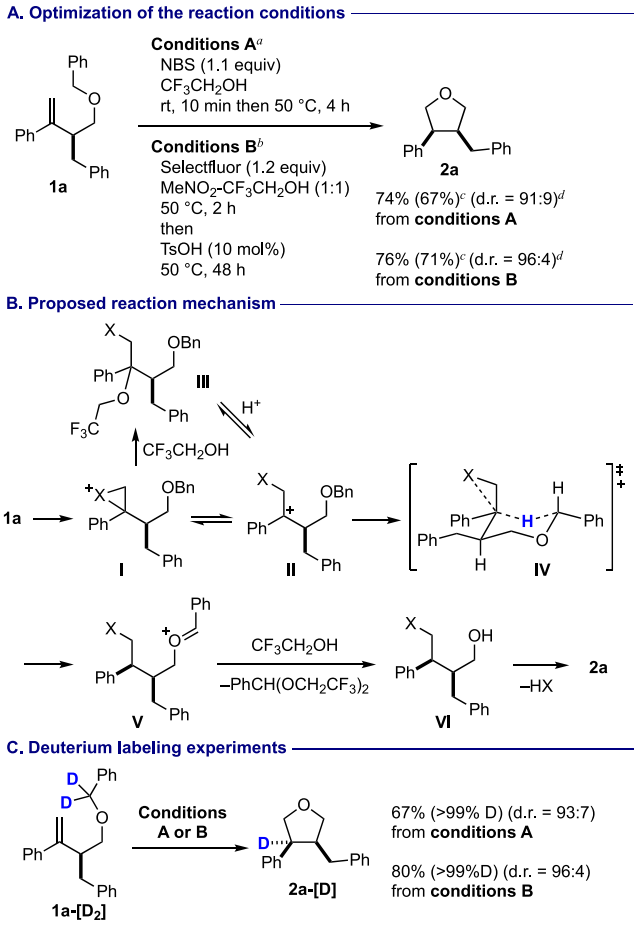
Scheme 2. Stereoselective Formation of 3,4-*cis*-Disubstituted Tetrahydrofuran 2a

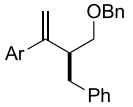
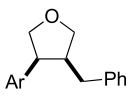
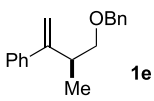
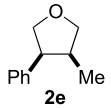
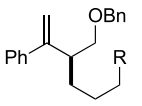
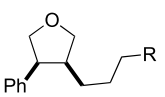
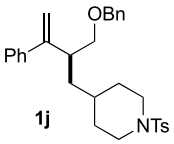
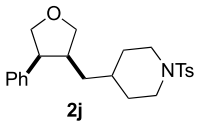


[a]Reaction conditions A: **1a** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), rt, 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **1a** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$–CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol %), 50 °C, 48 h. [c]The chemical yields from the reactions in 1 g scale (use of 3 mmol of **1a**). [d]The diastereomeric ratio was determined on the basis of ^{1}H NMR analysis.

4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) was found to be an alternative reagent, allowing the formation of **2a** in 76% yield with higher diastereoselectivity of 96:4. In this case, *p*-toluenesulfonic acid (TsOH) (10 mol %) was required to assist the furan ring closing step, and a longer reaction time was needed to complete the process (conditions B). The transformation is initiated by the formation of a halonium ion **I**, which is under equilibrium with the tertiary benzylic carbocation **II** probably via trifluoroethyl ethers **III**.[5] Subsequent 1,5-hydride shift from the benzylic position to the carbocation in **II** proceeds via a six-membered chairlike transition state **IV** in which the bulkier phenyl and benzyl groups adopt pseudo equatorial positions. Solvolysis of the resulting oxocarbenium ion **V** produces the diastereomerically enriched 4-halobutanol **VI**, which cyclizes by intramolecular nucleophilic substitution to form tetrahydrofuran **2a**.[6,7] The reaction of deuterated **1a**-[$\mathbf{D_2}$] resulted in deuterium incorporation at the C3 position of **2a**-[**D**], thus unambiguously proving the 1,5-hydride shift (Scheme 2C). This multistep conversion of homoallylic alcohol derivative **1a** into tetrahydrofuran **2a** could be regarded as *anti*-Markovnikov hydroetherification of aryl alkenes.

We then investigated the substituent effect on the synthesis of 3,4-*cis*-disubstituted tetrahydrofurans (Scheme 3). As for

Scheme 3. Synthesis of 3,4-*cis*-Disubstituted Tetrahydrofurans[a]

substrates (0.5 mmol)	products	yields (d.r.)
		
1b (Ar = 4-MeO-C_6H_4)	**2b**	**A**: 68% (96:4) **B**: 80% (>99:1)
1c (Ar = 2-Me-C_6H_4)	**2c**	**A**: 47% (>99:1) **B**: 35% (>99:1)
1d (Ar = 4-Br-C_6H_4)	**2d**	**A**: 63% (90:10) **B**: 69% (97:3)
 **1e**	 **2e**	**A**: 49% (94:6) **B**: 70% (97:3)
		
1f (R = OMe)	**2f**	**A**: 61% (91:9) **B**: 60% (99:1)
1g (R = Cl)	**2g**	**A**: 78% (91:9) **B**: 76% (95:5)
1h (R = CN)	**2h**	**A**: 67% (91:9) **B**: 62% (98:2)
1i (R = NPhth)	**2i**	**A**: 67% (95:5) **B**: 66% (98:2)
 **1j**	 **2j**	**A**: 71% (93:7) **B**: <18% (ND)

[a]Reaction conditions: **1** (0.5 mmol) under conditions A or B (see Scheme 2). Isolated yields and diastereomeric ratio of **2** are given.

the substituent on the alkene, both electron-rich and -deficient aryl groups could be installed (for **2b**–**2d**), whereas the use of a sterically hindered *ortho*-tolyl group rendered the process sluggish, providing the corresponding tetrahydrofuran **2c** in moderate yields under both reaction conditions A and B. Introduction of a methyl group at the allylic position of the substrate did not influence the diastereoselectivity (for **2e**). The method tolerated the presence of various functional groups such as methyl ether, chloride, cyanide, and phthalimide (for **2f**–**2i**). Construction of tetrahydrofuran **2j** having an *N*-tosylpiperidine moiety was successful under the reaction conditions A with NBS, while the use of Selectfluor (conditions B) gave a complex mixture of unidentified compounds probably due to the oxidation of the piperidine moiety by Selectfluor.

The present strategy allowed for the construction of 2,4-*trans*-disubstituted tetrahydrofuran **2k**, for which both reaction conditions A and B led to high diastereoselectivities (Scheme 4). Similarly, 2,3,4-trisubstituted bicyclic tetrahydrofurans **2l**

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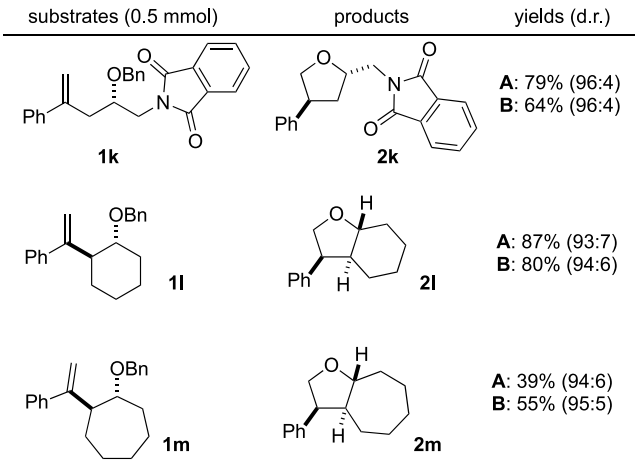
and **2m** could be synthesized, albeit with moderate efficiency in the case of **2m**.

Scheme 4. Synthesis of 2,4-Disubstituted and 2,3,4-Trisubstituted Bicyclic Tetrahydrofurans[a]



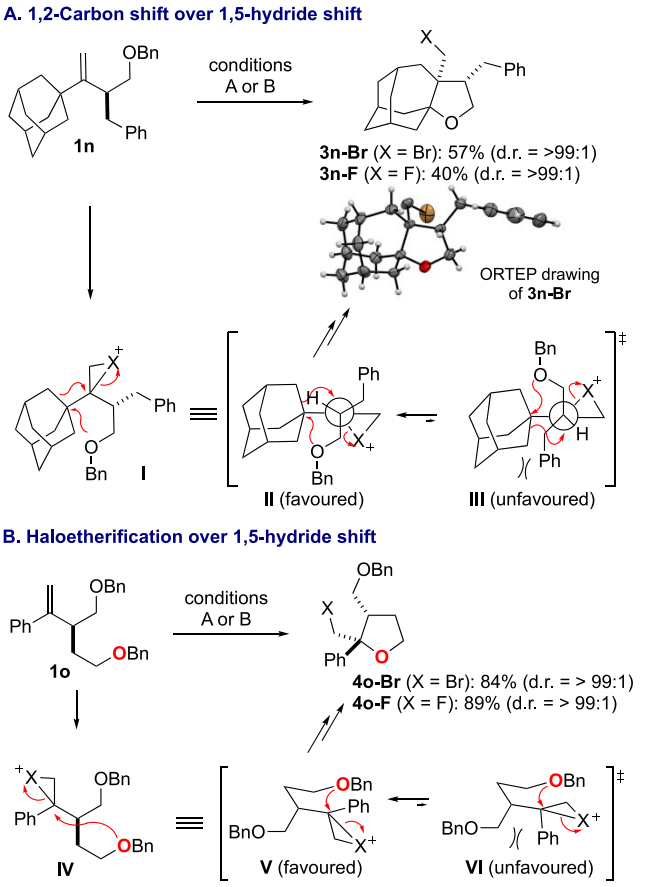
[a]Reaction conditions: **1** (0.5 mmol) under conditions A or B (see Scheme 2). Isolated yields and diastereomeric ratio of **2** are given.

During the course of the substrate scope study, we observed in several cases that the desired 1,5-hydride shift is interrupted. For example, the reactions of adamantyl derivative **1n** produced the intriguing polycyclic tetrahydrofurans **3n-Br** and **3n-F** having a halomethyl tether at the C3 position as a single diastereomer (Scheme 5A). In this case, a Wagner−Meerwein type 1,2-carbon shift to the halonium ion intermediates **I**[8] and concomitant cyclization of the OBn tether could account for the formation of **3n**. In this mechanistic scenario, conformation **II** would be energetically favored over conformation **III**. Substrate **1o** having a benzyloxyethyl tether at the allylic position gave the C2-halomethyl tetrahydrofurans **4o-Br** and **4o-F** as a single diastereomer (Scheme 5B). In this case, the nucleophilic attack of the ethereal oxygen to the halonium ion **IV** was more favorable than the 1,5-hydride shift.[9] The observed diastereoselectivity could be explained by the involvement of **V**, a conformer that would be more favorable than **VI** due to the presence of the phenyl group at a pseudo equatorial position.

Formation of tetrahydrofuran **2** from fluoroalcohol intermediates **VI** (Scheme 2) was unexpected, as such nucleophilic substitution at a nonactivated C(sp^3)-F position has rarely been reported in the literature.[10,11] Further modification of the reaction conditions B led to the development of an alternative stepwise protocol for the synthesis of fluoroalcohols as the major products (Scheme 6). A fluorohydroxylation step was first implemented by treating alkenes **1** with Selectfluor in the presence of water (5 equiv) in $MeNO_2$. The solvent system was then switched to 1,2-dichloroethane (DCE)−trifluoroethanol (4:1), and the resulting crude mixture was treated with trifluoromethanesulfonic acid (TfOH) (10 mol %) at 50 °C for a short period of time in order to prevent the substitution step. Under these conditions, fluoroalcohol **5a** could be obtained in good yield with high diastereoselectivity.

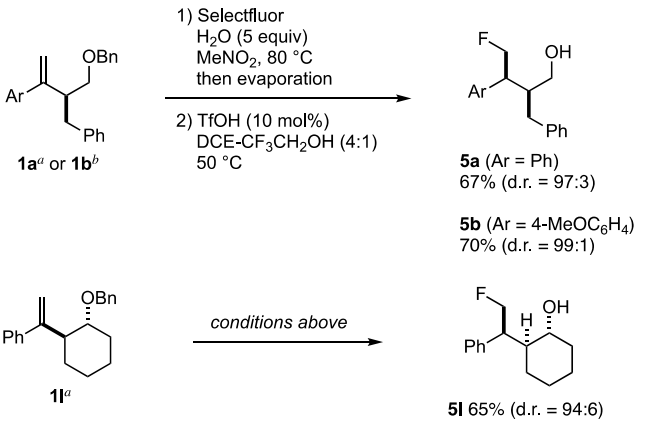
In summary, this work demonstrates synthesis of stereochemically defined tetrahydrofurans by a cascade process

Scheme 5. Interrupt of 1,5-Hydride Shift[a]



[a]Reaction conditions: **1** (0.5 mmol) under conditions A or B (see Scheme 2). Isolated yields and diastereomeric ratio of the products are given.

Scheme 6. Synthesis of Fluoroalcohols 5



[a]Reaction conditions: **1a** or **1l** (0.55 mmol), Selectfluor (0.5 mmol). Isolated yields were measured based on Selectfluor. [b]Reaction conditions: **1b** (0.5 mmol), Selectfluor (0.6 mmol). Isolated yield was measured based on **1b**.

involving a diastereoselective 1,5-hydride shift to a halonium ion intermediate as the key step. Overall, this transformation can be regarded as a formal intramolecular *anti*-Markovnikov hydroetherification of an aryl alkene, a reactivity scheme that has been rarely reported in the literature. Further application

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of the present method to the synthesis of complex molecules is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03548.

Experimental procedures, spectral data (PDF)

Accession Codes

CCDC 1956712 and 1956716 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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