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Diastereoselective Intramolecular Hydride Transfer under Brønsted Acid Catalysis

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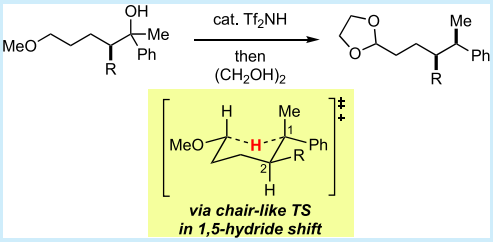
Supporting Information

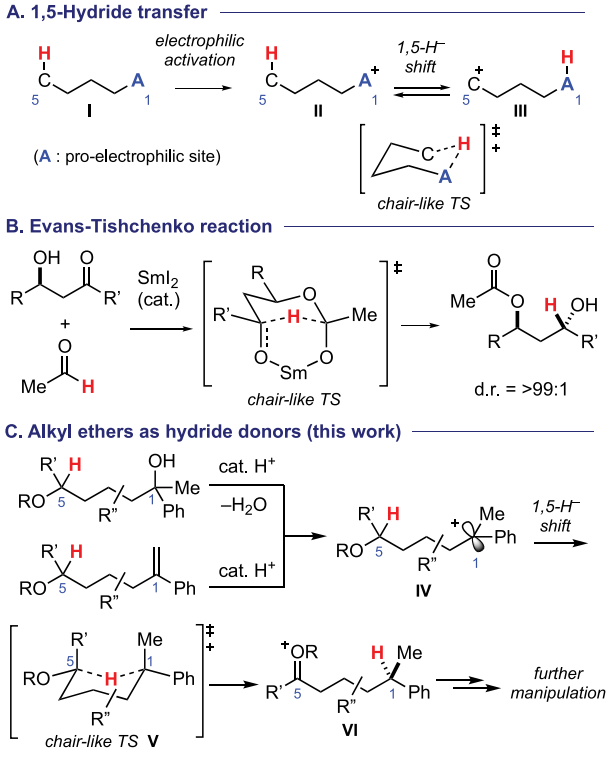
ABSTRACT: A diastereoselective hydride transfer process has been developed under Brønsted acid-catalyzed reaction conditions using methyl ethers or acetals as hydride donors and tertiary alcohols or alkenes as precursors of carbocation. The method enables construction of complex molecules having multiple stereogenic centers from rather simple and readily available starting materials with predictable diastereoselective control.



The stereocontrolled construction of stereogenic carbon centers is one of the most important areas of investigation in synthetic organic chemistry.[1,2] Despite the recent development of various strategies, it still remains a formidable challenge to perform predictable stereocontrol especially in the construction of acyclic aliphatic systems. One way to achieve high-level of stereocontrol in the creation of a stereogenic center is to leverage the geometric, steric, and electronic interplay in the transition state of the process. In this context, transformations based on intramolecular 1,5-hydride transfer[3] are particularly suitable to induce stereoinduction (Scheme 1A). From a general mechanistic point of view, such a process is initiated by the activation of a pro-electrophilic site (A) on the substrate (**I** → **II**), which triggers the intramolecular 1,5-hydride shift from a relatively electron-rich C−H bond onto the activated electrophilic site (A^+). This transfer results in the formation of a new carbocation **III**, thus rendering the overall transformation redox neutral in nature. This 1,5-hydride transfer step commonly proceeds via a well-ordered 6-membered ring chairlike transition state.[4] The Evans−Tishchenko reaction is one of the most beautiful examples of stereoinduction that takes advantage of 1,5-hydride transfer for the diastereoselective reduction of β-hydroxy ketones in the presence of SmI_2 and an aldehyde (Scheme 1B).[5] We reasoned that the 1,5-hydride transfer proceeding on carbocation **IV** derived from 5-alkoxypentan-1-ol or 6-alkoxyhex-1-ene derivatives[6] enables the predictable construction of a stereogenic center at position C1 (Scheme 1C).

The selectivity could be controlled by the presence of a remote substituent R″ through a 6-membered ring chairlike transition state **V**.[7] The resulting oxocarbenium ion **VI** could be further transformed into useful oxygen functional groups depending on the substitution pattern at position C5 (Scheme 1C). Herein, we report the execution of this concept for the stereocontrolled synthesis of aldehyde acetal, ketone, or ester derivatives from simple and readily available starting materials.

Scheme 1. 1,5-Hydride Transfer Processes



At the outset of the project, we examined the reactivity of methyl ether **1a** having a tertiary hydroxyl group at position

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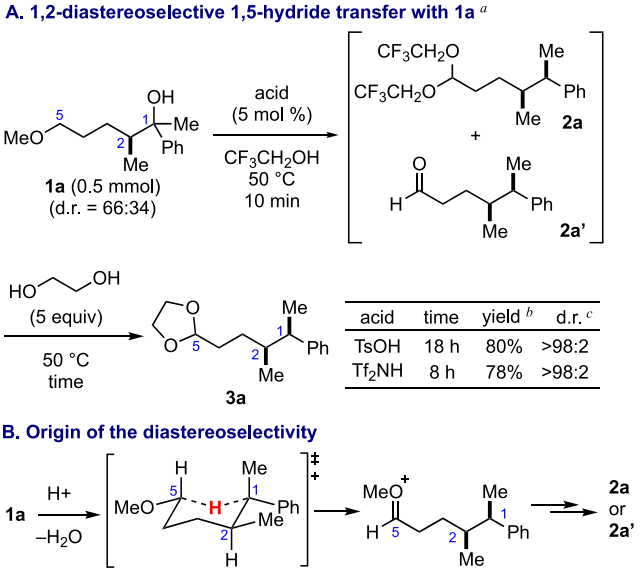
C1[8] and a methyl group at position C2 (Scheme 2A). We observed that the treatment of **1a** with 5 mol % of *p*-

Scheme 2. Diastereoselective 1,5-Hydride Transfer with 1a

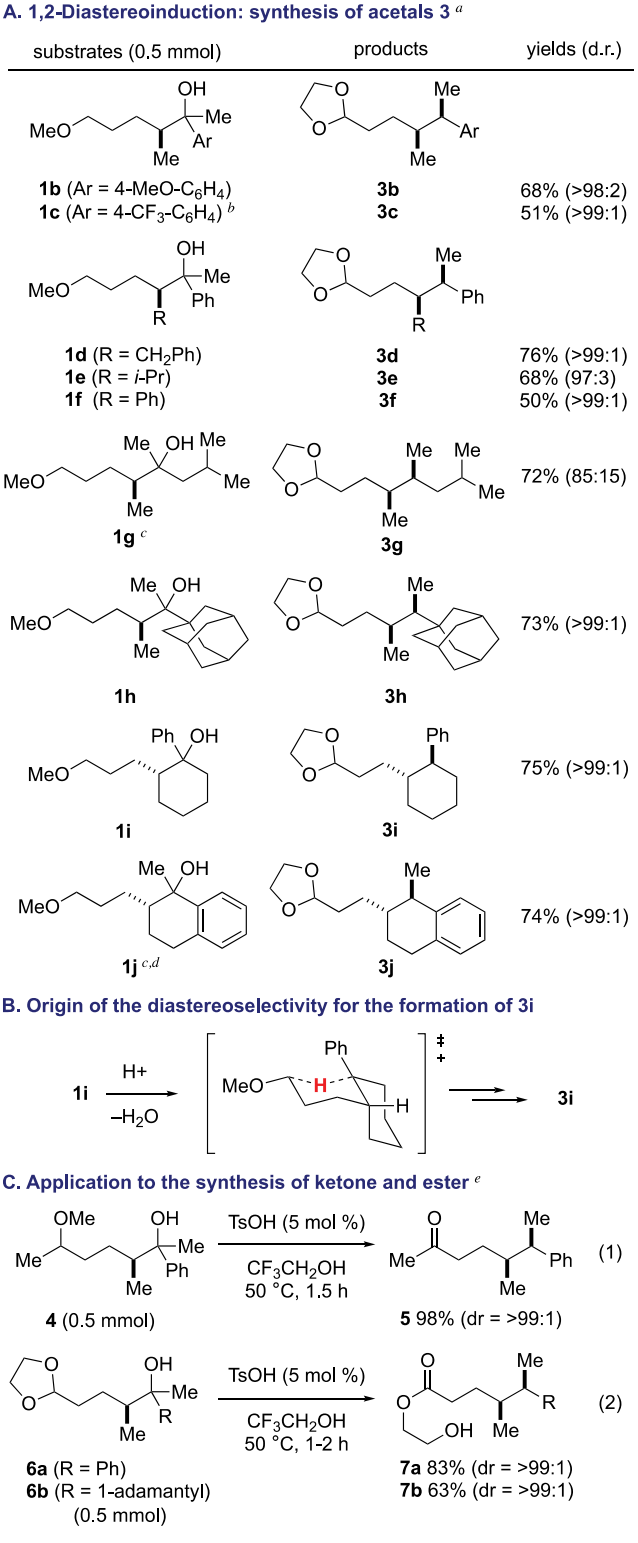


[a]Reaction conditions: **1a** (0.5 mmol), acids (5 mol %), CF_3CH_2OH (5 mL, 0.1 M), 50 °C 10 min, then ethylene glycol (5 equiv). [b]Isolated yields. [c]Diastereomeric ratio was determined on the basis of ^1H NMR analysis.

toluenesulfonic acid (TsOH) in trifluoroethanol at 50 °C rapidly produced bis(trifluoroethyl) acetal **2a** and aldehyde **2a′** (within 10 min).[9,10] Because of the instability of **2a** and **2a′**, the mixture was subsequently treated with ethylene glycol (5 equiv) to convert them into more stable 1,3-dioxolane **3a**, which was isolated in 80% yield with high 1,2-*syn* diastereoselectivity (>98:2). We found that the use of a stronger Brønsted acid, triflimide (Tf_2NH)[11] instead of TsOH, could accelerate the acetal formation (8 h instead of 18 h). The origin of the 1,2-*syn* diastereoselectivity could be rationalized by invoking a transient 6-membered ring transition state, in which larger substituents (Ph at C1 and Me at C2)[12] would be more favorably placed in pseudoequatorial positions (Scheme 2B).

We then investigated the substituent effect on the 1,2-diastereoinduction using various methyl ethers **1** (Scheme 3A). The process was not affected by the electronic nature of the aryl group at position C1: both electron-rich and -deficient arenes could be installed with high 1,2-*syn* diastereoselectivity (for **3b** and **3c**). As for the nature of C2 substituent, the sterically more demanding benzyl, isopropyl, and phenyl groups were tolerated (for **3d**–**f**) and no noticeable erosion of the diastereoselectivity was observed.[13] It is noteworthy that the current protocol allows for the use of non benzylic alcohols that are relatively less prone to electrophilic activation. Thus, alcohols **1g** and **1h** having isobutyl and 1-adamantyl groups, respectively, provided the corresponding 1,3-dioxolanes **3g** and **3h** in good yields despite the moderate diastereoselectivity observed in **3g** (d.r. = 85:15). The reactions of cyclic alcohols **1i** and **1j** proceeded smoothly to yield **3i** and **3j**, respectively. In both cases, a high 1,2-*trans* diastereoselectivity (>99:1) was obtained probably due to the involvement of a *cis*-decalin-like transition state (Scheme 3B). We also found that the method was applicable to the use of secondary alkyl ether **4** and 1,3-

Scheme 3. 1,2-Diastereoinduction



[a]Reaction conditions: **1** (0.5 mmol), Tf_2NH (5 mol %), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol (5 equiv). Isolated yields and diastereomeric ratio of **3** are given. [b]80 °C. [c]24 °C. [d]With Tf_2NH (10 mol %). [e]Reaction conditions: **4** or **6** (0.5 mmol), TsOH (5 mol %), CF_3CH_2OH (5 mL, 0.1 M), 50 °C. Isolated yields and diastereomeric ratio of **5** and **7** are given.

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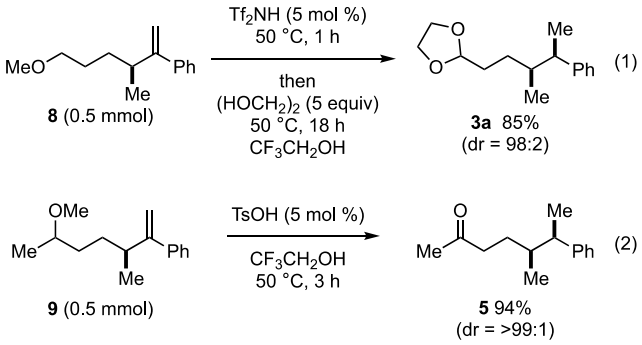
dioxolanes **6** as hydride donors for the efficient and highly diastereoselective construction of ketone **5** and glycol esters **7**, respectively (Scheme 3C).

Alkenes **8** and **9** were also proven to be viable sources of carbocations for the 1,5-hydride transfer process since the corresponding acetal **3a** and ketone **5** could be obtained in good yields and with high diastereoselectivity (Scheme 4).

Scheme 4. Diastereoselective 1,5-Hydride Transfer with Alkenes 8 and 9



We also found that the presence of a substituent at position C3 could induce a 1,3-*syn* diastereoselectivity during the 1,5-hydride transfer process (Scheme 5A). While the reactions of acyclic alcohols **10a−d** were efficient (65−81%) and various groups (alkyl, aryl, or vinyl) could be tolerated, the observed diastereomeric ratios for the formation of products **11a−d** (67:33−72:28) were not as high as those obtained in the case of 1,2-stereoinduction (97:3−99:1). On the other hand, cyclohexanol derivative **10e** could be transformed into the diastereomerically pure 1,3-*trans* cyclohexane **11e** presumably through a rigid bicyclic chair/chair-like transition state (Scheme 5B). In addition, we observed a higher diastereoselectivity of 93:7 in the conversion of alcohol **10f**,[14] which possesses methyl and phenyl substituents at positions C2 and C3, respectively. The corresponding acetal **11f** was isolated in 64% yield (Scheme 5C).[15] Notably, this 1,2,3-diastereoselective induction could be attained in almost a 8 mmol scale, thus demonstrating the scalability of the present protocol.

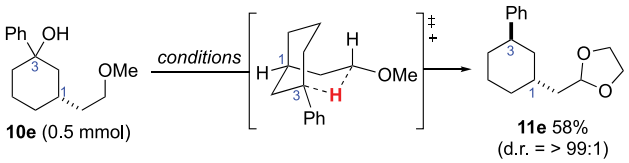
Finally, we examined the possibility to perform 1,4-diastereo induction with substrates possessing a substituent at position C4. The reaction with acyclic substrate **12a** proceeded smoothly to give acetal **13a** in 75% yield, but unfortunately with no diastereoinduction (Scheme 6A). In sharp contrast,

Scheme 5. 1,3- and 1,2,3-Diastereoinduction

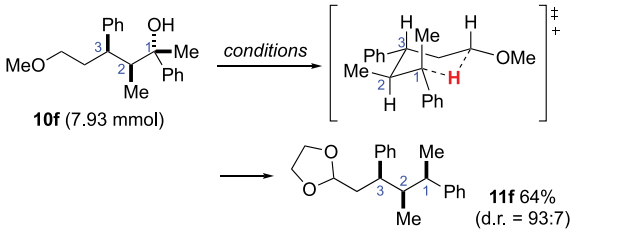
A. 1,3-Diastereoinduction with acylic substrates 10 [a]

substrates (0.5 mmol)	products	yields (d.r.)
10a (R = n-Bu)	**11a**	73% (72:28)
10b (R = *i*-Pr)	**11b**	70% (72:28)
10c (R = vinyl)	**11c**	81% (67:33)
10d (R = Ph)	**11d**	65% (72:28)

B. 1,3-Diastereoinduction with cyclohexanol 10e [b]



C. 1,2,3-Diastereoinduction with acyclic substrate 10f [c]

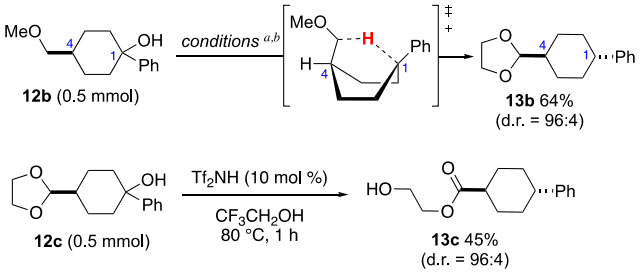


[a]Reaction conditions: **10** (0.5 mmol), Tf_2NH (5 mol %), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol (5 equiv). Isolated yields and diastereomeric ratio of **11** are given. [b]80 °C. [c]Reaction was conducted using 7.93 mmol (2.37 g) of **10f** with Tf_2NH (5 mol %) in CF_3CH_2OH (79 mL, 0.1 M) at 24 °C for 15 min, then ethylene glycol (5 equiv) at 50 °C.

Scheme 6. 1,4-Diastereoinduction

A. Reaction of acylic substrate 12a

B. 1,4-Diastereoinduction with cyclohexanols 12b and 12c



[a]Reaction conditions: **12** (0.5 mmol), Tf_2NH (5 mol %), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol (5 equiv). Isolated yields and diastereomeric ratio of **13** are given. [b]80 °C, 1 h.

the use of cyclohexanol derivative **12b** having a methoxymethyl tether at position C4 resulted in the formation of cyclohexane **13b** with high 1,4-*trans* diastereoselectivity (95:5). Similarly, diastereoselective 1,5-hydride transfer took place in the conversion of 1,3-dioxolane **12c** into ester **13c**. In these cases, the 1,5-hydride transfer step most likely proceeds via a boat-like transition state that would account for the observed 1,4-*trans* diastereoselectivity.[16,17]

In summary, this work demonstrates diastereoselective construction of tertiary stereogenic centers by taking advantage of 1,5-hydride transfer processes under Brønsted acid catalysis. This redox neutral process allows for enhancement of the molecular complexity from rather simple and readily available starting materials. Further application of the present method to the synthesis of complex molecules is currently ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00590.

Experimental procedures, spectral data (PDF)

Accession Codes

CCDC 1894803, 1894805, and 1894807−1894808 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 e-mailing 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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Notes

The authors declare no competing financial interest.

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(8) The stereochemistry of position C1 for the alcohol substrates was not determined except for compound **10f**. The diastereomeric ratio of the alcohol starting materials varies with the nature of the substituents. See the Supporting Information for more details.

(9) Acetal **2a** and aldehyde **2a′** were formed in 54% and 14% yields, respectively, according to ^{1}H NMR spectroscopy analysis of the crude residue.

(10) The initial optimization of the reaction conditions for the 1,5-hydride transfer was conducted using acetal **6a** and trifluoroethanol was found the optimal solvent for the process. See the Supporting Information for more details.

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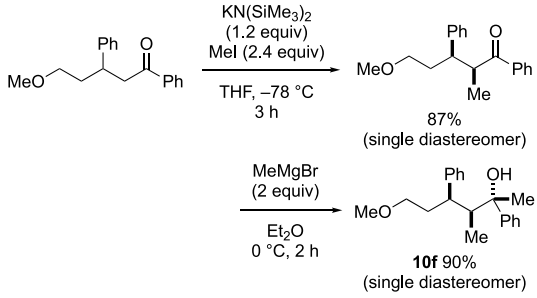
(12) The relative steric demands are evaluated on the basis of the A-values for a phenyl group (2.8 kcal/mol) and a methyl group (1.74 kcal/mol). For A-values of various substituents, see: Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley, 2001; p 444.

(13) The stereochemistry of the major isomer of **3f** was determined by X-ray crystallography analysis. See the Supporting Information for details.

(14) Synthesis of **10f** was accomplished by a sequence of diastereoselective α-methylation of ketone followed by addition of MeMgBr to the carbonyl group as shown below (for details, see the Supporting Information). The stereochemistry of **10f** was confirmed by X-ray crystallography analysis.



(15) The stereochemistry of the major isomer of **11f** was determined by the X-ray crystallography analysis of its 4-bromobenzoate derivative **11f′**. See the Supporting Information for details.

(16) Partial loss of diastereoselectivity (formation of 1,4-*cis* isomer) is most due to the epimerization of the oxocarbenium ion intermediates.

(17) The stereochemistry of the major isomer of **13b** was determined by the X-ray crystallography analysis. See the Supporting Information for details.

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