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# Highly Stereoselective Synthesis of Fused Tetrahydropyrans via Lewis-Acid-Promoted Double C(sp$^3$)−H Bond Functionalization

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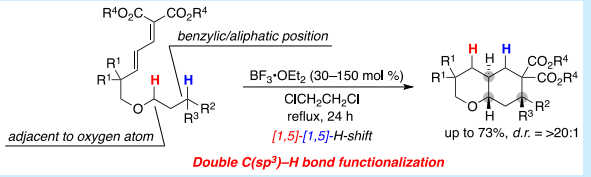
**ABSTRACT:** We have achieved a sequential hydride-shift-triggered double C(sp$^3$)−H bond functionalization at a position adjacent to an oxygen atom and a benzylic/aliphatic position through the employment of substrates with a dialkyl group in the alkyl chain, which enabled the highly diastereoselective synthesis of fused tetrahydropyrans.






The direct transformation of a C−H bond is a powerful methodology for the construction of organic molecules. Because of its utility from the perspective of atom economy[1] and step economy, much effort has been devoted to the development of new strategies.[2] In recent years, a more challenging transformation, namely, the double C−H bond functionalization, was developed.[3,4] Most of the methods reported so far deal with the functionalization of C(sp$^2$)−H/C(sp$^2$)−H bonds[3] and C(sp$^2$)−H/C(sp$^3$)−H bonds.[4] Examples of corresponding double functionalization of the strongest C(sp$^3$)−H bond are scarce,[5] and the development of new methods has been pursued.

Our continuous efforts for the development of new synthetic methods based on hydride-shift-triggered C(sp$^3$)−H bond functionalization (internal redox process)[6−11] have revealed that double C(sp$^3$)−H bond functionalization is achievable by the sequential utilization of the internal redox process (Figure 1).[8] In addition to the accomplishment of this challenging transformation, this method offers rapid access to multifunctionalized polyheterocycles. To make this sequential system a more useful and attractive synthetic tool, the achievement of analogous double C(sp$^3$)−H functionalization at a position adjacent to a heteroatom and a benzylic/aliphatic position (without an adjacent heteroatom) is highly desirable. The challenge of the planned reaction lies in the restricted conformation in the first hydride shift step. Previous studies by us and other groups have suggested that efficient overlapping between the lone pair of the heteroatom (X) and the $\sigma^*$ orbital of a C−H bond is important to promote the hydride shift.[6,7,10] In the previous method, a desired conformation like **A** is easy to take because the heteroatom is located outside the cyclic transition state structure (high conformational freedom). In sharp contrast, the required orbital overlapping would be insufficient in the planned reaction because the conformation of the heteroatom is restricted.

Herein, we describe the realization of a highly diastereoselective synthesis of fused tetrahydropyrans by double C(sp$^3$)−H bond functionalization at a position adjacent to an oxygen atom and a benzylic/aliphatic position (Scheme 1). When dialkyl ether derivatives with a dialkyl group in the alkyl chain were treated with a catalytic amount of $BF_3$·$OEt_2$, the expected [1,5]-[1,5]-hydride shift proceeded to afford fused tetrahydropyrans in good chemical yields with excellent diastereoselectivities (up to d.r. = >20:1).

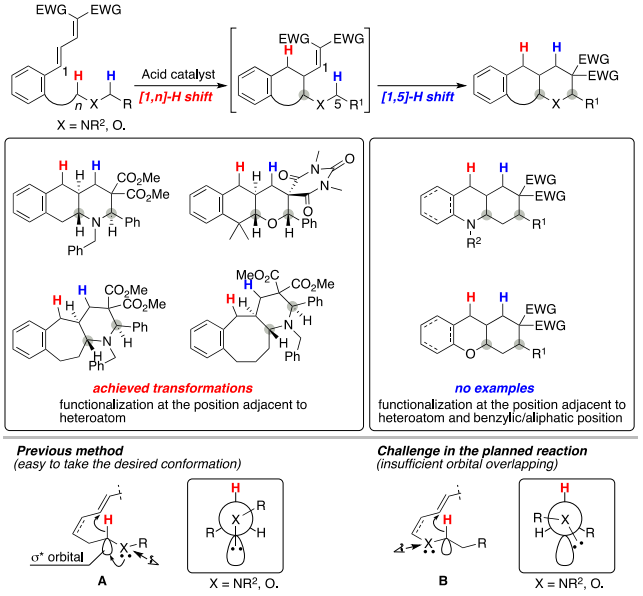



**Figure 1.** Double C(sp$^3$)−H bond functionalization developed by our group and challenge for the new sequential system.

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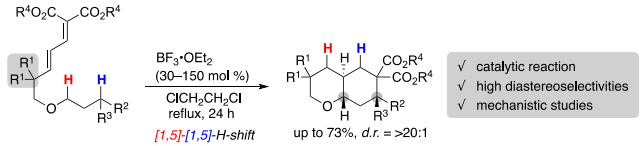
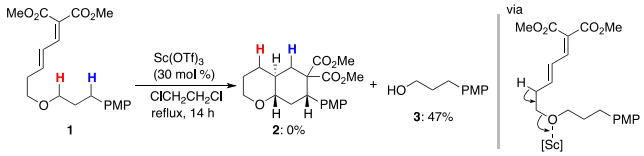
**Scheme 1. Double C($sp^3$)−H Bond Functionalization at the Position Adjacent to the Oxygen Atom and the Benzylic/Aliphatic Position**




Our study commenced with the reaction of dialky ether-type cinnamylidene malonate **1**, which is expected to be confomationally more flexible, enabling the desired orbital interaction compared to a phenol-type substrate (Scheme 2). When a

**Scheme 2. Initial Trial for the Planned Reaction**




solution of **1** in 1,2-dichloroethane was treated with 30 mol % of $Sc(OTf)_3$, **1** was almost completely consumed after 14 h. The resulting product was not desired fused pyran **2** but alcohol **3**, which was produced by the E2 elimination from **1** through the acid activation of ether oxygen. Other metal triflates, such as $Yb(OTf)_3$ and $Gd(OTf)_3$, were also ineffective, and substantial amounts of **3** were obtained in both cases (40−55%).

To suppress this unwanted reaction, we planned to use substrate **4** with a dialkyl group $\beta$ to the oxygen atom (Figure 2). This structural modification was expected to be effective

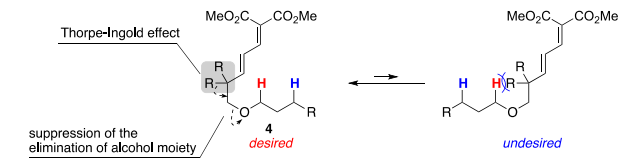
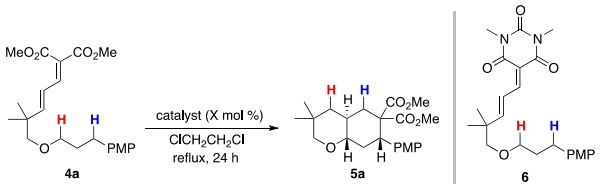



**Figure 2.** Reasons for using substrate **4** with a dialkyl moiety.

because it would not only suppress the elimination of the alcohol moiety due to the absence of $\beta$-hydrogens but also enhance the reactivity as a result of the Thorpe−Ingold effect.

Although the production of alcohol **3** was completely suppressed when substrate **4a** was subjected to the same reaction conditions as those in Scheme 2, desired fused pyran **5a** was not obtained. Instead, **4a** was completely recovered (entry 1, Table 1). Motivated by the suppression of the side reaction, extensive screening for the reaction conditions was conducted (Table 1). Various metal triflates, such as $Yb(OTf)_3$, $Gd(OTf)_3$, and $Zn(OTf)_2$, also resulted in the complete recovery of **4a** (entries 2−6). The same situation occurred when strong Brønsted acids, such as TfOH and $Tf_2NH$, were used (entries 7 and 8). Further screening for catalyst revealed that commonly used strong Lewis acids gave satisfactory results. Whereas $TiCl_4$ resulted in the recovery of **4a** (94%, entry 9), $SnCl_4$ gave fused pyran **5a** in 15% chemical yield (entry 10). Only two diastereomers were observed in this reaction even though **5a** had three stereogenic centers, and fortunately, one diastereomer was majored (d.r. = >20:1). $BF_3$·

**Table 1. Examination of Reaction Conditions**[a]




| | | | yield (%)[b] | | |
|---|---|---|---|---|---|
| entry | catalyst | X | 5a | d.r. | 4a |
| 1 | $Sc(OTf)_3$ | 30 | 0 | – | 98 |
| 2 | $Yb(OTf)_3$ | 30 | 0 | – | 95 |
| 3 | $Gd(OTf)_3$ | 30 | 0 | – | 98 |
| 4 | $Mg(OTf)_2$ | 30 | 0 | – | 98 |
| 5 | $Bi(OTf)_3$ | 30 | 0 | – | 98 |
| 6 | $Zn(OTf)_2$ | 30 | 0 | – | 98 |
| 7 | TfOH | 100 | 0 | – | 97 |
| 8 | $Tf_2NH$ | 100 | 0 | – | 98 |
| 9 | $TiCl_4$ | 100 | 0 | – | 94 |
| 10 | $SnCl_4$ | 100 | 15 | >20:1 | 0 |
| 11 | $BF_3·OEt_2$ | 100 | 61 | >20:1 | 0 |
| 12 | $BF_3·OEt_2$ | 30 | 68 | >20:1 | 0 |
| 13 | $BF_3·OEt_2$ | 20 | trace | – | 0 |
| 14[c] | $BF_3·OEt_2$ | 30 | 55 | >20:1 | 0 |
| 15 | $B(C_6F_5)_3$ | 30 | 0 | – | 94 |
| 16 | $BBr_3$ | 30 | 0 | – | 90 |

[a]Unless otherwise noted, all reactions were conducted with 0.10 mmol of **4a** in the presence of an acid catalyst (*X* mol %) in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature. [b]Isolated yield. [c]2.66 mmol scale.

$OEt_2$ turned out to be the most effective, and both good chemical yield and excellent diastereoselectivity were realized (61%, d.r. = >20:1, entry 11). Gratifyingly, the catalyst loading of $BF_3·OEt_2$ could be reduced to 30 mol % without sacrificing chemical yield and diastereoselectivity (68%, d.r. = >20:1, entry 12). A scale-up reaction was also acceptable (2.66 mmol, entry 14). Catalyst screening focusing on the boron Lewis acids suggested that $BF_3·OEt_2$ was an effective catalyst. Both $B(C_6F_5)_3$ and $BBr_3$ resulted in the recovery of **4a** (entries 15 and 16). Employment of the malonate moiety was essential to realize the target reaction; subjection of cinnamylidene barbiturate **6** under optimized reaction conditions (30 mol % of BF·$OEt_2$, $ClCH_2CH_2Cl$, reflux, 24 h) resulted in complete recovery of starting material.[12]

The relative stereochemistry of the major diastereomer was determined as described in **5a** by X-ray crystallographic analysis of the compound **8a**, which was synthesized from **5a** by a two-step sequence (reduction of two-ester moieties followed by acetal formation, Scheme 3),[13] and those of others shown in Figure 3 were surmised by analogy.

The substrate scope of this reaction is illustrated in Figure 3. Changing the ester portion of the malonate moiety from methyl to ethyl resulted in almost the same result (**5b**: 61%, d.r. = >20:1). The dialkyl moiety was not limited to the methyl group. Substrates with not only the diethyl group but also the cyclic groups, such as cyclopentyl and cyclohexyl moieties, participated in the reaction, and good chemical yields and excellent diastereoselectivities were realized (**5c−f**: 65−73%, d.r. = >20:1). In contrast to the wide acceptability of the dialkyl moiety, the *para*-methoxyphenyl (PMP) group was indispensable to achieving the catalytic and excellent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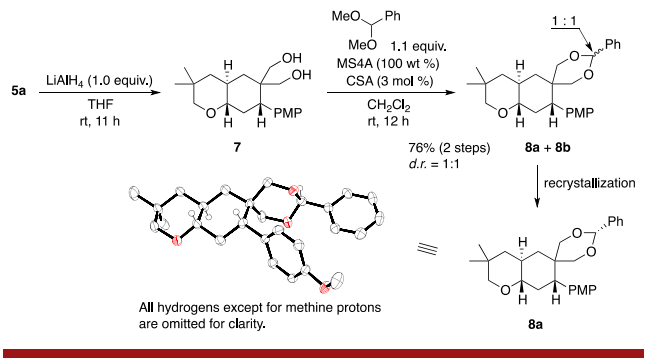
**Scheme 3. Determination of the Relative Stereochemistry of 5a**



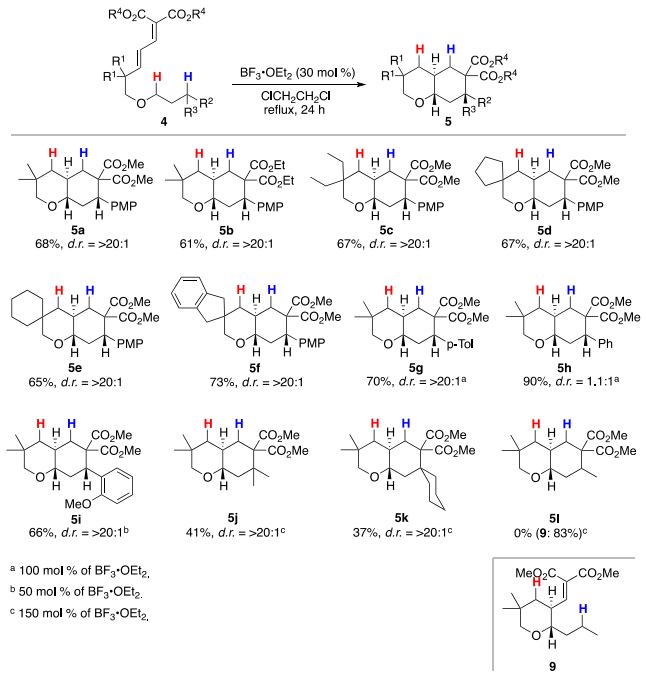




**Figure 3.** Substrate scope.

diastereoselective reaction. In the case of substrates **5g** and **5h** having a *para*-tolyl (*p*-Tol) group and a simple phenyl group, 100 mol % of $BF_3{\cdot}OEt_2$ was required for the completion of the reaction. Although excellent diastereoselectivity was observed for *p*-tolyl product **5g** (d.r. = >20:1), the diastereoselectivity was low (d.r. = 1.1:1) when phenyl-substituted substrate **4h** was employed. The substituent position was also important, and a substoichiometric amount of catalyst (50 mol %) was essential to achieve a good result (66%, d.r. = >20:1) in the case of substrate **4i** with an *ortho*-methoxyphenyl group. According to our previous report on the examination of the substituent effect on the benzylic hydride shift process, the low electron-donating ability and the steric hindrance in the aromatic ring considerably lowered the reactivity.[7b] These situations would apply to this reaction as well, leading to the requirement of an increased amount of catalyst in substrates **5g–i**. It is worth noting that this sequential system was applicable to the combination of hydride shifts at the position adjacent to the oxygen atom and the aliphatic position, giving **5j** and **5k** in moderate chemical yields with excellent diastereoselectivities (**5j**: 41%, d.r. = >20:1, **5k**: 37%, d.r. = >20:1, respectively). The employment of the branched substrate was essential to achieve the sequential reaction: subjection of substrate **4l** with a linear alkyl chain to the modified optimized reaction conditions (150 mol % of $BF_3{\cdot}OEt_2$, $CH_2CH_2Cl$, reflux, 24 h) resulted in exclusive formation of a single hydride shift adduct **9** (83%). The results in **5j** and **5k** offered us important information: the two diastereomers in **5h** were considered to be $\alpha$- and $\beta$-isomers at C-7 (adjacent to the $R^2/R^3$ group).

Our previous report on the highly diastereoselective synthesis of 1,3-disubstituted tetralins suggested that an acid-catalyzed interconversion between the $\alpha$- and $\beta$-isomers derived from the benzylic position easily took place via the strong electron-donating ability of the PMP group.[7d] Taking this result and the stereochemical information on **5j** and **5k** (*vide supra*) into account, the low diastereoselectivity of **5h** with a phenyl group could be well rationalized (Figure 4). In

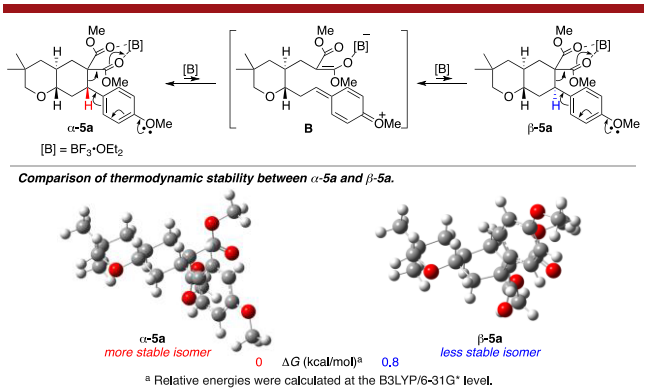
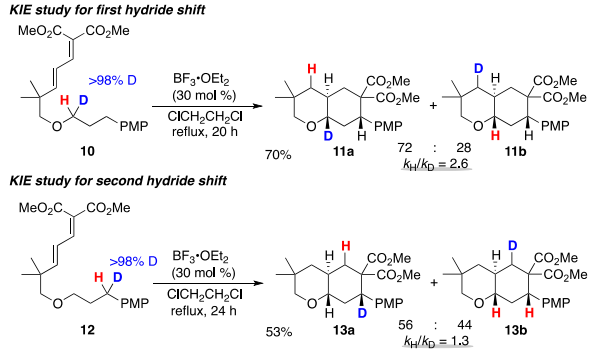



**Figure 4.** Rationalization for high diastereoselectivity.

contrast to PMP, *p*-Tol, and *ortho*-methoxyphenyl groups (strong electron-donating groups), the simple phenyl group could not induce the key interconversion between the two diastereomers, as shown in the upper part of Figure 4, and as a result, the diastereomeric ratio of **5h** remained at a low level. This assumption, i.e., thermodynamic control, was further supported by the comparison of the relative energies of the two diastereomers by DFT calculations (B3LYP/6-31G*), in which the major diastereomer ($\alpha$-isomer) was more stable than the minor one ($\beta$-isomer) due to the direction of the aromatic ring (equatorial vs axial).

Deuterium labeling experiments were conducted to clarify the reaction mechanism (Scheme 4). In contrast to the first hydride shift process, the primary kinetic isotope effect was not observed in the second hydride shift process ($k_H/k_D$ = 1.3 vs

**Scheme 4. Kinetic Studies**



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$k_H/k_D$ = 2.6 for the first hydride shift). These results suggested that the first hydride shift process would be the rate-determining step like the double C($sp^3$)−H bond functionalization at the position adjacent to the same heteroatom.[8]

In summary, we have achieved an expedient synthesis of fused tetrahydropyrans via the double C($sp^3$)−H bond functionalization at the position adjacent to an oxygen atom and the benzylic/aliphatic position. The employment of a substrate with a dialkyl group in the alkyl chain was the key to achieving the reaction, and various types of products were obtained in good chemical yields with excellent diastereoselectivities (up to d.r. = >20:1). Our previous studies and additional experiments provided important information on the reaction mechanism: (1) the first hydride shift process was the rate-determining step and (2) diastereoselectivity could be controlled thermodynamically. Multiple C−H bond functionalizations triggered by a sequential hydride shift/cyclization system are under way in our laboratory and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01867.

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, computational details, and Cartesian coordinates (PDF)

### Accession Codes

CCDC 1990657 contains 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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### Notes

The authors declare no competing financial interest.

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(13) See Supporting Information for details.



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