Highly diastereoselective synthesis of tricyclic fused-pyran by sequential hydride shift mediated double C(sp<sup>3</sup>)–H bond functionalization†

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Described herein is the Brønsted acid-catalyzed double C(sp<sup>3</sup>)–H bond functionalization of alkyl phenethyl ether derivatives. In this process, a [1,5]-[1,5]-hydride shift occurred successively to afford tricyclic fused pyran derivatives in excellent chemical yields with excellent diastereoselectivities (up to >20:1). The key to achieve this reaction was the introduction of two methyl groups at the benzylic position, which was effective in both hydride shift processes: (1) the Thorpe–Ingold effect for the first hydride shift and (2) conformational control in the second hydride shift.

Introduction

Development of an efficient synthetic method is a major topic of research interest in modern synthetic organic chemistry. Direct transformation of inert C–H bonds, in particular, has attracted much attention because of its high potential for the development of new trends in the synthesis of complex organic molecules.<sup>1</sup> Hydride shift triggered C(sp<sup>3</sup>)–H bond functionalization has recently emerged as a powerful tool for the rapid construction of various useful organic molecules.<sup>2</sup> Fig. 1 illustrates the details of this strategy. The key feature of this transformation is the [1,5]-hydride shift of the C(sp<sup>3</sup>)–H bond α to a heteroatom. Subsequent 6-endo cyclization to a cationic species A affords fused heterocycle 2.<sup>3–6</sup> As part of our ongoing effort to develop a new synthetic transformation method involving hydride shift triggered C(sp<sup>3</sup>)–H bond functionalization,<sup>7</sup> we have recently successfully applied this strategy to a sequential hydride shift system (double C(sp<sup>3</sup>)–H bond functionalization).<sup>8,9</sup> The key to achieving this reaction was the use of the reactive α,β-unsaturated trifluoromethyl ketone as the electrophilic moiety. This setting effectively promoted an unprecedented [1,4][1,5]-hydride shift sequence, affording linear tricyclic piperidines in excellent chemical yields and with excellent diastereoselectivities (eqn (1), Fig. 2).<sup>9</sup> The application of this sequential system to an oxygen analogue is also highly important because it would be a promising tool for rapid construction of multisubstituted tricyclic pyrans, which are found in some biologically active compounds. The two challenges to achieve this reaction are as follows: (1) the lower electron-donating ability of an oxygen atom than that of a nitrogen atom, which is disadvantageous for the hydride shift process, and (2) the propensity to eliminate the alkoxy group.<sup>10</sup>

We wish to report herein a solution to the issues related to the realization of the double C(sp<sup>3</sup>)–H bond functionalization in

![Fig. 1](image1.png)

**Fig. 1** C(sp<sup>3</sup>)–H functionalization by the internal redox process.

![Fig. 2](image2.png)

**Fig. 2** Double C(sp<sup>3</sup>)–H bond functionalization in alkyl phenethyl ether derivatives.

<sup>†</sup>Electronic supplementary information (ESI) available. CCDC 1838259, 1838261 and 1838262. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc02103a
alkyl phenethyl ether derivatives (eqn (2), Fig. 2). The key to achieving this functionalization was to introduce two methyl groups at the benzylic position, thereby promoting the desired [1,5]-[1,5]-hydride shift/cyclization sequence smoothly to furnish the corresponding tricyclic pyrans in excellent chemical yields with excellent diastereoselectivities (up to >20:1 d.r.).

Results and discussion

An initial trial was conducted with cinnamylidene barbiturate 3 bearing a 2-benzyloxyethyl moiety at the ortho position (Scheme 1). Treatment of 3 with 10 mol% Yb(OTf)₃, which exhibited excellent catalytic performance in the sequential internal redox reactions we previously developed,⁷ in reflexing ClCH₂CH₂Cl, the sequential [1,5]-hydride shift process proceeded to afford the tricyclic pyran derivative 9a in excellent chemical yield (90%). Only two diastereomers were observed in this reaction even though 9a has three stereogenic centers, and one diastereomer was slightly major (d.r. = 3.3:1). Other metal triflates such as Sc(OTf)₃, Gd(OTf)₃, and Dy(OTf)₃ also promoted the reaction albeit with lower diastereoselectivities (d.r. = <4.5:1, entries 2−4). The use of Mg(OTf)₂ or TiCl₄ resulted in the complete recovery of the starting material (entries 5 and 6). FeCl₃ promoted the reaction effectively to furnish 9a in 87% yield with 5.6:1 diastereoselectivity (entry 7). TFOH exhibited high reactivity as well as satisfactory diastereoselectivity (86%, d.r. = 13.0:1, entry 9), although the reactivity of Tf₂NH, also a strong Brønsted acid catalyst, was moderate (72%, d.r. = 5.0:1, entry 8). 2 mol% TFOH sufficed to complete the reaction with moderate diastereoselectivity (89%, d.r. = 6.7:1, entry 10). Excellent diastereoselectivity was realized even with a 2 mol% catalyst when the reaction was conducted in toluene (99%, d.r. = >20:1, entry 11). The structure of the major diastereomer was determined as described for 9a by X-ray crystallographic analysis, and those of others shown in Fig. 4 were surmised by analogy.¹¹,¹²

With the highly diastereoselective tricyclic pyran synthesis in our hand, the substrate scope of this reaction was examined (Fig. 4). Various substituents such as electron-donating groups (Me and OMe) and an electron-withdrawing group (F) were tolerated in this reaction, and the corresponding tricyclic pyrans 9b−f were obtained in excellent chemical yields with excellent diastereoselectivities (>94%, d.r. = >12.5:1). Although the diastereoselectivity was sufficient (d.r. = 11.2:1),

Fig. 3 Design of substrate 8 with a malonate moiety.
the chemical yield was modest (30%) in the case of the naphthyl substrate 9g owing to the detachment of the benzyl group.14 Both allyl ether 8h and ethyl ether 8i were also suitable substrates, and excellent diastereoselectivities were achieved for both substrates (d.r. >20 : 1). The construction of three contiguous stereogenic centers was also attainable, that is, the reaction of the substrate 8j with a monomethyl group at the benzylic position afforded the adduct 9j in 93% with 3.1 : 1 diastereoselectivity.11

To elucidate the reaction mechanism, additional experiments were conducted (Scheme 3). No primary kinetic isotope effect was observed in both hydride shift processes: The KIE (kH/D) values were determined to be 1.63 (for the first hydride shift) and 0.96 (for the second hydride shift). These results imply the reversibility of both hydride shift processes. To check their possible reversibility, the substrates 14 and 15 having the D atom in vinylic positions were subjected to the optimized reaction conditions. No incorporation of the D atom into the position adjacent to the oxygen atom was observed, which completely ruled out the reversibility of the hydride shift steps. Furthermore, the diastereomer ratio did not change even when the adduct 9a with low diastereoselectivity (d.r. = 6.7 : 1, entry 10 in Table 1) was subjected to slightly modified optimized reaction conditions (2 mol% TFOH, toluene, reflux, 48 h). Importantly, the relative stereochemistries of the two diastereomers of 9a were determined to be cis and trans in the ring junction \( \Delta H = 6.8 \text{ Hz in } 9a \text{ and } \Delta J = 11.6 \text{ Hz in } 9a \) (major diastereomer), which indicates that the diastereoselectivity was determined in the first hydride shift/cyclization process. The above results suggest that the excellent diastereoselectivities were achieved under kinetic control, and the rate-determining step would be the first cyclization step, and not the hydride shift processes as in the case of the sequential hydride shift system we have recently reported.8

Conclusions

In summary, we have developed a highly diastereoselective synthesis of fused tricyclic pyrans via double C(sp3)-H bond...
functionlization triggered by sequential hydride shift processes. The key to achieving this goal was the careful design of the substrate with two methyl groups at the benzylic position, and the desired sequential reaction proceeded smoothly with low catalyst loading of TfOH (only 2 mol%). Various tricyclic pyrans with electron-donating and -withdrawing substituents on the aromatic ring were obtained in excellent chemical yields with excellent diastereoselectivities (up to d.r. = 20:1). Additional experiments suggested that the rate-determining step was not the hydride shift step but the first cyclization step. Further investigation on the hydride shift/cyclization sequence, particularly the catalytic asymmetric version, is underway in our laboratory.

Conflicts of interest
There are no conflicts to declare.

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All of cinnamylidene barbiturates 8 were used as a mixture of E/Z isomer (E/Z = >4.3/1).

The low chemical yield of 9g was ascribed to the formation of 16 (58%), which was produced via cleavage of benzyl group, intramolecular Michael addition of oxygen atom followed by intramolecular Friedel–Crafts reaction.

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The structures of 9a, 9c, and 9j were unambiguously established by single-crystal X-ray analysis. CCDC-1838261, 1838259, and 1838262 contains the supplementary crystallographic data of 9a, 9c, and 9j.

The employment of barbituric acid moieties as an electrophilic portion was critical for the excellent results. The substrates with dimethyl malonate and 1,3-cyclohexanedione underwent the desired reactions smoothly to afford the tricyclic compounds, but their diastereomer ratio remained low to moderate (less than d.r. = <3.6 : 1).

13 Of cinnamylidene barbiturates 8 were used as a mixture of E/Z isomer (E/Z = >4.3/1).

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