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Double C(sp^3)–H Bond Functionalization Mediated by Sequential Hydride Shift/Cyclization Process: Diastereoselective Construction of Polyheterocycles

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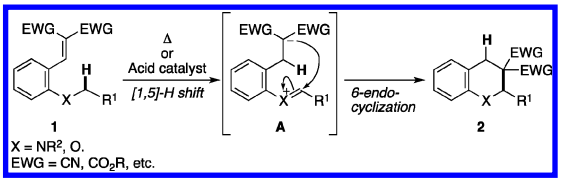
Supporting Information

ABSTRACT: Described herein are two novel types of double C(sp^3)–H bond functionalizations triggered by a sequential hydride shift/cyclization process: (1) construction of a bicyclo[3.2.2]nonane skeleton by a [1,6]- and [1,5]-hydride shift sequence and (2) sequential [1,4]- and [1,5]-hydride shift mediated construction of a linear tricyclic skeleton.

The development of methodology for the direct functionalization of relatively unreactive C–H bonds has become a major topic of research interest.[1] Recently, the C(sp^3)–H bond functionalization by a hydride shift/cyclization process, namely, the "internal redox process," has attracted much attention for its unique features (Scheme 1).[2] The key feature of this transformation is the [1,5]-hydride shift of the C(sp^3)–H bond α to the heteroatom. Subsequent *6-endo* cyclization to a cationic species affords heterocycle **2**.[3]

Scheme 1. C(sp^3)–H Functionalization by Internal Redox Process



Because of the potential synthetic utility, several groups including ours have developed new types of transformations and constructed useful skeletons.[4−8] However, in contrast to the dramatic advances in the process involving a [1,5]-hydride shift, the processes involving [1,4]- and [1,6]-hydride shifts, which would also offer various synthetically useful skeletons, have not been well investigated.[9,10] Furthermore, the sequential utilization of a [1,*n*]-hydride shift process (*n* = 4, 5, 6) is also a promising approach to construct complex polyheterocycles. Nevertheless, to the best of our knowledge, there is no precedent for the sequential hydride shift triggered double C(sp^3)–H bond functionalization.

We wish to report herein two types of double C(sp^3)–H bond functionalizations mediated by a sequential hydride shift/cyclization process (Figure 1). The interesting feature is that the reaction course ([1,4]- or [1,6]-hydride shift) is completely controlled by the electrophilic moiety of the substrate. A substrate with a *trans*-α,β-unsaturated trifluoroacetyl group (R^1 = H) affords a bicyclo[3.2.2]nonane skeleton by a sequential [1,6]- and [1,5]-hydride shift process (type I). On the other hand, a [1,4]- and [1,5]-hydride shift occurred successively in a substrate with a benzyl group at the position α to a trifluoroacetyl group (type II). Theoretical studies have revealed that the resonance stabilization in the benzylidene carbonyl moiety and the steric repulsion of the α-substituent (R^1) are the key to changing the reaction course.

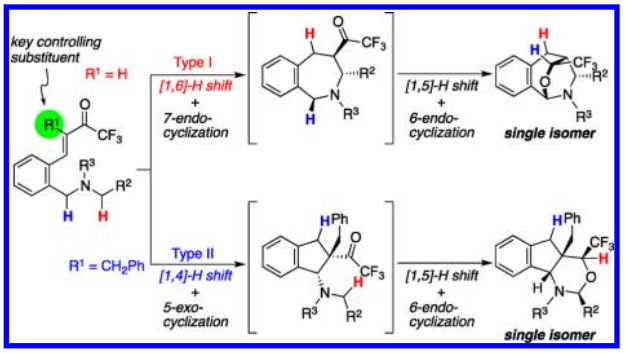


Figure 1. Sequential hydride shift processes.

To develop the desired sequential hydride shift/cyclization system, we selected benzylamine derivative **B** because of the potent hydride shift ability of the α-H of the N-atom (Figure 2).[4] The main challenge is twofold: (1) control of the two potentially competitive hydride shift processes ([1,4]-hydride shift vs [1,6]-hydride shift) and (2) selection of the appropriate electron-withdrawing group (EWG) that would trigger the second [1,5]-hydride shift. We were plagued by the latter issue because most of the internal redox reactions reported so far involve a 1,4-

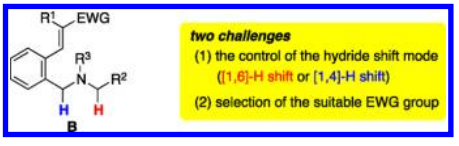


Figure 2. Two challenges in the reaction of benzylamine derivatives.

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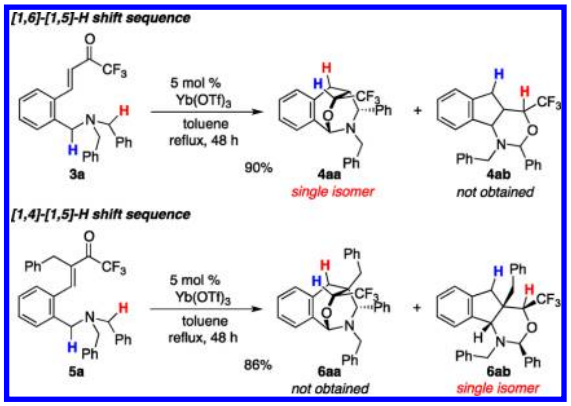

Figure 3. Two types of sequential hydride shift mediated double C(sp^3)−H bond functionalizations.

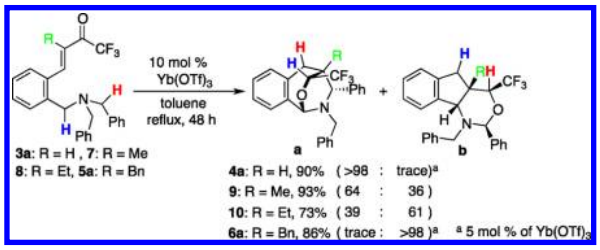

Figure 4. Effect of α-substituent of α,β-unsaturated trifluoroacetyl group.

reduction type hydride shift, and the 1,2-reduction type reaction is rare.[11] Model experiments revealed that the trifluoroacetyl group had excellent reactivity for the 1,2-reduction type internal redox process compared to aldehyde and methyl ketone (not shown, see Supporting Information (SI)).

Based on the above discussion and our previous studies of internal redox processes,[7] we selected a *N,N*-dibenzylbenzylamine derivative with a *trans*-α,β-unsaturated trifluoroacetyl group as the substrate (Figure 3).[12] We found that the key initial hydride shift process ([1,4]- or [1,6]-hydride shift) was completely controlled by tuning the electrophilic moiety (selection of the α-substituent of the trifluoroacetyl group). When substrate **3a** with a simple *trans*-α,β-unsaturated trifluoroacetyl group was subjected to the reaction conditions (5 mol % $Yb(OTf)_3$, toluene, reflux, 48 h), bicyclo[3.2.2]nonane-type compound **4aa** ([1,6]-hydride shift involved adduct) was obtained as the sole product (90%) and no appreciable **4ab** ([1,4]-hydride shift involved adduct) was observed. In sharp contrast, α-benzyl substrate **5a** underwent another sequential hydride shift process ([1,4]- and [1,5]-hydride shift) smoothly to furnish linear tricyclic compound **6ab** in excellent chemical yield (86%). Another interesting feature is that the three contiguous stereogenic centers in **4aa** and **6ab** were completely controlled, and the relative stereochemistries of each product were ambiguously established by X-ray analysis.[13]

Investigation of the electrophilic moiety revealed that the bulkiness of the α-substituent of the trifluoroacetyl group was the key to controlling the reaction course (Figure 4). Subjection of substrate **7**, bearing a methyl group at the α-position, to the optimum reaction conditions furnished bicyclo[3.2.2]nonane derivative **9a** in slight preference to linear tricyclic compound **9b** (93%, **9a**:**9b** = 64:36). The [1,4]-hydride shift involving adduct **10b** prevailed in substrate **8** with an α-ethyl group (73%, **10a**:**10b** = 39:61). The structures and relative stereochemistries of **9a** and **9b** were determined by X-ray analysis.

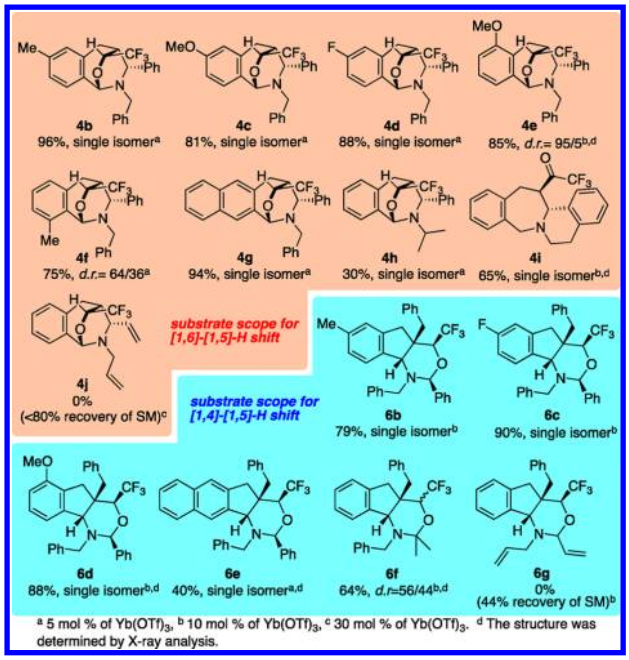

Figure 5. Substrate scope of sequential hydride shift processes.

The substrate scope of the two sequential hydride shift reactions is illustrated in Figure 5. As regards the [1,6]-[1,5]-sequential hydride shift process, bicyclo[3.2.2]nonane derivatives **4b**−**f** with electron-donating groups (methyl, methoxy) and an electron-withdrawing group (fluoro) were obtained in good chemical yields (up to 96%). Naphthyl-type product **4g** was obtained in excellent chemical yield (94%). The hydride shift occurred exclusively on the benzyl group in the presence of an isopropyl group to furnish **4h** in 30% yield. The acyclic nature of the *N,N*-dialkylamine moiety is important for the sequential hydride shift process; *i.e.*, an isoquinoline-type substrate **3i** afforded only 7-membered ring adduct **4i** (single hydride shift adduct) due to the restriction of the conformational mobility required for the second hydride shift process by the ring structure of the isoquinoline moiety. Furthermore, the use of at least one benzyl group on nitrogen was crucial in this reaction: no appreciable adduct was obtained from *N,N*-diallyl analogue **3j**.

The [1,4]-[1,5]-sequential hydride shift process has proven amenable to a range of substrates bearing a benzyl moiety,[14] affording tricyclic compounds (**6b**−**d**) in good to excellent chemical yields (79−90%, Figure 4). Naphthyl product **6e** was also obtained as a single diastereomer, albeit in low chemical yield (40%).[15] Interestingly, the second hydride shift ([1,5]-hydride shift) occurred exclusively on an isopropyl group in preference to a benzyl group (**6f**, 64%), whereas benzylic hydrogen migrated exclusively in the above sequential reaction. In this case as well, the presence of a benzyl group on nitrogen was essential and diallyl amine derivative **6g** was not obtained.

To elucidate the major factor controlling the reaction course, DFT calculations for the first hydride shift were carried out (Figures 6 and 7). The transition states (TSs) of the [1,4]-hydride shift (**TS1**) and the [1,6]-hydride shift (**TS2**) were compared using the protonated chemical models for **3a** (**TSa**), **5a** (**TSd**), **7** (**TSb**), and **8** (**TSc**). Increasing the bulkiness of the α-substituent (R^1) induced the reversal of the relative stability of TSs, in good agreement with the experimental results (Figure 6). **TS1a** (R^1 = H) was 2.7 kcal/mol less stable than **TS2a**. In contrast, **TS1d** with a sterically demanding benzyl group at the α-

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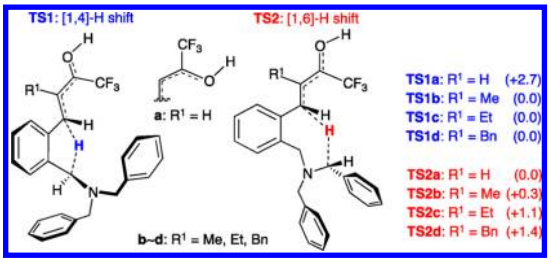

Figure 6. Relative energy differences (kcal/mol in parentheses) between **TS1** and **TS2** in series **a** (R^1 = H), **b** (R^1 = Me), **c** (R^1 = Et), and **d** (R^1 = Bn).

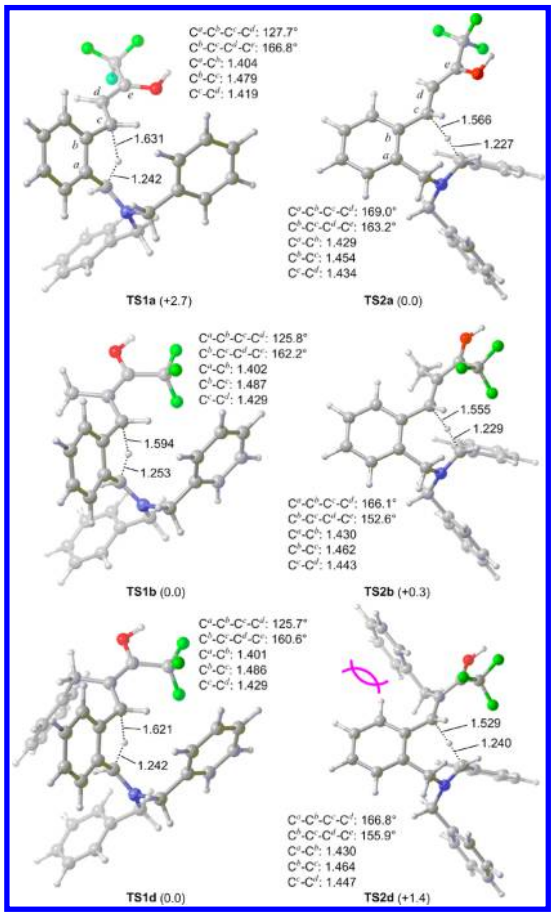

Figure 7. 3D structures of **TS1** and **TS2** in series **a** (R^1 = H), **b** (R^1 = Me), and **d** (R^1 = Bn). Bond lengths are shown in Å.

position was 1.4 kcal/mol more stable than **TS2d**. Relatively small energy differences between **TS1** and **TS2** were obtained in series **b** (R^1 = Me) and **c** (R^1 = Et).

The relative orientations between the olefin portion and the phenyl moiety are nearly orthogonal in **TS1** and parallel in **TS2** (Figure 7). **TS2a** is energetically more favored than **TS1a** mainly due to the resonance-stabilized structure in the benzylidene moiety (C^a–C^b–C^c–C^d). The steric repulsion between the α-methyl and phenyl groups would cause the deformation of the resonance-stabilized structure, thereby leading to a decrease in the energy difference between **TS1b** and **TS2b**. The sterically demanding benzyl group at the α-position would induce a large steric repulsion with the phenyl group (shown in purple curves in Figure 7) to overwhelmingly destabilize **TS2d** rather than **TS1d**.

The relative stereoselectivity in each sequential process could be well rationalized based on the results of a theoretical study by

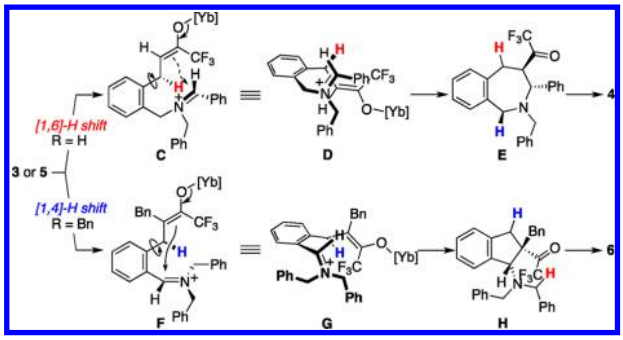

Figure 8. Rationalization of stereoselective formation of **4** and **6**.

Luo[5g] and Reinhoudt's early investigation.[4a] Luo suggested that the hydride shift process is the rate-determining step and subsequent cyclization occurred rapidly after the process according to the computational study. The primary kinetic isotope effects (k_H/k_D) of those two reactions (3.0 for [1,6]-hydride shift process, 2.6 for [1,4]-hydride shift process) also support this mechanism.[16−18] In addition, Reinhoudt's work[4a] and an enantioselective version of these types of processes developed by us[7f] and Luo[5f] revealed the highly stereoselective nature of the internal redox process; *i.e.*, the stereochemistry of the starting material was mostly transferred to the newly formed stereogenic center of the product. Based on this information, the stereoselectivity in both processes is explained as follows (Figure 8): the cyclization to the iminium cation, which was generated by the [1,6]- or [1,4]-hydride shift, by enolate species occurred from the same face of the transferred hydrogen to afford *trans*-**E** and *cis*-**H**, respectively. The severe steric repulsion between the CF_3 moiety and the adjacent substituent (Ph or Bn group) would control the direction of the trifluoroacetyl group, leading to the highly stereoselective [1,5]-hydride shift (reduction of trifluoroacetyl group). As a result, the corresponding adducts (**4** and **6**) were obtained with excellent stereoselectivities.

In summary, we have developed two types of double C(sp^3)–H bond functionalizations triggered by a sequential hydride shift/cyclization process. The interesting feature here is that simply changing the electrophilic moiety altered the reaction course. Theoretical studies revealed that the resonance stabilization in the benzylidene carbonyl moiety and the steric repulsion of the α-substituent (R^1) are the key to changing the reaction course. Further investigation of the hydride shift/cyclization sequence, particularly concerning the successive hydride shift system, is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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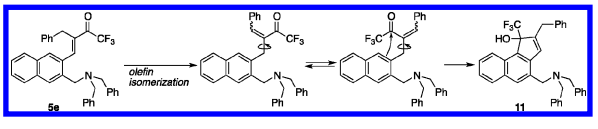
(12) The large coupling constant (J = 16.0 Hz) suggests the *E*-configuration of **3a**.

(13) Attempts to extend the present reaction to the catalyzed, enantioselective reaction with a chiral Yb-complex (with several Py-BOX ligands) were unsuccessful.

(14) The *E*-configuration of **5e** was determined by X-ray analysis, and those of other substrates were assigned by analogy.

(15) The low chemical yield of **6e** was ascribed to the formation of byproduct **11** (58%), which was produced by olefin isomerization followed by the Friedel−Crafts reaction.



(16) The results of the examination of the kinetic isotope effect were described in the SI.

(17) Subjecting products (**4aa** and **6ab**) under the optimum conditions led to complete recovery of starting materials, which ruled out the reversibility of these reactions.

(18) Crossover experiments for each sequential reaction suggested that the hydride shift occurred intramolecularly. See SI for details.

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