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Expeditious Construction of a Carbobicyclic Skeleton via sp^3-C−H Functionalization: Hydride Shift from an Aliphatic Tertiary Position in an Internal Redox Process

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Supporting Information

ABSTRACT: Described herein is the first example of an aliphatic, nonbenzylic hydride shift/cyclization sequence that contains two types of novel sp^3-C−H functionalization: (1) construction of a tetraline skeleton via [1,5]-hydride shift/cyclization and (2) [1,6]-hydride shift/cyclization to form a five-membered ring (indane derivatives).

Direct and selective functionalization of C−H bonds into C−C and/or C−X bonds (X = O, N, halogen, etc.) has become an important topic of research because it provides a powerful tool for the synthesis of numerous complex molecules.[1] Recently, much attention has been paid to sp^3-C−H bond functionalization mediated by an internal redox process, which involves a [1,5]-hydride shift from the α-carbon to the heteroatom, followed by cyclization (Scheme 1).[2] Although C−H functionalization is mostly promoted by transition-metal catalysts, the internal redox process typically proceeds under thermal conditions or, in some cases, under Brønsted or Lewis acid catalysis.[3,4]

As part of our recent program to develop new catalytic C−H functionalization methodologies, we have disclosed that imine derivatives are also viable substrates for this type of reaction[5] and that the substituent ortho to the oxygen atom has a beneficial effect on the reactivity.[6] The internal redox reactions involving the [1,5]-H shift reported to date have entailed the electronic assistance of an adjacent heteroatom for the stabilization of the carbocation generated by the hydride shift. Quite recently, however, it was found that benzylic hydrogen undergoes the hydride shift even in the absence of an adjacent heteroatom in the π-activation system.[7] The development of the hydride shift from an aliphatic, nonbenzylic position is still quite a challenging task, and its realization would improve the usefulness of the internal redox process in synthetic organic chemistry.

We document herein a novel hydride shift/cyclization reaction assisted by neither a heteroatom nor an arene (Figure 1). We found that the hydrogen on an aliphatic tertiary carbon can participate in the hydride shift process smoothly, driven by the generation of a stable tertiary carbocation intermediate. This communication deals with two types of novel sp^3-C−H functionalization: (1) construction of a tetrahydronaphthalene skeleton via [1,5]-hydride shift/cyclization (type I); (2) a [1,6]-hydride shift[4a,8] followed by interception of the resultant carbocation species using an internal arene to yield indane derivatives (type II). To the best of our knowledge, these represent the first

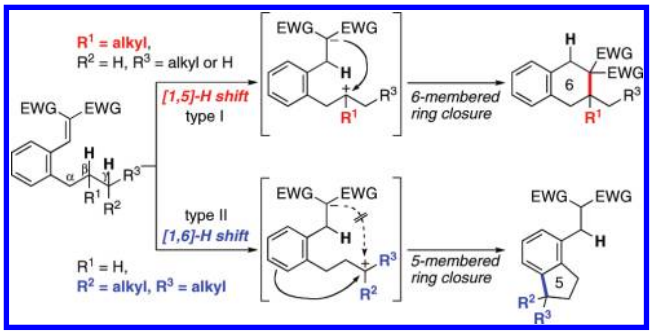
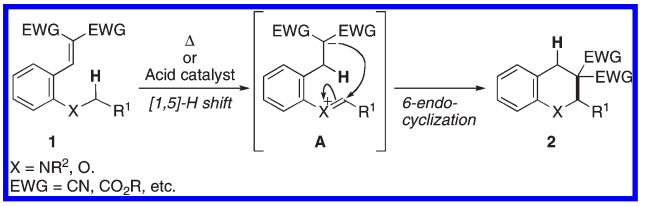


Figure 1. Two kinds of aliphatic, nonbenzylic internal redox processes.

Scheme 1. sp^3-C−H Functionalization via an Internal Redox Process



examples of a hydride shift occurring from an aliphatic, nonbenzylic position in the internal redox process.

The key to achieving this goal was determining how to trigger the hydride shift from an aliphatic position that has poor electron density. We found that treatment of benzylidene barbituric acid **3a** with 3 mol % $Sc(OTf)_3$[9] in refluxing $ClCH_2CH_2Cl$ for 24 h furnished the desired tetraline **4a** in excellent yield (96%; Figure 2). It should be noted that the H atom of the aliphatic, nonbenzylic sp^3 carbon participated in the [1,5]-hydride shift very smoothly even with the low catalyst loading (3 mol %).

Various substituents were tolerated in this reaction. For example, the unsymmetrical (ethyl- and methyl-substituted) product **4b** and the cyclohexyl and cyclopentyl derivatives **4c** and **4d** were obtained in excellent chemical yields (≥93%). Importantly, the substrate with a linear side chain did not give the desired product **4e**, even with a catalyst loading of 30 mol %. This result suggests that hydrogen, which generates a more stable carbocation (3° carbocation) intermediate, has a higher propensity to undergo the [1,5]-hydride shift. On the other hand,

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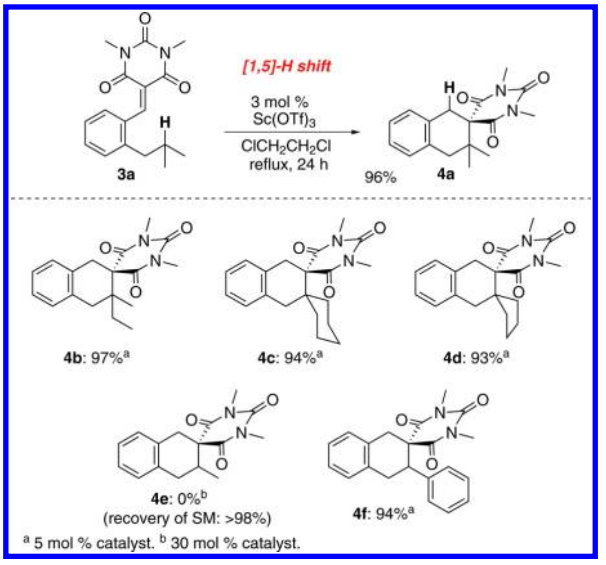
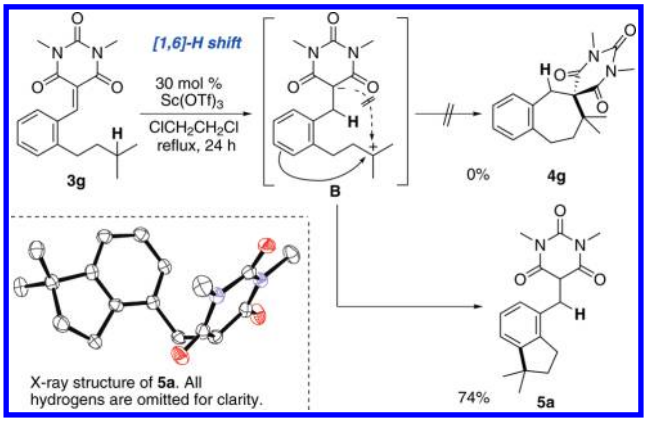


Figure 2. Substrate scope of C−H functionalization induced by the [1,5]-H shift.

Scheme 2. Unexpected Formation of Indane Derivatives via a [1,6]-H Shift/Cyclization Sequence



benzylic product **4f** was obtained in excellent yield with a low catalyst loading even in the absence of a methyl group (5 mol % catalyst loading, 94% yield), mainly as a result of the strong cation-stabilizing ability at the benzylic position.[10,11]

Inspired by the achievement of the aliphatic [1,5]-hydride shift process, we turned our attention to the development of the more challenging aliphatic [1,6]-H shift/cyclization reaction. Internal redox processes involving a [1,6]-H shift are quite rare and have been observed only in relatively reactive substrates with an adjacent nitrogen atom.[4a,8]

In order to satisfy the hydride shift requirement (the high stability of the resulting carbocation intermediate), we selected **3g** having a *gem*-dimethyl group at the γ-position as a suitable substrate. Upon treatment of **3g** with 30 mol % $Sc(OTf)_3$ in refluxing $ClCH_2CH_2Cl$, **3g** was consumed within 24 h. Surprisingly, the resulting product was not the expected seven-membered-ring adduct **4g** but rather indane derivative **5a** (74% yield; Scheme 2), whose structure was unambiguously established by single-crystal X-ray analysis. The unexpected product **5a** was probably produced by the Friedel−Crafts reaction of the internal

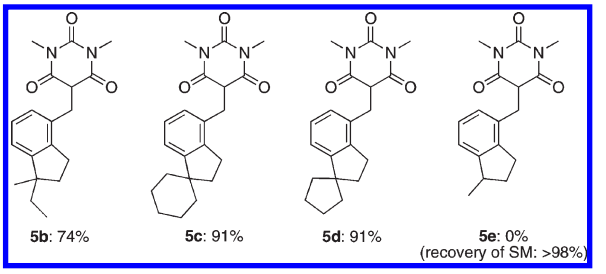
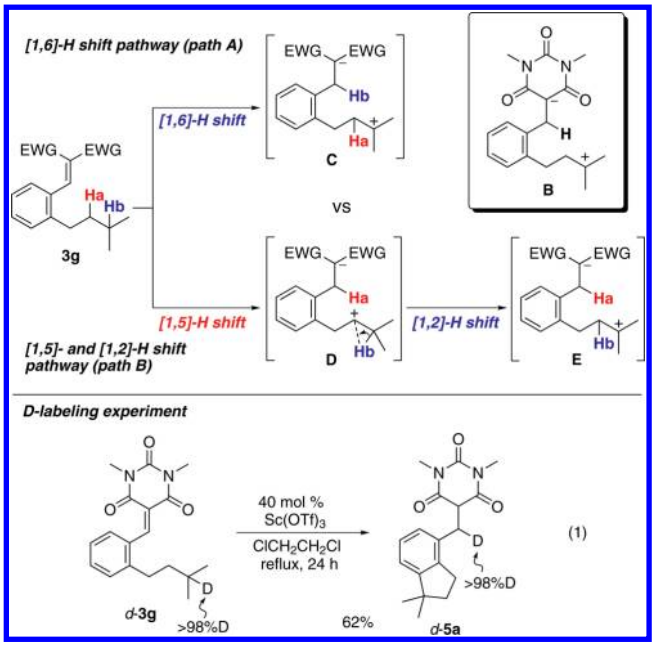


Figure 3. Substrate scope of C−H functionalization induced by the [1,6]-H shift.

Scheme 3. Clarification of the Reaction Mechanism of the [1,6]-H Shift/Cyclization Sequence



aromatic ring with the resulting carbocation **B** instead of the nucleophilic addition of the carbanion.[12] To the best of our knowledge, this type of internal redox reaction involving C−C bond formation between the carbocation and arene in the molecule was unprecedented until the report by Zhou and Zhang.[13]

The substrate scope of the [1,6]-H shift/cyclization sequence is shown in Figure 3.[14] 1,1-Ethylmethylindane **5b** and the cyclohexyl and cyclopentyl derivatives **5c** and **5d** were obtained in good to excellent chemical yields. Also in this case, the stabilization of the resulting γ-carbocation species was essential for triggering of the [1,6]-H shift (i.e., the substrate having a linear side chain led to almost complete recovery of the starting material).

Two reaction pathways could be assumed for the formation of the key γ-tertiary carbocation intermediate **B** (Scheme 3): (1) the [1,6]-hydride shift pathway (path A),[4a,8] and (2) the sequential hydride shift pathway (a [1,5]-H shift followed by a [1,2]-H shift, path B). In view of the results for **4e** and **5e**, path A is most likely because the latter path would contain a difficult hydride shift from a methylene moiety. To clarify the detailed reaction course, a D-labeling experiment was conducted (eq 1 in Scheme 3). D incorporation was observed only at the benzylic position (>98% D), unambiguously ruling out the sequential hydride shift pathway.[15]

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In summary, we have presented here the first examples of internal redox processes involving aliphatic, nonbenzylic hydride shift/cyclization sequences. The combination of benzylidene barbituric acids and $Sc(OTf)_3$ enabled us to trigger the desired [1,5]-hydride shift from the aliphatic position, affording tetraline derivatives. Substrates with a γ-dialkyl side chain underwent the unexpected [1,6]-hydride/cyclization process to furnish indane derivatives in good to excellent chemical yields (74−91%). Although most of the internal redox reactions reported to date involve the connection between the carbocation and the carbanion generated by the hydride shift, we have realized a novel bond-formation reaction: nucleophilic attack from the aromatic ring. Further investigations to develop new types of reactions by exploiting the aliphatic hydride/cyclization sequence are underway in our laboratory.

■ ASSOCIATED CONTENT

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

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(9) For internal redox reactions catalyzed by $Sc(OTf)_3$, see refs 2a, 2j, 4j, 4m, 6, and 7c.

(10) In order to obtain information about the reaction course, some D-labeling experiments were conducted. The results are described in the Supporting Information.

(11) For a theoretical study of the effect of the substituent on the stability of a carbocation, see: El-Nahas, A. M.; Clark, T. *J. Org. Chem.* **1995**, *60*, 6024.

(12) We assumed that there are two factors contributing to the predominant formation of a five-membered ring over a seven-membered ring: (1) Baldwin's rule and (2) steric repulsion between the bulky barbituric acid moiety and the dimethyl group around the tertiary carbocation in the transition state for the formation of a seven-membered ring.

(13) Zhou and Zhang reported a gold-catalyzed internal redox reaction involving C−C bond formation between a furanyl anion species and a carbocation generated by the hydride shift (see ref 2j).

(14) All of the reactions were performed with 0.1 mmol of **3** and 30 mol % $Sc(OTf)_3$ in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature.

(15) One of the reviewers suggested the intermolecular hydride shift mechanism. The crossover experiment of *d*-**3g** and a naphthyl-type substrate revealed that the hydride shift occurred intramolecularly. For more detailed information, see the Supporting Information. We thank the reviewer for the suggestion of this experiment.