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Expeditious synthesis of 1-aminoindane derivatives achieved by [1,4]-hydride shift mediated C(sp^3)–H bond functionalization†

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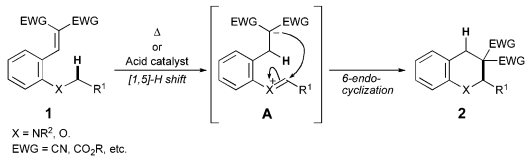
Described herein is a [1,4]-hydride shift mediated expeditious synthesis of 1-aminoindane derivatives. A wide variety of substrates could be employed in this reaction to afford various indane derivatives in good to excellent chemical yields. Examination of the amine moiety revealed that the sterically hindered amine is the key to achieving both low catalyst loading and excellent chemical yields.

The development of a method for the direct functionalization of relatively unreactive C–H bonds has become a major target of research.[1] Recently, the C(sp^3)–H bond functionalization by the hydride shift/cyclization process, namely, the "internal redox process," has attracted much attention due to 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 the cation species affords heterocycle **2**.[3] Although C–H bond functionalization is promoted by a transition metal catalyst in most cases, this type of C–H bond functionalization typically proceeds under thermal conditions or Brønsted or Lewis acid catalysis.

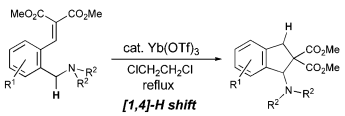
Recent advances in the internal redox process have enabled the construction of an array of useful skeletons.[4–7] An enantioselective variant of the reaction was also realized by using both a chiral metal catalyst and an organocatalyst, affording synthetically useful chiral tetrahydroquinoline derivatives with excellent enantioselectivities.[8] Contrary to the dramatic advances offered by the [1,5]-hydride shift process, the corresponding [1,4]-hydride shift process, which also generates synthetically useful skeletons, has not been well investigated. To the best of our knowledge, there are only two precedents in which two equivalents of a transition metal additive (CuBr)[9a] or strong electronic assistance from two heteroatoms[9b] was required.

We wish to report herein a [1,4]-hydride shift triggered C(sp^3)–H bond functionalization from simple benzylamine derivatives.



Scheme 1 C(sp^3)–H bond functionalization *via* an internal redox process.

In this process, the low catalyst loading of Yb(OTf)$_3$ (5 mol%) sufficed to promote the desired transformation to afford 1-aminoindane derivatives in good to excellent chemical yields.



(1)

The desired [1,4]-hydride shift process was realized when benzylidene malonate **3** was employed as the substrate. Upon treatment of **3a** with 5 mol% Yb(OTf)$_3$ in refluxing $ClCH_2CH_2Cl$, the desired reaction proceeded smoothly to afford indane derivative **4a** in a quantitative yield with a short reaction time (0.5 h).[10] The substrate scope of this reaction is summarized in Fig. 1. Investigation of the amine moiety revealed that the bulkiness of the substituent on the nitrogen atom played a critical role in the reactivity; whereas 30 mol% Yb(OTf)$_3$ was required to afford *N*,*N*-diethylamine derivative **4b** and 5 mol% of the same catalyst sufficed for *N*,*N*-diisopropylamine derivative **3a**. Relatively bulky amines, such as *N*,*N*-dibenzyl, diphenyl, and diallyl amines **3c–e**, underwent the reaction to give indanes **4c–e** in good to excellent chemical yields with a low catalyst loading (5 mol%).[11] This reactivity control by the steric effect was much more prominent in cyclic amine derivatives. Although almost no appreciable product was generated using piperidine substrate **3f** (30 mol% Yb(OTf)$_3$, 24 h), **3g** with 2,2,6,6-tetramethylpiperidine (an extremely bulky amine) enabled the smooth formation of desired adduct **4g** using a 5 mol% catalyst (ring-opened product **4h** was also obtained and the combined yield is shown in Fig. 1, **4g**:**4h** = 2.3:1). Isoquinoline derivative **4i** was obtained in moderate yield with a low catalyst loading (61%, 5 mol%).

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. CCDC 980641–980643. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00894d

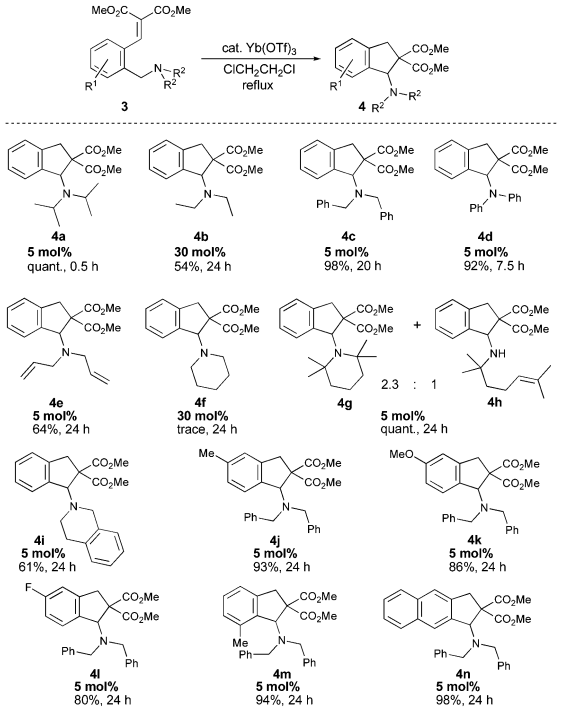
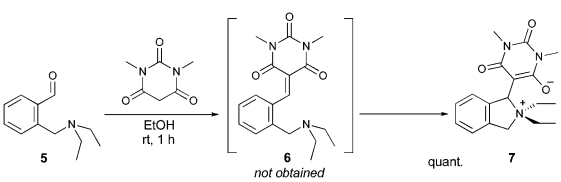


Fig. 1 Substrate scope of the [1,4]-H shift/cyclization sequence.

The substituent on the aromatic ring did not have an impact on the reaction, and the corresponding adducts (**4j–n**) were obtained in good to excellent chemical yields with the 5 mol% catalyst (the amine moiety was fixed to *N*,*N*-dibenzylamine).

Next, we attempted to decrease the catalyst loading of less reactive substrates (such as **3b** with an *N*,*N*-diethylamine moiety) by employing more reactive benzylidene barbiturate **6**. When aldehyde **5** was mixed with 1,3-dimethylbarbituric acid in EtOH at room temperature, **5** was almost completely consumed in 1 h. The resulting product, however, was not desired benzylidene barbiturate **6** but zwitterionic compound **7** (intramolecular cyclization adduct).[11] This result indicates that the nitrogen in **6** has the propensity to attack the activated electrophilic carbon of the hydride acceptor (Scheme 2).

Based on this result, the high reactivity of bulky amine derivatives could be rationalized by taking two factors into consideration: (1) control of the conformational behavior of the benzylamine moiety and (2) suppression of the intramolecular nucleophilic attack (Fig. 2). The desired [1,4]-hydride shift would be promoted *via* conformer **B**, wherein benzylic hydrogens would be located in the vicinity of the electrophilic α carbon of benzylidene malonate. In the case of **3a**, the conformational equilibrium would be shifted markedly to desired conformer **B** because of the steric repulsion between the bulky diisopropylamine moiety and the malonate group.



Scheme 2 Formation of a zwitterionic species.

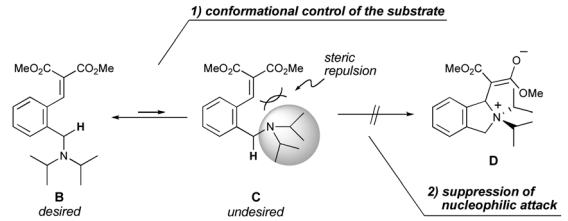


Fig. 2 Rationalization for enhancement of reactivity by the bulky amine moiety.

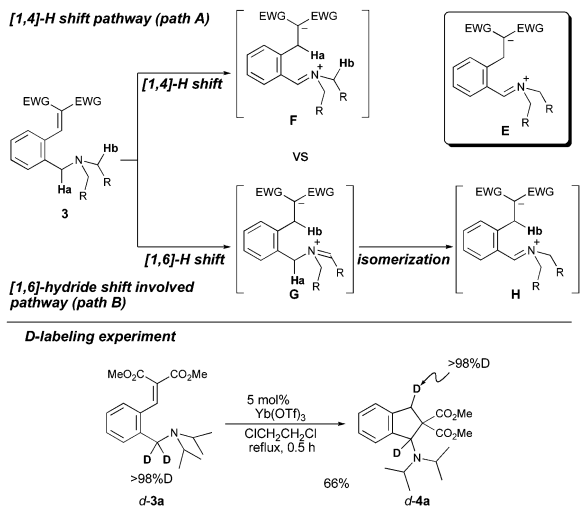
Furthermore, the bulky amine moiety would prevent the nucleophilic attack of nitrogen. As a result of these two factors, the reactivity of bulky amines was improved dramatically.[12]

Because benzylamine derivative **3** has some hydrogens adjacent to the nitrogen atom (Ha and Hb in Scheme 3), two reaction pathways could be assumed for the formation of key iminium cation intermediate **E** (Scheme 3): (1) the [1,4]-hydride shift pathway (path A) and (2) the pathway involving the [1,6]-hydride shift ([1,6]-H shift followed by isomerization, path B).

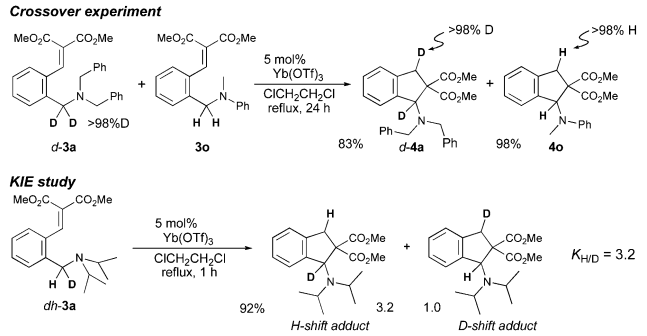
To clarify the detailed reaction course, a D-labeling experiment was conducted. The fact that deuterium incorporation was observed only at the benzylic position (>98% D) led us to unambiguously rule out the latter pathway.

Most of the internal redox reactions are considered to proceed *via* the intramolecular hydride shift process, although the intermolecular hydride shift mechanism is proposed in some cases.[6e,f] In order to ensure the intramolecular nature of the hydride shift process, we conducted a crossover experiment between *d*-**3a** and **3o** (Scheme 4). The deuterium incorporation was observed in only *d*-**4a**, which revealed that this hydride shift proceeded intramolecularly. Furthermore, the observation of the primary kinetic isotope effect ($k_{H/D}$ = 3.2) suggested that the hydride shift process was the rate-determining step in the reaction.

In summary, we have developed an expeditious synthesis of 1-aminoindane derivatives by [1,4]-hydride shift mediated



Scheme 3 Clarification of the reaction mechanism of the [1,4]-hydride shift/cyclization sequence.



Scheme 4 Crossover experiment and the kinetic study.

C(sp^3)–H bond functionalization. A wide variety of substrates were applicable to this reaction and various 1-aminoindane derivatives were obtained in good to excellent chemical yields. The salient feature of this reaction is that the bulky amine significantly enhanced the reactivity, which could be rationalized by two factors: (1) control of the conformational behavior of the benzylamine moiety and (2) suppression of the intramolecular nucleophilic attack. Detailed investigation of the reaction mechanism suggested that the [1,4]-hydride shift was the rate-determining step and occurred intramolecularly. Further investigation toward the development of new reactions by exploiting the [1,4]-hydride shift/cyclization sequence is underway in our laboratory.

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10 A detailed examination of the reaction conditions is described in ESI†.

11 The structures of **4a**, **4c**, and **7** were unambiguously established by single-crystal X-ray analysis. CCDC 980641(**4a**), 980642(**4c**) and 980643(**7**).

12 Subjection of the zwitterionic compound derived from *N*,*N*-dibenzylamine to the optimum conditions (10 mol% $Yb(OTf)_3$, $ClCH_2CH_2Cl$, reflux) resulted in a moderate chemical yield (55%) of the indane derivative. This clearly indicates the reversibility from zwitterionic compound to benzylidene barbiturate.