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Rapid Access to 3-Aryltetralin Skeleton via C(sp^3)–H Bond Functionalization: Investigation on the Substituent Effect of Aromatic Ring Adjacent to C–H Bond in Hydride Shift/Cyclization Sequence

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The concise construction of 3-aryltetralin skeleton via hydride shift mediated C–H bond functionalization was achieved. In this process, the benzylic [1,5]-H shift occurred smoothly to furnish tetralin derivatives in good to excellent chemical yields. The electronic and steric properties of the aromatic ring adjacent to the C–H bond influenced significantly the reactivity of this transformation.

The direct and selective replacement of carbon–hydrogen bonds with new bonds (C–H functionalization) represents an important and longstanding goal in synthetic organic chemistry.[1] Considering the high abundance of C–H bonds, the precise one-step substitution of C–H bonds with C–C and/or C–Y bonds (Y = O, N, etc.) without disruption of the surrounding molecular structure and the prefunctionalization to C–X bonds (X = halogen, OSO_2CF_3, etc.) offer a promising approach for the synthesis of various complex molecules.

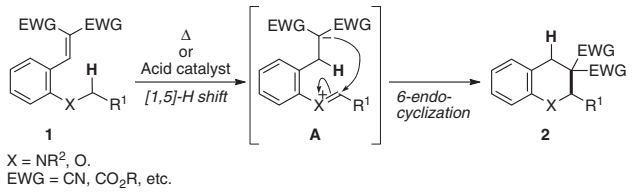
Recently, the C(sp^3)–H bond functionalization via hydride shift/cyclization, namely, "internal redox process," has attracted much attention for its unique features (Scheme 1).[2] Its key feature is the [1,5]-hydride shift of the C(sp^3)–H bond α to the heteroatom. Subsequent 6-endo cyclization affords heterocycle **2**. Although C–H functionalization is, in general, promoted by a transition-metal catalyst, this type of C–H functionalization process typically proceeds under thermal conditions or, in some cases, under the Brønsted or Lewis acid catalysis.[3–6]

Whereas a range of related reactions with heteroatom-containing substrates have been reported, the corresponding C-version had been overlooked until quite recently. This is because the key [1,5]-H shift required the electronic assistance of an adjacent heteroatom for the stabilization of the carbocation generated by the hydride shift. Recent work on the internal redox process has led to the realization of the benzylic, nonadjacent heteroatom hydride shift/cyclization sequence.[7] The groups of Chatani[7a] and He[7b] independently reported that the benzylic C–H bond without an adjacent heteroatom could also participate in this type of catalytic cycloisomerization reaction. Quite recently, our group has disclosed[8a] that the employment of benzylidene barbiturate as the electrophilic portion enabled the benzylic [1,5]-hydride shift of the C–H bond at the α-position of the phenethyl moiety, affording 3-phenyltetralin in excellent chemical yield.[8] Although there are several elegant pathways leading to benzylic C–H bond functionalization, details of the substituent effect of the aromatic ring adjacent to the C–H bond remain to be investigated.

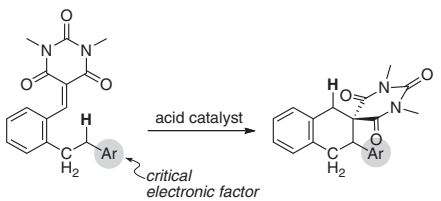
Herein we report our study of the benzylic hydride shift/transfer system, focusing on the substituent effect of he phenethyl aromatic ring (Scheme 2). We have found that the electronic nature of the aromatic group of the phenethyl moiety influenced significantly the reactivity, and the desired compounds were obtained in excellent chemical yields with low catalyst loading (as low as 0.5 mol %).

According to our previous report,[8a] various benzylidene barbiturates **5** were synthesized from salicylic acid derivatives. The preparation of *p*-tolyl analog **5b** is illustrated in Scheme 3 as a representative example. The Sonogashira coupling of triflate **3**, which is readily synthesized from commercially available salicylic acid, with *p*-tolyl acetylene afforded adduct **4** in 90% yield. Hydrogenation, reduction of the ester group, oxidation of the resulting alcohol, and condensation with 1,3-dimethylbarbituric acid gave **5b** in 76% yield from **4** (Scheme 3).

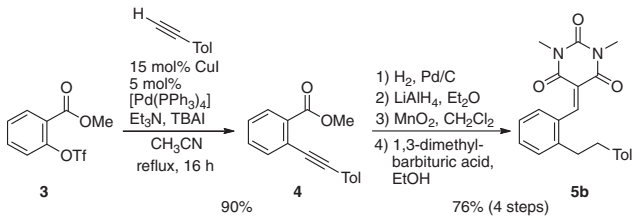
With the desired substrates in hand,[9] the substituent effect of the aromatic ring was surveyed under optimal conditions (cat. $Sc(OTf)_3$, $ClCH_2CH_2Cl$, reflux).[8a,10] Phenyl-substituted substrate **5a** underwent the internal redox process in 24 h by means of 5 mol % $Sc(OTf)_3$ (Table 1, Entry 1). Interestingly, the



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

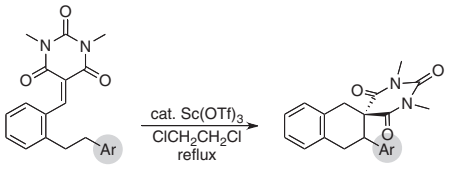


Scheme 2. Rapid access to tetralin skeleton.



Scheme 3. Preparation of benzylidene barbiturate.

Table 1. Investigation of the effect of aromatic ring on phenethyl moiety[a]



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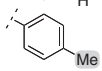
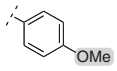
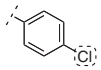
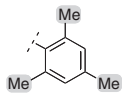
Entry	Ar		Catalyst loading /mol %	Time /h	Yield /%
1		**6a**	5	24	94
2		**6b**	5	2	98
3			1	10	95
4		**6c**	1	8	96
5			0.5	12	90
6		**6d**	30	24	88
7			5	24	25
8		**6e**	5	24	79
9			3	24	47
10		**6f**	5	24	96
11			1	24	6
12		**6g**	30	24	75
13			5	24	trace

[a]Unless otherwise noted, all reactions were performed with 0.2 mmol benzylidene barbiturate and a catalytic amount of $Sc(OTf)_3$ in $ClCH_2CH_2Cl$ (2.0 mL) at refluxing temperature.

electronic nature of the aromatic ring changed the reactivity significantly: the reaction of **5b** with *p*-tolyl group (electron-rich group) was completed within 2 h to give **6b** in excellent chemical yield (Entry 2 vs. Entry 1). In addition, the catalyst loading could be reduced to 1 mol % without sacrificing both chemical yield and reaction rate (95%, 10 h, Entry 3). Notably, even 0.5 mol % catalyst sufficed to afford **5c** with a *p*-methoxyphenyl group in excellent chemical yield (Entry 5). On the other hand, an electron-withdrawing substituent lowered the reactivity considerably: 30 mol % catalyst was required to achieve a satisfactory chemical yield for **6d** (Ar = *p*-chlorophenyl, 88%, 24 h, Entry 6).

Further investigation revealed that the steric factor also strongly affected the reactivity (Entries 8–13). To obtain **6f** (Ar = *o*-tolyl) in excellent chemical yield, a longer reaction time and an increased catalyst loading (24 h with 5 mol % catalyst) were required compared with *p*-tolyl **5b** (Entry 10 vs. Entry 3). Interestingly, **5g** with a mesityl group, which has high electron density compared with **5b**, showed considerably low reactivity: the chemical yield was at most 75% even with 30 mol % catalyst loading (Entry 12).

We assumed that the hyperconjugative interaction of the σ^* orbital of the C–H bond with neighboring substituents is

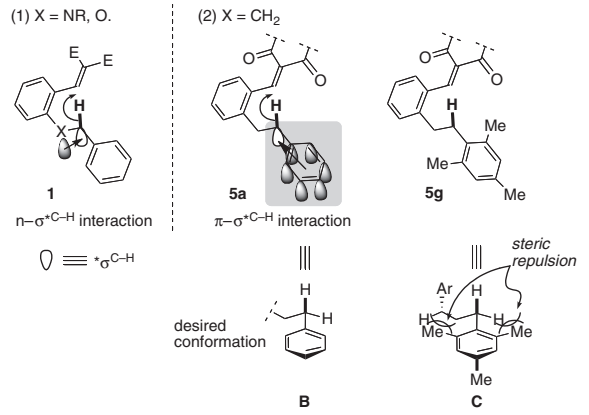


Figure 1. Rationalization of the difference of hydride transfer.

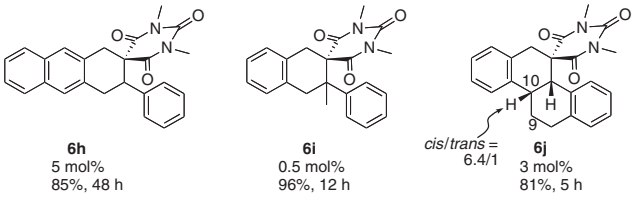


Figure 2. Further examination of substrate scope.

responsible for the promotion of the desired [1,5]-hydride shift (Figure 1). The electronic assistance from the n-orbital of heteroatom to the σ^{*C-H} orbital is the most important element in the case of heteroatom analog **1** (X = NR and O).[11] On the other hand, the orbital overlap between the π-orbital of the aromatic ring and the σ^{*C-H} orbital is the critical factor in **5a**, in good agreement with the result that the reactivity was changed by the electronic nature of the aromatic ring of the phenethyl moiety (Table 1).

Taking this into consideration, the low reactivity of **5g** could be well rationalized. For the efficient promotion of the desired [1,5]-hydride shift, the aromatic ring should be oriented vertical to the σ^{*C-H} orbital. The steric repulsion between the two *ortho*-methyl groups in the mesityl group and the methylene group in **5g** rendered desired conformer **C** unfavorable, lowering the reactivity.

Further investigation of the substrate scope is shown in Figure 2. Anthracene derivative **6h** was obtained in good yield (85%). It is notable that excellent chemical yield with low catalyst loading could be achieved in the case of **6i** (96% with 0.5 mol %). This was mainly due to the cooperative electronic assistance from the π orbital of the benzene ring and the σ^{C-H} orbital of the adjacent methyl group (hyperconjugation). Diastereoselective reaction was also attainable, giving desired tetracycle **6j** in good yield with fairly high selectivity (81%, cis/trans = 6.4/1).[12,13] This stereoselective transformation underscores the synthetic potential of the present methodology.

In summary, an $Sc(OTf)_3$-catalyzed internal redox process from simple phenethyl derivatives was achieved. We have found that the reactivity was strongly affected by the electronic nature of the aromatic group adjacent to the C–H bond, and the desired 3-aryltetralins were obtained in excellent chemical yields with low catalyst loadings (as low as 0.5 mol %). It is worthy of note

that the desired tetralines were obtained in good to excellent chemical yields even with low-reactive substrates (Ar = *p*-chlorophenyl or mesityl). The results described here offer important information for rationalizing the reactivity of the benzylic hydride shift/cyclization sequence.

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13 Due to the fixed configuration of the C-10 carbon, the nucleophilic attack mainly occurred from the same face of the aromatic ring in the cationic intermediate to afford *cis*-**6j**.

