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Transition-Metal-Free Self-Hydrogen-Transferring Allylic Isomerization

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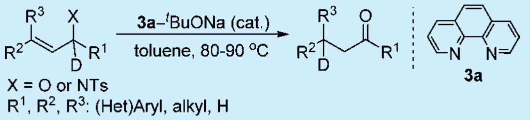
Supporting Information

ABSTRACT: Phenanthroline and *tert*-butoxide have been established as powerful radical initiators in reactions such as the $S_{RN}1$-type coupling reactions due to the cooperation of large heteroarenes and a special feature of *tert*-butoxide. The first phenanthroline-*tert*-butoxide-catalyzed transition-metal-free allylic isomerization is described. The resulting ketones are key intermediates for indenes. The control experiments rule out the base-promoted allylic anion pathway. The radical pathway is supported by experimental evidence that includes kinetic study, kinetic isotope effect, isotope-labeling experiments, trapping experiments, and EPR experiments.



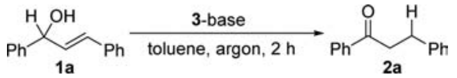
Transition-metal-free radical reactions such as $S_{RN}1$-type reactions have experienced a revival in recent years.[1−3] Besides $S_{RN}1$-type reactions, other radical reactions have also been reported.[4] The self-hydrogen transferring rearrangement and coupling reactions have already proven to be powerful approaches in organic synthesis.[5] Transition metals such as Rh, Ru, Ir, and Pd have been found to be necessary as catalysts for the allylic isomerization.[6−11] To date, the radical transition-metal-free isomerization of allylic alcohol has not yet been reported.

In the transition-metal-catalyzed isomerization of allylic alcohols, bases were normally found to be essential. We noted that a catalytic amount of 1,10-phenanthroline (**3a**) and ^{t}BuONa could catalyze the isomerization of **1a** to **2a** (Table 1, entries 1−3).[12−14] 1,10-Phenanthroline, which was normally considered a ligand, is essential in this reaction (entries 2 and 3). However, large heteroaromatic rings such as **3a** have proven to be good radical initiators in the presence of ^{t}BuONa.[2] By screening the reaction conditions, **3a**-^{t}BuONa (10 mol %) at 80 °C was chosen as the catalyst for the standard conditions in allylic isomerization (entry 7). The effect of transition metal traces was ruled out by ICP-AES analysis.

After establishing standard reaction conditions, the scope of this isomerization was investigated. First, various allylic alcohols with internal C═C bonds were examined. Several (hetero)aryl allylic alcohols have been subjected to the isomerization conditions, and generally high yields were obtained (Table 2). For example, allylic alcohols bearing styryl or 2-pyridyl groups gave the corresponding products **2c** or **2k** in high yields (entries 3 and 11). The 3-substitution on an allylic alcohol resulted in reducing the reaction rate due to the steric hindrance (entry 12). Next, various allylic alcohols bearing terminal C═C bonds were investigated. Generally, high yields were achieved. For example, pyridyl ketone **2s** was obtained in 84% yield (entry 19), which is comparable to that of **2k**. Ketones **2** are precursors for indenes. For example, **1a** was first isomerized to intermediate **2a**, followed by the annulation promoted by TfOH to afford indene **5a** in high yields (eq 1).

The isomerization of allylic amines has also been explored.[15] Amines **4a−4c** were subjected to the reaction conditions, and the corresponding ketones were obtained in high yields (Scheme 1). Imines were not observed in the reaction mixture.

Table 1. Reaction Conditions[a]



entry	base (mol %)	**3** (mol %)	temp (°C)	conv (%)[b]
1	–	**3a** (5)	90	0
2	^{t}BuONa (5)	–	90	9
3	^{t}BuONa (5)	**3a** (5)	90	97
4	^{t}BuONa (5)	**3b** (5)	90	84
5	^{t}BuONa (5)	**3c** (5)	90	17
6	^{t}BuONa (5)	**3d** (5)	90	15
7	^{t}BuONa (10)	**3a** (10)	80	96

[a]Reaction conditions: **1a** (0.5 mmol), toluene (1 mL), argon. [b]Determined by ^{1}H NMR.

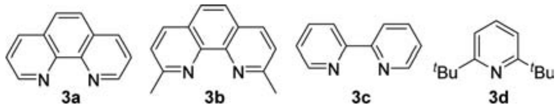


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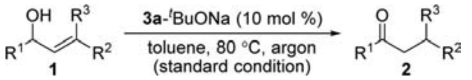
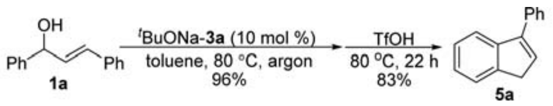
Table 2. Isomerization of Allylic Alcohols



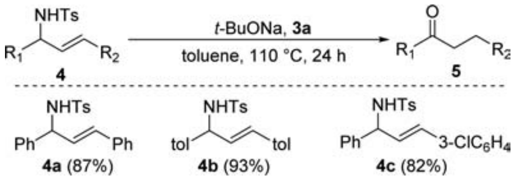
entry	R^1	R^2	R^3	**2**	*t*(h)	**2**(%)[a]
1	Ph	Ph	H	**2a**	1	96
2	Ph	4-FPh	H	**2b**	3	86
3[b]	Ph		H	**2c**	4	83
4	4-ClPh	Ph	H	**2d**	2	86
5	3-ClPh	Ph	H	**2e**	1	93
6[b]	4-MeOPh	Ph	H	**2f**	3	77
7[b]	4-MePh	Ph	H	**2g**	1	78
8[b]	4-MePh	4-MePh	H	**2h**	1	78
9[b]	4-MePh	4-FPh	H	**2i**	2	81
10	4-MePh	4-CF_3Ph	H	**2j**	2	95
11	Ph	2-Py	H	**2k**	3	86
12[b,c]	Ph	Ph	Me	**2l**	6	64
13[c,d]	*c*-propyl	Ph	H	**2m**	3	72
14[c,e]	*c*-Hexyl	Ph	H	**2n**	4	49
15[b]	3-ClPh	H	H	**2o**	3	80
16[d]	4-MePh	H	H	**2p**	4	74
17[b]	4-CF_3Ph	H	H	**2q**	2	88
18	2-Naph	H	H	**2r**	4	80
19[b]	2-Py	H	H	**2s**	1	84
20[b]	4-ClPh	H	H	**2t**	3	71

[a] Isolated yield. [b] ^{t}BuONa (20 mol %), **3a** (20 mol %). [c] At 110 °C. [d] ^{t}BuONa (50 mol %), **3a** (20 mol %). [e] ^{t}BuONa (50 mol %), **3a** (20 mol %).

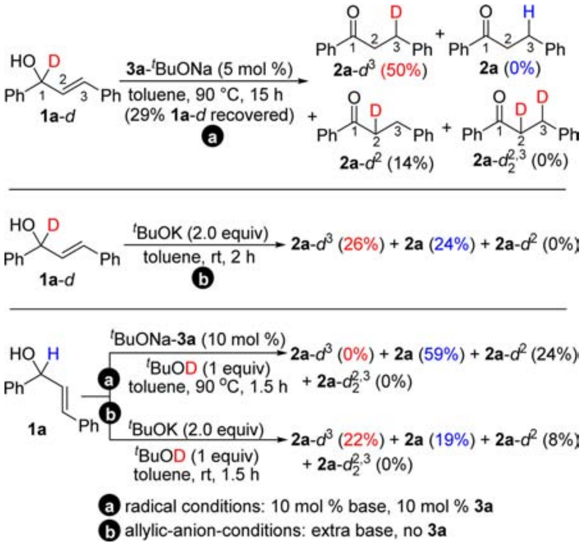


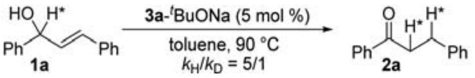
(1)

Scheme 1. Isomerization of Allylic Amines to Ketones



Scheme 2. Deuterium Labeling Experiments





(2)

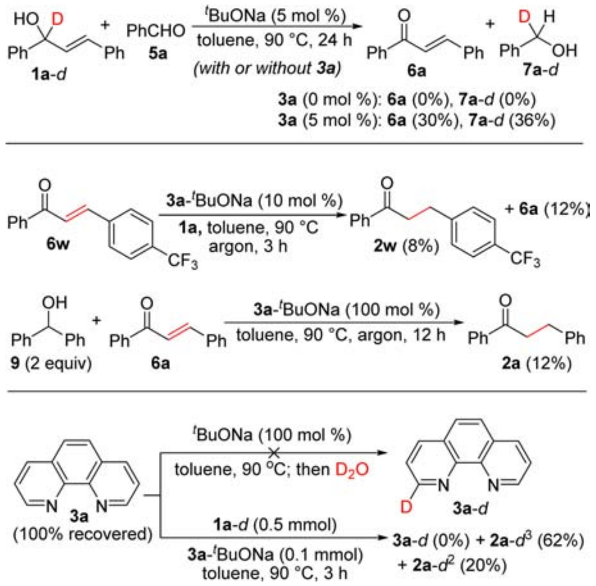
A kinetic isotope effect of 5/1 was established (eq 2), suggesting the C−H bond cleavage step probably to be the rate-determining step. The hydrides were relocated in either the 3- or 2-position in a ratio of 3.6:1, rather than only the 3-position as what has been reported in the metal-catalyzed version (Scheme 2). The deuteration experiments show that only monodeuterated products (**2a**-d^3 and **2a**-d^2) were observed. If **2a**-d^2 generated from deprotonation−reprotonation of product **2a**, the dideuterated product [**2a**-$d_2^{2,3}$] should also been observed. However, when **1a**-*d* was treated with 2 equiv of ^{t}BuOK without **3a**, a 1:1 mixture of **2a** and **2a**-d^3 was obtained.[13] In the cross deuteration experiments, **1a** was subjected to radical reaction conditions in the presence of 1 equiv of ^{t}BuOD and only **2a** was obtained in 59% yield without the observation of **2a**-d^3. When **1a** was treated with 2 equiv of ^{t}BuOK without **3a** under allylic-anion conditions in the presence of ^{t}BuOD, the nearly 1:1 mixture of **2a** and **2a**-d^3 was obtained. These findings directly show that the reaction catalyzed by **3a**-^{t}BuONa is different from that promoted by a stoichiometric base. The deuterium in the 3-position of **2a** under the former conditions thus should be transferred from **1a** itself other than ^{t}BuOH or the OH-group of **1a**.

Compared to the very low conversion obtained without **3a**, the reaction in the presence of **3a** gave the isomerization product **2a** in excellent yield (Table 1, entries 2 and 3). To explore the form of hydrogen in this isomerization, **1a**-*d* was subjected to the catalytic isomerization conditions in the presence of PhCHO under isomerization conditions and an almost 1:1 ratio of chalcone **6a** and **7a**-*d* was found, where **1a** and benzaldehyde worked as the hydride donor and acceptor, respectively. In contrast, without **3a** there was no **6a** or **7a** found. This result suggests that the hydrogen atom should be transferred via the form of a hydrogen atom or hydride other than a proton. The hydrogen transfer between **1a** and **6w** further proved this (Scheme 3).

In previous work, a dimer of **3a** was discussed as the catalytically active species.[3b] Actually, when **3b** (both sides are blocked by methyl groups) was used instead of **3a**, the isomerization of **1a** still works very well. The treatment of **3a** with 1 equiv of ^{t}BuONa and D_2O gave no deuterated **3a** (Scheme 3). Similarly, after the catalytic isomerization of **1a**, **3a** was quantitatively recovered as well. All of the above-mentioned information shows that **3a** itself other than its dimer works as a necessary catalytically active species.

In the kinetic study, a first-order dependence of initial rate on either ^{t}BuONa or **3a** was established, indicating that both ^{t}BuONa and **3a** are necessary to catalyze this isomerization reaction (Figure 1A). The first-order dependence of initial rate on **3a** directly illustrates the participation of **3a** in the catalysis as a catalyst rather than a chelating reagent for the Na^+ cation. The first-order dependence of initial rate on ^{t}BuONa shows that ^{t}BuO$^-$ is directly involved in the catalysis. The similar

Scheme 3. Hydrogen/Hydride v.s. Proton



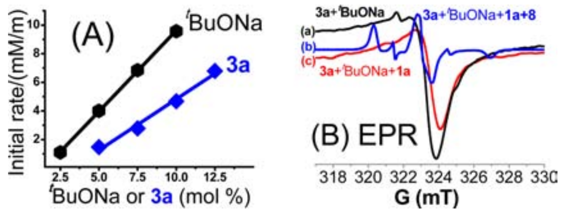
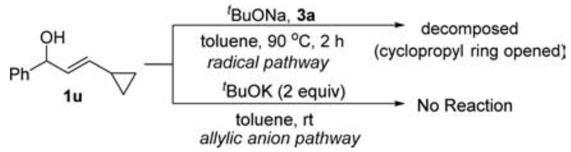


Figure 1. Kinetic study and EPR experiments. First-order dependence of initial rate on ^{t}BuONa and **3a**, respectively.

slopes of **3a** and ^{t}BuONa in Figure 1A indicate that these two species should work cooperatively.

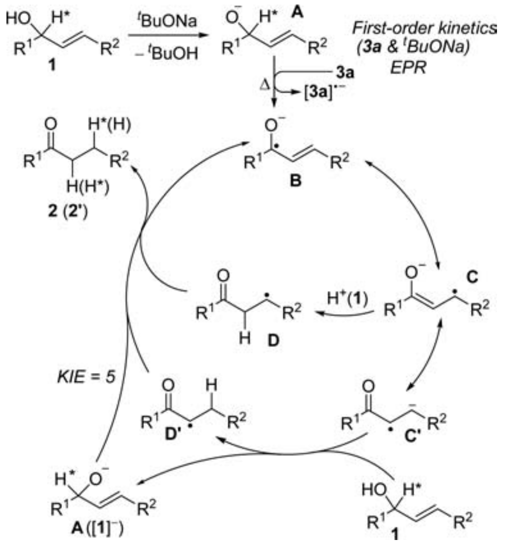
Radical scavengers such as *N*-^{t}Bu phenyl nitrone **8** and TEMPO inhibit the isomerization. TEMPO was recovered without change in the presence of ^{t}BuONa. A radical process was further confirmed by **1u** bearing a cyclopropyl ring as a radical clock, which decomposed in the presence of **3a**-^{t}BuONa but remained unchanged in excess ^{t}BuOK (Scheme 4). The existence of the radical species was further proven by the EPR experiment (Figure 1B). The mixture of **3a** and ^{t}BuONa gave radical signals (a and b) with substrate **1a**, indicating **3a** and alkoxide can produce a radical.[1,2] This radical could be trapped by *N*-^{t}Bu phenyl nitrone (signal c).

Scheme 4. Radical Trapping Experiments



Based on the systematic experimental evidence, a plausible working model is proposed (Scheme 5). The deprotonation of **1** with ^{t}BuONa affords intermediate **A**, followed by generation of radical anion **B** promoted by phenanthroline **3a**. Radical anion **B** further transforms to **C** by resonance. **C** and its resonance structure **C′** are both protonated with the hydroxyl group of **1** to afford **D** and **D′** with the regeneration of **A**. **D** and **D′** easily scrabble a hydrogen atom from **A** to regenerate **B**.

Scheme 5. Working Model



In this working model, either the 2- and 3-position can be deuterated, which is consistent with the deuterium-labeling experiments.

Alternatively, a base-promoted working model via an allylic-anion pathway might be proposed to explain the deuteration on either the 2- or 3-position.[12] In a few previous base-promoted allylic isomerizations, an excess of strong bases must be engaged and various reaction working models were proposed with no experimental evidence.[12−14] The catalytic amount of ^{t}BuONa (normally 5−10 mol %) will first deprotonate the more acidic OH-group of starting materials; thus, there is no extra base to deprotonate the less acidic *α*-H of **1a**. In fact, even when an excess amount of ^{t}BuONa was added, only **1a**-Na was observed by ^{1}H NMR. The existence of **2a**-d^2 could be argued by a base-promoted deuterium−proton exchange reaction of product **2a**. The enolate of **2a** cannot directly scrabble a proton from the less acidic *α*-*d* of **1a**-Na. In addition, the allylic-anion pathway could not explain the essential catalytic role of **3a**. Therefore, the base-promoted model should be ruled out.

In conclusion, a highly efficient phenanthroline-*tert*-butoxide-catalyzed transition-metal-free allylic isomerization of alcohols and amines has been developed. On the basis of systematic experimental study including kinetic study, EPR, deuterium-labeling experiments, and control experiments, a plausible reaction mechanism involving a radical pathway has been proposed. This phenanthroline-*tert*-butoxide-catalyzed isomerization provided a new approach for self-hydrogen transferring isomerization of allylic alcohols and allylic amines using as low as 5 mol % of **3a**-^{t}BuONa. We anticipate that this approach could be applied in other organic transformations, especially in a transition-metal-free process via a radical pathway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03124.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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