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Tandem O−H Insertion/[1,3]-Alkyl Shift of Rhodium Azavinyl Carbenoids with Benzylic Alcohols: A Route To Convert C−OH Bonds into C−C Bonds

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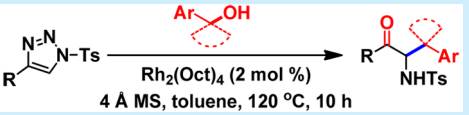
Supporting Information

ABSTRACT: Alcohols are among the most abundant and commonly used organic feedstock in industrial processes and academic research. The first tandem O−H insertion/[1,3]-alkyl shift reaction reported is between benzylic alcohols and rhodium azavinyl carbenoids derived from *N*-sulfonyl-1,2,3-triazoles, which provides a strategically novel way of cleaving C−OH bonds and forming C−C bonds. The substrate scope is broad, capable of covering 1°-, 2°-, and 3°-benzylic alcohols. Moreover, it constitutes a new and powerful synthetic method for constructing α-aminoketones. Mechanistic studies suggest that a [1,3]-alkyl shift of oxonium ylides is responsible for cleavage of the C−OH bonds.



Carbon−carbon bond-forming reactions are prevalent and of fundamental significance in the field of synthetic chemistry.[1] The utility of the "green" alcohols as the starting materials for forming carbon−carbon bonds is attracting massive attention, because they are among the most abundant, inexpensive, and environmentally benign chemicals. Instead of the traditional carbocation strategy,[2] dependence on the transition-metal catalysis has significantly expanded the horizon of this area in the past few decades. Many impressive strategies have emerged, for example, the ruthenium-catalyzed dehydrative C−H functionalization of alcohols,[3] the TM-catalyzed arylation/alkylation of benzyl alcohols with Grignard or arylboronic reagents,[4] the TM-catalyzed *C*-alkylation of ketones and secondary alcohols with alcohols by the borrowing of a hydrogen process,[5] sequential O−H insertion/[3,3]- or [2,3]-sigmatropic rearrangement of rhodium carbenoids with alcohols,[6,7] and the palladium-catalyzed allylic alkylation of ketones with allylic alcohols.[8] While these studies provide variable routes to exploit alcohols in C−C bond-forming reactions, the limited scope of alcohol substrates still remains a major drawback in applying these methods in synthetic practice.[3−8] Consequently, development of new alcohol-based C−C bond-forming reactions, especially those expanding the repertoire of the alcohols that can be used, is still a long-standing research goal.

Rhodium carbenoid insertion into O−H bonds, followed by sigmatropic rearrangement, has received considerable attention as an effective method for the cleavage of C−OH bonds to form C−C bonds.[6,7,9] These reactions are believed to proceed, mechanistically, via tandem formation of an oxonium ylide and sigmatropic rearrangement. Both [3,3]- and [2,3]-sigmatropic rearrangements have been utilized in such a reaction sequence, especially with applications in natural product synthesis.[6a,b,10] The groups of Wood,[6a−d] Mukarami,[6e] Fokin,[6f] and Lee[6g] have made leading contributions to the development of methods for O−H insertion/[3,3]-sigmatropic rearrangement (Figure 1a),

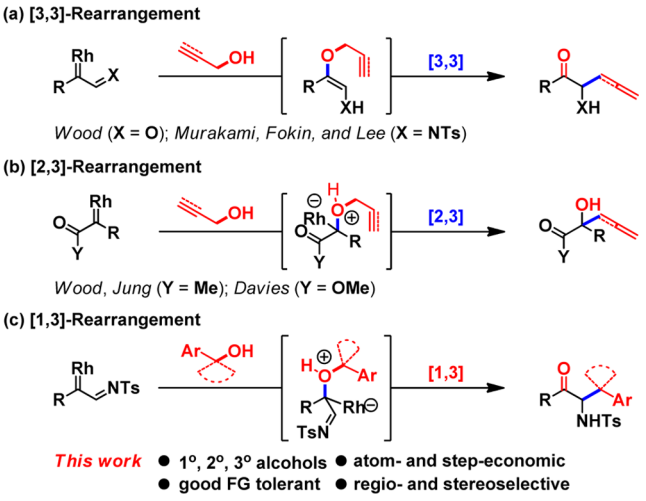


Figure 1. Tandem O−H insertion/sigmatropic rearrangement of rhodium carbenoids with alcohols.

while the [2,3]-sigmatropic rearrangement has been mainly exploited by Jung,[7a] Wood,[7b] and Davies[7c−h] (Figure 1b). Apparently, the dependence of either allylic or propargylic alcohols is necessary in all of these reactions. Therefore, expansion of this elegant strategy to general alcohols remains a hard task. The thermal [1,3]-alkyl shift of vinyl ethers was known in 1896 in the seminal report of Claisen[11] and recently

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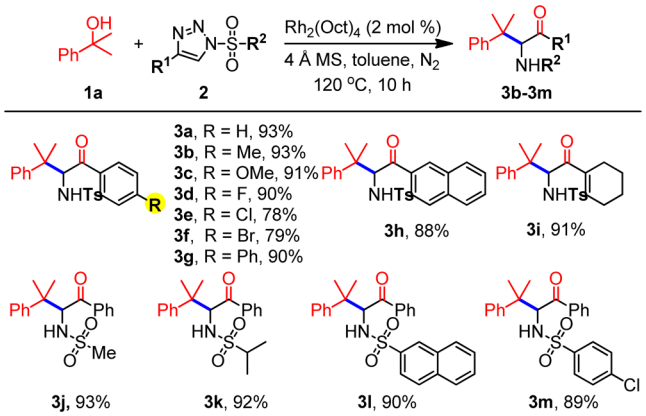
further developed by means of transition metal catalysis[12] or Brønsted acid catalysis.[13] In comparison with [3,3]- and [2,3]-sigmatropic rearrangement, the [1,3]-alkyl migration is less developed.[9] Here, we for the first time have incorporated a [1,3]-alkyl shift into the C−OH bond cleavage of alcohols by a strategically novel O−H insertion/[1,3]-alkyl shift reaction of benzylic alcohols with rhodium azavinyl carbenoids which were derived from *N*-sulfonyl-1,2,3-triazoles (Figure 1c).[14] Notably, 1°-, 2°-, and 3°-alcohols are all suitable for this reaction. To the best of our knowledge, this is the first [1,3]-alkyl shift reaction developed directly starting from alcohols. In addition, this reaction constitutes a new and powerful synthetic method for the synthesis of α-aminoketones.[15]

After identifying the optimal conditions (for details, please see the Supporting Information), we then explored the reaction scope with regard to *N*-sulfonyl-1,2,3-triazoles (Scheme 1). *N*-

Scheme 1. Scope of *N*-Sulfonyl-1,2,3-triazoles[a,b]

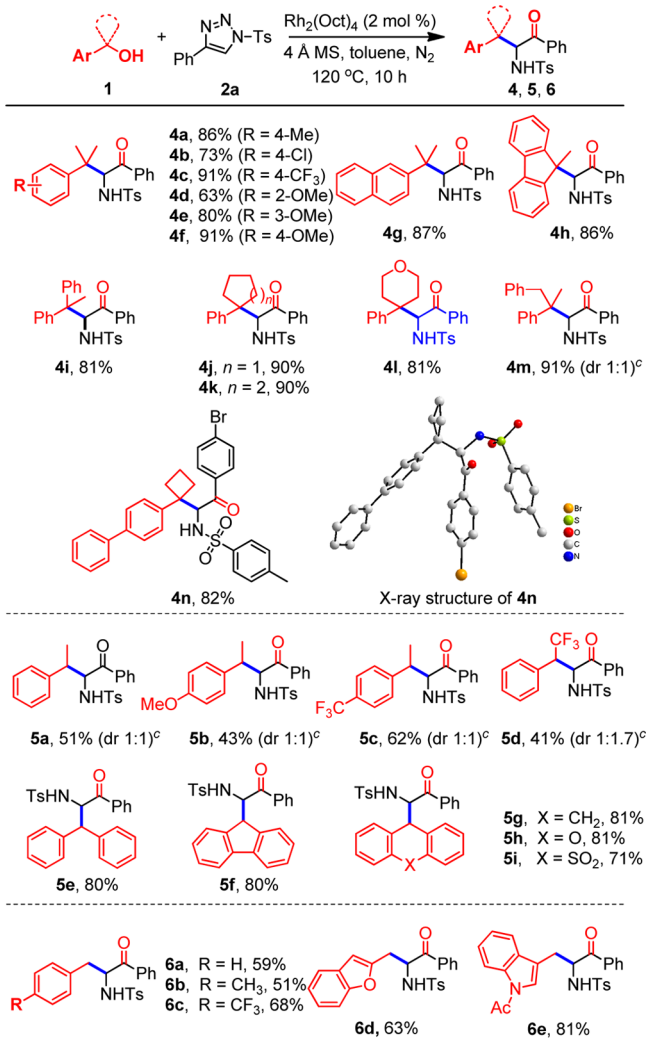


[a]Conditions: **1** (0.75 mmol), **2** (0.5 mmol), $Rh_2(Oct)_4$ (2 mol %), 4 Å MS (100 mg), toluene (3 mL), 120 °C, under N_2, 10 h. [b]Isolated yields.

Tosyl-1,2,3-triazoles substituted at C4 with a phenyl ring containing electron-donating or -withdrawing groups all afforded high yields of products (**3a**−**3g**, 78−93%). *N*-Tosyl-1,2,3-triazoles containing a fused aryl ring, such as naphthyl (**3h**, 88%), or an aliphatic cyclic system, such as cyclohexenyl (**3i**, 91%), also smoothly participated in the target reaction. Furthermore, variation of the sulfonyl units of 1,2,3-triazoles did not affect the reaction efficacy (**3j**−**3m**, 89−93% yields).

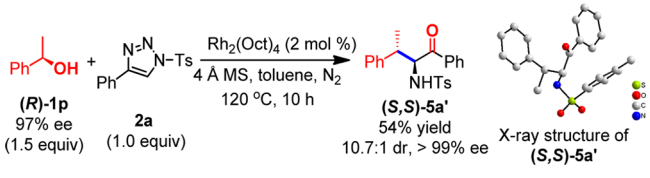
We next explored the scope of alcohols. As illustrated in Scheme 2, 3°-benzylic alcohols with electron-withdrawing (**4b** and **4c**) and electron-donating groups at the *o*/*m*/*p* positions were well tolerated (**4a**, **4d**−**4f**, 63−91%). Bulky tertiary alcohols, such as naphthyl (**4g**), fluorenyl (**4h**), and 1,1-diphenylethanol (**4i**), also smoothly underwent the target reaction to offer excellent product yields (81−92%). Furthermore, benzylic alcohols bearing aliphatic rings, such as cyclopentane (**4j**), cyclohexane (**4k**), and cyclobutane (**4n**), proved to be suitable. The structure of **4n** was further confirmed by single-crystal X-ray analysis. Similarly, a range of 2°-benzylic alcohols were reactive and resulted in the corresponding products in moderate-to-high yields (**5a**−**5i**, 41−81%). Next, the reaction scope was expanded to 1°-benzylic alcohols, which delivered the desired products (**6a**−**6c**), albeit in slightly decreased yields (51−68%). Alcohols derived from benzofuran (**6d**, 63%) and indole (**6e**, 81%) were also suitable for the target reaction.

Scheme 2. Scope of Alcohols[a]



[a]Conditions: **1** (0.75 mmol), **2** (0.5 mmol), $Rh_2(Oct)_4$ (2 mol %), 4 Å MS (100 mg), toluene (3 mL), 120 °C, under N_2, 10 h. [b]Isolated yields. [c]The dr values were identified by HPLC analysis.

To develop an asymmetric version of this reaction, we tested a series of chiral rhodium catalysts, including Rh_2(*S*-BNP)$_4$,[16] Rh_2(*S*-DOSP)$_4$,[17] and Rh_2(*S*-nttl)$_4$,[18] but no satisfying results were obtained. Therefore, we considered achieving high stereoselectivity by chiral induction using a chiral alcohol. Pleasingly, the alcohol (*R*)-**1p** (97% ee) produced the product **5a′** with high dr and ee values (dr = 10.7:1, ee >99%).



All α-aminoketone products structurally contained a benzylic motif at the α-carbon, thus providing a handle for further synthetic derivation. We investigated the cyclization under various conditions and eventually achieved the conversion of these α-aminoketones into tetrahydroisoquinolines **7** via reaction with dimethoxymethane in the presence of H_2SO_4 at 90 °C (Scheme 3).[19] The isoquinoline structure was

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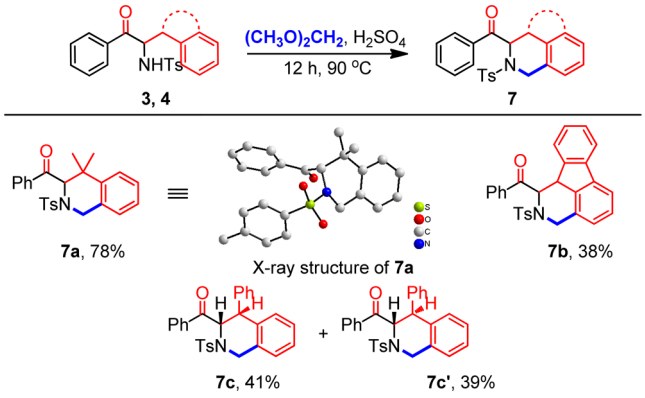
Scheme 3. Synthetic Utility of the Products[a,b]

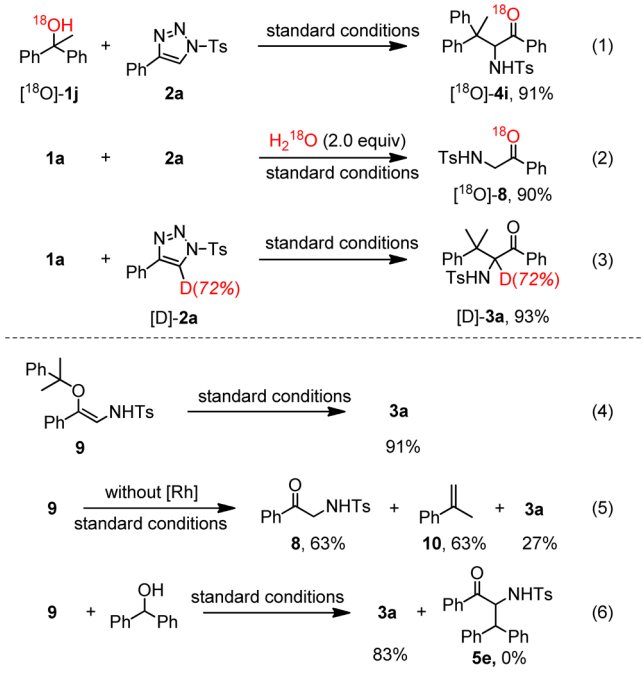


[a]Reaction conditions: **3** (0.5 mmol), dimethoxymethane (0.5 mL), H_2SO_4 (0.5 mL) at 90 °C. [b]Isolated yields.

unambiguously confirmed by single-crystal X-ray analysis of product **7a**. Notably, 1,2,3,4-tetrahydroisoquinoline is a privileged structure in many biological and medicinal compounds such as Solifenacin, a commercial antimuscarinic drug.[20]

We performed extensive experiments to elucidate the reaction mechanism (Scheme 4). First, we sought to identify

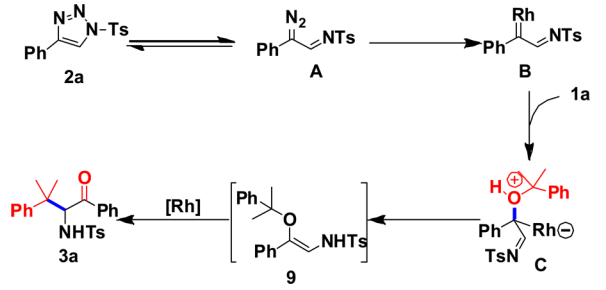
Scheme 4. Mechanistic Investigations



the source of the oxygen and hydrogen atoms in the products. A reaction using the oxygen isotope-labeled alcohol [^{18}O]-**1j** gives β-aminoketone [^{18}O]-**4i** (eq 1). Trace amount of water in the solvent was ruled out as the source of the oxygen atom through an experiment with $H_2{}^{18}O$, which afforded a H_2O-insertion product, [^{18}O]-**8**, as in Mukarami's report (eq 2).[21] These results suggest that the hydroxyl group of the alcohol is the source of the oxygen atom in the β-aminoketones. A reaction with deuterium-labeled triazole [D]-**2a** offered product [D]-**3a**, and equivalent quantities of deuterium were observed in both compounds (eq 3). Control experiments validated the involvement of the rhodium catalyst in the [1,3]-sigmatropic rearrangement step (eqs 4–6). The β-oxyenamine **9** was prepared separately and then subjected to the standard reaction conditions, which delivered **3a** in 91% yield, whereas the reaction without the rhodium catalyst afforded the thermal dissociation products **8** (63%) and **10** (63%), along with **3a** in small amounts (23%). Finally, a competition experiment was conducted by adding diphenylmethanol to the rearrangement reaction of **9**, which led to **3a** in 83% yield, without formation of the cross-reaction product **5e**. This result further suggests that the rhodium-catalyzed rearrangement of intermediate **9** occurs through an intramolecular process.

Based on these results and related precedents,[6,7,12] a plausible mechanism is proposed (Scheme 5). Initially, *N*-sulfonyl-1,2,3-

Scheme 5. Plausible Mechanism



triazole **2a** is converted to the α-diazo imine intermediate **A** via ring–chain tautomerization. This conversion is followed by reaction with the rhodium catalyst to afford α-imino rhodium carbenoid intermediate **B**, along with release of molecular nitrogen. Alcohol **1a** then adds to the electrophilic carbene center of **B** to generate zwitterionic intermediate **C**. Then, intermediate **C** released the rhodium to form the vinyl ether intermediate **9** which then undergoes a rhodium-induced [1,3]-alkyl shift to give product **3a**.[12]

In conclusion, we have developed a practical, general method for the construction of C–C bonds using alcohols and rhodium carbenoids, generated in situ from *N*-sulfonyl-1,2,3-triazoles. In contrast to the [2,3]-alkyl shifts typically observed with conventional rhodium carbenoids derived from α-diazocarbonyl precursors, and the [3,3]-alkyl shifts observed for rhodium azavinyl carbenoids derived from *N*-sulfonyl-1,2,3-triazoles, these reactions proceed via an unusual formal [1,3]-alkyl migration pathway. In addition, this atom-economic reaction provides a useful tool for the synthesis of a range of densely functionalized α-aminoketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02459.

Experimental procedures and spectra copies (PDF)

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Notes

The authors declare no competing financial interest.

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