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Pyridinyl Directed Alkenylation with Olefins via Rh(III)-Catalyzed C−C Bond Cleavage of Secondary Arylmethanols

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Supporting Information

ABSTRACT: Novel C−C bond cleavage of secondary alcohols through Rh(III)-catalyzed β-carbon elimination directed by a pyridinyl group is reported. A five-membered rhodacycle is proposed as a key intermediate, which undergoes further alkenylation with various olefins. This novel transformation shows high efficiency along with excellent selectivity in mild conditions. A wide range of functionalities are compatible. This study offers a new strategy to carry out C−C bond activation.

Transition-metal-catalyzed C−C bond cleavage has attracted much attention and emerged as a tremendous challenge in recent years.[1] Typically, in order to facilitate C−C bond cleavage, two basic strategies are employed. One is to use strained three- or four-membered-ring compounds, which undergo oxidative cyclometalation, forming more stable metallacyclic complexes, to release ring strain.[2] On the other hand, for the reaction of unstrained molecules, special driving forces for C−C bond cleavage are required to generate stable intermediates.[3,4] For example, tertiary alcohols have been successfully applied as substrates for catalytic selective C−C bond cleavage via β-carbon elimination, forming an organometallic intermediate and a ketone.[5] In comparison, catalytic C−C bond cleavage of secondary alcohols has rarely been reported.[6,7] Herein we demonstrate an unprecedented strategy to facilitate Rh(III)-catalyzed selective C−C bond activation of secondary alcohols directed by a pyridinyl group followed by C−C bond formation.

The major challenge remaining in cleaving the C−C bond adjacent to the hydroxyl group of secondary alcohols is to avoid hydrogen transfer, which is the typical transformation of secondary alcohols in the presence/absence of external oxidants (Scheme 1, path a).[8] In our design, a proper substrate for C−C bond cleavage should satisfy geometrical requirements by generating a thermodynamically favorable metallacyclic complex as the key intermediate, which has also been demonstrated in C−H activation.[9] The generated organometallic intermediates can potentially facilitate sequential functionalizations, such as olefination (Scheme 1, path b). This strategy offers a new concept for C−C bond activation.

Scheme 1. Rational Design To Form a C−M Intermediate through β-Carbon Elimination

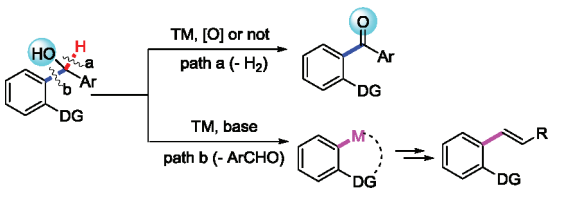
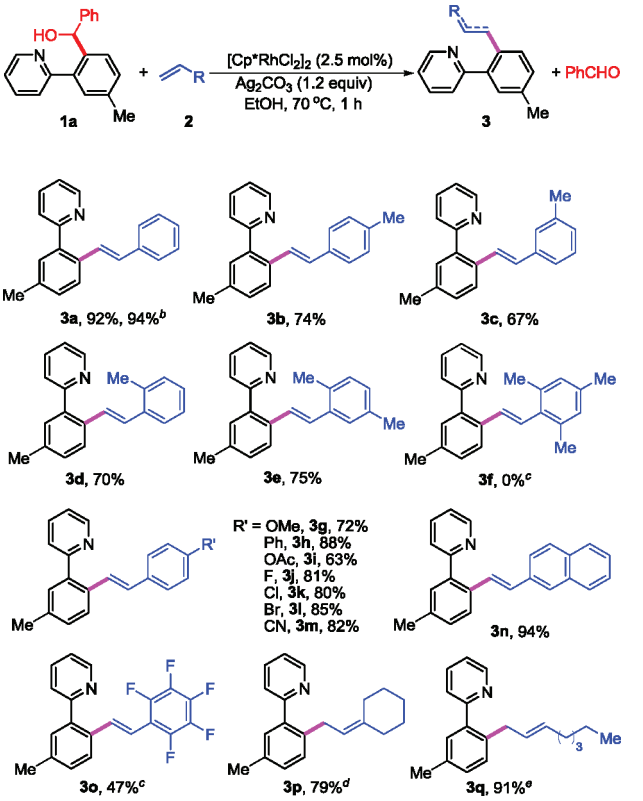


Table 1. Rh(III)-Catalyzed Alkenylation of 1a by Cross-Coupling with Different Alkenes through C−C Bond Cleavage[a]

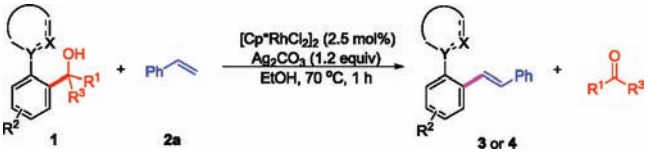


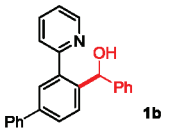
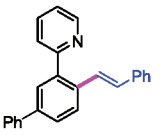
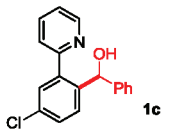
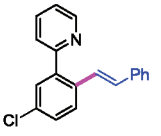
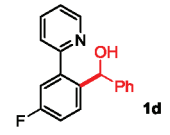
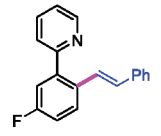
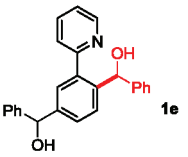
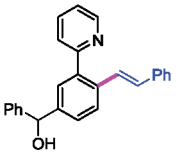
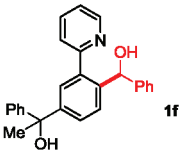
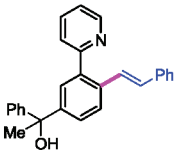
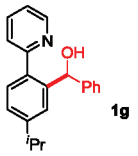
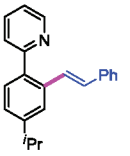
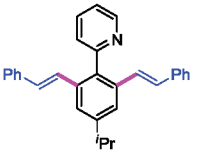
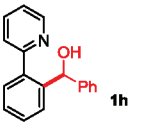
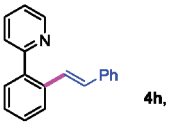
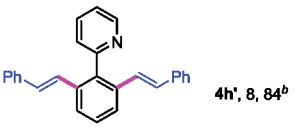
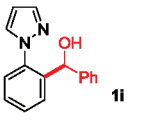
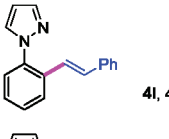
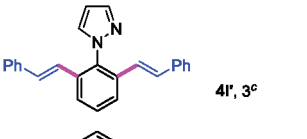
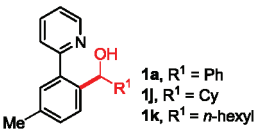
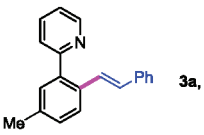
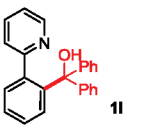
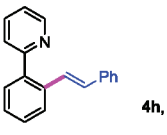
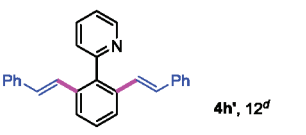
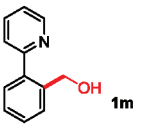
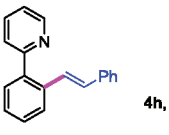
[a] Reactions conducted with 0.25 mmol of alcohol substrate **1a**, 2.5 mol % of $[Cp^*RhCl_2]_2$ as catalyst, 1.2 equiv of alkene, 1.2 equiv of Ag_2CO_3, and 1.0 mL of EtOH as solvent unless otherwise noted; isolated yields are given. [b] Reaction performed on 1.0 mmol scale. [c] Reaction ran for 3 h. [d] Reaction ran for 12 h. [e] E/Z = 6.7:1.

Received: June 7, 2011
Published: August 30, 2011

dx.doi.org/10.1021/ja205228y | J. Am. Chem. Soc. 2011, 133, 15244–15247

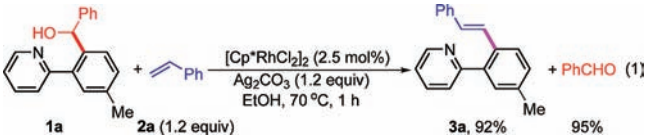
Table 2. Rh(III)-Catalyzed Alkenylation of Various Alcohols 1 by Cross-Coupling with Styrene through C−C Bond Cleavage[a]



entry	substrate	product, yield (%)
1	 1b	 4b, 80
2	 1c	 4c, 47
3	 1d	 4d, 33
4	 1e	 4e, 72
5	 1f	 4f, 85
6	 1g	 4g, 66
		 4g', 9
7	 1h	 4h, 72, 5[b]
		 4h', 8, 84[b]
8	 1i	 4l, 40[c]
		 4l', 3[c]
9	 1a, R[1] = Ph 1j, R[1] = Cy 1k, R[1] = *n*-hexyl	 3a, 92 75 60
10	 1l	 4h, 69[d]
		 4h', 12[d]
11	 1m	 4h, 0

[a] Reactions conducted with 0.25 mmol of alcohol substrate **1**, 2.5 mol % of $[Cp^*RhCl_2]_2$ as catalyst, 1.2 equiv of styrene, 1.2 equiv of Ag_2CO_3, and 1.0 mL of EtOH as solvent unless otherwise noted. Isolated yields are given. [b] 3.0 equiv each of styrene and Ag_2CO_3 were used. [c] Reaction ran for 5 h. [d] Reaction ran for 4 h.

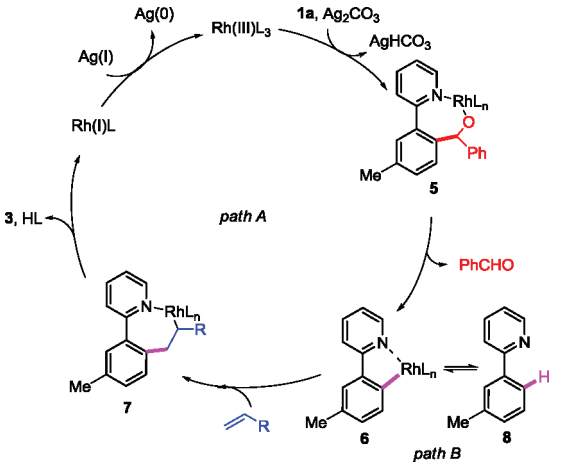
With this idea in mind, we initiated our study by examining the reactivity of 1-phenyl-(4-methyl-2-(pyridin-2-yl))benzyl alcohol (**1a**) with styrene (**2a**). After a series of screening, we found that employing $[Cp^*RhCl_2]_2$ ($Cp^* = \eta^5$-pentamethylcyclopentadienyl) as the catalyst, Ag_2CO_3 as the oxidant, and EtOH as the solvent afforded the desired alkenylated product **3a** in 92% isolated yield, along with 95% NMR yield of benzaldehyde (eq 1).[10]



Under the optimized conditions in hand, we explored the substrate scope of olefins (Table 1). Reaction with styrene provided satisfactory results, even on a larger scale (**3a**). Styrene bearing methyl substituents at different positions on the phenyl ring afforded good yields (**3b**−**e**). However, sterically hindered 2,4,6-trimethylstyrene inhibited this transformation (**3f**). Moreover, both electron-rich (**3g**−**i**) and electron-deficient styrene derivatives (**3j**−**m**) were excellent coupling partners. Notably,

dx.doi.org/10.1021/ja205228y |*J. Am. Chem. Soc.* 2011, 133, 15244–15247

Scheme 2. Plausible Mechanism for Rh(III)-Catalyzed C−C Bond Cleavage/Alkenylation of 1a with Olefins



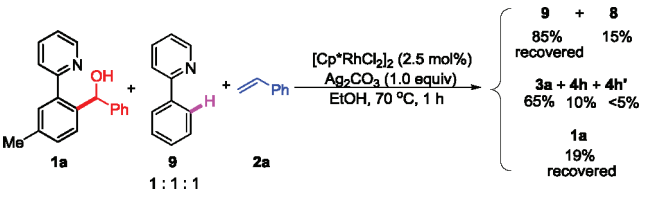
halogen substituents were well tolerated (**3k**,**l**), providing opportunities for further functionalization. In addition, 2-vinylnaphthalene also showed excellent reactivity (**3n**). Last, 2,3,4,5,6-pentafluorostyrene was tested, and the desired product was obtained albeit in lower yield (**3o**). Notably, aliphatic terminal alkenes, e.g., vinylcyclohexane and 1-octene, both reacted smoothly under this condition, affording double-bond-migrated products in high yields (**3p**,**q**), the result of β-hydride elimination from the other site, lacking π-conjugation from the phenyl ring of styrene substrates.

The substrate scope of alcohols was further investigated (Table 2). To our satisfaction, both electron-donating and -withdrawing groups on the phenyl ring of **1** showed moderate to good compatibility (entries 1−3). Again, halogen groups were tolerated (entry 2). Most importantly and interestingly, a secondary or tertiary alcohol motif at a nonchelating position remained intact in the reaction (entries 4 and 5), which exhibited exclusive selectivity controlled by the pyridinyl directing group. Furthermore, by simply adjusting the excess of styrene and oxidant, secondary alcohol substrates with a *para* or no substituent on the phenyl ring provided mono- and dialkenylated products selectively in good yields at 70 °C within 1 h (entries 6 and 7), showing better controllable selectivity than direct C−H activation.[9d] A pyrazolyl group could also be used to direct this Rh(III)-catalyzed C−C bond cleavage reaction (entry 8).[11,12]

A variety of aliphatic-substituted secondary alcohols other than diarylmethanols were examined to test the reactivity. To our delight, secondary alcohols bearing both aryl and aliphatic groups underwent β-C elimination and further alkenylation smoothly, generating aliphatic aldehydes as the byproducts (Table 2, entry 9, **1j**,**k**). Tertiary alcohols also exhibited good reactivity under these conditions (entry 10); however, primary alcohols were not suitable for this sequence of C−C bond cleavage/formation (entry 11).

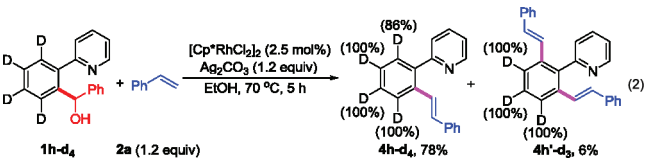
Based on previous studies, the reaction pathway shown in Scheme 2 was proposed. After the initial coordination of Rh(III) catalyst with N and O atoms of **1a**, Ag_2CO_3 might act as a base to facilitate the deprotonation process,[13] promoting β-C elimination to release benzaldehyde and generate five-membered rhodacycle **6**, which further undergoes alkene insertion and β-H elimination to produce the final alkenylated product **3** and Rh(I) species.[9d] The latter was subsequently oxidized by Ag(I) to regenerate Rh(III) species (path A). In fact, a five-membered rhodacyclic complex was

Scheme 3. Competition of Rh(III)-Catalyzed C−C Bond Cleavage versus C−H Activation



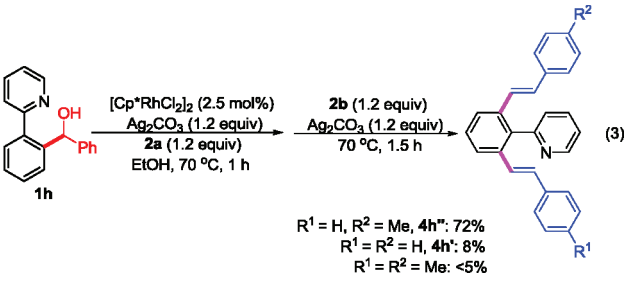
captured by cleaving the C-C bond of **1a** using stoichiometric $[Cp^*RhCl_2]_2$, which also showed excellent catalytic activity.[14]

On the other hand, since 2-*m*-tolylpyridine (**8**) was detected occasionally as a byproduct of the reaction of **1a**, a pathway via sequential protonation of rhodacycle **6**/Rh-catalyzed C−H alkenylation of **8** could also be considered (path B). This hypothesis was supported by a deuterium labeling experiment (eq 2), where partially deuterium labeled product **4h-d_4** was generated from C−D cleavage, as shown in path B.[14]



To distinguish the two pathways, a competition experiment was done, treating of 1 equiv each of alcohol **1a**, 2-phenylpyridine (**9**), and styrene in one pot under the standard reaction conditions, as shown in Scheme 3.[14] The results evidenced that alkenylation from C−C cleavage was much faster than from direct C−H activation. Thus, path A was proposed to be more facile than path B in Scheme 2.

Finally, "dual activation" of secondary alcohol **1h** was achieved by sequential C−C bond cleavage/C−H activation by stepwise addition of styrene (**2a**) and 4-methylstyrene (**2b**) in one pot under mild conditions, with good efficiency and outstanding selectivity (eq 3). This unique activity highlights the potential utility of this C−C cleavage in postsynthetic elaboration of complex natural products. Thus, rationally designed alcohol substrates and their alkenylated products can serve as versatile synthetic intermediates.



In summary, we have developed an unprecedented Rh(III)-catalyzed C−C bond cleavage reaction of secondary diarylmethanols with the assistance of a pyridinyl group through β-C elimination. The formed five-membered rhodacycle undergoes alkenylation through coupling with a variety of terminal alkenes. The pyridinyl group is essential to control the selectivity of C−C bond cleavage via chelation assistance. This novel strategy provides a mild and efficient method for "inert" C−C bond activation, showcasing the viability of late-stage modification of complex molecules toward a diversity-oriented synthesis.

dx.doi.org/10.1021/ja205228y |*J. Am. Chem. Soc.* 2011, 133, 15244–15247

Further studies to find other substrates and investigate alternative transformations are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for alcohol substrates, alkenylated products, mechanistic study experiments, and rhodacyclic intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

Support of this work by NSFC (Nos. 20672006, 20821062, 20832002, 20925207, 21002001, and GZ419) and the "973" Project from the MOST of China (2009CB825300) is gratefully acknowledged. H.L. thanks Zhi-Quan Lei for assistance in the preparation of alcohol substrates.

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(10) For condition screening table and more detailed explanations, see Supporting Information.

(11) The ketone from oxidation of **1i** was detected as the main byproduct.

(12) Other directing groups such as acetamide did not work; using a phenyl group instead of a pyridinyl group also afforded no C—C cleavage products. These resulted in oxidation of the starting alcohol substrates to the corresponding ketones.

(13) *O*-Silylated substrates, e.g., *O*-TBS-substituted **1a**, did not react in the standard conditions.

(14) For experimental details, see Supporting Information.