Communication

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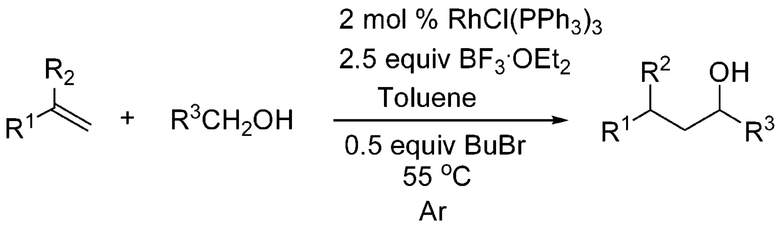

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COMMUNICATIONS

A Reaction for sp^3-sp^3 C−C Bond Formation via Cooperation of Lewis Acid-Promoted/Rh-Catalyzed C−H Bond Activation

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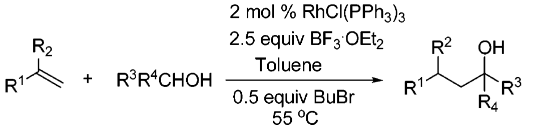
The sp^3-sp^3 C−C bond formation has been one of the most significant but challenging basic subjects in organic chemistry. The effects toward the direct and selective formation of the sp^3-sp^3 C−C bond via C−H bond activation have long been intriguing organic chemists. Since the landmark report of the ruthenium-catalyzed hydroarylation of alkenes by Murai and co-workers,[1] some good pioneering progresses have been achieved in this area.[2] As a continued research in our group on C−C bond formation via C−H bond activation,[3] recently we interestingly found that the combination of $BF_3{\cdot}OEt_2$ with Wilkinson catalyst $RhCl(PPh_3)_3$ could promote effectively a new cross-coupling reaction between the primary aliphatic alcohol and the olefin, which could be developed to a new method for the synthesis of secondary alcohol. To the best of our knowledge, this kind of intermolecular reaction of primary aliphatic alcohols with olefins via Rh-catalyzed/Lewis acid-assisted C−H bond activation has not been reported.[4] The most significant aspect of our work is the discovery that rhodium-catalyzed C−H bond activation of alcohols is feasible under Lewis acid-promoted conditions.

We commenced our studies in the experimental procedure: a mixture of styrene (1 equiv), ethanol (10 equiv), and $RhCl(PPh_3)_3$ (0.02 equiv) in freshly distilled solvent was stirred for 5 h at 55 °C under argon atmosphere. Subsequently, Lewis acid was added to the above reaction system, and the resulting mixture was further stirred for 24 h efficiently. Following this general procedure, various Lewis acids ($TiCl_4$, $Ti(Oi\text{-}Pr)_4$, $CuCl_2$, $BF_3{\cdot}OEt_2$, $BF_3{\cdot}N(n\text{-}Bu)_3$, BEt_3, and $B(Oi\text{-}Pr)_3$) and solvents (benzene, toluene, *n*-hexane, CH_3CN, DME, DMF, and DMSO) were examined (Scheme 1). As a result, the expected 4-phenylbutan-2-ol product could be obtained by use of styrene, ethanol, Wilkinson catalyst ($RhCl(PPh_3)_3$), and $BF_3{\cdot}OEt_2$ in the mole ratios of 1:10:0.02:2.5 in toluene, although the yield was merely 27%. Importantly, it should be noticed that this reaction did not work in the absence of Lewis acid $BF_3{\cdot}OEt_2$. Through further GC−MS analyses, the major byproducts in this reaction proved to mainly come from the Friedel−Crafts reaction between styrene and toluene[5] and, minorly, from the dimerization of styrene.[6] No ether product[7] resulting from the ethanol O−H addition with the olefin double bond was isolated. To optimize this reaction, BuBr (0.5 equiv) as an additive was chosen to suppress the undesired Friedel−Crafts reaction of olefin with toluene, and pleasingly, the good yield of 70% was afforded.

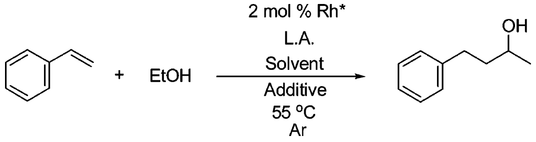
Table 1. Coupling of Alcohols with Olefins[a]



entry	olefin (R^1, R^2)	alcohol (R^3, R^4)	product	yield (%)[b]
1	$R^1 = Ph$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1a**	70
2	$R^1 = Ph$, $R^2 = H$	$R^3 = n\text{-}Pr$, $R^4 = H$	**1b**	70
3	$R^1 = Ph$, $R^2 = H$	$R^3 = i\text{-}Pr$, $R^4 = H$	**1c**	68
4	$R^1 = Ph$, $R^2 = H$	$R^3 = n\text{-}C_{13}H_{27}$, $R^4 = H$	**1d**	74
5	$R^1 = 2\text{-}MeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1e**	65
6	$R^1 = 3\text{-}MeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1f**	78
7	$R^1 = 4\text{-}MeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1g**	63
8	$R^1 = 2\text{-}OMeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$		*c*
9	$R^1 = 3\text{-}OMeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1h**	57
10	$R^1 = 4\text{-}OMeC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$		*c*
11	$R^1 = 4\text{-}(CH_2Cl)C_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1i**	71
12	$R^1 = 1\text{-naphthyl}$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1j**	73
13	$R^1 = 2\text{-}ClC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1k**	66
14	$R^1 = 2\text{-}BrC_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$	**1l**	64
15	$R^1 = 2\text{-}NO_2C_6H_4$, $R^2 = H$	$R^3 = CH_3$, $R^4 = H$		*d*
16	$R^1 = Ph$, $R^2 = Ph$	$R^3 = CH_3$, $R^4 = H$	**1m**	64
17	$R^1 = CH_3$, $R^2 = CH_3$	$R^3 = n\text{-}C_7H_{15}$, $R^4 = H$	**1n**	31[e]
18	$R^1 = Ph$, $R^2 = H$	$R^3 = CH_3$, $R^4 = CH_3$		*c*

[a] For detailed experimental operation, see Supporting Information. [b] Isolated yields of expected products. [c] Complicated products, and no expected products were isolated. [d] No reaction. [e] With 1 equiv of alcohol, 20 equiv of olefin, room temperature.

Scheme 1. Optimization Studies



Following the above optimized condition, some other alcohols and olefins, as depicted in Table 1, were further investigated, from which it could be seen that the coupling of a series of the primary aliphatic alcohols (entries 1−4) and various olefins (entries 5−7, 9, 11−14, 16, and 17) could proceed smoothly to afford the corresponding secondary alcohol products in good yields. In addition, the electronic effect of the substituents of aromatic olefins was also observed. For example, the substrates with an electron-rich group on the aromatic ring (entries 5−12) reacted rapidly, while those with the electron-withdrawing group (entries 13 and 14) reacted very slowly and usually a longer reaction time (>2 days) was required. The coupling reaction for 2-nitrostyrene (entry 15) bearing the strong electron-withdrawing group could not even occur under the present condition. Furthermore, aromatic olefins bearing the *ortho*- or *para*-substituent reacted more quickly than those bearing the *meta*-substituted group (entries 5−10); consequently, the 2 (or 4)-methoxy styrene reacted too rapidly to isolate the expected products. It is particularly notable that the disubstituted aromatic olefin (entry 16) gave the desired products in good isolated yield (64%). To expand the scope of substrates, we further examined the disubstituted aliphatic olefin (entry 17) and obtained the expected product, although the yield was merely 31%. However, the monosubstituted aliphatic olefin (*n*-hexene) was ineffective under this reaction condition, which maybe supported a possible

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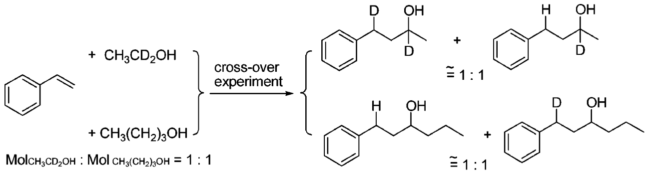
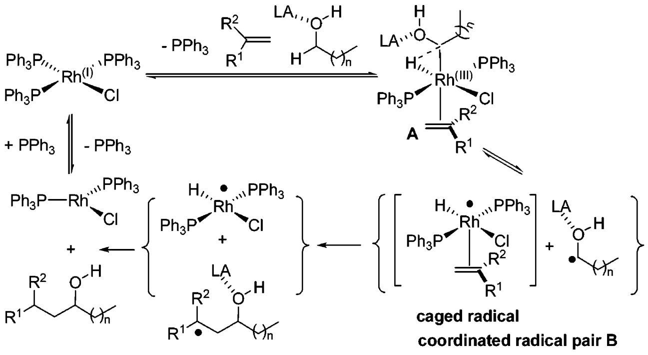
Scheme 2. Deuterium Crossover Experiment



Scheme 3. Plausible Reaction Mechanism



radical mechanism because the third alkyl radical was more stable than the secondary alkyl radical.

To propose a possible reaction mechanism, we conducted some more supporting experiments. For example, $RhCl_3/BF_3{\cdot}OEt_2$/toluene was tested and could be effective to this coupling reaction, which showed the formation of Rh(III) intermediates. Addition of PPh_3 (0.05 equiv) could prevent the reaction, indicating that the presence of PPh_3 could prohibit the ligand dissociation and exchange. The crossover experiment was performed using styrene and a 1:1 mixture of deuterated and undeuterated alcohols (Scheme 2). The resulting mixtures were isolated and analyzed by mass spectrometry to determine the isotopic distribution. This experiment result indicated that a possible radical reaction mechanism was involved, which would lead to a statistical distribution of the labels in the products.[8] Furthermore, formation of the expected adducts could be inhibited completely by the addition of radical scavenger (1,4-benzoquinone, TEMPO, and $FeCl_3$) in the system of ethanol with styrene (in the same experimental procedure as entry 1 in Table 1), which further confirmed the presence of a radical reaction mechanism. Besides, 4-phenylbutan-2-one could not have been observed in the cross-coupling of ethanol and styrene (entry 1, Table 1), and when acetaldehyde was used in place of the primary alcohol substrate, the corresponding coupling reaction with styrene could not proceed under the same condition. These experimental facts mentioned above indicated that the reaction could not undergo the reaction mechanism as reported:[9] first hydrogen transfer from alcohol to form aldehyde, and subsequent radical hydroacylation, followed by hydrogenation of ketone, to give the corresponding product.

On the basis of the above experimental results and the previously reported literature,[10] a tentative mechanism was thus proposed, as shown in Scheme 3, which involved the Lewis acid-promoted[11] direct C−H bond activation of alcohol by a Rh(I) species. The reaction first proceeded by coordination of Lewis acid with an oxygen atom, and then the oxidation addition of the C−H bond to $RhCl(PPh_3)_3$, followed by olefin coordination, to give the Rh(III) complexes A.[12] The formed Rh(III) complexes A then generated a coordinated radical pair B, which underwent the analogical Kharasch radical reaction[10d−h] to afford the secondary alcohol product by releasing the Rh(I) catalysts for the next cycle.

In summary, we have first successfully developed a new Rh-catalyzed/Lewis acid-promoted C−C bond formation with olefins via sp^3 C−H activation of aliphatic alcohols, which can be simply performed in good yields without the need to sacrifice any extra functional groups. The more detailed and widespread investigation of this new reaction is underway.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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