

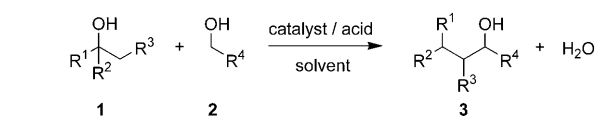
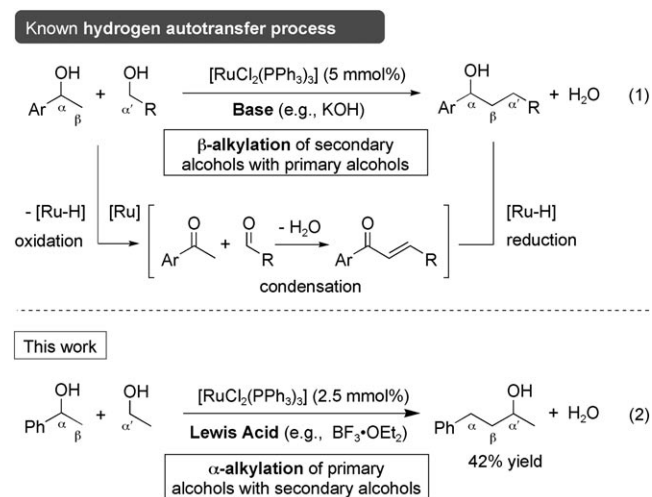
Cross-Coupling Reaction between Alcohols through sp^3 C–H Activation Catalyzed by a Ruthenium/Lewis Acid System

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The C–C bond formation is pivotal and fundamental to molecular architecture and complexity in organic chemistry; the direct C–C cross-coupling using alcohols is one of ideal reactions for achieving this goal, since it not only makes new C–C bonds,^[1–6] but also displays atom-economic and environmentally benign chemistry.^[7]

Some pioneering work on the transition-metal-catalyzed C–C cross-coupling directly utilizing alcohols has been made extensively under basic conditions.^[6] For example, ruthenium-catalyzed^[8]/base-mediated cross-coupling of secondary alcohols with primary alcohols exclusively afforded β -alkylated secondary alcohols [Eq. (1)],^[6a] wherein the “hy-

drogen autotransfer process” was proposed on the basis of the tandem oxidation-condensation-reduction processes.^[9] However, most recently we found that the coupling reaction of the same type of above-mentioned alcohols catalyzed by $[\text{RuCl}_2(\text{PPh}_3)_3]$ in the presence of Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$, as shown in Equation (2), mainly delivered a totally different isomeric product 4-phenyl-2-butanol, despite in moderate yield of 42%,^[10] instead of the above-obtained β -alkylation product in Equation (1). To our knowledge, this constitutes the first example concerning the chemoselective intermolecular α -alkylation of primary alcohols **2** with aliphatic alcohols **1** through transition-metal-catalyzed C–C cross-coupling (Scheme 1). In comparison with our previous report



concerning the olefin/alcohol coupling reaction,^[4] the significant difference and advantage of the present sequence include the following: 1) employment of easily available alcohols, especially tertiary alcohols, as green materials instead of alkenes; 2) discovery of new effective catalyst, $[\text{RuCl}_2(\text{PPh}_3)_3]$, for the cross-coupling between alcohols, but which is less effective in previous alkene/alcohol coupling; 3) formation of functionalized secondary alcohols as product in good to excellent yields. This Ru-catalyzed/Lewis acid promoted cross-coupling demonstrates a novel synthetic transformation directly from simple alcohols to advanced alcohols in an environmentally benign fashion. Herein, we present our experimental results in detail.

Initially to widely explore the above novel transformation commencing from easily available and handled alcohols, we selected 1,1-diphenylethanol (**1a**) and ethanol (**2a**) as substrates for our initial investigation with various transition-

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metal catalysts under different acid and solvent conditions (Table 1); we found that catalytic amounts of $[\text{RuCl}_2(\text{PPh}_3)_3]$ in the presence of 1.2 equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ as a nonme-

Table 1. Optimization of reaction conditions.^[a]

Entry	Catalyst	Acid	Solvent	Yield[%] ^[b]
1	IrCl_3	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	trace
2	RuCl_3	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	trace
3	$[\text{RhCl}(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	72
4	$[\text{Pd}(\text{OAc})_2(\text{PPh}_3)]$	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	22
5	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	82
6	$[\text{RuCpCl}(\text{PPh}_3)_2]$	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	64
7	$[\text{AuCl}(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	trace
8	$[\text{RuCl}_2(\text{PPh}_3)_3]$	InCl_3	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	15
9	$[\text{RuCl}_2(\text{PPh}_3)_3]$	TsOH	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	^[c]
10	$[\text{RuCl}_2(\text{PPh}_3)_3]$	SnCl_4	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	62
11	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	toluene	68
12	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	THF	^[c]
13	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	CH_3NO_2	60
14	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$	CH_3CN	^[c]
15	$[\text{RuCl}_2(\text{PPh}_3)_3]$	$\text{BF}_3 \cdot \text{OEt}_2$ ^[d]	$\text{Cl}(\text{CH}_2)_2\text{Cl}$	42

[a] For entries 1–14, the general reaction condition: 1,1-diphenylethanol **1a** (0.5 mmol) reacted with ethanol **2a** (0.75 mmol) in the presence of catalyst (0.0125 mmol) and acid (0.6 mmol) at 50°C for 5 h. [b] Yield of isolated product. [c] No desired product. [d] $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 equiv), 4 days.

tallic Lewis acid in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ gave the best result (82% yield, entry 5). Among the catalysts screened (entries 1–7), $[\text{RhCl}(\text{PPh}_3)_3]$ (entry 3) or $[\text{RuCpCl}(\text{PPh}_3)_2]$ (entry 6) could also catalyze this reaction despite a slightly lower yield, but the other transition-metal catalysts, such as $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)]$, IrCl_3 , RuCl_3 , and $[\text{AuCl}(\text{PPh}_3)_3]$ were not effective. The role of acid in this reaction was also investigated (entries 8–10), and surprisingly SnCl_4 as an alternative Lewis acid could give the desired product in 62% yield. The solvent was examined further, and it was found that toluene (entry 11) and nitromethane (entry 13) were good reaction media. However, the current reaction did not proceed at all in either THF (entry 12) or CH_3CN (entry 14). Notably, employing substoichiometric amounts of $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 equiv, entry 15) also gave rise to the formation of **3aa** in 42% yield, albeit in a less efficient manner, and this provides a potential access to an effective catalytic system for this reaction.

The current ruthenium-catalyzed/Lewis acid-promoted cross-coupling reaction between ethanol **2a** and the alkene 1,1-diphenylethene ($\text{Ph}_2\text{C}=\text{CH}_2$), instead of the tertiary alcohol **1a**, with the addition of a stoichiometric amount of water has been investigated. Surprisingly, the coupling reaction proceeded without apparent accelerating effect, and the desired product **3aa** was only afforded in a lower yield than that obtained by directly using tertiary alcohol **1a** (entry 5 of Table 1). In addition, the use of 4 Å molecule sieves as water scavenger was also subjected to our standard coupling reaction of **1a** and **2a**, but there is no evident influence on the isolated yield of **3aa** or the reaction rate. These prelimi-

nary experimental facts imply that the gradual in situ generation of water by dehydration of tertiary alcohols might have the subtle influence on this ruthenium catalyst system.

Following the above optimized conditions, the generality and scope of this cross-coupling were then investigated. As listed in Table 2, a series of primary alcohols **2b–2h** in the presence of **1a** or **1b** were subjected to the current protocol (entries 1–8), smoothly giving the desired α -alkylation products in good to excellent yields. It should be noted that an enantiopure primary alcohol **2d** with a chiral β -methyl group was investigated in the presence of **1a** (entry 3), and the chiral α -alkylation product **3ad** was readily afforded in 70% yield with a pair of epimers (2:1). From the results obtained, it could be seen that this cross-coupling reaction, to some extent, was independent upon the steric hindrance of

Table 2. α -Alkylation of various primary alcohols with tertiary alcohols.^[a]

Entry	Substrates	Product	Yield [%] ^[b]
1	1a + 2b	3ab	93
2	1a + 2c	3ac	91
3	1a + 2d	3ad	70 2:1
4	1a + 2e	3ae	92
5	1a + 2f	3af	71
6	1a + 2g	3ag	98
7	1b + 2g	3bg	93
8	1b + 2h	3bh	96

[a] The general reaction conditions: **1** (0.5 mmol) was treated with **2** (0.75 mmol) in the presence of $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.0125 mmol), and Lewis acid (0.6 mmol) at 50°C. [b] Yield of isolated product based on the tertiary alcohol **1** used.

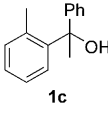
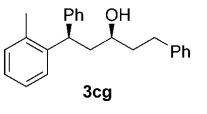
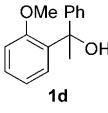
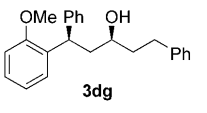
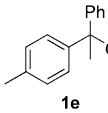
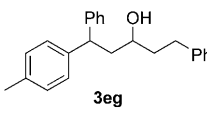
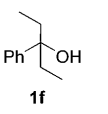
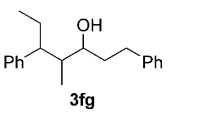
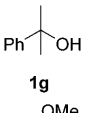
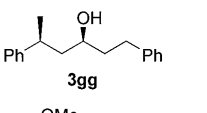
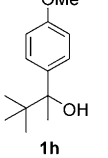
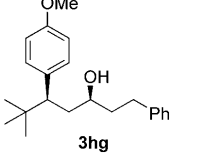
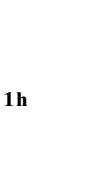
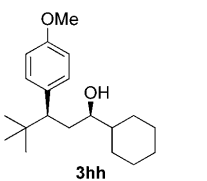
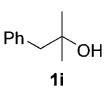
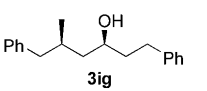
β - or γ -branched chain primary alcohols, such as **2c** (entry 2), **2d** (entry 3), **2h** (entry 8), and **2e** (entry 4). For most of the examples in Table 2, the reaction time needed was around 5 h, but the α -alkylation was accomplished by prolonging reaction time to 16 h when using long-chain primary alcohol **2f** (entry 5). In addition, some primary benzylic alcohols **2** (e.g., benzylic alcohol and 2,6-dichlorophenylmethanol) were also tested, but no positive results were obtained. We also examined the cross-coupling reaction of some secondary benzylic alcohols **1** (e.g., 1-phenylethanol and 1,2,3,4-tetrahydro-1-naphthol) with primary alcohols **2** (e.g., **2a**, **2b**, and **2g**), but the isolated yields of desired products were generally lower (around 30–40% yields) than using tertiary alcohols (**1a** and **1b** in Table 2).

To probe the stereoselectivity in the current C–C cross-coupling reactions, some tertiary alcohols **1c–1i** with different quaternary centers were subsequently investigated (entries 1–8, Table 3). Clearly, the level of diastereocontrol was found to be dependent to the relative bulkiness of R^1 and R^2 in **1**. While both R^1 and R^2 in **1** of Table 3 were aromatic groups, the *ortho*-substituent effect on benzene ring was observed. For example, the coupling reaction of tertiary alcohol **1c**, bearing an *ortho*-methylphenyl substituent, with **2g** gave the expected product **3cg** with a diastereomeric ratio (*syn:anti*) of 7:1 in 92% yield (entry 1, Table 3); the relative configuration of major product was assigned by comparison with a pure sample prepared by a known method.^[11] When **1d** was used, with a slightly less hindered *ortho*-methoxyphenyl group compared to **1c**, the *syn:anti* ratio dramatically decreased to 3:2 (entry 2), although the reaction yield remained almost unchanged. Certainly, no diastereomeric control could be achieved while employing the starting tertiary alcohol with *para*-substituted phenyl group such as **1e** (entry 3).

In addition, tertiary alcohols **1** containing the quaternary center attached by two aliphatic groups (i.e., R^1 and R^2) were also subjected to the current reaction under standard condition (entries 4–7). When 3-phenyl-3-pentanol (**1f**) and 3-phenyl-1-propanol (**2g**) were used in this coupling (entry 4), a moderate diastereoselectivity (*syn:anti*=5:1) and yield (55%) were obtained. Remarkably, however, only the *syn* diastereoisomer product was isolated for the case of **1g** (entry 5) and **1h** (entries 6,7), for which the high diastereoselectivity (*syn:anti*>99:1) demonstrated here presents a clue for mechanistically understanding the stereo process in this selective α -alkylation of primary alcohols through ruthenium-catalyzed/Lewis acid mediated cross-coupling with tertiary alcohols.

Moreover, one extending example of reaction of a tertiary alcohol with the quaternary center attached by three alkyl substituents (e.g., **1i** in the entry 8 of Table 3) was included, but the reaction proceeded slowly (16 h) and the expected product **3ig**, with a diastereomeric ratio of 8:1, was generated merely in 32% yield. In this case, the lower reaction yield might result from the fact that two olefin intermediates were generated in situ through the dehydration of **1i** under current conditions, but only the kinetic terminal olefin, 1-

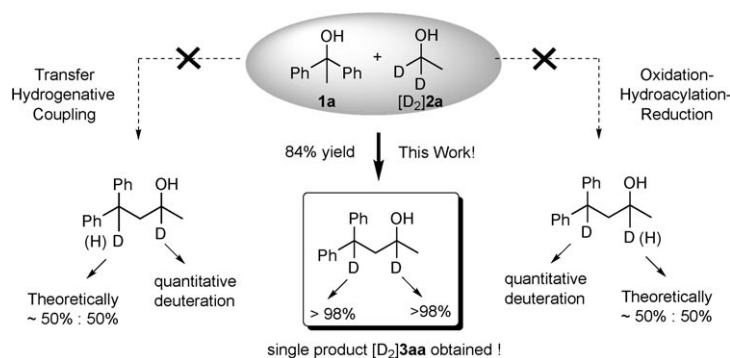
Table 3. α -Alkylation of primary alcohols with various tertiary alcohols.^[a]

Entry	Substrates	Product ^[b]	Yield [%] ^[c]
1			92 (7:1)
2			92 (3:2)
3			93 (1:1)
4			55 ^[d] (5:1)
5			76 (>99:1)
6			62 (>99:1)
7			88 (>99:1)
8			32 (8:1)

[a] Reaction conditions: **1** (0.5 mmol) was treated with **2** (0.75 mmol) in the presence of $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.0125 mmol), and Lewis acid (0.6 mmol) at 50 °C. [b] Major *syn* diastereoisomers with relative configuration were shown. [c] Yield of isolated product based on the tertiary alcohol **1** used. The *syn:anti* ratio of the two diastereoisomers is given in parentheses, and the assignment of relative configuration (see Scheme 1 in the Supporting Information). [d] Only two diastereoisomers were isolated, and the stereochemistry remains unknown currently.

benzyl-1-methylethene, could be slowly converted into the final cross-coupling product **3ig** presumably due to the steric effect of thermodynamic trisubstituted olefin.

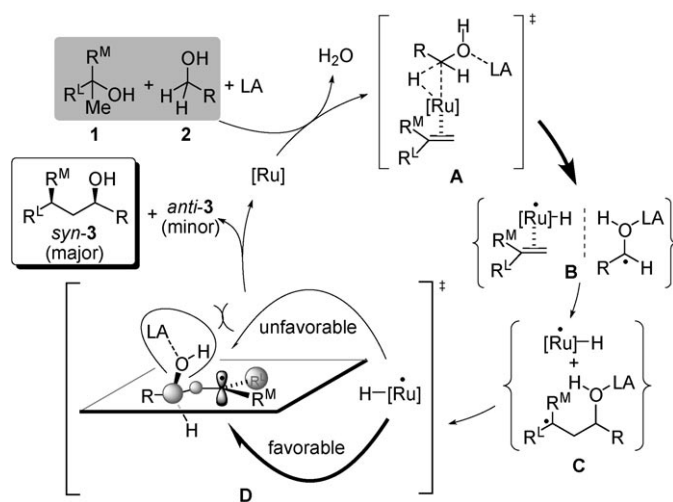
To elucidate the current C–C cross-coupling process, a supporting experiment by reaction of **1a** with ethanol-1,1- D_2 ($[\text{D}_2]\mathbf{2a}$) was conducted. As demonstrated in Scheme 2, the dideuterated coupling product $[\text{D}_2]\mathbf{3aa}$ with a deuterium purity of 98% was exclusively obtained in 84% yield, which clearly rules out the previously known “oxidation–hydroacylation–reduction”^[2] or “transfer–hydrogenative–coupling”^[3]



Scheme 2. Deuterium-labeled cross-coupling experiment.

sequences for our reaction.^[13] Additionally, when some radical scavengers such as 1,4-benzoquinone and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) were added to the system of **1a** with **2a**, the formation of the desired coupling product was inhibited completely, which confirmed the presence of a radical reaction mechanism.

On the basis of the above experimental results and our previous protocol promoted by Wilkinson catalyst [RhCl(PPh₃)₃],^[4a] a catalytic mechanism involving sp³ C–H activation is proposed in Scheme 3. The Lewis acid promoted, kinetically controlled dehydration of tertiary alcohol **1** was



Scheme 3. Proposed catalytic mechanism.

first reacted in situ to generate the alkene intermediate, and then the ruthenium-catalyzed/Lewis acid mediated activation of the α -C–H bond adjacent to the oxygen atom^[4,14] in primary alcohol **2** took place. Compared with our previous coupling system,^[4] the Lewis acid displays pivotal dual roles for not only accelerating the C–H bond activation, but also promoting the elimination of hydroxy in current reaction. After this rate-determined sp³ C–H activation in **A**, the formation of radical pair **B** followed by simultaneous free-radical addition results in the generation of **C**. Subsequently, the

metal hydride ([Ru]H) undergoes a stereoselective reductive attack through a less steric conformation in transition state **D**,^[15] preferentially giving the diastereoisomer *syn*-**3** as major product by releasing the ruthenium catalyst for the next catalytic cycle.

From the proposed mechanism mentioned above, some explanations to our experimental results could be addressed. For example, while employing the secondary alcohols [e.g., Eq. (2)], the chemical yields were generally lower than using tertiary alcohols (Tables 2 and 3), probably due to the fact that the generation of secondary radical species from **B** to **C** (Scheme 3) is less favorable than that of the tertiary one. Analogously, the formation of a less stable nonbenzylic radical species in **C** might be one of reasons for the longer reaction time of 16 h and the low yield of 32% (entry 8, Table 3).

In summary, we have developed a new Ru-catalyzed/acid-mediated C–C cross-coupling reaction between alcohols as green starting materials, and we have shown that various functionalized alcohols could be straightforwardly synthesized by sp³ C–H bond activation of primary alcohols. The stereoselectivity in this kind of coupling was investigated for the first time by using different tertiary alcohols. The current protocol provides a new strategy for the efficient access to a range of secondary alcohols by selective α -alkylation of primary alcohols using aliphatic alcohols, which can be simply performed in good yields. The widespread investigation on its asymmetric version as well as the study toward its mechanistic details is underway in our laboratory.

Experimental Section

Typical procedure: Cl(CH₂)₂Cl (4 mL), primary alcohol **2** (0.75 mmol) and [RuCl₂(PPh₃)₃] (12 mg, 0.0125 mmol) were sequentially added to a flame-dried 25 mL flask. The resulting mixture was stirred and heated from room temperature to 40 °C over a period of 10 min. The alcohol **1** (0.5 mmol) was added and stirring was continued at 40 °C for 10 min under an argon atmosphere; then freshly distilled BF₃·OEt₂ (0.02 mL, 0.15 mmol) was introduced into the reaction mixture. The resulting mixture was stirred at 40 °C for 20 min, and another portion of BF₃·OEt₂ (0.06 mL, 0.45 mmol) was added. The reaction was heated over an oil bath to 50 °C, and stirred at 50 °C for 5 h. After that, it was cooled to room temperature, and diluted with ethyl acetate (3 mL) followed by addition of saturated aqueous NaHCO₃ solution (2 mL). The organic layer was separated, and the aqueous phase was re-extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with H₂O (20 mL), and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified by the flash chromatography to afford the desired separable product **3**.

Acknowledgements

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Keywords: alcohols • C–C coupling • C–H activation • cross-coupling • ruthenium

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