Iron Catalysis

DOI: 10.1002/ange.200903960

Iron-Catalyzed $C(sp^3)–C(sp^3)$ Bond Formation through $C(sp^3)–H$ Functionalization: A Cross-Coupling Reaction of Alcohols with Alkenes**

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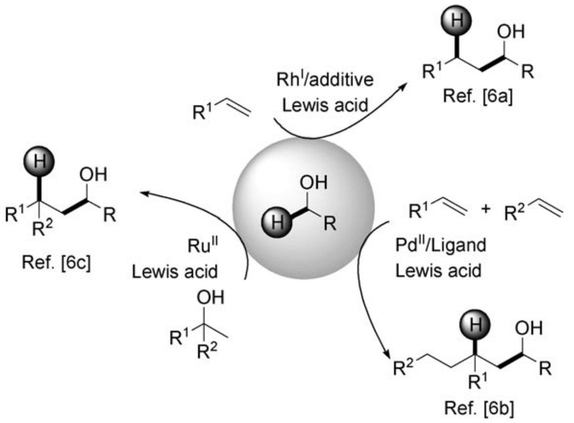
Iron as one of the most abundant metals on earth and has been increasingly explored in modern catalysis to discover its unique and novel reactivity towards carbon–carbon and carbon–heteroatom bond formation, which have been typically achieved by rare and expensive transition metal catalysts (e.g. Ru, Rh, and Pd). Owing to its inexpensive and environmentally friendly characteristics, considerable effort has been directed towards iron catalysis and as a result a series of novel iron-catalyzed organic transformations have been developed. These mainly involve $C(sp^2)–C(sp)$, $C(sp)–C(sp)$, and $C(sp^3)–N$ bond formations.[1,2] To our knowledge, however, iron-catalyzed $C(sp^3)–C(sp^3)$ bond-forming reactions through direct C–H functionalization remain rare.[3]

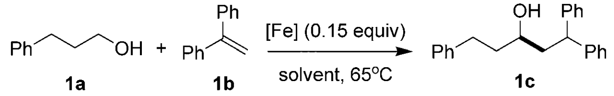
The formation of C–C bonds through direct C–H functionalization undoubtedly belongs to an important and challenging area of organic chemistry.[4] In particular, the direct C–C cross-coupling of alcohols with olefins through direct functionalization of a C–H bond at the α position is one of the most attractive reactions as it constructs a new C–C bond, directly introduces an active hydroxy functional group, and is atom economic involving few steps.[5] Recently, our research group has demonstrated that of a late-transition-metal catalyst (Rh, Ru, or Pd) and a Lewis acid can be used to copromote this kind of cross-coupling reaction (Scheme 1).[6] However, the chemical disadvantages of these protocols center around using such expensive and toxic transition metals as well as excess amounts of Lewis acids. An alternative catalytic system with more sustainable perspectives is therefore highly appealing. Herein, we present our preliminary experimental results of a novel $FeCl_3$-catalyzed $C(sp^3)–C(sp^3)$ bond-forming cross-coupling reaction of alcohols with alkenes.

To explore our iron catalysis system, 3-phenylpropanol (**1a**) and 1,1-diphenylethylene (**1b**) were selected as model substrates for screening iron catalysts and solvents for the general experimental procedure. As shown in Table 1, the solvents were firstly examined in the presence of a catalytic amount of $FeCl_3$ (Table 1, entries 1–5), and gratifyingly it was found that DCE (1,2-dichloroethane) gave 83% yield of **1c** (Table 1, entry 5). These control experiments indicated that DCE was essential to this coupling reaction; DCE was even effective as an additive in a reaction medium that could not



Scheme 1. Carbon–carbon cross-coupling reactions of alcohols with olefins through copromotion with late transition metals and Lewis acids.

Table 1: Optimization of cross-coupling reaction conditions.[a]



Entry	[Fe]	Solvent	**3 a** [%][b]
1	$FeCl_3$	toluene	trace
2	$FeCl_3$	THF	–
3	$FeCl_3$	DMF	–
4	$FeCl_3$	*n*BuBr	trace
5	**$FeCl_3$**	**DCE**	**83**
6	$FeCl_3$	*n*BuBr/DCE[c]	63
7	$FeCl_2$	DCE	22
8	$Fe(acac)_3$	DCE	–
9	$FeCl_3·6H_2O$	DCE	72
10	$Fe(ClO_4)_3·9H_2O$	DCE	36
11	$FeCl_3$ (0.02 equiv)	DCE	42
12	$FeCl_3$ (0.10 equiv)	DCE	64

[a] General reaction conditions: a mixture of alcohol **1a** (0.2 mmol), alkene **1b** (0.3 mmol), and solvent (2 mL) in the presence of iron catalyst (0.03 mmol) was stirred at 65 °C under argon for 8–12 hours. [b] Yield of isolated product. [c] 1.0 equivalent of DCE was added to 2 mL of *n*BuBr. acac = acetylacetonate, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

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[**] This work was supported by the NSFC (grant nos. 20621091, 20672048, and 20732002) and the "111" Program of the Chinese Education Ministry.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903960.

promote the present cross-coupling reaction (Table 1, entry 6). Subsequently, our evaluation turned to the iron salts. FeCl$_2$ and Fe(acac)$_3$ proved to be less effective (Table 1, entries 7–10), and decreasing the loading of FeCl$_3$ led to lower yields of **1c** (Table 1, entries 11 and 12).

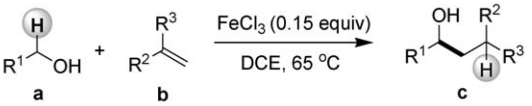
Also, in combination with FeCl$_3$ in DCE, we tested several ligands such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), NEt$_3$, and DACH (*trans*-1,2-diaminocyclohexane), which are commonly used for iron catalysis, and some additives such as lithium or copper salts,[7,8] but no significant improvement in yield was observed. As a result, FeCl$_3$ (0.15 equiv)/DCE was selected as the general catalysis system for our coupling reaction (Table 1, entry 5).

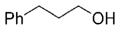
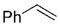
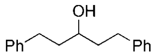
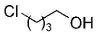
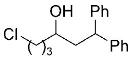
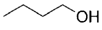
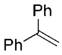
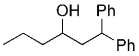
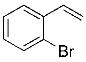
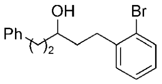
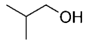
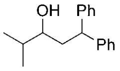
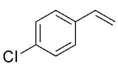
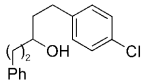
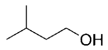
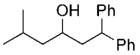
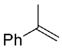
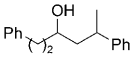
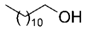
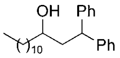
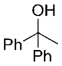
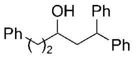
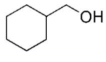
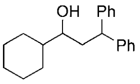
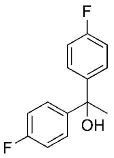
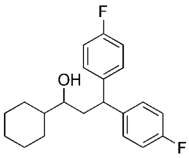
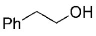
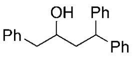
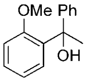
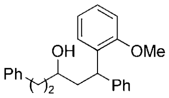
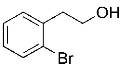
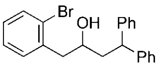
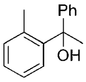
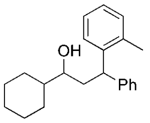
After the above optimization, the generality and substrate scope of this cross-coupling reaction were investigated. As indicated in Table 2, a series of primary alcohols **1a**–**9a** were treated with alkenes **1b**–**5b** or tertiary alcohols **6b**–**9b** as their precursors (which are more environmentally friendly and easily available than alkenes), and smoothly gave the desired secondary alcohols **1c**–**16c** in moderate to good yields. Notably, the coupling reaction using β-aryl alcohol **7a** or **8a** did not proceed to completion, even after 24 h, and the reaction only afforded 51 % and 48 % yield, respectively (Table 2, entries 7 and 8). Generally, our coupling reaction was carried out within 8 hours, but a prolonged reaction time (16–24 h) was essential for those reactions that involved the in situ formation of alkenes **b** from tertiary alcohols (Table 2, entry 13–16). For entries 12, 15, and 16 of Table 2, a substrate-based diastereoselectivity (> 99:1 to 1:1) was observed, thus highlighting the fact that the level of diastereocontrol was dependent to the relative bulkiness of the R^2 and R^3 groups in **b**.

To elucidate a possible reaction pathway, some additional experiments were carefully performed. For example, PhCH$_2$CH$_2$CHO instead of the starting alcohol **1a** was treated with the alkene **1b** under the standard reaction conditions, however, no hydroacylation reaction was observed. Clearly this result indicated that the known "oxidation/hydroacylation/reduction" or "transfer-hydrogenative coupling" process was not involved in our current cross-coupling reaction of alcohols **a** and alkenes **b**.[9,10]

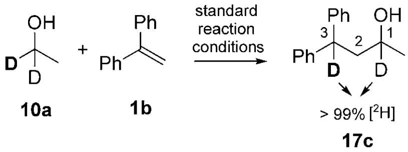
To further clarify the hydrogen transfer from alcohols **a** to alkenes **b**, several deuterium-labeling experiments were conducted. As shown in Scheme 2, 1,1-dideuterated ethanol **10a** and **1b** were subjected to the cross-coupling reaction, and only the 1,3-dideuterated product **17c** was obtained, in which

Table 2: Cross-coupling reaction of primary alcohols with various alkenes or tertiary alcohols.[a]



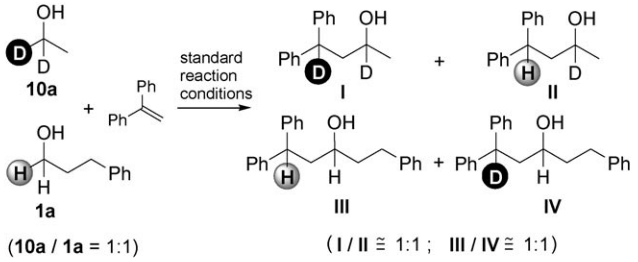
Entry	Substrate alcohol	Substrate alkene	Product	Yield [%][b]	Entry	Substrate alcohol	Substrate alkene	Product	Yield [%][b]
1	**1a** 	**2b** 	**2c** 	83	9	**9a** 	**1b**	**10c** 	53
2	**2a** 	**1b** 	**3c** 	81	10	**1a**	**3b** 	**11c** 	82
3	**3a** 	**1b**	**4c** 	72	11	**1a**	**4b** 	**12c** 	88
4	**4a** 	**1b**	**5c** 	78	12	**1a**	**5b** 	**13c** 	62 (>99:1)[d]
5	**5a** 	**1b**	**6c** 	70	13	**1a**	**6b** 	**1c** 	82
6	**6a** 	**1b**	**7c** 	77	14	**5a**	**7b** 	**14c** 	78
7	**7a** 	**1b**	**8c** 	51 (90)[c]	15	**1a**	**8b** 	**15c** 	58 (1:1)
8	**8a** 	**1b**	**9c** 	48 (92)[c]	16	**5a**	**9b** 	**16c** 	93 (1:1)

[a] Reaction conditions: alcohols **a** (0.2 mmol) were treated with alkenes **b** (0.3 mmol) in the presence of FeCl$_3$ (0.03 mmol) and DCE (2 mL) at 65 °C for 8–24 hours. [b] Yield of isolated product. [c] Yield based on the recovered starting material. [d] Only one diastereomer was isolated, and its relative stereochemistry is temporarily assigned as *syn* according to our previous report.[6c]



Scheme 2. Deuterium-labeled experiment using **10a**.

the deuterium at the C3 position of **17c** originated entirely from the α deuterium atom that was adjacent to the hydroxy group of **10a**. This reaction outcome is consistent with what we have observed previously[6] in this type of cross-coupling of alcohols and alkenens catalyzed by non-iron catalysts, and therefore additionally demonstrating that the pathway of our iron-catalyzed cross-coupling reaction was quite different from the "oxidation/hydroacylation/reduction" or "transfer-hydrogenative coupling" processes. Moreover, one crossover experiment was investigated using a 1:1 mixture of 1,1-dideuterated **10a** and undeuterated **1a** (Scheme 3), and afforded a statistical distribution of deuterium labels in the products: the isotopic distribution patterns were analyzed by ^{1}H NMR spectroscopy. This result implies that the hydrogen-transfer process from alcohol to alkene might proceed discretely in an intermolecular fashion.

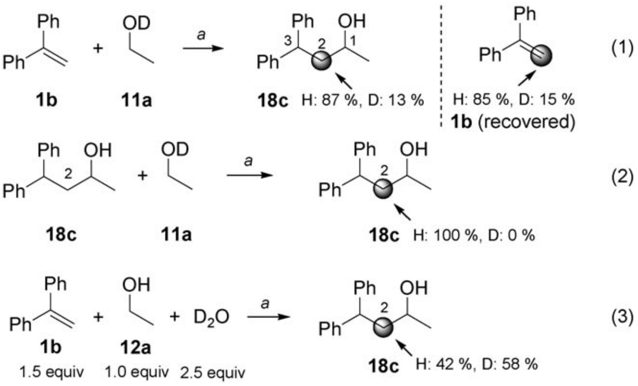


Scheme 3. Deuterium-labeled crossover experiment.

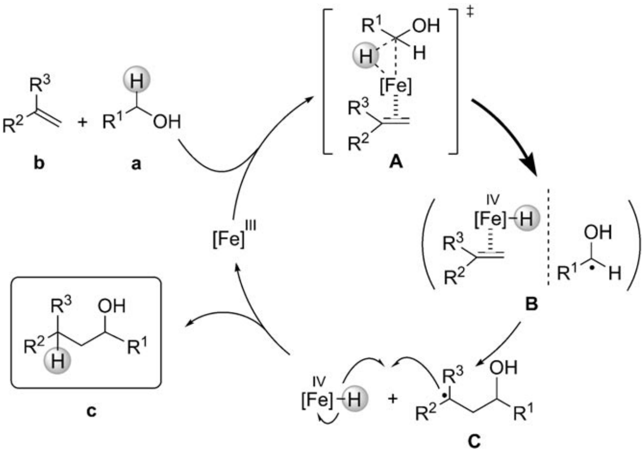
In addition to the above preliminary investigation using **10a** (Scheme 2), **11a** was also examined to probe the transfer of the active hydrogen atom [Eq. (1), Scheme 4]. Surprisingly, the C2-deuterated compound **18c** (H/D = 87:13) was obtained as well as **1b** (H/D = 85:15), which had partial deuteration of the terminal hxdrogen atom.[11] Notably, no C1- or C3-deuterated products were observed. One additional deuterium-labeling experiment [Eq. (2), Scheme 4] clearly excluded the possibity that the hydrogen atom at C2 of the deuterium-free cross-coupling product **18c** directly exchanged with the deuterium of **11a** in this coupling system. This fact demonstrated a preferential occurrence of the hydrogen exchange between the active hydrogen atom of alcohols and the terminal hydrogen atom of alkenes under the standard reaction condition.[12,13] Moreover D_2O, as an alternative active source of hydrogen, was subjected to the current reaction system [Eq. (3), Scheme 4], and the deuterium of D_2O could also be partially installed at the C2 position of the product. These above-mentioned results reveal that the active hydroxy hydrogen atom could undergo a fast iron-catalyzed regioselective hydrogen exchange between alkenes and alcohols under the current iron catalysis,[12] thus delivering the final C2-deuterated products.

Together with the experiments shown in Schemes 2–4, the ionic C–H bond dissociation at the α position of alcohols could be excluded unambiguously in our iron-catalyzed cross-coupling reaction, and a possible homolysis of the C–H bond at the α position in the alcohols catalyzed by iron was supported. In light of this mechanistic implication, the radical scavenger PhSH was subjected to the current cross-coupling reaction, and the positive inhibiting effect in this control experiment further indicates the presence of the free radical species resulting from homolysis.

According to the above experimental results and our previous reports,[6] a catalytic mechanism for this iron-catalyzed cross-coupling reaction is proposed in Scheme 5. Firstly, iron-initiated activation for cleavage of the C(sp^3)–H bond adjacent to oxygen[14] of alcohols **a** is involved in the formation of **A**. Then a radical pair **B** forms followed by simultaneous free-radical addition and disassociation to afford [Fe]^{IV}–H and a free-radical species **C**. Subsequently, the metal hydride ([Fe]^{IV}–H) undergoes an outer-sphere-type hydrogen transfer to give the coupling product **c**, thus regenerating the iron-catalyst [Fe]^{III} for the next catalytic cycle.



Scheme 4. Deuterium-labeled experiment probing the active hydrogen atom.[12] Reaction conditions: a) 1. standard reaction conditions, 2. aqueous work-up.



Scheme 5. Proposed catalytic mechanism.

In summary, we have developed a novel iron-catalyzed $C(sp^3)$-$C(sp^3)$ bond-forming reaction between alcohols and olefins through direct $C(sp^3)$–H functionalization, and various substrates proved to be well tolerated. This protocol provides an economical and convenient strategy for efficient access to structurally diverse secondary alcohols. An extensive investigation of this reaction is underway in our laboratory.

Experimental Section

Typical procedure: DCE (2 mL), alcohol **a** (0.2 mmol), and $FeCl_3$ (0.03 mmol) were sequentially added to a flame-dried 10 mL flask. The mixture was stirred for 20 min before alkene **b** or the related tertiary alcohol (0.3 mmol) was introduced. The resulting reaction mixture and stirred at 65 °C for a further 6–18 hours until the reaction was completed (as evident by TLC). The reaction mixture was cooled to room temperature and diluted with ethyl acetate (3 mL) and H_2O (2 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with H_2O (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford the desired product **c**.

Received: July 19, 2009
Revised: September 12, 2009

Keywords: alcohols · C–C coupling · C–H activation · cross-coupling · iron

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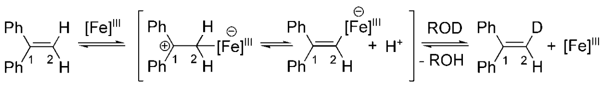

[13] Although this kind of H/D exchange processes haS been mentioned in some transition-metals-catalyzed transformations (such as Pd, Rh, Ru, and Ir), they have not yet been reported in Fe-catalyzed reactions, see: J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem.* **2007**, *119*, 7890–7911; *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765.

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