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Iron-Catalyzed Stereospecific Olefin Synthesis by Direct Coupling of Alcohols and Alkenes with Alcohols

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ABSTRACT

An efficient Fe(III)-catalyzed direct coupling of alkenes with alcohols and cross-coupling of alcohols with alcohols to give the corresponding substituted (*E*)-alkenes stereospecifically is demonstrated. Additionally, this reaction could be scaled up. The kinetic isotope effect (KIE) experiments indicated a typical secondary isotope effect in this process. Although benzylic alcohols were effective substrates, mild conditions, atom efficiency, environmental soundness, and stereospecificity are features that make this procedure very attractive.

Carbon–carbon bond formation by direct coupling of alcohols with other partners might be very attractive since it would be atom-efficient and environmentally benign since water is the major byproduct.[1] However, very few successful systems to generate a C–C bond by using alcohols as alternatives to halides as coupling partners have been achieved due to the poor leaving ability of the hydroxyl group.[2] Recently, some coupling reactions of alcohols with allyl, aryl, and alkynyl partners have been developed by us,[3] Kabalka,[4] Baba,[5] and others. Of particular interest are the coupling of alcohols with alkenyl reagents to prepare substituted olefins. Kabalka et al.[4c] reported a coupling of alcohols with vinylboron dihalides using a stoichiometric amount of *n*BuLi. In(III)- and Bi(III)-catalyzed couplings of alcohols with alkenylsilanes have been explored by Baba et al.[5e] These two systems prompted us to develop a direct coupling of alcohols with olefins. Although an acid-catalyzed reaction of 9-fluorenol with 9-alkylidene fluorenes has been reported 65 years ago, this system suffered from seriously limited substrate scopes.[6] Recently, an efficient Pd(II)-catalyzed coupling

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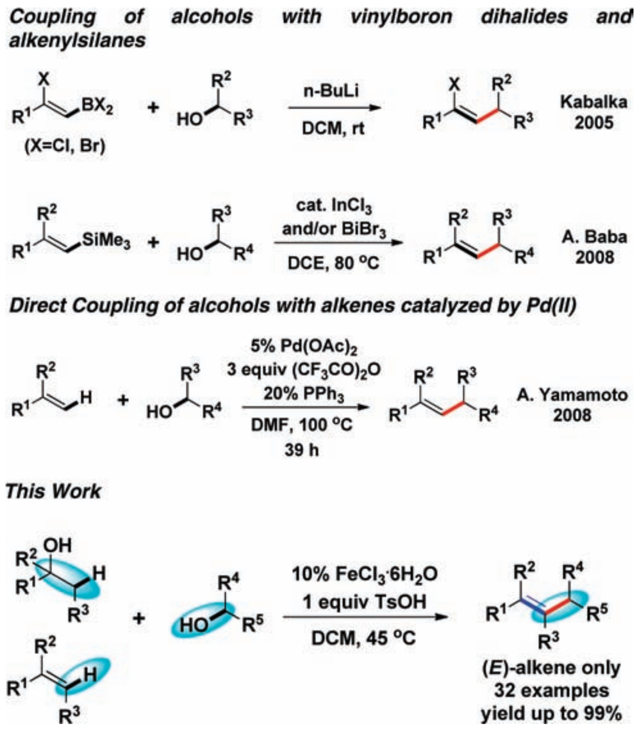
of alcohols with olefins was developed by Yamamoto et al.[7] However, substituted alkenes as the desired products were obtained in moderate yields by using a relatively high $(CF_3CO)_2O$ loading (3 equiv) and long reaction time (Scheme 1). We wish to report herein the first example of iron-catalyzed stereospecific substituted olefin synthesis by direct coupling of alcohols with alkenes and alcohols.[8]

Scheme 1. Direct Coupling of Alcohols with Some Partners To Give Substituted Olefins



Initially, we chose styrene and benzhydrol as model substrates to optimize suitable conditions for this reaction.

Inspired by the recent work of Jiao[9] and Sanz,[10] the coupling reaction was designed to be catalyzed by Lewis acids such as $FeCl_3$, $Fe(OTf)_3$, $AlCl_3$, $ZnCl_2$, etc. and mediated by Brønsted acids such as TsOH, TfOH, H_2SO_4, etc. It was found that the acids, catalysts, and solvent critically affect the reaction efficiency. The desired product was obtained in 66% isolated yield under the typical conditions: 2.0 equiv of styrene, 1.0 equiv of benzhydrol, 10 mol % $FeCl_3 \cdot 6H_2O$, 1.0 equiv of TsOH, CH_2Cl_2, 45 °C, 5 h (See Supporting Information). It is worth noting that (*E*)-prop-2-ene-1,1,3-triyltribenzene was obtained as the major product and the (*Z*)-isomer was not observed in this system.

To examine the scope of this system, the coupling reactions of various olefins with different types of benzylic alcohols were studied (Table 1). Styrene and its derivatives gave the desired products in moderate to quantitative yields. Neither aliphatic alkenes nor aliphatic alcohols were reactive in this reaction. The ^1H NMR spectra of all products except for **1n** (entry 14) indicated that only the *E* isomers formed. Coupling of styrene with various benzylic alcohols produced the corresponding substituted alkenes in moderate to good yields (entries 1–6). Both *p*-methylstyrene and *p*-chlorostyrene gave good yields of the (*E*)-aryl-substituted propenes (entries 7–10). Interestingly, a different major product was obtained by a mix of different ratios of α-methylstyrene and benzhydrol (entries 11 and 12). The **1m** was formed by coupling of benzhydrol with 1,1-diphenylethylene in 92% isolated yield (entry 13). Although it took place slowly, a more steric olefin such as 1-phenyl-1-cyclohexene gave the desired product in excellent yield (entry 14). 3-Benzhydryl-1, 2-dihydronaphthalene (**1o**) was isolated in 69% yield by the coupling of 1,2-dihydronaphthalene with benzhydrol (entry 15).

It is well-known that alkenes could be formed by dehydroxylation of the corresponding secondary and tertiary alcohols promoted by a Brønsted acid and/or a Lewis acid. Encouraged by these results, we began to design a series of cross couplings of benzylic alcohols. Fortunately, we successfully accomplished an efficient cross coupling of two types of benzylic alcohols to prepare various substituted alkenes with water as the only byproduct (Table 2).

To the best of our knowledge, this is the first example of the formation of olefins via cross coupling of two different benzylic alcohols. As indicated in Table 2, various benzylic alcohols (entries 1–5, 7–9) gave the desired products in moderate to good yields except for 1-(2-naphthyl)ethanol (entry 6). As expected, (3-(*p*-tolyl)but-1-ene-1,1-diyl)-dibenzene was produced as the major product by coupling of 1-(*p*-tolyl)ethanol with 1,1-diphenylethanol (entry 10). Homocoupling of the benzylic alcohols also gave the corresponding 1,3-diarylbut-1-ene derivatives in moderate to high yields (entries 11–17). Since diarylcarbenium ions are more stable than methylarylcarbenium ions, a selective

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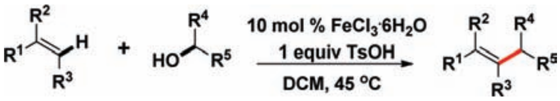
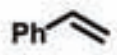
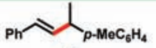
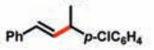
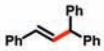
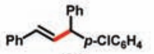
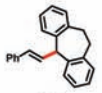
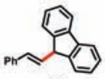
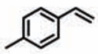
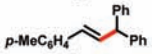
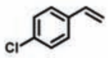
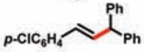
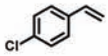
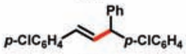
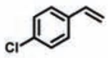
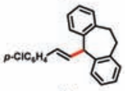
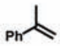
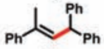
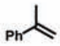
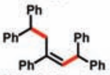
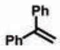
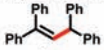
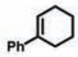
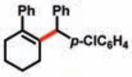
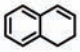
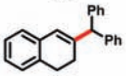
Table 1. Direct Coupling of Alcohols with Olefins[a]



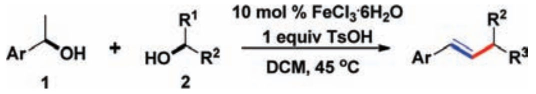
entry	olefin	product	t(h)[b]	Yield (%)[c]
1		 **1a**	5	81
2		 **1b**	42	67
3		 **1c**	5	66
4		 **1d**	11	83
5		 **1e**	5	65
6		 **1f**	5	43
7		 **1g**	2.5	89
8		 **1h**	24	80
9		 **1i**	3	88
10		 **1j**	5.5	78
11		 **1k**	5	88
12[d]		 **1l** (**1l**:**1k**=2:1)	2.5	99
13		 **1m**	2.5	92
14		 **1n**	45	93
15		 **1o**	11	69

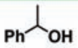
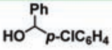
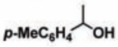
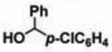
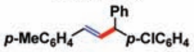
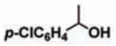
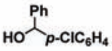
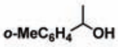
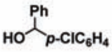
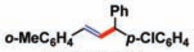
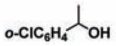
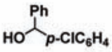
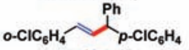
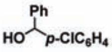
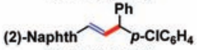
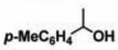
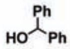
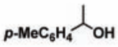
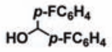
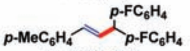
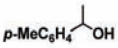
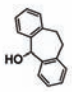
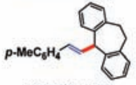
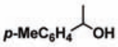
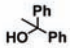
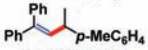
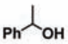
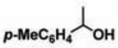
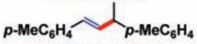
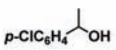
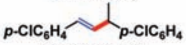
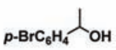
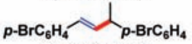
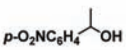
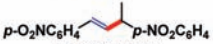
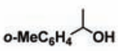
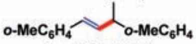
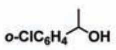
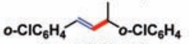
[a] Reaction conditions: benzylic alcohol (0.5 mmol), olefin (1.0 mmol), $FeCl_3 \cdot 6H_2O$ (0.05 mmol), TsOH (0.5 mmol), CH_2Cl_2 (15 mL), 45 °C, unless otherwise noted. [b] Reaction time, indicated by TLC. [c] Isolated yields. [d] Reaction conditions: benzylic alcohol (1.0 mmol), olefin (0.5 mmol), $FeCl_3 \cdot 6H_2O$ (0.05 mmol), TsOH (0.5 mmol), CH_2Cl_2 (15 mL), 45 °C.

dehydration occurred in the cross-coupling reactions. The stereoselectivity of the reaction of alcohol with alcohol is the same as that of the reaction of alcohol with olefin, only the *E* isomers were obtained as revealed by the NMR spectra of all the products in Table 2. Although aliphatic alcohols were not effective, water as a side product and exclusive *E* alkenes formation features make this system very interesting.

Under the typical conditions, this coupling reaction could be scaled up (Scheme 2). A mixture of (4-chlorophenyl)(phenyl)methanol (1.015 g, 4.6 mmol), styrene (0.965 g, 9.2 mmol), $FeCl_3 \cdot 6H_2O$ (125 mg, 0.46 mmol), and TsOH (885 mg, 4.6 mmol) was dissolved in 30 mL of CH_2Cl_2. The reaction was complete after stirring for 20 h at 45 °C. The solvent was recovered, and the mixture was purified by flash column chromatography (petroleum ether) to afford the desired product in 61% yield.

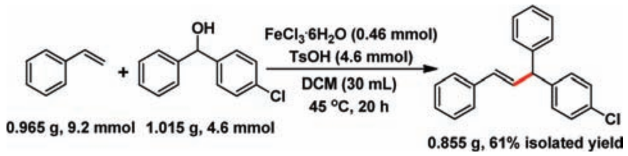
Table 2. Cross-Coupling/Homocoupling of Benzylic Alcohols[a]



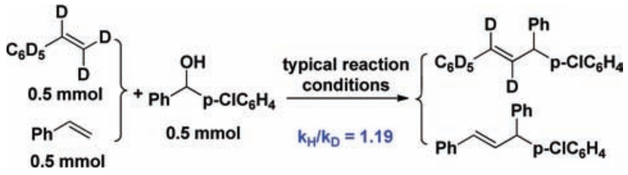
entry	alcohol **1**	alcohol **2**	product Yield[b] (t[c])
1			**1d** 59% (14.5h)
2			 **2a** 81% (4.5h)
3			**1i** 79% (10h)
4			 **2b** 78% (5h)
5			 **2c** 74% (40h)
6			 **2d** 26% (6.5h)
7			**1g** 61% (3h)
8			 **2e** 76% (6h)
9			 **2f** 78% (5h)
10			 **2g** 83% (12h)
11		-	 **2h** 80% (6h)
12		-	 **2i** 71% (5h)
13		-	 **2j** 81% (14h)
14		-	 **2k** 80% (23h)
15		-	 **2l** 86% (40h)
16		-	 **2m** 62% (18h)
17		-	 **2n** 58% (67h)

[a] Reaction conditions: alcohol **1** (1.0 mmol), alcohol **2** (0.5 mmol), $FeCl_3 \cdot 6H_2O$ (0.05 mmol), TsOH (0.5 mmol), CH_2Cl_2 (15 mL), 45 °C, unless otherwise noted. [b] Isolated yields. [c] Reaction time, indicated by TLC.

Scheme 2. Coupling of Benzylic Alcohol with Olefin Could Be Scaled up

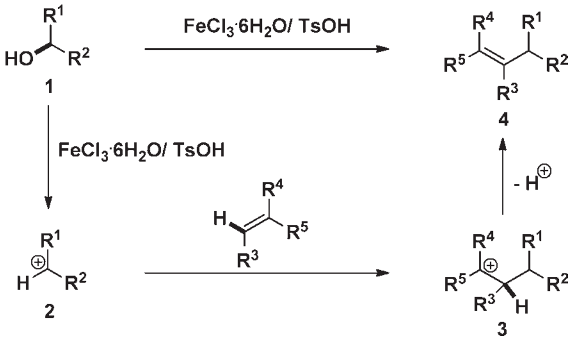


Scheme 3. Competing KIE Experiment



To gain mechanistic insight, a competing kinetic isotope effect (KIE) experiment was carried out (Scheme 3). As a result, a typical secondary KIE was observed since the $k_H/k_D = 1.19$ (see Supporting Information). It suggests that a carbocation intermediate should be involved in this reaction and the C−H bond cleavage is not the rate-determining step.[11] With these results in hand, a plausible mechanism for this catalytic coupling reaction is depicted in Scheme 4. A carbocation intermediate **2** would be generated from the benzylic alcohol mediated by $FeCl_3 \cdot 6H_2O$ and TsOH.[21,9] Electrophilic addition of olefin to **2** would form a new cationic intermediate **3**; this would be the rate-determine step which has been systematically studied by Mayr et al.[12] Then it would be followed by fast deprotonation to give the corresponding substituted alkenes **4**.[3]

Scheme 4. Proposed Mechanism for the Coupling of Alcohol with Olefin



In conclusion, we developed a novel iron-catalyzed stereospecific substituted olefin synthesis *via* direct coupling of benzylic alcohols with alkenes. Additionally, the $C(sp^3)-C(sp^2)$ bond formation could also be achieved by cross coupling of two different benzylic alcohols under the reaction conditions. Furthermore, this reaction could be scaled up. Although only benzylic alcohols were effective substrates, mild conditions, atom efficiency, environmental soundness, and stereospecificity are features make this procedure very attractive. Further investigation of this system is underway in our laboratory.

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Supporting Information Available. Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] (a) Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713. (b) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265. (c) Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109. (d) Sunko, D. E.; Hehre, W. J. *Prog. Phys. Org. Chem.* **1983**, *14*, 205.

[12] (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed.* **1994**, *33*, 938. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.