

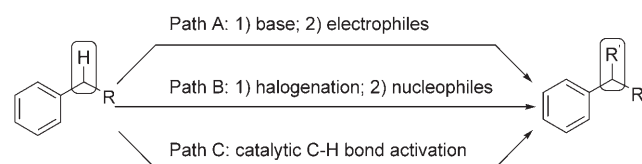
C–C Bond Formation

FeCl₂-Catalyzed Selective C–C Bond Formation by Oxidative Activation of a Benzylic C–H Bond**

Zhiping Li,* Lin Cao, and Chao-Jun Li*

The selective and efficient functionalization of C–H bonds has attracted much attention from both academia and industry in the past decade,^[1] and various methods, especially ones based on transition-metal catalysts, have been developed and applied in the synthesis of complex molecules.^[1,2] Although great progress has been made in this area, new processes for the construction of C–C bonds starting from C–H bonds are still highly desirable.

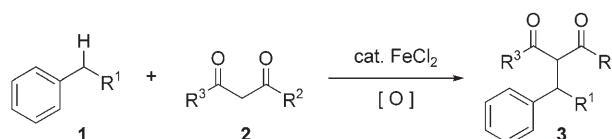
The synthesis of benzylic derivatives from starting materials containing a benzylic C–H bond is well known (Scheme 1, paths A and B), although multistep syntheses are still commonly used. Alternatively, various catalytic methods have been developed recently that allow the direct functionalization of benzylic C–H bonds (Scheme 1, path C).^[3,4]



Scheme 1. Various methods for the functionalization of benzylic C–H bonds.

Although transition-metal catalysts are widely used in organic synthesis, the use of more readily available and nontoxic catalysts instead of expensive and sensitive catalysts is highly desirable. The numerous advantages of iron make it highly attractive as a catalyst or reagent for chemical synthesis.^[5] Iron-catalyzed C–H bond oxidations in systems such

as the Gif^[6] and Fenton reactions^[7] are some of the best known examples of C–H functionalization. However, iron-catalyzed activation of C–H bonds followed by C–C bond formation is virtually unknown.^[8] Herein, we report an FeCl₂-catalyzed oxidative activation of a benzylic C–H bond which is followed by a cross-coupling reaction to form a C–C bond (Scheme 2).^[5,9,10]



Scheme 2. Iron-catalyzed functionalization of benzylic C–H bonds.

There are two main challenges in this type of reaction, namely to avoid homocoupling and to use a catalytic amount of metal catalyst. As a starting point, we chose diphenylmethane (**1a**) and benzoylacetone (**2a**) as standard substrates to investigate suitable reaction conditions for the desired reaction (Table 1). The desired product (**3a**) was isolated in 11 % yield with CoCl₂ as the catalyst and *tert*-butyl hydrogen

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

Entry	Catalyst (mol %)	Oxidant (equiv)	T [°C]	t [h]	Yield [%] ^[b]
1	CoCl ₂ (10)	TBHP (2)	100	5	11
2	CuBr/CoCl ₂ (10/10)	TBHP (2)	100	5	30
3	CuBr (10)	TBHP (2)	100	5	n.d. ^[c]
4	FeCl ₂ (20)	TBHP (2)	80	8	46
5	FeCl ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	66
6	FeCl ₂ (10)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	47
7	FeCl ₂ (20)	PhCOOO <i>t</i> Bu (2)	80	8	n.d. ^[c]
8	FeCl ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (1)	80	8	64
9	FeBr ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	49
10	FeCl ₃ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	56
11	Fe(OAc) ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	n.d. ^[c]
12 ^[d]	FeCl ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	46
13	FeCl ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (1)	RT	36	65
14	FeCl ₂ (20)	<i>t</i> BuOO <i>t</i> Bu (2)	RT	36	80
15	–	<i>t</i> BuOO <i>t</i> Bu (2)	80	8	n.d. ^[c]

[a] 1-Benzoylacetone (0.5 mmol), diphenylmethane (6.0 mmol), and TBHP (5–6 M in decane) under nitrogen, unless otherwise noted. [b] Yield of isolated product. [c] Not detected by NMR spectroscopy. [d] Only 1.0 mmol of diphenylmethane was used.

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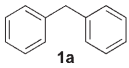
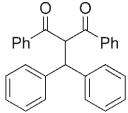
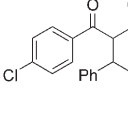
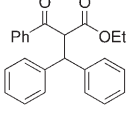
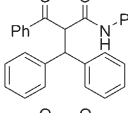
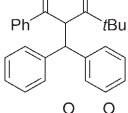
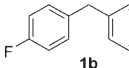
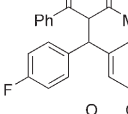
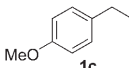
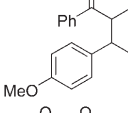
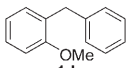
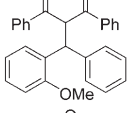
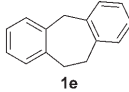
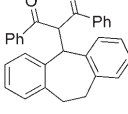
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peroxide (TBHP) as the oxidant (Table 1, entry 1). The yield of **3a** increased to 30% when CuBr and CoCl₂ were used as co-catalysts, while CuBr alone was not effective under the same reaction conditions (Table 1, entries 2 and 3, respectively). Further investigations showed that FeCl₂ is a more effective catalyst (Table 1, entry 4). The use of *tert*-butyl peroxide instead of TBHP as an oxidant increased the product yield to 66% (Table 1, entry 5). Other iron salts were either less effective than FeCl₂ or inactive (Table 1, entries 9–11).^[11]

The reaction was also found to proceed efficiently at room temperature, and **3a** was isolated in up to 80% yield on extending the reaction time (Table 1, entries 13 and 14).^[12] All the above coupling reactions are clean: only **1a**, **2a**, and the product (**3a**) are observed when the reactions are stopped, although a trace amount of benzophenone was also found on occasions.

Table 2: Alkylation of diaryl C–H bonds.^[a]

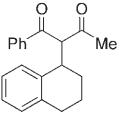
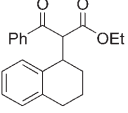
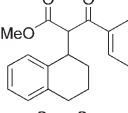
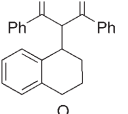
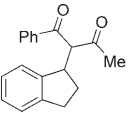
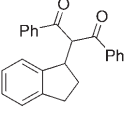
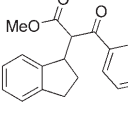
Entry	Diaryl substrate	Product	Yield [%] ^[b]
1			68
2	1a		65
3	1a		65
4	1a		84
5	1a		25
6			66
7			64
8			40
9			67

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), FeCl₂ (0.1 mmol), 80 °C, 8 h. [b] Yield of isolated product.

Various compounds were tested as substrates for the benzylic alkylation reaction under the optimized conditions. The benzylic C–H bonds of both more activated diaryl methanes (Table 2, **1a–1e**) and less activated cyclic substrates (Table 3, **1f** and **1j**) were found to react smoothly with 1,3-dicarbonyl compounds under these conditions. β-Ketone esters and a β-ketone amide were also found to react with diphenylmethane to give the desired products in good yields (Table 2, entries 1–4). A low yield was obtained when a *tert*-butyl-substituted 1,3-diketone was used (Table 2, entry 5), probably because of the steric effects of the *tert*-butyl substituent. Whereas no obvious electronic effect was observed with **1b**, which bears an electron-withdrawing *para*-fluoro group, or **1c**, which bears an electron-donating *para*-methoxy group, a very low yield was obtained with the *ortho*-substituted substrate **1e** (entries 6–8, respectively, in Table 2). 10,11-Dihydro-5H-dibenzo[a,d]cycloheptene (**1e**) was selectively transformed into **3j** (Table 2, entry 9).

The cyclic benzylic compounds **1f** and **1j** gave the expected oxidative coupling products in good yields (Table 3), although the desired products were obtained as an approximately 1:1 mixture of diastereomers from the

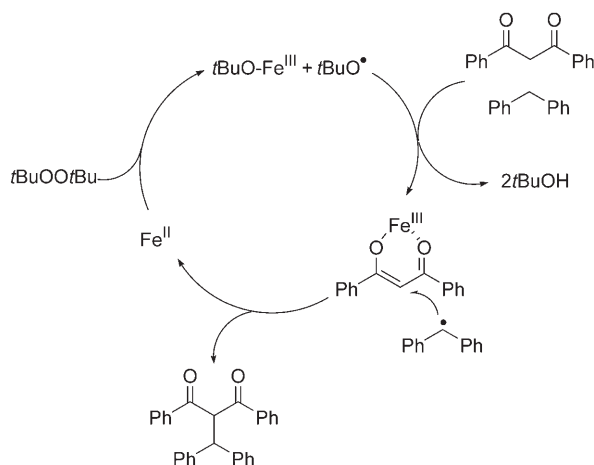
Table 3: Alkylation of cyclic benzylic C–H bonds.^[a]

Entry	Cyclic substrate	Product	Yield [%] ^[b]
1			71 (1.2:1)
2	1f		87 (1:1)
3	1f		78 (1:1)
4	1f		61
5			85 (1.2:1)
6	1j		60
7	1j		80 (1:1)

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), FeCl₂ (0.1 mmol), 80 °C, 8 h. [b] Yield of isolated product. The ratio of the two diastereomers is given in parentheses.

reaction with unsymmetrical dicarbonyl compounds (Table 3, entries 1–3, 5, and 7).

A tentative mechanism for the iron-catalyzed C–C bond formation of benzylic C–H bonds is shown in Scheme 3.



Scheme 3. A tentative mechanism for the FeCl_2 -catalyzed benzylic alkylation.

In summary, we have developed an efficient method for the construction of a C–C bond by an FeCl_2 -catalyzed functionalization of benzylic C–H bonds. The reaction has the following advantages: 1) C–C bonds can be formed directly from C–H bonds; 2) it proceeds under mild reaction conditions; and 3) it uses inexpensive iron as a catalyst. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

Experimental Section

General procedure for the synthesis of products **3**: Diphenylmethane (1 mL, 6.0 mmol) was added to a mixture of 1-benzoylacetone (81 mg, 0.5 mmol) and FeCl_2 (12.6 mg, 0.1 mmol) under nitrogen at room temperature and *tert*-butyl peroxide (0.188 mL, 1.0 mmol) was then added dropwise. The resulting mixture was stirred at room temperature for 36 h or at 80 °C for 8 h. The resulting solid was diluted with dichloromethane and purified by flash column chromatography on silica gel with dichloromethane/petroleum ether (2:1) as eluent. The band that eluted with $R_f = 0.5$ was collected to give the desired product **3a**. M.p. 149.8–150.7 °C; ^1H NMR (300 MHz, CDCl_3 , TMS): $\delta = 7.95$ (d, $J = 7.8$ Hz; 2H), 7.53–7.03 (m; 13H), 5.62 (d, $J = 12.0$ Hz; 1H), 5.10 (d, $J = 12.0$ Hz; 1H), 2.04 ppm (s; 3H); ^{13}C NMR (75.4 MHz, CDCl_3 , TMS): $\delta = 203.0$, 194.2, 141.7, 141.2, 136.9, 133.6, 129.0, 128.7, 128.6, 128.1, 127.7, 127.1, 126.7, 68.9, 51.5, 27.8 ppm.

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- [11] Other iron salts, such as FeI_2 , FeS , $\text{Fe}(\text{OEt})_3$, Fe_2O_3 , $\text{Fe}(\text{TMHD})_3$, and $\text{Fe}(\text{DBM})_3$ (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionato, DBM = dibenzoylmethanato) were found to be inactive under the same conditions.
- [12] Various solvents (CH_3CN , dmsol, thf, CH_2Cl_2 , CHCl_3 , dmf, Et_2O , toluene, etc.) were also tested in the reaction of 2 equiv of **1a** with dibenzoylmethane under the same reaction conditions at room temperature. The desired product (**3b**) was isolated in only about 15 % yield in CHCl_3 or Et_2O . No product was isolated with the other solvents.