DOI: 10.1002/anie.200701782

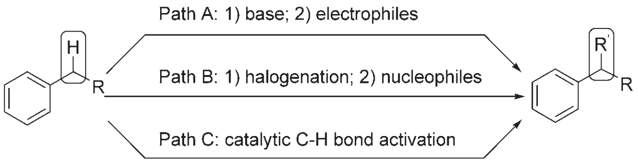
C–C Bond Formation

$FeCl_2$-Catalyzed Selective C–C Bond Formation by Oxidative Activation of a Benzylic C–H Bond[**]

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

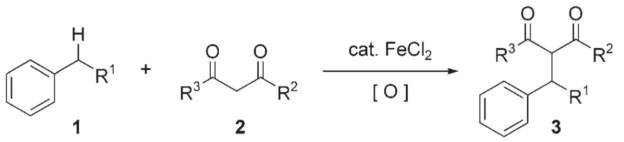
The selective and efficient functionalization of C–H bonds has attracted much attention from both academia and industry in the past decade,[1] and various methods, especially ones based on transition-metal catalysts, have been developed and applied in the synthesis of complex molecules.[1,2] Although 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.

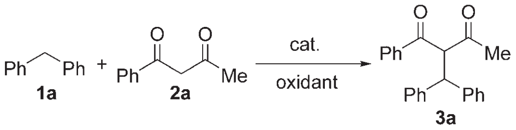
Although transition-metal catalysts are widely used in organic synthesis, the use of more readily available and nontoxic catalysts instead of expensive and sensitive catalysts is highly desirable. The numerous advantages of iron make it highly attractive as a catalyst or reagent for chemical synthesis.[5] 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 $FeCl_2$-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 $CoCl_2$ 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)	*t*BuOO*t*Bu (2)	80	8	66
6	$FeCl_2$ (10)	*t*BuOO*t*Bu (2)	80	8	47
7	$FeCl_2$ (20)	PhCOOO*t*Bu (2)	80	8	n.d.[c]
8	$FeCl_2$ (20)	*t*BuOO*t*Bu (1)	80	8	64
9	$FeBr_2$ (20)	*t*BuOO*t*Bu (2)	80	8	49
10	$FeCl_3$ (20)	*t*BuOO*t*Bu (2)	80	8	56
11	$Fe(OAc)_2$ (20)	*t*BuOO*t*Bu (2)	80	8	n.d.[c]
12[d]	$FeCl_2$ (20)	*t*BuOO*t*Bu (2)	80	8	46
13	$FeCl_2$ (20)	*t*BuOO*t*Bu (1)	RT	36	65
14	$FeCl_2$ (20)	*t*BuOO*t*Bu (2)	RT	36	80
15	–	*t*BuOO*t*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.

---

[*] Prof. Dr. Z. Li, L. Cao
Department of Chemistry, Renmin University of China
Beijing 100872 (China)
Fax: (+86) 10-6251-6444
E-mail: zpli@chem.ruc.edu.cn
Prof. Dr. C.-J. Li
Department of Chemistry, McGill University
801 Sherbrooke Street West, Montreal QC H3A 2K6 (Canada)
Fax: (+1) 514-398-3739
E-mail: cj.li@mcgill.ca

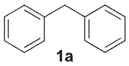
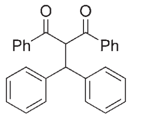
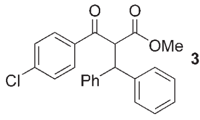
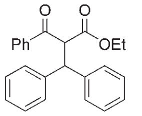
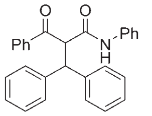
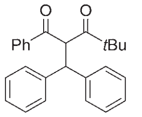
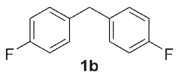
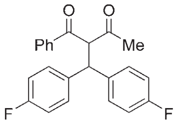
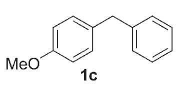
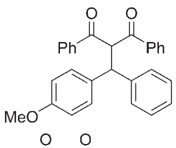
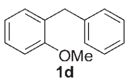
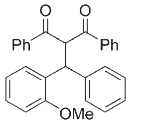
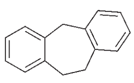
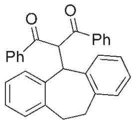
[**] We are grateful to the Scientific Research Starting Foundation of the Renmin University of China (to Z.L.) and the National Natural Science Foundation of China (grant no. 20602038). We also thank the Canada Research Chair (Tier I) foundation (to C.J.L.), and Prof. Zhenfeng Xi (Peking University) for helpful discussions and the supply of chemicals and instruments.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

peroxide (TBHP) as the oxidant (Table 1, entry 1). The yield of **3a** increased to 30% when CuBr and $CoCl_2$ 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 $FeCl_2$ 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 $FeCl_2$ 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]

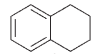
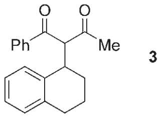
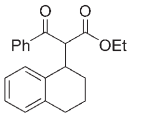
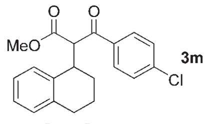
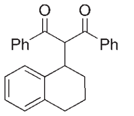
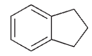
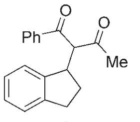
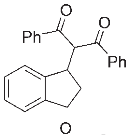
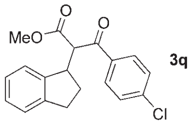
Entry	Diaryl substrate	Product	Yield [%][b]
1	 **1a**	 **3b**	68
2	**1a**	 **3c**	65
3	**1a**	 **3d**	65
4	**1a**	 **3e**	84
5	**1a**	 **3f**	25
6	 **1b**	 **3g**	66
7	 **1c**	 **3h**	64
8	 **1d**	 **3i**	40
9	 **1e**	 **3j**	67

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2$ (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-5*H*-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

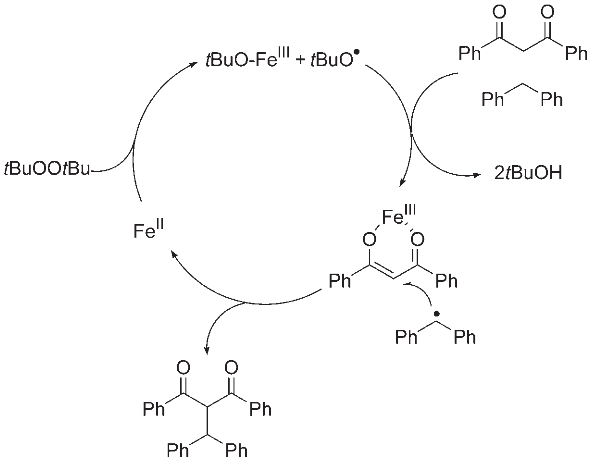
Table 3: Alkylation of cyclic benzylic C–H bonds.[a]

Entry	Cyclic substrate	Product	Yield [%][b]
1	 **1f**	 **3k**	71 (1.2:1)
2	**1f**	 **3l**	87 (1:1)
3	**1f**	 **3m**	78 (1:1)
4	**1f**	 **3n**	61
5	 **1j**	 **3o**	85 (1.2:1)
6	**1j**	 **3p**	60
7	**1j**	 **3q**	80 (1:1)

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2$ (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.

Received: April 23, 2007

Keywords: C–H activation · cross-coupling · iron · peroxides · redox chemistry

---

[1] K. Godula, D. Sames, *Science* **2006**, *312*, 67–72.

[2] *Handbook of C-H Transformations* (Ed.: D. Dyker), Wiley-VCH, Weinheim, **2005**.

[3] Intramolecular reactions: a) H. Ren, P. Knochel, *Angew. Chem.* **2006**, *118*, 3541–3544; *Angew. Chem. Int. Ed.* **2006**, *45*, 3462–3465; b) G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 6204–6210; carbenoid-induced insertion: c) H. M. L. Davies, S. J. Hedley, B. R. Bohall, *J. Org. Chem.* **2005**, *70*, 10737–10742; d) H. M. L. Davies, Q. Jin, P. Ren, A. Y. Kovalevsky, *J. Org. Chem.* **2002**, *67*, 4165–4169; Ir-catalyzed reactions: e) Y. Matsuo, A. Iwashita, E. Nakamura, *Chem. Lett.* **2006**, 858–859.

[4] For the "cation pool" method of electrochemistry, see: M. Okajima, K. Soga, T. Nokami, S. Suga, J. Yoshida, *Org. Lett.* **2006**, *8*, 5005–5007.

[5] Reviews: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) A. Furstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624–629.

[6] Reviews: a) P. Stavropoulos, R. Celenligil-Cetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, *34*, 745–752; b) D. H. R. Barton, D. Doller, *Acc. Chem. Res.* **1992**, *25*, 504–512.

[7] Reviews: a) C. Walling, *Acc. Chem. Res.* **1998**, *31*, 155–157; b) P. A. MacFaul, D. D. M. Wayner, K. U. Ingold, *Acc. Chem. Res.* **1998**, *31*, 159–162.

[8] There is only one report involving photolytic conditions: W. D. Jones, G. P. Foster, J. M. Putinas, *J. Am. Chem. Soc.* **1987**, *109*, 5047–5048.

[9] Iron-catalyzed cross-coupling reactions: a) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297–1299; b) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863; c) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687; d) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem.* **2005**, *117*, 1682–1685; *Angew. Chem. Int. Ed.* **2005**, *44*, 1654–1657; e) K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219–1222; f) L. K. Ottesen, F. Ek, R. Olsson, *Org. Lett.* **2006**, *8*, 1771–1773; g) K. Bica, P. Gaertner, *Org. Lett.* **2006**, *8*, 733–735; h) J. Kischel, K. Mertins, D. Michalik, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 865–870.

[10] Baran and co-workers have recently reported oxidative enolate coupling reactions in the presence of a stoichiometric amount of Fe^{III} or Cu^{II} (2 equiv) as the oxidant: a) P. S. Baran, M. P. DeMartino, *Angew. Chem.* **2006**, *118*, 7241–7244; *Angew. Chem. Int. Ed.* **2006**, *45*, 7083–7086; b) P. S. Baran, N. B. Ambhaikar, C. A. Guerrero, B. D. Hafensteiner, D. W. Lin, J. M. Richter, *ARKIVOC* **2006**, 310–325.

[11] Other iron salts, such as FeI_2, FeS, $Fe(OEt)_3$, Fe_2O_3, $Fe(TMHD)_3$, and $Fe(DBM)_3$ (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, dmso, 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.