DOI: 10.1002/anie.200900341

Iron Catalysis

Cross Dehydrogenative Arylation (CDA) of a Benzylic C–H Bond with Arenes by Iron Catalysis**

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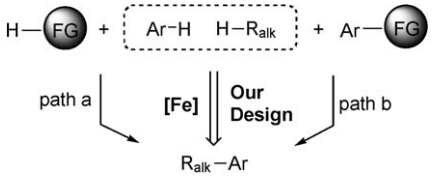
Selective C–H functionalization for the construction of C–C bonds is the most efficient and straightforward method to access complex molecules starting from easily available materials, which is considered the "holy grail" of organic chemistry.[1] Through C–H activation, highly functionalized and complex molecules can be produced with lower cost, minimum environmental impact, and fewer synthetic steps. During the past several years, this area has attracted significant interest from the chemical community, and spectacular achievements have been made.[2] Through the activation of $C(sp^2)$–H bonds, aromatic C(aryl)–C(aryl) and C–heteroatom bonds can be easily constructed with minimum functional-group manipulations.[3] More challenging is the direct functionalization of $C(sp^3)$–H bonds owing to their low reactivity, selectivity problems, and the lack of a coordination site for the transition-metal catalyst.[4] C–H bonds adjacent to heteroatoms or double bonds can be selectively activated because they are more reactive than isolated alkyl C–H bonds.[5] Recently, elegant examples of catalytic cross-coupling between aromatic and aliphatic substrates have appeared.[6] The Li group has reported the CuBr-catalyzed indolation of tetrahydroisoquinolines by the cross dehydrogenative coupling (CDC) between $C(sp^3)$–H and $C(sp^2)$–H bonds.[6a] Another impressive example was also reported by this group in which a simple unactivated alkane was coupled with a chelating arene under ruthenium catalysis.[6b] Additionally, an intramolecular cross-coupling between a C(aryl)–H bond and aliphatic C–H bond catalyzed by palladium was reported by Fagnou and Lie'gault using specific substrates.[6c]

Among the transition metals, iron is particularly attractive because of its low price, nontoxicity, and environmentally benign character, features of crucial importance in light of sustainable and green chemistry.[7] Collectively, iron-catalyzed C–H activation has numerous advantages. Although the iron-catalyzed formation of C–C and C–heteroatom bonds has become popular in recent years, the direct formation of C–C bonds through iron-catalyzed C–H bond activation has been reported only in limited cases.[8] In 1987 Jones et al. reported the iron-catalyzed activation of C(aryl)–H bonds and addition to isonitriles.[8a] More recently Nakamura and co-workers achieved an iron-catalyzed direct arylation of 2-arylpyridine derivatives with organozinc reagents through C–H activation.[8b] The Li group described iron-catalyzed C–C bond formation in the reaction of an active dicarbonyl methylene compound with coupling partners containing a benzylic C–H bond or a C–H bond adjacent to a heteroatom using peroxides as oxidants.[8c,d] Li et al. also reported an efficient direct alkylation of activated methylene with cycloalkanes.[8e] In all these examples, only one type of C–H bond was activated (path a and path b in Scheme 1). Herein we report an unprecedented iron-catalyzed cross-coupling between a benzylic $C(sp^3)$–H bond and the $C(sp^2)$–H bond of an electron-rich arene, in which two different types of C–H bonds are activated simultaneously (see the retrosynthetic analysis in Scheme 1).



Scheme 1. Cross dehydrogenative arylation by iron catalysis.

To initiate our study, diphenylmethane (**2a**) was chosen as a model substrate to react with simple arenes in the presence of an iron source and an oxidant. To understand the regioselectivity of the coupling with the arene counterpart, methyl *o*-methoxylbenzoate (**1a**) was chosen since both electron-withdrawing and electron-donating groups are present on the phenyl ring (Table 1). To our satisfaction, we found that when *t*BuOO*t*Bu was used as the oxidant, the reaction gave a single regioisomer (Table 1, entry 1). This result was very encouraging since there was potential complication in regiocontrol; these reaction conditions provided the baseline on which to improve. Screening of the oxidants quickly revealed that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was the best choice while other oxidants were much

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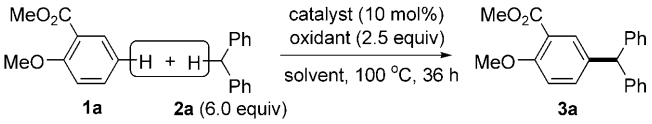
[**] This work was supported by a starter grant from Peking University, grants from the National Sciences of Foundation of China (nos. 20672006, 20821062, GZ419, J0630421) , and the "973" Project from the MOST of China (2009CB825300).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900341.

Table 1: Cross-coupling between **1a** and **2a** under various reaction conditions.[a]



1a **2a** (6.0 equiv) **3a**

Entry	Catalyst	Solvent	Oxidant	Yield [%][b]
1	$FeCl_2$	DCE	*t*BuOO*t*Bu	11
2	$FeCl_2$	DCE	dicumyl peroxide	0
3	$FeCl_2$	DCE	AcOO*t*Bu	0
4	$FeCl_2$	DCE	BQ	0
5	$FeCl_2$	DCE	$Cu(OAc)_2$	0
6	$FeCl_2$	DCE	DDQ	100 (94)[c]
7	$FeCl_2$	DMSO	DDQ	4
8	$FeCl_2$	DMF	DDQ	0
9	$FeCl_2$	chlorobenzene	DDQ	69
10	$FeCl_2$	dioxane	DDQ	66
11	none	DCE	DDQ	8
12	$NiCl_2$	DCE	DDQ	9
13	$CoCl_2$	DCE	DDQ	8
14	$PdCl_2$	DCE	DDQ	11
15	$CuCl_2$	DCE	DDQ	23
16	$FeBr_2$	DCE	DDQ	97
17	FeI_2	DCE	DDQ	21
18	$Fe(OAc)_2$	DCE	DDQ	84
19	$Fe(fumarate)_2$	DCE	DDQ	12

[a] Reaction conditions: 0.5 mmol of methyl 2-methoxybenzoate (**1a**), 3.0 mmol of diphenylmethane (**2a**), 0.05 mmol of catalyst, 1.25 mmol of oxidant in 1 mL of solvent. [b] Yield determined by GC methods using *n*-dodecane as the internal standard. [c] Yield of isolated product in brackets. BQ = 1,4-benzoquinone.

less effective (Table 1, entries 2–6). It is worth mentioning that the use of DDQ as the oxidant is more advantageous than peroxides for safety considerations. The addition of dichloroethane (DCE) as a cosolvent can reduce the amount of diphenylmethane (**2a**) needed to as low as 6 equiv and resulted in 94% yield of the desired product **3a**, whose structure was determined unambiguously by X-ray crystallography (Figure 1). Other solvents gave slightly lower yields (Table 1, entries 7–10). Importantly, other transition metals including cobalt, nickel, palladium, and copper did not accelerate the reaction as markedly as iron (Table 1, entries 11–15). The catalytic activity of the iron species highly depended on the counteranion (Table 1, entries 16–19). It should be noted that the reaction was also highly chemoselective. The cross-coupling did not take place at the phenyl group of the diphenylmethane. Furthermore, the benzylic C–H bond of the triarylmethane product **3a** did not engage in further transformation.

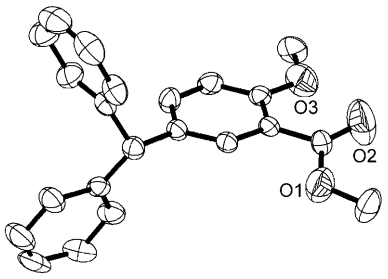


Figure 1. X-ray crystal structure of **3a**; ellipsoids depicted at the 30% probability level. Hydrogen atoms have been omitted for clarity.

Under the optimized conditions, a variety of electron-rich aromatic substrates were investigated, and the results are compiled in Figure 2. The reactions of various substituted

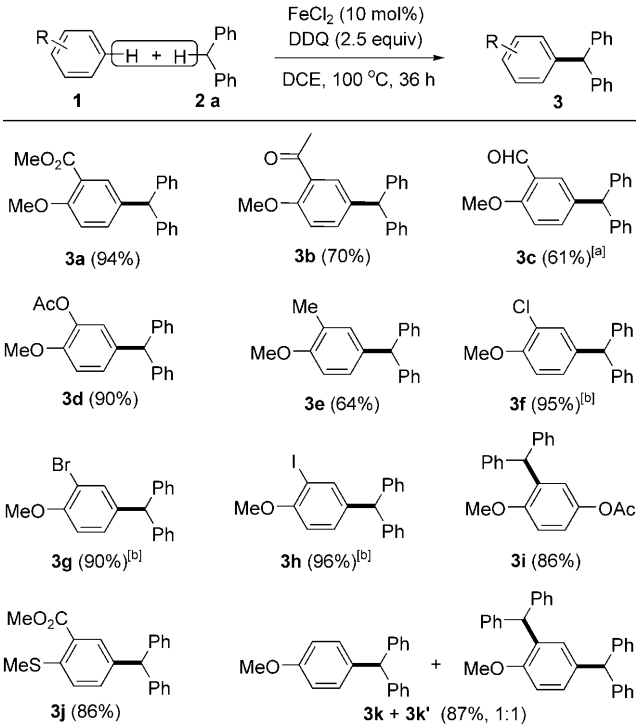
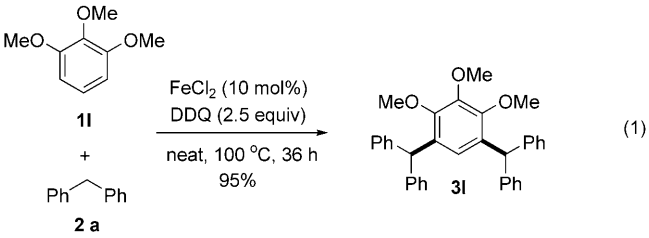


Figure 2. Products obtained by the iron-catalyzed cross dehydrogenative arylation of arenes **1** with **2a**. Reaction conditions: 0.5 mmol of **1**, 3.0 mmol of **2a**, 0.05 mmol of $FeCl_2$, 1.25 mmol of DDQ in 1 mL of DCE. Yields of isolated products are given. [a] Reaction conducted with 20 mol% $FeCl_2$. [b] Yield determined by NMR methods using CH_2Br_2 as an internal standard.

anisoles proceeded with a high level of regiocontrol. For example, orthoester-, acetoxy-, carbonyl-, methyl-, and halide-substituted anisoles reacted to give only one regioisomer (**3a**–**3h**). The *para*-substituted 4-acetoxyanisole also gave a single product (**3i**) in high yield. The regioselectivity could be controlled by a methylthio group instead of the methoxy group (**3j**). Simple anisole gave a mixture of mono- and dibenzylation products (**3k** + **3k′**). Various potentially labile functional groups were well tolerated and did not interfere with the catalyst. It is apparent that increased electron density on the aromatic ring improved the yield, which is in consistent with their nucleophilicity, thus suggesting a Friedel–Crafts-type reaction feature. *o*-Methylanisole does not follow this trend; this finding might be attributed to the over-oxidation of the methyl group, as we have observed some benzylic chlorination products in the crude reaction mixture.

Further increase of the electron density led to mainly dialkylation, as exemplified by the efficient reaction of 1,2,3-trimethoxybenzene (**1l**) with diphenylmethane (**2a**) [Eq. (1)].

During this process, four C–H bonds were cleaved and two new C–C bonds were constructed. These results demonstrated that the judicious tuning of the electronic character of the aromatic substrates is of crucial importance for the chemoselectivity.



(1)

We next examined the reaction with a series of substituted diphenylmethanes (Figure 3). All substrates **2** reacted uniformly with excellent regioselectivity. Steric effect influence the reactivity significantly. For example, the reaction of 1-benzyl-3-methylbenzene gave a slightly lower yield (**3n**), while the efficiency of 1-benzyl-2-methylbenzene was diminished considerably (**3o**). Similarly, electronic effect also played an important role. Electron-withdrawing groups on the diphenylmethane decreased the yields considerably (**3q**, **3r**, **3s**), presumably because they destabilize the proposed methylenyl cation intermediate generated by oxidation. Different functional groups such as fluoro, chloro, and ester were well tolerated with the current reaction system. Besides diarylmethanes, simple benzylic substrate such as mesitylene also worked well under the same conditions. The dimerization of mesitylene gave the desired product **3u** in a good turnover number based on the iron catalyst, albeit at higher temperatures [Eq. (2)].

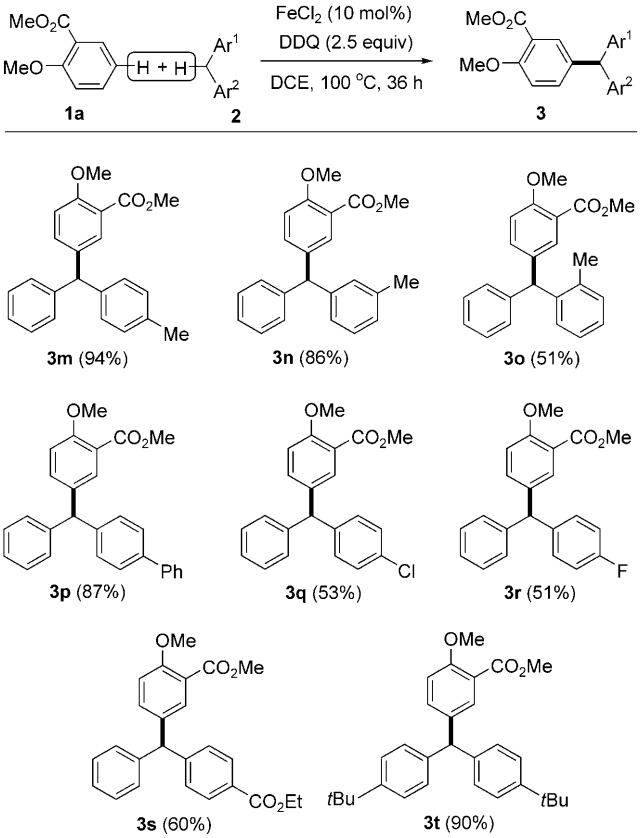
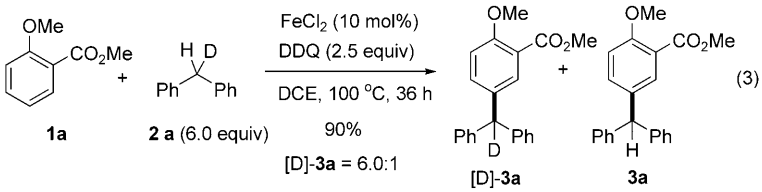
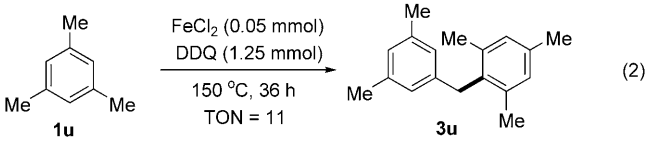


Figure 3. Products obtained by iron-catalyzed cross dehydrogenative arylation of different diarylmethanes **2** with **1a**. Reaction conditions: 0.5 mmol of **1a**, 3.0 mmol of **2**, 0.05 mmol of $FeCl_2$, 1.25 mmol of DDQ in 1 mL of DCE. Yields of isolated products are given.

We also conducted a preliminary mechanistic investigation to gain insight into this novel reaction. Since the homocoupling of diarylmethane was detected but no homocoupling product of the arene formed, it is very likely that the reaction is initiated by the preferential single-electron-transfer (SET) oxidation of the diarylmethane. In addition, a large intramolecular kinetic isotopic effect ($k_H/k_D = 6.0$) was determined [Eq. (3)], indicating that the cleavage of the benzylic C–H bond is involved in the rate-determining step. Furthermore, except for methyl *o*-methoxybenzoate (**1a**), which gave a small amount of the product (8% GC-MS yield) in the absence of the iron catalyst, all the other arenes did not give appreciable amount of products (<5% by GC-MS) when the reaction was conducted without iron catalyst, thus providing evidence that iron is involved in the catalytic cycle and promotes the efficiency. Based on these results, we assume that the reaction is initiated by the iron-assisted SET oxidation to form the benzyl radical, which could be further oxidized to the benzyl cation. A subsequent Friedel–Crafts-type process, followed by abstraction of the proton by the reduced hydroquinone, would deliver the coupling product and regenerate the catalyst (Scheme 2).

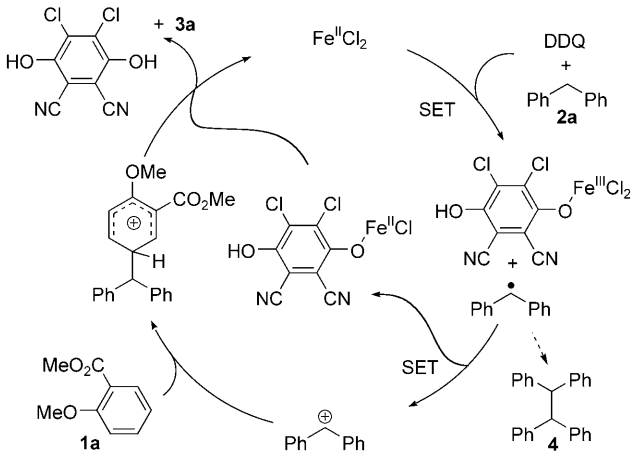


(3)



(2)

In summary, we have demonstrated an unprecedented iron-catalyzed oxidative cross-coupling between compounds containing benzylic $C(sp^3)$–H and aromatic $C(sp^2)$–H bonds. This novel reaction has the advantages of both C–H functionalization and iron chemistry. Considering the great potential of C–H functionalization and vast applicability of iron chemistry, we anticipate that this powerful combination may generate numerous synthetic possibilities. Further investigation of the detailed mechanism and application of this chemistry is currently underway in our lab.



Scheme 2. Proposed mechanism for the dehydrogenative arylation.

Experimental Section

General procedure for the cross dehydrogenative arylation (CDA) of benzylic C–H bonds with arenes: An oven-dried Schlenk tube was charged with DDQ (284 mg, 1.25 mmol), $FeCl_2$ (6.3 mg, 0.05 mmol), diarylmethane **2** (3.0 mmol), and arene **1** (0.5 mmol). The tube was evacuated and refilled with N_2, and this process was repeated three times. Then DCE was added and the reaction mixture was stirred at 100 °C for 36 h. The mixture was cooled down to room temperature and 1.4 g silica gel was added. After removal of the solvent, the residue was purified by flash column chromatography eluting with ethyl acetate and petroleum ether to afford the desired products **3**.

Received: January 19, 2009
Published online: April 16, 2009

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

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