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Iron-Catalyzed Direct Arylation through an Aryl Radical Transfer Pathway

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Biaryl compounds are omnipresent in Nature as well as in numerous biologically active compounds, including antibiotics[1] and various receptor inhibitors, and have been used to treat hypertension as well as bipolar disorders. Consequently, they have attracted much pharmaceutical interest,[2] as well as in other areas including material and supramolecular sciences.[3,4]

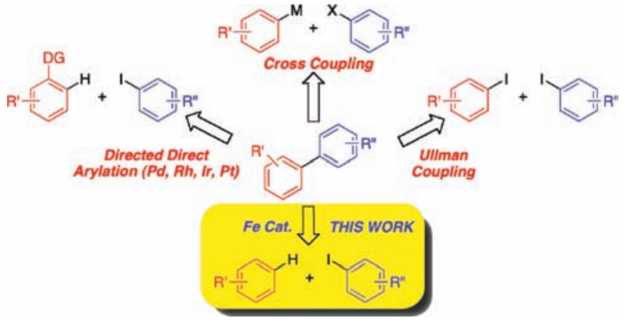
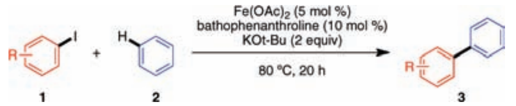


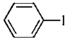
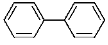
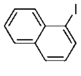
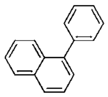
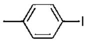
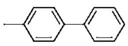
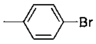
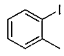
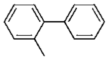
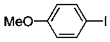
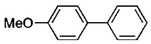
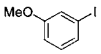
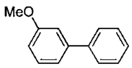
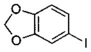
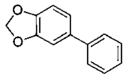
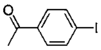
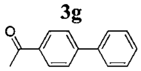
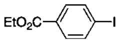
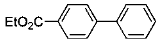
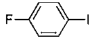
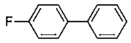
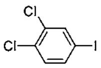
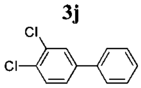
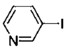
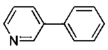
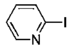
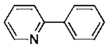
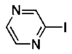
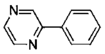
Figure 1. Various ways to prepare biaryl compounds.

The recent application of transition metals to direct functionalization processes has opened an opportunistic new class of carbon−carbon bond forming reactions.[5] Owing to the ubiquity of C−H bonds, the possibility of directly introducing a new functionality via a direct C−H bond transformation is a highly attractive strategy in synthesis.[6] Although several Rh, Pd, and Ru catalysts have proven to be highly effective in such direct coupling processes,[7] the development of new, cost-effective, and environmentally benign catalysts for the aforementioned transformations remains a significant challenge.[8] Iron has recently emerged as a promising alternative as a catalyst for direct C−C bond forming reactions due to their low cost, toxicity, and offer attractive industrial possibilities in terms of sustainable chemistry (Figure 1).[9,10]

While Fe catalysis has been investigated in the field of cross coupling reactions,[11] the envisaged direct arylation of arenes poses a challenge and often requires stoichiometric quantities of iron reagents.[12] In addition, Nakamura recently described the elegant use of an Fe catalyst to perform directed arylation reactions. However, drawbacks of these contributions are that they require not only a directing group, but also a large excess of Grignard reagent in conjunction with a stoichiometric amount of Zn salts.[9] Herein, we report our efforts toward the development of a high yielding, mild, iron-catalyzed direct arylation of unactivated arenes with aryl iodides *without the addition of a stoichiometric amount of metal reagent or the requirement of a directing group.*

Table 1. Iron-Catalyzed Direct Arylation of Benzene with Various Aryl and Heteroaryl Iodides[a]



entry	aryl halide	product	yield (%)
1	 **1a**	 **3a**	89
2	 **1b**	 **3b**	60
3	 **1c**	 **3c**	86
4	 **1d**		46
5[b]	 **1e**	 **3d**	80
6	 **1f**	 **3e**	93 (51)[c]
7	 **1g**	 **3f**	88
8	 **1h**	 **3g**	72
9[d]	 **1i**	 **3h**	69
10	 **1j**	 **3i**	40
11	 **1k**	 **3j**	86
12	 **1l**	 **3k**	53
13	 **1m**	 **3l**	85
14	 **1n**	 **3m**	85
15	 **1o**	 **3n**	79

[a] Reaction conditions: **1** (1 equiv), benzene (100 equiv), $Fe(OAc)_2$ (5 mol %), bathophenanthroline (10 mol %), KO*t*-Bu (2 equiv), 80 °C, 20 h. [b] Reaction performed at 125 °C. [c] Reaction performed at rt for 60 h. [d] Reaction performed at 90 °C.

Our optimization studies determined that a mixture of 4-iodotoluene (1 equiv), benzene (100 equiv), KO*t*-Bu (2 equiv), $Fe(OAc)_2$ (5 mol %), and bathophenanthroline (10 mol %) at a relatively mild 80 °C provided the desired tolyl biphenyl in 86% yield (Table 1, entry 3).[13] Interestingly the catalyst proved to be particularly

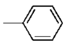
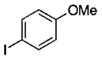
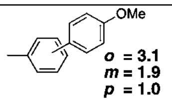
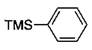
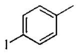
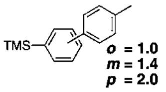
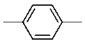
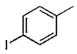
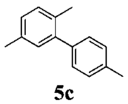
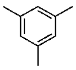
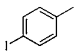
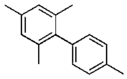
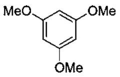
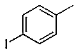
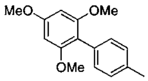
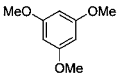
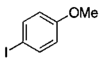
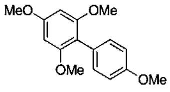
10.1021/ja910687u

efficient, as even a catalyst loading of 0.5 mol % furnished the product in 76% yield (GC) when performed at 125 °C.

With the optimal conditions in hand, we explored the scope of our method using commercially available aryl iodides as coupling partners for benzene. Gratifyingly, the reaction was found to be quite general. The reactions proceeded cleanly, and biaryls **3** were obtained in moderate to excellent yields (Table 1). In a few cases, trace amounts of biphenyl resulting from the coupling of two benzene molecules were detected, although this side product could be readily removed. Unsubstituted aryl iodides provided the biaryl products in good to excellent yields (entries 1, 2). 4-Iodotoluene reacted well under the standard reaction conditions, although 4-bromotoluene was found to be less effective (entries 3, 4) and 4-chlorotoluene proved unreactive. 2-Iodotoluene gave a very good yield when the reaction was performed at 125 °C (entry 5). Electron-rich iodides were exceptionally effective partners (entries 6−8). These species proved to be even effective at rt, as moderate yields were obtained with slightly prolonged reaction times. Electron-poor substrates were operative but provided slightly lower yields (entries 9−10), even iodides bearing enolizable centers (entry 9). Both F and Cl substitutions were tolerated (entries 11, 12). Gratifyingly, pyridyl and pyrazyl iodides provided the corresponding heterobiaryls with excellent results (entries 13−15).

Next, the coupling of different arene derivatives was examined. They combined with aryl iodides to afford the corresponding biaryl products in moderate to good yields (Table 2). Toluene provided a mixture of regioisomers favoring the *o*- position over the *m*- and *p*- positions with a moderate overall yield (Table 2, entry 1). PhTMS also provided a mixture of regioisomers, favoring the *p*- position over the *m*- and *o*- positions with a low overall yield, (entry 2). *p*-Xylene reacted successfully with **1c** furnishing **5c** in 81% yield (entry 3). Interestingly, hindered **4d** reacted with **1c** to afford **5d** in moderate yield (entry 4). Even **4f** reacted with both **1c** and **1f** giving the corresponding products in moderate yields.

Table 2. Iron-Catalyzed Direct Arylation of Arene Derivatives with Various Aryl Iodides[a]

entry	arene	aryl iodide	product	yield (%)
1	 **4a**	 **1f**	 **5a**	50[b]
2	 **4b**	 **1c**	 **5b**	28[b]
3	 **4c**	 **1c**	 **5c**	81
4	 **4d**	 **1c**	 **5d**	63
5	 **4e**	 **1c**	 **5e**	54
6	 **4f**	 **1f**	 **5f**	41

[a] Reaction conditions: **1** (1 equiv), arene (100 equiv), $Fe(OAc)_2$ (5 mol %), bathophenanthroline (10 mol %), KO*t*-Bu (2 equiv), 130 °C, 20 h. [b] Yield determined as a mixture of isomers.

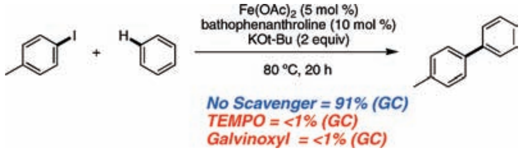
Recently, Bolm and Buchwald reported that reactions catalyzed with $FeCl_3$ may be positively affected by trace quantities of other metals, particularly Cu.[14] Cognizant of this possibility, we investigated whether a catalytic amount of Cu could influence the reaction outcome. $Fe(OAc)_2$ was examined in the direct coupling of benzene with 4-iodotoluene (Table 3). These findings suggest that the purity of $Fe(OAc)_2$ does not play a crucial role in the success of the transformation. Indeed, using $Fe(OAc)_2$ with high purity (99.995%, entry 1) yielded improved results with respect to reagent grade $Fe(OAc)_2$ (97%, entry 2). Both CuOAc and $Cu(OAc)_2$ were ineffective as catalysts (entries 3, 4). Furthermore, using Fe in conjunction with Cu proved to be detrimental, providing 57% and 48% yields with CuOAc and $Cu(OAc)_2$ respectively (entries 5, 6).

Table 3. Direct Arylation in Presence of Fe and Cu Catalysts[a]

entry	catalyst	purity (%)	commercial source	yield(%)[b]
1	$Fe(OAc)_2$	99.995	Aldrich	98 (87)[c]
2	$Fe(OAc)_2$	97	Strem	91
3	Cu(OAc)	99	Strem	6
4	$Cu(OAc)_2$	97	Strem	9
5	$Fe(OAc)_2$ + Cu(OAc)	99.995 + 99	Aldrich Strem	57
6	$Fe(OAc)_2$ + $Cu(OAc)_2$	99.995 + 97	Aldrich Strem	48

[a] Reaction conditions: **1** (1 equiv), benzene (100 equiv), cat. (5 mol %), bathophenanthroline (10 mol %), KO*t*-Bu (2 equiv), 80 °C, 20 h. [b] Yield determined by GCMS analysis using an internal standard. [c] Yield of isolated product.

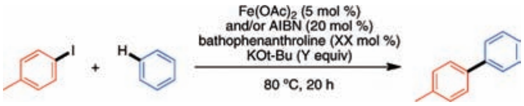
Scheme 1. Effect of Radical Inhibitors



To gain some understanding of the reaction, a KIE of 1.04 was determined. This result suggested that the C−H bond breaking event was not rate limiting. This was surprising and prompted us to consider a possible radical pathway, which is known to exhibit such low values in radical aromatic substitutions.[15] This was indeed supported by experiments performed in the presence of radical scavengers. Galvinoxyl and TEMPO (1 equiv) completely inhibited the reaction (Scheme 1). Other experiments (Table 4) demonstrated that *t*BuOK is likely less important in the radical transformation as has been reported (entry 2)[16] and that a metal-free version of the reaction using AIBN was possible; however, it was far less efficient (entry 3).

Due to the results shown in Tables 3 and 4 and Scheme 1, we believe that a plausible mechanistic pathway could be analogous to that reported in a metal-catalyzed living radical polymerization reaction (Figure 2).[17] The Fe-catalyzed radical direct coupling is believed to proceed via reversible activation of the aryl−halogen bond by via a one-electron oxidation of the metal center to form an initiating radical species and an oxidized metallo-intermediate. This intermediate is then transformed into the biaryl product via radical addition onto an arene (possibly precoordinated to Fe) and proximal abstraction of a halogen atom from the Fe^{III} complex. This regenerates the active form of the catalyst as well as HI that can be quenched by *t*BuOK. Although we cannot rule out a more prominent role of *t*BuOK, the presence of *t*BuOH is observed in the reaction mixture. As in the metal-catalyzed living radical polymerization, the reaction would rely on creating a dynamic equilibrium between a low concentration of growing radicals and a large amount of dormant species, which cannot propagate and/or self-terminate. As a result, side reactions are limited, and the process of direct coupling is efficient. Such a mechanism would explain the increased efficiency of electron-rich species, as they could stabilize radical intermediates, providing a positive β-effect.[15] This may explain the preference for *o*-substitution in toluene, due to the formation of a tertiary radical stabilized though additional hyperconjugation. In addition, the observed ratios are consistent with aryl radical substitutions onto toluene.[15]

Table 4. Direct Arylation in Presence of Fe and AIBN[a]



entry	catalyst	ligand	KO*t*-Bu	yield (%)[b]
1	$Fe(OAc)_2$	10 mol %	2 equiv	91
2	none	10 mol %	2 equiv	0
3	AIBN	none	2 equiv	17
4	$Fe(OAc)_2$ + AIBN	10 mol %	none	0

[a] Reaction conditions: **1** (1 equiv), benzene (100 equiv), cat. (5 mol %), bathophenanthroline (10 mol %), KO*t*-Bu (2 equiv), 80 °C, 20 h. [b] Yield determined by GCMS analysis using an internal standard.

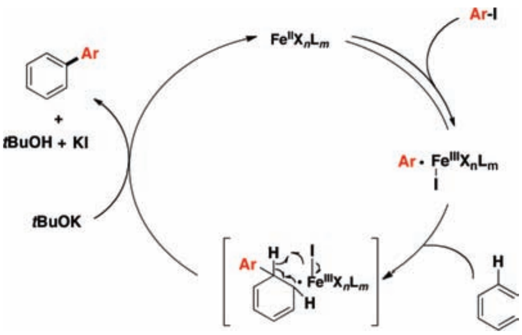


Figure 2. Proposed catalytic cycle.

In summary, we have demonstrated that the inexpensive and environmentally friendly catalytic system composed of $Fe(OAc)_2$ and bathophenanthroline is highly effective for the synthesis of biaryl compounds. Mechanistic evidence suggests that the transformation proceeds through an Fe-catalyzed radical process giving a metal-catalyzed radical living direct arylation.[17] This novel process constitutes a powerful and practical direct arylation protocol under mild conditions. Work is ongoing to determine the full extent of these reactions as well as a detailed mechanistic analysis of the process.

Acknowledgment. This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), Merck Frosst Canada Ltd., Boehringer Ingelheim (Canada), Ltd., the Canada Research Chair Program, the Canada Foundation for Innovation, and the Université de Montréal. J.J.M. is grateful to FQRNT for a doctoral scholarship.

Supporting Information Available: Experimental procedures, sample spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA910687U