


## Iron-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction

David Bézier<sup>a</sup> and Christophe Darcel<sup>a,\*</sup>

<sup>a</sup> UMR 6226 CNRS-Université de Rennes 1 “Sciences Chimiques de Rennes”, Equipe “Catalyse et Organométalliques”, Campus de Beaulieu, Bat 10C, Avenue du Général Leclerc, 35042 Rennes Cedex, France  
Fax: (+33)-2-2323-6939; e-mail: christophe.darcel@univ-rennes1.fr

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**Abstract:** An efficient, mild, and simple protocol for iron-catalyzed Suzuki–Miyaura type cross-coupling reaction between iodo- or bromoaryl derivatives and arylboronic acids was developed. In the presence of iron(III) chloride (10 mol%) and a stoichiometric amount of potassium fluoride, aryl iodides and bromides reacted with arylboronic acids in ethanol at 100 °C under air to give the corresponding bis-aryl compounds with good to excellent yields.

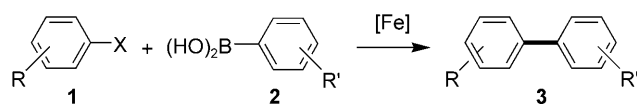
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For the construction of carbon-carbon bonds, some of the most common and powerful methods involve the use of transition metal-mediated reactions. Among these methods, the Suzuki–Miyaura cross-coupling reaction<sup>[1]</sup> has become one of the most useful and worthy synthetic methods for selective biaryl C–C bond formation,<sup>[2]</sup> which are often included as partial structures in natural products,<sup>[3]</sup> pharmaceuticals,<sup>[4]</sup> functional materials,<sup>[5]</sup> etc. This reaction is actually one of the most frequently used transition metal-catalyzed ones either in academic or in industrial areas. However, the most interesting features of organoboron reagents and their by-products are their low toxicity, making these compounds environmentally practical compared to other organometallic reagents, particularly organostannanes. Countless improvements on the original Suzuki–Miyaura protocol for the cross-couplings of aryl halides with arylboronic acids have been recorded. Important contributions include great improvements in substrate scope, catalyst/ligand systems and solvents, as well as enhanced experimental conditions. One important drawback in the palladium

series is certainly that the complexes are usually air-sensitive.

In the environmental context of today, one of the challenging issues for chemists is to develop cost-effective, green, mild, and efficient catalytic routes that minimize hazardous waste. On the other hand, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices can constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on the earth, and one of the most inexpensive and environmentally friendly ones. Despite the fact that the coordination chemistry of iron was widely developed in the past decades, it is really surprising that, until lately, iron was under-represented in the field of homogeneous catalysis relative to the other transition metals. However, the last few years have seen a rise in the use of iron as a catalyst,<sup>[6]</sup> and very efficient processes that are now able to compete with other metal-catalyzed ones have emerged in the hydrosilylation,<sup>[7]</sup> oxidation,<sup>[8]</sup> epoxidation<sup>[9]</sup> and even hydrogenation areas.<sup>[10]</sup> In the field of carbon-carbon bond formation *via* cross-coupling reactions of Grignard derivatives, an intensive work was accomplished since the pioneering reports of Kochi<sup>[11]</sup> and the iron-catalyzed cross-coupling methodology is able to compete with the palladium-catalyzed one.<sup>[12]</sup> Iron-catalyzed cross-coupling reactions were also realized with organometallic reagents such as zinc,<sup>[13]</sup> copper,<sup>[14]</sup> or manganese<sup>[15]</sup> derivatives. During the course of this work, a pioneering communication related to the cross-coupling reaction of phenylboronic acid with a limited number of bromoaryl derivatives catalyzed by pyridyliron complexes was published.<sup>[16]</sup>

In continuing our work on the use of iron as catalyst to promote environmentally benign synthetic methodologies,<sup>[17–19]</sup> we describe herein an cross-coupling reaction of halogenoaryl compounds (X = I, Br) with arylboronic acid in ethanol in the presence of a catalytic amount of FeCl<sub>3</sub> in combination with a stoichiometric amount of KF (Scheme 1).



**Scheme 1.** Iron-catalyzed Miyaura–Suzuki cross-coupling reaction.

In the initial attempts to improve this iron-catalyzed Suzuki–Miyaura type cross-coupling reaction, iodobenzene was chosen as a test substrate to optimize the reaction conditions (Scheme 1). An ethanol solution of iodobenzene was allowed to react with phenylboronic acid (2 equivalents) at 100 °C in the presence of a catalytic amount of iron salt (10 mol%) and 3.5 equivalents of KF. After warming in a sealed Schlenk tube at 100 °C for 16 h, the reaction afforded the cross-coupling product with complete conversion of the iodobenzene. We then carried out extensive investigations to define the best reaction conditions, and Table 1 lists representative data obtained for the cross-coupling reaction of iodobenzene with phenylboronic acid with various commercially available iron(II) and iron(III) salts.

First of all, on using acetate iron salts such as Fe(acac)<sub>2</sub> or Fe(acac)<sub>3</sub> as catalysts, only moderate GC yields were obtained (28 and 40%, respectively) (Table 1, entries 2 and 3). Interestingly, the use of Fe(OAc)<sub>2</sub> or FeSO<sub>4</sub>·7H<sub>2</sub>O gave satisfactory results (65% GC yield) (Table 1, entries 6 and 7). Iron halide salts seem to be then best catalyst precursors (Table 1, entries 8–11), and dry FeCl<sub>3</sub> was the best iron salt for the formation of the biphenyl compound (100% GC yield). (Table 1, entry 11) Interestingly,

**Table 1.** Iron salt screening for the Miyaura–Suzuki cross-coupling reaction of phenyl iodide with phenylboronic acid.

Entry	Iron salt (10 mol%) <sup>[a]</sup>	GC yield [%] <sup>[b]</sup>
1	–	0
2	Fe(acac) <sub>2</sub>	28
3	Fe(acac) <sub>3</sub>	40
4	Fe <sub>2</sub> O <sub>3</sub>	30
5	FeF <sub>2</sub>	16
6	FeSO <sub>4</sub> ·7H <sub>2</sub> O	65
7	Fe(OAc) <sub>2</sub>	65
8	FeBr <sub>2</sub>	75
9	FeCl <sub>2</sub>	75
10	FeF <sub>3</sub>	95
11	<b>FeCl<sub>3</sub></b>	<b>100</b>
12	FeCl <sub>3</sub> ·6H <sub>2</sub> O	22

<sup>[a]</sup> Experimental conditions: bromobenzene (0.5 mmol), phenylboronic acid (1 mmol), KF (1.75 mmol), iron salt (10 mol%) in 3 mL of ethanol for 16 h in a sealed tube.

<sup>[b]</sup> GC yield.

when a hydrated precursor FeCl<sub>3</sub>·6H<sub>2</sub>O was used, only 22% of the biphenyl derivative was obtained (Table 1, entry 12). A control experiment in the absence of an iron salt confirmed the crucial role which the iron catalyst plays in the described cross-coupling reaction as the reaction did not occur.

It must be also underlined that when the reaction was performed under argon, at 100 °C for 16 h in a sealed tube using FeCl<sub>3</sub> as catalyst in ethanol in the presence of KF, no conversion was observed. This result shows the crucial role of air in the iron-catalytic process.

To get more information on the optimal catalyst conditions, we carried out also intensive investigations to define the best solvent for this transformation. 6 different solvents were tested at reflux for 16 h using 10 mol% of FeCl<sub>3</sub> as catalyst. Table 2 lists representative data collected for the synthesis of biphenyl **3a** as a model reaction.

Among the different solvents screened, ethanol has been found to be a far better solvent: biphenyl **3a** was obtained with excellent GC yield (100%) (Table 2, entry 7). In some classical solvents such as toluene, ether, THF or methanol, surprisingly, no reaction took place (Table 2, entries 1–4). When the reaction was conducted in refluxing isopropyl alcohol or ethanol, only low conversions were observed, 10 and 25%, respectively (Table 2, entries 5 and 6). We also might point out the crucial role of the pressure on the cross-coupling process. When the reaction was performed in an open flask under reflux for 16 h, only 25% conversion was observed. On the contrary, when it was conducted in a sealed tube at 100 °C, 100% conversion was observed. It should be noted that the reaction was clean and only the cross-coupling product was detected on GC. Interestingly, reduction of the

**Table 2.** Investigation of solvents and additives on the model reaction.

Entry	Additive <sup>[a]</sup>	Solvent	Conditions	GC Yield [%] <sup>[b]</sup>
1	KF	THF	Reflux, 16 h	0
2	KF	Toluene	Reflux, 16 h	0
3	KF	Ether	Reflux, 16 h	0
4	KF	MeOH	Reflux, 16 h	0
5	KF	i-PrOH	Reflux, 16 h	10
6	KF	EtOH	Reflux, 16 h	25
7	<b>KF</b>	<b>EtOH</b>	<b>100 °C, 16 h<sup>[c]</sup></b>	<b>100</b>
8	KO- <i>t</i> -Bu	EtOH	100 °C, 16 h <sup>[c]</sup>	22
9	Cs <sub>2</sub> CO <sub>3</sub>	EtOH	100 °C, 16 h <sup>[c]</sup>	5
10	K <sub>3</sub> PO <sub>4</sub>	EtOH	100 °C, 16 h	0
11	KOAc	EtOH	100 °C, 16 h <sup>[c]</sup>	0
12	CsF	EtOH	100 °C, 16 h <sup>[c]</sup>	80

<sup>[a]</sup> Experimental conditions: bromobenzene (0.5 mmol), phenylboronic acid (1 mmol), additive (1.75 mmol, 3.5 equiv.), FeCl<sub>3</sub> (10 mol%) in 3 mL of solvent for 16 h.

<sup>[b]</sup> GC yield.

<sup>[c]</sup> Reaction performed on a sealed tube.

aryl halides was not observed and only trace amounts of biphenyl derivatives (<1%) resulting from the homocoupling of arylboronic acids were detected by GC-MS analysis.

In those conditions, a small pressure in the sealed reactor favoured the reaction. One very recent communication supported this opinion: Young and co-workers reported that the metal-catalyzed Suzuki–Miyaura cross-coupling reaction between bromobenzene and phenylboronic acid can be promoted at high pressure (15 kbar). In particular, using  $\text{FeCl}_3/2$ -(diphenylphosphino)pyridine as catalyst (5 mol%), 97% conversion was observed after 48 h at 100 °C.<sup>[20]</sup> They suggested that the main influence of pressure on the iron-catalyzed reaction should be the acceleration of the reduction of the metal to a catalytically active oxidation state. Usually, in iron-catalyzed cross-coupling reaction, a reducing agent such as a Grignard reagent is required to reduce the iron salt to its low valent state as the catalytically active species.<sup>[12d,e]</sup>

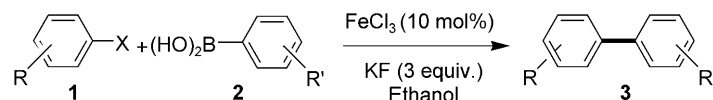
The nature of the additive has also a crucial role on the reaction. When  $\text{Cs}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ , or  $\text{KOAc}$  were used as additives (3.5 equivalents) instead of  $\text{KF}$ , the formation of only trace amount of the desired product **3a** was detected on GC. (Table 2, entries 9–11) With  $\text{KO}-t\text{-Bu}$  as additive, a better conversion was observed (22%) (Table 2, entry 8). Finally, when  $\text{CsF}$

was used, the biphenyl derivative **3a** was obtained with 80% GC yield (Table 2, entry 12).

We next examined the scope and limitations of this iron-catalyzed cross-coupling reaction with various types of iodo- and bromoaryl derivatives and arylboronic acids (Table 3). All reactions were carried out with 10 mol% of  $\text{FeCl}_3$  in HPLC grade ethanol at 90–100 °C in the presence of a stoichiometric amount of  $\text{KF}$  in a sealed tube. In general, all reactions were clean, and bis-aryl derivatives **3** were obtained in good yields.

The cross-coupling reaction of iodoaryl derivative was amenable to both electron-rich and electron-poor aromatic iodoaryl derivatives such as iodobenzene or *para*-substituted (Me, OMe,  $\text{CF}_3$ ) iodobenzenes, and the reaction gave the corresponding bis-aryl compounds **3** in good to excellent yields (75–98%; Table 3, entries 1–4). No great influence of the *para*-substituted group on the arylboronic acid partner was observed for the reaction with iodobenzene; both arylboronic acids which possess an electron-donating or electron-withdrawing group on the aryl ring gave the corresponding bis-aryl products **3** in good to excellent isolated yield (77–98%) (Table 3, entries 5–8). It must be pointed out, with *p*-fluoro and *p*-acetylphenylboronic acids, to avoid a degradation procedure of the starting compounds, that the reaction was conducted at 90 °C (Table 3, entries 6 and 8).

**Table 3.** Scope of the reaction.



Entry	Ar-X	Ar'-B(OH) <sub>2</sub>	Conditions <sup>[a]</sup>	Compound	Yield [%] <sup>[b]</sup>
1	Ph-I	Ph-B(OH) <sub>2</sub>	16 h/100 °C	Ph-Ph	<b>3a</b> 96
2	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -I	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -Ph	<b>3b</b> 75
3	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> -I	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> -Ph	<b>3c</b> 80
4	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -I	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -Ph	<b>3d</b> 98
5	Ph-I	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	16 h/100 °C	Ph-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -CF <sub>3</sub>	<b>3d</b> 98
6	Ph-I	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	30 h/90 °C	Ph-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -F	<b>3e</b> 77
7	Ph-I	<i>p</i> -OEt-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	16 h/100 °C	Ph-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OEt	<b>3f</b> 96
8	Ph-I	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	30 h/90 °C	Ph-C <sub>6</sub> H <sub>4</sub> - <i>p</i> -COMe	<b>3g</b> 85
9	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -Br	Ph-B(OH) <sub>2</sub>	16 h/100 °C <sup>c</sup>	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -Ph	<b>3h</b> 98
10	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -Br	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -Ph	<b>3d</b> 99
11	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Ph	<b>3g</b> 98
12	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Br	Ph-B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Ph	<b>3c</b> 35
13	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	16 h/90 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> -COMe	<b>3i</b> 99
14	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> -CF <sub>3</sub>	<b>3j</b> 97
15	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	30 h/90 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> -F	<b>3k</b> 97
16	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	36 h/100 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> -Me	<b>3l</b> 97
17	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	<i>p</i> -OEt-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> -OEt	<b>3m</b> 83
18	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -Br	1-NaphthylB(OH) <sub>2</sub>	16 h/100 °C	<i>p</i> -MeCO-C <sub>6</sub> H <sub>4</sub> -1-Naphthyl	<b>3n</b> 32

<sup>[a]</sup> Experimental conditions: aryl halide (0.5 mmol), arylboronic acid (1 mmol),  $\text{KF}$  (1.75 mmol, 3.5 equiv.),  $\text{FeCl}_3$  (10 mol%) in 3 mL of ethanol in a sealed tube.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup>  $\text{CsF}$  instead  $\text{KF}$ .

Interestingly, the cross-coupling reaction can be also successful with bromobenzene derivatives. *para*-Electron-withdrawing group substituted (NO<sub>2</sub>, MeCO, CF<sub>3</sub>) bromobenzenes, coupled with phenylboronic acid in excellent yields (98–99%) (Table 3, entries 9–11). Worthy of note is that an electron-rich bromobenzene, such as *p*-methoxybromobenzene, led to the bis-aryl product with a moderate yield (35%) (Table 3, entry 12). Even after a prolonged reaction time (60 h at 100 °C), no better result was obtained.

Next, the reaction of various boronic acids with an electron-poor bromobenzene was also examined using the present catalytic system. The reaction of bromobenzene with various *p*-electron-withdrawing groups (MeCO, F, CF<sub>3</sub>) and *p*-electron-donating (Me, OMe) substituted phenylboronic acids led to the corresponding cross-coupling compounds **3** with good to excellent isolated yields (83–99%) (Table 3, entries 13–17). Furthermore, it must also be underlined that, in our experimental conditions, hindrance hampers the reaction. Indeed, with a sterically hindered *ortho*-substituted bromobenzene such as *o*-trifluoromethyl-, *o*-nitro-, or *o*-acetyl bromobenzene, no reaction occurred after 16 h at 100 °C. In the case of a more sterically hindered arylboronic acid such as 1-naphthylboronic acid, only 32% yield for the coupling product with the *p*-acetyl bromobenzene was isolated (Table 3, entry 18).

In summary, we have developed an interesting and useful iron-catalyzed protocol for Suzuki–Miyaura coupling reactions. It proceeds at 100 °C under small pressure in ethanol in a sealed tube in the presence of a stoichiometric amount of potassium fluoride (3.5 equivalents) and 10 mol% of FeCl<sub>3</sub>. Although the literature enumerates a number of procedures for Suzuki cross-coupling reactions, the simplicity, environmental acceptability, and inexpensiveness of our procedure makes it a practical alternative. As a result of its ease of manipulation, low-cost, and benign character, the new iron catalyst described appears promising for large-scale applications. Studies to improve the catalyst performance and to expand the substrate scope of the method are currently in progress in our laboratory.

## Experimental Section

### General Procedure for Iron-Catalyzed Suzuki–Miyaura Reaction<sup>[21]</sup>

FeCl<sub>3</sub> (8.2 mg, 0.05 mmol, 10 mol%; 98% from Aldrich) was dissolved in in HPLC grade ethanol (3 mL). The aryl halide (0.5 mmol, 1 equiv.) and phenylboronic acid (122 mg, 1 mmol, 2 equiv.) were then added to the mixture which was stirred 10 min at room temperature. Finally, KF (102 mg, 1.75 mmol, 3.5 equiv.) was introduced and the reaction mixture was then warmed at 100 °C for 16 h in a sealed tube.

The reaction progress was monitored by GC. The mixture was cooled to room temperature, extracted with EtOAc (20 mL) and washed with distilled water (2 × 15 mL) and then dried over MgSO<sub>4</sub>. Then, the solvent was removed under vacuum, and the residue was purified by flash column (petroleum ether/ethyl acetate, 95:5), Bis-aryl derivatives were obtained as solids. <sup>1</sup>H and <sup>13</sup>C NMR data for the products were in accordance with literature values.

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