



trans-Tetrakis(pyridine)dichloroiron(II) as catalyst for Suzuki cross-coupling in ethanol and water

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ABSTRACT

Aryl bromides can be coupled with phenylboronic acid in moderate to excellent yields using a *trans*-tetrakis(pyridine)dichloroiron(II) catalyst. The Suzuki–Miyaura reaction can be carried out under air in ethanol and aqueous ethanol with low catalyst loading. Addition of TBAB dramatically increases the yields in aqueous ethanol or in water. *trans*-Tetrakis(pyridine)dichloroiron(II) offers an environmental and less expensive method for the synthesis of biaryl compounds. This is the first example of an iron–pyridine catalyst for Suzuki cross-coupling.

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Transition metal-catalyzed cross-coupling reactions are widely used methods for carbon–carbon bond formation.¹ The palladium-catalyzed Suzuki reaction has become an extremely useful process for the synthesis of biaryl moieties present in, for example, pharmaceuticals.^{2,3} Consequently, much attention has been focused on improving the reaction by designing novel ligands, such as sterically hindered electron-rich phosphine ligands,⁴ palladacycles,⁵ and chiral Schiff bases and diamines.⁶ However, most of the ligands are expensive or their complexes are air sensitive, which significantly limits their industrial applications. We have recently developed a ligandless version of the Suzuki reaction catalyzed by Pd/C in water.⁷ Compared to air-sensitive and expensive complexes, palladium on charcoal can be safely handled, restored and removed from the reaction mixture by simple filtration. Nickel complexes have also been reported to be excellent catalysts in Suzuki reactions, but appear to have a less general scope than Pd-catalysts.⁸ In addition to these two most commonly used metal-catalysts, other transition metals, for example iron, have recently been actively investigated in cross-coupling reactions.^{9,10} The development of efficient catalytic systems consisting of economical catalysts, mild bases, and environmentally friendly solvents remains a highly desirable goal.³ Iron salt catalysts have been used successfully in homo-coupling reactions of aryl–metal

reagents⁹ and aromatic Grignard reagents¹⁰ using 1–10 mol % iron. Ferrocene- and ferrocenium-based palladium pincer complexes have been used as catalysts in Suzuki reactions with low catalyst loading.¹¹ Iron complexed to *N,N,N*-bis(imino)pyridyl-type ligands has been used for ethylene and 1-hexene polymerization.¹² Iron chloride complexed with pyridine^{13–16} and bipyridine¹⁷ is known, but these iron complexes have not been used in cross-coupling reactions. FeCl₂py₄ has been used as a reactant when synthesizing larger iron complexes.¹⁸ Electronic and structural properties, such as Mössbauer spectra¹⁹ and crystal structures,¹⁴ have been investigated for FeCl₂py₄. FeCl₂py₄ has also found application for the oxygenation of cyclohexane,¹⁵ and FeCl₂py₄⁺ has been used as a catalyst for the transformation of aromatic amines by HOOH.¹⁶ [Fepy₃Cl₃]py complexes are known to be unstable in air.¹³ The instability, however, might arise from the dissociation of pyridine ligands. More information on iron-catalyzed reactions and reviews in this field of research can be found in papers by Fürstner and co-workers.^{20–22}

In this Letter, we report that FeCl₃·6H₂O forms complexes with pyridine or 2,6-dichloropyridine: *trans*-tetrakis(pyridine)dichloroiron(II) complex **1**²³ (Fig. 1), and an as yet still unidentified complex **2**, respectively, that exhibit excellent catalyst activity for simple biaryl synthesis in ethanol and in aqueous ethanol.

Unfortunately, we could only obtain X-ray diffraction quality crystals of complex **1**. The X-ray structure of **1**²⁴ had been previously published by Long and Clarke.¹⁴ To illustrate the catalytic activity and stability, both complexes were used as the catalyst for the formation of 4-nitro-, 4-acetyl-, and 4-methoxybiphenyl.

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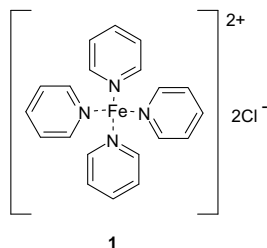


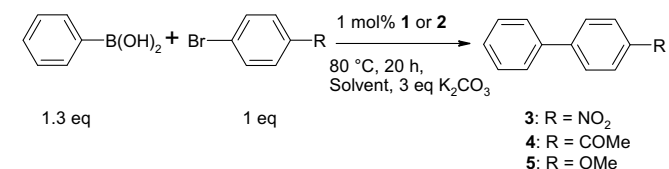
Figure 1. The isolated iron-pyridine complex **1**.

Reaction in air (Table 1, entries 4–6) compared to reactions performed under argon (Table 1, entries 1–3) led us to store both complexes under air, although we noticed some loss of catalytic activity. Although some iron(III)-pyridine complexes and FeCl_2py_4 are reported to need an inert atmosphere,¹³ compounds **1** and **2** seem to be reasonably stable in air. The difference in stabilities might arise due to different dissociation processes of the pyridine ligands. In our case, the initial iron species might be converted to $\gamma\text{-Fe}_2\text{O}_3$ as reported previously.²⁵ This would be the case, especially when reactions are performed under air. We noticed, however, that the yields were not significantly different although all the reactions presented in Table 2 were performed under argon. Therefore, at present, we do not speculate about the conversions of iron species before additional experiments have been performed.

Due to the fact that reactions proceeded with moderate to excellent yields when performed under argon, and that good yields could also be obtained if the reactions were performed under air, especially when the *para* substituent was nitro or acetyl (Table 1, entries 4–5), we concluded that it would perhaps also be possible to use complexes **1** and **2** in aqueous solvent systems (Table 2). We observed that when using a mixture of ethanol/water 1:1 (Table 2, entries 1–3), the yields were similar to those in neat ethanol under air (Table 1, entries 4–6). The catalyst activity did not vary greatly when ethanol was replaced by water as solvent (Table 2, entries 7–9).

Addition of tetrabutylammonium bromide (TBAB) accelerated the cross-coupling reaction in the aqueous environment. We believe that the addition of TBAB increased the organic substrate solubility and also activated the boronic acids by forming a boronate complex, as previously described.²⁶ We, therefore decided to use TBAB as the phase-transfer catalyst in aqueous reaction mixtures. Addition of 1.3 equiv of TBAB improved the yields in ethanol/water 1:1 (Table 2, entries 4–6) and in water (Table 2, entries 10–12).

Table 1
Suzuki reactions of phenylboronic acid with three aryl bromides using iron-pyridine catalysts **1** and **2** in ethanol



Entry	Atmosphere	Product R	Yield % using catalyst	
			1	2
1	Argon	NO ₂	99	99
2	Argon	COMe	99	99
3	Argon	OMe	19	48
4	Air	NO ₂	62	82
5	Air	COMe	50	86
6	Air	OMe	38	48

Table 2

Suzuki reactions with aryl bromides using iron-pyridine catalysts **1** or **2** in aqueous media under air^a

Entry	Solvent	Product R	Yield % using catalyst	
			1	2
1	Ethanol/water 1:1	NO ₂	57	96
2	Ethanol/water 1:1	COMe	66	99
3	Ethanol/water 1:1	OMe	5	48
4	Ethanol/water 1:1 + TBAB	NO ₂	100	98
5	Ethanol/water 1:1 + TBAB	COMe	100	80
6	Ethanol/water 1:1 + TBAB	OMe	12	49
7	Water	NO ₂	nr	28
8	Water	COMe	75	94
9	Water	OMe	43	7
10	Water + TBAB	NO ₂	81	100
11	Water + TBAB	COMe	100	100
12	Water + TBAB	OMe	63	59

Nr: no reaction. No remarkable difference in yields was observed when reactions were performed under argon instead.

^a The reaction was carried out using 1.0 equiv of aryl bromide, 1.3 equiv of phenylboronic acid, and 1 mol % of catalyst in the presence of 3.0 equiv of K_2CO_3 and 1.3 equiv of TBAB.

In conclusion, we have shown that an iron-pyridine complex can serve as an excellent catalyst for Suzuki–Miyaura coupling reactions performed under air in ethanol, aqueous ethanol, or water as solvent. Our result offers a less expensive preparation of biphenyls. This phosphine and palladium-free method is simple and can be used to generate products with low catalyst loading. The protocol not only represents the first example of an iron-pyridine catalyst suitable for biaryl coupling, but also demonstrates the versatility of iron catalysts and broadens the prospects of their applications in organic synthesis.

Preparation of trans-tetrakis(pyridine) dichloroiron(II) (1): $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 equiv) was dissolved in pyridine (18 equiv) and refluxed for 2 h under argon and filtered. Light yellow crystals (mp 242–245 °C) were obtained in 75% isolated yield, and used for X-ray analysis. The crystal structure was the same as that reported by Long and Clarke.¹⁴ Tetrakis(pyridine)dichloroiron(II) can be prepared starting from FeCl_2 and pyridine.²³ However, in this reference the exact structure of the complex was not reported.

Preparation of trans-tetrakis(2,6-dichloropyridine) dichloroiron(II) (2): $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1 equiv) was dissolved in acetonitrile, and 2,6-dichloropyridine (6.1 equiv) was added in one portion to the boiling reaction mixture. After addition, the reaction vessel was flushed with argon, and the reaction mixture was refluxed for 2 h under argon. Filtration and evaporation of the solvent yielded yellow micro crystals in 83% isolated yield. Reliable data for the melting point could not be obtained.

General Suzuki reaction procedure: The aryl bromide (0.56 mmol, 1 equiv), phenylboronic acid (0.728 mmol, 1.3 equiv), K_2CO_3 (232 mg, 1.68 mmol, 3 equiv), and catalyst (1 mol %) were dissolved in the appropriate solvent (3 ml), and thereafter the mixture was stirred for 24 h at 80 °C. The mixture was cooled to room temperature, EtOAc (~20 ml) was added and the reaction mixture was filtered through a 3G glass sinter. The organic layer was washed with distilled water (2 × 15 ml) and brine (2 × 15 ml) and then dried over MgSO_4 . Evaporation and purification by column chromatography yielded the products **3–5**. ¹H and ¹³C NMR data for the products were in accordance with literature values.⁵

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