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$FeCl_3/PPh_3$-catalyzed Sonogashira coupling reaction of aryl iodides with terminal alkynes

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ABSTRACT

Conditions for a $FeCl_3/PPh_3$-catalyzed and palladium-, copper-, amine free-Sonogashira coupling reaction of aryl halides with terminal alkynes are reported. The protocol was applicable to a wide variety of substituted aryl iodides and alkynes with different steric and electronic properties and gave excellent yields of the desired coupling products.

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Sonogashira coupling of terminal acetylenes with aryl halides is a widely used tool for the synthesis of a variety of intermediates in pharmaceuticals, agrochemicals and natural products.[1] After the first report on this reaction by Sonogashira and Hagihara in 1975 using a palladium catalyst in combination with copper,[2] several other modified protocols based on palladium systems were developed.[3] Palladium-catalyzed protocols have limitations due to the use of expensive Pd metal, which is also toxic and detrimental to the environment.[4] There is a rapidly growing demand for new catalytic systems which are effective, yet economical and environmentally friendly. Iron is one of the better potential candidates as it is cheaper, nontoxic and abundant.[5] In the last few years there has been growing awareness of iron-catalyzed cross-coupling reactions.[6] Recently Bolm and co-workers reported various iron-based catalytic systems for C–C,[7] C–N,[8] C–O[9] and C–S[10] bond formation reactions, and they were the first to introduce the iron-catalyzed Sonogashira reaction.[7] There are also a few reports on Fe–Cu co-catalyzed Sonogashira coupling reactions.[11]

While there has been significant growth in the area of iron-catalyzed cross-coupling methodologies.[12] Buchwald and Bolm[13] recently, demonstrated that the catalytic activity in some iron-catalyzed reactions is due to trace amounts of copper present as an impurity in iron salts. They arrived at this conclusion by demonstrating that yield decreases with higher-purity $FeCl_3$ and this is reversed by introducing trace amount of Cu_2O. These findings suggest that there is still much to learn about the role of iron in the catalysis of Sonogashira coupling reactions.[14]

In this work, we report an efficient and facile protocol for Sonogashira cross-coupling reactions catalyzed by $FeCl_3/PPh_3$. The reaction works as well with high-purity $FeCl_3$ as it does with lower grades, suggesting that iron is indeed the metal responsible for the observed catalytic activity.

The cross-coupling reaction of phenyl acetylene (**1**) with iodobenzene (**2**) was chosen as a model reaction to optimize different reaction parameters. Initially, the reaction was conducted for 120 h, giving a 98% yield of the desired diphenylacetylene **3a** (Table 1, entry 1). The reaction was studied at different time intervals, and it was observed that the product **3a** was obtained in 94% yield after 48 h (Table 1, entry 3). The utility of the different phosphine ligands shown in Figure 1 was investigated (Table 1, entries 3 and 5–9). Most of these ligands were found to be ineffective, with only L1 and L3 giving good yields (94% and 65%, respectively) (Table 1, entries 3 and 6).

The effects of different organic and inorganic bases were then screened (Table 1, entries 10–17) and inorganic bases were found to be superior to organic bases. It was observed that K_2CO_3 and K_3PO_4 showed similar results and gave good yields of the desired product (Table 1, entries 3 and 17). However, K_3PO_4 was preferred over K_2CO_3 for further study due to the ease of handling. The solvents acetonitrile, toluene *N*,*N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) were screened (Table 1, entries 18–20). It was observed that the reaction gave better results with the use of acetonitrile or toluene as a solvent. However, due to cost considerations and environmental aspects, toluene was our preferred solvent for further study (Table 1, entry 17 vs 18). The reaction temperature was also optimized to 135 °C. The reaction at lower temperature gave lower yield of **3a** (Table 2).

Decreasing the catalyst loading to 5% led to lower yield of **3a**. However, it should be noted that increasing catalyst loading above 15% did not affect the yield (Table 3).

In order to probe the role of iron and possible foreign metal contamination in reagents, test experiments were carried out in the absence of $FeCl_3$ and PPh_3 giving no reaction products (Table 4, entry 1). PPh_3 and K_3PO_4 without $FeCl_3$ were not able to catalyze the reaction (Table 4, entry 2), demonstrating that $FeCl_3$, PPh_3 and K_3PO_4 were all necessary. This indirectly confirms the absence of active metals in PPh_3, K_3PO_4 and toluene.

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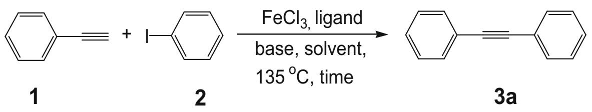
Table 1
Reagent screening for the iron-catalyzed coupling of phenyl acetylene (**1**) with iodobenzene (2)[a]



Entry	Ligand	Base	Solvent	*t* (h)	Yield of **3a**[b] (%)
Effect of time					
1	L1	K_2CO_3	PhMe	120	98
2	L1	K_2CO_3	PhMe	72	96
3	L1	K_2CO_3	PhMe	48	94
4	L1	K_2CO_3	PhMe	24	27
Effect of ligand					
5	L2	K_2CO_3	PhMe	48	Traces
6	L3	K_2CO_3	PhMe	48	65
7	L4	K_2CO_3	PhMe	48	Traces
8	L5	K_2CO_3	PhMe	48	12
9	L6	K_2CO_3	PhMe	48	0
Effecy of base					
10	L1	$[BMIM]OH^-$	PhMe	48	0
11	L1	Morpholine	PhMe	48	0
12	L1	Et_3N	PhMe	48	Traces
13	L1	DBU	PhMe	48	7
14	L1	K^tBuO	PhMe	48	Traces
15	L1	KOH	PhMe	48	10
16	L1	Cs_2CO_3	PhMe	48	70
Effect of solvent					
17	L1	K_3PO_4	PhMe	48	96
18	L1	K_3PO_4	ACN	48	96
19	L1	K_3PO_4	DMF	48	60
20	L1	K_3PO_4	NMP	48	85

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), commercial grade >95% $FeCl_3$ (0.15 mol %), ligand (0.30 mol %), base (2 mmol), solvent (3 mL/mmol), 135 °C under nitrogen.
[b] GC yield.

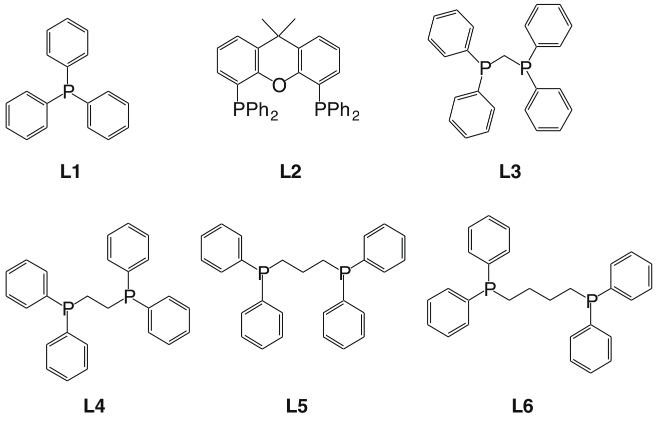


Figure 1. Various phosphine ligands.

Table 2
Influence of reaction temperature on iron-catalyzed Sonogashira coupling of phenylacetylene (**1**) with phenyl iodide (**2**)[a]

No.	Temp (°C)	Yield of **3a**[b] (%)
1	145	98
2	135	98
3	125	70
4	115	32
5	105	22
6	95	21
7	75	18
8	rt	12

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), $FeCl_3$ (0.15 mol %), PPh_3 (0.30 mol %), K_3PO_4 (2.0 mmol), toluene (3 mL/mmol), 48 h under nitrogen.
[b] GC yield.

Table 3
Influence of catalyst loading on iron-catalyzed Sonogashira coupling of phenylacetylene (**1**) with phenyl iodide (**2**)[a]

No.	$FeCl_3$ (mol %)	PPh_3 (mol %)	Yield of **3a**[b] (%)
1	5	10	38
2	10	20	72
3	15	30	98
4	20	40	98

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), K_3PO_4 (2.0 mmol), toluene (3 mL/mmol), 135 °C, 48 h under nitrogen.
[b] GC yield.

Table 4
Test experiment for the iron-catalyzed Sonogashira coupling of phenylacetylene (**1**) with phenyl iodide (**2**)[a]

No.	$FeCl_3$	PPh_3	K_3PO_4	**1**	**2**	Yield of **3a**[b] (%)
1	–	–	✓	✓	✓	0
2	–	✓	✓	✓	✓	Trace
3	✓	–	✓	✓	✓	Trace
4	✓	✓	–	✓	✓	0
5	✓	✓	✓	✓	✓	96

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), $FeCl_3$ (0.15 mol %), PPh_3 (0.30 mol %), K_3PO_4 (2.0 mmol), toluene (3 mL/mmol), 135 °C, 48 h under nitrogen.
[b] Yield of isolated product after column chromatography.

Table 5
Sonogashira coupling of phenyl acetylene (**1**) with iodobenzene (**2**) using different commercial sources of $FeCl_3$[a]

Entry	$FeCl_3$	Yield of **3a**[b] (%)
1	>95% (S.D fine chemicals)	96
2	>98% (Merck)	96
3	>99.99+% (Aldrich)	99

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), $FeCl_3$ (0.15 mol %), PPh_3 (0.30 mol %), K_3PO_4 (2.0 mmol), toluene (3 mL/mmol), 135 °C, 48 h under nitrogen.
[b] Yield of isolated product after column chromatography.

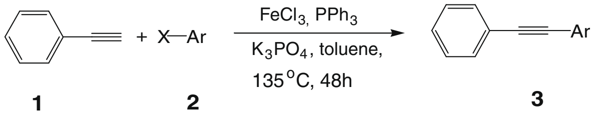
Finally, to gain insight into whether the reaction was catalyzed by trace impurities in $FeCl_3$, we carried out the same experiment with different sources of $FeCl_3$ (from >95% to 99.99+% purity) (Table 5, entries 1–3). Using higher purity $FeCl_3$ did not have a negative impact on the yield of **3a** (Table 5, entry 3), so the lowest grade of $FeCl_3$ (from S.D fine chemicals, purity >95%) was used for the subsequent substrate study.

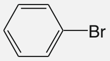
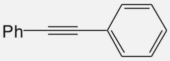
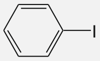
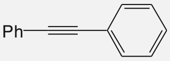
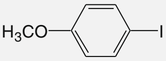
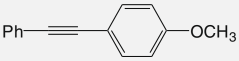
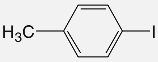
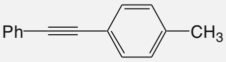
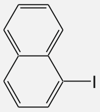
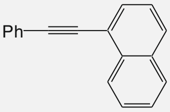
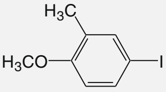
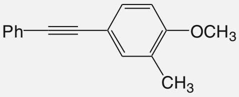
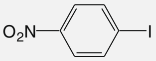
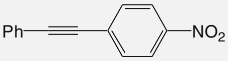
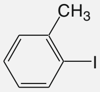
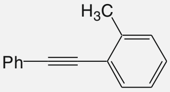
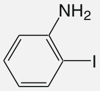
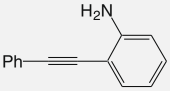
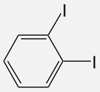
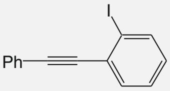
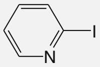
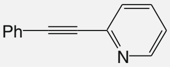
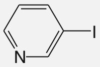
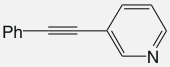
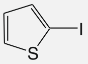
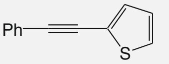
The optimized reaction conditions are phenylacetylene (**1**, 2 mmol), iodobenzene (**2**, 1 mmol), $FeCl_3$ (0.15 mol %), PPh_3 (0.30 mol %) and K_3PO_4 (2 mmol) in toluene (3 mL/mmol of iodobenzene) at 135 °C for 48 h.[15] These conditions were applied to the coupling of phenyl acetylene with a range of aryl- and heteroaryl halides (Table 6). There was no reaction of phenyl acetylene with bromobenzene (entry 1) or with *ortho*-substituted aryl iodides (entries 8–10). Electron-donating substituents gave good to excellent yields (entries 3, 4 and 6), and bulky 1-iodonaphthalene also gave 85% yield (entry 5). Electron-deficient 4-iodonitrobenzene, on the other hand, gave no desired product (entry 7). The reaction also worked well with heterocyclic aryl iodides 2-iodopyridine, 3-iodopyridine and 2-iodothiophene, giving good to excellent yields (entries 11–13).

The generality of the protocol was explored using reactions of various aliphatic, heteroaromatic and aromatic substituted alkynes

Table 6

Iron-catalyzed Sonogashira coupling of phenyl acetylene (**1**) with aryl halides[a]



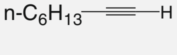
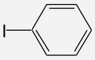
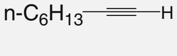
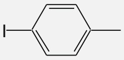
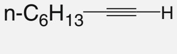
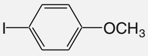
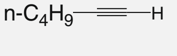
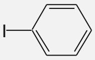
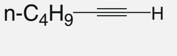
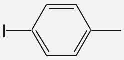
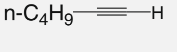
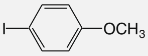
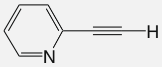
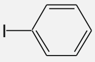
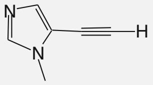
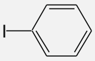
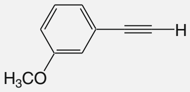
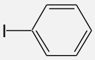
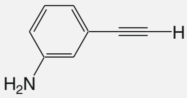
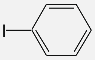
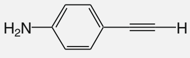
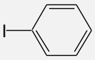
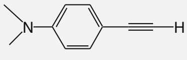
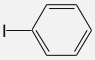
Entry	Aryl halide (**2**)	Product (**3**)		Yield[b] (%)
1			**3a**	Trace
2			**3a**	99
3			**3b**	98
4			**3c**	99
5			**3d**	85
6			**3e**	78
7			**3f**	0
8			**3g**	Trace
9			**3h**	Trace
10			**3i**	0
11			**3j**	69
12			**3k**	92
13			**3l**	96

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), FeCl$_3$ (0.15 mol %), PPh$_3$ (0.30 mol %), K$_3$PO$_4$ (2 mmol), toluene (3 mL/mmol), 135 °C, 48 h under nitrogen.

[b] Yield of isolated product after column chromatography.

Table 7

Iron-catalyzed Sonogashira coupling of terminal alkynes with aryl iodides[a]

Entry	Alkyne (**1**)	Aryl iodide (**2**)	Product (**3**)	Yield[b] (%)
1			**3m**	45[c]
2			**3n**	62[c]
3			**3o**	66[c]
4			**3p**	36[c]
5			**3q**	47[c]
6			**3r**	58[c]
7			**3s**	0
8			**3t**	0
9			**3u**	0
10			**3v**	0
11			**3w**	85[b]
12			**3x**	92[b]

[a] Reaction conditions: **1** (2 mmol), **2** (1 mmol), FeCl$_3$ (0.15 mol %), PPh$_3$ (0.30 mol %), K$_3$PO$_4$ (2.0 mmol), toluene (3 mL/mmol), 135 °C, 48 h under nitrogen.

[b] Yield of isolated product after column chromatography.

[c] GC Yield.

with aryl iodides (Table 7). Aliphatic alkynes were found to react smoothly with a series of aryl iodides in moderate to good yields (entries 1–6), with more electron-rich aryl halides giving better yields. Heteroaromatic alkynes were non-reactive towards the coupling reaction under optimized reaction conditions (entries 7 and 8). Surprisingly, alkynes substituted with electron-donating groups in their meta position (entries 9 and 10) were also non-reactive. On the other hand, the electron-rich alkynes 4-ethynyl aniline and 4-ethynyl-*N*,*N*-dimethylaniline gave 85% and 92% yield of the desired products (entries 11 and 12). These observations suggest that using aryl iodides or alkynes containing electron-donating groups in the para position leads to an increase in yield, while electron-withdrawing groups tend to decrease yield.

During all these studies no alkyne homo coupling products were observed in any reaction.

In summary, FeCl$_3$/PPh$_3$ has been shown to be an effective catalytic system for Sonogashira couplings. The reaction was optimized with respect to various parameters and enabled coupling reactions of various aryl iodides with different alkynes. Further investigations on the application of this catalytic system in other coupling reactions are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.063.

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15. *General procedure for the iron-catalyzed Sonogashira coupling*: toluene (3 ml/mmol), FeCl$_3$ (0.15 mol %), PPh$_3$ (0.30 mol %), K$_3$PO$_4$ (2.0 mmol), alkynes (**1**, 2.0 mmol) and aryl iodide (**2**, 1 mmol) were added in the reaction vial under nitrogen atmosphere. All the reactions were performed in closed vials with a Teflon-coated screw cap, and the reaction mixture was heated at 135 °C with stirring for 48 h in oil bath. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with diethyl ether. The resulting heterogeneous solution was filtered through a pad of silica and concentrated to afford the crude product, which was purified by column chromatography using petroleum ether as eluent or petroleum ether/ethyl acetate (98:2) eluent mixture to give the expected product. The identity and purity of the products were confirmed by ^{1}H NMR, ^{13}C NMR and GC–MS.