C–N Coupling

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Efficient Iron/Copper Co-Catalyzed Arylation of Nitrogen Nucleophiles**

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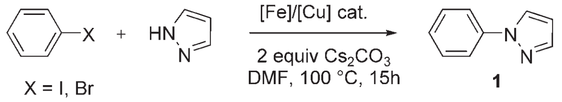
The formation of N–C bonds is one of the most important reactions in numerous syntheses of intermediates and targets throughout the chemical, pharmaceutical, and materials industries.[1] One of the main methods to create this type of bond is the copper-catalyzed N-arylation of nucleophiles with aryl halides (the Ullmann or Goldberg condensations).[2] Developed several decades before the corresponding nickel- and palladium-catalyzed arylations, this well-known method, however, suffers from several drawbacks such as high-temperature conditions and the use of stoichiometric amounts of copper.[1] Recently, we developed systems involving copper salts and new nitrogen and/or oxygen ligands[3,4] able to promote N-arylations under very mild conditions with respect to the classical Ullmann reaction. These conditions, often representing new landmarks in copper-catalyzed arylations for various nitrogen nucleophiles,[4a,d,e] were of particular interest in the field of industrial applications.

Other groups[1,5] also revisited the C–N bond formation by the Ullmann method. However, to our knowledge, iron complexes, which are cheap and environmentally friendly, used alone or associated with other metals have not been involved in forming this type of bond.[6] Herein, we report a very economically competitive system that allows N-arylation reactions[7] based on simple and cheap iron–copper co-catalysis. Indeed, we have found that differently substituted aryl halides react with various nitrogen heterocycles in the presence of a catalytic amount of [Fe(acac)$_3$] (acac = acetylacetonate) and copper salts under mild conditions to give the corresponding cross-coupling products. This novel system constitutes one of the rare examples of bimetallic catalysis[8] and the first involving both iron and copper in this type of N–C bond formation.

First, a set of experiments were carried out using pyrazole and iodo- or bromobenzene as model substrates. This preliminary survey, carried out in *N,N*-dimethylformamide (DMF) at 100 °C with cesium carbonate as base, allowed us to evaluate and optimize the most efficient catalytic system (Table 1). We observed that without a copper source, catalytic amounts of iron salts FeCl$_3$ or [Fe(acac)$_3$] were not able to promote the reaction (Table 1, entries 1 and 2). The other blank experiments in the absence of an iron additive but in the presence of a copper precatalyst also revealed no conversion of either aryl halide into product **1** (Table 1, entries 3–6).

Table 1: Preliminary survey of the iron/copper catalytic systems for the N-arylation of pyrazole with aryl iodides and bromides.



Entry	X	[Fe] cat. (0.3 equiv)	[Cu] cat. (0.1 equiv)	Yield [%][a]
1	Br, I	[Fe(acac)$_3$]	–	0
2	Br, I	FeCl$_3$	–	0
3	Br, I	–	CuI	0
4	Br, I	–	[Cu(acac)$_2$]	0
5	I	–	Cu	0
6	I	–	CuI + [Cu(acac)$_2$][b]	4
7	I	[Fe(acac)$_3$]	Cu	100
8	Br	[Fe(acac)$_3$]	Cu	83
9	Br	[Fe(acac)$_3$]	CuI	79
10	Br	[Fe(acac)$_3$]	CuO	91
11	Br	[Fe(acac)$_3$]	[Cu(acac)$_2$]	71
12	I	[Fe(acac)$_3$]	[Cu(acac)$_2$]	100
13	I	FeCl$_3$	Cu	0
14	I	FeCl$_3$	[Cu(acac)$_2$]	30
15	I	FeCl$_2$	[Cu(acac)$_2$]	0

[a] Yields obtained from gas chromatography (GC) using 1,3-dimethoxybenzene as internal standard. [b] 1:1 CuI/[Cu(acac)$_2$].

On the other hand, we were pleased to find that the coupling of pyrazole with iodobenzene was successful in the presence of catalytic amounts of both [Fe(acac)$_3$] and copper (100 % yield; Table 1, entry 7). This co-catalyzed N-arylation was also observed to proceed in very good yield from the less reactive but more economically interesting bromobenzene (Table 1, entry 8). Other copper sources with different oxidation states (0, I, II) tested with PhBr or PhI also led to the coupling product. Moreover, the reactions were totally selective with respect to aryl halides and pyrazole (Table 1, entries 7–12).

Note that the presence of the acetylacetonate ligand and its precomplexation with iron is also crucial for an efficient co-catalysis (compare entries 7–10 with 14, Table 1). In addition, the use of an iron(III) precatalyst appears to be important for the reaction to proceed (Table 1, entries 14 and 15; 0 % conversion with FeCl$_2$).

We then investigated the reaction scope of this Fe/Cu catalytic system and its tolerance of functional groups in the

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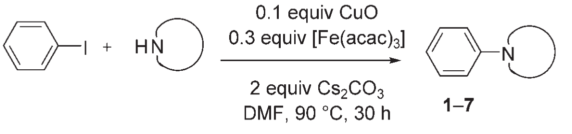
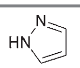
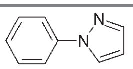
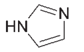
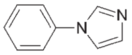
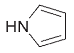
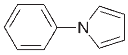
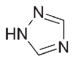
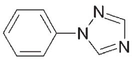
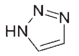
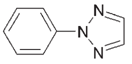
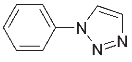
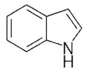
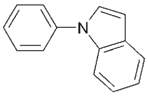
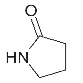
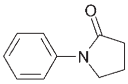
case of other nitrogen heterocycles (Table 2) and other aryl halides (Table 3). We rapidly noticed the broad field of application of the process and its remarkable functional group compatibility on both reagents.

Table 2: Iron/copper co-catalyzed N-arylation of azoles and a cyclic amide with iodobenzene (and bromobenzene).[a]



1–7

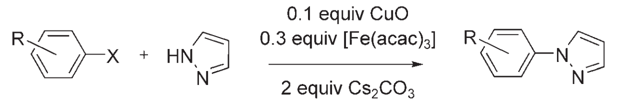
Entry		Product		Yield [%][b]
1			**1**	91
2			**2**	90
3			**3**	91
4			**4**	83
5		 	**5**	41 48
6			**6**	93
7			**7**	81

[a] The reaction also takes place with the aryl bromide. Yields of 80–95 % for compounds **1**–**7** were determined by GC using 1,3-dimethoxybenzene as internal standard. [b] Yield of isolated product.

With respect to the nitrogen heterocycle, we obtained and isolated in excellent yields (81–93 %) various molecules resulting from the cross-coupling between different azoles (pyrazole, imidazole, pyrrole, triazole, indole) or a cyclic amide derivative (pyrrolidin-2-one) with phenyl iodide (Table 2). On the basis of our first tests (Table 1), the reaction was performed in all cases under very mild temperature conditions (90 °C) in the presence of CuO and [Fe(acac)$_3$] as precatalysts and cesium carbonate as base (for the coupling with aryl bromides, see Table 2, footnote [a]).

In a second set of experiments, the scope of the process with respect to aryl iodides, bromides, or chlorides substituted with various electron-withdrawing and -donating substituents was investigated using pyrazole as a model N-nucleophilic substrate (Table 3). All the expected coupling products were selectively synthesized under our standard experimental conditions, whatever the nature of the substituents. Thus, aryl pyrazoles **1** and **8**–**14** were obtained at 90 °C in very good yields from aryl iodides with various electron-withdrawing and -donor substituents, or from bromobenzene or electron-poor aryl bromides (Table 3, entries 1–3 and 5–9). The arylation of electron-rich aryl bromides and iodoaniline in particular was more troublesome at 90 °C. However, good yields of coupling products **9**, **10**, **15**, and **16** were obtained at higher temperatures (120 °C; Table 3, entries 4 and 10–12, respectively).

Table 3: Iron/copper co-catalyzed N-arylation of pyrazole with different substituted aryl halides.



X = I, Br, Cl

1, 8–17

Entry	X	R	Product	Yield [%][a]
1	I	4-H	**1**	91
2	I	4-COOEt	**8**	93
3	I	4-OMe	**9**	98
4	I	4-NH_2	**10**	57[b]
5	Br	4-H	**1**	94
6	Br	4-NO_2	**11**	90
7	Br	4-CN	**12**	98
8	Br	4-Ph	**13**	93
9	Br	4-COMe	**14**	81
10	Br	4-Me	**15**	57[b]
11	Br	4-OMe	**9**	80[b]
12	Br	3-OMe	**16**	86[b]
13	Cl	4-CF_3	**17**	40[c]

[a] Yield of isolated product. [b] 120 °C for 24 h. [c] 140 °C for 24 h.

Note that an activated aryl chloride tested at 140 °C gave very encouraging results: the corresponding coupling product was isolated in 40 % yield (Table 3, entry 13). The arylation of nucleophiles from aryl chlorides indeed constitutes a challenge of considerable economic and environmental importance.

Overall, it is remarkable that there are no obvious side reactions in this co-catalyzed N-arylation. Therefore, the workup can be greatly simplified. By-products resulting from biaryl coupling or from the reduction of aryl halides were never observed.

In summary, we have presented here a first and original example of a cooperative bimetallic catalysis with Fe and Cu that allows the N-arylation of various nitrogen nucleophiles from differently substituted aryl halides (X = I, Br, Cl). The commercial availability and low cost of the precatalysts [Fe(acac)$_3$] and CuO, the mild conditions, experimental simplicity, and environmental friendliness are all features of our catalytic system. The catalytic system should find applications very soon once it has been adapted for the industrial scale, where financial and environmental issues are of greater concern. Work is in progress to broaden further the scope of this catalytic system (which also catalyzes C–C and C–O cross-coupling reactions),[7] especially for aryl chlorides, and to understand the mechanism. These results will be reported in due course.

Experimental Section

General procedure for the synthesis of **1**: A schlenk tube (evacuated and back-filled with nitrogen) was charged with [Fe(acac)$_3$] (212 mg, 0.6 mmol), CuO (16 mg, 0.2 mmol), 1*H*-pyrazole (205 mg, 3.0 mmol), and Cs$_2$CO$_3$ (1.3 g, 4.0 mmol). Iodobenzene (224 μL, 2.0 mmol, 1 equiv) or bromobenzene (212 μL, 2.0 mmol, 1 equiv) was added under nitrogen followed by anhydrous DMF (2 mL). The tube was sealed under nitrogen, and the mixture was heated to 90 °C and stirred for 30 h. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered. The filtrate was washed twice with water, and the combined aqueous phases were extracted twice with dichloromethane. The organic layers were combined, dried over Na$_2$SO$_4$, and concentrated to yield the crude product, which was further purified by silica gel chromatography (1:1 hexanes/dichloromethane) to yield 1-phenyl-1*H*-pyrazole (**1**) as an oil (270 mg, 94% yield). Selected data: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.95–7.96 (dd, 1H), 7.71–7.75 (m, 3H), 7.47–7.50 (m, 2H), 7.28–7.34 (m, 1H), 6.49–6.50 ppm (dd, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 141.09, 140.22, 129.45, 126.75, 126.46, 119.23, 107.61 ppm; HRMS: *m*/*z* calcd for C$_9$H$_8$N$_2$ [*M*+H]: 145.0766; found: 145.0766.

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[7] This catalytic system is protected: M. Taillefer, N. Xia, A. Ouali, US PATENT 60/818,334, **2006**. The application field described also concerns C−C, C−O, C−S, and C−P bond formation.

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