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On the Role of Metal Contaminants in Catalyses with FeCl₃

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Metal catalysis has a dominant role in modern organic chemistry. In particular, cross-coupling reactions allow bond formations, which have previously been impossible to perform.^[1] Precious metal catalysts dominate the field, but alternative systems based on nickel and copper salts have also, historically, been important. In particular, recent systems based on these metals have been described that provide products in a highly efficient manner.^[2]

In this context, one of us (C.B.) reported iron-catalyzed cross-couplings leading to arylated amides, phenols, thiols and alkynes.^[3,4] Commonly, 10 mol % of an iron salt in combination with 20 mol % of a ligand (a diamine or a diketone) in a solvent such as toluene at 135 °C (using closed vials) was used. It was noticed by chemists at RWTH and MIT (past and present) that the catalyst activity depended on the metal salt purity and even more so on its commercial source.^[5] Also, a parallel between the results with the iron systems and some of those realized with copper catalysts by S.L.B.'s group and that of Song was recognized. For example, as in the case of much of the chemistry from S.L.B.'s group, N,N'-dimethyl-1,2-diamines were superior ligands, and the best results were realized in conversions of aryl iodides.

These observations prompted us to collaborate to investigate whether it was possible that trace amounts of copper impurities were influencing these reactions. Thus, different sources of FeCl₃ (from >98–99.99% metal purity) were examined in the couplings of pyrazole, phenyl amide, phenol and thiophenol with aryl iodides. The literature data and the new results (obtained by B. Fors and R. Martin in the S.L.B. group) are shown below (Tables 1–4).

In all cases when >99.99% FeCl₃ was employed lower yields were obtained than when the reactions were run using >98% FeCl₃.^[6,7] Furthermore, when different sources of >98% FeCl₃ were used different results were observed. These findings suggest that both the purity and the source of the FeCl₃ play a crucial role in the success of these transformations.

In order to further investigate the cause of these findings, small amounts of Cu₂O were added to the reactions using >99.99% FeCl₃. With only 10 ppm of Cu₂O a significant increase in yield was observed in all cases.^[8,9] Moreover, in two cases examined, essentially

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identical results were obtained if the reaction was carried out in the absence of FeCl_3 , but in the presence of DMEDA and as little as 10 ppm of Cu_2O (Tables 1 and 2, last entries).

Although questions remain, we conclude that the outcome of the reported reactions with FeCl_3 may in certain cases be significantly affected by trace quantities of other metals, particularly copper. Considering that metal contaminants have also been found relevant in other processes involving metals (such as the chromium-mediated Nozaki-Hiyama-Kishi reaction,^[10] olefinations and Simmons-Smith reactions with organozinc reagents,^[11] and “metal-free” Suzuki^[12] and Sonogashira-coupling^[13]), we suspect that the presence of trace metal impurities may play a more important role than is generally assumed.

Acknowledgments

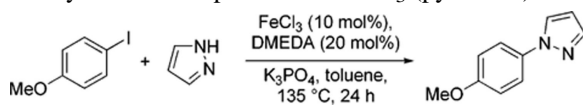
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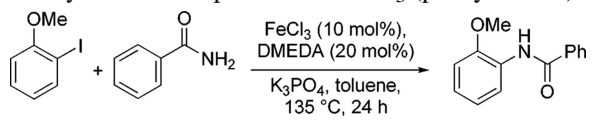
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Table 1

N-Arylation in the presence of FeCl₃ (pyrrazole).

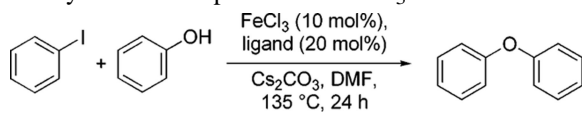
FeCl ₃	3C Yield (%)
>98% (Merck)	87 (ref. 3a)
>98% (Aldrich)	26
>99.99 (Aldrich)	9
>99.99% + 5 ppm Cu ₂ O	78
>99.99% + 10 ppm Cu ₂ O	79
no Fe + ligand + 5 ppm Cu ₂ O	77
no Fe + no ligand + 5 ppm Cu ₂ O	23

Table 2

N-Arylation in the presence of FeCl₃ (phenyl amide).

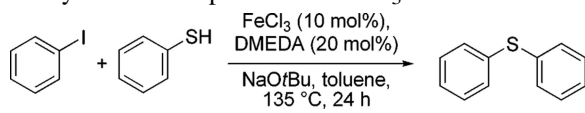
FeCl ₃	GC Yield (%)
>98% (Merck)	79(ref. 3c)
>98% (Aldrich)	16
>99.99 (Aldrich)	trace
>99.99% + 5 ppm Cu ₂ O	98
>99.99% + 10 ppm Cu ₂ O	99
no Fe + ligand + 5 ppm Cu ₂ O	97
no Fe + no ligand + 5 ppm Cu ₂ O	34

Table 3

O-Arylation in the presence of FeCl₃.

	FeCl ₃	GC Yield (%)
 = ligand	>98% (Merck)	85 (ref. 3d)
	>98% (Aldrich)	81
	>99.99 (Aldrich)	32
	>99.99% + 10 ppm Cu ₂ O	92
	>99.99% + 100 ppm Cu ₂ O	98
	>99.99% + 1000 ppm Cu ₂ O	99

Table 4

S-Arylation in the presence of FeCl₃.

FeCl ₃	GC Yield (%)
>98% (Merck)	91 (ref. 3f)
>98% (Aldrich)	4
>99.99 (Aldrich)	2
>99.99% + 10ppmCu ₂ O	42
>99.99% + 100 ppm Cu ₂ O	99
>99.99% + 1000 ppm Cu ₂ O	93