Iron or Copper?

DOI: 10.1002/anie.200902237

On the Role of Metal Contaminants in Catalyses with $FeCl_3$**

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arylation · copper · homogeneous catalysis · iron trichloride · metal impurities

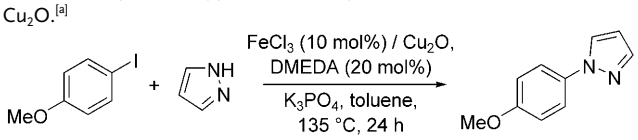
Metal catalysis has a dominant role in modern organic chemistry. In particular, cross-coupling reactions allow bond formations, which have previously been impossible to perform.[1] Precious metal catalysts dominate the field, but alternative systems based on nickel and copper salts have also, historically, 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 Aachen 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 $FeCl_3$ (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 in Tables 1–4.

In all cases when >99.99% $FeCl_3$ was employed lower yields were obtained than when the reactions were run using >98% $FeCl_3$.[6,7] Furthermore, when different sources of >98% $FeCl_3$ were used different results were observed. These findings suggest that both the purity and the source of the $FeCl_3$ play a crucial role in the success of these transformations.

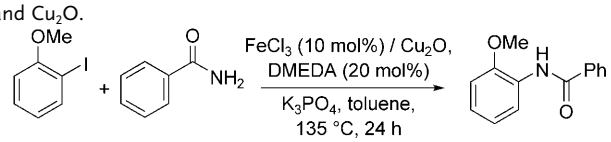
Table 1: N-Arylation of pyrrazole in the presence or absence of $FeCl_3$ and Cu_2O.[a]



$FeCl_3/Cu_2O$	Yield [%] (GC)
>98% (Merck)	87 (ref. [3a])
>98% (Aldrich)	26
>99.99 (Aldrich)	9
>99.99% + 5 ppm Cu_2O	78
>99.99% + 10 ppm Cu_2O	79
no Fe + ligand + 5 ppm Cu_2O	77
no Fe + no ligand + 5 ppm Cu_2O	23

[a] DMEDA = *N*,*N*′-Dimethylethylenediamine.

Table 2: N-Arylation of phenyl amide in the presence or absence of $FeCl_3$ and Cu_2O.



$FeCl_3/Cu_2O$	Yield [%] (GC)
>98% (Merck)	79 (ref. [3c])
>98% (Aldrich)	16
>99.99 (Aldrich)	trace
>99.99% + 5 ppm Cu_2O	98
>99.99% + 10 ppm Cu_2O	99
no Fe + ligand + 5 ppm Cu_2O	97
no Fe + no ligand + 5 ppm Cu_2O	34

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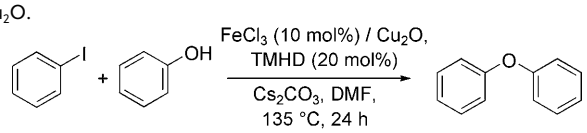
[**] C.B. is grateful to the Fonds der Chemischen Industrie for the financial support and thanks Prof. Dr. R. Dronskowski and L. Stork (Institute for Inorganic Chemistry, RWTH Aachen University) for substrate analyses by atom absorption spectroscopy. S.L.B. acknowledges the National Institutes of Health (GM46059 and 58160). We also thank Dr. A. Klapars and Prof. Dr. J. Antilla for insightful comments. Further, we are indebted to B. Fors and Dr. R. Martin for experimental results and Prof. Dr. A. Fürstner (MPI, Mülheim (Germany)) and Prof. Dr. M. Beller (LIKAT, Rostock (Germany)) for performing control experiments.

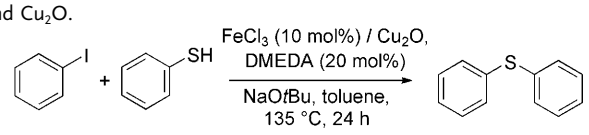
Table 3: O-Arylation of phenole in the presence or absence of $FeCl_3$ and Cu_2O.



$FeCl_3/Cu_2O$	Yield [%] (GC)
>98% (Merck)	85 (ref. [3d])
>98% (Aldrich)	81
>99.99 (Aldrich)	32
>99.99% + 10 ppm Cu_2O	92
>99.99% + 100 ppm Cu_2O	98
>99.99% + 1000 ppm Cu_2O	99

[a] TMHD = 2,2,6,6-Tetramethyl-3,5-heptanedione.

Table 4: S-Arylation of thiophenole in the presence or absence of $FeCl_3$ and Cu_2O.



$FeCl_3/Cu_2O$	Yield [%] (GC)
>98% (Merck)	91 (ref. [3f])
>98% (Aldrich)	4
>99.99 (Aldrich)	2
>99.99% + 10 ppm Cu_2O	42
>99.99% + 100 ppm Cu_2O	99
>99.99% + 1000 ppm Cu_2O	93

In order to further investigate the cause of these findings, small amounts of Cu_2O were added to the reactions using >99.99% $FeCl_3$. With only 10 ppm of Cu_2O a significant increase in yield was observed in all cases.[8,9] Moreover, in two cases examined, essentially 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.

Received: April 27, 2009
Published online: June 24, 2009

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[2] Reviews: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; d) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; e) M. Carril, R. SanMartin, E. Domínguez, *Chem. Soc. Rev.* **2008**, *37*, 639; f) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096; g) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; h) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.

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[4] Recently, it was reported that N-arylations in water with $FeCl_3$ under otherwise identical conditions as applied in ref. [3a] gave essentially the same results: Y.-C. Teo, *Adv. Synth. Catal.* **2009**, *351*, 720.

[5] The best results were achieved with $FeCl_3$ having a purity of >98% (from Merck). According to atom absorption spectroscopy the major contaminant in this sample is manganese (ca. 0.17%). Control experiments showed this to be catalytically inactive: A. Correa, M. Carril, C. Bolm, unpublished results. The copper content was determined to be 0.034%.

[6] This is consistent with observations reported for the N-arylations of sulfoximines (ref. [3b]).

[7] Also in iron-catalyzed alkylations of aromatic Grignard reagents the purity of the $FeCl_3$ is important. See: G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem.* **2007**, *119*, 4442; *Angew. Chem. Int. Ed.* **2007**, *46*, 4364.

[8] Prof. Dr. Per-Ola Norrby (University of Gothenburg, Sweden) kindly informed us about analogous observations found independently. For a summary of those findings, see: P.-F. Larsson, A. Correa, M. Carril, P-O. Norrby, C. Bolm, *Angew. Chem.* **2009**, *121*, 5801; *Angew. Chem. Int. Ed.* **2009**, *48*, 5691.

[9] For Fe/Cu co-catalyses (with commonly catalyst loadings in the 10 mol% range for both metals), see: a) M. Taillefer, N. Xia, A. Oualli, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934; b) R.-J. Song, C.-L. Deng, Y.-X. Xie, J.-H. Li, *Tetrahedron Lett.* **2007**, *48*, 7845; c) Z. Wang, H. Fu, Y. Jiang, Y. Zhao, *Synlett* **2008**, 2540; d) C. M. Rao Volla, P. Vogel, *Tetrahedron Lett.* **2008**, *49*, 5961; e) J. Mao, G. Xie, M. Wu, J. Guo, S. Ji, *Adv. Synth. Catal.* **2008**, *350*, 2477; f) H. Huang, H. Jiang, K. Chen, H. Liu, *J. Org. Chem.* **2008**, *73*, 9061; g) X. Ku, H. Huang, H. Jiang, H. Liu, *J. Comb. Chem.* **2009**, *11*, 338; h) S. Li, W. Jia, N. Jiao, *Adv. Synth. Catal.* **2009**, *351*, 569.

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[13] For an excellent highlight providing additional insight into the importance of trace metals in palladium-catalyzed Sonogashira reactions, see: H. Plenio, *Angew. Chem.* **2008**, *120*, 7060; *Angew. Chem. Int. Ed.* **2008**, *47*, 6954.

