Homogeneous Catalysis

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Iron-Catalyzed Alkylations of Aromatic Grignard Reagents**

Gérard Cahiez, Vanessa Habiak, Christophe Duplais, and Alban Moyeux*

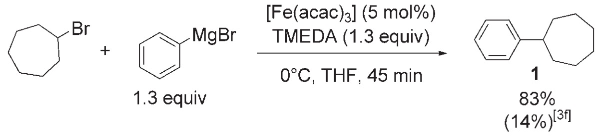
Sustainable development now plays an increasingly important role in the strategy of chemical industries. As a part of this preoccupation, the search for more economic and more eco-friendly new efficient synthetic methods is of vital concern. The development of iron-catalyzed cross-coupling reactions is one of the current promising fields of research, as these reactions are very attractive compared to the related palladium- or nickel-catalyzed procedures extensively used until now. This is well illustrated by the numerous results published by us[1] and others.[2] Note that for large-scale applications, it is not enough to use iron salts as catalysts; it is also important to use cheap ligands in small amounts as well as solvents that are compatible with industrial processes.

We recently became interested in the iron-catalyzed alkylation of aromatic Grignard reagents for large-scale applications. During the course of our studies, some related reports appeared in the literature. Hayashi and Nagano[3a] and Bedford et al.[3c,d] reported the cross-coupling reaction between primary and secondary alkyl bromides and aromatic Grignard reagents in the presence of catalytic amounts of $FeCl_3$. The group of Bedford also showed that a [FeCl(salen)] complex can be used as a catalyst.[3b] However, yields are generally lower than 80 % and the Grignard reagent has to be used in large excess and added at once. Moreover, the reactions are performed in diethyl ether under reflux. Therefore, these methods are not suitable for large-scale applications.

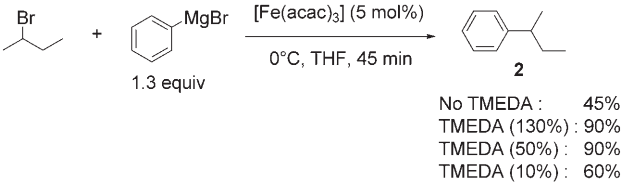
Two other reports suggested that the coupling could be carried out in THF. Fürstner[3e] showed that the complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ is a very efficient catalyst (TMEDA: *N,N,N′,N′*-tetramethylethylenediamine). From a mechanistic point of view, this elegant example is very interesting as it demonstrates that a Fe^{2-} species can be used successfully. However, the use of a sophisticated non-commercial iron complex is a major drawback for large-scale applications. The catalytic system used by Nakamura and co-workers[3f] ($FeCl_3$/TMEDA) seems more attractive. Nevertheless, it is necessary to use a large quantity of TMEDA (26 equiv relative to $FeCl_3$). Also, during our investigations we found that the use of $FeCl_3$ leads to variable yields according to its purity and its commercial origin (see Supporting Information). Moreover, this salt is not very easy to handle on a large scale as it is highly hygroscopic.

Herein, we report our results concerning two new catalytic systems that can be used on a large scale to perform this reaction very efficiently.

Nakamura and co-workers reported that the use of $[Fe(acac)_3]$ (acac: acetylacetonate) as a catalyst gave unsatisfactory yields of the substitution product.[4] We found this very surprising because during our investigations the reaction proceeded very efficiently in the presence of TMEDA and $[Fe(acac)_3]$, whatever the origin of the salt (Scheme 1). Moreover, these results concord well with our experience in the field of iron catalysis[1] as the use of $[Fe(acac)_3]$ in place of $FeCl_3$ has always led to more reproducible results and to similar or better yields. Note that only 10 equivalents of TMEDA are required when using $[Fe(acac)_3]$ as catalyst, instead of 26 equivalents of TMEDA with $FeCl_3$ (Scheme 2).



Scheme 1. Cross-coupling between phenylmagnesium bromide and cycloheptyl bromide in the presence of $[Fe(acac)_3]$.



Scheme 2. Influence of TMEDA on the iron-catalyzed cross-coupling reaction between phenylmagnesium bromide and *sec*-butyl bromide.

We were not satisfied by this result as the amount of TMEDA was still too high, and so we tested a vast array of ligands. The most interesting results were obtained with hexamethylenetetraamine (HMTA). Moreover, a single equivalent of this ligand suffices to increase the yield up to 80 % (Scheme 3). To the best of our knowledge, this is the first use of HMTA as a ligand in performing a transition-metal-catalyzed cross-coupling reaction. HMTA is very convenient for industrial applications as it is a cheap compound that is easily eliminated then degraded during the treatment of the effluents.

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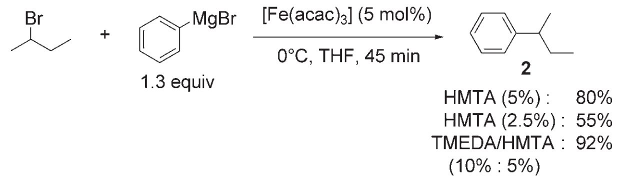
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

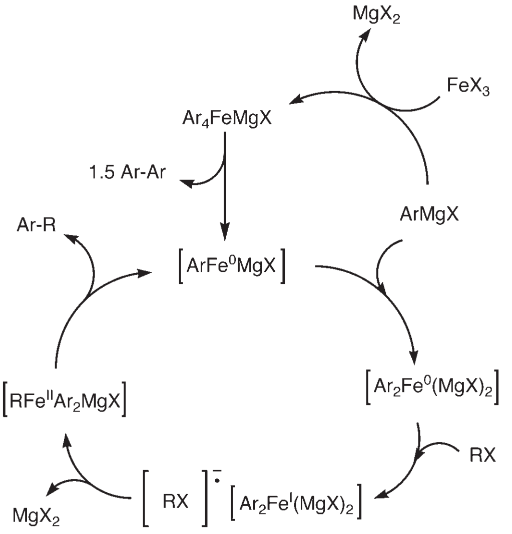


Scheme 3. Influence of HMTA or a combination of TMEDA and HMTA on the iron-catalyzed cross-coupling reaction between phenylmagnesium bromide and *sec*-butyl bromide.

However, with HMTA it is not possible to obtain the product in more than 80% yield. Fortunately, we discovered that by using both one equivalent of HMTA and two equivalents of TMEDA (Scheme 3) it is possible to obtain a better yield (92%) than in the presence of only one of these ligands, whatever their proportion. In fact, this new catalytic system based on a synergy between two ligands is clearly more convenient and reliable than the one previously described by Nakamura and co-workers ($FeCl_3$/TMEDA).[3f]

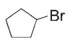
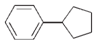
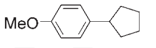
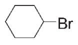
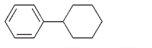
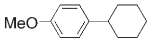
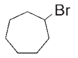
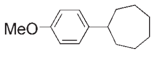
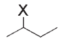
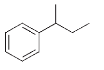
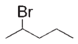
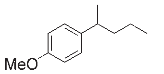
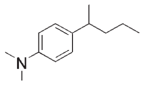
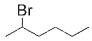
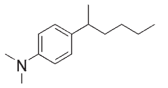
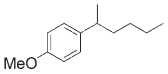
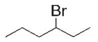
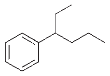
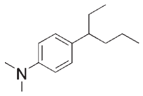
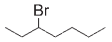
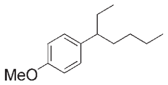
Recently, in an interesting report, Fu and co-workers[5a] showed that secondary alkyl halides do not react under palladium catalysis as the oxidative addition is too slow. They demonstrated that this lack of reactivity is mainly due to steric effects. Under iron catalysis, the coupling reaction is clearly less sensitive to such steric influences as both cyclic and acyclic secondary alkyl bromides were used successfully (Table 1). Such a difference could be explained by the mechanism proposed in Scheme 4. Contrary to Pd^0, which reacts with alkyl halides according to a concerted oxidative addition mechanism, the iron-catalyzed reaction could involve a two-step single-electron transfer.

Secondary alkyl bromides or iodides gave rise to similar yields (Table 1, entries 6 and 7). However, no reaction occurred with the corresponding chlorides (Table 1, entry 8). Our cross-coupling conditions were also successfully applied to primary alkyl halides (Table 2). Generally, the yields were lower than those obtained from secondary alkyl bromides, especially with long-chain alkyl bromides such as dodecyl bromide (Table 2, entries 5 and 6).



Scheme 4. Tentative mechanism for the iron-catalyzed coupling reaction.[6]

Table 1: Iron-catalyzed cross-coupling between aryl Grignard reagents and secondary alkyl halides.[a]

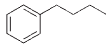
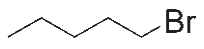
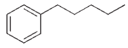
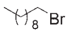
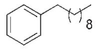
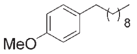
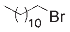
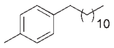
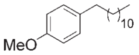
Entry	Alkyl halide	Product		Isolated yield [%]
1			**3**	91[b]
2			**4**	88[b]
3			**5**	90
4			**6**	89
5			**7**	83
			**2**	
6	X = I			94
7	X = Br			93
8	X = Cl			traces
9			**8**	93
10			**9**	88
11			**10**	67
12			**11**	88
13			**12**	71
14			**13**	85
15			**14**	74

[a] The aryl Grignard reagent (13 mmol) was added dropwise over 45 min to a solution of alkyl bromide (10 mmol), $[Fe(acac)_3]$ (0.5 mmol), TMEDA (1.0 mmol), and HMTA (0.5 mmol) in THF at 0 °C under stirring. [b] The reaction was performed on a 50 mmol scale.

During our investigations, we also tried to eliminate the drawbacks previously mentioned with $FeCl_3$. Indeed, this salt is interesting as it is a very cheap material. After several attempts, we finally discovered that it is very easy to obtain a complex $[(FeCl_3)_2(tmeda)_3]$ by adding 1.5 equivalents of TMEDA to a solution of $FeCl_3$ in THF at room temperature. The complex precipitates and can be isolated quantitatively by filtration. To our delight, only 1.5 mol% $[(FeCl_3)_2(tmeda)_3]$ was needed to perform the coupling between an aromatic Grignard reagent and a secondary alkyl halide very efficiently (Table 3, entries 1–4). The reaction can be extended to primary alkyl halides, but the yields are generally slightly lower (Table 3, entry 5).

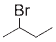
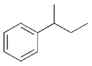
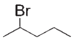
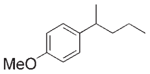
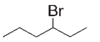
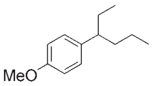
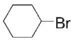
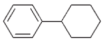
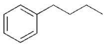
This procedure compares very advantageously to the one previously described by Nakamura and co-workers.[3f] The

Table 2: Iron-catalyzed cross-coupling between primary alkyl bromides and aromatic Grignard reagents.[a]

Entry	Alkyl halide	Product		Yield [%]
1			**15**	75[b]
2			**16**	70[b]
3			**17**	76
4			**18**	72
5			**19**	50
6			**20**	39

[a] The aryl Grignard reagent (13 mmol) was added dropwise over 45 min to a solution of alkyl bromide (10 mmol), [Fe(acac)$_3$] (0.5 mmol), TMEDA (1.0 mmol), and HMTA (0.5 mmol) in THF at 0 °C under stirring. [b] The reaction was performed on a 50 mmol scale.

Table 3: Cross-coupling between aryl Grignard reagents and secondary alkyl halides[a] in the presence of [(FeCl$_3$)$_2$(tmeda)$_3$].

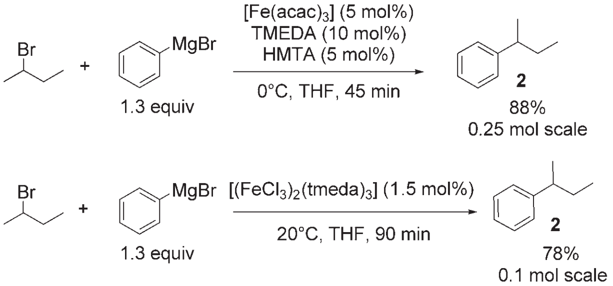
Entry	Alkyl halide	Product		Yield [%]
1			**2**	81
2			**9**	92
3			**21**	83
4			**5**	91
5			**15**	75

[a] The aryl Grignard reagent (13 mmol) was added dropwise over 45 min to a solution of alkyl bromide (10 mmol) and [(FeCl$_3$)$_2$(tmeda)$_3$] (0.15 mmol) in THF at room temperature under stirring.

amount of TMEDA required is dramatically lowered (from 120% to 5%) and 3% FeCl$_3$ is used instead of 5%. In addition, the yields are slightly better (5–10% higher) and the coupling is performed at room temperature instead of 0 °C. Finally, note that contrary to FeCl$_3$, the complex [(FeCl$_3$)$_2$(tmeda)$_3$] is not hygroscopic and can be stored at room temperature without any special precautions.

Finally, we applied our cross-coupling procedures on a large scale. The results (unoptimized yields) are described in Scheme 5.

In summary, we have disclosed herein two efficient eco-friendly iron-catalyzed procedures to couple secondary and primary alkyl halides with aromatic Grignard reagents, using two new catalytic systems, [Fe(acac)$_3$]/HMTA/TMEDA (1:1:2) and the complex [(FeCl$_3$)$_2$(tmeda)$_3$]. To the best of our knowledge, HMTA has never been employed as a ligand for cross-coupling reactions until now, while the second catalyst [(FeCl$_3$)$_2$(tmeda)$_3$] has not been described and is a non-hygroscopic and cheap complex that is very easy to prepare.



Scheme 5. Large-scale preparation of *sec*-butylbenzene.

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Keywords: cross-coupling · Grignard reagents · homogeneous catalysis · iron · sustainable chemistry

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[1] a) G. Cahiez, P. Y. Chavant, E. Metais, *Tetrahedron Lett.* **1992**, *33*, 5245; b) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; c) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199; d) C. Duplais, F. Bures, T. Korn, I. Sapountzis, G. Cahiez, P. Knochel, *Angew. Chem.* **2004**, *116*, 3028; *Angew. Chem. Int. Ed.* **2004**, *43*, 2968.

[2] For exhaustive reviews on iron-mediated coupling reactions, see: a) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; b) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; c) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2071.

[3] a) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297; b) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, 2822; c) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; d) R. B. Bedford, D. W. Bruce, R. M. Frost, M. Hird, *Chem. Commun.* **2005**, 4161; e) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, *116*, 4045; *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; f) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686.

[4] See reference [3f] and Table S2 in the Supporting Information.

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