ORGANIC LETTERS

2006
Vol. 8, No. 4
733−735

An Iron-Containing Ionic Liquid as Recyclable Catalyst for Aryl Grignard Cross-Coupling of Alkyl Halides

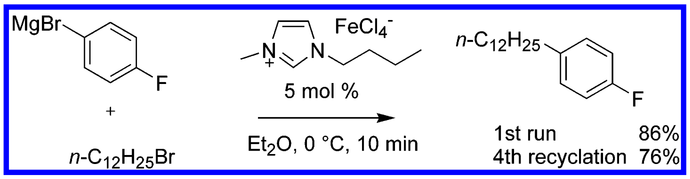
Katharina Bica and Peter Gaertner*

Department of Applied Synthetic Chemistry, Vienna University of Technology,
Getreidemarkt 9, A-1060 Vienna, Austria

peter.gaertner@tuwien.ac.at

Received December 7, 2005

ABSTRACT



The ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) was found to be a very effective and completely air stable catalyst for the biphasic Grignard cross-coupling with primary and secondary alkyl halides bearing β-hydrogens. After simply decanting the product in the ethereal layer, the ionic liquid catalyst was successfully recycled four times.

Since iron is one of the most inexpensive and nonpollutant metals on earth, the scope for iron-catalyzed chemistry is of substantial interest.[1,2] Recent advances in the field of iron-catalyzed cross-coupling chemistry include the original work of Kochi et al.[3] and of Cahiez and Avedissian,[4] considering alkenyl bromides, as well as recent papers of Fürstner and co-workers who used iron−salen precatalysts[5] and the tetrakisferrate complex $[Li(tmeda)_2]Fe(C_2H_4)_2$.[6] Nagano and Hayashi showed the utility of $Fe(acac)_3$ [7] in the coupling of $C(sp^3)-X$ compounds, whereas Fürstner used $Fe(acac)_3$ and anhydrous $FeCl_3$ for the coupling of aryl halides.[5,8] Several papers of Fürstner et al. dealt with the $Fe(acac)_3$-catalyzed coupling of aryl triflates[9] and enol triflates[10] as well as with acid chlorides[10,11] and propargyl epoxides.[12] Further studies on the use of various iron−salen catalysts were done by Bedford et al., who also discovered the use of anhydrous $FeCl_3$ in combination with appropiate amine ligands to diminish β-elimination.[13] The catalyst system $FeCl_3$/stoichiometric TMEDA for the coupling of Grignard and zinc reagents was also described by Nakamura et al.; nevertheless, slow addition of the Grignard reagent via a syringe pump was necessary.[14] In our current studies concerning the use of ionic liquids for transition metal catalyzed reactions,[15] we discovered that the iron-containing ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) is a very

---

(1) For a general review on iron-catalyzed organic reactions, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Shinokobu, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081.

(2) For a recent review on iron-catalyzed cross-coupling chemistry: Fürstner, A.; Rubén, M. *Chem. Lett.* **2005**, *34*, 624.

(3) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063. (c) Tamura, M.; Kochi, J. K. *Synthesis* **1971,** 303. (d) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351. (e) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (e) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (f) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11.

(4) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

(5) (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.

(6) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955.

(7) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(8) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

(9) Seidel, D.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950.

(10) (a) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (b) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Tenson, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358.

(11) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805. (b) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053.

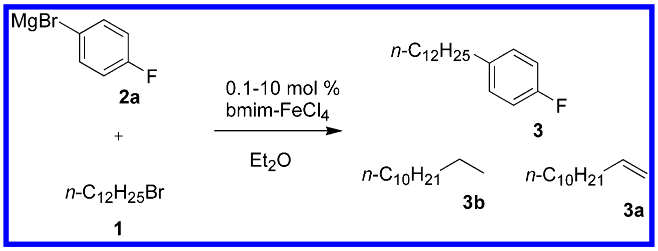
(12) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355.

(13) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161.

(14) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794.

10.1021/ol052965z CCC: $33.50

Table 1. Influence of Catalyst Concentration on the bmim-$FeCl_4$-Catalyzed Cross Coupling of 4-Fluorophenylmagnesium Bromide **2a** and Dodecyl Bromide **1**



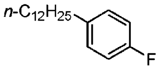
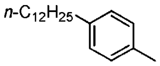
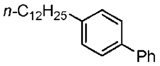
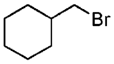
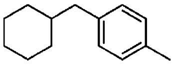
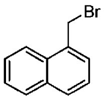
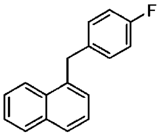
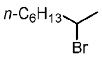
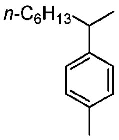
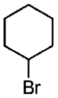
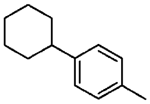
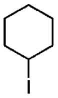
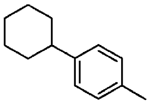
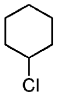
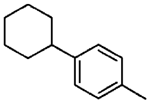
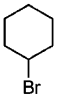
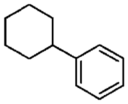
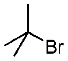
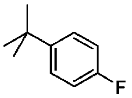
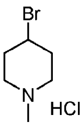
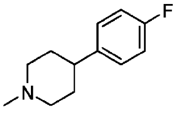
		yield		
entry[a]	bmim-$FeCl_4$ (mol %)	**3**[b] (%)	**3a**[b] (%)	**3b**[b] (%)
1	10	88.3	7.6	3.5
2	5	89.8	6.7	3.0
3	1	80.3	9.9	4.9
4	0.5	79.4	9.8	6.1
5	0.1	<0.1	0.5	0.4

[a] All reactions were carried out in Et_2O at 0 °C with 2 mmol of R-X and 3 mmol of ArMgX under air. [b] Determined by GC−MS using *n*-hexadecane as internal standard.

efficient catalyst for the Grignard cross coupling of alkyl halides. Bmim-$FeCl_4$ was easily prepared in a solid state reaction by mixing commercially available solid bmim-Cl and $FeCl_3 \cdot 6\ H_2O$, yielding the hydrophobic ionic liquid as a lower phase, and water, which can be easily separated.[16] This ionic liquid was already used on solid support as a catalyst for Friedel−Crafts acylation,[17] but, to the best of our knowledge, no application in cross-coupling chemistry either as catalyst nor as solvent has been reported so far. For initial screening of catalytic activity, we chose an alkyl halide bearing β-hydrogens and examined the coupling between dodecyl bromide and 4-fluorophenylmagnesium bromide using 10 mol % of bmim-$FeCl_4$ catalyst. The biphasic reaction was initially run in dry diethyl ether as cosolvent, but later studies showed that there is no difference using technical instead of anhydrous ether. Furthermore, the reaction proved to be completely air and moisture stable and could be carried out without inert atmosphere. Since addition of the Grignard solution was rather exothermic, cooling with an ice bath during the addition is recommended, although higher temperature did not have any negative influence on the conversion.

Reactions proceeded very fast within 10 min and gave product **3** in 88% yield and only small amounts of byproducts from β-elimination (**3a**) and reductive elimination (**3b**) (Table 1; entry 1) compared to analogous $Fe(acac)_3$-catalyzed

Table 2. Results of Various Aryl Grignard Cross-Couplings Catalyzed by bmim-$FeCl_4$

Entry[a]	RX	Ar-Met	Product	Yield[b]
1	n-$C_{12}H_{25}$Br	**2a**	 **3**	86
2	n-$C_{12}H_{25}$Br	**2b**	 **4**	73
3	n-$C_{12}H_{25}$Br	**2c**	 **5**	60
4		**2b**	 **6**	64
5		**2a**	 **7**	60
6		**2b**	 **8**	84
7		**2b**	 **9**	89
8		**2a**	 **9**	79
9		**2a**	 **9**	75
10		**2d**	 **10**	20[c]
11		**2a**	 **11**	0[d]
12		**2a**[e]	 **12**	79

[a] All reactions were carried out in Et_2O at 0 °C with 2 mmol of R-X and 3 mmol of ArMgX under air. [b] Isolated yield after flash chromatography, if not otherwise stated. [c] Yield calculated from GC−MS of crude product using *n*-hexadecane as internal standard. [d] No product could be observed on GC−MS analysis. [e] 5 mmol of ArMgX used.

---

(15) For a review: (a) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (b) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A* **2002**, *182−183*, 419. (c) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.

(16) (a) Hayashi, S.; Hamaguchi, H. *Chem. Lett.* **2004**, *33*, 1590. (b) Sitze, M. S.; Schreiter, E. R.; Patterson, E. V.; Freeman, R. G. *Inorg. Chem.* **2001**, *40*, 2298. (c) Zhang, Q.; Yang, J.; Lu, X.; Gui, J.; Huang, M. *Fluid Phase Equilib.* **2004**, *226*, 207.

(17) Valkenberg, M. H.; deCastro, C.; Holderich, W. F. *Appl. Catal. A* **2001**, *215*, 185.

reactions reported in the literature.[7] Best results were obtained with a catalyst concentration of 5 mol %, giving 90% yield whereas a lower catalyst concentration resulted in a slight increase of byproducts **3a** and **3b** and a decrease of the desired coupling product **3** (Table 1; entries 2−4). Changing the Grignard reagent to the electron rich *p*-tolylmagnesium bromide as well as to 4-biphenylmagnesium bromide the reaction proceeded also favorably, although with lower yields of 73 and 60%, respectively (Table 2; entries 2 and 3).

Moving to secondary alkyl halides, we observed a selective formation of the desired coupling product **8** and **9** without any occurrence of β-elimination or reductive elimination. Thus, we could achieve considerably higher yields in the coupling of 2-octyl bromide and cyclohexyl bromide with Grignard reagent **2b** (Table 2; entries 6 and 7) than reported in the literature for Fe(acac)$_3$ as a catalyst.[7] Both cyclohexyl iodide and chloride turned out to be suitable for the cross coupling even though the isolated yields of the coupling product **9** are slightly lower (Table 2; entries 8 and 9).

The use of phenyllithium instead of an aryl Grignard reagent led to a significant drop of yield, and for the first time the homocoupling product 1,1′-dicyclohexyl was detected in almost equal amount (Table 2; entry 10). Tertiary alkyl halides are less reactive: As Nagano and Hayashi have already reported for Fe(acac)$_3$ as catalyst,[7] no conversion at all could be detected using *tert*-butyl bromide (entry 11). Secondary alkyl halides incorperating a heterocyclic *N*-methyl piperidinyl structural motif proceeded also satisfyingly, yielding 79% of coupling product **12** (entry 12).

Ionic liquids have proved to be excellent solvents for catalyst immobilization via liquid−liquid biphasic catalysis.[18] In most cases, products and remaining starting materials can be simply removed by decantation while the catalyst trapped in the ionic liquid can be reused. Starting with 5 mol % of bmim-FeCl$_4$ and 0.5 mL of diethyl ether as cosolvent, we tried to recycle the iron-containing ionic liquid, surveying the initially optimized coupling of 4-fluorophenylmagnesium bromide and dodecyl bromide.

After complete reaction the ionic liquid and formed MgBr$_2$ were left to settle, and the upper ethereal layer containing the product was decanted. The remaining product was extracted by washing the residue twice with 0.5 mL of diethyl ether each. Fresh alkyl halide, *n*-hexadecane as internal standard and 0.5 mL of diethyl ether as cosolvent were added to the remaining bmim-FeCl$_4$ layer which had turned from black to orange during the washing steps. Successive addition of Grignard reagent gave an immediate color change to black, and the catalytic cycle was found to be active again. Although conversion of the alkyl halide is almost complete, the isolated yield of the desired coupling product **3** slightly decreased from 86% in the first run to 76% after the fifth one (Table 3; entries 1−5). This may be explained by the fact that small amounts of iron get removed from the ionic liquid phase during extraction (compare to Table 1).

Table 3. Recycling of bmim-FeCl$_4$ in the Cross-Coupling of 4-Fluorophenylmagnesium Bromide **2a** and Dodecyl Bromide **1**

entry[a]	run	conversion of **1**[b] (%)	yield of **3**[c] (%)
1	1	>99	86
2	2	>99	n.a.
3	3	96	77
4	4	93	n.a.
5	5	92	76

[a] All reactions were carried out in Et$_2$O at 0 °C with 2 mmol of R-X and 3 mmol of ArMgX under air. [b] Conversion calculated from GC−MS of crude product using *n*-hexadecane as internal standard. [c] Isolated yield after flash chromatography.

In summary, we have established a new, easily prepared, and recyclable catalyst for iron catalyzed Grignard cross-coupling of primary and especially of secondary alkyl halides under mild and air-stable conditions. Further aspects including stereoselective coupling using a chiral ionic liquid-derived iron catalyst as well as mechanistic details via Raman spectroscopy concerning the catalytically relevant iron species are currently under investigation.

Acknowledgment. We thank Prof. B. Lendl and M. López-Pastor for measuring Raman spectra.

Supporting Information Available: Representative experimental procedure and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052965Z

---

(18) Dupont, J.; deSouza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667.