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Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents

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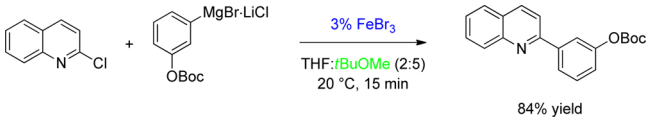
ABSTRACT



A simple, practical iron salt catalyzed procedure allows fast cross-couplings of *N*-heterocyclic chlorides and bromides with various electron-rich and -poor arylmagnesium reagents. A solvent mixture of THF and *t*BuOMe is found to be essential for achieving high yields mainly by avoiding homocoupling side reactions.

Fe-catalyzed cross-couplings have received a lot of attention due to the environmentally friendly properties of iron salts combined with their moderate prices.[1] Whereas alkyl-aryl,[2] alkyl-alkenyl,[3] aryl-alkenyl,[3b,c,4] and alkynyl[5] coupling reactions are well documented, the corresponding aryl−aryl cross-couplings are much more challenging due to the formation of homocoupling products[2a,6,7] or to the need for additional copper salts.[8] The use of iron fluorides in combination with carbene ligands improves such aryl−aryl cross-couplings dramatically as shown by M. Nakamura.[9] The cross-coupling of *N*-heterocyclic halides (chlorides or bromides) with arylmagnesium reagents is of special importance due to the potential biological activity of the resulting arylated heterocycles. For such reactions only a

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few examples have been reported and no general cross-coupling method has been available.[2a,b,9,10] Herein, we describe an efficient iron-catalyzed cross-coupling between *N*-heterocyclic chlorides and bromides with various arylmagnesium reagents using a simple iron salt as the catalyst system.

In preliminary experiments, we have examined the cross-coupling between 2-chloropyridine (**1a**) and PhMgCl (**2a**) (Scheme 1). Thus, catalytic amounts (5 mol %) of various iron salts such as $Fe(acac)_2$, $Fe(acac)_3$, or the related $Fe(TMHD)_3$ (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate; entries 1−3 of Table 1) and iron halides such as $FeCl_2$, $FeCl_3$, $FeBr_2$, or $FeBr_3$ (entries 4−7) as well as $Fe(OTf)_3$ (entry 8) gave only moderate yields of the desired cross-coupling product **3a** (46−63%) in THF at rt. Also, the use of iron fluorides and iodide led to only traces of product at rt (entries 9−11). Polar cosolvents such as NMP (*N*-methylpyrrolidone) hampered the cross-coupling (entry 12). Nonpolar solvents, e.g., *n*-hexane or toluene, did not display any considerable improvement (entries 13−14).[11] However, ethereal solvents such as diethyl ether or *t*BuOMe dramatically increased the GC yield up to 87% affording after isolation the arylated pyridine **3a** in 84% yield (entries 15−16). Since comparable yields are obtained using *t*BuOMe or Et_2O, we have pursued our investigations using the industry-friendly solvent *t*BuOMe. The use of such ethereal solvents proved to be a key determinant and allowed us to extend this cross-coupling to various other *N*-heterocycles. In order to study the reaction scope, we have first varied the *N*-heterocyclic chlorides or bromides and determined their reactions with PhMgCl (**2a**) in *t*BuOMe at rt.[12] Thus, we observed that

Scheme 1. Cross-Coupling of Pyridyl Chloride (**1a**) with PhMgCl (**2a**) in the Presence of Various Fe-Salts

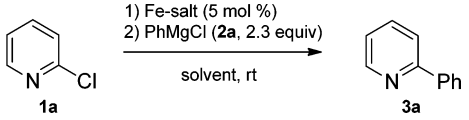
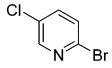
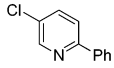
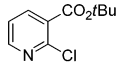
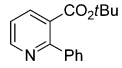
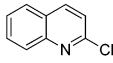
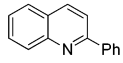
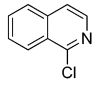
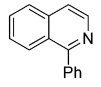
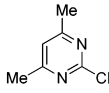
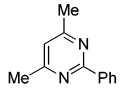
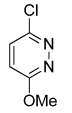
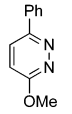


Table 1. Optimization of the Conditions for Reaction of Pyridyl Chloride (**1a**) with PhMgCl (**2a**) Catalyzed by Fe-Salts

entry	Fe-salt[a]	solvent	reaction time[b]	yield (%)[c]
1	$Fe(acac)_2$	THF	2 h	46
2	$Fe(acac)_3$	THF	2 h	55
3	$Fe(TMHD)_3$	THF	2 h	53
4	$FeCl_2$	THF	5 h	56
5	$FeCl_3$	THF	2 h	55
6	$FeBr_2$	THF	2 h	62
7	$FeBr_3$	THF	1.5 h	63
8	$Fe(OTf)_3$	THF	5 h	60
9	FeF_2	THF	20 h	traces[d]
10	FeF_3	THF	20 h	traces[d]
11	FeI_2	THF	20 h	traces[d]
12	$FeBr_3$	THF/NMP[e]	2 h	traces
13	$FeBr_3$	*n*-hexane	2 h	53
14	$FeBr_3$	toluene	1.5 h	14
15	$FeBr_3$	Et_2O	1.5 h	73, 87[f] (84)[f]
16	$FeBr_3$	*t*-BuOMe	1.5 h	75, 85[f] (82)[f]

[a] 5 mol % of Fe-salt was used. [b] Reaction time until reaction completion according to GC analysis. [c] Calibrated GC yield using undecane ($C_{11}H_{24}$) as internal standard. Numbers in brackets indicate isolated yields [d] Starting material was not consumed even after 20 h. [e] A mixture of THF/NMP (5:1) was used. The reaction of PhMgCl with NMP was dominant. [f] 3 mol % of $FeBr_3$ was used.

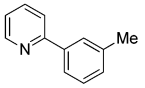
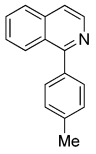
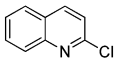
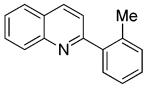
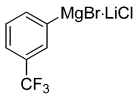
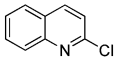
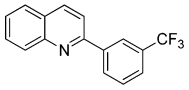
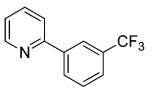
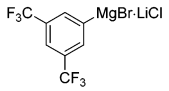
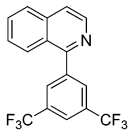
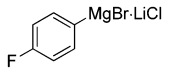
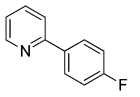
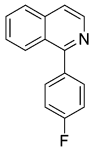
Table 2. Scope of Iron-Catalyzed Cross-Coupling of *N*-Heteroarylchlorides/-bromides (**1a**−**1j**) with PhMgCl (**2a**)

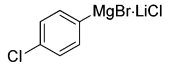
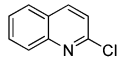
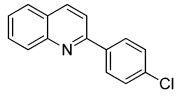
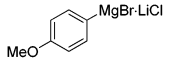
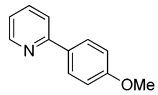
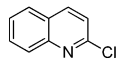
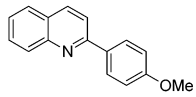
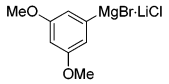
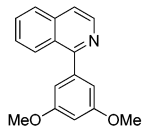
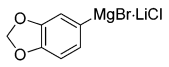
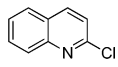
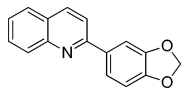
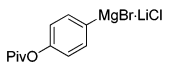
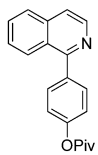
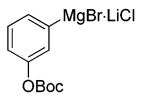
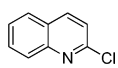
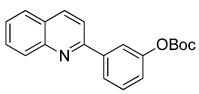
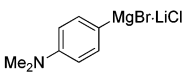
entry[a]	substrate	reaction time	product	yield (%)[b]
				
1	**1a**: X= Cl	1.5 h	**3a**	82
2	**1b**: X= Br	70 min	**3a**	83
				
3	**1c**	2 h	**3b**	84
				
4	**1d**	70 min	**3c**	78
				
5	**1e**	5 min	**3d**	60
				
6	**1f**	5 min	**3e**	88
				
7	**1g**	5 min	**3f**	90
				
8	**1h**	2 h	**3g**	76
				
9	**1i**	5 h	**3h**	22[c]
				
10	**1j**	3 h	**3i**	24[c]

[a] The reaction was performed on a 1 mmol scale with 3 mol % of $FeBr_3$ in THF/*t*BuOMe (ca. 2:5) at rt. [b] Isolated yield. [c] GC yield.

(3) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Fabre, J.-L.; Julia, M.; Verpeaux, J.-N. *Tetrahedron. Lett.* **1982**, *23*, 2469. (c) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (d) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253. (e) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem.* **2007**, *119*, 6641. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521. (f) Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, *10*, 2389. (g) Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496. (h) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656. (i) Nishikado, H.; Nakatsuji, H.; Ueno, K.; Nagase, R.; Tanabe, Y. *Synlett* **2010**, *14*, 2087. (j) Hashimoto, T.; Hatakeyama, T.; Nakamura, M. *J. Org. Chem.* **2012**, *77*, 1168.

Table 3. Iron-Catalyzed Cross-couplings of *N*-Heteroarylchlorides/-bromides with Various Grignard Reagents

entry[a]	Grignard reagent	substrate; reaction time	product; yield[b]
1	*m*-TolMgBr·LiCl **2b**	 **1b**; 1.5 h	 **3j**; 80%
2	*p*-TolMgBr·LiCl **2c**	 **1g**; 2 min	 **3k**; 93%
3	*o*-TolMgBr·LiCl **2d**	 **1f**; 45 min	 **3l**; 84%
4	 **2e**	 **1f**; 15 min	 **3m**; 92%
5	**2e**	 **1b**; 2 h	 **3n**; 66%
6	 **2f**	 **1g**; 5 h	 **3o**; 75%
7	 **2g**	 **1b**; 5 min	 **3p**; 68%
8	**2g**	 **1g**; 5 min	 **3q**; 90%

entry[a]	Grignard reagent	substrate; reaction time	product; yield[b]
9	 **2h**	 **1f**; 5 min	 **3r**; 84%
10	 **2i**	 **1b**; 10 min	 **3s**; 82%
11	**2i**	 **1f**; 5min	 **3t**; 87%
12	 **2j**	 **1g**; 5 min	 **3u**; 71%
13	 **2k**	 **1f**; 5min	 **3v**; 81%
14	 **2l**	 **1g**; 15 min	 **3w**; 80%
15	 **2m**	 **1f**; 15 min	 **3x**; 84%
16	 **2n**	**1f**; 5min	**3y**; 82%

[a] The reaction was performed on a 1 mmol scale with 3 mol % of $FeBr_3$ in THF/*t*BuOMe (ca. 2:5) at rt. [b] Isolated yield.

2-bromopyridine (**1b**) reacted with PhMgCl at a faster rate for completion than 2-chloropyridine (70 min instead of 90 min) and produced **3a** in the same yield (83%, entry 2 of Table 2). Substituted bromo- or chloropyridines such as 2-chloro-4-picoline (**1c**) and 2-bromo-5-chloropyridine (**1d**) reacted smoothly with similar reaction times leading to the pyridines **3b** and **3c** in 78−84% yield (entries 3 and 4). Interestingly, the presence of a *tert*-butoxycarbonyl group in position 3 (**1e**) dramatically increased the reaction rate leading to full conversion within 5 min (entry 5). The cross-coupling product **3d** was isolated in 60% yield. No starting chloride was detected, and the relatively moderate yield may be due to a polymerization of **1e**. The annulation of the pyridine ring with a benzene moiety also accelerated the reaction rate, and the cross-couplings of PhMgCl with

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2-chloroquinoline (**1f**) or 1-chloroisoquinoline (**1g**) were completed in 5 min and gave the expected phenylated *N*-heterocycles **3e** and **3f** in 88−90% yield (entries 6 and 7). The cross-coupling was also extended to diazines. Whereas the 2-chloropyrimidine derivative **1h** reacted with PhMgCl within 2 h providing the arylated pyrimidine **3g** in 76% yield (entry 8), the more sensitive chloropyridazine **1i** and -pyrazine **1j** required 3−5 h for the reaction to go to completion but led to the phenylated products in only 22−24% yields (entries 9 and 10).[13]

We have then varied the nature of the Grignard reagent[14] using typical *N*-heterocyclic chlorides and bromides (**1b**, **1f**, **1g**) as electrophiles (Table 3). In all cases, the Fe-catalyzed cross-couplings were fast (2 min to 5 h) and led to complete conversion. Both electron-rich and -poor substituents can be present in the Grignard reagent. We have examined first the substitution pattern of the arylmagnesium reagent and have found that *ortho*-, *meta*-, and *para*-substituted Grignard reagents can be used. Whereas *m*-TolMgBr·LiCl (**2b**) and *p*-TolMgBr·LiCl (**2c**) react at similar rates as the unsubstituted magnesium reagent, the presence of an *ortho*-methyl substituent in *o*-TolMgBr·LiCl (**2d**) reduced the reaction rate (compare entry 3 of Table 3 with entry 6 of Table 2). However, in all cases excellent yields (80−93%; entries 1−3 of Table 3) were obtained. Various electron-poor substituents such as a trifluoromethyl group (as in 3-trifluoromethyl- magnesium bromide **2e** and in 3,5-ditrifluorophenylmagnesium bromide **2f**; entries 4−6), a fluorine group (as in 4-fluorophenylmagnesium bromide **2g**; entries 7 and 8), and a chlorine group (as in **2h**; entry 9) were well tolerated in the cross-couplings providing the expected products in 66−92% yields (entries 4−9). Interestingly, also electron-rich substituents such as methoxy (see reagents **2i** and **2j**; entries 10−12), methylenedioxy (see reagent **2k**; entry 13), and pivalate groups (OPiv; see reagent **2l**; entry 14) were compatible with rapid iron-catalyzed cross-couplings. The more sensitive Boc-protected Grignard reagent **2m** also smoothly underwent cross-coupling with 2-chloroquinoline leading to the 2-arylated quinoline **3x** in 84% yield (entry 15). An amino substituent did not disturb the cross-coupling, and the Grignard reagent **2n** reacted with **1f** within 5 min providing the product **3y** in 82% yield (entry 16).

Even though the mechanism of this cross-coupling could not yet be elucidated, we noticed that the use of Fe(II) or Fe(III) salt led to similar results. Reducing the Fe(III) catalyst *in situ* with *i*PrMgCl prior to cross-coupling deactivated the catalytic system and hampered the coupling reaction. The use of an apolar cosolvent such as *t*BuOMe was found to be vital to achieving high yields mainly by avoiding homocoupling products.

In summary, we have developed a new practical iron-catalyzed sp^2-sp^2 cross-coupling between *N*-heterocyclic chlorides or bromides and various arylmagnesium reagents. This cross-coupling reaction tolerates several electron-withdrawing and -rich functionalities, such as dimethylamino, *tert*-butoxyoxycarbonyl (OBoc), or methoxy groups. Further studies to increased the reaction scope as well as mechanistic investigations are currently underway in our laboratories.

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Supporting Information Available. Experimental procedures and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The term "homocoupling" refers only to the homocoupling of the Grignard reagent.

(8) (a) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem.* **2005**, *117*, 1682. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654. (b) Kofink, C. C.; Blank, B.; Pagano, S.; Götz, N.; Knochel, P. *Chem. Commun.* **2007**, 1954.

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(11) The low yields in entries 1−14 of Table 1 are due to the fact that the reaction conversion never reaches 100% for these substrates.

(12) Since PhMgCl is prepared in THF, the cross-coupling reaction is in fact performed in a mixture of THF and *t*BuOMe (ca. 2:5).

(13) The use of other heterocyclic halides, such as 3- and 4-chloropyridine, 2-chlorothiophene, or 2-bromofuran, as well as standard haloarenes resulted in only low yields.

(14) The Grignard reagents were prepared by LiCl-mediated Mg insertion; see: Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; P. Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

The authors declare no competing financial interest.