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Catalysis

Practical Iron- and Cobalt-Catalyzed Cross-Coupling Reactions between N-Heterocyclic Halides and Aryl or Heteroaryl Magnesium Reagents

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Abstract: The reaction scope of iron- and cobalt-catalyzed cross-coupling reactions in the presence of isoquinoline (quinoline) in the solvent mixture *t*BuOMe/THF has been further investigated. Various 2-halogenated pyridine, pyrimidine, and triazine derivatives were arylated under these mild conditions in excellent yields. The presence of isoquinoline allows us to perform Fe-catalyzed cross-coupling reactions between 6-chloroquinoline and aryl magnesium reagents. Furthermore, it was found that the use of 10% *N*,*N*-dimethylquinoline-8-amine increases the yields of some Co-catalyzed cross-coupling reactions with chloropyridines bearing electron-withdrawing substituents.

Introduction

Iron-catalyzed cross-coupling reactions are of high synthetic interest due to the abundance of iron, its low toxicity, and moderate price, especially in comparison with Pd- or Rh-catalyzed cross-coupling reactions.[1,2] Although, the performance of Csp^2–Csp^3 cross-coupling reactions using an iron-catalyst is well-established,[3] the corresponding cross-couplings between Csp^2-centers is much more challenging due to the formation of homocoupling side products.[4] The use of copper reagents instead of magnesium derivatives suppresses most of the homocoupling side reactions, but the need for stoichiometric amounts of copper salts is a serious drawback.[5] Alternatively, the use of heterocyclic carbene (NHC) ligands in combination with iron fluorides also considerably reduces the amount of homocoupling as has been demonstrated by M. Nakamura.[6] This paved the route for a range of new aryl–aryl cross-coupling reactions.[7] Further, polar cosolvents, as shown by Cahiez[8] and Fürstner,[3b] lead to efficient cross-coupling reactions in some special cases. Recently, we have reported that a mixture of THF and *t*BuOMe, an ether of low polarity, improves Csp^2–Csp^2 cross-coupling reactions with only 3% $FeBr_3$.[9] Nevertheless, these reaction conditions are not satisfactory in the case of highly functionalized Grignard reagents and require often several hours of reaction time for reaching an acceptable conversion. Co-catalyzed cross-coupling reactions have also attracted a lot of attention over the last decades.[10] The high reactivity of several cobalt catalysts for various C–C bond-forming reactions was disclosed by Cahiez,[11] Oshima,[12] Gosmini,[13] and Cossy.[14] In 2009, M. Nakamura showed that the combination of NHC ligands and cobalt fluorides can also successfully be applied to biaryl cross-coupling reactions.[15] Alternatively, cobalt-catalyzed cross-coupling reactions of heterocyclic chlorides with aryl and heteroaryl magnesium halides are possible as well. The desired cross-coupled products were obtained in good yields, using diethyl ether as a solvent.[16] Cobalt-catalyzed cross-coupling reactions between polyfunctional arylcopper reagents and aryl bromides or chlorides have also been reported. The addition of 4-fluorostyrene to Bu_4NI in a solvent mixture DME/THF/DMPU (6:3:2) promotes such cross-coupling reactions.[17] Further extensions of this method allowed cobalt-catalyzed cross-coupling reactions between polyfunctional arylcopper reagents and aryl fluorides or tosylates.[18,19]

Results and Discussion

During the course of our investigations, we noted that the reaction of 1-chloroisoquinoline (**1a**) and PhMgCl (**2a**) in the presence of 3% $FeBr_3$ in the solvent mixture *t*BuOMe/THF takes only 5 min and provides the cross-coupled product, 1-phenylisoquinoline (**3a**) in 90% yield, whereas the cross-coupling of 2-chloropyridine (**1b**) under the same conditions requires 1.5 h for completion and gives 2-phenylpyridine (**3b**) in 82% yield (Scheme 1).

The reactivity difference of these substrates led us to postulate that the catalytically active iron species, generated in situ, may contain an isoquinoline fragment as a ligand.[20] To check this, we have performed the reaction between 2-chloropyridine (**1b**) and PhMgCl (**2a**) in the presence of 7% isoquinoline and

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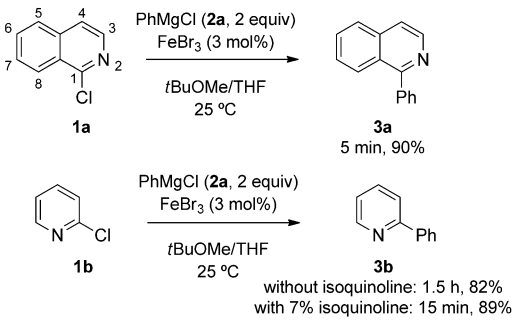
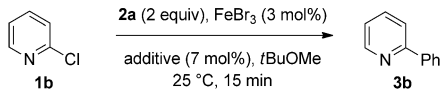


Scheme 1. Iron-catalyzed cross-couplings of 1-chloroisoquinoline (**1a**) or 2-chloropyridine (**1b**) with PhMgCl (**2a**).

have found that the arylated pyridine **3b** was obtained at a much faster rate (within 15 min) and with an increased isolated yield of 89% under these new reaction conditions (Scheme 1). Herein, we report our full investigations on the iron- and cobalt-catalyzed cross-coupling reactions promoted by N-heterocyclic ligands. We describe the reaction scope as well as some extensions allowing a direct aryl–aryl cross-coupling with some special substrates.

The accelerating effect of isoquinoline for performing cross-coupling reactions (see Scheme 1) led us to screen other ligands. We systematically examined various substituted quinolines and isoquinolines (Table 1). 1-Methylisoquinoline had a similar catalytic activity as isoquinoline (Table 1, entry 4). An erosion of the rate enhancement occurs when a methyl group is attached either to the 2- or 8-position (entries 5 and 6), and only a slight improvement was observed when the methyl group is attached to position 6 of the quinoline ring (entry 7). An electron-donating methoxy group had a positive effect, when it was placed at the 4- or 6-positions (entries 8 and 9) but had no effect, when it was attached to the 8-position (entry 10).

Table 1. Screening of various additives for the Fe-catalyzed cross-coupling reaction of 2-chloropyridine (**1b**) with PhMgCl (**2a**).



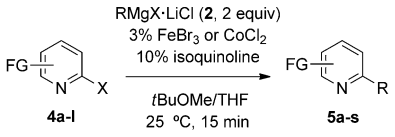
Entry[]	Additive	Yield of **3b** [%][a]
1	without additive	40
2	**isoquinoline**	**92 (89)**[b]
3	quinoline	75
4	**1-methylisoquinoline**	**91**
5	2-methylquinoline	67
6	8-methylquinoline	48
7	**6-methylquinoline**	**82**
8	4-methoxyquinoline	73
9	**6-methoxyquinoline**	**82**
10	8-methoxyquinoline	40
11	6-chloroquinoline	58
12	6-bromoquinoline	73

[a] Yield determined after 15 min by integration of a GC chromatogram and comparison against undecane as a calibrated internal standard. [b] Isolated yield after purification by flash column chromatograpy.

An electron-withdrawing group such as a chloride in position 6 decreases the catalytical activity of the quinoline ligand (Table 1, entry 11). Interestingly, 6-bromoquinoline undergoes a Br/Mg-exchange reaction with PhMgCl (**2a**), providing the debrominated quinoline, which gave similar results to quinoline (compare entries 3 and 12). Based on this small snapshot of all tested ligands, the following trend could be found. Electron-donating substituents give better results than electron-withdrawing ones. The 2-position of quinoline should not be substituted. Electron-donating groups placed in position 6 of quinoline are beneficial. Finally, chelating ligands such as bispyridine deactivate the iron catalyst, probably due to chelation. We have found that 10 mol% was the optimum amount of isoquinoline and that most reactions were complete within 15 min at 25 °C. Screening of various metal salts showed that isoquinoline was also a good ligand for Co-catalyzed cross-coupling reactions.

Both $FeBr_3$ and $CoCl_2$ had similar activity in combination with isoquinoline and both metal salts catalyze under these conditions the cross-couplings between N-heterocyclic halides and aryl- or heteroaryl-magnesium reagents.[21] Thus, 2-bromopyridine (**4a**) reacted with the heterocyclic Grignard reagent (**2b**), providing the desired pyridine (**5a**) in 61% isolated yield (Table 2, entry 1). TMS-substituted 2-bromopyridine (**4b**) undergoes Fe- and Co-catalyzed coupling reactions with various electron-rich (**2c**) and sulfur-containing Grignard reagents (**2d–f**) to furnish the respective 2,3-disubstituted bis(hetero)aromatics (**5b–e**) in 49–91% yields (entries 2–5). Also, 2-halogenated 6-methoxypyridines (**4c–d**) couple well with 4-fluorophenylmagnesium bromide (**2g**) as well as the indolylmagnesium reagent (**2b**) to furnish the coupling products (**5f–g**) in 65–75% yields (entries 6–7). Bis-halogenated pyridine (**4e**) undergoes cross-coupling reactions with the ester substituted phenylmagnesium bromide (**2h**) and the electron-rich nucleophile (**2i**) exclusively at position 2 (entries 8–9). We subsequently screened various substituted 3-arylated 2-halogenated pyridines (**4f–g**) in Fe- and Co-catalyzed Csp^2–Csp^2 cross-coupling reactions. The bromopyridines (**4f–g**) undergo high-yielding coupling reactions with Grignard reagents **2c**, **2g**, and **2i** that result in the 2,3-bisarylated pyridines (**5j–l**) in 68–82% yields (entries 10–12). 4-Thienyl-2-bromopyridine (**4h**) is well tolerated in these coupling reactions, resulting in various 2,4-bisarylated pyridines (**5m–o**) in 65–79% yields (entries 13–15). Polyhalogenated 4-arylated pyridines (**4i–k**) undergo Fe- and Co-catalyzed coupling reactions exclusively in position 2, using sterically demanding aromatic Grignard reagents like mesitylmagnesium bromide (**2m**) or the Grignard reagent **2h** leading to the products (**5p–r**) in 65–82% yields (entries 16–18). Sensitive functional groups, such as an alkyne, which may undergo carbometallation with Fe catalysis,[22] gave poor yields of cross-coupling products. However, it was found that the use of 3% $CoCl_2$ and 10% isoquinoline improved this yield and allowed the isolation of pyridine **5s** in 62% yield (entry 19). Oligomerisation reactions of the pyridyl halides may explain the low yields.

Table 2. Fe- and Co-catalyzed cross-coupling reactions between pyridine derivatives and aromatic Grignard reagents, utilizing isoquinoline as a ligand.



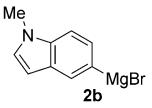
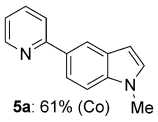
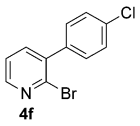
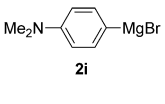
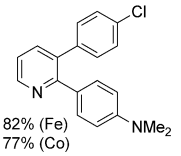
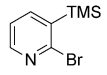
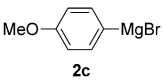
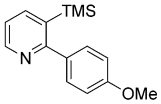
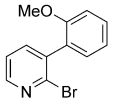
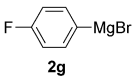
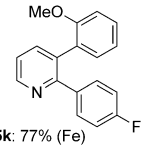
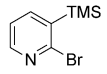
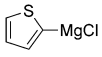
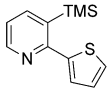
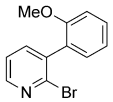
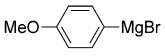
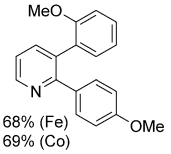
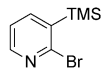
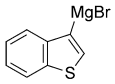
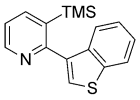
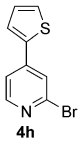
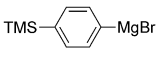
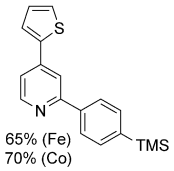
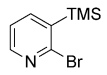
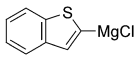
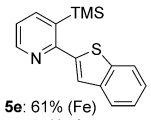
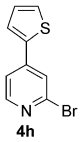
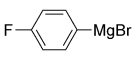
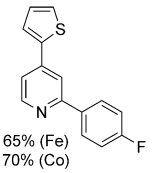
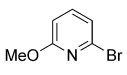
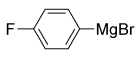
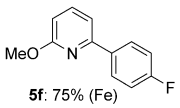
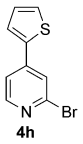
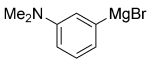
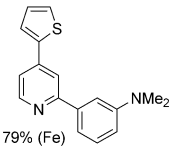
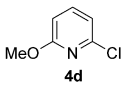
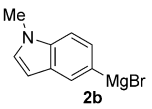
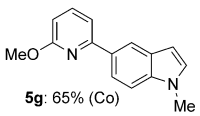
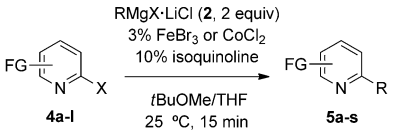
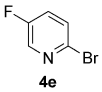
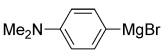
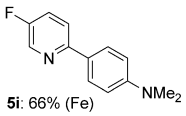
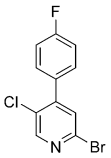
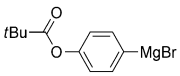
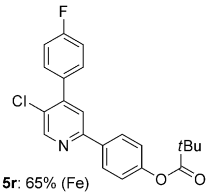
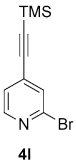
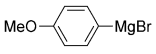
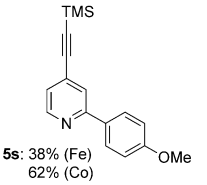
Entry	Starting material	Grignard reagent	Product[a]	Entry	Starting material	Grignard reagent	Product[a]
1	 **4a**	 **2b**	 **5a**: 61% (Co)	10	 **4f**	 **2i**	 **5j**: 82% (Fe) 77% (Co)
2	 **4b**	 **2c**	 **5b**: 91% (Fe) 85% (Co)	11	 **4g**	 **2g**	 **5k**: 77% (Fe) 79% (Co)
3	 **4b**	 **2d**	 **5c**: 63% (Fe) 49% (Co)	12	 **4g**	 **2c**	 **5l**: 68% (Fe) 69% (Co)
4[b]	 **4b**	 **2e**	 **5d**: 64% (Fe) 66% (Co)	13	 **4h**	 **2j**	 **5m**: 65% (Fe) 70% (Co)
5[c]	 **4b**	 **2f**	 **5e**: 61% (Fe) 66% (Co)	14	 **4h**	 **2g**	 **5n**: 65% (Fe) 70% (Co)
6	 **4c**	 **2g**	 **5f**: 75% (Fe)	15	 **4h**	 **2k**	 **5o**: 79% (Fe)
7[d]	 **4d**	 **2b**	 **5g**: 65% (Co)	16	**4i**	**2l**	**5p**: 71% (Fe) 79% (Co)
8	**4e**	**2h**	**5h**: 58% (Fe)	17[e]	**4j**	**2m**	**5q**: 82% (Co)

Table 2. (Continued)



Entry	Starting material	Grignard reagent	Product[a]	Entry	Starting material	Grignard reagent	Product[a]
9	 **4e**	 **2i**	 **5i**: 66% (Fe)	18	 **4k**	 **2h**	 **5r**: 65% (Fe)
				19[f]	 **4l**	 **2c**	 **5s**: 38% (Fe) 62% (Co)

[a] Isolated yield after purification by flash column chromatography. [b] The reaction was performed at 25 °C for 24 h. [c] The reaction was performed at 50 °C for 12 h, when 3% $FeBr_3$ was used and at 25 °C for 12 h, when 3% $CoCl_2$ was used. [d] The reaction was performed at 25 °C for 1 h. [e] The reaction was performed at 25 °C for 5 h. [f] The reaction was performed at 25 °C for 30 min.

The pyrimidine scaffold is often found in pharmaceutical compounds[23] and therefore is an important structure for cross-coupling reactions. Various pyrimidines were prepared using 3% of $FeBr_3$ and 3% of $CoCl_2$ in a combination with 10% of isoquinoline (Table 3).

Thus, 2-chloro-4,6-dimethylpyrimidine (**6a**) undergoes an iron-catalyzed cross-coupling reaction with electron-poor aromatic Grignard reagent (**2g**) in 71% yield (Table 3, entry 1). The more electron-rich pyrimidine (**6b**) is also a good substrate for this transformation (entry 2). An iron-catalyzed double-arylation of 4,6-dichloropyrimidine (**6c**) was performed with an excess of Grignard reagent (**2l**), furnishing the bis-arylated pyrimidine (**7c**) in 95% yield (entry 3). Arylated 2-bromopyrimidines (**6d**–**e**) participate in such reactions, leading to Fe- or Co-catalyzed cross-coupling reactions with the polyhalogenated and acetal-substituted aromatic Grignard reagents (**2o** and **2q**), as well as with phenylmagnesium bromide (**2n**) and 1-naphthylmagnesium bromide (**2p**) (entries 4–7).

The functionalization of triazines is of great importance, since these compounds are often used as building blocks in material chemistry[24] and as agrochemicals.[25]

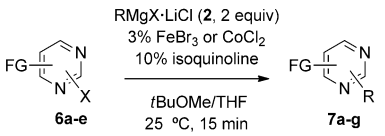
Various heteroatomic substituted 2-chlorinated triazines, like pyrrolidyl-substituted triazine (**8a**), ethoxy-substituted triazine (**8b**), and ethylthiotriazine **8c** were coupled with various (hetero)aromatic Grignard reagents, like 2-thienylmagnesium chloride (**2d**) or the acetal-substituted Grignard reagent (**2q**), resulting in arylated triazines (**9a**–**c**) in 61–84% yields (Table 4).

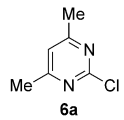
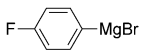
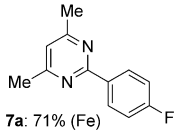
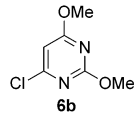
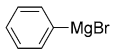
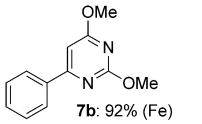
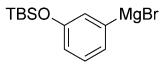
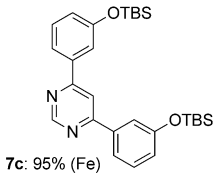
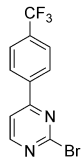
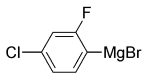
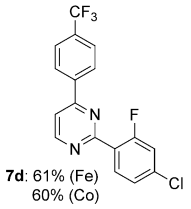
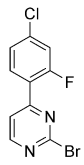
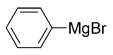
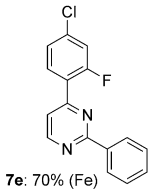
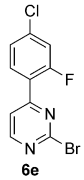
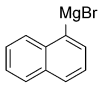
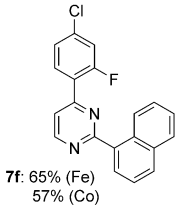
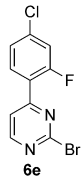
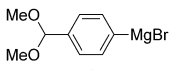
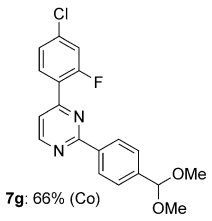
To demonstrate the effect of the isoquinoline ligand, several control experiments have been performed.[20] Thus, in the case of the chloropyrimidine (**6a**) the reactions with the arylmagnesium derivative (**2k**) performed in the presence of isoquinoline (10%) led to the desired product (**7h**) within 30 min at 25 °C in 63–78% yield. In the absence of isoquinoline only low yields of 11–26% were obtained. Longer reaction times (over 2 h) improve somewhat these low yields. Similarly, the 1,3,5-triazine (**8d**) reacts with *p*-anisylmagnesium halides (**2c**) in the presence of 3% $CoCl_2$ or $FeBr_3$ and isoquinoline (10%) leading to the triazine (**9d**) in 79–81% yields within 15 min at 25 °C. In the absence of isoquinoline, the triazine (**9d**) was only isolated in 54–55% yield (Scheme 2).

Also quinolines, like the polysubstituted 2-chloroquinoline **10a** can be coupled efficiently with 4-fluorophenylmagnesium bromide (**2g**) in 67% yield using 3% $CoCl_2$ and in 82% yield using 3% $FeBr_3$ (Table 5, entry 1). The aryl-substituted 2-bromoquinoline **10b** was arylated with 4-anisylmagnesium bromide (**2c**), resulting in bis-arylated quinoline (**11b**) in 78% yield (entry 2). 2,6-Dichloroquinoline (**10c**) undergoes regioselective coupling reactions in position 2 with electron-poor Grignard reagents **2g** and **2r** leading to the quinolines (**11c**–**d**) in 63–65% yields (entries 3–4).

During the course of our investigations, we found that not only the 2-position of halogenated quinolines, but also the 6-position can be functionalized using iron or cobalt catalysts in combination with isoquinoline as a ligand. 6-Chloro-2-phenylquinoline (**12**) undergoes an iron-catalyzed cross-coupling reaction with 4-fluorophenylmagnesium bromide (**2g**) in a moderate yield of 42%. The addition of 10 mol% isoquinoline accelerates this reaction considerably and also increases the yield of **13** to 88%. Compared to $CoCl_2$, $FeBr_3$ is the superior catalyst in this reaction. We were also able to couple the electron-rich

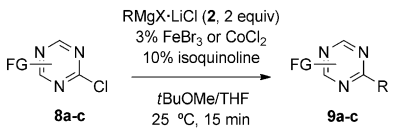
Table 3. Fe- and Co-catalyzed cross-coupling reactions between pyrimidine derivatives and aromatic Grignard reagents, utilizing isoquinoline as a ligand.

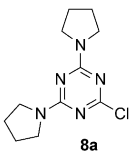
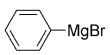
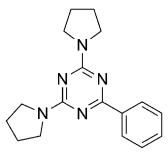
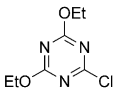
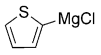
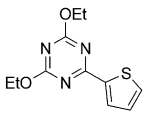
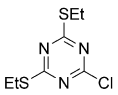
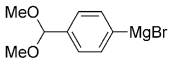
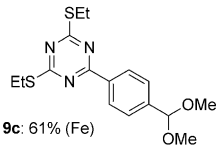


Entry	Starting material	Grignard reagent	Product[a]
1	 **6a**	 **2g**	 **7a**: 71% (Fe)
2	 **6b**	 **2n**	 **7b**: 92% (Fe)
3[b]	 **6c**	 **2l**	 **7c**: 95% (Fe)
4	 **6d**	 **2o**	 **7d**: 61% (Fe) 60% (Co)
5	 **6e**	 **2n**	 **7e**: 70% (Fe)
6	 **6e**	 **2p**	 **7f**: 65% (Fe) 57% (Co)
7	 **6e**	 **2q**	 **7g**: 66% (Co)

[a] Isolated yield after purification by flash column chromatography. [b] An excess of Grignard reagent **2l** (4 equiv) was used.

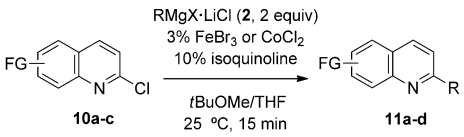
Table 4. Fe- and Co-catalyzed cross-coupling reactions between triazine derivatives and aromatic Grignard reagents, utilizing isoquinoline as a ligand.

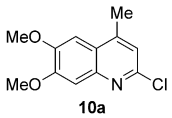
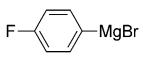
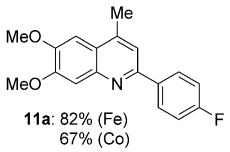
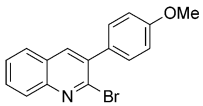
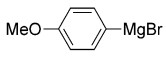
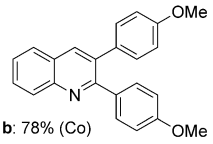
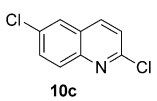


Entry	Starting material	Grignard reagent	Product[a]
1[b]	 **8a**	 **2n**	 **9a**: 76% (Fe)
2[c]	 **8b**	 **2d**	 **9b**: 84% (Fe) 79% (Co)
3	 **8c**	 **2q**	 **9c**: 61% (Fe)

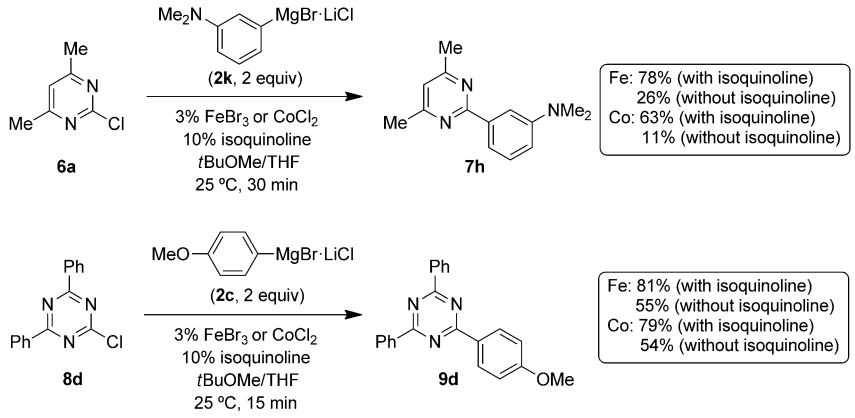
[a] Isolated yield after purification by flash column chromatography. [b] The reaction was performed at 50 °C for 12 h. [c] The reaction was performed at 25 °C for 12 h.

Table 5. Fe- and Co-catalyzed cross-coupling reactions between quinoline derivatives and aromatic Grignard reagents, utilizing isoquinoline as a ligand.

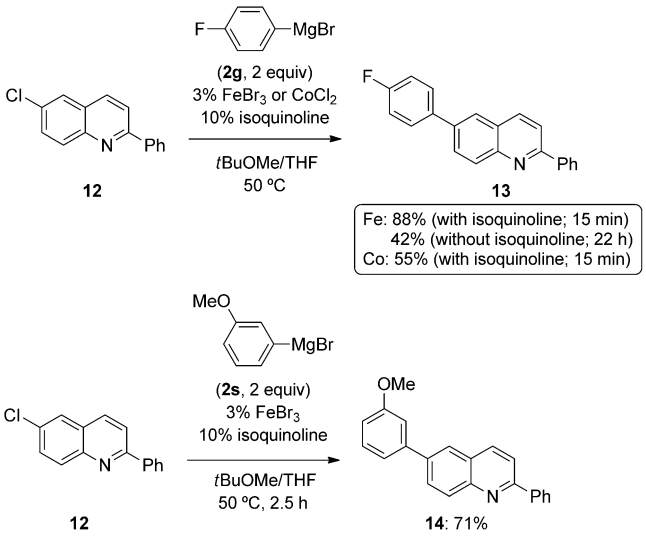


Entry	Starting material	Grignard reagent	Product[a]
1	 **10a**	 **2g**	 **11a**: 82% (Fe) 67% (Co)
2	 **10b**	 **2c**	 **11b**: 78% (Co)
3	 **10c**	**2g**	**11c**: 63% (Fe) 63% (Co)
4	**10c**	**2r**	**11d**: 65% (Fe)

[a] Isolated yield after purification by flash column chromatography.



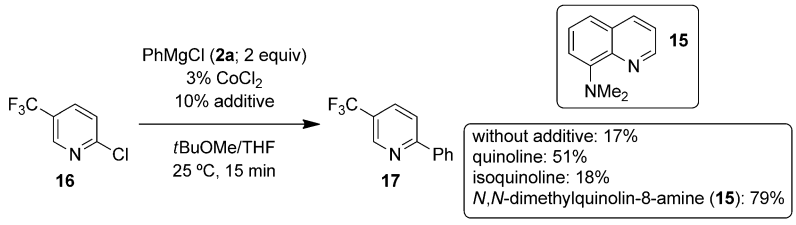
Scheme 2. Co- and Fe-catalyzed cross-coupling reactions with and without isoquinoline.



Scheme 3. Co- and Fe-catalyzed cross-coupling reactions between 6-chloroquinoline **12** and Grignard reagents **2g** and **2s**.

3-anisylmagnesium bromide (**2s**) with 6-chloro-2-phenylquinoline (**12**) and could isolate the 2,6-bisarylated quinoline **14** in 71% yield (Scheme 3).[26]

We have also observed that Co-catalyzed cross-coupling reactions with pyridines, bearing an electron-withdrawing group such as the CF_3 group, could be improved by using 10 mol% of *N*,*N*-dimethylquinoline-8-amine (**15**) instead of isoquinoline (Scheme 4). The cross-coupling reaction of the CF_3-substituted pyridine (**16**) afforded the expected cross-coupled product **17** after 15 min in 79% yield. Whereas in the presence of isoquinoline, a yield of only 18% was reached after 15 min at 25 °C.[27]



Scheme 4. Co-catalyzed cross-coupling reaction between pyridine **16** and PhMgCl (**2a**) utilizing *N*,*N*-dimethylquinolin-8-amine (**15**) as a ligand.

Conclusion

The scope of the iron-catalyzed cross-coupling reactions between electron-deficient 2-halogeno-*N*-heterocycles can be greatly improved by the presence of 10% isoquinoline or 10% quinoline. We have shown that 2-halogenopyridines, -pyrimidines, and -triazines are excellent substrates for such cross-coupling reactions. Furthermore, the presence of isoquinoline also improves aryl–aryl ring cross-coupling reactions if 6-halogenoquinolines are used. In some cases, Co-catalyzed cross-coupling reactions with electron-poor chloropyridines can be greatly improved by using 10% of *N*,*N*-dimethylquinolin-8-amine (**15**) as a new ligand. Further extension of this catalysis is underway in our laboratories.

Experimental Section

Representative procedure: Preparation of arylated quinoline 13 (Scheme 3)

A solution of the Grignard reagent **2g** (1 mL, 2 equiv, 1.0 M in THF containing 1 equiv LiCl) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and 6-chloro-2-phenylquinoline **12** (120 mg, 0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 50 °C for the 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an ethylenediaminetetraacetic acid (EDTA) (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite. After washing the pad of Celite with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield the crude compound, which was purified by column chromatography to yield **13** (120 mg, 88%) as a white solid.

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Keywords: cobalt · cross-coupling · Grignard reagents · N-heterocycles · iron

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[26] Interestingly, we did not observe the formation of the diarylation products for **10c** (Table 5, entries 3 and 4), probably due to the fact that cross-coupling at position 2 is faster than at position 6.
[27] Use of the *N*,*N*-dimethylquinoline-8-amine (**15**) results in rate-acceleration in the case of N-heterocyclic halides substituted with electron-withdrawing groups. In the case of the 2-chloro-5-trifluoromethylpyridine (**16**), this effect is most significant. When 3 mol% of $FeBr_3$ and 10 mol% of *N*,*N*-dimethylquinoline-8-amine (**15**) were used, pyridine **17** was obtained in 38% yield after a 15 min reaction time.

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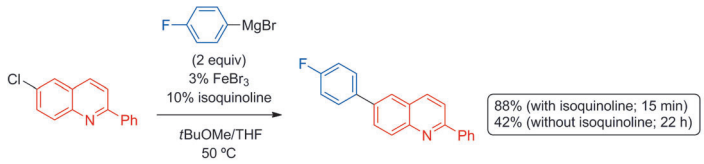

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Catalysis

*O. M. Kuzmina, A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel**

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Practical Iron- and Cobalt-Catalyzed Cross-Coupling Reactions between N-Heterocyclic Halides and Aryl or Heteroaryl Magnesium Reagents