Cross-Coupling

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Ligand-Accelerated Iron- and Cobalt-Catalyzed Cross-Coupling Reactions between N-Heteroaryl Halides and Aryl Magnesium Reagents**

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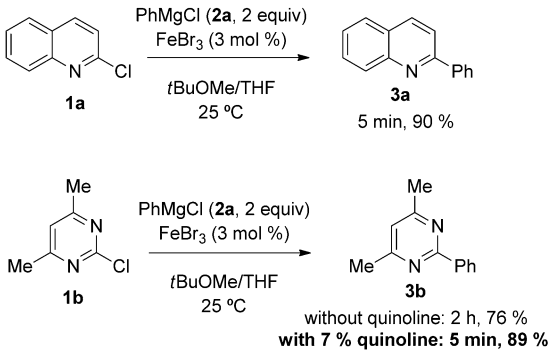
Transition-metal-catalyzed cross-coupling reactions are one of the most used C–C bond-forming reactions in the production of pharmaceuticals and agrochemicals.[1] A variety of Pd-catalyzed coupling reactions (for example, Suzuki, Negishi, Kumada cross-coupling) dominate this field because a large arsenal of bulky phosphine ligands lend generality to these reactions, and virtually any cross-coupling can be achieved by selecting the appropriate ligand.[2] However, the use of Pd has some drawbacks, as its price and toxicity (LD_{50} ($PdCl_2$, rabbit) 18.6 mg kg^{-1}) hamper its use in industrial applications. Cross-coupling reactions employing alternative transition metals, such as Fe and Co, are a viable alternative.[3] Recently, there has been much progress in Fe-catalyzed coupling reactions between C(sp^2) and C(sp^3) centers.[4] However, the formation of C(sp^2)–C(sp^2) bonds remains problematic because of homocoupling side reactions.[5] Nakamura and co-workers have shown that N-heterocyclic carbene (NHC) ligands can suppress the homocoupling reaction to less than 5% in conjunction with Fe- and Co-catalyzed aryl–aryl cross-coupling reactions.[6–8] Although this is a large improvement, NHC ligands are expensive, and even under optimized conditions, elevated temperatures and long reaction times are often required to complete the coupling reaction. Clearly, there is a need to discover new classes of ligands for Fe catalysis. Previously, we have reported that the use of *t*BuOMe as a co-solvent leads to a dramatic reduction of homocoupling and enables Fe-catalyzed aryl–heteroaryl coupling reactions to proceed at room temperature.[9] During the course of our work, we have made the serendipitous discovery that quinoline or isoquinoline can be used as a ligand to promote Fe-catalyzed cross-couplings in improved yield and reaction rate. Herein, we report the scope of this new ligand-accelerated cross-coupling and its extension from Fe catalysis to Co catalysis.

Thus, whereas the cross-coupling of 2-chloroquinoline (**1a**) with PhMgCl (**2a**) in the presence of 3% $FeBr_3$ in *t*BuOMe/THF is completed at 25 °C in 5 min (producing the phenylated product **3a** in 90% yield; Scheme 1), the cross-coupling of the 2-chloropyrimidine **1b** under the same reaction conditions requires 2 h for completion and provides the arylated pyrimidine **3b** in 76% yield. However, carrying out the same reaction in the presence of 7 mol% quinoline leads to a reaction completion within 5 min (about 50 times faster) and an increased yield of **3b** (89% yield of isolated product; Scheme 1).



Scheme 1. Rate acceleration and improved yield of Fe-catalyzed cross-couplings in the presence of quinoline.

Prompted by these results, we screened other ligands. We noted that NMP and TMEDA, which have been traditionally used for Fe catalysis, had a detrimental effect under our conditions (compare entries 1–4 of Table 1).[4c,l] We systematically examined substituted quinolines. Erosion of the rate enhancement occurs when a methyl group is attached to either the 2- or 8-position (entries 5 and 6), and only a slight improvement can be seen when a methyl group is placed at position 6 (entry 7). Benzo[*h*]quinoline and acridine even led to a decrease in yield (entries 8 and 9). Electron-donating groups have a positive effect, whereas electron-withdrawing groups decrease the catalytic activity of the quinoline core (compare entries 10–14). Finally, we discovered that isoquinoline gave the best results with a 92% yield after 15 min (entry 15). 1-Methyl isoquinoline had a similar catalytic

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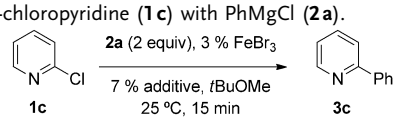
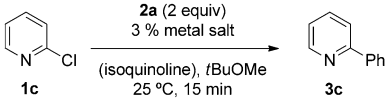
Table 1: Screening different additives for the Fe-catalyzed cross-coupling reaction of 2-chloropyridine (**1c**) with PhMgCl (**2a**).



Entry	Additive	Yield of **3c** [%][a]
1	without additive	40
2	quinoline	75
3	NMP[b]	0
4	TMEDA[c]	32
5	2-methylquinoline	67
6	8-methylquinoline	48
7	6-methylquinoline	82
8	benzo[*h*]quinoline	30
9	acridine	32
10	4-methoxyquinoline	73
11	6-methoxyquinoline	82
12	4-[(*tert*-butyldimethylsilyl)oxy]quinoline	75
13	6-[(*tert*-butyldimethylsilyl)oxy]quinoline	83
14	quinoline-3-carbonitrile	43
15	**isoquinoline**	**92 (89)**[d]
16	1-methylisoquinoline	91
17	1-benzyl-6,7-dimethoxyisoquinoline	28
18	2,9-diphenyl-1,10-phenanthroline	27
19	4-(dimethylamino)pyridine	25
20	styrene	40
21	1-methoxy-3-vinylbenzene	67
22	1-methoxy-4-vinylbenzene	68
23	2-vinylpyridine	37

[a] Yield determined after 15 min by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard. [b] NMP = *N*-methyl-2-pyrrolidone. [c] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene-1,2-diamine. [d] Yield of isolated product after purification by flash column chromatography.

Table 2: Performance of different transition metals with isoquinoline-promoted cross-coupling reactions.



Entry	Metal salt	Isoquinoline (mol%)	Yield of **3c**[a] [%]
1	$FeBr_3$	0	40
2	**$FeBr_3$**	**10**	**92 (89)**[b]
3	$CuBr_2$[c]	0	0
4	$CuBr_2$	10	2
5	$FeBr_3 + CuBr_2$	10	89
6	VCl_3	0	0
7	VCl_3	10	2
8	VCl_4	0	5
9	VCl_4	10	9
10	$MnCl_2$	0	28
11	$MnCl_2$	10	14
12	$CoCl_2$	0	46
13	**$CoCl_2$**	**10**	**90**

[a] Yield determined after 15 min by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard. [b] Yield of isolated product after purification by flash column chromatography. [c] Cu_2O was also used and gave the same results.

activity as isoquinoline, but surprisingly, electron-rich 1-benzyl-6,7-dimethoxyisoquinoline performed very poorly (compare entries 16 and 17). Two nitrogen-containing heterocycles hindered the reaction (entries 18 and 19). We previously showed that 4-fluorostyrene promotes Co-catalyzed coupling reactions.[10] However, styrene had no effect (entry 20), and various substituted styrene derivatives caused only a moderate rate enhancement (entries 21–23). Finally, we varied the amount of isoquinoline from 1–100% and found that 10% of the ligand was optimum. We also noted that isoquinoline (or quinoline) was not consumed during the cross-coupling.

With isoquinoline, we tested the ability of other metallic salts to undergo rate-enhanced cross-coupling reactions. In response to the current debate as to whether trace impurities of Cu in commercial samples of Fe salts can be the cause of catalytic activity,[11] we tested $CuBr_2$ and found none to minimal activity (compare entries 1,2 with entries 3,4 of Table 2). A mixture of $FeBr_3$ and $CuBr_2$ displayed no synergistic benefit, as the yield was essentially the same as when no Cu is added (entry 5). Vanadium salts also had very little catalytic activity (entries 6–9). We were pleased to find that isoquinoline can also be used as a ligand to enhance the yield of Co-catalyzed reactions (entries 12 and 13). As both Fe and Co had similar activity, we utilized both of these transition metals while exploring the scope of our new catalytic system.

Electron-poor pyridine **1d** reacted with the Grignard reagent **2b** to give product **3d** in 71% yield of isolated product in the presence of isoquinoline, but in its absence, the reaction proceeded with low conversion to give **3d** in only 10% yield. Thus, the addition of isoquinoline greatly increased the conversion. Second, pyrimidine **1e** coupled with Grignard compound **2c** after 10 min both with and without isoquinoline. However, more of the starting material was converted to insoluble polymeric by-products in the absence of isoquinoline. Thus, the second effect of isoquinoline was to minimize side products (Scheme 2).

Using isoquinoline as a ligand (10%), we were able to obtain the expected cross-coupling products with a variety of chloro- or bromo-substituted pyridines as well as with a fair range of Grignard reagents. Good yields of the substituted pyridines **3f**–**3m** (65–91%) were obtained, especially with electron-rich Grignard reagents (entries 1–6 of Table 3) as well as with electron-poor 4-fluorophenylmagnesium bromide **2j** to give pyridine **3l** (77–79% yield, entry 7). We were also able to couple the polyfunctional pyridine **1m** with the sensitive ester-substituted Grignard compound **2k** to produce pyridine **3m** in 65% yield (entry 8). Often both Co- and Fe-catalyzed couplings proceed with comparable yield, and it was difficult to favor one metal salt as a superior catalyst for all substrates. Pyrimidines, which are common motifs in pharmaceuticals, can be produced from the same set of Grignard reagents to yield functionalized N-heterocycles **3p**–**3s** in 60–95% yield (entries 11–14). Triazines are of great importance as building blocks for materials and as agrochemicals. Our new method allows various chlorotriazines to be cross-

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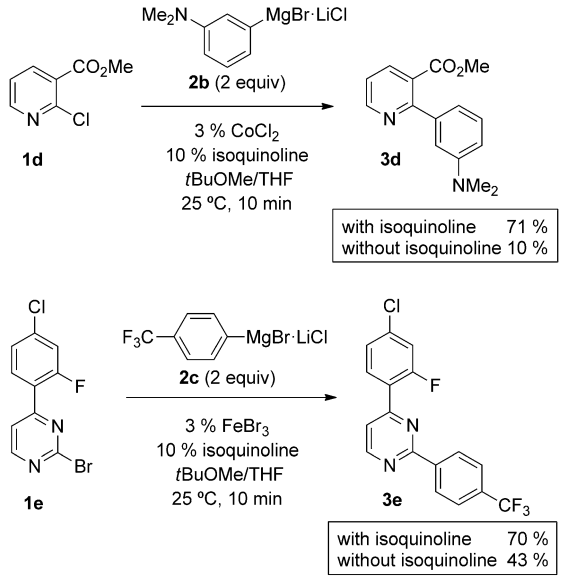
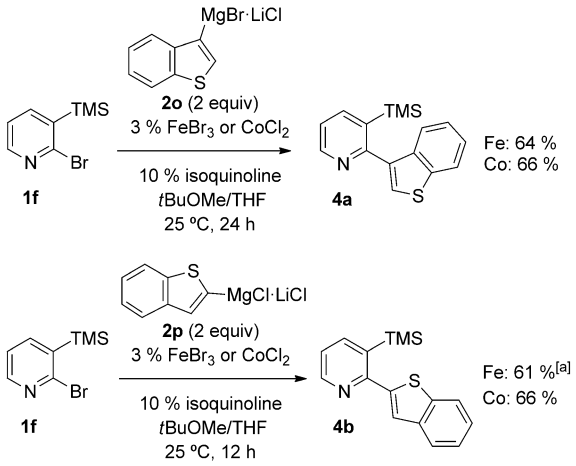


Scheme 2. Co- and Fe-catalyzed cross-coupling reactions with and without isoquinoline.

coupled with magnesium reagents, leading to the desired products (**3t**–**3w**) in 61-84% yield (entries 15–18).

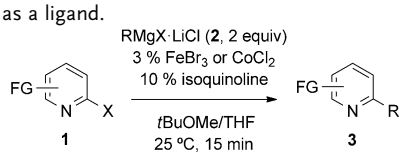
The synthesis of heteroaryl–heteroaryl coupling products is often challenging. In the case of Pd or Ni catalysis, deactivation of the catalyst is observed owing to chelation of the product with the catalyst.[12] However, we noted that both Fe- and Co-catalysts promoted by 10% isoquinoline allow smooth cross-coupling with either the 3-magnesiated benzothiophene **2o** or the 2-magnesiated heterocycle **2p** to afford heterobyaryl compounds **4a**,**b** in 61–66% yield of isolated product (Scheme 3).

Sensitive functional groups, such as alkynes, which are prone to undergo carbometallation with Fe catalysis,[13] gave poor yields of cross-coupling products. However, it was found that the use of 3% $CoCl_2$ and 10% isoquinoline improved the yield and allows the isolation of pyridine **6** in 62% yield (Scheme 4).



Scheme 3. Heteroaryl–heteroaryl cross-coupling reactions between bromopyridine **1f** and benzothiophene. [a] Reaction run at 50°C.

Table 3: Scope of Co- and Fe-catalyzed cross-coupling reactions utilizing isoquinoline as a ligand.



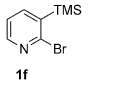
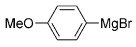
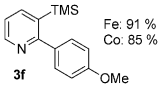
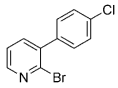
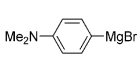
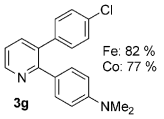
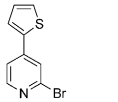
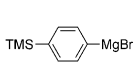
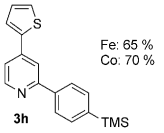
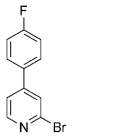
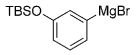
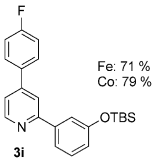
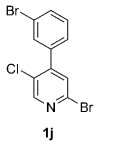
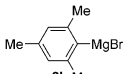
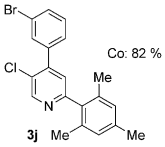
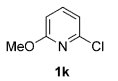
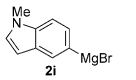
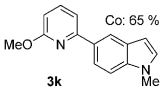
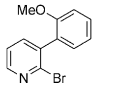
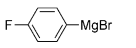
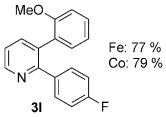
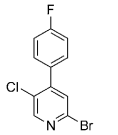
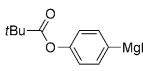
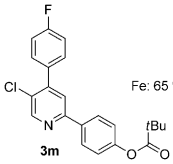
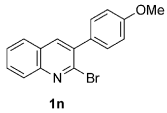
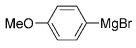
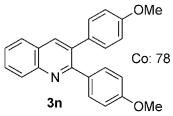
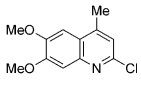
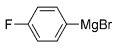
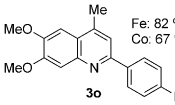
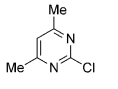
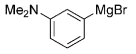
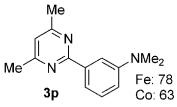
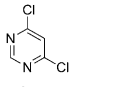
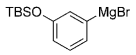
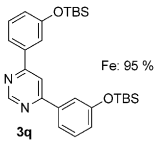
Entry	Starting Material	Grignard Reagent	Product[a]
1	 **1f**	 **2d**	 Fe: 91 % Co: 85 % **3f**
2	 **1g**	 **2e**	 Fe: 82 % Co: 77 % **3g**
3	 **1h**	 **2f**	 Fe: 65 % Co: 70 % **3h**
4	 **1i**	 **2g**	 Fe: 71 % Co: 79 % **3i**
5[b]	 **1j**	 **2h**	 Co: 82 % **3j**
6[c]	 **1k**	 **2i**	 Co: 65 % **3k**
7	 **1l**	 **2j**	 Fe: 77 % Co: 79 % **3l**
8	 **1m**	 **2k**	 Fe: 65 % **3m**
9	 **1n**	 **2d**	 Co: 78 % **3n**
10	 **1o**	 **2j**	 Fe: 82 % Co: 67 % **3o**
11[d]	 **1b**	 **2b**	 Fe: 78 % Co: 63 % **3p**
12[e]	 **1p**	 **2g**	 Fe: 95 % **3q**

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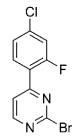
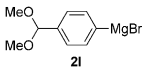
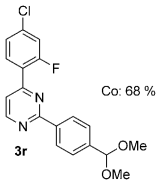
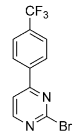
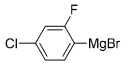
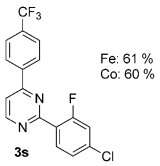
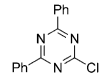
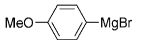
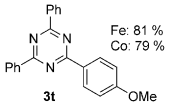
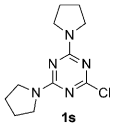
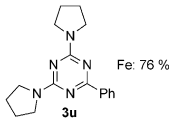
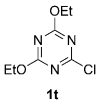
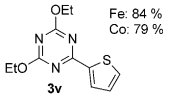
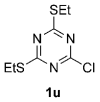
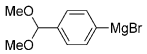
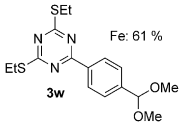
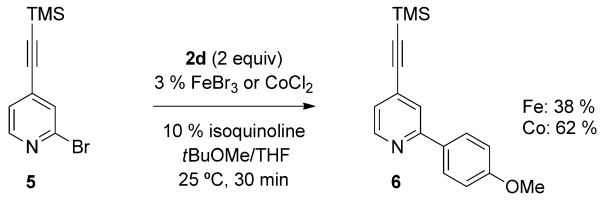
Table 3: (Continued)

Entry	Starting Material	Grignard Reagent	Product[a]
13	 **1e**	 **2l**	 Co: 68 % **3r**
14	 **1q**	 **2m**	 Fe: 61 % Co: 60 % **3s**
15	 **1r**	 **2d**	 Fe: 81 % Co: 79 % **3t**
16[f]	 **1s**	 **2a**	 Fe: 76 % **3u**
17[g]	 **1t**	 **2n**	 Fe: 84 % Co: 79 % **3v**
18	 **1u**	 **2l**	 Fe: 61 % **3w**

[a] Yield of isolated product after purification by flash column chromatography. [b] Reaction run at 25 °C for 5 h. [c] Reaction run at 25 °C for 1 h. [d] Reaction run at 25 °C for 30 min. [e] 4 equivalents of **2g** were used. [f] Reaction run at 50 °C for 12 h. [g] Reaction run at 25 °C for 12 h.

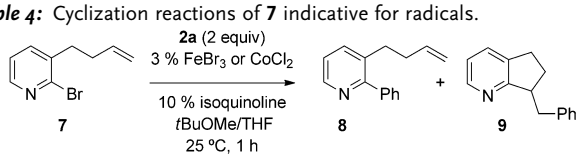


Scheme 4. Cross-coupling reactions of acetylene-containing pyridines.

To probe the mechanism of Fe- and Co-catalyzed cross-coupling reactions, we prepared the radical clock **7**.[14] Treatment of this unsaturated pyridine **7** with PhMgCl (**2a**), using either $FeBr_3$ or $CoCl_2$, produces a 4:1 mixture of the expected cross-coupling product **8** and the cyclized pyridine **9**, which is indicative of radical intermediates.

The addition of isoquinoline did not change the product ratio, but as expected, it improved the yields (compare entries 1–4 of Table 4). These results indicate that both Fe- and Co-catalyzed cross-couplings undergo the radical pathway, at least partially. Interestingly, the corresponding Pd- and Ni-catalyzed cross-couplings, using 3 % $[Pd(PPh_3)_4]$ or 3 % $[NiCl_2(dppe)]$ provided much less, if any, cyclized products.

Table 4: Cyclization reactions of **7** indicative for radicals.



Entry	Catalyst	**8**/**9**	Yield [%][a]
1	$FeBr_3$	80:20	47
2	$FeBr_3$/isoquinoline	80:20	62
3	$CoCl_2$	80:20	72
4	$CoCl_2$/isoquinoline	80:20	78
5[b]	$[Pd(PPh_3)_4]$	100:0	64
6	$[NiCl_2(dppe)]$	95:5	67

[a] Yield of isolated product after purification by flash column chromatography. [b] reaction was performed at 50 °C.

Further mechanistic studies for evaluating the catalytic oxidation state are underway in our laboratories.

In summary, we have demonstrated the ability of isoquinoline (and quinoline) to act as a new efficient ligand for Fe- and Co-catalyzed cross-couplings. It increases both the rate and yield of such reactions. By using only 10 % of isoquinoline, it is now possible to couple substrates bearing complex functional groups that would normally proceed in very low yield (see Table 3). We are currently exploring the use of other N-heterocycles and related compounds as ligands for Co- and Fe-catalysis to further increase the reaction scope of these cross-couplings.

Experimental Section

Representative procedure: Preparation of **3f** (entry 1 of Table 3): A solution of Grignard reagent **2d** (1 mL, 2 equiv, 1.0 M in THF with 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 2-chloro-3-(trimethylsilyl)pyridine **1f** (93 mg, 0.5 mmol, 1 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The solution was stirred at 25 °C for 15 min before being quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2, and EDTA (1.0 M, H_2O) was added. The mixture was stirred at 25 °C for 15 min before being filtered through a pad of Celite. After washing the Celite pad with CH_2Cl_2, brine 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 **3f** (117 mg, 91 %) as a colorless oil.

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