

Chemoselective sp^2 - sp^3 Cross-Couplings: Iron-Catalyzed Alkyl Transfer to Dihaloaromatics

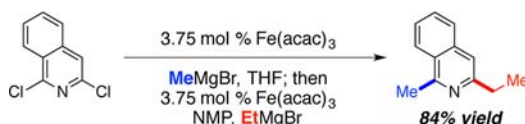
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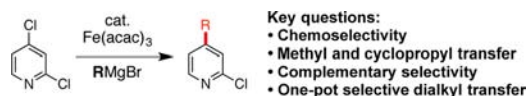
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ABSTRACT



The chemoselective functionalization of a range of dihaloaromatics with methyl, cyclopropyl, and higher alkyl Grignard reagents via iron-catalyzed cross-coupling is described. The site selectivity of C–X (X = halogen) activation is determined by factors such as the position of the halogen on the ring, the solvent, and the nucleophile. A one-pot protocol for the chemoselective synthesis of mixed dialkyl heterocycles is achieved solely employing iron catalysis.

Polysubstituted heteroaromatics serve as essential building blocks in the synthesis of natural products and pharmaceuticals.¹ These structures also prove to be valuable precursors to products derived from the ring opening of heterocycles such as furans, thiophenes, pyridines, and isoxazoles.² In a program dedicated toward accessing a variety of heteroaromatic scaffolds possessing methyl, cyclopropyl, and higher alkyl groups, we envisioned the chemoselective cross-coupling between readily available dihaloaromatics and alkyl Grignard reagents featuring iron catalysis (Figure 1).³



Key questions:
• Chemoselectivity
• Methyl and cyclopropyl transfer
• Complementary selectivity
• One-pot selective dialkyl transfer

Figure 1. Chemoselective Fe-catalyzed sp^2 - sp^3 cross-coupling to dihaloaromatics.

Previous studies on the chemoselective substitution of dichloro- and dibromoaromatics using transition-metal-catalyzed cross-coupling have relied mostly on the use of Pd and Ni catalysis, primarily targeting sp^2 - sp^2 bond formation processes.⁴ When lowered selectivity in such cross-coupling reactions is observed, a viable strategy involves the stepwise installation of two different halogen atoms in the starting material.⁵ In cases where the same halogen can be employed, the selectivity in such transformations has recently been ascribed to bond distortion energies (related to bond dissociation energies).⁶ The pioneering work of Kochi⁷ and subsequent studies by Kauffmann,^{8a} Fürstner^{8a,9} and von Wangelin¹⁰ led us to investigate the chemoselective cross-coupling of such

[†] Small Molecule Process Chemistry.

[‡] Small Molecule Analytical Chemistry.

[§] Safety Assessment.

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(3) We refer to this transformation as chemoselective, as it involves the discrimination between two reactive C–X bonds. See: Trost, B. M. *Science* **1983**, *219*, 245.

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(5) For a recent example, see: Conreux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.-P.; Balme, G. *Org. Lett.* **2007**, *9*, 271.

dihaloaromatics with alkyl nucleophiles employing iron catalysis. Although the selective functionalization of symmetrical dihaloaromatics using iron has been demonstrated,¹¹ the selective substitution of dihalogenated heterocycles with electronically or sterically dissimilar C–X bonds has been limited to the pyrimidine and purine nuclei.¹² Whether chemoselectivity could be achieved with a broader range of dihaloaromatics such as pyridones, pyridines, quinolines, isoquinolines, and carbocycles remained unanswered. Additionally, for substrates containing electronically similar C–X bonds, we investigated if factors beyond bond distortion energy may direct the selectivity in such transformations.

Extensive investigations by Fürstner et al. toward Fe-catalyzed cross-couplings between haloaromatics and alkyl magnesium reagents revealed that Grignards containing higher alkyls (those possessing β -hydrogens) were essential for efficient alkyl transfer.¹³ This is in contrast to vinyl bromides where incorporation of a methyl group can be achieved.^{7a,8} Despite this difference, we postulated that dihaloaromatics possessing lower LUMO energies could prove to be more reactive substrates for selective incorporation of this moiety. The evaluation of this hypothesis is reported herein.

Evaluation of the cross-coupling reaction on model substrate **1a** (Table 1) revealed that the coupling between MeMgBr and 3,5-dibromopyridone in the absence of a catalyst or in the presence of selected copper, manganese, palladium, nickel, or cobalt salts resulted in the formation of pyridone **2a** in low yield (Table 1, entries 1–11). In contrast, incorporation of FeCl₃ or Fe(acac)₃ provided significantly higher yields of the desired product **2a** (entries 12 and 13). Further evaluation of the reaction was conducted with Fe(acac)₃ due to its relative ease of handling.¹⁴ Lowering the catalyst loading to 3.75 mol % furnished pyridone **2a** in 76% yield (entry 14). Previous reports of Fe-catalyzed cross-coupling reactions demonstrated that the

Table 1. Selected Optimization Studies

entry ^a	catalyst	solvent	temp	yield ^b
1	none	THF	rt	0%
2	15 mol % MnBr ₂	THF	rt	4%
3	15 mol % Mn(acac) ₂	THF	rt	3%
4	15 mol % Mn(acac) ₃	THF	rt	2%
5	15 mol % Cu ₂ O	THF	rt	1%
6	15 mol % CuI	THF	rt	2%
7	15 mol % Co(acac) ₃	THF	rt	8%
8	15 mol % NiCl ₂ ·DME	THF	rt	26%
9	15 mol % Ni(dppf)Cl ₂	THF	rt	13%
10	15 mol % Ni(PPh ₃) ₂ Cl ₂	THF	rt	30%
11	15 mol % Pd(OAc) ₂	THF	rt	9%
12	15 mol % FeCl ₃	THF	rt	52%
13	15 mol % Fe(acac) ₃	THF	rt	56%
14	3.75 mol % Fe(acac) ₃	THF	rt	76%
15	3.75 mol % Fe(acac) ₃	THF/NMP	rt	44%
16	3.75 mol % Fe(acac) ₃	THF	0 °C	75%
17	3.75 mol % Fe(acac) ₃	THF/NMP	0 °C	44%
18	3.75 mol % Fe(acac) ₃	THF	rt	82% ^c

^a All reactions were conducted on a 0.75 mmol scale using 1.0 equiv of MeMgBr in THF at a concentration of 0.15 M where the Grignard reagent was added via syringe pump over 7.5 min. ^b Unless otherwise indicated, HPLC determined assay yields. ^c Isolated yield using 1.15 equiv of MeMgBr.

cosolvent *N*-methylpyrrolidone (NMP) can provide higher yields.¹⁵ Incorporation of this cosolvent revealed that at 0 °C and rt, the inclusion of NMP lowered the efficiency of the transformation (compare entries 14–17). An increase in the quantity of Grignard to 1.15 equiv led to the isolation of the desired product **2a** in 82% yield (entry 18).¹⁶

Selective incorporation of a methyl group on dihaloaromatics was then evaluated with a broader range of electrophiles (Table 2). In THF alone, dichloroisoquinolines **1b** and **1c** provided products in high selectivity with a preference for substitution at C-1 in 91% and 92% yield, respectively (entries 2 and 3). Dichloropyridine **1d** required the use of 4:1 THF/NMP to obtain the desired product in synthetically useful yields. Substitution at C-2 was favored affording compound **2d** in 77% yield (entry 4). 4,7-Dichloroquinoline **1e** and 2,6-dichlorobenzothiazole **1f**, both substrates that possess a halogen on separate rings, led to selective alkyl transfer at the more electron-deficient ring to afford **2e** in 96% yield and **2f** in 73% yield (entries 5 and 7). Of particular note, the reaction with **1e** was successful on 20 mmol scale (entry 6, 93% yield), demonstrating the practicality of this methodology.

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(16) When excess Grignard was added, the LC/MS trace suggested the formation of dimethylated and dimeric products. However, these products were not isolated and characterized in the present study. Meanwhile, iron salts from three different suppliers gave similar results in the cross-coupling reaction between MeMgBr and pyridone **1a**.

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(7) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, 93, 1487. (b) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, 40, 599. (c) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, 41, 502.

(8) (a) Kauffman, T. *Angew. Chem., Int. Ed.* **1996**, 35, 386. (b) Fürstner, A.; Krause, H.; Lehmann, C. E. *Angew. Chem., Int. Ed.* **2006**, 45, 440.

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(13) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, 130, 8773.

(14) Lots from three different suppliers provided equivalent results. For trace metal analysis of the lot used for the majority of experiments presented in this work, see Supporting Information.

Table 2. Fe-Catalyzed Methyl Transfer

entry ^a	dihaloaromatic	product	selectivity	% yield ^b
1			2a >20:1	82
2			2b >20:1 R = H	91
3			2c >20:1 R = F	92
4 ^c			2d ^d >20:1	77
5 ^c			2e >20:1	96
6 ^c			2f >20:1	93 ^e
7 ^c			2g >20:1	73 ^f
8 ^c			2h ^g : 2i 4:1 2h ^g : 2i 1:8 ^g	76
9 ¹⁷			2i: R, R' = Cl, Me	50

^a See Supporting Information for experimental details. ^b Isolated yield for the major product only. ^c High selectivity observed when the reaction was conducted without NMP. ^d Volatile compound. ^e Reaction conducted on a 20 mmol scale. ^f 1.38 equiv of MeMgBr used for 100% conversion. ^g Selectivity with just THF as reaction solvent.

Monohalogenated carbocyclic aromatics have previously been shown to be recalcitrant to methyl transfer using iron catalysis.¹³ Employing ester **1g** under our conditions, high selectivity was observed in the incorporation of the methyl group ortho to the ester in 54% yield (entry 8). During the course of our studies we observed that the treatment of pyridine **1h** with MeMgBr in the presence of 3.75 mol % Fe(acac)₃ in THF/NMP favored the formation of **2h** (entry 9). Interestingly, in the absence of NMP the formation of 2-chloro-4-methylpyridine **2i** was preferred.¹⁷

The Pd-catalyzed cross-coupling employing cyclopropylboronic acid,¹⁸ potassium cyclopropyl trifluoroborate,¹⁹ cyclopropyl MIDA boronates,²⁰ and tricyclopropylbismuth,²¹

(17) No background reaction was observed without Fe(acac)₃ for either solvent system. Product ratios after reaction workup may vary due to the lower boiling point of pyridine **2h** compared to compound **2i**.

(18) For selected examples, see: (a) Wallace, D. J.; Chen, C. *Tetrahedron Lett.* **2002**, 43, 6987. (b) Lemhadri, M.; Doucet, H.; Santelli, M. *Synth. Commun.* **2006**, 36, 121.

(19) For a recent example, see: Molander, G. A.; Beaumard, F.; Niethamer, T. K. *J. Org. Chem.* **2011**, 76, 8126.

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Table 3. Fe-Catalyzed Cyclopropyl Transfer

entry ^a	dihaloaromatic	product	selectivity	% yield ^b
1			3a >20:1	50
2			5.6:1 R = H	70
3			4.2:1 R = F	70
4			7:1	70
5			>20:1	90
6			3.6:1	76

^a See Supporting Information for experimental details. ^b Isolated yield for the major product only.

tricyclopropylindium,²² tributyl-stannylcyclopropane,²³ cyclopropylmagnesium,²⁴ and zinc halides²⁵ represents a powerful entry for the incorporation of a cyclopropyl group onto an aromatic ring.²⁶ In the context of iron catalysis, the cross-coupling between a commercially available cyclopropyl Grignard and monohaloheteroaromatics has previously been achieved.²⁷ Our work establishes that control in selectivity is in fact possible using a range of dihalides (Table 3).

The Fe-catalyzed addition of alkyl Grignards possessing β -hydrogens to simple chloroaromatics posed a significant challenge for the selective incorporation of higher alkyl groups, mainly due to competitive bis-addition. Nevertheless, for certain substrates the overaddition could be attenuated to afford the desired heterocycles, as exemplified by the formation of **4a–c** (Figure 2).

The ability to selectively incorporate a methyl group coupled with the facility of alkyl Grignards to add to haloaromatics proved to be a powerful means of accessing differentially alkylated heteroaromatics. As illustrated in Scheme 1, the chemoselective incorporation of two alkyl groups could be achieved in a one-pot process solely featuring iron catalysis.²⁸ Initial treatment of 1,3-dichloroisoquinoline **1b**

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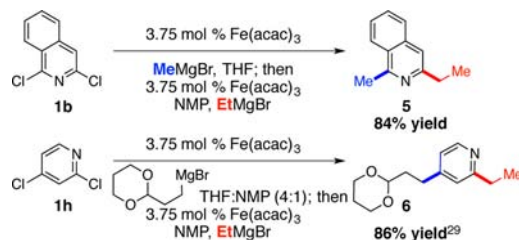
Figure 2. Fe-catalyzed sp^2 – sp^3 couplings with higher alkyls.

with MeMgBr in the presence of Fe(acac)₃ followed by additional iron and EtMgBr selectively furnished a differentially substituted 1,3-isoquinoline **5** in 84% yield. Analogously, sequential addition of two higher alkyl Grignards to 2,4-dichloropyridine **1h** in the presence of Fe(acac)₃ afforded a differentially substituted 2,4-dialkylpyridine **6** in 86% yield.²⁹

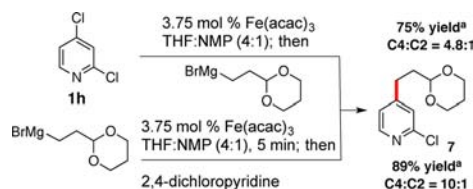
Electronic factors play a dominant role in the site selectivity of the alkyl transfer, and for most cases a similar selectivity pattern is observed compared to Pd catalysis.^{6,30} The methylation of 3,5-pyridone **1a** and pyridine **1h** exemplify the differences between Fe and the more commonly used Pd salts for selective cross-couplings.³¹ Significantly higher yields are obtained with pyridone **1a** employing Fe catalysis. With pyridine **1h** and MeMgBr, either constitutional isomer can be obtained employing Fe catalysis, depending on the choice of solvent. This complementary selectivity could not be achieved using Pd catalysis.

Recent mechanistic work on the addition of alkyl Grignards to electron-deficient aryl pseudohalides in the presence of iron salts suggests that the oxidative addition is irreversible.^{15b,32} Based on this proposal, we postulate that the chemoselective incorporation of an alkyl group into a dihaloaromatic depends upon the ability of one C–X bond to preferentially undergo insertion, though the nature of the iron species participating in the oxidative addition remains elusive. With pyridine **1h** employing 4:1 THF/NMP as the reaction solvent, the methyl incorporation occurs selectively to C-2, whereas, with cyclopropane and the higher alkyl Grignard, transfer occurs at C-4. This suggests that not only electronic but also steric factors influence the site of oxidative addition. These observations support the mechanism proposed by Kauffmann⁸ for 1-alkenyl bromides where transmetalation initially leads to an iron alkyl complex. Oxidative addition of this complex into a C–X bond and subsequent reductive elimination afford the desired product, converse to the catalytic cycle proposed for Pd-catalyzed cross-coupling reactions.³³

Scheme 1. One-Pot Selective Dialkyl Cross-coupling



Scheme 2. Preincubation of Grignard and Fe Allows for Enhanced Chemoselectivity^a



^a Isolated yield for major product only.

Consistent with this notion is our observation that preincubation of Fe(acac)₃ with the appropriate Grignard reagent (which presumably shifts the equilibrium toward a catalytically active iron alkyl superate complex initially proposed by Kauffmann) leads to an increase in site selectivity in the formation of pyridine **7** from 4.8:1 (75% yield) to 10:1 (89% yield) (Scheme 2).³⁴

In conclusion, we have developed a highly chemoselective sp^2 – sp^3 cross-coupling with a broad range of dihaloaromatics employing challenging methyl, cyclopropyl, and higher alkyl Grignards in the presence of Fe(acac)₃. These environmentally friendly and cost-effective iron salts can be used to achieve high levels of chemoselectivity. The synthetic potential of the method is highlighted by the sequential and selective incorporation of two alkyl groups on the aromatic backbone in a single pot. Further studies will focus on elucidating the factors governing chemoselectivity.

Acknowledgment. We thank Genentech colleagues K. L. Green for conducting selected experiments, C. C. Goretski for analyzing trace metals in commercially available Fe(acac)₃, and J. S. Stults for the X-ray structure.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(28) A sequential process has been demonstrated on 6-chloropyridin-2-yl trifluoromethanesulfonate: Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.

(29) Isolated as a mixture of regioisomeric products where the distribution results from the first alkyl transfer to afford compound **7**. The reaction yield reflects the combined yield of both isomers.

(30) The majority of Pd-catalyzed processes involve sp^2 – sp^2 cross-couplings starting from dibromo or diiodo aromatics.

(31) Pd-catalysis resulted in preferential substitution C-4:C-2 = 4:1.

(32) Guisán-Ceinos, M.; Tato, F.; Buñuel, E.; Calle, P.; Cárdenas, D. J. *Chem. Sci.* **2013**, *4*, 1098.

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(34) Olefins present in certain Grignard reagents or formed via β -hydride elimination processes may also contribute to differential selectivity for the Grignards investigated (see ref 15b).

The authors declare no competing financial interest.