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Cross-Coupling of Non-activated Chloroalkanes with Aryl Grignard Reagents in the Presence of Iron/*N*-Heterocyclic Carbene Catalysts

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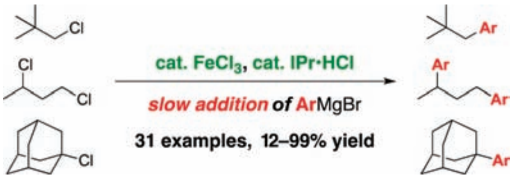
ABSTRACT



An efficient and high-yielding cross-coupling reaction of various primary, secondary, and tertiary alkyl chlorides with aryl Grignard reagents was achieved by using catalytic amounts of *N*-heterocyclic carbene ligands and iron salts. This reaction is a simple and efficient arylation method having applicability to a wide range of industrially abundant chloroalkanes, including polychloroalkanes, which are challenging substrates under conventional cross-coupling conditions.

Aryl and alkyl chlorides are abundant industrial feedstocks with annual global production on the order of millions of tons.[1] Significant progress has been made in the development of synthetically valuable cross-coupling reactions with aryl chlorides. These transformations are extremely important for preparing aromatic compounds in academic and industrial settings.[2] However, alkyl chlorides remain challenging substrates in cross-coupling reactions, and they are not commonly used as electrophilic coupling partners[3] because the kinetic and thermodynamic stability of non-activated sp^3 carbon−chlorine bonds toward transition-metal catalysts hampers efficient bond reorganizations between the coupling partners.[4] Recently, considerable effort has been devoted to achieving useful cross-coupling reactions with non-activated alkyl chlorides. Several catalysts have been reported,[5] but they are mostly limited to primary alkyl electrophiles, and only one method is applicable to secondary alkyl chlorides.[5f]

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Besides these other metal catalysts, iron catalysts have recently proved to be remarkably effective for coupling reactions of non-activated alkyl halides.[6−8] Nonetheless, these iron-catalyzed reactions are mainly applied to alkyl bromides and iodides. Alkyl chlorides, especially primary and tertiary ones, remain poor substrates with iron catalysts. This is partly, but critically, owing to the reaction mechanism of the iron-catalyzed cross-couplings of alkyl halides, which are most likely radical-mediated.[9]

Herein, we report a versatile metal-catalyzed cross-coupling method applicable to a variety of alkyl chlorides with aryl Grignard reagents. The reactions are easily carried out with catalytic amounts of $FeCl_3$ and *N*-heterocyclic carbene (NHC) ligands[10,11] by the *slow addition* technique developed by us previously[8a,m,n] (Figure 1).

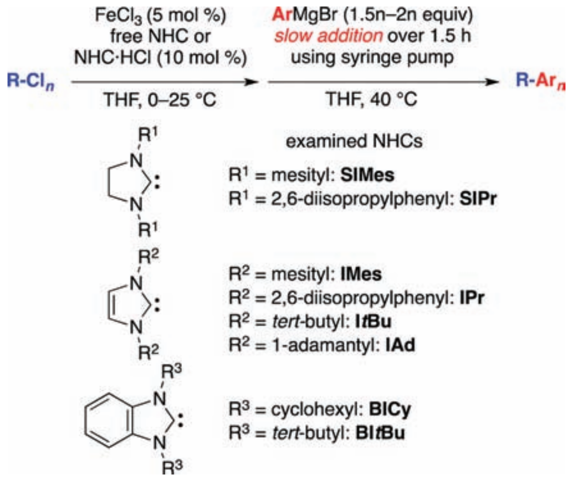

Figure 1. Coupling reaction between alkyl chlorides and aryl Grignard reagents in the presence of $FeCl_3$ and NHC ligands.

We began by studying coupling reactions between 1-chlorodecane and phenylmagnesium bromide in the presence of an iron salt[12] and an NHC ligand. Table 1 summarizes the outcomes of the reactions with various ligands and conditions.[13] Use of the IPr ligand and the slow addition technique were the keys to obtaining the cross-coupling product in high yield. In the absence of a ligand, the desired coupling product **2** was obtained in 20% yield along with significant amounts of alkene and alkane byproducts; thus, the product selectivity was quite low at 32% (Table 1, entry 1). While the widely used IMes did not work well (Table 1, entry 2), bulkier NHCs such as I*t*Bu, IAd, and IPr improved the product selectivity to as high as 80% and caused efficient conversion of **1** (Table 1, entries 3−5). A superior result was obtained when IPr·HCl was used as the NHC precursor (Table 1, entry 6). Furthermore, we found that without the slow addition technique, the reaction provided 1-decene as the major product in 47% yield and gave the desired product with only 25% selectivity (Table 1, entry 7). We tried to improve the reaction further with the NHC ligand SIPr, but it proved to be less effective than its unsaturated congener IPr (Table 1, entry 8). On the basis of these results, we selected IPr·HCl with the slow addition technique as the conditions for the rest of this study.

Table 2 presents the scope of the coupling reaction with a variety of alkyl chlorides. Primary alkyl chlorides were coupled with various aryl Grignard reagents to give the corresponding products in good to excellent yields.

Phenyl and *para*-substituted aryl Grignard reagents gave the coupling products in 83−92% yields (Table 2, entries 1−6). Excellent yields were obtained with the moderately sterically demanding 2-tolyl- and 1-naphthylmagnesium bromides (Table 2, entries 7, 8, and 13). Only the bulky mesityl Grignard failed to yield product (Table 2, entry 9). Sterics appear to hinder the reaction in cases of extreme crowding. As in entries 10 and 11 (Table 2), the steric hindrance at β-position to the reaction site did not much affect the chemical yield, suggesting that the substation proceeded via a non-S_N2 mechanism.

Entries 14−24 (Table 2) show that the cross-coupling of secondary alkyl chlorides proceeded smoothly to give the corresponding coupling products in excellent yields. The only poor reaction was again with the mesityl nucleophile. Otherwise, steric or electronic factors did not significantly

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(7) Seminal early studies on Fe-catalyzed cross-coupling reaction: (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489. (b) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449–5452. (c) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017–6028. (d) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700–1701. (e) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205. (f) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

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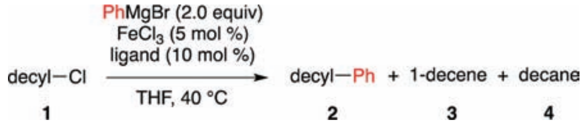
(10) Cazin, C. S. J., Ed.; *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Springer: New York, 2010; Vol. 32, Catalysis by Metal Complexes.

(11) Favorable effects of NHC ligands in iron-catalyzed cross-couplings of haloalkanes were reported previously: (a) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733–735. (b) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem., Int. Ed.* **2007**, *47*, 198–201. See also ref 8e.

(12) To avoid the risk of trace metal contamination, we used pure anhydrous $FeCl_3$ (99.99% from Aldrich), even though other iron salts, such as $Fe(acac)_3$ and $FeCl_2$, were found to be effective. Details are given in the Supporting Information. For the trace metal contamination in iron-catalyzed cross-couplings, see: (a) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5588. (b) Bedford, R. B.; Nakamura, M.; Gower, N. J.; Haddow, M. F.; Hall, M. A.; Huwe, M.; Hashimoto, T.; Okopie, R. A. *Tetrahedron Lett.* **2009**, *50*, 6110–6111.

(13) Other NHC or phosphine ligands as well as an excess amount of TMEDA were not effective. See the Supporting Information for details.

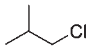
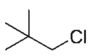
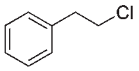
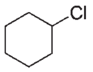
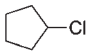
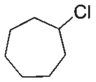
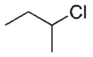
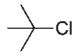
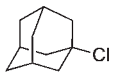
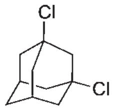
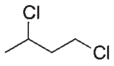
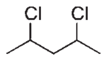
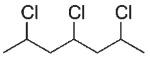
Table 1. Iron-Catalyzed Cross-Coupling Reaction of 1-Chlorodecane with Phenylmagnesium Bromide



		product yield (%)[b]				RSM[d]
entry[a]	ligand	**2**	**3**	**4**	coupling selectivity (%)[c]	**1**
1	none	20	18	24	32	31
2	IMes	31	18	31	39	0
3	I*t*Bu	78	6	11	82	0
4	IAd	72	3	14	81	0
5	IPr	78	3	16	80	0
6	IPr[e]	85	7	8	85	0
7	IPr[e,f]	23	47	21	25	0
8	SIPr	59	7	21	68	0

[a] Reactions were carried out on a 0.5−1.0 mmol scale under the conditions described in Figure 1. [b] Yields were determined by GC analysis using undecane as an internal standard. [c] % Selectivity of the coupling product **2** in all the products. [d] Recovery of starting material. [e] NHC free carbene was prepared in situ by mixing equimolar amounts of NHC·HCl and PhMgBr at 0 °C for 5 min. [f] PhMgBr was added at 0 °C in a single aliquot and heated to 40 °C for 1.5 h.

Table 2. Cross-Coupling Reaction of Various Alkyl Chlorides with Arylmagnesium Halides[a]

entry[b]	alkyl chloride	ArMgBr	yield[c] (%)
1[d]	decyl−Cl	Ar = Ph	84
2[d]		Ar = Ph[e]	84[f]
3[d]		Ar = 4-tolyl	85
4[d]		Ar = 4-MeO-C_6H_4	83
5[d]		Ar = 4-F-C_6H_4	92
6[d]		Ar = 2-naphthyl	84
7[d]		Ar = 1-naphthyl	98
8[d]		Ar = 2-tolyl	97
9[d]		Ar = mesityl	0[g]
10[d]		4-MeO-C_6H_4	69[h]
11[d]		4-MeO-C_6H_4	67[h]
12[d]		Ar = 4-MeO-C_6H_4	53[h]
13[d]		Ar = 1-naphthyl	95[h]
14		Ar = Ph	99
15		Ar = Ph[e]	96[h]
16		Ar = 4-MeO-C_6H_4	98
17		Ar = 4-F-C_6H_4	98
18		Ar = 2-tolyl	99
19		Ar = 2-naphthyl	98[h]
20[i]		Ar = 1-naphthyl	97[h]
21[i]		Ar = mesityl	trace[g]
22		Ph	99
23		Ph	96
24		4-MeO-C_6H_4	72
25[d]		4-MeO-C_6H_4	12[h]
26[d]		Ar = Ph	88
27[d]		Ar = 4-MeO-C_6H_4	90
28[d]		Ar = 4-F-C_6H_4	87
29		Ph	68
30		Ph	85
31		Ph	86
32[d]		Ph	61

[a] The reactions were carried out on a 1−3 mmol scale for monochloro compounds, 0.5 mmol scale for dichloro compounds, and 0.33 mmol scale for trichloro compounds under slow addition conditions. [b] 1.5 equiv of Grignard reagent was used per atom of chlorine present in the molecule unless otherwise noted. [c] Isolated yield. [d] 2.0 equiv of Grignard was used per atom of chlorine present in the molecule. [e] PhMgCl was used instead of PhMgBr. [f] GC yield with undecane as an internal standard. [g] *ca.* 99% of recovery of the starting material. [h] NMR yield determined with 1,1,2,2-tetrachloroethane as an internal standard. [i] 1.6 equiv of Grignard reagent was used.

affect the selectivity, probably because a secondary carbon−chlorine bond is more susceptible to homolytic cleavage than a primary one. Phenylmagnesium chloride also gave the desired products in good yields, showing that the bromide ion derived from the Grignard reagent had no role in the coupling reactions (Table 2, entries 2 and 15). While reactions with tertiary alkyl chlorides were somewhat inconsistent, cross-couplings with adamantyl chloride gave the corresponding products in high yields (Table 2, entries 26−28). Again, the electronic effects of the aryl substituents were negligible. Unfortunately, *tert*-butyl chloride gave the cross-coupling product in only 12% yield, although the chloride substrate was consumed smoothly (Table 2, entry 25).

The present method could be further applied to polychlorinated alkanes such as 1,3-dihalogenated compounds (Table 2, entries 29−31). In the presence of iron catalyst and Grignard reagents, these polychlorinated alkanes usually provide elimination and cyclization products.[14] It is interesting to note that the coupling reaction of 2,4,6-trichloroheptane, a model compound of polyvinyl chloride (PVC),[15] gave the triply arylated product in good yield, suggesting a role of this reaction in polymer functionalization.

To gain mechanistic insight into the cross-coupling reaction, we conducted a stereochemical study using diastereomerically pure α,*β*-[D_2]-*β*-adamantylethyl chloride **5**[5h] with PhMgBr under the standard conditions (Scheme 1). ^{1}H NMR analysis revealed that the reaction center completely epimerized to give a 1:1 mixture of diastereomers, suggesting a radical intermediate. This

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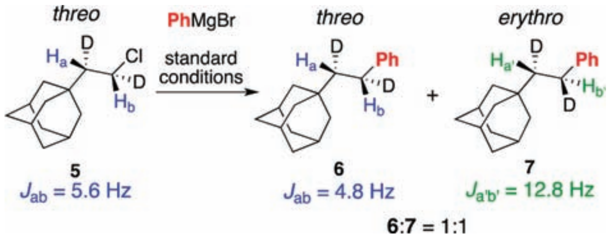
(15) Schilling, F. C.; Schilling, M. L. *Macromolecules* **1988**, *21*, 1530–1532.

was in stark contrast with the Cu-catalyzed cross-coupling reactions between alkyl chlorides and Grignard reagents reported by Kambe and Terao, where the reactions proceeded with almost complete inversion of the stereochemistry at the reaction center, inferring an S_N2 mechanism.[5h]

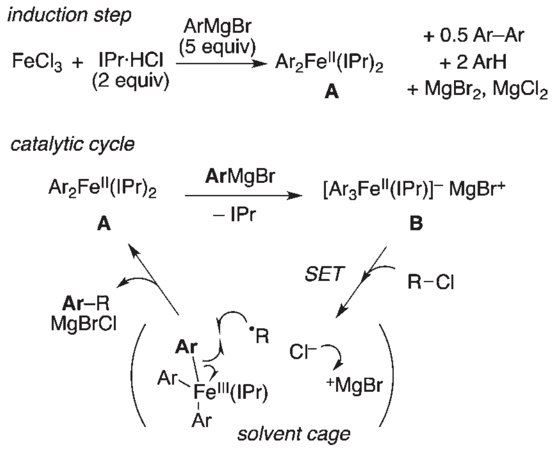
Scheme 1. Cross-Coupling Reaction of Diastereomerically Pure Alkyl Chloride to Study the Mechanism



On the basis of these observations and results reported previously by us and the other researchers, a plausible mechanism is postulated in Scheme 2. Initial reduction of $FeCl_3$ with an aryl Grignard reagent gives an iron(II) intermediate.[8h] We actually observed an induction period for the coupling reaction during the addition of ca. 5 equiv of ArMgBr to $FeCl_3$, in which 3 equiv were used for the partial reduction of $FeCl_3$ to generate the biaryl and the other 2 equiv were used to generate two NHC ligands from the corresponding imidazolium salt.[16] As shown in Scheme 2, the iron(II) intermediate can be best described as a neutral diaryliron possessing two NHC ligands,[17] such as **A**. While **A** may or may not be a reactive intermediate, we are currently assuming that a ferrate(II) intermediate **B** is the catalytically active species because of its higher reducing potential than the neutral species.[18] Thus, homolytic cleavage of the sp^3 carbon–chlorine bond and recombination of the resulting elusive radical with an aryl ligand occur in a solvent cage to give the coupling product while regenerating **A**.

In summary, we have developed an efficient iron-catalyzed cross-coupling reaction and demonstrated its scope with various primary, secondary, and tertiary alkyl chlorides and aryl Grignard reagents. The method was also effective for arylating polychloroalkanes that would form byproducts under other conditions. This direct arylation uses catalytic amounts of IPr and $FeCl_3$ with our slow addition method. Instead of requiring more costly bromo- and iodoalkanes, our technique works with less costly alkyl chlorides, extending the utility of the catalytic cross-coupling of non-activated alkyl halides.

Scheme 2. Plausible Mechanism for the Iron-Catalyzed Cross-Coupling Reaction



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Supporting Information Available. Detailed experimental procedures, characterization, and physical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] See the Supporting Information for details of the time course study.

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[18] Uchiyama, M.; Matsumoto, Y.; Nakamura, S.; Ohwada, T.; Kobayashi, N.; Yamashita, N.; Matsumiya, A.; Sakamoto, T. *J. Am. Chem. Soc.* **2004**, *126*, 8755–8759. See also ref 8h. Bedford proposed an SET/radical mechanism for cross-coupling of alkyl halides with aryl Grignard reagents in the presence of monodentate phosphine ligands as well as NHC ligands: see ref 8e.

The authors declare no competing financial interest.