Iron-Catalyzed Chemoselective Cross-Coupling of Primary and Secondary Alkyl Halides with Arylzinc Reagents

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Abstract: Functional-group-compatible cross-coupling reaction of alkyl halides with arylzinc reagents takes place under iron catalysis in the presence of TMEDA, producing a variety of aromatic compounds in good to excellent yield. The pronounced effect of a magnesium salt was found to be the key to the promotion of the iron-catalyzed coupling reaction.

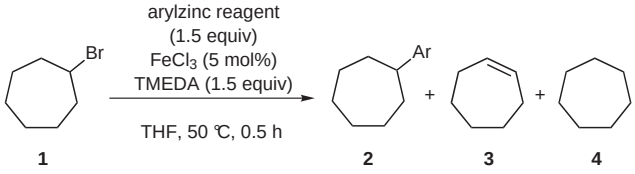
Key words: iron catalyst, zinc reagents, alkyl halides, cross-coupling, substitution

Iron has enormous practical advantages as a catalyst due to its low cost, ample supply, environmental friendliness, and lack of toxicity. Iron catalysis therefore is intensively studied now to achieve controlled organic synthesis, especially in cross-coupling reactions.[1,2] Considerable progress has been made recently by ourselves[3] and others[4] in this field. Iron catalysis not only improves known catalytic processes but also brings about new possibilities in synthesis; for instance, iron catalysis solved the long-standing synthetic problem[5,6] in the coupling of primary or secondary alkyl halides with organometallic compounds.[3] However, a drawback of the iron-catalyzed cross-coupling reaction of haloalkanes is that the nucleophilic partner has been limited largely to organomagnesium reagents,[7] in which electrophilic substituents can survive only at low temperatures.[8] Here, we report an iron-catalyzed cross-coupling of primary or secondary alkyl halides with arylzinc reagents, where the mild reactivity of the zinc reagents much improves the functional group tolerance and the synthetic practicability of the cross-coupling reaction.

We first examined various organozinc reagents generated by several methods. The results summarized in Table 1 show that a diorganozinc reagent (carbanion ligand/zinc, 2:1) is necessary (Table 1, entries 1 and 2) but not sufficient (Table 1, entry 4); the presence of a magnesium salt is mandatory for the cross-coupling reaction. Thus, we found that bromocycloheptane can be coupled with $Ph_2Zn{\cdot}2MgBrCl$ in the presence of a stoichiometric amount of TMEDA and 5 mol% of $FeCl_3$ (Table 1, entry 1). Both, PhZnCl or PhZnBr (Table 1, entries 2–4) prepared by transmetalation from a phenyl Grignard reagent or phenyllithium, and by the direct insertion of Rieke zinc with bromobenzene were inert under the same coupling conditions. Diphenylzinc prepared from $ZnCl_2$ and two equivalents of phenyl lithium did not react at all with bromocycloheptane under the reaction conditions (Table 1, entry 5). The results indicate that magnesium halide is essential for the reaction.

A subtle but practically important consequence of the use of zinc in place of the magnesium reagents is that the reagent can be mixed at once with other reactants as opposed to the required (to achieve high yield) slow addition of the Grignard reagent in our previous protocol.[3a] We tentatively ascribe this difference to the lower ligand transferability of the zinc reagent, which can avoid malfunction of the iron catalyst caused by further reaction with the nucleophile.

The requirement for a diarylzinc reagent is a clear drawback of the above reaction, as one of the two aryl groups cannot be utilized for the coupling. This problem can be resolved by the use of a mixed diorganozinc reagent bearing a Me_3SiCH_2 non-transferable ligand.[9] In this way, only one equivalent of an aryl nucleophile in the form of either an aryllithium or an arylzinc reagent is allowed to couple with one equivalent of bromocycloheptane in high yield (Table 1, entries 6 and 7).



Scheme 1 Iron-catalyzed cross-coupling between bromocycloheptane and arylzinc reagent.

In the absence of the catalyst, no coupling product was produced (data not shown). Though we used hygroscopic anhydrous $ZnCl_2$ for our initial studies, we subsequently found that air- and moisture-stable $ZnCl_2{\cdot}TMEDA$ complex[10] can be used with equal success and hence was used for the remaining studies.

The results of the cross-coupling of alkyl halides possessing various functional groups with arylzinc reagents (Scheme 1) are summarized in Table 2.[11] Iodo- and bromocyclohexane reacted smoothly to give cyclohexylbenzene in quantitative yield (Table 2, entries 1, 2).

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Table 1 Effect of Organozinc Reagents on the Iron-Catalyzed Cross-Coupling of Bromocycloheptane[a]

Entry	Arylzinc reagent	Yield (%)[b]			
		2	**3**	**4**	**1**
1	$ZnCl_2$/2PhMgBr	96	3	trace	0
2	$ZnCl_2$/PhMgBr	0	trace	trace	>95
3	PhZnBr (Mg free)	0	trace	trace	>95
4[c]	$ZnCl_2$/2PhLi	0	trace	trace	>95
5[c]	$ZnCl_2$/PhLi	0	trace	trace	>95
6[d]	$ZnCl_2$/PhMgBr/Me_3SiCH_2MgCl	95	4	trace	0
7[e]	$ZnCl_2$/PhLi/Me_3SiCH_2MgCl	92	7	0	0

[a] Reactions were performed by the addition of a THF solution of $FeCl_3$ (5 mol%) to a mixture of an alkyl halide (1.0 mmol), PhMgBr (3.0 equiv), $ZnCl_2$ (1.5 equiv), and TMEDA (1.5 equiv) in THF.
[b] Yield according to GC using a calibrated internal standard (decane).
[c] The solvent is THF–Bu_2O (2:1).
[d] The solvent is THF–Et_2O–Bu_2O (2:2:1).
[e] The solvent is THF–pentane–Bu_2O (2:2:1).

Chlorocyclohexane also takes part in the reaction with a slightly diminished yield and reaction rate (Table 1, entry 3). A steroidal chloride (100% α) reacted smoothly to give the phenylated product in high yield (Table 1, entry 4; α/β, 14:86).

The catalyst system tolerates functional groups such as alkenyl (data not shown), trimethylsilyl, and alkynyl groups (Table 2, entry 5), as well as esters (Table 2, entries 6–9) and nitriles (Table 2, entry 10). The rather unreactive glucose derivative (Table 2, entry 11) was completely consumed giving the product in 90% yield with almost no loss of the acetyl groups, when two equivalents of the diarylzinc reagent was used.

The method can be applied to cross-coupling with functionalized arylzinc reagents or heteroarylzinc reagents (Scheme 2, Table 3).[12] The coupling was achieved in good to quantitative yield by the use of the arylzinc reagents, $ArZnCH_2SiMe_3$ ($ArZnCH_2TMS$) prepared by the treatment of ArZnX (X = Br, I) with one equivalent of Me_3SiCH_2MgCl. The aryl zinc reagents bearing an electron-withdrawing group, such as ethoxycarbonyl and cyano groups, were found to be slightly less reactive than the corresponding phenyl reagent, but reactive enough to react with primary alkyl iodides (Table 3, entries 1, 2) and secondary alkyl bromides (Table 3, entries 3–5) in good yields. 2-Pyridylzinc also took part in the cross-coupling to give the product in 98% yield (Table 3, entry 6). Some other heteroaromatic organozinc reagents, which are prepared easily from the corresponding organolithium compounds gave 2-substituted benzofuran and indole in good yield (Table 3, entries 7, 8).

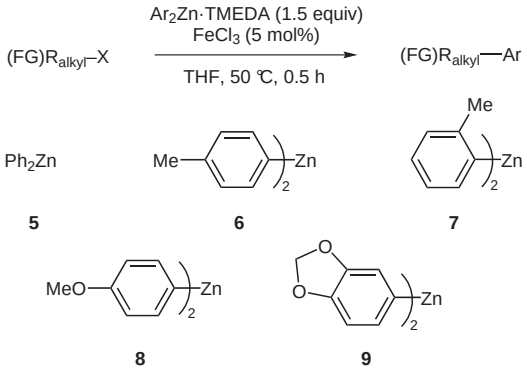
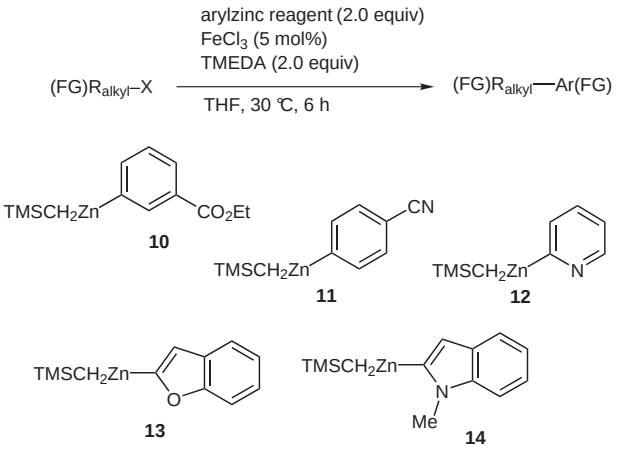
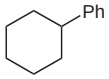
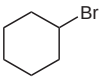
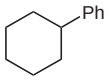
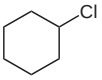
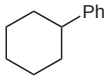
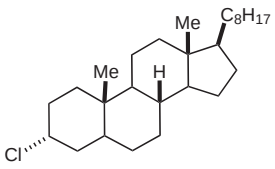
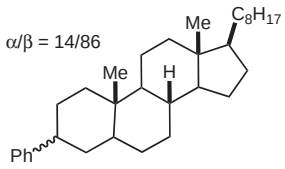
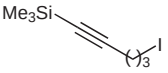
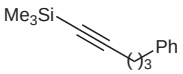
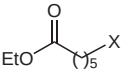
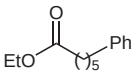
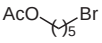
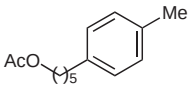
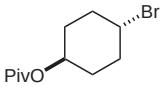
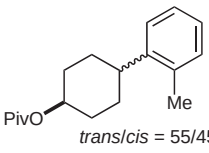
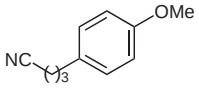
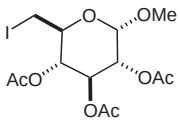
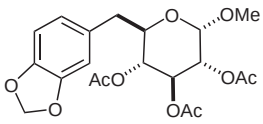


Figure 1

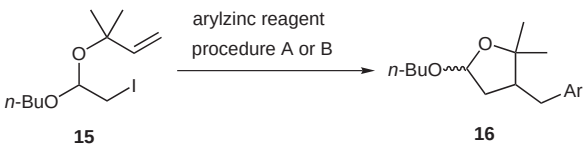


Scheme 2

Table 2 Iron-Catalyzed Cross-Coupling of Functionalized Alkyl Halides with Diarylzinc Reagents[a]

Entry	(FG)R_{alkyl}–X	Arylzinc[b]	Product	Yield (%)[c]
1		**5**		98
2		**5**		97
3[d]		**5**		88
4[e]		**5**		89
5		**5**		93
6		**5**		99
7				91
8		**6**		83
9		**7**	 *trans*/*cis* = 55/45	98
10		**8**		86
11[f]		**9**		90

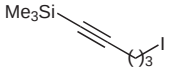
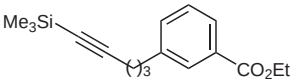
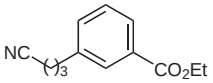
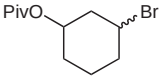
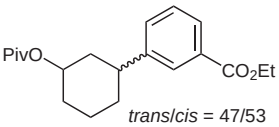
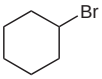
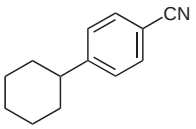
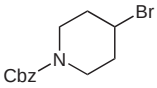
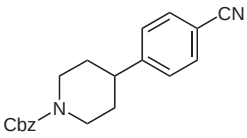
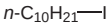
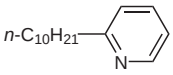
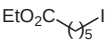
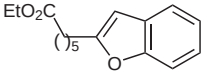
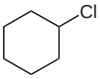
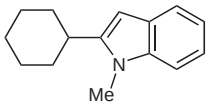
[a] Reactions were performed at 50 °C by the addition of a THF solution of $FeCl_3$ (5 mol%) to a THF solution of an alkylhalide, a diarylzinc reagent, and TMEDA under vigorous stirring.
[b] The diarylzinc reagent was prepared at ambient temperature, prior to the addition of the alkyl halide, by mixing ArMgBr (3.0 equiv) and $ZnCl_2$·TMEDA (1.5 equiv) unless otherwise noted.
[c] Isolated yield.
[d] The reaction time was 3 h.
[e] The reaction time was 12 h.
[f] $ZnCl_2$·TMEDA complex (2 equiv) and ArMgBr (4 equiv).



Scheme 3

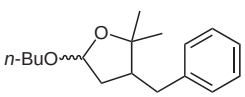
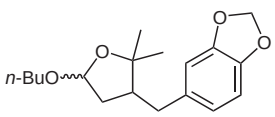
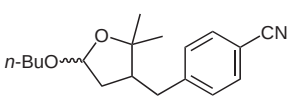
Cyclative cross-coupling[4a,13] could also be achieved in good yield and with high chemoselectivity (Scheme 3). When iodoacetal **5** was treated with a diarylzinc reagent, tandem 5-exo-cyclization/cross-coupling reaction gave the tetrahydrofuran derivative **6** (Table 4). This result suggests participation of radical related intermediates in the iron-catalyzed cross-coupling of organozinc reagent.[3]

Table 3 Iron-Catalyzed Cross-Coupling with Functionalized Arylzinc Reagents[a]

Entry	$(FG)R_{alkyl}$–X	Arylzinc[b]	Product	Yield (%)[c]
1		**10**		91
2		**10**		72
3	 *trans*/*cis* = 33/67	**10**	 *trans*/*cis* = 47/53	78
4		**11**		90
5[d]		**11**		79
6		**12**		98
7		**13**		89
8[e]		**14**		78

[a] Reactions were performed by the addition of a THF solution of $FeCl_3$ (5 mol%) to a mixture of an alkyl halide (1.0 mmol), an arylzinc reagent, and TMEDA under vigorous stirring.
[b] Arylzinc reagents were prepared by mixing ArZnX (X = Cl, Br, or I; THF solution, 2.0 equiv) and Me_3SiCH_2MgCl (ethereal solution, 2.0 equiv) at 0 °C for 1 h.
[c] Isolated yield.
[d] The reaction time was 24 h.
[e] The reaction time was 120 h (reflux).

Table 4 Iron-Catalyzed Tandem Cyclization/Coupling[11,12]

Entry	Aryl-zinc	Proce-dure	Product	Yield (%)[a]
1	**5**	A		76 (63:37)
2	**9**	A		86 (64:36)
3[b]	**11**	B		73 (63:37)

[a] Isolated yield. Diastereomeric ratios are in parentheses.
[b] The reaction time was 24 h.

Acknowledgment

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References

(1) (a) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176. (b) *Cross-Coupling Reactions. A Practical Guide*, *Topics in Current Chemistry*, Vol. 219; Miyaura, N., Ed.; Springer: Berlin, **2002**. (c) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.; Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.

(2) (a) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (d) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1654. (e) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2968. (f) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (g) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (h) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (i) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901; and references cited therein.

(3) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) See also: Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (c) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373.

(4) (a) Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822.

(5) (a) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. (b) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (d) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726. (e) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137.

(6) For overviews of the difficulty for cross-coupling of alkyl halides: (a) Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384. (b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187.

(7) An organomanganate and an organozincate have been used in the iron-catalyzed cross-coupling of aryl electrophiles; see ref. 2h.

(8) Boudier, A.; Bromm, L. O.; Lots, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

(9) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1496.

(10) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679.

(11) **Typical Experimental Procedure A (Table 2); 5-Phenyl-1-(trimethylsilyl)pent-1-yne:** In a dry reaction vessel, a mixture of $ZnCl_2$·TMEDA (379 mg, 1.5 mmol) and PhMgBr (0.93 M solution in THF, 3.22 mL, 3.0 mmol) was stirred for 1 h. To the resulting suspension was added 5-iodo-1-(trimethylsilyl)pent-1-yne (266 mg, 1.0 mmol), and then $FeCl_3$ (0.1 M solution in THF, 0.5 mL, 0.05 mmol) at 0 °C. The reaction mixture was stirred at 50 °C for 0.5 h. After quenching with a saturated aqueous solution of NH_4Cl, the mixture was filtered through a pad of Florisil®, and concentrated in vacuo. Purification by silica gel chromatography afforded 5-phenyl-1-(trimethylsilyl)pent-1-yne (201 mg, 93%); FTIR (neat): 2958 (w), 2902 (w), 2175 (w), 1478 (w), 1451 (s), 1395 (w), 1366 (s), 1268 (w), 1167 (w), 997 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 3 H), 7.21–7.17 (m, 2 H), 2.72 (t, *J* = 7.6 Hz, 2 H), 2.24 (t, *J* = 7.1 Hz, 2 H), 1.84 (tt, *J* = 7.6, 7.1 Hz, 2 H), 0.16 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.3, 128.2 (2 C), 128.0 (2 C), 125.5, 106.8, 87.4, 34.5, 30.0, 19.1, 0.0 (3 C); HRMS (EI, 70 eV): *m*/*z* calcd for $C_{14}H_{20}Si$ $[M]^+$, 216.1334; found, 216.1305; Anal. Calcd for $C_{14}H_{20}Si$: C, 77.71; H, 9.32. Found: C, 77.53; H, 9.13.

(12) **Typical Experimental Procedure B (Table 3); 4-(4-Cyanophenyl)-*N*-(benzyloxycarbonyl)piperidine:** In a dry reaction vessel, a mixture of ArZnBr (0.48 M solution in THF, 4.2 mL, 2.0 mmol) and Me_3SiCH_2MgCl (1.1 M solution in Et_2O, 1.8 mL, 2.0 mmol) was stirred at 0 °C for 1 h. To the resulting solution was added TMEDA (0.30 mL, 2.0 mmol), 4-bromo-*N*-(benzyloxycarbonyl)piperidine (298 mg, 1.0 mmol), and then $FeCl_3$ (0.1 M solution in THF, 0.5 mL, 0.05 mmol) at 0 °C. The reaction mixture was stirred at 30 °C for 6 h. After quenching with a saturated aqueous solution of NH_4Cl, the mixture was filtered through a pad of Florisil®, and concentrated in vacuo. Purification by silica gel chromatography afforded 4-(4-cyanophenyl)-*N*-(benzyloxycarbonyl)piperidine (253 mg, 79%); FTIR (neat): 3014 (w), 2943 (w), 2923 (w), 2856 (w), 2227 (m), 1688 (s), 1466 (m), 1455 (m), 1436 (m), 1273 (w), 1218 (s), 1125 (m), 1057 (m), 1009 (m), 917 (w), 838 (m), 760 (s), 702 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.6 Hz, 2 H), 7.39–7.26 (m, 7 H), 5.16 (br s, 2 H), 4.35 (br s, 2 H), 2.89 (br s, 2 H), 1.90–1.78 (m, 2 H), 1.70–1.58 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 150.8, 136.7, 132.4 (2 C), 128.5 (2 C), 128.0, 127.9 (2 C), 127.6 (2 C), 118.8, 110.3, 67.2, 44.3 (2 C), 42.7, 32.6 (2 C); Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.80; H, 6.42; N, 8.54.

(13) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374.