

Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents

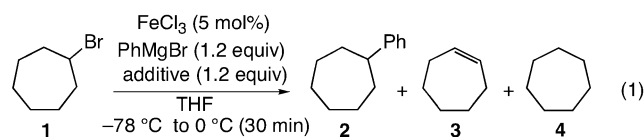
Masaharu Nakamura,^{*,†} Keiko Matsuo, Shingo Ito, and Eiichi Nakamura*

Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received January 15, 2004; E-mail: masaharu@chem.s.u-tokyo.ac.jp; nakamura@chem.s.u-tokyo.ac.jp

Despite its long history and widespread use,¹ C–C bond formation by nucleophilic substitution of an alkyl halide has not yet been a truly satisfactory synthetic method. The substitution on an sp³ carbon center generally suffers from limitations as to the scope of the alkylating agent, imperfect stoichiometry, and unsatisfactory product yield.² The alkylating agent is generally limited to a primary alkyl iodide or bromide because of the rather stringent requirement of the nucleophilic S_N2-type substitution. Recent reports on the use of secondary and tertiary alkyl halides under cobalt^{3a} or nickel catalysis^{3b} suggested a high potential for transition metal catalysis in this field.⁴ We report herein that iron catalysis^{5,6} allows us to achieve cross coupling between near stoichiometric amounts of an alkyl halide and an aryl Grignard reagent generally in excellent yield. The use of iron provides obvious practical and environmental merits, and the method allows the use of rather unreactive secondary bromides and chlorides on a synthetically useful scale.

Among the key factors that led to the discovery of the present iron catalysis, the use of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) was the most important to suppress the undesirable side reactions such as olefin formation by the loss of hydrogen halide from the halide substrate. Pertinent data are shown in Table 1 for the results obtained on a 1.0-mmol scale experiment: A 0.1 M solution of 5 mol % FeCl₃ in dry THF was added to a mixture of bromocycloheptane **1**, PhMgBr (1.2 equiv), and an additive in THF kept at –78 °C. The reaction mixture was allowed to stand for 30 min at 0 °C (eq 1). The product yield was determined by gas chromatographic analysis (GC) of the crude product using an internal standard (decane).



Without any additive, the reaction mainly gave cycloheptene **3** in 79% yield along with the formation of the cross-coupling product **2** in 5% yield (Table 1, entry 1). The formation of the olefinic product may suggest intervention of an unstable radical or an organoiron intermediate. Tertiary monoamines such as triethylamine and *N*-methylmorpholine showed no effect at all (entries 2 and 3), and a stronger base, 1,4-diazabicyclo[2.2.2]octane (DABCO), afforded **2** as the major product at the expense of reaction rate (entry 4). 1-Methyl-2-pyrrolidinone (NMP) that exerts favorable effects in some iron-catalysis⁵ behaved similarly (entry 5). Hence the high-yield production of the desired coupling product **2** in the presence of TMEDA was remarkable (entry 6). Phosphine ligands, alkyl Grignard reagents, and organozinc reagents were found to be unsuitable for the desired coupling reaction.⁷

Further examination of the reaction conditions on a larger scale revealed that slow addition of a mixture of the Grignard reagent

Table 1. Effect of Additives on the Product Selectivity and Yield

entry	additive	% yield ^a				Ph–Ph
		2	3	4	1	
1	none	5	79	0	4	6
2	Et ₃ N	3	78	0	11	5
3	<i>N</i> -methyl morpholine	8	72	0	4	5
4	DABCO	20	2	0	75	3
5	NMP	15	3	trace	79	4
6	TMEDA	71	19	3	trace	10

^a The reaction conditions are described in eq 1. The yield was determined by GC with decane as an internal standard.

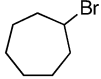
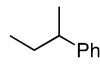
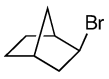
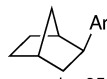
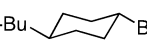
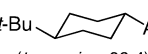
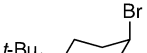
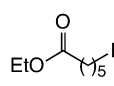
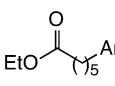
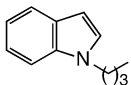
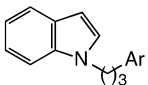
and TMEDA to a solution of the halide and the iron catalyst improves the product yield significantly (Table 2, entry 1). A typical procedure is given: To a mixture of bromocycloheptane **1** (8.85 g, 50 mmol) and FeCl₃ (25 mL of a 0.1 M THF solution, 5 mol %), a mixture of PhMgBr (72 mL, a 0.93 M THF solution, 67 mmol) and TMEDA (7.78 g, 67 mmol) was added at 0 °C with a syringe pump at such a rate that the reaction mixture was kept pale yellow rather than dark red (1.36 mL/min for 60 min in this case). The reaction mixture was stirred at 0 °C for 10 min after completion of the addition of PhMgBr/TMEDA. GC analysis (decane as an internal standard) indicated complete consumption of **1**, and the formation of **2**, **3**, **4**, and biphenyl in 97, 3, <0.1, and 5% yield, respectively. Distillation of the product mixture afforded phenylcycloheptane **2** in 90% yield (8.18 g, containing a small amount of biphenyl). The amount of the catalyst may be reduced to less than 1% at the expense of the reaction rate.

The scope of the reaction is illustrated in Table 2. Comparison among alkyl iodide, bromide, and chloride indicated that the reactivity decreases in this order. The iodide and the bromide reacted quickly at 0 °C to give the coupling product in quantitative yield. The corresponding chloride was inert under the reaction conditions and was completely consumed with 1.5 equiv of Grignard reagent at 25 °C (entries 2–4).

Comparison among a range of the Grignard reagents in the reaction with bromocyclohexane (entries 5–7) indicated that a normal or an electron-rich aryl Grignard reagent reacts rapidly to give the desired product with near 1:1 stoichiometry, while a reagent with an electron-withdrawing group reacts sluggishly: (4-Methoxyphenyl)magnesium bromide and (4-methylphenyl)magnesium bromide reacted with bromocyclohexane to give the corresponding arylated cyclohexanes in 99 and 96% yield respectively, but (4-trifluoromethylphenyl)magnesium bromide gave the coupling product in 67% yield along with the formation of the corresponding biaryl. 2-Naphthylmagnesium bromide smoothly reacted with bromocyclohexane and gave 2-cyclohexylnaphthalene in 96% yield (entry 8). The more hindered 1-naphthylmagnesium bromide gave a comparable result when 1.8 equiv of the reagent was used (entry 9). (2-Methylphenyl)magnesium bromide (1.2 equiv) gave the cross-coupling product in 98% yield (entry 10).

[†] PRESTO, Japan Science and Technology Agency (JST).

Table 2. Iron-Catalyzed Coupling Reaction of an Alkyl Halide with an Aryl Grignard Reagent^a

entry ^b	alkyl halide	ArMgBr	product	% yield ^{c,d}
1		Ar = Ph		96 (90) ^{e,f}
2		Ar = Ph		99 (X = I)
3				99 (X = Br) ^e
4				99 (X = Cl) ^g
5		Ar = 4-MeOC ₆ H ₄		99 ^e
6		Ar = 4-MeC ₆ H ₄		96 ^e
7		Ar = 4-CF ₃ C ₆ H ₄		67 ^{e,h}
8 ⁱ		Ar = 2-naphthyl		96
9 ^j		Ar = 1-naphthyl		97 ^j
10		Ar = 2-MeC ₆ H ₄		98 ^e
11		Ar = Ph		95 (X = I)
12				94 (X = Br)
13				84 (X = Cl) ^{g,k}
14	<i>n</i> -C ₈ H ₁₇ -X	Ar = Ph	<i>n</i> -C ₈ H ₁₇ -Ph	97 (X = I)
15				91 (X = Br)
16				45 (X = Cl) ^{g,k}
17		Ar = 4-MeOC ₆ H ₄	 (<i>exo:endo</i> = 95:5)	91
18 ^l		Ar = 4-MeOC ₆ H ₄	 (<i>trans:cis</i> = 96:4)	96 ^e
19 ^l		Ar = 4-MeOC ₆ H ₄	 (<i>trans:cis</i> = 96:4)	98
20		Ar = 4-MeOC ₆ H ₄		88 ^e
21		Ar = 4-MeOC ₆ H ₄		87 ^e

^a The reaction was carried out at a 1 mmol scale under the slow-addition conditions unless otherwise noted. ^b Reaction temperature was 0 °C in entries 1–3, 11, 14, and 17–21 and 25 °C in entries 4–10, 12, and 15 unless otherwise noted. ^c 1.2 equiv of Grignard reagent was used unless otherwise noted. ^d The yield refers to the one determined by GC or ¹H NMR with an internal standard unless otherwise noted. See details in Supporting Information. ^e Isolated yield. ^f The large-scale experiment in the text using 1.3 equiv of Grignard reagent. ^g 1.5 equiv of Grignard reagent was used. ^h 2.0 equiv of Grignard reagent was used. ⁱ Grignard reagent was added to a mixture of bromocyclohexane, FeCl₃, and TMEDA. ^j 1.8 equiv of Grignard reagent was used. ^k The reaction temperature was 40 °C. ^l 0.5 mmol scale.

Acyclic secondary alkyl halides gave similar results with those of cyclic ones, while 2-chlorobutane turned out to be less reactive and required 1.5 equiv of Grignard reagent and slightly higher temperature (40 °C) (entries 11–13). Interestingly, primary alkyl halides are much less reactive than the corresponding secondary halides. 1-Iodooctane and 1-bromooctane gave octylbenzene in high yield, but the corresponding chloride gave the desired product in only 45% yield because of the formation of octane and octenes (ca. 50% yield) (entries 14–16). Tertiary halides were consumed as rapidly as secondary halides but gave a mixture of the reduction and the elimination products. Combined with the fact that the reaction of (*S*)-2-bromooctane (99.5% ee) with PhMgBr took place

with complete loss of the optical purity, the results indicate that the reaction is not a simple nucleophilic substitution but rather involves a radical-related reaction.

Stereochemical probes provided further mechanistic insight. The arylation of *exo*-2-bromonorbornene proceeded in high yield with retention of the stereochemistry (entry 17). *trans*- and *cis*-1-Bromo-4-*tert*-butylcyclohexane reacted to give the product of the same diastereomeric composition rich (96%) in the more stable *trans*-product (entries 18–19). These results suggest that the intermediate responsible for the C–C bond-forming step undergoes stereochemical mutation and is rather bulky. One plausible possibility is an “iron-bound radical” intermediate as suggested for living radical polymerization under iron and ruthenium catalysis.^{8,9} This hypothesis would merit further consideration from mechanistic and synthetic viewpoints.

A useful feature of the present reaction is the functional group compatibility. Functional groups, such as alkoxycarbonyl and *N*-indolyl group (entries 20–21), as well as alkenyl and alkynyl groups (data not shown) in the alkylating reagent survive under the reaction.

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Science, and Technology of Japan for financial supports, a Grant-in-Aid for Specially Promoted Research, a Grant-in-Aid for Young Scientists (A) (KAKENHI 14703011) and 21st Century COE Program for Frontiers in Fundamental Chemistry. K.M. thanks Hayashi Memorial Foundation for Female Natural Scientists for a predoctoral fellowship.

Supporting Information Available: Experimental details and spectral data for new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Cf. Holleman, A. F. *Lehrbuch der Organischen Chemie*; Vereinigung Wissenschaftlicher Verleger: Berlin and Leipzig, 1920.
- (2) Cf. Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025–1030.
- (3) (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137–4139. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.
- (4) (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694. (b) Donkersvoort, J. D.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61–69. (c) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059. (d) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. (e) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647. A recent review see: Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387.
- (5) (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979. (b) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373–1375.
- (6) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489. (b) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017–6028. (c) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700–1701. (d) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205. (e) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901–1903. (f) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (g) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355–5357.
- (7) Other additives including phosphine ligands and other iron catalysts (FeF₃, Fe(BF₄)₃, Fe(acac)₃, FeCl₂, Fe(CO)₅) were not effective. See Supporting Information for details.
- (8) Wakioka, M.; Baek, K.-Y.; Ando, T.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2002**, *35*, 330–333 and references therein.
- (9) The iron-catalyzed cross-coupling of 6-bromo-1-hexene with PhMgBr gave exclusively hex-5-enylbenzene (65%) under the slow-addition conditions at 25 °C. Under the conditions shown in eq 1 (at 25 °C), however, the product of a 5-*exo*-radical-cyclization/coupling process was obtained in 10% yield along with the formation of hex-5-enylbenzene (52%).

JA049744T