ORGANIC
LETTERS

2009
Vol. 11, No. 2
277−280

A New Efficient Catalytic System for the Chemoselective Cobalt-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Primary and Secondary Alkyl Bromides

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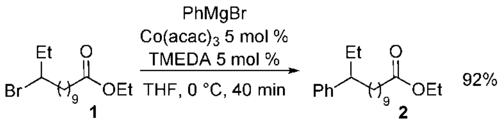
Received October 13, 2008

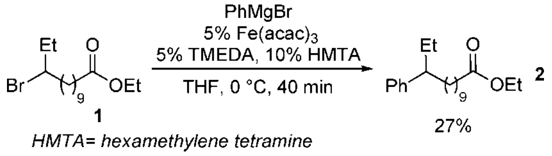
ABSTRACT



The cobalt-catalyzed alkylation of aromatic Grignard reagents is performed in good yields by using a new simple and efficient catalytic system: $CoCl_2$/TMEDA (1:1). Primary and secondary cyclic or acyclic alkyl bromides were used successfully. The reaction is highly chemoselective since ester, amide, and keto groups are tolerated. The procedure is inexpensive and very easy to carry out on a larger scale.

Cross-coupling reactions from nonactivated alkyl halides are still a very challenging area of investigation.[1] Recently, new efficient iron-catalyzed procedures for coupling aromatic or vinylic Grignard reagents and alkyl halides were discovered. Thus, we[2] and others[3] have shown that these reactions[4] can be a very attractive economical and eco-friendly alternative to the nickel- or palladium-catalyzed procedures previously described.[1] In addition, iron catalysis is generally more efficient, especially in the case of secondary alkyl halides that are not easy to couple under nickel or palladium catalysis.[5] However, in spite of considerable recent advances, the iron-catalyzed alkylation of aromatic Grignard reagents cannot be achieved chemoselectively from functionalized nonactivated secondary alkyl halides like ω-halogenoester **1**.[6] Thus, all our attempts to prepare ester **2** via an iron-catalyzed reaction resulted in poor yield even by using the efficient catalytic system that we recently described (Scheme 1).[2a]

Scheme 1



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(1) For reviews on the use of alkyl halides in transition-metal-catalyzed reactions, see: (a) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (b) Westrum, L. J. *Fine Chem.* November/December **2002**. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (d) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(2) (a) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364. (b) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253.

(3) For recent reports on the use of alkyl halides in iron-catalyzed cross-coupling reactions, see: (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (b) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822. (c) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104. (d) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161. (e) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (g) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521. (h) Dongol, K. G.; Koh, H.; Sau, M; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015.

10.1021/ol802362e CCC: $40.75

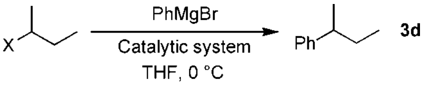
In a recent report, Nakamura[7] circumvented this problem by using a diarylzinc prepared by transmetalation from the corresponding aryl Grignard reagent.

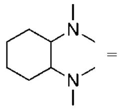
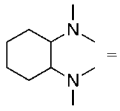
However, 1.5 equivalents of diarylzinc are required since only one of the two aryl groups of Ar_2Zn is transferred. Therefore, it is necessary to use 3 equivalents of the starting Grignard reagent. To improve the procedure, Nakamura proposed to use an organozinc compound $ArZnCH_2SiMe_3$ prepared by reacting $ZnCl_2$ successively with ArMgCl and Me_3SiCH_2MgCl. Indeed, this unsymmetrical diorganozinc reagent selectively transfers the aryl group. Unfortunately, it is less reactive than the corresponding diarylzinc, and 2 equivalents are necessary to obtain satisfactory yields. Moreover, Me_3SiCH_2MgCl is a very expensive material. Therefore, these procedures are not very attractive for large scale applications since at least 2 equivalents of the starting aryl Grignard reagent have to be used.

From both an economical and an environmental point of view, cobalt salts are not as convenient as iron or manganese[8] salts. However, they compare favorably to palladium or nickel salts and deserve to be considered when iron salts are not efficient. In 2006, Oshima[9] described the cobalt-catalyzed alkylation of aromatic Grignard reagents. A mixture $CoCl_2$/*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine is used as a catalytic system. As a rule, yields are excellent, and various primary and secondary alkyl iodides were coupled successfully under mild conditions. The procedure has been successfully applied to the synthesis of AH13205, an EP2-receptor agonist that lowers intraocular pressure. Nevertheless, it should be noted that the use of nonactivated alkyl bromides in place of the corresponding iodides results in lower yields (73% instead of 93%, Table 1, entries 4 and 6).

In light of the previous considerations and because of our background in this field,[10] we tried to prepare ester **2** from bromoester **1** via a cobalt-catalyzed coupling reaction. Therefore, we decided to reinvestigate this coupling reaction to improve the yield in the case of nonactivated alkyl bromides.

Table 1. Cobalt-Catalyzed Cross-Coupling of Phenylmagnesium Bromide with 2-Bromo- or 2-Iodobutane



entry	X	catalytic system 5 mol %	yield[a] (%)
1	I	$CoCl_2$	10
2	I	$Co(acac)_3$	14
3	I	$Co(acac)_3$/ TMEDA = 1:1	94
4	I	$CoCl_2$ /  = 1:1	93
5	Br	$Co(acac)_3$/ TMEDA = 1:1	92
6	Br	$CoCl_2$ /  = 1:1	73
7	Br	$Co(acac)_3$ / Et_3N = 1:5	15
8	Br	$Co(acac)_3$/DABCO = 1:1	37
9	Br	$Co(acac)_3$/ dppe = 1:3	traces

[a] The yield was determinated by GC with pentadecane as an internal standard.

The results obtained by reacting 2-iodo- and 2-bromobutane with phenylmagnesium bromide under cobalt catalysis are summarized in Table 1.

With cobalt chloride as a catalyst, 2-phenylbutane **3d** was formed in only 10% yield from 2-iodobutane (entry 1). In agreement with the results published by Oshima,[9] the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine allows an excellent yield (93%, entry 4). Unfortunately, from 2-bromobutane, the yield is significantly lower (73% instead of 93%, entries 4 and 6).

According to our experience in the case of the alkylation of aromatic Grignard reagents under iron catalysis,[2a] the use of a metal acetylacetonate instead of the corresponding chloride as a catalyst can give better yields of coupling product. Thus, we tried to use cobalt acetylacetonate in place of cobalt chloride. In the absence of ligand, yields obtained from both salts are very similar (entries 1 and 2). Surprisingly, we discovered that by using the complex $Co(acac)_3$/TMEDA (1:1) formed in situ, the yield jumps from 14% to 94% (entries 2 and 3). This was unexpected since Oshima had shown that, with cobalt chloride as a catalyst, TMEDA is clearly less efficient than *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (Table 2, entry 9 and note d).[9] This result is very interesting since commercial TMEDA is a very simple and inexpensive starting material compared to *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine.

Moreover, we were pleased to note that the new catalytic system allows similar yields from 2-iodo- and 2-bromobu-

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(4) For exhaustive reviews on iron-mediated coupling reactions see: (a) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(5) Palladium- or nickel-catalyzed alkylation reactions generally suffer from β-elimination processes from the intermediate alkyl−metal species formed during the reaction, thus limiting the scope of the possible halogenoalkanes used as a substrate.

(6) Several interesting exemples of reaction between ArMgX and primary functionalized alkyl halides in the presence of $[Fe(C_2H_4)_4][Li(tmeda)]_2$ as a catalyst were recently described by Fürstner.[4a] However, the yields are significantly lower when secondary functionalized unactivated alkyl bromides are used.

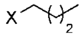
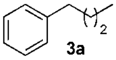
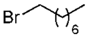
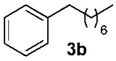
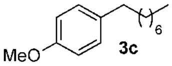
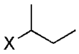
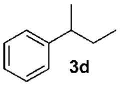
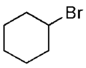
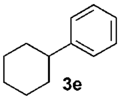
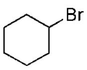
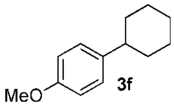
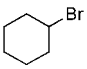
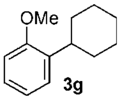
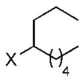
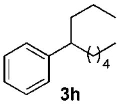
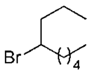
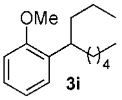
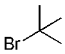
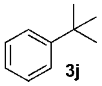
(7) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794.

(8) Manganese salts are also very attractive from both economical and environmental points of view. For Mn-catalyzed cross-coupling reactions, see: (a) Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2008**, in press. (b) Cahiez, G.; Gager, O.; Lecomte, F. *Org. Lett.* **2008**, ASAP.

(9) Tsuji, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886. For reviews on Co-catalyzed coupling reactions, see: (a) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (b) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (c) Iqbal, J.; Mukhopadhyay, M.; Mandal, A. K. *Synlett* **1997**, 876.

Table 2. Cobalt-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Simple Primary and Secondary Alkyl Bromides[a]

$$\text{Alk-Br} + \text{ArMgBr} \xrightarrow[\text{THF, 0°C, 40 min}]{\text{Co(acac)}_3\text{ 5 mol \%, TMEDA 5 mol \%}} \text{Alk-Ar}\ \ \mathbf{3}$$

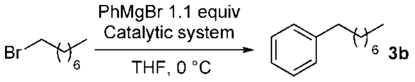
entry	alkyl halide	product	yield[b] (%)
1		 **3a**	95 (X = I)
2			94 (X = Br)
3			10 (X = Cl)
4		 **3b**	95
5		 **3c**	96
6		 **3d**	94 (X = I)
7			92 (X = Br)
8			4 (X = Cl)[c]
9		 **3e**	93[d]
10		 **3f**	97
11		 **3g**	88
12		 **3h**	98 (X = Br)
13			10 (X = OTs)
14		 **3i**	79
15		 **3j**	< 1

[a] All reactions were carried out by adding the aryl Grignard reagent (11 mmol) for 40 min to a mixture of the alkyl halide (10 mmol), Co(acac)$_3$ (0.5 mmol), and TMEDA (0.5 mmol) in THF at 0 °C. [b] Isolated yield. [c] 90% of 2-chlorobutane was recovered. [d] Oshima showed that only 43% yield is obtained when the coupling is performed by using 5% CoCl$_2$/TMEDA as a catalyst.[9]

tanes (Table 1, entries 3 and 5) contrary to the catalytic system used by Oshima[9] (entries 4 and 6). It is important from both an economical and a practical point of view since alkyl bromides are cheaper and more stable than the corresponding iodides. Some attempts to use various ligands such as triethylamine, DABCO, or dppe gave unsatisfactory results (entries 7–9).

As shown in Table 2, various aryl Grignard reagents were coupled successfully with primary and secondary cyclic or acyclic alkyl bromides in the presence of our new catalytic system.

Scheme 2. Cross-Coupling Reaction between Phenylmagnesium Bromide and 1-Bromooctane under Copper, Iron, and Cobalt Catalysis (0.1 mol Scale)



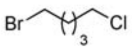
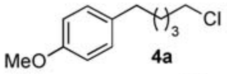
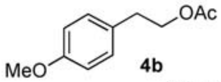
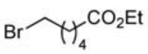
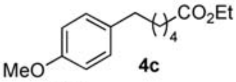
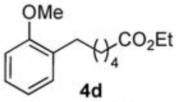
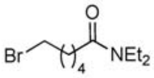
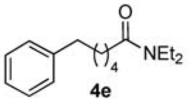
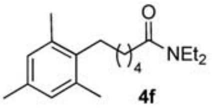
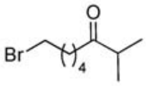
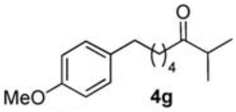
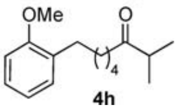
CuCl$_4$Li$_2$ 3 mol % : 70%
Fe(acac)$_3$/2TMEDA/HMTA 5 mol % : 92%
CoCl$_2$/TMEDA 5 mol % : 95%

As a rule, excellent yields are obtained. It should be underlined that only a slight excess (1.1 equiv) of the Grignard reagent was used. Alkyl iodides and bromides give similar yields (entries 1–2 and 6–7), whereas alkyl chlorides or tosylates only lead to poor results (entries 3, 8, and 13).

The reaction is not very sensitive to steric hindrance. Thus, it is possible to couple a secondary alkyl bromide with *o*-anisylmagnesium bromide in satisfactory yields (entry 14).

Table 3. Cross-Coupling of Aryl Grignard Reagents with Functionalized Primary Alkyl Bromides[a]

$$\text{Alk}_{\text{FG}}\text{-Br} + \text{ArMgBr} \xrightarrow[\text{THF, 0 °C, 40 min}]{\text{Co(acac)}_3\text{ 5 mol \%, TMEDA 5 mol \%}} \text{Alk}_{\text{FG}}\text{-Ar}\ \ \mathbf{4}$$

entry	alkyl halide	product **5**	yield[b] (%)
1		 **4a**	89
2		 **4b**	88
3		 **4c**	90
4		 **4d**	88
5		 **4e**	84
6		 **4f**	16
7		 **4g**	90
8		 **4h**	88

[a] All reactions were carried out as described previously (Table 2). [b] Isolated yield.

On the other hand, tertiary alkyl bromides cannot be used (entry 15). The starting material is consumed, but less than 1% of coupling product is formed.

Interestingly, the results presented in Scheme 2 show that, for preparative applications, the cobalt-catalyzed alkylation of aryl Grignard reagents compares favorably to the copper- or iron-catalyzed procedures.[11,2a]

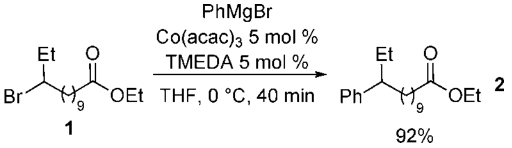
Encouraged by these results, we tried to extend the reaction to various functionalized primary alkyl bromides (Table 3). We were very pleased to note that the reaction is highly chemoselective. Thus, 1-bromo-5-chloropentane reacts selectively to afford the corresponding alkyl chloride in good yield (entry 1).

The reaction also tolerates the presence of various sensitive groups like an acetate (entry 2), an ester (entries 3−4), an amide (entries 5−6), or even a ketone (entries 7−8).

Interestingly, the coupling is also highly chemoselective in the case of a secondary alkyl bromide. Thus, we were able to prepare ester **2** from the corresponding secondary alkyl bromide **1** in excellent yield (Scheme 3).

To the best of our knowledge, this is the first report of a preparative metal-catalyzed cross-coupling between an aromatic Grignard reagent and a functionalized nonactivated secondary alkyl bromide such as **1**.

Scheme 3. Chemoselective Coupling from Functionalized Secondary Alkyl Bromide **1**



In summary, we disclosed herein an efficient cobalt-catalyzed cross-coupling reaction between aryl Grignard reagents and primary or secondary alkyl bromides. The reaction is highly chemoselective and proceeds under mild conditions. The new catalytic system is obtained by mixing two inexpensive starting materials, cobalt acetylacetonate and TMEDA. This simple procedure is very attractive for large-scale applications.

Acknowledgment. We thank the CNRS for financial support, the Ministère de l'Education Nationale et de la Recherche for financial support, and a grant to A. M. as well as the Fondation de France for a grant to C.D.

Supporting Information Available: Detailed experimental procedures and complete compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802362E

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