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Unexpected Cross-Coupling Reaction between *o*-Chloroaryl Ketones and Organomanganese Reagents

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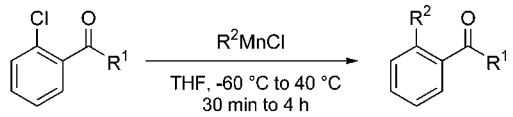
ABSTRACT



R^1, R^2= Alkyl or Aryl

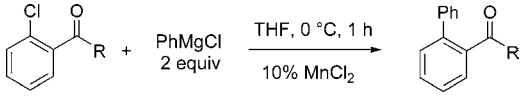
Alkyl- and arylmanganese reagents react with *o*-chloro or *o*-bromoaryl ketones to give the substituted ketones in high yields. The cross-coupling reaction is performed under mild conditions (−60 to +40 °C, 30 min to 4 h) and takes place with excellent chemoselectivity.

The discovery of new economically and environmentally friendly alternatives to palladium and nickel catalyzed-*cross*-coupling reactions between an organic halide and an organometallic compound is of current interest, especially for large-scale application. In this field, we have recently reported the first manganese-catalyzed cross-coupling reaction between activated aryl halides (X = Cl, Br, F) or activated aryl methyl ethers and organomagnesium reagents.[1]

Recently, we have tried to extend this reaction to a new family of activated aryl halides: the *o*-chloro or *o*-bromoaryl ketones.[2]

The first preliminary experiments were quite encouraging since in THF at 0 °C, phenylmagnesium chloride quickly reacts with *o*-chlorovalerophenone or *o*-chlorobenzophenone to lead to the corresponding coupling products in good yields (88−89%, Scheme 1).

Scheme 1. Mn-Catalyzed Cross-Coupling Reaction between PhMgCl and *o*-Chloroaryl Ketones



R = *n*-Bu, yield = 88%
R = Ph, yield = 89%

Unfortunately, all of our attempts to perform the reaction with a more reactive organomagnesium compound such as

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(1) (a) Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, *12*, 2138. It should be noted that organomanganese reagents have been used to perform various coupling reactions. For some leading references see the following. Acylation: (b) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369; **1992**, *33*, 4439. (c) Cahiez, G.; Razafintsalama, L.; Laboue, B.; Chau, F. *Tetrahedron Lett.* **1998**, *39*, 849. (d) Cahiez, G.; Métais, E. *Tetrahedron: Asymmetry* **1996**, *8*, 1373. Cu-catalyzed alkylation and Fe-catalyzed alkylation: (e) Cahiez, G.; Marquais, S. *Pure and Appl. Chem.* **1996**, *68*, 53. Pd-catalyzed arylation: (f) Riguet, E.; Alami, M.; Cahiez, G. *J. Organomet. Chem.* **2001**, *624*, 376. For reviews, see: (g) Cahiez, G. *Butyl Manganese Chloride in Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; Vol. 2, p 925. (h) Cahiez, G. Manganese (II) Chloride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; Vol. 5, p 3227. (i) Cahiez, G. *An. Quim.* **1995**, *91*, 561.

(2) Until now, only very few examples of coupling reactions were described with *o*-halogenoaryl ketones. Boronic acids/Pd catalyses: (a) Shen, W. *Tetrahedron Lett.* **1997**, *32*, 5575. (b) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1997**, *20*, 3855. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1943**, *65*, 504. (d) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1953**, *18*, 6797. (e) Feuerstein, M.; Doucet, H.; Santelli, M. *Synlett* **2001**, *9*, 1458. (f) Jensen, J. F.; Johannsen, M. *Org Lett.* **2003**, *5*, 3025. Vinylstannanes/Ni catalyses: (g) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2449; *Synthesis* **1998**, 1544.

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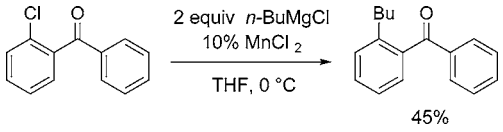
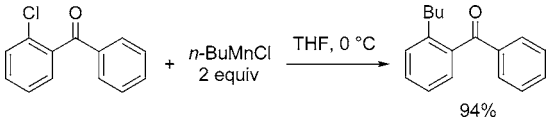
butylmagnesium chloride gave poor yields (45%) of substituted ketone since the Grignard reagent mainly reacts with the carbonyl group (Scheme 2).

Scheme 2. Mn-Catalyzed Reaction between *n*-BuMgCl and *o*-Chlorobenzophenone



Then, we tried to perform the reaction by using a milder organometallic. Surprisingly, an almost quantitative yield of cross-coupling product (94% isolated yield) was obtained by using butylmanganese chloride (Scheme 3). It should be

Scheme 3. Cross-Coupling Reaction between *n*-BuMnCl and *o*-Chlorobenzophenone

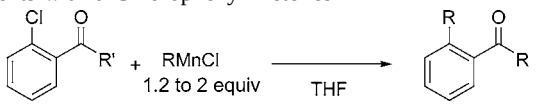


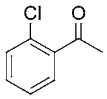
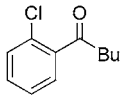
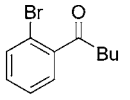
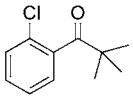
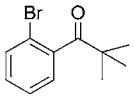
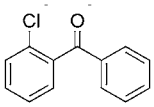
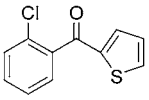
emphasized that it is the first example of a direct coupling reaction between organomanganese reagents and aryl halides.

The reaction has been applied successfully to various organomanganese reagents (Table 1). Thus, even in the case of the *o*-chloroacetophenone, which is a reactive ketone, the coupling reaction takes place highly chemoselectively with alkyl or arylmanganese chlorides to give excellent yields of substitution products (entries 1−6).

The reaction conditions have to be optimized depending on the nature of both substrate and organomanganese chloride. Thus, isopropylmanganese chloride reacts with *o*-chloroacetophenone in 30 min at −60 °C (entry 2), whereas 45 min at 20 °C is required in the case of phenylmanganese chloride (entry 6). For less reactive substrates, the reaction is still more difficult. For instance, with *tert*-butyl-*o*-chlorophenyl ketone it is necessary to warm to 50 °C for 6 h (entry 11). The reaction can also be performed with alkenylmanganese chlorides (entry 15), but all of our attempts to introduce a methyl or a *tert*-butyl group failed.

Table 1. Coupling Reactions of Various Organomanganese Reagents with *o*-Chlorophenyl Ketones



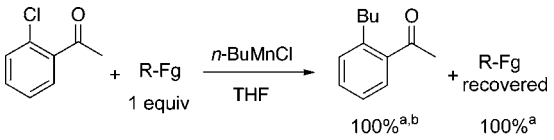
entry	ArCl	R from RMnX	yield of coupling product % reactions conditions
1		Et	**97**[a] -50 °C, 1 h
2		*i*-Pr	**90**[b] -60 °C, 30 min
3		*c*-Hex	**98**[b] 0 °C, 30 min
4		*n*-Bu	**97**[c] -10 °C, 30 min
5		*n*-Oct	**96**[b] 0 °C, 30 min
6		Ph	**63**[a] 20 °C, 45 min
7		*n*-Bu	**92**[a] 0 °C, 30 min
8		Ph	**90**[a] 0 °C, 45 min
9		*n*-Bu	**96**[a] 0 °C, 30 min
10		n-Bu	**90**[a] 40 °C, 1 h
11		Ph	**70**[a] 50 °C, 6 h
12		*n*-Bu	**97**[a] 40 °C, 1 h
13		*n*-Bu	**94**[a] 0 °C, 30 min
14		2-Naphtyl	**78**[a] 0 °C, 30 min
15			**67**[a] 50 °C, 30 min
16		*n*-Bu	**90**[a] 0 °C, 30 min
17		Ph	**66(83**[e]**)**[a,d] 45 °C, 3 h

[a] 2 equiv of RMnCl was used. [b] 1.2 equiv of RMnCl was used. [c] 1.3 equiv of *n*-BuMnCl was used. [d] Conversion rate: 93%. [e] GC yield.

(3) **General Procedure for the One-Pot Acylation−Substitution Sequence with 2′-Chlorobenzoyl Chloride (2′-Octyl Valerophenone, Scheme 1).** Under nitrogen, a 500 mL three-necked flask was charged with 2′-chlorobenzoyl chloride (7 g, 40 mmol), CuCl (120 mg, 1.2 mmol), and THF (60 mL). A solution of *n*-BuMnCl in THF (116 mL, 0.41 M, 48 mmol) and then a solution of *n*-OctMnCl in THF (146 mL, 0.41 M, 60 mmol) were added dropwise at −40 °C in, respectively, 1 h and 15 min. The mixture was allowed to warm to 0 °C. After the mixture was stirred for 15 min, 180 mL of 1 N HCl was added, and the resultant mixture was stirred at 20 °C for 30 min and extracted with Et_2O (2 × 150 mL). The combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ (150 mL) and brine (150 mL), dried ($MgSO_4$), and concentrated under vacuum. Purification by chromatography on silica gel (90:10 cyclohexane/ethyl acetate) gave 10.59 g (yield: 97%) of 2′-octyl valerophenone as a clear oil.

(4) **General Procedure for the Coupling Reaction of 2′-Chloroacetophenone with Organomanganese Reagents (2′-Butyl Acetophenone, Table 1, Entry 4).** Under nitrogen, to a solution of $MnCl_2$·2LiCl ($MnCl_2$: 8.19 g, 65 mmol; LiCl: 5.53 g, 130 mmol) in THF (130 mL) at −10 °C was slowly added a THF solution of butylmagnesium chloride (38.2 mL, 1.7 M, 65 mmol). Then, a solution of 2′-chloroacetophenone (7.72 g, 50 mmol) in THF (50 mL) was added dropwise over 15 min. After being stirred for 15 min, the reaction mixture was hydrolyzed at −10 °C with 1 N HCl (150 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under vacuum. Purification by chromatography on silica gel (95:5 cyclohexane/ethyl acetate) gave 8.54 g (yield: 97%) of (2′-butyl acetophenone) as a pale yellow oil.

Scheme 4. Reaction of *n*-BuMnCl with *o*-Chloroacetophenone in the Presence of Various Functionalized Compounds



[a] GC yield. All reactions were performed on a 50 mmol scale (1.3 equiv of *n*-BuMnCl, −10 °C, 30 min). [b]Isolated yields: 95−97%. [c]2 equiv of *n*-BuMnCl, −60 °C, 1 h. At −10 °C; recovered 5-nonanone: 91%, yield of coupling product: 98%.

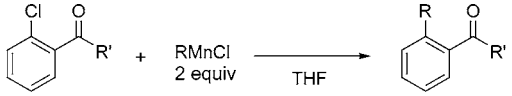
It is interesting to note that this reaction tolerates the presence of halogenoalkanes (X = Cl, Br or I) as well as aliphatic nitriles, esters, and ketones (Scheme 4). At −10 °C, the chemoselectivity is generally excellent. However, in the case of the 5-nonanone it is necessary to operate at −60 °C to avoid completely the attack of the ketone.

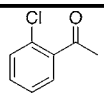
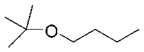
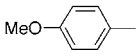
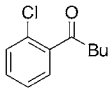
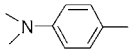
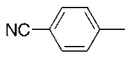
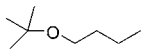
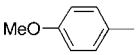
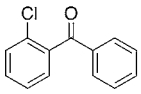
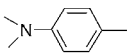
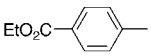
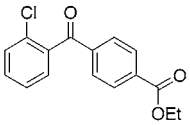
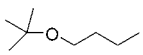
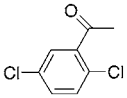
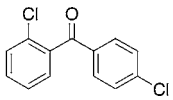
These encouraging results prompted us to prepare functionalized ketones (Table 2).

Thus, various functionalized organomanganese reagents such as 3-*tert*-butyloxypropylmanganese chloride (entries 1, 5, and 10) as well as 4-dimethylamino-, 4-methoxy-, 4-cyano-, and 4-carbethoxyphenylmanganese chlorides (entries 2−4 and 6−8) led to excellent yields of cross-coupling products. On the other hand, good yields were obtained when the starting *o*-chloroaryl ketone bears a COOEt group (entries 9 and 10). The reaction only occurs from *o*-halogenoaryl ketones; thus, 2,5-dichloroacetophenone and 2,4′-dichlorobenzophenone led to the *ortho*-substituted product selectively (entries 11 and 12).

It is well-known that organomanganese halides can be easily acylated even at low temperature in THF with or without a CuCl catalysis.[1b] We have thus tried to perform a one-pot acylation-substitution sequence with chlorobenzoyl chloride (Table 3).

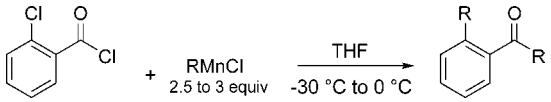
Table 2. Preparation of Functionalized Aromatic Ketones



entry	ArCl	R from RMnX	yield (%) reactions conditions
1			**73** 0 °C, 30 min
2			**92** 0 °C, 30min
3			**80** 0 °C, 30 min
4			**75**[a] -10 °C to 20 °C, 1 h
5			**74** 0 °C, 30 min
6			**77** 0 °C, 30 min
7			**81** 0 °C, 30 min
8			**39**[b] 0 °C, 2 h
9		*n*-Bu	**97** -40 °C, 1 h
10			**60** -5 °C, 1 h
11		*n*-Bu	**89** -30 °C, 30 min
12		*n*-Bu	**93** -30 °C, 1 h

[a] Conversion rate: 74%. [b] Isolated as the carboxylic acid; conversion rate: 92%.

Table 3. Reaction of 2-Chlorobenzoyl Chloride with Organomanganese Chlorides Reagents

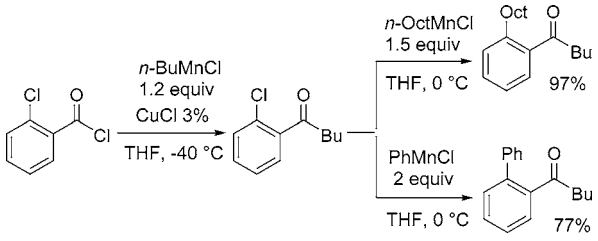


entry	RMnX	yield (%)
1	*n*-BuMnCl	99
2	*c*-HexMnCl	99
3	PhMnCl	99

By using 2.5−3 equiv of organomanganese chloride, the *ortho*-substituted phenyl ketones were actually obtained in quantitative yields (Table 3).

Furthemore, we were also able to perform selectively the acylation and then the substitution step. Thus, *o*-octyl valerophenone and *o*-phenyl valerophenone were obtained with excellent overall yields (Scheme 5).

Scheme 5. One-Pot Acylation−Substitution Procedure from *o*-Chlorobenzoyl Chloride



For a general procedure, see note 3.

In conclusion, we reported here a new efficient cross-coupling reaction between *ortho*-acylated aryl chlorides and organomanganese reagents (for a general procedure see ref 4). Yields are generally excellent, and the reaction occurs readily under very mild conditions with excellent chemoselectivity. We think this unexpected coupling reaction could be of great interest since to our knowledge very few examples of substitution of *o*-chloroaryl ketones are described in the literature.[2]

Acknowledgment. We thank the CNRS and the Ecole Supérieure de Chimie Organique et Minérale (ESCOM) for their financial support as well as Sanofi Chimie for its financial support and a grant to F.L.

Supporting Information Available: Experimental procedures and full characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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