

Communication

# Versatile palladium-catalyzed arylation of organomanganese chlorides by aryl bromides

Eric Riguet, Mouâd Alami<sup>1</sup>, Gérard Cahiez\*

Laboratoire de Synthèse Organique Sélective et de Chimie Organométallique CNRS-UCP-ESCOM, 13 boulevard de l'Hautail, F-95092 Cergy-Pontoise cedex, France

Received 16 October 2000; accepted 10 November 2000

Dedicated to Professor Jean Normant for his 65th birthday

## Abstract

In THF, a palladium-catalyzed cross-coupling reaction of organomanganese reagents with various aryl bromides including unreactive deactivated or hindered aryl bromides was performed successfully in the presence of a new catalytic system 1% PdCl<sub>2</sub>(dppp)–four equivalents DME. The scope of the reaction is very broad since many functional groups are tolerated, moreover, even hindered *O,O'*-di- or trisubstituted diaryls were obtained in high yields. It is interesting to note that hindered aryl bromides are more reactive than the corresponding aryl iodides. Alkyl, alkenyl and alkynylmanganese chlorides also react under similar conditions. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** Arylation; Cross-coupling reactions; Organomanganese reagents; Aryl bromides

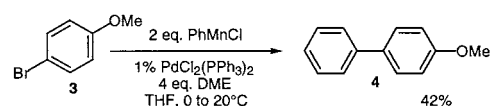
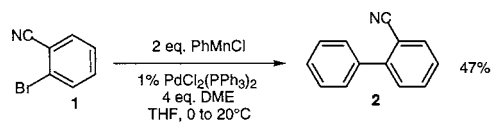
Previously [1], we reported that functionalized unsymmetrical biaryls can be prepared in high yields in THF by reacting arylmanganese chlorides with aryl halides or triflates (X = I, Br, OTf) in the presence of a new catalytic system 1% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>–four equivalents DME. We have shown that the presence of DME greatly accelerates the coupling reaction rate and improves the yields. Unfortunately, under these conditions, all our attempts to prepare unsymmetrical biaryls from unreactive aryl bromides such as hindered *ortho*-substituted aryl bromides (i.e. **1**) or deactivated aryl

bromides bearing an electron-donating group (i.e. **3**) resulted in unsatisfactory yields [2].

These results prompted us to undertake a more detailed study to extend the scope of this coupling reaction. Some preliminary experiments were performed in the case of the first coupling reaction described above (synthesis of **2** from **1**). A very interesting result was obtained by changing the nature of the catalyst (Table 1).

Table 1  
Synthesis of *ortho*-cyanobiphenyl **2** from phenylmanganese chloride and *ortho*-bromobenzonitrile **1**; influence of the nature of the catalyst PdL<sub>*n*</sub><sup>a</sup>

Entry	PdL <sub><i>n</i></sub>	Time (h)	Yield (%) <sup>b</sup>
1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	15	47
2	PdCl <sub>2</sub> (TMEDA)	24	0
3	PdCl <sub>2</sub> (PhCN) <sub>2</sub>	24	0
4	PdCl <sub>2</sub> (dppf)	24	0
5	PdCl <sub>2</sub> (dppb)	21	15
6	PdCl <sub>2</sub> (dppp)	3	98
7	Pd(OAc) <sub>2</sub> +dppp	7	91



\* Corresponding author. Fax: +33-01-307560 21.









<sup>1</sup> Present address: BIOCIS, Faculté de Pharmacie, rue Jean-Baptiste Clément, F-92296 Châtenay-Malabry, France.

<sup>a</sup> PhMnCl was prepared from PhMgCl, all reactions were performed at 20°C. For a general procedure see Ref. [4].

<sup>b</sup> Isolated yield based on **1**.

Table 2

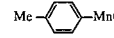
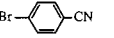
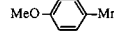
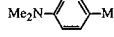
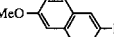
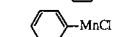
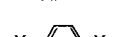
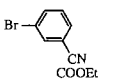
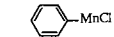
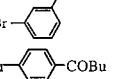
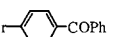
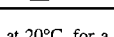
Preparation of unsymmetrical biaryls from PhMnCl<sup>a</sup> and hindered or deactivated aryl bromides

Entry	ArBr	Time (h)	Yield (%) <sup>b</sup>	
			PdCl <sub>2</sub> (dppp) <sup>d</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> <sup>e</sup>
8		2	98	47
9		0.1	96	-
10		3	95 <sup>c</sup>	-
11		72	94	-
12		7	93	-
13		4	91	42
14		20	96 <sup>d</sup>	28
15		1	95 <sup>c</sup>	-

a/ PhMnCl was prepared from PhMgCl, all reactions were performed at 20°C. For a general procedure see ref. 4. b/ Isolated yield based on aryl bromides. c/ 1% PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was used as catalyst. d/ GLC yield. e/ 1% PdCl<sub>2</sub>(dppf) was used as catalyst.

Table 3

Preparation of unsymmetrical biaryls from ArMnCl and functionalized aryl bromides<sup>a</sup>

Entry	RMnCl <sup>b</sup>	ArBr	Time (h)	Yield (%) <sup>c</sup>
16			0.6	98
17		"	1	98
18		"	0.5	96
19		"	0.3	90
20		"	0.5	96
21			1	90
22			0.5	95
23	"		< 0.05	75
24	"		< 0.05	83

a/ All reactions were performed at 20°C, for a general procedure see ref. 4. b/ Prepared from ArMgCl. c/ Isolated yield based on aryl bromides.

Indeed, in the presence of various palladium complexes PdCl<sub>2</sub>L<sub>2</sub> (L<sub>2</sub> = TMEDA, (PhCN)<sub>2</sub>, dppe, dppb) the yield of **2** was lower than with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>. On the other hand, in the presence of 1% PdCl<sub>2</sub>(dppp) the reaction occurred quickly (3 h) at room temperature to afford **2** in excellent yield (98%). Moreover, the formation of the homo-coupling product (biphenyl), which is often a very annoying side-product for such cross-coupling reactions, was almost completely avoided.

This very promising result encouraged us to extend the reaction to various unreactive aryl bromides bear-

ing an electron-donating group or/and a substituent in the *ortho*-position (Table 2). In all cases, excellent yields (91–98%) were obtained by varying only the reaction time [3]. The results obtained by using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> are clearly inferior (Entries 8, 13 and 14).

As expected, under similar reaction conditions, the coupling of arylmanganese chlorides with reactive aryl bromides bearing an electron-withdrawing group gave high yields (Table 3). Interestingly, the reaction is very chemoselective since even a reactive keto group is tolerated (Entries 23 and 24).

It should be noted that the reaction has also been performed successfully with aryl triflates which can be easily prepared from the corresponding phenols [4] (Table 4).

On account of the large scope of this coupling procedure, we have tried to synthesize various highly hindered *O,O'*-substituted biaryls (Tables 5 and 6). Indeed, these compounds are generally very difficult to obtain via a palladium-catalyzed aryl–aryl coupling since such reactions are not very efficient from sterically hindered organometallic and/or aryl halides [5]. At first, we have compared the reactivity of various *ortho*-substituted aryl bromides and iodides with phenylmanganese chloride (Table 5). In all cases aryl bromides led to better results (Entries 30–33). It is very surprising since, as a rule, it is accepted that aryl iodides are more reactive.

The difference of reactivity increases along with the steric hindrance. Thus, all our attempts to prepare *O,O'*-di- or trisubstituted biphenyls from aryl iodides were unsatisfactory whereas the corresponding aryl bromides gave excellent yields (Entries 34–37). A similar difference was observed by comparing aryl bromides and triflates (Entries 38 and 39). To our knowledge, it is the first time that such a difference of reactivity is reported.

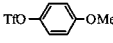
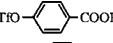
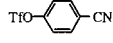
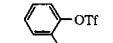
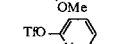
According to this observation, various *O,O'*-substituted biaryls were prepared in high yields from various *ortho*-substituted arylmanganese chlorides and *ortho*-substituted aryl bromides (Table 6). It should be underlined that this procedure is currently one of the most efficient for the preparation of such hindered diaryls [5].

Finally, under these reaction conditions, it is also possible to extend the scope of the reaction to benzyl, alkenyl, alkynyl and alkylmanganese chlorides (Table 7). However, in some cases, it is necessary to use PdCl<sub>2</sub>(dppf) as catalyst instead of PdCl<sub>2</sub>(dppp), for instance with alkyl derivatives having eliminable β-hydrogen atoms [6] (Entries 45 and 46).

In conclusion, we have reported a new catalytic system 1% PdCl<sub>2</sub>(dppp)–four equivalents DME to perform efficiently the coupling of organomanganese chlorides with aryl bromides or triflates. The reaction has a very large scope, thus, many functional groups such as esters, nitriles or ketones are tolerated and excellent yields were obtained from both electron-rich and elec-


















iron-poor substrates. This new procedure is especially interesting for the synthesis of hindered *O,O'*-substituted biaryls which were difficult to prepare until now by using a palladium-catalyzed cross-coupling reaction [5]. In addition, we have shown that, in our case,

Table 4  
Preparation of unsymmetrical biaryls from PhMnCl and aryl triflates<sup>a</sup>

Entry	ArBr	Yield, % <sup>b</sup>	
		(x equiv. PhMnCl, Time)	
		PdCl <sub>2</sub> (dppp)	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>
25		95 (2 eq., 10 min.)	14 <sup>c</sup> (3.5 eq., 72h)
26		98 (2 eq., 5 min.)	88 (3 eq., 2h)
27		98 (2 eq., 15 min.)	98 (2 eq., 15 min.)
28		90 (3.5 eq., 3h) <sup>d</sup>	-
29		88 (2 eq., 5 min.)	77 (3 eq., 48h)









a/ PhMnCl was prepared from PhMgCl, all reactions were performed at 20°C. For a general procedure see ref. 4. b/ Isolated yield based on aryl triflate. c/ GLC yield. d/ Reaction performed at 65°C.

Table 5  
Preparation of hindered *O,O'*-substituted unsymmetrical biaryls from ArMnCl and Ar'X; influence of the nature of Ar'X (X = Br, I and OTf)<sup>a</sup>

Entry	ArMnCl <sup>b</sup>	Ar'X	ArMnCl x equiv.	Reaction Conditions	Yield (%) <sup>c</sup>
30			2	3h, 20°C <sup>d</sup>	95 <sup>e</sup>
31			2	12h, 20°C <sup>d</sup>	96 <sup>e</sup>
32			2	3.5h, 20°C <sup>d</sup>	91
33			2	3.5h, 20°C <sup>d</sup>	50
34			3	19h, 65°C	93
35	"		3	48h, 65°C	35 <sup>e</sup>
36			2.5	4h, 65°C	93
37	"		2.5	48h, 65°C	0
38			2.5	12h, 20°C <sup>d</sup>	93
39	"		3.5	48h, 20°C	0





a/ All reactions were performed at 20°C, for a general procedure see ref. 4. b/ Prepared from ArMgCl. c/ Isolated yield based on Ar'X. e/ GLC yield.

Table 6  
Preparation of hindered *O,O'*-substituted unsymmetrical biaryls from RMnCl and aryl bromides<sup>a</sup>

Entry	RMnCl <sup>b</sup>	ArX	RMnCl x equiv.	Reaction Conditions	Yield (%) <sup>c</sup>
40			2.2	2h, 20°C	94
41	"		2	2h, 65°C	97
42	"		2	4h, 65°C	90
43			3.5	1h, 65°C	95
44			2.5	19h, 65°C	96

a/ For a general procedure see ref. 4. b/ Prepared from RMgCl. c/ Isolated yield based on ArX.

Table 7  
Pd-cross-coupling reaction from various non-aromatic organoman-ganese reagents and aryl bromides<sup>a</sup>

Entry	RMnCl <sup>b</sup>	ArBr	Time (h)	Yield (%) <sup>c</sup>
45	C <sub>6</sub> H <sub>17</sub> MnCl		0.3	91 <sup>d</sup>
46		"	0.5	93 <sup>d</sup>
47		"	1	91 <sup>e</sup>
48		"	0.6	92 <sup>e</sup>
49	C <sub>5</sub> H <sub>11</sub> ≡MnCl	"	24	91 <sup>d</sup>

a/ For a general procedure see ref. 4. b/ Prepared from RMgCl. c/ Isolated yield based on aryl bromide. e/ 1% PdCl<sub>2</sub>(dppf) was used as catalyst. f/ 1% PdCl<sub>2</sub>(dppp) was used as catalyst.

hindered aryl bromides are clearly more reactive than the corresponding iodides. It is, to our knowledge, the first report of such a reversal of reactivity. The use of this new catalytic system with various organometallic compounds (RMgX, RZnX) is currently under investigation.

## Acknowledgements

The CNRS and the Ecole Supérieure de Chimie Organique et Minérale (ESCOM) are gratefully acknowledged for financial support. Thanks are also to the ESCOM for a doctoral fellowship to E.R.

## References

- [1] E. Riguet, M. Alami, G. Cahiez, *Tetrahedron Lett.* 38 (1997) 4397.
- [2] For recent reviews about the transition metal-catalyzed aryl–aryl coupling reactions see: (a) S.P. Stanforth, *Tetrahedron* 54 (1998) 263–303. (b) F. Diederich, P.J. Stang (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, 1998.
- [3] General procedure: To a solution of  $\text{ArMnCl}$  [7] (7.4 mmol) in 5 ml of THF were added, at 0°C, 1.5 ml (14.8 mmol) of distilled DME, 1% of  $\text{PdCl}_2(\text{dppp})$  (0.037 mmol) and aryl bromide (3.7 mmol) in 2 ml of THF. After stirring (the reaction time and the temperature are indicated in Tables 1–7), the reaction mixture was hydrolyzed, at 0°C, with aqueous hydrochloric acid (1 M) and the aqueous layer was extracted twice with  $\text{Et}_2\text{O}$ . The combined organic layers were then dried over  $\text{MgSO}_4$  and the solvents were removed in vacuo. Pure unsymmetrical biaryl was isolated by simple filtration through silica gel.
- [4] For the preparation of triflates see: P.J. Stang, M. Hanack, L.R. Subramanian, *Synthesis* (1982) 85–126. For cross-coupling reactions from aryl triflates, see for instances: (a) T. Kamikawa, T. Hayashi, *Synlett* (1997) 163–64. (b) P.G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* 33 (1992) 4815–18.
- [5] See Ref. [2] and references quoted herein. Until now, few efficient procedures were reported to prepare hindered diaryls, see for instances; from arylboronic acids: (a) A.F. Littke, C. Dal, G.C. Fu, *J. Am. Chem. Soc.* 122 (2000) 4020–4028. (b) T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* (1992) 207–210; from arylstannanes: J.M. Saá, O. Martorell, *J. Org. Chem.* 58 (1993) 1963–1966.
- [6] It is known that the use of  $\text{PdCl}_2(\text{dppf})$  as a catalyst allows us to avoid or to limit the  $\beta$ -hydrogen elimination when an alkylmetal having eliminable  $\beta$ -hydrogen atoms is used. See for instance: T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* 106 (1984) 158–163.
- [7] For reviews on the preparation and the reactivity of organomanganese reagents see: (a) G. Cahiez, Butyl manganese chloride, in: L. Paquette (Ed.), *Encyclopedia of Reagents for Organic Synthesis*, vol. 2, Wiley, Chichester, 1995, pp. 925–928. (b) G. Cahiez, Manganese(II) chloride, in: L. Paquette, (Ed.), *Encyclopedia of Reagents for Organic Synthesis*, vol. 5, Wiley, Chichester, 1995, pp. 3227–3228. (c) G. Cahiez, *An. Quim.* 91 (1995) 561–578.