

Palladium-Catalyzed Selective Synthesis of Unsymmetrical Biaryls from Aryl Halides or Triflates and Organomanganese Reagents¹

Eric Riguet, Mouâd Alami* and Gérard Cahiez*

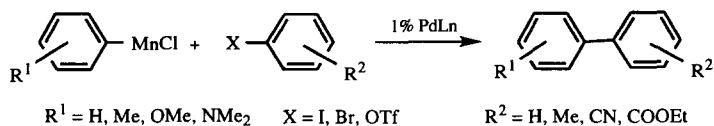
Ecole Supérieure de Chimie Organique et Minérale, Département de Chimie
 13, bd de l'Hautil, 95092 Cergy Pontoise, France

Abstract: Various functionalized unsymmetrical biaryls can be prepared in good to excellent isolated yields by palladium-catalyzed coupling reaction of aryl manganese chloride with aryl iodides, bromides or triflates. The reaction takes place rapidly and cleanly under mild conditions by using only 1% of palladium complexes. © 1997 Published by Elsevier Science Ltd.

Functionalized unsymmetrical biaryls are of great interest since they are found in various biologically active compounds² and materials having interesting physical properties.³ During the last few years, considerable attention has been paid to their preparation. The transition metal-catalyzed coupling reaction between an organometallic and an aryl halide or triflate is one of the most convenient route to prepare these compounds.⁴ Palladium complexes are particularly effective as catalysts to perform such heterocoupling reactions (Mg,⁵ Si,⁶ Sn,⁷ Zn,⁸ B⁹).

Recently, we have shown that transition metal-catalyzed (Cu, Fe) reactions of organomanganese reagents with alkyl and vinyl halides¹⁰ are very efficient and have a large scope. They are of interest for preparative organic chemistry since they give high yields of coupling products under mild conditions and are remarkably selective.^{10, 11}

Until now, nothing has been reported concerning the cross-coupling reactions of organomanganese halides with organic halides in the presence of palladium complexes. In connection with our interest in selective carbon-carbon bond formation mediated by a palladium catalyst,¹² we now describe our first results about the Pd-catalyzed reaction of organomanganese halides with functionalized aryl halides and triflates. In this letter we demonstrate the efficiency of this reaction and its application to the synthesis of functionalized unsymmetrical biaryls.



*Fax: (+33) 01.30.75.60.21

A palladium catalyst is essential to perform this cross coupling reaction (Table I, entry 1). Thus, the coupling of phenylmanganese chloride with *p*-bromobenzonitrile occurs at room temperature in THF in the presence of 1% PdCl₂(PPh₃)₂ to give 4-phenyl benzonitrile **1** in a 79% isolated yield within 2h (entry 2). The addition of a cosolvent to the reaction mixture allows to improve remarkably the yield of the cross coupling product (88 to 98% within 1.5 to 3h, entries 5 to 9). The best result was obtained in the presence of DME (4 equiv), under these conditions, **1** was isolated in excellent yield within 15 min (98%, entry 10). It is noteworthy that other palladium catalysts such as Pd(OAc)₂ + 2PPh₃ or Pd(PPh₃)₄ can be used successfully (98%, entries 12 and 14). In all cases, only 1% of palladium complex is sufficient to catalyze the reaction efficiently.

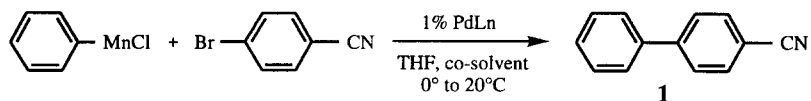


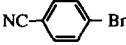
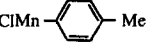
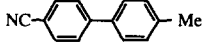
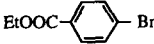
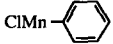

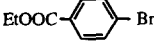

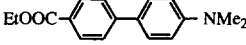

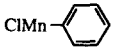
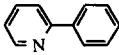
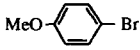
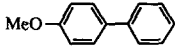
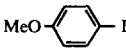
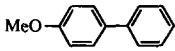

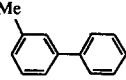
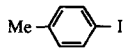
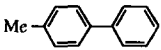
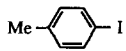
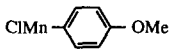
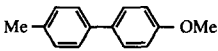
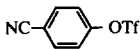
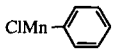
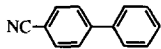
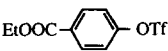
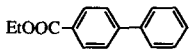

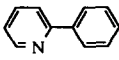
Table I: Reaction Conditions for the Cross-Coupling of *p*-Bromobenzonitrile with Phenylmanganese Chloride^a

Entry	Co-solvent ^b	PdL _n	Reaction time (h)	Yield ^c of 1 (%)
1	-	-	24	0
2	-	PdCl ₂ (PPh ₃) ₂	2	79
3	DABCO	"	18	58
4	dimethyl piperazine	"	6	40
5	TMEDA	"	2	90
6	Et ₃ N	"	2	88
7	NMP	"	3	88 ^d
8	DMPU	"	1	87
9	sulfolane	"	1.5	98
10	DME	"	0.25	98 ^e
11	"	PdCl ₂ + 2 PPh ₃	18	10
12	"	Pd(OAc) ₂ + 2 PPh ₃	2	98
13	"	Pd(OAc) ₂	18	48
14	"	Pd(PPh ₃) ₄	2	98

^{a/} To drive the reaction to completion, 2 equiv of PhMnCl were used. PhMnCl was prepared from PhMgCl.¹⁴ ^{b/} 4 equiv of co-solvent were used. ^{c/} Yield of isolated product. ^{d/} a 79% yield was obtained when PhMnCl was prepared from PhLi. ^{e/} a 70% yield was obtained when using 1.5 equiv of PhMnCl.

In order to demonstrate the efficiency of this new synthetic approach, a variety of unsymmetrical biaryls were thus synthesized in good to excellent yields starting from aryl iodides, bromides or triflates. As shown in table II, the reaction with 2-bromo pyridine or with aryl bromides bearing an electron-withdrawing group gave excellent yields of biaryls (91 to 99%, entries 15, 16, 17 and 18).

Table II: Pd-Catalyzed Cross-Coupling Reactions of ArX (X = I, Br or OTf) with Ar'MnCl Reagents.^a

Entry	ArX	Ar'MnCl ^b	Product ^c	Yield (%) ^d
15				91
16				99
17				91
18				96
19		"		42
20		"		91
21		"		93
22		"		97
23				93
24				98 ^e
25		"		88 ^e
26		"		77 ^e

^a/ To drive the reaction to completion, 2 equiv of ArMnCl were used. ^b/ ArMnCl were prepared from ArMgCl.¹⁴ ^c/ Satisfactory spectral data were obtained for all compounds see ref. 13. ^d/ Yield of isolated product. ^e/ 2.5 equiv of PhMnCl were used.

Nevertheless, with the substrates bearing an electron-donating group the reaction is slow and the yields are lower. Thus, only 42% of desired product were formed from *p*-bromoanisole (entry 19). However, by using the corresponding iodide the coupling products was rapidly obtained in nearly quantitative isolated yields within 10 min (91 to 97%, entries 20, 21, 22 and 23). It should be pointed out that under the same conditions aryl triflates reacts smoothly and give the biaryl products in good yields (entries 24, 25 and 26).

In conclusion, the procedure described herein provides a new synthetic and alternative approach to various functionalized unsymmetrical biaryls. It compares favourably with the previous procedures since excellent yields are rapidly obtained under mild conditions by using only 1% of palladium catalyst. Further developments will be reported in due course.

Acknowledgements: G.C. and M.A. belong to the CNRS. The *Ecole Supérieure de Chimie Organique et Minérale* (ESCOM) is gratefully acknowledged for financial support and for a doctoral fellowship to E.R. Thanks are also due to the CNRS for support of this research.

References and notes

- Organomanganese Reagents XXXV. For part XXXIV see: Cahiez G. and Métails E. *Tetrahedron Asymmetry* **1997**, in press.
- (a) Hallock, Y.F.; Manfredi, K.P.; Blunt, J.W.; Cardellina II, J.H.; Schäffer, M.; Gulden, K.P.; Bringmann, G.; Lee, A.Y.; Clardy, J.; François, G.; Boyd, M.R. *J. Org. Chem.* **1994**, *59*, 6349-6355. (b) Watanabe, T.; Kamikawa, K.; Uemura, M. *Tetrahedron Lett.* **1995**, *36*, 6695-6698. (c) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977-991.
- Bahl, A.; Grahn, W.; Stadler, S.; Feiner, F.; Bourhill, G.; Bräuchle, C.; Reisner, A.; Jones, P.G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1485-1487.
- Knight, D.W. in *Comprehensive Organic Synthesis*, Vol. 3; Trost, B.M.; Fleming, I.; Pattenden, G. Ed.; Pergamon Press: Oxford, **1991**, pp 481-520.
- (a) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1976**, *118*, 349-354. (b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669-679.
- Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711-1714.
- (a) Stille, J.K.; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524. (b) Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486. (c) Mitchell, T.N. *Synthesis* **1992**, 803-815. (d) Saà, J.M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963-1966.
- (a) Negishi, E.; King, A.O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348. (c) Amatore, C.; Jutand, A.; Negri, S. *J. Organomet. Chem.* **1990**, *390*, 389-398. (d) Erdik, E. *Tetrahedron* **1992**, *48*, 9577-9648. (e) Sibille, S.; Ratovelomanana, V.; Nédélec, J.Y.; Périchon, J. *Synlett* **1993**, 425-426. (f) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573-575 and references therein.
- (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
- Cu-catalyzed alkylation and Fe-catalyzed alkenylation of organomanganese reagents have been recently reported see: (a) Cahiez, G.; Marquais, S. *Synlett* **1993**, 45-47. (b) Cahiez, G. and Marquais, S. *Pure & Appl. Chem.* **1996**, *68*, 53-60. (c) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773-1776.
- For reviews see: (a) Cahiez, G. *Butyl Manganese Chloride in Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.; Ed., Wiley, Chichester **1995**, *2*, 925-928. (b) Cahiez, G. *Manganese (II) Chloride in Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.; Ed., Wiley, Chichester **1995**, *5*, 3227-3229. (c) Cahiez, G. *Anales de Química* **1995**, *91*, 561-578.
- (a) Linstrumelle, G.; Alami, M. (*E*) and (*Z*)-dichloroethylene in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.; Ed., Wiley, Chichester **1995**, *3*, 1710-1712. (b) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109-6112. (c) Crousse, B.; Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 4245-4248. (d) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *40*, 6403-6406. (e) Alami, M.; Ferri, F. *Synlett* **1996**, 755-756.
- Typical procedure:** To a solution of ArMnCl¹⁴ (7.4 mmol) in 5 mL of THF were added, at 0°C, 1.5 mL (14.8 mmol) of distilled DME, 1% of PdCl₂(PPh₃)₂ (0.037 mmol) and aryl bromide (3.7 mmol) in 2 mL of THF. After stirring at room temperature for 30 min, the reaction was hydrolyzed, at 0°C, with aqueous hydrochloric acid (1M) and extracted with Et₂O. The combined organic layers was then dried over MgSO₄ and the solvent was removed *in vacuo*. Pure unsymmetrical biaryl was isolated by simple filtration through silica gel.
- Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163-4176.

(Received in France 5 March 1997; accepted 9 May 1997)