



Communication

Manganese-catalyzed oxidative homo-coupling of aryl Grignard chlorides

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ABSTRACT

Manganese-catalyzed homo-coupling of aryl magnesium chlorides to give biphenyls was successfully achieved using manganese chloride as catalyst. A variety of aryl magnesium chlorides were efficiently converted into the corresponding symmetrical biaryls using 10 mol% MnCl_2 as catalyst in the presence of a stoichiometric amount of 1,2-dichloroethane. Since the aryl chlorides, from which the Grignard reagents were prepared, are cheaper and more readily available than the corresponding bromides and iodides this procedure should become the method of choice for preparing symmetrical biaryls.

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1. Introduction

Biaryl compounds are important building blocks for numerous agrochemicals, pharmaceuticals, natural products, conducting materials, and as ligands for asymmetric catalysis [1–3]. Thus efficient aryl–aryl bond forming reactions have been the theme of many research papers [4–14]. Symmetrical biaryl compounds are traditionally prepared by the Ullmann homo-coupling reaction, which involves the condensation of aryl halide molecules by a stoichiometric amount of copper at very high (>200 °C) temperatures [15]. More recently, biaryls have been prepared from arylboronic acids [16], arylstannanes [17] and arylzinc [18] reagents. Indeed, diverse metal catalysts including palladium [19–24] and nickel [25–28] have been employed in the homo-coupling reactions under relatively mild reaction conditions because of their extensive applicability and brilliant compatibility with many functional groups. There are, however, some limitations with partial catalysts with regards to expense, toxicity and the need in many cases to employ expensive and air sensitive phosphorus ligands. Therefore the discovery of new effective and environmental friendly procedures is of real current interest. Mayr and Knochel found a transition-metal-free homo-coupling of organomagnesium compounds [29]. Ackermann reported an efficient aryl–aryl coupling by using nickel complexes of air-stable phosphine oxides [30]. Cahiez and Rieke reported organomanganese-catalyzed cross-coupling reactions in the past 10 years [31–34]. Hoffman determined the stereochemistry of the transmetalation of Grignard reagents to manganese (II) [35]. Recently, Yuan developed the manganese-cat-

alyzed homo-coupling reaction of aliphatic halides in the presence of magnesium [36]. Although these newly developed methods are good for the preparation of biaryls, their use have been restricted to aryl bromides and iodides as starting material which somewhat limits their use due to cost and availability of starting material. In contrast to aryl iodides and bromides, aryl chlorides are cheap and more readily available though less reactive. Although aryl chlorides are well-known bulk chemical feedstocks, their coupling chemistry has proven difficult but it would be economically beneficial to a number of industrial processes. Up until now the homo-coupling reactions of aryl chlorides depends on highly active catalysts such as palladium or nickel complex [13,37–41]. To the best of our knowledge there have been no reports on the selective homo-coupling of organometallics by manganese catalysis from aryl magnesium chlorides. Herein, we report an efficient and practical reaction conditions for the manganese-catalyzed oxidative homo-coupling of aryl magnesium chlorides.

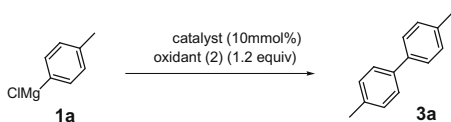
2. Results and discussion

To establish the generality of this method, the manganese-catalyzed oxidative homo-coupling reaction conditions of 4-methylphenylmagnesium chloride (**1a**) was examined, and the resulting yields are shown in Table 1. It was found that inexpensive 1,2-dichloroethane (**2a**) was an excellent oxidant for the homo-coupling, giving 4,4'-dimethylbiphenyl (**3a**) in high yields without any byproducts. Thus, in the presence of 10 mol% MnCl_2 and 1.2 equiv. of **2a**, the homo-coupling of the Grignard reagent **1a** was completed in 2 h, in THF at room temperature (entry 1), to afford a quantitative yield of the biaryl **3a**. When the temperature was decreased, the yield was consequently reduced (entries 2

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Table 1
Manganese catalyzed homo-coupling of 4-methylphenylmagnesium chloride (**1a**)^a



Entry	Temp/°C	Oxidant	Catalyst	Yield/%
1	rt	ClCH ₂ CH ₂ Cl (2a)	MnCl ₂	96
2	10	2a	MnCl ₂	80
3	0	2a	MnCl ₂	72
4	rt	BrCH ₂ CH ₂ Br (2b)	MnCl ₂	73
5	rt	2a	NiCl ₂	85
6	rt	2a	CuCl ₂	60
7	rt	2a	MgCl ₂	30
8	rt	2a	FeCl ₃	95(99[4])

^a The reactions were carried out with 10 mol % of catalyst.

and 3). Use of 1,2-dibromoethane (**2b**) also gave homo-coupling product **3a**, although the yield of **3a** dropped slightly (entry 4). Compared with those of other metal compounds the highest activity for formation of **3a** was observed for MnCl₂ and FeCl₃ [4].

Table 2 summarizes a diverse array of results obtained for the oxidative homo-coupling of other aryl Grignard chlorides under our standard reaction conditions. When chlorobenzene was used the yield was excellent (99%, entry 11). However, when a methyl group was introduced at an *o*-position of the aryl Grignard reagent, this results in a somewhat lowering of yield of the homo-coupling product (entry 2) implying homo-coupling reaction is sensitive to steric congestion at the reaction site. Although sterically demanding substrates **1b**, and **1d**, required longer reaction times, they still gave the corresponding biaryls in good yields. When an electron withdrawing group was introduced into the aryl chloride the yield of the biaryls remained high, (**3i**, 94%), which was contrary to literature precedent using palladium as catalyst [14]. Since the electron withdrawing groups slow down transmetalation this result implies

Table 2
Manganese -catalyzed oxidative homo-coupling of Grignard chlorides^a.

Entry	Aryl	Product	Time/h	Yield/% ^b
1	1a	3a	2	96%
2	1b	3b	12	87.4%
3	1c	3c	2	80.4%
4	1d	3d	12	73.5%
5	1e	3e	12	45.3%
6	1f	3f	12	54%
7	1g	3g	2	57.6%
8	1h	3h	12	60.6%
9	1i	3i	12	94%
10	1j	3j	2	99%

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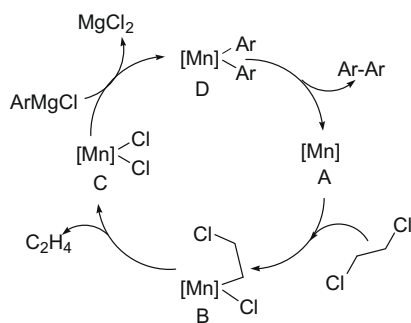
Table 2 (continued)

Entry	Aryl	Product	Time/h	Yield/% ^b
11			12	60%
12			12	0%
13			12	0%
14			12	68.4%
15			12	89.1%
16			12	67.5%

^a Unless otherwise noted, the reactions were carried out using aryl Grignard chlorides (10 mmol), 1,2-dichloroethane (12 mmol), and MnCl₂ (1 mmol) in THF. The reactions were carried out at room temperature for 2–12 h and the progress of the reaction was monitored by TLC.

^b Isolated yields after column chromatography.

that transmetalation is not the rate determining step. This may contribute to the substituted nitro group which was beneficial to the transmetalation reaction from organomagnesium compound



Scheme 1. Mechanism for manganese-catalyzed homo-coupling.

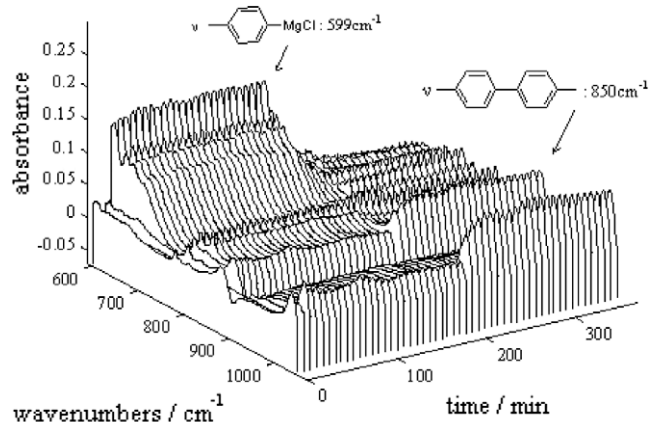
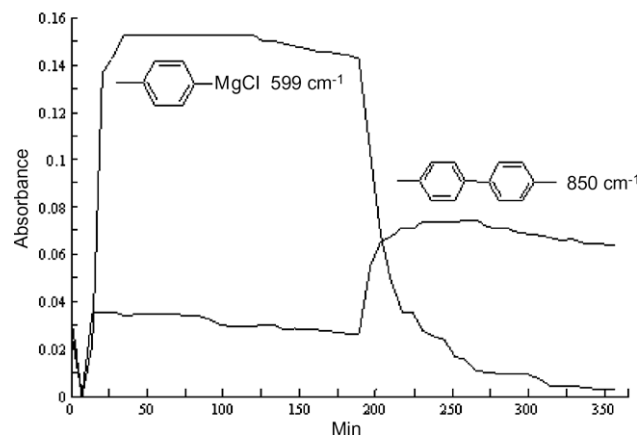


Fig. 1. Infrared spectra obtained during the preparation of 4,4'-dimethyl-biphenyl.

to organomanganese compound (Scheme 1). In contrast aryl chlorides containing electron donating groups gave slightly lower yields. The yields of 4-methoxy-, 2-methoxy-, and *N,N*-dimethyl-amino-phenylmagnesium chlorides, 4-methoxymethyl-protected phenolmagnesium chlorides were down when converted to the corresponding biaryls **3c**, **3d**, **3e**, **3f** and **3g**, respectively, under comparable conditions (entries 3–7). It is remarkable that both electron withdrawing or donating group at *para*-substituted position both gave good to excellent yields of the corresponding biaryls (**3c**, **3i**) (87.4% and 96%). Oxazoline groups on the aromatic ring or heteroaryl chlorides are difficult to couple, with coordination with the catalysts being a possible reason. (entries 11–13) [14]. Furthermore, this chemistry was extended to Grignard reagents derived from benzyl chloride **1n**, chloronaphthalene **1o** and chloro-ethyne **1p** and the yields obtained were moderate.

Fig. 2. IR monitoring during the entire reaction. The relative IR absorbance values are shown on the left axis for 4-methylphenylmagnesium chloride and corresponding 4,4'-dimethyl-biphenyl at 599 and 850 cm⁻¹, respectively.

By using *in situ* infrared technology, we try to continuously monitor the formation of the 4-methylphenylmagnesium chloride and the corresponding biaryls. Fig. 1 shows an IR spectrum “waterfall” plot obtained during the course of the reaction. The *in situ* IR data for RMgX and the homo-couplings were profiled for the entire reaction (Fig. 2). At the beginning of the reaction the Grignard reagents were formed quickly during the initiation period. After initiation the RMgX levels continue to rise until no aryl chloride was left. Absorbance for biaryls increased immediately after the catalyst was added as observed by the parallel profiles. The homo-couplings stopped increasing when the Grignard Reagents were consumed at 220 min. On-line monitoring by IR provided confidence that the homo-coupling was successfully generated by the increasing in absorbance at 850 cm^{-1} , as clearly shown in Fig. 1.

A mechanism for the manganese catalyzed homo-coupling of Grignard reagents is presented (Scheme 1), and is similar to the iron catalyzed reaction [4]. Reaction of the aryl Grignard with manganese chloride results in transmetallation affording a diarylmanganese intermediate D. Reductive elimination of the two aryl groups gives the homo-coupling product and reduced manganese. Oxidative addition of 1,2-dichloroethane to reduced manganese A forms an alkyl manganese intermediate B which undergoes β -halogen elimination [42] giving ethylene and regenerating the catalytically active species C.

Manganese complexes A and B should be considered as the important intermediates because the yield of biaryls was decreased seriously (96% to 23%, 96% to 12%) without the catalyst MnCl_2 or the oxidant 1,2-dichloroethane respectively.

3. Conclusion

In summary, we have developed a new and practical reaction system for oxidative homo-coupling for Grignard chlorides using MnCl_2 as a catalyst and 1,2-dichloroethane as a reoxidant. These results pave the way for the homo-coupling of various aryl Grignard chlorides and are readily amenable to a large-scale synthesis of biaryl compounds. Noteworthy features of this method include the following: lower cost of aryl Grignard chlorides, use of a commercially available, airstable catalyst MnCl_2 ; tolerance of nitro functionality; synthesis of hindered biaryls; coupling of sterically demanding chlorides; generally good to excellent yields. We believe this coupling reaction could be of great interest since to our knowledge no example of this selective homo-coupling of organometallics by manganese catalysis Grignard chlorides as feedstock are described in the literature.

4. Experimental

4.1. Representative procedure for the coupling reaction

4.1.1. The high activity magnesium

Freshly cut potassium (0.70 g, 18 mmol), MgCl_2 (1.14 g, 12 mmol), KI (1.99 g, 12 mmol), and THF (15 mL) were placed in an oven-dried 50-ml three-necked flask equipped with condenser, septum, heating mantle, magnetic stirring, and nitrogen atmosphere. The mixture was stirred and heated to reflux, where reduction of MgCl_2 occurred to give a dark black mixture. The mixture was refluxed for 3 h to ensure complete reaction of potassium, and was then cooled at room temperature for 0.5 h [43].

4.1.2. 4-Methylphenylmagnesium chloride

A solution of 4-chloro-toluene (1.27 g, 10 mmol) in THF (5 mL) was added dropwise to a 50 mL-flask, charged with activated magnesium (292 mg, 12 mmol), THF (15 mL) and nitrogen atmosphere.

The mixtures were refluxed for 4 h. The flask was then cooled to r.t. and the Grignard reagent **1a** was used directly in the following experiment. Yield of mono-Grignard reagent determined by quenching followed by HPLC analysis was 97%.

4.1.3. 4,4'-Dimethyl-biphenyl

The Grignard reagent solution (1a containing 9.7 mmol mono-Grignard chlorides) was added dropwise to a 50 mL-flask, charged with MnCl_2 (126 mg, 1 mmol), THF (10 mL), and 1,2-dichloroethane (1.19 g, 12 mmol), whilst maintaining the temperature at $25\text{ }^\circ\text{C}$ under an atmosphere of N_2 . After stirring for 2 h, the reaction mixtures were quenched with CH_3OH (2 mL). The suspension was filtered and the cake washed with THF. The combined organic layer was concentrated under reduced pressure to give 900 mg of crude 4,4'-dimethylbiphenyl. This crude material was purified by chromatography on silica gel (hexane: ethyl acetate, 50:1) to give 4,4'-dimethyl-biphenyl (844 mg, 96% yield) as a white solid. M.p.: $123\text{--}124\text{ }^\circ\text{C}$ (Lit.^[2a]: $125\text{ }^\circ\text{C}$).

^1H NMR (CDCl_3/TMS): δ 2.35 (s, 6H), 7.12–7.14 (d, $J = 7.9\text{ Hz}$, 4H), 7.36–7.38 (d, $J = 7.6\text{ Hz}$, 4H).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.12.021.

References

- [1] K.C. Nicolaou, C.N.C. Boddy, S. Brase, N. Winssinger, *Angew. Chem., Int. Ed.* 38 (1999) 2096.
- [2] L. Pu, *Chem. Rev.* 98 (1998) 2405.
- [3] J. Tsuji, in: *Palladium Reagents and Catalyst*, John Wiley and Sons, New York, 1995.
- [4] T. Nagano, T. Hayashi, *Org. Lett.* 7 (2005) 491.
- [5] A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* 124 (2002) 13856.
- [6] M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* 126 (2004) 3686.
- [7] I. Cepanec, M. Litvić, J. Udiković, I. Pogorelič, M. Lovrić, *Tetrahedron* 63 (2007) 5614.
- [8] S. Hidehiro, T. Hironori, T. Tatsuya, *J. Organomet. Chem.* 692 (2007) 368.
- [9] X. Xu, D. Cheng, W. Pei, *J. Org. Chem.* 71 (2006) 6637.
- [10] J.-H. Li, Y.-X. Xie, D.-L. Yin, *J. Org. Chem.* 68 (2003) 9867.
- [11] P.B. Silveira, V.R. Lando, J. Dupont, A.L. Monteiro, *Tetrahedron Lett.* 43 (2002) 2327.
- [12] N. Ma, Z. Duan, Y.-J. Wu, *J. Organomet. Chem.* 691 (2006) 5697.
- [13] I. Masahiko, O. Hiroki, S. Koichi, N. Nobue, O. Masaji, *Bull. Chem. Soc. Jpn.* 63 (1990) 80.
- [14] S. Kanth, R. Reddy, G.V. Yakaiah, T. Narsaiah, B. Rao, *Synthetic Commun.* 36 (2006) 3079.
- [15] F. Ullmann, *Ber.* 36 (1903) 2389.
- [16] N. Miyaura, A. Suzuki, *Chem. Rev.* 95 (1995) 2457.
- [17] V. Farina, *Pure Appl. Chem.* 68 (1996) 73.
- [18] E. Negishi, *Acc. Chem. Res.* 15 (1982) 340.
- [19] J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, M. Lemaire, *Tetrahedron* 54 (1998) 13793.
- [20] F.-T. Luo, A. Jeevanandam, M.K. Basu, *Tetrahedron Lett.* 39 (1998) 7939.
- [21] S. Venkatraman, C.-J. Li, *Org. Lett.* 1 (1999) 1133.
- [22] D.D. Hennings, T. Iwama, V.H. Rawal, *Org. Lett.* 1 (1999) 1205.
- [23] D.L. Boger, J. Goldberg, C.-M. Andersson, *J. Org. Chem.* 64 (1999) 2422.
- [24] J. Hassan, C. Hathroubi, C. Gozzi, M. Lemaire, *Tetrahedron* 57 (2001) 7845.
- [25] F. Massicot, R. Schneider, Y. Fort, S. Illy-Cherrey, O. Tillement, *Tetrahedron* 57 (2001) 531.
- [26] G.-Q. Lin, R. Hong, *J. Org. Chem.* 66 (2001) 2877.
- [27] J. Howarth, P. James, J. Dai, *Tetrahedron Lett.* 41 (2000) 10319.
- [28] F. Massicot, R. Schneider, Y. Fort, *J. Chem. Res.* (1999) 664.
- [29] A. Krasovskiy, A. Tishkov, V.D. Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* 45 (2006) 5010.
- [30] L. Ackermann, R. Born, J.H. Spatz, D. Meyer, *Angew. Chem. Int. Ed.* 44 (2005) 7216.
- [31] G. Cahiez, D. Luat, F. Lecomte, *Org. Lett.* 6 (2004) 4395.
- [32] R.D. Rieke, Y.S. Suh, S.H. Kim, *Tetrahedron Lett.* 46 (2005) 5961.
- [33] S.H. Kim, R.D. Rieke, *J. Org. Chem.* 65 (2000) 2322.
- [34] G. Cahiez, F. Lepifre, P. Ramiandrasoa, *Synthesis* (1999) 2138.
- [35] R.W. Hoffmann, B. Hoelzer, *J. Am. Chem. Soc.* 124 (2002) 4204.
- [36] Y. Yuan, Y.-B. Bian, *Appl. Organomet. Chem.* 22 (2008) 15.
- [37] I. Colon, D.R. Kelsey, *J. Org. Chem.* 51 (1986) 2627.

- [38] C.S. Chao, C.H. Cheng, C.T. Chang, *J. Org. Chem.* 48 (1983) 4904.
- [39] Q. Nida, M. Sudip, S. Yoel, *Adv. Synth. Catal.* 344 (2002) 1079.
- [40] M. Lourak, R. Vanderesse, Y. Fort, P. Caubere, *J. Org. Chem.* 54 (1989) 4840.
- [41] P. Bamfield, P.M. Quan, *Synthesis* 7 (1978) 537.
- [42] For β -Halogen elimination on manganese species, see: B.B. Snider, M.A. Dombroski, *J. Org. Chem.* 52 (1987) 5487.
- [43] R.D. Rieke, S.E. Bales, *J. Am. Chem. Soc.* 96 (1974) 1775.