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Simple and Efficient $TiCl_4$-Mediated Synthesis of Biaryls via Arylmagnesium Compounds

Atsushi Inoue, Kazuya Kitagawa, Hiroshi Shinokubo and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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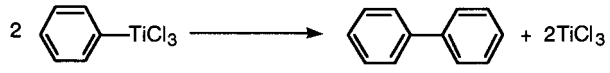
Abstract—Oxidative self-coupling reactions of various arylmagnesium bromides with $TiCl_4$ affords the corresponding symmetric biaryls in moderate to good yields at 0°C or lower. Tributylmagnesate-induced halogen–magnesium exchange of aryl halides followed by the coupling reaction provides biaryls in good yields under mild conditions. This method can achieve a one-pot synthesis of biaryls containing functional groups such as esters, amides, or nitriles. © 2000 Elsevier Science Ltd. All rights reserved.

Biaryls are recognized as an important class of compounds in organic synthesis because of their versatility in both ligand chemistry and materials chemistry. Biaryls are also found in various types of natural products which show unique biological activity. The synthesis of biaryls via coupling reactions has been the subject of numerous past and current investigations.[1] Biaryls are often prepared from aryl halides either by the classical Ullmann-type reaction[2,3] or by the transition metal-catalyzed coupling reaction of aryl halides with arylmetals.[4] Self-coupling reaction of arylmetallic reagents with oxidants such as Co(II), Cu(II) or V(V) also provides a convenient method for the synthesis of symmetric biaryls.[5,6]

Phenyltrichlorotitanium is known to decompose thermally to form biphenyl and titanium(III) chloride (Scheme 1).[7] However the yield of biphenyl was low and the synthetic application of this reaction has not yet been fully investigated. Herein we wish to report a simple procedure for coupling of various arylmagnesium compounds using titanium(IV) chloride as an oxidant. The coupling reaction can proceed under conditions so mild that this method can be successfully applied to the coupling of functionalized arylmagnesium reagents.

Titanium(IV) chloride was added dropwise at 0°C to a solution of phenylmagnesium bromide (**1a**) in THF and the reaction mixture was stirred for 30 min at 0°C. Aqueous workup and purification by silica gel column chromatography gave biphenyl (**2a**) in 82% yield (Scheme 2). The use of THF as a solvent is essential for successful coupling. The use of ether instead of THF provided biphenyl in lower yield (22%).

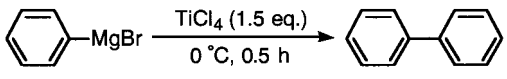


Scheme 1.

Various arylmagnesium bromides can be easily prepared from the corresponding aryl bromides and metallic magnesium. A one-pot synthesis of biaryls from aryl bromides has been developed. The results are shown in Table 1.

As shown in Table 1, 3,3- and 4,4′-disubstituted biaryls could be obtained in moderate to good yields (entries 2–5). In contrast, ortho-substituted arylmagnesium bromide gave 2,2′-disubstituted biaryl only in low yield (entry 6). In this reaction, the major product was anisole (50%), which was generated from hydrolysis of the starting Grignard reagent. In this case, however, an inverse-addition procedure was found to improve the yield of the desired biaryl. Thus, the addition of a THF solution of 2-methoxyphenylmagnesium bromide, prepared from the reaction of 2-bromoanisole with magnesium, to a solution of $TiCl_4$ in 1,2-dimethoxyethane provided 2,2′-dimethoxybiphenyl in 58% yield (Scheme 3).

We have also developed an alternative coupling method starting from aryl halides. Recently we reported the halogen–magnesium exchange reaction[8] of aryl bromides and aryl iodides with lithium trialkylmagnesate ($R_3Mg^-Li^+$).[9] This exchange reaction can generate an



Scheme 2.

Keywords: biaryls; coupling reactions; titanium(IV) chloride; arylmagnesium compound; aryl halides.

* Corresponding author. Tel.: +81-75753-5523; fax: +81-75753-4863; e-mail: oshima@fm1.kuic.kyoto-u.ac.jp

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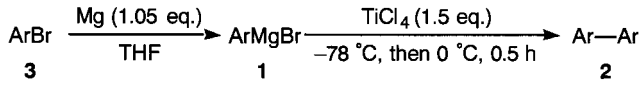
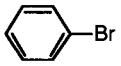
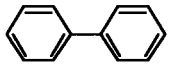
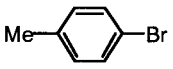
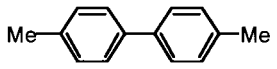
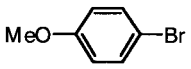
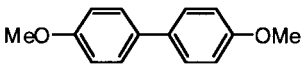
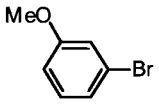
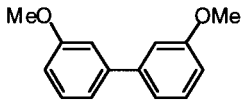
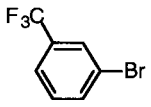
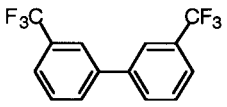
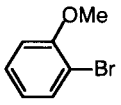
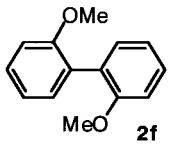
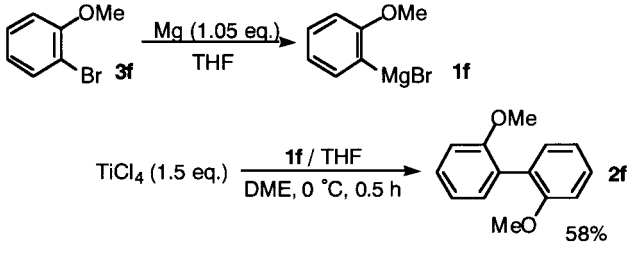
Table 1. The coupling reaction of arylmagnesium bromides prepared from aryl bromides and magnesium



Entry	Aryl Bromide	Product	Yield (%)
1	 **3a**	 **2a**	76
2	 **3b**	 **2b**	77
3	 **3c**	 **2c**	71
4	 **3d**	 **2d**	71
5	 **3e**	 **2e**	65
6	 **3f**	 **2f**	35

arylmagnesium ate-complex which would be a promising precursor for the oxidative coupling reaction. Indeed, the addition of $TiCl_4$ to the resulting arylmagnesium species provided biaryls in good yields. The results of this alternative one-pot procedure are summarized in Table 2. Both aryl bromides and aryl iodides can be converted to the corresponding biaryls efficiently. In the case of dibromobenzene, one of two bromines could be selectively metallated with tributylmagnesate to give 4,4′-dibromobiphenyl or 3,3′-dibromobiphenyl in good yield (entries 5 and 6).

It is worth noting that the exchange procedure has an advantageous feature: the exchange reaction with magnesate reagent proceeds at low temperatures to furnish functionalized arylmagnesium species efficiently. Thus, the subsequent $TiCl_4$-induced coupling reaction at low temperatures provided biaryls bearing functional groups such as an ester or amide (Scheme 4). In the case of *p*- or *m*-bromobenzonitrile, the inverse-addition technique (vide supra) improved the yields of the corresponding biaryls (Scheme 5). We suppose that biaryls arise from aryltitanium species via the transmetallation between magnesium ate-complex **5** and $TiCl_4$. Butylated products could not be found in the reaction mixture, although butyl group might be on the titanium species after the transmetallation.



Scheme 3.

This new coupling method can be successfully applied to intramolecular reactions. Treatment of substrates such as **6** with trialkylmagnesate followed by an addition of $TiCl_4$ afforded the desired coupling product **7** in moderate yields (Scheme 6).

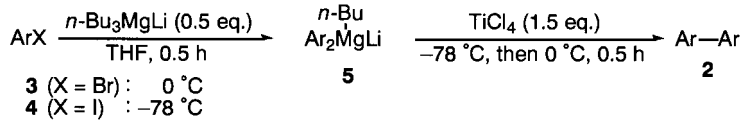
In conclusion, we have found that $TiCl_4$-induced self-coupling reaction of arylmagnesium species proceeds efficiently in THF under mild conditions and at low temperatures. This method can be successfully applied to the preparation of functionalized biaryls starting from aryl halides having various functional groups using the halogen–magnesium exchange reaction.

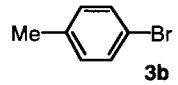
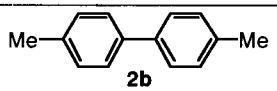
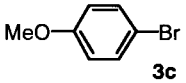
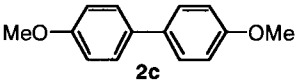
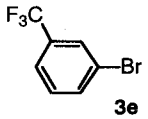
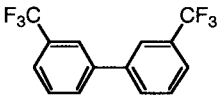
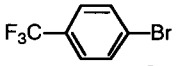
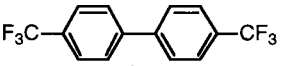
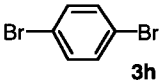
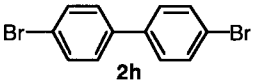
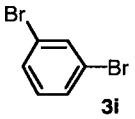
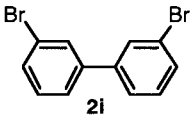
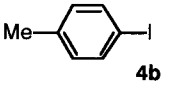
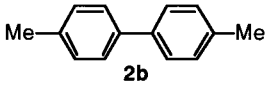
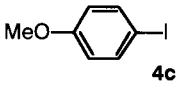
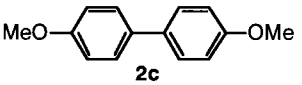
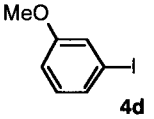
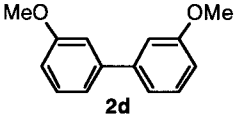
Experimental

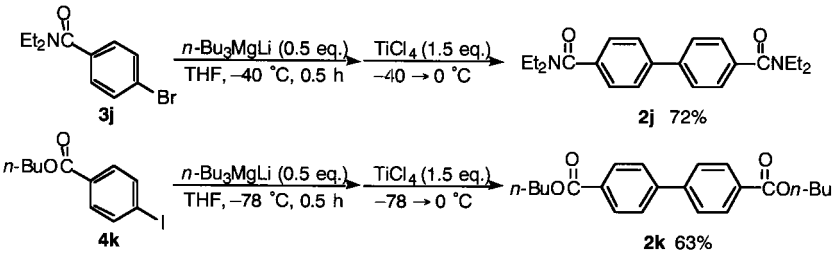
Instrumentation and materials

^1H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer, $CDCl_3$

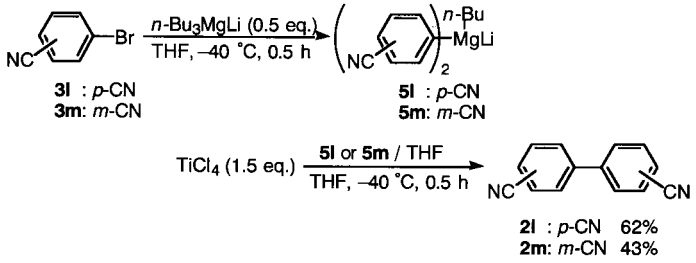
Table 2. The coupling reaction of arylmagnesium compounds prepared by halogen–magnesium exchange



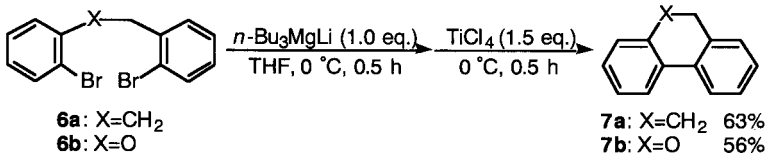
Entry	Aryl Halide	Product	Yield (%)
1	 **3b**	 **2b**	82
2	 **3c**	 **2c**	80
3	 **3e**	 **2e**	62
4	 **3g**	 **2g**	74
5	 **3h**	 **2h**	54
6	 **3i**	 **2i**	74
7	 **4b**	 **2b**	85
8	 **4c**	 **2c**	71
9	 **4d**	 **2d**	73



Scheme 4.



Scheme 5.



Scheme 6.

was used as a solvent, and chemical shifts are given in δ with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merk Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The analyses were carried out at the Elemental Analysis Center of Kyoto University.

Diethyl ether was dried over a slice of sodium. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were freshly distilled from sodium benzophenone ketyl before use. Titanium(IV) chloride was distilled and stored under argon. All reactions were carried out under an argon atmosphere.

General procedure for $TiCl_4$-mediated coupling reaction of aryl Grignard reagents

Magnesium turnings (51 mg, 2.1 mmol) and THF (3 mL) were placed in a flask under argon atmosphere. 3-Bromoanisole (**3d**, 0.37 g, 2.0 mmol) was added and stirred for 0.5 h at room temperature. THF (7 mL) was added and the mixture was cooled to −78°C. $TiCl_4$ (0.33 mL, 3.0 mmol) was added dropwise and the reaction mixture was stirred for 0.5 h at 0°C. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography provided 3,3′-dimethoxybiphenyl (**2d**, 0.15 g, 0.71 mmol) in 71% yield.

Procedure for the synthesis of 2,2′-disubstituted biaryl

A THF solution of 2-methoxyphenylmagnesium bromide, which was prepared from 2-bromoanisole (**3f**, 0.37 g, 2.0 mmol) and magnesium (51 mg, 2.1 mmol) as above, was added to a precooled solution of $TiCl_4$ (0.33 mL, 3.0 mmol) in DME (15 mL) at −78°C and the mixture was stirred for 0.5 h at 0°C. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexane/ethyl acetate=10/1) provided 2,2′-dimethoxybiphenyl (**2f**, 0.12 g, 0.58 mmol) in 58% yield.

One-pot procedure for the synthesis of functionalized biaryl

To a solution of butylmagnesium bromide (1.0 mL, 1.0 M THF solution, 1.0 mmol) in THF (5 mL) was added butyllithium (1.3 mL, 1.6 M hexane solution, 2.0 mmol) at 0°C and the mixture was stirred for 10 min. The solution was cooled to −40°C and a solution of 4-bromo-*N*,*N*-diethylbenzamide (**3j**, 0.51 g, 2.0 mmol) in THF (3 mL) was added dropwise. The mixture was stirred for 0.5 h. $TiCl_4$ (0.33 mL, 3.0 mmol) was added and the reaction mixture was warmed to 0°C gradually. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate) gave *N*,*N*,*N*′,*N*′-tetraethylbiphenyl-4,4′-dicarboxamide (**2j**, 0.23 g, 0.65 mmol) in 65% yield: IR (nujol) 1624, 1287, 1099, 845, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (bs, 3H), 1.24 (bs, 3H), 3.31 (bs, 3H), 3.55 (bs, 3H), 7.45 (d, J=8.4 Hz, 4H), 7.61 (d, J=8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 12.82, 14.12, 39.16, 43.21, 126.98, 127.17, 136.58, 141.22, 171.11. Found: C, 74.79; H, 8.07%. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01%.

Dibutyl biphenyl-4,4′-dicarboxylate (2k). IR (nujol) 1722, 1267, 1103, 846, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J=7.2 Hz, 6H), 1.49 (tq, J=7.4, 7.2 Hz, 4H), 1.77 (tt, J=6.6, 7.4 Hz, 4H), 4.35 (t, J=6.6 Hz, 4H), 7.68 (d, J=8.1 Hz, 4H), 8.12 (d, J=8.1 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 13.64, 19.17, 30.69, 64.94, 127.28, 130.14, 130.24, 144.42, 166.53. Found: C, 74.37; H, 7.54%. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39%.

Procedure for the synthesis of biphenyldicarbonitrile

To a solution of butylmagnesium bromide (1.0 mL, 1.0 M THF solution, 1.0 mmol) in THF (5 mL) was added butyllithium (1.3 mL, 1.6 M hexane solution, 2.0 mmol) at 0°C and the mixture was stirred for 10 min. The solution was cooled to −40°C and a solution of 4-bromobenzonitrile (**3l**, 0.36 g, 2.0 mmol) in THF (3 mL) was added dropwise. The mixture was stirred for 0.5 h. In another flask was placed THF (10 mL) and cooled to −40°C. $TiCl_4$ (0.33 mL, 3.0 mmol) was added and the mixture was stirred for 10 min. To this suspension was added dropwise the THF solution of arylmagnesate prepared above. The reaction mixture was stirred for 0.5 h at −40°C and then poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a white solid. Washing this solid with hexane gave biphenyl-4,4′-dicarbonitrile (**2l**, 0.13 g, 0.62 mmol) in 62% yield: IR (nujol) 2222, 1605, 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (d, J=8.7 Hz, 4H), 7.78 (d, J=8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 112.50, 118.45, 128.01, 132.97, 143.63. Found: C, 82.08; H, 3.79%. Calcd for $C_{14}H_8N_2$: C, 82.34; H, 3.95%.

Biphenyl-3,3′-dicarbonitrile (2m). IR (nujol) 2224, 786, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (dd, J=7.8, 7.8 Hz, 2H), 7.71 (d, J=7.8 Hz, 2H), 7.79 (d, J=7.8 Hz, 2H), 7.84 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 113.58, 118.38, 130.13,

130.75, 131.50, 131.90, 140.29. Found: C, 82.07; H, 3.85%. Calcd for $C_{14}H_8N_2$: C, 82.34; H, 3.95%.

Procedure for the intramolecular coupling

To a solution of butylmagnesium bromide (1.0 mL, 1.0 M solution in THF, 1.0 mmol) in THF (2 mL) was added butyllithium (1.3 mL, 1.6 M hexane solution, 2.0 mmol) at 0°C and the mixture was stirred for 10 min. A solution of 1,2-bis(2-bromophenyl)ethane (**6a**, 0.34 g, 1.0 mmol) in THF (3 mL) was added at 0°C and the mixture was stirred for 0.5 h at the temperature. $TiCl_4$ (0.33 mL, 3.0 mmol) was added dropwise at 0°C. The reaction mixture was stirred for further 0.5 h. The mixture was then poured into saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexane/ethyl acetate=20/1) afforded 9,10-dihydrophenanthrene (**7a**, 0.11 g, 0.63 mmol) in 63% yield along with dibenzyl (0.05 g, 0.29 mmol) in 29% yield.

2-Bromobenzyl 2-bromophenyl ether (6b). IR (nujol) 1594, 1298, 1252, 1060, 1026, 746, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s, 2H), 6.88 (ddd, J=1.5, 7.5, 7.8 Hz, 1H), 6.96 (dd, J=1.5, 8.1 Hz, 1H), 7.19 (ddd, J=1.5, 7.5, 7.5 Hz, 1H), 7.27 (ddd, J=1.5, 7.8, 8.1 Hz, 1H), 7.37 (ddd, J=1.5, 7.5, 7.8 Hz, 1H), 7.58 (dd, J=1.5, 7.8 Hz, 1H), 7.59 (dd, J=1.5, 7.5 Hz, 1H), 7.72 (dd, J=1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 69.97, 112.43, 113.74, 121.64, 122.45, 127.77, 128.59, 128.60, 129.23, 132.51, 133.58, 135.94, 154.79. Found: C, 45.53; H, 2.86%. Calcd for $C_{13}H_{10}Br_2O$: C, 45.65; H, 2.95%.

9,10-Dihydro-9-oxaphenanthrene (7b). IR (neat) 2840, 1607, 1487, 1440, 1245, 1198, 1018, 810, 753, 724, 651, 614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (s, 2H), 7.01 (dd, J=1.2, 8.1 Hz, 1H), 7.07 (ddd, J=1.5, 7.5, 7.8 Hz, 1H), 7.16 (dd, J=1.5, 7.5 Hz, 1H), 7.25 (ddd, J=1.5, 7.5, 8.1 Hz, 1H), 7.29 (ddd, J=1.5, 7.5, 7.5 Hz, 1H), 7.39 (ddd, J=1.5, 7.5, 7.8 Hz, 1H), 7.71 (dd, J=1.5, 7.8 Hz, 1H), 7.75 (dd, J=1.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 68.43, 117.44, 122.07, 122.21, 123.01, 123.36, 124.73, 127.73, 128.51, 129.53, 130.19, 131.50, 154.89. Found: C, 85.73; H, 5.55%. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53%.

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