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# Control of Reactive Site in Palladium-Catalyzed Grignard Cross-Coupling of Arenes Containing both Bromide and Triflate

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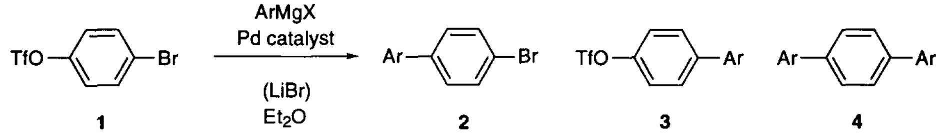
**Abstract:** Reaction of 4-bromophenyl triflate (**1**) with phenylmagnesium bromide in the presence of 5 mol % of $PdCl_2$(dppp) gave 97% yield of 4-bromobiphenyl (**2a**), which was formed by selective replacement of triflate in **1** by phenyl. On the other hand, bromide in **1** was substituted with the phenyl Grignard reagent selectively by use of $PdCl_2$(meo-mop)$_2$ to give 4-biphenyl triflate (**3a**) in high yield. The selective substitution was demonstrated to take place at the oxidative addition step to a palladium(0) species in a stoichiometric reaction of **1** with palladium(0) phosphine complexes. © 1997 Elsevier Science Ltd.

The transition metal-catalyzed cross-coupling of aromatic electrophiles with organometallic reagents is recognized to be a versatile method for the construction of aromatic molecules.[1] In the palladium-catalyzed cross-coupling, aromatic iodides are generally more reactive than the corresponding bromides or triflates, iodides undergoing the substitution preferentially.[1] On the other hand, it is difficult to control the reactivity of aryl bromides and triflates in the palladium-catalyzed cross-coupling reactions.[2] One successful example is the reaction of 4-bromophenyl triflate with tributyl(vinyl)tin where the coordination number of phosphine ligand in a palladium-triphenylphosphine catalyst controls the selectivity.[3,4,5] Here we report that selective replacement of either triflate or bromide by Grignard reagents is achieved by use of 1,3-bis(diphenylphosphino)propane (dppp) or 2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (meo-mop) as a ligand in palladium-catalyzed Grignard cross-coupling.[6]

Scheme 1



**a**: Ar = Ph. **b**: Ar = 2-MeC$_6$H$_4$. **c**: Ar = 4-ClC$_6$H$_4$

Effects of phosphine ligands on the reactivity and selectivity were examined in the palladium-catalyzed cross-coupling of 4-bromophenyl triflate (**1**) with phenylmagnesium bromide (Scheme 1). It was found that the triflate group in **1** is selectively substituted with phenyl group in the presence of palladium catalysts coordinated with bisphosphines. Of the bisphosphine complexes, $PdCl_2$(dppp) was most selective and catalytically active.[7] Thus, the reaction of **1** (1.0 mmol) with phenylmagnesium bromide (1.2 mmol) in the presence of lithium bromide (1.0 mmol) and $PdCl_2$(dppp) (0.05 mmol) in ether (0.4 mL) at 0 °C for 30 min gave 97% yield of 4-bromobiphenyl (**2a**) together with a small amount (3%) of *p*-terphenyl (**4a**) (entry 1 in Table 1). None of the 4-biphenyl triflate (**3a**), which would be formed by phenylation of bromide in **1**, was detected. In the absence of

Table 1. Cross-coupling of 4-bromophenyl triflate (**1**) with phenylmagnesium bromide in the presence of palladium-phosphine complexes[a]

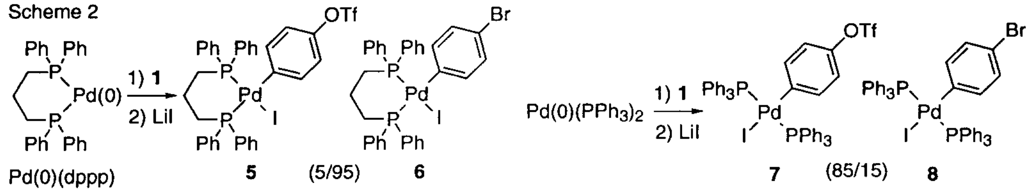
| entry | catalyst | additive | conditions temp (°C) | conditions time (h) | rec **1** | yield (%)[b] of **2a** | **3a** | **4a** |
|---|---|---|---|---|---|---|---|---|
| 1 | $\mathrm{PdCl_2(dppp)}$ | LiBr | 0 | 0.5 | 0 | 97 | 0 | 3 |
| 2 | $\mathrm{PdCl_2(dppp)}$ | – | 0 | 2 | 24 | 74 | 0 | 1 |
| 3 | $\mathrm{PdCl_2(dppe)}$ | LiBr | 0 | 2 | 40 | 59 | 0 | 0 |
| 4 | $\mathrm{PdCl_2(dppb)}$ | LiBr | 0 | 2 | 5 | 96 | 1 | 0 |
| 5 | $\mathrm{PdCl_2(dppf)}$ | LiBr | 0 | 2 | 40 | 46 | 4 | 7 |
| 6 | $\mathrm{PdCl_2(PPh_3)_2}$ | LiBr | 0 | 2 | 81 | 5 | 14 | 2 |
| 7 | $\mathrm{PdCl_2(PPh_3)_2}$[c] | LiBr | 20 | 2 | 30 | 16 | 35 | 7 |
| 8 | $\mathrm{PdCl_2(PPh_3)_2}$[c] | – | 20 | 2 | 3 | 9 | 43 | 11 |
| 9 | $\mathrm{PdCl_2(P(}o\mathrm{\text{-}tol)_3)_2}$[c] | – | 20 | 2 | 55 | 0 | 23 | 2 |
| 10 | $\mathrm{PdCl_2(meo\text{-}mop)_2}$[c] | LiBr | 20 | 2 | 19 | 2 | 62 | 10 |
| 11 | $\mathrm{PdCl_2(meo\text{-}mop)_2}$[c] | – | 20 | 2 | 6 | 0 | 68 | 4 |

[a] The cross-coupling was carried out with 1.2 equiv of the Grignard reagent in the presence or absence of 1 equiv of lithium bromide and 5 mol % of catalyst in ether unless otherwise noted. [b] Isolated yield by silica gel preparative TLC. 4-Bromobiphenyl (**2a**) was obtained as a mixture with a small amount of biphenyl, and the yield of **2a** was calculated on the basis of GLC and $^1$H NMR analyses of the mixture. [c] With 2.0 equiv of the Grignard reagent.

lithium bromide, the cross-coupling was slower but the selectivity in forming **2a** was still high[8,9,10] (entry 2), indicating that lithium bromide is not responsible for the high triflate-selectivity. Palladium complexes coordinated with 1,2-bis(diphenylphosphino)ethane (dppe) and 1,4-bis(diphenylphosphino)butane (dppb) also catalyzed the substitution of triflate forming **2a** with high selectivity, though the reaction is slower than that catalyzed by $\mathrm{PdCl_2(dppp)}$ (entries 3 and 4). Use of monodentate phosphine ligands reversed the selectivity, **1** undergoing the cross-coupling at bromide site to give 4-biphenyl triflate (**3a**) preferentially. The selectivity forming **3a** is not so high with triphenylphosphine complex, which gave 43% of **3a** together with 9% of **2a** at highest selectivity. (entries 6–8). The selectivity and catalytic activity were improved by use of sterically more bulky phosphine ligands. Highest yield forming **3a** was 68%, which was observed in the reaction catalyzed by $\mathrm{PdCl_2(meo\text{-}mop)_2}$[11,12] (entry 11).

The selective substitution of either triflate or bromide in the Grignard cross-coupling should be determined at oxidative addition step in the catalytic cycle. The effects of phosphine ligands on the selectivity at the oxidative addition step were demonstrated in a stoichiometric reaction of palladium(0) phosphine complexes with 4-bromophenyl triflate (**1**) (Scheme 2). Thus, a palladium(0) species coordinated with bisphosphine dppp, which was generated by treatment of a mixture of $\mathrm{[PdCl(\pi\text{-}C_3H_5)]_2}$ and dppp (1 equiv to Pd) with one equiv of dimethyl sodiomalonate in THF, was allowed to react with **1** at 0 °C for 1 h. Anion exchange by addition of

Scheme 2



excess lithium iodide to the reaction mixture gave 60% yield of the palladium(II) complexes, PdI(Ar)(dppp),[13] where Ar group consists of 4-trifluoromethanesulfonyloxyphenyl (**5**) and 4-bromophenyl (**6**) in a ratio of 5 to 95, indicating that triflate group participated in the oxidative addition preferentially. Structures of **5** and **6** were assigned by comparison with authentic samples prepared by reaction of the Pd(0)–dppp with 4-iodophenyl triflate and 4-iodophenyl bromide, respectively. Reverse selectivity was observed in the oxidative addition of **1** to a palladium(0) complex coordinated with triphenylphosphine, which gave palladium(II) complexes (69% yield) containing 4-trifluoromethanesulfonyloxyphenyl (**7**) and 4-bromophenyl (**8**) in a ratio of 85 to 15.[14] The oxidative addition shown above is the first example of successful control of the leaving group-selectivity by a proper choice of phosphine ligand on palladium.

The selective substitution of triflate group on **1** was also observed in the cross-coupling with 2-methylphenyl and 4-chlorophenyl Grignard reagents in the presence of $PdCl_2(dppp)$ as a catalyst to give over 90% yield of the corresponding monoarylation products, **2b** and **2c**, respectively (Table 2, entries 1 and 2). Aromatic compounds **9a-e**, which contain both triflate and bromide on benzene, naphthalene, or biphenyl skeleton, also underwent the selective substitution of the triflate group (Scheme 3). Replacement of triflate by phenyl took place with high selectivity in the reaction with phenylmagnesium bromide in the presence of $PdCl_2(dppp)$, bromide remaining intact (entries 3–7).

Scheme 3

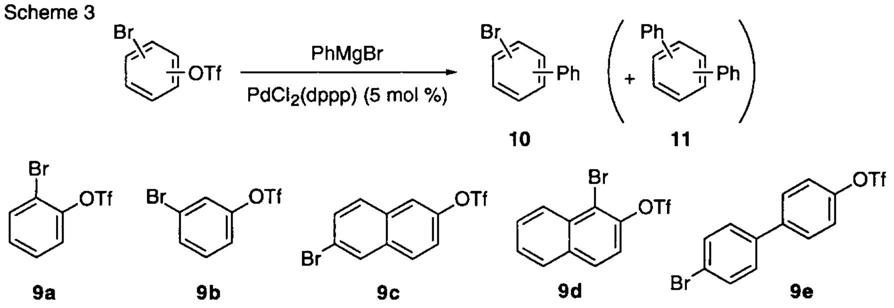


Table 2. Cross-coupling of bromoaryl triflates **1** and **9** with Grignard reagents in the presence of $PdCl_2(dppp)$[a]

| entry | triflate | Ar in ArMgBr (equiv) | conditions temp (°C) | time (h) | yield (%)[b] of coupling products[c] | |
|---|---|---|---|---|---|---|
| 1 | **1** | 2-$MeC_6H_4$ (1.5) | 0 | 2 | 91 (**2b**) | 3 (**4b**) |
| 2 | **1** | 4-$ClC_6H_4$ (1.3) | 0 | 2 | 95 (**2c**) | 3 (**4c**) |
| 3 | **9a** | Ph (1.5) | 20 | 12 | 82 (**10a**) | 2 (**11a**) |
| 4 | **9b** | Ph (1.3) | 0 | 2 | 92 (**10b**) | 4 (**11b**) |
| 5 | **9c** | Ph (1.3) | 0 | 2 | 92 (**10c**) | 3 (**11c**) |
| 6 | **9d** | Ph (2.0) | 30 | 24 | 84 (**10d**) | 2 (**11d**) |
| 7 | **9e** | Ph (1.5) | 0 | 1 | 99 (**10e**) | 0 (**11e**) |

[a] All reactions were carried out in the presence of 1 equiv of lithium bromide and 5 mol % of $PdCl_2(dppp)$. [b] Isolated yield by silica gel preparative TLC. In entries 1-6, cross-coupling products **2** and **10** were obtained as a mixture with a small amount of biphenyls formed by homo-coupling of the Grignard reagents, and the yields were calculated on the basis of GLC and $^1H$ NMR analyses of the mixture. [c] No arylated triflates, which would result from monosubstitution of bromide, were detected.

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13. $PdI(4\text{-}TfOC_6H_4)$(dppp) (**5**): $^1H$ NMR ($CDCl_3$, 500 MHz): δ 1.91 (m, 2 H), 2.42 (m, 2 H), 2.55 (m, 2 H), 6.49 (dd, *J*(H,H) = 8.3, *J*(H,P) = 1.5 Hz, 2 H), 6.98 (ddd, *J*(H,H) = 8.3, *J*(H,P) = 7.8, *J*(H,P) = 2.0 Hz, 2 H), 7.16-7.46 (m, 16 H), 7.78 (m, 4 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 109 MHz): δ -9.59 (d, *J* = 52.5 Hz, 1 P), 10.85 (d, *J* = 52.5 Hz, 1 P). $PdI(4\text{-}BrC_6H_4)$(dppp) (**6**): $^1H$ NMR ($CDCl_3$, 500 MHz): δ 1.90 (m, 2 H), 2.41 (m, 2 H), 2.53 (m, 2 H), 6.66 (dd, *J*(H,H) = 8.4, *J*(H,P) = 2.0 Hz, 2 H), 6.76 (ddd, *J*(H,H) = 8.4, *J*(H,P) = 7.8, *J*(H,P) = 2.0 Hz, 2 H), 7.16-7.45 (m, 16 H), 7.79 (m, 4 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 109 MHz): δ -9.40 (d, *J* = 52.5 Hz, 1 P), 11.17 (d, *J* = 52.5 Hz, 1 P).
14. *trans*-$PdI(4\text{-}TfOC_6H_4)(PPh_3)_2$ (**7**): $^1H$ NMR ($CDCl_3$, 500 MHz): δ 6.16 (d, *J*(H,H) = 8.5 Hz, 2 H), 6.68 (dt, *J*(H,H) = 8.5, *J*(H,P) = 1.5 Hz, 2 H), 7.25-7.37 (m, 18 H), 7.49-7.54 (m, 12 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 161 MHz): δ 23.26 (s). *trans*-$PdI(4\text{-}BrC_6H_4)(PPh_3)_2$ (**8**): $^1H$ NMR ($CDCl_3$, 500 MHz): δ 6.33 (d, *J*(H,H) = 8.3 Hz, 2 H), 6.42 (dt, *J*(H,H) = 8.3, *J*(H,P) = 2.0 Hz, 2 H), 7.25-7.36 (m, 18 H), 7.49-7.53 (m, 12 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 161 MHz): δ 23.32 (s).

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