# Palladium-Catalyzed Cross-Coupling Reaction of Organobismuth Compounds with Aryl and Alkenyl Chlorides

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*Received 8 June 2004*

**Abstract:** Cross-coupling reactions of hypervalent organobismuth compounds, 6-*tert*-butyl-5,6,7,12-tetrahydrodibenz[*c*,*f*][1,5]azabismocines, with aryl and alkenyl chlorides are efficiently catalyzed by the Pd(OAc)$_2$/dppf [dppf = 1,1′-bis(diphenylphosphino)ferrocene] system.

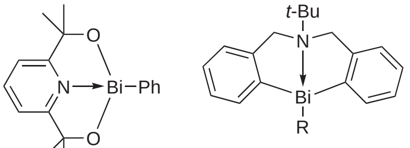
**Key words:** cross-coupling, organometallic reagents, bismuth, palladium, hypervalent

Transition metal-catalyzed cross-coupling reactions of organometallic compounds with organic halides and triflates are one of the most important reactions to make C-C bonds.[1] Recently, enormous development has been achieved in this methodology and a number of active catalyst systems have been developed to enable the efficient coupling of aryl chlorides, which are generally cheaper and more easily available, but less reactive than the corresponding bromides and iodides.[2,3]

We became interested in using organobismuth compounds in organic synthesis because bismuth is a low toxic element and the use of organobismuth compounds in organic synthesis was limited.[4] Recently, we have reported that organobismuth compounds are capable reagents for the cross-coupling reaction with organic triflates, iodides and bromides.[5] In particular, hypervalent organobismuth compounds, 6-*tert*-butyl-5,6,7,12-tetrahydrodibenz[*c*,*f*][1,5]azabismocines,[6] have proved to be highly reactive and recoverable reagents for the cross-coupling reaction with aryl bromides.[5d] Herein, we wish to report the first application of organobismuth compounds to the cross-coupling reaction with aryl and alkenyl chlorides.

The performance of three organobismuth compounds, BiPh$_3$, **1** (Figure 1),[5a,c,7] and **2a** for the cross-coupling reaction with aryl chlorides was evaluated by the reaction with 4-chlorobenzonitrile (**3a**) in the presence of 10 mol% of Pd(PPh$_3$)$_4$ in NMP (NMP = 1-methyl-2-pyrrolidinone) at 100 °C for 12 hours. BiPh$_3$ and **1** afforded the cross-coupled product in very low yields and the addition of CsF showed no improvement (Table 1, entries 1–4). On the other hand, **2a** gave the cross-coupled product in moderate yield and the yield was improved by the addition of CsF (Table 1, entries 5 and 6).

Table 2 shows the representative results of the effect of phosphine ligands on the reaction of **2a** with **3a** and 2-chloronaphthalene (**3b**). The reaction of **2a** with **3a** efficiently proceeded when bidentate phosphines with relatively large bite angles[8] were used (Table 2, entries 1, 2, and 4–6), and 10 mol% of dppf showed the best result. Among monodentate phosphines tested, PCy$_3$ (Cy = cyclohexyl) showed the highest activity (Table 2,

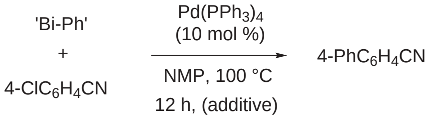


**1**

**2a**: R = Ph
**2b**: R = Me
**2c**: R = -C(CH$_3$)=CH$_2$
**2d**: R = -C≡CPh
**2e**: R = Cl

**Figure 1** Structures of organobismuth compounds **1** and **2a**–**e**

**Table 1** Cross-Coupling Reaction of Organobismuth Compounds, BiPh$_3$, **1**, and **2a** with 4-Chlorobenzonitrile



| Entry | ‘Bi-Ph’ | Additive (equiv) | Yield (%)[a] |
|---|---|---|---|
| 1[b] | BiPh$_3$ | – | 2 |
| 2[b] | BiPh$_3$ | CsF (4) | 0 |
| 3[c] | **1** | – | 6 |
| 4[c] | **1** | CsF (2) | 8 |
| 5[c] | **2a** | – | 66 |
| 6[c] | **2a** | CsF (2) | 82 |

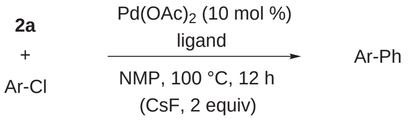
[a] Yields were determined by GC using hexadecane as an internal standard.
[b] BiPh$_3$, 0.13 mmol; ArCl, 0.41 mmol; NMP, 3 mL.
[c] **1** or **2a**, 0.30 mmol; ArCl, 0.25 mmol; NMP, 3 mL.

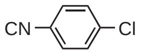
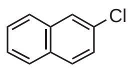
***SYNLETT*** 2004, No. 11, pp 1921–1924
Advanced online publication: 06.08.2004
DOI: 10.1055/s-2004-831298; Art ID: U16604ST

entry 10), which, however, was not as high as the reaction with dppf. P($t$-Bu)$_3$, which is effective for Suzuki–Miyaura and some other cross-coupling reactions,[9] was not very suitable for the reaction of **2a** (Table 2, entries 11–13). For the less reactive **3b**, cross-coupled product was obtained in a moderate yield when dppf was used and the addition of CsF (2 equiv) considerably improved the yield (Table 2, entries 14, 15). $Ph_2P(CH_2)_4PPh_2$ and $Ph_2P(CH_2)_5PPh_2$ were less efficient than dppf for the reaction of **3b** (Table 2, entries 16, 17).

Table 3 summarizes the scope and limitation of the cross-coupling reaction of 6-*tert*-butyl-5,6,7,12-tetrahydrodibenz[*c*,*f*][1,5]azabismocines with aryl and alkenyl chlorides catalyzed by the Pd(OAc)$_2$–dppf system.[10] Phenyl compound **2a** and methyl compound **2b** efficiently reacted with electron-deficient and -neutral aryl chlorides in the absence (Table 3, entries 1, 2 and 10–15) or in the presence of CsF (Table 3, entries 6, 7), while **2a** did not react with a deactivated aryl chloride, 4-chlorotoluene, efficiently (Table 3, entry 16). Pyridyl, thienyl and alkenyl chlorides also smoothly coupled with **2a** (Table 3, entries 17–21). Isopropenyl compound **2c** also reacted with **3a** and **3b** under the same reaction conditions as those for **2a** and **2b**, although the yields were moderate (Table 3, entries 3 and 8). On the other hand, phenylethynyl compound **2d** is much less reactive than **2a**–**c** and required the addition of CsF and higher reaction temperature even in the reaction with **3a** (Table 3, entry 4) and did not give the cross-coupled product in the reaction with **3b** (Table 3, entry 9).

**Table 2** Effect of Phosphine Ligands on the Cross-Coupling Reaction of **2a** with Aryl Chlorides



| Entry | ArCl | Ligand (mol%) | CsF | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  | dppf (20) | No | 88 |
| 2 | | dppf (10) | No | 93 |
| 3 | | $Ph_2P(CH_2)_2PPh_2$ (10) | No | 25 |
| 4 | | $Ph_2P(CH_2)_3PPh_2$ (10) | No | 85 |
| 5 | | $Ph_2P(CH_2)_4PPh_2$ (10) | No | 90 |
| 6 | | $Ph_2P(CH_2)_5PPh_2$ (10) | No | 92 |
| 7 | | $PPh_3$ (40) | No | 41 |
| 8 | | P($o$-tolyl)$_3$ (40) | No | Trace |
| 9 | | P(2-furyl)$_3$ (40) | No | Trace |
| 10 | | P(Cy)$_3$ (40) | No | 72 |
| 11 | | P($t$-Bu)$_3$ (40) | No | 13 |
| 12 | | P($t$-Bu)$_3$ (30) | No | 60 |
| 13[b] | | P($t$-Bu)$_3$ (20) | No | 24 |
| 14 |  | dppf (10) | No | 66 |
| 15 | | dppf (10) | Yes | 93 |
| 16 | | $Ph_2P(CH_2)_4PPh_2$ (10) | Yes | 65 |
| 17 | | $Ph_2P(CH_2)_5PPh_2$ (10) | Yes | 10 |

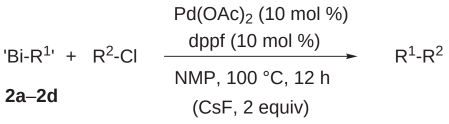
[a] Yields were determined by GC using hexadecane as an internal standard.
[b] $Pd_2(dba)_3$ (5 mol%) was used instead of Pd(OAc)$_2$.

As reported previously,[5d] the cyclic 5,6,7,12-tetrahydrodibenz[*c*,*f*][1,5]azabismocine structure is stable and the bismuth compound can be recovered almost quantitatively as chloride **2e**, which can easily be converted to **2a**–**d** and reused.[6c,10]

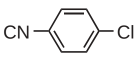
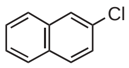
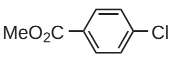
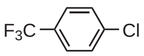
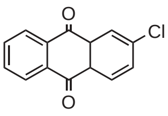
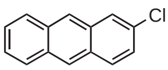
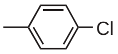
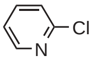
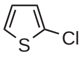
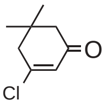
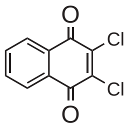
Figure 2 shows a plausible reaction mechanism of the present cross-coupling reaction. The cross-coupling reaction of **2** seems to follow a typical reaction cycle of the cross-coupling reaction of organometallic compounds with organic halides and triflates like the cross-coupling reaction of 1.

In order to gain information on the cause of the reactivity difference among BiPh$_3$, **1**, and **2**, the following two sets of experiments were carried out. The first was the reaction of these Bi-Ph compounds with $(Ph_3P)_2PdCl(C_6H_4CN)$,[11] which is associated with path (ii) in Figure 2. The yield of 4-biphenylcarbonitrile after heating in DMF-$d_7$ at 100 °C for one hour in the presence of two equivalents of PPh$_3$ was 44%, 59%, and quantitative, respectively, for BiPh$_3$, **1**, and **2a**, suggesting the exceptionally high reactivity of **2a**. The other set of experiments was intended to examine the possible Bi-C oxidative addition, which is envisioned to lead to catalyst decomposition [path (iv), Figure 2]. The $^{31}$P NMR spectrum of a 1:1 mixture of BiPh$_3$, **1** or **2a** and Pd(PPh$_3$)$_4$ in DMF-$d_7$ revealed the palladium species decomposing upon heating at 100 °C, the rate being in the order BiPh$_3$>**1**>**2a**.[12] In this set of experiments, we were unable to detect the species coming from Bi-C oxidative addition with Pd(PPh$_3$)$_4$. However, the oxidative addition of Bi-C bonds of **1** and **2a** towards a Pt(0) complex does take place, **1** being much more reactive than **2a**.[13] We presume that the decomposition of Pd(PPh$_3$)$_4$ is triggered by Bi-C oxidative addition to Pd(0), which is probably reversible and can be competitive with the desired oxidative addition of C-Cl bonds. On the basis of these experiments, we conclude that the higher efficiency of **2a** probably results from (1) the higher ability to transfer the organic group on the bismuth atom in the transmetallation step [path (ii), Figure 2] and (2) the lower ability of the Bi-C bond for oxidative addition to the Pd(0) species that leads to the decomposition of the catalyst [path (iv), Figure 2].

**Table 3** Cross-Coupling Reaction of **2a**–**d** with Various Aryl and Alkenyl Chlorides



$$\underset{\textbf{2a–2d}}{\text{'Bi-R}^{1\text{'}}} + \text{R}^2\text{-Cl} \xrightarrow[\substack{\text{NMP, 100 °C, 12 h}\\ \text{(CsF, 2 equiv)}}]{\substack{\text{Pd(OAc)}_2\text{ (10 mol \%)}\\ \text{dppf (10 mol \%)}}} \text{R}^1\text{-R}^2$$

| Entry | 2a–d | R$^2$-Cl | CsF | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **2a** |  | No | Quant. |
| 2 | **2b** | | No | (92) |
| 3 | **2c** | | No | 62 |
| 4[b] | **2d** | | Yes | 58 |
| 5 | **2a** |  | No | 66 |
| 6 | **2a** | | Yes | 93 |
| 7 | **2b** | | Yes | (95) |
| 8 | **2c** | | Yes | (53) |
| 9 | **2d** | | Yes | 0 |
| 10 | **2a** |  | No | 92 |
| 11 | **2a** |  | No | 79 |
| 12 | **2a** |  | No | Quant. |
| 13 | **2b** | | No | 75 |
| 14 | **2a** |  | No | Quant. |
| 15 | **2b** | | No | (99) |
| 16 | **2a** |  | Yes | (10) |
| 17 | **2a** |  | No | 92 |
| 18 | **2a** |  | No | 42 |
| 19 | **2a** | | Yes | 58 |
| 20 | **2a** |  | No | 90 |
| 21[c] | **2a** |  | No | 61[d] |

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[a] Isolated yields. GC yields using hexadecane as an internal standard are shown in parentheses.

[b] Reaction temperature: 120 °C.

[c] 20 mol% of Pd(OAc)$_2$ and dppf were used.

[d] Yield of diphenylated product.

Although the effect of CsF was not clearly understood, coordination of the fluoride anion to the bismuth center may take place, which facilitates the transfer of organic group in the transmetallation step and retards the direct oxidative addition of Bi-C bond to Pd(0) species.

In conclusion, bismuth compounds **2a**–**d** are useful and easily recoverable reagents for the cross-coupling reaction with aryl chlorides. For relatively reactive aryl chlorides, the addition of coordinating additives such as CsF or bases is not necessary, which is often required for the cross-coupling reaction of other organometallic reagents.

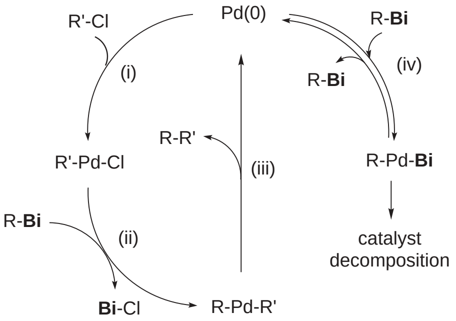

**Figure 2** A plausible mechanism of the reaction of **2a**–**d** with aryl and alkenyl chlorides

## Acknowledgment

This work was partially supported by the Japan Science and Technology Corporation (JST) through the CREST (Core Research for Evolutional Science and Technology) program. O.Y. thanks JST for a postdoctoral fellowship.

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(10) **Typical Procedure:** A mixture of **2a** (161 mg, 0.30 mmol), 4-$CF_3C_6H_4Cl$ (46 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and dppf (14 mg, 0.025 mmol) in 3 mL of NMP was heated at 100 °C for 12 h under $N_2$. The crude mixture was dissolved in EtOAc (90 mL) and washed with aq HCl (4 M, 3 × 10 mL) and $H_2O$ (10 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was separated with a short pad of silica gel, eluting with EtOAc–hexane (1:10) to give a mixture containing cross-coupled product and then with $CH_2Cl_2$–EtOAc (1:1) to give pure **2e** (145 mg, 98%). The former mixture was further purified with PTLC to give 4-trifluoromethylbiphenyl (45 mg, 79%).

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(12) The $^{31}P$ NMR spectrum of each of the mixture at r.t. showed a broad signal suggesting a rapid exchange of coordinated and uncoordinated $PPh_3$. The signals shifted upfield gradually and reached that of free $PPh_3$ after complete decomposition.

(13) (a) Shimada, S.; Tanaka, M. unpublished results.
(b) Oxidative addition of **1** toward $Pt(PEt_3)_3$ takes place even at –50 °C and is complete within 1 h at 0 °C, while that of **2a** toward $Pt(PEt_3)_3$ is slow at r.t. and is not complete, and seems to reach equilibrium at about 60% conversion.