Practical and Convenient Suzuki–Miyaura Coupling Reaction and α-Arylation Using Diphenylcyclopropylphosphine Ligands

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Abstract: A new ligand, diphenylmethylcyclopropylphosphine, has successfully been applied in the palladium-catalyzed Suzuki–Miyaura coupling and α-arylation of ketones with aryl chlorides in moderate to high yields. An asymmetric coupling between anisyl chloride and 2-methylindan-1-one was also tested as the first trial, giving 80% yield and 41% ee with 1 mol% of Pd.

Key words: cross-coupling, halides, ligands, palladium

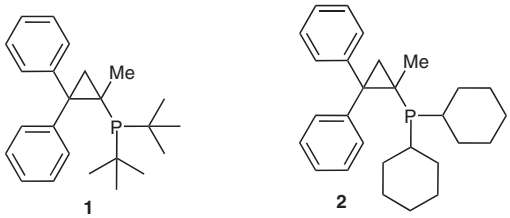

Figure 1 Structures of phosphine ligands

Palladium-catalyzed coupling reactions of aryl halides provide a general route to a wide range of substituted arenes and have often been used as a key reaction for constructing carbon–carbon bonds due to the versatility and reliability.[1] Therefore, much work has been devoted to the development of the coupling reactions.[2–13,15] The previous work has mainly focused on enhancing reactivity toward aryl halides to employ aryl chlorides and sulfonates as coupling partners, and also milder reaction conditions in the various coupling reactions such as Buchwald–Hartwig amination,[2] Suzuki–Miyaura coupling,[3] and α-arylation.[4] Initial work by Hartwig,[5] Buchwald,[6] Fu,[7] Beller,[8] and Nolan[9] showed effective catalyst systems incorporating sterically hindered alkylphosphines or carbene ligands in the coupling reactions. Li,[10] Verkade,[11] and Koie[12] as well as other groups[13] have also studied the coupling reactions with their new systems. Recently, we reported amination of various aryl chlorides using a new diphenylmethylcyclopropylphosphine (**1**)[14] as the ligand, which was designed based on combining two structural characteristics that new phosphine ligands have in common.[15] As part of our continuing efforts to aim at developing practical and convenient coupling reactions, Suzuki–Miyaura coupling and α-arylation of aryl chlorides were attempted. We herein report that ligand **1**/palladium catalyst catalyzes Suzuki–Miyaura coupling and α-arylation. We also report an initial study of asymmetric α-arylation of ketone with aryl chloride using optically pure ligand **2** (Figure 1).

To investigate the performance of phosphine **1**, we first examined its stability, because it is important that it is stable to molecular oxygen and moisture, especially from the industrial perspective. Phosphines **1** and **2** were stable enough to be treated under air. When the solid phosphines were exposed to air for several months, no change was observed. In addition, the purity of a solution of phosphine **1** in toluene was >99% after the solution was stirred at 30 °C for 16 hours, although a trace amount of the phosphine oxide was detected by HPLC (<0.3%). In the case at 50 °C, the purity was >98%.

We next examined Suzuki–Miyaura coupling and α-arylation with ligand **1**. As shown Table 1, the ligand **1**/Pd system was effective in the cross-coupling of various aryl chlorides. For the Suzuki–Miyaura coupling, electron-rich and electron-poor aryl chlorides coupled with arylboronic acids in high yields. In the presence of 0.5 mol% of $[(\pi\text{-allyl})PdCl]_2$ and 2 mol% of ligand **1**, reaction of 4-anisyl and 2,5-dimethoxyphenyl chlorides with arylboronic acids afforded the corresponding biaryls in 96% and 93% yields, respectively (entries 3 and 4). An aryl chloride with an ester group was also a suitable coupling partner (entry 2). In the reaction of sterically hindered substrates, 2,6-dimethylphenyl chloride and 2-tolylboronic acid, although bulky ligand **1** was less effective, use of ligand **2** that had less bulkiness gave a better result with a longer reaction time (entry 5). In the case of phenyl tosylate, the isolated yield was moderate and further optimization of the reaction conditions was needed (entry 6). The catalyst system was also applicable for the reaction of electron-rich aryl chlorides with ketones. The reaction of 4-chloroanisole and 2-chlorotoluene with propiophenones using 1 mol% of Pd selectively proceeded to give the corresponding monoarylated products in 90% and 81% yields, respectively (entries 7 and 8). In the case of 2-methylindan-1-one, the coupling product was obtained in 91% yield (entry 9). However, for arylation of phenyl tosylate, the product was not observed under these conditions (entry 10).

Asymmetric coupling reactions of aryl halides to produce new chiral quaternary carbon centers such as arylation of ketones has attracted much attention. Buchwald's group

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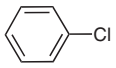
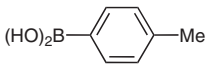
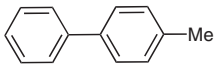
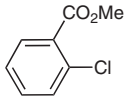
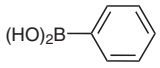
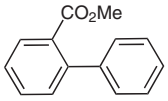
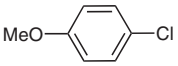
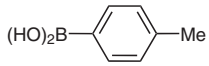
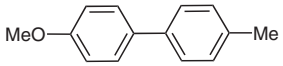
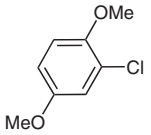
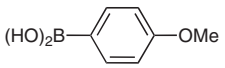
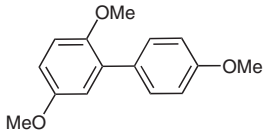
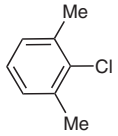
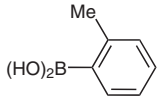
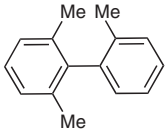
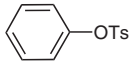
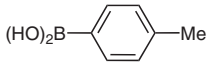
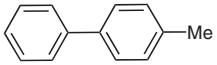
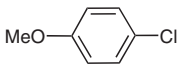
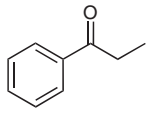
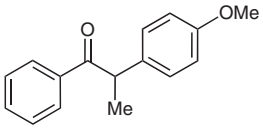
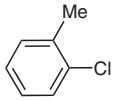
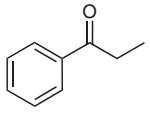
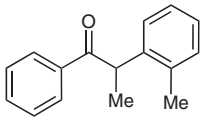
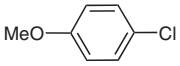
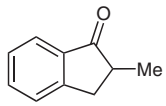
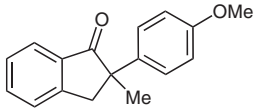
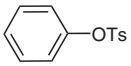
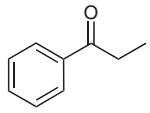
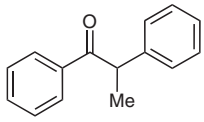
Table 1 Coupling Reactions of Aryl Chlorides and Tosylates with Arylboronic Acids and Ketones[20,21]

Entry	Aryl halide	Coupling partner	Conditions[a]	Product	Yield (%)[b]
1			A		94
2			A		96
3			A		96
4			A		93
5[c]			A		87
6			A		41[d]
7			B		90
8			B		81
9			B		91
10			B		NR

[a] Conditions A: aryl halide (1.0 equiv), arylboronic acid (1.5 equiv), $[(\pi\text{-allyl})PdCl]_2$ (0.5 mol%), ligand **1** (2 mol%), K_2CO_3 (2 equiv), toluene, 80 °C, 3 h. Conditions B: aryl halide (1.0 equiv), ketone (1.1 equiv), $[(\pi\text{-allyl})PdCl]_2$ (0.5 mol%), ligand **1** (2 mol%), NaO*t*-Bu (1.2 equiv), toluene, 80 °C, 16–18 h.

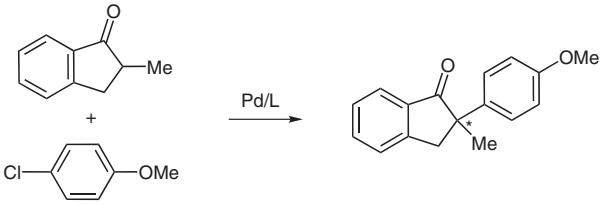
[b] Isolated yield.

[c] Reaction was conducted with ligand **2** as ligand for 8 h.

[d] GC conversion was 47%.

reported asymmetric arylation by an atropoisomeric binaphthylphosphine/Pd system, which enjoyed high enantioselectivity.[16] However, the reaction was mainly limited to the reaction of aryl bromides. Ligands **1**[17] and **2**[18] originally have chiral carbons next to the phosphorus in contrast to achiral phosphine ligands specially designed for coupling reactions of less active aryl halides. We also tried asymmetric arylation with optically pure ligand **2**,[19] which was obtained by optical resolution of the racemic oxide by HPLC and subsequent reduction. Under the same conditions, the reaction of 4-anisyl chloride with indanone gave the coupling product in 80% yield and with 41% ee (Equation 1). Although the high yield was obtained, it was ineffective for good enantioselectivity. We believe this study would lead to the next step of these ligands.

In conclusion, we demonstrated that, with diphenylmethylcyclopropylphosphines as the ligand, practical and effective Suzuki–Miyaura coupling and α-arylation of ketones including asymmetric reaction can take place. Further improvements are now under investigation.



Equation 1 Asymmetric coupling of 2-methylindanone and 4-anisyl chloride

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(14) As a series of BRIDPs, ligands **1** and **2** are commercially available from Strem Chemicals, Inc. and Sigma-Aldrich.

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(16) (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Paluchi, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (c) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.

(17) For optically pure phosphine **1**, it is now under investigation.

(18) Phosphine ligand **2** was prepared with the same manner as ligand **1**, see ref. 15a. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99–1.40 (m, 11 H), 1.01 (d, *J* = 1.7 Hz, 3 H), 1.55–1.93 (m, 13 H), 7.00 (t, *J* = 7.6 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 2 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 7.28–7.37 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4 (d, *J* = 4.4 Hz), 23.9 (d, *J* = 17.1 Hz), 26.52, 26.54, 27.0 (d, *J* = 12.6 Hz), 27.36, 27.44 (d, *J* = 3.9 Hz), 27.9 (d, *J* = 4.0 Hz), 28.3 (d, *J* = 15.5 Hz), 29.5, 30.1 (d, *J* = 8.9 Hz), 31.8 (d, *J* = 20.1 Hz), 32.7 (d, *J* = 15.5 Hz), 34.2 (d, *J* = 25.3 Hz), 34.6 (d, *J* = 15.8 Hz), 40.6 (d, *J* = 10.9 Hz), 125.9, 126.1, 127.9, 128.2, 129.8 (d, *J* = 2.5 Hz), 130.3 (d, *J* = 1.3 Hz), 143.8 (d, *J* = 8.8 Hz), 143.9. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 11.21. ESI-HRMS: *m/z* calcd for $C_{28}H_{37}P$ [M + Na]$^+$: 427.2531; found [M + Na]$^+$: 427.2534.

(19) Optically pure phosphine **2** was prepared by oxidation of phosphine with H_2O_2, HPLC resolution and the following reduction by Cl_3SiH.

Oxidation of Phosphine Ligand 2

H_2O_2 (30% in H_2O, 1.26 g, 11.1 mmol) was added dropwise to a solution of phosphine **2** (3.00 g, 7.42 mmol) in toluene (15 mL) at 0 °C. After the mixture was stirred at 35 °C for 2 h, an organic phase was separated, washed with 20% aq Na_2SO_3 and H_2O, dried over anhyd $MgSO_4$, and concentrated under reduced pressure to give a crude oxide (3.14 g, quantitative yield) as a white solid. The crude was used for chiral resolution without further purification. ^{1}H

NMR (500 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 11.8 Hz, 3 H), 1.15–1.32 (m, 7 H), 1.33–2.23 (m, 16 H), 2.52 (dd, *J* = 4.7, 12.9 Hz, 1 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 7.14–7.21 (m, 3 H), 7.24–7.32 (m, 2 H), 7.39–7.50 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.9, 20.0, 23.51, 23.53, 23.9, 24.5, 25.36, 25.40, 25.91, 25.95, 25.98, 26.11, 26.12, 26.25, 26.3, 26.6, 26.7, 27.28, 27.34, 27.37, 27.44, 27.53, 27.55, 28.37, 28.39, 35.4, 35.9, 38.8, 39.3, 40.46, 40.48, 126.1, 126.4, 127.6, 128.5, 129.6, 129.9, 141.64, 141.66, 143.4 (observed complexity due to P–C splitting). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 49.88. ESI-HRMS: *m/z* calcd for $C_{28}H_{37}PO$ [M + H]$^+$: 241.2660; found [M + H]$^+$: 241.2656.

HPLC Resolution of Racemic Oxide of Phosphine 2

The optically pure oxide was obtained by HPLC resolution with a Chiralcel OD-H column (250 mm × 20 mm, hexane–2-PrOH = 96:4, flow rate = 10 mL/min).

Reduction of Oxide of Phosphine 2

Under a nitrogen atmosphere, $SiCl_3H$ (2.26 g, 16.7 mmol) was added dropwise to a solution of optically pure phosphine oxide (1.00 g, 2.38 mmol) and *N*,*N*-dimethylaniline (2.31 g, 19.0 mmol) in xylene (16 mL) at 85 °C. After stirring at 115 °C for 1.5 h, remaining $SiCl_3H$ was removed from the reaction solution by distillation. The solution was washed with 20% aq NaOH and H_2O, dried over anhyd $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by recrystallization from toluene (1.5 mL) and MeOH (6 mL) to give the optically pure phosphine **2** as a white solid (0.49 g, 51%).

(20) **Typical Procedure for the Coupling Reaction of Aryl Halides with Arylboronic Acids**

A solution of powdered K_2CO_3 (2.0 equiv), [(π-allyl)PdCl]$_2$ (0.5 mol%) and ligand (2.0 mol%) in toluene (0.5 M) was stirred for 15 min at r.t. Arylboronic acid (1.5 equiv) and aryl halide (1.0 equiv) were added to the premixed solution. The mixture was stirred at 80 °C for the time specified. After cooling to r.t., the reaction solution was diluted with toluene, washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the concentrate by column chromatography on SiO_2 gave the coupling product.

4-Methoxy-4′-methylbiphenyl (Table 1, Entry 3)

Purification by flash chromatography (hexane–toluene = 2:1) gave a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 3.84 (s, 3 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.50 (d, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 55.3, 114.1, 126.6, 127.9, 129.4, 133.7, 136.3, 138.0, 158.9.

(21) **Typical Procedure for the Coupling Reaction of Aryl Halides with Ketones**

A solution of NaO*t*-Bu (1.2 equiv), [(π-allyl)PdCl]$_2$ (0.5 mol%) and ligand (2.0 mol%) in toluene (0.5 M) was stirred for 15 min at r.t. Aryl halide (1.0 equiv) and ketone (1.1 equiv) were added to the solution. The mixture was stirred at 80 °C for the time specified. After cooling to r.t., the reaction solution was diluted with toluene, washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the concentrate by column chromatography on SiO_2 gave the coupling product.

2-(4-Methoxyphenyl)propiophenone (Table 1, Entry 7)

Purification by flash chromatography (hexane–EtOAc = 8:1) gave a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.9 Hz, 3 H), 3.75 (s, 3 H), 4.64 (q, *J* = 6.9 Hz, 1 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.33–7.41 (m, 2 H), 7.42–7.51 (m, 1 H), 7.90–7.98 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 46.9, 55.2, 114.4, 128.4, 128.7, 128.8, 132.7, 133.5, 136.5, 158.5, 200.5.