Versatile Suzuki–Miyaura Coupling Reaction Using Diphenylvinylphosphine Ligands

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Abstract: The scope of the utility of diphenylvinylphosphine ligands has been extended to include the Suzuki–Miyaura coupling reaction. A catalyst composed of phosphines and palladium efficiently mediates the reactions of a variety of aryl halides with arylboronic acids to afford the corresponding biphenyls in good to excellent yields.

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

The Suzuki-Miyaura coupling reaction of aryl halides with arylboronic acids is one of the most convenient and useful tools for carbon-carbon bond formation affording aromatic compounds such as unsymmetrical biaryls.¹ There has been a considerable interest in the coupling, since the C–C bond formation is often used in a key step in processes for pharmaceuticals, fine chemicals and new materials. The coupling generally shows promise giving the desired coupling products with high yields and selectivity from starting materials having a wide range of functional groups. In addition, a recent advance was the emergence of new supporting ligands, which greatly enhanced the range of applicable aryl halides. Among the ligands, bulky phosphines especially impacted the coupling chemistry.^{2,3} The representative examples include tris-tert-butylphosphine by Fu⁴ and diadamantyl phosphines by Beller,⁵ biaryl-based phosphines by Buchwald,⁶ and pentaphenylated ferrocenyl phosphines by Hartwig.⁷ The increased electron density of the phosphines facilitates the oxidative addition and allows the use of otherwise inactive aryl chlorides.⁸



Figure 1 Structure of diphenylvinylphosphines

While various phosphines have been developed, we have also reported a new class of ligands, 2,2-diphenylvinylphosphines 1a-c (Figure 1), which are effective for ar-

SYNLETT 2007, No. 20, pp 3206–3208 Advanced online publication: 21.11.2007 DOI: 10.1055/s-2007-992371; Art ID: U08407ST © Georg Thieme Verlag Stuttgart · New York omatic amination of aryl bromides and chlorides.⁹ The ligands have appropriate steric bulk and electron-richness as those mentioned, and an interaction between a palladium center and the *cis*-phenyl group on the ligands gives the catalyst the stability in the reaction as reported by Buchwald.⁶ In the course of our study, application of the ligands to Suzuki–Miyaura coupling was attempted due to our strong ongoing interest. In this communication, we report the Suzuki–Miyaura coupling of various aryl halides using the ligands **1a–c**.^{10,11}

We first examined the coupling of 4-bromoanisole with phenylboronic acid in the presence of 2 mol% of ligand 1b and 1 mol% of $Pd(OAc)_2$.¹² The reaction was successfully carried out in 2.5 hours to afford 4-methoxybiphenyl in 92% isolated yield (Table 1, entry 1). When 0.1 mol% and 0.02 mol% of Pd were used, the yields were 89% and 80%, respectively. The effect of substituents was investigated with various aryl halides and arylboronic acids. In entries 2–4, the reaction of aryl bromides with electronrich and -poor substituents proceeded smoothly to give the corresponding biphenyls in excellent yields, whereas coupling of sterically hindered 2-bromo-1,3,5-trimethylbenzene with 2-tolylboronic acid was slightly less effective (entry 5). Under the same condition, aryl chlorides were examined in entries 6-10. Substrates with functional groups sensitive to basic conditions such as ester and nitrile were applicable to the reaction, and the corresponding coupling products were obtained in high yields (entries 6–8). In the reaction of electron-rich substrates, 4-anisyl and 2-tolyl chlorides effectively coupled with arylboronic acids with 87% and 93% yields, respectively (entries 9 and 10). We also examined aryl triflates. Coupling of 4-anisyl and 2,5-dimethylphenyl triflates with arylboronic acids successfully completed to afford the products in excellent yields (entries 11 and 12). These results show that the ligand is versatile not only for amination but also for the Suzuki-Miyaura coupling.

Chemoselective monocoupling of dihaloarene is of interest because the products could be scaffolds for subsequent reactions. We conducted reactions of *p*-bromoiodo- and *p*-bromochlorobenzene with anisylboronic acid using the ligand **1a**/Pd system under the same condition as listed in Table 1. In the coupling of bromoiodobenzene, anisylboronic acid selectively coupled at the position of the iodo group to give the corresponding bromobiaryl in 84% yield. On the other hand, in the case of bromochloroben-

Table 1 Coupling of Aryl Halides with Arylboronic Acids^a

ntry	Aryl halide	Arylboronic acid	Time (h)	Yield (%) ^b
1 ^{c,d}	MeO	(HO) ₂ B	2.5	92
2	Br	(HO) ₂ B	2.5	96
3	MeO ₂ C-Br	(HO) ₂ B	2.0	92
4	CO ₂ Me Br	(HO) ₂ B-Me	1.0	93
5	Me Me Me	(HO) ₂ B	2.0	84
5		(HO) ₂ B	2.0	99
,	CO ₂ Me	(HO) ₂ B-Me	2.0	85
3	CI_N_CI	(HO) ₂ B-OMe	2.5	93
e	MeO-CI	(HO) ₂ B	3.0	87
)	Me Cl	(HO) ₂ B	3.0	93
	MeO-OTf	(HO) ₂ B	3.0	96
2	Me OTf	(HO) ₂ B	3.0	99

^a Reaction conditions: aryl halide (1 equiv), arylboronic acid (1.2 equiv), Pd(OAc)₂ (1 mol%), ligand **1a** (2 mol%), KF (2 equiv), toluene, 80 °C. ^b Isolated yields.

^c When the reaction was performed with Pd(OAc)₂ (0.1 mol%) and ligand **1a** (0.2 mol%) at 80 °C for 3 h, the yield was 89%.

^d When the reaction was performed with Pd(OAc)₂ (0.02 mol%) and ligand **1a** (0.04 mol%) at 80 °C for 48 h, the yield was 80%.

^e A 1:1 complex of $[(\pi-allyl)PdCl]_2$ and ligand **1c** was used as catalyst.

zene, chlorobiaryl was selectively obtained in 91% yield (Equation 1).

In conclusion, we have demonstrated the Suzuki–Miyaura coupling using the catalyst system composed of 2,2-diphenylvinylphosphines and the palladium species, which was applicable to various aryl halides. In the reac-



Equation 1 Coupling of 1,4-dihaloarenes

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tion of dihaloarenes, the catalyst selectively afforded the corresponding monohalobiaryl in high yields.

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- (10) For the preparation of **1b** and **1c**, see ref. 9. Representative Procedure for the Preparation of 1a: A solution of 2-bromo-1,1-diphenylpropene⁹ (25.0 g, 91.5 mmol) and magnesium turnings (2.35 g, 96.1 mmol) in THF (100 mL) was stirred at r.t. under a nitrogen atmosphere. After addition of a piece of iodine, the solution was refluxed for 2 h. Then chlorodiisopropylphosphine (16.8 g, 109.8 mmol) was added dropwise at the same temperature and the mixed solution was refluxed for 18 h. After cooling to r.t., H_2O was added to the solution and the organic phase was extracted with toluene. The extract was dried over anhyd MgSO₄ and concentrated under reduced pressure. The concentrate was purified by recrystallization from MeOH (100 mL) to give the title compound (18.8 g, 66%) as a white solid. ¹H NMR (300 MHz, CDCl₃): $\delta = 1.07$ (dd, J = 2.0, 7.1Hz, 6 H), 1.12 (dd, J = 5.7, 6.3 Hz, 6 H), 1.80–2.04 (m, 2 H), 1.86 (d, J = 2.1 Hz, 3 H), 7.08–7.33 (m, 10 H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 17.2$ (d, J = 4.6 Hz), 20.8 (d, J = 1.1 Hz), 21.0 (d, J = 8.0 Hz), 24.4 (d, J = 14.3 Hz), 126.4, 126.5, 127.5, 128.1, 128.6, 130.2 (d, J = 3.5 Hz), 133.4 (d, J = 21.8 Hz), 143.5 (d, J = 8.6 Hz), 143.9 (d, J = 10.3 Hz), 155.3 (d, J = 32.0 Hz). ³¹P NMR (121 MHz, CDCl₃): $\delta = 5.44$. HRMS (ESI): $m/z [M + H]^+$ calcd for C₂₁H₂₇P: 311.1929; found: 311.1916.
- (11) Ligands **1a–c** are solids stable enough to moisture and oxidation by molecular oxygen that they could be to be handled under air.
- (12) **Typical Procedure for the Coupling Reaction:** Aryl halide (1.0 equiv) and arylboronic acid (1.2 equiv) were added to a solution of KF (2.0 equiv), Pd(OAc)₂ (1.0 mol%) and ligand (2.0 mol%) in toluene (0.5 M) at r.t. under a nitrogen atmosphere. The solution was stirred at 80 °C for 1–3 h. After cooling to r.t., the solution was diluted with toluene, washed with H₂O and brine, dried over anhyd MgSO₄ and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography to give the coupling products. **4-Methoxybiphenyl (Table 1, entry 1)**: ¹H NMR (200 MHz, CDCl₃): δ = 3.85 (s, 3 H), 7.04–6.93 (m, 2 H), 7.60–7.23 (m, 7 H). ¹³C NMR (50 MHz, CDCl₃): δ = 55.3, 114.2, 126.6, 126.7, 128.1, 128.7, 133.8, 140.8, 159.1.

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