

Palladium Charcoal-Catalyzed Suzuki–Miyaura Coupling To Obtain Arylpyridines and Arylquinolines

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A phosphine ligand, such as PPh₃ or 2-(dicyclohexylphosphino)biphenyl, is essential for the Pd/C-catalyzed Suzuki–Miyaura coupling of halopyridines and haloquinolines, although it has been reported that the reaction of phenyl chlorides can be catalyzed by nonpre-reduced Pd/C without any additives. In the reactions of bromopyridines, bromoquinolines, 2-chloropyridines, and 2-chloroquinolines, PPh₃ was effective enough to provide coupling products in good yields. However, in the reactions of 3-chloropyridine, 4-chloropyridine, and 6-chloroquinoline, sterically hindered 2-(dicyclohexylphosphino)biphenyl was indispensable as a ligand.

Introduction

Suzuki–Miyaura coupling is a well-known synthetic tool for C–C bond formation.¹ This reaction has often been used to obtain a wide variety of biaryl compounds, which are used in pharmaceuticals, herbicides, and light-emitting materials. In such cases, homogeneous palladium complexes are generally used as a catalyst. However, the reaction with a heterogeneous catalyst such as Pd/C has also recently been investigated.² Compared to air-sensitive and expensive homogeneous palladium catalysts, palladium charcoal can be safely handled and removed from the reaction mixture by simple filtration. The recovered palladium charcoal can be purified and reused as palladium metal. These features are great advantages in an industrial process.

In 1994, the Roche group reported palladium charcoal-catalyzed Suzuki–Miyaura coupling of phenyl bromides and phenylboronic acids that proceeded without any additives.^{2a} They noted that there were two types of Pd/C, which differed with regard to the degree of the reduction of palladium. One, in which the degree of palladium reduction is low [mainly Pd(II)], is shown as [Pd(II)/C], and the other, in which the degree of palladium reduction is high [mainly Pd(0)], is shown as [Pd(0)/C]. In 2001, Köhler and co-workers successfully coupled phenyl chlorides with an electron-withdrawing

TABLE 1. Yields of Pd/C(0)-Catalyzed Suzuki–Miyaura Coupling with TBAB

| entry | 1 | TBAB (equiv) | 3 | yield (%) ^a |
|-------|---------------------------------------------|--------------|---------------------------------------------|------------------------|
| 1 | 1a : X = 2-Br, R = H | 0 | 3a : Y = 2-Ph, R = H | 21 |
| | | 0.1 | | 67 |
| 2 | 1b : X = 3-Br, R = H | 0 | 3b : Y = 3-Ph, R = H | 54 |
| | | 0.1 | | 85 |
| 3 | 1c : X = 4-Br, R = H ^b | 0 | 3c : Y = 4-Ph, R = H | 55 |
| | | 0.3 | | 67 |
| | | 1.5 | | 95 |
| 4 | 1d : X = 2-Cl, R = 3-NO ₂ | 0 | 3d : Y = 2-Ph, R = 3-NO ₂ | 49 |
| | | 0.1 | | 67 |
| | | 0.3 | | 87 |
| 5 | 1e : X = 2-Cl, R = 5-CN | 0 | 3e : Y = 2-Ph, R = 5-CN | 34 |
| | | 1.5 | | 69 |
| 6 | 1f : X = 2-Cl, R = 5-NO ₂ | 0 | 3f : Y = 2-Ph, R = 5-NO ₂ | 24 |
| | | 0.3 | | 38 |
| | | 1.5 | | 79 |

^a Isolated yield. ^b 4-Bromopyridinium hydrochloride was used as a starting material.

(1) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (d) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213. (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (g) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (h) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (i) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (j) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993.

(2) (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277. (b) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555. (c) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, *7*, 1118. (d) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571. (e) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721. (f) Gala, A.; Stanford, J.; Jenkins, J.; Kugelman, M. *Org. Process Res. Dev.* **1997**, *1*, 163. (g) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248.

group.^{2c} In their paper, the reactive catalyst for Suzuki–Miyaura coupling was characterized by high Pd dispersion (e.g. >50%), a low degree of Pd reduction (no pre-reduction before use), and high water content (>50%). However, there has been no previous report on the Suzuki–Miyaura coupling of heteroaromatic halides with Pd/C. We report here the Suzuki–Miyaura coupling of halopyridines and haloquinolines using Pd/C.

Results and Discussion

First, we examined reactions using Pd(0)/C in the absence of an additive. According to the Roche method, halopyridine **1** was treated with phenylboronic acid (**2**) (1.9 equiv) in the presence of Pd(0)/C (4.5 mol %), using

TABLE 2. Yields of Pd/C(0)-Catalyzed Suzuki–Miyaura Coupling with PPh₃

| entry | substrate | ligand | product | yield (%) ^a |
|-------|---------------------------------------------|------------------|---------------------------------------------|--------------------------|
| 1 | 1a : X = 2-Br, R = H | PPh ₃ | 3a : Y = 2-Ph, R = H | 85 |
| 2 | 1b : X = 3-Br, R = H | PPh ₃ | 3b : Y = 3-Ph, R = H | 90 |
| 3 | 1c : X = 4-Br, R = H ^b | PPh ₃ | 3c : Y = 4-Ph, R = H | 60 |
| 4 | 1d : X = 2-Cl, R = 3-NO ₂ | PPh ₃ | 3d : Y = 2-Ph, R = 3-NO ₂ | 94 |
| 5 | 1e : X = 2-Cl, R = 5-CN | PPh ₃ | 3e : Y = 2-Ph, R = 5-CN | 90 |
| 6 | 1f : X = 2-Cl, R = 5-NO ₂ | PPh ₃ | 3f : Y = 2-Ph, R = 5-NO ₂ | 85 |
| 7 | 1g : X = 2-Cl, R = H | none | 3a : Y = 2-Ph, R = H | no reaction ^d |
| | | PPh ₃ | | 82 |
| 8 | 1h : X = 2-Cl, R = 3-CN | none | 3g : Y = 2-Ph, R = 3-CN | 16 |
| | | PPh ₃ | | quant |
| 9 | 1i : X = 2-Cl, R = 5-CF ₃ | none | 3h : Y = 2-Ph, R = 3-CF ₃ | 30 |
| | | PPh ₃ | | 85 |
| 10 | 4a : X = 2-Cl | None | 6a : Y = 2-Ph | no reaction ^d |
| | | PPh ₃ | | 91 |
| 11 | 4b : X = 3-Br | none | 6b : Y = 3-Ph | no reaction ^d |
| | | PPh ₃ | | 82 |
| 12 | 5 | none | 7 | 36 |
| | | PPh ₃ | | 72 |
| 13 | 1j : X = 2-Cl, R = 6-OMe | PPh ₃ | 3i : Y = 2-Ph, R = 6-OMe | 25 |
| 14 | 1k : X = 2-Cl, R = 3-NH ₂ | PPh ₃ | 3j : Y = 2-Ph, R = 3-NH ₂ | 19 |
| 15 | 1l : X = 3-Cl, R = H | PPh ₃ | 3b : Y = 3-Ph, R = H | 2 |
| 16 | 1m : X = 4-Cl, R = H ^c | PPh ₃ | 3c : Y = 4-Ph, R = H ^b | 9 |
| 17 | 4c : X = 6-Cl | PPh ₃ | 6c : Y = 6-Ph | no reaction |

^a Isolated yield. ^b 4-Bromopyridinium hydrochloride was used as a starting material. ^c 4-Chloropyridinium hydrochloride was used as a starting material. ^d In the reactions without PPh₃, 1.9 equiv of PhB(OH)₂ was used.

Na₂CO₃ (3.7 equiv) as a base in DME–H₂O at 80 °C overnight. The coupling product **3³** was obtained in 21–54% yield {Table 1, entries 1–6 (TBAB 0 equiv)}. To improve the yields of the products, TBAB was added to the reaction, since TBAB has been reported to work effectively.⁴ Although the yields were improved {Table 1, entries 1, 2, and 4 (TBAB 0.1 equiv)}, larger amounts of TBAB were needed depending on the substrate structure {Table 1, entries 3, 5, and 6 (TBAB 1.5 equiv)}.

Second, following the Roche method, 18 mol % of PPh₃ was added to the mixture⁵ of halopyridine **1**, phenylboronic acid (**2**) (1.2 equiv), Pd(0)/C (4.5 mol %), and Na₂CO₃ (3.7 equiv) in DME–H₂O. The reaction mixture was then heated at 80 °C overnight. The reactions of bromopyridines **1a–c**, 2-chloropyridine (**1g**), 2-chloropy-

ridines with an electron-withdrawing group **1d–f**, **1h**, and **1i**, and haloquinoline **4a,b**, proceeded smoothly and gave the products in good yields (Table 2, entries 1–12). However, the reactions of 2-chloropyridines with an electron-donating group **1j,k** gave unsuccessful results (Table 2, entries 13 and 14). In the case of 3-chloropyridine (**1l**) and 4-chloropyridine (**1m**), the yields of the products were extremely low (Table 2, entries 15 and 16).⁶ Furthermore, the reaction did not take place with 6-chloroquinoline (**4c**). The reactivity of the substrate showed the same tendency as was seen in the reaction with a homogeneous catalyst; i.e., chloropyridines with an electron-withdrawing group were more reactive than those with an electron-donating group. Unlike the reported reaction of phenyl chlorides,^{2c} a phosphine ligand was essential for the reaction of halopyridines. It has been reported that the Pd/C-catalyzed Heck reaction is accompanied by a Pd leaching process,⁷ in which Pd leaches into a solution, catalyzes the reaction, and reprecipitates on the charcoal at the end of the reaction. Thus, in Pd/C-catalyzed Suzuki–Miyaura coupling, Pd may also leach into solution and become an active species by interacting with phosphine ligands.⁸

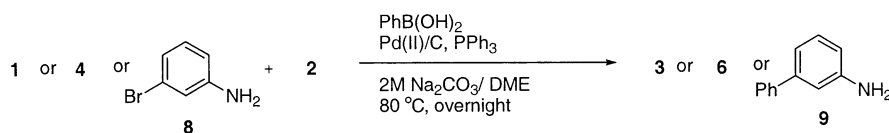
(3) Compounds **3a–c** are commercially available from Tokyo Kasei Kogyo Co., Ltd. Compounds **3d**, **3e**, and **3f** are described in the following citations a, b, and c, respectively. (a) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117. (b) Shiano, M.-J.; Liu, K.-H.; Lin, P.-Y. *Heterocycles* **1993**, *38*, 507. (c) Tohda, Y.; Eiraku, M.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashima, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820.

(4) (a) Ishikura, M.; Kamada, M.; Terashima, M. *Heterocycles* **1984**, *22*, 265. (b) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, *4*, 466. (c) Castant, A.-S.; Colobert, F.; Desmurs, J.-R.; Schlama, T. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 481–487. (d) Botella, L.; Najera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179. (e) Zapf, A.; Beller, M. *Chem. Eur. J.* **2000**, *6*, 1830. (f) Zim, D.; Monterio, A. L.; Dopont, J. *Tetrahedron Lett.* **2000**, *41*, 8199. (g) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

(5) The effects of the molar ratio of Pd and PPh₃ were examined. In the Roche method, the molar ratio of Pd and PPh₃ was 1:4. When the reaction of 2-chloropyridine was carried out in the presence of Pd and PPh₃ at molar ratios of 1:2 and 1:6, the respective yields were 80% and 77%.

(6) Compound **6a** is commercially available from Sigma-Aldrich Co. Compounds **3g**, **3h**, **3i**, **3j**, **6b**, **6c**, and **7** are described in the following reports a, b, c, d, e, f, and g, respectively. (a) Court, J.; Vidal, S.; Bonnier, J.-M. *Bull. Soc. Chem. Fr.* **1972**, 3107. (b) WO 02/02714 A2. (c) Dufournet, R.; Court, J.; Bonnier, J.-M. *Bull. Soc. Chem. Fr.* **1974**, 1112. (d) Jpn. Kokai Tokkyo Koho. JP-H08-310972-A2. (e) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713. (f) Kaslow, C. E.; Hayer, M. *J. Am. Chem. Soc.* **1951**, *73*, 4986. (g) Miller, R. B.; Svoboda, J. *J. Synth. Commun.* **1994**, *24*, 1187.

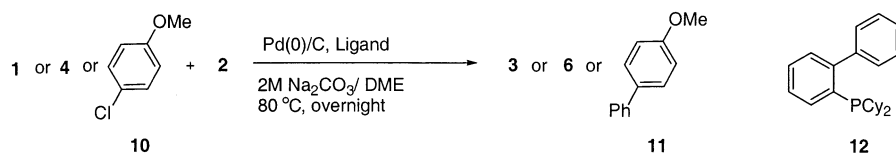
(7) Heidenreich, R.-G.; Krauter, J. G. E.; Pietsch, J.; Köhler, K. J. *Mol. Catal. A: Chem.* **2002**, *182–183*, 499–509.

TABLE 3. Yields of Pd/C(II)-Catalyzed Suzuki–Miyaura Coupling with PPh₃

| entry | substrate | product | yield (%) |
|-------|---------------------------------------------|---------------------------------------------|-----------------|
| 1 | 1j : X = 2-Cl, R = 6-OMe | 3i : X = 2-Ph, R = 6-OMe | 90 |
| 2 | 1k : X = 2-Cl, R = 3-NH ₂ | 3j : X = 2-Ph, R = 3-NH ₂ | 97 |
| 3 | 1l : X = 3-Cl, R = H | 3b : X = 3-Ph, R = H | 2 |
| 4 | 1m : X = 4-Cl, R = H ^a | 3c : X = 4-Ph, R = H | 9 |
| 5 | 4c : X = 6-Cl | 6c : X = 6-Ph | NR ^c |
| 6 | 8 | 9 | 97 ^b |

^a 4-Chloropyridinium hydrochloride was used as a starting material. ^b When Pd(0)/C was used, the yield was 20%. ^c NR = no reaction.

TABLE 4. Ligand Effects on Pd/C(0)-Catalyzed Suzuki–Miyaura Coupling



| entry | substrate | ligand | product | yield (%) |
|-------|-----------------------------|-----------|-----------------------------|-----------------|
| 1 | 1l : X = 3-Cl, R = H | dppp | 3b : X = 3-Ph, R = H | NR ^b |
| 2 | 1l : X = 3-Cl, R = H | dppb | 3b : X = 3-Ph, R = H | NR ^b |
| 3 | 1l : X = 3-Cl, R = H | 12 | 3b : X = 3-Ph, R = H | 88 |
| 4 | 1m : X = 4-Cl, R = H | 12 | 3c : X = 4-Ph, R = H | 92 |
| 5 | 4c : X = 6-Cl | 12 | 6c : X = 6-Cl | 77 |
| 6 | 10 | 12 | 11 | 80 ^a |

^a Pd(II)/C was used. When Pd(0)/C was used, the yield was 8%. ^b NR = no reaction.

Third, the combination of Pd(II)/C and PPh₃ was used in the reaction of 2-chloropyridines with an electron-donating group **1j,k**, 3-chloropyridine (**1l**), 4-chloropyridine (**1m**), 6-chloroquinoline (**4c**), and 3-bromoaniline (**8**). As described above, Pd(II)/C has been shown to be more reactive than Pd(0)/C.^{2c} Therefore, it was expected that the combination of Pd(II)/C and PPh₃ would be effective for the reaction of less-reactive substrates. In fact, the reactions of 2-chloropyridines with an electron-donating group and 3-bromoaniline (**8**) gave high yields (Table 3, entries 1, 2, and 6).⁹ However, the products were not obtained in good yields (Table 3, entries 3–5) in the reactions of 3-chloropyridine (**1l**), 4-chloropyridine (**1m**), and 6-chloroquinoline (**4c**).

Finally, to improve the yields in the reactions of less-reactive pyridines such as 3-chloropyridine (**1l**), 4-chloropyridine (**1m**), and 6-chloroquinoline (**4c**), ligand

effects were studied by using 3-chloropyridine (**1l**) with Pd(0)/C. Although the reactions in the presence of dppb (9 mol %) or dppp (9 mol %) instead of PPh₃ (18 mol %) resulted in unsatisfactory conversion (Table 4, entries 1 and 2), the sterically hindered ligand 2-(dicyclohexylphosphino)biphenyl (9 mol %)^{10,11} dramatically improved the yield (Table 4, entries 1 and 3). It has been reported that bulky and electron-rich ligands increase the yields of homogeneous Suzuki–Miyaura coupling reactions.^{10c} Electron-rich phosphine ligands facilitate oxidative addition, and the steric bulk around the metal promotes reductive elimination. Thus, during the Pd/C-catalyzed reaction, 2-(dicyclohexylphosphino)biphenyl (**12**) would interact with the leaching Pd and show the same effects. The combination of Pd(0)/C and 2-(dicyclohexylphosphino)biphenyl was also effective for the reactions of 4-chloropyridine and 6-chloroquinoline (Table 4, entries 4 and 5).¹² Although this combination was not effective enough for the reaction of 4-methoxyphenyl chloride, the combination of Pd(II)/C and 2-(dicyclohexyl-

(8) The Pd content in the recovered Pd/C and crude product was measured in the Pd/C-catalyzed coupling of 2-chloroquinoline (**4a**) and phenylboronic acid (**2**). To a solution of 2-chloroquinoline (3.60 g, 22.0 mmol) and phenylboronic acid (3.23 g, 26.4 mmol) in DME (25 mL) were added 2 M K₂CO₃ (30 mL) and NE Chemcat STD 5% Pd/C (water content 55.4%) (2.62 g, 0.12 mmol; Pd content is 61 mg), and the reaction mixture was stirred at 80 °C for 9 h. After the reaction was completed, Pd/C was filtered, washed twice with 30 mL of AcOEt, and dried under reduced pressure to give 2.22 g of Pd/C. The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to give crude product (5.35 g). The Pd contents of the recovered Pd/C and crude product were measured by a flame atomizer, and found to be 2.11% (47 mg) and 0.24% (13 mg), respectively. Thus, 80% of the Pd in the original Pd/C was recovered in the filtered Pd/C, and 20% contaminated the crude product. Coordination between Pd and nitrogen made the amount of Pd in the crude product greater in heteroaromatic compounds.

(9) Compound **9** is commercially available from Tokyo Kasei Kogyo Co., Ltd.

(10) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (b) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(11) In the reaction of 3-chloropyridine in the presence of Pd and 2-(dicyclohexylphosphino)biphenyl in a molar ratio of 1:4 and 1:1, the product was obtained in respective yields of 75% and 82%.

(12) The reactions of **1j** and **1k** were carried out with the Pd(0)/C-phosphine **12** system, and gave the products in respective yields of 87% yield and 79%. It is assumed that more-reactive halopyridines and haloquinolines, such as **1a–i**, **4a,b**, and **5**, would also give the products in good yields.

phosphino)biphenyl was effective in this case (Table 4, entry 6).¹³

Conclusion

In conclusion, we studied Suzuki–Miyaura coupling catalyzed by palladium charcoal and found that a phosphine ligand was indispensable for the reaction of halo-pyridines and haloquinolines. The sterically hindered ligand 2-(dicyclohexylphosphino)biphenyl was extremely effective in this reaction. Industrial-scale manipulation of this process is now under investigation.¹⁴

Acknowledgment. The authors are grateful for the assistance of Mr. Masaki Shimada.

(13) Compound **11** is commercially available from Tokyo Kasei Kogyo Co., Ltd.

Supporting Information Available: Experimental data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The coupling reaction of 3-amino-2-chloropyridine and triphenylboroxine was carried out at a 100-g scale in the presence of 0.45 mol % of Pd in *n*-butanol, which was more suitable than DME for an industrial process. A flask was charged with triphenylphosphine (8.28 g, 32 mmol), 3-amino-2-chloropyridine (232 g, 1.8 mol), triphenylboroxine (225 g, 0.72 mol), KHCO₃ (216 g, 2.16 mol), Degussa E 106 NE/W 10% Pd/C (water content 50.8%) (17.6 g, 8.1 mmol), *n*-butanol (684 mL), and H₂O (1080 mL). After the reaction mixture was stirred at reflux for 9 h under nitrogen, Pd/C was filtered off and rinsed with *n*-butanol (300 mL). The organic layer was separated, washed with water, and evaporated to give a brown oil, which was purified by distillation to give 3-amino-2-phenylpyridine (243 g, yield 79%) as a white solid (bp 138–140 °C/1.0 mmHg, mp; 61–63 °C). Contamination of the product by Pd was not detected by a flame atomizer.