A Mixed Naphthyl-Phenyl Phosphine Ligand Motif for Suzuki, Heck, and Hydrodehalogenation Reactions

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Dedicated to Richard Heck who let fly the first arrow of transition-metal-catalyzed reactions for organic synthesis

Abstract: Nap-Phos, representing a new naphthyl-phenyl biaryl-type phosphine ligand class and available by a short synthesis (4 steps, 71% overall yield), effectively catalyzes the Suzuki–Miyaura (including highly hindered cases), hydrodehalogenation, and Heck reactions.

Key words: cross-coupling, Suzuki–Miyaura, homogenous catalysis, Heck reaction, phosphorus ligand, hindered biaryls, dehydrohalogenation

In the last decade, the inspiration gained from the discoveries of the now-eminent transition-metal-catalyzed name reactions[1] has been translated into extensive application to synthetic problems, especially in pharmaceutical industry practice[2] and has witnessed increased mechanistic understanding,[1c] to further drive the development of highly active and selective catalysts.

Recognition that ligand variation constitutes the most powerful tool in deriving the new catalytic advantage[3] has resulted in a continuous superfluity of reports aimed to explore and exploit the subtle crosstalk between steric and electronic parameters which determine the properties of the catalyst.[4] In the growing catalogue of available ligands, the phosphine-based systems are dominant,[4] arguably followed by the N-heterocyclic carbenes;[5] however, a variety of others are being developed, including ligandless protocols.[6]

Although 'no universal guidelines'[4b] as yet exist for phosphine ligands, insight into the critical contributions of steric bulk and electron-donating ability of the ligand on catalytic activity is emerging[7] concurrently with wide-ranging application, especially with respect to the Suzuki–Miyaura methodology.[8] Thus, at the forefront of current work, ligands such as S-Phos,[6] X-Phos,[6] and Cy-MAP[9] (Figure 1) display high catalytic activity in Suzuki–Miyaura reactions of hindered biaryls even at room temperature and extremely low (ppm) catalyst loading.

We report on the design and synthesis of a new monodentate P-ligand (Nap-Phos, **7**) and its application to the Suzuki–Miyaura, hydrodehalogenation, and Heck reactions. Of the approximately 60 known biaryl phosphines frameworks,[4b] Nap-Phos is, to the best of our knowledge, the first mixed naphthyl-phenyl P-ligand and is prepared by non-metalation/metal–halogen exchange routes. Our results, by implication, support concurring evidence of the importance of bulk and electronic criteria in the P-ligand structure and provide a new basis for future ligand development for transition metal catalysis.

Cognizant of the difficulties associated with the construction of unsymmetrical, hindered *ortho*-substituted biaryl P-ligand cores by direct coupling reactions,[4,6a,10] we sought, in our approach to Nap-Phos (**7**), an effective short synthesis whose accent was on the introduction of *ortho*-P-functionality by a non-coupling route[10b] subsequent to aryl–aryl bond formation. In addition, a process, which was based on commercial starting materials and amenable to scale-up, was aspired.

Thus (Scheme 1), treatment (1 mmol scale) of naphthoquinone (**1a**) and 2-bromonaphthoquinone (**1b**) under oxidative Heck[11] and Suzuki[6] conditions with the boronic

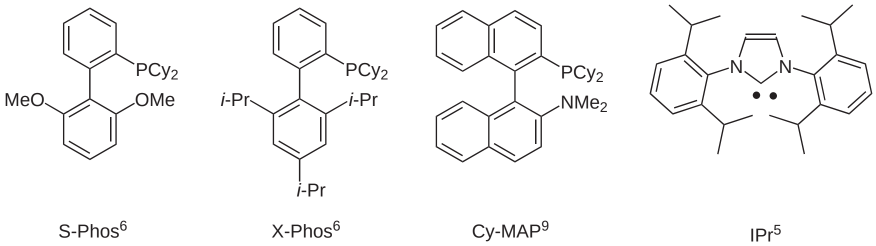

Figure 1 Some effective ligands for the Suzuki–Miyaura reaction.

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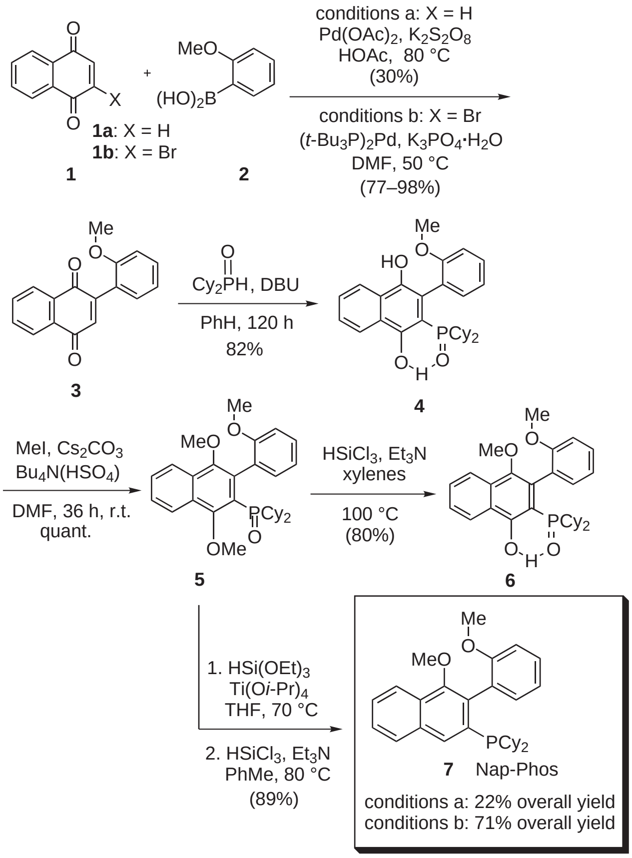


Scheme 1 The synthesis of Nap-Phos (**7**) in 4 steps and 71% overall yield.

acid **2** gave the aryl naphthoquinone **3** in 30% and 98% yields, respectively, from commercially available materials. The Suzuki conditions furnished **3** in 77% yield on a preparative (15 mmol) scale. Treatment with dicyclohexylphosphine oxide in the presence of DBU[12] afforded the phosphine oxide (**4**, 82% yield),[13] which was precipitated from the reaction mixture with pentane and used without additional purification. Methylation under mild conditions afforded the dimethyl ether phosphinoxide **5** in quantitative yield. Attempts to reduce **5** to the corresponding phosphine, with the intent to investigate its ligand properties, failed but provided a remarkable result.

Under conventional $HSiCl_3/Et_3N$ conditions,[10b] the demethylated product **6** was obtained, likely the result of phosphinoxide–$HSiCl_3$ coordination followed by hydride reductive cleavage.[14] Compound **6** resisted reduction to the corresponding phosphine by several established procedures.[15] To circumvent this difficulty, the 1-OMe group was cleaved by taking advantage of the presumed coordination effect. Thus, treatment of **5** with Ti(*i*-PrO)$_4$ and (EtO)$_3$SiH to derive titanium hydride in situ[16] afforded the corresponding 1-desmethoxy compound (81% yield) which, upon standard reduction with $HSiCl_3/Et_3N$, gave **7** in 71% overall yield from the phosphinoxide **5**.

Results of Suzuki–Miyaura cross-coupling reactions using Nap-Phos (**7**) are summarized in Table 1. For unhindered cross-couplings, excellent yields of biaryl products were obtained at somewhat above ambient temperatures, even for unactivated aryl chlorides[17,22] (entries 1 and 2). As expected from previous results[6] more hindered coupling partners require higher temperatures, aprotic solvents, and higher ligand loading (entries 3–8). These reaction conditions were optimized for the coupling of 2,6-dimethylbromobenzene with 2,4,6-trimethylphenyl boronic acid (entry 3) using 5:1 ratio of ligand:[Pd] at 150 °C. These conditions proved also effective for an unactivated heterocyclic bromide (entry 9). Of significant note, due to the connection to directed *ortho*-metalation (D*o*M) chemistry,[18] the high-yield coupling of a highly hindered benzamide was achieved (entry 8).[19]

In a second application of Nap-Phos, aryl bromide hydrodebromination, a fundamental synthetic reaction of considerable environmental relevance,[20b,c] has been demonstrated. The above Suzuki coupling results indicating the ready activation of the carbon–halogen bond by the Nap-Phos-Pd catalyst are reflected in facile hydrodebromination (Table 2): quantitative yields of products were observed in 40–100 °C temperature ranges using 2 mol% of [Pd]–ligand (1:1) catalyst precursor. Interestingly (entry 4), deuteriodehalogenation using excess CD_3OD and H_2O is inefficient at 40 °C but suggests hydride transfer with concomitant formation of formaldehyde.

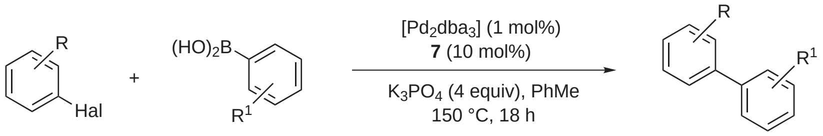
In another preliminary study, the application of Nap-Phos in the venerable Heck reaction[21,22] has also been realized (Table 3). Thus, using typical Heck reaction conditions,[21] products are obtained even for sterically hindered and deactivated aryl bromides (entries 1 and 2) and *ortho*-substituted aromatics and heteroaromatics (entries 3–5) derived by D*o*M tactics.[18]

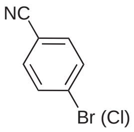
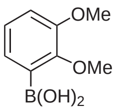
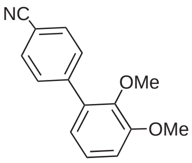
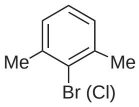
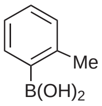
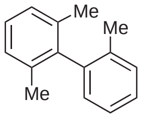
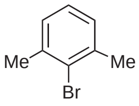
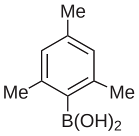
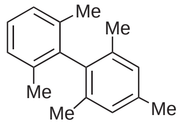
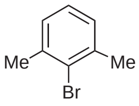
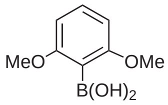
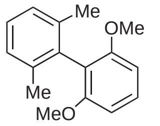
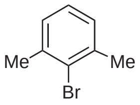
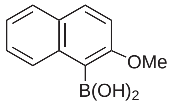
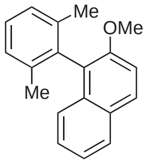
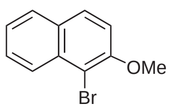
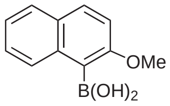
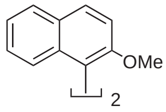
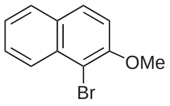
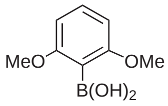
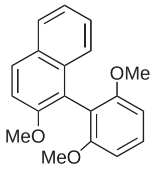
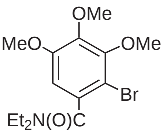
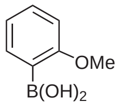
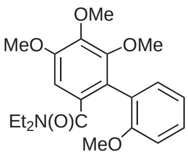
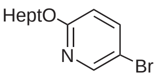
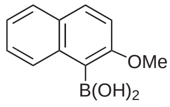
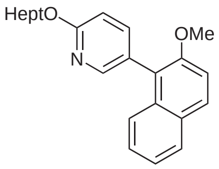
In conclusion, the efficacy of the first mixed naphthyl-phenyl ligand, Nap-Phos (**7**) in Suzuki–Miyaura, hydrodebromination, and Heck reactions has been demonstrated. In the Suzuki protocol, Nap-Phos appears to be of similar high activity to the current benchmark, S-Phos and gives comparable results[23] for difficult cases (entries 2–7, Table 1). Moreover, highly substituted sterically hindered bromo benzamides[19] (entry 8) and deactivated heteroaromatic bromides (entries 9) afford excellent yields of coupled products. The new catalytic reductive hydrodebromination methodology provides an effective and simple alternative to traditional, generally more harsh, procedures.[20a,b] The biaryl amide Suzuki (entry 8, Table 1) and Heck (entries 3–5, Table 3) products are retrosynthetically related to D*o*M chemistry,[18] a fact which invites further synthetic exploration. Further studies of Nap-Phos (**7**) and related new ligands is in progress.[24]

Dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphinoxide

A dried Schlenk tube containing a magnetic stirring bar was charged with **5** (3.92 g, 7.7 mmol) and anhyd THF (50 mL). The flask was capped with a rubber septum and evacuated and backfilled with argon. This sequence was repeated three times. Then

Table 1 Suzuki–Miyaura Cross-Coupling Reaction Using Nap-Phos (**7**)



Entry	Ar–Hal	Ar–$B(OH)_2$	Product	Yield (%)[a]
1				98[b], 98[b,c] (98)[b]
2				98[b] (98)[b]
3				76
4				70
5				71
6				58[d]
7				62[d]
8				98[d]
9				80[d]

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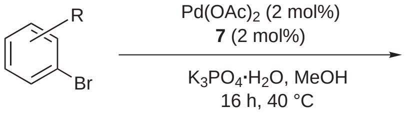
[a] Isolated yields obtained after silica gel chromatography or micro distillation. Products of the reactions of entries 2–4 contain about 4 mol% of boronic acid homocoupling by-products according to GC-MS.

[b] Conditions: $Pd(OAc)_2$ (2 mol%), Nap-Phos (**7**, 2 mol%), $K_3PO_4 \cdot H_2O$, anhyd MeOH, 40 °C.

[c] DMF as solvent, 40 °C.

[d] Mesitylene as solvent, 150 °C.

Table 2 Catalytic Hydrodehalogenation Using Nap-Phos (**7**)



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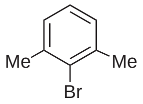
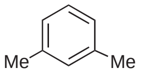
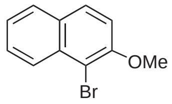
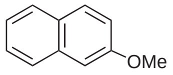
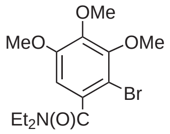
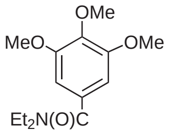
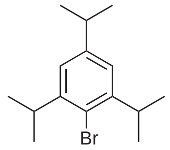
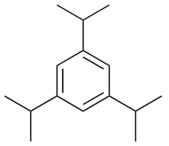
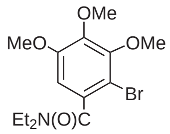
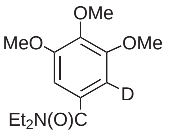
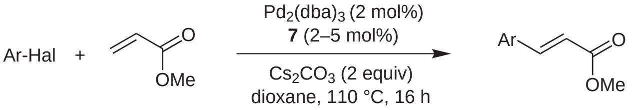
1			quant[a]
2			quant
3			quant[b]
4			quant[a]
5			40[c]

[a] Yield based on GC-MS analysis.
[b] Reaction at 100 °C.
[c] When CD_3OD or CD_3OH was used as solvent at 40 °C, the corresponding deuterated product was obtained in 40% yield with above 95% d_1-incorporation (NMR analysis).

Table 3 Heck Reaction Using Nap-Phos (**7**)



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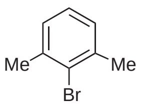
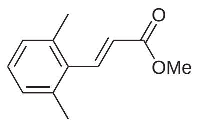
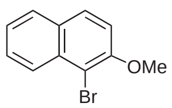
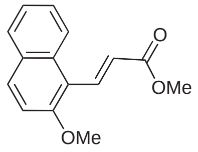
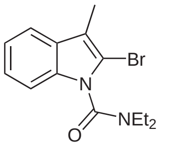
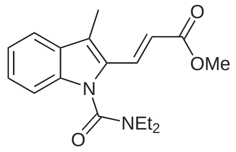
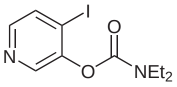
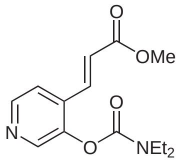
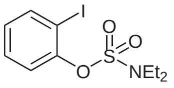
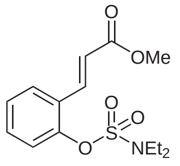
1			85
2			80[a]
3			84
4			40
5			42

[a] E:Z = 4.3:1 as determined by GC-MS and ^1H NMR analysis.

$HSi(OEt_3)$[16] (18.0 g, 20 mL, 108 mmol) and $Ti(i\text{-}PrO)_4$ (4.4 g, 4.6 mL, 16 mmol) were sequentially added through the septum, and the reaction mixture was slowly heated to 100 °C with vigorous stirring during which time pyrophoric SiH_4 was liberated. *Caution:* SiH_4 is a pyrophoric gas and should be diluted at the outlet with argon. The septum was replaced with a glass cap, the tube was sealed, and the reaction mixture was vigorously stirred and heated at 100–110 °C until **5** was almost completely consumed (^{31}P NMR analysis). After cooling to r.t., the mixture was evaporated under high vacuum, the resulting solid residue was impregnated with silica gel (6 g) and the material was subjected to column chromatography (40:1 hexane–EtOAc to 5:3:0.2 hexane–EtOAc–MeOH as eluents) to give **5** (0.08 g, 2%), **6** (0.04 g, 1%), dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphinoxide (3.0 g, 81%), and **7** (0.18 g, 5%). Pure dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphinoxide was obtained by recrystallization from hexane–EtOAc, colourless crystals, mp 197–198 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 48.3. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, 1 H, J = 12.1 Hz), 8.07 (d, 1 H, J = 8.1 Hz), 8.02 (d, 1 H, J = 8.1 Hz), 7.61 (~t, 1 H, J = ca. 7.9 Hz), 7.57 (~t, 1 H, J = ca. 7.6 Hz), 7.48 (~t, 1 H, J = ca. 7.6 Hz), 7.18 (d, 1 H, J = 7.1 Hz), 7.08 (t, 1 H, J = 7.1 Hz), 7.02 (d, 1 H, J = 8.0 Hz), 3.75 (s, 3 H), 3.63 (s, 3 H), 1.94–0.97 (m, 22 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 154.4 (d, 1 C, J_{C-P} = 12.4 Hz), 133.5 (d, 1 C, J_{C-P} = 12.4 Hz), 132.0 (d, 1 C, J_{C-P} = 5.1 Hz), 131.2, 130.2 (d, 1 C, J_{C-P} = 79.8 Hz), 129.9, 129.3, 129.0 (d, 1 C, J_{C-P} = 2.2 Hz), 127.7, 127.3 (d, 1 C, J_{C-P} = 10.3 Hz), 126.7, 126.0 (d, 1 C, J_{C-P} = 2.2 Hz), 122.5, 120.0, 110.4, 61.7, 55.3, 37.9 (d, 1 C, J_{C-P} = 66.5 Hz), 37.8 (d, 1 C, J_{C-P} = 65.1 Hz), 27.02, 26.99, 26.92, 26.89, 26.82, 26.69, 26.59, 26.57, 26.51, 26.46, 26.38, 26.28, 26.25, 25.77, 25.63, 25.59. IR (film): 1172, 1105 (P=O) cm^{-1}. HRMS (EI): m/z calcd for $C_{30}H_{37}O_3P$: 476.2480; found: 476.2475.

Dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphine (7)

To a stirred solution of dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphinoxide (3.5 g, 6.9 mmol) in degassed toluene (100 mL) under argon was sequentially added Et_3N (50 mL) and $HSiCl_3$ (6.7 g, 5 mL, 50 mmol). The flask was sealed and the mixture was stirred and heated at 80 °C for 16–18 h (the completion of the reaction was ascertained by ^{31}P NMR analysis). After cooling to r.t., toluene (100 mL) and then 30% aq NaOH (50 mL) were added under vigorous stirring. After 20 min, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give a residue which was purified by column chromatography (40:1 hexane–EtOAc as eluent) to give **7** (2.6 g, 77% yield) as a pale yellow solid which undergoes slow oxidation in air. ^{31}P NMR (162 MHz, C_6D_6): δ = –10.2. ^1H NMR (400 MHz, C_6D_6): δ = 8.35 (d, 1 H, J = 8.1 Hz), 8.10, 7.85 (d, 1 H, J = 8.1 Hz), 7.52 (d, 1 H, J = 7.1 Hz), 7.44–7.36 (m, 3 H), 7.14 (~t, 1 H, J = ca. 7.5 Hz), 6.82 (d, 1 H, J = 8.1 Hz), 3.56 (s, 3 H), 3.50 (s, 3 H), 2.35–0.93 (m, 22 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 157.5, 154.1 (d, 1 C, J_{C-P} = 8.8 Hz), 136.3 (d, 1 C, J_{C-P} = 22.0 Hz), 135.2 (d, 1 C, J_{C-P} = 32.2 Hz), 134.1, 133.2 (d, 1 C, J_{C-P} = 2.1 Hz), 128.9, 128.8, 128.3, 128.2 (d, 1 C, J_{C-P} = 2.9 Hz), 128.1, 126.2 (d, 1 C, J_{C-P} = 14.6 Hz), 122.8, 119.8, 110.1, 60.6, 54.5, 35.2 (d, 1 C, J_{C-P} = 144.9 Hz), 35.0 (d, 1 C, J_{C-P} = 144.2 Hz), 30.9, 30.7, 30.32, 30.27, 30.18, 30.09, 29.23, 29.15, 27.57, 27.50, 27.44, 27.43, 27.39, 27.35, 27.28, 26.86, 26.85, 26.49. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}O_2P$ + [H^+]: 461.2609; found: 461.2588.

In a simple procedure, the mixture obtained in the preparation of dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphth-2-yl]phosphinoxide as described above, after fast filtration through a plug of silica gel, was subjected to directly to the $HSiCl_3/Et_3N$/PhMe/80 °C/18 h conditions to give, after normal work-up, **7** in 90% yield.

Suzuki–Miyaura Cross-Coupling Reaction – General Procedure

A Schlenk tube containing a magnetic stirring bar, powdered $K_3PO_4·H_2O$ (3 mmol, 3 equiv), aryl boronic acid (2 mmol, 2 equiv) and MeOH (4 mL) was capped with a glass stopper and then evacuated and backfilled with argon. This sequence was repeated three times. The aryl halide (1.0 mmol, 1.0 equiv; aryl halides which were solids at r.t. were added as sat. solutions in MeOH or C_6H_6) and a solution of ligand **7** (0.02 mmol, 0.02 equiv) in C_6H_6 (0.2 mL) were then added followed by a solution of $Pd(OAc)_2$ (0.02 mmol, 0.02 equiv) in MeOH (1 mL). After 10 min, the reaction mixture was heated at 40 °C with stirring until the aryl halide was completely consumed as judged by GC analysis but not longer then 18 h. The reaction mixture was cooled to r.t., diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (2 × 15 mL). The organic extract was dried (Na_2SO_4) and concentrated in vacuo, and the crude material obtained was purified by flash chromatography on silica gel.

Suzuki–Miyaura Cross-Coupling Reaction – Hindered Aromatics

The above cross coupling procedure was used with the following changes: anhyd K_3PO_4 (3 equiv) was used in lieu of $K_3PO_4·H_2O$, $Pd_2(dba)_3$ (2 mol%) was employed instead of a solution of $Pd(OAc)_2$, a 5:1 ligand–[Pd] ratio was applied, and reaction was carried out in 1,3,5-$Me_3C_6H_3$ or 1,4-$Me_2C_6H_4$ or PhMe at 150 °C for 18 h.

Hydrodehalogenation Reaction

The general procedure for the cross coupling reaction described above was used with the exclusion of the aryl boronic acid as follows: $K_3PO_4·H_2O$ (3 mmol, 3 equiv), and MeOH (4 mL) aryl halide (1.0 mmol, 1.0 equiv), ligand **7** (0.02 mmol, 0.02 equiv) in C_6H_6 (0.2 mL), $Pd(OAc)_2$ (0.02 mmol, 0.02 equiv) in MeOH (1 mL), 40 °C, 18 h.

Heck Reaction

The general procedure for the cross-coupling reaction was used with the following changes in reagents: anhyd Cs_2CO_3 (3 equiv) was used in lieu of $K_3PO_4·H_2O$, methyl acrylate (2 equiv) was used instead of the boronic acid, $Pd_2(dba)_3$ (1 mol%) was used instead of a solution of $Pd(OAc)_2$, a 2:1 ligand–[Pd] ratio was employed, and reaction was carried out in dry dioxane at 150 °C for 18 h or at 200 °C under MW irradiation for 1 h.

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References and Notes

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: Weinheim, **2002**. (c) For mechanistic aspects, see: Kozuch, S.; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319.

(2) See, for example: (a) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205. (b) Rouhi, A. M. *Chem. Eng. News* **2004**, *82 (Sept. 6)*, 49. (c) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337; especially p. 2345.

(3) Review: Wilkinson, M. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Org. Biomol. Chem.* **2005**, *3*, 2371.

(4) Reviews: (a) Clarke, M. L.; Heydt, M. *Organometallics* **2005**, *24*, 6475. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405. (c) Valentine, D. H. Jr.; Hillhouse, J. H. *Synthesis* **2003**, 2437.

(5) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.

(6) (a) For an excellent overview and comprehensive list of references, see: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. For additional impact of SPhos on Suzuki–Miyaura chemistry, see: (b) Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871. (c) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (d) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3484.

(7) The significance of an η^1-Pd-C(ipso) interaction to the lifetime of the catalyst is being investigated, see ref. 6 and: Kočovský, P.; Vyskočil, S.; Cisařová, I.; Sejbal, J.; Tilerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714.

(8) (a) For an outstanding critical review on the Heck and Suzuki reactions focusing on the active species, which presents a detailed analysis of P-ligands, see: Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (b) For a review on hydrophilic P-based ligands, see: Shaughnessy, K. H. *Eur. J. Chem.* **2006**, 1827.

(9) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(10) For a practical synthesis of biphenyl phosphine ligands using a Grignard–benzyne reaction, see: (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334. (b) For recent work, see: Baillie, C.; Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 9085; and references cited therein.

(11) Schenck, H. V.; Nilsson, P.; Andappan, M. S.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212.

(12) Villemin, D.; Racha, F. *Tetrahedron Lett.* **1986**, *27*, 1789.

(13) As established by X-ray single crystal (Figure 2) and NMR analysis, compound **4** shows strong intra- and intermolecular hydrogen bonds in the solid state and in solution. The (C1)O–H–O=P intramolecular bond distances are 1.079 Å and 1.533 Å, respectively, while intermolecular (C4′)O–H–O=P bond distances are 1.046 Å and 1.794 Å, respectively. The ^{31}P NMR spectrum reveals a low field shifted phosphorus signal at δ = 67.9 ppm and the ^{1}H NMR spectrum (anhyd DMSO-d_6) exhibits two widely separated signals for the hydroxyl hydrogens at δ = 13.66 ppm and δ = 7.95 ppm confirming the presence of only one intramolecular (C1)OH–O=P hydrogen bond. A similar phenomenon was observed in benzene-d_6 solution. Crystallographic data (excluding structure factors) for the structure of **4** have been deposited with the Cambridge

Crystallographic Data Centre as supplementary publication no. CCDC-609270. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

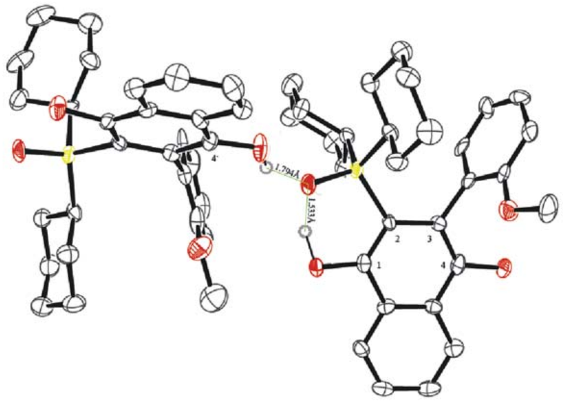

Figure 2 X-ray crystal structure of **4**. For clarity, hydrogen atoms are excluded except those involved in hydrogen bonding.

(14) For similar nucleophilic aromatic substitutions driven by coordination effects, see: (a) Meyers, A. I.; Hummelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. (b) Review: Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Merier, A. *Tetrahedron* **2004**, *60*, 4459. (c) For recent work, see: Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y. M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955.

(15) Reduction attempts on **5** using MeI/LiAlH$_4$ and PhSiH$_3$ were also unsuccessful. See: Imamoto, T.; Kikuchi, S.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87.

(16) (a) Coumhe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625; and references cited therein. (b) Replacement of (EtO)$_3$SiH with the more economical and non-toxic polyhydromethylsiloxane (PMHS), as suggested in the above reference, was similarly effective (110 °C, 56 h) but caused problems of incomplete separation of polymeric siloxanes in column chromatography.

(17) Use of an equimolar ligand **7**:Pd(OAc)$_2$ ratio produced a very active catalyst, leading to 50% product formation in 15 min in DMF or MeOH at 40 °C (Table 1, entry 1).

(18) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. (b) Macklin, T.; Snieckus, V. In *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, **2005**, 106.

(19) For previous cross-coupling of hindered benzamides which required special conditions and led to poorer yields, see: Fu, J.-m.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459.

(20) (a) Monguchi, M.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, *62*, 7926. (b) Review: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009. (c) Morra, M. J.; Borek, V.; Koolpe, J. *J. Environ. Qual.* **2000**, *29*, 706; and refs cited therein.

(21) Reviews: (a) Qadir, M.; Möchel, T.; Hii, K. K. *Tetrahedron* **2000**, *56*, 7975. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783.

(22) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(23) For hindered examples, Table 1, entry 2: S-phos (93%),[6a] Nap-Phos: (98%); entry 3: S-phos (82%),[6a] Nap-Phos: (76%); entry 4: S-phos (86%),[6a] Nap-Phos (70%).

(24) A preliminary PM3 modeling study shows a low racemization barrier (20 kcal/mol) for Nap-Phos which precludes its use as a chiral ligand in cross coupling reactions under conditions described herein. Few chiral non-racemic atropisomeric ligand motifs are known. For discussion, see ref. 14c.