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Asymmetric Suzuki–Miyaura cross-coupling of aryl chlorides with enhancement of reaction time and catalyst turnover

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ABSTRACT

A series of new chiral phosphonite ligands were evaluated for the palladium-catalyzed asymmetric Suzuki–Miyaura cross-coupling reactions of aryl chlorides. Ligand **4** gave 91% yield and 78% ee with 0.5 mol % catalyst loading for the coupling of aryl boronic acid and aryl chloride in 5 h. When the catalyst loading was lowered to 0.1 mol % the same reaction gave 75% yield and 76% ee.

The Suzuki–Miyaura cross-coupling reaction is one of the most widely used method for preparing biaryl bonds.[1] The widespread availability of aryl chlorides contributes to the utility of this reaction in synthetic organic chemistry.[1a–d] The asymmetric variant remains an important challenge[2] due to the importance of axially chiral biaryls in synthetic applications,[3a–d] including pharmaceutical,[3e,f] material,[3g] and supramolecular[3h] chemistry. So far a few examples on catalytic enantioselective versions have been reported.[4–6]

Recently, Lassaletta and Uozumi reported on highly efficient asymmetric cross-couplings. Lassaletta and co-workers utilized a novel C2-symmetric bis-hydrazone ligand,[7a] and Uozumi developed a polymer-supported catalyst.[7b] While their procedures achieved valuable enantioselectivities there is still room for improvement especially in terms of catalyst loadings and reaction times. In these prior works a minimum of 5 mol % of catalyst and 24 h of reaction time was necessary, though Uozumi was able to reuse their catalyst 4 times.

We previously reported on the pentaarylbenzene phosphine ligand **1** palladium-catalyzed Suzuki–Miyaura coupling of aryl chlorides.[8] The well-organized array of aromatic rings was demonstrated to play an enhancing role in the catalytic cycle.[9,10] Phosphine **1** catalyzed the reaction of 2-chloro-3-methoxybenzaldehyde with *ortho*-tolylboronic acid to form the unsymmetrical tri-*ortho*-substituted biaryl[11] in >99% yield with 0.1 mol % catalyst loading (Scheme 1).

In this Letter, we describe three new phophonites that promote the asymmetric cross-coupling of aryl chlorides with low catalyst loading and short reaction time. The pentatolylbenzene moiety feature found in **1** was appended with chiral biaryls to give **2**, **3**, and **4** (Fig. 1). Phosphonite **4** was found to give the axially chiral tri-*ortho*-substituted biaryl[12] in 75% yield and 76% ee with a 0.1 mol % catalyst loading (catalyst turnover = 750) and 5 h reaction time.

The chiral phosphonite **2**,[13] **3**,[14] and **4**[15] were synthesized from bromide **6**[16] via iodide **5**[10a] as shown in Scheme 2. Lithiation of iodide **5** smoothly occurred in toluene at −78 °C, and it was followed by reaction with 1,2-dibromobenzene, giving **6** in 89% yield.[8] Initial efforts to convert **6** to the desired ligands **2**, **3**, and **4** proved difficult presumably due to the sterically hindered carbanion.[17] After several attempts, the use of phosphorous trichloride was found to give access to desired phophonites. The addition of PCl_3 followed by (*R*)-1,1′-binaphthyl-2,2′-diol was conducted in one-pot under an argon atmosphere. Purification by silica gel column chromatography gave **2** in 43% yield. Similarly the reactions of (*R*)-3,3′-dimethyl-1,1′-binaphthyl-2,2′-diol[14] and (*S*)-9,10′-biphenanthrene-9′,10-diol[15] afforded **3** in 69% yield and **4** in 70% yield. These compounds readily dissolved in $CHCl_3$, CH_2Cl_2, benzene, toluene, and THF. Compounds **2**, **3**, and **4** proved to be stable solids as confirmed by the lack of observed phosphorous oxide in ^{31}P NMR after workup and purification. Presumably the large pentatolylbenzene moiety provides a degree of robustness to these ligands, protecting the phosphorous lone-pair from oxidation.[18]

At the outset of our study the availability of **2** led us to investigate its performance as a chiral ligand in palladium-catalyzed asymmetric Suzuki–Miyaura reactions. The reactions were carried out in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$ (dba = dibenzylideneacetone) and **2** (Scheme 3). As coupling partners, 2-(2-chloro-3-methoxyphenyl)-1,3-dioxolane **7** and *ortho*-tolylboronic acid **8** were chosen because of their availability. The chemical yield and enantiomeric excess of the axially chiral product (*S*)-2-(6-methoxy-2′-methyl biphenyl-2-yl)-1,3-dioxolane[19] were surveyed in several conditions (Table 1).[20]

In entries 1 and 2, the catalyst system at 75 °C in THF and KF smoothly gave the coupling adduct in 96% yield, although the yield at 50 °C decreased to 44%. In entries 2–4, the ratio of **2** to palladium (P/Pd ratio) was varied between 1.2, 2.0, and 3.0 to little effect. In entry 5 the reaction proceeded with 0.1 mol % catalyst loading,

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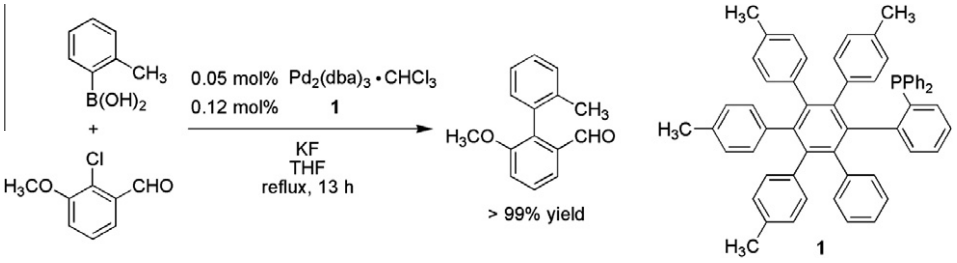


Scheme 1. Synthesis of a biaryl in the presence of **1**.

giving 99% yield and 40% ee. Of the bases evaluated in entries 6–11, the significance of CsF is striking, giving coupling in 96% yield and 46% ee. In entry 14, 92% yield and 45% ee were produced with a catalyst loading of 0.1 mol %.

The configurational stability of (*S*)-2-(6-methoxy-2′-methyl biphenyl-2-yl)-1,3-dioxolane at the reaction temperature of the coupling was surveyed. The mixture of (*S*)/(*R*) = 66:34 ratio was refluxed in THF for 12 h, to give 68:32. In addition, (*S*)/(*R*) = 68:32 was heated in toluene for 12 h at 90 °C, to give 66:34. There is virtually no erosion of ee under these conditions thus we presume that the biaryl has kept its configuration under the reaction conditions.

Next, we evaluated the performance of ligands **2**, **3**, and **4** (Table 2). In the reaction of halide **7** with boronic acid **8** with THF and KF under P/Pd = 2, phosphonite **3** gave 65% ee compared to **2** (41% ee) (entries 1 and 2). When the mol % of ligand **3** and **4** rose to 1.5 (P/Pd = 3) the starting material **7** disappeared by TLC monitoring within 5 h, and the product was given in 69% ee and 72% ee, respectively (entries 3 and 4). Conducting the reaction in toluene with CsF the % ee values were 74 with **3** and 78 with **4** (entries 5 and 6). This is slightly better as compared with the % ee using THF and KF. In entry 7, the catalyst loading of 0.1 mol % with **4** achieved 75% yield and 76% ee, consuming the starting material **7** within 5 h. The coupling partners of arylboronic acid were changed to *o*-anisylboronic acid **10** (entries 8 and 9)[21] and 1-naphthylboronic acid **11** (entries 10 and 11). Although the starting halide **7** was consumed within 5 h through entries 8–11, the highest enantioselectivities recorded was 52% ee.[22] Asymmetric cross-coupling of 2-chloro-3-methoxy benzonitrile **9**[23] with 1-naphthylboronic acid **11** in entry 12 was carried out with phosphonite **4**, and the reaction proceeded within 3 h in 87% yield and 33% ee.

In summary, chiral phosphonite **2**, **3**, and **4** were developed and evaluated for the asymmetric Suzuki–Miyaura cross-coupling

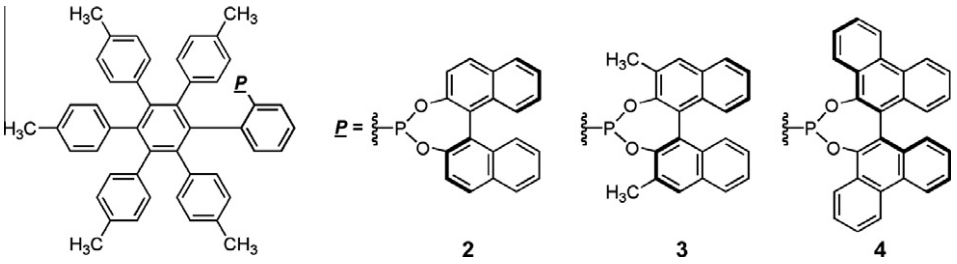
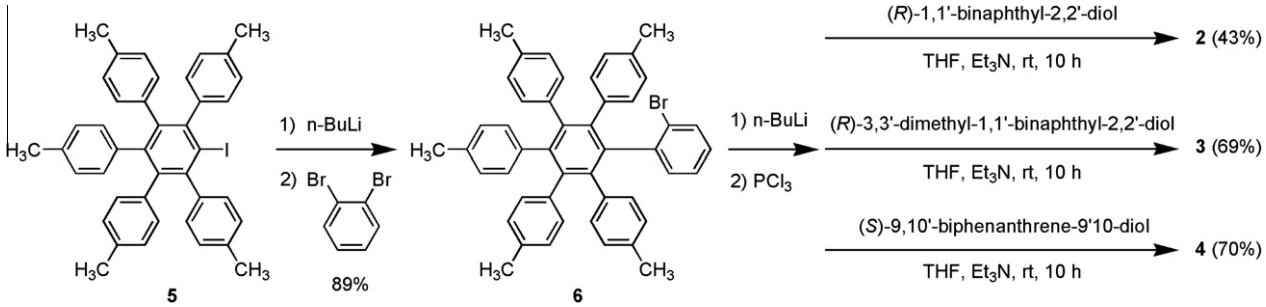
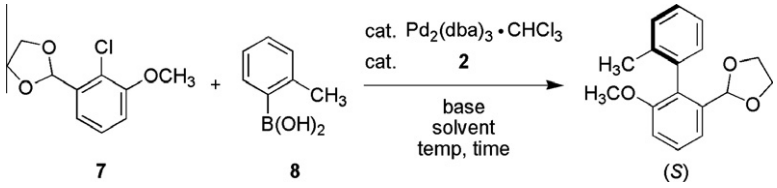


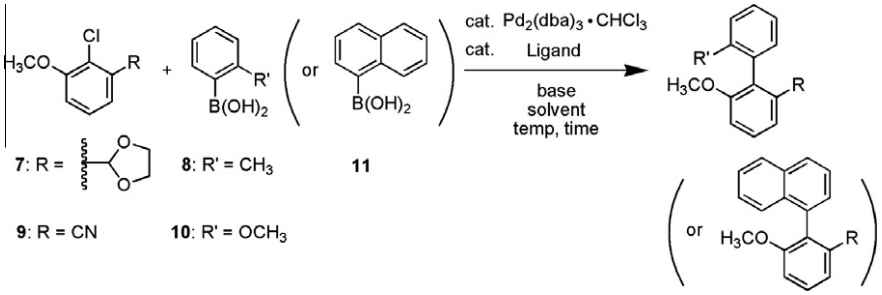
Figure 1. Phosphonite **2**, **3**, and **4**.



Scheme 2. Synthetic routes to **2**, **3**, and **4**.



Scheme 3. Asymmetric Suzuki–Miyaura reaction of **7** with **8**.



Scheme 4. Asymmetric Suzuki–Miyaura reaction with aryl chlorides.

Table 1
Effect of chiral ligand **2** on the asymmetric coupling conducted via Scheme 3[a]

Entry	Mol % of $Pd_2(dba)_3$	Mol % of **2**	Base	Solvent	Temp[b] (°C)	Time[c] (h)	Yield (%)	ee[d] (%)
1	0.5	1.2	KF	THF	50	5	44	30 (*S*)
2	0.5	1.2	KF	THF	75	5	96	33 (*S*)
3	0.5	2.0	KF	THF	75	7	99	42 (*S*)
4	0.5	3.0	KF	THF	75	5	97	34 (*S*)
5[e]	0.05	0.12	KF	THF	75	7	99	40 (*S*)
6	0.5	1.2	KF	Toluene	75	3.5	84	47 (*S*)
7	0.5	1.2	K_2CO_3	Toluene	75	4	37	48 (*S*)
8	0.5	1.2	Na_2CO_3	Toluene	75	4	24	50 (*S*)
9[f]	0.5	1.2	Cs_2CO_3	Toluene	75	6	16	59 (*S*)
10	0.5	1.2	$(C_2H_5)_3N$	Toluene	75	5	33	43 (*S*)
11	0.5	1.2	CsF	Toluene	75	5	96	46 (*S*)
12	0.5	1.2	CsF	Toluene	90	4	99	48 (*S*)
13	0.5	1.2	CsF	Toluene	110	4	>99	42 (*S*)
14	0.05	0.12	CsF	Toluene	90	4	92	45 (*S*)

[a] All reactions were performed in accordance with the representative procedure in Ref. 20, unless otherwise noted.
[b] Oil bath temperature.
[c] The reactions were stopped when the complete formation of Pd black was observed and/or when the starting materials disappeared on TLC monitoring.
[d] The absolute configuration is shown in parenthesis.
[e] The concentration of the aryl chloride was 0.83 M.
[f] The starting aryl chloride was recovered in 79%.

Table 2
Effect of **2**, **3**, and **4** on the asymmetric coupling conducted via Scheme 4[a]

Entry	Base/solvent	Ligand	Mol % of $Pd_2(dba)_3$	Mol % of ligand	Halide	Arylboronic acid	Temp[b] (°C)	Time[c] (h)	Yield (%)	ee[d] (%)
1	KF/THF	**2**	0.25	1.0	**7**	**8**	75	7	84	41 (*S*)
2	KF/THF	**3**	0.25	1.0	**7**	**8**	75	6	79	65 (*S*)
3	KF/THF	**3**	0.25	1.5	**7**	**8**	75	4	90	69 (*S*)
4	KF/THF	**4**	0.25	1.5	**7**	**8**	75	5	94	72 (*R*)
5	CsF/toluene	**3**	0.25	1.0	**7**	**8**	90	4	93	74 (*S*)
6	CsF/toluene	**4**	0.25	1.0	**7**	**8**	90	5	91	78 (*R*)
7	CsF/toluene	**4**	0.05	0.2	**7**	**8**	90	5	75	76 (*R*)
8[e]	CsF/toluene	**3**	0.25	1.0	**7**	**10**	90	5	92	37 (*S*)
9[e]	CsF/toluene	**4**	0.25	1.0	**7**	**10**	90	5	91	47 (*R*)[g]
10[f]	CsF/toluene	**3**	0.25	1.0	**7**	**11**	90	4	63	47
11[f]	CsF/toluene	**4**	0.25	1.0	**7**	**11**	90	4	55	52[h]
12	CsF/toluene	**4**	0.25	1.0	**9**	**11**	90	3	87	33[i]

[a] All reactions were performed in accordance with the representative procedure in Ref. 20, unless otherwise noted.
[b] Oil bath temperature.
[c] The reactions were stopped when the starting aryl chloride was consumed on TLC monitoring.
[d] The absolute configuration is shown in parenthesis.
[e] The absolute configuration was determined on the basis of the proline-derived diamine in Ref. 21
[f] The values of % yield and % ee were calculated after the recrystallization was operated.
[g] $[\alpha]_D^{21} = -16.9$ (*c* 0.50, $CDCl_3$).
[h] $[\alpha]_D^{22} = -2.24$ (*c* 0.49, $CDCl_3$).
[i] $[\alpha]_D^{22} = +39.8$ (*c* 0.50, $CDCl_3$).

reaction of aryl chlorides. These new phosphonite ligands afforded a catalytic system with very low loading (0.5 mol %) and with shortened reaction times compared to previous studies (now ca. 5 h). Under these conditions up to 91% yield and 78% ee were achieved for one set of coupling partners. Additionally, the asymmetric coupling of **7** with **8** with 0.1 mol % catalyst loading and ligand **4** within 5 h gave the resulting chiral biaryl in 75% yield and 76% ee. These results demonstrate a significant advance in the efficiency of the asymmetric cross-coupling reaction of aryl chlorides with aryl boronic acids to give chiral biaryls. Ongoing efforts to en-

hance the enantiomeric excess capability of chiral phosphonite ligands while retaining low catalyst loading and shortened reaction times will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.051.

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12. The phosphonite **2**, **3**, and **4** were applied in the formation of tetra-*ortho*-substituted biaryl: a cross-coupling reaction with 2-(2-chloro-3-methoxyphenyl)-1,3-dioxolane of 2,4,6-trimethylphenylboronic acid. However, any coupling adduct was not observed.
13. *Synthetic procedure for phosphonite* **2**, **3** *and* **4**: To a solution of **6** (136 mg, 0.20 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (0.21 mmol, 1.59 M in hexane) dropwise over 3 min, and the mixture was stirred for 2 h. PCl_3 (29 mg, 0.21 mmol) was slowly added over 2 min, and the reaction was allowed to warm to room temperature. After stirring for 4.5 h, the solvent was thoroughly removed in vacuo, and to the residue was added THF (2 mL) and appropriate chiral diol (0.24 mmol), and then Et_3N (42 mg, 0.42 mmol). After stirring for 10 h at ambient temperature, all the volatiles were evaporated. The mixture was dissolved in benzene (30 mL), and washed with water (30 mL × 2), and brine (30 mL), and dried over Na_2SO_4. Purification by silica gel column chromatography gave a desired molecule. Data of **4** are as follows: yield 70% as a white solid material; $[\alpha]_D^{26}$ −272 (*c* 1.00, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6) δ 9.06 (d, *J* = 7.9 Hz, 1H), 8.54–8.44 (m, 4H), 7.79 (t, *J* = 7.2, 7.2 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.57–6.51 (m, 32H), 5.95 (t, *J* = 7.5, 7.5 Hz, 1H), 1.98 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H), 1.70 (d, *J* = 5.6 Hz, 6H). ^{13}C NMR (100 MHz, C_6D_6) δ 148.4, 148.36, 147.0, 146.6, 143.0, 142.7, 142.0, 141.9, 141.50, 141.46, 140.5, 140.1, 139.5, 139.4, 139.2, 139.14, 139.1, 139.0, 136.2, 135.58, 135.57, 135.42, 135.37, 134.1, 133.4, 133.33, 133.28, 133.1, 132.9, 132.82, 132.76, 132.7, 132.5, 132.3, 132.1, 132.0, 131.2, 130.1, 130.1, 129.8, 129.5, 129.3, 129.18, 129.16, 129.14, 129.13, 129.0, 128.9, 127.8, 128.6, 128.5, 128.4, 128.0, 127.5, 127.3, 126.6, 126.3, 126.0, 124.2, 124.0, 123.94, 123.90, 123.8, 123.0, 121.5, 121.4, 22.0, 21.6, 21.5. ^{31}P NMR (162 MHz, C_6D_6) δ 184.1. MS (FAB) *m*/*z*: 1019 ([M+H]$^+$), 927 ([M−C_7H_7]$^+$). Anal. Calcd for $C_{75}H_{55}O_2P$: C, 88.38; H, 5.44. Found: C, 88.28; H, 5.46.
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20. *The typical procedure of asymmetric cross-coupling reactions* (Table 1, *entry 2*): KF (87 mg, 1.5 mmol) was dried in vacuo in a Schlenk flask with heating (heat gun), then 2-(2-chloro-3-methoxyphenyl)-1,3-dioxolane (107 mg, 0.5 mmol), *o*-tolylboronic acid (102 mg, 0.75 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mg, 0.0025 mmol), and phosphonite **2** (5.5 mg, 0.006 mmol) were added. The whole system was evacuated and backfilled with argon three times, and 1 mL of THF was added. The reaction mixture was stirred at room temperature for 10 min, and then conducted in refluxing THF (oil bath temperature 75 °C) for 5 h. After the reaction, the mixture was diluted with 10 mL of EtOAc, and filtered through a pad of celite and florisil. Purification by silica gel column chromatography gave a desired biaryl[19] (129 mg, 96%) as white needles. The ee was determined by HPLC analysis to be 33% with Daicel Chiralcel OJ (eluted with hexane/^{i}PrOH 75:25, 270 nm, flow rate 0.5 mL/min, column temperature 298 K, and retention times: 14.24 min for *R* with 33.7%; 18.95 min for *S* with 66.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (m, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.28–7.21 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 5.35 (s, 1H), 4.04–3.95 (m, 2H), 3.80–3.72 (m, 2H), 3.67 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 137.6, 137.2, 135.6, 130.68, 130.65, 129.7, 128.9, 127.8, 125.5, 118.8, 111.5, 101.6, 65.69, 65.57, 56.0, 20.3. MS (EI) *m*/*z*: 270 (M$^+$, 100%). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.52; H, 6.75.
21. (a) Bracegirdle, A.; Clayden, J.; Lai, L. W. *Beilstein J. Org. Chem.* **2008**, *4*, 47; b According to Ref. 21a, the product in Table 2 of entry 9 reacted with (*S*)-(+)-2-(anilinomethyl)pyrrolidine to be transformed into diastereo-mixtures. The major isomer afforded the identical assignment with ^{1}H NMR data of a biaryl bearing axial chirality (*R*).
22. The biaryl product in entries 10 and 11 was purified by recrystallization one time to remove small amounts of unclear byproducts.
23. Unfortunately, the derivatives from the cross-coupling reactions of 2-chrolo-3-methoxy benzonitrile **9** with *ortho*-tolylboronic acid **8**, *ortho*-methoxyphenylylboronic acid **10**, and *ortho*-formylphenylboronic acid did not have enough rotation barriers to maintain the axial chirality. The spectra of HPLC indicate that these bialys are racemic compounds even at 298 K.