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Biphenylene-Substituted Ruthenocenylphosphine for Suzuki–Miyaura Coupling of Aryl Chlorides

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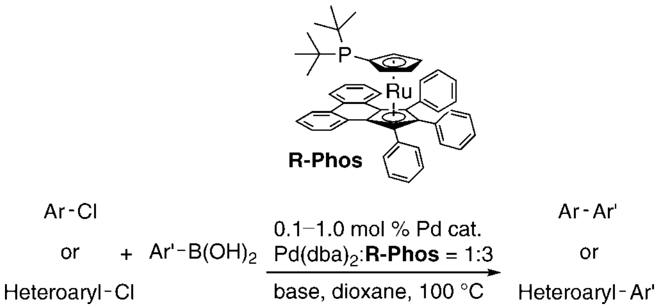
ABSTRACT



High activity in the palladium-catalyzed Suzuki−Miyaura reactions of aryl chlorides with arylboronic acids was furnished using biphenylene-substituted di-*tert*-butylruthenocenylphosphine (R-Phos) as a supporting ligand. Substrate combinations even for the construction of highly hindered tetra-*ortho*-substituted biaryls can be achieved in good to excellent yields with low catalyst loadings in short reaction times.

The use of bulky and electron-rich phosphines and N-heterocyclic carbenes (NHCs) as supporting ligands is now a well-recognized strategy for generating active palladium catalysts for cross-coupling reactions.[1] Excellent phosphine ligands have also been realized using a biaryl backbone involving the lower arene ring *ortho* to phosphine as the key structural element.[2,3] X-ray crystallographic and/or computational studies of palladium complexes bearing such active biaryl-based monophosphine ligands showed that these ligands serve as unique bidentate phosphine−arene ligands and not as simple monodentate phosphine ligands resulting from an interaction between the lower arene ring and the phosphine-ligated palladium center.[3] Buchwald proposed the importance of such the Pd-arene interaction to assist the generation of monophosphine−Pd^0 complexes believed to be catalytic species in the oxidative addition step, with concomitant improvement of their inherent instability associated with the highly coordinatively unsaturated palladium center. In this paper, we describe the development of a

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(1) For recent reviews on effective ligands for palladium-catalyzed cross-coupling reactions, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201. (c) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.

(2) For some recent examples of active biaryl-based monophosphine ligands, see: (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (b) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844. (c) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096. (d) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354. (e) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (f) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 137. (g) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, *9*, 203. (h) Barluenga, J.; Morlel, P.; Aznar, F.; Valdes, C. *Org. Lett.* **2007**, *9*, 275. (i) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597. (j) McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3785. (k) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, *72*, 8422. (l) Biscoe, M. R.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7232. (m) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (n) Zheng, N. Z.; Anderson, K, W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7509.

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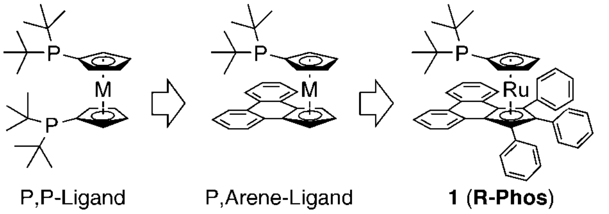
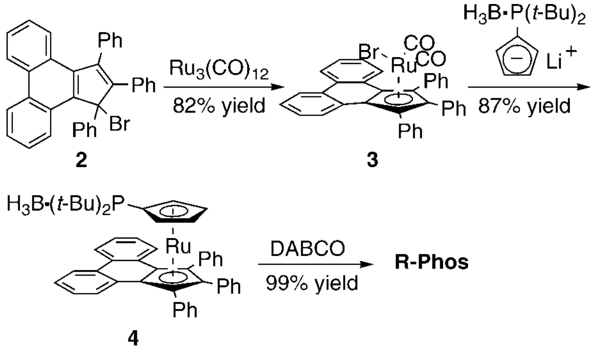
biphenylene-substituted di-*tert*-butylruthenocenylphosphine **1** (R-Phos) designed as a novel phosphine−arene ligand and its high ability to activate the palladium catalyst for Suzuki−Miyaura reactions of aryl chlorides with arylboronic acids,[4] even for the construction of highly hindered tetra-*ortho*-substituted biaryls.

The suggested process leading to the development of R-Phos is illustrated in Scheme 1. The ligand architecture of R-Phos is based on 1,1′-bis(phosphino)metallocene, a well-established bidentate bisphosphine ligand. We anticipated that a phosphine−arene ligand derived from a bidentate bisphosphine ligand by replacement of one phosphino group with an arene group (e.g., the biphenylene group in this study) would have the ability to adopt the chelate geometry in the complex, as has the parent ligand, and therefore would serve as a bidentate ligand for realizing the interaction between the arene ring and the phosphine-ligated palladium center. Furthermore, R-Phos may possess at least two structural advantages for the Pd−arene interaction: (1) the plane biphenylene group fixed parallel to the lower Cp ring, which would be the most preferable conformation for the chelate geometry, and (2) the three phenyl rings incorporated on the lower Cp ring whose steric bulk would control the phosphine-ligated palladium atom to locate on the less sterically demanding biphenylene group. R-Phos can be readily prepared starting from bromocyclopentadiene **2**[5] (Scheme 2). As a metallocene scaffold, we chose ruthenocene, rather than ferrocene, in view of the ready accessibility of its precursor, the bromodicarbonyl ruthenium complex **3**.[6]

Scheme 1. Ligand Design Leading to R-Phos



Scheme 2. Synthesis of R-Phos



In the initial investigation of the performance of R-Phos, we evaluated the Suzuki−Miyaura reactions of aryl chlorides in the presence of 0.1 mol % Pd.[7–9] For a test reaction, we chose 2-chloro-1,3-dimethylbenzene (**5a**) and 2-methylphenylboronic acid (**6a**) as a moderately hindered substrate combination. Actually, there have been only a few ligands found to be effective for this substrate combination with less than 0.1 mol % of Pd.[3e,4g] To obtain a larger proportion of the coordinatively unsaturated active palladium catalyst, a 1:1 ratio of Pd/R-Phos was chosen for preparing the catalyst system.[10] However, under this condition, the cross-coupling product **7a** was obtained in only modest yield (Table 1, entry 1). Even at an early stage of the reaction, the formation of Pd black was observed, indicating decomposition of the active catalyst. Thus, to improve the longevity of the active catalyst, we increased the Pd/R-Phos ratio.[11] As expected, with a 1:2 ratio of Pd/R-Phos, the amount of Pd black was effectively decreased and the yield was clearly improved (Table 1, entry 2). Then, we further increased the Pd/R-Phos

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(4) For recent examples of metallocene-based monophosphine ligands for palladium-catalyzed cross-coupling reactions, see: (a) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (b) Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408. (c) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (d) Pickett, T. E.; Roca, F. X.; Richards, C. J. *J. Org. Chem.* **2003**, *68*, 2592. (e) Jensen, J. F.; Johannsen, M. *Org. Lett.* **2003**, *5*, 3025. (f) Pickett, T. E.; Roca, F. X.; Richards, C. J. *J. Org. Chem.* **2003**, *68*, 2592. (g) Kwong, F. Y.; Chan, K. S.; Yeung, C. H.; Chan, A. S. C. *Chem. Commun.* **2004**, 2336. (h) Baille, C.; Zhang, L.; Xiao, J. *J. Org. Chem.* **2004**, *69*, 7779. (i) Weng, Z.; Teo, S.; Koh, L. L.; Hor, T. S. A. *Organometallics* **2004**, *23*, 4342. (j) Teo, S.; Weng, Z.; Hor, T. S. A. *Organometallics* **2006**, *25*, 1199. (k) Thimmaiah, M.; Fang, S. *Tetrahedron* **2007**, *63*, 6879.

(5) Dennis, G. D.; Edwards-Davis, D.; Field, L. D.; Masters, A. F.; Maschmeyer, T.; Ward, A. J.; Buys, I. E.; Turner, P. *Aust. J. Chem.* **2006**, *59*, 135.

(6) We could not prepare the iron analogue according to similar procedure using $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$.

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(8) For recent reviews on the Suzuki−Miyaura reaction, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (e) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(9) For a review on palladium-catalyzed cross-coupling reactions of aryl chlorides, see ref 1a.

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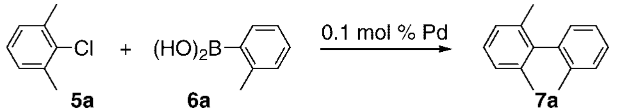
(11) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.

Table 1. Effect of the Pd/R-Phos Ratio on Suzuki−Miyaura Coupling[a]



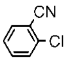
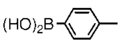
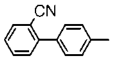
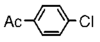
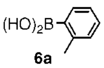
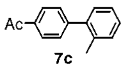
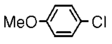
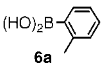
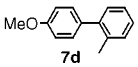
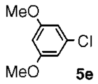
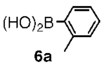
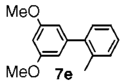
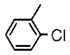
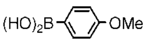
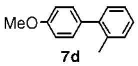
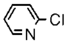
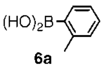
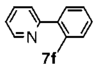
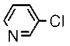
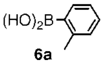
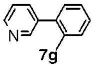
entry	Pd/R-Phos	*t*	Pd black	yield[f] (%)	TOF (h^{-1})
1[b]	1:1	4.5 h	+++	36	80
2[c]	1:2	4 h	+	65	163
3[d]	1:3	35 min	−	97 (3[g])	1662
4[e]	1:5	4 h	−	96 (3[g])	240

[a] Conditions: 1.0 mmol of aryl chloride **5a**, 1.5 equiv of arylboronic acid **6a**, 0.1 mol % Pd(dba)$_2$, 3 equiv of $K_3PO_4 \cdot H_2O$, dioxane, 100 °C. [b] 0.1 mol % of R-Phos. [c] 0.2 mol % of R-Phos. [d] 0.3 mol % of R-Phos. [e] 0.5 mol % of R-Phos. [f] ^{1}H NMR yield. [g] Yield of homocoupling product (2,2′-dimethylbiphenyl).

ratio to 1:3 and found that the formation of Pd black was completely suppressed and the reaction was dramatically accelerated to provide the desired coupling product in 97% yield in less than 35 min (Table 1, entry 3), which was exemplified by 20 and 10 times higher TOF than those of entries 1 and 2.[12] It is noteworthy that a further slight increase in the Pd/R-Phos ratio (1:5) resulted in an extremely slow reaction; however, no Pd black and decrease in the yield were observed (Table 1, entry 4).

Under the optimized conditions, an electronically broad spectrum of aryl chlorides **5b**−**h** also efficiently cross-coupled with arylboronic acids in the presence of only 0.1 mol % of Pd in good to excellent yields in short reaction times (Table 2). On the other hand, in contrast to the success in the coupling of **5a** and **6a** (Table 1, entry 3), the combination of sterically hindered 2,6-dimethylphenylboronic acid (**6d**) and 2-chlorotoluene (**5f**) gave the same product in only modest yield after 5 h under the same conditions (Table 3, entry 1). Even with 0.5 mol % of Pd, the yield was only slightly improved (Table 3, entry 2). GC monitoring of the reaction showed the formation of a significant amount of *m*-xylene, suggesting the serious competition of the undesired protodeboronation, a well-known drawback associated with sterically hindered arylboronic acids.[13] In fact, this transformation with excess boronic acid afforded nearly quantitative yield in only 40 min (Table 3, entry 3). Thus, to decrease the extent of protodeboronation, we reduced the amount of the proton source in the reaction system by replacing $K_3PO_4 \cdot H_2O$ with an anhydrous one.[14] As expected, with this modified method, 1.5 equiv of boronic acid was sufficient to effect this coupling in good yield (Table 3, entry 4).

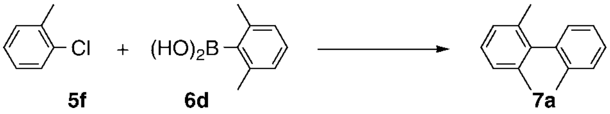
Table 2. Suzuki−Miyaura Coupling with 0.1 mol % of Pd Catalyst[a]

entry	ArCl	Ar′B(OH)$_2$	*t*	product	yield (%)
1	 **5b**	 **6b**	15 min	 **7b**	97
2[b]	 **5c**	 **6a**	1 h	 **7c**	99
3	 **5d**	 **6a**	1.5 h	 **7d**	76
4	 **5e**	 **6a**	30 min	 **7e**	99
5	 **5f**	 **6c**	1 h	 **7d**	96
6	 **5g**	 **6a**	15 min	 **7f**	95
7	 **5h**	 **6a**	20 min	 **7g**	100

[a] Conditions: 1.0 mmol of aryl chloride **5**, 1.5 equiv of arylboronic acid **6**, 0.1 mol % of Pd(dba)$_2$, 0.3 mol % of R-Phos, 3 equiv of $K_3PO_4 \cdot H_2O$, dioxane, 100 °C. [b] THF, reflux.

To evaluate the versatility of our catalytic system further, we examined the construction of tetra-*ortho*-substituted biaryls from aryl chlorides, which has emerged as an extremely difficult task in Suzuki−Miyaura reactions.[3b,14,15] In our initial investigation, the reaction of **5a** with 3 equiv of 2,4,6-trimethylphenylboronic acid (**6e**) was executed in the presence of 1.0 mol % of Pd, and we found that the

Table 3. Suzuki–Miyaura Coupling of Sterically Hindered Arylboronic Acid **6d**[a]



entry	Pd (mol %)	base	*t*	yield (%)
1[b]	0.1	$K_3PO_4 \cdot H_2O$	5 h	27
2[c]	0.5	$K_3PO_4 \cdot H_2O$	5 h	56
3[c,d]	0.5	$K_3PO_4 \cdot H_2O$	40 min	95
4[c]	0.5	K_3PO_4	4 h	80

[a] Conditions: 1.0 mmol of aryl chloride **5f**, 1.5 equiv of arylboronic acid **6d**, 3 equiv of base, dioxane, 100 °C. [b] 0.1 mol % of Pd(dba)$_2$, 0.3 mol % of R-Phos. [c] 0.5 mol % of Pd(dba)$_2$, 1.5 mol % of R-Phos. [d] 3 equiv of arylboronic acid **6d**.

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(12) For some examples of the beneficial effect of increasing the ligand/Pd ratio on catalytic activity, see: (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690.

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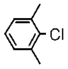
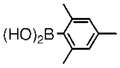
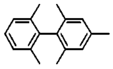
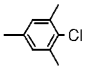
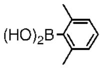
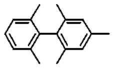
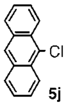
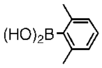
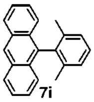
(14) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.

(15) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Anders, M. *Tetrahedron* **2005**, *61*, 7438.

desired biphenyl **7h** was obtained in 94% yield in 2 h (Table 4, entry 1). The same coupling product **7h** could also be furnished from the alternative substrate combination in good yield under the same condition (Table 4, entry 2). The reaction of 9-chloroanthracene (**5j**) proceeded much more rapidly to furnish the coupling product **7i** in 85% yield within 20 min (Table 4, entry 3).

Table 4. Suzuki−Miyaura Coupling for the Construction of Tetra-*ortho*-substituted Biaryls[a]

entry	ArCl	Ar'B(OH)$_2$	*t*	product	yield[d] (%)
1[b]	 **5a**	 **6e**	2 h	 **7h**	94 (4[e])
2[c]	 **5i**	 **6d**	2 h	 **7h**	80 (6[f])
3[c]	 **5j**	 **6d**	20 min	 **7i**	85 (3[f])

[a] Conditions: 1 mol % of Pd(dba)$_2$, 3 mol % of R-Phos, 1 equiv of aryl chloride **5**, 3 equiv of arylboronic acid **6**, 3 equiv of K_3PO_4, dioxane, 100 °C. [b] 1.0 mmol of aryl chloride. [c] 0.5 mmol of aryl chloride. [d] ^{1}H NMR yield. [e] Yield of homocoupling product (2,2′,4,4′,6,6′-hexamethylbiphenyl). [f] Yield of homocoupling product (2,2′,6,6′-tetramethylbiphenyl).

In summary, we described the design, development, and high activity of a biphenylene-substituted ruthenocene-based phosphine, R-Phos, as a supporting ligand for palladium-catalyzed Suzuki−Miyaura reactions of aryl chlorides with arylboronic acids. In particular, at a 1:3 Pd/R-Phos ratio, substrate combinations even for the construction of highly hindered tetra-*ortho*-substituted biaryls can be achieved in good to excellent yields with low catalyst loadings in short reaction times. Taking these results together with the high activity of the catalyst, our catalytic system is operationally simple and practical and requires no special handling such as the use of a glovebox. In actuality, R-Phos in the solid state can be handled in air at least during catalyst preparation. Furthermore, commercially available aryl chlorides, arylboronic acids, and bases can be used without further purification. Further work to expand the scope of substrates and understand the origin of the activation ability of R-Phos for Suzuki−Miyaura reactions is underway in our laboratory. Studies toward the application of our catalyst system to additional palladium-catalyzed cross-coupling processes are also ongoing.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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