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Air-Stable PinP(O)H as Preligand for Palladium-Catalyzed Kumada Couplings of Unactivated Tosylates

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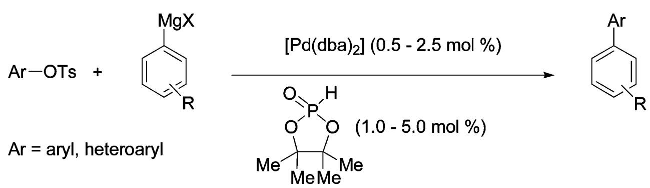
ABSTRACT



Air-stable and easily accessible PinP(O)H enables highly efficient palladium-catalyzed Kumada cross-coupling reactions of aryl tosylates. The in situ generated catalyst proved applicable not only to electron-rich and electron-poor carbocyclic tosylates but also to heterocyclic tosylates, such as pyridine and quinoline derivatives. The results described herein constitute the first use of air-stable secondary phosphine oxides as preligands for transition-metal-catalyzed coupling reactions between organometallic species and tosylates.

Palladium-catalyzed coupling reactions between organic electrophiles and organometallic reagents are reliable and versatile tools for the regioselective formation of carbon−carbon bonds involving two sp^2-hybridized carbons.[1,2] Usually, aryl triflates, bromides, and more recently chlorides[3] are employed as electrophiles.[4] Diversely substituted aryl tosylates are readily available from the corresponding phenols and inexpensive reagents. Therefore, and because of their significantly increased stability toward hydrolysis when compared to the corresponding triflates, they constitute attractive substrates in cross-coupling reactions. However, this superior stability translates into an inferior reactivity in palladium-catalyzed coupling chemistry. Consequently, the conversion of electronically unactivated aryl tosylates usually requires electron-rich tertiary phosphines as stabilizing ligands.[5] Specifically, generally applicable palladium-catalyzed cross-coupling reactions between organomagnesium reagents and unactivated aryl tosylates were only reported for a palladium complex derived from an electron-rich analogue of a Josiphos ligand.[6,7]

Recently, we reported on the use of heteroatom-substituted[8] secondary phosphine oxides, *H*-phosphonates and their derivatives, as modular and air-stable preligands for cross-coupling reactions using aryl and vinyl chlorides[9,10] or fluorides,[11] as well as direct arylation reactions employing chlorides[12] and tosylates.[13−15] In continuation of our studies, we report on palladium-catalyzed Kumada cross-coupling

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(2) Beller, M., Bolm, C., Eds., *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004.
(3) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.
(4) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004.
(5) Selected examples: (a) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P. O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, DOI: 10.1002/anie.200600442. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819. (c) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996 and references cited herein.
(6) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704−8705.
(7) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364−9370.
(8) For seminal work on the use of alkyl-substituted secondary phosphine oxides, see: (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. Kumada coupling reactions: (b) Li, G. Y. *J. Organomet. Chem.* **2002**, *653*, 63−68. (c) Li, G. Y.; Marshall, W. J. *Organometallics* **2002**, *21*, 590−591.
(9) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444−2447.
(10) Ackermann, L.; Gschrei, C. J.; Althammer, A.; Riederer, M. *Chem. Commun.* **2006**, 1419−1421.

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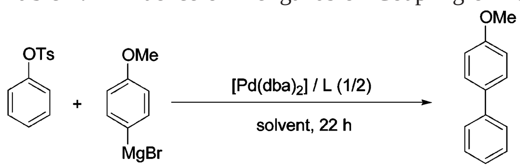
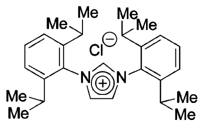
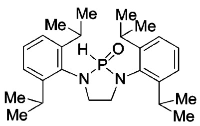
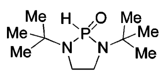
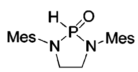
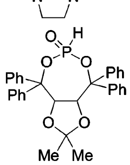
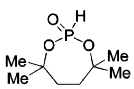
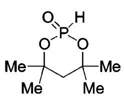
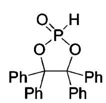
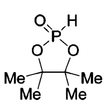
Table 1. Influence of Preligands on Coupling of Tosylate **1a**[a]



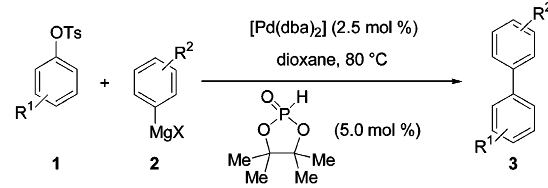
1a **2a** **3a**

entry	ligand			$[Pd(dba)]_2$ (mol %)	isolated yield
1	---	---	A/B	5.0	---
2		**4**	A	1.0	(40 %)[b]
3		**5**	B	5.0	(< 3 %)[b]
4		**6**	B	5.0	(15 %)[b]
5		**7**	B	5.0	49 %
6		**8**	B	5.0	83 %
7			A	0.5	90 %
8		**9**	A	1.0	80 %
9		**10**	A	1.0	88 %
10		**11**	A	1.0	68 %
11		**12**	A	0.5	93 %

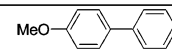
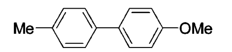
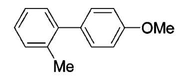
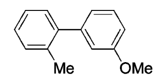
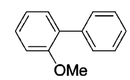
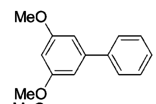
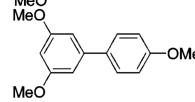
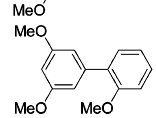
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $[Pd(dba)_2]$ (0.5−5.0 mol %), ligand (1.0−10.0 mol %). A: dioxane (4.0 mL), 80 °C. B: THF (4.0 mL), 60 °C. Yields of isolated products. [b] Determined by GC analysis.

reactions of differently substituted (hetero)aryl tosylates employing an air-stable and easily accessible preligand. The results presented herein constitute the first use of air-stable secondary phosphine oxides as preligands in transition-metal-catalyzed cross-couplings between organometallic reagents and aryl tosylates.

Table 2. Cross-Coupling with Electron-Rich Aryl Tosylates[a]



1 **2** **12** **3**

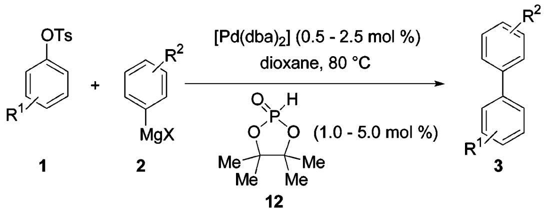
entry	R^1	R^2	product	isolated yield
1	4-MeO	H		93 %
2	4-Me	4-MeO		94 %
3	2-Me	4-MeO		92 %
4	2-Me	3-MeO		86 %
5	2-MeO	H		93 %
6	3,5-$(MeO)_2$	H		95 %
7	3,5-$(MeO)_2$	4-MeO		95 %
8	3,5-$(MeO)_2$	2-MeO		93 %

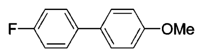
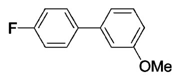
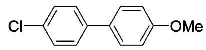
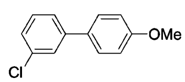
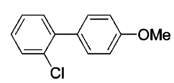
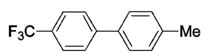
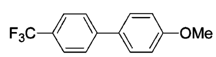
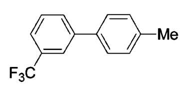
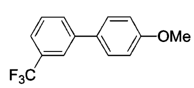
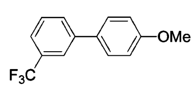
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $[Pd(dba)_2]$ (2.5 mol %), **12** (5.0 mol %), dioxane (4.0 mL), 80 °C, 22 h, yields of isolated products.

At the outset of our studies, we screened a variety of preligands in the cross-coupling reaction of electronically unactivated tosylate **1a** (Table 1). Imidazolium chloride **4** as precursor for a sterically congested *N*-heterocyclic carbene (entry 2) and diaminophosphine oxides **5**−**7** (entries 3−5) provided unsatisfactory results. As observed for Kumada couplings with chlorides,[10] TADDOLP(O)H (**8**)[16] enabled more efficient conversion of tosylate **1a** (entry 6). Among a variety of solvents, dioxane proved superior. Importantly, the catalyst loading could be significantly reduced (entry 7). As TADDOLP(O)H (**8**) is prepared in several steps and exhibits a high molecular weight, we desired to develop a more easily accessible preligand. On the basis of the modular ligand design, we identified a number of cyclic[17] *H*-phosphonates derived from vicinal diols that enable cross-coupling reactions of electronically unactivated tosylate **1a**

(11) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216−7219.
(12) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123−3125.
(13) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619−2622.
(14) Ackermann, L. *Synthesis* **2006**, 1557−1571.
(15) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209−214.
(16) Enders, D.; Tedeschi, L.; Bats, J. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4605−4607.

Table 3. Cross-Coupling with Electron-Poor Aryl Tosylates[a]



entry	R[1]	R[2]	[Pd(dba)]$_2$ (mol %)	product	isolated yield
1	4-F	4-MeO	2.5		93 %
2	4-F	3-MeO	2.5		78 %
3	4-Cl	4-MeO	2.5		88 %
4	3-Cl	4-MeO	2.5		87 %
5	2-Cl	4-MeO	2.5		89 %
6	4-CF$_3$	4-Me	0.5		91 %
7	4-CF$_3$	4-MeO	0.5		92 %
8	3-CF$_3$	4-Me	0.5		87 %
9	3-CF$_3$	4-MeO	0.5		94 %
10	3-CF$_3$	4-MeO	1.0		95 %[b]

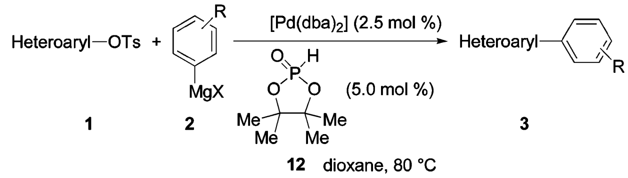
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), [Pd(dba)$_2$] (0.5−2.5 mol %), **12** (1.0−5.0 mol %), dioxane (4.0 mL), 80 °C, 22 h, yields of isolated products. [b] Performed at ambient temperature.

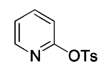
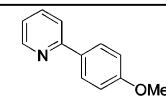
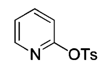
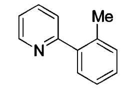
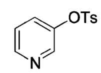
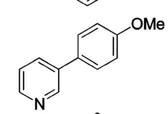
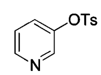
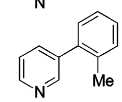
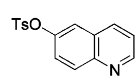
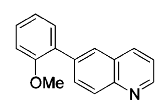
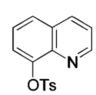
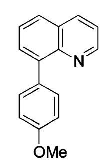
(entries 8−11). Interestingly, most efficient catalysis was accomplished with air-stable *H*-phosphonate PinP(O)H **12**[18] (entry 11), which is synthesized on a multigram scale in a single reaction from inexpensive pinacol.

With an improved and highly economical catalyst for Kumada cross-couplings of tosylates in hand, we explored the scope of this transformation.[19]

(17) Acyclic *H*-phosphonate (EtO)$_2$P(O)H and alkyl-substituted secondary phosphine oxide (1-Ad)$_2$P(O)H proved inferior, giving 11% and 58% conversion, respectively, using 5 mol % [Pd(dba)$_2$] in THF at 60 °C under otherwise identical reaction conditions.

Table 4. Cross-Coupling with Heteroaromatic Tosylates[a]



entry	1	R	product	isolated yield
1		4-MeO		99 %
2		2-Me		92 %
3		4-MeO		98 %
4		2-Me		85 %
5		2-MeO		98 %
6		4-MeO		91 %[b]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), [Pd(dba)$_2$] (2.5 mol %), **12** (5.0 mol %), dioxane (4.0 mL), 80 °C, 22 h, yields of isolated products. [b] GC conversion.

Diversely substituted electron-rich and thereby electronically deactivated aryl tosylates were efficiently converted (Table 2). Therefore, a mechanism based on a simple nucleophilic susbtitution is less likely. High yields of isolated products were observed even for tosylates bearing ortho-substituents (entries 3−5) or two electron-releasing functionalities (entries 6−8).

The palladium catalyst derived from air-stable PinP(O)H (**12**) proved also applicable to electron-poor aryl tosylates **1** (Table 3). Interestingly, the tosylate was a superior leaving

(18) Munoz, A.; Hubert, C.; Luche, J.-L. *J. Org. Chem.* **1996**, *61*, 6015−6017.

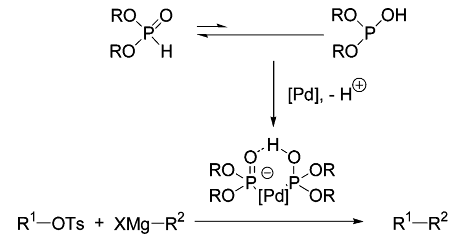
(19) **Representative Procedure.** A solution of [Pd(dba)$_2$] (2.9 mg, 0.005 mmol, 0.5 mol %) and PinP(O)H (**12**) (1.6 mg, 0.010 mmol, 1.0 mol %) in dry dioxane (4.0 mL) was stirred under N_2 for 5 min at ambient temperature and then treated with **2a** (3.0 mL, 0.5 M in THF, 1.50 mmol). The resulting mixture was stirred for 5 min at ambient temperature. Thereafter, **1a** was added, and the resulting suspension was stirred at 80 °C for 22 h. At ambient temperature, aqueous HCl (2.0 mL, 2.0 N), Et_2O (50 mL), and H_2O (30 mL) were added. The separated aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O = 200/1) to yield **3a** (171 mg, 93%) as a colorless solid (mp 85.1−85.4 °C).

group when compared to a fluoride (entries 1 and 2) or even a chloride[7] substituent (entries 3−5).

Nitrogen-containing heterocycles are ubiquitous in biologically active compounds, but the use of substrates bearing *N*-heterocyclic moieties was shown to be detrimental to the catalytic activity of the Josiphos-based palladium complex.[7,20] On the contrary, a palladium catalyst derived from air-stable PinP(O)H (**12**) proved applicable to heterocyclic tosylates (Table 4). Thereby, the synthesis of regioselectively substituted heterocycles, such as pyridine (entries 1−4) and quinoline (entries 5−7) derivatives, was achieved.

As for the working mode of the catalyst, we propose a formation of a hydrogen-bond-stabilized bidentate as outlined in Scheme 1.[14] This likely leads to a heterobimetallic[21] complex in the presence of a Grignard reagent.[14,22]

Scheme 1. Tautomerization and Complex Formation of *H*-Phosphonates Used as Preligands in Catalysis



In conclusion, we have reported on the unprecedented use of a secondary phosphine oxide as preligand for cross-coupling reactions between aryl tosylates and organometallic reagents. Importantly, the catalyst derived from easily accessible PinP(O)H proved applicable to Kumada cross-coupling reactions of electron-rich as well as electron-poor aryl tosylates, including heteroaromatic electrophiles.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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