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Phosphine Oxides as Preligands in Ruthenium-Catalyzed Arylations via C–H Bond Functionalization Using Aryl Chlorides

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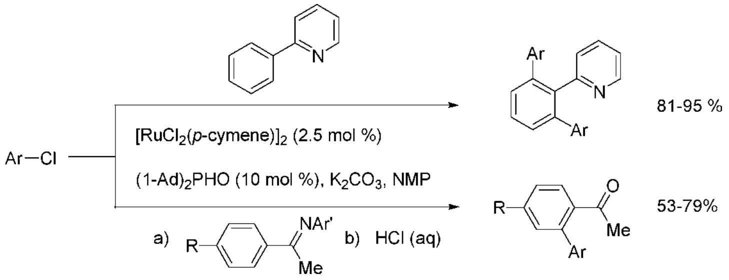
ABSTRACT



The use of air-stable, electron-rich phosphine oxides as preligands allows for unprecedented general ruthenium-catalyzed arylation reactions of pyridines and imines through C–H-bond activation using aryl chlorides. The catalytic system derived from a sterically hindered adamantyl-substituted phosphine oxide proves highly efficient and tolerates a number of important functional groups.

Transition-metal-catalyzed cross-coupling reactions of organometallic reagents such as organoboron or -tin compounds with aryl halides constitute reliable tools for the syntheses of biaryls.[1] However, the organometallic starting materials are frequently not commercially available, are expensive, and give rise to undesired byproducts. These problems can potentially be circumvented by developing protocols for the direct cross-coupling of organic compounds via C−H-bond functionalization. Comparably few examples of such intermolecular transformations have been described.[2] Methodologies for both the directed ortho-arylation of benzene derivatives[3−5] and the regioselective arylation of heterocyclic compounds[6] using aryl iodides and bromides have been developed. More readily available aryl chlorides, on the contrary, have only rarely been used. Particularly, a general protocol for ruthenium-catalyzed arylations[5,7] employing inexpensive, but less reactive, aryl chlorides has proven elusive.[8]

Recently, Sames et al. showed elegantly that an anionic phosphido ligand, formed in-situ from PPh$_3$ through C−P-

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(1) de Meijere, A., Diederich, F., Eds. *Metal-catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.

(2) (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212−237.

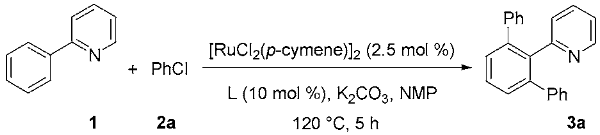
(3) Palladium-catalysis: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742. (b) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407−10408. (c) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236−5243. (d) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156−4157; and references therein.

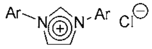
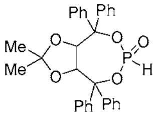
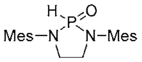
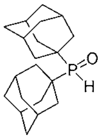
(4) Rhodium-catalysis: (a) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669−8682. (b) Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665−8668; and references therein.

(5) Ruthenium-catalysis: (a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579−2581. (b) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783−1785. (c) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698−1699. (d) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113−3119.

10.1021/ol051216e CCC: $30.25

Table 1. C−H Bond Activation of Pyridine **1** Employing Aryl Chloride **2a**[a]

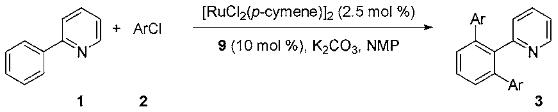


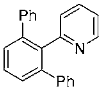
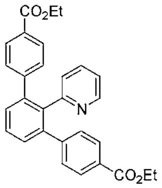
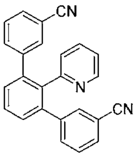
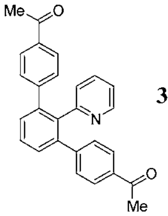
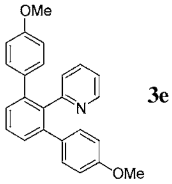
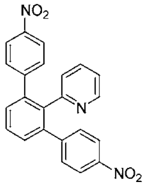
entry	ligand		yield (%)[b]
1		**4**	42
2	Ph_2PHO	**5**	54
3		**6**	8
4		**7**	61
5	tBu_2PHO	**8**	61
6		**9**	72
7			61[c]
8			> 98[d]

[a] Reaction conditions: **1** (1.0 mmol), **2a** (2.2 mmol), K_2CO_3 (3.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), ligand (10 mol %), NMP (2 mL); Ar = 2,6-$(i\text{-Pr})_2C_6H_3$. [b] Determined by GC-analysis. [c] NMP (2 mL), H_2O (1 mL), 20 h. [d] 24 h.

bond cleavage, gives rise to the catalytically active species in a ruthenium-catalyzed arylation of pyridine with iodobenzene.[9] Anionic P-bonded ligands are also obtained by reaction of air-stable phosphine oxides[10] with transition-metal complexes.[11] Consequently, such preligands[12] were probed in ruthenium-catalyzed arylation reactions through C−H-bond activation using aryl chlorides.

Table 2. Scope of Directed C−H Bond Activation of Pyridine **1**[a]



entry	Ar	t (h)	product		isolated yield
1	Ph **2a**	24		**3a**	95 %
2	4-$EtO_2CC_6H_4$ **2b**	8		**3b**	85 %
3	3-NCC_6H_4 **2c**	8		**3c**	81 %
4	4-$MeCOC_6H_4$ **2d**	10		**3d**	83 %
5	4-$MeOC_6H_4$ **2e**	24		**3e**	87 %
6	4-$O_2NC_6H_4$ **2f**	18		**3f**	---

[a] Reaction conditions: **1** (1.0 mmol), **2** (2.2 mmol), K_2CO_3 (3.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), **9** (10 mol %), NMP (2 mL), 120 °C.

On the outset of the studies a range of different ligands were tested in the ruthenium-catalyzed directed arylation of 2-phenylpyridine[5a] (**1**) using chlorobenzene (**2a**) (Table 1). While N-heterocyclic carbene precursor **4**[13,14] (entry 1) as well as phosphine oxides **5**, **6**,[15] **7**,[12] and **8**[16] (entries 2−5) enabled diarylation, the adamantyl-derivative **9** gave more

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(6) Selected examples: (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286−5287. (b) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700−1701. (c) Gallagher, W.; Maleczka, R. E. *J. Org. Chem.* **2003**, *68*, 6775−6779. (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275. (e) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607−3610. (f) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35−38. (g) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyn, V. *Org. Lett.* **2004**, *6*, 1159−1162. (h) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284−5285; and references therein.

(7) Kakiuchi, F.; Chatani, N. In *Ruthenium in Organic Synthesis*; Murahashi; S.-I., Ed.; Wiley-VCH: Weinheim 2004; pp 219−255.

(8) For a single low-yielding example, see ref 5b.

(9) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648−3649.

(10) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883−5886.

(11) (a) Beaulieu, W. B.; Rauchfuss, T. B.; Roundhill, D. M. *Inorg. Chem.* **1975**, *14*, 1732−1734. (b) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643−3650. (c) For the synthesis of a related ruthenium complex, see: Chan, E. Y. Y.; Zhang, Q.-F.; Sau, Y.-K.; Lo, S. M. F.; Sung, H. H. Y.; Williams, I. D.; Haynes, R. K.; Leung, W.-H. *Inorg. Chem.* **2004**, *43*, 4921−4926.

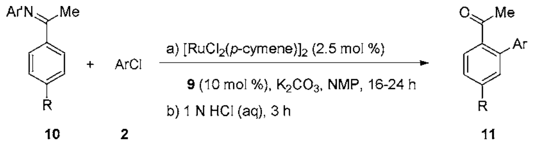
(12) For the use of diaminophosphine oxides in Suzuki-reactions, see: Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444−2447.

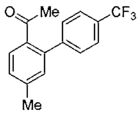
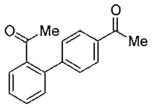
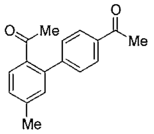
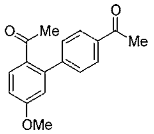
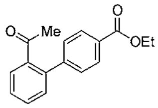
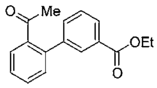
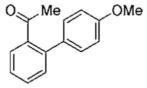
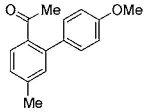
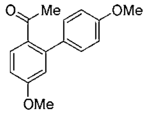
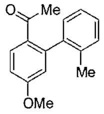
(13) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.

(14) For studies on the use of in-situ generated carbene complexes from this laboratory, see: (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824−2825. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 439−442.

(15) Enders, D.; Tedeschi, L.; Bats, J. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4605−4607.

Table 3. C−H Bond Functionalization with Aryl Chlorides **2**[a]



entry	R	Ar	product		isolated yield
1	Me **10a**	4-$F_3CC_6H_4$ **2g**		**11a**	75 %
2	H **10b**	4-$MeCOC_6H_4$ **2d**		**11b**	79 %
3	Me **10a**	4-$MeCOC_6H_4$ **2d**		**11c**	77 %
4	MeO **10c**	4-$MeCOC_6H_4$ **2d**		**11d**	56 %
5	H **10b**	4-$EtO_2CC_6H_4$ **2b**		**11e**	72 %
6	H **10b**	3-$EtO_2CC_6H_4$ **2h**		**11f**	54 %
7	H **10b**	4-$MeOC_6H_4$ **2e**		**11g**	74 %
8	Me **10a**	4-$MeOC_6H_4$ **2e**		**11h**	77 %
9	MeO **10c**	4-$MeOC_6H_4$ **2e**		**11i**	69 %
10	MeO **10c**	2-MeC_6H_4 **2i**		**11j**	65 %[b]

[a] Reaction conditions: **10** (1.0 mmol), **2** (1.2−2.2 mmol), K_2CO_3 (2.0−3.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), **9** (10 mol %), NMP (2 mL), 120 °C, 3 Å mol-sieves, Ar′ = 4-$MeOC_6H_4$. [b] $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), **9** (20 mol %).

efficient catalysis (entries 6−8). Note that **9** is directly accessible from inexpensive adamantane on a multigram scale in two reaction steps.[17] Reagent grade K_2CO_3 was employed as stoichiometric base without the need for prior drying, proving the tolerance of the catalytic system to the presence of water (entry 7).

The optimized catalyst allowed for quantitative conversion of both electron-poor (Table 2, entries 2−4) and electron-rich aryl chlorides (entry 5) with good to excellent isolated yields. Importantly, a wide variety of important functional groups, such as an ester (entry 2), a cyano group (entry 3), and an enolizable ketone (entry 4), were tolerated by the catalytic system. However, nitro-substituted aryl chloride **2f** was not converted.

Given the practical importance of imines for organic synthesis, phosphine oxide **9** was probed as preligand in the ruthenium-catalyzed functionalization of differently substituted ketimines with aryl chlorides (Table 3).[5b] Subjection of ketimines **10** and aryl chlorides **2** to the reaction conditions yielded selectively the monoarylated products. The corresponding ketones were isolated after hydrolysis in high yields. Again, electron-poor (entries 1−6) as well as electron-rich aryl chlorides (entries 7−10) could be employed. Not only meta- but also ortho-substituted aryl chlorides were efficiently converted (entries 6 and 10). The functional group tolerance of the catalytic system constitutes a valuable asset of the present protocol.

In summary, the use of air-stable adamantyl-substituted secondary phosphine oxide **9** as preligand enables unprecedented ruthenium-catalyzed diarylation of pyridines and mono-arylation of imines via C−H-bond functionalization using diversely substituted aryl chlorides. The catalytic system shows good tolerance of functional groups, such as enolizable ketones, nitriles, and esters. Mechanistic studies as well as further applications of the present catalytic system are ongoing and will be reported in due course.

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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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(16) Examples for the use in cross-coupling reactions: (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (b) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147−1150; and references therein.

(17) Goerlich, J. R.; Fischer, A.; Jonas, P. G.; Schmutzler, R. *Z. Naturforsch.* **1994**, *49b*, 801−811.