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C−H Bond Arylations and Benzylations on Oxazol(in)es with a Palladium Catalyst of a Secondary Phosphine Oxide

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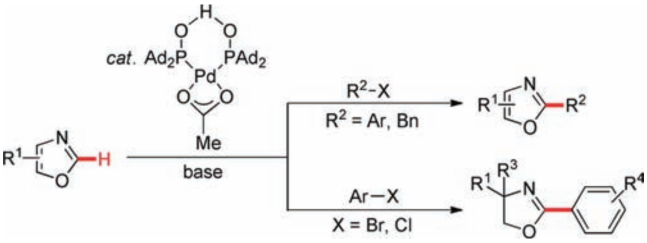
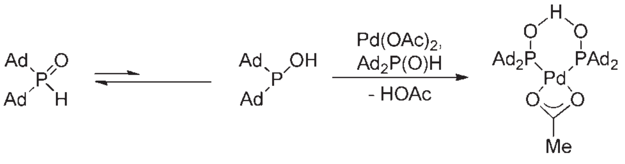
ABSTRACT



An air-stable, well-defined palladium complex derived from secondary phosphine oxide (SPO) $(1\text{-}Ad)_2P(O)H$ enabled efficient C−H bond functionalizations with ample scope, which set the stage for direct arylations and benzylations of (benz)oxazoles, as well as unprecedented palladium-catalyzed C−H bond arylations on nonaromatic oxazolines.

Secondary phosphine oxides (SPOs) are air- and moisture-stable preligands, which form in a self-assembly process late transition metal complexes bearing hydrogen bond-stabilized bidentate ligands (Scheme 1).[1] In recent years, these complexes were shown to be remarkably active catalysts for traditional cross-coupling reactions between aryl (pseudo)halides and organometallic reagents.[2] For instance, particularly palladium(II) complex **1** allowed for challenging arylations of 2-pyridyl Grignard reagents with low nucleophilicities.[3]

Scheme 1. Synthesis of Complex **1** via a Self-Assembly Process



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Within our program directed toward more sustainable syntheses without prefunctionalized starting materials,[4] we observed that complex **1** serves as efficient catalyst for economically and ecologically more attractive direct C−H bond functionalizations.[5−7] Thus, phosphinous acid complex **1** allowed among others for efficient direct benzylations of azoles, as well as first palladium-catalyzed direct arylations[8] of challenging oxazolines—versatile building blocks in organic synthesis.[9]

At the outset of our studies, we evaluated the efficacy of representative palladium catalysts in the direct

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(1) Reviews: (a) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (b) Ackermann, L. *Synthesis* **2006**, 1557–1571. (c) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (d) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883–5886. See also: (e) Nemoto, T.; Hamada, Y. *Tetrahedron* **2011**, *67*, 667–687.

(2) For representative examples, see: (a) Hu, D.-F.; Weng, C.-M.; Hong, F.-E. *Organometallics* **2011**, *30*, 1139–1147. (b) Ackermann, L.; Kapdi, A. R.; Schulzke, C. *Org. Lett.* **2010**, *12*, 2298–2301. (c) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276. (d) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381–384. (e) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638–7650. (f) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167. (g) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601–8604. (h) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516. See also: (i) Ackermann, L.; Kapdi, A. R.; Fenner, S.; Kornhaass, C.; Schulzke, C. *Chem.—Eur. J.* **2011**, *17*, 2965–2971. (j) Ackermann, L.; Potukuchi, H. K. *Synlett* **2009**, 2852–2856.

(3) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.—Eur. J.* **2010**, *16*, 3300–3303.

(4) (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (b) Ackermann, L. *Synlett* **2007**, 507–526.

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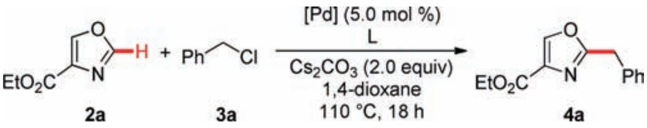
Table 1. Optimization of Direct Benzylation of Oxazole **2a**[a]



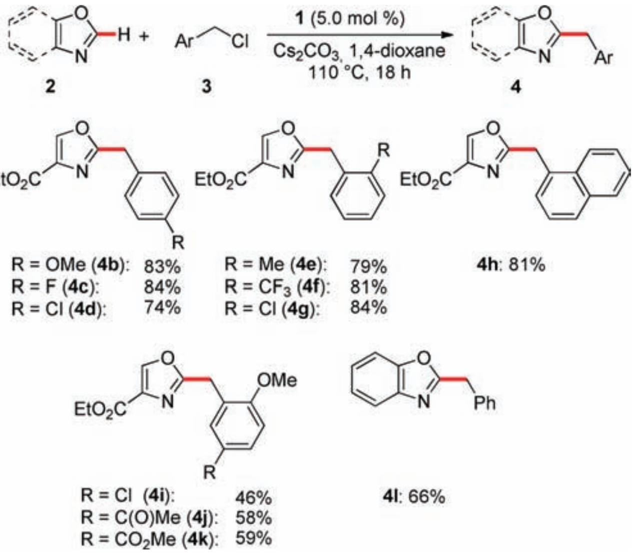
entry	[Pd]	L (mol %)	yield
1	–	–	–
2	$[Pd_2(dba)_3]$	–	–
3	$[Pd_2(dba)_3]$	X-Phos (10)	54%
4	$[Pd_2(dba)_3]$	SHIPrCl (5.0)	75%
5	$[Pd_2(dba)_3]$	HIPrCl (5.0)	59%
6	$[Pd_2(dba)_3]$	Xantphos (5.0)	(15%)[b]
7	$[Pd_2(dba)_3]$	dppf (5.0)	16%
8	$[Pd_2(dba)_3]$	*rac*-BINAP (5.0)	32%
9	$[Pd_2(dba)_3]$	dppe (5.0)	74%
10	$Pd(OAc)_2$	HIPrCl (10)	61%
11	$Pd(OAc)_2$	John-Phos (10)	62%
12	$Pd(OAc)_2$	Dave-Phos (10)	43%
13	$Pd(OAc)_2$	dppe (5.0)	51%
14	$[Pd(SIPr)(3\text{-}ClPy)Cl_2]$	–	69%
15	**1**	–	97%

[a] Reaction conditions: **2a** (1.0 mmol), **3a** (1.0 mmol), [Pd] (5.0 mol %), L (5.0–10 mol %), Cs_2CO_3 (2.0 mmol), 1,4-dioxane (3.0 mL), 110 °C, 18 h; X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; (S)HIPr = *N*,*N*′-bis-(2,6-diisopropylphenyl)imidazol(in)ium; John-Phos = 2-(dicyclohexylphosphino)biphenyl; Dave-Phos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; isolated yields. [b] GC-conversion.

benzylation[10] of oxazole **2a** (Table 1). Among various palladium catalysts, promising results were accomplished with in situ generated or preformed palladium complexes derived from N-heterocyclic carbenes (entries 4, 5, 10, and 14) or bidentate ligand dppe (entries 9, and 13). However, palladium(II) complex **1** provided a significantly improved yield of desired product **4a** (entry 15).

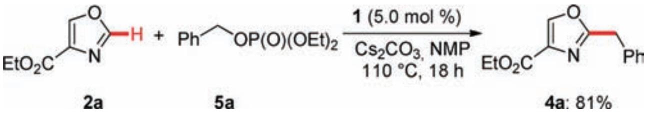
Subsequently, we tested air-stable complex **1** in the direct benzylation of heteroarenes **2** with differently substituted benzyl chlorides **3** (Scheme 2). Hence, we observed that valuable electrophilic functional groups were well tolerated by the catalyst.

Scheme 2. Scope of Direct Benzylation of Azoles **2**



Moreover, complex **1** also proved applicable to the challenging conversion of benzyl phosphate **5a** as electrophile (Scheme 3). Importantly, the yield of product **4a** turned out to be improved as compared to a previously reported catalytic system (dppe as the ligand: 69%).[10g]

Scheme 3. Direct Benzylation with Phosphate **5a** as Electrophile



It is noteworthy that subsequent direct benzylations[10h] and alkylations on product **4l** occurred even in the absence

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(5) Select recent reviews on metal-catalyzed C–H bond functionalizations: (a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992–2002. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (f) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (g) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (h) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (k) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (l) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (m) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352–10361. (n) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (o) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096–2098. (p) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev* **2009**, *38*, 3242–3272. (q) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (r) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (s) Ackermann, L.; Vicente, R; Kapdi, A. *Angew. Chem., Int. Ed* **2009**, *48*, 9792–9826. (t) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (u) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (v) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (w) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (x) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (y) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and references cited therein.

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(7) For SPO $(1\text{-}Ad)_2P(O)H$ as preligand in ruthenium-catalyzed C–H bond functionalizations, see: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125.

(8) For a very recent example of palladium-catalyzed direct *alkynylation*, see: Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868–1871.

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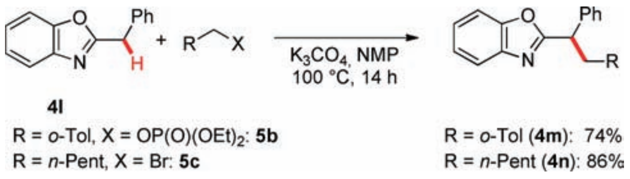
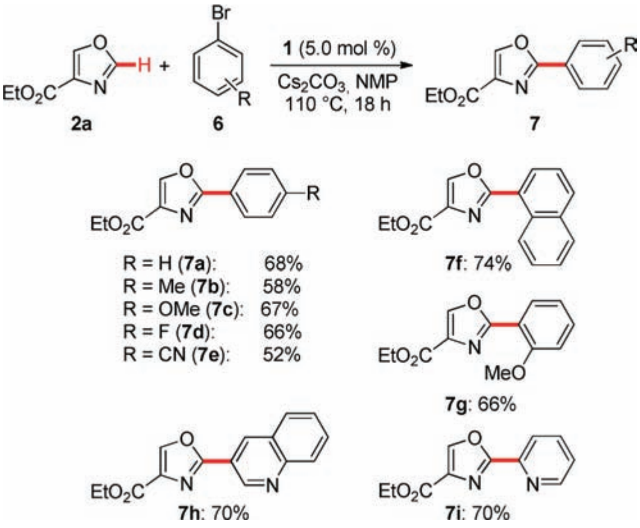
Scheme 4. Metal-Free Direct Benzylation and Alkylation of a C(sp^3)−H Bond



of transition metal catalysts at the activated benzhydryl-type position (Scheme 4).

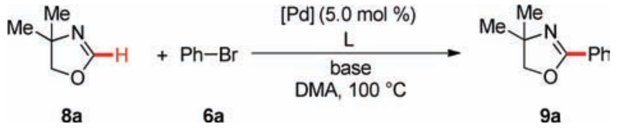
The well-defined complex **1** was not limited to direct benzylations, but allowed for efficient C−H bond arylations[11] on oxazole **2a** as well (Scheme 5). Notably, the catalysts broad substrate scope included sterically demanding *ortho*-substituted electrophiles as well as heteroaryl bromides **6**.

Scheme 5. Scope of Direct Arylations



In recent years, significant progress was made in direct arylations of heteroarenes.[5,11] On the contrary, a palladium-catalyzed[12] C−H bond arylation of nonaromatic oxazolines was as of yet not reported, despite of their practical importance as key intermediates in synthetic organic chemistry.[9] Consequently, we tested different ligands in the direct arylation of oxazoline **8a** (Table 2). Interestingly, complex **1** outperformed palladium complexes derived from representative mono- or bidentate phosphine ligands (entries 1−6), including Xantphos (entry 4), which was previously employed for palladium-catalyzed direct alkynylations.[8] Among a variety of bases, LiO*t*-Bu provided most satisfactory results, whereas the use of K$_2$CO$_3$, Cs$_2$CO$_3$, Rb$_2$CO$_3$ or K$_3$PO$_4$ gave no desired product **9a**.[13] We believe that the remarkably high catalytic activity exerted by complex **1** is due to the bidentate,

Table 2. Optimization of Direct Arylation on Oxazoline **8a**[a]



entry	[Pd]	L (mol %)	base (equiv)	yield (%)
1	Pd(OAc)$_2$	–	LiO*t*-Bu (2.0)	11
2	Pd(OAc)$_2$	PCy$_3$ (10)	LiO*t*-Bu (2.0)	23
3	Pd(OAc)$_2$	*rac*-BINAP (5.0)	LiO*t*-Bu (2.0)	37
4	Pd(OAc)$_2$	Xantphos (5.0)	LiO*t*-Bu (2.0)	35
5	Pd(OAc)$_2$	dppf (5.0)	LiO*t*-Bu (2.0)	24
6	Pd(OAc)$_2$	dppp (5.0)	LiO*t*-Bu (2.0)	53
7	**1**	–	KO*t*-Bu (2.5)	18
8	**1**	–	NaO*t*-Bu (2.5)	31
9	**1**	–	LiO*t*-Bu (2.5)	70

[a] Reaction conditions: **8a** (0.5 mmol), **6a** (1.0 mmol), [Pd] (5.0 mol %), base, DMA, 100 °C, 14−20 h; isolated yields.

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(10) Direct benzylations under basic reaction conditions were only recently developed. [Ru]: (a) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969. (b) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (c) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877. [Pd]: (d) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163. (e) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650. (f) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100. (g) Ackermann, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724–726. (h) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360–1363. (i) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 12307–12311. (j) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. A review: (k) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.

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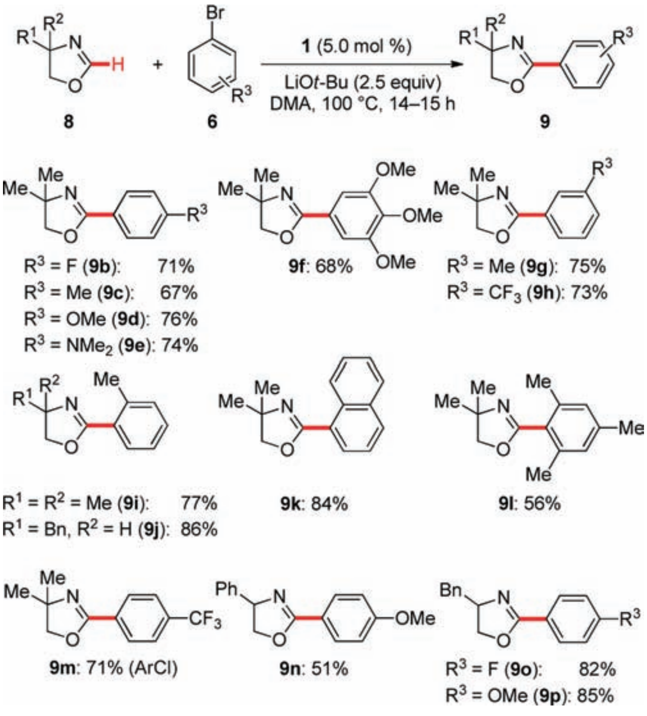
(12) For an example of an elegant rhodium-catalyzed C−H bond functionalization, see: (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35–38. (b) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500.

(13) This result is indicative of a reaction manifold involving an initial in situ deprotonation with the base LiO*t*-Bu.

monoanionic nature of the self-assembled, sterically demanding ligand.

Scheme 6. Scope of Direct Arylations of Oxazolines **8**



With optimized reaction conditions in hand, we probed the scope of direct arylations of oxazolines **8** employing aryl halides **6** (Scheme 6). Interestingly, complex **1** proved applicable to C−H bond arylations with functionalized as well as sterically congested *ortho*-substituted aryl bromides or chlorides **6**. Likewise, differently substituted oxazolines **8** were found to be viable substrates.

In summary, we have reported on the use of an air-stable palladium complex derived from a sterically hindered SPO preligand for high-yielding C−H bond functionalizations of heterocycles. Thus, a phosphinous acid complex enabled efficient direct arylations and benzylations of (benz)oxazoles, as well as first palladium-catalyzed direct arylations of oxazolines with ample scope.

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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.