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Air-Stable Secondary Phosphine Oxide as Preligand for Palladium-Catalyzed Intramolecular α-Arylations with Chloroarenes

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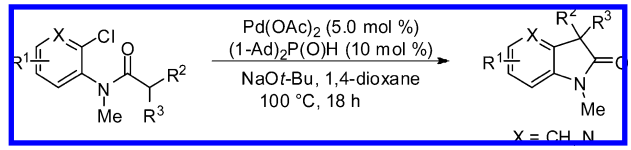
ABSTRACT



A palladium catalyst derived from air-stable secondary phosphine oxide $(1\text{-Ad})_2P(O)H$ enabled efficient intramolecular α-arylations of amides with aryl chlorides, which allowed for the synthesis of diversely substituted (aza)oxindoles.

Oxindoles constitute an important structural motif in various natural products and biologically active compounds.[1,2] While traditional methodologies are available to access this valuable heterocyclic moiety,[1,3] significant progress was represented by the development of complementary transition metal-catalyzed syntheses.[1,2] Particularly, pioneering studies by Miura,[4] Buchwald,[5] and Hartwig[6] set the stage for broadly applicable protocols for arylations of α-C−H acidic compounds,[7,8] which were shown to be applicable to intramolecular[9] arylations of amides.[10] While these efforts provided a modular access to substituted oxindoles, palladium-

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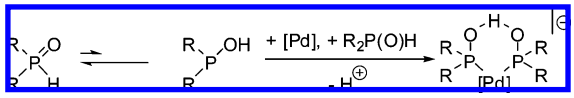
catalyzed intramolecular arylations of amides with inexpensive aryl chlorides[11] were thus far only accomplished with palladium complexes derived from either electron-rich *N*-heterocyclic carbenes or phosphine PCy_3, as developed by Hartwig.[12]

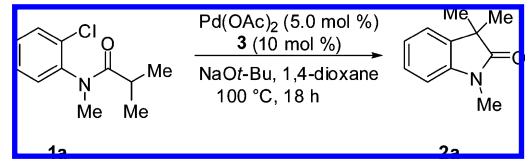
In recent years, secondary phosphine oxides (SPO) were introduced as air-stable preligands for transition metal-catalyzed cross-coupling reactions (Scheme 1).[13,14] During our studies on the development of heteroatom-substituted secondary phosphine oxide (HASPO) preligands for catalytic cross-coupling chemistry,[15,16] we observed that SPOs[17] can be employed as preligands for palladium-catalyzed α-arylations. Herein, we wish to report on these findings, which involve intramolecular arylations of amides with unactivated aryl chlorides for the synthesis of substituted (aza)oxindoles.

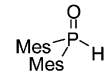
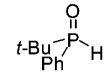
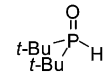
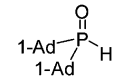
Scheme 1. Tautomerization and Complex Formation of Secondary Phosphine Oxide (SPO) Preligands



At the outset of our studies we probed representative air-stable SPO preligands in the palladium-catalyzed intramolecular α-arylation of amide **1a** (Table 1).

Table 1. Air-Stable Secondary Phosphine Oxide Preligands **3** for the α-Arylation of Amide **1a**[a]



entry	3		yield
1	---		2%[b]
2		**3a**	< 5%[b]
3		**3b**	27%[b]
4		**3c**	68%
5			84%
6		**3d**	82%[c]
7			92%[d]

[a] Reaction conditions: **1a** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol %), preligand (10 mol %), NaO*t*-Bu (1.2 mmol), 1,4-dioxane (2.0 mL), 18 h; yields of isolated product. [b] GC-conversion. [c] PhMe (2.0 mL) as solvent. [d] 20 mmol scale.

Unfortunately, aryl-substituted SPOs **3a** and **3b** provided unsatisfactory results, even when bearing sterically demanding substituents (entries 2, and 3). Catalysts generated in situ from sterically hindered alkyl-substituted SPOs **3c** and **3d** displayed significantly improved activities, with $(1\text{-Ad})_2P(O)H$ (**3d**)[18] providing superior results (entries 4 and 5). A comparable catalytic efficacy was observed when conducting reactions in toluene as solvent (entry 6). Likewise, a reaction performed on larger scale proceeded efficiently (entry 7). It is noteworthy that a valuable asset of preligand **3d** is represented by its nonhygroscopic nature, which renders its handling more convenient, when being compared with preligand **3c**.

With an optimized catalytic system in hand, we explored its scope in the α-arylation of differently substituted amides **1** (Table 2). Notably, a variety of intramolecular arylations were achieved with chlorides as electrophiles, giving access to substituted oxindoles **2** (entries 1−13). Notably, the use of less expensive $PdCl_2$ as palladium precursor gave rise to a comparable isolated yield of oxindole **2i** (entries 9 and 10). Further, preligand **3d** enabled the palladium-catalyzed α-arylation with chloride **1m** (entry 14) yielding a 3-alkoxy-substituted oxindole, which constitutes an indispensable core structure of a wide range of biologically active compounds.[2]

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(11) (a) Littke, A. F. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 25−68. (b) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283–2321.

(12) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415. See also: (b) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193–195. (c) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704–2705. (d) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484–8487. (e) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569–5572, and references cited therein.

(13) For reviews, see: (a) Ackermann, L. *Synthesis* **2006**, 1557–1571. (b) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (c) Ackermann, L. In *Trivalent Phosphorus Compounds in Asymmetric Catalysis, Synthesis and Applications*; Börner, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 831−847. (d) Ackermann, L.; Althammer, A. *Chem. Unserer Zeit* **2009**, *43*, 74–83.

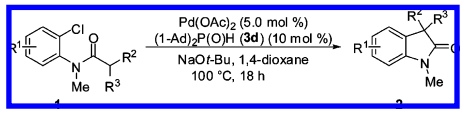
(14) For representative examples of SPO preligands in catalytic cross-coupling reactions, see: (a) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381–384. (b) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638–7650. (c) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167. (d) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698. (e) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415–2419. (f) Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737–2740. (g) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053. (h) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601–8604. (i) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147–1150. (j) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650. (k) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516.

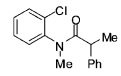
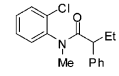
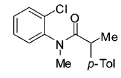
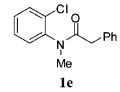
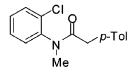
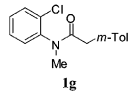
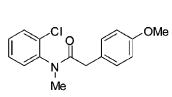
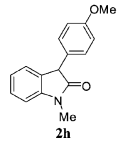
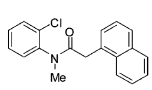
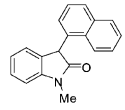
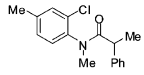
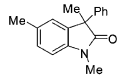
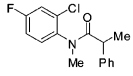
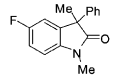
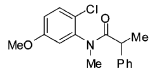
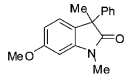
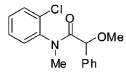
(15) Ackermann, L. *Synlett* **2007**, 507–526.

(16) For selected examples, see: (a) Ackermann, L.; Barfüβer, S. *Synlett* **2009**, 808–812. (b) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457–3460. (c) Ackermann, L.; Gschrei, C. J.; Althammer, A.; Riederer, M. *Chem. Commun.* **2006**, 1419–1421. (d) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622. (e) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216–7219. (f) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444–2447.

(17) For the use of a diaminochlorophosphine for palladium-catalyzed α-arylations, see: Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627–7630.

Table 2. Scope of Palladium-Catalyzed Oxindole Synthesis[a]



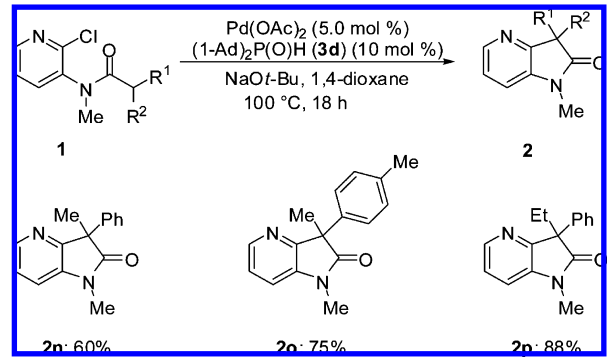
entry	1	2	yield
1	 **1b**	 **2b**	89%
2	 **1c**	 **2c**	91%
3	 **1d**	 **2d**	91%
4	 **1e**	 **2e**	66%
5			64%[b]
6	 **1f**	 **2f**	65%
7	 **1g**	 **2g**	60%
8	 **1h**	 **2h**	62%
9	 **1i**	 **2i**	61%
10			61%[c]
11	 **1j**	 **2j**	80%
12	 **1k**	 **2k**	88%
13	 **1l**	 **2l**	92%
14	 **1m**	 **2m**	45%

[a] Reaction conditions: **1** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol %), **3d** (10 mol %), NaO*t*-Bu (1.2 mmol), 1,4-dioxane (2.0 mL), 18 h; yields of isolated product. [b] Using the corresponding bromoarene. [c] $PdCl_2$ (5.0 mol %) as precatalyst.

While this transformation proceeded less efficiently, it represents, to the best of our knowledge, a first example of a 3-alkoxyoxindole synthesis through catalytic intramolecular α-arylation with an aryl chloride[19] as electrophile.

Finally, we explored the unprecedented use of intramolecular palladium-catalyzed α-arylations for the preparation of azaoxindoles. Thus, we were delighted to observe that 2-chloropyridines **1** proved to be viable precursors for 4-azaoxindoles **2n**−**p** under our optimized reaction conditions (Scheme 2).

Scheme 2. Palladium-Catalyzed Syntheses of Azaoxindoles **2**



In summary, we reported on the first use of air-stable secondary phosphine oxides (SPO) for catalyzed arylation reactions of α-C−H acidic compounds, which turned out to be applicable to intramolecular transformations of various amides with aryl chlorides, and enabled the synthesis of azaoxindoles among others.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H 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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