

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

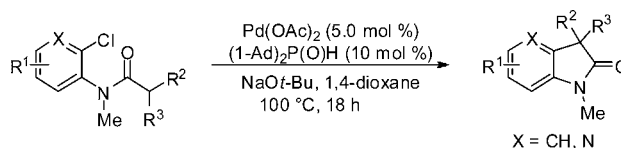
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ABSTRACT



A palladium catalyst derived from air-stable secondary phosphine oxide $(1\text{-Ad})_2\text{P}(\text{O})\text{H}$ 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 Hartwig⁶ set the stage for broadly applicable protocols for arylations of α -C–H acidic com-

pounds,^{7,8} which were shown to be applicable to intramolecular⁹ arylations of amides.¹⁰ While these efforts provided a modular access to substituted oxindoles, palladium-

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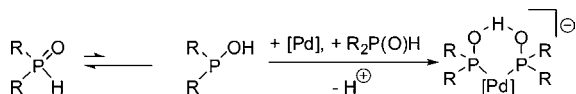
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catalyzed intramolecular arylations of amides with inexpensive aryl chlorides¹¹ were thus far only accomplished with palladium complexes derived from either electron-rich *N*-heterocyclic carbenes or phosphine PCy₃, as developed by Hartwig.¹²

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

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



our studies on the development of heteroatom-substituted secondary phosphine oxide (HASPO) preligands for catalytic cross-coupling chemistry,^{15,16} we observed that SPOs¹⁷ 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.

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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		82% ^c
7		93% ^d

^a Reaction conditions: **1a** (0.50 mmol), Pd(OAc)₂ (5.0 mol %), preligand (10 mol %), NaOt-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-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 PdCl₂ 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

Table 2. Scope of Palladium-Catalyzed Oxindole Synthesis^a

entry	1	2	yield
1			89%
2			91%
3			91%
4			66%
5			64% ^b
6			65%
7			60%
8			62%
9			61%
10			61% ^c
11			80%
12			88%
13			92%
14			45%

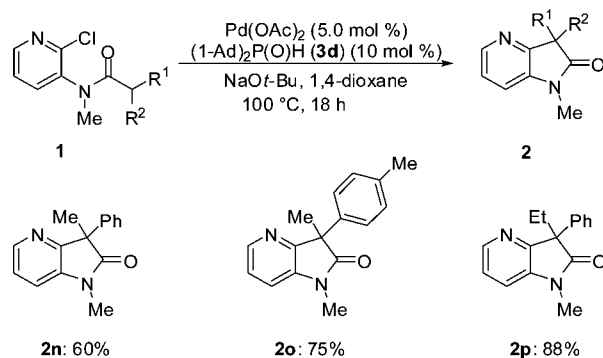
^a Reaction conditions: **1** (0.50 mmol), Pd(OAc)₂ (5.0 mol %), **3d** (10 mol %), NaOt-Bu (1.2 mmol), 1,4-dioxane (2.0 mL), 18 h; yields of isolated product.
^b Using the corresponding bromoarene. ^c PdCl₂ (5.0 mol %) as precatalyst.

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 chloride¹⁹ 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 ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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