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Palladium-Catalyzed α -Arylation of Benzylic Phosphine Oxides

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Abstract

A novel approach to prepare diarylmethyl phosphine oxides from benzyl phosphine oxides via deprotonative cross-coupling processes (DCCP) is reported. The optimization of the reaction was guided by High-Throughput Experimentation (HTE) techniques. The Pd(OAc)₂/Xantphos-based catalyst enabled the reaction between benzyl diphenyl or dicyclohexyl phosphine oxide derivatives and aryl bromides in good to excellent yields (51–91%).

Organophosphorus compounds, such as phosphine oxides, exhibit a wide range of applications in medicinal chemistry,¹ biochemistry,² agrochemistry,³ material science,⁴ catalysis (as catalysts and as ligands)⁵ and organic synthesis (from Arbusov to Wadsworth-Horner-Emmons reactions). They are also known flame-retardants⁶ and metal extractants.⁷ Considering these diverse applications, it is not surprising that the synthesis of organophosphorus compounds has attracted much attention.

Among organophosphorus compounds, α -diarylmethyl phosphine oxides exhibit particularly interesting properties.⁸ Surprisingly, very few methods have been reported for their synthesis. Classical methods involve the use of Michaelis-Arbuzov or Michaelis-Becker reactions (Scheme 1).⁹ These approaches, however, suffer from limited commercial availability of the requisite halogenated diarylmethanes or protected diarylmethanols. Diarylmethanes can also serve as precursors, but a three-step synthesis under harsh reaction conditions is needed to obtain the desired products (Scheme 1).^{9b} In this Letter, the first examples of palladium-catalyzed direct α -arylation of benzyl phosphine oxides are reported.

Recently, transition-metal-catalyzed cross-coupling reactions with phosphorus compounds have emerged as a powerful route to construct P–C bonds.¹⁰ In contrast, few examples of α -arylation of phosphorus compounds have been reported to date. These involve the deprotonation of significantly more acidic protons on (RO)₂P(=O)CH₂–EWG (EWG = keto, cyano or sulfonyl) compared to those of benzyl diphenylphosphine oxide, where the pK_a in DMSO is around 29.¹¹ Hagadorn and Hlavinka developed a method to deprotonate

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Supporting Information Available Procedures, characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(MeO)₂P(O)Me using Zn(tmp)₂¹² and coupled it with bromobenzene in a palladium-catalyzed process.

Recently, our research group has introduced methods for the functionalization of weakly acidic *sp*³-hybridized C–H bonds (*pK*_a's 28–35 in DMSO) of diarylmethanes, sulfoxides, sulfones, amides and amine derivatives via deprotonative cross-coupling processes (DCCP).¹³ Encouraged by the success of these reactions, we focused our effort on the cross-coupling of benzyl phosphine oxides with aryl bromides. To initiate these investigations, 6 bases [LiN(SiMe₃)₂, NaN(SiMe₃)₂, KN(SiMe₃)₂, LiOtBu, NaOtBu, and KOtBu], 4 solvents [CPME (cyclopentyl methyl ether), dioxane, THF, and toluene], 2 palladium sources [Pd(OAc)₂ and Pd(dba)₂] and 2 ligands [NiXantphos (**L1**, Table 1) and *N*-(dicyclohexylphosphino)-2-2'-tolyindole (**L2**)] were chosen based on our previous experience.¹² These initial variables were tested using microscale High-Throughput Experimentation (HTE) techniques (see Supporting Information for details). An interesting cation effect was observed – the catalysis only proceeded smoothly when NaN(SiMe₃)₂ or NaOtBu were utilized as bases. In contrast, the potassium and lithium bases were totally ineffective (less than 5% yield). The leading results from the screen were NaN(SiMe₃)₂, Pd(dba)₂/NiXantphos or Pd(OAc)₂/NiXantphos as the catalyst in CPME. On laboratory scale, unfortunately, these conditions led to **3a** in only 30% and 42% yield, respectively (Table 1, entries 1 and 2). As the choice of ligand is very important in DCCP, 23 mono- and bi-dentate ligands were screened using NaN(SiMe₃)₂ as a base and Pd(OAc)₂ as catalyst in CPME at 80 °C (see Supporting Information for details). Among those, CataCXium A (**L3**) and Xantphos (**L4**) gave the best results. On laboratory scale, Xantphos proved to be more effective, producing **3a** in 56% yield (Table 1, entry 4 vs 2–3). However, unreacted **1a** was present. To push the reaction to completion, the temperature was increased from 80 °C to 110 °C, leading to the desired product **3a** in 88% crude yield (entry 5). A decrease in the palladium/Xantphos loading from 10/20 mol % to 5/10 mol % was successfully achieved and the arylated product **3a** was isolated in 85% yield (entry 6). We observed some degradation of **1a** with NaN(SiMe₃)₂. Therefore, NaOtBu was employed and led to increased yield of the desired product **3a** (90% yield) (entry 7).

With the optimal conditions in hand, the substrate scope of aryl bromides in the arylation of benzyldiphenylphosphine oxide (**1a**) was investigated (Scheme 2). In general, aryl bromides containing electron-donating, electron-withdrawing as well as sterically hindered substituents exhibited good to excellent yields. Bromobenzene **2b** underwent coupling in 79% yield while electron-donating 4-*tert*-butyl and 4-methoxy bromobenzene led to the desired products (**3a** and **3c**) in 90% and 91% yield, respectively. The cross-coupling reactions proceeded smoothly between **1a** with aryl bromides bearing electron-withdrawing groups, such as 4-fluoro (**2d**) and 4-chloro (**2f**) bromobenzene generating the arylation products in 83% and 54% yield respectively. With the 3-bromobenzotrifluoride **2e**, the use of NaOtBu did not afford the expected product. Instead, the product underwent P–C bond-cleavage leading exclusively to the 1-benzyl-3-(trifluoromethyl)benzene and *tert*-butyl diphenylphosphinate, Ph₂PO(*O-t*Bu). Formation of this byproduct was suppressed by using a non-nucleophilic base, NaH, which led to α -arylation product **3e** in 71% yield. In the case of more sterically demanding 2-bromotoluene and 1-bromonaphthalene, longer reaction times and higher reaction concentrations (from 0.1 M to 0.2 M) were necessary, providing **3g** and **3h** in 51 and 66% yield, respectively. The scalability of the cross-coupling was evaluated by performing the reaction with 4-*tert*-butyl bromobenzene on a 3.42 mmol (1.0 g) scale leading to the desired product **3a** in 83% yield.

We next turned to the substrate scope of benzyldiphenylphosphine oxides (Scheme 3). In this study, diphenylphosphine oxides possessing 4-methoxybenzyl (**1b**) or 4-fluorobenzyl (**1c**) were coupled with aryl bromides containing electron-donating and withdrawing groups.

Under our optimized conditions, products were isolated in 61–87% yields. In addition, (naphthalen-1-ylmethyl)diphenylphosphine oxide (**1d**) and (2-methylbenzyl)diphenylphosphine oxide (**1e**) furnished the products **3g** and **3h** in 85% and 78% yield respectively. These yields are significantly better than those obtained in Scheme 2 for the synthesis of these products. Finally, diphenyl(phenyl(pyridine-3-yl)methyl)phosphine oxide **3n**, an example of heterocycle-containing substrates, was isolated in 75% yield when NaH was utilized as base. It is noteworthy that this compound has been demonstrated to be a potent inhibitor of the Kv1.5 potassium channel and a possible treatment for atrial fibrillation.^{8a} The prior synthesis provided only 2% yield of this biologically interesting compound, whereas the yield was significantly improved employing our method.

Dialkyl phosphine oxides are less acidic than their diaryl analogues and, therefore, are more challenging to prepare. Nonetheless, many important ligands used in transition-metal-catalyzed reactions possess bulky *P*-alkyl substituents.¹⁴ We, therefore, decided to apply our method to prepare benzyl phosphine oxides bearing bulky alkyl substituents. As shown in Scheme 4, benzyldicyclohexylphosphine oxide underwent DCCP with **2a** to give the desired product in 84% yield using sodium hydride as a base.

The α -diarylmethyl phosphine oxides prepared herein can be envisioned as precursors for the synthesis of new phosphine ligands. Unfortunately, using trichlorosilane and triethylamine to reduce the phosphine oxide moiety resulted in no reaction. In contrast, the reaction proceeded smoothly with a catalytic amount of Ti(O^{*i*}Pr)₄ and triethoxysilane, furnishing the expected phosphine **4a** in 91% yield (Scheme 5).¹⁵

In summary, we have developed the first α -arylation of benzyl phosphine oxide derivatives with aryl bromides. The combination of Pd(OAc)₂ and Xantphos under basic conditions catalyzed the reaction, providing access to these useful compounds in good yield. NaO^{*t*}Bu or NaH bases enabled the deprotonation of the weakly acidic α -protons of phosphine oxides and promoted the transmetalation to palladium. This work broadens the scope of weakly acidic substrates that can be employed in deprotonative cross-coupling processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Synthesis of Diarylmethyl Phosphine Oxides

Scheme 2.

Substrate Scope of Aryl Bromides in Pd-Catalyzed α -Arylation with Benzyldiphenylphosphine Oxide (**1a**)

^a **1a**: 3.42 mmol, **2a**: 6.84 mmol, NaOtBu : 6.84 mmol, CPME: 34 mL. ^b NaOtBu was replaced by NaH . ^c 48 h, 0.2 M.

Scheme 3.

Substrate Scope of Benzyldiphenylphosphine Oxides in Pd-Catalyzed α -Arylations with Aryl Bromides

^a 48 h, 0.2 M. ^b 3 equiv NaH, 32 h.

Scheme 4.

α -Arylation of Benzyldicyclohexylphosphine Oxide with 4-*tert*-Butyl Bromobenzene

Scheme 5.
Reduction of the Phosphine Oxide **3a** to Phosphine **4a**

Table 1

Optimization of α -Arylation of Benzyldiphenylphosphine Oxide with 4-*tert*-Butyl Bromobenzene

NiXantphos (L1)		N-(Dicyclohexylphosphino)-2-(2'-tolyl)indole (L2)

CataCXium A (L3)		Xantphos (L4)

entry	catalyst	ligand	base	catalyst/ligand/mol %	temp / °C	yield ^a / %
1	Pd(dba) ₂	L1	NaHMDS	10/20	80	30
2	Pd(OAc) ₂	L1	NaHMDS	10/20	80	42
3	Pd(OAc) ₂	L3	NaHMDS	10/20	80	48
4	Pd(OAc) ₂	L4	NaHMDS	10/20	80	56
5	Pd(OAc) ₂	L4	NaHMDS	10/20	110	88
6	Pd(OAc) ₂	L4	NaHMDS	5/10	110	85 ^b
7	Pd(OAc) ₂	L4	NaOtBu	5/10	110	90 ^b

^aYield determined by ¹H NMR integration of crude reaction mixture using 0.1 mmol of CH₂Br₂ as internal standard.

^b Isolated yield after chromatographic purification.