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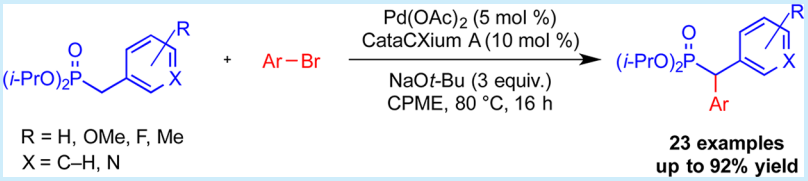
Palladium-Catalyzed α-Arylation of Benzylic Phosphonates

Sonia Montel, Ludovic Raffier, Yuying He, and Patrick J. Walsh*

Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information



ABSTRACT: A new synthetic route to access diarylmethyl phosphonates is presented. The transformation enables the introduction of aromatic groups on benzylic phosphonates via a deprotonative cross-coupling process (DCCP). The $Pd(OAc)_2$/CataCXium A-based catalyst afforded a reaction between benzyl diisopropyl phosphonate derivatives and aryl bromides in good to excellent isolated yields (64–92%).

Phosphonates and their derivatives are a class of organophosphorus compounds that exhibit a wide range of applications in medicinal[1] and agricultural chemistry.[2] They are also flame retardants, metal extractants,[3] and reagents in the Horner–Wadsworth–Emmons (HWE) reaction.[4] Given the interest in phosphonates, and their applications as reagents to prepare a host of useful molecules (Figure 1),[5] there is a significant demand for their synthesis.

Despite the widespread use of dialkyl (diarylmethyl)phosphonates, only a few methods for their synthesis have been reported. Classical preparations include Michaelis–Arbuzov or Michaelis–Becker reactions,[6] which are dependent on the limited availability of the starting diarylmethyl halides. Recently, a Friedel–Crafts type reaction has been developed by Chakravarty et al. starting from diethyl (hydroxy(aryl)methyl)-phosphonates to obtain diethyl (diarylmethyl)phosphonates (Figure 2A).[7] The products were obtained in good yields, although the scope suffers from the usual limitations of Friedel–Crafts reactions. To date, some examples of α-arylation of activated phosphonates have been reported.[8] They involved the deprotonation of relatively acidic methylene C–H's (pK_a around 17 in DMSO) sandwiched between phosphonates and a second electron-withdrawing group (Figure 2B–D). One example of palladium-catalyzed α-arylation of dimethyl methylphosphonate in 70% yield has been reported by Hagadorn and Hlavinka using $Zn(tmp)_2$ as the base (Figure 2E).[9] This approach employs an irreversible deprotonation, rather than a reversible deprotonation employed in our work.[10] In this Letter, we disclose the first general palladium-catalyzed direct α-arylation of dialkyl benzyl phosphonates (Figure 2F). These substrates (pK_a = 27.6 in DMSO) are around 10 orders of magnitude less acidic than those in Figure 2B–D, making their arylation considerably more challenging.

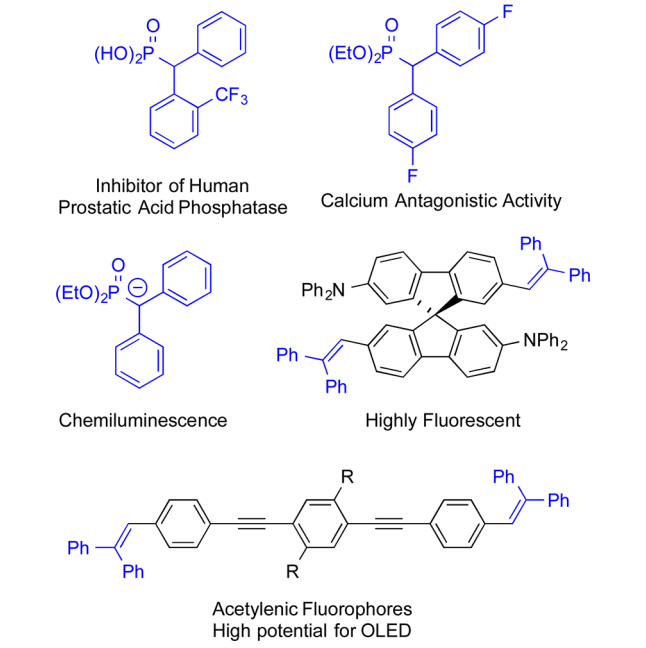


Figure 1. Examples of interesting molecules obtained from dialkyl (diarylmethyl)phosphonates.

Our group is interested in the functionalization of weakly acidic sp^3 C–H bonds via deprotonative cross-coupling processes (DCCP). Substrates employed to date include diarylmethanes, sulfoxides, sulfones, amides,[11,12] and most recently phosphine oxides.[13] Encouraged by the utility of phosphonates, and the lack of general methods to α-arylate weakly acidic members of these compounds, we set out to develop the arylation of benzylic phosphonates. Based on our

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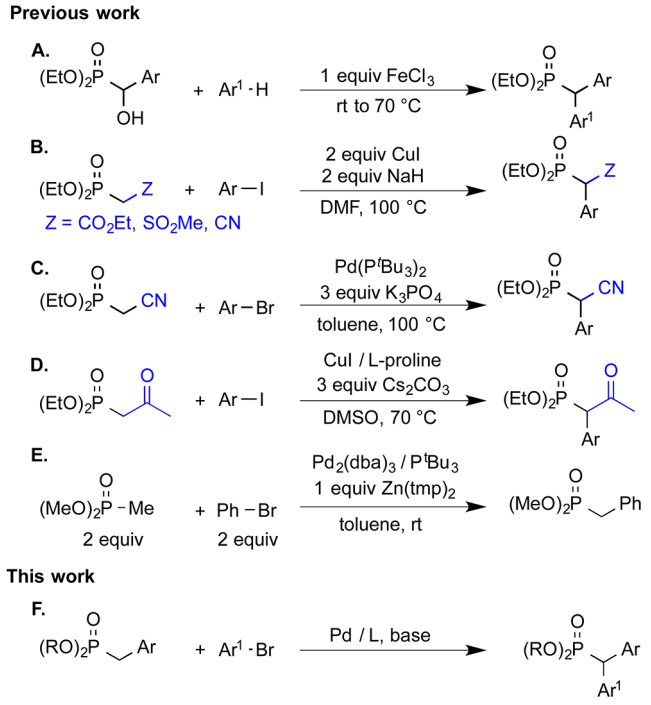
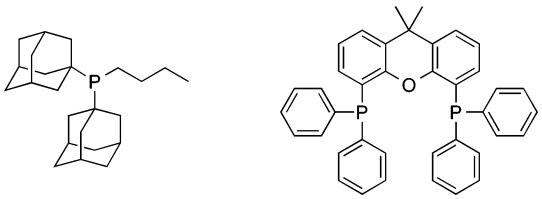


Figure 2. α-Arylation and Friedel–Crafts type reaction of phosphonates.

previous observations in the arylation of phosphine oxides,[13] our investigations were initiated using six bases [LiO*t*-Bu, NaO*t*-Bu, KO*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$], two palladium sources [$Pd(OAc)_2$ and $Pd(dba)_2$], two ligands [CataCXium A (**L1**)[14] and Xantphos (**L2**),[15] Figure 3], and four solvents [CPME (cyclopentyl methyl



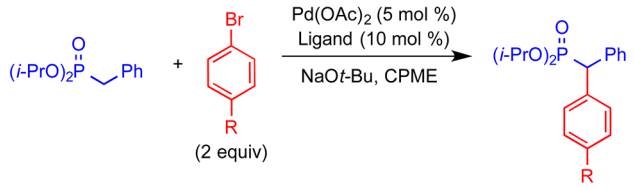
CataCXium A (**L1**) Xantphos (**L2**)

Figure 3. Structures of CataCXium A (**L1**) and Xantphos (**L2**).

ether), 1,4-dioxane, THF, and DME], using microscale (10 μmol) High-Throughput Experimentation (HTE) techniques (see Supporting Information).

From this microscale screen, two hits were obtained with NaO*t*-Bu, $Pd(OAc)_2$ and CataCXium A (**L1**, Figure 3) or Xantphos (**L2**, Figure 3) in CPME at 80 °C. On laboratory scale (0.2 mmol), these two systems led to the desired arylation product in 85% and 84% yield, respectively (Table 1, entries 1–2). Changing the concentration from 0.1 to 0.2 M resulted in an increase in the yields to 99% and 98%, respectively (entries 3–4). To differentiate these two catalysts, reactions with an electron-rich and -poor aryl bromide were tested. While CataCXium A (**L1**) generated the desired products in 99% yield with 4-methoxy bromobenzene and with 4-fluoro bromobenzene (entries 5 and 7), the use of Xantphos (**L2**) resulted in a drop in the yield to 79% and 88%, respectively (entries 6 and 8). Based on these results, CataCXium A (**L1**)

Table 1. Optimization of α-Arylation of Benzyl Diisopropyl Phosphonate with Bromobenzene, 4-Methoxy Bromobenzene, and 4-Fluoro Bromobenzene



entry	R	ligand	base (equiv)	temp (°C)	concn (mol/L)	yield[a] (%)
1	H	**L1**	3	80	0.1	85%
2	H	**L2**	3	80	0.1	84%
3	H	**L1**	3	80	0.2	99%
4	H	**L2**	3	80	0.2	98%
5	OMe	**L1**	3	80	0.2	99%
6	OMe	**L2**	3	80	0.2	79%
7	F	**L1**	3	80	0.2	99%
8	F	**L2**	3	80	0.2	88%
9	H	**L1**	2	80	0.2	70%
10	H	**L1**	3	50	0.2	24%

[a]Yields determined by ^{1}H NMR of the crude reaction mixtures using CH_2Br_2 as the internal standard.

was chosen as the more suitable ligand for this reaction. Interestingly, Xantphos proved to be a better ligand for the α-arylation of phosphine oxides.[13] Note that attempts to reduce the amount of base or the temperature resulted in a drop in the yield (entries 9 and 10).

The optimized reaction conditions in Table 1 were then used to determine the substrate scope of aryl bromides **2a–j** (Scheme 1). Bromobenzene underwent a reaction to give **3a** in 91% isolated yield. It is noteworthy that an 88% yield was obtained when the reaction was carried out with 1 g of phosphonate **1a** and bromobenzene, indicating that the catalyst and conditions are scalable. Reaction with 4-*tert*-butyl bromobenzene afforded compound **3b** in 82% yield. No difficulty was noted with electron-donating groups, such as 4-methoxy bromobenzene and 4-bromo-*N*,*N*-dimethylaniline, which resulted in the formation of products **3c** and **3d** in 86% and 82% yield, respectively. Reaction with electron-withdrawing groups also proceeded well. With 4-fluoro bromobenzene, **3e** was isolated in 82% yield. Similar reactivity was observed with 4-chloro bromobenzene, although a longer reaction time was required to reach complete conversion. Sterically hindered 2-methyl bromobenzene and 1-bromonaphthalene afforded products **3g** and **3h** both in 89% isolated yield. Finally, introduction of heteroaromatics 5-bromobenzofuran and 5-bromo-*N*-methyl indole were achieved in 80% and 71% yield, respectively.

The substrate scope of the diisopropyl benzyl phosphonate was then studied (Scheme 2). The benzyl group in **1a** was replaced with 4-methoxybenzyl (**1b**), 4-fluorobenzyl (**1c**), 2-methylbenzyl (**1d**), and 3-methylpyridyl (**1e**) groups. In each case, the substrate was coupled with neutral, electron-rich, and electron-poor aryl bromides (bromobenzene, 4-methoxy bromobenzene, and 4-fluoro bromobenzene). Phosphonate **1b**, possessing a 4-methoxybenzyl group, afforded coupled products **3c**, **3k**, and **3l** in 60–82% yield. It is noteworthy that a longer reaction time and/or a higher temperature was required for these substrates, probably due to the lower acidity of the benzylic protons of **1b**. Compounds **3e**, **3l**, and **3m** were

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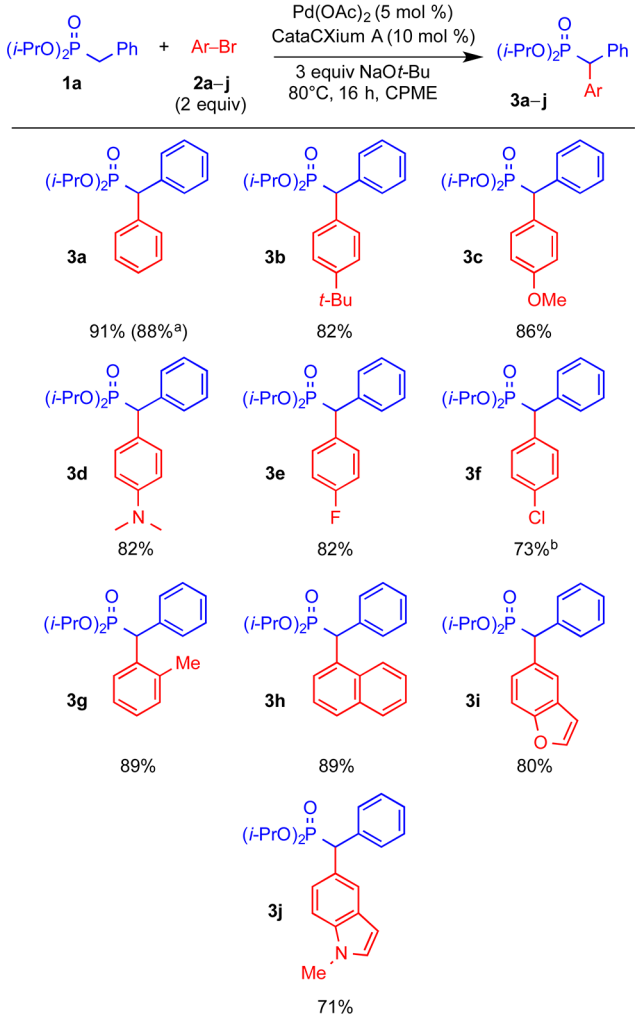
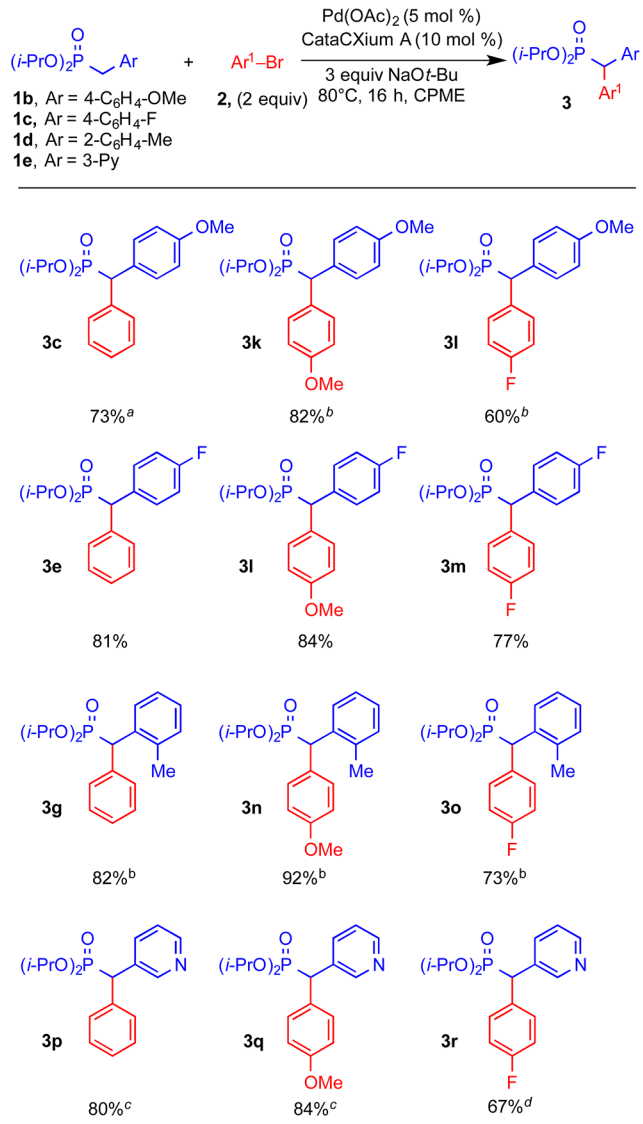
Scheme 1. Substrate Scope of Aryl Bromides 2a–j in Pd-Catalyzed α-Arylation of Diisopropyl Benzyl Phosphonate 1a



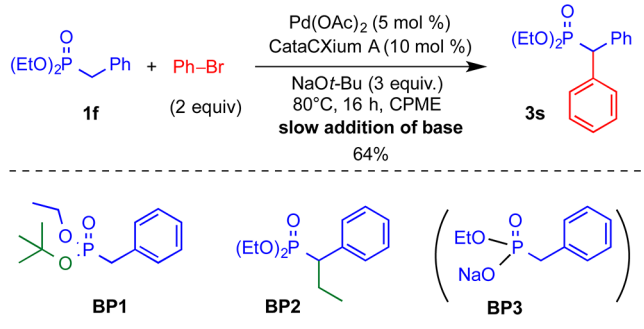
[a] **1a**: 3.90 mmol, 1.0 g. [b] 32 h reaction time.

Scheme 2. Substrate Scope of Diisopropyl Benzyl Phosphonate in the Pd-Catalyzed α-Arylation with Aryl Bromides



[a] 32 h reaction time. [b] 24 h reaction time, 110 °C. [c] 24 h reaction time. [d] 48 h reaction time.

Scheme 3. α-Arylation of Diethyl Benzylphosphonate 1f with Bromobenzene



obtained from 4-fluoro benzyl phosphonate (**1c**) in 77–84% yield. Sterically hindered 2-methyl benzyl phosphonate (**1d**) afforded **3g**, **3n**, and **3o** in 73–92% yield. A longer reaction time and a higher temperature were, however, needed to reach complete conversion. Finally, coupling products **3p–r** were obtained from 3-pyridyl containing phosphonate **1e** in 67–84% yield after 24 h or 48 h of reaction time.

Replacement of the isopropyl moieties of **1a** has also been considered. Ethoxy groups are among the most commonly employed substituents on the phosphorus atom in phosphonate chemistry. We, therefore, applied our α-arylation conditions to diethyl benzylphosphonate **1f** (Scheme 3). Unfortunately, the coupling did not proceed smoothly. Only a 30% yield of the product was obtained, along with the formation of a byproduct, *tert*-butyl ethyl benzylphosphonate **BP1** (~ 20% yield), and some degradation of the starting material. Changing the base did not solve the problem, as degradation was observed with all bases employed. Only the nature of the major byproduct formed differed: *tert*-butyl ethyl benzylphosphonate **BP1** when *tert*-butoxide bases (Li, Na, K) were employed and diethyl (1-phenylpropyl)phosphonate **BP2** when the $MN(SiMe_3)_2$ (M = Li, Na, K) bases were used. Formation of **BP2** presumably also gives rise to **BP3**, but this charged species was not isolated. After extensive optimization, slow addition of sodium *tert*-butoxide to the reaction media (0.1 mL/h, see Supporting

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Information for details) avoided the degradation of the diethyl benzylphosphonate **1f** and decreased the formation of the byproduct **BP1**. The product **3s** was isolated in 64% yield.

In summary, we have developed the first Pd-catalyzed α-arylation of benzylic phosphonates with aryl bromides. Despite the perceived similarity between phosphine oxides and phosphonates, different catalysts gave the best results for each substrate class. For phosphonates, the combination of $Pd(OAc)_2$, CataCXium A, and NaO*t*-Bu in CPME enabled access to useful diarylmethyl phosphonates in good to excellent yields through a deprotonative cross-coupling process.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pwalsh@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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