

Green, Palladium-Catalyzed Synthesis of Benzylic *H*-Phosphinates from Hypophosphorous Acid and Benzylic Alcohols

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Benzylic alcohols cross-couple directly with concentrated H_3PO_2 by using Pd/xantphos (1 or 2 mol-%). Depending on the substrate, DMF at 110 °C or *t*-AmOH at reflux with a Dean–Stark trap can be used. A broad range of benzylic alcohols react successfully to give moderate to good yields of the products. The preparation of other organophosphorus compounds (phosphinic and phosphonic acids) is also

demonstrated. Asymmetric reaction with (*R*)-1-(2-naphthyl)-ethanol provides the corresponding *H*-phosphinic acid in 77 % ee. The methodology provides a green, PCl_3 -free route to benzylic-*H*-phosphinic acids.

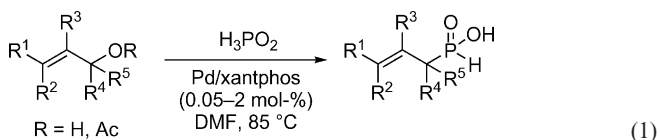
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Introduction

Phosphorus trichloride is the main building block in the “organophosphorus economy”;^[1] however, the chlorine atoms are not typically retained in the final products. Phosphorus–carbon bond-forming reactions are the object of intense studies because of the fact that organophosphorus compounds have a major impact in everyday life, from phosphane ligands in catalysis, to phosphonates and phosphinates as extractants, flame retardants, and biologically active molecules.^[2] Our research focuses on hypophosphorous compounds and *H*-phosphinic acid derivatives as flexible intermediates in the preparation of a variety of phosphorus functionalities.^[3] *H*-Phosphinic acids are nearly ideal for this purpose because they can be derivatized to most of the important phosphorus-containing functionalities.^[4]

Herein we describe the first cross-coupling of benzylic alcohols without any prior activation (as ester, carbonate, or halide derivative compounds, which are often less available than the parent alcohol) to prepare *H*-phosphinates. There are a few examples of benzylic acetate couplings,^[5] which include in situ activation,^[5a] but none that proceed through the benzylic alcohol directly.^[6] Recently, we described the synthesis of allylic-*H*-phosphinates from H_3PO_2 and allylic acetates^[7] or alcohols^[8] [Equation (1)]. Realizing that this type of reaction should constitute a general pattern of reactivity, similar to that of benzylic acetates, we investigated benzylic alcohols in place of allylic alcohols in order

to achieve the “green”, catalytic synthesis of benzylic-*H*-phosphinates without the need for any prior activation. Preparation from H_3PO_2 is ideal in terms of atom-economy (the by-product is water). On the basis of our previous work on allylic alcohols,^[8] we expected a similar reaction (Fisher esterification, Pd-catalyzed ionization, rearrangement, and ultimately P–C bond formation) to be reasonable for benzylic alcohols. Indeed, this proved to be the case.^[9]



Results and Discussion

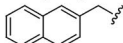
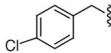
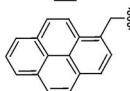
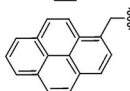
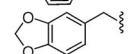
Initially, we investigated the reaction of 1- and 2-naphthylmethanol on the basis of Fiaud's success with the corresponding acetates.^[5b,5c] Using Pd/xantphos (1 mol-%) and DMF at 110 °C, we obtained good yields for the cross-coupling (82% and 93% isolated yields, respectively; Table 1, Entries 1 and 2).

Table 1 shows that these conditions were also satisfactory for other substrates (Table 1, Entries 3–8a). No P–C bond formation was observed in the absence of catalyst. However, some substrates reacted inefficiently or not at all. Our recent discovery of *tert*-amyl alcohol (*t*-AmOH) as a reaction solvent to promote the P^{V} to P^{III} tautomeric equilibrium necessary for P–H bond activation^[8] provided another set of conditions that often succeeded when DMF gave poor results (Table 1, Entries 8b–16).

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Table 1. Scope of the palladium-catalyzed benzylation.^[a]

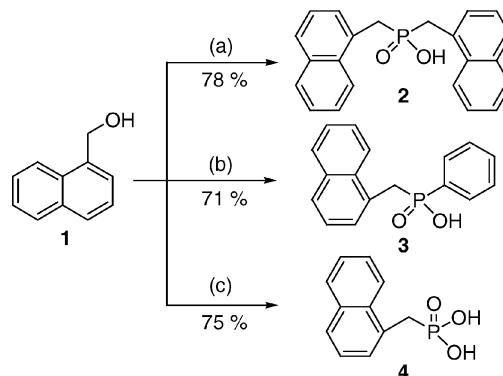
1) H₃PO₂ (2 equiv.) ArCH₂OH $\xrightarrow{\hspace{1.5cm}}$ Ar-CH₂-P(O)(OR)H Pd/xantphos (1 mol-%) solvent, heat 2) workup				
Entry	ArCH ₂ =	R =	Isolated Yield [%] ^[b]	
1		H	82	
2		H	93	
3		H	50	
4a		H	81	
4b		Bu	38	
5		Bu	37	
6		H	84	
7		Bu	57	
8a		H	82	
8b		H	79	
9		H	53	
R¹ =				
10		H	Bu	56
11		2-Me	NH ₄	41
12		3-Me	NH ₄	54
13		4-Me	NH ₄	65
14		3-CbzNH	H	79
15		4-Ph	H	66
16		3-MeO	NH ₄	32

[a] In all cases, 1 mol-% Pd was used under N₂. Entries 1–8a: DMF, 110 °C; Entries 8b–16: *t*-AmOH, reflux, Dean–Stark trap. [b] Isolated after extractive workup (R = H), ammonium salt precipitation (R = NH₄), or esterification with (BuO)₄Si (R = Bu).

As shown in Table 1, a broad range of substrates were converted into the corresponding *H*-phosphinic acids directly. This reaction provides a valuable and straightforward route to benzylic *H*-phosphinic acids and their derivatives. Alternate synthetic methods are much less desirable.^[10] In Table 1, the acids were often isolated after a simple extractive workup or by precipitation as the ammonium salt. With some hydrophilic *H*-phosphinic acids, esterification^[11] was necessary in order to isolate the pure products. With *t*-AmOH as the solvent, some side reactions are also sometimes observed, through elimination followed by hydrophosphinylation.^[12] In this case, esterification or precipitation is necessary to obtain pure coupling products. Overall, the direct benzylation of H₃PO₂ is a novel and efficient catalytic reaction, which alleviates the use of atom-wasteful procedures.

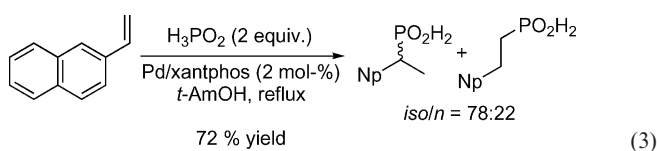
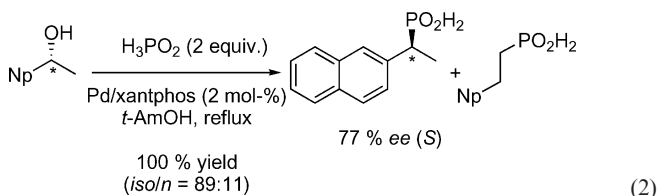
Scheme 1 illustrates some catalytic transformations in which this benzylation can be employed to prepare other compounds: (a) the catalytic benzylation of an *H*-phosphinic acid (compounds **2** and **3**), and (b) the one-pot ben-

zylation–oxidation reaction to produce phosphonic acids in a catalytic and environmentally friendly manner (compound **4**).^[13] The catalytic allylation of benzylic-*H*-phosphinic acids can also be achieved.^[14]



Scheme 1. Tandem transformations through benzylation. Reagents and conditions: (a) concentrated H₃PO₂ (0.5 equiv.), Pd₂(dba)₃ (dba = dibenzylideneacetone) (0.5 mol-%), xantphos (1.1 mol-%), *t*-AmOH, Dean–Stark, reflux, N₂, 16 h; (b) PhP(O)(OH)H (1.0 equiv.), Pd₂(dba)₃ (0.5 mol-%), xantphos (1.1 mol-%), *t*-AmOH, reflux, N₂, 17 h; (c) concentrated H₃PO₂ (2.0 equiv.), Pd₂(dba)₃ (0.5 mol-%), xantphos (1.1 mol-%), DMF 110 °C, N₂, 15 h; then open to air, 110 °C, 8 h.

The possibility for an asymmetric variant of this benzylation was then examined with the commercially available chiral (*R*)-1-(2-naphthyl)ethanol (>97% *ee*). The corresponding *H*-phosphinic acid was obtained in 77% *ee* [Equation (2)]. In this case, some competing racemic side reaction is taking place, most likely by β-hydrogen elimination–hydrophosphinylation. A control reaction with 2-vinylnaphthalene [Equation (3)] reveals the formation of a mixture of racemic (1-naphthalen-2-yl-ethyl)phosphinic acid and (1-naphthalen-2-yl-ethyl)phosphinic acid (*iso/linear* 78:22), which indicates that some asymmetric induction is still observed when starting from the alcohol, perhaps via the undissociated alkene (if the alkene dissociates, the enantiomeric excess would be expected in the range 50–55%). This approach does provide a significantly enantio-enriched *H*-phosphinic acid (the enantiomeric excess is comparable to or better than that of other asymmetric reactions with benzylic electrophiles),^[5b,5e] which can be a precursor to a variety of other organophosphorus compounds.



Conclusions

In conclusion, we have demonstrated the first cross-coupling of benzylic alcohols and its application to the formation of *H*-phosphinic acids and some derivatives. The reaction appears to be quite general and should be useful in the “green” preparation of organophosphorus building blocks. Preliminary results on the asymmetric variant are presented. Future work will be aimed at studying and improving the asymmetric benzylation of H_3PO_2 , as well as investigating the mechanism and scope of the reaction in more detail. The environmentally friendly, halogen-free preparation of building blocks is an important objective, which continues to be a major focus in our laboratory.

Experimental Section

General Procedure for the Catalytic Benzylation of H_3PO_2 with Benzylic Alcohols: $\text{Pd}_2(\text{dba})_3$ (0.5 mol-%, 0.01 mmol) and xantphos (1.1 mol-%, 0.022 mmol) were added to a benzylic alcohol (1 equiv., 2.0 mmol) and concentrated H_3PO_2 (2 equiv., 4.0 mmol) dissolved in *t*-AmOH (0.2 M, 10.0 mL) or in DMF (0.2 M, 10.0 mL) at room temperature. The reaction mixture was heated at reflux (Dean–Stark trap) under N_2 for 13–15 h when *t*-AmOH was used or heated at 110 °C under N_2 for 17 h for DMF. After the reaction mixture was cooled, the product was then isolated as the acid, the ammonium salt, or the butyl ester (see details in Supporting Information).

Supporting Information (see footnote on the first page of this article): General experimental procedures and detailed spectroscopic data for all products, mechanistic experiments, and details for Equation (2) are presented (106 pages).

Acknowledgments

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