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

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Abstract

Benzylic alcohols cross-couple directly with concentrated H₃PO₂ 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 reacted successfully in moderate to good yields. The preparation of other organophosphorus compounds (phosphinic and phosphonic acids) is also demonstrated.

Asymmetric reaction with (*R*)-1-(2-naphthyl)ethanol provided the corresponding *H*-phosphinic acid in 77% *ee*. The methodology provides a green, PCl₃-free, entry into benzylic-*H*-phosphinic acids.

Keywords

Phosphorus; Cross-Coupling; Phosphinic; Alcohols; Palladium; Homogeneous Catalysis

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 due to the fact that organophosphorus compounds have a major impact in everyday life, from phosphine ligands in catalysis, to phosphonates and phosphinates, as extractants, flame-retardants, and biologically active molecules.^[2] Our research is focusing 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]

(1)

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] including in situ activation,^[5a] but none which proceed on the benzylic alcohol directly.^[6] Recently, we described the synthesis of allylic-*H*-phosphinates from H₃PO₂ and allylic acetates^[7] or alcohols^[8] (Eq. 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 H₃PO₂ is ideal in terms of atom-economy (the by-product is water). Based on 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, based on Fiaud's success with the corresponding acetates.^[5b, 5c] Using Pd/xantphos 1 mol-%, DMF at 110°C, we were gratified with good yields of cross-coupling (82% and 93% isolated yields, respectively: Table 1, entries 1 and 2).

Table 1 shows that these conditions were also satisfactory with 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 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 which often succeeded when DMF gave poor results (Table 1, entries 8b–16).

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 entry into 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 work-up, or by precipitation as the ammonium salt. With some hydrophilic *H*-phosphinic acids, esterification^[11] was necessary in order to isolate 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 benzylation-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]

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

(2)

(3)

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 aim at studying and improving the asymmetric benzylation of H_3PO_2 , as well as investigating the mechanism and scope of the reaction in more details. 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

To a benzylic alcohol (1 equiv, 2.0 mmol) and concentrated H_3PO_2 (2 equiv, 4.0 mmol) dissolved in *t*-amylOH (0.2 M, 10.0 mL), or in DMF (0.2 M, 10.0 mL), were added Pd_2dba_3 (0.5 mol-%, 0.01 mmol) and xantphos (1.1 mol-%, 0.022 mmol) at room temperature. The reaction mixture was refluxed (Dean-Stark trap) under N_2 for 13–15 h, in the case of *t*-amylOH; or heated at 110°C under N_2 for 17 h, in the case of DMF. After cooling down the

reaction mixture, the product was then isolated as the acid, the ammonium salt, or the butyl ester (see details in Supporting Information).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Tandem transformations through benzylation. Reagents and conditions: a) conc. H_3PO_2 (0.5 equiv), Pd_2dba_3 (0.5 mol-%), xantphos (1.1 mol-%), *t*-AmOH, Dean-Stark, reflux, N_2 , 16 h; b) $\text{PhP}(\text{O})(\text{OH})\text{H}$ (1.0 equiv), Pd_2dba_3 (0.5 mol-%), xantphos (1.1 mol-%), *t*-AmOH, reflux, N_2 , 17 h; c) conc. H_3PO_2 (2.0 equiv), Pd_2dba_3 (0.5 mol-%), xantphos (1.1 mol-%), DMF 110°C, N_2 , 15 h; then open to air, 110°C, 8 h.

Table 1

Scope of the palladium-catalyzed benzylation^[a]

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	
<hr/>
	R ¹ =		
10		H	Bu	56
11		2-Me	NH ₄	41
12		3-Me	NH ₄	54

Entry	ArCH ₂ =	R=	Isolated Yield (%) ^[b]
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 work-up (R = H), ammonium salt precipitation (R = NH₄), or esterification with (BuO)₄Si (R = Bu).