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A novel approach to phosphonic acids from hypophosphorous acid

Karla Bravo-Altamirano and Jean-Luc Montchamp *

Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, Texas 76129, USA

Abstract

A novel access to phosphonic acids via Pd-catalyzed tandem carbon-phosphorus bond formation – oxidation processes was developed. The procedures involve atom-economical and environmentally friendly functionalization reactions of hypophosphorous acid (H_3PO_2) and *H*-phosphinic acids [$\text{RP}(\text{O})(\text{OH})(\text{H})$].

Keywords

phosphonic acid; *H*-phosphinic acid; hypophosphorous acid

Over the last few years, the quest for synthetic efficiency has gained remarkable importance, partly due to the need to reduce waste.¹ Given the increasing biological and synthetic impact of organophosphorus compounds,² it has become crucial to develop atom-economical methods that address the functionalization of P-H bonds from basic feedstocks. Homogeneous catalysis is an ever increasingly useful and versatile alternative for the construction of C-P bonds.³ Indeed, metal-catalyzed P-H bond activation has already shown some potential in the synthesis of various phosphines (free and protected),⁴ phosphonates,⁵ phosphine oxides,⁶ phosphinates,⁷ and more recently *H*-phosphinates.⁸ Our laboratory has demonstrated that in spite of being powerful reducing agents, hypophosphorous compounds ($\text{ROP}(\text{O})\text{H}_2$) can effectively participate in metal-catalyzed processes involving C-P bond formation, leading to *H*-phosphinic acids and their derivatives.⁹ Of particular relevance are the Pd-catalyzed addition of hypophosphorous acid (H_3PO_2) across unsaturated carbon linkages,^{8a–b} and the Pd-catalyzed dehydrative allylic substitution of H_3PO_2 with allylic alcohols,¹⁰ which are both unique and highly atom-efficient transformations. *H*-phosphinic acids [$\text{RP}(\text{O})(\text{OH})(\text{H})$] are characterized by the presence of a phosphinylidene [$\text{P}(\text{O})(\text{H})$] moiety that works as a bridge between the P(V) and P(III) forms via a tautomeric equilibrium,¹¹ and provides them with a unique versatility for further functionalization.^{8c,12}

Guided by the prospect of exploiting the flexibility of *H*-phosphinates as synthons for the preparation of other organophosphorus compounds, we became interested in developing new reactions that involve formal P-H bond activation processes, particularly those which can fulfill “green chemistry” requirements.¹³ In this regard, we discovered that *H*-phosphinates were sensitive towards oxidation into phosphonic acids, particularly under an air atmosphere and in the presence of catalytic amounts of transition metals. Since phosphonic acids have been extensively studied as phosphate analogs in catalytic enzymatic pathways, and their biological,

* Corresponding author. Tel.: +1-817-257-6201; fax: +1-817-257-5851; e-mail: j.montchamp@tcu.edu.

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biochemical, and synthetic importance are diverse,¹⁴ a convenient direct synthesis of these important compounds is highly desirable.

The literature syntheses of phosphonic acids generally involve the preparation of the phosphonate alkyl esters, which requires an additional deprotection step by treatment with trimethylsilyl bromide,¹⁵ or acidic hydrolysis at high temperatures.¹⁶ However, surprisingly few methods for their direct preparation via C-P bond formation have been described, such as the low-yielding free-radical mediated addition of phosphorous acid (H_3PO_3) to olefins,¹⁷ where polymerization is difficult to avoid.^{17,18} Another viable approach to phosphonic acids uses tris(trimethylsilyl) phosphite [$\text{P}(\text{OTMS})_3$] in Arbuzov reactions with electrophiles (i.e. iodides, bromides, triflates, aziridine and oxazolidine ring-opening, etc),¹⁹ as well as in Ni-catalyzed cross-couplings with aryl iodides and bromides.²⁰ This approach is not convenient because it requires strict anhydrous conditions and wasteful silylation. Furthermore, the synthesis of pure $\text{P}(\text{OTMS})_3$ is cumbersome.^{19a} On the other hand, phosphonic acids have also been previously prepared from *H*-phosphinic acids, however the strong oxidizing agents and/or harsh conditions that are usually required are major drawbacks,^{12a,21} along with the fact that, until recently, few effective synthetic methodologies for *H*-phosphinates were available.²²

Initially, we studied a simultaneous P-H bond functionalization starting from H_3PO_2 . This consisted of a one pot, one step hydrophosphinylation^{8a} – oxidation process (Scheme 1), avoiding in this way the isolation of the intermediate *H*-phosphinic acid **1**.

A series of experiments was performed in order to investigate the influence of the catalyst, solvent, temperature, air and water in the outcome of the reaction (Table 1). In a typical procedure, a DMF solution of freshly concentrated H_3PO_2 was heated with 1-octene in the presence of Pd_2dba_3 (1 mol%) and xantphos (2 mol%) under an air atmosphere. At 110°C, we observed a smooth conversion of the *in situ* formed octyl-*H*-phosphinic acid **3** into the corresponding phosphonic acid **4** (entry 1), along with minor amounts of H_3PO_3 and H_3PO_4 . The use of undried, reagent grade DMF (110°C) proved to be optimum, and a decrease in the temperature and/or replacement of DMF by CH_3CN significantly slowed down the oxidation step (entries 2 and 3). When the reaction was performed with anhydrous DMF under a nitrogen atmosphere, *H*-phosphinic acid **3** was the main product (entry 4). However, the presence of oxygen completely reverses this behavior and leads mainly to the oxidized product **4** (entry 6). As expected, the C-P bond-forming step proceeds very inefficiently with H_3PO_2 in the absence of Pd catalyst (entry 7). Other experiments probed the influence of stoichiometry and catalyst loading (entries 8 and 9). It was found that 1.5 – 2 equiv of H_3PO_2 and 2 mol% of Pd provide excellent yields of the phosphonic acid **4** (entry 8), while lowering the amount of catalyst markedly decreases the yield of **4**, and *H*-phosphinic acid **3** becomes the exclusive product (entry 9). This, along with control experiments performed on isolated *H*-phosphinic acids,²³ supports an active role of the Pd catalyst in the oxidation step. Remarkably, the reaction still proceeds in excellent yield when conducted with the commercially available aqueous solution of H_3PO_2 (50 wt. %) (entry 10). It should be noted that the use of concentrated versus aqueous H_3PO_2 did not show a significant impact on the formation of **4** (entry 4 vs. 5), contrary to the presence of nitrogen versus air in the reaction atmosphere (entries 4 vs. 6 and 5 vs. 10). Additionally, the concentration of the reactants also plays a key role, and 0.5 to 1 M appears to be optimum.

Pursuant to the design of a more general tandem C-P bond formation – oxidation process using H_3PO_2 as precursor, other Pd-catalyzed reactions that lead to *H*-phosphinic acids were conducted under the optimized conditions for the hydrophosphinylation-oxidation of 1-octene (Method A). Various unsaturated substrates, allylic alcohols and aryl halides were examined in hydrophosphinylation,^{8a} allylation¹⁰ and cross-coupling reactions,²⁴ respectively.

However, we discovered that the presence of oxygen during the C-P bond-forming step was not always optimum in all cases. Therefore a stepwise process (Method B) where the *H*-phosphinic acid is preformed under our published conditions (under N₂, with concentrated H₃PO₂) followed by *in situ* Pd-catalyzed oxidation (under air) provided overall better yields of products than the simultaneous version (Table 2). In accordance with the literature, Pd₂dba₃/xantphos (2 mol% Pd) worked efficiently as a catalytic system for hydrophosphinylation and allylation reactions (entries 1–8), while Pd(OAc)₂/dppp (2 mol%) with Et₃N as base (3 eq) proved successful in cross-coupling (entries 9–11). The products were generally isolated in moderate to good yields by an aqueous extractive workup and, if required, recrystallization was performed (entries 9–11). However, *N*-containing phosphonic acids (entries 4–5) are soluble in water and ion-exchange chromatography was required for their isolation.

Even though the mechanism of this transformation is not completely clear at this time, it could proceed either, via a direct P-H bond activation where the palladium inserts into the P-H bond of the *H*-phosphinic acid^{3b–c,3f} or, most probably, through an indirect process where the metal complex first activates molecular oxygen present in the solution forming a highly reactive species (as a radical), that in turn reacts with the *H*-phosphinic acid.²⁵ Further work will be required to delineate the mechanism of the reaction. In summary, an efficient step- and atom-economical method to access phosphonic acids was developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Table 1
Optimization of the tandem hydrophosphinylation – oxidation of 1-octene^a

entry	H ₃ PO ₂ ^b aq/concd (equiv)	Pd/L (mol %)	air/N ₂	solvent	T (°C)	31P NMR and/or [isolated] ^c yields (%)	
						3	4
1	concd (1)	2	air	DMF	110	0	74 [72]
2	concd (1)	2	air	DMF	85	34	53
3	concd (1)	2	air	CH ₃ CN	82	46	34
4	concd (1)	2	N ₂	DMF (anh) ^d	110	82	10
5	aq (1)	2	N ₂	DMF	110	45	31
6	concd (1)	2	air	DMF (anh), ^{de}	110	13	77
7	concd (1)	0	air	DMF	110	6	0
8	Concd (1.5-2)	2	air	DMF	110	0	100 [100]
9	concd (2)	0.05	air	DMF	110	100	0
10	aq (2)	2	air	DMF	110	0	100 [100]

^a Unless otherwise noted, reactions were conducted in a one-step mode, using reagent grade, undried solvents [0.5 M]. Reaction times: 20–24 h.

^b Concentrated H₃PO₂ was obtained by rotary evaporation of the commercial aqueous solution (50 wt. %). See Supplementary data for details.

^c Isolated yield after extractive workup.

^d Freshly vacuum-distilled DMF (from CaH₂).

^e Drierite trap was used to avoid moisture from air.

Table 2
Synthesis of phosphonic acids via tandem C-P bond formation – oxidation reactions

entry	substrate	method ^d	catalyst	base (equiv)	product	1 st step time (h)	2 nd step time (h)	isolated yield, ^b [NMR yield] (%)
1a 1b	Hex	A B	Pd ₂ dba ₃ / xaniphos	-	Oct-P(OH) ₃	20 12	- 24	100 100
2a 2b		A B	Pd ₂ dba ₃ / xaniphos	-		50 12	- 64	81 97
3	Ph	A	Pd ₂ dba ₃ / xaniphos	-	Ph-CH ₂ -P(OH) ₃	50	-	95
4	CbzHN	B	Pd ₂ dba ₃ / xaniphos	-	CbzHN-CH ₂ -P(OH) ₃	12	50	86 ^c
5	PhHN	B	Pd ₂ dba ₃ / xaniphos	-	PhHN-CH ₂ -P(OH) ₃	12	20	[81]
6	Pr	B	Pd ₂ dba ₃ / xaniphos	-	Pr-CH ₂ -P(OH) ₃	12	50	91
7	Ph	B	Pd ₂ dba ₃ / xaniphos	-	Ph-CH=CH-P(OH) ₃	12	22	89
8		B	Pd ₂ dba ₃ / xaniphos	-		15	50	[92]
9		B	Pd(OAc) ₂ / dppp	Et ₃ N (3)		15	22	82 ^d
10		B	Pd(OAc) ₂ / dppp	Et ₃ N (3)		15	22	55 ^d
11		B	Pd(OAc) ₂ / dppp	Et ₃ N (3)		15	42	52 ^d

entry	substrate	method ^d	catalyst	base (equiv)	product	1 st step time (h)	2 nd step time (h)	isolated yield, ^b [NMR yield] (%)
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^a See Supplementary data for details of the procedures. Method A: one step, 2 equiv 50% aqueous H₃PO₂, DMF, 110°C, air. Method B: two steps, 2 equiv concentrated H₃PO₂; 1st step: P-C bond formation: DMF, 85°C, N₂; 2nd step: oxidation: DMF, 110°C, air.

^b Unless otherwise noted, products were isolated in good purity (>95%) by a simple extractive workup.

^c Purified by ion-exchange chromatography.

^d Purified by recrystallization.