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Environmentally Benign Synthesis of H-Phosphinic Acids Using a Water-Tolerant, Recyclable Polymer-Supported Catalyst

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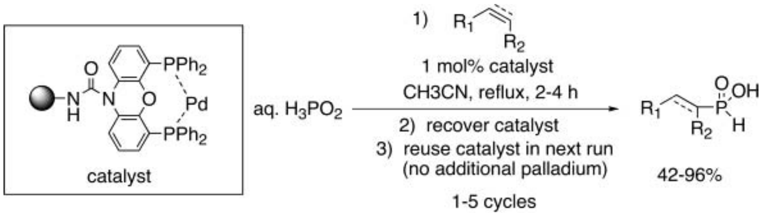
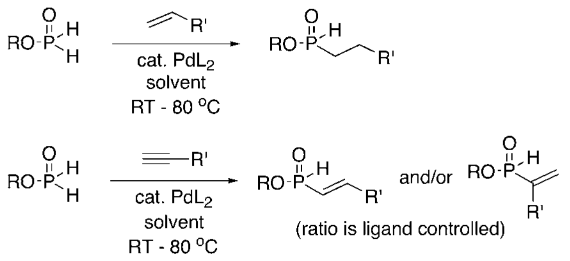
ABSTRACT



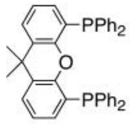
A reusable polymer-supported hydrophosphinylation catalyst is described for the preparation of H-phosphinic acids. The polystyrene-based ligand is prepared in one step from commercially available compounds. The polymeric catalyst generally gives good yields for a variety of substrates and is water- and air-tolerant, although the scope of alkenes and alkynes which can be employed is somewhat narrower than with our original xantphos/Pd$_2$dba$_3$ catalyst.

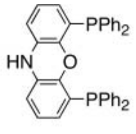
We recently reported a new palladium-catalyzed phosphorus−carbon bond-forming reaction in which hypophosphorous compounds undergo addition to alkenes and alkynes (Scheme 1).[1] Various ligands, in particular 9,9-dimethyl-4,5-bis-(diphenylphosphino)xanthene (xantphos **1**) and 1,1′-bis-(diphenylphosphino)ferrocene (dppf), were employed successfully. In a continuing effort to improve this methodology, we became interested in the development of a polymer-supported hydrophosphinylation catalyst. Immobilized catalysts are receiving increased attention because of the simplified product purification and the potential for recycling. Many approaches have been successfully employed to attach a ligand on a solid support for the catalysis of a wide variety of reactions, and several recent reviews are available on the subject.[2] Herein we detail the preparation and synthetic application of a recyclable hydrophosphinylation catalyst which can be employed under mild conditions, even in the presence of water.

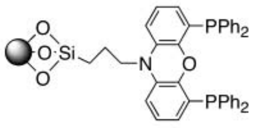
Scheme 1



R = Alk, PhNH$_3$, H; L$_2$ = ligand = xantphos, dppf, DPEphos, 2 PPh$_3$


xantphos **1**


nixantphos **2**


Van Leeuwen's ligand **3**

Van Leeuwen and co-workers have pioneered the use of xantphos-type ligands (**1**, **2**), particularly for highly selective

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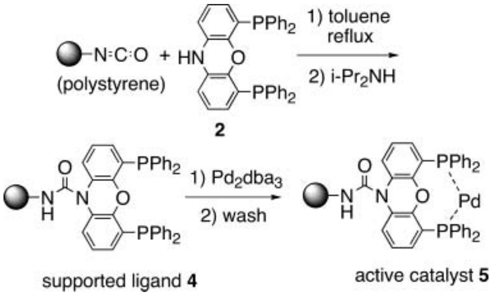
Scheme 2

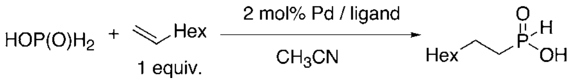


hydroformylation reactions.[3] They have also reported a powerful catalyst based on the xantphos motif immobilized on a silicate matrix **3**.[4] To our knowledge, their immobilized catalyst has never been tested in hydrophosphinylation reactions. We have focused on a different approach, which relies on a single step for the synthesis of a robust polystyrene-supported ligand **4** from commercially available reagents (Scheme 2). Reaction of excess polystyryl isocyanate (Aldrich or Chemtech) with nixantphos **2** (Strem) in refluxing toluene directly produces the desired urea-linked ligand. As expected, the phenoxazine nitrogen in **2** is quite unreactive and conversions are relatively low (ca. 40%). The use of refluxing mesitylene does not significantly improve the yield. The remaining isocyanate functionalities are reacted with diisopropylamine. Unreacted nixantphos is recovered essentially pure by washing the polymer and removing the volatile components, and it can be recycled. Loadings of 0.10−0.33 mmol/g are typically achieved, and no significant differences between batches are observed in the subsequent reactions. The active catalyst **5** is then obtained by treating polymer **4** with Pd_2dba_3 and washing, if it is not prepared in situ (Scheme 2). The catalyst is air-stable and does not require particular handling precautions.

As shown in Table 1, catalyst **5** successfully catalyzes the hydrophosphinylation of 1-octene with commercial 50 wt % aqueous H_3PO_2. When concentrated H_3PO_2 is employed, it is prepared by removing the water in vacuo for 20−30 min. Xantphos **1** and even nixantphos **2** are excellent ligands for the reaction, but catalyst **5** gives comparable results with 1-octene. The use of 10% Pd−C with xantphos also gives satisfactory results although the yields are 10−20% lower than with the homogeneous system, high amounts of water significantly suppress the reaction, and the reaction time increases. As expected, the P−C bond-forming reaction does not take place in the absence of ligand, and transfer hydrogenation occurs instead. Dppf is completely unsatisfactory to conduct hydrophosphinylation with H_3PO_2 (Table 1), whereas it was a good ligand with alkyl phosphinates.[1] Catalyst **5** uniformly gives good yields of addition and appears significantly more water-tolerant than its homogeneous counterpart **1**/Pd_2dba_3 (Table 1). Hydrophosphinylation of 1-octene with catalyst **5** also takes place with BuOP(O)H_2 in refluxing acetonitrile (100% NMR yield) or with $PhNH_3OP(O)H_2$ (100% in CH_3CN, 81% in DMF at 85 °C).[5] In addition, the hydrophosphinylation can even be conducted in air (yields in parentheses in Table 1). Overall, the results shown in Table 1 for 1-octene indicate that the polymer-supported catalyst **4**/Pd_2dba_3 is at least as good as the homogeneous system under a variety of conditions and that it is significantly more air and water tolerant.

As expected, various substrates reacted successfully under the influence of **5** (Table 2). More importantly, catalyst **5** can be used directly in multiple runs without further addition of palladium (Table 2), except when DMF is used as the reaction solvent. With DMF, extensive leaching of the palladium apparently occurs, and the recovered polymer **4**

Table 1. Catalyst Comparison in the Hydrophosphinylation of 1-Octene with H_3PO_2[a]



	concd H_3PO_2		50% aq H_3PO_2		aq H_3PO_2/CH_3CN/H_2O 10:1	
catalyst	rt	reflux	rt	reflux	rt	reflux
xantphos/Pd_2dba_3	88 (62)	100 (86)	79	97	68	64
nixantphos/Pd_2dba_3	91				0	
dppf/Pd_2dba_3		0				
10% Pd−C	0	0				
xantphos/10% Pd−C	83	78	69	58	0	35
ligand 4/Pd_2dba_3	93 (73)	100 (85)	82 (61)	99 (100)	89	78
ligand 4/10% Pd−C			77			
ligand 4/5% Pd−C	64	89	(64)	80		
ligand 4/Pd(OAc)$_2$	93	95 (92)				

[a] All yields are NMR yields which are determined by integration of all the resonances in the ^{31}P NMR spectra. The yields are accurate within 10% of the value indicated, reproducible, and representative of at least two runs. Numbers in parentheses correspond to runs conducted in air. Reactions were conducted with 1.5−2.0 equiv of H_3PO_2. Reactions at room temperature require 12−18 h. Reactions at reflux are usually complete in 2−3 h. Runs conducted in 10:1 CH_3CN/H_2O require extended reaction times.

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(1) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.

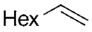
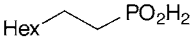
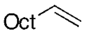
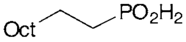
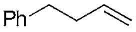
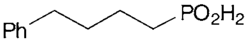
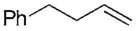
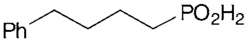
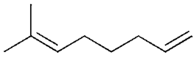
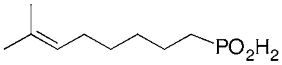
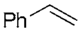
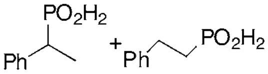
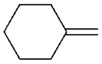
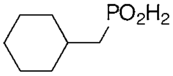
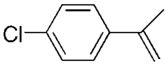
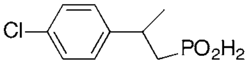
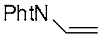
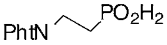
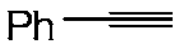
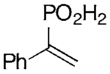
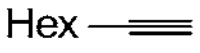
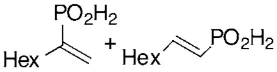
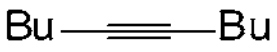
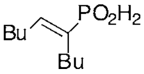
(2) For example: (a) Bräse, S.; Lauterwasser, F.; Ziegert, R. E. *Adv. Synth. Catal.* **2003**, *345*, 869. (b) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217. (c) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717. (d) Clapham, B.; Reger, T. S.; Janda, K. D.*Tetrahedron* **2001**, *57*, 4637. (e) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000.

(3) (a) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443. (c) van der Veen, L.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1999**, *18*, 4765. (d) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

(4) (a) van Leeuwen, P. W. N. M.; Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J. *J. Mol. Catal. A* **2002**, *182−183*, 107. (b) Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2001**, *123*, 8468. (c) Sandee, A. J.; van der Veen, L. A.; Reek, J. N. H.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; van Leeuwen P. W. N. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3231.

(5) Results not shown.

Table 2. Hydrophosphinylation Scope with Catalyst **5**[a]

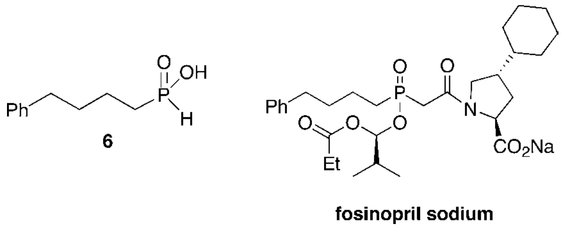
entry	substrate	product	H_3PO_2	conditions	number of runs	isolated yield %
1			50% aq	reflux, N_2	3	70
2			50% aq	reflux, N_2	4	50
3			50% aq	reflux, N_2	3	96
4[b]			50% aq[b]	reflux, N_2[b]	5[b]	82[b]
5			50% aq	reflux, N_2	4	68
6			50% aq	reflux, N_2	5	90[c]
7			conc.	reflux, N_2	1	92
8			50% aq	reflux, N_2	1	91
9			conc.	reflux, N_2	1	61
10			conc.	RT, N_2	1	42[d]
11			conc.	reflux, N_2	1	53[e]
12			conc.	reflux, N_2	1	46

[a] All yields are isolated. General conditions: all reactions were conducted in CH_3CN. Concentrated H_3PO_2 was obtained by concentration at room temperature, in vacuo for 20−30 min. 1 equiv of alkene was added to 2 equiv of 50% aq H_3PO_2 in the presence of 0.5 mol % Pd_2dba_3 and 1.1−1.2 mol % **4**. When multiple runs are conducted, the catalyst is reused directly after filtration. Reaction times vary from 3 to 12 h. [b] Entry 4 was conducted with 5% Pd−C/**4** (0.18 mmol/g). [c] Branched/linear ratio is 1:2. [d] Branched only. [e] Branched/linear ratio is 2:1.

must then be retreated with Pd_2dba_3 prior to subsequent runs.[5] Generally, acetonitrile was found to be the ideal solvent, although other solvents, such as ethyl acetate, toluene, or dichloromethane, can also be used. With alkenes, catalyst **5** gives high yields of products with commercial 50 wt % aqueous H_3PO_2 (Table 2, entries 1−3 and 5, 6, and 9). However, alkynes, especially internal alkynes, give lower yields (Table 2, entries 10−12) than with the homogeneous system[1] **1**/Pd_2dba_3, and concentrated H_3PO_2 should be employed to obtain the highest yields.

In these experiments, gas chromatographic analysis shows mainly unreacted alkyne as the balance of material, as opposed to products resulting from the possible competing transfer hydrogenation. Thus, the low reactivity of internal alkynes with catalyst **5** may be due to increased steric requirements for the heterogeneous catalyst, instead of an increase in competing reduction (transfer hydrogenation). 1,2-Disubstituted alkenes are completely unreactive (<5%, whereas **1**/Pd_2dba_3 gives 45% yield on *trans*-4-octene). Interestingly, a doubly heterogeneous system of **4** and Pd−C also gives useful results (Table 1). In this case, the optimum loading must be determined for each batch of ligand **4** (5% Pd−C is optimum with **4** at a loading of 0.18 mmol/g). This combination can easily be reused and provides generally good results (Table 2, entry 4).

With less reactive substrates, concentrated H_3PO_2 in refluxing CH_3CN should be employed for optimum results (Table 2, entries 7, 9−12). The hydrophosphinylation of terminal alkenes is successful even at room temperature (Table 1) but requires 12−18 h, instead of 2−3h at reflux, to reach completion. The reaction of 4-phenyl-1-butene (Table 2, entries 3−4) is particularly interesting because the product, (4-phenylbutyl)phosphinic acid **6**, is an intermediate in the synthesis of the commercial heart drug Monopril (fosinopril sodium, Figure 1). The commercial process (Bristol-Myers Squibb) employs a modified Nifant'ev thermal radical addition for the preparation of **6**.[6] Our reusable



6

fosinopril sodium

Figure 1. Synthetic intermediate and Fosinopril sodium.

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(6) Anderson, N. G.; Coradetti, M. L.; Cronin, J. A.; Davies, M. L.; Gardineer, M. B.; Kotnis, A. S.; Lust, D. A.; Palaniswamy, V. A. *Org. Process Res. Dev.* **1997**, *1*, 315.

catalyst, straightforward purification, and lower number of H_3PO_2 equivalents are advantages of our procedure. The product derived from *N*-vinylphthalimide (entry 9) is also an interesting synthon for the preparation of DNA analogues, a project currently underway in our laboratory, even if in this case too, Pd_2dba_3/**1** gives higher yields. Phosphorous acid (H_3PO_3) does not undergo our palladium-catalyzed reaction; thus, phosphonic acids are not accessible directly. However, the H-phosphinic acid products are readily oxidized (for example with H_2O_2) to the corresponding phosphonic acids.[7] H-Phosphinic acids have been relatively underexploited in the synthesis of various organophosphorus compounds, in part because of the paucity of convenient methods to access them. Thus, our catalytic P−C bond formation should be useful to access other derivatives in a straightforward manner.[8]

In conclusion, we have developed a new polymer-supported recyclable hydrophosphinylation catalyst. The reaction can be conducted under mild conditions even in the presence of water and air. Various unsaturated substrates undergo the addition of H_3PO_2 in good to excellent yields. The scope of the reactions catalyzed by **5** is narrower than with our original homogeneous system, but tolerance to water is significantly enhanced, and both purification and recycling are straightforward. Since the catalyst can be recovered and reused, this methodology represents an environmentally friendly and atom-economical approach toward H-phosphinic acids.

Application to deuterium labeling can also be conducted, and even if at this time deuterium incorporation only reaches 75−80%,[5] this shows promise for radiolabeling with T_3PO_2. Owing to its ease of preparation and its broad reactivity profile, catalyst **5** should prove useful for the environmentally benign synthesis of various organophosphorus compounds. Our palladium-catalyzed hydrophosphinylation also represents a useful alternative to radical-based methodologies.[9] Further studies are currently in progress to develop better polymer-supported hydrophosphinylation catalysts in order to improve the yields and regioselectivity of the reaction with alkyne substrates, and to increase deuterium incorporation. The related preparation of polymer-supported chiral ligands for asymmetric P−C bond formation is also an intriguing possibility.

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Supporting Information Available: Experimental procedures, spectroscopic data, and representative NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0484198

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(7) For example: (a) Vitharana, D.; France, J. E.; Scarpetti, D.; Bonneville, G. W.; Majer, P.; Tsukamoto, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1609. (b) Khomutov, A. R.; Osipova, T. I.; Khurs, E. N.; Alferov, K. V.; Khomutov, R. M. *Russ. Chem. Bull.* **1996**, *45*, 1961. (c) Sasaki, M. *Agric. Biol. Chem.* **1986**, *50*, 741. (d) Frank, A. W. *Chem. Rev.* **1961**, *61*, 389 and references therein.

(8) For example, see: (a) *Methoden der Organischen Chemie (Houben-Weyl)*; Sasse K., Ed.; Thieme: Stuttgart, 1964; Band XII/1, pp 294−337. (b) *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz, M., Ed.; Thieme: Stuttgart, 1982; Vol. E2. (c) Frank, A. W. In *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley: New York, 1972; Vol. 4, Chapter 10. (d) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000.

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