

Cite this: *Green Chem.*, 2012, **14**, 2699

www.rsc.org/greenchem

## Solvent- and catalyst-free regioselective hydrophosphanation of alkenes†

Francisco Alonso,\*<sup>a</sup> Yanina Moglie,<sup>a</sup> Gabriel Radivoy<sup>b</sup> and Miguel Yus<sup>a</sup>

Received 13th June 2012, Accepted 10th August 2012

DOI: 10.1039/c2gc35898k

**The hydrophosphanation of alkenes, an atom-economy process typically promoted by radicals or metal species, has been shown to take place in the absence of a catalyst, under solvent-free conditions and in a regioselective manner.**

Organophosphorus compounds are widely used in the chemical, agrochemical, and pharmaceutical industries.<sup>1</sup> In particular, phosphane ligands are of paramount importance in organic synthesis, especially in homogeneous and asymmetric catalysis.<sup>2</sup> In recent years, increasing attention has also been devoted to the design of metal–phosphane complexes with anticancer activity, as potential substitutes of the current platinum drugs.<sup>3</sup> The traditional methods for the synthesis of phosphanes include (a) the reaction of an organometallic reagent with a phosphorus halide or a phosphane bearing a good leaving group, (b) reaction of a metal phosphide with an organic electrophile, (c) reduction of a phosphorus halide or oxide, and (d) from elemental phosphorus.<sup>4</sup> The direct addition of the P–H bond to alkenes is, however, a more suitable approach from the green chemistry and atom economy point of view since no by-products are formed. This reaction, known as hydrophosphanation,<sup>5</sup> has been much less studied than the hydrophosphinylation<sup>6</sup> and hydrophosphorylation<sup>7</sup> counterparts.

The hydrophosphanation of alkenes was initially conducted under base catalysis or radical activation, leading to the anti-Markovnikov products.<sup>5c</sup> In contrast, the acid-promoted reaction was barely documented and led to the Markovnikov products.<sup>8</sup> A new era for the addition of phosphanes to alkenes began with the advent of the transition-metal catalysed methodologies.<sup>5</sup> Pioneering work in the late nineties was developed by Glueck *et al.* on the platinum-catalysed anti-Markovnikov hydrophosphanation of the activated alkene acrylonitrile.<sup>9</sup> In the early 21st century, the group of Marks described the utility of lanthanocenes as catalysts for the intramolecular hydrophosphanation of primary and secondary alkenyl phosphanes.<sup>10</sup> Soon after, the ytterbium-catalysed addition of diphenylphosphane to isoprene and two styrenes was reported by Takaki *et al.*<sup>11</sup> In 2002, the

group of Beletskaya reported the first intermolecular hydrophosphanation of styrenes catalysed by nickel and palladium complexes.<sup>12</sup> The process was high yielding though suffered from some lack of atom economy under rather harsh reaction conditions, involving 5 mol% Ni[P(OEt)<sub>3</sub>]<sub>4</sub>, 2 equiv. of styrene, 1 equiv. of Et<sub>3</sub>N, in benzene at 130 °C for 20 h. Some years later, Barret *et al.* introduced a β-diketoimidato-stabilised calcium amide which effectively catalysed the addition of diphenylphosphane to styrene, isoprene, and 1,3-cyclohexadiene in C<sub>6</sub>D<sub>6</sub> (25–75 °C, 16–36 h).<sup>13</sup> Chiral organopalladium(II) complexes, prepared by Leung *et al.*, allowed the asymmetric hydrophosphanation of vinyl phosphanes, aromatic enones, functionalised allenes and alkyldiene malonate esters.<sup>14</sup> Recently, Corma *et al.* presented the first hydrophosphanation of styrenes catalysed by a metal salt: (CuOTf)<sub>2</sub>·toluene (10 mol%) in 1,4-dioxane-d<sub>8</sub> at 100 °C for 18–24 h.<sup>15</sup> Other diverse metal salts, preferably FeCl<sub>2</sub> and FeCl<sub>3</sub>, have been also shown to promote the addition of secondary phosphanes to alkenes.<sup>16</sup> The formation of the anti-Markovnikov products is a common feature for all these metal-catalysed strategies.<sup>17</sup>

Notwithstanding the utility of the aforementioned methods, expensive and, in some cases, toxic catalytic systems are applied often under harsh conditions. The oxidation of the resulting phosphane to the corresponding phosphane oxide is another inconvenience commonly encountered, which can be enhanced by the presence of the metal. The use of neutral conditions is also desirable in order to minimise side-reactions (*e.g.* polymerisation, self-condensation) and avoid the aqueous work-up, which increases the risk of oxidation. In this sense, Gaumont *et al.* designed an elegant approach to the unique uncatalysed hydrophosphanation of inactivated alkenes (styrenes excluded), starting from secondary phosphane–borane complexes.<sup>18</sup> The addition occurred in toluene under neutral conditions and either classical or microwave heating (50–80 °C).

Our interest in the transition-metal catalysed addition of H–H bonds across carbon–carbon multiple bonds<sup>19</sup> led us to the discovery of the uncatalysed addition of secondary phosphanes to alkenes under solvent-free conditions. We initially studied the solvent effect on the addition of diphenylphosphane to styrene as a model reaction. The experiments were conducted in common organic solvents at 70 °C, under an argon atmosphere in order to prevent the *in situ* oxidation of the reagent diphenylphosphane to the corresponding phosphane oxide. Among them, CH<sub>2</sub>Cl<sub>2</sub>, MeCN, and EtOH were found to be very inappropriate solvents (Table 1, entries 1, 6, and 7, respectively), whereas marginal-to-low conversions into the product were obtained in THF, toluene, DMSO or DMF (Table 1, entries 2–5). In contrast, quantitative

<sup>a</sup>Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo 99, 03080 Alicante, Spain. E-mail: falonso@ua.es; Fax: (+34)965903549; Tel: (+34)965903548

<sup>b</sup>Departamento de Química, Instituto de Química del Sur (INQUISUR-CONICET), Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina

†Electronic supplementary information (ESI) available: General remarks, experimental procedure, physical and spectroscopic data of new compounds, and NMR spectra. See DOI: 10.1039/c2gc35898k

**Table 1** Uncatalysed addition of diphenylphosphane to styrene in different solvents<sup>a</sup>

Entry	Solvent	Conversion <sup>b</sup> (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	0
2	THF	2
3	PhMe	13
4	DMSO	7
5	DMF	19
6	MeCN	0
7	EtOH	0
8	None	>99

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), diphenylphosphane (0.5 mmol), solvent (1 mL), 70 °C, 24 h, Ar atmosphere. <sup>b</sup> Determined by GLC.

conversion was recorded for the reaction carried out in the absence of a solvent (Table 1, entry 8). Solvent-free organic synthesis is one of the most promising steps toward waste prevention and environmental protection.<sup>20</sup>

We next extended this uncatalysed solvent-free protocol to a variety of alkenes.<sup>‡</sup> All reactions were performed with new magnetic bars in order to rule out any catalysis by traces of metals. Among the styrenes tested, styrene (product **2a**) was found to react faster than the *p*-halostyrenes (products **2b** and **2c**), albeit similar good yields were reached in all cases. The process was also high yielding for *p*-methoxy- and *p*-acetoxystyrene (**2d** and **2e**, respectively). The hydrophosphanation of vinyl pyridines furnished the expected heterocyclic products **2f** and **2g**; the former is a P,N-bidentate ligand known as pyphos, which has found application in homogeneous transition-metal catalysis.<sup>21</sup> Yields around 90% were recorded in the hydrophosphanation of either 2-vinylnaphthalene or 4-vinyl-1,1'-biphenyl (**2h** and **2i**, respectively). Interestingly, the much less reactive gem-disubstituted alkene isopropenyl benzene successfully reacted under the standard conditions, giving rise to **2j** in 79% yield. Moreover, diphenylphosphane could be also added to *N*-vinyl compounds, such as *N*-vinylphthalimide or *N*-vinylpyrrolidin-2-one, though longer time was needed in order to attain good yields (**2k** and **2l**, respectively). A P,S-bidentate ligand (**2m**), also applied in catalysis,<sup>22</sup> was nicely prepared from phenyl vinyl sulphide. In contrast, vinyl ethers were rather reluctant to react under the standard conditions. We next studied the hydrophosphanation of some activated alkenes such as methyl vinyl ketone, ethyl acrylate, and acrylonitrile. We were delighted to observe that reactions proceeded at room temperature (7 h) with similar yields as at 70 °C, though were faster by heating (1–3 h). 4-(Diphenylphosphanyl)butan-2-one (**2n**) was obtained in lower yield due to some by-product formation involving two molecules of the substrate. This side reaction was not observed in the case of **2o**. It is noteworthy that the addition of diphenylphosphane to acrylonitrile, a reaction deeply studied under platinum catalysis,<sup>9</sup> was effectively accomplished in the absence of a catalyst, even at room temperature (**2p**).

We must remark that conversions in the range 96–>99% were generally achieved except for the alkene precursors of

**Table 2** Solvent- and catalyst-free hydrophosphanation of alkenes<sup>a</sup>

1	2
<b>2a</b> (4 h, 82%)	<b>2b</b> (16 h, 85%)
<b>2c</b> (16 h, 82%)	<b>2d</b> (8 h, 88%)
<b>2e</b> (8 h, 85%)	<b>2f</b> (16 h, 80%)
<b>2g</b> (16 h, 74%)	<b>2h</b> (16 h, 91%)
<b>2i</b> (16 h, 90%)	<b>2j</b> (16 h, 79%)
<b>2k</b> (24 h, 70%)	<b>2l</b> (24 h, 78%)
<b>2m</b> (16 h, 85%)	<b>2n</b> (1 h, 70%) (7 h at rt)
<b>2o</b> (3 h, 77%) (7 h at rt)	<b>2p</b> (3 h, 81%) (7 h at rt)

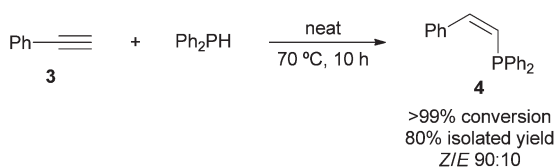
<sup>a</sup> Reaction conditions: **1** (0.5 mmol), diphenylphosphane (0.5 mmol), 70 °C or rt, Ar atmosphere; reaction time and isolated yield in parentheses.

compounds **2c** and **2i–2l**. Minor amounts of the corresponding phosphane oxides (10–15%) were detected in some cases as a result of the addition of partially oxidised diphenylphosphane and/or spontaneous oxidation of the product **2**. Nevertheless,

**Table 3** Addition of diphenylphosphane to styrene

Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield <sup>a</sup> (%)
1 <sup>23</sup>	<i>t</i> -BuOK (20)	DMSO	rt	1	83
2 <sup>12a</sup>	Ni[P(OEt) <sub>3</sub> ] <sub>4</sub> (5)	C <sub>6</sub> H <sub>6</sub>	130	20	>99 <sup>b</sup>
3 <sup>13a</sup>	Ca complex (10)	C <sub>6</sub> D <sub>6</sub>	75	20	95 <sup>c</sup>
4 <sup>15</sup>	(CuOTf) <sub>2</sub> ·PhMe (10)	Dioxane-d <sub>8</sub>	100	18–24	92 <sup>b</sup>
5 <sup>16</sup>	FeCl <sub>2</sub> (30)	MeCN	60	12	97 <sup>d</sup>
6 <sup>e</sup>	None	None	70	4	82

<sup>a</sup> Isolated yield unless otherwise stated. <sup>b</sup> <sup>31</sup>P NMR yield. <sup>c</sup> Conversion by NMR. <sup>d</sup> Isolated as the borane complex. <sup>e</sup> This communication.

**Scheme 1** Uncatalysed solvent-free addition of diphenylphosphane to phenylacetylene.

easy and quick purification by column chromatography provided the pure tertiary phosphanes. Furthermore, all reactions were shown to be highly regioselective, exclusively affording the anti-Markovnikov products. Table 3 clearly shows more evidence about how advantageous the title reaction is in the hydrophosphanation of styrene when compared with the reported catalytic procedures.

We checked that the addition of radical traps, such as cumene, TEMPO or 2,6-di-*tert*-butylphenol, did not inhibit the hydrophosphanation of styrenes (>96% conversion) and no products derived from their reaction with diphenylphosphanyl radicals were detected. In addition, no cyclisation product was formed by the addition of diphenylphosphane to hepta-1,6-diene, with all these results practically discarding any free-radical process.

Finally, we proved the potential application of this simple methodology to the synthesis of vinyl phosphanes. As an example, the solvent- and catalyst-free hydrophosphanation of phenylacetylene yielded the diphenyl(styryl)phosphane **4** in a regio- and stereoselective manner, mainly following an anti-Markovnikov anti-addition (Scheme 1).

## Conclusions

We have demonstrated the feasibility of the uncatalysed direct addition of phosphanes to alkenes when carried out in the absence of a solvent. Styrenes, *N*- and *S*-vinyl compounds, as well as activated alkenes, underwent this atom-economy addition in moderate-to-high isolated yields (70–91%) at 70 °C or room temperature (in the latter case). The process is highly regioselective producing all tertiary phosphanes in an anti-Markovnikov fashion. These results emphasize how important it is to perform control experiments in the absence of a catalyst and the crucial role that the concentration effect can play in solvent-free

reactions. Further studies on the substrate scope of this simple methodology are under way.

## Acknowledgements

This work was generously supported by the Spanish Ministerio de Ciencia e Innovación (MICINN; CTQ2007-65218 and Consolider Ingenio 2010-CSD2007-00006), the Generalitat Valenciana (GV; PROMETEO/2009/039), and Fondo Europeo de Desarrollo Regional (FEDER). Y. M. acknowledges the Instituto de Síntesis Orgánica (ISO) of the Universidad de Alicante for a grant.

## Notes and references

‡ General procedure: Diphenylphosphane (0.5 mmol, 87  $\mu$ L) and the alkene (0.5 mmol) were stirred under argon during the specified time at 70 °C or room temperature (see Table 2). The progress of the reaction was monitored by TLC and GLC until total or steady conversion was achieved. The resulting mixture was subjected to column chromatography (silica gel, hexane–EtOAc) to give the pure phosphanes **2**.

- L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley-Interscience, New York, 2000.
- For recent reviews and monographs, see: (a) *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*, ed. A. Börner, Wiley-VCH, Weinheim, 2008; (b) P. E. Goudriann, P. W. N. M. van Leeuwen, M.-N. Birkholz and J. N. H. Reek, *Eur. J. Inorg. Chem.*, 2008, 2939–2958; (c) S. Lühr, J. Holz and A. Börner, *ChemCatChem*, 2011, **3**, 1708–1730; (d) J. Wassenaar and J. N. H. Reek, *Org. Biomol. Chem.*, 2011, **9**, 1704; (e) F. L. Lam, F. K. Kwong and A. S. C. Chan, *Top. Organomet. Chem.*, 2011, **36**, 29–66; (f) *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, ed. P. C. J. Kamer and P. W. N. M. van Leeuwen, John Wiley & Sons, Chichester, 2012.
- A. A. Nazarov and P. J. Dyson, in *Phosphorus Compounds, Advanced Tools in Catalysis and Materials Science, Catalysis by Metal Complexes*, ed. M. Peruzzini and L. Gonsalvi, Springer, Dordrecht, 2011, ch. 13, vol. 37.
- (a) M. L. Clarke and J. M. J. Williams, in *Organophosphorus Reagents. A Practical Approach in Chemistry*, ed. P. J. Murphy, Oxford University Press, Oxford, 2004, ch. 2; (b) E. Hey-Hawkins and A. A. Karasik, in *Science of Synthesis*, ed. F. Mathey, Georg Thieme Verlag, Stuttgart, 2009, vol. 42, pp. 71–108; (c) B. A. Trofimov and N. K. Gusarova, *Mendeleev Commun.*, 2009, **19**, 295–302.
- For reviews, see: (a) C. Baillie and J. Xiao, *Curr. Org. Chem.*, 2003, **7**, 477–514; (b) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079–3159; (c) O. Delacroix and A. C. Gaumont, *Curr. Org. Chem.*, 2005, **9**, 1851–1882.
- For a microreview, see: L. Coudray and J.-L. Montchamp, *Eur. J. Org. Chem.*, 2008, 3601–3613.
- For an account on the hydrophosphorylation of alkynes, see: V. P. Ananikov, L. L. Khemchyan and I. P. Beletskaya, *Synlett*, 2009, 2375–2381.
- (a) M. C. Hoff and P. Hill, *J. Org. Chem.*, 1959, **24**, 356–359; (b) B. D. Dombek, *J. Org. Chem.*, 1978, **43**, 3408–3409.
- (a) D. K. Wicht, I. V. Kourkine, B. M. Lew, J. Mulei Nthenge and D. S. Glueck, *J. Am. Chem. Soc.*, 1997, **119**, 5039–5040; (b) D. K. Wicht, I. V. Kourkine, I. Kovacic and D. S. Glueck, *Organometallics*, 1999, **18**, 5381–5394; (c) C. Scriban, I. Kovacic and D. S. Glueck, *Organometallics*, 2005, **24**, 4871–4874; (d) I. Kovacic, C. Scriban and D. S. Glueck, *Organometallics*, 2006, **25**, 536–539; (e) C. Scriban, D. S. Glueck, L. N. Zakharov, W. Scott Kassel, A. G. DiPasquale, J. A. Golen and A. L. Rheingold, *Organometallics*, 2006, **25**, 5757–5767.
- (a) M. R. Douglass and T. J. Marks, *J. Am. Chem. Soc.*, 2000, **122**, 1824–1825; (b) M. R. Douglass, C. L. Stern and T. J. Marks, *J. Am. Chem. Soc.*, 2001, **123**, 10221–10238; (c) A. Motta, I. L. Fragalà and T. J. Marks, *Organometallics*, 2005, **24**, 4995–5003.
- K. Takaki, M. Takeda, G. Koshiji, T. Shishido and K. Takehira, *Tetrahedron Lett.*, 2001, **42**, 6357–6360.

- 12 (a) M. O. Shulyupin, M. A. Kazankova and I. P. Beletskaya, *Org. Lett.*, 2002, **4**, 761–763; (b) M. A. Kazankova, M. O. Shulyupin, A. A. Borisenko and I. P. Beletskaya, *Russ. J. Org. Chem.*, 2002, **38**, 1532–1537; For the Pd- and Ni-catalysed hydrophosphanation of vinyl ethers, see: (c) M. A. Kazankova, M. O. Shulyupin and I. P. Beletskaya, *Synlett*, 2003, 2155–2158; (d) M. O. Shulyupin, I. G. Trostyanskaya, M. A. Kazankova and I. P. Beletskaya, *Russ. J. Org. Chem.*, 2006, **42**, 17–22.
- 13 (a) M. R. Crimmin, A. G. M. Barret, M. S. Hill, P. B. Hitchcock and P. A. Procopiu, *Organometallics*, 2007, **26**, 2953–2956; (b) Improved catalytic activity by related calcium or ytterbium complexes has been very recently reported: H. Hu and C. Cui, *Organometallics*, 2012, **31**, 1208–1211.
- 14 (a) W.-C. Yeo, L. Tang, B. Yan, S.-Y. Tee, L. L. Koh, G.-K. Tan and P.-H. Leung, *Organometallics*, 2005, **24**, 5581–5585; (b) Y. Zhang, L. Tang, S. A. Pullarkat, F. Liu, Y. Li and P.-H. Leung, *J. Organomet. Chem.*, 2009, **694**, 3500–3505; (c) Y. Huang, S. A. Pullarkat, Y. Li and P.-H. Leung, *Chem. Commun.*, 2010, **46**, 6950–6952; (d) Y. Huang, S. A. Pullarkat, M. Yuan, Y. Ding, Y. Li and P.-H. Leung, *Organometallics*, 2010, **29**, 536–542; (e) C. Xu, G. J. H. Kennard, F. Hennesdorf, Y. Li, S. A. Pullarkat and P.-H. Leung, *Organometallics*, 2012, **31**, 3022–3026.
- 15 A. Leyva-Pérez, J. A. Vidal-Moya, J. R. Cabrero-Antonino, S. S. Al-Deyab, S. I. Al-Resayes and A. Corma, *J. Organomet. Chem.*, 2011, **696**, 362–367.
- 16 M. Taillefer, L. Routaboul and A. C. Gaumont, *FR Pat.*, 2965809, 2012.
- 17 The Pd- and Ni-catalysed hydrophosphanation of vinyl ethers is an exception, which gave the Markovnikov products.<sup>12c,d</sup>
- 18 (a) D. Mimeau, O. Delacroix and A.-C. Gaumont, *Chem. Commun.*, 2003, 2928–2929; (b) D. Mimeau, O. Delacroix, B. Join and A.-C. Gaumont, *C. R. Chim.*, 2004, **7**, 845–854.
- 19 Si–H addition: (a) F. Alonso, R. Buitrago, Y. Moglie, J. Ruiz-Martínez, A. Sepúlveda-Escribano and M. Yus, *J. Organomet. Chem.*, 2011, **696**, 368–372; (b) F. Alonso, R. Buitrago, Y. Moglie, A. Sepúlveda-Escribano and M. Yus, *Organometallics*, 2012, **31**, 2336–2342; P–H addition: unpublished results.
- 20 (a) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025–1074; (b) K. Tanaka, *Solvent-Free Organic Synthesis*, Wiley-VCH, Weinheim, 2003.
- 21 See, for instance: R. L. Rogers, J. L. Moore and T. Rovis, *Angew. Chem., Int. Ed.*, 2007, **46**, 9301–9304.
- 22 See, for instance: C. Pisano, A. Mezzetti and G. Consiglio, *Organometallics*, 1992, **11**, 20–22.
- 23 T. Bunlaksananusorn and P. Knochel, *Tetrahedron Lett.*, 2002, **43**, 5817–5819. According to Corma *et al.*,<sup>15</sup> the corresponding phosphane oxide was the major product isolated under those conditions.