Palladium-catalysed regioselective addition reaction of ethyl phenylphosphinate with terminal acetylenes: ligand- and solvent-dependent regioselectivity†‡

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Palladium–1,2-bis(diphenylphosphino)ethane complex catalyses regioselective Markovnikov addition of ethyl phenylphosphinate to terminal alkynes in toluene, while the use of tri-*tert*-butylphosphine as the ligand or ethanol as the solvent leads to regioselectivity reversal.

α,β-Unsaturated phosphorus(V) compounds are a useful class of intermediates that undergo myriad synthetic organic transformation reactions.[1] They are envisioned to be useful as flame retardants and monomers for flame retardant polymers.[2] They have also been recognised as excellent matrix metalloproteinase (MMP) inhibitors.[3] Synthesis of this important class of compounds remains a great interest and several synthetic protocols have been developed.[4] One of us has also been engaged in exploring transition metal catalysts for the synthesis of organophosphorus(V) compounds and developed novel addition reactions of hydrogen phosphonates, secondary phosphine oxides and related compounds with alkynes, alkenes and other unsaturated compounds.[5] A great feature of these reactions lies in the high regioselectivity; for instance, the palladium-catalysed reaction of hydrogen phosphonate, H–P(O)$(OR)_2$, with terminal alkynes forms branched products regioselectively. On the other hand, the reaction of diphenylphosphine oxide, H–P(O)Ph_2, with terminal alkynes forms linear products. These results show the branched- and linear-directing nature of alkoxy and phenyl groups bound to the phosphorus centre, respectively. Because of the conflicting nature of the alkoxy and phenyl groups, the reaction of hydrogen phosphinates such as H–P(O)Ph(OR) does not proceed regioselectively unless an acidic additive such as diphenylphosphinic acid is present in the reaction system, which can be a serious drawback for commercial implementation, as was described in a patent application.[5l] This communication discloses three protocols for the palladium-catalysed regioselective addition of ethyl phenylphosphinate, (EtO)PhP(O)H (**1**), to terminal alkynes without the use of acidic additives, furnishing either linear (anti-Markovnikov) or branched (Markovnikov) adducts, depending on the ligand and the solvent.

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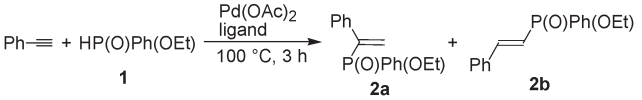
‡ Electronic supplementary information (ESI) available: General experimental information and spectral and analytical data of new compounds. See DOI: 10.1039/b703165c

The performance of phosphine ligands in the addition reaction between **1** and phenylacetylene run at 100 °C for 3 h in toluene using $Pd(OAc)_2$ as precatalyst is summarized in Table 1.[6] Unless otherwise noted, phosphine ligands were used at a P : Pd ratio of 3 : 1.

The reaction using PPh_3 as the ligand did not proceed selectively, ending up with the formation of **2a** and **2b** in an approximately 2 : 1 ratio although the reaction proceeded smoothly (entries 1 and 2). The reaction using $PPhMe_2$ was not regioselective either (entries 4 and 5) as was disclosed in the patent application.[5l] However, the regioselectivity for **2a** increased dramatically when chelating phosphines were used (entries 7–13). The more strongly chelating and more sterically demanding ones

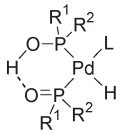
Table 1 Ligand effect in the reaction of phenylacetylene with ethyl phenylphosphinate[a]



Entry	Ligand	Conversion of **1**[b,c] (%)	Yield[b] (%) **2a**	Yield[b] (%) **2b**	Selectivity of **2a**[d] (%)
1	PPh_3	>99	51.9	28.2	64.8
2	PPh_3[e]	99	48.1	27.4	63.7
3	PPh_2Me	100	63.9	22.4	74.4
4	$PPhMe_2$	100	63.9	35.6	64.2
5	$PPhMe_2$[e]	100	57.4	41.6	57.9
6	PMe_3	45	10.9	24.3	31.0
7	dppe	99	89.0	0.94	99.0
8	dppp	93	63.7	5.7	91.7
9	dppb	99	52.6	9.4	84.8
10	dppf	86	55.1	18.0	75.3
11	xantphos	100	78.9	16.0	83.1
12	dmpe	64	34.2	4.0	89.5
13	dcpe	7.9	3.1	Trace	99.0
14	P^tBu_3	100	32.1	44.8	41.7
15	P^tBu_3[e]	99	44.7	40.0	52.8
16	P^tBu_3[f]	99	18.6	68.4	21.4
17	P^tBu_3[g]	99	13.5	75.0	15.3
18	P^tBu_3[h]	99	9.5	81.8	10.4
19	PEt_3	78	31.4	22.8	57.9
20	PEt_3[f]	73	24.1	40.2	37.5
21	PEt_3[g]	70	17.4	32.4	34.9

[a] Reactions were performed using **1** (1.33 mmol), phenylacetylene (1.39 mmol), $Pd(OAc)_2$ (5 mol%) and a phosphine ligand (P : Pd = 3 : 1) in 5 mL toluene at 100 °C for 3 h. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture in toluene-d_8 using *p*-dimethoxybenzene as internal standard. [c] Conversion of **1**. [d] Regioselectivity = 100 × **2a**/(**2a** + **2b**). [e] P/Pd = 1.5. [f] P/Pd = 5. [g] P/Pd = 9. [h] P/Pd = 20.

appear superior as far as the regioselectivity is concerned as the results obtained with 1,2-bis(diphenylphosphino)ethane (dppe), 1,2-bis(dicyclohexylphosphino)ethane (dcpe) suggest, while less strongly chelating ones with larger bite angles or less sterically demanding ones were inferior, which was seen with 1,2-bis-(dimethylphosphino)ethane (dmpe), 1,4-bis(diphenylphosphino)-butane (dppb), 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos). In view of the reaction with dcpe being very slow, we conclude that dppe is the ligand of choice, with which adduct **2a** can be obtained in a high yield regioselectively without the aid of additives such as diphenylphosphinic acid.§ The origin of the selective formation of **2a** is ambiguous at this moment. However, we speculate that the regioselectivity is associated with the structure of the intermediate. In palladium-catalysed addition of diphenylphosphine oxide using monodentate phosphine ligands, the involvement of species **3** was established.[5b] It is reasonable to presume that a similar species **4** is involved in the addition reaction of ethyl phenylphosphinate catalysed by monodentate phosphine palladium complexes. Since species **4** is ligated by only one phosphine ligand, the use of strongly chelating phosphines such as dppe may not allow generation of such species.



3: $R^1 = R^2 = Ph$
4: $R^1 = Ph$, $R^2 = OEt$
(L = phosphine ligand)

Use of sterically bulky and electron rich *t*-Bu_3P has been known to enable otherwise sluggish reactions to proceed efficiently in a diverse range of palladium complex-catalysed reactions.[7] With this in mind, it is interesting to note that if the desired isomer is the linear one **2b**, *t*-Bu_3P is the ligand of choice, in particular when a large phosphine : palladium ratio is employed. The reaction under the standard conditions (P : Pd = 3 : 1) was not selective (entry 14). When the ratio was decreased to 1.5, the selectivity for **2a** increased (entry 15). On the contrary, when the ratio was increased up to 20, the regioselectivity for **2a** gradually decreased, eventually furnishing an 89.6% regioselectivity for **2b** at a ratio of 20 without significant loss of the catalytic activity (entries 14–18). PEt_3, less sterically demanding and less basic than *t*-Bu_3P, also displayed the same trends upon variation of the ratio (entries 19–21), but the dependence was not so significant as compared with *t*-Bu_3P.

The intramolecular hydrogen bonding in species **4** is anticipated to be influenced by protic solvents, which hopefully affects the regioselectivity. Indeed, the use of ethanol has proved to be another tool to enhance the selectivity for the linear isomer **2b** although the reaction was somewhat slow as seen in Table 2. The experiments were run by using $Pd(OAc)_2$ and PPh_3. As already mentioned, the reaction in toluene was not regioselective. Other solvents such as THF, *n*-octane, chlorobenzene, propionitrile, showed similar regioselectivities although marginal variation was observed. However, ethanol, the only protic solvent examined, behaved differently from the other solvents, leading to the formation of the linear product **2b** with a regioselectivity in excess of 80%.

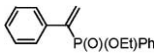
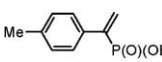
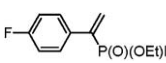
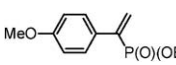
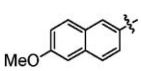
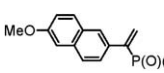
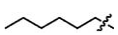
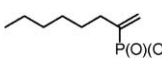
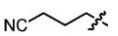
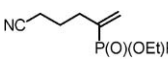
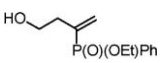
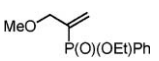
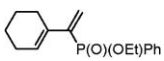
As demonstrated in Table 3, the palladium–dppe catalyst system proficiently hydrophosphinylates a wide range of structurally diverse terminal acetylenes with **1**, affording high yields of the branched adducts by regioselective attack of the phosphorus at the internal carbon of the triple bond. All aromatic acetylenes displayed excellent regioselectivities. Note that the products are straightforward precursors for phosphorus analogues of arylpropionic acids, which attract strong interest due to their biological activity.[8] Reactivity and regioselectivity for aliphatic acetylene were somewhat low. Functionalities such as cyano and hydroxy groups were tolerant toward the reaction, and satisfactory results were obtained as well. The reaction of propargyl methyl ether was not

Table 2 Solvent effect in the reaction of phenylacetylene with ethyl phenylphosphinate[a]

Entry	Solvent	Conversion of **1**[b,c] (%)	Yield[b] (%)		Selectivity of **2a**[c] (%)
			2a	**2b**	
1	Toluene	>99	51.9	28.2	64.8
2	Octane	99	55.8	27.5	67.0
3	Chlorobenzene	99	39.0	17.6	68.9
4	THF	99	49.0	28.9	62.9
5	Propionitrile	99	38.2	33.6	53.2
6	2-Butanone	99	50.9	33.8	60.0
7	Ethanol	79	12.8	56.6	18.5

[a] Reactions were performed using **1** (1.33 mmol), phenylacetylene (1.39 mmol), $Pd(OAc)_2$ (5 mol%) and PPh_3 (P : Pd = 3 : 1) in 5 mL toluene at 100 °C for 3 h. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture in toluene-d_8 using *p*-dimethoxybenzene as internal standard. [c] Regioselectivity = 100 × **2a**/(**2a** + **2b**).

Table 3 Hydrophosphinylation of alkynes with ethyl phenylphosphinate[a]

Alkyne R =	Time[b]/h	Product	Yield (%)[c,d]	Selectivity[c,e] (%)
	3		89.0 (78.5)	99.0
	3		87.2 (76.1)	99.1
	3		91.3 (72.4)	>99
	3		74.9 (67.6)	>99
	5		87.6 (75.5)	>99
	5.5		79.0	93.7
	3		88.3 (68.8)	>99
	8.5[f]		71.8	96.5
	8.5		51.3	83.3
	3		84.5	>99

[a] *Procedure and conditions*: **1** (1.33 mmol), alkyne (1.39 mmol), $Pd(OAc)_2$ (5 mol%) and dppe (7.5 mol%) (P : Pd = 3 : 1) in 3 mL toluene at 100 °C. [b] Reaction time. Unless otherwise noted, the conversion of alkynes was near complete. [c] Yield of the branched product. [d] Determined by ^1H NMR spectroscopy. The figures in parentheses are isolated yields. [e] Selectivity = 100 × branched/(branched + linear). [f] Conversion of the alkyne was 89.4%.

clean. Analysis by ^{31}P NMR spectroscopy displayed many unidentified signals, some of which may have come from the cleavage of the propargyl–O bond.[9] Cyclohexenylacetylene, a conjugated enyne, reacted exclusively at the triple bond with an excellent regioselectivity. However, sterically bulky and internal acetylenes such as trimethylsilylacetylene and diphenylacetylene were inert under the present conditions.

In summary, the regioselectivity of hydrophosphinylation of terminal acetylenes is highly dependent on the structure of the phosphine ligand. The use of dppe furnishes branched products highly regioselectively while the use of t-Bu_3P affords linear products preferentially. The reaction with PPh_3 ligand is also linear selective when run in ethanol. Mechanistic aspects, in particular the structures of intermediates will be reported shortly.

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Notes and references

§ *Representative procedure*: To a mixture of $Pd(OAc)_2$ (0.0148 g, 0.066 mmol) and dppe (1.5 equivalents relative to palladium) in dry toluene (3 mL) under nitrogen were added ethyl phenylphosphinate (0.226 g, 1.33 mmol) and phenylacetylene (0.142 g, 1.39 mmol). The solution was heated at 100 °C for 3 h to produce a transparent yellow solution, which was evaporated. The residue was purified using column chromatography on silica gel (*i*-PrOH : hexane = 1 : 9) to afford a colourless oil. The major regioisomer **2a** could be separated by Kugelrohr distillation (145 °C/0.226 mm Hg, 325 mg).

1 For a review, see: (*a*) T. Minami and J. Motoyoshiya, *Synthesis*, 1992, 333; (*b*) for recent examples, see: A. A. Thomas and K. B. Sharpless, *J. Org. Chem.*, 1999, **64**, 8379; (*c*) S. M. Ruder and M. Ding, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1771; (*d*) E. Mizushima, L.-B. Han, T. Hayashi and M. Tanaka, *Jpn. Pat.*, 3610371, 2004; (*e*) O. M. Demchuk, K. M. Pietrusiewicz, A. Michrowska and K. Grela, *Org. Lett.*, 2003, **5**, 3217; (*f*) Y. Kobayashi and A. D. William, *Adv. Synth. Catal.*, 2004, **346**, 1749; (*g*) D. Leca, K. Song, M. Albert, M. G. Gonçalves, L. Fensterbank, E. Lacôte and M. Malacria, *Synthesis*, 2005, 1405; (*h*) A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos and K. Grela, *J. Am. Chem. Soc.*, 2004, **126**, 9318; (*i*) M. S. Rahman, M. Oliana and K. K. Hii, *Tetrahedron: Asymmetry*, 2004, **15**, 1835; (*j*) M. Alajarin, C. Lopez-Leonardo and P. Llamas-Lorente, *Lett. Org. Chem.*, 2004, **1**, 145; (*k*) I. V. Saratovskikh and V. V. Ragulin, *Russ. J. Gen. Chem.*, 2005, **75**, 1077; (*l*) Y. Ono and L.-B. Han, *Tetrahedron Lett.*, 2006, **47**, 421.

2 (*a*) F. J. Welch and H. J. Paxton, *J. Polym. Sci., Part A: Gen. Pap.*, 1965, **3**, 3427; (*b*) F. J. Welch and H. J. Paxton, *J. Polym. Sci., Part A: Gen. Pap.*, 1965, **3**, 3439; (*c*) J. R. Shukla, *US Pat.*, 4241145, 1980; (*d*) S. V. Levchik and E. D. Weil, *Polym. Int.*, 2005, **54**, 11.

3 (*a*) A. A.-Z. Al-Quntar, O. Baum, R. Reich and M. Srebnik, *Arch. Pharm. Pharm. Med. Chem.*, 2004, **337**, 76; (*b*) M. R. Harnden, A. Parkin, M. J. Parratt and R. M. Perkins, *J. Med. Chem.*, 1993, **36**, 1343.

4 For recent reviews, see: (*a*) V. M. Dembitsky, A. A. A. A. Quntar, A. Haj-Yehia and M. Srebnik, *Mini-Rev. Org. Chem.*, 2005, **2**, 91; (*b*) M. Tanaka, *Top. Curr. Chem.*, 2004, **232**, 25. For recent examples, see: (*c*) M. Niu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2007, 272; (*d*) S. Thielges, P. Bisseret and J. Eustache, *Org. Lett.*, 2005, **7**, 681; (*e*) L.-B. Han and C.-Q. Zhao, *J. Org. Chem.*, 2005, **70**, 10121; (*f*) P. Ribiere, K. Bravo-Altamirano, M. I. Antczak, J. D. Hawkins and J.-L. Montchamp, *J. Org. Chem.*, 2005, **70**, 4064; (*g*) J. J. Stone, R. A. Stockland, Jr., J. M. Reyes, Jr., J. Kovach, C. C. Goodman and E. S. Tillman, *J. Mol. Catal. A: Chem.*, 2005, **226**, 11; (*h*) M. Maffei, *Curr. Org. Synth.*, 2004, **1**, 355; (*i*) O. Tayama, A. Nakano, T. Iwahama, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2004, **69**, 5494; (*j*) S. Deprèle and J.-L. Montchamp, *Org. Lett.*, 2004, **6**, 3805; (*k*) G. W. Kabalka and S. K. Guchhait, *Org. Lett.*, 2003, **5**, 729; (*l*) D. Gelman, L. Jiang and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 2315; (*m*) N. S. Gulykina, T. M. Dolgina, G. N. Bondarenko and I. P. Beletskaya, *Russ. J. Org. Chem.*, 2003, **39**, 797; (*n*) K. Takaki, G. Koshoji, K. Komeyama, M. Takeda, T. Shishido, A. Kitani and K. Takehira, *J. Org. Chem.*, 2003, **68**, 6554; (*o*) A. A. Quntar, V. M. Dembitsky and M. Srebnik, *Org. Lett.*, 2003, **5**, 357; (*p*) A. Peng and Y. Ding, *Synthesis*, 2003, 205; (*q*) K. Takaki, K. Komeyama and K. Takehira, *Tetrahedron*, 2003, **59**, 10381; (*r*) M. Lera and C. J. Hayes, *Org. Lett.*, 2001, **3**, 2765.

5 (*a*) L.-B. Han and M. Tanaka, *J. Am. Chem. Soc.*, 1996, **118**, 1571; (*b*) L.-B. Han, N. Choi and M. Tanaka, *Organometallics*, 1996, **15**, 3259; (*c*) L.-B. Han, N. Choi and M. Tanaka, *J. Am. Chem. Soc.*, 1996, **118**, 7000; (*d*) L.-B. Han, R. Hua and M. Tanaka, *Angew. Chem., Int. Ed.*, 1998, **37**, 94; (*e*) R. Hua and M. Tanaka, *Chem. Lett.*, 1998, 431; (*f*) L.-B. Han and M. Tanaka, *Chem. Lett.*, 1999, 863; (*g*) L.-B. Han, F. Mirzaei, C.-Q. Zhao and M. Tanaka, *J. Am. Chem. Soc.*, 2000, **122**, 5407; (*h*) C. Q. Zhao, L.-B. Han and M. Tanaka, *Organometallics*, 2000, **19**, 4196; (*i*) L. B. Han, C.-Q. Zhao and M. Tanaka, *J. Org. Chem.*, 2001, **66**, 5929; (*j*) C.-Q. Zhao, L.-B. Han, M. Goto and M. Tanaka, *Angew. Chem., Int. Ed.*, 2001, **40**, 1929; (*k*) F. Mirzaei, L.-B. Han and M. Tanaka, *Tetrahedron Lett.*, 2001, **42**, 297; (*l*) L.-B. Han, C.-Q. Zhao and M. Tanaka, *Int. Pat.*, WO2002/064604, 2002; (*m*) L.-B. Han, C.-Q. Zhao, S.-y. Onozawa, M. Goto and M. Tanaka, *J. Am. Chem. Soc.*, 2002, **124**, 3842; (*n*) L.-B. Han, C. Zhang and M. Tanaka, *Int. Pat.*, WO2003/097654, 2003.

6 It has been known that palladium acetate is reduced to generate Pd(0) species when treated with a phosphine, see: (*a*) C. Amatore, A. Jutand and M. A. M'Barki, *Organometallics*, 1992, **11**, 3009; (*b*) C. Amatore, E. Carré, A. Jutand and M. A. M'Barki, *Organometallics*, 1995, **14**, 1818.

7 (*a*) T. Yamamoto, M. Nishiyama and Y. Koie, *Tetrahedron Lett.*, 1998, **39**, 2367; (*b*) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020; (*c*) T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729; (*d*) V. P. W. Böhm and W. A. Herrmann, *Eur. J. Org. Chem.*, 2000, 3679; (*e*) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020; (*f*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (*g*) J. P. Stambuli, R. Kuwano and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2002, **41**, 4746; (*h*) A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer and D. L. Hughes, *Org. Lett.*, 2003, **5**, 4191; (*i*) A. Köllhofer, T. Pullmann and H. Plenio, *Angew. Chem., Int. Ed.*, 2003, **42**, 1056; (*j*) I. D. Hills and G. C. Fu, *J. Am. Chem. Soc.*, 2004, **126**, 13178; (*k*) J. F. Hartwig, *Synlett*, 2006, 1283; (*l*) S. Shekhar and J. F. Hartwig, *Organometallics*, 2007, **26**, 340.

8 (*a*) K. W. Jung and K. D. Janda, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2281; (*b*) N. S. Gulyukina, T. M. Dolgina, G. N. Bondarenko, I. P. Beletskaya, N. A. Bondarenko, J.-C. Henry, D. Lavergne, V. Ratovelomanana-Vidal and J.-P. Genet, *Russ. J. Org. Chem.*, 2002, **38**, 573; (*c*) N. S. Goulioukina, T. M. Dolgina, I. P. Beletskaya, J.-C. Henry, D. Lavergne, V. Ratovelomanana-Vidal and J.-P. Genet, *Tetrahedron: Asymmetry*, 2001, **12**, 319; (*d*) J.-C. Henry, D. Lavergne, V. Ratovelomanana-Vidal and J.-P. Genet, *Tetrahedron Lett.*, 1998, **39**, 3473; (*e*) N. A. Bondarenko, I. N. Lermontova, G. N. Bondarenko, N. S. Gulyukina, T. M. Dolgina, S. O. Bachurin and I. P. Beletskaya, *Pharm. Chem. J.*, 2003, **37**, 226.

9 (*a*) C. Chowdhury, B. M. Sukhendu and A. Basudeb, *Tetrahedron Lett.*, 2005, **46**, 8531; (*b*) H. Miyabe, Y. Yamaoka, T. Naito and Y. Takemoto, *J. Org. Chem.*, 2004, **69**, 1415; (*c*) M. Pal, K. Parasuraman and K. R. Yaleswarapu, *Org. Lett.*, 2003, **5**, 349; (*d*) J.-R. Labrosse, P. Lhoste and D. Sinou, *Tetrahedron Lett.*, 1999, **40**, 9025; (*e*) S. Cacchi, G. Fabrizi and L. Moro, *Tetrahedron Lett.*, 1998, **39**, 5101; (*f*) N. Monteiro, A. Arnold and G. Blame, *Synlett*, 1998, 1111.

