

# Celebrating 20 Years of *SYNLETT* – Special Essay: General Procedure for the Palladium-Catalyzed Selective Hydrophosphorylation of Alkynes

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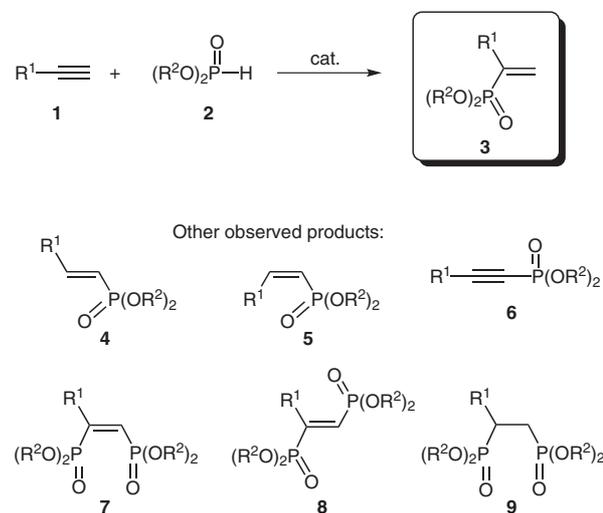
**Abstract:** A novel catalytic system has been developed to accomplish the hydrophosphorylation of terminal and internal alkynes with high isolated yields (up to 96%) and excellent regio- and stereo-selectivity (>99:1). The key factor was to apply a low-ligated palladium/triphenylphosphane (1:2) catalytic system in the presence of a catalytic amount of trifluoroacetic acid. The catalytic system so developed has been applied successfully to permit the formation of diverse alkenylphosphonates utilizing a variety of available H-phosphonates and alkynes.

**Key words:** addition reactions, alkynes, palladium, homogenous catalysis, phosphorylations

Transition-metal-catalyzed element–hydrogen (E–H) addition to unsaturated compounds is a rapidly developing area of synthetic chemistry for constructing carbon–element bonds in an atom-economic manner.<sup>1,2</sup> Recent studies have highlighted catalytic E–H addition to triple bonds of alkynes as an area of special interest, providing several opportunities for easy access to heterofunctionalized vinylic derivatives. Carbon–phosphorus bond formation via phosphorus–hydrogen addition to alkynes has been successfully implemented as a route to alkenylphosphonates,<sup>3</sup> some of which are biologically active,<sup>4,5</sup> while others act as versatile reagents in synthesis<sup>6</sup> or are established building blocks in polymer sciences.<sup>7</sup>

The transition-metal-catalyzed hydrophosphorylation of alkynes was discovered by Han and Tanaka in 1996.<sup>8</sup> Phosphane complexes of palladium were found to catalyze the addition of H-phosphonates **2** to alkynes **1** leading to the formation of Markovnikov products **3** (Scheme 1). After Han and Tanaka's discovery, several studies appeared<sup>3,9,10</sup> giving the impression that a solution to the problem of the selective hydrophosphorylation of alkynes had been found. However, a deeper look at the published material revealed a rather complicated picture. While the addition of the simplest H-phosphonate, dimethyl phosphonate [(MeO)<sub>2</sub>P(O)H], to oct-1-yne was possible with a special *cis*-[Me<sub>2</sub>Pd(PPh<sub>2</sub>Me)<sub>2</sub>] catalyst leading to Markovnikov/anti-Markovnikov ( $\alpha/\beta$ ) selectivity of 95:5,<sup>8</sup> the involvement of the more sterically hindered diethyl phosphonate reagent in the addition reaction

decreased the selectivity to 90:10. Furthermore, use of the traditional catalyst [Pd(PPh<sub>3</sub>)<sub>4</sub>] gave poor selectivity of 86:14 (67 °C, THF, 18 h).<sup>8</sup> Changing from linear to cyclic H-phosphonates resulted in the formation of completely different species, and compound **3** was observed only as a minor product.<sup>11</sup> It has also been reported that a diphenylphosphinic acid additive may influence the regioselectivity of the reaction, but the proposed mechanism is rather questionable.<sup>12</sup>



**Scheme 1** Alkyne hydrophosphorylation reaction leading to Markovnikov product **3** and possible byproducts

In addition to desired compounds **3**, a broad range of species **4–9** have been observed in the reaction as byproducts and sometimes as major products (Scheme 1). For example, species **4** and **5** were formed as byproducts in palladium-catalyzed reactions or as major products in rhodium- or nickel-catalyzed reactions.<sup>8–16</sup> In addition to the catalytic pathway, some contribution to the formation of **4** and **5** originates from nucleophilic or free-radical addition without the involvement of a transition-metal catalyst.<sup>13,14</sup> The formation of alkynylphosphonates **6** as byproducts was observed under [Pd(PPh<sub>3</sub>)<sub>4</sub>]-catalyzed conditions.<sup>15</sup> Dehydrogenative addition of two molecules of an H-phosphonate leading to products **7** and **8** (sometimes with high yields) was observed with various palladium catalysts {e.g., PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, and [Pd(PPh<sub>3</sub>)<sub>4</sub>]}.<sup>11,16</sup> The formation of compounds **9** was suggested to proceed via the pal-

ladium-catalyzed addition of H-phosphonates **2** to vinylic products **3** (in moderate to high yields),<sup>15</sup> thus decreasing the yield of vinylphosphonates **3**. The reaction leading to byproducts **9** was also observed under metal-free conditions.<sup>11,14,15</sup>

Thus, a number of side reactions, either involving a metal complex or proceeding in a concurrent noncatalytic fashion, introduce significant difficulties in achieving high selectivity towards the formation of products **3**. It appears that the catalytic systems described so far have succeeded in selective transformation only for a specific combination of starting reagents, while attempts to create a general synthetic procedure have suffered from the high sensitiv-

ity of the reaction yield and selectivity to the nature of the metal, ligand, H-phosphonate, and alkyne.<sup>3,8-11</sup> The system has to be optimized each time the structure of the H-phosphonate or alkyne is changed.

For practical reasons, substituents with pronounced structural variation are required. For instance, the alkyl group of the H-phosphonate would be phenyl and benzyl for biological activity enhancement, C<sub>n</sub>H<sub>2n+1</sub> with n > 6 for micelle precursors and incorporation into a hydrophobic environment, and branched and cyclic alkyl residuals for material science applications. Obviously, designing a catalytic system for each particular case would be time-consuming and inefficient.

## Biographical Sketches



**Valentine Ananikov** received his diploma in 1996 from Donetsk State University (Donetsk, Ukraine), his Ph.D. degree in 1999, and his Doctor of Chemistry degree in 2003 from the ND Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (Moscow, Russian Federation). In 2004, he became Professor of the High Chemistry College of the Russian

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has been supported by grants from the President of Russia (2004, 2007). In 2008, he was elected as a corresponding member of the Russian Academy of Sciences. His scientific interests are focused on transition-metal-catalyzed addition reactions to unsaturated molecules, the development of new NMR spectroscopic methods, and theoretical studies of catalytic reactions.



**Levon Khemchyan** became a Ph.D. student at the ND Zelinsky Institute of Organic Chemistry of the

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on transition-metal-catalyzed carbon–phosphorus bond formation.

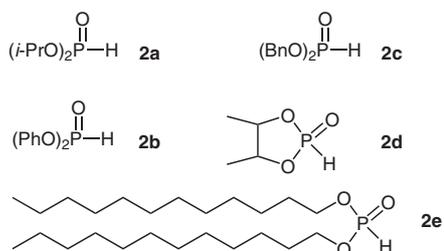
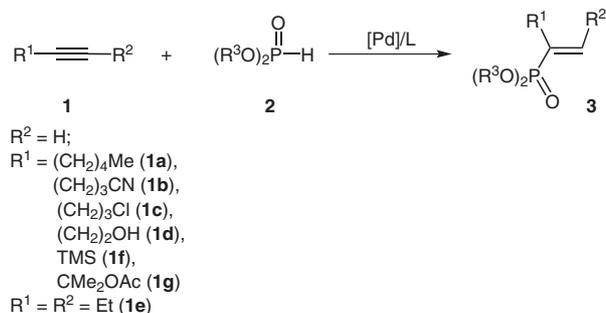


**Irina Beletskaya** received her diploma degree in 1955, her Ph.D. degree in 1958, and her Doctor of Chemistry degree in 1963 from Moscow State University (Moscow, Russian Federation). The subject for the latter was electrophilic substitution at saturated carbon. She became Full Professor at Moscow State University in 1970, and in 1974 she became a corresponding member of the Academy of Sciences (USSR), of which

she became a full member (Academician) in 1992. She is currently Head of the Laboratory of Organoelement Compounds in the Department of Chemistry at Moscow State University. Irina Beletskaya is Chief Editor of the Russian Journal of Organic Chemistry. She was President of the Organic Chemistry Division of IUPAC from 1989 to 1991. She has been a recipient of the Lomonosov Prize (1979), the Mendeleev Prize

(1982), the Nesmeyanov Prize, (1991), the Demidov Prize (2003), the State Prize (2004), and the International Arbusov Prize (2007). She is the author of more than 600 articles and 4 monographs. Her current scientific interests are focused on transition-metal catalysis in organic synthesis, organic derivatives of lanthanides, and carbanions and nucleophilic aromatic substitution.

To overcome these limitations, we have carried out a series of mechanistic studies and have found a general catalytic system for the highly selective formation of Markovnikov products **3** independent of the nature of H-phosphonates **2** and alkynes **1a–e** containing typical organic functional groups (Scheme 2). The limits of the performance of our developed catalytic system were tested with sterically hindered reagents **2a** and **2e**, by varying the electronic properties of the substituents, e.g. use of phosphonates **2b** and **2c**, and through the use of activated<sup>17</sup> five-membered cyclic H-phosphonate **2d**.



**Scheme 2** Palladium-catalyzed, regioselective alkyne hydrophosphorylation investigated in our studies

In the case of the hydrophosphorylation of hept-1-yne (**1a**) using isopropyl derivative **2a** under typical palladium-catalyzed conditions, the reaction resulted in low product yield (63%) and very poor selectivity (~3:1) (Table 1, entry 1). The <sup>31</sup>P{<sup>1</sup>H} NMR spectrum of the crude mixture of the reaction contained a number of signals and indicated the formation of several byproducts.<sup>18</sup> With insight from the mechanistic study, we evaluated the effects of a base, water, radical scavengers, and acids. The addition of a base deteriorated the catalytic reaction, with the yield dropping from 63 to 25% (entries 1 and 2, respectively). Approximately half of reagent **2a** remained unreacted, with a noticeable increase in the byproduct formation from 19 to 28%. A quantity of water as small as 50  $\mu$ L added to the reaction mixture caused the yield to drop to 26% (entry 3). Moreover, in this case, the remaining amount of reagent **2a** was completely converted into byproducts without the possibility for recycling. To avoid the possible influence of water, we utilized dried THF throughout subsequent studies.

We estimated the contribution of the free-radical pathway by addition of  $\gamma$ -terpinene, which is known to behave as a radical trap in transition-metal-catalyzed reactions.<sup>19</sup> A

**Table 1** The Influence of Various Additives on the Yield and Selectivity of Diisopropyl Phosphonate (**2a**) Addition to Hept-1-yne (**1a**)<sup>a</sup>

Entry	Additive	Yield <sup>c</sup> (%)		
		Product <b>3a</b>	Unreacted <b>2a</b>	Other products <sup>f</sup>
1	None	63	18	19
2	Et <sub>3</sub> N <sup>b</sup>	25	47	28
3	H <sub>2</sub> O <sup>c</sup>	26	0	74
4	$\gamma$ -terpinene <sup>d</sup>	67	10	23
5	H <sub>2</sub> SO <sub>4</sub> <sup>b</sup>	56	32	12
6	AcOH <sup>b</sup>	59	22	19
7	HO <sub>2</sub> C–CO <sub>2</sub> H <sup>b</sup>	60	8	32
8	BzOH <sup>b</sup>	71	13	16
9	TFA <sup>b</sup>	85	7	8

<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), Ph<sub>3</sub>P (12 mol%), THF (0.5 mL), 100 °C, 3 h.

<sup>b</sup> Using 10 mol% of the additive.

<sup>c</sup> Using 50  $\mu$ L of the additive.

<sup>d</sup> Using 20 mol% of the additive.

<sup>e</sup> Determined by <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy.

<sup>f</sup> Overall amount of phosphorus-containing byproducts.

rather small change in the product yield indicated a very minor contribution of side reactions involving free-radical species (Table 1, entry 4).

Sulfuric acid and acetic acid decreased the yield of product **3a** (Table 1, entries 5 and 6, respectively). Oxalic acid also decreased the product yield and increased the amount of byproducts (entry 7). Benzoic acid was found to improve the addition reaction in terms of better product yield (71%) and smaller amounts of impurities (entry 8). Remarkably, excellent performance of the catalytic system was observed in the presence of trifluoroacetic acid (TFA), resulting in 85% product yield and only 8% of byproducts (entry 9).

Thus, this investigation highlights the rather complicated nature of the acid effect in which both the influence on the yield of the catalytic reaction and on the amount of impurities formed have to be taken into account.

The performance of the catalytic hydrophosphorylation reaction was studied in various solvents (THF, benzene, CH<sub>2</sub>Cl<sub>2</sub>, MeCN, and DMSO).<sup>18</sup> In all cases, the addition of TFA increased the product yield, while triethylamine suppressed product formation. Benzene and THF were found to be the best solvents in which to carry out the hydrophosphorylation reaction.

To verify the possible influence of the acid on the final product yield, we next investigated the catalytic reactions with different amounts of TFA. Thus, 85% yield of product **3a** and 11% yield of overall impurities were observed with 5 mol% of TFA (Table 2, entry 1). Increasing the amount of TFA to 10 mol% slightly decreased the amount of impurities (entry 2). The maximum product yield of

**Table 2** The Influence of the Amount of Acid on the Yield and Selectivity of Diisopropyl Phosphonate (**2a**) Addition to Hept-1-yne (**1a**)<sup>a</sup>

Entry	Amount of TFA (mol%)	Yield <sup>b</sup> (%)		
		Product <b>3a</b>	Unreacted <b>2a</b>	Other products <sup>c</sup>
1	5	85	4	11
2	10	85	7	8
3	20	89	5	6
4	30	84	10	6
5	50	75	19	6

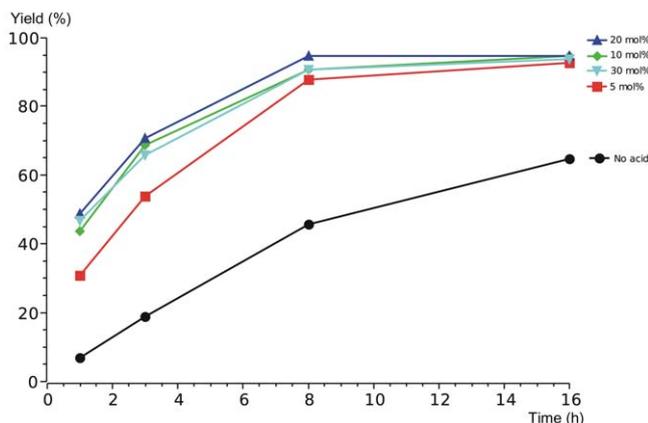
<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), Ph<sub>3</sub>P (12 mol%), THF (0.5 mL), 100 °C, 3 h.

<sup>b</sup> Determined by <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy.

<sup>c</sup> Overall amount of phosphorus-containing byproducts.

89% was observed with 20 mol% of TFA (entry 3). Further increase in the amount of acid led to a decrease in the product yield, but retained the trace level of impurities (entries 4 and 5).

The NMR spectroscopic monitoring of the catalytic reaction performed at a lower temperature (50 °C) showed that TFA not only enhanced the yield of the product, but also increased the rate of the reaction. A graphical representation of observed acid affect is shown in Figure 1. For practical reasons, we have chosen a compromise value of 10 mol% of TFA to be used in the catalytic system.

**Figure 1** The yield of palladium-catalyzed diisopropyl phosphonate (**2a**) addition to hept-1-yne (**1a**) using various amounts of TFA (30, 20, 10, and 5 mol% and no acid) at 50 °C

The choice of ligand was crucial to achieving high selectivity in the studied reaction. The following ligands were evaluated in the catalytic reaction: triphenyl-, tris(4-methoxyphenyl)-, tris(2-methoxyphenyl)-, tris(2,6-dimethoxyphenyl)-, tri-2-tolyl-, benzyl(diphenyl)-, methyl(diphenyl)-, ethyl(diphenyl)-, cyclohexyl(diphenyl)-, dimethyl(phenyl)-, tributyl-, dicyclohexyl(phenyl)-, and tricyclohexylphosphane, bis-phosphino ligands (dppe, dppb, dppm), and triphenyl and tributyl phosphite.<sup>18</sup> The

best performance was observed with triphenylphosphane which gave complete conversion of the starting materials and high selectivity of the reaction. A comparison of the results for acid-free and acid-containing catalytic systems revealed the superior performance of the latter.<sup>18</sup>

The next important characteristic of the catalytic system was the amount of ligand needed to achieve high activity. An equimolar palladium/ligand (Pd/L) ratio led to only 27% of the product after 8 hours at 50 °C (Table 3, entry 1). The best performance of the catalytic reaction, 94% product yield, was observed using a ratio (Pd/L) of 1:2 (entry 2). Changing the ratio to 1:4 and 1:8 resulted in 81 and 41% yield of the product, respectively, with some increase in the amount of impurities to 11 and 12% (entries 3 and 4, respectively). Therefore, the ratio (Pd/L) of 1:2 should be considered for the catalytic system of choice.

**Table 3** The Influence of the Palladium/Ligand Ratio on the Yield and Selectivity of Diisopropyl Phosphonate (**2a**) Addition to Hept-1-yne (**1a**) at 50 °C<sup>a</sup>

Entry	Ratio (Pd/L) <sup>b</sup>	Yield <sup>c</sup> (%)		
		Product <b>3a</b>	Unreacted <b>2a</b>	Other products <sup>d</sup>
1	1:1	27	72	1
2	1:2	94	4	2
3	1:4	81	8	11
4	1:8	41	47	12

<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), given amount of ligand (Ph<sub>3</sub>P), TFA (10 mol%), THF (0.5 mL), 50 °C, 8 h.

<sup>b</sup> The reaction did not take place in the absence of the ligand.

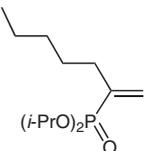
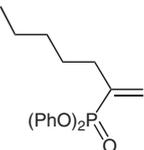
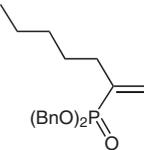
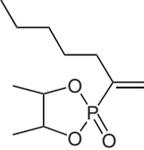
<sup>c</sup> Determined by <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy.

<sup>d</sup> Overall amount of phosphorus-containing byproducts.

With an optimized synthetic procedure in hand,<sup>20</sup> we investigated the scope of the hydrophosphorylation reaction using various alkynes. For product separation, a simple purification procedure based on flash chromatography was utilized.<sup>21–23</sup> In the cases of alkynes **1a–c**, the catalytic reaction was carried out at 50 °C and resulted in excellent product yields of 91–94% and 85–91% isolated yields (Table 4, entries 1–3). Monosubstituted alkyne **1d** bearing a terminal hydroxy group on the alkyl substituent was less reactive and required a higher temperature of 70 °C (entry 4). The reaction with internal alkyne **1e** was the slowest and required an even higher temperature of 120 °C (entry 5). A remarkable feature of the developed catalytic system is the excellent regio- and stereoselectivity possible within the large temperature range of 50–120 °C. A (3/4) regioselectivity of >99:1 was observed for the reactions of alkynes **1a–d** (entries 1–4, respectively), and *syn*-addition stereoselectivity of >99:1 was found for the reaction of substrate **1e** (entry 5). Carrying out the reaction at somewhat higher temperatures and for a longer time made it possible to decrease catalyst loading. For the synthesis of product **3a**, the reaction with 1.5 mol% of the catalyst was carried out at 70 °C for 24 hours and resulted in 92% yield



**Table 5** Palladium-Catalyzed Addition of H-Phosphonates **2a–e** to Hept-1-yne (**1a**)<sup>a</sup>

Entry	H-Phosphonate <b>2</b>	Product <b>3</b>	Yield <sup>b</sup> (%)
1	<b>2a</b>		94 (91)
2	<b>2b</b>	<b>3a</b> 	99 (92) <sup>c</sup>
3	<b>2c</b>	<b>3f</b> 	94 (85) <sup>d</sup>
4	<b>2d</b>	<b>3g</b> 	99 (96) <sup>e</sup>
5	<b>2e</b>	<b>3h</b> 	99 (87)
		<b>3i</b> 	

<sup>a</sup> Reaction conditions: **1a** (1 mmol), H-phosphonate (1 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3 mol%), Ph<sub>3</sub>P (12 mol%), TFA (10 mol%), THF (0.5 mL), 50 °C, 8 h.

<sup>b</sup> Determined by <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy; isolated yields are in parentheses and the overall amount of impurities in all cases was <10%.

<sup>c</sup> From the reaction at 70 °C.

<sup>d</sup> After a reaction time of 4 h.

<sup>e</sup> After a reaction time of 2 h.

scope of the preparative synthesis of alkenylphosphonates.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (20) **Palladium-Catalyzed Hydrophosphorylation; General Procedure:** Under argon, Pd<sub>2</sub>(dba)<sub>3</sub> (31.1 mg, 3.0 × 10<sup>-5</sup> mol) and Ph<sub>3</sub>P (31.5 mg, 1.2 × 10<sup>-4</sup> mol) were placed into a septum-sealed tube equipped with a magnetic stir bar, followed by the addition of THF (0.5 mL) through the septum, and the mixture was stirred for 3 min. When the color of the solution became brown, the H-phosphonate (1.0 × 10<sup>-3</sup> mol) and alkyne (1.0 × 10<sup>-3</sup> mol) were added to the mixture through the septum. Then, TFA (11.4 mg, 1.0 × 10<sup>-4</sup> mol) was added, and the tube was capped with a PTFE-sealed screw cap. The mixture was stirred at 50 °C (see Tables 4 and 5 for additional details relating to the ratio of the reagents or conditions). After completion of the reaction, the color of the solution remained brown or changed to light brown.
- (21) **Compound Isolation and Purification:** After completion of the reaction, the products were purified by dry-column flash chromatography on silica gel, see ref. 23. Hexane–EtOAc (for **3a-c**, **3e-i**, **4a**, and **10**) and hexane–EtOAc–EtOH (for **3d**) gradient elution was applied. After drying in a vacuum, the pure products were obtained. The products were isolated as colorless or light-yellow oils, and their isolated yields given in Tables 4 and 5 were calculated based on the initial amount of the corresponding H-phosphonate.
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