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$NiCl_2$-Catalyzed Hydrophosphinylation

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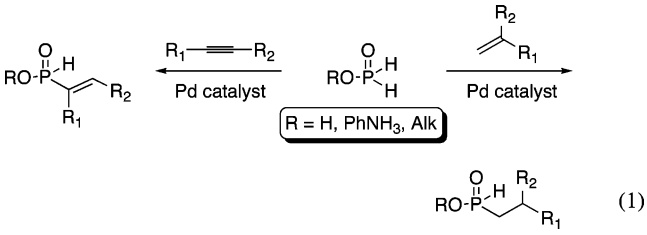
A new nickel-based catalytic system has been developed for phosphorus−carbon bond formation. The addition of alkyl phosphinates to alkynes is catalyzed by nickel chloride in the absence of added ligand. The reaction generally proceeds in high yields, even with internal alkynes, which were poor substrates in our previously reported palladium-catalyzed hydrophosphinylation of alkyl phosphinates. The method is useful for the preparation of *H*-phosphinate esters and their derivatives. The one-pot synthesis of various important organophosphorus compounds is also demonstrated. The reaction can be conducted with microwave heating.

Introduction

We reported recently a novel palladium-catalyzed phosphorus−carbon bond-forming reaction via the addition of hypophosphorous compounds to various unsaturated substrates (eq 1).[1] Catalytic P−C bond formation is



(1)

an increasingly active field, but the reactions that use hypophosphorous acid or its derivatives as starting materials have been overlooked. Undoubtedly, this is the result of the well-known transition-metals-catalyzed transfer hydrogenation[2] expected and observed with these reagents, which suggested that P−C bond formation would be difficult. However, we showed that addition does take place in very high yield, if the correct catalyst is employed.[1] More recently, we also described a reusable catalyst system, which gave good results with commercially available aqueous H_3PO_2.[3] Although our palladium-catalyzed hydrophosphinylation has a broad scope and proceeds with low catalyst loadings or can now be conducted with a reusable catalyst, we became interested in exploring still cheaper and, more importantly, possibly more reactive nickel-based catalysts. Herein, we report the development of a simple and inexpensive nickel chloride catalyzed alkyne hydrophosphinylation.[4]

With the exception of PH_3,[5] the compounds usually employed in transition-metal-catalyzed reactions do not contain more than one P−H bond,[6] and therefore the possibility for transfer hydrogenation[2] is removed or drastically decreased. Various researchers have described addition reactions involving compounds containing a single P−H bond. For example, Beletskaya has reported the addition of secondary phosphines to styrenes.[7] Marks also developed the hydrophosphination of unsaturated compounds using lanthanide catalysts.[8] Tanaka developed the catalytic addition reactions of *H*-phosphonates and secondary phosphine oxides using rhodium or palladium catalysts.[9] Maybe more relevant to the present

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(3) Deprèle, S.; Montchamp, J.-L. *Org. Lett.* **2004**, *6*, 3805.
(4) Preliminary results were presented at the 228th National Meeting of the ACS, Philadelphia, August 22−26, 2004; poster 581.
(5) Metal-catalyzed PH_3 addition and related: (a) Costa, E.; Pringle, P. G.; Smith, M. B.; Worboys, K. *J. Chem. Soc., Dalton Trans.* **1997**, 4277. (b) Costa, E.; Pringle, P. G.; Worboys, K. *Chem. Commun.* **1998**, 49. (c) Wicht, D. K.; Kourkine, I. V.; Kovacik, I.; Glueck, D. S.; Concolino, T. E.; Yap, G. P. A.; Incarvito, C. D.; Rheingold, A. L. *Organometallics* **1999**, *18*, 5381. (d) Trofimov, B. A.; Arbuzova, S. N.; Gusarova, N. K. *Russ. Chem. Rev.* **1999**, *68*, 215.

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work, Han and co-workers recently described the nickel-catalyzed addition of dimethyl phosphite, diphenyl phosphine oxide, and ethyl *H*-phenylphosphinate to alkyne.[10] However, the reaction is a Tanaka-like addition, which does not have to contend with transfer hydrogenation pathways, and only two alkynes were tested.[10] Additionally, all of these P−C bond forming reactions lead to a specific phosphorus-containing functional group, which does not have the synthetic flexibility offered by *H*-phosphinates.[11]

Results and Discussion

During the development of our palladium hydrophosphinylation, we tested various ligand and catalyst combinations.[1] Although Cl_2NiL_2/MeLi did produce some addition product in the reaction of $BuOP(O)H_2$ with 1-octene,[1] the yields were considerably lower than several of our Pd-based catalysts (Table 1, entries 1 and 2 versus entries 3 and 6). Further studies showed that the yields of alkene hydrophosphinylation could be significantly improved (Table 1, entries 7 and 8) up to 60−70%, by adjusting temperature and solvent, but these results were still not sufficiently good to compete with our palladium-catalyzed reaction.[1,3] Despite much experimentation, the yields could not be improved significantly beyond the 70% mark.

TABLE 1. Comparison of Pd versus Ni as Catalyst in Hydrophosphinylation with $ROP(O)H_2$[a]

entry	substrate	R	solvent	catalyst[d]	NMR yield, %[e]
1[b]	1-octene	Bu	CH_3CN, reflux	Pd_2dba_3/xantphos	100
2[b]	1-octene	Bu	$PhCH_3$, reflux	Cl_2Pd(dppf)	100
3	1-octene	Bu	$PhCH_3$, reflux	Cl_2Ni(dppf)/MeLi	33
4	1-octene	Bu	$PhCH_3$, reflux	Cl_2Ni(dppf)	38
5	1-octene	Bu	CH_3CN, reflux	Cl_2Ni(dppf)	14
6	1-octene	Et	$PhCH_3$, reflux	Cl_2Ni(dppp)	20
7	1-octene	Et	$PhCH_3$, rt	Cl_2Ni(dppp)	69
8	1-octene	Et	$PhCH_3$, rt	$Cl_2Ni(PPh_3)_2$	65
9[c]	1-octene	Et	$PhCH_3$, rt	$NiCl_2$	25
10[c]	4-octyne	Et	CH_3CN, reflux	Pd_2dba_3/xantphos	40
11[c]	4-octyne	Et	CH_3CN, reflux	$NiCl_2$	100

[a] Best conditions. [b] See ref 1. [c] This work. [d] Catalyst loadings vary from 1 to 4 mol %. [e] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra.

However, we discovered that the situation was very different in the case of alkynes (Table 1, entry 11 versus 5). With palladium, internal alkynes are poor substrates with alkyl phosphinates (even if H_3PO_2 and $PhNH_3{\cdot}OP(O)H_2$ do react in good yield), whereas with nickel both terminal and internal alkynes are excellent substrates. A notable feature of our reaction is the fact that inexpensive $NiCl_2$ (2−4 mol %) is an excellent catalyst. In fact, as little as 0.5 mol % $NiCl_2$ still delivered a quantitative yield of alkenyl-*H*-phosphinate in 12 h, in refluxing acetonitrile. Of course, no P−C bond formation is observed in the absence of the nickel catalyst. Other readily available nickel sources were tested, and several gave satisfactory results (Table 2). It is interesting to note that $PdCl_2$ is a very poor catalyst (entry 12), even if it is not surprising based on our previous work on the palladium-catalyzed hydrophosphinylation.[1] The fact that $Ni(cod)_2$ is not necessary is significant since this complex is highly air-sensitive and requires careful handling. With the Ni(II) catalysts, it is likely that $ROP(O)H_2$ serves as the reducing agent to form a catalytically active Ni(0) species that could be complexed by excess alkyl phosphinate present in the reaction mixture. There was no significant difference between various nickel halide precatalysts (Table 2, entries 1−6), but other nickel sources were not satisfactory (Table 2, entries 8−11). Interestingly, various usually adverse reaction conditions were well-tolerated, including moisture and even air (Table 2, entries 13−15). Nickel chloride hydrate was also tested (Table 2, entry 2) since 1 equiv of water did not interfere with the reaction, and as expected the reaction took place in excellent yield. Although anhydrous $NiCl_2$ was generally selected for our subsequent study, the hydrate gave similar results in every instance where it was tested.

A competition experiment was conducted with an equimolar amount of 1-octene and 4-octyne. The internal alkyne smoothly undergoes hydrophosphinylation reaching 88% yield, whereas P−C bond formation from the

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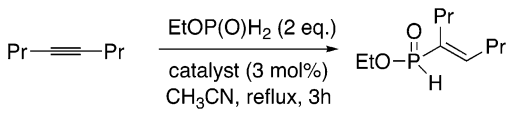
TABLE 2. Comparison of Nickel Catalyst and Influence of Additives



entry	catalyst	additive	NMR yield, %[a] (isolated yield, %)
1	$NiCl_2$	none	100 (75)
2	$NiCl_2 \cdot 6H_2O$	none	99 (84)
3	$NiBr_2$	none	97
4	NiI_2	none	99
5	$NiCl_2(PPh_3)_2$	none	100 (83)
6	$NiBr_2(PPh_3)_2$	none	100
7	$Ni(acac)_2$	none	94
8	$Ni(OAc)_2 \cdot H_2O$	none	47
9	$NiCp_2$	none	15
10	Ni powder	none	11
11	Ni on SiO_2/Al_2O_3[b]	none	8
12	$PdCl_2$	none	11
13	$NiCl_2$	H_2O (1 equiv)	100 (80)
14	$NiCl_2$	EtOH (3 equiv)	100 (81)
15	$NiCl_2$	O_2[c]	100 (86)

[a] NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra. [b] 65 wt % Ni. [c] Open to air with a drierite trap.

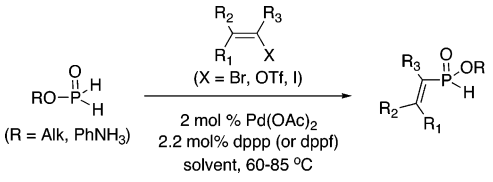
alkene never reaches more than a few percent. However, the alkene does disappear slowly presumably with formation of isomerized and reduced products. Similar results were obtained when a competition experiment was conducted with 4-octene and 4-octyne.

Various alkyl phosphinates ($ROP(O)H_2$, R = Me, Et, Bu, *i*-Pr) react in high yield (Table 3, entries 1a−1c, 2a) and the method used for their synthesis[12] does not appear to significantly affect the outcome. We have found that several variations of our silicate-based methodology for the preparation of alkyl phosphinates[12] are equally successful. In fact, stock solutions of alkyl phosphinates appear stable at room temperature and under nitrogen for at least 2 months, and these alkylphosphinate stock solutions can also be used in the present reaction. The alkyl phosphinate can also be formed in situ in a single reaction step (entry 1d), instead of preforming it prior to the hydrophosphinylation. Interestingly, even the use of the trifluoroacetate salt of an aminosilicate is also possible, the hydrophosphinylation still taking place in high yield (Table 3, entries 2b, 6b, 7b, 11, 12). As we previously showed in other reactions,[12] this method of alkyl phosphinate preparation allows removal of the silicate byproducts by extraction and therefore simplifies the workup. Here, the products can often be obtained in better than 90% purity by a simple aqueous workup. Isolated yields are sometimes improved because the crude reaction mixture is purer (Table 3, entries 2b vs 2a and 7b vs 7a).

Whereas alkyl phosphinates react very well, both H_3PO_2 and $PhNH_3OP(O)H_2$ fail to undergo the nickel-catalyzed reaction to any significant extent (less than 20% yield). Again, this contrasts with the palladium-catalyzed version of our reaction.[1,3] The solvent is also important: acetonitrile was found to be ideal, toluene was generally satisfactory, but tetrahydrofuran gave only low yields.

The scope of our nickel-catalyzed alkyne hydrophosphinylation is very broad (Table 3). Internal and terminal alkynes react in general to form the product in high yields. With unsymmetrical alkynes, the regioselectivity is often poor (ranging from 1:1 to 3:1) and the low isolated yields reflect the difficulty in separating the two regioisomers. With terminal alkynes, our previously reported palladium-catalyzed reaction is more selective for linear products with Pd_2dba_3/xantphos and highly selective for the branched isomer with $Cl_2Pd(PPh_3)_2$/MeLi (eq 1).[1,13] However, some substrates still display useful regioselectivities with the nickel catalysts when significant steric or electronic biases are present. For example, alkynes with a terminal *tert*-butyl or trimethylsilyl group react regioselectively to afford the β-substituted *H*-phosphinate (entries 5, 12, and 13). In the case of 2,4-hexadiyne, high regioselectivity is also observed (entry 8). Other alkynes substituted with a phenyl, alkene, or ethoxy group tend to give a significant amount of the "branched" product where addition takes place at the substituted carbon. Intrinsically, terminal alkynes give the linear product as the major isomer (entry 11), but inductively electron-withdrawing substituents increase the amount of the branched isomer (entries 6, 9, 10). In all the cases, excellent stereospecificity for syn addition (*E*-isomer) is observed.

Although regiocontrol is often difficult to achieve in the present reaction, we have already provided a regio- and stereospecific alternative to prepare alkenyl *H*-phosphinates using the palladium-catalyzed cross-coupling of anilinium hypophosphite[14] and alkenyl phosphinates[15] (eq 2). Nonetheless, the direct addition to an alkyne is often more convenient because the starting material is more generally available than the corresponding alkenyl halide.



(2)

Even acetylene gas bubbled through the reaction mixture at room temperature can cleanly afford the corresponding *H*-vinyl phosphinate (entry 4); however, we were not able to isolate the product in reasonable yield because of the polarity and ease of hydrolysis of vinyl-*H*-phosphinates. Further optimization of this particular reaction will be conducted because the corresponding vinyl-*H*-phosphinates are generally difficult to obtain, although it would be a useful synthon for the preparation of a variety of compounds. *O*-Ethyl vinylphosphinate has been prepared previously by Maier using a multistep sequence from $ClCH_2CH_2PCl_2$.[16]

As shown in Table 3, a variety of alkynes react in satisfactory yields. With a propargylic chloride (entry 14),

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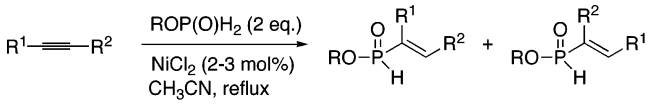
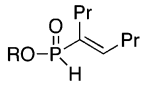
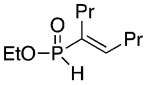
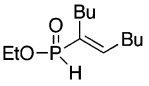
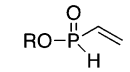
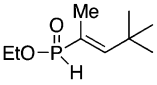
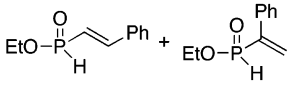
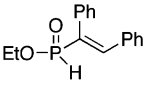
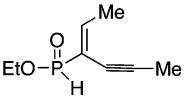
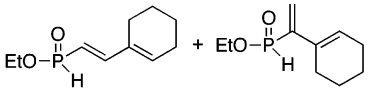
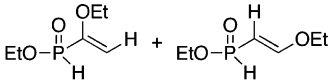
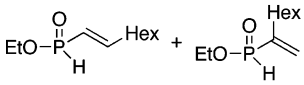
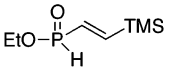
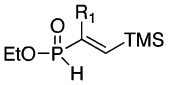
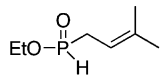
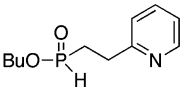
TABLE 3. $NiCl_2$-Catalyzed Hydrophosphinylation of Alkynes[a]



Entry	R^1	R^2	R	Reaction time	Reagent for $ROP(O)H_2$ formation	Product(s)	Isolated Yield %[a]
1a	Pr	Pr	Me	38	$(MeO)_4Si$		90
1b			*i*-Pr	13	$(i\text{-}PrO)_4Si$		96
1c			Bu	2.5	$(BuO)_4Si$		100
1d			Bu	16[b]	$(BuO)_4Si$[b]		90[b]
2a	Pr	Pr	Et	7	$Me_2Si(OEt)_2$		75
2b				13	$(EtO)_3Si(CH_2)_3NH_2$		100
3	Bu	Bu	Et	12	$Me_2Si(OEt)_2$		76[c]
4a	H	H	Et	1	$(EtO)_3Si(CH_2)_3NH_2$		[d]
4b			Et_2CHCH_2		$(Et_2CHCH_2O)_4Si$		[e]
5	*t*-Bu	Me	Et	12	$Me_2Si(OEt)_2$		77
6a	Ph	H	Et	6	$Me_2Si(OEt)_2$		40
6b			Et	5	$(EtO)_3Si(CH_2)_3NH_2$		100 (1:1)
7a	Ph	Ph	Et	4.5	$Me_2Si(OEt)_2$		85
7b				1.5	$(EtO)_3Si(CH_2)_3NH_2$		93
8	MeC≡C	Me	Et	3	$Me_2Si(OEt)_2$		57
9	1-cyclo hexenyl	H	Et	12	$Me_2Si(OEt)_2$		63 (1.5:1)
10	EtO	H	Et	18	$Me_2Si(OEt)_2$		42/0 (3:1)
11	Hex	H	Et	13	$(EtO)_3Si(CH_2)_3NH_2$		100 (3:1)
12	TMS	H	Et	2.5	$(EtO)_3Si(CH_2)_3NH_2$		75
13a	Bu	TMS	Et	13	$Me_2Si(OEt)_2$		64
13b	Pr			20			46
14	Me_2CCl	H	Et	3	$Me_2Si(OEt)_2$		55[f]
15	2-Pyr	H	Bu	24	$(BuO)_4Si$		32

[a] All yields are isolated. Ratios in parentheses indicate regioselection determined on the crude reaction mixture. All reactions were conducted in refluxing reagent grade CH_3CN. Details can be found in Experimental Section. [b] One-pot process where esterification and hydrophosphinylation take place simultaneously (see text). [c] Conducted on a 50 mmol scale. [d] ^{31}P NMR yield: 43%, conducted at room temperature. [e] ^{31}P NMR yield: 31%, conducted at room temperature. [f] Approximately 85% pure.

an allylic product was obtained as the major product, apparently through the allene intermediate. Interestingly, in the case of 2-ethynylpyridine, the saturated product is obtained cleanly (entry 15). At this time, the mechanistic details of this reaction remain unclear.

The reactivity of two particularly interesting substrates was tested (Scheme 1). With cyclohexylallene, the reaction proceeds normally to provide the corresponding allylic-*H*-phosphinate in 59% NMR yield, but the isolated yield was low (29%).[17] With cinnamyl chloride, cinnamyl-*H*-phosphinate is cleanly obtained in 70% yield (100%

(17) Allenes also undergo the palladium-catalyzed hydrophosphinylation: unpublished results.

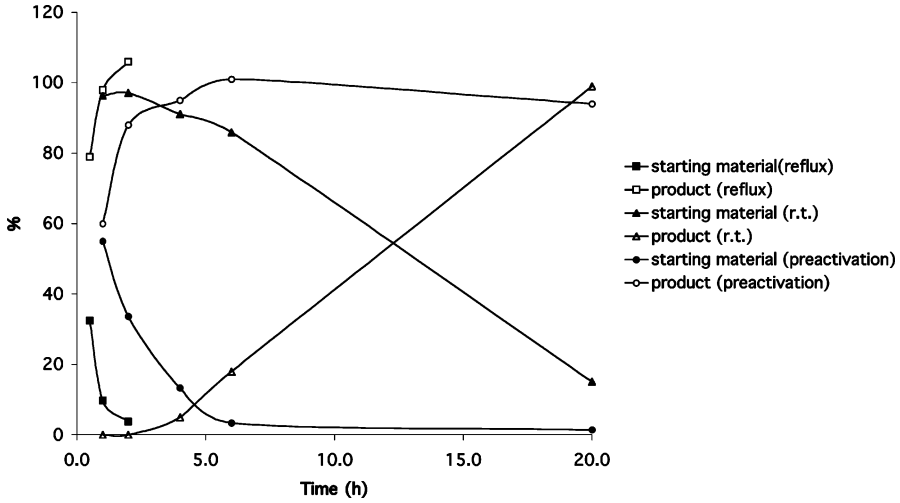
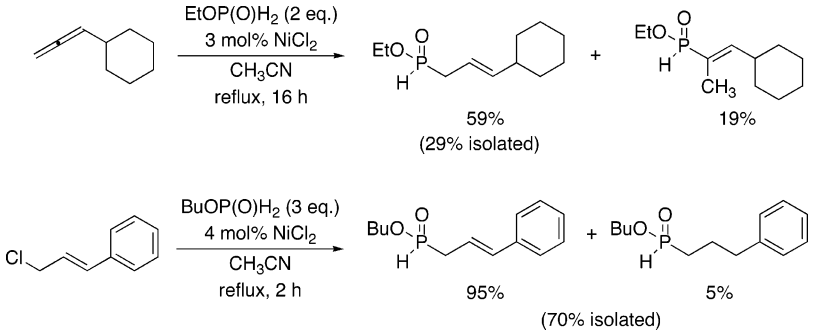


FIGURE 1. Hydrophosphinylation of 4-Octyne with $EtOP(O)H_2$

SCHEME 1. $NiCl_2$-Catalyzed Hydrophosphinylation of Cycloxexylallene and Cinnamyl Chloride



NMR yield, 95:5 allyl/reduced), which suggests a direct cross-coupling reaction. The latter reaction type was previously observed and studied in some detail in our cross-coupling work,[15] and we are currently developing a general allylic cross-coupling reaction with alkyl phosphinates.[18] Taken together, both results support an allene intermediate in the reaction of the propargyl chloride (Table 3, entry 14).

We have also studied the influence of the temperature on the rate of our hydrophosphinylation (Figure 1). The various runs were followed by both ^{31}P NMR (product formation) and GC chromatography (alkyne disappearance).[19] Remarkable agreement was observed (perfect agreement would be mirror images around the 50% mark), which also validated the ^{31}P NMR yield measurements. The validity of the NMR yields was also checked using authentic samples (see Supporting Information). Whereas the thermal reaction generally proceeds to completion within a few hours, we noted that at room temperature the reaction reached completion in about 20 h, after an induction period (Figure 1). Reasoning that it could be due to the slow formation of a catalytically active nickel(0) species (through reduction of the Ni(II) precursor), we looked for a preactivation procedure. When nickel chloride was heated for 15 min with the alkyl phosphinate in the absence of the alkyne and then the resulting mixture allowed to cool to room temperature for 15 min before alkyne addition, the reaction proceeded much more rapidly reaching completion within 6 h. This room-temperature protocol was also the one employed with acetylene gas (Table 3, entry 4).

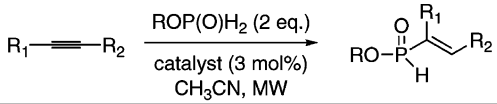
Because the thermal reaction gave excellent results, we studied the feasibility of a microwave process. Reactions conducted under microwave irradiation are currently receiving a great deal of attention because of the very short reaction times involved.[20] As expected, excellent hydrophosphinylation yields can be obtained in minutes in a microwave reactor (Table 4). Conditions did not affect significantly the regioselectivity of the reaction. With phenylacetylene, the microwave reaction appears slightly more regioselective than the thermal reaction (see Table 3, entry 6). The corresponding products can be isolated in good yields (Table 4).

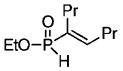
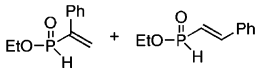
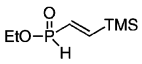
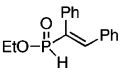
Next, we turned our attention to representative synthetic applications of this reaction. Since various functional group transformations of *H*-phosphinates are well-established in the literature,[21] some one-pot tandem functionalizations were investigated. A variety of reactions can be conducted on pure *H*-phosphinate esters,[21] so focus was placed exclusively on one-pot reactions without intermediate purification, to maximize practicality and broad applicability. Since the *H*-phosphinates are often difficult to purify thus decreasing the isolated yield,[13] a tandem sequence of reactions could be a clear

(18) Bravo-Altamirano, K.; Montchamp, J.-L. Unpublished results.
(19) See Supporting Information for experimental details.

(20) Reviews: (a) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Loupy, A.; Petit, A.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213.

TABLE 4. Nickel-Catalyzed Hydrophosphinylation with Microwave Heating[a]

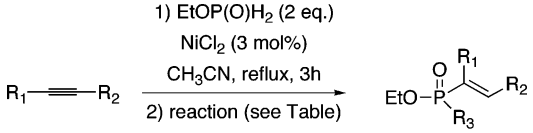


R^1	R^2	catalyst	time (mn)	temp. (°C)	power (W)	P (bars)	product	NMR yield % [isomeric ratio] (isolated %)
Pr	Pr	$NiCl_2$	1	125	25	2		93
Pr	Pr	$NiCl_2$	10	80	15	0		43
Pr	Pr	$NiCl_2$	5	100	25-30	1		100 (81)
Pr	Pr	$NiCl_2.6H_2O$	5	100	20	0		100 (73)
Ph	H	$NiCl_2$	5	80	15	0		91 [2.8 / 1] (41)[b]
Ph	H	$NiCl_2$	1	100	20	0		97 [2.5 / 1]
TMS	H	$NiCl_2$	10	80	15	0		72 (41)
Ph	Ph	$NiCl_2$	5	100	25	0		100 (83)

[a] General procedure for the hydrophosphinylation of alkynes by microwave irradiation (using a commercial instrument): To the alkyne (1.25 mmol) and the catalyst (0.025−0.037 mmol, 2−3 mol % relative to the alkyne) was added a solution of $EtOP(O)H_2$ (2.5 mmol) in CH_3CN (5 mL, 0.5 M) at room temperature. The mixture was prestirred for 30 s before being irradiated under normal adsorption. The mixture was then concentrated in vacuo. The residue was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$ and then brine. Drying on $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (hexanes, 100% v/v to EtOAc, 100% v/v). [b] Branched only.

advantage. Some examples of tandem reactions are shown in Table 5. As expected, alkenylphosphonate diesters are readily obtained by oxidative esterification (Table 5, entries 1 and 7). Unsymmetrical phosphonate diesters or phosphonate monoesters should also be accessible using a similar approach. More interestingly, tandem cross-coupling (Table 5, entry 2), conjugate addition (Table 5, entries 3 and 6), and alkylation (Table 5, entries 4 and 5) can all be conducted to provide acceptable yields (generally 50−60%) of unsymmetrically disubstituted phosphinate esters. The lower yield obtained in entry 6 presumably comes from the sensitivity of the enyne product, but the hydrophosphinylation step is highly regioselective (see Table 3, entry 8).

TABLE 5. Tandem One-Pot Alkyne Hydrophosphinylation-Functionalization



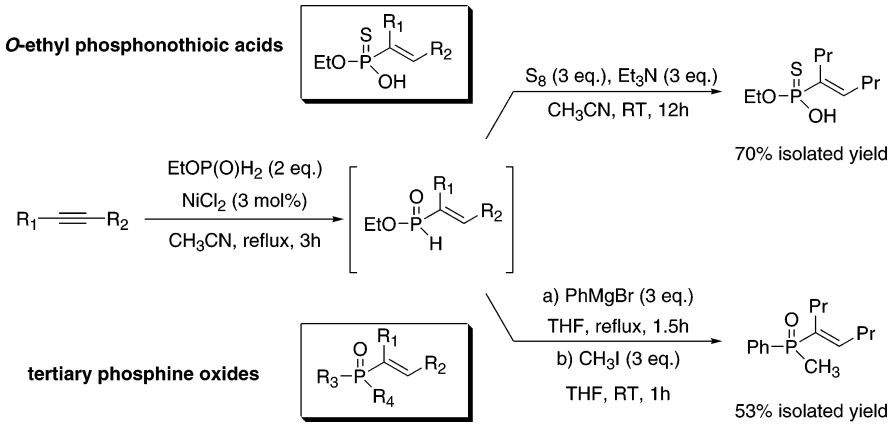
entry	R^1	R^2	R^3	second reaction[a]	isolated yield, %
1	Pr	Pr	OEt	A	48
2	Pr	Pr	Ph	B	58
3	Pr	Pr	CH_2CH_2CN	C	63
4	Pr	Pr	allyl	D	76
5	Pr	Pr	Me	E	62
6	C≡CMe	Me	$CH_2CH_2CO_2Bn$	F	32
7	Me	*t*-Bu	OEt	A	57

[a] Reactions: (A) EtOH (55 equiv), CCl_4 (33 equiv), Et_3N (10 equiv), room temperature, 12 h. (B) PhI (3 equiv), Et_3N (6 equiv), 2 mol % $Cl_2Pd(PPh_3)_2$, reflux, 12 h. (C) acrylonitrile (3 equiv), DBU (3 equiv), room temperature, 6 h. (D) allyl chloride (3 equiv), BSA (6 equiv), reflux, 3 h. (E) Me_2SO_4 (2 equiv), BSA (6 equiv), room temperature, 3 h. (F) benzyl acrylate (3 equiv), DBU (3 equiv), room temperature, 6 h.

Other tandem reactions are shown in Scheme 2. Phosphonothioic acids can easily be obtained by simply treating the crude hydrophosphinylation mixtures with elemental sulfur. The product can even be obtained in good purity using a simple extractive workup with hexane. The resolution of phosphonothioic acids with chiral amines has been reported in the literature as a way to access P-chiral compounds.[22] Thus the methodology we are developing for the preparation of *H*-phosphinate esters could ultimately become useful for the preparation of P-chiral ligands. Scheme 2 also shows an

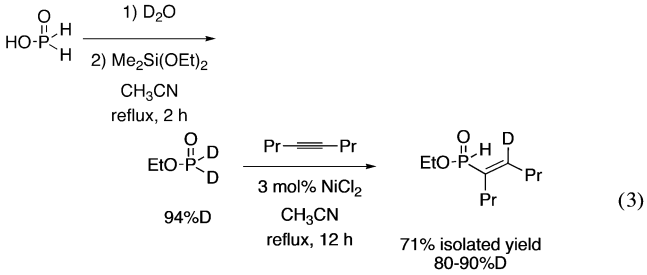
(21) See also ref 11. For some representative examples of specific functional group transformations for *H*-phosphinate esters, see: (a) Karanewsky, D. S.; Badia, M. C. *Tetrahedron Lett.* **1986**, *27*, 1751. (b) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385. (c) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389. (d) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297. (e) Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313. (f) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *Tetrahedron Lett.* **2001**, *42*, 4491. (g) Thottathil, J. K.; Przybyla, C. A.; Moniot, J. L. *Tetrahedron Lett.* **1984**, *25*, 4737. (h) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502. (i) McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319. (j) Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275. (k) Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743. (l) Bartlett, P. A.; Giangiodano, M. A. *J. Org. Chem.* **1996**, *61*, 3433. (m) Fatima Fernandez, M.; Vlaar, C. P.; Fan, H.; Liu, Y.-H.; Fronczek, F. R.; Hammer, R. P. *J. Org. Chem.* **1995**, *60*, 7390. (n) Seo, K.; Yamashita, M.; Oshikawa, T.; Kobayashi, J.-i. *Carbohydr. Res.* **1996**, *281*, 307. (o) Emmick, T. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459. (p) Hall, R. G.; Riebli, P. *Synlett* **1999**, 1633. (q) Xu, Y.; Wei, H.; Xia, J. *Liebigs Ann. Chem.* **1988**, 1139. (r) Schuman, M.; Lopez, X.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299. (s) Luke, G.; Shakespeare, W. C. *Synth. Commun.* **2002**, *32*, 2951. (t) Zeiss, H.-J. *Tetrahedron* **1992**, *48*, 8263.

SCHEME 2. Phosphonothioate and Tertiary Phosphine Oxide via Tandem Reactions



interesting and potentially very useful example of three phosphorus−carbon bond-forming reactions in a single pot. After hydrophosphinylation, a Grignard reagent displaces the ester group,[21o−q] and the resulting secondary phosphine oxide anion can be trapped with an electrophile. In this case, a solvent switch from acetonitrile to THF was required after the first step, to be compatible with the Grignard reagent, but no intermediate purification was conducted during the entire sequence. Such access to functionalized phosphine oxides could be particularly useful since the reduction of tertiary phosphine oxides is very well-precedented and leads to tertiary phosphines.[23]

Although we have not yet studied the mechanism of this novel nickel-catalyzed hydrophosphinylation, it is likely to proceed similarly to that of the palladium version.[1] One experiment that was conducted was the hydrophosphinylation of an internal alkyne with EtOP(O)D_2 (eq 3). Deuterated ethyl phosphinate was prepared



(3)

in 94% isotopic purity from D_3PO_2 (itself obtained by exchanging H_3PO_2 with D_2O) using our alkoxysilane esterification. As expected, the deuterium is incorporated via a syn addition in 80−90% isotopic purity.

In conclusion, we have developed a novel nickel-catalyzed phosphorus−carbon bond-forming reaction. Although the regioselectivity needs to be improved and some mechanistic issues remain to be clarified, the practical aspects of this reaction should prove a useful tool in the synthesis of alkenyl *H*-phosphinates and their derivatives. The fact that inexpensive $NiCl_2$ (or its hydrate) is employed catalytically makes this novel P−C bond-forming reaction particularly convenient. We also demonstrated conditions that employ microwave heating to produce the alkenyl phosphinates in high yield in a few minutes. Since the alkenyl-*H*-phosphinates are now readily available, their reactivity and use for the preparation of other compounds can be investigated. Along these lines, the one-pot elaboration of the hydrophosphinylation products was also demonstrated for a variety of common reactions to provide access to functionalized organophosphorus compounds. Taken with our previously reported palladium-catalyzed hydrophosphinylation,[1,3] radical-based hydrophosphinylation,[24] and palladium cross-coupling of aryl[15,25] and alkenyl halides,[14,15] this methodology further expands the scope of *H*-phosphinic acid derivatives that can be obtained. Thus access to a wide variety of functionalized *H*-phosphinates should significantly enhance the synthetic usefulness of these intermediates, for example, in the preparation of biologically active compounds or phosphine ligands.

Experimental Section

Experimental Procedures for Table 3. General Procedure for the Hydrophosphinylation of Alkynes with a Stock Solution of ROP(O)H_2. To the alkyne (2.5 mmol) and the catalyst (0.05−0.075 mmol, 2−3 mol % relative to the alkyne) was added a solution of EtOP(O)H_2 (5 mmol) in CH_3CN (10 mL, 0.5 M) at room temperature. The mixture was stirred at reflux until completion of the reaction (NMR monitoring on a sample of the crude reaction mixture). The mixture was then concentrated in vacuo. The residue was diluted with EtOAc and washed with 1 M aqueous $NaHSO_4$ and then brine. Drying on $MgSO_4$ and concentration afforded the crude compound, which was purified by radial chromatography (hexanes, 100% v/v to EtOAc, 100% v/v). The product was generally obtained as a light yellow oil.

Representative Procedure with Alternate Workup: Preparation of Ethyl (1-Propyl-pent-1-enyl) Phosphinate (Table 3, entry 2a). To a solution of EtOP(O)H_2 (0.5 M, 10 mL, 5 mmol) in CH_3CN (prepared from $(EtO)_2SiMe_2$ as described above) was added 4-octyne (0.37 mL, 2.5 mmol) and

(22) (a) Aaron, H. S.; Braun, J.; Shryne, T. M.; Frack, H. F.; Smith, G. E.; Uyeda, R. T.; Miller, J. I. *J. Am. Chem. Soc.* **1960**, *82*, 596. (b) Krawiecka, B.; Michalski, J. *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **1971**, *19*, 377.

(23) Reduction of phosphine oxides to phosphines: (a) Kagan, H. B.; Sasaki, M. *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: New York, 1990; Vol. 1, Chapter 3. (b) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625. (c) Imamoto, T.; Takeyama, T.; Kusumoto, T. *Chem. Lett.* **1985**, 1491. (d) Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87 and references therein.

(24) Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745.

(25) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510.

nickel chloride (0.01 g, 0.075 mmol, 3 mol %), at room temperature. The solution was refluxed under N_2 for 7 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 31.8 ppm. The mixture was then diluted with EtOAc and washed with dilute aqueous HCl (1 ×), the resulting aqueous phase was extracted with EtOAc (3 ×). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 ×) and brine. Drying and concentration afforded the crude compound, which was purified by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc). The product was obtained as a colorless oil (0.510 g, 100%). ^1H NMR ($CDCl_3$) δ 6.99 (d, J = 542 Hz, 1 H), 6.36 (dt, J = 26 Hz, J = 6 Hz, 1 H), 3.89−4.1 (m, 2 H), 2.0−2.27 (m, 4 H), 1.3−1.52 (m, 4 H), 1.12−1.3 (m, 3 H), 0.72−1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 146.9 (d, J_{PCC} = 14 Hz), 131.6 (d, J_{PC} = 124 Hz), 61.7 (d, J_{POC} = 7 Hz), 30.3 (d, J_{PCC} = 18 Hz), 28.1 (d, J_{PCCC} = 12 Hz), 22.4, 21.7, 16.1 (d, J_{POCC} = 3 Hz), 13.9, 13.6; ^{31}P NMR ($CDCl_3$) δ 32.2 (dm, J = 543 Hz). HRMS (EI) calcd for $C_{10}H_{21}O_2P$ (M^+) 204.1279, obsd 204.1275.

Representative Procedure for One-Pot Hydrophosphinylation with Anilinum Hypophosphite: Preparation of Butyl (1-Propyl-pent-1-enyl) Phosphinate (Table 3, entry 1d). To a suspension of $PhNH_3OP(O)H_2$ (0.800 g, 5 mmol), $(BuO)_4Si$ (1.122 g, 3.5 mmol), and 4-octyne (0.37 mL, 2.5 mmol) in CH_3CN (10 mL) was added $NiCl_2$ (0.01 g, 0.075 mmol, 3 mol %). The reaction mixture was then refluxed for 16 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 31.2 ppm (100%). The mixture was then diluted with EtOAc and washed successively with diluted HCl (1 ×). The resulting aqueous phase was extracted with EtOAc (3 ×), and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 ×) and brine. Drying, concentration, and purification by radial chromatography (2 mm thickness, hexanes/EtOAc 3:1, v/v, EtOAc) afforded the product as a colorless oil (0.521 g, 90%).

Representative Procedure with Aminosilicate/TFA: Preparation of Ethyl (*trans*-2-Trimethylsilyl-vinyl) Phosphinate (Table 3, entry 12). To a solution of concentrated H_3PO_2 (5 mmol) in HPLC grade CH_3CN (10 mL) were added 3-aminopropyl)triethoxysilane (1.107 g, 5 mmol), trimethylsilylacetylene (0.35 mL, 2.5 mmol), trifluoroacetic acid (0.39 mL, 5 mmol), and nickel chloride (0.01 g, 0.075 mmol, 3 mol %), at room temperature. The solution was refluxed under N_2 for 2.5 h. After cooling to room temperature, ^{31}P NMR analysis showed the product at 25.3 ppm (98%). The mixture was then diluted with EtOAc and washed successively with diluted aqueous HCl (1 ×). The aqueous phase was then extracted with EtOAc (3 ×) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1 ×) and brine. Drying and concentration afforded the product as a colorless oil (0.350 g, 75%).

Tandem Reactions (Table 4). Diethyl (1-Propyl-pent-1-enyl) Phosphonate (Table 4, entry1).[26] To 4-octyne (0.275 g, 2.50 mmol) and $NiCl_2$ (9.7 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added CCl_4 (8 mL, 12.7 g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9 g, 29 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (299 mg, 48%) as an oil. ^1H NMR ($CDCl_3$, Me_4Si) δ 6.48 (dt, J = 24 Hz, J = 7 Hz, 1 H), 3.97 (q, J = 7 Hz, 2 H), 2.05−2.18 (m, 4 H), 1.25−1.40 (m, 4 H), 1.24 (t, J = 7 Hz, 6 Hz), 0.86 (dt, J = 3 Hz, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 147.6 (J_{PCC} = 10 Hz), 129.4 (J_{PC} = 175 Hz), 61.5 (J_{POC} = 6 Hz), 30.7 (J_{PCCC} = 19 Hz), 29.6 (J_{PCC} = 11 Hz), 22.6 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.5 (J_{POCC} = 7 Hz), 14.3, 14.0; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 23.47; MS (EI$^+$) *m/z* 248 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{12}H_{25}O_3P$ 248.1541, obsd 248.1534.

Ethyl Phenyl-(1-propyl-pent-1-enyl) Phosphinate (Table 4, entry 2). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture were added iodobenzene (1.5 g, 7.51 mmol), $Cl_2Pd(PPh_3)_2$ (35 mg, 0.05 mmol, 1.9 mol %), and triethylamine (1.52 g, 15.1 mmol) at room temperature. The resulting mixture was stirred at reflux overnight. The solution was concentrated, partitioned between 1 M $NaHSO_4$ and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (419 mg, 58%) as an oil. ^1H NMR ($CDCl_3$, Me_4Si) δ 7.64 (ddd, J = 11.7 Hz, J = 1.5 Hz, J = 0.6 Hz, 2 H), 7.29−7.45 (m, 3 H), 6.39 (dt, J = 22.3 Hz, J = 7.3 Hz, 1 H), 3.91/3.91 (ddq, J = 22.4 Hz, J = 10.1 Hz, J = 7.0 Hz, 1 H/1 H), 1.96−2.10 (m, 4 H), 1.25−1.40 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.0−1.2 (m, 2 H), 0.79 (t, J = 7.3 Hz, 3 H), 0.70 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 146.4 (J_{PCC} = 10 Hz), 131.9 (J_{PC} = 127.5 Hz), 131.5 (J_{PCCCC} = 3 Hz), 131.3 (J_{PCC} = 10 Hz), 131.0 (J_{PC} = 131 Hz), 128.0 (J_{PCCC} = 12 Hz), 60.2 (J_{POC} = 6 Hz), 30.3 (J_{PCCC} = 17 Hz), 28.9 (J_{PCC} = 12 Hz), 22.5 (J_{PCCC} = 2 Hz), 21.6 (J_{PCCCC} = 1 Hz), 16.1 (J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 35.89; MS (EI$^+$) *m/z* 280 ([*M*]$^+$); HRMS (EI$^+$) calcd for $C_{16}H_{25}O_2P$ 280.1592, obsd 280.1588.

Ethyl (2-Cyano-ethyl)-(1-propyl-ent-1-enyl) Phosphinate (Table 4, entry 3). To 4-octyne (0.282 g, 2.56 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 2.9 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture was added acrylonitrile (0.403 g, 7.6 mmol) and DBU (1.1 g, 7.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solution was quenched with 1 M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (415 mg, 63%) as an oil. ^1H NMR ($CDCl_3$, Me_4Si) δ 6.58 (dt, J = 21.4 Hz, J = 7.3 Hz), 3.95−4.16 (m, 1 H), 3.82−3.96 (m, 1 H), 2.56−2.70 (m, 2 H), 1.35−1.60 (m, 4 H), 1.32 (t, J = 7.3 Hz), 0.98 (t, J = 7.0 Hz), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 149.8 (J_{PCC} = 9 Hz), 130.7 (J_{PC} = 118 Hz), 119.0 (J_{PCCC} = 17 Hz), 60.7 (J_{POC} = 6 Hz), 31.1 (J_{PCCC} = 16 Hz), 29.5 (J_{PCC} = 12 Hz), 24.5 (J_{PC} = 97 Hz), 23.2 (J_{PCCCC} = 2 Hz), 22.1 (J_{PCCC} = 2 Hz), 16.6 (J_{POCC} = 6 Hz), 14.5, 14.1, 10.8 (J_{PCC} = 2 Hz); ^{31}P NMR ($CDCl_3$, Me_4Si) δ 43.25; MS (EI$^+$) *m/z* 257 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{13}H_{24}NO_2P$ 257.1545, obsd 257.1547.

Ethyl Allyl-(1-propyl-pent-1-enyl) Phosphinate (Table 4, entry 4). To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.1 mg, 0.078 mmol, 3 mol %) was added 10 mL (5 mmol) of $EtOP(O)H_2$ (0.5M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 3 h. To the reaction mixture was added at room temperature BSA (1.46 g, 7.2 mmol) and, after 5 min of stirring, allyl chloride (0.582 g, 7.61 mmol). To the mixture was stirred at reflux for 3 h. The reaction mixture was then cooled, quenched by saturated $NaHCO_3$, extracted with EtOAc, and the combined organic phases were washed with brine. Drying over $MgSO_4$, and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (475 mg, 76%) as an oil. ^1H NMR ($CDCl_3$, Me_4Si) δ 6.48 (dt, J = 21.1 Hz, J = 7.3 Hz, 1 H), 5.7−5.85 (m, 1 H), 5.1−5.22 (m, 2 H), 3.85−4.2 (m, 2 H), 2.5−2.75 (m, 2 H), 2.1−2.25 (m, 4 H), 1.35−1.55 (m, 4 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.95 (t, J = 7.3

(26) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1991**, *21*, 2341.

Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 147.7 (d, J_{PCC} = 9 Hz), 130.7 (d, J_{PC} = 116 Hz), 127.3 (d, J_{PCC} = 9 Hz), 119.5 (d, J_{PCCC} = 13 Hz), 59.8 (d, J_{POC} = 6 Hz), 34.0 (d, J_{PC} = 94 Hz), 30.1 (d, J_{PCCC} = 13 Hz), 29.1 (d, J_{PCC} = 12 Hz), 22.4 (d, J_{PCCCC} = 1 Hz), 21.6 (d, J_{PCCC} = 1 Hz), 16.8 (d, J_{POCC} = 7 Hz), 13.9, 13.5; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 45.18; MS (EI$^+$) *m/z* 244 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{13}H_{25}O_2P$ 244.1592, obsd 244.1587.

Ethyl Methyl-(1-propyl-pent-1-enyl) Phosphinate (Table 4, entry 5). To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of EtOP(O)H_2 (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added at room temperature BSA (1.46 g, 7.2 mmol) and, after 5 min of stirring, dimethyl sulfate (0.633 g, 5.02 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by saturated $NaHCO_3$ and extracted with EtOAc, and the combined organic phases washed with brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (343 mg, 62%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 6.55 (dt, J = 21.4 Hz, J = 7.3 Hz, 1 H), 3.8−4.05 (m, 2 H), 2.1−2.25 (m, 4 H), 1.49 (d, J = 13.8 Hz, 3 H), 1.35−1.55 (m, 4 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 147.0 (d, J_{PCC} = 9 Hz), 132.5 (d, J_{PC} = 118 Hz), 59.9 (d, J_{POC} = 6 Hz), 30.8 (d, J_{PCCC} = 16 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.0 (d, J_{PCCCC} = 1 Hz), 22.2 (d, J_{PCCC} = 1 Hz), 14.5, 14.5 (d, J_{PC} = 99 Hz), 14.1; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 45.77; MS (EI$^+$) *m/z* 218 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{11}H_{23}O_2P$ 218.1436, obsd 218.1438.

Benzyl 3-[Ethoxy-(1-ethylidene-but-2-ynyl)-phosphinoyl]propionate (Table 4, entry 6). To 2,4-hexadiyne (0.199 g, 2.55 mmol) and $NiCl_2$ (7.0 mg, 0.054 mmol, 2.1 mol %) was added 10 mL (5 mmol) of EtOP(O)H_2 (0.5M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added benzyl acrylate (1.22 g, 7.5 mmol) and DBU (1.12 g, 7.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. The solution was quenched with 1M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (271 mg, 32%) as an oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 7.3−7.4 (br, 5 H), 6.9−7.1 (m, 1 H), 5.13 (s, 2 H), 4.05−4.2 (m, 1 H), 3.85−4.1 (m, 2 H), 2.55−2.8 (m, 2 H), 2.1−2.3 (m, 2 H), 1.95−2.05 (m, 6 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 172.1 (d, J_{PCCC} = 19 Hz), 152.1 (d, J_{PC} = 8 Hz), 135.7, 128.6, 128.3, 128.2, 117.3 (d, J_{PC} = 128 Hz), 95.5 (d, J_{PCCC} = 8 Hz), 73.0 (d, J_{PCC} = 13 Hz), 66.6, 60.7 (d, J_{POC} = 7 Hz), 26.7 (d, J_{PCC} = 2 Hz), 22.5 (d, J_{PC} = 106 Hz), 17.3 (d, J_{PCCC} = 14 Hz), 16.4 (d, J_{POCC} = 7 Hz), 4.6 (d, J_{PCCCC} = 2 Hz); ^{31}P NMR ($CDCl_3$, Me_4Si) δ 41.41; MS (EI$^+$) *m/z* 334 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{18}H_{23}O_4P$ 334.1334, obsd 334.1340.

Diethyl (1,3,3-Trimethyl-but-1-enyl) Phosphonate (Table 4, entry 7). To 4,4-dimethyl-2-pentyne (0.240 g, 2.50 mmol) and $NiCl_2$ (9.8 mg, 0.076 mmol, 3.0 mol %) was added 10 mL (5 mmol) of EtOP(O)H_2 (0.5M solution in CH_3CN) at room temperature. The solution was stirred at reflux for 24h. To the reaction mixture was added CCl_4 (8 mL, 12.7 g, 83 mmol), ethanol (8 mL, 6.3 g, 137 mmol), and triethylamine (4 mL, 2.9 g, 29 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. The solution was quenched with 1M $NaHSO_4$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (354 mg, 57%) as an oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 6.54 (ddd, J = 27 Hz, J = 1.47 Hz, J = 0.59 Hz, 3 H), 3.9−4.1 (m, 4 H), 1.88 (ddd, J = 15.8 Hz, J = 1.47 Hz, J = 0.59 Hz, 3 H), 1.28 (t, J = 7 Hz, 6 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 155.8 (d, J_{PCC} = 4 Hz), 123.2 (d, J_{POC} = 175 Hz), 61.7 (d, J_{POC} = 6 Hz), 34.5 (d, J_{PCCC} = 21 Hz), 30.2, 16.5 (d, J_{POCC} = 6 Hz), 13.5 (d, J_{PCC} = 10 Hz); ^{31}P NMR ($CDCl_3$, Me_4Si) δ 24.44; MS (EI$^+$) *m/z* 234 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{11}H_{23}O_3P$ 234.1585, obsd 234.1380.

Tandem Reactions (Scheme 2). (1-Propyl-pent-1-enyl)-phosphonothioic Acid *O*-Ethyl Ester. To 4-octyne (0.281 g, 2.55 mmol) and $NiCl_2$ (10.0 mg, 0.077 mmol, 3 mol %) was added 10 mL (5 mmol) of EtOP(O)H_2 (0.5M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. To the reaction mixture was added sulfur (0.24 g, 7.5 mmol) and triethylamine (0.762 g, 7.53 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The solution was extracted with hexane, the acetonitrile layer was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude compound. Purification over silica gel (hexanes, 100% v/v to hexanes/EtOAc, 90/10% v/v) produced the expected compound (424 mg, 70%) as a brown oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 6.66 (dt, J = 27.5 Hz, J = 7.2 Hz, 1 H), 6.4−6.65 (s br, 1 H), 4.05−4.2 (m, 2 H), 2.25−2.4 (m, 2 H), 2.1−2.25 (m, 2 H), 1.4−1.6 (m, 4 H), 1.33 (t, J = 7.0 Hz, 3H), 0.95 (dt, J = 2.3 Hz, J = 7.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 146.6 (d, J_{PCC} = 14 Hz), 134.1 (d, J_{PC} = 141 Hz), 62.3 (d, J_{POC} = 6 Hz), 30.9 (d, J_{PCCC} = 20 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1, 22.2, 16.3 (d, J_{POCC} = 8 Hz), 14.5, 14.2; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 85.69; MS (EI$^+$) *m/z* 236 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{10}H_{21}O_2PS$ 236.1000, obsd 236.0992.

Methyl-phenyl-(1-propyl-pent-1-enyl)phosphine Oxide. To 4-octyne (0.279 g, 2.5 mmol) and $NiCl_2$ (9.9 mg, 0.076 mmol, 3 mol %) was added 10 mL (5 mmol) of EtOP(O)H_2 (0.5 M solution in CH_3CN) at room temperature. The solution was stirred at reflux overnight. The mixture was then concentrated in high vacuo. The residue was diluted with 5 mL of dry THF. To the mixture at 0 °C was added 7.5 mL (7.5 mmol) of phenylmagnesium bromide (1 M solution in THF). The mixture was warmed to room temperature and then stirred at reflux for 1 h 30. After addition at 0 °C of methyl iodide (1.08 g, 7.61 mmol), the mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then quenched by 10 mL of 1 M HCl, extracted with EtOAc and the combined organic phases washed with 1 M sodium thiosulfate and then brine. Drying over $MgSO_4$ and concentration afforded the crude compound. Purification over silica gel (hexanes, 100% v/v to EtOAc, 100% v/v) produced the expected compound (334 mg, 53%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 7.65−7.8 (m, 2 H), 7.4−7.55 (m, 3 H), 6.41 (dt, J = 21.1 Hz, J = 7.3 Hz, 1 H), 2.0−2.25 (m, 4 H), 1.8 (d, J = 12.9 Hz, 3 H), 1.42−1.46 (m, 2 H), 1.20−1.35 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 144.5 (d, J_{PCC} = 9 Hz), 134.4 (d, J_{PC} = 94 Hz), 133.9 (d, J_{PC} = 98 Hz), 131.4 (d, J_{PCCCC} = 3 Hz), 130.4 (d, J_{PCC} = 10 Hz), 128.5 (d, J_{PCCC} = 12 Hz), 30.8 (d, J_{PCCC} = 15 Hz), 29.5 (d, J_{PCC} = 12 Hz), 23.1, 22.1, 14.9 (d, J_{PC} = 72 Hz), 14.3, 13.9; ^{31}P NMR ($CDCl_3$, Me_4Si) δ 33.74 (m); MS (EI$^+$) *m/z* 250 ([M]$^+$); HRMS (EI$^+$) calcd for $C_{15}H_{23}OP$ 250.1487, obsd 250.1488

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

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