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Phospha-Michael Additions to Activated Internal Alkenes: Steric and Electronic Effects

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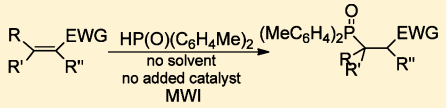
Supporting Information

ABSTRACT: The addition of P(O)−H bonds to internal alkenes has been accomplished under solvent-free conditions without the addition of a catalyst or radical initiator. Using a prototypical secondary phosphine oxide, a range of substrates including cinnamates, crotonates, coumarins, sulfones, and chalcones were successfully functionalized. Highly activated acceptors such as isopropylidenemalononitrile and ethyl 2-cyano-3-methyl-2-butenoate underwent the phospha-Michael reaction upon simple trituration of the reagents at room temperature, whereas less activated substrates such as ethyl cinnamate and methyl crotonate required heating (>150 °C) in a microwave reactor to achieve significant consumption of the starting alkenes. For the latter alkenes, a competing reaction involving disproportionation of the ditolylphosphine oxide into ditolylphosphinic acid and ditolylphosphine was observed at the high temperatures needed to promote the addition reaction.

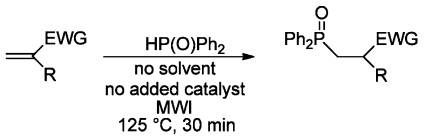


internal alkenes = coumarins, cinnamates, chalcones, crotonates

INTRODUCTION

The addition of P−H bonds to alkenes and alkynes remains one of the most effective methods for constructing organophosphorus compounds.[1−12] The resulting phosphonate, phosphine oxide, and phosphonic acid containing compounds are high-value targets with applications in medicine,[13−22] material science,[23,24] and organic synthesis.[25−28] Historically, this reaction has been catalyzed by strong bases,[29] radical initiators,[30] UV light,[8] and transition metal catalysts.[1−8]

We recently reported the microwave-assisted addition of a prototypical secondary phosphine oxide to terminal alkenes under solvent-free conditions without the addition of a catalyst or radical initiator (eq 1).[31] A range of terminal alkenes were



(1)

EWG = P(O)(OEt)$_2$, CO$_2$Bu, CO$_2$Me, CN, C(O)Me, SO$_2$Et
R = H, Me

employed in this chemistry, and moderate to excellent yields were obtained for most substrates at 125 °C. In many cases, the chemistry was remarkably clean, and near quantitative conversions were observed by NMR before any purification. Although a number of terminal alkenes worked well, only a few internal alkenes with a single type of electron-withdrawing group were screened. Although the phospha-Michael additions were successful with these internal alkenes, the substrate scope was extremely limited. To address this issue, we have extended the chemistry to a wide range of internal alkenes.

RESULTS AND DISCUSSION

To investigate whether or not conjugated internal alkenes could be used in these phospha-Michael reactions, we screened a model system comprised of ethyl cinnamate as the representative alkene and ditolylphosphine oxide as the secondary phosphine oxide. Ditolylphosphine oxide was selected as the substrate for these reactions, as the methyl groups provided an uncluttered resonance in the ^{1}H NMR spectrum that was used to monitor the consumption of the secondary phosphine oxide. Using the same reaction conditions that were successful for the phospha-Michael reactions involving terminal alkenes (solvent free, 125 °C, 30 min), irradiating a 1:1 mixture of the model substrates afforded low conversion. A temperature profile revealed that heating the reaction mixture for 30 min at 180 °C afforded moderate yields of the addition product.[32] Analyzing the ^{1}H NMR spectra of the crude material revealed incomplete consumption of the cinnamate, whereas the ^{31}P NMR spectrum showed the presence of ditolylphosphinic acid in addition to what appeared to be unreacted ditolylphosphine oxide. The formation of the phosphinic acid is likely due to disproportionation of ditolylphosphine oxide into ditolylphosphinic acid and ditolylphosphine.[33−35] The latter was rapidly oxidized to ditolylphosphine oxide upon exposure to air, resulting in apparently unreacted starting material. Performing the reaction at lower temperatures to minimize this side reaction led to lower yields of the phospha-Michael adduct. Increasing the temperature above 200 °C afforded increased amounts of the phosphinic acid. Heating the reaction at 190 °C for 35 min generated the highest yield of the phospha-Michael adduct and the smallest amount of the phosphinic acid. The Michael

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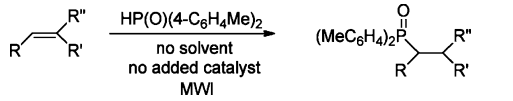
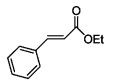
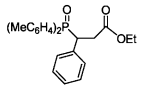
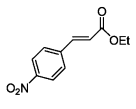
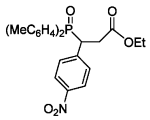
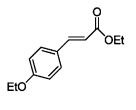
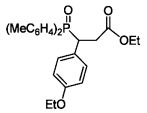
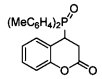
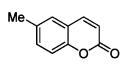
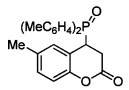
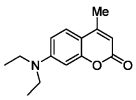
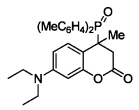
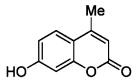
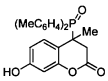
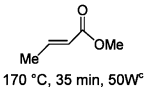
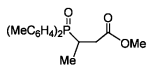
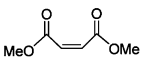
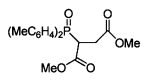
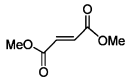
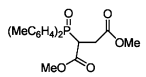
acceptor did not contribute to this process, as heating the phosphine oxide (200 °C, 35 min) without the addition of the Michael acceptor also consumed the ditolylphosphine oxide and generated ditolylphosphinic acid and ditolylphosphine.

Once a successful system for the phospha-Michael addition of ditolylphosphine oxide to ethyl cinnamate was identified, the chemistry was extended to functionalized cinnamates and related internal alkenes (Table 1). For cinnamates, the addition chemistry was moderately tolerant of electronic changes to the acceptor. Using ethyl cinnamate as the reference point, slightly lower yields of the addition product were obtained using a nitro-substituted cinnamate, while similar yields of the addition product were found when a methoxy group was incorporated into ethyl cinnamate. Breaking the conjugation of the molecule by exchanging the aromatic group on the alkene for an alkyl group (Table 1, entry 8) did not change the outcome of the reaction and high yields of the addition product were obtained. Cyclic Michael acceptors, coumarin and 6-methyl coumarin, were also successfully used in the phospha-Michael reaction. Furthermore, adding a second electron-withdrawing group to the β-position of the Michael acceptor (Table 1, entries 9, 10) resulted in near quantitative yields (by NMR) of the Michael adducts after irradiating the reagents at reduced temperatures (110 °C, 35 min). While the addition reaction was moderately tolerant of electron withdrawing or donating groups, the addition reaction was completely suppressed when the steric bulk of the substrate was increased by incorporating a second substituent to the β-position of the internal alkene (Table 1, entries 6, 7).

Table 1. Addition of Ditolylphosphine Oxide to Cinnamates, Crotonates, and Related Internal Alkenes[a]



	Substrate	Product	#	Yield[b]
1			1	91
	180 °C, 30 min, 150W[c]			
2			2	66
	170 °C, 35 min, 130W[c]			
3			3	82
	180 °C, 30 min, 75W[c]			
4			4	73
	130 °C, 35 min, 100W[c]			
5			5	71
	130 °C, 35 min, 100W[c]			
6			6	0
	130-200 °C, 30-60 min, 100 - 200W[c]			
7			7	0
	130-200 °C, 30-60 min, 100 - 200W[c]			
8			8	70
	170 °C, 35 min, 50W[c]			
9			9	89
	110 °C, 35 min, 50W[c]			
10			9	74
	110 °C, 35 min, 50W[c]			

[a]Reactions were carried out without solvent using 0.43 mmol of ditolylphosphine oxide. [b]Yields are based upon isolated material. [c]Initial microwave power levels.

As mentioned above, the addition reaction between ditolylphosphine oxide and coumarins was completely suppressed when a second substituent was added to the β-position of the alkene (Table 1). To investigate whether or not the addition of a second electron-withdrawing group could overcome this steric issue, a range of substrates incorporating malonates and malononitriles was investigated. As shown in Table 3, the addition of the second nitrile or ester group strongly activated the alkene, and the phospha-Michael reaction proceeded at reduced temperatures when compared to the analogous reaction shown in Table 2. For example, cinnamonitrile (Table 2 entry 8) required heating to 175 °C to induce the phospha-Michael addition, whereas the same reaction involving benzylidenemalononitrile (Table 3 entry 2) proceeded at 65 °C. While this chemistry tolerated having two alkyl substituents in the β-position of the Michael acceptor,

The chemistry was extended to other internal alkenes containing a single activating group such as chalcones and cinnamonitriles (Table 2). For the chalcones, the lowest effective reaction temperatures were between 120 and 130 °C (20−35 min). Under these conditions, nearly quantitative conversions into the addition products were observed with only trace amounts of the phosphinic acid. Similar to the reactions involving the cinnamates, substrates bearing either electron-withdrawing or electron-donating groups were successfully functionalized in these reactions. Of particular interest was the use of an unprotected phenol in the chemistry. Historically, protection/deprotection strategies were required when substrates bearing phenols were used in phospha-Michael reactions promoted by strong bases or transition metal catalysts. This was not necessary in our microwave assisted chemistry as evidenced by the high yields of the addition product obtained using a representative phenol (Table 2, entry 1). Moving to nitrile-functionalized substrates gave similar results. Both cinnamonitrile and 4-dimethylaminocinnamonitrile were successfully used in these reactions. For these substrates, the reaction temperatures were similar to the cinnamates and methyl crotonate (170−190 °C). While most of the internal alkenes screened gave good to excellent yields of the addition products, using phenyl *trans*-styryl sulfone as the Michael acceptor was less successful (Table 2, entry 7). Although a range of conditions was screened, a significant amount of secondary products was observed in the ^{1}H and ^{31}P NMR spectra from reactions involving this sulfone. Despite this complex mixture, the addition product was able to be purified by column chromatography.

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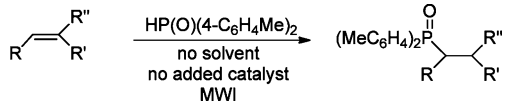
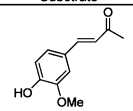
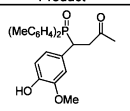
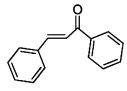
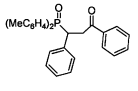
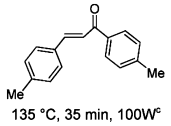
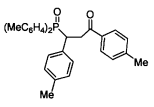
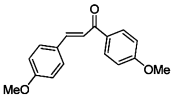
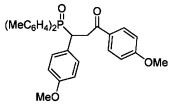
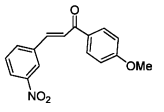
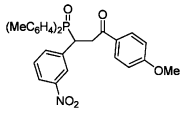
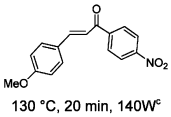
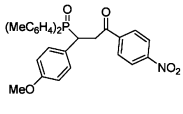
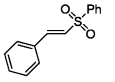
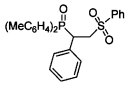
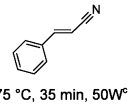
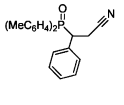
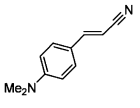
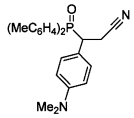
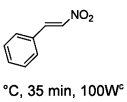
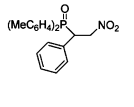
Table 2. Addition of Ditolylphosphine Oxide to Chalcones and Related Compounds[a]

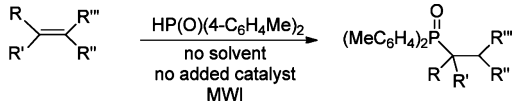


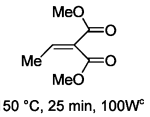
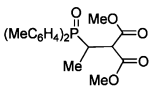
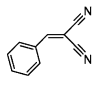
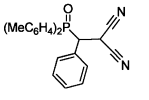
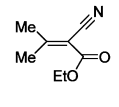
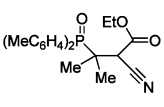
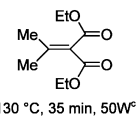
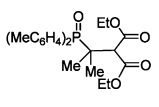
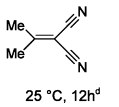
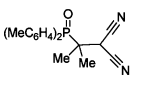
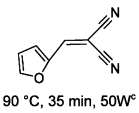
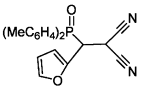
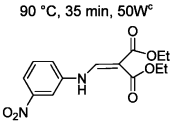
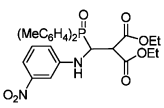
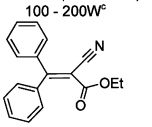
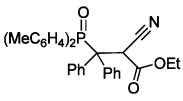
	Substrate	Product	#	Yield[b]
1	 130 °C, 35 min, 50W[c]		**10**	82
2	 135 °C, 35 min, 100W[c]		**11**	84
3	 135 °C, 35 min, 100W[c]		**12**	94
4	 135 °C, 35 min, 100W[c]		**13**	79
5	 130 °C, 20 min, 150W[c]		**14**	90
6	 130 °C, 20 min, 140W[c]		**15**	76
7	 125 °C, 35 min, 50W[c]		**16**	49
8	 175 °C, 35 min, 50W[c]		**17**	70
9	 200 °C, 35 min, 150W[c]		**18**	87
10	 130 °C, 35 min, 100W[c]		**19**	68

[a]Reactions were carried out without solvent using 0.43 mmol of ditolylphosphine oxide. [b]Yields are based upon isolated material. [c]Initial microwave power levels.

analogous reactions with two aryl groups led to complete recovery of the starting materials (Table 3, entry 8). Increasing the temperature of the reaction simply resulted in high amounts of phosphinic acid and no consumption of the alkene. In some cases, the phospha-Michael reaction proceeded at ambient temperature without irradiation. For example, simply triturating isopropylidenemalononitrile or ethyl 2-cyano-3-methyl-2-butenoate with ditolylphosphine oxide at 25 °C for 12 h afforded high yields of the adducts (Table 3, entries 3, 5).

Table 3. Addition of Ditolylphosphine Oxide to Internal Alkenes Containing Multiple Activating Groups[a]



	Substrate	Product	#	Yield[b]
1	 150 °C, 25 min, 100W[c]		**20**	90
2	 65 °C, 45 min, 50W[c]		**21**	72
3	 25 °C, 12h[d]		**22**	90
4	 130 °C, 35 min, 50W[c]		**23**	96
5	 25 °C, 12h[d]		**24**	82
6	 90 °C, 35 min, 50W[c]		**25**	87
7	 130-200 °C, 30-60 min, 100 - 200W[c]		**26**	0
8	 130-200 °C, 30-60 min, 100 - 200W[c]		**27**	0

[a]Reactions were carried out without solvent using 0.43 mmol of ditolylphosphine oxide. [b]Yields are based upon isolated material. [c]Initial microwave power levels. [d]No irradiation.

To investigate whether or not the phospha-Michael chemistry could be carried out using conventional heating, the addition reactions were carried out using a preheated oil bath. Heating benzylidenemalononitrile and dimethyl fumarate with ditolylphosphine oxide at 65 °C (1 h) and 110 °C (35 min) under solvent-free conditions afforded excellent yields (91 and 85%) of the phospha-Michael adducts with minimal amounts of secondary products.

In addition to probing the effectiveness of the microwave-assisted protocol with a range of Michael acceptors, the steric and electronic limits of this reaction were also established from the standpoint of the secondary phosphine oxide (Table 4). For this set of experiments, 1,3-diphenyl-2-propenone was used as the model Michael acceptor, and a range of $HP(O)R_2$ donors were screened. Irradiation of a 1:1 mixture of the Michael acceptor and $HP(O)(C_6H_4X)_2$ (X = OMe, H, CF_3) species at 130 °C for 35 min afforded the Michael adducts in excellent yields. No reduction in conversion was observed using either

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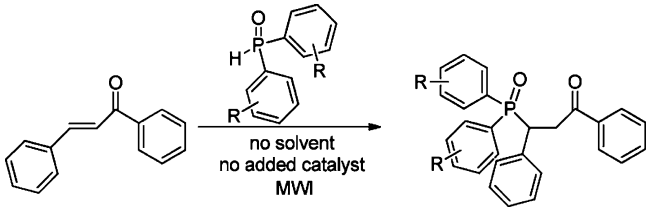
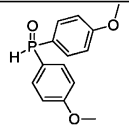
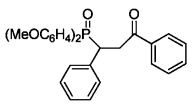
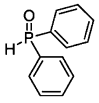
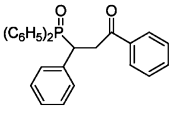
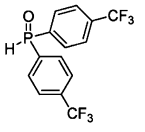
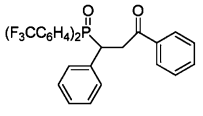
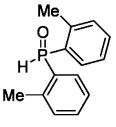
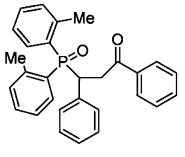
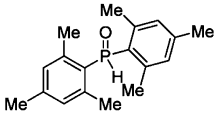
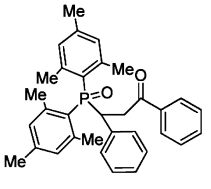
Table 4. Addition of Functionalized Secondary Phosphine Oxides to *trans*-Chalcone[a]



	Substrate	Product	#	Yield[b]
1	 130 °C, 35 min, 100W[c]		28	95
2	 130 °C, 35 min, 100W[c]		29	89
3	 130 °C, 35 min, 100W[c]		30	80
4	 130 °C, 35 min, 100W[c]		31	89
5	 200 °C, 35 min, 200W[c]		32	15[d]

[a]Reactions were carried out without solvent using 0.30−0.49 mmol of the secondary phosphine oxide. [b]Yields are based upon isolated material. [c]Initial microwave power levels. [d]Determined by NMR spectroscopy.

electron-donating or electron-withdrawing groups. The steric limits of this reaction were investigated by successively adding methyl groups in the ortho positions of diphenylphosphine oxide. Adding a single methyl group to each of the aromatic rings in $HP(O)Ph_2$ did not appreciably inhibit the reaction, and high yields of the addition product were obtained. However, adding a second methyl group (Table 4, entry 5) successfully inhibited the reaction, and no addition product was observed at 130 °C. Increasing the temperature of the reaction to 200 °C for 35 min resulted in 15% conversion into the Michael adduct. It was also noteworthy that no dimesitylphosphinic acid was observed in these reactions. The incorporation of the sterically imposing mesityl groups inhibited the disproportionation reaction and mostly unreacted starting materials were observed at the end of the reaction.

CONCLUSION

In summary, we have developed a protocol for the addition of P(O)−H bonds to internal alkenes without using a radical initiator, strong base, or metal catalyst. This methodology was successful with a range of internal alkenes such as cinnamates, coumarins, crotonates, sulfones, chalcones, and cinnamonitriles. Furthermore, the presence of unprotected phenols did not complicate the chemistry, and high yields of the phospha-Michael adducts were obtained. For all of the reactions described herein that require heating above 130 °C, developing a successful phospha-Michael reaction for these internal alkenes involved maximizing the addition chemistry while minimizing the disproportionation of the secondary phosphine oxide.

EXPERIMENTAL SECTION

General Considerations. Unless specified, all solvents were dried using a Grubbs-type solvent purification system. The phosphine oxides were prepared according to literature procedures and purified by column chromatography.[36,37] The chalcones were prepared by condensation reactions and compared with literature ^1H NMR values.[38−42] The remaining chemicals were obtained from commercial sources and used as received. ^1H and $^{13}C\{^1H\}$ chemical shifts were determined by reference to residual nondeuterated solvent resonances. All coupling constants are given in Hertz. $^{31}P\{^1H\}$ NMR spectra were referenced to external H_3PO_4 (0 ppm). ^{19}F NMR spectra were referenced to C_6F_6 (−164.9). Microwave catalyzed reactions were carried out in sealed vessels using a CEM Discover equipped with an external IR (surface) temperature sensor. The temperatures reached and maintained in these reactions are listed below as well as in Tables 1−4.

General Method for Phospha-Michael Reactions. *Microwave Heating (Method A).* A reactor vial (10 mL) was charged with the phosphine oxide, Michael acceptor, and a magnetic stirring bar. After exchanging the air for nitrogen, the reagents were triturated and irradiated (unless specified). The initial power setting listed for each reaction was maintained until the desired temperature was reached. The power was then reduced for the remainder of the reaction to maintain the temperature. No ramping periods were used in these reactions; thus, the reaction time listed is the total irradiation time (not the time at the desired temperature). For reactions involving solid reagents, the solids needed to melt before a significant temperature increase was observed. For the reactions studied herein, this typically occurred within 4 min. Care must be taken not to use initial high levels of microwave power (to rapidly melt the solids), as significant decomposition was observed under those conditions. Following irradiation, the residue was cooled to room temperature and purified by column chromatography. When liquid Michael acceptors were used, they were injected into the reaction flask following the exchange of air for nitrogen.

Conventional Heating (Method B). A reactor vial (10 mL) was charged with the phosphine oxide, Michael acceptor, and a magnetic stirring bar. After exchanging the air for nitrogen, the reagents were triturated and plunged into a preheated oil bath at the desired temperature for the specified time.

Ethyl 3-[Bis(4-methylphenyl)phosphinyl]-3-phenylpropanoate (1). The general procedure (method A) was followed with ethyl cinnamate (73.5 μL g, 0.44 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 180 °C; time = 30 min; initial power level = 150 W. Chromatography: silica (19 g), hexane/THF 1:1. R_f = 0.35, yield = 0.16 g of a white powder (91%), mp = 155−158 °C. Anal. Calcd for $C_{25}H_{27}O_3P$: C, 73.87; H, 6.70. Found: C, 73.67; H, 6.90. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.81 (m, 2H), 7.32 (m, 4H), 7.27 (m, 2H), 7.16 (m, 3H), 7.04 (m, 2H), 4.02 (ddd, 1H, J = 11.4, 8.1, 3.3), 3.91 (q, 2H, J = 7.0), 3.06 (ddd, 1H, J = 16.8, 11.1, 5.9), 2.88 (ddd, 1H, J = 16.2, 9.0, 3.5), 2.41 (s, 3H), 2.26 (s, 3H), 1.02 (t, 3H, J = 7.2); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 171.5 (d, J = 17.3), 142.4 (d, J = 2.3), 141.8 (d, J = 2.7), 135.4 (d, J = 5.6), 131.4 (d, J = 8.3), 131.1 (d, J = 9.0), 129.8 (d, J = 5.6), 129.6 (d, J = 11.8), 128.8 (d, J = 12.4), 128.3 (d, J = 102.7), 128.2 (d, J = 1.7), 128.1 (d, J = 97.1), 127.1 (d, J = 2.3), 60.7 (s), 43.1 (d, J = 67.9), 35.0 (s), 21.6 (d, J = 1.2), 21.5 (d, J = 1.2), 13.9 (s); $^{31}P\{^1H\}$($CDCl_3$, 25 °C) δ 32.8 (s).

Ethyl 3-[Bis(4-methylphenyl)phosphinyl]-3-(4-nitrophenyl)-propanoate (2). The general procedure (method A) was followed with ethyl 4-nitrocinnamate (0.096 g, 0.43 mmol) and ditolylphosphine

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oxide (0.10 g, 0.43 mmol). Temperature = 170 °C; time = 35 min; initial power level = 130 W. Chromatography: silica (19.0 g), EtOAc/hexane (gradient 30:70−80:20). R_f = 0.84 (EtOAc/hexane = 80:20). Yield = 0.13 g of a white powder (66%), mp = 211−214 °C. Anal. Calcd For $C_{25}H_{26}NO_5P$: C, 66.51; H, 5.80. Found: C, 66.24; H, 5.74. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 8.03 (m, 2H), 7.81 (m, 2H), 7.47 (m, 2H), 7.35 (m, 4H), 7.09 (m, 2H), 4.14 (ddd, 1H, J = 11.4, 8.1, 3.3), 3.93 (m, 2H), 3.09 (ddd, 1H, J = 17.1, 11.4, 5.7), 2.89 (ddd, 1H, J = 16.8, 9.0, 3.0), 2.43 (s, 3H), 2.29 (s, 3H), 1.05 (t, 3H, J = 7.2); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 170.9 (d, J = 16.9), 147.0 (d, J = 2.7), 143.7 (d, J = 5.6), 142.9 (d, J = 2.7), 142.5 (d, J = 2.9), 131.2 (d, J = 9.0), 130.8 (d, J = 9.7), 130.6 (d, J = 5.0), 129.8 (d, J = 11.8), 129.2 (d, J = 12.4), 127.6 (d, J = 103.3), 127.3 (d, J = 99.4), 123.3 (d, J = 1.7), 61.1 (s), 43.2 (d, J = 65.8), 34.8 (s), 21.6 (s), 21.5 (s), 14.0 (s); ^{31}P{^{1}H}($CDCl_3$, 25 °C) δ 31.8 (s).

3-[Bis(4-methylphenyl)phosphinyl]-3-(4-ethoxyphenyl)-propanoate (3). The general procedure (method A) was followed with ethyl 4-ethoxycinnamate (0.095 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 180 °C; time = 30 min; initial power level = 75 W. Chromatography: (silica) 19.0 g; hexane/THF 1:1. R_f = 0.26 (hexane/THF = 50:50). Yield = 0.16 g of a white powder (82%), mp = 121−124 °C. Anal. Calcd for $C_{27}H_{31}O_4P$: C, 71.98; H, 6.94. Found: C, 72.20; H, 6.65. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.77 (m, 2H), 7.31 (m, 4H), 7.16 (m, 2H), 7.05 (m, 2H), 6.69 (m, 2H), 3.92 (m, 5H), 3.00 (ddd, 1H, J = 16.3, 11.3, 6.1), 2.83 (ddd, 1H, J = 16.3, 8.7, 3.4), 2.39 (s, 3H), 2.26 (s, 3H), 1.35 (t, 3H, J = 7.0), 1.03 (t, 3H, J = 7.1); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 171.6 (d, J = 17.6), 158.1 (d, J = 2.3), 142.3 (d, J = 2.7), 141.7 (d, J = 2.8), 131.4 (d, J = 8.9), 131.1 (d, J = 9.2), 130.8 (d, J = 5.4), 129.5 (d, J = 11.6), 128.9 (d, J = 12.1), 128.4 (d, J = 102.5), 128.3 (d, J = 96.6), 127.0 (d, J = 5.5), 114.3 (d, J = 1.6), 63.3 (s), 60.7 (s), 42.2 (d, J = 69.2), 35.2 (s), 21.6 (d, J = 0.9), 21.5 (d, J = 1.0), 14.8 (s), 14.0 (s); ^{31}P{^{1}H}($CDCl_3$, 25 °C) δ 32.5 (s).

4-[Bis(4-methylphenyl)phosphinyl]-3,4-dihydro-2*H*-1-benzopyran-2-one (4). The general procedure (method A) was followed with coumarin (0.064 g, 0.44 mmol) and ditolylphosphine oxide (0.1 g, 0.43 mmol). Temperature = 130 °C; time = 35 min; initial power level = 100 W. Chromatography: (silica) 19.0 g; hexane/THF (gradient 20:80−0:100). R_f = 0.47 (hexane/THF = 20:80). Yield = 0.12 g (73%) of a white powder, mp = 268−272 °C. Anal. Calcd for $C_{23}H_{21}O_3P$: C, 73.39; H, 5.62. Found: C, 73.40; H, 5.96. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.69 (m, 2H), 7.41 (m, 2H), 7.32 (m, 2H), 7.25−7.19 (m, 3H), 6.99 (d, 1H, J = 8.1), 6.87 (t, 1H, J = 7.5), 6.67 (dt, 1H, J = 7.7, 2.0), 3.88 (ddd, 1H, J = 9.9, 8.0, 1.8), 3.21 (ddd, 1H, J = 16.8, 9.5, 1.8), 2.95 (ddd, 1H, J = 29.7, 16.7, 8.0), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 165.6 (d, J = 3.0), 152.6 (d, J = 4.6), 143.12 (d, J = 2.7), 143.10 (d, J = 2.7), 131.8 (d, J = 9.1), 131.6 (d, J = 9.3), 129.7 (d, J = 12.0), 129.5 (d, J = 4.0), 129.3 (d, J = 12.1), 129.2 (d, J = 3.0), 126.6 (d, J = 99.9), 125.5 (d, J = 100.5), 123.9 (d, J = 2.6), 117.6 (d, J = 2.5), 117.5 (d, J = 5.6), 37.9 (d, J = 66.0), 28.8 (d, J = 2.1), 21.66 (d, J = 1.3), 21.65 (d, J = 1.3); ^{31}P{^{1}H} ($CDCl_3$, 25 °C) δ 31.3 (s).

6-Methyl-4-[bis(4-methylphenyl)phosphinyl]-3,4-dihydro-2*H*-1-benzopyran-2-one (5). The general procedure (method A) was followed with 6-methyl coumarin (0.069 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C; time = 35 min; initial power level = 100 W. Chromatography: (silica) 19.0 g; hexane/THF (gradient 50:50−0:100). R_f = 0.79 (hexane/THF = 20:80). Yield = 0.12 g (71%) of a white powder, mp = 275−277 °C. Anal. Calcd for $C_{24}H_{23}O_3P$: C, 73.83; H, 5.94. Found: C, 73.53; H, 6.01. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.68 (m, 2H), 7.41 (m, 2H), 7.33 (m, 2H), 7.21 (m, 2H), 7.02 (m, 1H), 6.87 (m, 1H), 6.41 (s, 1H), 3.79 (ddd, 1H, J = 12.1, 8.0, 2.0), 3.19 (ddd, 1H, J = 16.8, 9.5, 1.8), 2.94 (ddd, 1H, J = 30.0, 16.8, 8.2), 2.43 (s, 3H), 2.40 (s, 3H), 2.09 (s, 3H); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 165.8 (d, J = 3.1), 150.4 (d, J = 4.6), 143.07 (d, J = 2.8), 143.04 (d, J = 2.8), 133.3 (d, J = 2.7), 131.9 (d, J = 9.1), 131.6 (d, J = 9.2), 130.0 (d, J = 4.0), 129.7 (d, J = 3.0), 129.6 (d, J = 12.0), 129.2 (d, J = 12.1), 126.6 (d, J = 99.7), 125.6 (d, J = 100.4), 117.2 (d, J = 2.5), 117.0 (d, J = 4.8), 38.1 (d, J = 66.0), 28.8 (d, J = 2.1), 21.64 (d, J = 1.2), 21.62 (d, J = 1.3), 20.5 (s); ^{31}P{^{1}H} (CDCl3, 25 °C) δ 31.1(s).

Methyl 3-[Bis(4-methylphenyl)phosphinyl]butanoate (8). The general procedure (method A) was followed with methyl crotonate (46.0 μL, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 170 °C; time = 35 min; initial power level = 50 W. Chromatography: (silica) 19.0 g; ETOAc. R_f = 0.37 (EtOAc). Yield = 0.10 g of a colorless waxy solid (70%). Anal. Calcd for $C_{19}H_{23}O_3P$: C, 69.08; H, 7.02. Found: C, 69.35; H, 6.91. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.68 (m, 4H), 7.27 (m, 4H), 3.62 (s, 3H), 2.92 (m, 1H), 2.62 (ddd, 1H, J = 16.4, 10.1, 3.0), 2.43 (ddd, 1H, J = 16.5, 10.9, 5.5), 2.38 (s, 3H), 2.37 (s, 3H), 1.18 (dd, 3H, J = 16.0, 7.0); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 172.7 (d, J = 17.8), 142.24 (d, J = 2.7), 142.18 (d, J = 2.8), 131.1 (d, J = 9.1), 131.0 (d, J = 9.1), 129.5 (d, J = 12.2), 129.4 (d, J = 12.3), 128.4 (d, J = 98.2), 128.3 (d, J = 99.6), 51.9 (s), 34.3 (s), 29.4 (d, J = 73.3), 21.55 (d, J = 1.2), 21.54 (d, J = 1.2), 12.9 (d, J = 2.7); ^{31}P{^{1}H} ($CDCl_3$, 25 °C) δ 36.0(s).

Dimethyl-2-[bis(4-methylphenyl)phosphinyl]succinate (9). The general procedure (method A) was followed with methyl fumarate (0.062 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 110 °C; time = 35 min; initial power level setting 50 W. Chromatography: silica (5.0 g), ETOAc. R_f = 0.41 (EtOAc). Yield = 0.145 g of a white powder (89%), mp = 94−95 °C. Anal. Calcd for $C_{20}H_{23}O_5P$: C, 64.17; H, 6.19. Found: C, 64.41; H, 6.03. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.71 (m, 4H), 7.29 (m, 4H), 4.00 (ddd, 1H, J = 14.5, 11.3, 3.1), 3.64 (s, 3H), 3.44 (s, 3H), 3.13 (ddd, 1H, J = 17.5, 11.8, 5.8), 2.77 (ddd, 1H, J = 17.6, 8.50, 3.14), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 172.0 (d, J = 15.7), 169.3 (d, J = 3.3), 143.0 (d, J = 2.7), 142.9 (d, J = 2.7), 131.6 (d, J = 9.7), 131.4 (d, J = 9.7), 129.5 (d, J = 12.8), 129.2 (d, J = 12.4), 127.6 (d, J = 104.9), 126.8 (d, J = 104.9), 52.3 (s), 52.2 (s), 44.8 (d, J = 58.4), 30.8 (s), 21.63 (d, J = 1.1), 21.61 (d, J = 1.1); ^{31}P{^{1}H} ($CDCl_3$, 25 °C) δ 29.9 (s). The title compound was also prepared using dimethyl maleate (54.4 μL, 0.43 mmol): Temperature = 110 °C; time = 35 min; power = 50 W. Yield = 0.12 g (74%). The title compound was also prepared using method B. Triturating methyl fumarate (0.062 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol) at 110 °C for 35 min afforded 85% of the phospha-Michael adduct as determined by ^{1}H NMR spectroscopy using anisole as an internal standard.

4-[Bis(4-methylphenyl)phosphinyl]-4-[4-hydroxy-3-methoxyphenyl]butan-2-one (10). The general procedure (method A) was followed with 3-methoxy-4-hydroxybenzalacetone (0.083 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C; time = 35 min; power = 50 W. Chromatography: silica (19.0 g), THF/hexane (70:30). R_f = 0.28 (THF/hexane 70:30). Yield = 0.15 g of a white powder (82%), mp = 158−161 °C. Anal. Calcd for $C_{25}H_{27}O_4P$: C, 71.08; H, 6.44. Found: C, 71.11; H, 6.23. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.78 (m, 2H), 7.33 (m, 4H), 7.06 (m, 2H), 6.85 (m, 1H), 6.74 (m, 2H), 5.65 (s, 1H), 4.09 (ddd, 1H, J = 10.4, 7.7, 2.8), 3.75 (s, 3H), 3.24 (ddd, 1H, J = 17.8, 10.3, 5.1), 2.89 (ddd, 1H, J = 17.8, 10.9, 2.8), 2.41 (s, 3H), 2.28 (s, 3H), 1.96 (s, 3H); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 205.8 (d, J = 13.0), 146.6 (d, J = 1.9), 145.0 (d, J = 2.4), 142.4 (d, J = 2.7), 141.8 (d, J = 2.7), 131.3 (d, J = 8.9), 131.1 (d, J = 9.2), 129.6 (d, J = 11.6), 128.8 (d, J = 12.1), 128.4 (d, J = 102.7), 128.3 (d, J = 96.7), 127.4 (d, J = 5.6), 122.7 (d, J = 6.4), 114.5 (d, J = 1.7), 112.4 (d, J = 5.1), 55.8 (s), 43.7 (s), 40.8 (d, J = 69.7), 30.7 (s), 21.6 (d, J = 0.9), 21.4 (d, J = 1.0); ^{31}P{^{1}H} ($CDCl_3$, 25 °C) δ 34.4 (s).

3-[Bis(4-methylphenyl)phosphinyl]-1,3-diphenylpropan-1-one (11). The general procedure (method A) was followed with (*E*)-1,3-diphenyl-2-propenone (0.090 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 135 °C; time = 35 min; power = 100 W. Chromatography: silica (19.0 g), hexane/THF (1:1). R_f = 0.27 (hexane/THF 1:1). Yield = 0.16 g of a white powder (84%), mp = 187−189 °C. Anal. Calcd for $C_{29}H_{27}O_2P$: C, 79.43; H, 6.21. Found: C, 79.08; H, 6.53. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.85 (m, 4H), 7.47 (m, 1H), 7.40 (m, 2H), 7.35 (m, 4H), 7.30 (m, 2H), 7.15 (m, 2H), 7.09 (m, 1H), 7.04 (m, 2H), 4.43 (ddd, 1H, J = 9.9, 7.2, 2.6), 3.99 (ddd, 1H, J = 18.0, 10.8, 4.2), 3.38 (ddd, 1H, J = 18.0, 11.4, 2.4),

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2.36 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 196.8 (d, J = 13.4), 142.4 (d, J = 2.7), 141.7 (d, J = 2.9), 136.5 (s), 136.3 (d, J = 5.6), 133.2 (s), 131.3 (d, J = 8.9), 131.0 (d, J = 9.5), 129.9 (d, J = 6.2), 129.6 (d, J = 11.8), 128.8 (d, J = 11.8), 128.7 (d, J = 102.7), 128.5 (s), 128.4 (d, J = 97.0), 128.2 (d, J = 2.3), 128.1 (s), 126.9 (d, J = 2.3), 41.2 (d, J = 69.1), 39.2 (s), 21.5 (s), 21.4 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 34.5 (s).

3-[Bis(4-methylphenyl)phosphinyl]-1,3-bis(4-methylphenyl)propan-1-one (12). The general procedure (method A) was followed with *trans*-4,4′-dimethylchalcone (0.105 g, 0.44 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 135 °C; time = 35 min; power = 100 W. Chromatography: silica (5.5 g), hexane/THF (gradient 90:10−20:80). R_f = 0.35 (hexane/THF 50:50). Yield = 0.19 g of a white powder (94%), mp = 191−193 °C. Anal. Calcd for $C_{31}H_{31}O_2P$: C, 79.81; H, 6.70. Found: C, 79.58; H, 6.33. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.82 (m, 2H), 7.72 (m, 2H), 7.37 (m, 2H), 7.27 (m, 4H), 7.15 (m, 2H), 7.05 (m, 2H), 6.95 (m, 2H), 4.40 (ddd, 1H, J = 9.9, 7.2, 2.6), 3.93 (ddd, 1H, J = 17.7, 10.5, 4.2), 3.31 (ddd, 1H, J = 18.0, 11.1, 2.3), 2.36 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 196.5 (d, J = 13.4), 144.0 (s), 142.2 (d, J = 2.9), 141.6 (d, J = 2.9), 136.4 (d, J = 2.1), 134.1 (s), 133.2 (d, J = 5.7), 131.3 (d, J = 9.0), 131.1 (d, J = 9.0), 129.7 (d, J = 5.6), 129.6 (d, J = 11.8), 129.1 (s), 129.0 (d, J = 1.7), 128.9 (d, J = 102.7), 128.8 (d, J = 11.8), 128.7 (d, J = 96.5), 128.2 (s), 40.7 (d, J = 69.5), 39.1 (s), 21.57 (s), 21.53 (s), 21.47 (s), 21.0 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 34.5 (s).

3-[Bis(4-methylphenyl)phosphinyl]-1,3-bis(4-methoxyphenyl)propan-1-one (13). The general procedure (method A) was followed with *trans*-4,4′-dimethoxychalcone (0.116 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 135 °C; time = 35 min; power = 100 W. Chromatography: silica (5.0 g), hexane/THF (gradient 90:10−10:90). R_f = 0.45 (hexane/THF 40:60). Yield = 0.17 g of a white powder (79%), mp = 198−200 °C. Anal. Calcd for $C_{31}H_{31}O_4P$: C, 74.68; H, 6.27. Found: C, 74.94; H, 6.25. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.82 (m, 4H), 7.32 (m, 6H), 7.05 (m, 2H), 6.82 (m, 2H), 6.69 (m, 2H), 4.38 (ddd, 1H, 9.7, 7.1, 2.2), 3.90 (ddd, 1H, J = 17.4, 10.4, 4.2), 3.26 (ddd, 1H, J = 17.7, 11.1, 2.0), 3.79 (s, 3H), 3.68 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 195.4 (d, J = 13.4), 163.6 (s), 158.4 (d, J = 2.3), 142.2 (d, J = 2.7), 141.6 (d, J = 2.9), 131.2 (d, J = 8.9), 131.0 (d, J = 9.5), 130.9 (d, J = 6.2), 130.4 (s), 129.7 (s), 129.6 (d, J = 11.2), 128.9 (d, J = 102.6), 128.8 (d, J = 11.8), 128.6 (d, J = 96.4), 128.3 (d, J = 5.6), 113.7 (d, J = 1.2), 113.6 (s), 55.4 (s), 55.1 (s), 40.3 (d, J = 70.1), 38.8 (s), 21.5 (s), 21.4(s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 34.7 (s).

3-[Bis(4-methylphenyl)phosphinyl]-1-(4-methoxyphenyl)-3-(3-nitrophenyl)propan-1-one (14). The general procedure (method A) was followed with *trans*-4′-methoxy-3-nitrochalcone (0.125 g, 0.44 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C; time = 20 min; power = 150 W. Chromatography: silica (19.0 g), gradient EtOAc/hexane (30:70−80:20). R_f = 0.54 (EtOAc/hexane = 80:20). Yield = 0.20 g of a white powder (90%), mp = 202−204 °C. Anal. Calcd for $C_{30}H_{28}NO_5P$: C, 70.17; H, 5.50. Found: C, 69.83; H, 5.48. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 8.13 (m, 1H), 7.95 (m, 1H), 7.86 - 7.78 (m, 5H), 7.38−7.31 (m, 5H), 7.06 (m, 2H), 6.84 (m, 2H), 4.51 (ddd, 1H, J = 10.8, 7.0, 2.4), 3.96 (ddd, 1H, J = 18.1, 10.7, 4.3), 3.81 (s, 3H), 3.35 (ddd, 1H, J = 18.1, 10.5, 2.4), 2.38 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 194.6 (d, J = 13.0), 163.9 (s), 147.8 (d, J = 1.9), 142.8 (d, J = 2.8), 142.3 (d, J = 2.8), 138.8 (d, J = 5.4), 135.5 (d, J = 5.0), 131.1 (d, J = 9.0), 130.6 (d, J = 9.3), 130.4 (s), 129.8 (d, J = 11.8), 129.2 (d, J = 1.2), 129.1 (d, J = 12.1), 129.1 (d, J = 2.0), 127.9 (d, J = 103.2), 127.5 (d, J = 98.8), 125.1 (d, J = 5.8), 121.9 (d, J = 2.2), 113.8 (s), 55.5 (s), 41.3 (d, J = 67.6), 38.3 (s), 21.6 (d, J = 1.1), 21.4 (d, J = 1.1); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 34.6 (s).

3-[Bis(4-methylphenyl)phosphinyl]-3-(4-methoxyphenyl)-1-(4-nitrophenyl)propan-1-one (15). The general procedure (method A) was followed with *trans*-4′-nitro-4-methoxychalcone (0.125 g, 0.44 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C; time = 20 min; power = 140 W. Chromatography: silica (19.0 g), EtOAc/hexane (gradient 10:90−80:20). R_f = 0.74 (EtOAc/hexane = 80:20). Yield = 0.17 g of a white powder (76%), mp = 210−215 °C. Anal. Calcd for $C_{30}H_{28}NO_5P$: C, 70.17; H, 5.50. Found: C, 70.28; H, 5.40. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 8.21 (m, 2H), 7.96 (m, 2H), 7.81 (m, 2H), 7.34−7.27 (m, 6H), 7.07 (m, 2H), 6.70 (m, 2H), 4.31 (ddd, 1H, J = 10.3, 7.3, 2.9), 3.92 (ddd, 1H, J = 18.0, 10.4, 5.0), 3.71 (s, 3H), 3.39 (ddd, 1H, J = 17.9, 10.3, 2.8), 2.38 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 196.0 (d, J = 13.7), 158.7 (d, J = 2.3), 150.4 (s), 142.6 (d, J = 2.7), 141.9 (d, J = 2.7), 140.9 (s), 131.2 (d, J = 9.0), 131.0 (d, J = 9.0), 130.8 (d, J = 5.4), 129.7 (d, J = 11.8), 129.1 (s), 129.0 (d, J = 11.7), 128.3 (d, J = 101.0), 128.3 (d, J = 99.5), 127.7 (d, J = 5.6), 123.7 (s), 113.9 (d, J = 1.5), 55.1 (s), 40.6 (d, J = 69.4), 39.9 (s), 21.6 (d, J = 1.2), 21.5 (d, J = 1.2); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 33.0 (s).

Bis(4-methylphenyl)[1-phenyl-2-(phenylsulfonyl)ethane]-phosphine Oxide (16). The general procedure (method A) was followed with phenyl *trans*-styryl sulfone (0.11 g, 0.45 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 125 °C; time = 35 min; power = 50 W. Chromatography: silica (19.0 g), hexane/THF (4:6). R_f = 0.39. Yield = 0.10 g of a white powder (49%), mp = 284−286 °C. Anal. Calcd for $C_{28}H_{27}O_3PS$: C, 70.87; H, 5.73. Found: C, 70.94; H, 5.79. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.82 (m, 2H), 7.44 (m, 2H), 7.38 (m, 3H), 7.22 (m, 2H), 7.16 (m, 2H), 7.02−6.94 (m, 7H), 4.09 (ddd, 1H, J = 11.3, 9.1, 1.9), 4.01 (ddd, 1H, J = 14.9, 12.6, 2.6), 3.56 (ddd, 1H, J = 14.9, 9.8, 1.7), 2.46 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.1 (d, J = 2.8), 142.2 (d, J = 2.9), 139.6 (s), 133.1 (s), 132.2 (d, J = 6.0), 131.4 (d, J = 8.9), 131.0 (d, J = 9.5), 130.0 (d, J = 11.8), 129.8 (d, J = 5.2), 128.8 (d, J = 12.4), 128.8 (s), 128.1 (d, J = 2.1), 127.7 (s), 127.4 (d, J = 2.6), 127.4 (d, J = 104.5), 126.7 (d, J = 98.1), 56.3 (s), 42.5 (d, J = 63.0), 21.7 (d, J = 1.1), 21.5 (d, J = 1.2); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 33.0 (s).

3-[Bis(4-methylphenyl)phosphinyl]-3-phenylpropanenitrile (17). The general procedure (method A) was followed with cinnamonitrile (54.0 μL, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 175 °C; time = 35 min; power = 50 W. Chromatography: silica (19.0 g), hexane/THF (gradient 90:10−30:70). R_f = 0.27 (hexane/THF 50:50). Yield = 0.11 g of a white powder (70%), mp = 225−228 °C. Anal. Calcd for $C_{23}H_{22}NOP$: C, 76.86; H, 6.17. Found: C, 76.90; H, 6.55. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.78 (m, 2H), 7.37 (m, 2H), 7.29−7.24 (m, 7H), 7.06 (m, 2H), 3.70 (ddd, 1H, J = 11.8, 7.8, 3.9), 3.11 (ddd, 1H, J = 17.2, 12.0, 6.9), 2.87 (ddd, 1H, J = 17.3, 6.5, 3.7), 2.44 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.2 (d, J = 2.8), 142.5 (d, J = 2.9), 133.5 (d, J = 5.2), 131.2 (d, J = 9.0), 131.1 (d, J = 9.4), 129.9 (d, J = 11.8), 129.4 (d, J = 5.3), 129.0 (d, J = 12.5), 128.8 (d, J = 1.7), 128.2 (d, J = 2.2), 127.1 (d, J = 98.2), 127.0 (d, J = 105.0), 117.8 (d, J = 19.0), 43.8 (d, J = 66.0), 21.6 (d, J = 1.1), 21.5 (d, J = 1.2), 19.5 (d, J = 2.3); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 31.3 (s)

3-[Bis(4-methylphenyl)phosphinyl]-3-[(4-dimethylamino)-phenyl]propanenitrile (18). The general procedure (method A) was followed with (4-dimethylamino)cinnamonitrile (0.074 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 200 °C; time = 35 min; power = 150 W. Chromatography: silica (19.0 g), hexane/THF (1:1). R_f = 0.26. Yield = 0.15 g of a white powder (87%), mp = 204−208 °C. Anal. Calcd for $C_{25}H_{27}N_2OP$: C, 74.61; H, 6.76. Found: C, 74.90; H, 7.06. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.74 (m, 2H), 7.34 (m, 4H), 7.13 (m, 2H), 7.08 (m, 2H), 6.60 (m, 2H), 3.63 (ddd, 1H, J = 12.0, 8.4, 3.6), 3.02 (ddd, 1H, J = 18.9, 12.0, 6.9), 2.91 (s, 6H), 2.85 (ddd, 1H, J = 17.4, 6.6, 3.8), 2.43 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 150.2 (d, J = 1.8), 142.9 (d, J = 2.9), 142.2 (d, J = 2.9), 131.3 (d, J = 8.9), 131.2 (d, J = 9.7), 130.1 (d, J = 5.0), 129.8 (d, J = 11.5), 129.0 (d, J = 12.4), 127.7 (d, J = 96.8), 127.5 (d, J = 104.5), 120.4 (d, J = 5.0), 118.2 (d, J = 19.3), 112.6 (d, J = 1.5), 42.9 (d, J = 68.2), 40.4 (s), 21.6 (d, J = 1.2), 21.5 (d, J = 1.4), 19.7 (d, J = 3.3); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 31.5 (s)

(2-Nitro-1-phenylethyl)-bis(4-methylphenyl)phosphine Oxide (19). The general procedure (method A) was followed with β-nitrostyrene (0.064 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C; time = 35 min; power = 100 W. Chromatography: silica (19.0 g), hexane/THF (gradient 90:10−10:90). R_f = 0.37 (hexane/THF 50:50). Yield = 0.11 g of a white powder (68%), mp = 192−194 °C. Anal. Calcd for $C_{22}H_{22}NO_3P$: C, 69.65; H, 5.84. Found: C, 69.39; H, 5.92. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.85 (m, 2H), 7.39 (m, 2H), 7.29 (m, 4H), 7.21 (m, 3H), 7.06 (m, 2H), 5.07 (ddd, 1H, J = 13.8, 11.8, 3.8), 4.75 (ddd, 1H, J = 13.8,

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6.0, 3.3), 4.36 (ddd, 1H, J = 11.9, 10.4, 3.4), 2.44 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.3 (d, J = 2.9), 142.6 (d, J = 2.9), 132.0 (d, J = 5.6), 131.2 (d, J = 9.7), 131.1 (d, J = 9.5), 130.0 (d, J = 11.9), 129.5 (d, J = 5.1), 129.1 (d, J = 12.4), 128.7 (d, J = 1.7), 128.2 (d, J = 2.3), 127.0 (d, J = 104.4), 127.0 (d, J = 98.8), 76.0 (d, J = 5.6), 46.1 (d, J = 63.9), 21.6 (d, J = 1.2), 21.5 (d, J = 1.1); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 30.2

Dimethyl 2-(1-[Bis(4-methylphenyl)phosphinyl]ethyl)-malonate (20). The general procedure (method A) was followed with dimethyl ethylidenemalonate (61.0 μL, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 150 °C; time = 25 min, 100 W. Chromatography: silica (5.6 g), EtOAc. R_f = 0.57. Yield = 0.15 g of a colorless gel (90%). Anal. Calcd for $C_{21}H_{25}O_5P$: C, 64.94; H, 6.49. Found: C, 64.67; H, 6.73. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.69 (m, 4H), 7.29 (m, 4H), 3.81 (dd, 1H, J = 9.6, 6.6), 3.69 (s, 3H), 3.48 (s, 3H), 3.29 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.24 (dd, 3H, J = 15.6, 7.2); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 168.6 (d, J = 9.7), 168.1 (d, J = 8.9), 142.4 (d, J = 2.7), 142.3 (d, J = 2.9), 131.4 (d, J = 9.0), 131.3 (d, J = 9.5), 129.4 (d, J = 11.8), 129.3 (d, J = 11.8), 128.4 (d, J = 98.6), 127.7 (d, J = 99.8), 52.6 (s), 52.5 (s), 50.4 (s), 33.0 (d, J = 71.1), 21.6 (d, J = 1.2), 21.5 (d, J = 1.1), 11.1 (d, J = 1.7); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 34.2 (s).

2-([Bis(4-methylphenyl)phosphinyl]phenylmethyl)-propanedinitrile (21). The general procedure (method A) was followed with benzylidenemalononitrile (0.067 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 65 °C; time = 45 min; power = 50 W. Chromatography: silica (19.0 g), hexane/THF (1:1). R_f = 0.21 (hexane/THF 1:1). Yield = 0.12 g of a white powder (72%), mp = 196−198 °C. Anal. Calcd for $C_{24}H_{21}N_2OP$: C, 74.99; H, 5.51. Found: C, 75.16; H, 5.30. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.81 (m, 2H), 7.39−7.28 (m, 9H), 7.07 (m, 2H), 4.69 (t, 1H, J = 7.5), 3.95 (t, 1H, J = 7.8), 2.44 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.8 (d, J = 2.9), 143.0 (d, J = 2.9), 131.4 (d, J = 9.6), 131.3 (d, J = 9.4), 131.0 (d, J = 4.0), 130.0 (d, J = 12.3), 129.8 (d, J = 5.2), 129.3 (d, J = 1.8), 129.2 (d, J = 1.0), 129.1 (d, J = 12.8), 126.8 (d, J = 100.6), 126.1 (d, J = 107.4), 111.5 (d, J = 8.5), 111.3 (d, J = 8.6), 47.3 (d, J = 63.2), 24.8 (d, J = 1.7), 21.7 (d, J = 1.2), 21.5 (d, J = 1.2); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 28.8 (s). The title compound was also prepared following method B. Trituration of benzylidenemalononitrile (0.067 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol) at 65 °C for 1 h afforded 91% of the phospha-Michael adduct as determined by ^1H NMR spectroscopy using anisole as an internal standard.

Ethyl 2-Cyano-3-[bis(4-methylphenyl)phosphinyl]-3-methyl-buanoate (22). The general procedure (method A) was followed with ethyl 2-cyano-3-methyl-2-butenoate (0.066 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 25 °C; time = 12 h; no irradiation. Chromatography: silica (19.0 g), hexane/THF (gradient 90:10−50:50). R_f = 0.36 (hexane/THF 50:50). Yield = 0.15 g of a white powder (90%), mp = 191−193 °C. Anal. Calcd for $C_{22}H_{26}NO_3P$: C, 68.92; H, 6.83. Found: C, 69.28; H, 6.63. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.90 (m, 4H), 7.32 (m, 4H), 4.14 (m, 1H), 4.03 (m, 1H), 3.99 (d, 1H, J = 7.8), 2.41 (s, 3H), 2.40 (s, 3H), 1.53 (d, 3H, J = 15.0), 1.42 (d, 3H, J = 14.4), 1.26 (t, 3H, J = 7.2); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 164.5 (d, J = 7.9), 143.0 (d, J = 2.8), 142.8 (d, J = 2.8), 132.4 (d, J = 8.6), 132.3 (d, J = 8.6), 129.4 (d, J = 9.0), 129.3 (d, J = 9.0), 126.5 (d, J = 97.0), 126.3 (d, J = 95.6), 114.8 (d, J = 9.5), 62.7 (s), 43.2 (d, J = 3.6), 40.0 (d, J = 68.8), 22.1 (s), 21.6 (s), 21.5 (s), 20.2 (s), 13.8 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 33.5 (s).

Diethyl 2-(2-[Bis(4-methylphenyl)phosphinyl]propan-2-yl)-malonate (23). The general procedure (method A) was followed with diethyl isopropylidenemalonate (86.0 μL, 0.44 mmol) and ditolylphosphine oxide (0.100 g, 0.43 mmol). Temperature = 130 °C; time = 35 min; power = 50 W. Chromatography: silica (5.6 g); hexane/EtOAc (30:70). R_f = 0.18 (hexane/EtOAc 30:70). Yield = 0.18 g of a white powder (96%), mp = 92−94 °C. Anal. Calcd for $C_{24}H_{31}O_5P$: C, 66.96; H, 7.26. Found: C, 67.24; H, 7.40. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.89 (m, 4H), 7.28 (m, 4H), 3.99 (m, 4H), 3.85 (d, 1H, J = 7.5), 2.39 (s, 6H), 1.49 (d, 6H, J = 15.5), 1.19 (d, 6H, J = 7.2); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 167.1 (d, J = 10.4), 142.1 (d, J = 2.7), 132.5 (d, J = 8.3), 129.0 (d, J = 11.5), 127.4 (d, J = 94.0), 61.2 (s), 54.4 (d, J = 2.4), 40.1 (d, J = 69.4), 21.5 (d, J = 0.8), 20.4 (s), 13.9 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 35.3 (s).

2-(2-[Bis(4-methylphenyl)phosphinyl]propan-2-yl)-propanedinitrile (24). The general procedure (method A) was followed with isopropylidenemalononitrile (48.0 μL, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 25 °C; time = 12 h; no irradiation. Chromatography: silica (19.0 g), hexane/THF (gradient 90:10−40:60). R_f = 0.39 (50:50). Yield = 0.12 g of a white powder (82%), mp = 134−138 °C. Anal. Calcd for $C_{20}H_{21}N_2OP$: C, 71.41; H, 6.29. Found: C, 71.76; H, 6.23. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.90 (m, 4H), 7.35 (m, 4H), 4.49 (d, 1H, J = 7.0), 2.42 (s, 6H), 1.52 (d, 6H J = 13.9); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.5 (d, J = 2.9), 132.1 (d, J = 8.7), 129.7 (d, J = 12.0), 125.5 (d, J = 98.2), 111.1 (d, J = 8.4), 40.3 (d, J = 67.5), 30.6 (d, J = 4.3), 21.6 (d, J = 1.0), 21.3 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 31.7 (s).

2-([Bis(4-methylphenyl)phosphinyl](furan-2-yl)methyl)-propanedinitrile (25). The general procedure (method A) was followed with (2-furanylmethylene)malononitrile (0.062 g, 0.43 mmol) and ditolylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 90 °C; time = 35 min; power = 50 W. Chromatography: silica (5.6 g), hexane/THF (50:50). R_f = 0.50 (hexane/EtOAc 50:50). Yield = 0.14 g of a white powder (87%), mp = 161−163 °C. Anal. Calcd for $C_{22}H_{19}N_2O_2P$: C, 70.58; H, 5.12. Found: C, 70.34; H, 5.43. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 7.71 (m, 2H), 7.41 (m, 2H), 7.36 (m, 3H), 7.20 (m, 2H), 6.34 (m, 1H), 6.32 (m, 1H), 4.82 (dd, 1H, J = 4.1, 4.1), 4.35 (dd, 1H, J = 12.8, 4.1), 2.43 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 143.9 (d, J = 2.9), 143.7 (d, J = 3.9), 143.6 (d, J = 2.3), 143.6 (d, J = 2.7), 131.9 (d, J = 10.1), 131.2 (d, J = 9.7), 129.9 (d, J = 12.2), 129.2 (d, J = 13.0), 126.6 (d, J = 103.2), 124.7 (d, J = 106.6), 111.9 (d, J = 5.1), 111.5 (d, J = 10.0), 111.4 (d, J = 2.3), 110.9 (d, J = 5.9), 42.4 (d, J = 64.0), 23.1 (d, J = 2.3), 21.71 (s), 21.66 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 28.2 (s).

3-[Bis(4-methoxyphenyl)phosphinyl]-1,3-diphenyl-1-propanone (28).[43] The general procedure (method A) was followed with (*E*)-1,3-diphenyl-2-propenone (0.079 g, 0.38 mmol) and bis(4-methoxyphenyl)phosphine oxide (0.10 g, 0.38 mmol). Temperature = 130 °C; time = 35 min; power = 100 W. Chromatography: silica (19.0 g), hexane/THF (gradient 40:60−100:0). R_f = 0.43 (hexane/THF 20:80). Yield = 0.17 g of a white powder (95%). mp = 180−183 °C. Anal. Calcd for $C_{29}H_{27}O_4P$: C, 74.03; H, 5.78. Found: C, 74.29; H, 5.49.

3-(Diphenylphosphinyl)-1,3-diphenyl-1-propanone (29).[43,44] The general procedure (method A) was followed with (*E*)-1,3-diphenyl-2-propenone (0.105 g, 0.50 mmol) and diphenylphosphine oxide (0.10 g, 0.49 mmol). Temperature = 130 °C; time = 35 min; power = 100 W. Chromatography: silica (19.0 g), EtOAc. R_f = 0.49 (EtOAc). Yield = 0.18 g of a white powder (89%). mp = 239−241 °C (lit. = 238 °C).[44]

3-[Bis[(4-trifluoromethyl)phenyl]phosphinyl]-1,3-diphenyl-1-propanone (30). The general procedure (method A) was followed with (*E*)-1,3-diphenyl-2-propenone (0.062 g, 0.30 mmol) and bis[(4-trifluoromethyl) phenyl]phosphine oxide (0.10 g, 0.30 mmol). Temperature = 130 °C; time = 35 min; power = 100 W. Chromatography: silica (19.0 g), hexane/THF (gradient 40:60−50:50). R_f = 0.46 (hexane/THF 60:40). Yield = 0.13 g of a white powder (80%), mp = 234−237 °C. Anal. Calcd for $C_{29}H_{21}F_6O_2P$: C, 63.74; H, 3.87. Found: C, 63.65; H, 3.85. Spectral data: ^1H ($CDCl_3$, 25 °C) δ 8.12 (m, 2H), 7.84 (m, 2H), 7.78 (m, 2H), 7.63 (m, 2H), 7.53 (m, 3H), 7.39 (m, 4H), 7.16 (m, 3H), 4.58 (ddd, 1H, J = 9.3, 6.6, 2.7), 3.98 (ddd, 1H, J = 15.0, 9.6, 5.4), 3.40 (ddd, 1H, J = 15.0, 12.0, 2.8); $^{13}C\{^1H\}$ ($CDCl_3$, 25 °C) δ 196.1 (d, J = 12.2), 136.1 (s), 135.5 (d, J = 98.2), 135.4 (d, J = 92.5), 135.1 (d, J = 5.6), 134.2 (qd, J = 33.1, 2.8), 133.7 (s), 133.6 (qd, J = 32.6, 2.7), 131.8 (d, J = 8.9), 131.4 (d, J = 8.9), 129.8 (d, J = 6.2), 128.7 (d, J = 2.7), 128.7 (s), 128.1 (s), 127.6 (d, J = 2.3), 126.0 (dq, J = 11.3, 3.7), 125.2 (dq, J = 11.8, 3.9), 123.4 (q, J = 272.5), 40.7 (d, J = 70.1), 38.9 (s); $^{31}P\{^1H\}$ ($CDCl_3$, 25 °C) δ 32.5 (s)

3-[Bis(2-methylphenyl)phosphinyl]-1,3-diphenyl-1-propanone (31). The general procedure (method A) was followed with (*E*)-1,3-diphenyl-2-propenone (0.091 g, 0.44 mmol) and bis(2-methyl phenylphosphine oxide (0.10 g, 0.43 mmol). Temperature = 130 °C;

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time = 35 min; power = 100 W. Chromatography: silica (19.0 g), hexane/THF (50:50). R_f = 0.69 (hexane/THF 50:50). Yield = 0.17 g of a white powder (89%), mp = 140−142 °C. Anal. Calcd for $C_{29}H_{27}O_2P$: C, 79.43; H, 6.21. Found: C, 79.16; H, 6.32. Spectral data: ^{1}H ($CDCl_3$, 25 °C) δ 7.92 (m, 2H), 7.82 (m, 1H), 7.51 (m, 2H), 7.39 (m, 5H), 7.29 (m, 1H), 7.20 (m, 2H), 7.11−7.01 (m, 4H), 6.93 (m, 1H), 4.69 (ddd, 1H, J = 10.5, 6.9, 1.9), 4.18 (ddd, 1H, J = 18.6, 10.8, 3.8), 3.71 (ddd, 1H, J = 18.6, 10.8, 2.0), 2.39 (s, 3H), 2.15 (s, 3H); ^{13}C{^{1}H} ($CDCl_3$, 25 °C) δ 197.0 (d, J = 13.0), 143.3 (d, J = 7.4), 141.8 (d, J = 8.5), 136.6 (d, J = 4.5), 136.5 (s), 133.4 (s), 132.7 (d, J = 10.7), 132.5 (d, J = 10.1), 131.8 (d, J = 2.7), 131.2 (s), 131.2 (d, J = 13.0), 131.1 (d, J = 92.0), 131.0 (d, J = 10.1), 130.1 (d, J = 96.5), 129.7 (d, J = 5.6), 128.6 (s), 128.2 (s), 127.0 (d, J = 2.9), 125.6 (d, J = 11.2), 125.0 (d, J = 12.4), 39.9 (s), 39.5 (d, J = 69.5), 21.4 (d, J = 3.9), 21.0 (d, J = 3.5); ^{31}P{^{1}H} ($CDCl_3$, 25 °C) δ 37.8 (s).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Greenberg, S.; Stephan, D. W. *Chem. Soc. Rev.* **2008**, *37*, 1482−1489.
(2) Tanaka, M. Homogeneous catalysis for H−P bond addition reactions. In *New Aspects in Phosphorus Chemistry IV*; Springer-Verlag: Berlin, 2004; Vol. *232*, pp 25−54.
(3) Keglevich, G.; Sipos, M.; Takacs, D.; Ludanyi, K. *Heteroat. Chem.* **2008**, *19*, 288−292.
(4) Enders, D.; Saint-Dizier, A.; Lannou, M. I.; Lenzen, A. *Eur. J. Org. Chem.* **2005**, 29−49.
(5) Xu, Q.; Han, L. B. *J. Organomet. Chem.* **2011**, *696*, 130−140.
(6) Coudray, L.; Montchamp, J. L. *Eur. J. Org. Chem.* **2008**, 3601−3613.
(7) Nagata, S.; Kawaguchi, S.; Matsumoto, M.; Kamiya, I.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 6637−6640.
(8) Ide, D. M.; Eastlund, M. P.; Jupe, C. L.; Stockland, R. A. Jr. *Curr. Org. Chem.* **2008**, *12*, 1258−1278.
(9) Staubitz, A.; Robertson, A. P. M; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023−4078.
(10) Negishi, E.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151−3182.
(11) Mimeau, D.; Delacroix, O.; Join, B.; Gaumont, A. C. *C. R. Chim.* **2004**, *7*, 845−854.
(12) Mimeau, D.; Gaumont, A. C. *J. Org. Chem.* **2003**, *68*, 7016−7022.
(13) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472.
(14) Berlicki, L.; Obojska, A.; Forlani, G.; Kafarski, P. *J. Med. Chem.* **2005**, *48*, 6340−6349.
(15) Bertenshaw, S. R.; Rogers, R. S.; Stern, M. K.; Norman, B. H.; Moore, W. M.; Jerome, G. M.; Branson, L. M.; McDonald, J. F.; McMahon, E. G.; Palomo, M. A. *J. Med. Chem.* **1993**, *36*, 173−176.
(16) Bigge, C. F.; Johnson, G.; Ortwine, D. F.; Drummond, J. T.; Retz, D. M.; Brahce, L. J.; Coughenour, L. L.; Marcoux, F. W.; Probert, A. W. *J. Med. Chem.* **1992**, *35*, 1371−1384.
(17) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158−169.
(18) Boëdec, A.; Sicard, H.; Dessolin, J.; Herbette, G.; Ingoure, S.; Raymond, C.; Belmant, C.; Kraus, J. *J. Med. Chem.* **2008**, *51*, 1747−1754.
(19) Boyer, S. H.; Jiang, H.; Jacintho, J. D.; Reddy, M. V.; Li, H.; Li, W.; Godwin, J. L.; Schulz, W. G.; Cable, E. E.; Hou, J.; Wu, R.; Fujitaki, J. M.; Hecker, S. J.; Erion, M. D. *J. Med. Chem.* **2008**, *51*, 7075−7093.
(20) Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7*, 629−647.
(21) Yang, Y.; Coward, J. K. *J. Org. Chem.* **2007**, *72*, 5748−5758.
(22) Feng, Y.; Coward, J. K. *J. Med. Chem.* **2006**, *49*, 770−788.
(23) Baumgartner, T.; Reau, R. *Chem. Rev.* **2006**, *106*, 4681−4727.
(24) Monge, S.; Canniccioni, B.; Graillot, A.; Robin, J. J. *Biomacromolecules* **2011**, *12*, 1973−1982.
(25) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652−663.
(26) Fernandez-Perez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119−2176.
(27) Metcalf, W. W.; van der Donk, W. A. *Annu. Rev. Biochem.* **2009**, *78*, 65−94.
(28) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99.
(29) Bunlaksananusorn, T.; Knochel, P. *Tetrahedron Lett.* **2002**, *43*, 5817−5819.
(30) Semenzin, D.; Etemad-Moghadam, G.; Albouy, D.; Diallo, O.; Koenig, M. *J. Org. Chem.* **1997**, *62*, 2414−2422.
(31) Stockland, R. A. Jr.; Taylor, R. I.; Thompson, L. E.; Patel, P. B. *Org. Lett.* **2005**, *7*, 851−853.
(32) The use of classic radical inhibitors such as 4-methoxyphenol did not quench the reaction. Furthermore, the use of 3-methoxy-4-hydroxybenzalacetone as the Michael acceptor successfully generated compound **10** in excellent yields.
(33) Skolimowski, J. J.; Quin, L. D.; Hughes, A. N. *J. Org. Chem.* **1989**, *54*, 3493−3496.
(34) Miller, R. C. *J. Org. Chem.* **1959**, *24*, 2013−2069.
(35) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 3690−3694.
(36) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 4277−4280.
(37) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550−5554.
(38) Wu, X. F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596−14602.
(39) Ducki, S.; Rennison, D.; Woo, M.; Kendall, A.; Chabert, J. F. D.; McGown, A. T.; Lawrence, N. J. *Bioorg. Med. Chem.* **2009**, *17*, 7698−7710.
(40) Narender, T.; Papi Reddy, K. *Tetrahedron Lett.* **2007**, *48*, 3177−3180.
(41) Supuran, C. T.; Popescu, A.; Ilisiu, M.; Costandache, A.; Banciu, M. D. *Eur. J. Med. Chem.* **1996**, *31*, 439−447.
(42) Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, *9*, 707−710.
(43) Feng, J. J.; Chen, X. F.; Shi, M.; Duan, W. L. *J. Am. Chem. Soc.* **2010**, *132*, 5562−5563.
(44) Trepohl, V. T.; Mori, S.; Itami, K.; Oestreich, M. *Org. Lett.* **2009**, *11*, 1091−1094.