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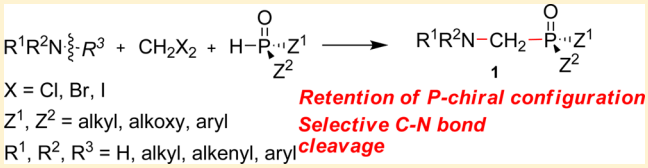
Catalyst-Free and Selective C−N Bond Functionalization: Stereospecific Three-Component Coupling of Amines, Dichloromethane, and >P(O)H Species Affording α-Aminophosphorus Compounds

Yalei Zhao,[§] Xiuling Chen,[§] Tieqiao Chen, Yongbo Zhou,* Shuang-Feng Yin,* and Li-Biao Han

State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha, 410082, People's Republic of China

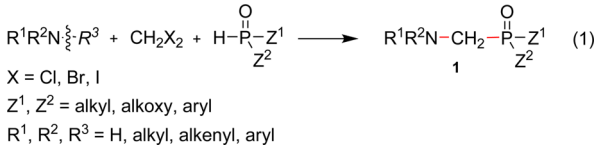
Supporting Information

ABSTRACT: Catalyst-free and selective C−N bond functionalization has been achieved through three-component coupling of amines, dihalomethane, and >P(O)H species. This reaction takes place stereospecifically with retention of configuration at phosphorus, which can produce various new optically active phosphorus analogues of α-amino acids.



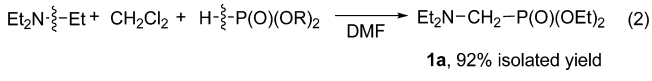
INTRODUCTION

Carbon−nitrogen (C−N) bonds are abundant in numerous organic compounds including natural products and fine chemicals.[1] It would therefore be important and useful to develop a method for C−N bond cleavage for constructing new compounds by organic synthesis.[2] However, C−N bonds are generally stable, which makes their functionalization difficult.[3] Considerable efforts have been devoted to resolve the challenge.[2,3] However, among the reported systems, transition metals and their complexes are generally required as catalysts to accomplish the cleavage and further functionalization of C−N bonds.[2,3] The limited availability and difficult removal of transition metals from products led to the development of alternative green metal-free catalytic systems, but they remain scarce.[4,5] Due to the interest in C−N activation and further functionalization, and combined with our previous work,[6] we accidentally discovered a catalyst-free and selective C−N cleavage, leading to an efficient alternative synthesis method to α-aminophosphorus compounds. α-Aminophosphorus compounds are structural analogoues to natural α-amino acids, which have wide applications in the research fields of physiological processes in living organisms, as well as diagnostic and therapeutic studies.[7] Over the past half century, numerous methods for the preparation of such compounds have been developed with the Kabachnik−Fields reaction and Pudovik reaction being the most popular choices.[8,9] However, in those systems, transition metals are generally required or the scope of starting materials is limited to aldehydes (ketones) or imines. Especially, there is no precedent for the stereospecific synthesis of P-chiral α-aminophosphorus compounds. Herein we report that, without the aid of any catalysts, selective C−N bond functionalization is achieved: by simply combining an amine, a >P(O)H compound (H-phosphonate, H-phosphinate, or secondary phosphine oxide), and dihalomethane, a one-pot three-component coupling reaction takes place stereospecifically and selectively to afford the α-aminophosphorus compounds **1** in high yields (eq 1).



RESULTS AND DISCUSSION

When a mixture of $(EtO)_2P(O)H$ (0.5 mmol), CH_2Cl_2 (0.5 mL), and Et_3N (1.5 mmol) in DMF (0.5 mL) is heated at 100 °C for 12 h, the unsymmetrical substituted product α-aminophosphonate **1a** is selectively obtained in 92% yield through C−N bond cleavage (eq 2). The use of other methylene halides also



produces the corresponding α-aminophosphonate **1a** in good to excellent yields under the same reaction conditions (CH_2Br_2, 91%; CH_2I_2, 86%; CH_2BrCl, 75%), but no corresponding coupling products can be obtained when dihalomethane is switched to other haloalkanes, such as $CHCl_3$, CH_3CHCl_2, $ClCH_2CH_2Cl$, or $CH_3CCl_2CH_3$. This reaction is highly solvent-dependent. In addition to DMF, under similar reaction conditions, **1a** can also be obtained from DMSO and MeCN in excellent yields, respectively. However, the reaction hardly proceeds in EtOAc, hexane, toluene, THF, dioxane, and ethanol.

As shown in Table 1, this reaction can be successfully applied to other substrates, indicating that this is a general method for

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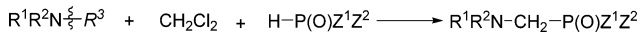
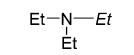
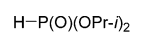
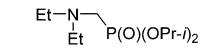
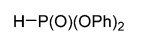
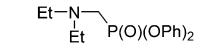
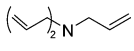
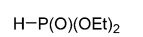
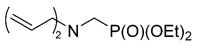
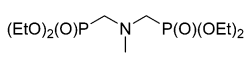
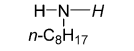
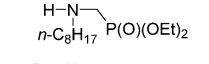
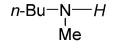
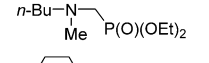
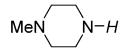
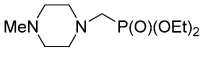
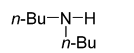
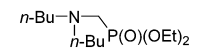
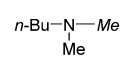
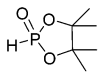
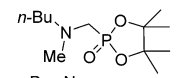
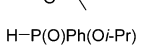
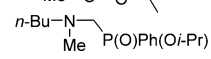
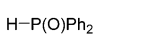
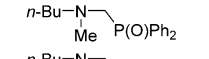
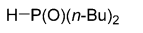
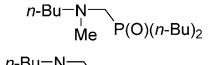
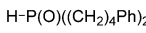
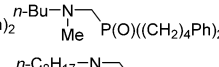
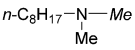
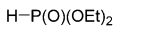
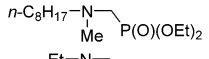
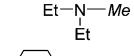
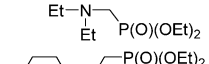
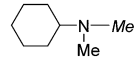
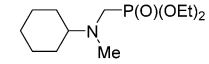
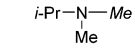
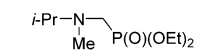
Table 1. One-Pot Three-Component Coupling Reactions Forming α-Aminophosphorus Compounds[a]



entry	amine	$H-P(O)Z^1Z^2$	product		% yield (selectivity)[b]
1				**1b**	95
2				**1c**	69
3				**1d**	73
4				**1e**	77
5				**1f**	81(98)
6				**1g**	96(98)
7				**1h**	93(98)
8				**1i**	92(98)
9			**1g**		95(98)
10				**1j**	90(98)
11				**1k**	91(98)
12				**1l**	94(98)
13				**1m**	93(98)
14				**1n**	91(98)
15				**1o**	87(98)
16				**1a**	83(85)
17				**1p**	92(99)
18				**1q**	80(96)
19				**1r**	89(99)
20				**1s**	89(99)
21				**1t**	82(96)
22			**1t**		65(85)
23			**1t**		70(67)

[a]A mixture of $HP(O)Z^1Z^2$ (0.5 mmol), amine (1.5 mmol), and CH_2Cl_2 (0.5 mL) in DMF (0.5 mL) was heated overnight in a sealed glass tube (75 °C for primary and secondary amines, 100 °C for tertiary amines). [b]Isolated yield based on $HP(O)Z^1Z^2$ used. Selectivity was determined on the basis of the ratio of the products calculated from ^{31}P NMR and/or GC analysis results of the mixture.

the preparation of a variety of α-aminophosphorus compounds. Besides $(EtO)_2P(O)H$, $(i\text{-}PrO)_2P(O)H$ and $(PhO)_2P(O)H$ can also react efficiently with Et_3N to give the corresponding coupling products **1b** and **1c** in satisfactory yields (entries 1 and 2). As to symmetrical tertiary amines, in addition to Et_3N, the use of triallylamine also produces the corresponding α-aminophosphonate in a good yield (entry 3). Moreover, for both triethylamine and triallylamine, only one of the three C−N bonds of the amine is cleaved to give the corresponding coupling products. The reaction with polyamine is noteworthy. For example, the use of urotropine produces a bisphosphorylamino compound selectively in high yields (entry 4). For primary and secondary amines, the N−H bond cleavage takes place predominantly to produce the corresponding coupling products (entries 5−8). No coupling products from the C−N bond cleavage can be detected from these reactions. In addition, such a high selectivity is also observed in the C−N bond cleavage with tertiary amines. For example, with *n*-$BuNMe_2$, regardless of the tiny electronic and steric difference between *n*-Bu and Me, an almost exclusive cleavage takes place at the N−Me bond to produce *n*-$BuMeNCH_2P(O)(OEt)_2$ in 95% yield (entry 9). Besides $HP(O)(OEt)_2$, other >P(O)H species, such as a cyclic H-phosphonate (entry 10), a H-phosphinate (entry 11), and secondary phosphine oxides (entries 12−14) all react efficiently and selectively with *n*-$BuNMe_2$ to give the corresponding α-aminophosphorus compounds in high yields. As expected, high selectivity for C−N bond cleavage (N−Me cleavage) is gained for dimethyloctylamine (entry 15), and a good selectivity preferring N−Me cleavage (85% selectivity) is also observed for diethylmethylamine $MeNEt_2$ (entry 16). Moreover, selective N−Me bond cleavages are achieved for amines bearing secondary alkyl groups (entries 17 and 18), and cyclic amines such as 1-methylpiperidine and 4-methylmorpholine (entries 19 and 20). However, with *t*-$BuNMe_2$ (entry 21), the selective cleavage of N−*t*-Bu rather than N−Me is observed. The selectivity is 96% preferring the N−*t*-Bu cleavage, which is striking considering the nearly perfect selective N−Me bond cleavage for *i*-$PrNMe_2$ (entry 16). Similarly, in the cases of Me_2NCH_2Ph and $Me_2NCH_2CH{=}CH_2$, which simultaneously bear two N−Me bonds, preferred cleavages for the $N-CH_2Ph$ (85% selectivity) and N−allyl bond (67% selectivity) occur (entries 20 and 21). Therefore, the ease of N−R cleavage in the coupling reactions follows the decreasing order of H, *t*-Bu, allyl, benzyl > Me > primary and secondary alkyl groups.[10]

Importantly, this one-pot three-component coupling reaction takes place highly stereospecifically to produce the corresponding P-chiral aminophosphorus compounds, a new class of phosphorus analogues of amino acids. They are difficult to be synthesized in high yields through other methods by employing the easily accessible optically pure P-chiral H-phosphinates as substrates (Table 2).[11a] One can see that (R_P)-**2a** and (R_P)-**2b** react efficiently with a variety of amines to produce the corresponding optically pure (S_P)-α-aminophosphinates selectively. The absolute configuration at the phosphorus atom of the product from dimethylcyclohexylamine with (R_P)-**2b** was determined unambiguously by X-ray analysis (Figure 1), showing that this three-component coupling takes place with retention of the configuration at phosphorus. On the other hand, from the reaction of **2a** (R_P/S_P = 60/40) with dimethylcyclohexylamine, the corresponding coupling product can be obtained with the same diastereomer's ratio, confirming that this coupling reaction proceeds stereospecifically. It is noted that this reaction also presents a rare example for stereospecific substitution reactions of optically active hydrogen phosphorus compounds because epimerization usually occurs during such reactions.[11b,c] This simple three-component coupling, taking place highly stereospecifically, has not been recognized previously.

The reaction mechanism of the above three-component coupling reaction was investigated thoroughly. First, the stoichiometry of the reaction was determined exactly by using

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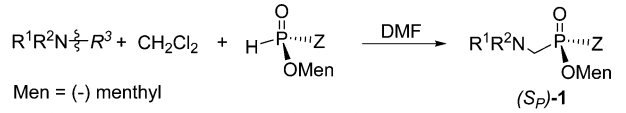
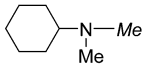
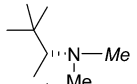
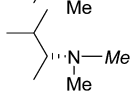
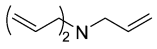
Table 2. One-Pot Three-Component Coupling Reactions Forming P-Chiral Aminophosphorus Compounds[a]



R^1R^2N-$\overset{S}{S}$-R^3	(R_P)-**2**	(S_P)-**1**	% yield (selectivity)[b]	ee (%)[c]
n-Bu–N(Me)–Me	(R_P)-**2a**	(S_P)-**1a**	95(98)	> 99
	(R_P)-**2b**	(S_P)-**1b**	94(98)	> 99
	(R_P)-**2a**	(S_P)-**1c**	96(99)	> 99
	(R_P)-**2b**	(S_P)-**1d**	95(99)	> 99
		(S_P)-**1e**	93(95)	> 99
		(S_P)-**1f**	90(96)	> 99
n-C_8H_{17}–N(H)–Me	(R_P)-**2a**	(S_P)-**1g**	75(99)	> 99
Me–N(Me)–CH_2Ph		(S_P)-**1h**	65(85)	> 99
Et_2N–Et		(S_P)-**1i**	98	> 99
		(S_P)-**1j**	72	> 99

[a]A mixture of (R_P)-**2** (0.2 mmol), amine (0.6 mmol), and CH_2Cl_2 (0.3 mL) in DMF (0.3 mL) was heated overnight in a sealed glass tube (75 °C for primary and secondary amines, 100 °C for tertiary amines). [b]Isolated yield based on (R_P)-**2** used. Selectivity was determined on the basis of the ratio of the products calculated from ^{31}P NMR and/or GC of the mixture. [c]Enantiomeric excess determined by ^1H and ^{31}P NMR.

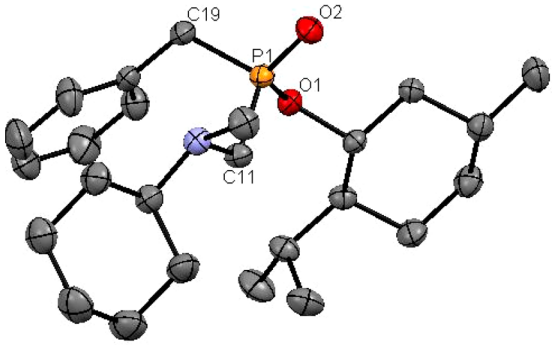
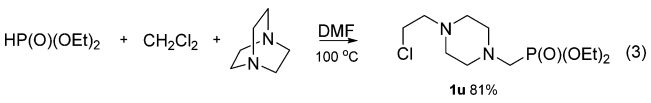


Figure 1. ORTEP drawing of (S_P)-**1d**. Hydrogen atoms are omitted for clarity; ellipsoids are drawn at 50% probability. Selected bond lengths (Å) and angles (deg): C11–P1 = 1.8134(13), C19–P1 = 1.8033(12), O1–P1 = 1.5933(10), O2–P1 = 1.4812(9), C1–O1–P1 = 121.91(7), O2–P1–O1 = 115.56(5), O2–P1–C19 = 112.44(6), O1–P1–C19 = 101.48(5), O2–P1–C11 = 114.82(6), O1–P1–C11 = 103.82(5), C19–P1–C11 = 107.47(6).

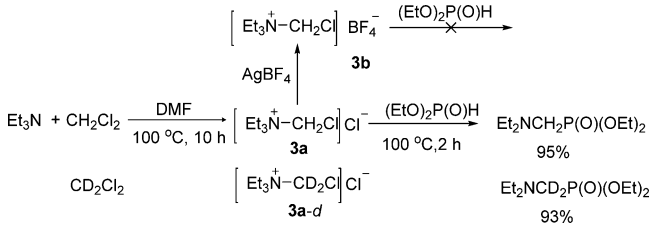
1,4-diazabicyclo[2.2.2]octane (DABCO) (eq 3). Heating a mixture of DABCO (1.5 mmol), $(EtO)_2P(O)H$ (0.5 mmol), and CH_2Cl_2 (0.5 mL) in DMF (0.5 mL) at 100 °C overnight resulted in a halogenated α-aminophosphorus compound in



81% yield based on $(EtO)_2P(O)H$. This result indicates that one α-aminophosphonate is produced, accompanied by one chloroalkane in the present system.

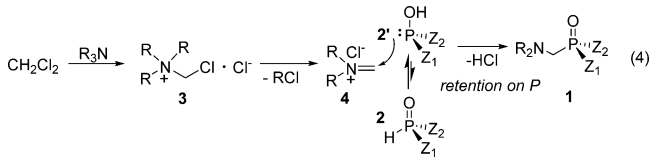
On the other hand, under the reaction conditions, CH_2Cl_2 reacts with Et_3N to form the corresponding 1-chloro-*N*,*N*,*N*-triethylmethaniminium chloride **3a** in 89% yield (reaction conditions: 100 °C in DMF for 10 h) as colorless crystals.[12] Importantly, the α-aminophosphonate can be obtained quantitatively by heating **3a** with an equal amount of diethyl phosphite in DMF at 100 °C for 2 h (Scheme 1). Instead of

Scheme 1. Reactions of Triethylamine with Dichloromethane Forming 3



CH_2Cl_2, an experiment using CD_2Cl_2 as the substrate confirms that the two protons of the methylene group of dichloromethane are not affected during the reaction, showing that the proton for the formation of the ammonium chloride comes from the hydrogen phosphonate. Moreover, the presence of the two chloro atoms in **3a** are essential for this reaction because the replacement of one chloro atom by BF_4, without nucleophilicity, fails to produce the α-aminophosphonate with $(EtO)_2P(O)H$ under similar reaction conditions.

On the basis of these observations and the literature,[13] the reaction sequences for the stereospecific three-component coupling are illustrated in eq 4. First, methaniminium chloride **3**



formed by the reaction of R_3N with CH_2Cl_2 is decomposed to produce methyleneammonium chloride **4**.[10] Intermediate **4** is an electrophile[14] which subsequently is attacked by the phosphorus of **2′**, a tautomer of **2**,[8e,k,15] to give the product with retention of configuration at phosphorus.

In summary, we have demonstrated a general and efficient three-component coupling of amines, dichloromethane, and >P(O)H species, producing the important α-aminophosphorus compounds in high yields. This reaction takes place stereospecifically with retention of configuration at phosphorus, which can readily produce various new chiral optically active phosphorus analogues of amino acids. This reaction also provides a novel C–N bond functionalization without the aid of any catalysts.

EXPERIMENTAL SECTION

General Information. Except where otherwise noted, all reactions were carried out in oven-dried Schlenk tubes under N_2 atmosphere with dry solvents under anhydrous conditions. Dry solvents were obtained by purification according to standard methods. Reagents were used as received unless otherwise noted. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a 500 MHz spectrometer (500 MHz for ^1H,

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125 MHz for ^{13}C, and 202 MHz for ^{31}P NMR spectroscopy) or a 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P NMR spectroscopy). $CDCl_3$ or C_6D_6 was used as the solvent. Chemical shifts for ^{1}H NMR are referred to internal Me_4Si (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity, integration, and coupling constant (Hz). Data for ^{13}C NMR are reported in ppm relative to the center line of a triplet at 77.0 ppm for chloroform-*d*, and those for ^{31}P NMR were relative to H_3PO_4 (85% solution in D_2O, 0 ppm). The electron ionization (EI) and electrospray ionization (ESI) methods are used as the ionization method for the HRMS measurement, and the mass analyzer type is TOF for EI and ion trap for ESI.

General Procedure for Synthesis of α-Aminophosphorus Compounds. An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with a mixture of $R_2P(O)$-H (0.5 mmol), amine (1.5 mmol), and dichloromethane (0.5 mL) in 0.5 mL of DMF under N_2 atmosphere and stirred at a selected temperature (75 °C for primary and secondary amine, 100 °C for tertiary amine) for 12 h. After completion of the reaction, saturated solution of Na_2CO_3 (10 mL) was added to the reaction mixture and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was passed through a short silica chromatography (particle size 40−50 μm) or preparative GPC to afford the pure products.

General Procedure for Synthesis of P-Chiral Aminophosphinates. An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with a mixture of P-chiral H-phosphinates (0.2 mmol), amine (0.6 mmol), and dichloromethane (0.3 mL) in 0.3 mL of DMF under N_2 atmosphere and stirred at a selected temperature (75 °C for primary amine, 100 °C for tertiary amine) for 12 h. After the reaction was finished, Na_2CO_3 saturated solution (5 mL) was added to the reaction mixture and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum, and the resulting residue was subjected to silica chromatography through a short column (particle size 40−50 μm) or preparative GPC to afford the pure products.

Synthesis of Ammonium Chloride and Ammonium Tetrafluoroborate. An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with a mixture of Et_3N (1.5 mmol) and dichloromethane (0.5 mL) in 0.5 mL of DMF under N_2 atmosphere stirred at 100 °C for 10 h. The mixture was then cooled to room temperature, and removal of the volatiles under vacuum afforded a white solid. Recrystallization of the crude product from MeOH and Et_2O gave 1-chloro-*N*,*N*,*N*-triethylmethaniminium chloride **3a** as a colorless crystal in 89% yield. Similarly, using dichloromethane-d_2 as substrate resulted in **3a**-*d*.

For the synthesis of ammonium tetrafluoroborate, in a glass tube was dissolved **3a** (0.2 mmol) in 0.5 mL of DMSO-d_6, and $AgBF_4$ (0.2 mol) was added under N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and then removal of the solid by filtration afforded the corresponding ammonium tetrafluoroborate **3b** quantitatively.

^{1}H, ^{13}C, and ^{31}P NMR Spectral Data of the Products. *Diethyl (N,N-Diethylaminomethyl)phosphonate (**1a**).*[16] Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (3/1) to afford a pale yellow liquid.Yield: 102.6 mg, 92%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11−4.19 (m, 4H), 2.86 (d, 2H, J_{P-H} = 10.8 Hz), 2.71 (q, 4H, J = 7.2 Hz), 1.32−1.35 (m, 6H), 1.05 (t, 6H, J = 7.2 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 26.77; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 61.8 (d, J_{P-C} = 6.9 Hz), 47.7 (d, J_{P-C} = 162.8 Hz), 48.2 (d, J_{P-C} = 8.6 Hz), 16.3 (d, J_{P-C} = 5.8 Hz), 11.4. **1a**−*d*: ^{1} H NMR ($CDCl_3$, 400 MHz): δ 4.10−4.15 (m, 4H), 2.66 (q, 4H, J = 5.7 Hz), 1.31 (t, 6H, J = 5.6 Hz), 1.01 (t, 6H, J = 5.6 Hz).

*Diisopropyl (N,N-Diethylaminomethyl)phosphonate (**1b**).*[16] Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (3/1) to afford a colorless liquid. Yield: 119.2 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62−4.70 (m. 2H), 2.70 (d, 2H, J = 10.8 Hz), 2.60 (q, 4H, J = 7.0 Hz), 1.24 (d, 12H, J = 10.4 Hz), 0.94 (t, 6H, J = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.17; ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.1 (d, J_{P-C} = 2.0 Hz), 49.8 (d, J_{P-C} = 163.7 Hz), 48.2 (d, J_{P-C} = 8.8 Hz), 24.1 (d, J_{P-C} = 3.5 Hz), 24.0 (d, J_{P-C} =5.0 Hz), 11.6.

*Diphenyl (N,N-Diethylaminomethyl)phosphonate (**1c**).* Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (3/1) to afford a colorless liquid. Yield: 110.1 mg, 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, 4H, J = 8.0 Hz), 7.20 (d, 4H, J = 8.4 Hz), 7.15 (t, 2H, J = 7.2 Hz), 3.21 (d, 2H, J = 9.2 Hz), 2.76 (q, 4H, J = 7.2 Hz), 1.05 (t, 6H, J = 8.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.87; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (d, J_{P-C} = 9.7 Hz), 129.6, 125.0, 120.6 (d, J_{P-C} = 4.3 Hz), 49.2 (d, J_{P-C} =163.0 Hz), 48.4 (d, J_{P-C} = 8.9 Hz), 11.7. HRMS (EI) *m*/*z*: [M] Calcd for $C_{17}H_{22}NO_3P$ 319.1337; found 319.1335.

*Diethyl (N,N-Diallylaminomethyl)phosphonate (**1d**).*[17] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 90.2 mg, 73%. ^{1}H NMR (400 MHz, C_6D_6) δ 5.75−5.86 (m, 2H), 5.13 (dd, 2H, J_1 = 2.0 Hz, J_2 = 17.2 Hz), 5.03 (dd, 2H, J_1 = 2.0 Hz, J_2 = 10.4 Hz), 3.96−4.06 (m, 4H), 3.25 (d, 4H, J = 6.4 Hz), 2.83 (d, 2H, J = 10.8 Hz), 1.07 (t, 6H, J = 7.6 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 24.90; ^{13}C NMR (100 MHz, C_6D_6) δ 135.8, 117.8, 61.7 (d, J_{P-C} = 6.6 Hz), 58.3 (d, J_{P-C} = 8.6 Hz), 49.1 (d, J_{P-C} = 162.1 Hz), 16.7 (d, J_{P-C} = 5.7 Hz).

*N,N-Bis(diethoxyphosphinoylmethyl)-N-methylamine (**1e**).*[18] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 63.7 mg, 77%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11−4.22 (m, 8H), 3.06 (d, 4H, J_{P-H} =9.2 Hz), 2.63 (s, 3H), 1.34 (t, 12H, J = 7.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 25.41; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 61.8 (t, J_{P-C} = 3.4 Hz), 53.4 (dd, $J_{1\ P-C}$ = 10.0 Hz, $J_{2\ P-C}$ = 156.7 Hz), 45.8 (t, J_{P-C} = 6.9 Hz), 16.4 (t, J_{P-C} = 2.9 Hz).

*Diethyl N-Octylaminomethylphosphonate (**1f**).*[19] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 113.1 mg, 81%. ^{1}H NMR (400 MHz, C_6D_6) δ 3.96−4.10 (m, 4H), 2.87 (d, 2H, J_{P-H} = 12.4 Hz), 2.45 (t, 2H, J = 6.8 Hz), 1.36 (br, 1H), 1.29 (br, 4H), 1.21 (br, 8H), 1.09 (t, 6H, J = 7.2 Hz), 0.90 (t, 3H, J = 6.4 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 26.15; ^{13}C NMR (100 MHz, C_6D_6) δ 61.8 (d, J_{P-C} = 6.7 Hz), 51.7 (d, J_{P-C} = 16.2 Hz), 46.2 (d, J_{P-C} = 153.5 Hz), 32.3, 30.2, 29.9, 29.7, 27.5, 23.1, 16.7 (d, J_{P-C} = 5.7 Hz), 14.4.

*Diethyl (N-Butylmethylaminomethyl)phosphonate (**1g**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 113.8 mg, 96%. ^{1}H NMR (400 MHz, C_6D_6) δ 3.98−4.08 (m, 4H), 2.67 (d, 2H, J_{P-H} = 10.8 Hz), 2.32−2.37 (m, 5H), 1.21−1.36 (m, 4H), 1.09 (t, 6H, J = 6.8 Hz), 0.86 (t, 3H, J = 6.8 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 24.69; ^{13}C NMR (100 MHz, C_6D_6) δ 61.6 (d, J_{P-C} = 5.7 Hz), 59.5 (d, J_{P-C} = 13.4 Hz), 54.0 (d, J_{P-C} = 163.0 Hz), 44.2 (d, J_{P-C} = 6.7 Hz), 29.9, 20.6, 16.7 (d, J_{P-C} = 5.7 Hz), 14.2. HRMS (EI) *m*/*z*: [M] Calcd for $C_{10}H_{24}NO_3P$ 237.1494; found 237.1490.

*Diethyl (4-Methylpiperazin-1-yl)methylphosphonate (**1h**).*[20] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 116.3 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07−4.20 (m, 4H), 2.76 (d, 2H, J_{P-H} = 11.2 Hz), 2.66 (br, 4H), 2.42 (br, 4H), 2.25 (s, 3H), 1.32 (t, 6H, J = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.37; ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.1 (d, J_{P-C} = 6.7 Hz), 55.1, 54.8, 54.0 (d, J_{P-C} = 172.5 Hz), 45.9, 16.6 (d, J_{P-C} = 4.8 Hz).

*Diethyl (N,N-Dibutylaminomethyl)phosphonate (**1i**).*[21] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 128.5 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06−4.15 (m, 4H), 2.83 (d, 2H, J_{P-H} = 10.0 Hz), 2.54 (t, 4H, J = 6.8 Hz), 1.36−1.43 (m, 4H), 1.24−1.33 (m, 10H), 0.88 (t, 6H, J = 7.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.10; ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.8 (d, J_{P-C} = 6.7 Hz), 55.2 (d, J_{P-C} = 8.4 Hz), 50.0 (d, J_{P-C} = 161.1 Hz), 29.1, 20.41, 16.5 (d, J_{P-C} = 5.7 Hz), 14.1.

*2-(N-Butylmethylaminomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (**1j**).* Following the general procedure, the crude

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product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 118.4 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (d, 2H, J_{P-H} = 9.6 Hz), 2.50 (t, 2H, J = 7.2 Hz), 2.39 (s, 3H), 1.49 (s, 6H), 1.39−1.48 (m, 2H), 1.37 (s, 6H), 1.26−1.35 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.09; ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.0 (d, J_{P-C} = 1.9 Hz), 58.6 (d, J_{P-C} = 12.4 Hz), 54.1 (d, J_{P-C} = 147.7 Hz), 44.0 (d, J_{P-C} = 5.7 Hz), 29.5, 25.0 (d, J_{P-C} = 3.8 Hz), 24.2 (d, J_{P-C} = 4.7 Hz), 20.4, 14.1. HRMS (EI) m/z: [M] Calcd for $C_{12}H_{26}NO_3P$ 263.1650; found 263.1656.

*Isopropyl (N-Butylmethylaminomethyl)phenylphosphinate (**1k**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 128.9 mg, 91%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.91−7.98 (m, 2H), 7.10−7.16 (m, 3H), 4.53−4.64 (m, 1H), 2.71−2.84 (m, 2H), 2.34 (s, 3H), 2.17−2.32 (m, 2H), 1.28 (d, 3H, J = 6.4 Hz), 1.03−1.21 (m, 4H), 0.97 (d, 3H, J = 6.0 Hz), 0.76 (t, 3H, J = 7.6 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 35.97; ^{13}C NMR (100 MHz, C_6D_6) δ 133.3 (d, J_{P-C} = 121.1 Hz), 132.5 (d, J_{P-C} = 8.6 Hz), 131.7 (d, J_{P-C} = 2.9 Hz), 127.9, 69.3 (d, J_{P-C} = 6.7 Hz), 59.6 (d, J_{P-C} = 12.4 Hz), 57.4 (d, J_{P-C} = 121.1 Hz), 44.4 (d, J_{P-C} = 4.7 Hz), 29.8, 24.7 (d, J_{P-C} = 2.8 Hz), 24.1 (d, J_{P-C} = 4.7 Hz), 20.4, 14.2. HRMS (EI) m/z: [M] Calcd for $C_{15}H_{26}NO_2P$ 283.1701; found 283.1710.

*Diphenyl (N-Butylmethylaminomethyl)phosphine Oxide (**1l**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 141.6 mg, 94%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.84−7.89 (m, 4H), 7.16 (br, 4H), 7.06−7.08 (m, 2H), 3.02 (d, 2H, J_{P-H} = 6.4 Hz), 2.39 (s, 3H), 2.37 (t, 2H, J = 6.8 Hz), 1.18−1.25 (m, 2H), 1.07−1.16 (m, 2H), 0.78 (t, 3H, J = 7.2 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 24.74; ^{13}C NMR (100 MHz, C_6D_6) δ 134.5 (d, J_{P-C} = 94.3 Hz), 131.6 (d, J_{P-C} = 8.6 Hz), 131.4 (d, J_{P-C} = 1.9 Hz), 128.5 (d, J_{P-C} = 10.4 Hz), 60.0 (d, J_{P-C} = 10.5 Hz), 58.5 (d, J_{P-C} = 87.7 Hz), 44.6 (d, J_{P-C} = 5.7 Hz), 29.7, 20.5, 14.2. HRMS (EI) m/z: [M] Calcd for $C_{18}H_{24}NOP$ 301.1596; found 301.1595.

*Dibutyl (N-Butylmethylaminomethyl)phosphine Oxide (**1m**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 121.5 mg, 93%. ^{1}H NMR (400 MHz, C_6D_6) δ 2.31−2.36 (m, 7H), 1.42−1.58 (m, 8H), 1.24−1.33 (m, 8H), 0.89 (t, 3H, J = 7.2 Hz), 0.83 (t, 6H, J = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.22; ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.4 (d, J_{P-C} = 9.5 Hz), 56.6 (d, J_{P-C} = 81.1 Hz), 44.7 (d, J_{P-C} = 4.8 Hz), 30.0, 27.5 (d, J_{P-C} = 64.8 Hz), 24.7 (d, J_{P-C} = 13.4 Hz), 24.3 (d, J_{P-C} = 3.8 Hz), 20.7, 14.3, 13.9. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{32}NOPNa$ 284.2114; found 284.2113.

*Bis(4-phenylbutyl)(N-butylmethylaminomethyl)phosphine Oxide (**1n**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 188.1 mg, 91%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.11−7.16 (m, 6H), 7.01−7.05 (m, 4H), 2.38−2.45 (m, 4H), 2.56−2.29 (m, 7H), 1.36−1.50 (m, 12H), 1.21−1.27 (m, 4H), 0.834 (t, 3H, J = 6.8 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 42.78; ^{13}C NMR (100 MHz, C_6D_6) δ 142.4, 128.7, 128.7, 126.2, 60.4 (d, J_{P-C} = 10.5 Hz), 56.7 (d, J_{P-C} = 80.0 Hz), 44.7 (d, J_{P-C} = 4.8 Hz), 35.8, 33.3 (d, J_{P-C} = 12.4 Hz), 29.9, 27.7 (d, J_{P-C} = 63.8 Hz), 21.9 (d, J_{P-C} = 2.8 Hz), 20.7, 14.3. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{26}H_{40}NOPNa$ 436.2740; found 436.2736.

*Diethyl (N-Octylmethylaminomethyl)phosphonate (**1o**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 127.6 mg, 87%. ^{1}H NMR (400 MHz, C_6D_6) δ 3.97−4.09 (m, 4H), 2.70 (d, 2H, J_{P-H} = 10.8 Hz), 2.36−2.39 (m, 5H), 1.25−1.40 (m, 12H), 1.10 (t, 6H, J = 6.8 Hz), 0.90 (t, 3H, J = 6.8 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 24.67; ^{13}C NMR (100 MHz, C_6D_6) δ 61.6 (d, J_{P-C} = 6.7 Hz), 59.8 (d, J_{P-C} = 13.3 Hz), 54.0 (d, J_{P-C} = 162.9 Hz), 44.2 (d, J_{P-C} = 6.7 Hz), 32.3, 30.0, 29.8, 27.9, 27.6, 23.1, 16.7 (d, J_{P-C} = 5.7 Hz), 14.4. HRMS (EI) m/z: [M] Calcd for $C_{14}H_{32}NO_3P$ 293.2120; found 293.2109.

*Diethyl (N-Cyclohexylmethylaminomethyl)phosphonate (**1p**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 121.1 mg, 92%. ^{1}H NMR (400 MHz, C_6D_6) δ 4.02−4.12 (m, 4H), 2.74 (d, 2H, J_{P-H} = 11.2 Hz), 2.44 (s, 3H) 2.23−2.30 (m, 1H), 1.45−1.67 (m, 6H), 1.11 (t, 6H, J = 6.8 Hz), 0.84−1.10 (m, 4H); ^{31}P NMR (162 MHz, C_6D_6) δ 25.36; ^{13}C NMR (100 MHz, C_6D_6) δ 64.4 (d, J_{P-C} = 14.3 Hz), 61.7 (d, J_{P-C} = 6.7 Hz), 50.4 (d, J_{P-C} = 167.8 Hz), 39.8 (d, J_{P-C} = 3.8 Hz), 28.6, 26.5, 26.1, 16.7 (d, J_{P-C} = 5.7 Hz). HRMS (EI) m/z: [M] Calcd for $C_{12}H_{26}NO_3P$ 263.1650; found 263.1643.

*Diethyl (N-Isopropylmethylaminomethyl)phosphonate (**1q**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 89.3 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09−4.18 (m, 4H), 2.82−2.92 (m, 1H), 2.73 (d, 2H, J_{P-H} = 10.8 Hz), 2.38 (s, 3H), 1.32 (t, 6H, J = 7.2 Hz), 0.97 (d, 6H, J = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.34; ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.0 (d, J_{P-C} = 6.7 Hz), 55.3 (d, J_{P-C} = 14.3 Hz), 48.6 (d, J_{P-C} = 168.7 Hz), 39.7 (d, J_{P-C} = 2.8 Hz), 17.6, 16.5 (d, J_{P-C} = 5.7 Hz). HRMS (EI) m/z: [M] Calcd for $C_9H_{22}NO_3P$ 223.1337; found 223.1331.

*Piperidin-1-ylmethylphosphonic Acid Diethyl Ester (**1r**).*[22] Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (4/1) to afford a pale yellow liquid. Yield: 104.6 mg, 89%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11−4.21 (m, 4H), 2.78 (d, 2H, J_{P-H} = 11.2 Hz), 2.62 (br, 4H), 1.57−1.63 (m, 4H), 1.42−1.44 (m, 2H); 1.34 (t, 6H, J = 7.0 Hz,); ^{31}P NMR (CDCl3, 162 MHz): δ 25.85; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 62.0 (d, J_{P-C} = 6.7 Hz), 56.2 (d, J_{P-C} = 9.5 Hz), 53.8 (d, J_{P-C} = 160.4 Hz), 25.9, 23.6, 16.5 (d, J_{P-C} = 5.8 Hz).

*Diethyl (Morpholinomethyl)phosphonate (**1s**).*[22] Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (4/1) to afford a pale yellow liquid. Yield: 105.5 mg, 89%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11−4.21 (m, 4H), 3.71 (t, 4H, J = 4.8 Hz), 2.78 (d, 2H, J_{P-H} = 12.0 Hz), 2.65 (t, 4H, J = 4.6 Hz), 1.34 (t, 6H, J = 7.2 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 24.95; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.6, 61.8 (d, J_{P-C} = 6.7 Hz), 55.0 (d, J_{P-C} = 10.4 Hz), 54.1 (d, J_{P-C} = 163.0 Hz), 16.2 (d, J_{P-C} = 5.6 Hz).

*Diethyl (N,N-Dimethylaminomethyl)phosphonate (**1t**).*[23] Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 79.9 mg, 82%. ^{1}H NMR (400 MHz, C_6D_6) δ 3.96−4.07 (m, 4H), 2.57 (d, 2H, J_{P-H} = 11.6 Hz), 2.23 (s, 6H), 1.07 (t, 6H, J = 7.6 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 24.16; ^{13}C NMR (100 MHz, C_6D_6) δ 61.7 (d, J_{P-C} = 6.6 Hz), 55.7 (d, J_{P-C} = 162.9 Hz), 47.5 (d, J_{P-C} = 11.5 Hz), 16.7 (d, J_{P-C} = 5.7 Hz).

*Diethyl [4-(2-Chloroethyl)piperazin-1-yl]methylphosphonate (**1u**).* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 120.9 mg, 81%. ^{1}H NMR (400 MHz, C_6D_6) δ 3.95−4.10 (m, 4H), 3.14 (t, 2H, J = 6.8 Hz), 2.60 (d, 2H, J_{P-H} = 11.6 Hz), 2.55 (br, 4H), 2.31 (t, 2H, J = 7.2 Hz), 2.17 (t, 4H, J = 4.8 Hz), 1.09 (t, 6H, J = 7.2 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 23.61; ^{13}C NMR (100 MHz, C_6D_6) δ 61.7 (d, J_{P-C} = 6.7 Hz), 59.9, 54.7 (d, J_{P-C} = 163.9 Hz), 55.3 (d, J_{P-C} = 10.5 Hz), 53.4, 41.3, 16.7 (d, J_{P-C} = 5.7 Hz). HRMS (EI) m/z: [M + H]$^+$ Calcd for $C_{11}H_{25}ClN_2O_3P$ 299.1286; found 299.1283.

*(S_P)-(−)-Menthyl Phenyl(N-butylmethylaminomethyl)-phosphinate (S_P)-**1a**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 72.1 mg, 95%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.96−8.04 (m, 2H), 7.08−7.16 (m, 3H), 4.50−4.58 (m, 1H), 2.76−2.88 (m, 2H), 2.53−2.65 (m, 1H), 2.36 (s, 3H) 2.19−2.34 (m, 2H), 1.86−1.92 (m, 1H), 1.34−1.52 (m, 3H), 1.15−1.23 (m, 2H), 1.06−1.14 (m, 6H), 1.02 (d, 3H, J = 6.8 Hz), 0.80−0.99 (m, 2H), 0.77 (t, 3H, J = 7.2 Hz), 0.61−0.68 (m, 1H), 0.59 (d, 3H, J = 6.0 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 35.21; ^{13}C NMR (100 MHz, C_6D_6) δ 130.2 (d, J_{P-C} = 121.0 Hz), 128.0 (d, J_{P-C} = 9.5 Hz), 127.5 (d, J_{P-C} = 2.8 Hz), 123.9, 71.6 (d, J_{P-C} = 7.6 Hz), 55.6 (d, J_{P-C} = 12.4 Hz), 53.5 (d, J_{P-C} = 122.0 Hz), 45.2 (d, J_{P-C} = 4.7 Hz), 40.2 (d, J_{P-C} = 4.8 Hz),

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39.5, 30.2, 27.3, 25.6, 21.9, 19.0, 17.9, 17.2, 16.2, 12.0, 10.0. HRMS (EI) m/z: [M] Calcd for $C_{22}H_{38}NO_2P$ 379.2640; found 379.2628.

*(S_P)-(−)-Menthyl Benzyl(N-butylmethylaminomethyl)-phosphinate (S_P)-**1b**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 73.9 mg, 94%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.41−7.44 (m, 2H), 7.14−7.17 (m, 2H), 7.03−7.08 (m, 1H), 4.35−4.43 (m, 1H), 3.12−3.32 (m, 2H), 2.43−2.58 (m, 3H), 2.32 (s, 3H) 2.17−2.28 (m, 2H), 1.87−1.92 (m, 1H), 1.35−1.48 (m, 3H), 1.22−1.35 (m, 5H), 0.97−1.14 (m, 2H), 0.85−0.93 (m, 9H), 0.78−0.82 (m, 1H), 0.75 (d, 3H, J = 6.4 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 46.36; ^{13}C NMR (100 MHz, C_6D_6) δ 133.5 (d, J_{P-C} = 7.6 Hz), 130.7 (d, J_{P-C} = 5.7 Hz), 128.5 (d, J_{P-C} = 1.9 Hz), 126.7 (d, J_{P-C} = 2.8 Hz), 75.8 (d, J_{P-C} = 6.7 Hz), 59.8 (d, J_{P-C} = 11.4 Hz), 56.4 (d, J_{P-C} = 114.4 Hz), 49.1 (d, J_{P-C} = 5.8 Hz), 44.2, 43.9 (d, J_{P-C} = 6.6 Hz), 37.1 (d, J_{P-C} = 83.9 Hz), 34.4, 31.6, 29.8, 26.0, 23.1, 22.2, 21.3, 20.8, 15.9, 14.3. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{41}NO_2P$ 394.2869; found 394.2870.

*(S_P)-(−)-Menthyl Phenyl(N-cyclohexylmethylaminomethyl)-phosphinate (S_P)-**1c**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 75.1 mg, 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.86 (m, 2H), 7.49−7.53 (m, 1H), 7.42−7.46 (m, 2H), 4.27−4.36 (m, 1H), 2.81−3.00 (m, 2H), 2.38 (s, 3H), 2.22−2.35 (m, 2H), 1.50−1.80 (m, 8H), 1.26−1.42 (m, 2H), 0.94−1.17 (m, 10H), 0.89 (d, 3H, J = 6.8 Hz), 0.79−0.85 (m, 1H), 0.76 (d, 3H, J = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.61; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8 (d, J_{P-C} = 123.9 Hz), 131.9 (d, J_{P-C} = 8.6 Hz), 131.7, 127.9 (d, J_{P-C} = 11.5 Hz), 76.2 (d, J_{P-C} = 9.5 Hz), 64.3 (d, J_{P-C} = 11.4 Hz), 53.4 (d, J_{P-C} = 125.8 Hz), 48.9 (d, J_{P-C} = 5.7 Hz), 43.3, 39.8 (d, J_{P-C} = 2.9 Hz), 34.1, 31.5, 28.7, 27.7, 25.8 (d, J_{P-C} = 6.6 Hz), 25.7, 22.9, 22.0, 21.2, 15.8. HRMS (EI) m/z: [M] Calcd for $C_{24}H_{40}NO_2P$ 405.2797; found 405.2789.

*(S_P)-(−)-Menthyl Benzyl(N-cyclohexylmethylaminomethyl)-phosphinate (S_P)-**1d**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 77.1 mg, 95%. The purified product was dissolved in hexane and allowed to stand at −30 °C overnight afforded a white solid. A crystal suitable for X-ray crystallography was obtained from recrystallization of the solid from hexane at −30 °C (rt and then slowly cooled to −30 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.34 (m, 2H), 7.27−7.29 (m, 2H), 7.19−7.23 (m, 1H), 4.14−4.22 (m, 1H), 3.16−3.32 (m, 2H), 2.62 (d, 2H, J_{P-H} = 9.6 Hz), 2.38 (s, 3H), 2.26−2.34 (m, 1H), 1.96−2.04 (m, 1H), 1.67−1.80 (m, 6H), 1.61 (d, 3H, J = 12.8 Hz), 1.31−1.39 (m, 1H), 1.22−1.29 (m, 2H), 1.13−1.18 (m, 3H), 1.00−1.05 (m, 1H), 0.91−0.97 (m, 2H), 0.87 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 6.4 Hz), 0.77 (d, 3H, J = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.97; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (d, J_{P-C} = 9.5 Hz), 130.2 (d, J_{P-C} = 5.7 Hz), 128.3 (d, J_{P-C} = 2.8 Hz), 126.5 (d, J_{P-C} = 2.8 Hz), 76.2 (d, J_{P-C} = 7.6 Hz), 64.5 (d, J_{P-C} = 12.4 Hz), 52.6 (d, J_{P-C} = 118.2 Hz), 48.7 (d, J_{P-C} = 5.8 Hz), 43.7, 38.5, 36.1 (d, J_{P-C} = 85.8 Hz), 34.1, 31.5, 28.2 (d, J_{P-C} = 13.8 Hz), 26.3, 26.0 (d, J_{P-C} = 5.8 Hz), 25.6, 22.8, 22.0, 21.1, 15.6. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{42}NO_2PNa$ 442.2845; found 442.2839.

*(S_P)-(−)-Menthyl Benzyl(((S)-3,3-dimethylbutan-2-yl)(methyl)-aminomethyl)phosphinate (S_P)-**1e**.* Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (3/1) to afford a colorless liquid. Yield: 78.3 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.34 (m, 5H), 4.11−4.19 (m, 1H), 3.15−3.38 (m, 2H), 2.62−2.78 (m, 2H), 2.37−2.39 (m, 1H), 2.35 (s, 3H), 1.99−2.07 (m, 1H), 1.53−1.61 (m, 3H), 1.21−1.32 (m, 3H), 0.94 (s, 9H), 0.86−0.92 (m, 7H), 0.74−0.79 (m, 7H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.77; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4 (d, J_{P-C} = 7.9 Hz), 130.2 (q, J_{P-C} = 5.5 Hz), 128.3 (d, J_{P-C} = 2.5 Hz), 126.5 (d, J_{P-C} = 2.9 Hz), 76.1 (d, J_{P-C} = 8.0 Hz), 68.8 (d, J_{P-C} = 11.3 Hz), 56.2 (d, J_{P-C} = 113.6 Hz), 48.6 (d, J_{P-C} = 5.5 Hz), 43.5, 40.1 (d, J_{P-C} = 3.9 Hz), 36.2, (d, J_{P-C} = 83.2 Hz), 35.8, 34.0, 31.4, 27.9, 25.6, 22.7, 21.9, 21.1, 15.5, 6.5. HRMS (EI) m/z: [M + H] Calcd for $C_{25}H_{45}NO_2P$ 422.3182; found 422.3164.

*(S_P)-(−)-Menthyl Benzyl(((S)-3-methylbutan-2-yl)(methyl)-aminomethyl)phosphinate (S_P)-**1f**.* Following the general procedure, the crude product was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (3/1) to afford a colorless liquid. Yield: 73.2 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.33 (m, 5H), 4.11−4.19 (m, 1H), 3.17−3.35 (m, 2H), 2.55−2.67 (m, 2H), 2.26(s, 3H), 2.16−2.22 (m, 1H), 1.94−1.99 (m, 1H), 1.69 (d, 1H, J = 12.4 Hz), 1.58 (d, 3H, J = 11.6 Hz), 1.20−1.37 (m, 3H), 1.05 (d, 3H, J = 6.4 Hz), 0.85−0.98 (m, 11H), 0.77 (t, 6H, J = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.73; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5 (d, J_{P-C} = 7.9 Hz), 130.2 (q, J_{P-C} = 5.5 Hz), 128.3 (d, J_{P-C} = 2.4 Hz), 126.5 (d, J_{P-C} = 3.0 Hz), 76.1 (d, J_{P-C} = 7.0 Hz), 66.5 (d, J_{P-C} = 11.8 Hz), 54.0 (d, J_{P-C} = 116.1 Hz), 48.6 (d, J_{P-C} = 5.6 Hz), 43.6, 36.0 (d, J_{P-C} = 3.9 Hz), 35.9 (d, J_{P-C} = 84.6 Hz), 34.0, 31.9, 31.4, 25.5, 22.7, 21.9, 21.1, 21.0, 20.4, 15.5, 9.2. HRMS (EI) m/z: [M] Calcd for $C_{24}H_{42}NO_2P$ 407.2953; found 407.2939.

*(S_P)-(−)-Menthyl Phenyl(N-octylaminomethyl)phosphinate (S_P)-**1g**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 63.1 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.83 (m, 2H), 7.45−7.52 (m, 1H), 7.40−7.44 (m, 2H), 4.28−4.36 (m, 1H), 3.00−3.11 (m, 2H), 2.55−2.59 (m, 2H), 2.19−2.26 (m, 1H), 1.79−1.85 (m, 1H), 1.57−1.65 (m, 2H), 1.36 (t, 3H, J = 12.4 Hz), 1.20 (br, 12H), 0.96−1.04 (m, 2H), 0.92−0.94 (m, 3H), 0.83−0.87 (m, 6H), 0.69−0.80 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.33; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2 (d, J_{P-C} = 121.1 Hz), 132.1(d, J_{P-C} = 2.9 Hz), 131.6 (d, J_{P-C} = 9.5 Hz), 128.3 (d, J_{P-C} = 12.4 Hz), 76.9 (d, J_{P-C} = 7.6 Hz), 51.5 (d, J_{P-C} = 14.3 Hz), 49.3 (d, J_{P-C} = 105.6 Hz), 48.9 (d, J_{P-C} = 5.7 Hz), 43.4, 34.1, 31.9, 31.5, 29.8, 29.5, 29.3, 27.1, 25.8, 22.9, 22.7, 21.9, 21.2, 15.8, 14.1. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{45}NO_2P$ 422.3182; found 422.3183.

*(S_P)-(−)-Menthyl Phenyl(N,N-dimethylaminomethyl)phosphinate (S_P)-**1h**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 43.8 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.86 (m, 2H), 7.51−7.55 (m, 1H), 7.43−7.48 (m, 2H), 4.27−4.35 (m, 1H), 2.77−2.90 (m, 2H), 2.30 (s, 6H), 2.22−2.28 (m, 1H), 1.74−1.80 (m, 2H), 1.58−1.68 (m, 2H), 1.25−1.41 (m, 2H), 0.98−1.56 (m, 1H), 0.95 (d, 3H, J = 7.2 Hz), 0.88 (d, 3H, J = 6.8 Hz), 0.77−0.84 (m, 1H), 0.75 (d, 3H, J = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.04; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8 (d, J_{P-C} = 122.0 Hz), 131.9 (d, J_{P-C} = 2.9 Hz), 131.6 (d, J_{P-C} = 9.6 Hz), 128.3 (d, J_{P-C} = 12.4 Hz), 76.6 (d, J_{P-C} = 8.5 Hz), 59.6 (d, J_{P-C} = 120.1 Hz), 48.9 (d, J_{P-C} = 5.7 Hz), 47.8 (d, J_{P-C} = 10.4 Hz), 43.3, 34.1, 31.5, 25.7, 22.9, 22.0, 21.2, 15.9. HRMS (EI) m/z: [M] Calcd for $C_{19}H_{32}NO_2P$ 337.2171; found 337.2169.

*(S_P)-(−)-Menthyl Phenyl(N,N-diethylaminomethyl)phosphinate (S_P)-**1i**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a pale yellow liquid. Yield: 71.6 mg, 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.85 (m, 2H), 7.48−7.52 (m, 1H), 7.40−7.44 (m, 2H), 4.25−4.34 (m, 1H), 2.84−2.95 (m, 2H), 2.53−2.62 (m, 4H), 2.26−2.33 (m, 1H), 1.75−1.80 (m, 1H), 1.57−1.67 (m, 2H), 1.26−1.39 (m, 2H), 0.94−1.05 (m, 2H), 0.944 (d, 3H, J = 6.8 Hz), 0.83−0.88 (m, 9H), 0.77−0.81 (m, 1H), 0.74 (d, 3H, J = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.26; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9 (d, J_{P-C} = 121.0 Hz), 131.9 (d, J_{P-C} = 9.5 Hz), 131.7 (d, J_{P-C} = 2.9 Hz), 127.9 (d, J_{P-C} = 12.4 Hz), 76.3 (d, J_{P-C} = 7.6 Hz), 53.3 (d, J_{P-C} = 122.0 Hz), 48.9 (d, J_{P-C} = 5.7 Hz), 48.5 (d, J_{P-C} = 7.6 Hz), 43.3, 34.1, 31.5, 25.7, 22.9, 22.0, 21.2, 15.8, 11.6. HRMS (EI) m/z: [M] Calcd for $C_{21}H_{36}NO_2P$ 365.2484; found 365.2469.

*(S_P)-(−)-Menthyl Phenyl(N,N-diallylaminomethyl)phosphinate (S_P)-**1j**.* Following the general procedure, the crude product was purified by preparative GPC using $CHCl_3$ as eluent to afford a colorless liquid. Yield: 56.1 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.83 (m, 2H), 7.49−7.54 (m, 1H), 7.41−7.46 (m, 2H), 5.54−5.64 (m, 2H), 5.02−5.07 (m, 4H), 4.26−4.34 (m, 1H), 3.08−3.25 (m, 4H), 2.84−2.98 (m, 2H), 2.24−2.35 (m, 1H), 1.74−1.79 (m, 2H), 1.58−1.68 (m, 2H), 1.26−1.41 (m, 2H), 0.98−1.02 (m, 1H), 0.95 (d, 3H, J = 7.2 Hz), 0.87 (d, 3H, J = 6.8 Hz), 0.78−0.85 (m, 1H),

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0.75 (d, 3H, J = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.24; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.1 (d, J_{P-C} = 123.0 Hz), 132.3 (d, J_{P-C} = 8.5 Hz), 132.2 (d, J_{P-C} = 2.8 Hz), 128.4 (d, J_{P-C} = 12.3 Hz), 118.1, 76.7 (d, J_{P-C} = 7.6 Hz), 58.6 (d, J_{P-C} = 7.6 Hz), 52.7 (d, J_{P-C} = 121.0 Hz), 49.3 (d, J_{P-C} = 5.8 Hz), 43.7, 34.5, 31.8, 26.0, 23.3, 22.3, 21.6, 16.2. HRMS (EI) m/z: [M] Calcd for $C_{23}H_{36}NO_2P$ 389.2484; found389.2468.

*1-Chloro-N,N,N-triethylmethaniminium Chloride (**3a**).* ^{1}H NMR (400 MHz, DMSO-d_6 δ 5.41 (s, 2H), 3.42 (q, 6H, J = 7.3 Hz), 1.27 (t, 9H, J = 7.2 Hz). (**3a**–*d*). ^{1}H NMR (400 MHz, DMSO-d_6 δ3.42 (q, 6H, J = 7.3 Hz), 1.28 (t, 9H, J = 7.2 Hz).

*1-Chloro-N,N,N-triethylmethaniminium Tetrafluoroborate (**3b**).* ^{1}H NMR (400 MHz, DMSO-d_6 δ 5.33 (s, 2H), 3.40 (q, 6H, J = 7.2 Hz), 1.27 (t, 9H, J = 7.2 Hz).

■ ASSOCIATED CONTENT

Supporting Information

CIF files of chiral α-aminophosphonate, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhouyb@hun.edu.cn.

*E-mail: sf_yin@hnu.edu.cn. Fax: (+) 86-731-88821171.

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

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