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Copper/DIPEA-Catalyzed, Aldehyde-Induced Tandem Decarboxylation−Coupling of Natural α-Amino Acids and Phosphites or Secondary Phosphine Oxides

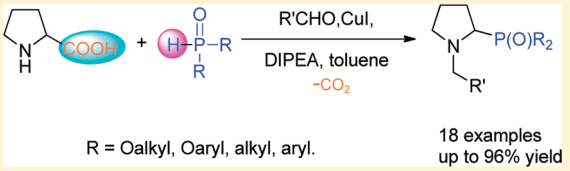
Dongxu Yang,[†] Depeng Zhao,[†] Lijuan Mao,[†] Linqing Wang,[†] and Rui Wang*[,†,‡]

[†]Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Medicine, State Key Laboratory of Applied Organic Chemistry, and Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou 730000, P. R. China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China

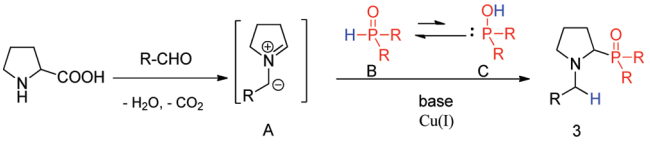
Supporting Information

ABSTRACT: A copper/DIPEA-catalyzed, aldehyde-induced intermolecular decarboxylative coupling reaction of natural α-amino acids and phosphites or secondary phosphine oxides was developed. In this process, a series of potentially useful ligands for organic synthesis and biologically important unnatural amino acid derivatives (tertiary amino phosphorus compounds) were obtained.



Phosphorus−containing compounds have received intense interest in recent years because of their wide applications as ligands for metal-catalyzed C−C bond formation[1] and their potential biological activities.[2] In particular, α-amino phosphonates have been widely used owing to their extensive role as antibacterial agents,[3] antiviral agents,[4] and enzyme inhibitors[5] and their catalytic antibody activities.[6] The addition of phosphorus nucleophiles to imine catalyzed by Lewis acid is one of the most convenient and traditional methods to provide such compounds.[7] Recently, a copper-catalyzed aerobic phosphonation of *N*-protected tetrahydroisoquinoline based on cross-dehydrogenative coupling (CDC) reactions was reported.[8] This method provides a new route to synthesize α-amino phosphonates but is limited to a narrow range of substrates. Very recently, Li's research group reported a C−C bond-forming reaction based on a copper- or iron-catalyzed oxidative decarboxylative coupling of sp^3-hybridized carbons with *N*-benzylproline.[9] Most rencently, Yang's and Liang's group reported the first example of copper-catalyzed decarboxylative coupling of *N*-benzylproline with $Ph_2P(O)H$ compounds to construct C−P bonds.[10] This new reaction expands the scope and synthetic utility of the catalytic decarboxylative coupling reactions previously developed. However, this method still suffers from a fundamental drawback as Li's work:[9] these methods need other oxidants[9] or transition metals[10] besides copper to facilitate the reaction. In 2010, Seidel and Li's group successfully improved the method involving a new reaction pathway, respectively, and they both reported an interesting aldehyde-induced intermolecular tandem decarboxylation−coupling of secondary α-amino acids with alkynes to afford propargylic amino derivatives, releasing H_2O and CO_2 as the only byproducts.[11,12] In these methods, the carboxylic acids provide the possibility for site-specific functionalization of the α-amino acids skeletons, using decarboxylative coupling reactions to generate amine derivatives. On this basis, and considering our interest in building phosphorus-containing compounds,[13] we decided to try to develop a new way of synthesis of α-amino phosphonates. We propose a model for the decarboxylative three components coupling reaction which is outlined in Scheme 1.

Scheme 1. Proposed Mechanism for the Decarboxylative Three-Component Coupling Reaction



Previous research indicated the condensation of proline with an aldehyde resulted in the formation of azomethine ylide **A**,[10,11] and the phosphite can be activated by employing an appropriate base since the equilibrium between **B** and **C** could shift toward the reactive phosphinous acid **C**. Then protonation of the dipole by the pronucleophile phosphinous acid **C** results in the formation of ion pairs which then convert into products **3**. Furthermore, in order that this work has a wider range of applications, we also tried to use other phosphorus nucleophiles, such as diaryl phosphine oxides and even the less reactive dialkyl phosphine oxides, to synthesize α-amino phosphine oxides.

We began by establishing reaction conditions for a Cu (I)-catalyzed decarboxylation−coupling phosphonation. Initially, the reaction of 1.0 equiv of diethyl phosphite **1a**, 1.5 equiv of proline **2a**, 1.4 equiv of *p*-cyanobenzaldehyde, and 30 mol % of

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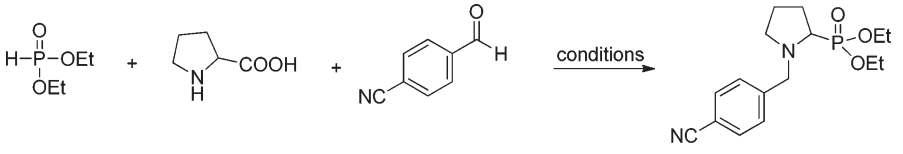
Table 1. Optimization of the Reaction Conditions



1a **2a** **3a**

entry[a]	catalyst	additive	solvents	temp (°C)	time (h)	yield[b] (%)
1	CuCl		toluene	100	10	33
2	CuBr		toluene	100	10	42
3	CuI		toluene	100	10	37
4	CuBr		toluene	130	10	43
5	CuI		toluene	130	10	57
6	CuBr		toluene	130	20	66
7	CuI		toluene	130	20	68
8	CuI	DIPEA (30%)	toluene	130	10	72
9	CuI	TEA (30%)	toluene	130	10	60
10	CuI	DMA (30%)	toluene	130	10	60
11	CuI	TMEDA (30%)	toluene	130	10	72
12	CuI	DMAP (30%)	toluene	130	10	56
13	CuI	DIPEA (30%)	xylene	130	10	67
14	CuI	DIPEA (30%)	$CF_3-C_6H_3$	130	10	12
15	CuI	DIPEA (30%)	DMF	130	10	37
16	CuI	DIPEA (30%)	DMSO	130	10	N.R
17	CuI	DIPEA (30%)	toluene	130	10	71[c]
18	CuI	DIPEA (30%)	toluene	130	20	92 (83)[d]
19	CuI	DIPEA (30%)	toluene	130	24	91
20	CuI	DIPEA (30%)	toluene	130	24	77[e]

[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale in 2.5 mL of toluene under air with 1.0 equiv of **1a** (0.3 mmol), 1.5 equiv of **2a** (0.45 mmol), 1.4 equiv of *p*-cyanobenzaldehyde (0.42 mmol), and 0.3 equiv of catalyst . [b] Reported yields were based on **1a** and determined by ^{31}P NMR with use of an internal standard. [c] The reaction was carried out under argon protection. [d] The yield was given in the parentheses. [e] The reaction was carried out by using 0.15 equiv of CuI.

CuCl as the catalyst stirred in toluene at 100 °C for 10 h under air. The desired product **3a** was obtained in 33% yield (Table 1, entry 1). When other Cu (I) salts were used as catalysts, the yields were not significantly improved (entries 2 and 3). To further improve the yield, the reaction was performed at 130 °C for 10 h, and a moderate yield was obtained using CuI as catalyst (entry 5). When the reaction time was extended to 20 h, the yield increased to 68%. To our great delight, when *N*,*N*-diisopropylethylamine (DIPEA) or tetramethylethylenediamine (TMEDA) was added to the reaction, the conversion was significantly enhanced; the desired product **3a** was obtained in 72% yield when the reaction was carried out for 10 h. Solvent screening indicated that toluene was still the best solvent for this reaction, and when the reaction time was extended to 20 h, the desired product was obtained in 92% yield (entry 18). However, lowering the catalyst loading of CuI to 15 mol % resulted in a decrease in yield (entry 20). We also found that when the reaction was carried out under nitrogen atmosphere, the result was not improved indeed (entry 17).

With the optimal conditions established above, we then examined the scope of the decarboxylation−coupling reaction of the substrates **1** and **2**, and the results are summarized in Table 2. Diethyl phosphite offered excellent yield by NMR, and dimethyl and dipropyl phosphites were also employed with high efficiency under the same reaction conditions (Table 2, entries 1−3). The diphenyl phosphite even offered an almost quantitative yield by the NMR test (entry 4).

At the same time, we also constructed of P−C bonds employing phosphine oxides using this new decarboxylation−coupling method and also achieved excellent results. Diethyl-, diallyl-, and diphenylphosphine oxides performed smoothly reactions and got almost quantitative yields (entries 5−7). After expanding the scope of phosphorus nucleophiles, we then developed several different amino acids substrates. When cyclic amino acid pipecolic acid **2b** was used, the corresponding product **3h** was obtained in a moderate yield (entry 8). We suspect that perhaps the substrate's conformation of six-membered ring is not conducive to the transformation. For catenarian amino acid *N*-benzylvaline **2c**, the corresponding product **3i** was formed in excellent yield (entry 9). The isopropyl did not prevent the site-specific functionalization of the α-amino acids skeletons. Similarly, *N*-benzylleuine **2d** was also applicable to the current transformation and provides the corresponding product **3j** in good yield (entry 10).

Subsequently, our investigations were focused on the use of various aldehydes. As illustrated in Table 3, the use of benzaldehydes bearing electron-withdrawing groups gave the corresponding products **3l**, **3m**, and **3n** in good yields, respectively (entries 2−4). Fortunately, benzaldehydes bearing electron-donating

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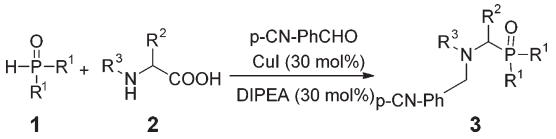
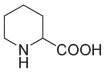
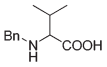
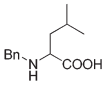
Table 2. Substrate Scope of the Phosphorus Nucleophiles (1) and Amino Acids (2)[a]



Entry	1 (R^1)	2 (R^2, R^3)	Product (3)	Yield (%)[a]
1	**1a OEt**	**2a**	**3a**	92 (83)
2	**1b OMe**	**2a**	**3b**	93 (83)
3	**1cOnPr**	**2a**	**3c**	87 (81)
4	**1d OPh**	**2a**	**3d**	99 (79)
5	**1e Et**	**2a**	**3e**	99 (94)
6	**1f allyl**	**2a**	**3f**	99 (96)
7	**1g Ph**	**2a**	**3g**	99 (87)
8	**1a**	 **2b**	**3h**	45 (32)[b]
9	**1a**	 **2c**	**3i**	95 (81)
10	**1a**	 **2d**	**3j**	82 (69)

[*] Reported yields were based on **1** and determined by ^{31}P NMR with use of an internal standard. Yields are given in parentheses. [b] The reaction was performed for 48 h under the same conditions. [a] Reactions were performed on a 0.3 mmol scale in 2.5 mL of toluene with 1.0 equiv of phosphorus nucleophiles **1**, 1.5 equiv of amino acids **2**, 1.4 equiv of *p*-cyanobenzaldehyde, and 0.3 equiv of catalyst in a 130 °C oil bath for 20 h.

groups had no ill effect on the yields of the products (entries 6, 8, and 9). However, benzaldehydes with ortho-substituted phenyl were less reactive (entries 5 and 7). When the ortho-substituent was nitro, the reaction did not even proceed due to the hard steric hindrance (entry 7).

In summary, a copper/DIPEA-catalyzed, aldehyde-induced tandem decarboxylation−coupling of natural α-amino acids and phosphites or secondary phosphine oxides has been developed. In this process, a broad range of potential ligands for organic synthesis and biologically important non-natural amino acid derivatives (tertiary amino phosphorus compounds) can be readily accessible. The use of natural α-amino acids as materials, cheap copper salt as the catalyst, and the site-specific functionalization are some of the numerous advantages of this new method.

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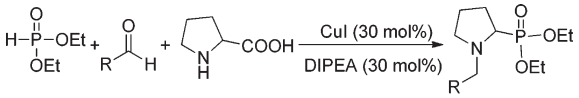
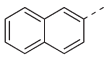
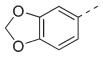
Table 3. Substrate Scope and Limits of the Aldehyde (3)*



Entry	Aldehyde (R)	Product (3)	Yield (%)
1	Ph	**3k**	72 (57)
2	*p* – Cl – Ph	**3l**	79 (62)
3	*p* – Br – Ph	**3m**	82 (71)
4	*p* – NO_2 – Ph	**3n**	87 (85)
5	*o* – Me – Ph	**3o**	52 (33)
6	*m* – Me – Ph	**3p**	72 (69)
7	*o* – NO_2 – Ph	**3q**	N.R[a]
8		**3r**	77 (76)
9		**3s**	83 (80)

*Reactions were performed on a 0.3 mmol scale in 2.5 mL of toluene with 1.0 equiv of **1a**, 1.5 equiv of **2a**, 1.4 equiv of aldehydes, and 0.3 equiv of catalyst in a 130 °C oil bath for 20 h. [a] The product **3q** was not isolated.

EXPERIMENTAL SECTION

^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{31}P NMR (121 MHz) spectra were obtained in $CDCl_3$. The chemical shifts are reported in ppm relative to internal standard TMS (^{1}H NMR), to residual signals of the solvents ($CHCl_3$, 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR), and to external standard 85% H_3PO_4 (^{31}P NMR). IR spectra were recorded on FT-IR, and only major peaks are reported.

General Procedure (Table 2, Entry 1). CuI (0.09 mmol, 17.0 mg) was added to a solution of proline (**2a**, 0.45 mmol, 52.0 mg) in toluene (2.5 mL). The mixture was stirred for 10 min at room temperature, and then *N*,*N*-diisopropylethylamine (0.09 mmol, 11.6 mg, 15.7 uL), 4-cyanobenzaldehyde (0.42 mmol, 55.0 mg), and diethyl phosphite (**1a**, 0.3 mmol, 38.4 μL) were added to the reaction mixture. The reaction was then put in a 130 °C oil bath as soon as possible, stirred for 20 h, and then cooled to room temperature. The resulting suspension was diluted with CH_2Cl_2, and then it was washed with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. After concentration of the solvents, the residue was purified on a silica gel column (PE/EA, 4:1 to 1:1) to afford the corresponding product **3a** in 83% yield upon isolation as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 4.50 (d, J = 13.8 Hz, 1H), 4.29−4.01 (m, 4H), 3.44 (d, J = 13.8 Hz, 1H), 2.96 (t, J = 6.9 Hz, 1H), 2.92−2.78 (m, 1H), 2.23−2.00 (m, 3H), 1.87−1.71 (m, 2H), 1.41−1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 132.0, 129.1, 119.0, 110.6, 62.8 (d, J = 6.8 Hz), 61.6 (d, J = 7.4 Hz), 60.8, 59.9, 58.5, 54.5 (d, J = 15.1 Hz), 26.9, 24.5 (d, J = 6.0 Hz), 16.6 (dd, J = 9.1, 5.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.60; IR (neat) 3451, 2979, 2227, 1228, 1026, 963, 794 cm^{-1}; HRMS (ESI) $C_{16}H_{23}N_2O_3P$ [M + Na]$^+$ calcd 345.1339, found 345.1328.

[1-(4-Cyanobenzyl)pyrrolidin-2-yl]phosphonic acid dimethyl ester (3b): yellow oil, the product was isolated using the same procedure as **3a** and obtained in 83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 4.48 (d, J = 13.7 Hz, 1H), 3.86 (d, 10.3 Hz, 3H), 3.78 (d, 10.3 Hz, 3H), 3.46 (d, J = 13.7 Hz, 1H), 3.02 (t, J = 7.8 Hz, 1H), 2.97−2.83 (m, 1H), 2.25−1.99 (m, 3H), 1.85−1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 132.1, 129.2, 119.0, 110.7, 60.2 (d, J = 51.8 Hz), 58.3, 54.5 (d, J = 14.9 Hz), 53.8, 52.5 (d, J = 7.4 Hz), 26.9, 24.0 (d, J = 6.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.71; IR (neat) 3405, 2955, 2228, 1228, 1684, 1232, 1033, 824 cm^{-1}; HRMS (ESI) $C_{14}H_{19}N_2O_3P$ [M + H]$^+$ calcd 295.1206, found 295.1208.

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[1-(4-Cyanobenzyl)pyrrolidin-2-yl]phosphonic acid dipropyl ester (3c): yellow oil; 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 4.53 (d, J = 13.8 Hz, 1H), 4.08 (dq, J = 20.6, 6.7 Hz, 4H), 3.45 (d, J = 13.9 Hz, 1H), 3.01 (dd, J = 9.0, 6.6 Hz, 1H), 2.91 (ddd, J = 9.1, 6.0, 3.3 Hz, 1H), 2.26 − 1.99 (m, 3H), 1.86 − 1.75 (m, 2H), 1.72 −1.51 (m, 4H), 0.95 (td, J = 7.4, 4.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 131.9, 129.1, 119.0, 110.5, 68.3 (d, J = 7.2 Hz), 67.1 (d, J = 7.5 Hz), 60.7, 59.8, 58.4, 54.4 (d, J = 15.2 Hz), 26.8 (d, J = 2.4 Hz), 24.4 (d, J = 6.0 Hz), 24.0 (d, J = 8.1 Hz), 10.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.47 ppm. IR (neat): 3453, 2968, 2227, 1229, 998, 851 cm^{-1}; HRMS (ESI) $C_{18}H_{27}N_2O_3P$ [M + H]$^+$ calcd 351.1832, found 351.1830.

[1-(4-Cyanobenzyl)pyrrolidin-2-yl]phosphonic Acid Diphenyl Ester (3d). The product **3d** was isolated on a silica gel column (PE:EA, 15:1 to 4:1) to get the corresponding yellow oil: 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.2 Hz, 2H), 7.38−7.21 (m, 8H), 7.21−7.09 (m, 4H), 4.56 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 3.46−3.28 (m, 1H), 3.05−2.90 (m, 1H), 2.54−2.18 (m, 3H), 2.15−1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.0, 129.7 (d, J = 13.3 Hz), 129.3, 125.1 (d, J = 13.3 Hz), 120.6 (d, J = 4.2 Hz), 120.7 (d, J = 4.2 Hz), 119.1, 110.6, 61.2, 60.0, 58.9, 54.5 (d, J = 15.4 Hz), 27.3, 24.7 (d, J = 5.6 Hz), 24.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.89; IR (neat) 2969, 2227, 1489, 1192, 933, 766 cm^{-1}; HRMS (ESI) $C_{24}H_{23}N_2O_3P$ [M + H]$^+$ calcd 419.1524, found 419.1519.

4-[2-(Diethylphosphinoyl)pyrrolidin-1-ylmethyl]benzonitrile (3e). The product **3e** was isolated on a silica gel column (PE:EA, 2:1 to 0:1) to obtain the corresponding yellow oil: 94% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.57 (d, J = 14.2 Hz, 1H), 3.49 (d, J = 14.2 Hz, 1H), 3.09 (dd, J = 9.7, 6.2 Hz, 1H), 2.94 (ddd, J = 9.5, 6.5, 3.3 Hz, 1H), 2.26 − 2.07 (m, 2H), 1.99 − 1.68 (m, 7H), 1.25 (dt, J = 16.2, 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 131.9, 128.8, 118.9, 110.3, 61.7, 60.6 (d, J = 10.7 Hz), 54.9 (d, J = 10.8 Hz), 26.2, 24.1 (d, J = 5.5 Hz), 19.4, 18.5, 17.1, 16.3, 5.6 (d, J = 18.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 53.30; IR (neat) 3412, 2970, 2226, 1607, 1458, 1149, 764 cm^{-1}; HRMS (ESI) $C_{16}H_{23}N_2OP$ [M + H]$^+$ calcd 291.1621, found 291.1613.

4-[2-(Diallylphosphinoyl)pyrrolidin-1-ylmethyl]benzonitrile (3f). The product **3f** was isolated on a silica gel column (PE:EA, 2:1 to 1:3) to obtain the corresponding yellow oil; 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 6.06−5.81 (m, 2H), 5.38−5.12 (m, 4H), 4.53 (d, J = 14.2 Hz, 1H), 3.52 (d, J = 14.2 Hz, 1H), 3.16 (dd, J = 10.0, 6.1 Hz, 1H), 3.05−2.91 (m, 1H), 2.92−2.73 (m, 1H), 2.75−2.55 (m, 3H), 2.32−2.08 (m, 2H), 2.02−1.88 (m, 1H), 1.88−1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 131.9, 128.7, 127.6 (d, J = 21.9 Hz), 120.0 (d, J = 10.6 Hz), 118.8, 110.4, 61.8, 60.6 (d, J = 8.4 Hz), 54.7 (d, J = 10.7 Hz), 32.3 (d, J = 59.2 Hz), 30.4 (d, J = 61.5 Hz), 26.1, 24.1 (d, J = qS.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 46.79; IR (neat) 3403, 2965, 2226, 1603, 1179, 911, 727 cm^{-1}; HRMS (ESI) $C_{18}H_{23}N_2OP$ [M + H]$^+$ calcd 315.1621, found 315.1612.

4-[2-(Diphenylphosphinoyl)pyrrolidin-1-ylmethyl]benzonitrile (3g). The product **3g** was isolated on a silica gel column (PE:EA, 4:1 to 1:2) to obtain the corresponding yellow oil: 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−7.92 (m, 2H), 7.92−7.77 (m, 2H), 7.57−7.40 (m, 8H), 7.27 (d, J = 8.1 Hz, 2H), 3.94 (d, J = 13.6 Hz, 1H), 3.77−3.58 (m, 1H), 3.39 (d, J = 13.6 Hz, 1H), 3.01−2.77 (m, 1H), 2.37−2.18 (m, 2H), 2.18−1.95 (m, 1H), 1.78−1.62 (m, 1H), 1.62−1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.359, 132.0−31.3 (m), 131.1, 130.3, 128.8, 128.2 (d, J = 11.0 Hz), 118.8, 110.3, 63.9, 62.6, 61.0, 54.7 (d, J = 9.1 Hz), 27.1, 24.4 (d, J = 3.4 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.61; IR (neat) 3456, 2982, 2227, 1244, 1025, 957 cm^{-1}; HRMS (ESI) $C_{24}H_{23}N_2OP$ [M + H]$^+$ calcd 387.1621, found 387.1633.

[1-(4-Cyanobenzyl)piperidin-2-yl]phosphonic acid diethyl ester (3h): yellow oil; 32% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 4.30 (d, J = 14.7 Hz, 1H), 4.23−4.05 (m, 4H), 3.77 (d, J = 14.8 Hz, 1H), 3.16−2.85 (m, 2H), 2.27 (dd, J = 12.1, 5.8 Hz, 1H), 2.03−1.62 (m, 3H), 1.60−1.46 (m, 3H), 1.34 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 132.0, 129.0, 123.0, 110.5, 61.6 (d, J = 30.7 Hz) 59.3, 57.3, 50.5, 25.9, 24.4, 22.3, 16.6, 13.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.81; IR (neat) 3453, 2979, 2227, 1218, 1025, 953, 790 cm^{-1}; HRMS (ESI) $C_{17}H_{25}N_2O_3P$ [M + Na]$^+$ calcd 359.1495, found 359.1499.

[1-[Benzyl(4-cyanobenzyl)amino]-2-methylpropyl]phosphonic Acid Diethyl Ester (3i). The product **3i** was isolated on a silica gel column (PE:EA, 4:1 to 2:1) to obtain the corresponding yellow oil: 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.37−7.22 (m, 5H), 4.28−4.10 (m, 4H), 4.07−3.67 (m, 4H), 2.56 (dd, J = 15.8, 8.4 Hz, 1H), 2.16−1.99 (m, 1H), 1.35 (td, J = 7.0, 5.3 Hz, 6H), 1.02 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 139.0, 132.0, 129.7, 129.4, 128.3, 127.2, 119.0, 110.7, 63.1, 61.5, 61.0 (d, J = 22.1 Hz), 55.9, 55.4, 28.3 (d, J = 7.0 Hz), 28.0, 21.6 (d, J = 10.4 Hz), 21.0, 16.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.37; IR (neat) 3456, 2982, 2227, 1244, 1025, 957 cm^{-1}; HRMS (ESI) $C_{23}H_{31}N_2O_3P$ [M + Na]$^+$ calcd 437.1965, found 437.1952.

[1-[Benzyl-(4-cyanobenzyl)amino]-3-methylbutyl]phosphonic Acid Diethyl Ester (3j). The product **3j** was isolated on a silica gel column (PE:EA, 4:1 to 2:1) to obtain the corresponding yellow oil: 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.36−7.28 (m, 4H), 7.28−7.21 (m, 1H), 4.23−4.05 (m, 4H), 4.06−3.72 (m, 4H), 2.93 (ddd, J = 15.9, 10.1, 3.5 Hz, 1H), 1.91−1.78 (m, 1H), 1.78− 1.60 (m, 1H), 1.35 (td, J = 7.0, 2.9 Hz, 6H), 0.87 (d, J = 6.7 Hz, 3H), 0.42 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 139.1, 132.0, 129.7, 129.3, 128.3, 127.3, 119.0, 110.7, 61.5, 61.2 (d, J = 7.6 Hz), 55.2, 54.5 (d, J = 24.0 Hz), 52.5, 36.8, 24.2 (d, J = 11.2 Hz), 23.5, 20.9, 16.6, 11.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.90; IR (neat) 3463, 2956, 2227, 1242, 1051, 956 cm^{-1}; HRMS (ESI) $C_{24}H_{33}N_2O_3P$ [M + H]$^+$ calcd 429.2302, found 429.2299.

(1-Benzylpyrrolidin-2-yl)phosphonic acid diethyl ester (3k): colorless oil; 57% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 4H), 7.26−7.22 (m, 1H), 4.44 (d, J = 13.0 Hz, 1H), 4.32−4.09 (m, 4H), 3.41 (d, J = 13.0 Hz, 1H), 2.99 (dd, J = 9.7, 6.1 Hz, 1H), 2.95−2.84 (m, 1H), 2.29−2.17 (m, 1H), 2.14−1.98 (m, 2H), 1.87−1.62 (m, 2H), 1.34 (td, J = 7.0, 3.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 128.8, 128.1, 126.7, 62.6 (d, J = 7.0 Hz), 61.7 (d, J = 7.1 Hz), 60.5, 60.1, 58.2, 54.2 (d, J = 15.1 Hz), 26.9, 24.3 (d, J = 6.0 Hz), 16.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.16; IR (neat) 3450, 2976, 1450, 1234, 1028, 961, 702 cm^{-1}; HRMS (ESI) $C_{15}H_{24}NO_3P$ [M + H]$^+$ calcd 298.1567, found 298.1572.

[1-(4-Chlorobenzyl)pyrrolidin-2-yl]phosphonic acid diethyl ester (3l): colorless oil; 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.26 (m, 4H), 4.40 (d, J = 13.1 Hz, 1H), 4.29−4.08 (m, 4H), 3.37 (d, J = 13.1 Hz, 1H), 2.97 (dd, J = 9.5, 6.3 Hz, 1H), 2.93−2.84 (m, 1H), 2.25−1.99 (m, 3H), 1.87−1.65 (m, 2H), 1.33 (td, J = 7.1, 3.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 132.4, 130.0, 128.2, 62.7 (d, J = 6.8 Hz), 61.6 (d, J = 7.3 Hz), 60.5, 59.5, 58.2, 54.3 (d, J = 15.3 Hz), 26.9, 24.4 (d, J = 6.0 Hz), 16.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.90; IR (neat) 3461, 2977, 1489, 1232, 1027, 961, 801 cm^{-1}; HRMS (ESI) $C_{15}H_{23}ClNO_3P$ [M + H]$^+$ calcd 332.1177, found 332.1172.

[1-(4-Bromobenzyl)pyrrolidin-2-yl]phosphonic acid diethyl ester (3m): colorless oil; 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.32−7.22 (m, 2H), 4.38 (d, J = 13.2 Hz, 1H), 4.28−4.12 (m, 4H), 3.36 (d, J = 13.2 Hz, 1H), 2.97 (dd, J = 9.5, 6.4 Hz, 1H), 2.92−2.83 (m, 1H), 2.24−2.04 (m, 3H), 1.84−1.63 (m, 2H), 1.33 (td, J = 7.1, 3.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 131.2, 130.4, 120.5, 62.7 (d, J = 7.0 Hz), 61.7 (d, J = 7.3 Hz), 60.6, 59.5, 58.3,

54.3 (d, J = 15.2 Hz), 26.9, 24.4 (d, J = 5.9 Hz), 16.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.87; IR (neat) 3456, 2977, 1486, 1234, 1027, 963, 800 cm^{-1}; HRMS (ESI) $C_{15}H_{23}BrNO_3P$ $[M + H]^+$ calcd 376.0672, found 376.0667.

[1-(4-Nitrobenzyl)pyrrolidin-2-yl]phosphonic acid diethyl ester (3n): yellow oil; 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 4.56 (d, J = 13.9 Hz, 1H), 4.33−4.04 (m, 4H), 3.52 (d, J = 14.0 Hz, 1H), 3.16−2.96 (m, 1H), 2.93 (ddd, J = 9.1, 5.9, 3.4 Hz, 1H), 2.31−2.02 (m, 3H), 1.87−1.74 (m, 2H), 1.34 (dt, J = 12.8, 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.9, 129.1, 123.4, 62.8 (d, J = 7.0 Hz), 61.6 (d, J = 7.3 Hz), 60.8, 59.6 (d, J = 2.1 Hz), 58.5, 54.5 (d, J = 15.1 Hz), 26.8 (d, J = 2.4 Hz), 24.5 (d, J = 6.0 Hz), 16.5 (d, J = 9.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.52; IR (neat) 3450, 2978, 1520, 1346, 1026, 961, 741 cm^{-1}; HRMS (ESI) $C_{15}H_{23}N_2O_3P$ $[M + H]^+$ calcd 343.1427, found 343.1427.

[1-(2-Methylbenzyl)pyrrolidin-2-yl]phosphonic acid diethyl ester (3o): colorless oil; 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.28 (m, 1H), 7.19−7.05 (m, 3H), 4.44 (d, J = 13.0 Hz, 1H), 4.30−4.05 (m, 4H), 3.36 (d, J = 13.0 Hz, 1H), 3.01−2.91 (m, 1H), 2.92−2.83 (m, 1H), 2.40 (s, 3H), 2.26−2.03 (m, 3H), 1.80−1.69 (m, 2H), 1.32 (td, J = 7.1, 4.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.0, 130.0, 129.4, 126.7, 125.4, 62.5 (d, J = 6.9 Hz), 61.5 (d, J = 7.5 Hz), 61.2, 58.9, 58.6 (d, J = 2.7 Hz), 54.6 (d, J = 15.4 Hz), 26.9 (d, J = 2.2 Hz), 24.3 (d, J = 6.0 Hz), 19.3, 16.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.21; IR (neat) 3464, 2977, 1233, 1027, 961, 790 cm^{-1}; HRMS (ESI) $C_{16}H_{26}NO_3P$ $[M + H]^+$ calcd 312.1723, found 312.1729.

[1-(3-Methylbenzyl)pyrrolidin-2-yl]phosphonic acid diethyl ester (3p): colorless oil; 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.08 (m, 3H), 7.05 (d, J = 6.8 Hz, 1H), 4.40 (d, J = 13.0 Hz, 1H), 4.29−4.12 (m, 4H), 3.37 (d, J = 13.0 Hz, 1H), 3.05−2.85 (m, 2H), 2.34 (s, 3H), 2.22 (td, J = 9.3, 6.8 Hz, 1H), 2.17−2.00 (m, 2H), 1.79−1.62 (m, 2H), 1.34 (td, J = 7.1, 3.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 137.6, 129.6, 127.9, 127.5, 125.9, 62.6 (d, J = 7.0 Hz), 61.7 (d, J = 7.5 Hz), 60.6, 60.2, 58.3, 54.3 (d, J = 15.2 Hz), 26.9, 24.3 (d, J = 6.1 Hz), 21.4, 16.6 (d, J = 4.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.24; IR (neat) 3452, 2978, 2232, 1458, 1232, 1028, 962, 748 cm^{-1}; HRMS (ESI) $C_{16}H_{26}NO_3P$ $[M + H]^+$ calcd 312.1723, found 312.1733.

(1-Naphthalen-2-ylmethylpyrrolidin-2-yl)phosphonic acid diethyl ester (3r): colorless oil; 76% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.76 (m, 3H), 7.74 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.49−7.39 (m, 2H), 4.60 (d, J = 13.0 Hz, 1H), 4.33−4.14 (m, 4H), 3.56 (d, J = 13.0 Hz, 1H), 3.05 (dd, J = 9.6, 6.0 Hz, 1H), 3.00−2.85 (m, 1H), 2.28 (td, J = 9.3, 6.9 Hz, 1H), 2.19−1.99 (m, 2H), 1.85−1.67 (m, 2H), 1.35 (td, J = 7.0, 5.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 133.3, 132.6, 127.7, 127.6, 127.6, 127.3, 127.0, 125.8, 125.4, 62.7 (d, J = 6.7 Hz), 61.7 (d, J = 7.1 Hz), 60.7, 60.4, 58.4, 54.4 (d, J = 15.0 Hz), 27.0, 24.4 (d, J = 5.8 Hz), 16.6 (d, J = 5.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.16; IR (neat) 3461, 2977, 1231, 1027, 960, 755, 547 cm^{-1}; HRMS (ESI) $C_{19}H_{26}NO_3P$ $[M + H]^+$ calcd 348.1723, found 348.1712.

(1-Benzo[1,3]dioxol-5-ylmethylpyrrolidin-2-yl)phosphonic acid diethyl ester (3s): colorless oil; 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.75 (q, J = 8.1 Hz, 2H), 5.93 (s, 2H), 4.33 (d, J = 12.9 Hz, 1H), 4.28−4.07 (m, 4H), 3.32 (d, J = 12.9 Hz, 1H), 2.98−2.84 (m, 2H), 2.29−2.16 (m, 1H), 2.15−1.97 (m, 2H), 1.85−1.68 (m, 2H), 1.33 (tt, J = 9.2, 4.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.4, 133.3, 121.8, 109.3, 107.8, 100.8, 62.7 (d, J = 6.9 Hz), 61.8, 60.4, 59.9, 58.1, 54.2 (d, J = 15.1 Hz), 26.9, 24.4, 16.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.13; IR (neat) 3428, 2978, 1489, 1443, 1240, 1033, 807 cm^{-1}; HRMS (ESI) $C_{16}H_{24}NO_5P$ $[M + H]^+$ calcd 342.1465, found 342.1454.

■ ASSOCIATED CONTENT

Supporting Information. Detailed spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
wangrui@lzu.edu.cn

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