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Diastereo- and enantioselective nitro-Mannich reaction of α-substituted nitroacetates to *N*-phosphoryl imines catalyzed by *cinchona* alkaloid thiourea organocatalysts†

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The asymmetric nitro-Mannich reaction of *N*-phosphoryl imines with α-substituted nitroacetates was performed by using *cinchona* alkaloid thioureas as organocatalysts in toluene at −20 °C. The present method was highly tolerable to functionalized *N*-phosphoryl imines and provided a reliable synthetic route to obtain the corresponding β-nitro ethylphosphoramidates with adjacent quaternary and tertiary chiral centers in high yield (up to 86%) and high enantiostereoselectivity (up to 99% ee) and diastereoselectivity (up to 99 : 1, *anti*-selectivity).

Introduction

The catalytic asymmetric nucleophilic addition of nitroalkanes to the C=N bond of imines, called the catalytic asymmetric nitro-Mannich reaction, is a useful carbon–carbon bond-forming process that can provide chiral β-nitroamines with two contiguous nitrogen-bearing stereogenic centers.[1] The development of C–C bond-forming reactions that create two new stereogenic centers with high diastereo- and enantioselectivity in a single step can open new routes to valuable building blocks or biologically active compounds.[2] The concurrent synthesis of adjacent quaternary and tertiary stereogenic centers is even more appealing since it allows the assembly of highly functionalized molecules such as 1,2-diamines, α-amino carbonyl compounds[3] and biologically active compounds.[4] As a result, considerable effort has been directed toward the development of catalytic asymmetric versions of the nitro-Mannich reaction over the past several years. In their pioneering work, Shibasaki and co-workers have described a chiral ytterbium[5] and aluminum[6] catalyzed enantioselective addition of nitroalkanes to *N*-phosphinoyl imines. Jørgensen also reported enantioselective addition of nitro compounds to imines catalyzed by chiral bisoxazoline–Cu^{II} complexes. The optically active β-nitro-α-amino esters with two new stereogenic centers have been obtained with excellent diastereo- and enantioselectivity.[1d,7]

Beyond these metal-catalyzed variants, enantioselective organocatalytic nitro-Mannich reactions have also been developed. Takemoto and co-workers reported the enantioselective addition of nitromethane to a variety of aromatic *N*-phosphinoyl imines catalyzed by bifunctional thiourea catalysts.[8] Furthermore, Johnston developed a chiral bis-amidine triflate salt that effects the diastereoselective addition of nitroethane to a range of electron-deficient *N*-Boc imines.[9] However, despite these important advances, the applications of α-substituted nitroacetates in this field, in which adjacent quaternary and tertiary chiral centers must be constructed concurrently, are rarely explored.[10]

Phosphoramidate derivatives have attracted attention because of their pharmaceutical applications and excellent inhibitory bioactivities, such as anticancer and antivirus activities.[11] On the other hand, the 1,2-diamine structural motif is important in biologically active natural products,[12] in medicinal chemistry,[13] and more recently as a core unit in chiral auxiliaries and chiral ligands for use in asymmetric catalysis.[14] Some general and asymmetric synthetic methods exist for the preparation of 1,2-diamine derivatives;[12a] however, phosphoramidites bearing 1,2-diamine derivatives have rarely been described. Particularly, the presence of a quaternary stereocenter in a highly substituted phosphoramidite unit, will interact with certain proteases and resist proteolytic degradation. Continuing with our interest in the chemistry of aminophosphorus derivatives,[15] here we report the first example of β-nitro ethylphosphoramidates with an adjacent synthesis of quaternary and tertiary chiral centers promoted by *cinchona* alkaloid

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thiourea organocatalysts. The reactions proceeded with good yields and high diastereo- and enantioselectivities.

Results and discussion

Bifunctional organocatalysts possessing thioureas and tertiary amine groups have been utilized successfully in a number of 1,2 or 1,4-addition reactions.[16] Recently our laboratory has identified a family of chiral carbohydrate combined thiourea organocatalysts that catalyze asymmetric aldol reactions[15a] and the Biginelli reaction[17] with high levels of enantioselectivity. Based on previous achievements in organocatalysis, we began our investigation by developing a catalytic asymmetric nitro-Mannich reaction. Bifunctional thioureas (**1–3**) with diversely structured scaffolds were chosen as the catalyst candidates (Fig. 1).[18]

Initially, the reaction of benzaldehyde-derived *N*-phosphoryl imine **4a**[19] with methyl 2-nitropropanoate **5a** was conducted in the presence of a catalytic amount of **1a** (10 mol%) in toluene at −20 °C. There was no product **6a** detected with saccharide-derived thiourea catalyst **1a** (Table 1, entry 1). The use of *N*,*N*-dimethyl-protected thiourea catalyst **1b** gave β-nitro ethylphosphoramidate **6a** in good yield with moderate enantioselectivity. However, the diastereoselectivity of the major isomer was low (51 : 49 d.r.; Table 1, entry 2). This result suggested that a tertiary amine thiourea structure is essential to effect this reaction. Next, we explored the 3,5-bis(trifluoromethyl)phenylthiourea **2** and *cinchona*-based thioureas **3a** and **3b** as catalysts, and found that the desired products were obtained in yields of 60–80%, and with the highest diastereo- and enantioselectivities (Table 1, entries 3–5).

With the best thiourea catalyst **3a** being identified, we next optimized the other reaction parameters, such as solvent, temperature, and catalyst loading. Among the various solvents tested, dichloromethane, methanol, tetrahydrofuran and trichloromethane afforded moderate to good yields of the expected product **6a** with high diastereo- and enantioselectivities (Table 1, entries 6–9). The most suitable solvent was found to be toluene. When the reaction was carried out at 0 °C using **3a** as the catalyst, a lower enantiomeric excess value of 97% was obtained (Table 1, entry 10). In addition, decreasing the amount of the catalyst from 10 to 5 mol% did not affect the stereoselectivity and resulted in a higher yield (Table 1, entry 11). Under similar reaction conditions, the use of quinine-derived catalyst **3b** gave the product **6a** with a high level of stereoselectivity and with the opposite sense of asymmetric induction (Table 1, entry 5). Thus, the optimal reaction conditions for this transformation were determined to be 0.3 mmol of *N*-phosphoryl imine **4a**, 1.5 equivalents of methyl 2-nitropropanoate **5a** and 5 mol% of **3a** in 2 mL toluene as the solvent at −20 °C.

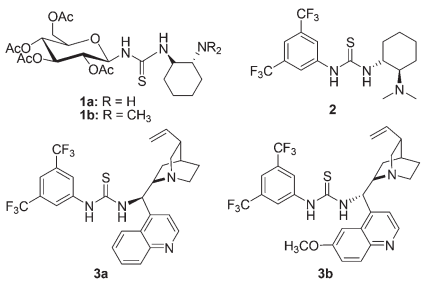
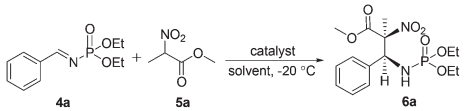


Fig. 1 The catalysts' structures.

Table 1 Screening of catalysts[a]



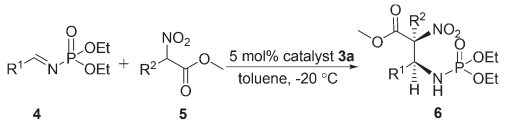
4a 5a 6a

Entry	Catalyst	Solvent	Time [h]	Yields[b] [%]	d.r. (*anti*/*syn*)[c]	ee[c] [%]
1	**1a**	$PhCH_3$	17	—	—	—
2	**1b**	$PhCH_3$	17	60	51 : 49	56
3	**2**	$PhCH_3$	17	65	89 : 11	97
4	**3a**	$PhCH_3$	17	80	>99 : 1	98
5	**3b**	$PhCH_3$	17	77	96 : 4	−99
6	**3a**	CH_2Cl_2	32	68	91 : 9	99
7	**3a**	MeOH	32	40	94 : 6	92
8	**3a**	THF	32	64	85 : 15	96
9	**3a**	$CHCl_3$	24	60	90 : 10	95
10[d]	**3a**	$PhCH_3$	32	70	87 : 13	97
11[e]	**3a**	$PhCH_3$	17	82	>99 : 1	98

[a] Unless otherwise specified all reactions were carried out using diethyl benzylidenephosphoramidate **4a** (0.3 mmol, 1 equiv.) and methyl 2-nitropropanoate **5a** (0.45 mmol, 1.5 equiv.) in 3 mL solvent with 10 mol% of catalyst at −20 °C. [b] Yield of isolated product of **6a** after column chromatography. [c] Determined by HPLC (Chiralcel AD-H). [d] The reaction was performed at 0 °C. [e] 5 mol% of catalyst **3a** was used.

Having optimized the reaction conditions, the reaction scope for *N*-phosphoryl imines **4**[19] and α-substituted nitroacetates **5** was investigated. The results were summarized in Table 2. In general the major chiral isomers **6** could be directly isolated in pure form in good to high yields. A variety of aromatic *N*-phosphoryl imines **4** bearing diverse electron-withdrawing or electron-donating substitutions were found to be suitable coupling partners with methyl 2-nitropropanoate **5a**. Good results were obtained with excellent diastereo- and enantioselectivities (Table 2, entries 1–11). The *ortho*-, *meta*- and *para*-positions of the substituents on the phenyl ring have almost no influence on the stereoselectivity. When heteroaryl imine **4l** and cinnamylidene *N*-phosphoryl imine **4m** were employed as substrates, the reactions gave the corresponding products with excellent stereoselectivities and moderate yields (Table 2, entries 12–13). Other α-substituted nitroacetates were also studied; the α-ethyl derivative **5b** gave lower diastereoselectivities in the reaction with *ortho*- and *meta*-chloro substituent *N*-phosphoryl imines with longer reaction time (Table 2, entries 14–15). To date, results using imines from aliphatic aldehydes such as acrolein are less satisfactory (Table 2, entry 16).[20] In addition, the X-ray crystal structure of **6a** revealed the configuration, and the relative *anti*-selectivity and its

Table 2 Scope of the reaction[a]



4 5 6

Entry	R^1	R^2	Product	Time [h]	Yield[b] [%]	d.r.[c]	ee[c] [%]
1	Ph (**4a**)	Me (**5a**)	**6a**	17	82	>99 : 1	98
2	*o*-FC_6H_4 (**4b**)	Me (**5a**)	**6b**	17	86	94 : 6	99
3	*o*-BrC_6H_4 (**4c**)	Me (**5a**)	**6c**	17	81	87 : 13	97
4	*m*-FC_6H_4 (**4d**)	Me (**5a**)	**6d**	17	72	92 : 8	96
5	*m*-ClC_6H_4 (**4e**)	Me (**5a**)	**6e**	17	82	91 : 9	98
6	*m*-BrC_6H_4 (**4f**)	Me (**5a**)	**6f**	17	70	96 : 4	95
7	*p*-FC_6H_4 (**4g**)	Me (**5a**)	**6g**	17	75	91 : 9	99
8	*p*-ClC_6H_4 (**4h**)	Me (**5a**)	**6h**	17	85	91 : 9	99
9	*p*-BrC_6H_4 (**4i**)	Me (**5a**)	**6i**	17	80	89 : 11	98
10	*p*-MeC_6H_4 (**4j**)	Me (**5a**)	**6j**	17	70	90 : 10	98
11	*m*-$CH_3C_6H_4$ (**4k**)	Me (**5a**)	**6k**	17	74	>99 : 1	>99
12[d]	Furyl (**4l**)	Me (**5a**)	**6l**	17	75	>99 : 1	>99
13	*trans*-PhCH=CH (**4m**)	Me (**5a**)	**6m**	17	65	>99 : 1	96
14	*o*-ClC_6H_4 (**4n**)	Et (**5b**)	**6n**	42	68	55 : 45	90
15	*m*-ClC_6H_4 (**4e**)	Et (**5b**)	**6o**	42	71	72 : 28	93
16	CH_2=CH (**4o**)	Me (**5a**)	**6p**	36	—	—	—

[a] Reaction conditions: phosphoramidate **4** (0.3 mmol), 2-nitropropanoate **5** (0.45 mmol), in 3 mL of toluene at −20 °C in the presence of 5 mol% of catalyst **3a**. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC analysis. [d] Determined after one recrystallization.

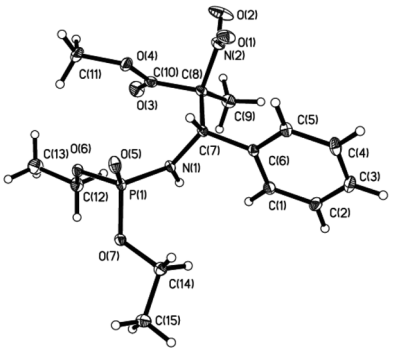
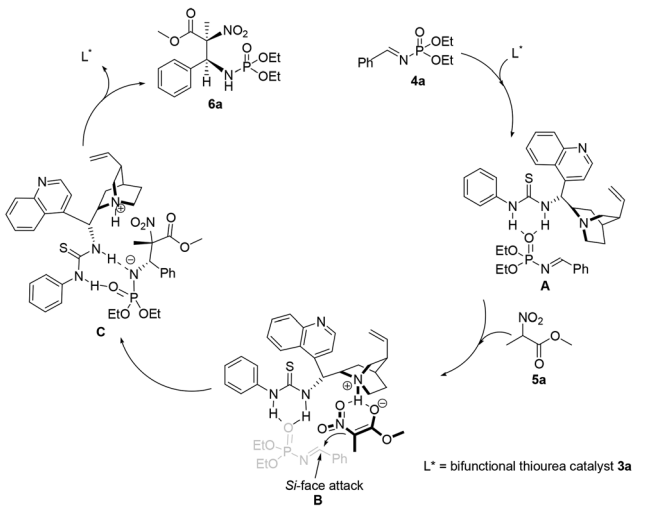


Fig. 2 X-ray crystal structure of **6a**.



Scheme 1 Plausible reaction mechanism.

stereochemistry at the quaternary stereogenic center was successfully determined to be the *S* configuration (Fig. 2).[21]

In Scheme 1 a proposal for the catalytic cycle of the new nitro-Mannich reaction is suggested to account for the catalytic activity, and for the diastereo- and enantioselectivity. According to our observations, a double hydrogen bonding interaction may be formed between the two N–H groups of the thiourea and the P=O group of the *N*-phosphoryl imine as complex **A** to increase its electrophilicity. When methyl 2-nitropropanoate **5a** was added to the mixture, another double hydrogen bonding interaction would occur between the protonated tertiary amine group and the carbonyl and nitro groups of the α-substituted nitroacetate (intermediate **B**). Subsequently, the *Si*-face attack of the electrophilic imine through the *Si*-face of the enolate is restricted by the *cinchona* alkaloid scaffold of the catalyst and affords the desired Mannich adduct **6** with (*S*,*S*) configuration (intermediate **C**). The mechanism indicates that the thiourea and *cinchona* alkaloid scaffold of the bifunctional catalyst play a significant role in controlling the enantioselectivity of the addition reaction.

In order to further investigate the mechanism, the formation of **6a** was followed by ^{31}P NMR spectroscopy as shown in Fig. 3.[22] The starting material diethyl benzylidenephosphoramidate **4a** in toluene showed ^{31}P NMR at 7.68 ppm. After catalyst **3a** (0.0085 g, 5 mol%) and methyl 2-nitropropanoate **5a** were added to the solution of **4a**, the single peak changed from 7.68 to 8.26 ppm, which can be assigned to complex **A**, and a new single peak at 5.67 ppm appeared. The new single peak was assigned to the intermediate **C**. The expected nucleophilic addition product was formed (single peak at 5.67 ppm) in 1.5 hours (complex **C**). As time passed, the ^{31}P NMR signals

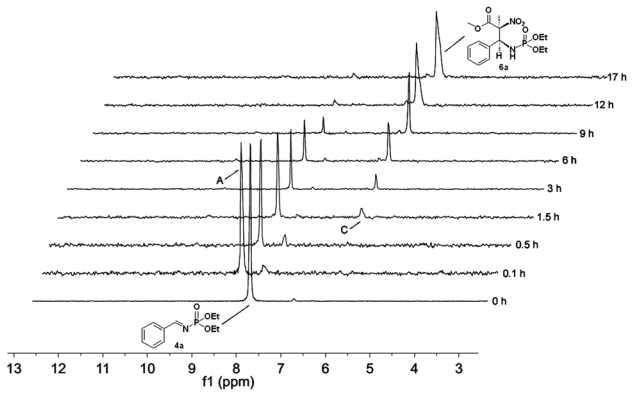


Fig. 3 Time elapsed ^{31}P NMR spectra for the synthesis of **6a** (ppm).

of the starting material disappeared gradually, and the signals of **6a** (single peaks at 5.67 ppm) increased. The reaction was almost completed after 17 h according to the ^{31}P NMR spectra (Fig. 3).

Conclusions

In conclusion, we have presented the highly stereoselective nitro-Mannich reaction of α-substituted nitroacetate and *N*-phosphoryl aldimines by employing bifunctional thiourea–tertiary amine catalysts. This methodology provides facile access to substituted β-nitro ethylphosphoramidate derivatives with adjacent quaternary and tertiary chiral centers with good to excellent diastereo- and enantioselectivities. Further application of these catalysts to other asymmetric reactions and expansion of the new bifunctional organocatalysts are currently underway in our laboratory.

Experimental

General remarks

All reactions were carried out under an inert atmosphere and in heat-dried glassware. Solvents were dried and distilled prior to use according to the standard methods. Flash column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 121 MHz for ^{31}P). Chemical shifts were reported in ppm downfield from internal $Si(CH_3)_4$. HPLC analyses were recorded on a chiral column Daicel Chiralcel AD-H column or a AS-H column, at 220 nm. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were recorded on a LCQ advantage spectrometer with ESI resource. HR-MS were recorded on APEXII and ZAB-HS spectrometer. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter. Melting points were determined on a T-4 melting point apparatus (uncorrected).

General procedure for the synthesis of β-nitro ethylphosphoramidates 6. To a solution of *N*-phosphoryl imines **4** (0.3 mmol) and chiral catalyst **3a** (0.015 mmol, 5 mol%) in toluene (3.0 mL) was added 2-nitropropanoate **5** (0.45 mmol, 1.5 equiv.) at −20 °C under a nitrogen atmosphere. The mixture was stirred for the corresponding time at −20 °C (monitored by TLC). Then saturated NH_4Cl aq. (3 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude products **6**, which were purified by flash column chromatography on silica gel [petroleum ether (60–90 °C)–ethyl acetate, 1 : 1 (v/v)] to provide pure products **6**.

Methyl 3-((diethylphosphoryl)amino)-2-methyl-2-nitro-3-phenylpropanoate (6a). White solid; mp 114–117 °C; $[\alpha]_D^{20}$ = 48.8° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30–7.38 (m, 5H), 4.92 (dd, J = 11.5, 9.7 Hz, 1H), 4.83 (t, J = 11.5 Hz, 1H), 3.73–3.95 (m, 6H), 3.50–3.65 (m, 1H), 1.70 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.96, 136.74, 128.74, 128.61, 128.50, 94.89 (d, J = 8.1 Hz), 62.49 (d, J = 5.0 Hz), 62.37 (d, J = 5.0 Hz), 62.00, 53.60, 22.56, 16.00 (d, J = 7.5 Hz), 15.77 (d, J = 7.5 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.86, 5.67; HRMS (MALDI) calculated for $[C_{15}H_{23}N_2O_7P + H]^+$: 375.1321, found 375.1315.

Methyl 3-((diethylphosphoryl)amino)-3-(2-fluorophenyl)-2-methyl-2-nitropropanoate (6b). White solid; mp 68–71 °C; $[\alpha]_D^{20}$ = 56.4° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28–7.39 (m, 2H), 7.12–7.21 (m, 1H), 7.01–7.12 (m, 1H), 5.37 (dd, J = 11.4, 10.4 Hz, 1H), 4.75 (t, J = 11.4 Hz, 1H), 3.79–4.01 (m, 6H), 3.57–3.71 (m, 1H), 1.74 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.81, 160.20 (d, J = 247.2 Hz), 130.46, 129.46, 124.68, 124.36, 115.50 (d, J = 22.9 Hz), 94.81 (d, J = 7.9 Hz), 62.64 (d, J = 5.3 Hz), 62.39 (d, J = 5.4 Hz), 54.33 (s), 53.64 (s), 21.36 (d, J = 2.6 Hz), 15.98 (d, J = 7.4 Hz), 15.67 (d, J = 7.5 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.65, 5.39; HRMS (MALDI) calculated for $[C_{15}H_{22}FN_2O_7P + H]^+$: 415.1046, found 415.1044.

Methyl 3-((diethylphosphoryl)amino)-3-(2-bromophenyl)-2-methyl-2-nitropropanoate (6c). White solid; mp 80–83 °C; $[\alpha]_D^{20}$ = 9.8° (c = 0.01, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49–7.65 (m, 1H), 7.25–7.38 (m, 2H), 7.11–7.24 (m, 1H), 5.66 (t, J = 10.3 Hz, 1H), 4.91 (t, J = 11.6 Hz, 1H), 3.76–4.07 (m, 6H), 3.44–3.61 (m, 1H), 1.75 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.00 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 166.72, 136.60, 133.05, 130.22, 128.57, 128.41, 125.33, 96.43 (d, J = 8.8 Hz), 62.79 (d, J = 5.6 Hz), 62.41 (d, J = 5.5 Hz), 57.85, 54.00, 20.60, 16.12 (d, J = 7.7 Hz), 15.74 (d, J = 7.7 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.27, 5.14; HRMS (MALDI) calculated for $[C_{15}H_{22}BrN_2O_7P + Na]^+$: 475.0246, found 475.0242.

Methyl 3-((diethylphosphoryl)amino)-3-(3-fluorophenyl)-2-methyl-2-nitropropanoate (6d). White solid; mp 90–93 °C; $[\alpha]_D^{20}$ = 51.2° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27–7.38 (m, 1H), 6.97–7.20 (m, 3H), 4.92 (dd, J = 11.5, 9.4 Hz, 1H), 4.79 (t, J = 11.5 Hz, 1H), 3.75–3.99 (m, 6H), 3.51–3.75 (m, 1H), 1.71 (s, 3H),1.21 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.87, 162.64 (d, J = 247.3 Hz),

139.38, 130.11, 124.47, 115.75, 115.43, 94.72 (d, J = 7.9 Hz), 62.59 (d, J = 5.3 Hz), 62.48 (d, J = 5.2 Hz), 61.48, 53.72, 22.27, 15.99 (d, J = 7.4 Hz), 15.79 (d, J = 7.4 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.88, 5.66; HRMS (MALDI) calculated for $[C_{15}H_{22}FN_2O_7P + Na]^+$: 415.1046, found 415.1043.

Methyl 3-((diethoxyphosphoryl)amino)-3-(3-chlorophenyl)-2-methyl-2-nitropropanoate (6e). White solid; mp 89–92 °C; $[\alpha]_D^{20}$ 50.8° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35–7.43 (m, 1H), 7.28–7.35 (m, 3H), 4.66–4.99 (m, 2H), 3.75–3.99 (m, 6H), 3.58–3.74 (m, 1H), 1.72 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.84, 138.90, 134.52, 129.83, 128.90, 128.74, 126.83, 94.70 (d, J = 8.1 Hz), 62.63 (d, J = 5.3 Hz), 62.50 (d, J = 5.2 Hz), 61.44, 53.73, 22.28, 16.00 (d, J = 7.4 Hz), 15.79 (d, J = 7.4 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.87 (s), 5.65 (s); HRMS (MALDI) calculated for $[C_{15}H_{22}ClN_2O_7P + Na]^+$: 431.0751, found 431.0748.

Methyl 3-((diethoxyphosphoryl)amino)-3-(3-bromophenyl)-2-methyl-2-nitropropanoate (6f). White solid; mp 73–75 °C; $[\alpha]_D^{20}$ = 50.8° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.50–7.56 (m, 1H), 7.43–7.50 (m, 1H), 7.28–7.34 (m, 1H), 7.19–7.25 (m, 1H), 4.88 (dd, J = 11.5, 9.2 Hz, 1H), 4.79 (t, J = 11.5 Hz, 1H), 3.76–3.97 (m, 6H), 3.62–3.72 (m, 1H), 1.72 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.83, 139.15, 131.85, 131.66, 130.11, 127.25, 122.61, 94.69 (d, J = 7.8 Hz), 62.64 (d, J = 5.2 Hz), 62.52 (d, J = 5.2 Hz), 61.45, 53.74, 22.38, 16.02 (d, J = 7.5 Hz), 15.81 (d, J = 7.5 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.87, 5.64; HRMS (MALDI) calculated for $[C_{15}H_{22}BrN_2O_7P + Na]^+$: 475.0246, found 475.0243.

Methyl 3-((diethylphosphoryl)amino)-3-(4-fluorophenyl)-2-methyl-2-nitropropanoate (6g). White solid; mp 99–102 °C; $[\alpha]_D^{20}$ = 28.0° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34–7.42 (m, 2H), 7.01–7.11 (m, 2H), 4.93 (dd, J = 11.5, 9.2 Hz, 1H), 4.80 (t, J = 11.5 Hz, 1H), 3.77–3.98 (m, 6H), 3.62–3.73 (m, 1H), 1.72 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.94, 162.73 (d, J = 248.6 Hz), 132.70, 130.35, 115.55, 94.84 (d, J = 8.1 Hz), 62.58 (d, J = 5.3 Hz), 62.49 (d, J = 5.3 Hz), 61.38, 53.67, 22.48, 16.02 (d, J = 7.4 Hz), 15.84 (d, J = 7.4 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 6.05, 5.84; HRMS (MALDI) calculated for $[C_{15}H_{22}FN_2O_7P + Na]^+$: 415.1046, found 415.1044.

Methyl 3-((diethylphosphoryl)amino)-3-(4-chlorophenyl)-2-methyl-2-nitropropanoate (6h). White solid; mp 103–105 °C; $[\alpha]_D^{20}$ = 48.0° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28–7.38 (m, 4H), 4.90 (dd, J = 11.5, 9.3 Hz, 1H), 4.79 (t, J = 11.5 Hz, 1H), 3.75–3.98 (m, 6H), 3.61–3.73 (m, 1H), 1.70 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.87, 135.33, 134.74, 129.96, 128.76, 94.73 (d, J = 7.9 Hz), 62.64 (d, J = 5.3 Hz), 62.54 (d, J = 5.3 Hz), 61.40 (d, J = 2.2 Hz), 53.71, 22.38, 16.02 (d, J = 7.4 Hz), 15.85 (d, J = 7.4 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.85, 5.63; HRMS (MALDI) calculated for $[C_{15}H_{22}ClN_2O_7P + Na]^+$: 431.0751, found 431.0747.

Methyl 3-((diethylphosphoryl)amino)-3-(4-bromophenyl)-2-methyl-2-nitropropanoate (6i). White solid; mp 104–107 °C; $[\alpha]_D^{20}$ = 26.2° (c = 0.01, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36–7.57 (m, 2H), 7.08–7.21 (m, 2H), 4.89 (dd, J = 11.4, 10.0 Hz, 1H), 4.66 (t, J = 11.4 Hz, 1H), 3.78–4.00 (m, 6H), 3.64–3.78 (m, 1H), 1.74 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 166.53, 135.54, 131.68, 130.07, 122.92, 95.88 (d, J = 8.5 Hz), 62.70, 62.62 (d, J = 5.8 Hz), 60.15, 53.84, 20.63, 16.03 (d, J = 7.2 Hz), 15.87 (d, J = 7.2 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.98, 5.77; HRMS (MALDI) calculated for $[C_{15}H_{22}BrN_2O_7P + Na]^+$: 475.0246, found 475.0244.

Methyl 3-((diethylphosphoryl)amino)-2-methyl-2-nitro-3-(*p*-tolyl)propanoate (6j). White solid; mp 100–103 °C; $[\alpha]_D^{20}$ = 44.0° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23–7.27 (m, 2H), 7.14–7.19 (m, 2H), 4.87–4.95 (m, 1H), 4.81 (t, J = 11.4 Hz, 1H), 3.77–3.99 (m, 6H), 3.57–3.66 (m, 1H), 2.36 (s, 3H), 1.71 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.07 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 166.00, 138.59, 133.69, 129.26, 128.35, 94.97 (d, J = 8.1 Hz), 62.47 (d, J = 5.1 Hz), 62.37 (d, J = 4.9 Hz), 61.74, 53.57, 22.60, 21.09, 16.03 (d, J = 7.4 Hz), 15.80 (d, J = 7.4 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 6.07, 5.87; HRMS (MALDI) calculated for $[C_{16}H_{25}N_2O_7P + Na]^+$: 411.1297, found 411.1293.

Methyl 3-((diethoxyphosphoryl)amino)-2-methyl-2-nitro-3-(*m*-tolyl)propanoate (6k). White solid; mp 102–105 °C; $[\alpha]_D^{20}$ = 50.9° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24–7.29 (m, 2H), 7.12–7.17 (m, 2H), 4.84–4.92 (m, 1H), 4.75–4.83 (m, 1H), 3.74–3.96 (m, 6H), 3.54–3.63 (m, 1H), 2.34 (s, 3H), 1.69 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H), 1.03 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 164.96, 137.24, 135.64, 128.41, 128.23, 127.47, 124.38, 93.86 (d, J = 8.0 Hz), 61.43 (d, J = 5.0 Hz), 61.30 (d, J = 5.1 Hz), 60.96, 52.52, 21.63, 20.41, 14.98 (d, J = 7.6 Hz), 14.74 (d, J = 7.6 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.71; HRMS (MALDI) calculated for $[C_{16}H_{25}N_2O_7P + Na]^+$: 411.1297, found 411.1295.

Methyl 3-((diethylphosphoryl)amino)-3-(furan-2-yl)-2-methyl-2-nitropropanoate (6l). White solid; mp 84–87 °C; $[\alpha]_D^{20}$ = 74.0° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34–7.37 (m, 1H), 6.28–6.46 (m, 2H), 5.11 (dd, J = 11.8, 9.9 Hz, 1H), 4.34 (t, J = 11.8 Hz, 1H), 3.70–4.02 (m, 7H), 1.76 (s, 3H), 1.11–1.29 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.71, 150.11, 142.65, 110.79, 109.77, 94.05 (d, J = 7.8 Hz), 62.66, 62.62, 55.51, 53.70, 21.40, 16.07, 15.96 (d, J = 7.5 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.98; HRMS (MALDI) calculated for $[C_{13}H_{21}N_2O_8P + Na]^+$: 387.0933, found 387.0935.

Methyl 3-((diethylphosphoryl)amino)-2-methyl-2-nitro-5-phenylpent-4-enoate (6m). White solid; mp 57–60 °C; $[\alpha]_D^{20}$ = 6.4° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30–7.47 (m, 5H), 6.71 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.8, 8.5 Hz, 1H), 4.44 (dd, J = 20.4, 9.0 Hz, 1H), 3.81–4.11 (m, 8H), 1.89 (s, 3H), 1.22–1.33 (m, 6H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 166.28, 135.71, 135.57, 128.73, 128.50, 126.70, 124.43, 95.05 (d, J = 7.3 Hz), 62.76, 62.69 (d, J = 4.7 Hz), 60.82, 53.61, 21.66, 16.17, 16.07 (d, J = 7.3 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 6.73; HRMS (MALDI) calculated for $[C_{17}H_{25}N_2O_7P + Na]^+$: 423.1297, found 423.1295.

Methyl 2-((2-chlorophenyl)((diethylphosphoryl)amino) methyl)-2-nitrobutanoate (6n). White solid; mp 59–62 °C; $[\alpha]_D^{20}$ = 7.0°

(c = 0.01, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36–7.41 (m, 1H), 7.23–7.31 (m, 2H), 7.12–7.18 (m, 1H), 5.57–5.75 (m, 1H), 4.65–4.85 (m, 1H), 3.77–4.03 (m, 6H), 3.43–3.62 (m, 1H), 2.16–2.30 (m, 1H), 1.82–1.99 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.62, 135.10, 134.06, 129.92, 129.65, 127.94, 127.63, 100.74 (d, J = 8.4 Hz), 62.70 (d, J = 5.5 Hz), 62.40 (d, J = 5.5 Hz), 55.59, 53.57, 27.09, 16.09 (d, J = 7.5 Hz), 15.75 (d, J = 7.5 Hz), 9.12; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.34, 5.19; HRMS (MALDI) calculated for $[C_{16}H_{24}ClN_2O_7P + Na]^+$: 445.0907, found 445.0905.

Methyl 2-((3-chlorophenyl)((diethylphosphoryl)amino)-methyl)-2-nitrobutanoate (6o). White solid; mp 58–60 °C; $[\alpha]_D^{20}$ = 27.6° (c = 0.005, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22–7.35 (m, 3H), 7.13–7.20 (m, 1H), 4.93–5.03 (m, 1H), 4.67–4.78 (m, 1H), 3.79–3.97 (m, 6H), 3.63–3.74 (m, 1H), 1.95–2.09 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 165.64, 139.07, 134.58, 129.90, 128.96, 128.18, 126.21, 98.34, 62.60 (d, J = 5.3 Hz), 62.50 (d, J = 5.1 Hz), 60.98, 53.49, 29.59, 15.99 (d, J = 7.5 Hz), 15.81 (d, J = 7.5 Hz), 9.02; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 5.75, 5.60; HRMS (MALDI) calculated for $[C_{16}H_{24}ClN_2O_7P + H]^+$: 423.1088, found 423.1086.

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