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Chiral phosphoric acid catalyzed 1,3-dipolar cycloadditions of aldehydes, diethyl α-aminomalonate, and nitroalkenes

Wenqiang Luo, Yongjun Lin, Dengshan Yang, Long He *

Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, Nanchong 637002, PR China

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ABSTRACT

A one-pot three component 1,3-dipolar cycloaddition reaction of an aldehyde, α-aminomalonate, and nitroalkene has been developed through binaphthol derived chiral phosphoric acids. This reaction represents one of the most enantioselective catalytic approaches to access structurally diverse pyrrolidine derivatives.

1. Introduction

Five-membered heterocycles, in particular highly substituted pyrrolidines, have features that are widely found within a wide variety of biologically active unnatural products, and in numerous natural alkaloids (Fig. 1).[1] Furthermore, they also serve as chiral building blocks or intermediates in the synthesis of natural alkaloids and medicinally relevant compounds, as well as organocatalysts in asymmetric catalysis.[2] Consequently, the development of efficient methods to construct enantiomerically pure pyrrolidine frameworks is undoubtedly appealing in organic synthesis.

Among the synthetic approaches to access pyrrolidine structural motifs,[3,4] the 1,3-dipolar cycloaddition reaction of azomethine ylides with electronically poor olefins represents one of the most efficient synthetic methods to construct these valuable heterocycles.[5,6] Chiral phosphoric acids containing a strongly acidic hydroxyl and Lewis basic phosphoryl oxygens pioneered by Akiyama et al. and Terada's et al.,[7] as efficient bifunctional catalysts have been widely applied to a large number of highly enantioselective organic transformations over the past few years.[8,9] Nitroalkenes (electronically poor olefins) are broadly applicable to asymmetric reactions. Cycloaddition reactions of nitroalkenes with azomethine ylides catalyzed by metal-complexes and chiral thioureas have also been reported on.[6f,6m,6n,10] Despite this great success, the chiral phosphoric acid catalyzed cycloaddition of nitroalkenes has not received as much attention. Herein we report a highly diastereo- and enantioselective one-pot, three-component reaction of aldehydes, α-aminomalonates, and nitroalkenes to the synthesis of multi-substituted pyrrolidine derivatives in the presence of phosphoric acid (see Fig. 2).

2. Results and discussion

Initially, we started our investigation using 4-nitrobenzaldehyde **3a**, ethyl α-aminomalonate **4**, and *trans*-β-nitrostyrene **5a** in CH_2Cl_2 at room temperature in the presence of 3 Å molecular sieves catalyzed by 10 mol % of chiral biphosphoric acid **1** developed by Gong et al.[9a] Unfortunately, chiral phosphoric acid **1**, which exhibited high enantioselectivity in reactions with maleates, when catalyzing the reaction of nitroalkenes resulted in racemic products (entry 1). A catalyst survey of monophosphoric acids revealed that a substantial change of the 3,3′-subtituents had a significant effect on the reactivity and enantioselectivity of the cycloaddition. As shown in Table 1, most of the catalysts tested afforded high yields but with disappointing enantioselectivities (entries 2 to 10 and 12). Phosphoric acid **2j** gave the best result in the model reaction (88% yield), however, poor enantioselectivity was observed (54% ee, entry 11). It is worth noting that this reaction exhibited excellent diastereoselectivity (>95/5) by ^{1}H NMR analysis of the crude product.

Studying the effect of temperature showed that the enantioselectivity could be improved by performing the reaction at low temperature (entries 12–15). The enantioselectivity was increased to 68% ee when the reaction was carried out at −10 °C (entry 14), although the enantioselectivity did not improve and the yield decreased at lower temperatures. Screening of different solvents indicated that chloroform was the optimal choice (entries 16 to 18 and 14), affording the cycloaddition product **6a** in 80% yield and with 73% ee.

* Corresponding author. Tel.: +86 817 2568636.
E-mail address: longhe@cwnu.edu.cn (L. He).

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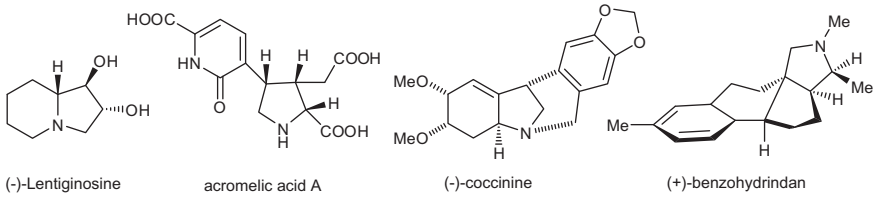


Figure 1. Representative natural products bearing the pyrrolidine framework.

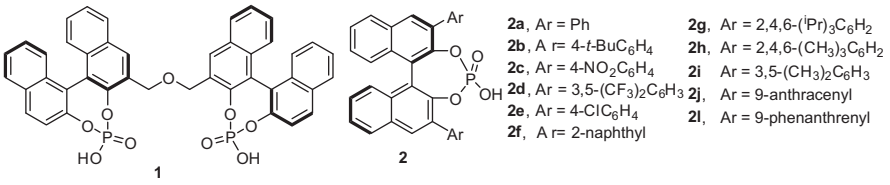
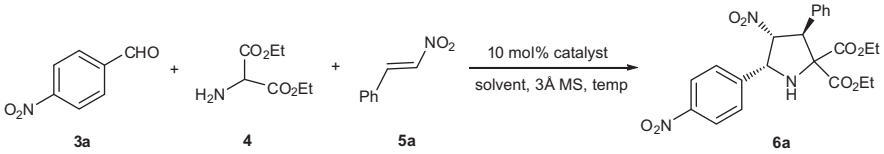


Figure 2. Chiral phosphoric acids evaluated in this study.

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Temp (°C)	Solvent	Yield[b] (%)	ee[c] (%)
1	**1**	25	CH_2Cl_2	77	1
2	**2a**	25	CH_2Cl_2	74	7
3	**2b**	25	CH_2Cl_2	77	7
4	**2c**	25	CH_2Cl_2	77	2
5	**2d**	25	CH_2Cl_2	78	24
6	**2e**	25	CH_2Cl_2	88	1
7	**2f**	25	CH_2Cl_2	77	2
8	**2g**	25	CH_2Cl_2	84	4
9	**2h**	25	CH_2Cl_2	60	9
10	**2i**	25	CH_2Cl_2	33	1
11	**2j**	25	CH_2Cl_2	88	54
12	**2k**	25	CH_2Cl_2	89	24
13	**2j**	0	CH_2Cl_2	80	63
14	**2j**	−10	CH_2Cl_2	79	68
15	**2j**	−25	CH_2Cl_2	45	68
16	**2j**	−10	1,2-DCE	76	70
17	**2j**	−10	$CHCl_3$	80	73
18	**2j**	−10	Toluene	71	26

[a] The reaction was carried out on a 0.1 mmol scale in a solvent (1 mL) with 3 Å MS (100 mg) for 24–96 h, and the ratio of **3a**/**4**/**5a** was 1.2:1:2.
[b] Isolated yield.
[c] ee values were determined by HPLC analysis and the absolute configuration was assigned by comparing specific rotations with literature values.[10b]

With the optimal conditions in hand, we first explored the generality of the current protocol, the cycloaddition between 4-nitrobenzaldehyde, ethyl α-aminomalonate, and different nitroalkenes with electron withdrawing substituents, as well as electron donating substituents on the phenyl motif. All of the reactions proceeded smoothly and furnished the desired cycloaddition adducts **6b**–**6h** in high yields and with moderate to good enantioselectivities (entries 1–7). The cycloaddition of a variety of aldehydes also takes place with moderate to high enantioselectivities (entries 8–13). However, electron rich benzaldehydes and alkyl-substituted nitroolefins failed to afford the desired product in the current catalytic system (entries 14–15).

3. Conclusion

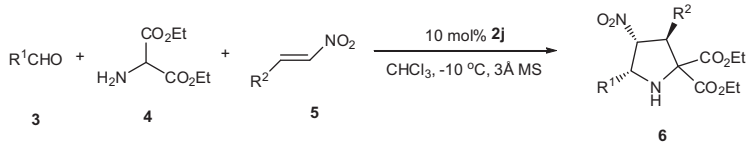
In conclusion, we have developed a chiral phosphoric acid catalyzed one-pot, three component 1,3-dipolar cycloaddition reaction of aldehydes, ethyl α-aminomalonate, and a variety of nitroalkenes, providing multi-substituted pyrrolidine derivatives in high yields and with excellent diastereoselectivities with moderate to high enantioselectivities.

4. Experimental

4.1. General

NMR spectra were recorded on a Brucker-400 MHz spectrometer. Melting points were determined on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump, UV detection monitored at 254 nm or 205 nm). Chiralpak columns were purchased from Daicel Chemical

Table 2
Generality for nitroalkenes and aldehydes[a]



Entry	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	4-$NO_2C_6H_4$	4-BrC_6H_4	**6b**	84	77
2	4-$NO_2C_6H_4$	3-$NO_2C_6H_4$	**6c**	90	65
3	4-$NO_2C_6H_4$	4-ClC_6H_4	**6d**	85	70
4	4-$NO_2C_6H_4$	4-CNC_6H_4	**6e**	81	74
5	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	**6f**	71	70
6	4-$NO_2C_6H_4$	3-BrC_6H_4	**6g**	74	56
7	4-$NO_2C_6H_4$	3-ClC_6H_4	**6h**	71	57
8	4-BrC_6H_4	C_6H_5	**6i**	92	62
9	4-BrC_6H_4	4-BrC_6H_5	**6j**	88	70
10	4-ClC_6H_4	C_6H_5	**6k**	90	53
11	4-CNC_6H_4	4-BrC_6H_5	**6l**	86	84
12	4-CNC_6H_4	C_6H_5	**6m**	76	74
13	C_6H_5	C_6H_5	**6n**	42	23
14	4-$CH_3OC_6H_4$	C_6H_5	**6o**	—	—
15	4-$NO_2C_6H_4$	*i*-Pr	**6p**	—	—[d]

[a] The reaction was carried out on a 0.1 mmol scale in $CHCl_3$ (1 mL) with 3 Å MS (100 mg) at −10 °C for 48–96 h, and the ratio of **3**/**4**/**5** was 1.2:1:2.
[b] Isolated yield.
[c] ee values were determined by HPLC analysis and the absolute configuration was assigned by comparing specific rotations with literature values.[10b]
[d] None of the desired product was isolated, only affording the product from the intermolecular cycloaddition of azomethine ylides.

Industries, LTD. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin–Elmer-343 polarimeter.

4.2. General procedure for the asymmetric 1,3-dipolar cycloaddition reactions (Table 2)

To a solution of an aldehyde (0.12 mmol), catalyst **2j** (0.01 mmol), and 3 Å molecular sieves (100 mg) in $CHCl_3$ (1.0 mL) was added the amino ester (0.1 mmol), and then the nitroalkene (0.2 mmol). The reaction mixture was stirred at −10 °C until the reaction was complete (monitored by TLC). The reaction mixture was then filtered to remove the molecular sieves, and the solid powder was washed with ethyl acetate (5.0 mL). The resultant solution was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with ethyl acetate (5 mL × 3). The combined organic layers were then dried over anhydrous Na_2SO_4. After evaporation under reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 4:1–2:1) to yield pure products.

4.3. Diethyl 4-nitro-5-(4-nitrophenyl)-3-phenylpyrrolidine-2,2-dicarboxylate 6a

White solid, mp 128–130 °C, yield: 76%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.78 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.28 (d, J = 5.4 Hz, 1H), 3.53–3.58 (m, 1H), 3.90–3.95 (m, 1H), 4.29–4.41 (m, 2H), 5.13 (d, J = 7.0 Hz, 1H), 5.59–5.67 (m, 2H), 7.30–7.35 (m, 5H), 7.61 (d, J = 8.6 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.31, 51.84, 62.25, 62.36, 63.39, 75.92, 93.42, 123.64, 128.33, 128.51, 128.53, 128.79, 134.45, 144.07, 148.23, 168.22, 171.06; IR (KBr): γ 3366, 2977, 1716, 1612, 1574, 1514, 1445, 1333, 1283, 1194, 1103, 1063, 862, 712; Enantiomeric excess: 72%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.98 min (minor), t_R = 26.67 min (major); $[\alpha]_D^{20}$ = +29.3 (c 0.43, CH_2Cl_2).

4.4. Diethyl 3-(4-bromophenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6b

White solid, mp 142–145 °C, yield: 84%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.86 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.28 (d, J = 5.4 Hz, 1H), 3.61–3.70 (m, 1H), 3.92–3.95 (m, 1H), 4.27–4.43 (m, 2H), 5.05 (d, J = 7.7 Hz, 1H), 5.56–5.67 (m, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.42, 13.99, 51.12, 62.44, 62.47, 62.87, 92.72, 122.71, 123.64, 128.37, 130.25, 131.91, 133.16, 143.98, 148.25, 168.05, 170.90; IR (KBr): γ 3364, 2953, 1719, 1586, 1547, 1335, 1282, 1202, 1102, 1003, 896, 724, 671; Enantiomeric excess: 77%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.26 min (minor), t_R = 34.47 min (major); $[\alpha]_D^{20}$ = +55.4 (c 0.39, CH_2Cl_2).

4.5. Diethyl 4-nitro-3-(3-nitrophenyl)-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6c

White solid, mp 155–158 °C, yield: 90%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.79 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 3.27 (d, J = 5.5 Hz, 1H), 3.60–3.68 (m, 1H), 3.92–4.00 (m, 1H), 4.20–4.36 (m, 2H), 5.09 (d, J = 8.6 Hz, 1H), 5.56 (q, J = 8.8 Hz, 1H), 5.68 (t, J = 8.8 Hz, 1H), 7.47 (q, J = 8.1 Hz, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 8.11–8.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$); 12.48, 12.95, 50.09, 61.35, 61.59, 61.69, 74.25, 91.18, 122.37, 122.56, 122.63, 127.50, 127.82, 134.31, 135.05, 142.83, 147.30, 147.35, 166.79, 169.58; IR (KBr): 3353, 3094, 2970, 2925, 1738, 1626, 1568, 1500, 1456, 1332, 1264, 1206, 1140, 1060, 867, 745, 657; Enantiomeric excess: 65%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 25.56 min (minor), t_R = 52.41 min (major); $[\alpha]_D^{20}$ = +47.1 (c 0.87, CH_2Cl_2).

4.6. Diethyl 3-(4-chlorophenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6d

Colorless foam, yield: 85%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.86 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 3.28 (d, J = 5.3 Hz, 1H), 3.62–3.70 (m, 1H), 3.95–4.03 (m, 1H), 4.26–4.43 (m, 2H), 5.07 (d, J = 7.7 Hz, 1H), 5.57–5.67 (m, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 12.40, 12.97, 50.04, 61.40, 61.45, 61.85, 74.53, 91.79, 122.61, 127.35, 127.91, 128.93, 131.62, 133.60, 142.99, 147.22, 167.05, 169.89; IR (KBr): γ 3356, 2977, 1742, 1685, 1591, 1437, 1371, 1288, 1229, 1105, 1040, 857, 773, 707; Enantiomeric excess: 70%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.51 min (minor), t_R = 34.38 min (major); $[\alpha]_D^{20}$ = +27.8 (c 0.78, CH_2Cl_2).

4.7. Diethyl 3-(4-cyanophenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6e

White solid, mp 136–138 °C, yield: 81%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.85 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 3.31 (d, J = 5.6 Hz, 1H), 3.59–3.68 (m, 1H), 3.97–4.05 (m, 1H), 4.27–4.43 (m, 2H), 5.14 (d, J = 8.0 Hz, 1H), 5.59–5.62 (m, 1H), 5.68 (q, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.48, 13.97, 51.35, 62.51, 62.67, 62.72, 75.45, 92.13, 112.62, 118.06, 123.67, 128.41, 129.57, 132.42, 139.42, 143.75, 148.31, 167.84, 170.57; IR (KBr): γ 3368, 3072, 2984, 2927, 2234, 1736, 1698, 1629, 1478, 1426, 1361, 1281, 1222, 1182, 1102, 1043, 865, 813, 762, 689; Enantiomeric excess: 74%, determined by HPLC (Daicel Chirapak IA-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.30 min (minor), t_R = 45.10 min (major); $[\alpha]_D^{20}$ = +61.4 (c 0.7, CH_2Cl_2).

4.8. Diethyl 3-(4-methoxyphenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6f

White solid, mp 134–136 °C, yield: 71%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.85 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.26 (d, J = 5.4 Hz, 1H), 3.61–3.68 (m, 1H), 3.38 (s, 3H), 3.93–4.00 (m, 1H), 4.28–4.41 (m, 2H), 5.04 (d, J = 7.4 Hz, 1H), 5.56–5.66 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 9.2 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.46, 14.01, 51.21, 55.35, 62.26, 62.29, 63.00, 75.72, 93.43, 114.14, 123.61, 126.07, 128.34, 129.68, 144.25, 148.19, 159.71, 168.31, 171.22; IR (KBr): γ 3353, 2979, 2875, 1747, 1618, 1587, 1558, 1528, 1449, 1359, 1270, 1230, 1041, 881, 822; Enantiomeric excess: 70%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 27.51 min (minor), t_R = 41.98 min (major); $[\alpha]_D^{20}$ = +46.4 (c 0.7, CH_2Cl_2).

4.9. Diethyl 3-(3-bromophenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6g

White solid, mp 164–167 °C, yield: 74%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.86 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.29 (d, J = 5.2 Hz, 1H), 3.67–3.74 (m, 1H), 3.95–4.01 (m, 1H), 4.29–4.41 (m, 2H), 5.06 (d, J = 7.4 Hz, 1H), 5.58–5.67 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 7.20 (q, J = 7.8 Hz, 2H), 7.35–7.44 (m, 2H), 7.45 (d, J = 6.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.42, 13.99, 51.29, 62.47, 62.51, 62.98, 75.63, 92.83, 122.76, 123.63, 127.48, 128.40, 130.31, 131.52, 131.68, 136.52, 143.93, 148.26, 167.97, 170.86; IR (KBr): γ 3322, 2979, 2890, 1725, 1601, 1545, 1518, 1474, 1346, 1287, 1207, 1145, 1112, 1046, 858, 778, 694; Enantiomeric excess: 56%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.79 min (minor), t_R = 27.73 min (major); $[\alpha]_D^{20}$ = +24.5 (c 0.4, CH_2Cl_2).

4.10. Diethyl 3-(3-chlorophenyl)-4-nitro-5-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate 6h

White solid, mp 154–157 °C, yield: 71%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.85 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.29 (d, J = 5.3 Hz, 1H), 3.65–3.69 (m, 1H), 3.94–3.98 (m, 1H), 4.27–4.38 (m, 2H), 5.07 (d, J = 7.5 Hz, 1H), 5.57–5.67 (m, 2H), 7.23–7.33 (m, 4H), 7.60 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.39, 13.98, 51.31, 62.45, 62.51, 62.98, 75.61, 92.82, 123.62, 126.91, 128.73, 134.69, 136.25, 143.95, 148.25, 167.99, 170.86; IR (KBr): γ 3348, 2977, 1738, 1658, 1591, 1378, 1258, 1223, 1105, 1040, 855, 707; Enantiomeric excess: 57%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.21 min (minor), t_R = 26.66 min (major); $[\alpha]_D^{20}$ = +25.9 (c 0.66, CH_2Cl_2).

4.11. Diethyl 5-(4-bromophenyl)-4-nitro-3-phenylpyrrolidine-2,2-dicarboxylate 6i

White solid, mp 138–140 °C, yield: 92%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.76 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 3.21 (d, J = 5.4 Hz, 1H), 3.49–3.57 (m, 1H), 3.86–3.93 (m, 1H), 4.26–4.39 (m, 2H), 5.11 (d, J = 6.9 Hz, 1H), 5.44–5.48 (m, 1H), 5.57 (q, J = 7.0 Hz, 1H), 7.29–7.33 (m, 7H), 7.45 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.32, 14.00, 51.93, 62.07, 62.23, 63.83, 75.94, 93.55, 122.92, 128.33, 128.59, 128.94, 131.6, 134.91, 135.79, 168.43, 171.11; IR (KBr): γ 3375, 3001, 2924, 1746, 1565, 1481, 1462, 1362, 1267, 1211, 1140, 1044, 1012, 845, 745, 705; Enantiomeric excess: 62%, determined by HPLC (Daicel Chirapak IA-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.47 min (minor), t_R = 14.72 - min (major); $[\alpha]_D^{20}$ = 24.1 (c 0.86, CH_2Cl_2).

4.12. Diethyl 3,5-bis(4-bromophenyl)-4-nitropyrrolidine-2,2-dicarboxylate 6j

White solid, mp 104–106 °C, yield: 88%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.84 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 3.21 (d, J = 5.4 Hz, 1H), 3.58–3.67 (m, 1H), 3.91–3.99 (m, 1H), 4.23–4.39 (m, 2H), 5.04 (d, J = 7.6 Hz, 1H), 5.42–5.45 (m, 1H), 5.55 (q, J = 8.0 Hz, 1H), 7.21 (d, J = 6.8 Hz, 2H), 7.26 (q, J = 8.4 Hz, 2H), 7.44–7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.43, 13.99, 51.18, 62.27, 62.35, 63.31, 75.52, 92.83, 122.51, 123.00, 128.98, 130.32, 131.66, 131.82, 133.64, 135.74, 168.26, 170.94; IR (KBr): γ 3365, 2983, 2926, 1745, 1554, 1489, 1410, 1364, 1285, 1201, 1155, 1071, 1031, 1011, 858, 807, 737; Enantiomeric excess: 70%, determined by HPLC (Daicel Chirapak IA-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.02 min (minor), t_R = 17.08 min (major); $[\alpha]_D^{20}$ = +43.4 (c 1.0, CH_2Cl_2).

4.13. Diethyl 5-(4-chlorophenyl)-4-nitro-3-phenylpyrrolidine-2,2-dicarboxylate 6k

White solid, mp 142–144 °C, yield: 90%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.77 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 3.21 (d, J = 5.4 Hz, 1H), 3.49–3.58 (m, 1H), 3.86–3.94 (m, 1H), 4.27–4.39 (m, 2H), 5.12 (d, J = 6.9 Hz, 1H), 5.46–5.50 (m, 1H), 5.57 (q, J = 7.2 Hz, 1H), 7.29–7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.32, 13.99, 51.93, 62.06, 62.23, 63.79, 75.94, 93.62, 128.33, 128.60, 128.63, 128.70, 134.69, 134.93, 135.25, 168.44, 171.12; IR (KBr): γ 3357, 2981, 1739, 1549, 1490, 1442, 1366, 1279, 1211, 1155, 1087, 1052, 1009, 849, 761, 698; Enantiomeric excess: 53%, determined by HPLC (Daicel Chirapak IA-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.03 min (minor), t_R = 13.39 min (major); $[\alpha]_D^{20}$ = +19.3 (c 0.76, CH_2Cl_2).

4.14. Diethyl 3-(4-bromophenyl)-5-(4-cyanophenyl)-4-nitropyrrolidine-2,2-dicarboxylate 6l

Yield: 86%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.86 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 3.25 (d, J = 5.5 Hz, 1H), 3.62–3.67 (m, 1H), 3.96–4.00 (m, 1H), 4.26–4.39 (m, 2H), 5.03 (d, J = 7.9 Hz, 1H), 5.51–5.54 (m, 1H), 5.61 (q, J = 8.1 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.42, 13.98, 51.08, 62.41, 62.44, 63.08, 75.47, 92.67, 112. 81, 118.42, 122.67, 128.17, 130.25, 131.89, 133.21, 142.11, 168.09, 170.90; IR (KBr): γ 3357, 2993, 2235, 1727, 1609, 1549, 1484, 1406, 1374, 1283, 1211, 1147, 1048, 1008, 853, 809; Enantiomeric excess: 84%, determined by HPLC (Daicel Chirapak IA-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.61 min (minor), t_R = 31.59 min (major); $[\alpha]_D^{20}$ = +59.3 (c 0.82, CH_2Cl_2).

4.15. Diethyl 5-(4-cyanophenyl)-4-nitro-3-phenylpyrrolidine-2,2-dicarboxylate 6m

Colorless foam, yield: 76%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.77 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 3.25 (d, J = 5.5 Hz, 1H), 3.53–3.57 (m, 1H), 3.89–3.93 (m, 1H), 4.28–4.40 (m, 2H), 5.11 (d, J = 7.1 Hz, 1H), 5.53–5.56 (m, 1H), 5.62 (q, J = 7.7 Hz, 1H), 7.30–7.35 (m, 5H), 7.54 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13.31, 13.99, 51.81, 62.22, 62.33, 63.61, 93.38, 112.74, 118.47, 128.14, 128.48, 128.53, 128.78, 132.26, 134.49, 142.20, 168.26, 171.06; IR (KBr): γ 3356, 2921, 2227, 1755, 1561, 1458, 1362, 1287, 1219, 1135, 1032, 853, 745, 698; Enantiomeric excess: 74%, determined by HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.35 min (minor), t_R = 18.84 -min (major); $[\alpha]_D^{20}$ = +28.6 (c 0.67, CH_2Cl_2).

4.16. Diethyl-4-nitro-3,5-diphenylpyrrolidine-2,2-dicarboxylate 6n

Colorless foam, yield: 42%; (Flash column chromatography eluent, petroleum ether/ethyl acetate 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.76 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 3.22 (d, J = 5.4 Hz, 1H), 3.51–3.56 (m, 1H), 3.86–3.91 (m, 1H), 4.27–4.39 (m, 2H), 5.14 (d, J = 6.7 Hz, 1H), 5.48–5.52 (m, 1H), 5.58–5.62 (m, 1H), 7.28–7.36 (m, 8H), 7.40–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); 13,4, 13.9, 50.9, 62.3, 62.4, 62.9, 74.5, 93.0, 115.6, 115.8, 123.6, 128.5, 130.2, 130.3, 144.0, 148.2, 161.4, 163.9, 168.1, 171.0; IR (KBr): γ 3357, 2983, 2928, 2235, 1737, 1486, 1406, 1364, 1281, 1211, 1048, 819; Enantiomeric excess: 23%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.45 min (major), t_R = 16.36 min (minor); $[\alpha]_D^{20}$ = 26.6 (c 0.43, CH_2Cl_2).

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