

## **A g ( I ) / S E C - A M I N E - A M I D P H O S - C A T A L Y Z E D ENDO-STEREOSELECTIVE SYNTHESIS OF FULLY SUBSTITUTED PYRROLIDINES VIA 1,3-DIPOLAR CYCLOADDITION BASED ON AZOMETHINE YLIDES**

**Haifei Wang,<sup>1</sup> Chen Zhang,<sup>1</sup> Jialin Liu,<sup>1</sup> Xinluo Song,<sup>1</sup> and Haiyun Jiang<sup>2\*</sup>**

<sup>1</sup>College of Life Science and Chemistry, Hunan University of Technology, Zhuzhou 412007, P. R. of China. <sup>2</sup>College of Packaging and Materials Engineering, Hunan University of Technology, Zhuzhou 412007, P. R. China.  
E-mail:jhyun@163.com

**Abstract** – Cooperative catalysis using multifunctional organic scaffolds in combination with transition-metal ions is emerging as a powerful tool in asymmetric synthesis. In this report, a series of multifunctional amidophosphanes derived from substituted 1,2-benzenediamine or 2-aminobenzylamine and chiral  $\alpha$ -amino acids, in combination with silver(I) salts, have been developed to cooperatively catalyze the azomethine ylides-involved 1,3-dipolar cycloaddition with maleates. Under optimal conditions, fully substituted *endo*-pyrrolidines were obtained in high to excellent yields (up to 92% yield) and enantioselectivities (up to 94% ee).

### **INTRODUCTION**

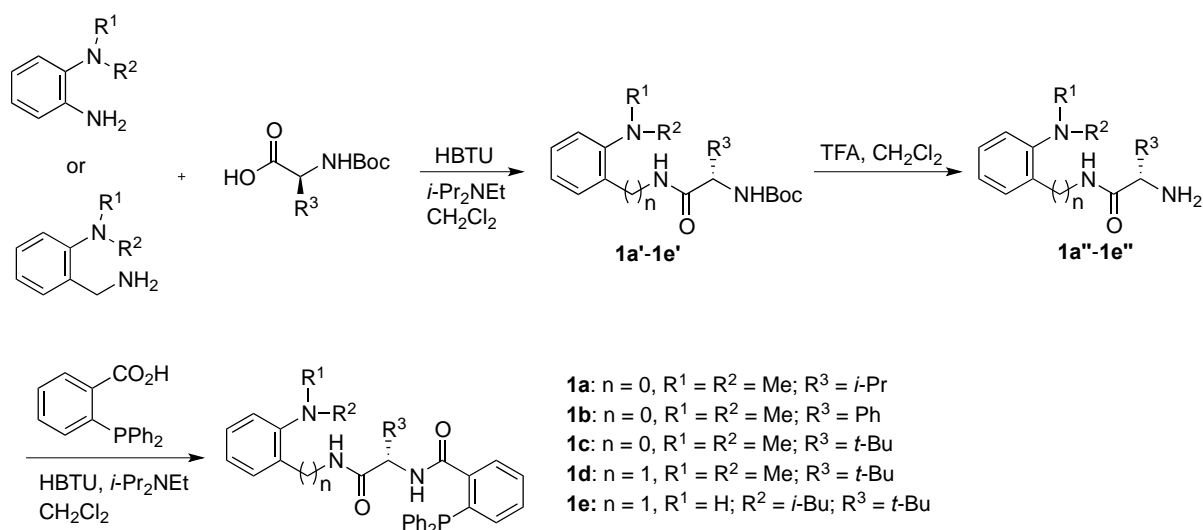
Chiral pyrrolidine derivatives are prevalent in natural products and biologically active molecules and also play a significant role in acting as chiral ligands or organocatalysts.<sup>1</sup> Owing to the importance of this structural motif, the catalytic enantioselective construction of various substituted pyrrolidines has received increasing attention, and great progress has been made in recent years.<sup>2</sup> Among these, chiral metal complexes-catalyzed azomethine ylides-involved 1,3-dipolar cycloaddition with electron-deficient alkenes is one of the most effective strategies for the preparation of such medicinally useful and synthetically challenging molecules with different stereochemical selectivities.<sup>3</sup> Since the first asymmetric version of 1,3-dipolar cycloaddition for affording fully substituted pyrrolidine derivatives reported by Zhang et al. via the AgOAc/xylyl-FAP/*i*-Pr<sub>2</sub>NEt catalytic system,<sup>4a</sup> a relatively broad range of chiral metal complex catalysts, including Ag(I),<sup>4</sup> Cu(I)/Cu(II),<sup>5</sup> Zn(II),<sup>6</sup> Ni(II),<sup>7</sup> Ca(II),<sup>8</sup> and Au(I),<sup>9</sup> in

combination with different bidentate ligands (such as P,P-ligands, P,N-ligands, P,S-ligands, N,N-ligands, and N,O-ligands, et al.), have been successfully applied in the azomethine ylides-involved 1,3-dipolar cycloaddition to construct structurally and stereochemically rich pyrrolidine derivatives. In spite of the aforementioned enormous achievements, it is still necessary to develop novel multifunctional catalytic systems that can be easily prepared with different phosphines. Recently, we have developed a class of amide-induced multidentate amidophosphane precatalysts derived from different scaffolds (such as cinchona alkaloids, chiral 1,2-diphenylethylenediamines and  $\alpha$ -amino acids) serving as the desired multifunctional precatalysts in combination with Ag(I) ions to cooperatively catalyze azomethine ylides-involved 1,3-dipolar cycloadditions with high diastereo- and enantioselectivities.<sup>10</sup> In order to develop inexpensive multifunctional amidophosphanes with different skeletons and expand its application, we herein report a class of substituted 1,2-benzenediamine or 2-aminobenzylamine and chiral  $\alpha$ -amino acids-derived multifunctional amidophosphanes containing two amide bonds as the H-bond donors, a *tert*- or *sec*-amine as the base, and a *tert*-phosphine ligand in combination with Ag(I) to cooperatively catalyze azomethine ylides-involved 1,3-dipolar cycloaddition with maleates to construct fully substituted *endo*-pyrrolidine derivatives with four contiguous stereocenters and high to excellent *endo/exo*-diastereo- and enantioselectivities.

## RESULTS AND DISCUSSION

### 1. Synthesis of Amidophosphanes 1a–e

As illustrated in Scheme 1, multifunctional amidophosphane precatalysts **1a–e** were easily prepared from substituted 1,2-benzenediamine or 2-aminobenzylamine and different natural  $\alpha$ -amino acids via three steps according to our reported procedures.<sup>10a</sup> Among these, amidophosphanes **1a–c** were synthesized



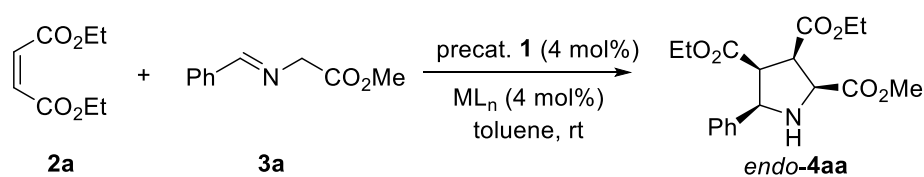
Scheme 1. Synthesis of amidophosphanes **1a–e**

from *N,N'*-dimethyl-1,2-benzenediamine and *N*-Boc-L-valine or *N*-Boc-L-phenylglycine or *N*-Boc-L-*tert*-leucine, respectively, while amidophosphanes **1d–e** from the corresponding substituted 2-aminobenzylamine and *N*-Boc-L-*tert*-leucine.

## 2. Optimization of 1,3-Dipole Cycloaddition Reaction Conditions

In our initial investigation,  $\alpha$ -iminoester **3a** and diethyl maleate **2a** were chosen as the model substrates to evaluate the 1,3-dipole cycloaddition reaction catalyzed cooperatively by silver(I) oxide and different amidophosphanes **1a–e** (Table 1, entries 1–5). Through the screening of amidophosphanes, we were pleased to find that the precatalyst **1e** derived from 2-aminobenzylamine and *L*-*tert*-leucine, with a terminal isobutylamino group, gave relatively satisfactory reactivity and enantioselectivity in combination with Ag<sub>2</sub>O (Table 1, entry 5). To further optimize the process, different metal salts, such as Ag<sub>2</sub>CO<sub>3</sub>, AgF, PhCO<sub>2</sub>Ag, AgOTf, and Cu(OTf)<sub>2</sub>, were also studied (entries 6–10). Disappointingly, the yields and

Table 1. Optimization of asymmetric 1,3-dipole cycloaddition reaction conditions



Entry	Precat. <b>1</b>	ML <sub>n</sub>	Time	Yield (%) <sup>a</sup>	Ee (%) <sup>b</sup>
1	<b>1a</b>	Ag <sub>2</sub> O	3	78	56
2	<b>1b</b>	Ag <sub>2</sub> O	3	82	54
3	<b>1c</b>	Ag <sub>2</sub> O	3	80	60
4	<b>1d</b>	Ag <sub>2</sub> O	3	86	87
5	<b>1e</b>	Ag <sub>2</sub> O	3	90	92
6	<b>1e</b>	Ag <sub>2</sub> CO <sub>3</sub>	3	88	91
7	<b>1e</b>	AgF	6	78	68
8	<b>1e</b>	PhCO <sub>2</sub> Ag	6	74	64
9	<b>1e</b>	AgOTf	10	trace	nd <sup>c</sup>
10	<b>1e</b>	Cu(OTf) <sub>2</sub>	10	trace	nd <sup>c</sup>
11 <sup>d</sup>	<b>1e</b>	Ag <sub>2</sub> O	4	87	92

<sup>a</sup>Isolated yield based on **2a**. <sup>b</sup>Determined by HPLC. <sup>c</sup>Not determined.

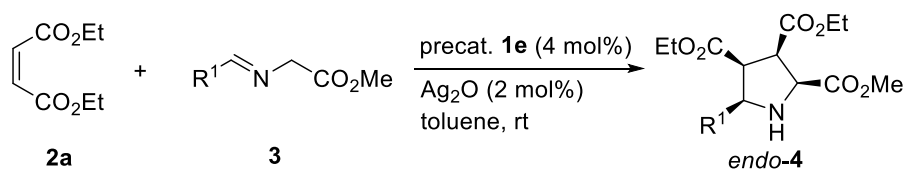
<sup>d</sup>Temperature = -5 °C.

enantioselectivities of *endo*-**4aa** adduct have not been greatly improved compared with the catalytic system Ag<sub>2</sub>O/**1e**. Next, through lowering the reaction temperature from room temperature to -5 °C, the enantioselectivity has not been improved with a prolonged reaction time (4 h, 92% ee, entry 11). Thus, the optimal conditions for the 1,3-dipole cycloaddition is Ag<sub>2</sub>O/**1e**/toluene at room temperature.

### 3. Substrate Scope of Asymmetric 1,3-Dipolar Cycloaddition

After the optimal reaction conditions were established, we proceeded to evaluate the scope of 1,3-dipole cycloaddition of various iminoesters **3** and diethyl maleate **2a**. As shown in Table 2, iminoesters **3a–j** from aromatic aldehydes bearing both electron-donating and -withdrawing groups regardless of their positions participated efficiently to react with diethyl maleate **2a**, affording the desired adducts **4aa–4aj** exclusively with 72–90% yields and 86–93% enantioselectivities (entries 1–10). Notably, iminoesters **3k** and **3l** containing heteroatoms in their aromatic rings can also effectively work with moderate to high yields (60–81%) and enantioselectivities (80–83% ee, entries 11–12).

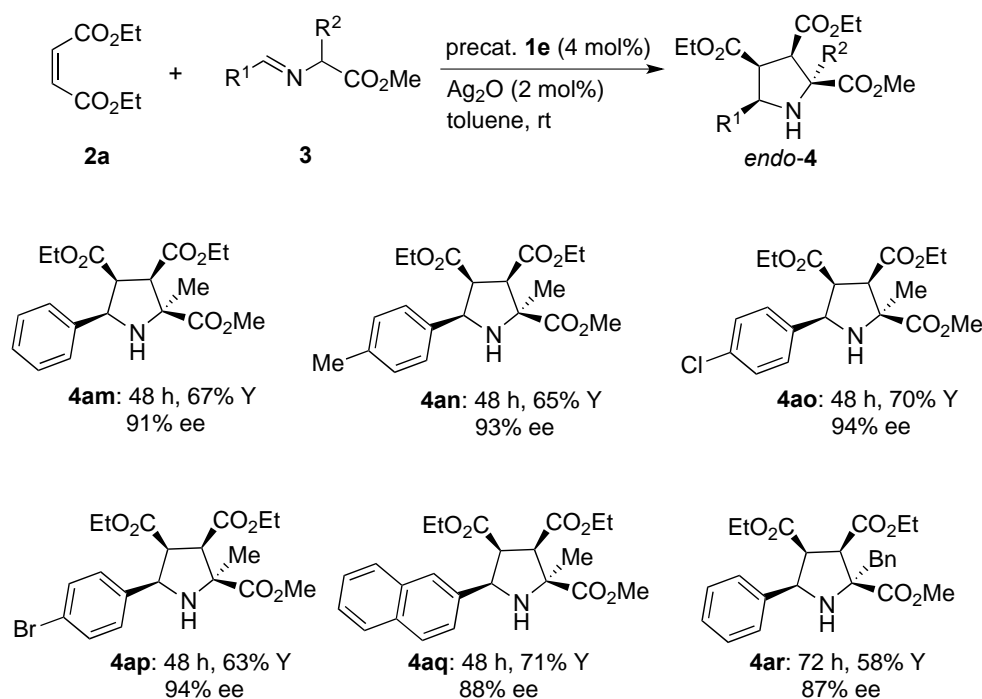
Table 2. Substrate scope of the synthesis of chiral fully substituted *endo*-pyrrolidines



Entry	<b>3</b> , R <sup>1</sup>	Time (h)	<b>4</b> , Yield (%) <sup>a</sup>	Ee (%) <sup>b</sup>
1	<b>3a</b> , C <sub>6</sub> H <sub>5</sub>	4	<b>4aa</b> , 90	92
2	<b>3b</b> , 4-MeC <sub>6</sub> H <sub>4</sub>	3	<b>4ab</b> , 85	88
3	<b>3c</b> , 4-MeOC <sub>6</sub> H <sub>4</sub>	4	<b>4ac</b> , 86	93
4	<b>3d</b> , 4-FC <sub>6</sub> H <sub>4</sub>	2	<b>4ad</b> , 90	91
5	<b>3e</b> , 4-ClC <sub>6</sub> H <sub>4</sub>	2	<b>4ae</b> , 88	90
6	<b>3f</b> , 3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	4	<b>4af</b> , 72	87
7	<b>3g</b> , 2-ClC <sub>6</sub> H <sub>4</sub>	3	<b>4ag</b> , 86	93
8	<b>3h</b> , 4-BrC <sub>6</sub> H <sub>4</sub>	2	<b>4ah</b> , 83	87
9	<b>3i</b> , 1-naphthyl	5	<b>4ai</b> , 90	92
10	<b>3j</b> , 2-naphthyl	6	<b>4aj</b> , 89	86
11	<b>3k</b> , 2-furyl	2	<b>4ak</b> , 81	83
12	<b>3l</b> , 2-thienyl	10	<b>4al</b> , 60	80

<sup>a</sup>Isolated yield based on **2a**. <sup>b</sup>Determined by HPLC.

Subsequently, the substrate scope and limitation of 1,3-dipole cycloaddition between the 2-substituted iminoesters **3** and diethyl maleate **2a** were also investigated. As depicted in Scheme 2, alanine-derived iminoesters **3m–q** were well tolerated with **2a** under the Ag<sub>2</sub>O/**1e** catalytic system, delivering the expected *endo*-pyrrolidines **4am–4aq** with a C2-quaternary stereocenter, with sole *endo*-selectivity and excellent enantioselectivities (88–94% ee). Furthermore, the phenylalanine-derived iminoester **3r** has also been successfully examined, affording the *endo*-adduct **4ar** with 58% yield and 87% enantioselectivity, albeit requiring prolonged reaction time.



Scheme 2. Substrate scope of *endo*-pyrrolidines with a C2-quaternary stereocenter

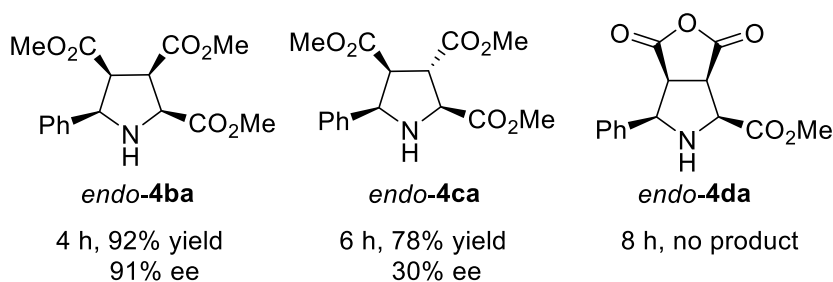
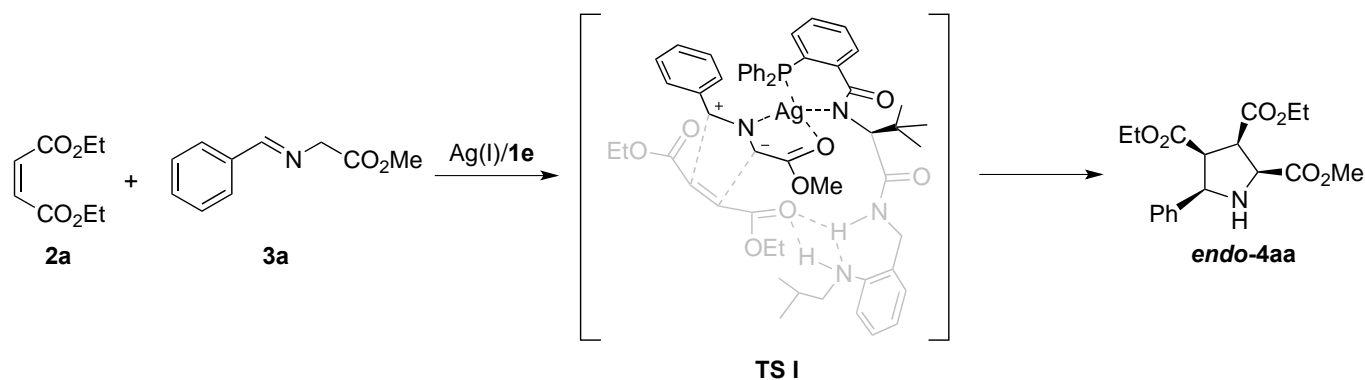


Figure 1. Cycloaddition of **3a** with other dipolarophiles

We also probed other three dipolarophiles as outlined in Figure 1. Dimethyl maleate as a popular dipolarophile was used to react with  $\alpha$ -iminoester **3a** with 92% yield and 91% ee. For dimethyl fumarate, much lower enantioselectivity was observed with 30% ee. However, when maleic anhydride was also used to react with  $\alpha$ -iminoester **3a** in 8 h, no desired product was obtained.

According to the above results and literatures,<sup>10a,11</sup> a postulated transition state stereinduction model is depicted in Scheme 3. The coordination of amide nitrogen and phosphorous in precatalyst **1e** and 1,3-dipole produced *in situ* derived from  $\alpha$ -iminoester **3a** by deprotonation to silver(I) would define the position of the two reactions by synergetic mechanism. The additional multiple hydrogen bond interaction between secondary amine, amide and ester oxygen could further refine the stereochemical environment, ultimately leading to the stereoscopic configuration of *endo*-**4aa**.



Scheme 3. Postulated catalyst activation mode

## CONCLUSION

In conclusion, we have developed the Ag(I)/*sec*-amine-Amidphos **1e**-catalyzed azomethine ylides-involved 1,3-dipolar cycloaddition with maleates and dimethyl fumarate, achieving fully substituted *endo*-**4** pyrrolidines in moderate to excellent yields (58%–92%) and enantioselectivities (30%–94%) under mild conditions, especially for the heterocyclic and 2-substituted iminoesters. Further investigations on mechanistic aspects and other applications are in progress.

## EXPERIMENTAL

### 1. Materials and Instruments

Most chemical reagents were purchased from Adamas-beta® Co., Ltd. (Shanghai, China), aladdin® Co., Ltd. (Shanghai, China) and Sigma-Aldrich Co. (St. Louis, Missouri, USA) and were used as received without further purification. <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded on a Bruker AV-400 spectrometer in CDCl<sub>3</sub>. CDCl<sub>3</sub> served as the internal standard ( $\delta = 7.26$ ) for <sup>1</sup>H NMR and ( $\delta = 77.0$ ) for <sup>13</sup>C-NMR. Chiral HPLC was performed on a Agilent 1260 apparatus equipped with a spectrophotometric detector (monitoring at 205–230 nm) with Daicel chiral AS-H, AD-H and OD-H columns. High-resolution mass spectrometry was recorded on Shimadzu LCMS-IT-TOF mass spectrometer. Optical rotations were measured on an Insmark IP-digi300/2 polarimeter. All reactions were monitored by thin-layer chromatography (TLC) plates (Qingdao Marine Chemistry Company, Qingdao, China). Flash column

chromatography was completed by using silica gel 200–300 (particle size 0.0040–0.0750 mm) (Qingdao Marine Chemistry Company, Qingdao, China).

## 2. General procedure of the synthesis of amidophosphanes 1a–e

### (*S*)-*N*-(1-((2-(Dimethylamino)phenyl)amino)-3-methyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (**1a**)

**Typical procedure:** compound **1a'** was prepared according to the reported procedure.<sup>10a</sup> **1a'** (335 mg, 1 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and TFA (1 mL) was dropwise added at 0 °C. Then, the reaction mixture was stirred for 7 h at rt. All volatile compounds were removed in vacuo and the residue was dissolved in water and treated with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 ×) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and then evaporation of the solvent, the crude free amine was obtained without purification for the next step. To a solution of the free amine in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU; 417 mg, 1.1 mmol), followed by the addition of *N,N*-diisopropylethylamine (367 μL, 2.2 mmol) and 2-(diphenylphosphino)benzoic acid (306 mg, 1 mmol). The reaction mixture was then stirred for 6 h at rt. The mixture was combined with CH<sub>2</sub>Cl<sub>2</sub> and water, and the organic layer was separated, washed with saturated aqueous NaHCO<sub>3</sub> solution (2 ×), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed in vacuo to afford the crude product as a colorless oil, which was purified by flash chromatography (20% EtOAc in hexanes) yielding precatalyst **1a** as a white solid (371 mg, 71%).

Mp 91–93 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -17.9 (c 0.85, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.78 (brs, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 7.66–7.65 (m, 1H), 7.40–7.06 (m, 15H), 6.96 (t, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.52 (dd, *J* = 7.2, 7.6 Hz, 1H), 2.60 (s, 6H), 2.17–2.12 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 6H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.9, 168.8, 143.1, 140.7, 140.5, 137.3, 137.2, 137.1, 136.8, 136.6, 134.3, 134.0, 133.8(d), 133.7, 133.0, 130.4, 128.7(d), 128.6, 128.5(d), 128.4, 127.7, 127.6, 125.0, 124.1, 120.2, 119.4, 59.8, 44.9, 31.7, 19.1, 18.4; <sup>31</sup>P-NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  -9.6; HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>P<sub>1</sub>: 524.2467; found: 524.2472.

### (*S*)-*N*-(2-((2-(Dimethylamino)phenyl)amino)-2-oxo-1-phenylethyl)-2-(diphenylphosphino)benzamide (**1b**)

Catalyst **1b** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1b'** (369 mg, 1.0 mmol), which yielded **1b** as a white solid (412 mg, 74%).

Mp 104–106 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +44.3 (c 1.24, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.68 (brs, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.71–7.69 (m, 1H), 7.48 (d, *J* = 5.6 Hz, 1H), 7.45–7.38 (m, 3H), 7.33–7.24 (m, 14H), 7.12–7.08 (m, 2H), 7.06–7.02 (m, 1H), 6.98–6.96 (m, 1H), 5.62 (d, *J* = 6.4 Hz, 1H), 2.38 (s, 6H);

$^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.3, 167.5, 143.0, 140.5, 140.3, 137.8, 137.3, 137.2, 137.1, 136.9(d), 136.7, 134.3, 134.0, 133.9, 133.8, 133.7, 132.8, 130.4, 129.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.4, 125.0, 124.1, 120.0, 119.2, 58.5, 44.6;  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -9.7; HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{35}\text{H}_{33}\text{N}_3\text{O}_2\text{P}_1$ : 558.2310; found: 558.2315.

**(S)-N-(1-((2-(Dimethylamino)phenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-2-(diphenylphosphino)-benzamide (1c)**

Catalyst **1c** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1c'** (349 mg, 1.0 mmol), which yielded **1c** as a white solid (446 mg, 80%).

Mp 98-99 °C;  $[\alpha]_{\text{D}}^{25}$  +13.2 ( $c$  1.40,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.74 (brs, 1H), 8.39 (d,  $J$  = 8.0 Hz, 1H), 7.63-7.62 (m, 1H), 7.40-7.21 (m, 12H), 7.17-7.06 (m, 3H), 7.00-6.91 (m, 1H), 6.85 (d,  $J$  = 9.2 Hz, 1H), 4.49 (d,  $J$  = 9.2 Hz, 1H), 2.61 (s, 6H), 1.03 (s, 9H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.7, 168.4, 142.9, 140.7, 140.4, 137.4, 137.3, 137.2, 137.0, 136.8, 134.2, 134.1, 133.9(d), 133.8, 133.6, 133.2, 130.3, 128.6, 128.5, 128.4(d), 128.3, 127.5(d), 125.3, 124.0, 120.5, 119.1, 62.0, 45.2, 35.5, 26.9, 26.6;  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -9.0; HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{33}\text{H}_{37}\text{N}_3\text{O}_2\text{P}_1$ : 538.2623; found: 538.2632.

**(S)-N-(1-((2-(Dimethylamino)benzyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-2-(diphenylphosphino)-benzamide (1d)**

Catalyst **1d** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1d'** (363 mg, 1.0 mmol), which yielded **1d** as a white solid (386 mg, 70%).

Mp 112-114 °C;  $[\alpha]_{\text{D}}^{25}$  -36.0 ( $c$  1.08,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61-7.60 (m, 1H), 7.38 (t,  $J$  = 7.6 Hz, 1H), 7.33-7.23 (m, 13H), 7.14-7.01 (m, 1H), 6.97-6.94 (m, 1H), 6.75 (d,  $J$  = 8.8 Hz, 1H), 4.60 (dd,  $J$  = 5.6, 15.2 Hz, 1H), 4.50 (dd,  $J$  = 4.8, 15.2 Hz, 1H), 4.29 (d,  $J$  = 8.8 Hz, 2H), 2.68 (s, 6H), 0.91 (s, 9H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.8, 168.7, 152.4, 141.3, 137.4, 137.3, 136.3, 134.4, 133.9, 133.8, 133.7, 133.6, 131.5, 130.3, 129.7, 128.7, 128.6, 128.5(d), 128.4(d), 127.6(d), 123.8, 119.6, 61.4, 44.6, 41.1, 35.0, 26.7;  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -9.9; HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_2\text{P}_1$ : 552.2780; found: 552.2772.

**(S)-2-(Diphenylphosphino)-N-(1-((2-(isobutylamino)benzyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-benzamide (1e)**

Catalyst **1e** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1e'** (391 mg, 1.0 mmol), which yielded **1e** as a white solid (370 mg, 64%).

Mp 124-126 °C;  $[\alpha]_{\text{D}}^{25}$  -47.2 ( $c$  1.13,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (d,  $J$  = 5.6 Hz, 1H), 7.44-7.13 (m, 13H), 6.97 (t,  $J$  = 6.4 Hz, 2H), 6.58-6.49 (m, 4H), 4.84 (brs, 1H), 4.36-4.28 (m, 3H), 2.89



(d,  $J = 6.4$  Hz, 2H), 1.93-1.86 (m, 1H), 0.96 (d,  $J = 6.4$  Hz, 6H), 0.85 (s, 9H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.5, 168.8, 146.8, 141.3, 141.0, 136.7, 134.4, 133.9, 133.8, 133.7, 133.6, 130.7, 130.4, 129.4, 128.9, 128.8(d), 128.7, 128.6, 128.5, 127.9(d), 121.0, 115.6, 110.1, 61.6, 51.7, 40.8, 34.7, 27.9, 26.6, 20.7, 20.6;  $^{31}\text{P-NMR}$  (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -10.8; HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_2\text{P}_1$ : 580.3093; found: 580.3098.

### 3. General procedure of 1,3-dipole cycloaddition catalyzed by $\text{Ag}_2\text{O}/\mathbf{1e}$

Precatalyst **1e** (4.63 mg, 0.008 mmol) and  $\text{Ag}_2\text{O}$  (0.92 mg, 0.004 mmol) were dissolved in toluene (1.4 mL). The reaction mixture was stirred for 1 h at rt, followed by the addition of maleates **2a** (34.4 mg, 0.2 mmol) or **2b** (28.8 mg, 0.2 mmol) and iminester substrates **3** (0.24 mmol). Once starting material had been consumed (monitored by TLC), the mixture was purified by column chromatography to give the corresponding cycloaddition product **4**, which was then directly analyzed by chiral HPLC.

#### (2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**4aa**)<sup>10a</sup>

Yield: 63 mg (90%);  $[\alpha]_{\text{D}}^{30} +50.2$  ( $c$  1.08,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.25 (m, 5H), 4.47 (d,  $J = 6.8$  Hz, 1H), 4.16-4.11 (m, 3H), 3.81 (s, 3H), 3.76-3.62 (m, 3H), 3.59 (t,  $J = 7.6$  Hz, 1H), 3.43 (brs, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 0.80 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 170.4, 170.25, 137.0, 128.2, 127.6, 126.7, 65.3, 62.1, 61.0, 60.3, 52.7, 52.2, 51.2, 14.0, 13.5; The ee value was 92%,  $t_{\text{r}} = 5.71$  and 9.67 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $^i\text{PrOH}$ /hexane 50:50, flow rate = 0.8 mL/min).

#### (2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate (**4ab**)<sup>10a</sup>

Yield: 62 mg (85%);  $[\alpha]_{\text{D}}^{30} +40.7$  ( $c$  1.20,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (d,  $J = 7.6$  Hz, 2H), 7.10 (d,  $J = 7.6$  Hz, 2H), 4.43 (d,  $J = 6.4$  Hz, 1H), 4.14-4.09 (m, 3H), 3.79 (s, 3H), 3.75-3.64 (m, 3H), 3.57-3.53 (m, 2H), 2.30 (s, 3H), 1.23 (t,  $J = 7.2$  Hz, 3H), 0.83 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 170.4, 170.2, 137.2, 133.9, 128.9, 126.6, 65.1, 62.1, 61.0, 60.3, 52.8, 52.2, 51.3, 21.0, 14.0, 13.6; The ee value was 88%,  $t_{\text{r}} = 6.30$  and 12.49 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $^i\text{PrOH}$ /hexane 50:50, flow rate = 0.8 mL/min).

#### (2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (**4ac**)<sup>10a</sup>

Yield: 65mg (86%);  $[\alpha]_{\text{D}}^{30} +45.8$  ( $c$  1.06,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (d,  $J = 8.4$  Hz, 2H), 6.85 (d,  $J = 8.4$  Hz, 2H), 4.43 (d,  $J = 6.8$  Hz, 1H), 4.15-4.10 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.71-3.67 (m, 3H), 3.55 (t,  $J = 6.8$  Hz, 1H), 3.22 (brs, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 0.86 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 170.5, 170.3, 159.0, 129.2, 128.0, 113.6, 64.9, 62.1, 61.0, 60.3, 55.2, 52.8, 52.2, 51.1, 14.0, 13.6; The ee value was 93%,  $t_{\text{r}} = 7.78$  and 14.19 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $^i\text{PrOH}$ /hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4ad)<sup>10a</sup>**

Yield: 67 mg (90%);  $[\alpha]_D^{30} +47.4$  (c 1.20, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33-7.32 (m, 2H), 7.01-6.99 (m, 2H), 4.44 (d,  $J = 6.8$  Hz, 1H), 4.12-4.09 (m, 3H), 3.78 (s, 3H), 3.74-3.62 (m, 3H), 3.57-3.53 (m, 1H), 3.18 (brs, 1H), 1.22 (t,  $J = 7.2$  Hz, 3H), 0.83 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 170.3, 163.4, 160.9, 133.1, 133.0, 128.6, 128.5, 115.2, 115.0, 64.6, 62.1, 61.1, 60.4, 52.7, 52.2, 51.1, 14.0, 13.6; The ee value was 91%,  $t_r = 7.00$  and 11.05 min (Chiralcel AS-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4ae)<sup>10a</sup>**

Yield: 67 mg (88%);  $[\alpha]_D^{30} +43.9$  (c 1.10, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33-7.28 (m, 4H), 4.44 (d,  $J = 6.8$  Hz, 1H), 4.16-4.10 (m, 3H), 3.80 (s, 3H), 3.76-3.68 (m, 3H), 3.60-3.56 (m, 1H), 3.27 (brs, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 0.87 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.8, 170.1, 135.8, 133.4, 128.3, 128.3, 64.6, 62.0, 61.1, 60.4, 52.5, 52.2, 51.1, 14.0, 13.6; The ee value was 90%,  $t_r = 7.26$  and 11.64 min (Chiralcel AS-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-Methyl 5-(3,4-Dichlorophenyl)-pyrrolidine-2,3,4-tricarboxylate (4af)<sup>10c</sup>**

Yield: 60 mg (72%);  $[\alpha]_D^{30} +46.8$  (c 1.00, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.48 (s, 1H), 7.38 (d,  $J = 8.0$  Hz, 1H), 7.22 (d,  $J = 8.4$  Hz, 1H), 4.39 (d,  $J = 6.8$  Hz, 1H), 4.14-4.08 (m, 3H), 3.79 (s, 3H), 3.78-3.67 (m, 3H), 3.59-3.55 (m, 1H), 3.27 (brs, 1H), 1.22 (t,  $J = 6.8$  Hz, 3H), 0.89 (t,  $J = 7.2$  Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 170.7, 170.0, 137.8, 132.3, 131.6, 130.2, 129.1, 126.3, 64.0, 61.9, 61.2, 60.6, 52.3, 52.2, 51.1, 14.0, 13.6$ . The ee value was 87%,  $t_r = 7.75$  and 13.00 min (Chiralcel AS-H,  $\lambda = 230$  nm, <sup>i</sup>PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(2-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4ag)<sup>10c</sup>**

Yield: 66 mg (86%);  $[\alpha]_D^{30} +58.4$  (c 1.24, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.48 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.35 (dd,  $J = 7.6, 1.6$  Hz, 1H), 7.28-7.20 (m, 2H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.14-4.08 (m, 3H), 3.92 (dd,  $J = 8.4, 6.8$  Hz, 1H), 3.83 (s, 3H), 3.77 (dd,  $J = 8.8, 8.4$  Hz, 1H), 3.70-3.60 (m, 2H), 3.40 (brs, 1H), 1.21 (t,  $J = 7.2$  Hz, 3H), 0.78 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.1, 170.3, 169.9, 134.5, 133.3, 129.1, 128.8, 127.4, 126.7, 62.0, 61.1, 61.0, 60.3, 52.3, 51.0, 50.2, 14.0, 13.5; The ee value was 93%,  $t_r = 7.98$  and 14.57 min (Chiralcel AS-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate (4ah)<sup>10a</sup>**

Yield: 64 mg (83%);  $[\alpha]_D^{30} +45.8$  (c 1.00, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.46-7.43 (m, 2H), 7.27-7.24 (m, 2H), 4.42 (d,  $J = 7.2$  Hz, 1H), 4.16-4.10 (m, 3H), 3.80 (s, 3H), 3.80-3.55 (m, 4H), 3.27-3.26

(m, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 0.87 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 170.2, 136.3, 131.3, 128.6, 121.5, 64.7, 62.1, 61.1, 60.5, 52.5, 52.3, 51.1, 14.0, 13.6; The ee value was 87%,  $t_r = 7.53$  and 12.28 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(naphthalen-1-yl)pyrrolidine-2,3,4-tricarboxylate (4ai)<sup>10a</sup>**

Yield: 72 mg (90%);  $[\alpha]_D^{30} +187.6$  (c 1.24,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.4$  Hz, 1H), 7.84 (d,  $J = 8.0$  Hz, 1H), 7.75 (d,  $J = 8.0$  Hz, 1H), 7.59 (d,  $J = 7.2$  Hz, 1H), 7.53-7.40 (m, 3H), 5.14 (d,  $J = 6.8$  Hz, 1H), 4.20-4.06 (m, 3H), 3.93-3.82 (m, 2H), 3.84 (s, 3H), 3.45-3.31 (m, 3H), 1.17 (t,  $J = 7.2$  Hz, 3H), 0.37 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 170.2, 170.0, 133.4, 132.3, 131.0, 128.8, 128.2, 126.1, 125.4, 125.1, 123.2, 122.7, 61.5, 61.2, 60.9, 59.9, 52.2, 52.1, 51.3, 13.9, 13.1; The ee value was 92%,  $t_r = 10.19$  and 18.58 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tri carboxylate (4aj)<sup>10a</sup>**

Yield: 71 mg (89%);  $[\alpha]_D^{30} +24.5$  (c 1.00,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83-7.78 (m, 4H), 7.47-7.44 (m, 3H), 4.61 (dd,  $J = 6.4, 2.4$  Hz, 1H), 4.19 (d,  $J = 8.8$  Hz, 1H), 4.13 (q,  $J = 7.2$  Hz, 2H), 3.83 (s, 3H), 3.79-3.75 (m, 1H), 3.71-3.53 (m, 3H), 3.42 (brs, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 0.67 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 170.4, 170.2, 134.5, 133.1, 132.7, 128.0, 127.8, 127.5, 126.1, 125.9, 125.4, 124.9, 65.4, 62.0, 61.1, 60.3, 52.7, 52.3, 51.5, 14.0, 13.5; The ee value was 86%,  $t_r = 8.07$  and 21.18 min (ChiralcelAS-H,  $\lambda=205\text{nm}$ ,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(furan-2-yl)pyrrolidine-2,3,4-tricarboxylate (4ak)<sup>10a</sup>**

Yield: 54 mg (81%);  $[\alpha]_D^{30} +24.6$  (c 1.20,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33-7.32 (m, 1H), 6.33-6.31 (m, 2H), 4.47 (d,  $J = 6.8$  Hz, 1H), 4.12 (q,  $J = 7.2$  Hz, 2H), 4.22 (d,  $J = 8.8$  Hz, 1H), 3.94-3.85 (m, 2H), 3.78 (s, 3H), 3.62 (dd,  $J = 8.0, 8.8$  Hz, 1H), 3.50 (t,  $J = 7.6$  Hz, 1H), 3.24 (brs, 1H), 1.23 (t,  $J = 7.2$  Hz, 3H), 1.03 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 170.2, 170.0, 151.0, 141.8, 110.4, 107.2, 62.0, 61.1, 60.7, 59.5, 52.3, 51.5, 50.8, 14.0, 13.8; The ee value was 83%,  $t_r = 6.77$  and 14.34 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(thiophen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4al)<sup>10a</sup>**

Yield: 43 mg (60%);  $[\alpha]_D^{30} +30.5$  (c 1.00,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 (d,  $J = 4.8$  Hz, 1H), 7.02-7.01 (m, 1H), 6.94-6.92 (m, 1H), 4.59 (d,  $J = 6.8$  Hz, 1H), 4.13-4.10 (m, 3H), 3.86-3.82 (m, 2H), 3.77 (s, 3H), 3.67 (dd,  $J = 9.2, 8.0$  Hz, 1H), 3.67 (dd,  $J = 8.0, 6.8$  Hz, 1H), 3.34 (brs, 1H), 1.23 (t,  $J = 7.2$  Hz, 3H), 0.96 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 170.2, 169.9, 139.9, 126.7,

124.9, 124.5, 61.9, 61.3, 61.1, 60.6, 52.8, 52.2, 51.3, 14.0, 13.6; The ee value was 80%,  $t_r = 7.04$  and 14.35 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4am)<sup>10a</sup>**

Yield: 48mg (67%);  $[\alpha]_D^{30} +39.8$  (c 1.08, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37-7.24 (m, 5H), 4.63 (d,  $J = 6.4$  Hz, 1H), 4.20 (q,  $J = 7.2$  Hz, 2H), 3.79 (s, 3H), 3.78-3.65 (m, 2H), 3.47 (t,  $J = 7.2$  Hz, 1H), 3.28 (d,  $J = 6.8$  Hz, 1H), 1.68 (s, 3H), 1.29 (t,  $J = 7.2$  Hz, 3H), 0.80 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 170.5, 170.5, 137.3, 128.2, 127.7, 126.9, 68.6, 63.7, 61.0, 60.2, 58.0, 53.2, 52.5, 28.3, 14.1, 13.6; The ee value was 91%,  $t_r = 7.57$  and 11.01 min (Chiralcel AD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 2-methyl-5-(p-tolyl)pyrrolidine-2,3,4-tricarboxylate (4an)<sup>10a</sup>**

Yield: 49 mg (65%);  $[\alpha]_D^{30} +34.5$  (c 1.45, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 (d,  $J = 8.0$  Hz, 2H), 7.08 (d,  $J = 7.6$  Hz, 2H), 4.56 (d,  $J = 6.4$  Hz, 1H), 4.17 (q,  $J = 7.2$  Hz, 2H), 3.77 (s, 3H), 3.77-3.66 (m, 3H), 3.43 (t,  $J = 6.8$  Hz, 1H), 3.25 (d,  $J = 6.8$  Hz, 1H), 2.29 (s, 3H), 1.65 (s, 3H), 1.28 (t,  $J = 7.2$  Hz, 3H), 0.81 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.4, 170.6, 170.5, 137.2, 134.2, 128.8, 126.7, 68.5, 63.5, 60.9, 60.1, 58.0, 53.2, 52.5, 28.3, 21.0, 14.0, 13.6; The ee value was 93%,  $t_r = 7.57$  and 10.21 min (Chiralcel AD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-chlorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4ao)<sup>10a</sup>**

Yield: 56 mg (70%);  $[\alpha]_D^{30} +39.4$  (c 1.30, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 (d,  $J = 8.4$  Hz, 2H), 7.28 (d,  $J = 8.8$  Hz, 2H), 4.59 (d,  $J = 6.8$  Hz, 1H), 4.20 (q,  $J = 7.2$  Hz, 2H), 3.80 (s, 3H), 3.78-3.69 (m, 2H), 3.61 (brs, 1H), 3.46 (t,  $J = 6.8$  Hz, 1H), 3.27 (d,  $J = 7.2$  Hz, 1H), 1.66 (s, 3H), 1.30 (t,  $J = 7.2$  Hz, 3H), 0.86 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 170.5, 170.3, 136.2, 133.4, 128.5, 128.4, 68.6, 63.0, 61.1, 60.3, 57.8, 53.0, 52.6, 28.2, 14.1, 13.7; The ee value was 94%,  $t_r = 9.27$  and 10.14 min (Chiralcel OD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-bromophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4ap)<sup>10b</sup>**

Yield: 56 mg (63%);  $[\alpha]_D^{30} +31.6$  (c 1.20, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 (d,  $J = 8.4$  Hz, 2H), 7.19 (d,  $J = 8.0$  Hz, 2H), 4.51 (d,  $J = 6.8$  Hz, 1H), 4.12 (q,  $J = 7.2$  Hz, 1H), 3.71 (s, 3H), 3.74-3.59 (m, 3H), 3.39 (t,  $J = 7.2$  Hz, 1H), 3.19 (d,  $J = 6.8$  Hz, 1H), 1.59 (s, 3H), 1.22 (t,  $J = 7.2$  Hz, 3H), 0.79 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 170.5, 170.3, 136.7, 131.3, 128.8, 121.5, 77.3, 77.0,

76.7, 68.6, 63.0, 61.1, 60.3, 57.8, 52.9, 52.6, 28.1, 14.1, 13.7; The ee value was 94%,  $t_r = 9.26$  and  $14.11$  min (Chiralcel AD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 2-methyl-5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4aq)<sup>10a</sup>**

Yield 59 mg (71%);  $[\alpha]_D^{30} +17.6$  (c 0.93, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.85-7.77 (m, 4H), 7.53-7.44 (m, 3H), 4.77 (d,  $J = 6.4$  Hz, 1H), 4.23-4.18 (m, 2H), 3.81 (s, 1H), 3.70-3.55 (m, 4H), 3.33 (d,  $J = 7.2$  Hz, 1H), 1.72 (s, 3H), 1.30 (t,  $J = 7.2$  Hz, 3H), 0.66 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 170.5, 134.8, 133.1, 132.8, 128.0, 127.9, 127.5, 126.1, 125.9, 125.5, 125.0, 68.5, 63.7, 61.0, 60.2, 58.3, 53.1, 52.6, 28.5, 14.1, 13.5; The ee value was 88%,  $t_r = 18.17$  and  $19.94$  min (Chiralcel OD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 2-benzyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4ar)<sup>10a</sup>**

Yield: 51 mg (58%);  $[\alpha]_D^{30} +28.6$  (c 1.24, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.46-7.44 (m, 2H), 7.31-7.26 (m, 8H), 4.26 (q,  $J = 7.2$  Hz, 2H), 4.11 (d,  $J = 5.6$  Hz, 1H), 3.76-3.67 (m, 2H), 3.74 (s, 3H), 3.60 (brs, 1H), 3.30-3.17 (m, 4H), 1.38 (t,  $J = 7.2$  Hz, 3H), 0.79 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.1, 170.8, 170.2, 137.6, 136.1, 131.1, 128.2, 128.0, 127.5, 126.9, 126.7, 72.5, 63.8, 61.0, 60.0, 54.3, 52.4, 52.3, 44.9, 14.1, 13.6; The ee value was 87%,  $t_r = 6.56$  and  $9.36$  min (Chiralcel AD-H,  $\lambda = 210$  nm,  $i$ PrOH/hexane 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4ba)<sup>10a</sup>**

Yield: 59 mg (92%);  $[\alpha]_D^{30} +67.4$  (c 1.10, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35-7.26 (m, 5H), 4.49 (d,  $J = 6.8$  Hz, 1H), 4.17 (d,  $J = 8.8$  Hz, 1H), 3.82 (s, 3H), 3.75-3.70 (m, 1H), 3.70 (s, 3H), 3.58 (t,  $J = 7.2$  Hz, 1H), 3.23 (s, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.1, 170.9, 170.8, 137.0, 128.3, 127.7, 126.6, 65.4, 62.1, 52.5, 52.4, 52.1, 51.3, 50.9; The ee value was 91%,  $t_r = 7.47$  and  $15.21$  min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i$ PrOH/hexane 50:50, flow rate = 0.8 mL/min).

**(2S,3S,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4ca)<sup>10a</sup>**

Yield: 50 mg (78%);  $[\alpha]_D^{30} +14.2$  (c 1.20, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34-7.26 (m, 5H), 4.66 (d,  $J = 8.0$  Hz, 1H), 4.21 (d,  $J = 6.8$  Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.67-3.64 (m, 1H), 3.58 (dd,  $J = 8.0, 4.4$  Hz, 1H), 3.20 (s, 3H), 2.85 (brs, 1H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.5, 172.0, 171.6, 138.0, 128.6, 128.2, 127.8, 127.0, 126.7, 65.3, 63.2, 53.7, 52.5, 52.5, 51.5, 50.6; The ee value was 30%,  $t_r = 15.71$  and  $28.93$  min (Chiralcel OD-H,  $\lambda = 220$  nm,  $i$ PrOH/hexane 20:80, flow rate = 1.0 mL/min).

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