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## CHIRAL 1,2-DIAMINOCYCLOHEXANE- $\alpha$ -AMINO ACID-DERIVED AMIDPHOS/Ag(I)-CATALYZED DIVERGENT ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF AZOMETHINE YLIDES

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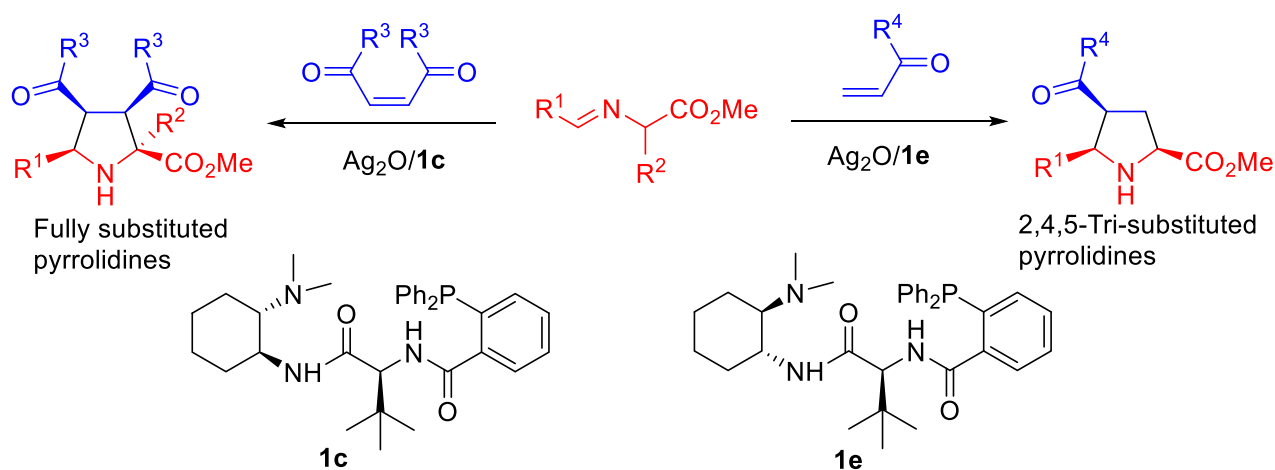
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**Abstract** – A series of chiral 1,2-diaminocyclohexane- $\alpha$ -amino acid-derived amidophosphanes in combination with silver(I) salts, have been developed to cooperatively catalyze the azomethine ylides-involved 1,3-dipolar cycloaddition with different electron-deficient alkenes. Among these, the (1*S*,2*S*)-1,2-cyclohexanediamine-*L*-*tert*-leucine-derived amidphos/Ag(I) has been demonstrated as being a highly efficient catalytic system in the *cis*-1,2-disubstituted electron-deficient olefins-involved 1,3-dipolar cycloaddition of azomethine ylides, including a series of aromatic, heteroaromatic, aliphatic, and 2-substituted azomethine ylides, affording various fully substituted pyrrolidines in high to excellent yields (up to 97% yield) and enantioselectivities (up to 97% ee). Interestingly, the (1*R*,2*R*)-1,2-cyclohexanediamine-*L*-*tert*-leucine-derived amidphos/Ag(I) can efficiently catalyze terminal electron-deficient olefin-involved 1,3-dipolar cycloaddition, giving a series of 2,4,5-tri-substituted pyrrolidines with up to 92% yield and 92% ee.

## INTRODUCTION

Various substituted chiral pyrrolidines, as important five-membered nitrogen heterocycle skeletons, are frequently encountered in many natural products, pharmaceuticals, chiral organocatalysts and ligands.<sup>1</sup> In the last two decade, remarkable progress has been made in chiral metal complexes-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient alkenes for constructing different substituted pyrrolidines.<sup>2</sup> To the best of our knowledge, in the chiral metal complexes catalytic systems, these ligands

mainly focus on bidentate P,P-ligands,<sup>3</sup> P,N-ligands,<sup>4</sup> P,S-ligands,<sup>5</sup> N,N-ligands,<sup>6</sup> and N,O-ligands,<sup>7</sup> et al. Recently, amidophosphanes developed by our group as the multifunctional ligands in combination with silver(I) ions have been successfully applied in azomethine ylides-involved 1,3-dipolar cycloaddition with high to excellent diastereo- and enantioselectivities.<sup>8</sup> A series of amidophosphane precatalysts with different chiral scaffolds including cinchona alkaloids, chiral 1,2-diphenylethylenediamines and  $\alpha$ -amino acids have been devised. Owing to the excellent catalytic performance of amidophosphanes, it was commendable to exploit other chiral skeleton types of amidophosphanes. Chiral 1,2-diaminocyclohexanes, as rich and easily available chiral sources, which are widely derived as organic small molecule catalysts and ligands to widely applied in the field of asymmetric synthesis,<sup>9</sup> has not been reported related applications in amidphos/Ag(I)-catalyzed asymmetric 1,3-dipolar cycloaddition. Therefore, it is necessary to develop the chiral 1,2-diaminocyclohexanes-derived amidophosphane precatalysts and expand its field of application. Here, we report a class of chiral 1,2-diaminocyclohexane- $\alpha$ -amino acid-derived amidophosphanes in combination with Ag(I) to divergently enantioselectively catalyzed 1,3-dipolar cycloaddition of azomethine ylides with *cis*-1,2-disubstituted electron-deficient olefins and terminal electron-deficient olefins to construct fully substituted *endo*-pyrrolidine derivatives with four contiguous stereocenters and 2,4,5-tri-substituted *endo*-pyrrolidines with moderate to excellent enantioselectivities, respectively (Scheme 1).

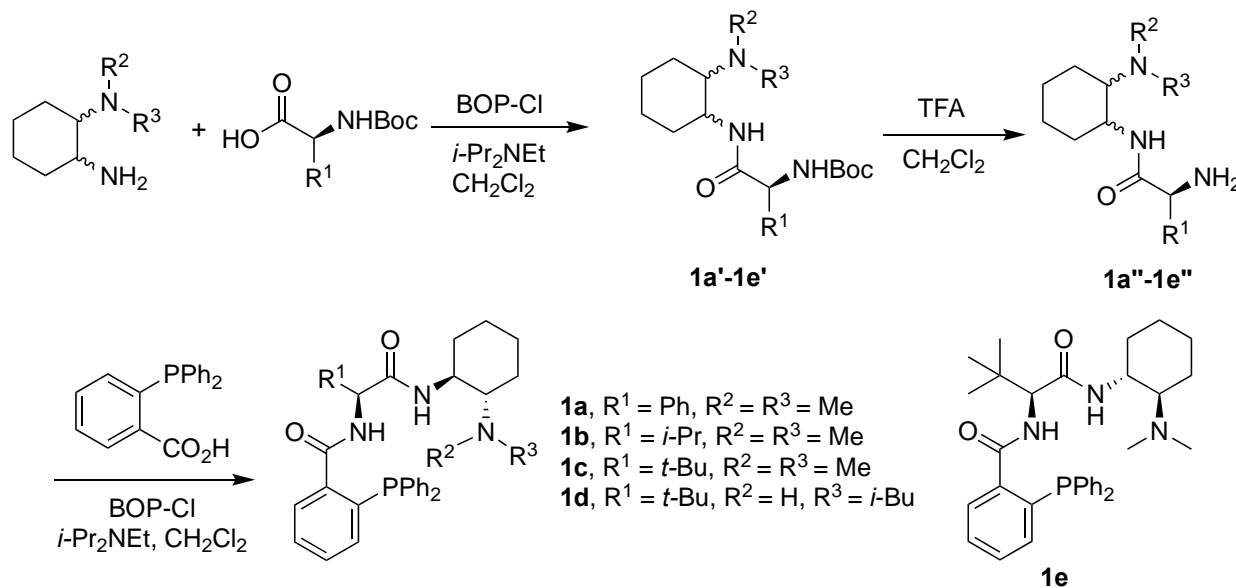


Scheme 1. Divergent enantioselective azomethine ylides-involved 1,3-dipolar cycloaddition

## RESULTS AND DISCUSSION

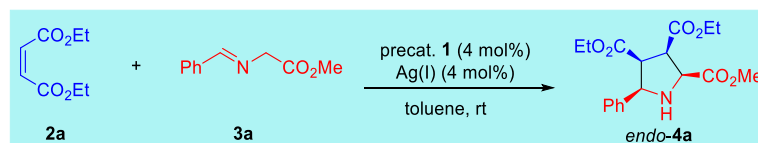
According to our reported procedures, a series of amidophosphanes **1a–e** were successfully obtained from chiral (1*R*,2*R*)- or (1*S*,2*S*)-1,2-cyclohexanediamine and natural  $\alpha$ -amino acids (Scheme 2).<sup>8a</sup> Amidophosphanes **1a–d** were synthesized with corresponding substituted (1*S*,2*S*)-1,2-cyclohexanediamines and different natural  $\alpha$ -amino acids, including *N*-Boc-(*S*)-phenylglycine,

*N*-Boc-(*S*)-valine and *N*-Boc-(*S*)-*tert*-leucine. On the other hand, the amidophosphane **1e** has also been obtained based on the two starting materials of (1*R*,2*R*)-1-amino-2-(dimethylamino)cyclohexane and *N*-Boc-(*S*)-*tert*-leucine.



Scheme 2. Synthesis of amidophosphanes **1a–e**

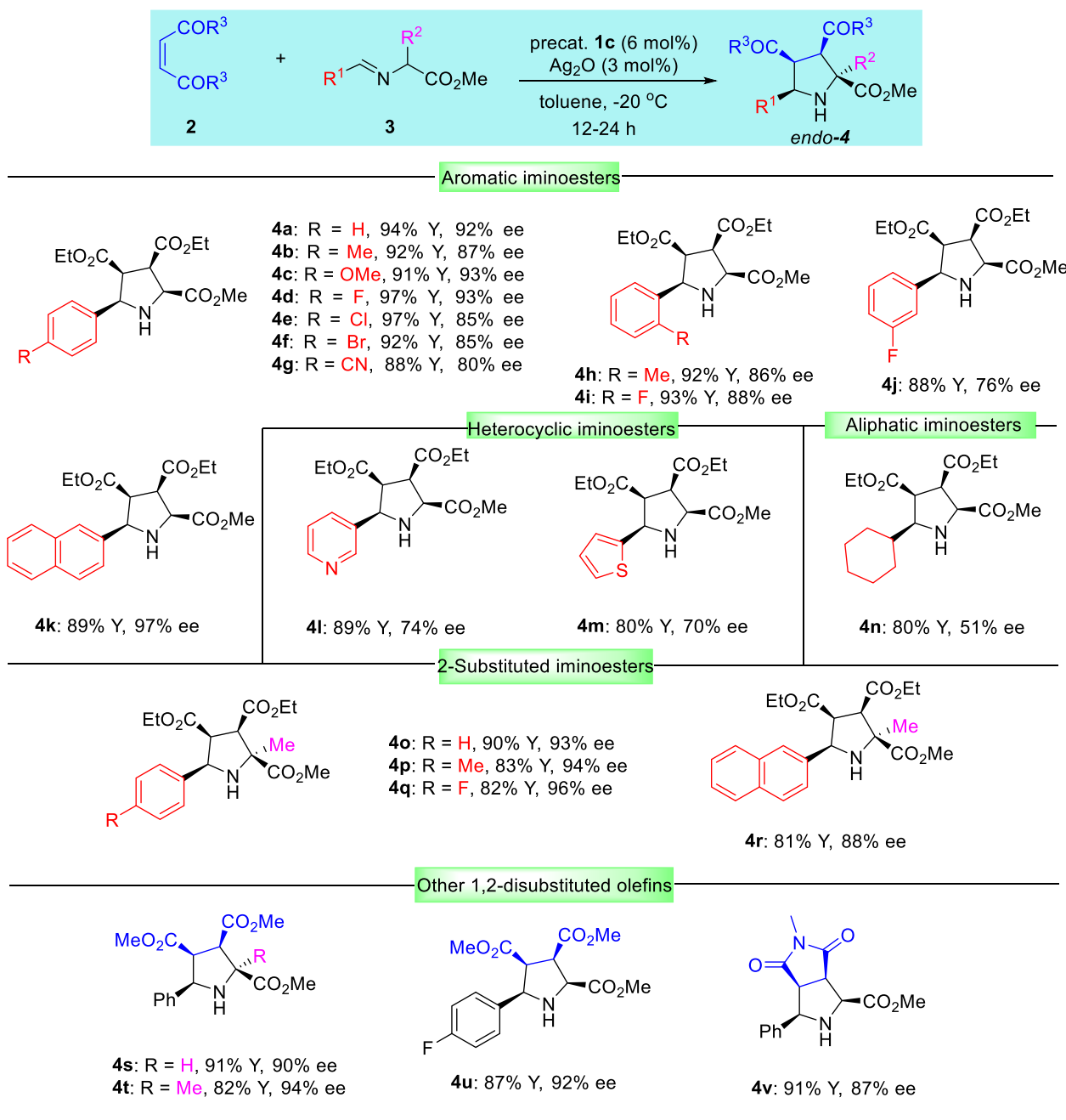
We initiated the study by choosing diethyl maleate **2a** and  $\alpha$ -iminoester **3a** as model substrates to optimize the reaction conditions (Table 1). At first, different amidophosphane ligands **1a–1e** in combination with Ag<sub>2</sub>CO<sub>3</sub> were tested in toluene at room temperature (Table 1, entries 1-5). Among those, ligand **1c** derived from (1*S*,2*S*)-1-amino-2-(dimethylamino)cyclohexane and *L*-*tert*-leucine was found to be the optimal precatalyst (95% yield, 80% ee). In order to further improve the enantioselectivity of the cycloadduct, various silver salts were explored, and Ag<sub>2</sub>O was chosen for further optimizations (Table 1, entries 6-9). Next, when the reaction temperature was reduced to  $-5$  °C, the enantioselectivity was increased to 85% ee (Table 1, entry 10). Further lowering the reaction temperature to  $-20$  °C resulted in 91% enantioselectivity and a prolonged reaction time (Table 1, entry 11). To our delight, increasing the catalyst loading furnished 92% enantioselectivity in 12 h (Table 1, entry 12). Therefore, the best result was obtained with Ag<sub>2</sub>O (3 mol%)/ **1c** (6 mol%) in toluene at  $-20$  °C.

Table 1. Optimization of asymmetric 1,3-dipole cycloaddition reaction conditions<sup>a</sup>

Entry	Precat <b>1</b>	Ag(I)	Time (h)	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	<b>1a</b>	Ag <sub>2</sub> CO <sub>3</sub>	3	92	78
2	<b>1b</b>	Ag <sub>2</sub> CO <sub>3</sub>	4	93	78
3	<b>1c</b>	Ag <sub>2</sub> CO <sub>3</sub>	4	95	80
4	<b>1d</b>	Ag <sub>2</sub> CO <sub>3</sub>	4	92	78
5	<b>1e</b>	Ag <sub>2</sub> CO <sub>3</sub>	5	90	63
6	<b>1c</b>	Ag <sub>2</sub> O	3	96	81
7	<b>1c</b>	AgF	4	92	70
8	<b>1c</b>	AgOAc	5	90	46
9	<b>1c</b>	AgOTf	24	Trace	n.d. <sup>d</sup>
10 <sup>e</sup>	<b>1c</b>	Ag <sub>2</sub> O	6	93	85
11 <sup>f</sup>	<b>1c</b>	Ag <sub>2</sub> O	18	93	91
12 <sup>g</sup>	<b>1c</b>	Ag <sub>2</sub> O	12	94	92

<sup>a</sup>Conditions: iminoester **3a** (0.30 mmol), diethyl maleate **2a** (0.20 mmol), Ag<sub>2</sub>CO<sub>3</sub> (2 mmol%), precat (4 mmol%), toluene (1.4 mL). <sup>b</sup>Isolated yields based on **2a**. <sup>c</sup>Determined by HPLC. <sup>d</sup>Not determined. <sup>e</sup>Run at -5 °C. <sup>f</sup>Run at -20 °C. <sup>g</sup>Ag<sub>2</sub>O (3 mmol%), precat. **1c** (6 mmol%).

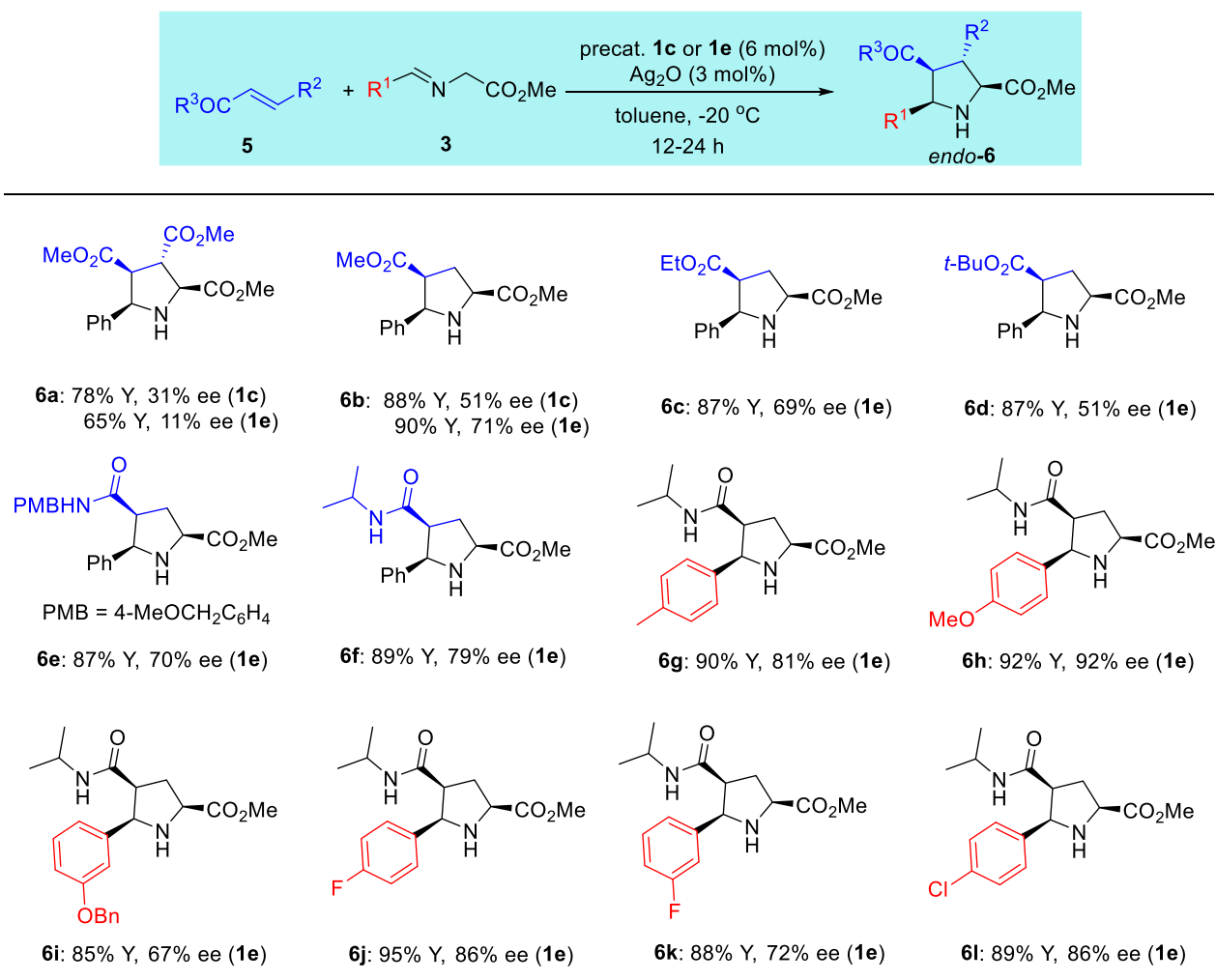
Having established the optimal condition, we next explored the substrate scope of 1,3-dipolar cycloaddition.<sup>10</sup> As shown in Scheme 3,  $\alpha$ -iminoesters **3a-k** from aromatic aldehydes bearing both electron-donating and -withdrawing groups regardless of their positions efficiently gave the desired cycloaddition products **4a-k** with good to excellent yields and enantioselectivities (88-97% yields, 76-97% ee). Subsequently,  $\alpha$ -iminoesters **3l** and **3m** with an array of heteroaryl groups, including thienyl and piperidinyl groups, also worked well with moderate to high yields (80-89% yields) and enantioselectivities (70-74% ee). Noticeably, for employing aliphatic cyclohexyl iminoester, the adduct **4n** was successfully obtained with 51% ee and 80% yield. Moreover, the 1,3-dipole cycloaddition between the 2-substituted  $\alpha$ -iminoesters **3o-3r** and diethyl maleate **2a** has been explored to produce adducts **4o-r** with a quaternary center at the 2-position in high yields and excellent enantioselectivities (81-90% yields, 88-96% ee). Besides diethyl maleate, dimethyl maleate and *N*-methylmaleimide were also applied in 1,3-dipolar cycloaddition reaction to provide corresponding adduct **4s-v** with 82-91% yields and 87-94% ee.



Scheme 3.  $\text{Ag}_2\text{O}/\mathbf{1c}$ -catalyzed cycloaddition of various  $\alpha$ -iminoesters **3** with **2<sup>a</sup>**. <sup>a</sup>Reaction conditions:  $\alpha$ -iminoesters **3** (0.30 mmol), **2** (0.20 mmol),  $\text{Ag}_2\text{O}$  (3 mol%), precat. **1c** (6 mol%), isolated yield based on **2**, ee value determined by HPLC.

Subsequently, cycloaddition of dimethyl fumarate with  $\alpha$ -iminoester **3a** in the presence of precat. **1c** and **1e** was investigated. However, adduct **6a** was obtained with low enantioselectivity (31% ee for **1c** and 11% ee for **1e**). Interestingly, when methyl acrylate was used, it was found that precat. **1e** is a more efficient precatalyst with 90% yield and 71% ee than precat. **1c** with 88% yield and 51% ee.<sup>11</sup> Inspired by this result, we next explored  $\text{Ag}_2\text{O}/\mathbf{1e}$ -catalyzed 1,3-dipolar cycloaddition of other terminal olefins **5** with  $\alpha$ -iminoesters **3**, and corresponding adducts **6c-f** were obtained with moderate enantioselectivities (51-79%

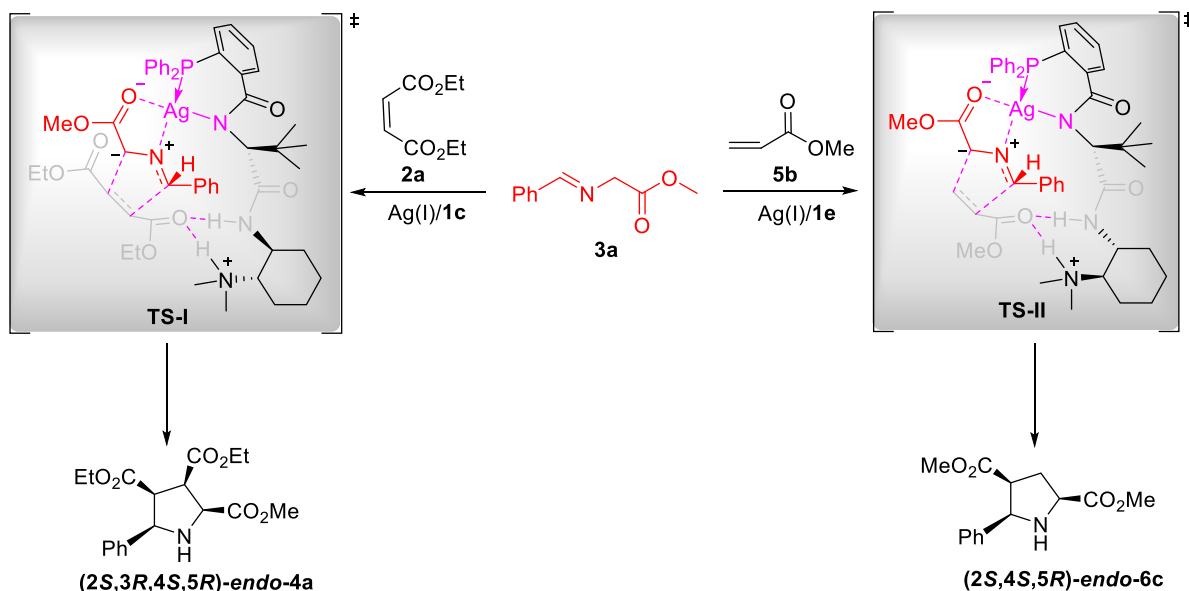
ee) and good yields (87-89%).<sup>10</sup> It is noteworthy that N-isopropyl substituted acrylamide **5f** afforded relatively higher results for adduct **6f** with 89% yield and 79% ee. We then evaluated the 1,3-dipolar cycloaddition of acrylamide **5f** with different  $\alpha$ -iminoesters **3**. A series of  $\alpha$ -iminoesters **3** were well tolerated under the Ag<sub>2</sub>O/**1e** catalytic system, delivering the expected 2,4,5-tri-substituted pyrrolidines **6g-l** with high yield (85-95%) and moderate to high enantioselectivities (67-92% ee).



Scheme 4. Ag<sub>2</sub>O/**1c** or **1e**-catalyzed cycloaddition of various  $\alpha$ -iminoesters **3** with **5**<sup>a</sup>. <sup>a</sup>Reaction conditions:  $\alpha$ -iminoesters **3** (0.30 mmol), **5** (0.20 mmol), Ag<sub>2</sub>O (3 mol%), precat. **1c** or **1e** (6 mol%), isolated yield based on **5**, ee value determined by HPLC.

On the basis of aforementioned results and literature reports,<sup>8c</sup> the plausible transition state stereoselection models are depicted in Figure 5. The coordination of the amide nitrogen and tertiary phosphine in precat. **1c** or **1e** and the nitrogen and oxygen atoms in iminoester **3a** to silver(I) would form the reactive silver-linked iminoester dipole, which attack the diethyl maleate **2a** or methyl acrylate **5b** through the cycloaddition from *Re*-face (C1) of iminoester **3a**, with additional hydrogen bonds between the protonated tertiary amine and the amide hydrogen atom in precat. **1c** or **1e** and the ester oxygen atom

to generate transition mode TS-I or TS-II, leading to the formation of (2*S*,3*R*,4*S*,5*R*)-*endo*-**4a** or (2*S*,4*S*,5*R*)-*endo*-**6c**. In addition, we found the stereoselectivities of adducts *endo*-**4a** and *endo*-**6c** are mainly affected not only by the chiral  $\alpha$ -amino acid skeleton, but also by the chiral matching or mismatching between  $\alpha$ -amino acids and 1,2-diaminocyclohexanes. Further experimental and theoretical studies are underway.



Scheme 5. Proposed stereoinduction models

In conclusion, we have developed a series of chiral 1,2-diaminocyclohexane- $\alpha$ -amino acid-derived amidophosphanes in combination with silver(I) salts successfully applied the azomethine ylides-involved 1,3-dipolar cycloaddition with different electron-deficient alkenes. These results indicate (1*S*,2*S*)-1,2-cyclohexanediamine-*L*-*tert*-leucine-derived amidphos **1c**/Ag<sub>2</sub>O catalytic system can efficiently catalyzed the 1,3-dipolar cycloaddition of *cis*-1,2-disubstituted olefins **2** and  $\alpha$ -iminoesters **3** to afford fully substituted pyrrolidines in high to excellent yields and enantioselectivities, whereas (1*R*,1*R*)-1,2-cyclohexanediamine-*L*-*tert*-leucine-derived amidphos **1e**/Ag<sub>2</sub>O serves as a relatively efficient catalytic system for the asymmetric 1,3-dipolar cycloaddition of terminal electron-deficient olefin **5** and  $\alpha$ -iminoesters **3** to deliver the 2,4,5-tri-substituted pyrrolidines with moderate to high enantioselectivities and yields. Further investigations on mechanistic aspects and other applications are in progress.

## EXPERIMENTAL

### 1. General Information

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 and AD-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. Preparation of the Catalysts

### N-((S)-2-(((1S,2S)-2-(Dimethylamino)cyclohexyl)amino)-2-oxo-1-phenylethyl)-2-(diphenylphosphino)-benzamide (**1a**)

**Typical procedure:** The *tert*-butyl (*S*)-((1*S*,2*S*)-2-(dimethylamino)cyclohexylcarbamoyl)(phenyl)-methylcarbamate **1a'** (375 mg, 1.0 mmol) prepared from *N*-Boc-*L*-phenylglycine and (1*S*,2*S*)-*N*',*N*'-dimethylcyclohexane-1,2-diamine according to the reported procedure<sup>8a</sup> was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and trifluoroacetic acid (5 mL) was dropped at 0 °C. The reaction mixture was then stirred for 4 h at rt. All volatile compounds were removed in vacuo and the residue was dissolved in water and treated with saturated Na<sub>2</sub>CO<sub>3</sub> solution. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and then evaporation of the solvent to afford the free amine **1a''** as colourless oil which was used directly in the next step without further purification. To a stirred solution of crude **1a''** in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at rt was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP-Cl, 531 mg, 1.2 mmol), followed by the addition of diisopropylethylamine (0.2 mL, 1.2 mmol) and 2-(diphenylphosphino)benzoic acid (306 mg, 1 mmol). The reaction mixture was then stirred for 12 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 NaHCO<sub>3</sub>, and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed in vacuo to afford the crude product as colourless oil, the crude product was purified by flash chromatography (35% EtOAc in hexanes) yielding **1a** (394 mg, 70%) as a white solid. Mp 109–110 °C;  $[\alpha]_D^{30}$  97.5 (*c* 0.80, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.85 (s, 1H), 7.76 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.34–7.26 (m, 13H), 7.14 (d, *J* = 7.6 Hz, 3H), 6.9–6.90 (m, 2H), 5.05 (s, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.35 (s, 1H), 2.78 (s, 1H), 2.67 (d, *J* = 3.6 Hz, 3H), 2.45 (d, *J* = 3.2 Hz, 3H), 1.99 (s, 2H), 1.84–1.72 (m, 5H), 1.33–1.23 (m, 4H). <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.9, 170.0, 139.2, 138.9, 134.6, 134.1, 133.8, 133.6, 133.4, 131.4, 129.7, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 127.2, 68.4, 62.0, 48.8, 42.6, 38.5, 37.1, 30.6, 24.3, 23.6, 22.7;



$^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -9.9; HRMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{35}\text{H}_{38}\text{N}_3\text{O}_2\text{P}$ : 564.2774, found: 564.2782.

**N-((S)-1-(((1S,2S)-2-(Dimethylamino)cyclohexyl)amino)-3-methyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1b)**

Catalyst **1b** was prepared according to the procedure used to synthesize catalyst **1a**,

starting from **1b'** (341 mg, 1.0 mmol) to yield the desired product as a white solid (397 mg, 75%). Mp 72–73 °C;  $[\alpha]_{\text{D}}^{30}$  25.3 ( $c$  0.95,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (dd,  $J$  = 7.2, 2.8 Hz, 1H), 7.39–7.37 (m, 1H), 7.35–7.26 (m, 12H), 6.97 (dd,  $J$  = 6.8, 4.0 Hz, 1H), 6.67 (d,  $J$  = 8.4 Hz, 1H), 6.42 (s, 1H), 4.34–4.30 (m, 1H), 3.49–3.42 (m, 1H), 2.48–2.45 (m, 1H), 2.28–2.24 (m, 1H), 2.18 (s, 6H), 2.01–2.03 (m, 1H), 1.84–1.79 (m, 2H), 1.68–1.65 (m, 1H), 1.27–1.10 (m, 4H), 0.87 (s, 3H), 0.86 (s, 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 168.6, 141.3, 141.1, 137.5, 137.4, 136.6, 136.4, 134.4, 133.9, 133.7, 130.3, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 127.7, 127.6, 66.4, 58.9, 51.4, 39.9, 32.5, 31.5, 25.3, 24.7, 21.3, 18.8, 18.2;  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -10.0; HRMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{32}\text{H}_{40}\text{N}_3\text{O}_2\text{P}$ : 530.2931, found: 530.2934.

**N-((S)-1-(((1S,2S)-2-(Dimethylamino)cyclohexyl)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'** (355 mg, 1.0 mmol) to yield the desired product as a white solid (391 mg, 72%). Mp 82–83 °C;  $[\alpha]_{\text{D}}^{30}$  80.6 ( $c$  0.80,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62–7.59 (m, 1H), 7.39–7.37 (m, 1H), 7.35–7.23 (m, 11H), 6.98–6.95 (m, 1H), 6.81 (d,  $J$  = 9.2 Hz, 1H), 6.37 (s, 1H), 4.31 (d,  $J$  = 9.2 Hz, 1H), 3.4–3.41 (m, 1H), 2.52–2.49 (m, 1H), 2.18 (s, 6H), 1.85–1.82 (m, 2H), 1.68–1.65 (m, 1H), 1.26–1.07 (m, 5H), 0.95 (s, 9H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 168.5, 141.3, 141.0, 137.7, 137.6, 137.5, 136.7, 136.5, 134.4, 133.9, 133.7, 133.6, 133.5, 130.2, 128.6, 128.5, 128.4, 128.4, 128.3, 127.4, 66.3, 61.1, 51.3, 39.8, 35.1, 32.2, 26.5, 25.2, 24.5, 21.1, 15.2.  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  -9.9; HRMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{33}\text{H}_{42}\text{N}_3\text{O}_2\text{P}$ : 544.3087, found: 544.3089.

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

Catalyst **1d** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1d'** (383 mg, 1.0 mmol) to yield the desired product as a white solid (429 mg, 75%). Mp 67–68 °C;  $[\alpha]_{\text{D}}^{30}$  23.3 ( $c$  1.80,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62–7.0 (m, 1H), 7.38 (td,  $J$  = 7.6, 1.2 Hz, 1H), 7.32–7.30 (m, 7H), 7.26–7.21 (m, 4H), 6.98–6.95 (m, 1H), 6.70 (d,  $J$  = 8.8 Hz, 1H), 6.20 (d,  $J$  = 7.2 Hz, 1H), 4.28 (d,  $J$  = 8.8 Hz, 1H), 3.51 (qd,  $J$  = 10.8, 4.0 Hz, 1H), 2.50 (dd,  $J$  = 11.2, 6.8 Hz, 1H), 2.28 (td,  $J$  = 10.2, 3.6 Hz, 1H), 2.21 (dd,  $J$  = 11.2, 6.8 Hz, 1H), 2.14–2.04 (m, 2H), 1.72–1.58 (m, 4H), 1.31–1.06 (m,

4H), 0.93 (s, 9H), 0.85 (d,  $J = 6.4$  Hz, 6H);  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 168.9, 141.4, 141.1, 137.1, 136.0, 135.8, 134.5, 133.8, 133.6, 130.4, 128.8, 128.7, 128.6, 127.7, 61.8, 60.8, 54.3, 53.5, 34.5, 32.2, 31.4, 28.9, 26.7, 24.6, 20.7;  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ -10.6; HRMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{35}\text{H}_{46}\text{N}_3\text{O}_2\text{P}$   $[\text{M}+\text{H}]^+$  572.3400, found: 572.3406.

**N-((S)-1-(((1R,2R)-2-(Dimethylamino)cyclohexyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1e)**

Catalyst **1e** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1e'** (355 mg, 1.0 mmol) to yield the desired product as a white solid (407 mg, 75%) Mp 101–102 °C;  $[\alpha]_{\text{D}}^{30}$  -10.4 ( $c$  0.80,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (dd,  $J = 6.8, 3.6$  Hz, 1H), 7.39 (t,  $J = 7.6$  Hz, 1H), 7.35–7.22 (m, 11H), 6.98 (dd,  $J = 7.2, 3.6$  Hz, 1H), 6.86 (d,  $J = 6.4$  Hz, 1H), 6.78 (d,  $J = 7.2$  Hz, 1H), 4.23 (d,  $J = 7.6$  Hz, 1H), 3.71–3.62 (m, 2H), 2.51–2.47 (m, 1H), 2.25 (s, 6H), 1.80–1.83 (m, 2H), 1.69 (d,  $J = 7.6$  Hz, 1H), 1.29–1.25 (m, 2H), 1.20–1.14 (m, 2H), 0.94 (s, 9H);  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 169.4, 152.2, 141.0, 140.7, 137.1, 137.0, 136.5, 136.3, 134.5, 133.9, 133.7, 133.7, 133.5, 130.5, 128.9, 128.7, 128.6, 128.5, 128.5, 127.7, 127.7, 66.9, 62.1, 50.00, 39.7, 34.1, 32.1, 26.6, 24.6, 24.5, 21.6.  $^{31}\text{P}$ -NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ -10.4; HRMS (ESI):  $m/z$   $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{33}\text{H}_{42}\text{N}_3\text{O}_2\text{P}$ : 544.3087, found: 544.3092.

**3. Representative procedure of 1,3-dipole cycloaddition**

Under argon atmosphere, precatalyst **1c** or **1e** (0.012 mmol) and  $\text{Ag}_2\text{O}$  (0.006 mmol) were dissolved in toluene (1.4 mL). The reaction mixture was stirred for 1 h at rt, followed by the addition of maleates **2** or **5** (0.20 mmol) and iminester substrates **3** (0.30 mmol) at  $-20$  °C. Once starting material had been consumed (monitored by TLC), the mixture was purified by column chromatography to give the corresponding cycloaddition product **4** or **6**, which was then directly analyzed by chiral HPLC.

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4a)**<sup>8a</sup>

White solid, Mp 118–119 °C; yield 94%;  $[\alpha]_{\text{D}}^{30}$  +52.1 ( $c$  1.00,  $\text{CH}_2\text{Cl}_2$ ); The ee value was 92%,  $t_{\text{R}}$  (major) = 5.71 min,  $t_{\text{R}}$  (minor) = 9.55 min (Chiralcel AS-H,  $\lambda = 205$  nm,  $i\text{PrOH}/\text{hexanes} = 50:50$ , flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate (4b)**<sup>8a</sup>

White solid, Mp 115–116 °C; yield 92%;  $[\alpha]_{\text{D}}^{30}$  +46.8 ( $c$  1.04,  $\text{CH}_2\text{Cl}_2$ ); The ee value was 87%,  $t_{\text{R}}$  (major) = 6.33 min,  $t_{\text{R}}$  (minor) = 14.35 min, (Chiralcel AS-H,  $\lambda = 210$  nm,  $i\text{PrOH}/\text{hexanes} 50:50$ , flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (4c)**<sup>8a</sup>

White solid, Mp 84–86 °C; yield 91%;  $[\alpha]_{\text{D}}^{30} +47.5$  (*c* 1.02, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 93%, *t<sub>R</sub>* (major) = 7.28 min, *t<sub>R</sub>* (minor) = 13.97 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 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 (4d)**<sup>8a</sup>

White solid, Mp 101–103 °C; yield 97%;  $[\alpha]_{\text{D}}^{30} +51.4$  (*c* 1.05, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 93%, *t<sub>R</sub>* (major) = 7.46 min, *t<sub>R</sub>* (minor) = 12.94 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 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 (4e)**<sup>8a</sup>

White solid, Mp 117–118 °C; yield 97%;  $[\alpha]_{\text{D}}^{30} +47.0$  (*c* 1.03, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 85%, *t<sub>R</sub>* (major) = 7.44 min, *t<sub>R</sub>* (minor) = 12.77 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 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 (4f)**<sup>8a</sup>

A white solid, Mp 104–105 °C; yield 92%;  $[\alpha]_{\text{D}}^{30} +46.8$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 85%, *t<sub>R</sub>* (major) = 5.98 min, *t<sub>R</sub>* (minor) = 9.33 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (4g)**<sup>8a</sup>

White solid, Mp 123–124 °C; yield 88%;  $[\alpha]_{\text{D}}^{30} +26.2$  (*c* 0.70, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 80%, *t<sub>R</sub>* (major) = 4.75 min, *t<sub>R</sub>* (minor) = 5.41 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(*o*-tolyl)pyrrolidine-2,3,4-tricarboxylate (4h)**

White solid, Mp 76–77 °C; yield 92%;  $[\alpha]_{\text{D}}^{30} +71.88$  (*c* 1.30, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.35 (m, 1H), 7.16–7.11 (m, 3H), 4.56 (d, *J* = 6.4 Hz, 1H), 4.13–4.06 (m, 3H), 3.82 (s, 3H), 3.70 (dt, *J* = 15.2, 8.4 Hz, 2H), 3.63–3.51 (m, 2H), 3.07 (brs, 1H), 2.35 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  171.1, 170.2, 135.6, 134.8, 130.0, 127.5, 125.9, 125.3, 62.0, 61.5, 61.0, 60.3, 52.2, 51.0, 50.8, 19.6, 13.9, 13.4; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>19</sub>H<sub>25</sub>NO<sub>6</sub>: 364.1755, found 364.1758; The ee value was 86%, *t<sub>R</sub>* (major) = 5.01 min, *t<sub>R</sub>* (minor) = 9.38 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(2-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4i)**

White solid, Mp 85–86 °C; yield 93%;  $[\alpha]_{\text{D}}^{30} +104.22$  (*c* 1.15, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40 (t, *J* = 7.2 Hz, 1H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01–6.96 (m, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.09–4.04 (m, 3H), 3.78 (s, 3H), 3.93–3.62 (m, 4H), 3.18 (brs, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 170.4, 169.9, 161.3, 158.9, 129.1,

127.2, 124.2, 124.1, 123.9, 114.8, 114.6, 61.2, 61.0, 60.3, 58.9, 58.8, 52.2, 51.4, 51.2, 13.9, 13.5; HRMS (ESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{18}H_{22}FNO_6$   $[M+H]^+$  368.1504, found: 368.1506; The ee value was 88%,  $t_R$  (major) = 5.68 min,  $t_R$  (minor) = 10.65 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(3-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4j)**

White solid, Mp 99–100 °C; yield 88%;  $[\alpha]_D^{30}$  +51.0 (*c* 1.25,  $CH_2Cl_2$ );  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.30–7.25 (m, 1H), 7.15–7.08 (m, 2H), 6.9–6.92 (m, 1H), 4.44 (d, *J* = 6.8 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 3.78–3.68 (m, 3H), 3.58 (dd, *J* = 8.0, 7.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H);  $^{13}C$ -NMR (101 MHz,  $CDCl_3$ )  $\delta$  170.9, 170.20, 170.17, 163.8, 161.4, 139.9, 129.8, 122.4, 114.2, 64.7, 62.0, 61.2, 60.5, 52.5, 52.3, 51.2, 14.0, 13.6; HRMS (ESI):  $m/z$   $[M+H]^+$  calcd. for  $C_{18}H_{22}FNO_6$   $[M+H]^+$  368.1504, found: 368.1506; The ee value was 76%,  $t_R$  (major) = 5.46 min,  $t_R$  (minor) = 8.88 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4k)<sup>8a</sup>**

White solid, Mp 122–124 °C; yield 89%;  $[\alpha]_D^{30}$  +28.9 (*c* 1.06,  $CH_2Cl_2$ ); The ee value was 97%,  $t_R$  (major) = 8.43 min,  $t_R$  (minor) = 18.83 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(pyridin-3-yl)pyrrolidine-2,3,4-tricarboxylate (4l)<sup>8c</sup>**

White solid, Mp 100–101 °C; yield: 89%;  $[\alpha]_D^{30}$  +44.2 (*c* 0.65,  $CH_2Cl_2$ ); The ee value was 74%,  $t_R$  (major) = 6.27 min,  $t_R$  (minor) = 7.13 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-(thiophen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4m)<sup>8a</sup>**

White solid, Mp 85–86 °C; yield 80%;  $[\alpha]_D^{30}$  +32.6 (*c* 1.10,  $CH_2Cl_2$ ); The ee value was 70%,  $t_R$  (major) = 5.63 min,  $t_R$  (minor) = 10.95 min (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes = 50:50, flow rate = 1.0 mL/min).

**(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-methyl 5-cyclohexylpyrrolidine-2,3,4-tricarboxylate (4n)<sup>8a</sup>**

White solid, Mp 80–81 °C; yield: 80%;  $[\alpha]_D^{30}$  +14.7 (*c* 0.90,  $CH_2Cl_2$ ); The ee value was 51%,  $t_R$  (minor) = 5.31 min,  $t_R$  (major) = 6.07 min (Chiralcel AD-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 20:80, flow rate = 1 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4o)<sup>8a</sup>**

Colorless oil, yield 90%;  $[\alpha]_D^{30}$  +40.8 (*c* 1.20,  $CH_2Cl_2$ ); The ee value was 93%,  $t_R$  (minor) = 7.92 min,  $t_R$  (major) = 12.14 min, (Chiralcel AD-H,  $\lambda$  = 205 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

**(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 2-methyl-5-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate (4p)<sup>8a</sup>**

Colorless oil, yield 83%;  $[\alpha]_{\text{D}}^{30} +25.8$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 94%,  $t_{\text{R}}$  (minor) = 7.45 min,  $t_{\text{R}}$  (major) = 10.28 min, (Chiralcel AD-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-3,4-Diethyl 2-methyl 5-(4-fluorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4q)**<sup>8a</sup>

White solid, Mp 87–88 °C; yield 82%;  $[\alpha]_{\text{D}}^{30} +41.2$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 96%,  $t_{\text{R}}$  (minor) = 8.14 min,  $t_{\text{R}}$  (major) = 12.11 min, (Chiralcel AD-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 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 (4r)**<sup>8a</sup>

Colorless oil, yield 81%;  $[\alpha]_{\text{D}}^{30} +21.8$  (*c* 0.95, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 88%,  $t_{\text{R}}$  (minor) = 18.2 min,  $t_{\text{R}}$  (major) = 19.9 min, (Chiralcel OD-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4s)**<sup>8a</sup>

White solid, yield 91%; Mp 94–95 °C;  $[\alpha]_{\text{D}}^{30} +72.8$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 90%,  $t_{\text{R}}$  (major) = 7.47 min,  $t_{\text{R}}$  (minor) = 15.2 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-Trimethyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4t)**<sup>8a</sup>

Colorless oil, yield 82%;  $[\alpha]_{\text{D}}^{30} +80.6$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>) The ee value was 94%,  $t_{\text{R}}$  (minor) = 18.56 min,  $t_{\text{R}}$  (major) = 19.70 min, (Chiralcel OD-H,  $\lambda$  = 205 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

**(2S,3R,4S,5R)-Trimethyl 5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4u)**

White solid, Mp 94–95 °C; yield 87%;  $[\alpha]_{\text{D}}^{30} +69.7$  (*c* 0.95, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33–7.29 (m, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 4.45 (d, *J* = 6.8 Hz, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H), 3.71–3.9 (m, 1H), 3.67 (s, 3H), 3.56–3.52 (m, 1H), 3.24 (s, 3H), 2.83 (s, 1H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  171., 170.8, 170.7, 163.3, 132.9, 128.5, 115.22, 64.6, 62.1, 52.4, 52.4, 52.1, 51.4, 50.7; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>18</sub>FNO<sub>6</sub>: 340.1191, found: 340.1198; The ee value was 92%,  $t_{\text{R}}$  (major) = 8.52 min,  $t_{\text{R}}$  (minor) = 14.74 min, (Chiralcel AS-H,  $\lambda$  = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).

**(1S,3R,3aS,6aR)-Methyl 5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4v)**<sup>8a</sup>

White solid, yield 91%; Mp 164–165 °C;  $[\alpha]_{\text{D}}^{30} +70.6$  (*c* 1.20, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 87%,  $t_{\text{R}}$  (minor) = 9.41 min,  $t_{\text{R}}$  (major) = 15.12 min, (Chiralcel AS-H,  $\lambda$  = 205 nm, *i*PrOH/hexanes 50:50, flow rate = 1.0 mL/min).

**(2S,3S,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (6a)**<sup>8a</sup>

Catalyzed by **1c**: colorless oil, yield 78%;  $[\alpha]_D^{30} +6.6$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 31%, *t<sub>R</sub>* (major) = 8.13 min, *t<sub>R</sub>* (minor) = 13.57 min (Chiralcel OD-H,  $\lambda = 220$  nm, *i*PrOH/hexanes = 40:60, flow rate = 1.0 mL/min).

Catalyzed by **1e**: Colorless oil, yield 65%;  $[\alpha]_D^{30} +3.9$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 11%, *t<sub>R</sub>* (major) = 8.12 min, *t<sub>R</sub>* (minor) = 13.47 min (Chiralcel OD-H,  $\lambda = 220$  nm, *i*PrOH/hexanes = 40:60, flow rate = 1.0 mL/min).

**(2S,4S,5R)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (6b)**<sup>8f</sup>

Catalyzed by **1c**: white solid, Mp 70–71 °C; yield 88%;  $[\alpha]_D^{30} +23.8$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 51%, *t<sub>R</sub>* (major) = 8.81 min, *t<sub>R</sub>* (minor) = 11.97 min, (Chiralcel AS-H,  $\lambda = 205$  nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

Catalyzed by **1e**: white solid, Mp 72–73 °C; yield 90%;  $[\alpha]_D^{30} +31.5$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 71%, *t<sub>R</sub>* (major) = 8.85 min, *t<sub>R</sub>* (minor) = 12.03 min, (Chiralcel AS-H,  $\lambda = 205$  nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

**(2S,4S,5R)-4-Ethyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (6c)**<sup>8f</sup>

White solid, Mp 69–70 °C; yield 87%;  $[\alpha]_D^{30} +15.1$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 69%, *t<sub>R</sub>* (major) = 6.61 min, *t<sub>R</sub>* (minor) = 9.20 min, (Chiralcel AS-H,  $\lambda = 205$  nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

**(2S,4S,5R)-4-tert-Butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (6d)**<sup>8f</sup>

White solid, Mp 68–69 °C; yield 87%;  $[\alpha]_D^{30} +12.3$  (*c* 0.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 51%, *t<sub>R</sub>* (major) = 5.30 min, *t<sub>R</sub>* (minor) = 6.54 min, (Chiralcel AS-H,  $\lambda = 205$  nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

**(2S,4S,5R)-Methyl 4-((4-methoxybenzyl)carbamoyl)-5-phenylpyrrolidine-2-carboxylate (6e)**<sup>8c</sup>

White solid, Mp 82–83 °C; yield 87%;  $[\alpha]_D^{30} +25.6$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 70%, *t<sub>R</sub>* (minor) = 8.29 min, *t<sub>R</sub>* (major) = 10.78 min. (Chiralcel AD-H,  $\lambda = 205$  nm, *i*PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 4-(isopropylcarbamoyl)-5-phenylpyrrolidine-2-carboxylate (6f)**<sup>8e</sup>

White solid, Mp 107–108 °C; yield 89%;  $[\alpha]_D^{30} +45.6$  (*c* 1.10, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 79%, *t<sub>R</sub>* (minor) = 4.98 min, *t<sub>R</sub>* (major) = 6.19 min (Chiralcel AD-H,  $\lambda = 205$  nm, *i*PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 4-(isopropylcarbamoyl)-5-(*p*-tolyl)pyrrolidine-2-carboxylate (6g)**<sup>8e</sup>

White solid, Mp 100–101 °C; yield 90%;  $[\alpha]_D^{30} +45.1$  (*c* 0.75, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 81%, *t<sub>R</sub>* (minor) = 5.33 min, *t<sub>R</sub>* (major) = 6.47 min (Chiralcel AD-H,  $\lambda = 205$  nm, *i*PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 4-(isopropylcarbamoyl)-5-(4-methoxyphenyl)pyrrolidine-2-carboxylate (6h)**<sup>8c</sup>

White solid, Mp 99–100 °C; yield 92%;  $[\alpha]_{\text{D}}^{30} +11.2$  (*c* 0.80, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 92%,  $t_{\text{R}}(\text{minor}) = 6.53$  min,  $t_{\text{R}}(\text{major}) = 7.29$  min (Chiralcel AD-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 5-(3-(benzyloxy)phenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6i)**

Colorless oil, yield 85%;  $[\alpha]_{\text{D}}^{30} +17.9$  (*c* 1.80, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.43–7.30 (m, 5H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.04 (s, 2H), 4.40 (d, *J* = 6.4 Hz, 1H), 4.00 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.80 (s, 3H), 3.72–3.67 (m, 1H), 3.01–2.97 (m, 1H), 2.57–2.53 (m, 1H), 2.35–2.34 (m, 1H), 2.14 (brs, 1H), 0.81–0.78 (m, 6H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 171.6, 158.7, 140.0, 136.9, 129.4, 128.5, 127.9, 127.5, 119.1, 113.4, 69.9, 65.0, 58.1, 52.3, 50.0, 40.6, 33.7, 22.2; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: 397.2122, found: 397.2127; The ee value was 67%,  $t_{\text{R}}(\text{minor}) = 6.77$  min,  $t_{\text{R}}(\text{major}) = 11.90$  min (Chiralcel AD-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 5-(4-fluorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6j)**<sup>8c</sup>

White solid, Mp 126–127 °C; yield 95%;  $[\alpha]_{\text{D}}^{30} +48.7$  (*c* 0.95, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 86%,  $t_{\text{R}}(\text{minor}) = 5.06$  min,  $t_{\text{R}}(\text{major}) = 5.99$  min (Chiralcel AD-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 5-(3-fluorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6k)**

White solid, Mp 126–127 °C; yield 88%;  $[\alpha]_{\text{D}}^{30} 41.75$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.29–7.24 (m, 1H), 7.10 (t, *J* = 1.0 Hz, 2H), 6.92 (td, *J* = 8.4, 2.1 Hz, 1H), 6.14 (d, *J* = 7.5 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.01 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.80 (s, 3H), 3.74–3.67 (m, 1H), 3.0–2.99 (m, 1H), 2.61–2.53 (m, 1H), 2.35–2.29 (m, 2H), 2.22 (brs, 1H), 0.82 (dd, *J* = 2.0, 4.8 Hz, 6H); <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  173.9, 171.3, 163.9, 161.5, 141.0, 129.8, 122.3, 114.3, 113.7, 64.6, 58.0, 52.3, 50.0, 40.7, 33.6, 22.3; HRMS (ESI): *m/z* [M+H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub>: 309.1609, found: 309.1615; The ee value was 72%,  $t_{\text{R}}(\text{minor}) = 5.10$  min,  $t_{\text{R}}(\text{major}) = 6.30$  min (Chiralcel AD-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane = 20:80, flow rate = 1 mL/min).

**(2S,4S,5R)-Methyl 5-(4-chlorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6l)**<sup>8c</sup>

White solid, Mp 128–129 °C; yield 89%;  $[\alpha]_{\text{D}}^{30} +51.3$  (*c* 0.90, CH<sub>2</sub>Cl<sub>2</sub>); The ee value was 86%,  $t_{\text{R}}(\text{minor}) = 5.70$  min,  $t_{\text{R}}(\text{major}) = 6.68$  min (Chiralcel AD-H,  $\lambda = 205$  nm, <sup>i</sup>PrOH/hexane = 20:80, flow rate = 1 mL/min).

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## SUPPORTING INFORMATION

Supplementary data (complete experimental procedures, and characterization of new products,  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra, and HPLC chromatograms, etc.) associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27443/104/1>.

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10. The absolute configurations of these cycloadducts were assigned by HPLC and optical rotation comparisons with the reported data (see ref. 8a, c, f, e and Supporting Information).
11. Optimization of reaction condition for 1,3-dipolar cycloaddition of the methyl acrylate, see the Supporting Information Table S1.