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

Haifei Wang,[1] Chuliang Gong,[1] Zhipeng Zhou,[1] Qingxia Zhou,[1] Youshi Liu,[1]* and Jie Luo[2]*

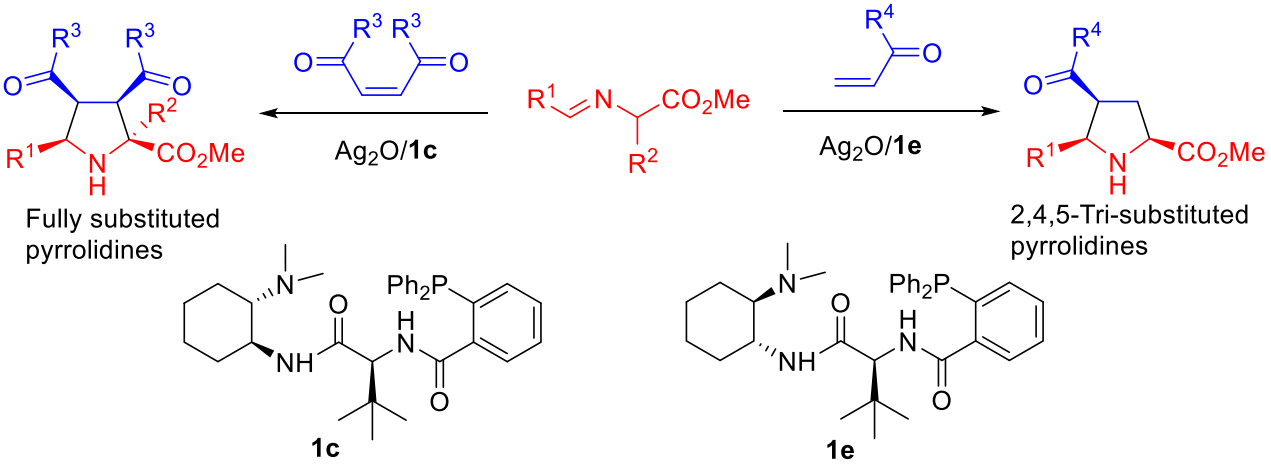
[1]College of Life Science and Chemistry, Hunan University of Technology, Zhuzhou 412007, P. R. of China; [2]College of Packaging and Materials Engineering, Hunan University of Technology, Zhuzhou 412007, P. R. of China; E-mail:471606483@qq.com; luojie84@hotmail.com

Abstract – A series of chiral 1,2-diaminocyclohexane-α-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.[1] 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.[2] To the best of our knowledge, in the chiral metal complexes catalytic systems, these ligands

mainly focus on bidentate P,P-ligands,[3] P,N-ligands,[4] P,S-ligands,[5] N,N-ligands,[6] and N,O-ligands,[7] 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.[8] A series of amidophosphane precatalysts with different chiral scaffolds including cinchona alkaloids, chiral 1,2-diphenylethylenediamines and α-amino acids have been devised. Owning 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,[9] 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-α-amino acid-derived amidophosphanes in combination with Ag(I) to divergently enantiocatalyzed 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).

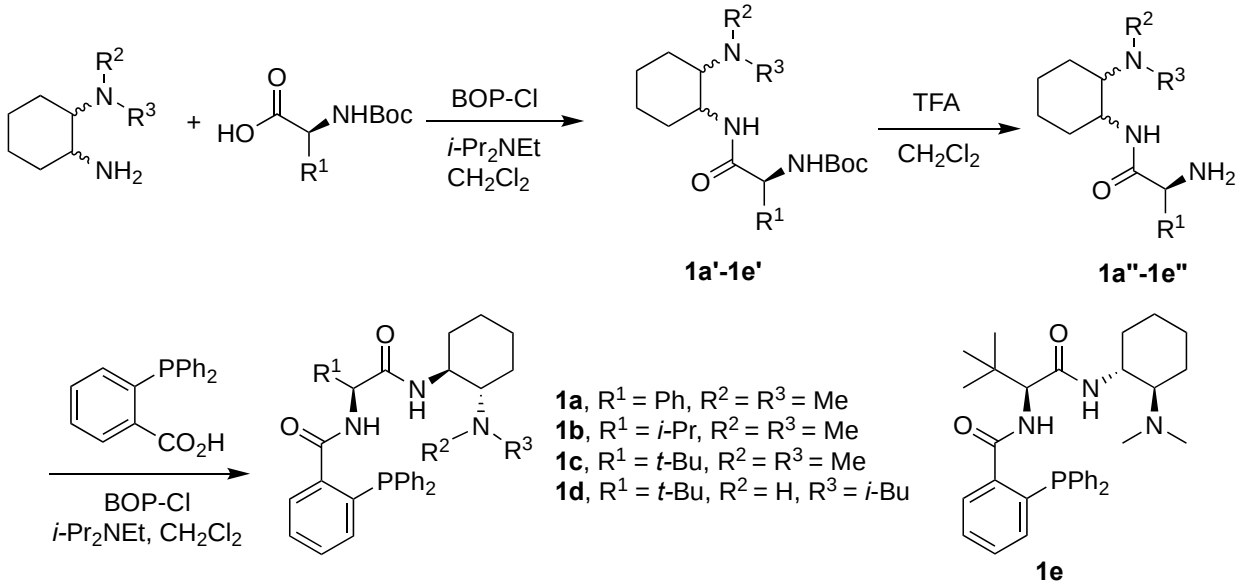


Scheme 1. Divergent enantioseletive azomethine ylides-involved 1,3-dipolar cycloaddition

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 α-amino acids (Scheme 2).[8a] Amidophosphanes **1a–d** were synthesized with corresponding substituted (1*S*,2*S*)-1,2-cyclohexanediamines and different natural α-amino acids, including *N*-Boc-(*S*)-phenylglycine,

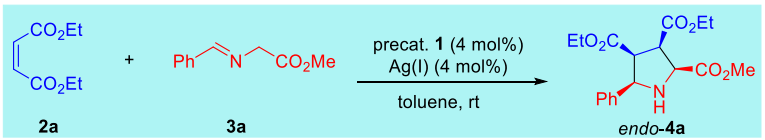
N-Boc-(*S*)-valine and *N*-Boc-(*S*)-*tert*-leucine. On the other hand, the amidophosphane **1e** has also been obtain based on the two starting materials of (1*R*,2*R*)-1-amino-2-(dimethylamino)cyclohexane and *N*-Boc-(*S*)-*tert*-leucine.



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

We initiated the study by choosing diethyl maleate **2a** and α-iminoester **3a** as model substrates to optimize the reaction conditions (Table 1). At first, different amidophosphane ligands **1a-1e** in combination with Ag_2CO_3 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_2O 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_2O (3 mol%)/ **1c** (6 mol%) in toluene at −20 °C.

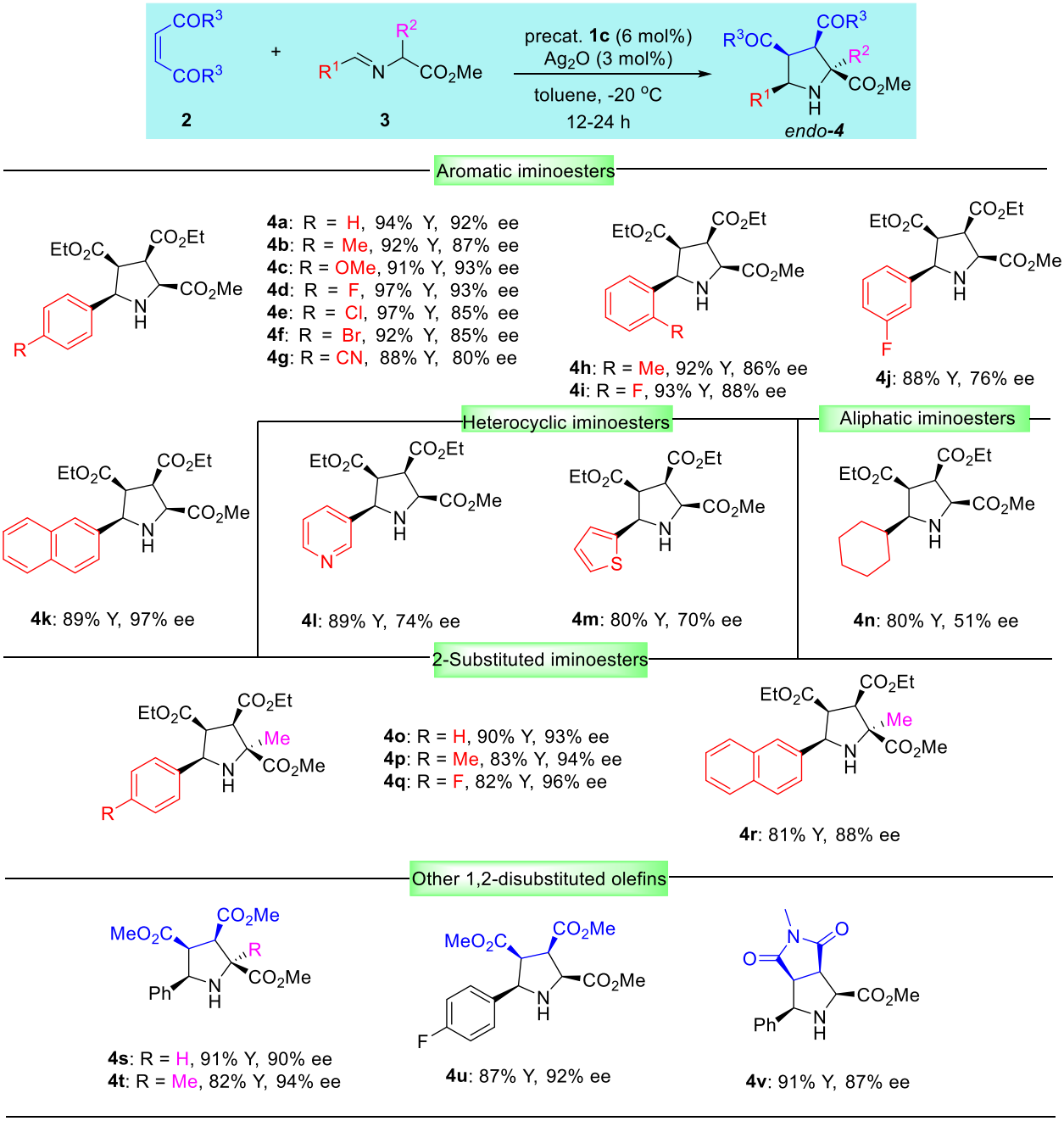
Table 1. Optimization of asymmetric 1,3-dipole cycloaddition reaction conditions[a]



Entry	Precat **1**	Ag(I)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	Ag_2CO_3	3	92	78
2	**1b**	Ag_2CO_3	4	93	78
3	**1c**	Ag_2CO_3	4	95	80
4	**1d**	Ag_2CO_3	4	92	78
5	**1e**	Ag_2CO_3	5	90	63
6	**1c**	Ag_2O	3	96	81
7	**1c**	AgF	4	92	70
8	**1c**	AgOAc	5	90	46
9	**1c**	AgOTf	24	Trace	n.d.[d]
10[e]	**1c**	Ag_2O	6	93	85
11[f]	**1c**	Ag_2O	18	93	91
12[g]	**1c**	Ag_2O	12	94	92

[a]Conditions: iminoester **3a** (0.30 mmol), diethyl maleate **2a** (0.20 mmol), Ag_2CO_3 (2 mmol%), precat (4 mmol%), toluene (1.4 mL). [b]Isolated yields based on **2a**. [c]Determined by HPLC. [d]Not determined. [e]Run at −5 °C. [f]Run at −20 °C. [g]Ag_2O (3 mmol%), precat. **1c** (6 mmol%).

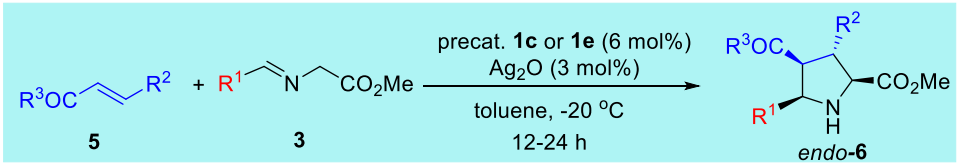
Having established the optimal condition, we next explored the substrate scope of 1,3-dipolar cycloaddition.[10] As shown in Scheme 3, α-iminoesters **3a-k** from aromatic aldehydes bearing both electron-donating and -withdrawing groups regardless of their positions efficiently gave the desired cycloaddition products **4a-k** with good to excellent yields and enantioselectivities (88-97% yields, 76-97% ee). Subsequently, α-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 cycloadditon between the 2-substituted α-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.

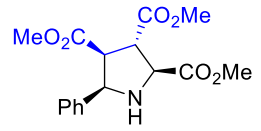


Scheme 3. Ag_2O/**1c**-catalyzed cycloaddition of various α-iminoesters **3** with **2**[a]. [a]Reaction conditions: α-iminoesters **3** (0.30 mmol), **2** (0.20 mmol), Ag_2O (3 mol%), precat. **1c** (6 mol%), isolated yield based on **2**, ee value determined by HPLC.

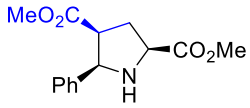
Subsequently, cycloaddition of dimethyl fumarate with α-iminoester **3a** in the presence of precat. **1c** and **1e** was investigated. However, addcut **6a** was obtained with low enantioselectivity (31% ee for **1c** and 11% ee for **1e**). Interestingly, when methyl acrylate was used, it was found that precat. **1e** is a more efficient precatalyst with 90% yield and 71% ee than precat. **1c** with 88% yield and 51% ee.[11] Inspired by this result, we next explored Ag_2O/**1e**-catalyzed 1,3-dipolar cycloaddition of other terminal olefins **5** with α-iminoesters **3**, and corresponding adducts **6c-f** were obtained with moderate enantioselectivities (51-79%

ee) and good yields (87-89%).[10] 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 α-iminoesters **3**. A series of α-iminoesters **3** were well tolerated under the Ag_2O/**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).

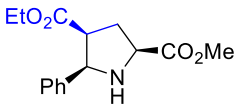




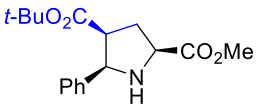
6a: 78% Y, 31% ee (**1c**)
65% Y, 11% ee (**1e**)



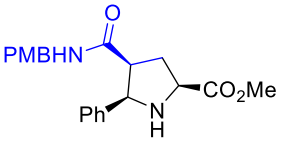
6b: 88% Y, 51% ee (**1c**)
90% Y, 71% ee (**1e**)



6c: 87% Y, 69% ee (**1e**)

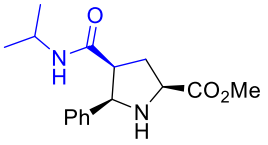


6d: 87% Y, 51% ee (**1e**)

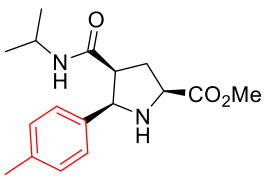


PMB = 4-MeOCH$_2$C$_6$H$_4$

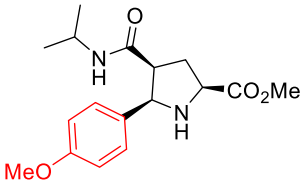
6e: 87% Y, 70% ee (**1e**)



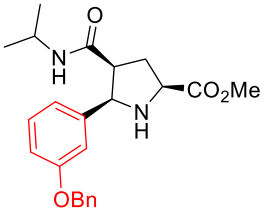
6f: 89% Y, 79% ee (**1e**)



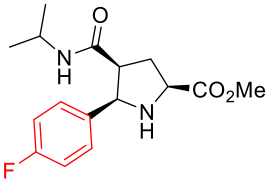
6g: 90% Y, 81% ee (**1e**)



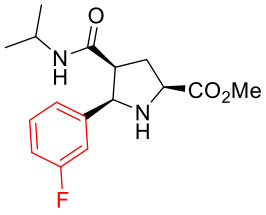
6h: 92% Y, 92% ee (**1e**)



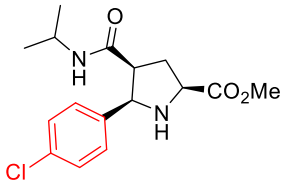
6i: 85% Y, 67% ee (**1e**)



6j: 95% Y, 86% ee (**1e**)



6k: 88% Y, 72% ee (**1e**)

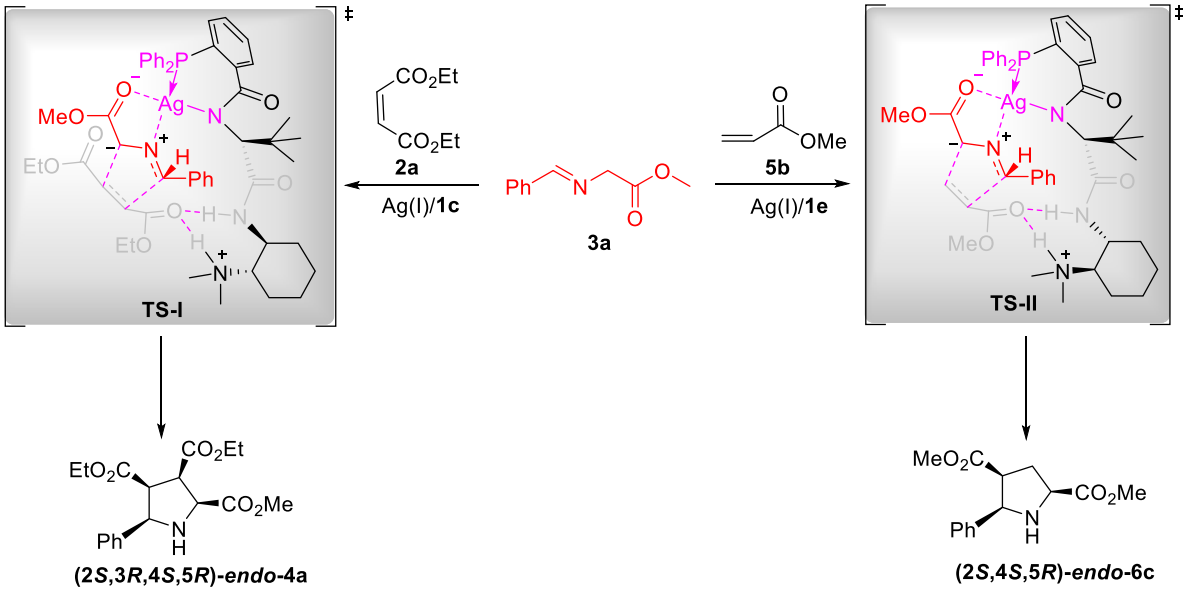


6l: 89% Y, 86% ee (**1e**)

Scheme 4. Ag_2O/**1c** or **1e**-catalyzed cycloaddition of various α-iminoesters **3** with **5**[a]. [a]Reaction conditions: α-iminoesters **3** (0.30 mmol), **5** (0.20 mmol), Ag_2O (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,[8e] the plausible transition state stereoinduction 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 α-amino acid skeleton, but also by the chiral matching or mismatching between α-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-α-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_2O catalytic system can efficiently catalyzed the 1,3-dipolar cycloaddition of *cis*-1,2-disubstituted olefins **2** and α-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_2O serves as a relatively efficient catalytic system for the asymmetric 1,3-dipolar cycloaddition of terminal electron-deficient olefin **5** and α-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. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-400 spectrometer

in $CDCl_3$. $CDCl_3$ served as the internal standard (δ = 7.26) for ^{1}H- NMR and (δ = 77.0) for ^{13}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-(((1*S*,2*S*)-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[8a] was dissolved in CH_2Cl_2 (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_2CO_3 solution. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. 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_2Cl_2 (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_2Cl_2 and water and the organic layer was separated, washed with saturated $NaHCO_3$, and dried over Na_2SO_4. 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_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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}P-NMR (162 MHz, $CDCl_3$) δ -9.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{35}H_{38}N_3O_2P$: 564.2774, found: 564.2782.

N-((*S*)-1-(((1*S*,2*S*)-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; $[\alpha]_D^{30}$ 25.3(*c* 0.95, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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}C-NMR (100 MHz, $CDCl_3$) δ 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}P-NMR (162 MHz, $CDCl_3$) δ -10.0; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{32}H_{40}N_3O_2P$: 530.2931, found: 530.2934.

N-((*S*)-1-(((1*S*,2*S*)-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; $[\alpha]_D^{30}$ 80.6 (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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}C-NMR (100 MHz, $CDCl_3$) δ 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}P-NMR (162 MHz, $CDCl_3$) δ-9.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{33}H_{42}N_3O_2P$: 544.3087, found:544.3089.

2-(Diphenylphosphino)-N-((*S*)-1-(((1*S*,2*S*)-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; $[\alpha]_D^{30}$ 23.3 (*c* 1.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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}C-NMR (101 MHz, $CDCl_3$) δ 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}P-NMR (162 MHz, $CDCl_3$) δ-10.6; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{35}H_{46}N_3O_2P$ $[M+H]^+$ 572.3400, found: 572.3406.

N-((*S*)-1-(((1*R*,2*R*)-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; $[\alpha]_D^{30}$ -10.4 (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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}C-NMR (101 MHz, $CDCl_3$) δ 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}P-NMR (162 MHz, $CDCl_3$) δ-10.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd. for $C_{33}H_{42}N_3O_2P$: 544.3087, found: 544.3092.

3. Representative procedure of 1,3-dipole cycloaddition

Under argon atmosphere, precatalyst **1c** or **1e** (0.012 mmol) and Ag_2O (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.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4a)[8a]

White solid, Mp 118–119 °C; yield 94%; $[\alpha]_D^{30}$ +52.1 (*c* 1.00, CH_2Cl_2); The ee value was 92%, t_R (major) = 5.71 min, t_R (minor) = 9.55 min (Chiralcel AS-H, λ = 205 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-(*p*-tolyl)pyrrolidine-2,3,4-tricarboxylate (4b)[8a]

White solid, Mp 115–116 °C; yield 92%; $[\alpha]_D^{30}$ +46.8 (*c* 1.04, CH_2Cl_2); The ee value was 87%, t_R (major) = 6.33 min, t_R (minor) = 14.35 min, (Chiralcel AS-H, λ = 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-(4-methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (4c)[8a]

White solid, Mp 84–86 °C; yield 91%; $[\alpha]_D^{30}$ +47.5 (c 1.02, CH_2Cl_2); The ee value was 93%, t_R (major) = 7.28 min, t_R (minor) = 13.97 min, (Chiralcel AS-H, λ = 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-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4d)[8a]

White solid, Mp 101-103 °C; yield 97%; $[\alpha]_D^{30}$ +51.4 (c 1.05, CH_2Cl_2); The ee value was 93%, t_R (major) = 7.46 min, t_R (minor) = 12.94 min, (Chiralcel AS-H, λ = 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-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4e)[8a]

White solid, Mp 117-118 °C; yield 97%; $[\alpha]_D^{30}$ +47.0 (c 1.03, CH_2Cl_2); The ee value was 85%, t_R (major) = 7.44 min, t_R (minor) = 12.77 min, (Chiralcel AS-H, λ = 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-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate (4f)[8a]

A white solid, Mp 104–105 °C; yield 92%; $[\alpha]_D^{30}$ +46.8 (*c* 1.10, CH_2Cl_2); The ee value was 85%, t_R (major) = 5.98 min, t_R (minor) = 9.33 min (Chiralcel AS-H, λ = 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-(4-cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (4g)[8a]

White solid, Mp 123–124 °C; yield 88%; $[\alpha]_D^{30}$ +26.2 (*c* 0.70, CH_2Cl_2); The ee value was 80%, t_R (major) = 4.75 min, t_R (minor) = 5.41 min (Chiralcel AS-H, λ = 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-(*o*-tolyl)pyrrolidine-2,3,4-tricarboxylate (4h)**

White solid, Mp 76–77 °C; yield 92%; $[\alpha]_D^{30}$ +71.88 (*c* 1.30, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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* $[M+H]^+$ calcd. for $C_{19}H_{25}NO_6$: 364.1755, found 364.1758; The ee value was 86%, t_R (major) = 5.01 min, t_R (minor) = 9.38 min (Chiralcel AS-H, λ = 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-(2-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4i)

White solid, Mp 85–86 °C; yield 93%; $[\alpha]_D^{30}$ +104.22 (*c* 1.15, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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, λ = 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); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, λ = 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)[8a]

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, λ = 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)[8c]

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, λ = 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)[8a]

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, λ = 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)[8a]

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, λ = 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)[8a]

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, λ = 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)[8a]

Colorless oil, yield 83%; $[\alpha]_D^{30}$ +25.8 (*c* 1.00, CH_2Cl_2); The ee value was 94%, t_R (minor) = 7.45 min, t_R (major) = 10.28 min, (Chiralcel AD-H, λ = 210 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 5-(4-fluorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4q)[8a]

White solid, Mp 87–88 °C; yield 82%; $[\alpha]_D^{30}$ +41.2 (*c* 1.00, CH_2Cl_2); The ee value was 96%, t_R (minor) = 8.14min, t_R (major) = 12.11 min, (Chiralcel AD-H, λ = 210 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-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (4r)[8a]

Colorless oil, yield 81%; $[\alpha]_D^{30}$ +21.8 (*c* 0.95, CH_2Cl_2); The ee value was 88%, t_R (minor) = 18.2 min, t_R (major) = 19.9 min, (Chiralcel OD-H, λ = 210 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

(2*S*,3*R*,4*S*,5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (4s)[8a]

White solid, yield 91%; Mp 94–95 °C; $[\alpha]_D^{30}$ +72.8 (c 1.10, CH_2Cl_2); The ee value was 90%, t_R (major) = 7.47 min, t_R (minor) = 15.2 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).

(2*S*,3*R*,4*S*,5*R*)-Trimethyl 2-methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4t)[8a]

Colorless oil, yield 82%; $[\alpha]_D^{30}$ +80.6 (c 1.10, CH2Cl2) The ee value was 94%, t_R (minor) = 18.56 min, t_R (major) = 19.70 min, (Chiralcel OD-H, λ = 205 nm, *i*PrOH/hexanes 15:85, flow rate = 0.8 mL/min).

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

White solid, Mp 94–95 °C; yield 87%; $[\alpha]_D^{30}$ +69.7 (c 0.95, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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* $[M+H]^+$ calcd. for $C_{16}H_{18}FNO_6$: 340.1191, found: 340.1198; The ee value was 92%, t_R (major) = 8.52 min, t_R (minor) = 14.74 min, (Chiralcel AS-H, λ = 210 nm, *i*PrOH/hexanes 50:50, flow rate = 0.8 mL/min).

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

White solid, yield 91%; Mp 164–165 °C; $[\alpha]_D^{30}$ +70.6 (*c* 1.20, CH_2Cl_2); The ee value was 87%, t_R (minor) = 9.41 min, t_R (major) = 15.12 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 50:50, flow rate = 1.0 mL/min).

(2*S*,3*S*,4*S*,5*R*)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (6a)[8a]

Catalyzed by **1c**: colorless oil, yield 78%; $[\alpha]_D^{30}$ +6.6 (*c* 1.10, CH_2Cl_2); The ee value was 31%, t_R (major) = 8.13 min, t_R (minor) = 13.57 min (Chiralcel OD-H, λ= 220 nm, iPrOH/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_2Cl_2); The ee value was 11%, t_R (major) = 8.12 min, t_R (minor) = 13.47 min (Chiralcel OD-H, λ= 220 nm, iPrOH/hexanes = 40:60, flow rate = 1.0 mL/min).

(2*S*,4*S*,5*R*)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (6b)[8f]

Catalyzed by **1c**: white solid, Mp 70–71 °C; yield 88%; $[\alpha]_D^{30}$ +23.8 (*c* 1.10, CH_2Cl_2); The ee value was 51%, t_R (major) = 8.81 min, t_R (minor) = 11.97 min, (Chiralcel AS-H, λ = 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_2Cl_2); The ee value was 71%, t_R (major) = 8.85 min, t_R (minor) = 12.03 min, (Chiralcel AS-H, λ = 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)[8f]

White solid, Mp 69–70 °C; yield 87%; $[\alpha]_D^{30}$ +15.1 (*c* 1.10, CH_2Cl_2); The ee value was 69%, t_R (major) = 6.61 min, t_R (minor) = 9.20 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

(2*S*,4*S*,5*R*)-4-*tert*-Butyl 2-methyl 5-phenylpyrrolidine-2,4-dicarboxylate (6d)[8f]

White solid, Mp 68–69 °C; yield 87%; $[\alpha]_D^{30}$ +12.3 (*c* 0.10, CH_2Cl_2); The ee value was 51%, t_R (major) = 5.30 min, t_R (minor) = 6.54 min, (Chiralcel AS-H, λ = 205 nm, *i*PrOH/hexanes 20:80, flow rate = 1.0 mL/min).

(2*S*,4*S*,5*R*)-Methyl 4-((4-methoxybenzyl)carbamoyl)-5-phenylpyrrolidine-2-carboxylate (6e)[8e]

White solid, Mp 82–83 °C; yield 87%; $[\alpha]_D^{30}$ +25.6 (c 1.10, CH_2Cl_2); The ee value was 70%, t_R (minor) = 8.29 min, t_R (major) = 10.78 min. (Chiralcel AD-H, λ = 205 nm ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

(2*S*,4*S*,5*R*)-Methyl 4-(isopropylcarbamoyl)-5-phenylpyrrolidine-2-carboxylate (6f)[8e]

White solid, Mp 107–108 °C; yield 89%; $[\alpha]_D^{30}$ +45.6 (*c* 1.10, CH_2Cl_2); The ee value was 79%, t_R(minor) = 4.98 min, t_R(major) = 6.19 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

(2*S*,4*S*,5*R*)-Methyl 4-(isopropylcarbamoyl)-5-(*p*-tolyl)pyrrolidine-2-carboxylate (6g)[8e]

White solid, Mp 100–101 °C; yield 90%; $[\alpha]_D^{30}$ +45.1 (*c* 0.75, CH_2Cl_2); The ee value was 81%, t_R (minor) = 5.33 min, t_R (major) = 6.47 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

(2*S*,4*S*,5*R*)-Methyl 4-(isopropylcarbamoyl)-5-(4-methoxyphenyl)pyrrolidine-2-carboxylate (6h)[8e]

White solid, Mp 99–100 ºC; yield 92%; $[\alpha]_D^{30}$ +11.2 (*c* 0.80, CH_2Cl_2); The ee value was 92%, t_R(minor) = 6.53 min, t_R(major) = 7.29 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

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

Colorless oil, yield 85%; $[\alpha]_D^{30}$ +17.9 (*c* 1.80, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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* $[M+H]^+$ calcd. for $C_{23}H_{28}N_2O_4$: 397.2122, found: 397.2127; The ee value was 67%, t_R(minor) = 6.77 min, t_R(major) = 11.90 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

(2*S*,4*S*,5*R*)-Methyl 5-(4-fluorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6j)[8e]

White solid, Mp 126–127 ºC; yield 95%; $[\alpha]_D^{30}$ +48.7 (*c* 0.95, CH_2Cl_2); The ee value was 86%, t_R(minor) = 5.06 min, t_R(major) = 5.99 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

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

White solid, Mp 126–127 ºC; yield 88%; $[\alpha]_D^{30}$ 41.75 (*c* 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 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* $[M+H]^+$ calcd. for $C_{16}H_{21}FN_2O_3$: 309.1609, found: 309.1615; The ee value was 72%, t_R(minor) = 5.10 min, t_R(major) = 6.30 min (Chiralcel AD-H, λ = 205 nm, ^{i}PrOH/hexane = 20:80, flow rate = 1 mL/min).

(2*S*,4*S*,5*R*)-Methyl 5-(4-chlorophenyl)-4-(isopropylcarbamoyl)pyrrolidine-2-carboxylate (6l)[8e]

White solid, Mp 128–129 ºC; yield 89%; $[\alpha]_D^{30}$ +51.3 (*c* 0.90, CH_2Cl_2); The ee value was 86%, t_R(minor) = 5.70 min, t_R(major) = 6.68 min (Chiralcel AD-H, λ = 205 nm, ^{i}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}H and ^{13}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.