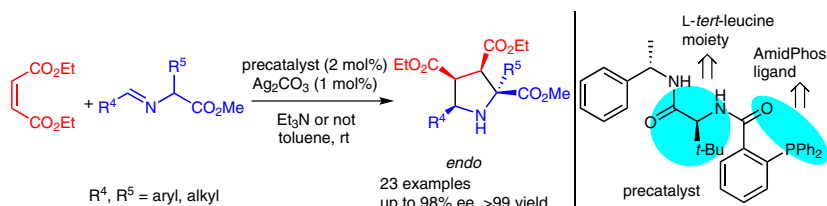


L-tert-Leucine-Derived AmidPhos–Silver(I) Chiral Complexes for the Asymmetric [3+2] Cycloaddition of Azomethine Ylides

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Received: 07.12.2016
Accepted after revision: 06.01.2017
Published online: 02.02.2017
DOI: 10.1055/s-0036-1588137; Art ID: st-2016-w0827-l

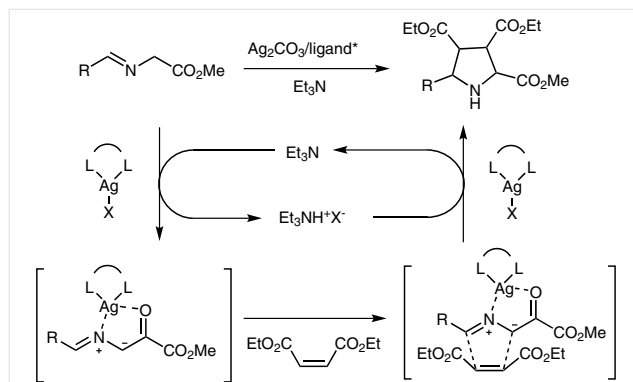
Abstract The L-tert-leucine-derived AmidPhos/silver(I) catalytic system has been developed for the asymmetric [3+2] cycloaddition of azomethine ylides with electronic-deficient alkenes with or without Et_3N . Under optimal conditions, highly functionalized *endo*-4-pyrrolidines were obtained with modest to high yields (up to 99% yield) and enantioselectivities (up to 98% ee).

Key words L-tert-leucine, amidophosphane, silver(I), [3+2] cycloaddition, azomethine ylide

Five-membered nitrogenous heterocycles, in particular, the highly substituted pyrrolidines are useful building blocks for biologically active molecules,¹ as the structural motifs are widely present in many natural alkaloids and pharmaceutically useful agents. In recent years, synthesis of this five-membered heterocyclic compounds have been the focus of attention.² The 1,3-dipolar cycloaddition reaction of azomethine ylides to electron-deficient alkenes is one of the most useful tool for constructing highly substituted pyrrolidines. Since the first catalytic asymmetric 1,3-dipolar cycloaddition reported by Zhang employing the $\text{AgOAc}/\text{xylyl-FAP}/i\text{-Pr}_2\text{NEt}$ system,³ several examples of the formation of optically pure pyrrolidines based on a combination of chiral metal Lewis acids and organic or inorganic bases have thus far been reported to catalyze the process with high *endo/exo* diastereo- and enantioselectivities.^{4–6} Despite these impressive advances, there are still some problems that need to be explored for the reaction. First, the effect of the extra bases on the substrates adaptability has hardly been systematically studied.⁷ Second, synthesis of pyrrolidine derivatives containing aliphatic, heterocyclic

substituents and 2-quaternary stereocenter with high enantioselectivities with small amounts of catalysts loading are still limited.⁸

In previous papers, the most accepted mechanism for the 1,3-dipolar cycloaddition reaction of azomethine ylides to electron-deficient alkenes has been proposed.⁹ Coordination of the iminoester to a chiral metal catalyst, followed by deprotonation with base to form the reactive metal-bound azomethine ylide dipole, which reacts with dipolarophiles, was followed by elimination of cycloadduct to regenerate the chiral catalyst (Scheme 1). Thus, for the catalytic system, an excess amount of base such as a tertiary amine or an inorganic base was involved. However, a few researchers reported that extra bases are not necessary for their catalytic systems, because the metal salt bearing a moderately charged with a basic ligand anion would facilitate deprotonation of the iminoester to generate the azomethine ylide.^{4c,9b,10} Whether such a catalytic system require an extra base or not, we believe that the deprotonation of the iminoester can be accelerated by a suitable base, which is advantageous to improve the reaction rate and enantioselectivity.



Scheme 1 Mechanism of Ag_2CO_3 -catalyzed 1,3-dipolar cycloaddition

tivities, especially for those slower reaction substrates containing aliphatic, heterocyclic, and α -substituted iminoesters. Here, we examined the substrate adaptability of 1,3-dipolar cycloaddition reaction of azomethine ylides to dipolarophiles catalyzed by the chiral *L*-tert-leucine-derived AmidPhos/Ag₂CO₃ catalytic system by small amounts of catalyst loading with or without base.

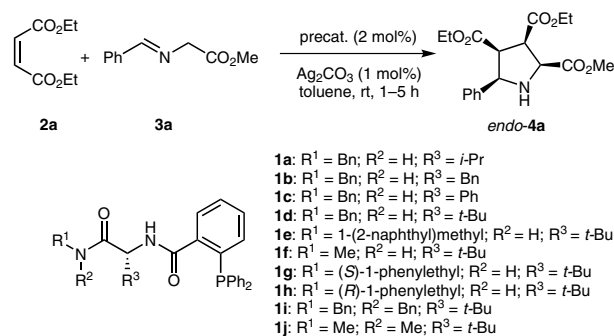
Recently, our group reported a new Ag₂CO₃/CA-AA-AmidPhos catalytic system which was applied to asymmetric 1,3-dipolar cycloaddition of azomethine ylides.¹¹ Through the studies of the reactivity of precatalyst in the cycloaddition, we found the Ag₂CO₃/*L*-valine-derived amidophosphane **1a** system can efficiently catalyze the cycloaddition of iminoesters **3a** with diethyl maleate in toluene at room temperature with high enantioselective (84% ee) in the absence of base (Table 1, entry 1), only the *endo* isomer **4a** was detected by ¹H NMR analysis of reaction mixtures.

Encouraged by these results, the effect of ligands derived from amino acids on the conversions and the enantioselectivities was investigated in toluene (Table 1).¹² Phenylalanine- and phenylglycine-derived ligands **1b,c** were not very effective by comparison with ligand **1a** with slightly lower enantioselectivities (Table 1, entries 2 and 3). Delightfully, high enantioselectivity (88% ee) was achieved with the *L*-tert-leucine-derived ligand **1d** (Table 1, entry 4). Next, the influence of the size and chirality of substituent on the terminal amide group was also studied (Table 1, entries 5–8). Four ligands were synthesized by replacing the benzyl group in **1d** to 1-(2-naphthyl)methyl (**1e**), methyl (**1f**), (*S*)-1-phenylethyl (**1g**), and (*R*)-1-phenylethyl (**1h**), respectively. We were pleased to find that the precatalyst **1g**, with a (*S*)-1-phenylethyl moiety incorporated, afforded the desired adduct with >99% yield and 94% ee (Table 1, entry 7). However, when two hydrogen atoms on the terminal amide group are replaced by dibenzyl and dimethyl groups, respectively, the enantioselectivities were sharply decreased (Table 1, entries 9 and 10).

To further optimize the process, different bases were also studied. When the reaction was run with K₂CO₃, the enantioselectivity was maintained, and the yield was slightly decreased (Table 1, entry 11). Extra Et₃N had no particular effect on the yield and ee value (Table 1, entry 12). Other organic bases were also used under the same conditions, lower enantioselectivities (87–93% ee) were obtained (Table 1, entries 13–16). Thus, the optimal conditions for the asymmetric cycloaddition of azomethine ylides are Ag₂CO₃/**1g**/toluene with or without Et₃N at room temperature.

1,3-Cycloaddition reaction of various iminoesters **3** and diethyl maleate (**2a**) in the presence of ligand **1g** was investigated under the optimized experimental conditions with or without Et₃N. Usually the increase in reaction rate will bring a lower selectivity, but the chiral silver AmidPhos ca-

Table 1 Screening Studies of Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Diethyl Maleate **2a**^a



Entry	Precat.	Base ^b	Yield (%) ^c	ee (%) ^d
1	1a	–	97	84
2	1b	–	84	70
3	1c	–	85	83
4	1d	–	97	88
5	1e	–	90	90
6	1f	–	89	84
7	1g	–	>99	94
8	1h	–	96	89
9	1i	–	72	25
10	1j	–	69	–24
11	1g	K ₂ CO ₃	91	94
12	1g	Et ₃ N	>99	94
13	1g	DBU	90	87
14	1g	DABCO ^e	74	92
15	1g	<i>i</i> -Pr ₂ NEt	96	93
16	1g	DMAP ^e	72	92

^a Reaction conditions: iminoester **3** (0.3 mmol), diethyl maleate (0.31 mmol), Ag₂CO₃ (1 mol%), precatalyst (2 mol%), toluene (1.4 mL).

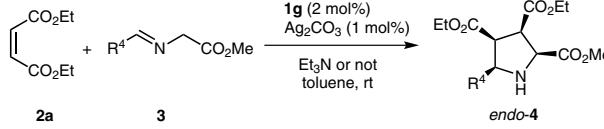
^b Base (5 mol%).

^c Isolated yields based on **3a**.

^d Determined by HPLC.

^e No response after 5 h.

talysis performance of the 1,3-dipolar cycloaddition showed extraordinary results. As shown in Table 2, α -iminoesters **3a–g** from aromatic aldehydes with different steric hindrance and electronic properties reacted with diethyl maleate (**2a**) to afford the corresponding *endo*-**4a–f** adducts exclusively in high yields (84–99%) and excellent enantioselectivities (91–98% ee) in the presence of ligand **1g** with or without Et₃N (Table 2, entries 1–7). Notably, when R⁴ was heteroaromatic groups (Table 2, entries 8 and 9), aliphatic cyclohexyl (Table 2, entry 10), the *endo*-**4h–j** adducts were successfully obtained with increased yields (56–85%) and higher enantioselectivities (92–93% ee) in 6–24 hours with extra Et₃N compared to Ag₂CO₃/**1g** catalytic system (Table 2, entries 8–10).

Table 2 Variation of the R⁴ Substituent on **3** for the Cycloaddition with Diethyl Maleate **2a**^a


Entry	R ⁴	Base ^b	Time (h)	Yield (%) ^c	ee (%) ^d
1	3a Ph	–	3	4a >99	94
		Et ₃ N	3	4a >99	94
2	3b 4-MeC ₆ H ₄	–	6	4b 84	91
		Et ₃ N	6	4b 85	91
3	3c 4-MeOC ₆ H ₄	–	24	4c 91	96
		Et ₃ N	18	4c 91	98
4	3d 4-FC ₆ H ₄	–	20	4d >99	96
		Et ₃ N	18	4d >99	96
5	3e 4-ClC ₆ H ₄	–	5	4e >99	94
		Et ₃ N	5	4e >99	94
6	3f 4-BrC ₆ H ₄	–	36	4f 87	92
		Et ₃ N	18	4f 89	93
7	3g 1-naphthyl	–	4	4g 90	91
		Et ₃ N	4	4g 90	91
8	3h 2-furyl/H	–	24	4h 70	82
		Et ₃ N	8	4h 80	93
9	3i 3-pyridyl, H	–	24	4i 77	84
		Et ₃ N	6	4i 85	92
10	3j cyclohexyl, H	–	48	4j 38	86
		Et ₃ N	24	4j 56	92
11	3k 2-naphthyl	–	4	4k 88	96
12	3l 3,4-ClC ₆ H ₃	–	30	4l 65	87
13	3m 2-ClC ₆ H ₄	–	30	4m 87	90

^a Reaction conditions: iminoester **3** (0.3 mmol), diethyl maleate (0.31 mmol), Ag₂CO₃ (1 mol%), precatalyst **1g** (2 mol%), toluene (1.4 mL).¹³

^b Et₃N (5 mol%).

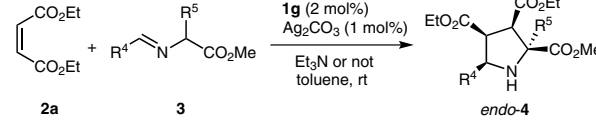
^c Isolated yields based on **4**.

^d Determined by HPLC.

In addition, when R⁴ was 2-naphthyl, 3,4-ClC₆H₃, and 2-ClC₆H₄, the *endo*-**4k–m** adducts were also successfully obtained with high enantioselectivities (87–96% ee) and yields (65–88%) by using Ag₂CO₃/**1g** catalytic system without Et₃N (Table 2, entries 11–13).

The scopes and limitations of the protocol with regard to the 2-substituted azomethine ylides **3** and the maleates **2** were also explored in a similar manner as shown in Table 3. The reaction of iminoesters **3n–p** derived from alanine with the maleates **2** using Ag₂CO₃/**1g** catalytic system without Et₃N led to pyrrolidines **4n–p** with a quaternary center at the 2-position with sole *endo* selectivities and excellent enantioselectivities ranging from 91–92% (Table 3, entries 1–

3). When the Ag₂CO₃/**1g** catalytic system was added Et₃N, slightly improved reactivity and enantioselectivity (94–96% ee) were obtained (Table 3, entries 1–3).

Table 3 Ag₂CO₃/**1g**-Catalyzed Enantioselective Cycloaddition of Various 1,3-Dipolar **3n–s** with **2a**^a


Entry	3 R ⁴ , R ⁵	Base ^b	Time (h)	Yield (%) ^c	ee (%) ^d
1	3n Ph, Me	–	24	4n 98	91
		Et ₃ N	18	4n >99	96
2 ^e	3n Ph, Me	–	24	4o 76	92
		Et ₃ N	18	4o 83	96
3	3p 4-MeC ₆ H ₄ , Me	–	40	4p 67	91
		Et ₃ N	30	4p 79	94
4	3q Ph, Bn	–	48	4q 89	88
		Et ₃ N	24	4q >99	94
5	3r Ph, 3-indolylmethyl	–	48	4r 56	74
		Et ₃ N	24	4r 65	87
6	3s Ph, Ph	–	72 ^f	4s 22	62
		Et ₃ N	72 ^g	4s 47	82

^a Reaction conditions: iminoester **3** (0.3 mmol), diethyl maleate (0.31 mmol), Ag₂CO₃ (1 mol%), precatalyst **1g** (2 mol%), toluene (1.4 mL).

^b Et₃N (5 mol%).

^c Isolated yields based on **4**.

^d Determined by HPLC.

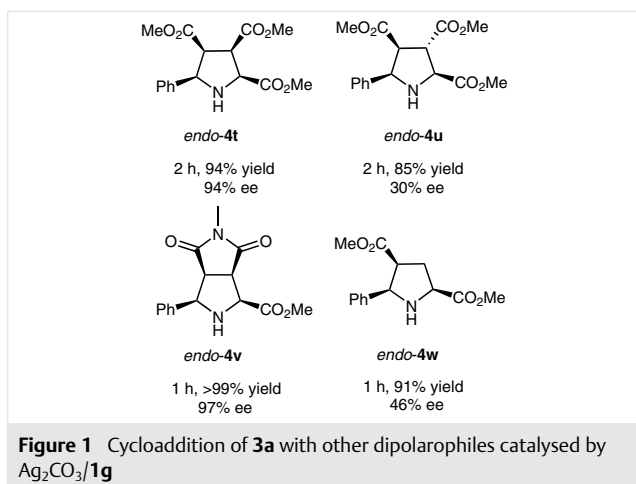
^e Dimethyl maleate **2b** was used.

^f No reaction completely.

^g *endo/exo* >92:8.

Furthermore, we also examined the iminoesters derived from phenylalanine (Table 3, entry 4), tryptophan (Table 3, entry 5), and phenylglycine (Table 3, entry 6) with or without Et₃N. We found the Et₃N had significantly positive influences on the reaction rate, yields, and enantioselectivities. Especially, when R⁵ was benzyl or 3-indolylmethyl group, the reaction time was sharply shortened to 24 hours with higher enantioselectivities (94%, 87% ee; Table 3, entries 4 and 5). Moreover, when R⁵ was Phenyl group, the enantioselectivity was also increased from 62% to 82% with extra Et₃N, albeit the reaction did not go to completion (Table 3, entry 6).

We also probed other four dipolarophiles in the cycloaddition with **3a** as outlined in Figure 1. Only the *endo* adducts were isolated in all cases. The iminoester **3a** reacted perfectly with dimethyl maleate in 94% ee. For dimethyl fumarate and methyl acrylate, much lower enantioselectivities were observed with 30% and 46% ee, respectively. *N*-Methylmaleimide as a popular dipolarophile in the reported literature was also used to react with α-iminoester **3a** with 99% yield and 97% ee.^{7b}



In conclusion, we have developed the *L*-tert-leucine-derived AmidPhos-silver(I) catalytic system for the asymmetric [3+2] cycloaddition of azomethine ylides with diethyl maleate in high yields and excellent levels of enantioselectivities by using a combination of 2 mol% of ligand **1g** and 1 mol% of Ag_2CO_3 with or without Et_3N . The study showed the addition of extra Et_3N greatly accelerated the reaction rate, increase the yields and the enantioselectivities as well, especially for heterocyclic, aliphatic, and 2-substituted azomethine ylides. In addition, dimethyl maleate, dimethyl fumarate, *N*-methylmaleimide, and methyl acrylate were also used to react with α -iminoester **3a** with high yield and modest to high enantioselectivities. Further investigation of the reaction scope and detailed mechanism study are under way.

Acknowledgment

We are grateful to the Natural Science Foundation of China (No. 21202042), the Hunan Provincial Natural Science Foundation of China (Nos. 13JJ4090, 2015JJ3063), the Natural Science Foundation of Hunan University of Technology (No. 2014HZX01), Zhuzhou Municipal Science and Technology Program and Graduate student innovation fund of Hunan Province (CX2016B642) for support of this research.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588137>.

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- (12) **Synthesis of the Representative Ligand 1g**
The **1g** (334 mg, 1 mmol), which was synthesized according to the procedure of the Supporting Information, was dissolved in CH₂Cl₂ (10 mL) and TFA (1 mL) was added dropwise at 0 °C. Then the reaction mixture was stirred for 18 h at r.t. All volatile compounds were removed in vacuo, and the residue was dissolved in water and treated with the sat. Na₂CO₃ solution. The resulting mixture was extracted with CH₂Cl₂ (3×), and the combined organic layers were dried over Na₂SO₄. After filtration and then evaporation of the solvent, the crude free amine was obtained without purification for the next step. To the solution of the free amine in CH₂Cl₂ (8 mL) was added *O*-benzotriazole-1-*N,N,N',N'*-tetraethyluronium hexafluorophosphate (HBTU, 417 mg, 1.1 mmol), followed by the addition of diisopropylethylamine (367 μL, 2.2 mmol) and 2-(diphenylphosphino)benzoic acid (306 mg, 1 mmol). The reaction mixture was then stirred for 18 h at r.t. The mixture was combined with CH₂Cl₂ and water, and the organic layer was separated, washed with sat. NaHCO₃ (2×), and dried over Na₂SO₄. The solvent was removed in vacuo to afford the crude product as colorless oil, which was purified by flash chromatography (15% EtOAc in hexane) yielding the ligand **1g**. White solid (407 mg, 78%); mp 77–79 °C; [α]_D³⁰ –25.6 (c 0.88, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.63–7.62 (m, 1 H), 7.40–7.20 (m, 17 H), 7.02–6.95 (m, 1 H), 6.71–6.70 (m, 1 H), 6.62 (br s, 1 H), 5.12–5.08 (m, 1 H), 4.38–4.35 (m, 1 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 0.84 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃; C–P coupling not removed): δ = 169.3, 168.9, 143.0, 136.7, 134.5, 133.9, 133.8, 133.7, 133.6, 130.5, 129.1, 128.8, 128.6, 128.6, 128.6, 128.5, 127.8, 127.8, 127.3, 126.3, 61.3, 49.1, 34.7, 26.6, 21.8. ³¹P NMR (162 MHz, CDCl₃) δ = –10.4. ESI-HRMS: *m/z* calcd for C₃₃H₃₅N₂O₂P [M + H]⁺: 523.2509; found: 523.2511.
- (13) **General Procedure of 1,3-Dipole Cycloaddition**
Ligand of **1g** (3.132 mg, 0.006 mmol) and Ag₂CO₃ (0.83 mg, 0.003 mmol) were dissolved in toluene (1.4 mL). The reaction mixture was stirred for 1 h at r.t., followed by the addition of the activated olefins (0.33 mmol), Et₃N (0.015 mmol), and imine substrate (0.3 mmol). Once starting material was consumed

(monitored by TLC), the mixture purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by chiral HPLC.

(2S,3R,4S,5R)-3,4-Diethyl 2-Methyl 5-(Pyridin-3-yl)pyrrolidine-2,3,4-tricarboxylate (4i)

White solid, yield 89 mg (85%); mp 102–105 °C; [α]_D³⁰ +50.2 (c 0.90, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 8.60–8.52 (m, 2 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 7.29–7.26 (m, 1 H), 4.51 (d, *J* = 6.4 Hz, 1 H), 4.17–4.12 (m, 3 H), 3.81 (s, 3 H), 3.78–3.63 (m, 4 H), 3.37 (br s, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.84 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.7, 170.2, 170.0, 149.0, 148.9, 134.3, 133.1, 123.2, 62.8, 62.2, 61.2, 60.6, 52.4, 52.3, 50.9, 14.0, 13.6. The ee value was 92%, *t*_R (major) = 9.28 min, *t*_R (minor) = 10.83 min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH–hexanes = 50:50, flow rate = 0.8 mL/min). ESI-HRMS: *m/z* calcd for C₁₇H₂₂N₂O₆ [M + H]⁺: 351.1551; found: 351.1554.

(2S,3R,4S,5R)-3,4-Diethyl 2-Methyl 5-(3,4-Dichlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4l)

White solid, yield 81 mg (65%); mp 127–128 °C; [α]_D³⁰ +46.8 (c 1.00, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.48 (s, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 4.39 (d, *J* = 6.8 Hz, 1 H), 4.14–4.08 (m, 3 H), 3.79 (s, 3 H), 3.78–3.67 (m, 3 H), 3.59–3.55 (m, 1 H), 3.27 (brs, 1 H), 1.22 (t, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 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 (major) = 7.75 min, *t*_R (minor) = 13.00 min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH–hexanes = 50:50, flow rate = 0.8 mL/min). ESI-HRMS: *m/z* calcd for C₁₈H₂₁Cl₂N₁O₆ [M + H]⁺: 418.0819; found: 418.0824.

(2S,3R,4S,5R)-3,4-Diethyl 2-Methyl 5-(2-Chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4m)

Colorless oil, yield 100 mg (87%); [α]_D³⁰ +60.1 (c 1.02, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.48 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.28–7.20 (m, 2 H), 4.72 (d, *J* = 6.8 Hz, 1 H), 4.14–4.08 (m, 3 H), 3.92 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.83 (s, 3 H), 3.77 (dd, *J* = 8.8, 8.8 Hz, 1 H), 3.70–3.60 (m, 2 H), 3.40 (br s, 1 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 0.78 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 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 90%, *t*_R (major) = 8.22 min, *t*_R (minor) = 16.46 min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH–hexanes = 50:50, flow rate = 0.8 mL/min). ESI-HRMS: *m/z* calcd for C₁₈H₂₂Cl₁N₁O₆ [M + H]⁺: 384.1208; found: 384.1212.

(2R,3R,4S,5R)-3,4-Diethyl 2-Methyl 2,5-Diphenylpyrrolidine-2,3,4-tricarboxylate (4s)

Colorless oil, yield 60 mg (47%); [α]_D³⁰ +15.1 (c 0.90, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, *J* = 7.6 Hz, 2 H), 7.45–7.37 (m, 4 H), 7.35–7.25 (m, 4 H), 4.49 (d, *J* = 7.2 Hz, 1 H), 4.36–4.22 (m, 2 H), 4.05 (br s, 1 H), 3.91 (d, *J* = 8.0 Hz, 1 H), 3.70 (s, 3 H), 3.69–3.64 (m, 1 H), 3.55–3.44 (m, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 0.75 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 172.7, 171.5, 170.2, 139.4, 137.8, 128.7, 128.6, 128.2, 128.1, 128.1, 127.8, 127.8, 126.6, 126.4, 76.0, 63.9, 61.2, 60.3, 57.2, 53.6, 52.7, 14.0, 13.5. The ee value was 82%, *t*_R (minor) = 9.13 min, *t*_R (major) = 10.87 min (Chiralcel AD-H, λ = 210 nm, *i*-PrOH–hexanes = 15:85, flow rate = 0.8 mL/min). ESI-HRMS: *m/z* calcd for C₂₄H₂₇N₁O₆ [M + H]⁺: 426.1911; found: 426.1914.