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A Chiral Secondary Amine–Amidophosphane Precatalyst for Silver-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions

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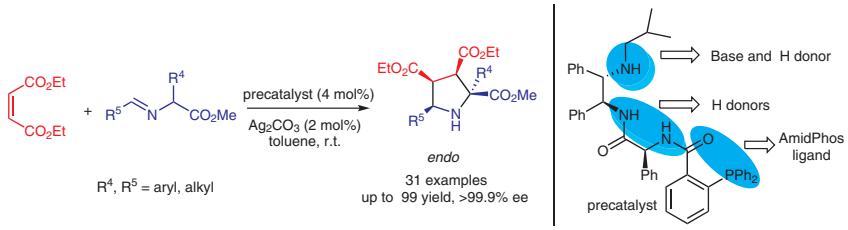

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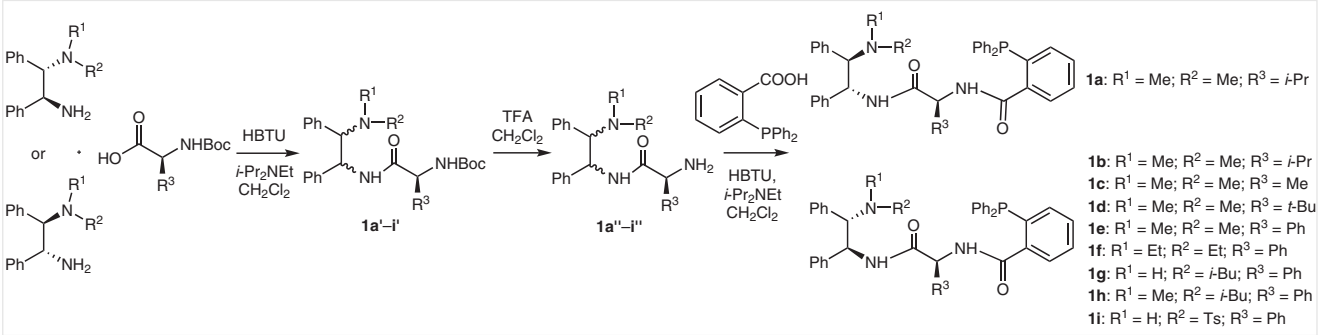
Abstract A class of multifunctional amidophosphanes derived from chiral 1,2-diphenylethylenediamines and natural α-amino acids has been developed. Among these, in combination with silver(I) salts, a chiral secondary amine–amidophosphane precatalyst has been demonstrated as being a highly efficient multifunctional precatalyst in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides, including a series of heterocyclic, aliphatic, and 2-substituted azomethine ylides, and aromatic α,β-unsaturated aldehyde derived imino esters with different electron-deficient alkenes, as well as the three-component reaction of α-imino esters generated in situ by using *N*,*N*′-diisopropylcarbodiimide as dehydrating agent. Under optimal conditions, highly functionalized *endo*-adducts were obtained in high to excellent yields (up to 99% yield) and enantioselectivities (up to >99.9% ee).

Key words secondary amine, amidophosphanes, silver carbonate, 1,3-dipolar cycloaddition, pyrrolidines

The catalytic asymmetric 1,3-dipolar cycloaddition reaction can be considered as one of the most powerful and reliable tools for the enantioselective synthesis of five-membered heterocyclic compounds.[1] The asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient olefins is of particular interest because it allows the preparation of enantiomerically enriched pyrrolidine structures,[2] which are widely present in many biologically active natural products and pharmaceutically useful agents.[3] To date, several effective chiral metal complex catalysts of silver,[4] copper,[5] zinc,[6] nickel,[7] calcium,[8] gold,[9] and organocatalysts[10] have been reported as successfully catalyzing the process for constructing highly substituted pyrrolidines with high *endo*/*exo* diastereo- and enantioselectivity. However, despite intensive efforts in recent years by several research groups who have developed a number of very efficient protocols for performing this reaction with chiral metal complexes as catalysts, there remains a great need for a new cooperative catalytic system using multifunctional organic scaffolds in combination with transition-metal ions to achieve this important transformation.

Cooperative catalysis using multifunctional organic scaffolds in combination with transition-metal ions is emerging as a powerful tool in asymmetric synthesis and has allowed the development of unprecedented transformations in terms of reactivity and stereocontrol.[11] In our previous papers, we have made a breakthrough in the use of multifunctional amidophosphanes derived from different scaffolds of cinchona alkaloid–α-amino acids or double α-amino acids in combination with transition-metal ions to cooperatively catalyze 1,3-dipolar cycloadditions of azomethine ylides with high diastereo- and enantioselectivities.[4f,g] In view of the excellent performance of amidophosphanes, it was advisable to develop a different skeleton type of multifunctional amidophosphane and expand its application prospects. Herein, we report a chiral secondary amine–amidophosphane precatalyst derived from (1*S*,2*S*)-1,2-diphenylethylenediamine and (*S*)-phenylglycine, containing a terminal secondary amine serving the dual role of base and H-bond donor, two amide moieties as H-bond donors, and a phosphine ligand, in combination with silver(I) to cooperatively catalyze 1,3-dipolar cycloadditions of azomethine ylides, including heterocyclic, aliphatic, and 2-substituted azomethine ylides, and aromatic α,β-unsaturated aldehyde derived imines, as well as the three-component reaction of α-imino esters generated in situ, with high to excellent diastereo- and enantioselectivity.

Initially, multifunctional amidophosphane precatalysts **1a–i** were easily synthesized from chiral (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diphenylethylenediamine and natural α-amino acids, as illustrated in Scheme 1. Amidophosphane **1a** was prepared via three steps starting from (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenyl-1,2-ethanediamine and *N*-Boc-(*S*)-valine according



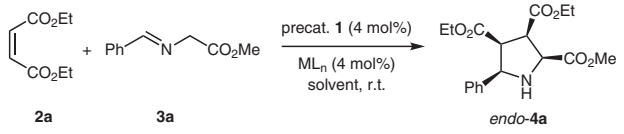
Scheme 1 Synthesis of amidophosphanes **1a–i**

to our reported procedures.[4f] Other amidophosphanes **1b–i** were prepared according to the procedure used to synthesize precatalyst **1a**, starting from the corresponding substituted (1*S*,2*S*)-1,2-diphenylethylenediamines and different natural α-amino acids, to yield the desired products.

To investigate the 1,3-dipolar cycloaddition reaction, azomethine ylide **3a** (from glycine) and diethyl maleate (**2a**) were selected as the model substrates to evaluate the reaction parameters (Table 1). In our initial investigation, we found the catalytic system Ag_2CO_3/amidophosphane **1a**, derived from (1*R*,2*R*)-1,2-diphenylethylenediamine and (*S*)-valine, can efficiently catalyze the cycloaddition of imino ester **3a** with diethyl maleate (**2a**) in toluene at room temperature in high yield (88%) and enantioselectivity (62% ee); only *endo*-**4a** was detected by ^{1}H NMR analysis of reaction mixtures (entry 1). To further understand the effect of central chirality on the enantioselectivity and absolute configuration of the product, amidophosphane **1b** derived from (1*S*,2*S*)-1,2-diphenylethylenediamine and (*S*)-valine was used, and an improvement in enantioselectivity was observed, with the same absolute configuration (86% ee, entry 2).

Encouraged by these results, the effect of ligands **1c–e** derived from the same (1*S*,2*S*)-1,2-diphenylethylenediamine and different α-amino acids on the conversion and the enantioselectivity was investigated in toluene (entries 3–5). Ligands **1c**,**d** derived from (*S*)-alanine and (*S*)-*tert*-leucine, respectively, were not very effective, by comparison with ligand **1b**, with slightly lower enantioselectivities (entries 3 and 4). Delightfully, high enantioselectivity (90% ee) was achieved with the (*S*)-phenylglycine-derived ligand **1e** (entry 5). Next, the influence of substituents on the terminal amino group was also studied (entries 6 and 7). When the terminal dimethylamino group was replaced by a diethylamino group, the enantioselectivity was slightly decreased (85% ee, entry 6). We were pleased to find that precatalyst **1g**, with a terminal isobutylamino group, afforded the desired adduct in 94% yield and 98% enantioselectivity (entry 7). However, when precatalyst **1h** (derived from precatalyst **1g** by replacing the terminal amino hydrogen by a methyl group) was used, the enantioselectivity was sharply decreased to 78% ee, albeit with the same reaction rate (entry 8). Precatalyst **1i** with a 4-tolylsulfonamido group afforded a dual detrimental effect on the enantioselectivity and the reaction rate, by comparison with precatalyst **1g**

Table 1 Optimization of the Conditions for the Reaction of Azomethine Ylide **3a** with Diethyl Maleate (**2a**)[a]



Entry	Precatalyst **1**	ML_n	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	Ag_2CO_3	toluene	3	88	62
2	**1b**	Ag_2CO_3	toluene	3	92	86
3	**1c**	Ag_2CO_3	toluene	3	89	74
4	**1d**	Ag_2CO_3	toluene	3	85	70
5	**1e**	Ag_2CO_3	toluene	3	87	90
6	**1f**	Ag_2CO_3	toluene	3	90	85
7	**1g**	Ag_2CO_3	toluene	3	94	98
8	**1h**	Ag_2CO_3	toluene	3	95	78
9	**1i**	Ag_2CO_3	toluene	21	86	78
10	**1g**	Ag_2O	toluene	2	93	96
11	**1g**	AgF	toluene	4	89	83
12	**1g**	AgOAc	toluene	4.5	75	69
13	**1g**	AgOTf	toluene	10	trace	–
14	**1g**	$Cu(OTf)_2$	toluene	10	trace	–
15	**1g**	Ag_2CO_3	EtOAc	3	88	89
16	**1g**	Ag_2CO_3	CH_2Cl_2	3	82	78
17	**1g**	Ag_2CO_3	Et_2O	4	93	92
18	**1g**	Ag_2CO_3	*t*-BuOMe	3	88	93
19	**1g**	Ag_2CO_3	THF	5	78	86

[a] Reaction conditions: imino ester **3a** (0.24 mmol), diethyl maleate (**2a**, 0.2 mmol), ML_n (4 mol%), precatalyst **1** (4 mol%), toluene (1.4 mL).
[b] Isolated yield based on **2a**.
[c] Determined by HPLC.

(78% ee, 21 h; entry 9). These results strongly suggest that the terminal secondary isobutylamino group on precatalyst **1g** has the dual role of base and H donor.

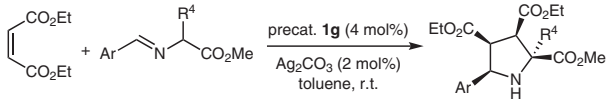
Furthermore, screening metal salts, such as Ag_2O, AgF, AgOAc, AgOTf, and $Cu(OTf)_2$, showed that Ag_2CO_3 gave optimal results in terms of yield and enantioselectivity of adduct **4a** (Table 1, entries 10–14). Screening solvents revealed toluene to be optimal of those tried in terms of both yield and enantioselectivity (entries 15–19). Thus, the optimal conditions for the asymmetric 1,3-dipolar cycloaddition of the azomethine ylide were established as Ag_2CO_3/**1g**/toluene at room temperature.

With the optimal reaction conditions in hand, we examined the scope of the substrates. As shown in Table 2, α-imino esters **3a–i** from aromatic aldehydes with different steric hindrance and electronic properties reacted with diethyl maleate (**2a**) to afford the corresponding *endo*-**4a–i** adducts exclusively in high yields (85–99%) and excellent enantioselectivities (94 to >99.9% ee) in the presence of precatalyst **1g** (entries 1–9).[12] Notably, when Ar was a heteroaromatic group (entries 10–12), the *endo*-**4j–l** adducts were successfully obtained with high yields (73–95%) and excellent enantioselectivities (96 to >99.9% ee). The scope and limitations of the protocol with regard to the 2-substituted azomethine ylides **3m–r** and diethyl maleate (**2a**) were also explored in a similar manner (entries 13–18). The reaction of imino esters **3m–q** derived from alanine with **2a** using the Ag_2CO_3/**1g** catalytic system led to pyrrolidines **4m–q** with a quaternary center at the 2-position, with sole *endo* selectivity and excellent enantioselectivity (98% ee, entries 13–17). Furthermore, imino ester **3r** derived from phenylalanine has also been examined, albeit requiring prolonged reaction time, which yielded the cycloaddition product **4r** without loss of enantioselectivity (98% ee, entry 18).

Next, we tried to expand our methodology to reactions of imino esters prepared from aliphatic aldehydes and aromatic α,β-unsaturated aldehydes (Table 3). Usually, 1,3-dipolar cycloaddition reactions using aliphatic imines, especially primary alkyl imines, are recognized to be very difficult, as such imines are easily converted into enamines in the presence of base, leading to undesired side reactions such as self-condensation. In fact, successful examples of asymmetric 1,3-dipolar cycloadditions of aliphatic aldehyde derived imino esters with high enantioselectivities are quite limited.[4b] As shown in Table 3, we first tested the 1,3-dipolar cycloaddition reaction of imino esters **3s–w** bearing a branched or cyclic alkyl substituent with diethyl maleate (**2a**) to afford the desired cycloadducts **4s–w** in 46–70% yield and 76–87% enantioselectivity under the standard reaction conditions (entries 1–5). Delightfully, when primary alkyl imino ester **3x** derived from hydrocinnamaldehyde was used, the *endo*-**4x** adduct was successfully obtained with high enantioselectivity (90% ee), albeit in moderate yield (65%, entry 6). Significantly, regardless of the substituent on the aromatic ring with different steric hindrance and electronic properties, a wide range of imino esters **3y–ze** derived from aromatic α,β-unsaturated aldehydes were also tolerated, leading to the formation of the desired adducts **4y–ze** in high yields (73–94%) and excellent enantioselectivities (92–98% ee, entries 7–13).[13] Notably, to the best of our knowledge, the azomethine ylides generated from glycine and the α,β-unsaturated aldehydes have not previously been systematically evaluated as substrates for 1,3-dipolar addition with diethyl maleate (**2a**) catalyzed by a chiral metal complex.

We next transferred our attention to evaluate the three-component 1,3-dipolar cycloaddition of α-imino esters generated in situ from aromatic aldehydes and free glycine ester dissolved in toluene with diethyl maleate (**2a**) in a one-pot fashion.[14] As shown in Table 4, when no additive was added, only a trace of product **4a** was observed (entry 1). Then, we investigated the effect of water-absorbing additives. DIC was found to be the best water-absorbing additive, superior to all other inorganic and organic additives

Table 2 Ag_2CO_3/**1g** Catalyzed Cycloaddition of Various Aromatic Aldehyde Derived Imino Esters **3a–r** with Diethyl Maleate (**2a**)[a]

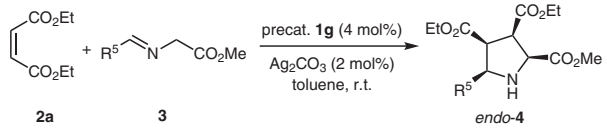


2a **3** *endo*-**4**

Entry	**3** (Ar/R^4)	Time (h)	**4**, Yield (%)[b]	ee (%)[c]
1	**3a** (C_6H_5/H)	3	**4a**, 94	98
2	**3b** (4-MeC_6H_4/H)	4.5	**4b**, 98	>99.9
3	**3c** (4-MeOC_6H_4/H)	7	**4c**, 88	>99.9
4	**3d** (4-FC_6H_4/H)	2	**4d**, 95	98
5	**3e** (4-ClC_6H_4/H)	2	**4e**, 99	99
6	**3f** (4-BrC_6H_4/H)	2	**4f**, 95	98
7	**3g** (4-NCC_6H_4/H)	1	**4g**, 85	94
8	**3h** (1-naphthyl/H)	2	**4h**, 94	>99.9
9	**3i** (2-naphthyl/H)	3	**4i**, 98	>99.9
10	**3j** (2-furyl/H)	6	**4j**, 76	>99.9
11	**3k** (2-thienyl/H)	6	**4k**, 95	96
12	**3l** (3-pyridyl/H)	5	**4l**, 73	97
13	**3m** (C_6H_5/Me)	40	**4m**, 91	98
14	**3n** (4-FC_6H_4/Me)	40	**4n**, 88	98
15	**3o** (4-ClC_6H_4/Me)	40	**4o**, 91	98
16	**3p** (4-BrC_6H_4/Me)	40	**4p**, 95	98
17	**3q** (2-naphthyl/Me)	40	**4q**, 90	98
18	**3r** (C_6H_5/Bn)	56	**4r**, 80	98

[a] Reaction conditions: imino ester **3** (0.24 mmol), diethyl maleate (**2a**, 0.2 mmol), Ag_2CO_3 (2 mol%), precatalyst **1g** (4 mol%), toluene (1.4 mL).
[b] Isolated yield based on **2a**.
[c] Determined by HPLC.

Table 3 Ag_2CO_3/**1g** Catalyzed Cycloaddition of Aliphatic and Unsaturated Aldehyde Derived Imino Esters **3s–ze** with Diethyl Maleate (**2a**)[a]



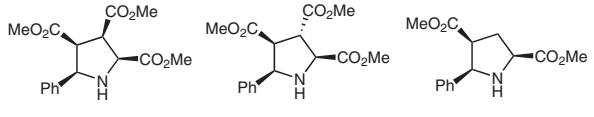
2a **3** *endo*-**4**

Entry	**3** (R^5)	Time (h)	**4**, Yield (%)[b]	ee (%)[c]
1	**3s** (*i*-Pr)	24	**4s**, 70	76
2	**3t** (*i*-Bu)	31	**4t**, 57	84
3	**3u** (*t*-Bu)	48	**4u**, 50	87
4	**3v** (neopentyl)	10	**4v**, 68	82
5	**3w** (cyclohexyl)	24	**4w**, 46	78
6	**3x** ($C_6H_5CH_2CH_2$)	24	**4x**, 65	90
7	**3y** (C_6H_5CH=CH)	10	**4y**, 89	98
8	**3z** (2-$MeOC_6H_4CH$=CH)	28	**4z**, 82	92
9	**3za** (2-FC_6H_4CH=CH)	10	**4za**, 94	97
10	**3zb** (4-FC_6H_4CH=CH)	9	**4zb**, 92	96
11	**3zc** (4-ClC_6H_4CH=CH	10	**4zc**, 81	93
12	**3zd** (4-BrC_6H_4CH=CH)	10	**4zd**, 86	96
13	**3ze** (2-furylCH=CH)	16	**4ze**, 73	94

[a] Reaction conditions: imino ester **3** (0.24 mmol), diethyl maleate (**2a**, 0.2 mmol), Ag_2CO_3 (2 mol%), precatalyst **1g** (4 mol%), toluene (1.4 mL).
[b] Isolated yield based on **2a**.
[c] Determined by HPLC.

tested, such as $MgSO_4$, 4 Å molecular sieves, and DCC (entries 2–5). However, under the same conditions, when methyl glycinate hydrochloride and Et_3N (0.30 mmol) were used, almost no product was observed (entry 6). Delightfully, under the action of DIC serving as water-absorbing additive, regardless of the substituent on the benzene ring with different steric hindrance and electronic properties, adducts **4b–f** derived from free glycine ester were successfully obtained in a one-pot process in satisfactory yields (89–99%) and, in two cases with slightly decreased enantioselectivity relative to **4a** (92–96% ee, entries 7–11).

We also probed another three dipolarophiles, as outlined in Figure 1. Only the *endo*-adducts were isolated in all cases. Dimethyl maleate, as a popular dipolarophile in the literature, was used in the reaction with α-imino ester **3a** to provide **4zf** in 94% yield and with 96% ee. For the reactions



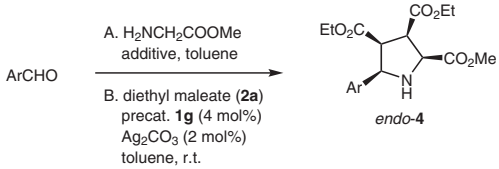
4zf, yield: 94%
ee: 96%

4zg, yield: 91%
ee: 28%

4zh, yield: 82%
ee: 56%

Figure 1 Cycloadducts of **3a** with other dipolarophiles

Table 4 Ag_2CO_3/**1g** Catalyzed Three-Component Reaction of α-Imino Esters Generated in situ[a]



endo-**4**

Entry	Ar	Additive	Time (h)[b]	**4**, Yield (%)[c]	ee (%)[d]
1[e]	C_6H_5	–	12 + 12	**4a**, trace	–
2[f]	C_6H_5	$MgSO_4$	10 + 6	**4a**, 70	88
3[g]	C_6H_5	4 Å MS	12 + 6	**4a**, trace	–
4	C_6H_5	DCC	4 + 3	**4a**, 83	95
5	C_6H_5	DIC	3 + 3	**4a**, 94	95
6[h]	C_6H_5	DIC	3 + 10	**4a**, trace	–
7	4-MeC_6H_4	DIC	3 + 5	**4b**, 94	92
8	4-$MeOC_6H_4$	DIC	3 + 6	**4c**, 89	95
9	4-FC_6H_4	DIC	3 + 3	**4d**, 96	92
10	4-ClC_6H_4	DIC	3 + 3	**4e**, 99	96
11	4-BrC_6H_4	DIC	3 + 4	**4f**, 95	95

[a] Reaction conditions: aldehyde (0.30 mmol), methyl glycinate (0.30 mmol), additive (0.30 mmol), diethyl maleate (**2a**, 0.2 mmol), Ag_2CO_3 (2 mol%), precatalyst **1g** (4 mol%), toluene (1.4 mL); DCC = *N*,*N*′-dicyclohexylcarbodiimide; DIC = *N*,*N*′-diisopropylcarbodiimide.
[b] Reaction time for the two steps.
[c] Isolated yield based on **2a**.
[d] Determined by HPLC.
[e] No additive was added.
[f] $MgSO_4$ (4 equiv) was added.
[g] 4 Å MS (100 mg) were added.
[h] Methyl glycinate hydrochloride (0.30 mmol) and Et_3N (0.30 mmol) were used.

of dimethyl fumarate and methyl acrylate with **3a**, adducts **4zg** and **4zh** with relatively lower enantioselectivities of 28% and 56% ee, respectively, were observed.

In conclusion, we have developed a series of multifunctional amidophosphane precatalysts derived from chiral 1,2-diphenylethylenediamines and α-amino acids. Among these, the (1*S*,2*S*)-1,2-diphenylethylenediamine and (*S*)-phenylglycine-derived secondary amine–amidophosphane **1g** served as a highly efficient multifunctional precatalyst in combination with silver carbonate to cooperatively catalyze the 1,3-dipolar cycloaddition of azomethine ylides **3** and diethyl maleate (**2a**), furnishing highly functionalized *endo*-**4** adducts in moderate to excellent yields (46–99%) and enantioselectivities (76 to >99.9%) under mild conditions, especially for heterocyclic, aliphatic, and 2-substituted azomethine ylides, and aromatic α,β-unsaturated aldehyde derived imino esters. In addition, the catalytic system Ag_2CO_3/**1g**/toluene has also been successfully applied in three-component reactions of α-imino esters generated in situ under the conditions using DIC as dehydrating agent

and with other electron-deficient alkenes. Additional investigations into the substrate scope and mechanistic aspects are in progress.

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AV-400 spectrometers, unless otherwise noted. $CDCl_3$ served as internal standard (^{1}H NMR, δ = 7.26; ^{13}C NMR, δ = 77.0). High-performance liquid chromatography was carried out using an Agilent 1260 apparatus which was equipped with a spectrophotometric detector (monitoring at 205–230 nm) and using a Daicel chiral AS-H column, OD-H column, or AD-H column. High-resolution mass spectrometry was recorded with a Micromass LCMS-IT-TOF instrument. Optical rotations were measured on an Insmark IP-digi300/2 polarimeter. All reactions were carried out under N_2 atmosphere in oven-dried glassware with magnetic stirring. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. All reagents, unless stated otherwise, were of commercial origin and were used without further purification.

N-((*S*)-1-(((1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl)amino)-3-methyl-1-oxobutan-2-yl)-2-(diphenylphosphino)benzamide (1a); Typical Procedure

Compound **1a′** was prepared according to the reported procedure.[4f] **1a′** (439 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (1 mL) was dropwise added 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 saturated Na_2CO_3 solution. The resulting mixture was extracted with CH_2Cl_2 (3 ×) and the combined organic layers were dried over Na_2SO_4. After filtration and then evaporation of the solvent, the crude free amine was obtained without purification for the next step. To a solution of the free amine in CH_2Cl_2 (8 mL) was added *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU; 417 mg, 1.1 mmol), followed by the addition of *N*,*N*-diisopropylethylamine (367 µL, 2.2 mmol) and 2-(diphenylphosphino)benzoic acid (306 mg, 1 mmol). The reaction mixture was then stirred for 6 h at r.t. The mixture was combined with CH_2Cl_2 and water, and the organic layer was separated, washed with saturated $NaHCO_3$ solution (2 ×), and dried over Na_2SO_4. The solvent was removed in vacuo to afford the crude product as a colorless oil, which was purified by flash chromatography (20% EtOAc in hexanes) yielding precatalyst **1a** as a white solid (514 mg, 82%).

Mp 93–95 °C; $[\alpha]_D^{30}$ +20.8 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 2 H), 7.38–7.18 (m, 15 H), 7.12–6.98 (m, 8 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 5.08 (dd, *J* = 11.2, 3.6 Hz, 1 H), 4.53 (dd, *J* = 8.4, 5.6 Hz, 1 H), 3.68 (d, *J* = 11.2 Hz, 1 H), 2.12 (s, 6 H), 2.12–2.04 (m, 1 H), 0.84 (d, *J* = 7.2 Hz, 3 H), 0.82 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 171.1, 168.7, 141.2, 141.0, 140.5, 137.6, 137.5, 137.4, 136.6, 136.4, 134.5, 133.9, 133.8, 133.7, 132.1, 130.3, 129.7, 128.7, 128.6, 128.5, 128.5, 128.4, 127.9, 127.7, 127.7, 127.5, 127.5, 126.9, 73.2, 58.5, 54.8, 40.5, 31.8, 19.1, 18.0.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –10.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{43}N_3O_2P$: 628.3093; found: 628.3095.

N-((*S*)-1-(((1*S*,2*S*)-2-(Dimethylamino)-1,2-diphenylethyl)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′** (439 mg, 1.0 mmol), which yielded **1b** as a white solid (502 mg, 80%).

Mp 105–107 °C; $[\alpha]_D^{30}$ –76.8 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 3.6 Hz, 1 H), 7.55–7.52 (m, 1 H), 7.36–7.20 (m, 15 H), 7.12–7.01 (m, 7 H), 6.99–6.96 (m, 1 H), 6.52 (d, *J* = 8.8 Hz, 1 H), 5.09 (dd, *J* = 11.2, 4.0 Hz, 1 H), 4.50 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.65 (d, *J* = 11.2 Hz, 1 H), 2.14 (s, 6 H), 2.12–2.07 (m, 1 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 170.4, 168.8, 141.3, 141.0, 140.6, 137.5, 137.5, 137.4, 137.4, 136.5, 136.3, 134.5, 133.9, 133.7, 132.3, 130.3, 129.7, 128.7, 128.6, 128.5, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 127.3, 126.8, 73.5, 59.0, 54.6, 40.7, 31.2, 19.1, 18.2.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –10.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{43}N_3O_2P$: 628.3093; found: 628.3096.

N-((*S*)-1-(((1*S*,2*S*)-2-(Dimethylamino)-1,2-diphenylethyl)amino)-1-oxopropan-2-yl)-2-(diphenylphosphino)benzamide (1c)

Catalyst **1c** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1c′** (411 mg, 1.0 mmol), which yielded **1c** as a white solid (413 mg, 69%).

Mp 109–111 °C; $[\alpha]_D^{30}$ –65.6 (*c* 1.40, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.53 (m, 2 H), 7.31–7.21 (m, 15 H), 7.09–6.94 (m, 8 H), 6.93 (br s, 1 H), 5.09 (d, *J* = 10.4 Hz, 1 H), 4.59–4.54 (m, 1 H), 3.69 (d, *J* = 10.4 Hz, 1 H), 2.14 (s, 6 H), 1.25 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 171.7, 168.4, 140.6, 140.6, 140.3, 137.3, 137.2, 137.1, 137.1, 136.7, 136.5, 134.0, 134.0, 133.8, 133.8, 132.5, 130.3, 129.7, 128.8, 128.7, 128.6, 128.5, 128.5, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4, 126.9, 73.4, 54.6, 49.2, 40.6, 18.2.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –9.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{39}N_3O_2P$: 600.2780; found: 600.2783.

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

Catalyst **1d** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1d′** (453 mg, 1.0 mmol), which yielded **1d** as a white solid (417 mg, 65%).

Mp 103–104 °C; $[\alpha]_D^{30}$ –64.3 (*c* 1.12, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.44 (m, 2 H), 7.33–7.18 (m, 15 H), 7.11–6.95 (m, 8 H), 6.53 (d, *J* = 9.2 Hz, 1 H), 5.05 (dd, *J* = 11.2, 3.2 Hz, 1 H), 4.55 (d, *J* = 9.6 Hz, 1 H), 3.60 (d, *J* = 11.2 Hz, 1 H), 2.15 (s, 6 H), 1.01 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 170.0, 168.9, 141.8, 141.5, 140.5, 137.7, 137.6, 137.5, 136.4, 136.2, 134.6, 133.8, 133.7, 133.6, 133.5, 132.0, 130.2, 129.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 127.9, 127.7, 127.6, 127.3, 127.2, 126.7, 73.6, 61.1, 54.6, 40.7, 34.9, 26.5.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –10.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{41}H_{45}N_3O_2P$: 642.3249; found: 642.3253.

N-((*S*)-2-(((1*S*,2*S*)-2-(Dimethylamino)-1,2-diphenylethyl)amino)-2-oxo-1-phenylethyl)-2-(diphenylphosphino)benzamide (1e)

Catalyst **1e** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1e′** (473 mg, 1.0 mmol), which yielded **1e** as a white solid (489 mg, 74%).

Mp 122–124 °C; $[\alpha]_D^{30}$ –1.9 (*c* 0.80, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.08 (m, 28 H), 6.94–6.93 (m, 3 H), 5.50 (d, *J* = 5.6 Hz, 1 H), 4.85 (d, *J* = 10.4 Hz, 1 H), 3.55 (d, *J* = 10.8 Hz, 1 H), 1.78 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 169.8, 168.1, 140.4, 138.4, 137.5, 137.4, 137.2, 136.9, 136.7, 134.3, 133.9, 133.9, 133.7, 133.7, 132.2, 130.3, 129.6, 128.9, 128.5, 128.4, 128.4, 128.0, 128.0, 127.7, 127.7, 127.3, 127.1, 127.0, 73.3, 57.6, 54.9, 40.1.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –9.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{43}H_{41}N_3O_2P$: 662.2936; found: 662.2934.

N-((*S*)-2-(((1*S*,2*S*)-2-(Diethylamino)-1,2-diphenylethyl)amino)-2-oxo-1-phenylethyl)-2-(diphenylphosphino)benzamide (1f)

Catalyst **1f** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1f′** (501 mg, 1.0 mmol), which yielded **1f** as a white solid (449 mg, 65%).

Mp 142–143 °C; $[\alpha]_D^{30}$ +16.5 (*c* 1.12, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (C–P coupling not removed) = 7.58–7.41 (m, 5 H), 7.33–7.07 (m, 23 H), 6.97–6.90 (m, 3 H), 5.54 (d, *J* = 6.0 Hz, 1 H), 4.89 (d, *J* = 10.0 Hz, 1 H), 3.77 (d, *J* = 10.8 Hz, 1 H), 2.37 (q, *J* = 7.2 Hz, 2 H), 1.95 (q, *J* = 7.2 Hz, 2 H), 0.68 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 168.0, 140.8, 140.7, 140.4, 138.2, 137.8, 137.6, 137.4, 137.3, 136.9, 136.7, 134.3, 133.9, 133.9, 133.7, 133.7, 130.2, 129.5, 129.1, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 127.2, 127.0, 68.8, 57.5, 54.9, 42.7, 13.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –9.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{45}H_{45}N_3O_2P$: 690.3249; found: 690.3255.

2-(Diphenylphosphino)-*N*-((*S*)-2-(((1*S*,2*S*)-2-(isobutylamino)-1,2-diphenylethyl)amino)-2-oxo-1-phenylethyl)benzamide (1g)

Catalyst **1g** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1g′** (501 mg, 1.0 mmol), which yielded **1g** as a white solid (482 mg, 70%).

Mp 112–116 °C; $[\alpha]_D^{30}$ +53.7 (*c* 1.26, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 1 H), 7.34–6.86 (m, 30 H), 5.56 (d, *J* = 6.4 Hz, 1 H), 4.93–4.90 (m, 1 H), 3.86 (d, *J* = 4.0 Hz, 1 H), 2.07–1.98 (m, 2 H), 1.48 (br s, 1 H), 0.88–0.83 (m, 1 H), 0.71 (d, *J* = 6.0 Hz, 3 H), 0.69 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 169.1, 168.2, 140.7, 140.5, 140.0, 139.9, 137.9, 137.4, 137.3, 137.1, 137.0, 136.7, 136.4, 134.3, 133.9, 133.9, 133.7, 133.7, 130.3, 129.0, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.9, 127.4, 127.2, 127.2, 126.5, 66.9, 59.1, 57.8, 55.1, 28.3, 20.5, 20.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –10.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{45}H_{45}N_3O_2P$: 690.3249; found: 690.3253.

2-(Diphenylphosphino)-*N*-((*S*)-2-(((1*S*,2*S*)-2-(isobutyl(methyl)amino)-1,2-diphenylethyl)amino)-2-oxo-1-phenylethyl)benzamide (1h)

Catalyst **1h** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1h′** (515 mg, 1.0 mmol), which yielded **1h** as a white solid (435 mg, 62%).

Mp 124–126 °C; $[\alpha]_D^{30}$ +5.52 (*c* 0.87, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.55 (m, 3 H), 7.44–7.42 (m, 2 H), 7.34–7.17 (m, 18 H), 7.15–7.06 (m, 5 H), 6.96–6.90 (m, 3 H), 5.54 (d, *J* = 6.4 Hz, 1 H), 4.84 (dd, *J* = 11.2, 6.0 Hz, 1 H), 3.61 (d, *J* = 10.8 Hz, 1 H), 1.99–1.94 (m, 1 H), 1.74–1.57 (m, 2 H), 1.51 (s, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 169.9, 167.9, 140.7, 140.6, 140.4, 138.4, 137.7, 137.6, 137.3, 137.2, 136.9, 136.7, 134.3, 133.9, 133.8, 133.7, 133.6, 132.7, 130.2, 129.6, 128.9, 128.4, 128.4, 128.3, 128.3, 128.2, 128.0, 127.8, 127.7, 127.7, 127.6, 127.2, 127.0, 72.4, 63.2, 57.4, 55.3, 34.7, 25.4, 20.8, 20.7.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –9.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{46}H_{47}N_3O_2P$: 704.3406; found: 704.3410.

2-(Diphenylphosphino)-*N*-((*S*)-2-(((1*S*,2*S*)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)-2-oxo-1-phenylethyl)benzamide (1i)

Catalyst **1i** was prepared according to the procedure used to synthesize catalyst **1a**, starting from **1i′** (599 mg, 1.0 mmol), which yielded **1i** as a white solid (457 mg, 58%).

Mp 139–140 °C; $[\alpha]_D^{30}$ +49.3 (*c* 0.93, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.62 (m, 1 H), 7.50–7.48 (m, 1 H), 7.35–6.85 (m, 31 H), 6.66 (d, *J* = 7.2 Hz, 2 H), 6.01 (br s, 1 H), 5.58 (d, *J* = 6.8 Hz, 1 H), 5.20 (dd, *J* = 8.4, 8.0 Hz, 1 H), 4.56 (d, *J* = 8.0 Hz, 1 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (C–P coupling not removed) = 170.4, 168.6, 142.6, 140.7, 140.5, 137.4, 137.4, 137.1, 136.8, 136.6, 136.5, 136.4, 135.7, 135.5, 134.3, 133.8, 133.7, 133.6, 133.5, 130.5, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 127.9, 127.9, 127.8, 127.5, 127.4, 126.9, 62.4, 58.8, 58.2, 21.3.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –11.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{48}H_{43}N_3O_4PS$: 788.2712; found: 788.2718.

Ag_2CO_3/1g Catalyzed Cycloaddition of Various Imino Esters 3; General Procedure

Precatalyst **1g** (5.51 mg, 0.008 mmol) and Ag_2CO_3 (1.09 mg, 0.004 mmol) were dissolved in toluene (1.4 mL). The reaction mixture was stirred for 1 h at r.t., followed by the addition of diethyl maleate (**2a**; 34.4 mg, 0.2 mmol) and imine substrate **3** (0.24 mmol). Once starting material had been consumed (monitored by TLC), the mixture was purified by column chromatography to give the corresponding cycloaddition product **4**, which was then directly analyzed by chiral HPLC.

Ag_2CO_3/1g Catalyzed Three-Component Reaction of α-Imino Esters Generated in Situ (Table 4); General Procedure

To the aromatic aldehyde (1.5 equiv) was added a solution of methyl glycinate (1.5 equiv) (by washing methyl glycinate hydrochloride dichloromethane solution with a mixture of aqueous 1 N NaOH and brine (1:1), followed by drying over Na_2SO_4, filtration, and concentra-

tion) in toluene (50 mg/mL) followed by dried *N*,*N*′-diisopropylcarbodiimide (37.8 mg, 0.3 mmol). This suspension was tumbled for 3 h. Under N_2 atmosphere, a solution of precatalyst **1g** (5.51 mg, 0.008 mmol) and Ag_2CO_3 (1.09 mg, 0.004 mmol) in toluene (0.5 mL), which was stirred for 1 h at r.t., was added to the above solution by syringe, followed by the addition of diethyl maleate (**2a**; 34.4 mg, 0.2 mmol). Once starting material had been consumed (monitored by TLC), the mixture was purified by column chromatography to give the corresponding cycloaddition product *endo*-**4**, which was then directly analyzed by chiral HPLC.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-Phenylpyrrolidine-2,3,4-tricarboxylate (4a)[4f]

White solid; yield: 66 mg (94%); 98% ee [t_R = 5.72 (major), 10.90 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 120–121 °C; $[\alpha]_D^{30}$ +58.1 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 4.47 (d, *J* = 6.8 Hz, 1 H), 4.16–4.11 (m, 3 H), 3.81 (s, 3 H), 3.76–3.62 (m, 3 H), 3.59 (t, *J* = 7.6 Hz, 1 H), 3.43 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.4, 170.25, 137.0, 128.2, 127.6, 126.7, 65.3, 62.1, 61.0, 60.3, 52.7, 52.2, 51.2, 14.0, 13.5.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(*p*-Tolyl)pyrrolidine-2,3,4-tricarboxylate (4b)[4f]

White solid; yield: 71 mg (98%); >99.9% ee [t_R = 6.36 (major) min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 115–117 °C; $[\alpha]_D^{30}$ +52.3 (*c* 1.24, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 7.6 Hz, 2 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 4.43 (d, *J* = 6.4 Hz, 1 H), 4.14–4.09 (m, 3 H), 3.79 (s, 3 H), 3.75–3.64 (m, 3 H), 3.57–3.53 (m, 2 H), 2.30 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.4, 170.2, 137.2, 133.9, 128.9, 126.6, 65.1, 62.1, 61.0, 60.3, 52.8, 52.2, 51.3, 21.0, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Methoxyphenyl)pyrrolidine-2,3,4-tricarboxylate (4c)[4f]

White solid; yield: 67 mg (88%); >99.9% ee [t_R = 8.38 (major) min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 84–86 °C; $[\alpha]_D^{30}$ +50.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 4.43 (d, *J* = 6.8 Hz, 1 H), 4.15–4.10 (m, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.71–3.67 (m, 3 H), 3.55 (t, *J* = 6.8 Hz, 1 H), 3.22 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.5, 170.3, 159.0, 129.2, 128.0, 113.6, 64.9, 62.1, 61.0, 60.3, 55.2, 52.8, 52.2, 51.1, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (4d)[4f]

White solid; yield: 70 mg (95%); 98% ee [t_R = 7.39 (major), 11.89 (minor) min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 101–103 °C; $[\alpha]_D^{30}$ +48.6 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.32 (m, 2 H), 7.01–6.99 (m, 2 H), 4.44 (d, *J* = 6.8 Hz, 1 H), 4.12–4.09 (m, 3 H), 3.78 (s, 3 H), 3.74–3.62 (m, 3 H), 3.57–3.53 (m, 1 H), 3.18 (br s, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.3, 163.4, 160.9, 133.1, 133.0, 128.6, 128.5, 115.2, 115.0, 64.6, 62.1, 61.1, 60.4, 52.7, 52.2, 51.1, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (4e)[4f]

White solid; yield: 76 mg (99%); 99% ee [t_R = 6.89 (major), 11.44 (minor) min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 117–118 °C; $[\alpha]_D^{30}$ +49.7 (*c* 1.14, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4 H), 4.44 (d, *J* = 6.8 Hz, 1 H), 4.16–4.10 (m, 3 H), 3.80 (s, 3 H), 3.76–3.68 (m, 3 H), 3.60–3.56 (m, 1 H), 3.27 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.1, 135.8, 133.4, 128.3, 128.3, 64.6, 62.0, 61.1, 60.4, 52.5, 52.2, 51.1, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Bromophenyl)pyrrolidine-2,3,4-tricarboxylate (4f)[4f]

White solid; yield: 81 mg (95%); 98% ee [t_R = 7.42 (major), 12.33 (minor) min (Chiralcel AS-H, λ = 230 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 108–110 °C; $[\alpha]_D^{30}$ +53.8 (*c* 1.14, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 7.27–7.24 (m, 2 H), 4.42 (d, *J* = 7.2 Hz, 1 H), 4.16–4.10 (m, 3 H), 3.80 (s, 3 H), 3.80–3.55 (m, 4 H), 3.27–3.26 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.2, 136.3, 131.3, 128.6, 121.5, 64.7, 62.1, 61.1, 60.5, 52.5, 52.3, 51.1, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (4g)[4f]

White solid; yield: 64 mg (85%); 94% ee [t_R = 12.69 (major), 16.60 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 140–142 °C; $[\alpha]_D^{30}$ +35.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 4.50 (d, *J* = 7.2 Hz, 1 H), 4.15–4.11 (m, 3 H), 3.79 (s, 3 H), 3.77–3.67 (m, 3 H), 3.63–3.60 (m, 1 H), 3.22 (br s, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.84 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.0, 169.9, 143.0, 132.0, 127.8, 118.5, 111.5, 64.6, 62.0, 61.3, 60.6, 52.4, 52.3, 51.1, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(1-Naphthyl)pyrrolidine-2,3,4-tricarboxylate (4h)[4f]

White solid; yield: 75 mg (94%); >99.9% ee [t_R = 11.49 (major) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 77–79 °C; $[\alpha]_D^{30}$ +212.4 (*c* 1.04, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 7.2 Hz, 1 H), 7.53–7.40 (m, 3 H), 5.14 (d, *J* = 6.8 Hz, 1 H), 4.20–4.06 (m, 3 H), 3.93–3.82 (m, 2 H), 3.84 (s, 3 H), 3.45–3.31 (m, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 0.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.2, 170.0, 133.4, 132.3, 131.0, 128.8, 128.2, 126.1, 125.4, 125.1, 123.2, 122.7, 61.5, 61.2, 60.9, 59.9, 52.2, 52.1, 51.3, 13.9, 13.1.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(2-Naphthyl)pyrrolidine-2,3,4-tricarboxylate (4i)[4f]

White solid; yield: 78 mg (98%); >99.9% ee [t_R = 11.41 (major) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 122–124 °C; $[\alpha]_D^{30}$ +32.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.78 (m, 4 H), 7.47–7.44 (m, 3 H), 4.61 (dd, *J* = 6.4, 2.4 Hz, 1 H), 4.19 (dd, J = 8.8, 2.0 Hz, 1H), 4.13 (qd, *J* = 7.2, 1.6 Hz, 2 H), 3.83 (s, 3 H), 3.79–3.75 (m, 1 H), 3.71–3.53 (m, 3 H), 3.42 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 0.67 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.4, 170.2, 134.5, 133.1, 132.7, 128.0, 127.8, 127.5, 126.1, 125.9, 125.4, 124.9, 65.4, 62.0, 61.1, 60.3, 52.7, 52.3, 51.5, 14.0, 13.5.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(2-Furyl)pyrrolidine-2,3,4-tricarboxylate (4j)[4f]

White solid; yield: 52 mg (76%); >99.9% ee [t_R = 7.21 (major) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 104–106 °C; $[\alpha]_D^{30}$ +24.6 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.32 (m, 1 H), 6.33–6.31 (m, 2 H), 4.47 (d, *J* = 6.8 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.07 (d, *J* = 8.8 Hz, 1 H), 3.94–3.85 (m, 2 H), 3.78 (s, 3 H), 3.62 (dd, *J* = 8.0, 8.8 Hz, 1 H), 3.50 (t, *J* = 7.6 Hz, 1 H), 3.24 (br s, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.03 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.2, 170.0, 151.0, 141.8, 110.4, 107.2, 62.0, 61.1, 60.7, 59.5, 52.3, 51.5, 50.8, 14.0, 13.8.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(2-Thienyl)pyrrolidine-2,3,4-tricarboxylate (4k)[4f]

White solid; yield: 67 mg (95%); 96% ee [t_R = 7.22 (major), 17.67 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 88–90 °C; $[\alpha]_D^{30}$ +36.7 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 4.8 Hz, 1 H), 7.02–7.01 (m, 1 H), 6.94–6.92 (m, 1 H), 4.59 (d, *J* = 6.8 Hz, 1 H), 4.13–4.10 (m, 3 H), 3.86–3.82 (m, 2 H), 3.77 (s, 3 H), 3.67 (dd, *J* = 9.2, 8.0 Hz, 1 H), 3.53 (dd, *J* = 8.0, 6.8 Hz, 1 H), 3.34 (br s, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.2, 169.9, 139.9, 126.7, 124.9, 124.5, 61.9, 61.3, 61.1, 60.6, 52.8, 52.2, 51.3, 14.0, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(3-Pyridyl)pyrrolidine-2,3,4-tricarboxylate (4l)[4g]

White solid; yield: 51 mg (73%); 97% ee [t_R = 9.11 (major), 10.62 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 102–105 °C; $[\alpha]_D^{30}$ +54.2 (*c* 1.40, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 2-Methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4m)[4f]

Colorless oil; yield: 66 mg (91%); 98% ee [t_R = 7.81 (minor), 11.70 (major) min (Chiralcel AD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +40.8 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5 H), 4.63 (d, *J* = 6.4 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.78–3.65 (m, 2 H), 3.47 (t, *J* = 7.2 Hz, 1 H), 3.28 (d, *J* = 6.8 Hz, 1 H), 1.68 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.5, 170.5, 137.3, 128.2, 127.7, 126.9, 68.6, 63.7, 61.0, 60.2, 58.0, 53.2, 52.5, 28.3, 14.1, 13.6.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Fluorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4n)[4f]

White solid; yield: 67 mg (88%); 98% ee [t_R = 8.24 (minor), 12.53 (major) min (Chiralcel AD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

Mp 87–88 °C; $[\alpha]_D^{30}$ +41.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 2 H), 7.00–6.96 (m, 2 H), 4.59 (d, *J* = 6.4 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.77 (s, 3 H), 3.69–3.66 (m, 2 H), 3.58 (br s, 1 H), 3.44 (t, *J* = 7.2 Hz, 1 H), 3.25 (d, *J* = 7.2 Hz, 1 H), 1.64 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.6, 170.4, 163.4, 161.0, 133.4, 128.8, 128.7, 115.2, 114.9, 68.6, 63.0, 61.0, 60.2, 57.6, 53.0, 52.5, 28.1, 14.0, 13.7.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Chlorophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4o)[4f]

Colorless oil; yield: 72 mg (91%); 98% ee [t_R = 9.73 (minor), 10.43 (major) min (Chiralcel OD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +39.2 (*c* 1.24, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 4.59 (d, *J* = 6.8 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.78–3.69 (m, 2 H), 3.61 (br s, 1 H), 3.46 (t, *J* = 6.8 Hz, 1 H), 3.27 (d, *J* = 7.2 Hz, 1 H), 1.66 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.5, 170.3, 136.2, 133.4, 128.5, 128.4, 68.6, 63.0, 61.1, 60.3, 57.8, 53.0, 52.6, 28.2, 14.1, 13.7.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-(4-Bromophenyl)-2-methylpyrrolidine-2,3,4-tricarboxylate (4p)[4h]

Colorless oil; yield: 84 mg (95%); 98% ee [t_R = 9.78 (minor), 10.77 (major) min (Chiralcel OD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +31.6 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.3 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 4.51 (d, *J* = 6.6 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.71 (s, 3 H), 3.70–3.46 (m, 3 H), 3.39 (t, *J* = 6.9 Hz, 1 H), 3.19 (d, *J* = 7.1 Hz, 1 H), 1.59 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.79 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.5, 170.3, 136.7, 131.3, 128.8, 121.5, 68.6, 63.0, 61.1, 60.3, 57.8, 52.9, 52.6, 28.1, 14.1, 13.7.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 2-Methyl-5-(2-naphthyl)pyrrolidine-2,3,4-tricarboxylate (4q)[4f]

Colorless oil; yield: 74 mg (90%); 98% ee [t_R = 17.88 (minor), 19.69 (major) min (Chiralcel OD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +22.5 (*c* 0.90, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.77 (m, 4 H), 7.53–7.44 (m, 3 H), 4.77 (d, *J* = 6.4 Hz, 1 H), 4.23–4.13 (m, 3 H), 3.81 (s, 3 H), 3.70–3.55 (m, 4 H), 3.33 (d, *J* = 7.2 Hz, 1 H), 1.72 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.66 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 170.5, 134.8, 133.1, 132.8, 128.0, 127.9, 127.5, 126.1, 125.9, 125.5, 125.0, 68.5, 63.7, 61.0, 60.2, 58.3, 53.1, 52.6, 28.5, 14.1, 13.5.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 2-Benzyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (4r)[4f]

White solid; yield: 70 mg (80%); 98% ee [t_R = 6.08 (minor), 9.91 (major) min (Chiralcel AD-H, λ = 210 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

Mp 77–78 °C; $[\alpha]_D^{30}$ +34.4 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H), 7.31–7.26 (m, 8 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 4.11 (d, *J* = 5.6 Hz, 1 H), 3.76–3.67 (m, 2 H), 3.74 (s, 3 H), 3.60 (br s, 1 H), 3.30–3.17 (m, 4 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 0.79 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 170.8, 170.2, 137.6, 136.1, 131.1, 128.2, 128.0, 127.5, 126.9, 126.7, 72.5, 63.8, 61.0, 60.0, 54.3, 52.4, 52.3, 44.9, 14.1, 13.6.

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

Colorless oil; yield: 44 mg (70%); 76% ee [t_R = 7.85 (major), 9.05 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 10:90, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +8.6 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12–3.97 (m, 5 H), 3.69 (s, 3 H), 3.51 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.15 (dd, *J* = 7.2, 5.6 Hz, 1 H), 2.68–2.64 (m, 2 H), 1.63–1.60 (m, 1 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.1, 169.8, 70.1, 61.2, 60.9, 60.4, 52.1, 49.4, 29.6, 21.4, 20.6, 14.0, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{26}NO_6$: 316.1760; found: 316.1764.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-Isobutylpyrrolidine-2,3,4-tricarboxylate (4t)

White solid; yield: 38 mg (57%); 84% ee [t_R = 6.08 (major), 6.76 (minor) min (Chiralcel AD-H, λ = 205 nm, *i*-PrOH/hexanes, 15:85, flow rate = 1 mL/min)].

Mp 84–85 °C; $[\alpha]_D^{30}$ +7.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15–4.06 (m, 4 H), 3.98 (d, *J* = 9.6 Hz, 1 H), 3.74 (s, 3 H), 3.54 (dd, *J* = 9.2, 8.0 Hz, 1 H), 3.25–3.22 (m, 1 H), 3.16 (dd, *J* = 7.6, 6.0 Hz, 1 H), 2.79 (brs, 1 H), 1.79–1.74 (m, 1 H), 1.46–1.43 (m, 2 H), 1.25 (t, *J* = 6.8 Hz, 3 H), 1.21 (t, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 4.4 Hz, 3 H), 0.89 (d, *J* = 4.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 171.1, 170.1, 67.7, 61.0, 60.5, 60.4, 52.2, 51.6, 50.7, 39.5, 25.8, 23.0, 22.4, 14.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_6$: 330.1917; found: 330.1921.

(2*S*,3*R*,4*S*,5*R*)-3,4-Diethyl 2-Methyl 5-*tert*-Butylpyrrolidine-2,3,4-tricarboxylate (4u)

Colorless oil; yield: 33 mg (50%); 87% ee [t_R = 6.12 (major), 6.81 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +18.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11–4.00 (m, 5 H), 3.74 (s, 3 H), 3.45 (dd, *J* = 10.4, 7.2 Hz, 1 H), 3.08 (dd, *J* = 6.8, 4.8 Hz, 1 H), 2.96 (br s, 1 H), 2.79 (d, *J* = 4.0 Hz, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 0.98 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 171.4, 169.6, 72.7, 60.8, 60.5, 52.2, 52.1, 47.8, 32.6, 27.4, 14.0, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_6$: 330.1917; found: 330.1919.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-Neopentylpyrrolidine-2,3,4-tricarboxylate (4v)

White solid; yield: 47 mg (68%); 82% ee [t_R = 6.70 (major), 7.16 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 15:85, flow rate = 0.8 mL/min)].

Mp 56–57 °C; $[\alpha]_D^{30}$ +7.1 (*c* 1.32, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16–4.06 (m, 4 H), 4.01 (d, *J* = 9.6 Hz, 1 H), 3.73 (s, 3 H), 3.52 (dd, *J* = 10.0, 8.0 Hz, 1 H), 3.20 (dd, *J* = 7.2, 4.0 Hz, 1 H), 3.12 (dd, *J* = 7.6, 6.0 Hz, 1 H), 2.95 (br s, 1 H), 1.52 (dd, *J* = 14.4, 4.0 Hz, 1 H), 1.40 (dd, *J* = 14.4, 7.6 Hz, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 0.94 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.1, 170.0, 61.6, 61.0, 60.5, 59.4, 52.2, 52.0, 51.4, 44.0, 30.3, 29.8, 14.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_6$: 344.2073; found: 344.2077.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-Cyclohexylpyrrolidine-2,3,4-tricarboxylate (4w)[4f]

White solid; yield: 33 mg (46%); 78% ee [t_R = 6.32 (minor), 7.60 (major) min (Chiralcel AD-H, λ = 205 nm, *i*-PrOH/hexanes, 15:85, flow rate = 1 mL/min)].

Mp 81–83 °C; $[\alpha]_D^{30}$ +11.6 (*c* 1.10, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25–4.17 (m, 1 H), 4.13–4.06 (m, 3 H), 4.02 (d, *J* = 10.0 Hz, 1 H), 3.74 (s, 3 H), 3.52 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.18 (dd, *J* = 7.2, 4.8 Hz, 1 H), 2.79 (dd, *J* = 10.0, 4.8 Hz, 1 H), 2.73 (br s, 1 H), 2.06 (d, *J* = 12.8 Hz, 1 H), 1.87 (d, *J* = 12.4 Hz, 1 H), 1.73–1.63 (m, 3 H), 1.41–1.32 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.21–1.11 (m, 3 H), 1.09–0.94 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 171.2, 169.9, 68.8, 61.2, 60.9, 60.4, 52.1, 52.0, 49.1, 39.0, 31.5, 30.9, 26.2, 25.7, 14.2, 14.0.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-Phenethylpyrrolidine-2,3,4-tricarboxylate (4x)

Colorless oil; yield: 49 mg (65%); 90% ee [t_R = 8.54 (major), 9.63 (minor) min (Chiralcel OD-H, λ = 205 nm, *i*-PrOH/hexanes, 25:75, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +10.5 (*c* 1.10, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.28 (m, 2 H), 7.20–7.17 (m, 3 H), 4.18–4.08 (m, 4 H), 3.98 (d, *J* = 9.6 Hz, 1 H), 3.78 (s, 3 H), 3.55 (dd, *J* = 9.2, 8.0 Hz, 1 H), 3.24–3.14 (m, 2 H), 2.86–2.76 (m, 3 H), 1.94–1.86 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 171.0, 170.0, 141.1, 128.3, 128.2, 125.9, 61.5, 60.9, 60.5, 52.1, 51.5, 50.4, 33.3, 32.1, 14.1, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{28}NO_6$: 378.1917; found: 378.1919.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-Styryl)pyrrolidine-2,3,4-tricarboxylate (4y)

Colorless oil; yield: 67 mg (89%); 98% ee [t_R = 8.20 (major), 13.31 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +7.8 (*c* 1.02, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 6.61 (d, *J* = 15.6 Hz, 1 H), 6.27 (dd, *J* = 15.6, 8.0 Hz, 1 H), 4.17–4.02 (m, 6 H), 3.76 (s, 3 H), 3.57 (t, *J* = 8.0 Hz, 1 H), 3.44 (t, *J* = 8.0 Hz, 1 H), 2.98 (br s, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.5, 170.2, 136.3, 133.5, 128.5, 127.8, 126.5, 125.7, 63.3, 62.5, 61.0, 60.7, 52.3, 52.0, 50.4, 14.1, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_6$: 376.1760; found: 376.1765.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-2-Methoxystyryl)pyrrolidine-2,3,4-tricarboxylate (4z)

Colorless oil; yield: 66 mg (82%); 92% ee [t_R = 9.05 (major), 21.00 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +4.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.6 Hz, 1 H), 7.24–7.19 (m, 1 H), 6.97–6.87 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.25 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.17–4.03 (m, 6 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.59 (dd, *J* =16.0, 8.0 Hz, 1 H), 3.44 (dd, *J* = 8.0, 8.0 Hz, 1 H), 2.88 (br s, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.6, 170.4, 156.7, 128.8, 128.4, 126.9, 126.0, 125.4, 120.5, 110.7, 63.9, 62.6, 61.0, 60.7, 55.3, 52.3, 52.3, 50.5, 14.1, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{28}NO_7$: 406.1866; found: 406.1867.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-2-Fluorostyryl)pyrrolidine-2,3,4-tricarboxylate (4za)

Colorless oil; yield: 74 mg (94%); 97% ee [t_R = 7.37 (major), 13.33 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +6.2 (*c* 1.10, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 1 H), 7.21–7.16 (m, 1 H), 7.07–6.97 (m, 2 H), 6.75 (d, *J* = 16.0 Hz, 1 H), 6.36 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.16–4.01 (m, 6 H), 3.75 (s, 3 H), 3.56 (t, *J* = 8.0 Hz, 1 H), 3.45 (t, *J* = 8.0 Hz, 1 H), 2.53 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 170.2, 161.4, 158.9, 129.1, 129.0, 128.6, 128.6, 127.5, 127.5, 125.8, 125.8, 124.1, 124.1, 124.0, 115.7, 115.5, 63.5, 62.6, 61.0, 60.8, 52.3, 52.1, 50.3, 14.0, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}FNO_6$: 394.1666; found: 394.1664.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-4-Fluorostyryl)pyrrolidine-2,3,4-tricarboxylate (4zb)

Colorless oil; yield: 72 mg (92%); 96% ee [t_R = 7.40 (major), 9.65 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +5.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 8.4, 5.2 Hz, 2 H), 6.97 (t, *J* = 8.8 Hz, 2 H), 6.56 (d, *J* = 16.0 Hz, 1 H), 6.20 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.16–4.02 (m, 6 H), 3.76 (s, 3 H), 3.56 (t, *J* = 8.0 Hz, 1 H), 3.43 (t, *J* = 8.0 Hz, 1 H), 2.80 (br s, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.11 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 170.2, 163.6, 161.2, 132.5, 132.5, 132.2, 128.0, 128.0, 125.6, 115.5, 115.3, 63.2, 62.6, 61.1, 60.7, 52.3, 52.0, 50.3, 14.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}FNO_6$: 394.1666; found: 394.1665.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-4-Chlorostyryl)pyrrolidine-2,3,4-tricarboxylate (4zc)

Colorless oil; yield: 66 mg (81%); 93% ee [t_R = 12.12 (major), 14.72 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 25:75, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +7.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 9.2 Hz, 2 H), 7.25 (d, *J* = 9.2 Hz, 2 H), 6.56 (d, *J* = 15.6 Hz, 1 H), 6.28 (dd, *J* = 15.6, 8.0 Hz, 1 H), 4.16–4.02 (m, 6 H), 3.77 (s, 3 H), 3.56 (t, *J* = 8.0 Hz, 1 H), 3.44 (t, *J* = 8.0 Hz, 1 H), 2.69 (br s, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 170.1, 134.9, 133.4, 132.1, 128.7, 127.7, 126.7, 63.1, 62.6, 61.1, 60.8, 52.3, 52.1, 50.3, 14.2, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}ClNO_6$: 410.1370; found: 410.1372.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-4-Bromostyryl)pyrrolidine-2,3,4-tricarboxylate (4zd)

Colorless oil; yield: 78 mg (86%); 96% ee [t_R = 10.65 (minor), 18.71 (major) min (Chiralcel AD-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 1.5 mL/min)].

$[\alpha]_D^{30}$ +9.1 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.52 (d, *J* = 15.6 Hz, 1 H), 6.29 (dd, *J* = 15.6, 8.0 Hz, 1 H), 4.16–4.01 (m, 6 H), 3.75 (s, 3 H), 3.55 (t, *J* = 8.0 Hz, 1 H), 3.43 (t, *J* = 8.0 Hz, 1 H), 2.59 (br s, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 170.1, 135.3, 132.1, 131.6, 128.0, 126.8, 121.6, 63.1, 62.6, 61.1, 60.7, 52.3, 52.0, 50.3, 14.2, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}BrNO_6$: 454.0865; found: 454.0868.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diethyl 2-Methyl 5-((*E*)-2-(2-Furyl)vinyl)pyrrolidine-2,3,4-tricarboxylate (4ze)

Colorless oil; yield: 53 mg (73%); 94% ee [t_R = 8.54 (major), 12.65 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

$[\alpha]_D^{30}$ +5.2 (*c* 1.04, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 1.2 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1 H), 6.23 (d, *J* = 3.2 Hz, 1 H), 6.19 (dd, *J* = 15.6, 7.6 Hz, 1 H), 4.15–4.02 (m, 6 H), 3.77 (s, 3 H), 3.56 (t, *J* = 7.6 Hz, 1 H), 3.41 (t, *J* = 7.6 Hz, 1 H), 2.62 (br s, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.4, 170.3, 151.9, 142.2, 124.0, 121.7, 111.2, 108.5, 63.1, 62.4, 61.1, 60.8, 52.3, 52.0, 50.5, 14.1, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}NO_7$: 366.1553; found: 366.1555.

(2*S*,3*R*,4*S*,5*R*)-Trimethyl 5-Phenylpyrrolidine-2,3,4-tricarboxylate (4zf)[4f]

White solid; yield: 60 mg (94%); 96% ee [t_R = 7.42 (major), 16.18 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 50:50, flow rate = 0.8 mL/min)].

Mp 94–95 °C; $[\alpha]_D^{30}$ +68.4 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.17 (d, *J* = 8.8 Hz, 1 H), 3.82 (s, 3 H), 3.75–3.70 (m, 1 H), 3.70 (s, 3 H), 3.58 (t, *J* = 7.2 Hz, 1 H), 3.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.9, 170.8, 137.0, 128.3, 127.7, 126.6, 65.4, 62.1, 52.5, 52.4, 52.1, 51.3, 50.9.

(2*S*,3*S*,4*S*,5*R*)-Trimethyl 5-Phenylpyrrolidine-2,3,4-tricarboxylate (4zg)[4f]

Colorless oil; yield: 58 mg (91%); 28% ee [t_R = 14.98 (major), 29.14 (minor) min (Chiralcel OD-H, λ = 220 nm, *i*-PrOH/hexanes, 20:80, flow rate = 1.0 mL/min)].

$[\alpha]_D^{30}$ +6.2 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5 H), 4.66 (d, *J* = 8.0 Hz, 1 H), 4.21 (d, *J* = 6.8 Hz, 1 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.67–3.64 (m, 1 H), 3.58 (dd, *J* = 8.0, 4.4 Hz, 1 H), 3.20 (s, 3 H), 2.85 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.0, 171.6, 138.0, 128.6, 128.2, 127.8, 127.0, 126.7, 65.3, 63.2, 53.7, 52.5, 52.5, 51.5, 50.6.

(2*S*,4*S*,5*R*)-Dimethyl 5-Phenylpyrrolidine-2,4-dicarboxylate (4zh)[4f]

White solid; yield: 43 mg (82%); 56% ee [t_R = 12.43 (major), 19.37 (minor) min (Chiralcel AS-H, λ = 205 nm, *i*-PrOH/hexanes, 10:90, flow rate = 1.0 mL/min)].

Mp 72–73 °C; $[\alpha]_D^{30}$ +17.6 (*c* 1.20, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 5 H), 4.53 (d, *J* = 8.0 Hz, 1 H), 3.98 (t, *J* = 8.0 Hz, 1 H), 3.81 (s, 3 H), 3.30 (dd, *J* = 14.4, 6.8 Hz, 1 H), 3.20 (s, 3 H), 2.94 (br s, 1 H), 2.40 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 172.8, 138.9, 128.0, 127.4, 126.5, 65.6, 59.7, 52.0, 51.0, 49.5, 33.1.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609492.

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