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Enantioselective Ag(I)-catalyzed [3+2] cycloaddition of azomethine ylides using a chiral ferrocene-based phosphine–phosphoramidite ligand having a stereogenic *P*-center

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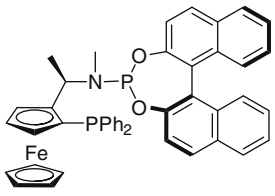
ABSTRACT

A series of chiral ferrocene-based phosphine–phosphoramidite ligands (PPFAPhos) have been employed in the Ag(I)-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides with dimethyl maleate. The results showed that the ligand with a stereogenic *P*-center in the phosphino moiety displayed the best diastereo- and enantioselectivities, in which up to 99% enantiomeric excesses and 99/1 *endo*/*exo* selectivities have been achieved.

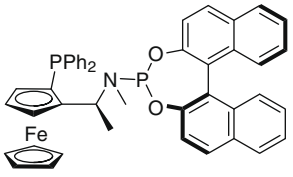
1. Introduction

The asymmetric 1,3-dipolar cycloadditions of azomethine ylides with electronic-deficient olefins represent one of the most important methods for the stereoselective construction of biologically and synthetically important pyrrolidine derivatives.[1] Following the pioneering work by Grigg et al. on the use of chiral transition metal complexes,[2] which require a stoichiometric amount of the metal complex, in the past few years some impressive advances have been made in the catalytic asymmetric [3+2] azomethine ylide cycloadditions by employing a variety of metal catalytic systems combining several ligand types and metal sources[3–5] or chiral organocatalysts.[6] Despite this important progress, there remains a need for the development of novel catalysts for this interesting reaction.

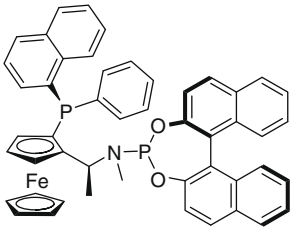
Recently, we have reported a new family of unsymmetrical hybrid chiral ferrocene-based phosphine–phosphoramidite ligands, PPFAPhos (as shown in Fig. 1), which showed excellent enantioselectivities and catalytic activities in the Rh-catalyzed asymmetric hydrogenation of a variety of functionalized olefins including enamides, dimethyl itaconate, α-dehydroamino acid esters, and β-dehydroamino acid esters.[7,8] This ligand class has the advantages of easy accessibility, modularity, and stability toward air and moisture, which makes this ligand class highly practical for both academic and industrial applications. However, research in the use of this ligand class is limited to catalytic asymmetric hydrogenation, and its potential in other catalytic reactions is still unexplored to date. Very recently, Nájera and Sansano et al. have reported that monodentate phosphophosphoramidite ligands can be successfully employed in Ag-catalyzed asymmetric [3+2] azomethine ylide cycloadditions.[3j] We therefore surmised that unsymmetrical hybrid phosphine–phosphoramidite ligands may also be effective for this reaction. As a result, we herein report our investigations on the use of the complexes of PPFAPhos ligands with AgOAc in the catalytic asymmetric 1,3-cycloadditions of azomethine ylides with dimethyl maleate, in which up to 99% ee and good yields for *endo*-adducts can be achieved.



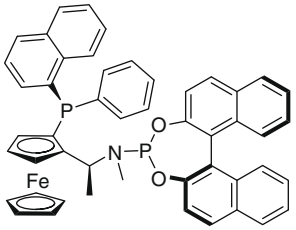
(R_c,S_{Fc},R_a)-PPFAPhos **1a**



(S_c,R_{Fc},R_a)-PPFAPhos **1b**



(S_c,R_{Fc},S_a,R_P)-PPFAPhos **1c**



(S_c,R_{Fc},R_a,R_P)-PPFAPhos **1d**

Figure 1. Ferrocene-based phosphine–phosphoramidite ligands, PPFAPhos **1a–d** evaluated in this study.

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2. Results and discussion

As we have reported, chiral ferrocene-based phosphine–phosphoramidite ligands (PPFAPhos) can be prepared from Ugi's amine via a modular procedure.[7] With these ligands in hand (Fig. 1), we tested their application in the Ag-catalyzed asymmetric [3+2] cycloaddition.

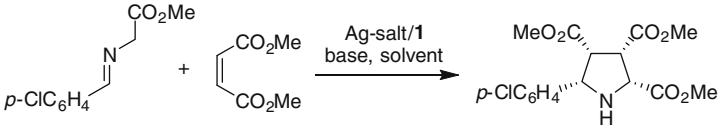
The cycloaddition of *N*-(4-chlorobenzylidene)glycine methyl ester **2a** with dimethyl maleate in the presence of catalytic amounts of Et_3N and AgOAc (3 mol %) was selected as a model reaction for the screening process, and some representative results are listed in Table 1. Initially, the effect of the ligand structure on the stereoselectivity and reaction activity was investigated in Et_2O at 0 °C. The first attempt, using (R_c,S_{Fc},R_a)-PPFAPhos **1a** bearing the matched chiral elements in the Rh-catalyzed asymmetric hydrogenation, afforded the desired product *endo*-**3a** in good yields, however, the enantioselectivities were low (48% ee) (entry 1). Higher enantioselectivities (63% ee) were observed when (S_c,R_{Fc},R_a)-PPFAPhos **1b** with the unmatched chiral elements was employed in the reaction (entry 2). The introduction of a stereogenic *P*-center into the phosphino moiety of these ligands resulted in dramatically changed enantioselectivity. The use of ligand (S_c,R_{Fc},S_a,R_P)-PPFAPhos **1c** has a positive effect in enantioselectivity in which better ee values (81%) were achieved, whereas (S_c,R_{Fc},R_a,R_P)-PPFAPhos **1d** led to lower enantioselectivities (41% ee) (entries 3 and 4). Lowering the reaction temperature to −25 °C, caused the enantioselectivity to further improve to 95% ee (entry 5). The results also indicated that silver salts significantly affected the reactivity and enantioselectivity (entries 5–8). Thus, the reaction can proceed smoothly with AgO_2CCF_3 or $AgBF_4$, but giving very low enantioselectivities (entries 6 and 7). Using $AgPF_6$ instead of AgOAc resulted in a dramatic decrease in reactivity (entry 8).

The nature of the solvents used in the cycloaddition reaction proved to have a remarkable influence in both catalytic activity and enantioselectivity. When the reaction was performed in THF, the yields were dropped to 49% though good enantioselectivity remained (entry 9). Using CH_2Cl_2 and toluene as the solvents, the decreased reactivity and enantioselectivity were observed (entries 10 and 11). We finally investigated the effect of the base additives in this cycloaddition. The results disclosed that Et_3N is the best base additives, superior to all other bases used such as *i*-Pr_2NEt, DBU, and DABCO (entries 13–15). The reaction without any base additives also gave good enantioselectivity, however, the yields were somewhat low (entry 12).

To explore the scope of the AgOAc/(S_c,R_{Fc},S_a,R_P)-PPFAPhos **1c** catalytic system, the [3+2] cycloadditions of various iminoesters **2a–l** prepared from glycinate and aromatic aldehydes with dimethyl maleate were carried out under the optimized reaction conditions (10 mol % Et_3N as the base additive, Et_2O as the solvent, −25 °C for 15 h),[7] and the results are summarized in Table 2. The results indicated that the reaction gave high yields and excellent levels of diastereoselectivity with the *endo*-adducts being obtained predominantly in all cases. However, the enantioselectivity was highly dependent on the characteristics of the aromatic ring. Thus, the substrates with a strong electron-withdrawing substituent, such as *p*-NO_2 or *p*-CF_3 afforded the corresponding cycloadducts in almost perfect enantioselectivities, whereas those with an electron-donating group such as *p*-Me, only gave moderate enantioselectivity (78% ee) (entries 7–9). For *meta*- or unsubstituted substrates as well as 1-naphthylmethylidene glycinate, the reaction gave somewhat lower enantioselectivities than that for **2a** (entries 10–12). The highest ee of 99% was obtained with *N*-(4-trifluoromethylbenzylidene)glycine methyl ester **2h** (entry 8).

Our attempts to use several other dipolarophiles such as *N*-phenylmaleimide, and *tert*-butyl acrylate proved to be unsuccessful (Scheme 1). In both cases, low enantioselectivities were achieved. However, the reaction with dimethyl fumarate also gave good enantioselectivity (84% ee).

Table 1
AgOAc-catalyzed asymmetric [3+2] cycloaddition of *N*-(4-chlorobenzylidene)glycine methyl ester **2a** with dimethyl maleate[a]

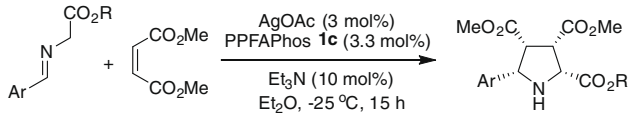


2a *endo*-**3a**

Entry	Ligand	Ag-salt	*T* (°C)	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	**1a**	AgOAc	0	Et_2O	Et_3N	86	48
2	**1b**	AgOAc	0	Et_2O	Et_3N	93	63
3	**1c**	AgOAc	0	Et_2O	Et_3N	94	81
4	**1d**	AgOAc	0	Et_2O	Et_3N	90	41
5	**1c**	AgOAc	−25	Et_2O	Et_3N	94	95
6	**1c**	AgO_2CCF_3	−25	Et_2O	Et_3N	95	<5
7	**1c**	$AgBF_4$	−25	Et_2O	Et_3N	88	<5
8	**1c**	$AgPF_6$	−25	Et_2O	Et_3N	<5	n.d.[d]
9	**1c**	AgOAc	−25	THF	Et_3N	49	94
10	**1c**	AgOAc	−25	CH_2Cl_2	Et_3N	25	85
11	**1c**	AgOAc	−25	PhMe	Et_3N	83	75
12	**1c**	AgOAc	−25	Et_2O	—[e]	79	93
13	**1c**	AgOAc	−25	Et_2O	*i*-Pr_2NEt	98	88
14	**1c**	AgOAc	−25	Et_2O	DBU	93	<5
15	**1c**	AgOAc	−25	Et_2O	DABCO	83	86

[a] Reactions were performed in 1.5 mL of solvent with 0.23 mmol of substrate **2a**, 10 mol % of base additives, and 3 mol % of catalyst prepared in situ from AgOAc and 1.1 equiv of PPFAPhos at indicated reaction temperature for 15 h. Reaction time for entries 1–4 is 3 h. *endo*-Adducts were achieved predominantly in all reactions.
[b] Isolated yields.
[c] Enantiomeric excesses were determined by chiral HPLC (Chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min).
[d] Not determined due to low conversion.
[e] No base additives.

Table 2
Ag(I)-catalyzed asymmetric [3+2] of iminoester **2a–l** with dimethyl maleate using (S_c,R_{Fc},S_a,R_P)-PPFAPhos **1c**[a]



2 *endo*-**3**

Entry	Substrate (Ar, R)	*endo*/*exo*[b]	Yield[c] (%)	ee[d] (%)
1	**2a** (*p*-ClC_6H_4, Me)	94/6	94	95
2	**2b** (*p*-ClC_6H_4, Et)	97/3	94	90
3	**2c** (C_6H_5, Me)	99/1	96	84
4	**2d** (C_6H_5, Et)	95/5	96	85
5	**2e** (*p*-FC_6H_4, Me)	92/8	94	87
6	**2f** (*p*-BrC_6H_4, Me)	99/1	96	94
7	**2g** (*p*-$NO_2C_6H_4$, Me)	95/5	98	98
8	**2h** (*p*-$CF_3C_6H_4$, Me)	99/1	96	99
9	**2i** (*p*-MeC_6H_4, Me)	99/1	95	78
10	**2j** (*m*-$NO_2C_6H_4$, Me)	98/2	93	90
11	**2k** (*m*-$CF_3C_6H_4$, Me)	97/3	94	90
12	**2l** (1-naphthyl, Me)	97/3	94	90

[a] Reactions were performed in 1.5 mL of Et_2O with 0.23 mmol of substrates **2**, 10 mol % of Et_3N, and 3 mol % of catalyst prepared in situ from AgOAc and 1.1 equiv of PPFAPhos **1c** at −25 °C for 15 h.
[b] *endo*/*exo*-Ratio was determined by ^1H NMR.
[c] Isolated yields.
[d] Enantiomeric excesses were determined by chiral HPLC.

3. Conclusion

In conclusion, AgOAc/(S_c,R_{Fc},S_a,R_P)-PPFAPhos complex was found to be an efficient catalyst for asymmetric 1,3-dipolar cycloadditon of azomethine ylides with dimethyl maleate. The results disclosed show that the *endo*-adducts were predominantly produced with ee values of up to 99%, while the enantioselectivity was highly dependent on the characteristics of the substituent in the aromatic ring of iminoester substrates. However, the present catalyst system is less efficient for the asymmetric 1,3-dipolar cycloadditon of azomethine ylides with other dipolarophiles such as *N*-phenylmaleimide and *tert*-butyl acrylate, in which low enantioselectivities were obtained.

4. Experimental

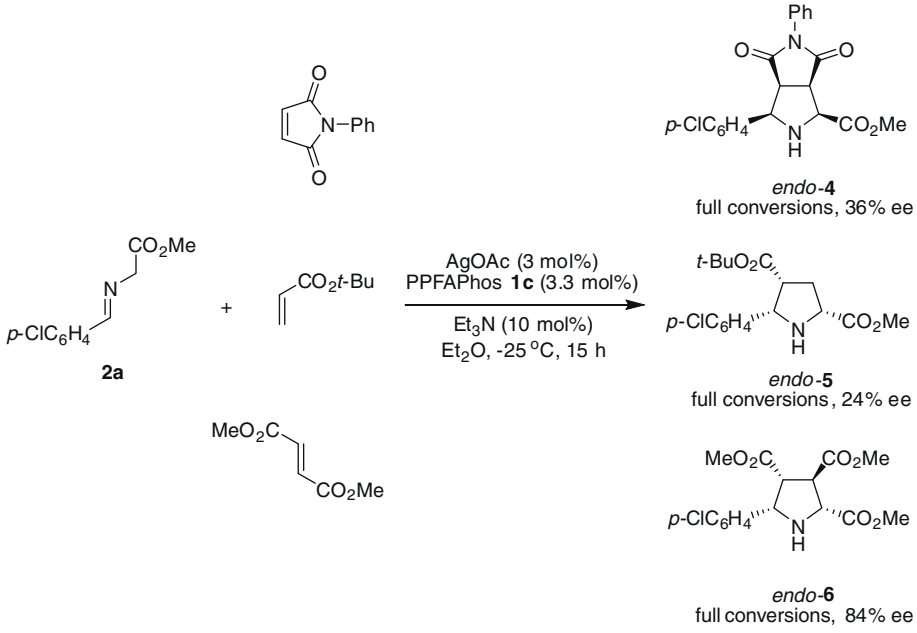
4.1. General

All synthetic reactions and manipulations were performed in a nitrogen or argon atmosphere using standard Schlenk techniques. Solvents were reagent grade, dried, and distilled before use following the standard procedures. Chiral ferrocene-based phosphine–phosphoramidite ligands, PPFAPhos, were synthesized according to the literature procedure.[7] Iminoesters **2a–l** are known compounds, which were prepared according to the literature methods.[3a] All other chemicals were obtained commercially.

^1H and ^{13}C NMR spectra were recorded on BRUKER DEX-400 spectrometer. Chemical shift values (δ) are denoted in ppm and are referenced to residue protons in deuterated solvents for ^1H NMR ($CDCl_3$: 7.27 ppm) and to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Optical rotations were recorded using a JASCO P-1020 high sensitive polarimeter. Enantiomeric excesses were determined by HPLC analysis with a chiral column (Chiralpak AS-H, 0.46 mm × 25 cm) for **3–6**.

4.2. General procedure for Ag(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides

(S_c,R_{Fc},S_a,R_P)-PPFAPhos **1c** (0.0075 mmol) and AgOAc (1.2 mg, 0.007 mmol) were placed in a dried Schlenk tube under a nitrogen atmosphere and Et_2O (1.0 mL) was added. The mixture was stirred at room temperature for about 1 h. After it was cooled to −25 °C, iminoester substrate (0.23 mmol) was added as a solution in Et_2O (0.5 mL) followed by dimethyl maleate (0.28 mmol) and Et_3N (0.023 mmol). After the reaction was stirred at −25 °C for 15 h, the mixture was passed through a short column of silica gel and the diastereometric ratio (*endo*/*exo*) was determined by the NMR spectroscopic analysis of the crude product. The pure adducts were then purified by column chromatography on silica gel, and were submitted to ee analysis by HPLC with a chiral column.



Scheme 1. AgOAc-catalyzed asymmetric [3+2] cycloaddition of *N*-(4-chlorobenzylidene)glycine methyl ester **2a** with *N*-phenyl maleimide, *t*-butyl acrylate, and dimethyl fumarate.

4.2.1. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate 3a

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (s, 4H), 4.45 (d, J = 6.8 Hz, 1H), 4.15 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.69–3.74 (m, 1H), 3.69 (s, 3H), 3.55–3.59 (m, 1H), 3.28 (s, 3H), 3.06 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.5, 52.2, 52.3, 52.5, 62.1, 64.6, 128.2, 128.5, 133.6, 135.8, 170.7, 170.9; 95% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 7.9 and 10.4 min); $[\alpha]_D^{22} = -33.8$ (c 1.0, $CHCl_3$).

4.2.2. (2*R*,3*S*,4*R*,5*S*)-5-(4-Chlorophenyl)pyrrolidine-2-carboxylic ethyl ester-3,4-dicarboxylic dimethyl ester 3b

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (s, 4H), 4.47 (d, J = 7.2 Hz, 1H), 4.24–4.29 (q, J = 7.2 Hz, 2H), 4.13 (d, J = 7.2 Hz, 1H), 3.72 (s, 3H), 3.46–3.58 (m, 1H), 3.28 (s, 3H), 2.80 (br, 1H), 1.24–1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 50.8, 51.5, 52.1, 52.4, 61.5, 62.3, 64.7, 128.3, 128.5, 133.5, 136.0, 170.5, 170.6, 170.8. 90% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 6.6 and 13.9 min); $[\alpha]_D^{22} = -40.9$ (c 1.2, $CHCl_3$).

4.2.3. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-phenylpyrrolidine-2,3,4-tricarboxylate 3c

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12–7.55 (m, 5H), 4.49 (d, J = 6.8 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 3.81 (s, 3H), 3.70–3.75 (m, 1H), 3.51–3.60 (m, 1H), 3.30 (br, 1H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.0, 51.3, 52.1, 52.4, 52.5, 62.2, 65.4, 126.7, 127.7, 128.3, 137.1, 170.8, 170.9, 171.1; 84% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 7.6 and 17.6 min); $[\alpha]_D^{23} = -58.0$ (c 1.0, $CHCl_3$).

4.2.4. (2*R*,3*S*,4*R*,5*S*)-5-Phenylpyrrolidine-2-carboxylic ethyl ester-3,4-dicarboxylic dimethyl ester 3d

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.36 (s, 5H), 4.53 (t, J = 7.2 Hz, 1H), 4.25–4.31 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.2 Hz, 1H), 3.71–3.74 (m, 1H), 3.71 (s, 3H), 3.55–3.59 (m, 1H), 3.24 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 50.9, 51.3, 52.0, 52.6, 61.5, 62.4, 65.5, 126.8, 127.7, 128.3, 137.2, 170.6, 170.8; 85% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 5.9 and 16.3 min); $[\alpha]_D^{23} = -48.3$ (c 0.9, $CHCl_3$).

4.2.5. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate 3e

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.36 (m, 2H), 7.00–7.04 (m, 2H), 4.51 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.71–3.74 (m, 1H), 3.71 (s, 3H), 3.55–3.59 (m, 1H), 3.28 (s, 3H), 3.06 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.8, 51.5, 52.2, 52.4, 52.5, 62.2, 64.7, 115.1, 115.4, 128.5, 128.6, 170.8, 170.9; 87% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 8.3 and 14.1 min); $[\alpha]_D^{23} = -58.4$ (c 1.1, $CHCl_3$).

4.2.6. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(4-bromophenyl)pyrrolidine-2,3,4-tricarboxylate 3f

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.46 (m, 2H), 7.23–7.25 (m, 2H), 4.32 (d, J = 6.8 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.70–3.74 (m, 1H), 3.70 (s, 3H), 3.55–3.59 (m, 1H), 3.28 (s, 3H), 3.00 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.5, 52.2, 52.5, 62.1, 64.7, 121.7, 128.6, 131.5, 136.3, 170.7, 170.9; 94% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 7.9 and 11.1 min); $[\alpha]_D^{23} = -47.2$ (c 0.8, $CHCl_3$).

4.2.7. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(4-nitrophenyl)pyrrolidine-2,3,4-tricarboxylate 3g

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19–8.21 (m, 2H), 7.57–7.59 (m, 2H), 4.61 (d, J = 5.6 Hz, 1H), 4.20–4.25 (m, 1H), 3.89 (s, 3H), 3.76–3.82 (m, 1H), 3.71 (s, 3H), 3.65–3.69 (m, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.6, 52.1, 52.3, 52.6, 62.0, 64.4, 123.5, 127.9, 145.1, 147.4, 170.3, 170.5, 170.8; 98% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 14.6 and 21.3 min); $[\alpha]_D^{23} = -52.6$ (c 1.0, $CHCl_3$).

4.2.8. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(4-trifluoromethylphenyl)pyrrolidine-2,3,4-tricarboxylate 3h

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58–7.60 (m, 2H), 7.49–7.51 (m, 2H), 4.53 (d, J = 6.8 Hz, 1H), 4.16–4.18 (m, 1H), 3.82 (s, 3H), 3.73–3.79 (m, 1H), 3.70 (s, 3H), 3.61–3.68 (m, 1H), 3.25 (s, 3H), 2.81 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.5, 52.2, 52.5, 62.1, 64.8, 125.2, 125.3, 127.3, 141.5, 170.6, 170.6, 170.9; 99% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 5.8 and 7.1 min); $[\alpha]_D^{23} = -39.5$ (c 1.0, $CHCl_3$).

4.2.9. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-*p*-tolylpyrrolidine-2,3,4-tricarboxylate 3i

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, J = 7.5 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 4.46 (d, J = 6.8 Hz, 1H), 4.17 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 3.68–3.74 (m, 1H), 3.68 (s, 3H), 3.53–3.57 (m, 1H), 3.27 (s, 3H), 2.38 (br, 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 51.1, 51.4, 52.1, 52.5, 62.1, 65.2, 126.6, 129.0 (d, J = 24 Hz), 133.9, 137.4, 170.8, 170.9; 78% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 1.0 mL/min, t_R = 6.2 and 11.7 min); $[\alpha]_D^{23} = -45.7$ (c 0.8, $CHCl_3$).

4.2.10. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(3-nitrophenyl)pyrrolidine-2,3,4-tricarboxylate 3j

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (m, 1H), 8.14–8.16 (m, 1H), 7.72–7.79 (m, 1H), 7.47–7.59 (m, 1H), 5.34–5.37 (t, J = 5.6 Hz, 1H), 4.59 (d, J = 7.2 Hz, 1H), 3.83 (s, 3H), 3.75–3.79 (m, 1H), 3.71 (s, 3H), 3.65–3.69 (m, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.6, 52.0, 52.3, 52.5, 62.0, 64.3, 122.3, 122.8, 129.3, 133.0, 140.0, 148.1, 170.4, 170.5, 170.8; 90% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 10.9 and 15.3 min); $[\alpha]_D^{23} = -51.6$ (c 1.2, $CHCl_3$).

4.2.11. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(3-trifluoromethylphenyl)pyrrolidine-2,3,4-tricarboxylate 3k

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.70 (m, 4H), 4.53 (d, J = 6.8 Hz, 1H), 4.18 (d, J = 8.8 Hz, 1H), 3.82 (s, 3H), 3.72–3.76 (m, 1H), 3.70 (s, 3H), 3.62–3.66 (m, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.9, 51.4, 52.2, 52.5, 62.1, 64.8, 123.9, 124.6, 128.9, 130.2, 130.5, 138.5, 170.6, 170.8; 90% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 5.8 and 8.5 min); $[\alpha]_D^{23} = -47.7$ (c 1.0, $CHCl_3$).

4.2.12. Trimethyl (2*R*,3*S*,4*R*,5*S*)-5-(1-naphthyl)pyrrolidine-2,3,4-tricarboxylate 3l

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79–7.83 (m, 4H), 7.42–7.50 (m, 3H), 4.64 (d, J = 6.4 Hz, 1H), 4.23 (d, J = 5.2 Hz, 1H), 3.88 (s, 3H), 3.77–3.84 (m, 1H), 3.71 (s, 3H), 3.67–3.71 (m, 1H), 3.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.3, 51.4, 52.2, 52.5, 62.2, 65.5, 124.8, 125.6, 126.0, 126.2, 127.6, 128.0, 128.1, 132.8, 133.2, 134.5, 170.7, 170.9, 171.1; 90% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 50/50, detector: 205 nm, 0.8 mL/min, t_R = 7.8 and 14.4 min); $[\alpha]_D^{23} = -38.1$ (c 0.9, $CHCl_3$).

4.2.13. Methyl (1*S*,3*R*,3a*S*,6a*R*)-3-(4-chlorophenyl)-4,6-dioxo-5-phenyl-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylate 4

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11–7.39 (m, 9H), 4.57 (m, 1H), 4.13 (m, 1H), 3.86 (s, 3H), 3.71–3.72 (m, 1H), 3.54–3.55 (m, 1H), 2.42 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.0, 49.1, 52.3, 61.8, 63.4, 125.8, 126.1, 126.5, 128.5, 128.6, 128.7, 1289.1, 129.2, 131.5, 134.0, 135.4, 170.0, 173.5, 175.0; 36% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 30/70, detector: 230 nm, 0.8 mL/min, t_R = 21.6 and 53.8 min); $[\alpha]_D^{20} = +47.4$ (*c* 1.0, $CHCl_3$).

4.2.14. (2*R*,4*R*,5*S*)-5-(4-Chlorophenyl)-pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester 5

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30–7.33 (m, 4H), 4.46 (d, *J* = 8.0 Hz, 1H), 3.96 (t, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.22–3.27 (m, 1H), 2.67 (br, 1H), 2.28–2.47 (m, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.5, 33.8, 50.0, 52.2, 59.7, 64.8, 80.8, 128.2, 128.7, 133.1, 138.0, 171.5, 173.5; 24% ee, HPLC (chiralpak AS-H column, *i*-PrOH/hexane 10/90, detector: 230 nm, 0.8 mL/min, t_R = 7.6 and 10.5 min); $[\alpha]_D^{20} = -2.2$ (*c* 1.0, $CHCl_3$).

4.2.15. Trimethyl (2*R*,3*R*,4*R*,5*S*)-5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate 6

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.30 (m, 4H), 4.62 (d, *J* = 8 Hz, 1H), 4.19 (d, *J* = 8 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.65–3.68 (m, 3H), 3.55–3.58 (m, 3H), 3.26 (s, 3H), 2.75 (br, 1H); ^{13}C NMR: δ 50.4, 51.7, 52.4, 52.6, 53.5, 63.1, 64.5, 128.3, 128.4, 128.6, 128.9, 133.7, 136.9, 171.4, 171.9, 172.5; 84% ee, (chiralpak AS-H column, *i*-PrOH/hexane 10/90, 215 nm, 1.0 mL/min, t_R = 17.2 and 19.1 min); $[\alpha]_D^{22} = -11.4$ (*c* 1.0, $CHCl_3$).

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