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Chiral thiophosphoramide and selenophosphoramide ligands in the Cu(I)-promoted catalytic enantioselective 1,3-dipolar cycloaddition reactions of azomethine ylides and pyrrole-2,5-dione derivatives

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Abstract—Chiral C_2-symmetric diphenylthiophosphoramide ligand **L1** prepared from C_2-symmetric (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine was found to be a fairly effective chiral ligand for Cu(I)-promoted 1,3-dipolar cycloaddition of imines and pyrrole-2,5-dione derivatives to give the corresponding adducts in moderate enantioselectivities and good yields.

1. Introduction

Previously we have reported that optically active diphenylphosphoramides, diphenylthiophosphoramides and diphenylselenophosphoramides of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, or (*R*)-1,1′-binaphthyl-2,2′-diamine (BINAM) are easily available, relatively stable, recoverable, and effective chiral ligands in a variety of catalytic, asymmetric C–C bond formation reactions to give the corresponding products in good yields with high ee.[1] These results have promoted us to explore more catalytic, asymmetric reactions using these interesting chiral ligands. Herein we report that these chiral ligands are also fairly effective in the copper(I)-promoted 1,3-dipolar cycloaddition of azomethine ylides (from imines) and pyrrole-2,5-dione derivatives, which allows the stereoselective synthesis of pyrrolidines or proline derivatives in moderate enantioselectivities.[2]

2. Results and discussion

Diphenylthiophosphoramides and diphenylselenophosphoramides **L1**–**L4** as well as their derivatives **L5**–**L6** were synthesized from the reaction of diphenylthiophosphinic or diphenylselenophosphinic chlorides as well as their analogues with (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine in the presence of diisopropylethylamine or triethylamine in dichloromethane, respectively (Fig. 1).[3] Initial examinations using imine **1a** and 1-phenylpyrrole-2,5-dione **2a** as the substrates in the presence of chiral diphenylthiophosphoramide ligand **L1** and various metal salts were aimed at determining the optimal conditions, with the results of these experiments being summarized in Table 1. We found that using $Cu(CH_3CN)_4ClO_4$ (5 mol %) as a catalyst and Et_3N (10 mol %) as a base gave the corresponding 1,3-dipolar cycloaddition product *endo*-**3a**, which was obtained in moderate to good yields and 5–55% ee in a variety of solvents in the presence of **L1** (5.5 mol %) at 0 °C (Table 1, entries 1–5).[4] Dichloromethane is the solvent of choice. Next, we utilized DBU and $^i Pr_2NEt$ as bases for this reaction under otherwise identical conditions, and found that *endo*-**3a** was formed in 83% yield and 69% ee when using $^i Pr_2NEt$ as the base (Table 1, entries 6 and 7). Using either AgOAc or AgOTf (5 mol %) as a catalyst and $^i Pr_2NEt$ as

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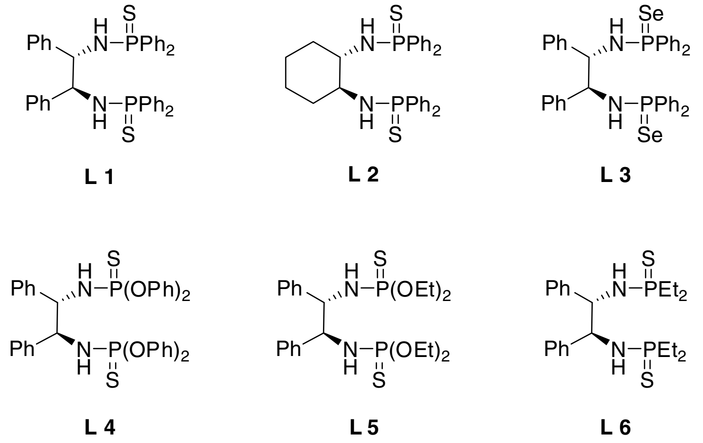
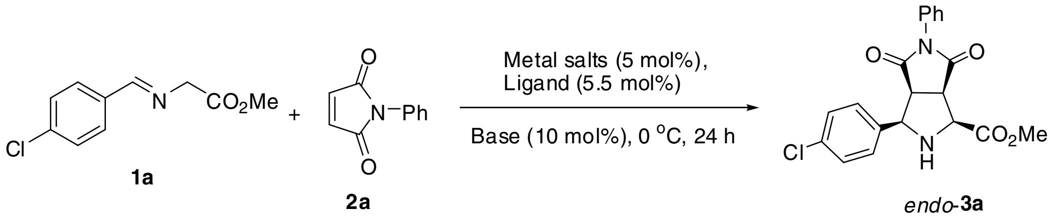


Figure 1.

Table 1. Optimization of the reaction conditions in the 1,3-dipolar cycloaddition of azomethine ylides (from imines) and 1-phenylpyrrole-2,5-dione



Entry	Ligand	Lewis acid	Base	Solvent	Yield[a] (%)	ee[b] (%)
1	**L1**	$Cu(CH_3CN)_4ClO_4$	Et_3N	Toluene	85	28
2	**L1**	$Cu(CH_3CN)_4ClO_4$	Et_3N	THF	47	37
3	**L1**	$Cu(CH_3CN)_4ClO_4$	Et_3N	CH_3CN	76	5
4	**L1**	$Cu(CH_3CN)_4ClO_4$	Et_3N	Ether	83	9
5	**L1**	$Cu(CH_3CN)_4ClO_4$	Et_3N	CH_2Cl_2	84	55
6	**L1**	$Cu(CH_3CN)_4ClO_4$	DBU	CH_2Cl_2	30	10
7	**L1**	$Cu(CH_3CN)_4ClO_4$	^{i}Pr$_2$NEt	CH_2Cl_2	83	69
8	**L1**	AgOAc	^{i}Pr$_2$NEt	CH_2Cl_2	78	64
9	**L1**	AgOTf	^{i}Pr$_2$NEt	CH_2Cl_2	54	69
10	**L1**	$Cu(OTf)_2$	^{i}Pr$_2$NEt	CH_2Cl_2	Trace	
11	**L1**	$Zn(OTf)_2$	^{i}Pr$_2$NEt	CH_2Cl_2	Trace	

[a] Isolated yields.

[b] Determined by chiral HPLC.

the base afforded *endo*-**3a** in 78% and 54% yields as well as 64% and 69% ee, respectively, in CH_2Cl_2 at 0 °C in the presence of **L1** (5.5 mol %) (Table 1, entries 8 and 9). It should be noted that copper salts, $Cu(OTf)_2$ and $Zn(OTf)_2$, did not catalyze this reaction under the standard conditions (Table 1, entries 10 and 11). The best reaction conditions are to carry out the reaction in CH_2Cl_2 using $Cu(CH_3CN)_4ClO_4$ (5 mol %) as a catalyst and ^{i}Pr$_2$NEt (10 mol %) as the base in the presence of **L1** (5.5 mol %). In this reaction, ^{i}Pr$_2$NEt acts as a base to generate the azomethine ylide.[2e] The possible transition state of this reaction has been provided in Figure 2. We believe that diphenylthiophosphoramide ligand **L1** is an (*S*,*S*)-bidentate ligand to the Cu center and its steric effect played a very important role for achieving higher ee.

With the optimized conditions in hand, we next examined the temperature effects on this reaction. As can be seen in Table 2, lowering the reaction temperature to −40 °C slightly improved the ee of **3a** to 74%, although no improvement could be realized at −10 °C and −25 °C (Table 2, entries 1–3). Other chiral thiophosphoramide ligands **L2**, **L4**–**L6** and chiral diphenylselenophosphoramide ligand **L3** produced *endo*-**3a** in lower enantioselectivities under the standard conditions and no enantioselectivity could be observed if using **L4** as a chiral ligand (Table 2, entries 4–8). Therefore, **L1** is the best chiral ligand in this reaction.

The generality of this $Cu(CH_3CN)_4ClO_4$/**L1**-catalyzed enantioselective 1,3-dipolar cycloaddition reaction was examined using a variety of imines and 1-methylpyrrole-2,5-dione, 1-benzylpyrrole-2,5-dione, and 1-phenylpyrrole-2,5-dione. The results are summarized in Table 3. All reactions proceeded smoothly to give the corresponding products **3** in good yields and moderate ee under the optimal conditions (Table 3). As for imine **1** bearing an electron-donating methyl group on the benzene ring or having no substituent on the benzene ring, the correspond-

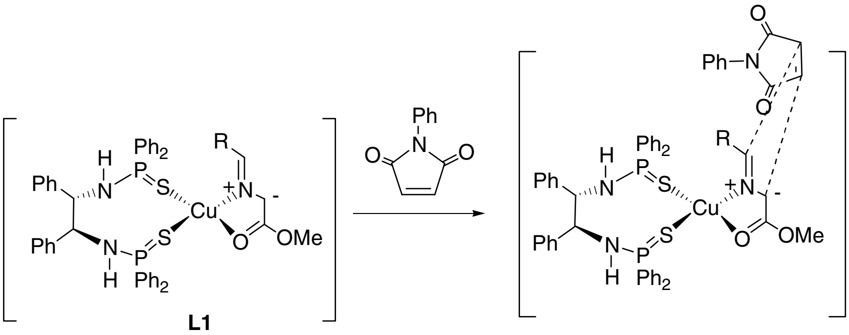
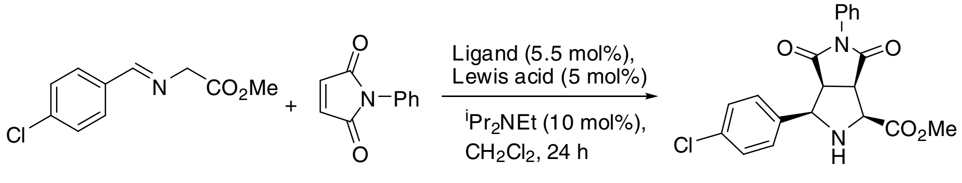


Figure 2.

Table 2. Optimization of the reaction conditions in the 1,3-dipolar cycloaddition of azomethine ylides (from imines) and 1-phenylpyrrole-2,5-dione



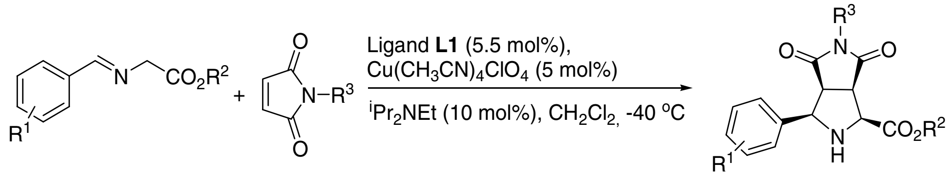
endo-**3a**

Entry	Ligand	Lewis acid	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	**L1**	$Cu(CH_3CN)_4ClO_4$	−10	81	65
2	**L1**	$Cu(CH_3CN)_4ClO_4$	−25	78	63
3	**L1**	$Cu(CH_3CN)_4ClO_4$	−40	82	74
4	**L2**	$Cu(CH_3CN)_4ClO_4$	0	87	48
5	**L3**	$Cu(CH_3CN)_4ClO_4$	0	65	47
6	**L4**	$Cu(CH_3CN)_4ClO_4$	0	48	0
7	**L5**	$Cu(CH_3CN)_4ClO_4$	0	86	7
8	**L6**	$Cu(CH_3CN)_4ClO_4$	0	90	17

[a] Isolated yields.

[b] Determined by chiral HPLC.

Table 3. Enantioselective 1,3-dipolar cycloaddition of azomethine ylides (from imines) and 1-phenylpyrrole-2,5-dione catalyzed by $Cu(CH_3CN)_4ClO_4$ in the presence of **L1**



1 **2** endo-**3**

Entry	R¹	R²	R³	Product	Yield[a] (%)	ee[b] (%)
1	*p*-Cl	Me	Ph	**3a**	82	74
2	*p*-Br	Me	Ph	**3b**	85	58
3	*o*-Cl	Me	Ph	**3c**	82	57
4	H	Me	Ph	**3d**	89	47
5	*p*-Me	Me	Ph	**3e**	76	26
6	*p*-Cl	Et	Ph	**3f**	72	62
7	*m*-Br	Me	Ph	**3g**	60	52
8	H	Me	Me	**3h**	77	79
9	*p*-Cl	Me	Me	**3i**	86	77
10	*p*-Cl	Me	Benzyl	**3j**	83	68

[a] Isolated yields.

[b] Determined by chiral HPLC.

ing 1,3-dipolar cycloaddition adducts **3e** and **3f** were obtained in 47% and 26% ee, respectively (Table 3, entries 4 and 5). In other cases, 1,3-dipolar cycloaddition adducts **3** were formed in 55–77% ee (Table 3, entries 1–3, 6, and

7). Using either 1-methylpyrrole-2,5-dione or 1-benzylpyrrole-2,5-dione as the substrate, the corresponding 1,3-dipolar cycloaddition adducts **3** were obtained in similar enantioselectivities (Table 3, entries 8–10).

3. Conclusion

In conclusion, chiral C_2-symmetric diphenylthiophosphoramide **L1**, prepared from C_2-symmetric (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine, has been found to be a fairly effective chiral ligand for Cu(I)-promoted 1,3-dipolar cycloaddition of imines and pyrrole-2,5-dione derivatives to give the corresponding adducts in moderate enantioselectivities. These results will allow us to design and synthesize new effective sulfur-containing chiral ligands for this interesting asymmetric 1,3-dipolar cycloaddition reaction. Efforts are currently underway to elucidate the mechanistic details of this asymmetric 1,3-dipolar cycloaddition reaction and to disclose the exact structure of the active species in this catalytic system.

4. Experimental

4.1. General methods

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ at 20 °C by using a Perkin–Elmer-241 MC polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard; *J*-values are given in Hz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. The organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses with an Italian Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai $60F_{254}$ silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. All 1,3-dipolar cycloaddition reactions were performed under argon using standard Schlenk techniques. Enantiomeric excesses of *sec*-alcohols were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel AD, AS, and OD) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation. Diphenylthiophosphinic and diphenylselenophosphinic chlorides were prepared upon heating chlorodiphenylphosphine with selenium at 120 °C for 6 h. 1-Phenylpyrrole-2,5-dione **2a** was synthesized according to the literature procedures.[5]

4.2. General procedure for the synthesis of α-imino esters

To a suspension of the corresponding amino acid ester hydrochloride (23.9 mmol) and $MgSO_4$ (25.0 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3.4 mL, 23.9 mmol). The mixture was stirred at room temperature for 1 h, then the corresponding aldehyde (20.0 mmol) was added. The reaction was stirred at room temperature overnight, and then the resulting precipitate was removed by filtration. The filtrate was washed with water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting pure imino esters were used in 1,3-dipolar cycloadditions without further purification.

4.3. General procedure for the preparation of chiral diphenylthiophosphoramides and diphenylselenophosphoramides L1–L6

To a solution of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (212 mg, 1.0 mmol) and triethylamine (303 mg, 3.0 mmol, 0.42 mL) in dichloromethane (20 mL) was added diphenylthiophosphinic chloride (504 mg, 2.0 mmol) at 0 °C. After stirring the reaction mixture for 10 h, the solvent was removed under reduced pressure. The crude product was extracted with ether and washed with water (3 × 50 mL), 10% Na_2CO_3 (50 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The residue was recrystallized from dichloromethane and hexane (4:1) to give **L1** as colorless crystals (534 mg, 86%).

4.3.1. Ligand L1. This is a known compound.[3a] Yield: (534 mg, 86%). White solid. Mp: 230.0–230.3 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 4.45–4.55 (m, 2H), 5.65–5.69 (m, 2H), 6.87 (d, $J = 7.8$ Hz, 4H), 7.03–7.15 (m, 10H), 7.26–7.29 (m, 2H), 7.40–7.46 (m, 4H), 7.50–7.52 (m, 2H), 7.60–7.66 (m, 4H), 7.83–7.90 (m, 4H); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ +66.0; $[\alpha]_D^{20} = +92.7$ (*c* 0.94, CH_2Cl_2).

4.3.2. Ligand L2. This is a known compound.[3b] Yield: (475 mg, 89%). White solid. Mp: 139.9–140.0 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.05–1.60 (6H), 1.80–1.87 (m, 2H), 3.26–3.36 (m, 2H), 4.00–4.04 (m, 2H), 7.31–7.37 (m, 4H), 7.44–7.51 (m, 8H), 7.76–7.83 (m, 4H), 8.02–8.09 (m, 4H); $[\alpha]_D^{20} = +20.8$ (*c* 1.28, CH_2Cl_2).

4.3.3. Ligand L3. This is a known compound.[3c] Yield: (644 mg, 87%). White solid. Mp: 170–172 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 4.55–4.69 (m, 2H), 5.62–5.67 (m, 2H), 6.89 (d, $J = 7.8$ Hz, 4H), 7.02–7.12 (m, 10H), 7.22–7.27 (m, 2H), 7.40–7.46 (m, 4H), 7.49–7.52 (m, 2H), 7.57–7.64 (m, 4H), 7.87–7.94 (m, 4H); $[\alpha]_D^{20} = +117.2$ (*c* 1.17, CH_2Cl_2).

4.3.4. Ligand L4. Yield: (495 mg, 70%). White solid. Mp: 130.0–130.1 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 4.27–4.34 (m, 2H), 4.90–4.98 (m, 2H), 6.89–6.92 (m, 4H), 6.95–6.98 (m, 4H), 7.05–7.29 (m, 22H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 61.6 (d, $J_{C\text{–}P} = 7.5$ Hz), 121.03, 121.09, 121.15, 121.2, 125.06, 125.08, 125.22, 125.24, 127.98, 128.02, 128.3, 129.32, 129.34, 129.49, 129.51, 138.5 (d, $J_{C\text{–}P} = 3.5$ Hz), 150.6 (d, $J_{C\text{–}P} = 7.5$ Hz), 150.8 (d, $J_{C\text{–}P} = 8.0$ Hz); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ

+63.5; IR ($CHCl_3$) ν 1590, 1489, 1455, 1188, 918 cm^{-1}; HRMS(ESI) calcd for $C_{38}H_{35}N_2O_4P_2S_2$ ($M+H^+$): 709.1514, found: 709.1513. $[\alpha]_D^{20} = -47.8$ (*c* 0.86, CH_2Cl_2).

4.3.5. Ligand L5. Yield: (412 mg, 80%). White solid. Mp: 70.2–70.9 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.02 (t, $J = 6.9$ Hz, 6H), 1.26 (t, $J = 6.9$ Hz, 6H), 3.53–3.64 (m, 2H), 3.86–4.02 (m, 8H), 4.44–4.55 (m, 2H), 6.95–6.98 (m, 4H), 7.18–7.28 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 15.4 (d, $J_{C-P} = 9.2$ Hz), 15.8 (d, $J_{C-P} = 8.6$ Hz), 61.1 (d, $J_{C-P} = 6.8$ Hz), 62.9 (d, $J_{C-P} = 4.7$ Hz), 63.1 (d, $J_{C-P} = 5.2$ Hz), 127.51, 127.55, 128.0, 139.3 (d, $J_{C-P} = 2.7$ Hz); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ +71.6; IR (CH_2Cl_2) ν 2970, 2839, 1738, 1454, 1376, 1167, 972 cm^{-1}; HRMS(ESI) calcd for $C_{22}H_{35}N_2O_4P_2S_2$ ($M+H^+$): 517.1514, found: 517.1515. $[\alpha]_D^{20} = -18.8$ (*c* 1.16, CH_2Cl_2).

4.3.6. Ligand L6. Yield: (352 mg, 78%). White solid. Mp: 154.7–155.8 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 0.76 (dt, $J = 7.5$, 20.1 Hz, 6H), 1.31 (dt, $J = 7.5$, 19.5 Hz, 6H), 1.59–1.71 (m, 4H), 2.09–2.21 (m, 4H), 4.41–4.49 (m, 2H), 4.76–4.80 (m, 2H), 6.93–6.97 (m, 4H), 7.11–7.13 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 6.8 (d, $J_{C-P} = 3.2$ Hz), 6.9 (d, $J_{C-P} = 4.4$ Hz), 24.0 (d, $J_{C-P} = 6$–5.1 Hz), 27.2 (d, $J_{C-P} = 68.4$ Hz), 60.7 (d, $J_{C-P} = 5.1$ Hz), 127.1, 127.7, 127.9, 141.3 (d, $J_{C-P} = 3.8$ Hz); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ +82.0; IR ($CHCl_3$) ν 2970, 2841, 1738, 1455, 1376, 1167, 973 cm^{-1}; HRMS(ESI) calcd for $C_{22}H_{35}N_2P_2S_2$ ($M+H^+$): 453.1717, found: 453.1714. $[\alpha]_D^{20} = +76.5$ (*c* 0.87, CH_2Cl_2).

4.4. Typical reaction procedure

The catalyst was prepared by stirring $Cu(CH_3CN)_4ClO_4$ (4.9 mg, 0.015 mmol, 5 mol %) and ligand **L1** (11.9 mg, 0.0165 mmol, 5.5 mol %) in CH_2Cl_2 (2 mL) for 1 h at room temperature. The reaction mixture was then cooled to −40 °C, after which imine substrate **1** (0.30 mmol), 1-phenylpyrrole-2,5-dione **2** (0.45 mmol, 1.5 equiv) and base (0.03 mmol, 10 mol %) were subsequently added and the resulting mixture was stirred at −40 °C for 24 h. When the reaction was complete, as monitored by TLC, the corresponding pure adduct was purified by column chromatography on silica gel (petroleum ether/ethyl acetate/1% triethylamine).

4.5. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*p*-chlorophenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3a

This is a known compound.[6] A white solid. Mp: 140.7–148.9 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.48–2.50 (m, 1H), 3.56 (t, $J = 8.1$ Hz, 1H), 3.74 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 4.14 (dd, $J = 4.8$, 6.6 Hz, 1H), 4.58 (dd, $J = 4.8$, 7.8 Hz, 1H), 7.14 (d, $J = 7.8$ Hz, 2H), 7.31–7.43 (m, 7H); $[\alpha]_D^{20} = +91.5$ (*c* 0.80, CH_2Cl_2) for 74% ee; Chiralcel AS-H, hexane/*i*PrOH = 50:50, 1.5 mL/min, 220 nm, $t_{major} = 8.33$ min, $t_{minor} = 30.61$ min.

4.6. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*p*-bromophenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3b

A white solid. Mp: 175.6–176.7 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.47–2.50 (m, 1H), 3.56 (t, $J = 8.4$ Hz, 1H), 3.75 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 4.11–4.16 (m, 1H), 4.56 (dd, $J = 4.8$, 8.4 Hz, 1H), 7.12–7.15 (m, 2H), 7.31–7.50 (m, 7H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 47.9, 49.0, 52.3, 61.7, 63.3, 122.2, 126.0, 128.6, 128.8, 129.1, 131.4, 131.5, 135.8, 169.9, 173.5, 174.9; IR (CH_2Cl_2) ν 3333, 2948, 2837, 1747, 1713, 1489, 1381, 1206, 1010 cm^{-1}; MS (ESI) *m*/*z*: 451 [$M+Na^+$]. Anal. Calcd for $C_{20}H_{17}BrN_2O_4$ requires: C, 55.96; H, 3.99; N, 6.53. Found: C, 56.66; H, 3.64; N, 6.25. $[\alpha]_D^{20} = +76.4$ (*c* 1.07, CH_2Cl_2), for 58% ee; Chiralcel AD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 230 nm, $t_{minor} = 12.14$ min, $t_{major} = 24.24$ min.

4.7. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*o*-chlorophenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3c

A white solid. Mp: 153.0–154.8 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.41–2.44 (m, 1H), 3.75 (t, $J = 7.2$ Hz, 1H), 3.84–3.90 (m, 4H), 4.18 (dd, $J = 4.8$, 6.3 Hz, 1H), 4.88 (dd, $J = 4.8$, 8.1 Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.25–7.43 (m, 6H), 7.67–7.70 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 46.5, 47.7, 52.3, 60.5, 61.4, 126.0, 126.9, 127.2, 128.4, 128.9, 129.2, 131.5, 133.3, 134.9, 144.9, 170.0, 173.3, 175.1; IR (CH_2Cl_2) ν 3333, 1748, 1713, 1500, 1383, 1206 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}ClN_2O_4$ ($M+Na^+$): 407.0775, found: 407.0770. $[\alpha]_D^{20} = +42.2$ (*c* 0.83, CH_2Cl_2) for 57% ee; Chiralcel AD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 230 nm, $t_{major} = 11.93$ min, $t_{minor} = 30.13$ min.

4.8. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3,5-diphenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3d

This is a known compound.[4] A white solid. Mp: 178.2–180.5 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.51–2.54 (m, 1H), 3.57 (t, $J = 8.4$ Hz, 1H), 3.73 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 4.12–4.16 (m, 1H), 4.61 (dd, $J = 5.1$, 8.4 Hz, 1H), 7.14 (d, $J = 7.2$ Hz, 2H), 7.29–7.47 (m, 8H); $[\alpha]_D^{20} = +44.1$ (*c* 0.73, CH_2Cl_2) for 47% ee; Chiralcel AD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 230 nm, $t_{minor} = 13.79$ min, $t_{major} = 22.21$ min.

4.9. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*p*-methylphenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3e

A white solid. Mp: 176.9–177.5 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.33 (s, 3H), 2.49 (br, 1H), 3.54 (t, $J = 8.4$ Hz, 1H), 3.72 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 4.11–4.15 (m, 1H), 4.58 (dd, $J = 4.8$, 8.7 Hz, 1H), 7.14–7.18 (m, 4H), 7.29–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.2, 48.3, 49.3, 52.3, 61.8, 64.1, 126.1, 126.9, 128.4, 129.0, 129.2, 131.5, 133.5, 138.0, 170.1, 173.7, 175.2; IR (CH_2Cl_2) ν 3333, 2956, 2844, 1748, 1714, 1500, 1382, 1206 cm^{-1}; MS (ESI) *m*/*z*: 387 [$M+Na^+$]. Anal. Calcd for $C_{21}H_{20}N_2O_4$ requires: C, 69.22; H, 5.53, N, 7.28%. Found: C, 69.13; H, 5.29, N, 7.49. $[\alpha]_D^{20} = +42.2$ (*c* 0.83, CH_2Cl_2), for 26% ee; Chiralcel AD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 230 nm, $t_{minor} = 14.09$ min, $t_{major} = 30.21$ min.

4.10. (1*S*,3*R*,3a*S*,6a*R*)-Ethyl-4,6-dioxo-3-(*p*-chlorophenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3f

A white solid. Mp: 75.7–76.9 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.37 (t, $J = 7.2$ Hz, 1H), 2.48–2.50 (m, 1H), 3.56 (t, $J = 8.1$ Hz, 1H), 3.74 (t, $J = 7.5$ Hz, 1H), 4.12 (dd, $J = 4.8$, 6.3 Hz, 1H), 4.30–4.38 (m, 2H), 4.57 (dd, $J = 4.8$, 6.0 Hz, 1H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.31–7.42 (m, 7H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 14.1, 47.9, 49.2, 61.5, 61.9, 63.4, 126.0, 128.4, 128.56, 128.63, 129.1, 131.4, 134.0, 135.2, 169.4, 169.8, 173.5, 174.8; IR (CH_2Cl_2) ν 3336, 2983, 2844, 1716, 1597, 1492, 1381, 1205 cm^{-1}; MS (ESI) *m*/*z*: 421 $[M+Na^+]$. Anal. Calcd for $C_{21}H_{19}ClN_2O_4$ requires: C, 63.24; H, 4.80; N, 7.02. Found: C, 63.42; H, 4.55; N, 6.94. $[\alpha]_D^{20} = +111.5$ (*c* 1.08, CH_2Cl_2) for 62% ee; Chiralcel OD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 230 nm, $t_{major} = 18.93$ min, $t_{minor} = 26.58$ min.

4.11. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*m*-bromophenyl)-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3g

A white solid. Mp: 157.2–157.3 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.51 (br, 1H), 3.56 (t, $J = 8.4$ Hz, 1H), 3.74 (t, $J = 6.9$ Hz, 1H) 3.87 (s, 3H), 4.13 (dd, $J = 4.5$, 6.6 Hz, 1H), 4.57 (dd, $J = 4.5$, 9.0 Hz, 1H), 7.14–7.24 (m, 3H), 7.34–7.46 (m, 5H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 47.9, 49.0, 52.3, 61.6, 63.2, 122.7, 126.0, 126.1, 128.6, 129.1, 130.0, 131.4, 131.5, 139.3, 145.3, 169.8, 173.5, 174.9; IR (CH_2Cl_2) ν 3337, 2948, 2837, 1747, 1713, 1500, 1382, 1206 cm^{-1}; MS (ESI) *m*/*z*: 451 $[M+Na^+]$. Anal. Calcd for $C_{20}H_{17}BrN_2O_4$ requires: C, 55.96; H, 3.99; N, 6.53. Found: C, 56.05; H, 3.67; N, 6.36. $[\alpha]_D^{20} = +58.3$ (*c* 0.80, CH_2Cl_2) for 52% ee; Chiralcel OD-H, hexane/*i*PrOH = 50:50, 1 mL/min, 230 nm, $t_{major} = 19.51$ min, $t_{minor} = 36.26$ min.

4.12. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-5-methyl-4,6-dioxo-3-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3h

This is a known compound.[4] A white solid. Mp: 152.1–153.7 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.42 (br, 1H), 2.88 (s, 3H), 3.43 (t, $J = 8.4$ Hz, 1H), 3.57 (t, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 4.04–4.08 (m, 1H), 4.50 (dd, $J = 4.8$, 8.7 Hz, 1H), 7.35 (s, 5H); $[\alpha]_D^{20} = +30.5$ (*c* 0.60, CH_2Cl_2) for 79% ee; Chiralcel AD-H, hexane/*i*PrOH = 50:50, 0.7 mL/min, 220 nm, $t_{major} = 29.54$ min, $t_{minor} = 33.29$ min.

4.13. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-5-methyl-4,6-dioxo-3-(*p*-chlorophenyl)-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3i

A white solid. Mp: 210.7–211.1 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.32 (br, 1H), 2.81 (s, 3H), 3.35 (t, $J = 8.1$ Hz, 1H), 3.50 (t, $J = 7.2$ Hz, 1H), 3.81 (s, 3H), 3.98 (d, $J = 6.6$ Hz, 1H), 4.40 (d, $J = 8.7$ Hz, 1H), 7.20–7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 25.0, 47.8, 49.1, 52.3, 61.4, 63.1, 128.4, 128.6, 133.9, 135.2, 170.0, 174.5, 175.8; IR (CH_2Cl_2) ν 3341, 2933, 1749, 1698, 1437, 1215 cm^{-1}; MS (ESI) *m*/*z*: 345 $[M+Na^+]$. Anal. Calcd for $C_{15}H_{15}ClN_2O_4$ requires: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.73; H, 4.53; N, 8.54. $[\alpha]_D^{20} = +86.2$ (*c* 0.75, CH_2Cl_2) for 77% ee; Chiralcel AS-H, hexane/*i*PrOH = 50:50, 1.5 mL/min, 220 nm, $t_{major} = 7.40$ min, $t_{minor} = 35.47$ min.

4.14. (1*S*,3*R*,3a*S*,6a*R*)-Methyl-4,6-dioxo-3-(*p*-chlorophenyl)-5-benzyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate *endo*-3j

A white solid. Mp: 155.4–155.7 °C; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.29 (br, 1H), 3.37 (t, $J = 8.1$ Hz, 1H), 3.56 (t, $J = 7.2$ Hz, 1H), 3.88 (s, 3H), 4.04 (d, $J = 7.2$ Hz, 1H), 4.41–4.61 (m, 3H), 7.04–7.17 (m, 4H), 7.31 (s, 5H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 42.6, 47.9, 49.0, 52.3, 61.6, 63.3, 127.9, 128.42, 128.44, 128.5, 129.0, 133.7, 134.9, 135.5, 169.9, 174.1, 175.4; IR (CH_2Cl_2) ν 3348, 2956, 5852, 1749, 1704, 1398, 1207 cm^{-1}; MS (ESI) *m*/*z*: 421 $[M+Na^+]$. Anal. Calcd for $C_{21}H_{19}ClN_2O_4$ requires: C, 63.24; H, 4.80; N, 7.02. Found: C, 63.07, H, 4.68, N, 6.83. $[\alpha]_D^{20} = +69.5$ (*c* 0.62, CH_2Cl_2), for 68% ee; Chiralcel AS-H, hexane/*i*PrOH = 50:50, 1.5 mL/min, 220 nm, $t_{major} = 7.04$ min, $t_{minor} = 25.33$ min.

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