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$Cu(OTf)_2$/trisoxazoline catalyzed asymmetric Friedel–Crafts reaction of pyrroles with alkylidene malonates

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ABSTRACT

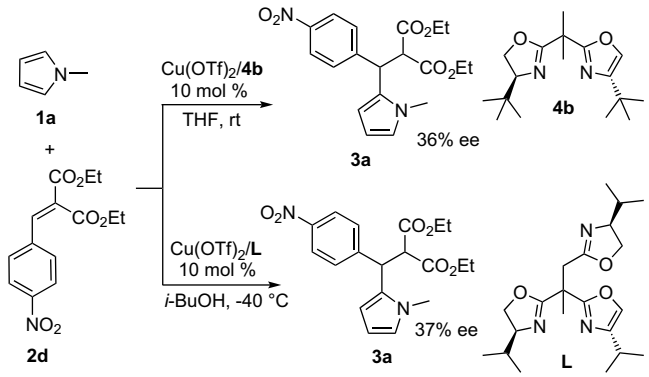
In the presence of catalytic amount of $Cu(OTf)_2$/trisoxazoline, an enantioselective Friedel–Crafts reaction of *N*-methyl pyrrole with alkylidene malonates has been developed and up to 66% ee is achieved.

1. Introduction

In the past decades, increasing attention has been paid to asymmetric Friedel–Crafts reaction[1,2] of indoles[3] and pyrroles[4] with electron-deficient olefins owing to its potential applications in the synthesis of molecules that have been widely identified as 'privileged' structure or pharmacophore. Of the developed asymmetric alkylations of indoles and pyrroles with alkylidene malonates, indoles always gave better enantioselectivities than pyrroles. For example, Jørgensen et al.[5] reported that enantioselective Friedel–Crafts reaction of indoles with alkylidene malonates gave up to 66% ee using bisoxazoline **4b**/$Cu(OTf)_2$ as a catalyst. Under the same conditions, however, pyrroles only gave up to 36% ee (Scheme 1). Recently, our laboratory developed a pseudo C_3-symmetric trisoxazoline (TOX)[6–8] by sidearm approach and found that TOX/Cu(II) is an efficient catalyst for the asymmetric Friedel–Crafts reaction of indoles with alkylidene malonates (Scheme 1). Unfortunately, the ee is less than 37% ee by employing pyrroles instead of indoles. Very recently, we modified the ligands and found that trisoxazoline/$Cu(OTf)_2$ complexes could catalyze the enantioselective alkylation of pyrroles with alkylidene malonates with up to 66% ee under optimized conditions. Herein, we wish to report these results in details.

2. Result and discussion

Initially, diethyl 2-benzylidenemalonate **2a** was selected as a model substrate for optimizing the reaction conditions. We first examined the effects of solvents on the enantioselective alkylation of *N*-methyl pyrrole. As shown in Table 1, the reaction proceeded smoothly in both polar and nonpolar solvents screened. In alcohols, the reaction was facilitated and gave reasonable yields (entries 1–5).



Scheme 1. Enantioselective alkylation of *N*-methyl pyrrole with alkylidene malonate.

The optimal one was *t*-BuOH. Noticeably, more bulky alcohols afforded better enantioselectivities (MeOH<EtOH<*i*-BuOH<*i*-PrOH<*t*-BuOH), suggesting the plausible coordination of alcohol to copper center of the active species.[6e] In halogenated solvents, the reaction also worked well but gave the opposite enantiomer (entries 6–8). THF, dioxane, and toluene slowed down the reaction (entries 9–14). For all the solvents screened, the optimal was *t*-BuOH.

To further improve the enantioselectivity, bisoxazoline, and trisoxazoline ligands in Figure 1 were synthesized and screened using $Cu(OTf)_2$ as a catalyst. As summarized in Table 2, the pendant groups strongly influence both the enantioselectivities and the yields. For example, bisoxazolines **4b** and **4c** gave the desired product in moderate to good yields with 26% and 11% ees, respectively (entries 2, 3) while bisoxazolines **4a** and **4d**, with coordination groups as sidearms, furnished moderate yields and moderate enantioselectivities (entries 1, 4).

Monooxazoline **5** only gave 11% ee. Compared with monooxazolines and bisoxazolines, trisoxazolines **6a**–**6d** gave better ees

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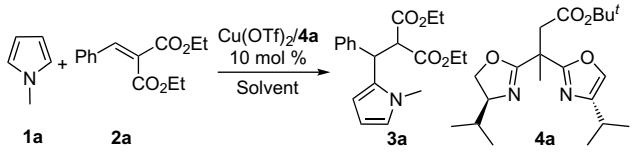
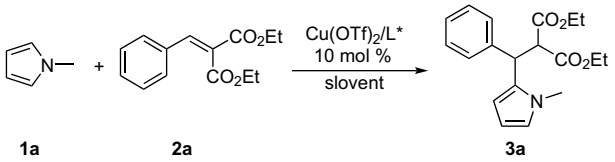
Table 1
Influence of reaction conditions on the Friedel–Crafts reaction of *N*-methyl pyrrole[a]



Entry	Solvent	*T* (°C)	Time (h)	Conv.[b] (%)	ee[c] (%)
1	MeOH	15	22	90	3
2	EtOH	15	30	94	28
3	*i*-BuOH	15	21	50	35
4	*i*-PrOH	15	10	67	37
5	*t*-BuOH	20	10	70	41
6	CH_2Cl_2	15	41	78	−24
7	DCE	15	30	83	−30
8	$CHCl_3$	15	48	56	−4
9	*i*-Pr_2O	15	41	85	34
10	THF	15	77	25	45
11	Dioxane	15	96	37	8
12	Ether	15	29	40	46
13	*n*-Bu_2O	15	23	15	14
14	Toluene	15	48	61	8

[a] Unless otherwise noted, all reactions were carried out with 10 mol % of $Cu(OTf)_2$ and 12 mol % of ligand in solvent (2.5 mL).
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC analysis.

Table 2
Effects of ligands on the Friedel–Crafts reaction[a]



Entry	L*	Solvent	*T* (°C)	Time (h)	Conv.[b] (%)	ee[c] (%)
1	**4a**	*t*-BuOH	20	10	70	41
2	**4b**	*i*-BuOH	15	10	56	26
3	**4c**	*i*-PrOH	15	17	>99	11
4	**4d**	*t*-BuOH	20	15	72	46
5	**5**	*t*-BuOH	20	72	48	11
6	**6a**	*t*-BuOH	20	72	77	50
7	**6b**	*t*-BuOH	20	11	93	50
8	**6c**	*t*-BuOH	20	11	85	53
9	**6d**	*t*-BuOH	20	15	99	58
10	**6d**	*i*-PrOH	15	17	99	47
11[d]	**6d**	*t*-BuOH/Et_2O	15	15	83	57
12[d]	**6d**	*t*-BuOH/Et_2O	0	40	72	66
13[d]	**6d**	*t*-BuOH/Et_2O	−20	65	47	60

[a] Unless otherwise noted, all reactions were carried out with 10 mol % of $Cu(OTf)_2$ and 12 mol % of ligand in solvent (2.5 mL).
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC analysis.
[d] 1.5/1, v/v.

(entries 6–9). Of the trisoxazolines examined, trisoxazoline **6d** was the optimal. To further improve the selectivities, a mixed solvent of *t*-BuOH and Et_2O (1.5/1, v/v) was examined at 15 °C. It was found that both the yield and the ee were affected slightly (entry 9 vs 11). Lowering the reaction temperature to 0 °C improved the ee value to 66% (entry 12). Further lowering the reaction temperature decreased both conversion and ee value (entry 13).

Under the optimized conditions, a variety of pyrrole derivatives **1** and alkylidene malonates **2** were tested to investigate the generality of the present reaction. The results are summarized in Table 3. In a mixed solvent of *t*-BuOH/Et_2O (1.5/1, v/v) at 0 °C, various alkylidene malonates **2** reacted smoothly with *N*-methyl pyrrole in moderate to good yields with moderate enantioselectivities. The ester groups of the malonate strongly affected both the yields and the ees (entries 1 and 2). For example, the benzyl ester gave lower ee than the ethyl ester (entries 1 and 2). Substituents on aryl groups also influenced the enantioselectivities and the yields (entries 1, 3–6, 12). Pyrrole worked well to give moderate yield and moderate ee (entry 7). Dimethyl 2-(3-methylbutylidene)malonate worked well to give the corresponding product in 27% yield with 26% ee (entry 8). For *N*-allyl pyrrole and *N*-benzyl pyrrole, the desired products were obtained in moderate yields with moderate ee values (entries 9–10). When *N*-Boc pyrrole was employed, the reaction was very sluggish even if the reaction time was prolonged to 5 days (entry 11).

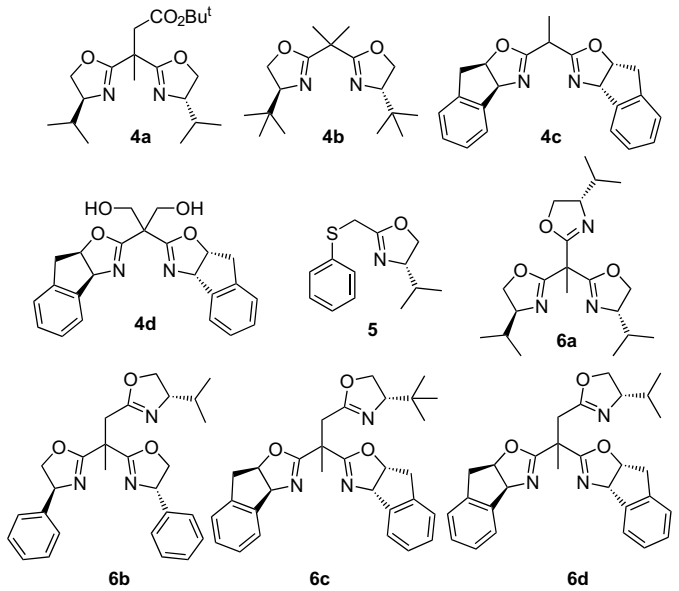
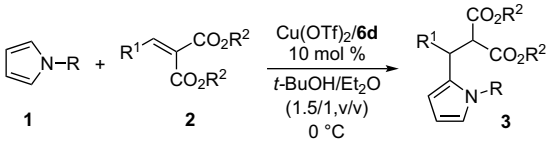


Figure 1. Chiral Ligands.

Table 3
Friedel–Crafts reactions of pyrrole derivatives to alkylidene malonates[a]



Entry	R	R^1	R^2	**3**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	Ph	Et	**3a**	65	73	66
2	Me	Ph	Bn	**3b**	58	91	39
3	Me	*m*-NO_2–C_6H_4	Et	**3c**	58	96	58
4	Me	*p*-NO_2–C_6H_4	Me	**3d**	70	70	52
5	Me	*o*-Cl–C_6H_4	Et	**3e**	70	30	40
6	Me	*p*-Br–C_6H_4	Et	**3f**	58	63	66
7	H	Ph	Et	**3g**	72	57	40
8[d,e]	H	*i*-Bu	Me	**3h**	11	27	26
9[d,f]	Allyl	Ph	Et	**3i**	5 d	43	20
10[d,f]	Bn	Ph	Et	**3j**	34	70	41
11	Boc	Ph	Et	—	5d	—	—
12	Me	*p*-MeO–C_6H_4	Me	**3k**	90	53	64

[a] Unless otherwise noted, all reactions were carried out with 10 mol % of $Cu(OTf)_2$ and 12 mol % of ligand in solvent (2.5 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Compound **4a** was used.
[e] *i*-BuOH as a solvent, rt.
[f] *i*-PrOH as a solvent, −20 °C.

3. Conclusion

In summary, we have developed a direct $Cu(OTf)_2$/trisoxazoline-catalyzed asymmetric Friedel–Crafts reaction between pyrrole derivatives and alkylidene malonates. Up to 66% ee was obtained, which represents the best example for this reaction. Compared with bisoxazolines, trisoxazolines provided better enantioselectivities.

4. Experimental section

4.1. General

All reactions were carried out in air atmosphere. Commercial grade solvents and reagents were dried and purified by standard procedures, as specified in "*Purification of Laboratory Chemicals*".

4.1.1. Synthesis of compound ***6d***

To a solution of compound **4c** (726 mg, 2.11 mmol) in anhydrous THF (30 mL) was added dropwise *t*-BuLi (2.5 mL, 1.7 M in hexanes, 4.25 mmol) within 15–20 min at −78 °C. The resulting yellow solution was stirred for further 1 h at −78 °C. Then a solution of 2-chloromethyl oxazoline (747 mg, 4.64 mmol) in THF (10 mL) was added dropwise at −78 °C over 10 min. The solution was slowly warmed to room temperature and was stirred for about 10 h. The mixture was diluted with CH_2Cl_2 (20 mL) and was washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/acetone=1/10) to afford the desired product **6d**. Yield: 602 mg (60%). $[\alpha]_D^{20}$ −265.2 (*c* 0.690, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.46 (m, 2H), 7.25–7.20 (m, 6H), 5.53 (dd, *J*=4.2, 8.1 Hz, 2H), 5.29–5.24 (m, 2H), 3.62–3.54 (m, 1H), 3.46–3.23 (m, 4H), 3.04–2.94 (m, 2H), 2.90 (s, 2H), 1.54–1.42 (m, 4H), 0.79 (d, *J*=6.6 Hz, 3H), 0.70 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 167.1, 163.2, 141.7, 141.5, 140.0, 139.5, 128.2, 128.1, 127.2, 127.0, 125.5, 125.0, 124.8, 83.4, 83.3, 76.4, 76.3, 71.7, 69.2, 40.6, 39.5, 39.4, 34.5, 32.1, 20.7, 18.5, 17.9; IR (film): 2958, 2911, 2859, 1650, 1479, 1453, 1165, 1095, 991, 751 cm^{-1}; MS (ESI, *m*/*z*): 470 ($M+H^+$); HRMS (ESI): Exact mass calcd for $C_{29}H_{32}N_3O_3^+$: 470.2437. Found: 470.2438.

4.1.2. Synthesis of compound ***6c***

Similar procedure to that of the synthesis of compound **6d**. Yield: 53%; $[\alpha]_D^{20}$ −283.2 (*c* 0.740, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.46 (m, 2H), 7.27–7.20 (m, 6H), 5.53 (dd, *J*=3.9, 8.1 Hz, 2H), 5.26 (m, 2H), 3.56–3.52 (m, 2H), 3.41–3.23 (m, 3H), 3.00–2.91 (m, 4H), 1.49 (s, 3H), 0.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 167.2, 163.2, 141.7, 141.6, 140.1, 139.6, 128.3, 128.1, 127.3, 127.1, 125.6, 125.0, 124.9, 83.4, 83.3, 76.5, 76.4, 75.5, 67.8, 40.6, 39.6, 39.5, 34.5, 33.2, 26.8, 25.6, 20.7; IR (film): 2955, 1652, 1648, 1459, 1097, 999, 753, 669 cm^{-1}; MS (ESI, *m*/*z*): 484 ($M+H^+$); HRMS (ESI): Exact mass calcd for $C_{30}H_{34}N_3O_3^+$: 484.2592. Found: 484.2594.

*4.1.3. General procedure for the Friedel–Crafts reaction (**3a** as an example)*

A mixture of $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and ligand **6d** (14 mg, 0.03 mmol) was stirred in *t*-BuOH (1.5 mL) at room temperature for 0.5 h. Then **2a** (62 mg, 0.25 mmol) in ether (1 mL) was added. The resulting mixture was stirred at 0 °C for 20 min and *N*-methyl pyrrole (0.044 mL, 0.3 mmol) was added. After the reaction was complete (monitored by TLC), the mixture was filtered rapidly through a glass funnel with a thin layer of silica gel and eluted with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate) to afford the desired product **3a**. Yield. 73%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=10/90, 0.7 mL/min, 230 nm; t_R (minor)=13.88 min, t_R (major)=15.94 min), 66% ee, $[\alpha]_D^{20}$ −110.7 (*c* 0.850, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.20 (m, 5H), 6.48–6.46 (m, 1H), 6.13–6.12 (m, 1H), 6.04–6.02 (m, 1H), 4.72 (d, *J*=12.0 Hz, 1H), 4.17–4.08 (m, 3H), 3.91 (q, *J*=6.9 Hz, 2H), 3.41 (s, 3H), 1.17 (t, *J*=6.9 Hz, 3H), 0.94 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.6, 139.1, 132.1, 128.6, 128.4, 128.1, 127.0, 122.0, 106.4, 105.2, 61.5, 61.3, 58.2, 43.1, 33.7, 13.9, 13.6; IR (film): 1756, 1735, 703 cm^{-1}; MS (EI, *m*/*z*): 329 (M^+, 13), 170 (100), 171 (15), 42 (8), 210 (8), 168 (6), 128 (6), 182 (5); Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.97; H, 7.18; N, 3.95.

4.1.4. Dibenzyl 2-((1-methyl-pyrrol-2-yl)(phenyl)methyl)-malonate ***3b***

Yield: 91%; ee is determined by HPLC analysis (Chiralcel OD-H, *i*-PrOH/hexane=10/90, 1.0 mL/min, 230 nm; t_R (minor)=6.15 min, t_R (major)=6.75 min), 39% ee, $[\alpha]_D^{20}$ −67.9 (*c* 1.200, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.13 (m, 13H), 6.98–6.96 (m, 2H), 6.46 (s, 1H), 6.12–6.11 (m, 1H), 6.04–6.02 (m, 1H), 5.10–4.99 (m, 2H), 4.74–4.90 (m, 3H), 4.23 (d, *J*=12.0 Hz, 1H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.4, 167.3, 139.0, 135.2, 134.9, 131.9, 128.6, 128.43, 128.36, 128.18, 128.15, 128.1, 128.0, 127.1, 122.1, 106.6, 105.5, 67.3, 67.2, 58.4, 43.2, 33.7; IR (film): 1749, 1735, 1455, 1305, 1172, 1146, 747, 692 cm^{-1}; MS (ESI, *m*/*z*): 454 ($M+H^+$); HRMS (ESI): Exact mass calcd for $C_{29}H_{27}NO_4Na^+$: 476.1836. Found: 476.1832.

4.1.5. Diethyl 2-((1-methyl-pyrrol-2-yl)(3-nitrophenyl)-methyl)malonate ***3c***

Yield: 96%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=40/60, 0.7 mL/min, 230 nm; t_R (major)=8.77 min, t_R (minor)=11.51 min), 58% ee, $[\alpha]_D^{20}$ −99.9 (*c* 0.975, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15–8.13 (m, 1H), 8.08–8.04 (m, 1H), 7.62–7.60 (m, 1H), 7.47–7.42 (m, 1H), 6.50 (t, *J*=2.1 Hz, 1H), 6.19 (m, 1H), 6.06 (t, *J*=3.0 Hz, 1H), 4.87 (d, *J*=11.4 Hz, 1H), 4.17–4.10 (m, 3H), 4.00–3.93 (m, 2H), 3.45 (s, 3H), 1.17 (t, *J*=6.9 Hz, 3H), 1.02 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.03, 166.97, 148.2, 141.8, 134.8, 130.6, 129.4, 123.4, 122.5, 122.1, 107.0, 106.0, 61.72, 61.67, 57.9, 42.4, 33.7, 13.8, 13.7; IR (film): 2981, 1745, 1735, 1531, 1352, 1023, 746, 713 cm^{-1}; MS (EI, *m*/*z*): 374 (M^+, 10), 215 (100), 169 (19), 255 (15), 216 (14), 168 (13), 357 (11), 42 (6); Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.75; H, 5.92; N, 7.06.

4.1.6. Dimethyl 2-((1-methyl-pyrrol-2-yl)(4-nitrophenyl)-methyl)malonate ***3d***

Yield: 70%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=30/70, 0.7 mL/min, 230 nm; t_R (minor)=14.20 min, t_R (major)=15.18 min), 52% ee, $[\alpha]_D^{20}$ −96.7 (*c* 1.450, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J*=8.7 Hz, 2H), 7.42 (d, *J*=9.0 Hz, 2H), 6.51 (dd, *J*=1.8 Hz, 2.4 Hz, 1H), 6.17–6.15 (m, 1H), 6.07–6.05 (m, 1H), 4.88 (d, *J*=11.7 Hz, 1H), 4.15 (d, *J*=11.7 Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 167.4, 147.0, 146.8, 130.4, 129.5, 123.8, 122.9, 107.1, 106.0, 57.5, 53.0, 52.8, 42.7, 33.8; IR (film): 2954, 1752, 1739, 1606, 1522, 1435, 1349, 1145, 862, 703 cm^{-1}; MS (EI, *m*/*z*): 346 (M^+, 16), 215 (100), 169 (30), 216 (16), 168 (10), 255 (9), 167 (6), 42 (6); Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.84; H, 5.27; N, 7.76.

4.1.7. Diethyl 2-((2-chlorophenyl)(1-methyl-pyrrol-2-yl)-methyl)malonate ***3e***

Yield: 30%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=30/70, 0.7 mL/min, 230 nm; t_R (major)=7.38 min, t_R (minor)=11.69 min), 40% ee, $[\alpha]_D^{20}$ −78.6 (*c* 1.200, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.30 (m, 2H), 7.21–7.08 (m, 2H), 6.47–6.46 (m, 1H), 6.12–6.11 (m, 1H), 6.03–6.01 (m, 1H), 5.37 (d, *J*=11.4 Hz, 1H), 4.17–4.08 (m, 3H), 4.01–3.90 (m, 2H), 3.54 (s, 3H), 1.15 (t, *J*=6.9 Hz, 3H), 0.99 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 167.1,

137.3, 133.4, 132.2, 130.2, 129.5, 128.1, 127.2, 122.1, 106.8, 105.9, 61.5, 58.0, 38.1, 34.1, 13.9, 13.6; IR (film): 2981, 1752, 1735, 1473, 1368, 1304, 1143, 1035, 756, 711 cm^{-1}; MS (EI, *m*/*z*): 363 (M^+, 13), 204 (100), 206 (34), 42 (14), 205 (12), 169 (11), 244 (10), 168 (10); Anal. Calcd for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.79; H, 5.94; N, 3.60.

4.1.8. Diethyl 2-((4-bromophenyl)(1-methyl-pyrrol-2-yl)-methyl)malonate **3f**

Yield: 63%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=30/70, 0.7 mL/min, 230 nm; t_R (minor)=8.85 min, t_R (major)=11.40 min), 65% ee, $[\alpha]_D^{20}$ −122.5 (*c* 1.300, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, *J*=8.7 Hz, 2H), 7.11 (d, *J*=8.7 Hz, 2H), 6.49–6.47 (m, 1H), 6.12–6.10 (m, 1H), 6.03 (t, *J*=3.3 Hz, 1H), 4.71 (d, *J*=11.4 Hz, 1H), 4.12 (q, *J*=7.5 Hz, 2H), 4.05 (d, *J*=11.7 Hz, 1H), 3.95 (q, *J*=7.2 Hz, 2H), 3.40 (s, 3H), 1.16 (t, *J*=7.2 Hz, 3H), 1.01 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.45, 167.39, 138.4, 131.6, 130.4, 122.3, 121.0, 106.7, 105.5, 61.7, 61.6, 58.1, 42.5, 33.8, 13.9, 13.7; IR (film): 2980, 1755, 1730, 1488, 1368, 1303, 1178, 1010, 717 cm^{-1}; MS (EI, *m*/*z*): 409 ($M+H^+$, 10), 248 (100), 250 (83), 44 (34), 42 (15), 249 (15), 168 (14), 43 (14), 169 (14); Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 56.17; H, 5.58; N, 3.22.

4.1.9. Diethyl 2-(phenyl(1H-pyrrol-2-yl)methyl)malonate **3g**

Yield: 57%; ee is determined by HPLC analysis (Chiralcel OD-H, *i*-PrOH/hexane=10/90, 1.0 mL/min, 254 nm; t_R (major)=5.73 min, t_R (minor)=6.83 min), 40% ee, $[\alpha]_D^{20}$ −13.3 (*c* 0.850, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.26–7.29 (m, 5H), 6.65–6.67 (m, 1H), 6.06–6.09 (m, 1H), 5.93–5.95 (m, 1H), 4.79 (d, *J*=10.8 Hz, 1H), 4.12–4.19 (m, 3H), 3.93 (q, *J*=6.9 Hz, 2H), 1.19 (t, *J*=7.2 Hz, 3H), 0.96 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 167.5, 139.7, 130.9, 128.5, 128.2, 127.1, 117.5, 108.0, 106.5, 61.8, 61.5, 57.9, 44.2, 13.9, 13.7; IR (film): 1744, 3386 cm^{-1}; MS (EI, *m*/*z*): 315 (M^+, 8), 156(100), 196 (12), 157 (10), 44 (7), 154 (6), 167 (6), 128 (6); Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.59; H, 6.72; N, 4.25.

4.1.10. Dimethyl 2-(3-methyl-1-(1H-pyrrol-2-yl)butyl)malonate **3h**

Yield: 27%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=30/70, 0.6 mL/min, 238 nm; t_R (major)=9.30 min, t_R (minor)=15.86 min), 26% ee, $[\alpha]_D^{20}$ +1.2 (*c* 0.440, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.77 (br s, 1H), 6.67–6.66 (m, 1H), 6.07 (dd, *J*=2.7, 6.0 Hz, 1H), 5.92 (br s, 1H), 3.70 (s, 3H), 3.63–3.61 (m, 4H), 3.54–3.46 (m, 1H), 1.82–1.73 (m, 1H), 1.47–1.25 (m, 2H), 0.89–0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 169.33, 169.28, 130.6, 117.0, 107.6, 106.3, 57.5, 52.6, 52.5, 41.7, 36.6, 25.5, 23.4, 21.4; IR (film): 3404, 2956, 2870, 1737, 1436, 1158, 1028, 721 cm^{-1}; MS (EI, *m*/*z*): 267 [M^+], 120 (100), 135 (54), 80 (50), 101 (48), 59 (40), 93 (31), 136 (30), 132 (29); HRMS (EI): Exact mass calcd for $C_{14}H_{21}NO_4$: 267.1471. Found: 267.1470.

4.1.11. Diethyl 2-((1-allyl-pyrrol-2-yl)(phenyl)methyl)malonate **3i**

Yield: 43%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=10/90, 0.6 mL/min, 238 nm; t_R (minor)=10.10 min, t_R (major)=13.53 min), 20% ee, $[\alpha]_D^{20}$ −20.4 (*c* 0.7033, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.16 (m, 5H), 6.52–6.50 (m, 1H), 6.16–6.15 (m, 1H), 6.08 (t, *J*=3.3 Hz, 1H), 5.78–5.66 (m, 1H), 5.08 (dd, *J*=1.2, 10.5 Hz, 1H), 4.89 (dd, *J*=1.8, 17.4 Hz, 1H), 4.71 (d, *J*=12.0 Hz, 1H), 4.29–4.27 (m, 2H), 4.17–4.07 (m, 3H), 3.89 (q, *J*=7.2 Hz, 2H), 1.18 (t, *J*=7.2 Hz, 3H), 0.93 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.61, 167.56, 139.4, 133.9, 131.9, 128.7, 128.4, 127.1, 121.2, 116.8, 106.9, 105.7, 61.5, 61.4, 58.4, 49.0, 43.0, 13.9, 13.7; IR (film): 2983, 2936, 1757, 1735, 1701, 1478, 1369, 1305, 1179, 1034, 703 cm^{-1}; MS (EI, *m*/*z*): 355 [M^+], 196 (100), 194 (72), 195 (56), 118 (40), 69 (20), 115 (19), 197 (19), 117 (18); HRMS (EI): Exact mass calcd for $C_{21}H_{25}NO_4$: 355.1784. Found: 355.1777.

4.1.12. Diethyl 2-((1-benzyl-pyrrol-2-yl)(phenyl)methyl)-malonate **3j**

Yield: 70%; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=10/90, 0.6 mL/min, 238 nm; t_R (minor)=11.09 min, t_R (major)=18.61 min), 41% ee, $[\alpha]_D^{20}$ −14.1 (*c* 2.2133, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.06 (m, 8H), 6.85–6.82 (m, 2H), 6.47–6.46 (m, 1H), 6.20–6.19 (m, 1H), 6.10–6.08 (m, 1H), 4.89 (ABd, *J*=16.8 Hz, 1H), 4.83(ABd, *J*=16.5 Hz, 1H), 4.64 (d, *J*=11.4 Hz, 1H), 4.17–4.02 (m, 3H), 3.80 (q, *J*=6.9 Hz, 2H), 1.10 (t, *J*=7.2 Hz, 3H), 0.85 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.22, 167.19, 139.1, 137.6, 132.0, 128.3, 128.2, 128.0, 126.9, 126.7, 126.4, 121.6, 107.0, 105.7, 61.2, 61.0, 58.3, 49.8, 42.8, 13.7, 13.4; IR (film): 2981, 2936, 1757, 1496, 1480, 1455, 1364, 1298, 1028, 707 cm^{-1}; MS (EI, *m*/*z*): 405 [M^+], 246 (100), 91 (83), 247 (22), 115 (22), 69 (20), 168 (17), 244 (16), 167 (16); HRMS (EI): Exact mass calcd for $C_{25}H_{27}NO_4$: 405.1940. Found: 405.1948.

4.1.13. Dimethyl 2-((1-methyl-pyrrol-2-yl)(4-methoxy-phenyl)methyl)malonate **3k**

Yield: 53%; mp 89–91 °C; ee is determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane=10/90, 0.6 mL/min, 230 nm; t_R (minor)=13.18 min, t_R (major)=14.83 min), 64% ee, $[\alpha]_D^{20}$ −134.5 (*c* 0.570, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, *J*=8.7 Hz, 2H), 6.77 (d, *J*=8.7 Hz, 2H), 6.47 (d, *J*=1.8 Hz, 1H), 6.08 (t, *J*=1.2 Hz, 1H), 6.03 (d, *J*=3 Hz, 1H), 4.69 (d, *J*=12 Hz, 1H), 4.09 (d, *J*=12 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.49 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.2, 167.0, 157.5, 131.2, 130.1, 128.5, 121.2, 112.9, 105.5, 104.1, 57.2, 54.1, 51.7, 51.5, 41.5, 32.8; IR (film): 2952, 2925, 2840, 1756, 1738, 1507, 1539, 1495, 1488, 1471, 1246, 1208, 709 cm^{-1}; MS (EI, *m*/*z*): 331 (M^+, 12), 200 (100); HRMS (EI): Exact mass calcd for $C_{18}H_{21}NO_5$: 331.1420. Found: 331.1425.

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Supplementary data

Spectral data for key compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.023.

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