DOI: 10.1002/ejoc.201100205

Metal-Free Asymmetric 1,3-Dipolar Cycloaddition of *N*-Arylmaleimides to Azomethine Ylides Catalyzed by Chiral Tertiary Amine Thiourea

Jian-Fei Bai,[a,b] Liang-Liang Wang,[a,b] Lin Peng,[a,b] Yun-Long Guo,[a,b] Jun-Nan Ming,[a] Fei-Ying Wang,[a] Xiao-Ying Xu,*[a] and Li-Xin Wang*[a]

Keywords: Cycloaddition / Organocatalysis / Diastereoselectivity / Enantioselectivity / Azomethine ylides

The first metal-free asymmetric 1,3-dipolar cycloaddition of *N*-arylmaleimides to azomethine ylides catalyzed by chiral tertiary amine thiourea to form multiply substituted pyrrolidines in excellent yields (up to 89 %) and enantioselectivities (up to 96 % *ee*) is presented. This procedure allows a rapid diversity-oriented synthesis of chiral pyrrolidine derivatives with high optical purity.

Introduction

Optically active five-membered nitrogen heterocycles are important motifs in natural alkaloids, pharmaceutically active substances, and key intermediates in total syntheses.[1] The significance of these structures has inspired chemists to develop new asymmetric strategies to access these interesting five-membered heterocycles.[2] Among them, the catalytic asymmetric 1,3-dipolar cycloaddition of activated alkenes to azomethine ylides is a straightforward way to construct functionalized pyrrolidines.[3] Over the past years, a variety of chiral metal catalysts including copper,[4] silver,[5] nickel,[6] zinc,[7] calcium,[8] and gold[9] have been successfully developed, which are generally used in combination with chiral ligands to afford moderate to high enantio-/diastereoselectivities. However, the development of more efficient and environmentally friendly methodologies in asymmetric catalysis, especially metal-free small molecular catalysis, is still a challenge.[10] In 2007, Vicario and coworkers reported the organocatalytic enantioselective cycloaddition of azomethine ylides to α,β-unsaturated aldehydes in good enantioselectivities.[10a] Subsequently, Gong and coworkers reported a Brønsted acid catalyzed three-component 1,3-dipolar cycloaddition between aldehydes, amino esters, and dipolarophiles.[10c] Additionally, nitroalkenes were also evaluated in this conversion.[10g] In the same year, Chen reported the organocatalytic, one-pot, three-component reaction of aldehydes, diethyl aminomalonate, and nitroalkenes catalyzed by a bifunctional tertiary amine-urea.[10e] Despite intense efforts, an organocatalytic asymmetric version of 1,3-dipolar cycloaddition of azomethine ylides has remained elusive. To date, there has been no report of organocatalytic asymmetric 1,3-dipolar cycloaddition of azomethine to maleimides, which could afford biological or clinical heterocycles with important and easily transformable succinimide motifs.[11] It is still desirable and challenging to develop new catalytic systems that bring about this useful transformation.

Recently, bifunctional thiourea catalysts have been investigated extensively in organocatalysis as a particular tool to activate both donors and acceptors simultaneously.[12] In our previous work, thiourea was shown to activate maleimides effectively through hydrogen bonds.[13a] Inspired by this concept, we recognized that the tertiary amine group would activate the α-imino esters as bases to produce azomethine ylides,[10e] whereas the thiourea group would activate *N*-arylmaleimides through double hydrogen bonds. Thus, the synergistic interactions through chiral tertiary amine thiourea bifunctional catalysis would ensure high stereoselectivities in the subsequent dipolar cycloaddition, affording the corresponding optically active products through a postulated transition state (TS) shown in Figure 1. As a part of our continuing interests in asymmetric syntheses,[13] herein, we wish to report the first organocatalytic asymmet-

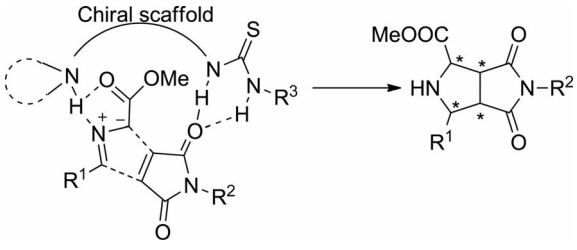


Figure 1. Proposed transition state.

[a] Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences,
Chengdu 610041, P. R. of China
Fax: +86-028-8525-5208
E-mail: wlxioc@cioc.ac.cn
xuxy@cioc.ac.cn
[b] Graduate University of Chinese Academy of Sciences, Beijing 10039, P. R. of China

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100205.

ric 1,3-dipolar cycloaddition of *N*-arylmaleimides and azomethine ylides promoted by chiral tertiary amine thiourea catalysts, yielding multiply substituted pyrrolidines in excellent enantioselectivities (up to 96% *ee*). This procedure allows a rapid diversity-oriented synthesis of chiral pyrrolidine derivatives.

Results and Discussion

Based on the above hypothesis, a series of catalysts with various substituents **1a**–**g** (Figure 2) were synthesized and evaluated.[14] We chose *N*-benzylideneglycine methyl ester (**2a**) and *N*-phenylmaleimide (**3a**) as the model reaction substrates to screen a range of chiral tertiary amine thioureas and found that the adduct *endo*-**4a** was obtained with highly variable yield as shown in Table 1.[15] For catalysts **1a** and **1b**, only moderate yields and low enantioselectivities were obtained (Table 1, entries 1 and 2). Catalyst **1a**, with cyclohexanediamine as a chiral scaffold, afforded better yield and enantioselectivity (61% yield, 63% *ee*) than catalyst **1b**, with a diphenyldiamine scaffold (21% yield, 7% *ee*; Table 1, entry 1 vs. 2). Catalysts **1c**–**f**, with cyclic substitution on the nitrogen atom, afforded better enantioselectivities (up to 91% *ee*; Table 1, entries 3–6) than those with methyl substitutions (Table 1, entries 1 and 2). More acidic N–H thiourea groups seem to have a detrimental effect on the catalytic activity. Catalysts **1c** and **1e**, with no substitutions on the phenyl ring, gave better enantioselectivities than those with 3,5-bis(trifluoromethyl) groups (Table 1, entries 3 vs. 5, and 4 vs. 6). Catalysts **1e** and **1f** afforded good enantioselectivities but poor yields (Table 1, entries 5 and 6). When the commonly used cinchona alkaloid based thioureas **1g** and **1h** were evaluated, almost racemic adducts were obtained (Table 1, entries 7 and 8). Catalyst **1c** thus gave the best enantioselectivity with an acceptable yield, and was selected for further optimization.

Other reaction conditions, such as substrate loadings, solvents, and additives, were then screened (Table 2). Excessive loading of azomethine ylides (**2a**) is unfavorable and the enantioselectivities decreased gradually with increasing ylide loadings (Table 2, entries 1–3). In contrast, use of an excess amount of *N*-phenylmaleimide (**3a**) gave better yields, while the enantioselectivities remained almost unchanged (Table 2, entries 1, 4, and 5). A molecular ratio of 1:1.5 reactants **2a** and **3a** gave the highest enantioselectivity (91% *ee*; Table 2, entry 4) and was chosen for further optimization. Solvents were also found to have remarkable effects on the enantioselectivities (Table 2, entries 6–13); CH_2Cl_2 gave the highest *ee* (93%) with moderate yield (64%, Table 1, entry 4) and was chosen as the most suitable solvent. It was reported in the literature[10e] that addition of molecular sieves (4 Å) can have a positive effect on the reaction yield of similar transformations. We also observed that when molecular sieves (4 Å) was added, the yield increased remarkably and the enantioselectivity was not decreased (69% yield, 93% *ee*; Table 2, entry 14). Generally, the yields were clearly affected by both the catalyst loading and the reaction time. The highest yield was obtained when the reaction was undertaken in the presence of 25 mol-% **1c** for 72 h (85% yield; Table 2, entry 16). Based on the above results, optimal reaction conditions (1.0 equiv. **2a** and

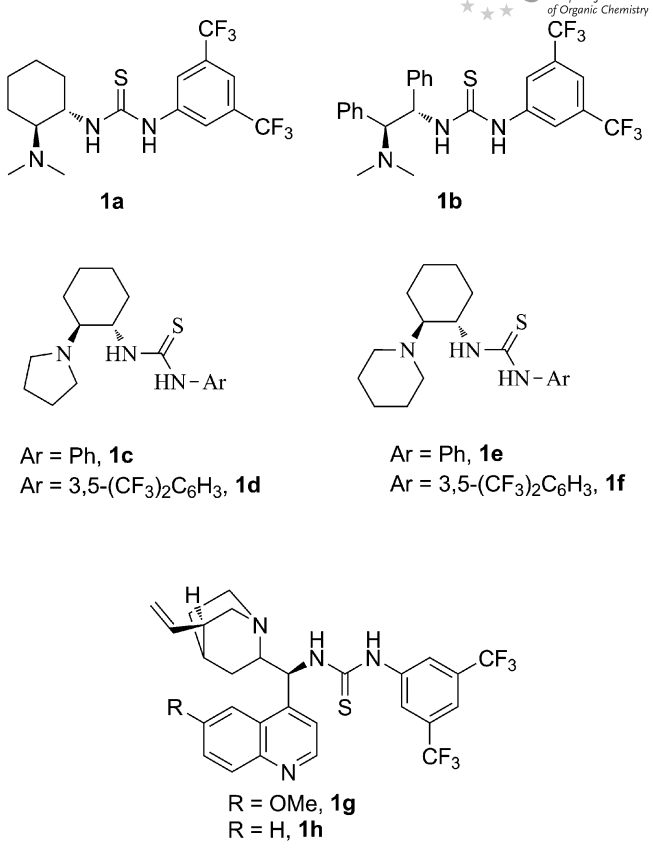
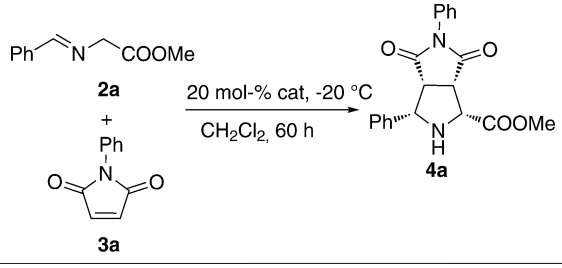


Figure 2. Organocatalysts assessed in this study.

Table 1. 1,3-Dipolar cycloaddition reaction of **2a** and **3a**.[a]

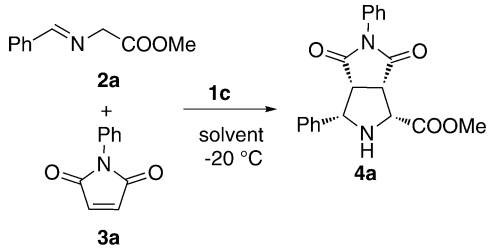


Entry	Cat.	Yield [%][b]	*ee* [%][c,d]
1	**1a**	61	63
2	**1b**	21	7
3	**1c**	50	91
4	**1d**	68	76
5	**1e**	19	82
6	**1f**	26	73
7	**1g**	82	7
8	**1h**	83	1

[a] Reagents and conditions: **2a** (0.20 mmol), **3a** (0.20 mmol), anhydrous CH_2Cl_2 (0.8 mL), –20 °C, 60 h. [b] Isolated yield of the *endo* isomer. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] The absolute configuration of the known compound **4a** was determined by optical rotation comparisons with reported data.[4i]

1.5 equiv. **3a** in CH_2Cl_2 with 25 mol-% catalyst **1c** and 4 Å molecular sieves at –20 °C) were established.

Table 2. Optimization of the reaction conditions.[a]

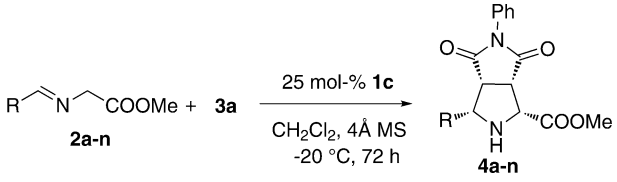


Entry	**2a**/**3a** ratio	Solvent	Yield [%][b]	*ee* [%][c,d]
1	1:1	CH_2Cl_2	50	91
2	2:1	CH_2Cl_2	62	87
3	5:1	CH_2Cl_2	58	80
4	1:1.5	CH_2Cl_2	64	93
5	1:2	CH_2Cl_2	61	91
6	1:1.5	$CHCl_3$	65	78
7	1:1.5	$ClCH_2CH_2Cl$	63	89
8	1:1.5	Et_2O	55	80
9	1:1.5	toluene	62	80
10	1:1.5	xylene	65	83
11	1:1.5	THF	52	73
12	1:1.5	DMF	33	67
13	1:1.5	CH_3CN	60	89
14[e]	1:1.5	CH_2Cl_2	69	93
15[e,f]	1:1.5	CH_2Cl_2	79	95
16[e,f,g]	1:1.5	CH_2Cl_2	85	93

[a] Reagents and conditions: **2a** (0.20 mmol), **3a** (0.20 mmol), anhydrous solvent (0.8 mL), –20 °C, 60 h. [b] Isolated yield of the *endo* isomer. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] The absolute configuration of the known compound **4a** was determined by comparison of the optical rotation with reported data.[4i] [e] MS (4 Å, 300 mg) was added. [f] **1c** (25 mol-%) was added. [g] The reaction time was 72 h.

Under the optimal conditions, the scope of the reaction was investigated; the substituents of azomethine ylides **2** and *N*-arylmaleimides **3** are listed in Table 3 and Table 4. All the reactions proceeded smoothly and all the substrates gave moderate to good yields (up to 89%) and satisfactory enantioselectivities (up to 96% *ee*). The electronic nature and position of the substituents on the azomethine ylides phenyl ring had some influence on the enantioselectivities. Strong electron-withdrawing groups on the phenyl ring of **2** decreased the yields and enantioselectivities remarkably (Table 3, entries 2, 9, and 12), whereas electron-rich groups on the phenyl ring of **2** gave the highest enantioselectivity (96% *ee*; Table 3, entry 5). 1-Naphthyl and 2-furyl azomethine ylides also worked well (Table 3, entries 13 and 14) and gave good results. The electronic property and position of the substituents on the arylmaleimides phenyl ring affected the enantioselectivities slightly. All reactions gave high yields and excellent enantioselectivities (up to 87% yield and 95% *ee*; Table 4), except with *N*-1-naphthyl maleimide **3j**, which gave lower yield (66%) and enantioselectivity (88% *ee*; Table 4, entry 10). Disappointedly, the aliphatic *N*-substituted maleimide **3k** gave poor enantioselectivity (30% *ee*; Table 4, entry 11).

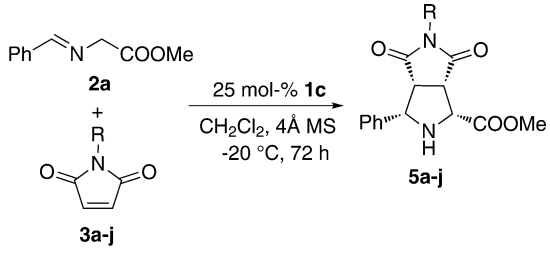
Table 3. Scope of azomethine ylides.[a]



Entry	R	**2**	**4**	Yield [%][b]	*ee* [%][c]
1	Ph	**2a**	**4a**	85	93
2	4-$NO_2C_6H_4$	**2b**	**4b**	77	67
3	4-BrC_6H_4	**2c**	**4c**	89	90
4	4-ClC_6H_4	**2d**	**4d**	84	95
5	4-$CH_3OC_6H_4$	**2e**	**4e**	79	96
6	4-$CH_3C_6H_4$	**2f**	**4f**	72	90
7	3-ClC_6H_4	**2g**	**4g**	72	86
8	3-BrC_6H_4	**2h**	**4h**	85	90
9	3-$NO_2C_6H_4$	**2i**	**4i**	64	85
10	3-$CH_3C_6H_4$	**2i**	**4j**	75	93
11	2-$CH_3OC_6H_4$	**2k**	**4k**	71	87
12	2-$NO_2C_6H_4$	**2l**	**4l**	51	70
13	1-naphthyl	**2m**	**4m**	86	90
14	2-furyl	**2n**	**4n**	82	91

[a] Reagents and conditions: **2** (0.30 mmol), **3a** (0.45 mmol), MS (4 Å, 300 mg), anhydrous CH_2Cl_2 (1.0 mL), –20 °C, 72 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis.

Table 4. Scope of *N*-arylmaleimides.[a]



Entry	R	**3**	**5**	Yield [%][b]	*ee* [%][c]
1	Ph	**3a**	**5a**	85	93
2	4-FC_6H_4	**3b**	**5b**	84	87
3	4-ClC_6H_4	**3c**	**5c**	81	92
4	4-$NO_2C_6H_4$	**3d**	**5d**	70	73
5	4-$CH_3OC_6H_4$	**3e**	**5e**	74	95
6	4-$CH_3C_6H_4$	**3f**	**5f**	85	90
7	3-FC_6H_4	**3g**	**5g**	87	85
8	2-FC_6H_4	**3h**	**5h**	73	90
9	2-$CH_3C_6H_4$	**3i**	**5i**	82	82
10	1-naphthyl	**3j**	**5j**	66	88
11	CH_3	**3k**	**5k**	75	30

[a] Reagents and conditions: **2a** (0.30 mmol), **3** (0.45 mmol), MS (4 Å, 300 mg), CH_2Cl_2 (1.0 mL), –20 °C, 72 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis.

Conclusions

We have developed a highly enantioselective formal 1,3-dipolar cycloaddition reaction between azomethine ylides and *N*-arylmaleimides catalyzed by chiral tertiary amine thiourea. This protocol has provided a new approach to the preparation of functionalized pyrolidines in excellent yields (up to 89%) and enantioselectivities (up to 96% *ee*), and

holds great potential in the environmentally friendly synthesis of highly substituted five-membered nitrogen heterocycles.

Experimental Section

General Methods: All regents were obtained from commercial suppliers and used without further purification. Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F. Perrin, D. D. Butterworth Heinemann, 1997). NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light. Enantiomeric excess was determined by HPLC analysis on Chiralpak AS-H column. The absolute configurations of the known products were assigned by HPLC and by comparison of the optical rotation with the reported data;[4i] those of other adducts were deduced on the basis of those results.

General Procedure for the Synthesis of α-Imino Esters: Et_3N (3.6 g, 36 mmol) was added to a suspension of the corresponding amino acid ester hydrochloride (36 mmol) and $MgSO_4$ (60 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 1 h, then the corresponding aldehyde (30 mmol) was added. The reaction was stirred at room temperature overnight, then the resulting precipitate was removed by filtration. The filtrate was washed twice with water (30 mL), the aqueous phase was extracted once with CH_2Cl_2 (30 mL) and the combined organic phase was washed with brine three times, dried with Na_2SO_4, and concentrated. The resulting imino esters were used in 1,3-dipolar cycloaddition reactions without further purification.

Preparation of Catalysts: The catalysts **1a**–**h** were prepared according to literature methods.[14,16]

1-Phenyl-3-[(1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl]thiourea (1c): Isothiocyanatobenzene (0.8 g, 6.0 mmol, 1.0 equiv.) was added to a solution of (1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexanamine (1.0 g, 6.0 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature. The resulting solution was stirred overnight, then concentrated in vacuo and purified by chromatography (PE/EtOAc/NEt_3, 5:1 to 1:1) to afford 1-phenyl-3-[(1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl]thiourea (**1c**; 1.55 g, 85% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (t, *J* = 7.38 Hz, 2 H), 7.26–7.18 (m, 3 H), 6.84 (br. s, 1 H), 3.84 (m, 1 H), 2.95–2.54 (m, 6 H), 1.81–1.63 (m, 7 H), 1.37–1.18 (m, 4 H) ppm.

The catalysts **1d**, **1e**, and **1f** were prepared in a similar manner to **1c**.

General Procedure for Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides Catalyzed by Chiral Tertiary Amine Thiourea: A mixture of imino esters (0.30 mmol), *N*-arylmaleimides (0.45 mmol), the catalyst **1c** (0.075 mmol), and 4 Å molecular sieves (300 mg) were stirred in CH_2Cl_2 (1.0 mL) at –20 °C for 72 h (reaction was monitored by TLC). After evaporation under reduced pressure, the residue was purified through column chromatography on silica gel (petroleum ether/ethyl acetate = 1.5:1) to yield pure products.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 4,6-Dioxo-3,5-diphenyloctahydropyrrolo-[3,4-*c*]pyrrole-1-carboxylate (4a): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 85% yield as a white solid. $[\alpha]_D^{20}$ = –93.4(*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.47–7.41 (m, 2 H), 7.30–7.28 (m, 6 H), 7.14 (d, *J* = 7.4 Hz, 2 H), 4.63 (d, *J* = 8.75 Hz, 1 H), 4.16 (d, *J* = 6.63 Hz, 1 H), 3.87 (s, 3 H), 3.73 (t, *J* = 7.6 Hz, 1 H), 3.57 (t, *J* = 8.7 Hz, 1 H), 2.39 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.0, 173.6, 170.0, 136.6, 131.6, 128.9, 128.6, 128.5, 127.0, 126.1, 64.2, 61.8, 52.3, 49.4, 48.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}N_2NaO_4$ [M + Na] 373.1159; found 373.1153. Enantiomeric excess: 93%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 15.5 min, t_R (major) = 25.5 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(4-Nitrophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4b): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 77% yield as a white solid. $[\alpha]_D^{20}$ = –118.9 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.20 (d, *J* = 8.67 Hz, 2 H), 7.64 (d, *J* = 8.64 Hz, 2 H), 7.42–7.28 (m, 3 H), 7.11 (d, *J* = 7.29 Hz, 2 H), 4.69 (d, *J* = 8.49 Hz, 1 H), 4.19 (d, *J* = 6.78 Hz, 1 H), 3.88 (s, 3 H), 3.77 (t, *J* = 7.56 Hz, 1 H), 3.64 (t, *J* = 8.25 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 67%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 37.5 min, t_R (major) = 61.1 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(4-Bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4c): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 89% yield as a white solid. $[\alpha]_D^{20}$ = –131.6 (*c* = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49–7.46 (m, 2 H), 7.42–7.35 (m, 5 H), 7.13 (d, *J* = 7.12 Hz, 2 H), 4.55 (d, *J* = 8.65 Hz, 1 H), 4.13 (d, *J* = 6.70 Hz, 1 H), 3.87 (s, 3 H), 3.73 (t, *J* = 6.98 Hz, 1 H), 3.55 (t, *J* = 8.1 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 22.4 min, t_R (major) = 48.7 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(4-Chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4d): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 84% yield as a white solid. $[\alpha]_D^{20}$ = –126.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.33 (m, 7 H), 7.10 (d, *J* = 8.75 Hz, 2 H), 4.61 (d, *J* = 8.74 Hz, 1 H), 4.14 (d, *J* = 6.59 Hz, 1 H), 3.87 (s, 3 H), 3.72 (t, *J* = 7.58 Hz, 1 H), 3.56 (t, *J* = 8.40 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 95%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 21.6 min, t_R (major) = 45.2 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(4-Methoxyphenyl)-4,6–dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4e): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 79% yield as a white solid. $[\alpha]_D^{20}$ = –7.1 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.42–7.29 (m, 5 H), 7.15 (d, *J* = 7.1 Hz, 2 H), 6.88 (d, *J* = 8.67 Hz, 2 H), 4.58 (d, *J* = 8.80 Hz, 1 H), 4.14 (d, *J* = 6.6 Hz, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.72 (t, *J* = 6.9 Hz, 1 H), 3.53 (t, *J* = 8.3 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 96%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 29.7 min, t_R (major) = 48.5 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 4,6-Dioxo-5-phenyl-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4f): This is a known com-

pound.[4i] The product was obtained according to the general procedure as described above in 72% yield as a white solid. $[\alpha]_D^{20}$ = –147.1 (c = 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, J = 7.53 Hz, 1 H), 7.39–7.29 (m, 4 H), 7.11 (d, J = 7.48 Hz, 2 H), 6.98–6.93 (m, 1 H), 6.89 (d, J = 8.20 Hz, 1 H), 4.73 (t, J = 7.62 Hz, 1 H), 4.16 (t, J = 6.41 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.79–3.71 (m, 2 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 21.9 min, t_R (major) = 40.5 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(3-Chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4g): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 72% yield as a white solid. $[\alpha]_D^{20}$ = –97.8 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (s, 1 H), 7.43–7.15 (m, 6 H), 7.13 (d, J = 7.26 Hz, 2 H), 4.58 (d, J = 8.82 Hz, 1 H), 4.14 (d, J = 6.48 Hz, 1 H), 3.87 (s, 3 H), 3.73 (t, J = 7.11 Hz, 1 H), 3.56 (t, J = 8.16 Hz, 1 H), 2.39 (br. s, 1 H, NH) ppm. Enantiomeric excess: 86%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 20.4 min, t_R (major) = 40.9 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(3-Bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4h): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 85% yield as a white solid. $[\alpha]_D^{20}$ = –89.9 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.65 (s, 1 H), 7.45–7.30 (m, 5 H), 7.25–7.22 (m, 1 H), 7.14 (d, J = 8.01 Hz, 2 H), 4.56 (d, J = 8.77 Hz, 1 H), 4.12 (d, J = 6.4 Hz, 1 H), 3.86 (s, 3 H), 3.72 (t, J = 7.3 Hz, 1 H), 3.55 (t, J = 8.3 Hz, 1 H), 2.04 (br. s, 1 H, NH), Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 22.5 min, t_R (major) = 45.1min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(3-Nitrophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4i): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 64% yield as a white solid. $[\alpha]_D^{20}$ = –115.2 (c = 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.33 (s, 1 H), 8.16–8.13 (m, 1 H), 7.80 (d, J = 7.62 Hz, 1 H), 7.42–7.34 (m, 4 H), 7.13 (d, J = 7.14 Hz, 2 H), 4.68 (d, J = 8.49 Hz, 1 H), 4.18 (d, J = 6.72 Hz, 1 H), 3.87 (s, 3 H), 3.76 (t, J = 7.26 Hz, 1 H), 3.63 (t, J = 8.1 Hz, 1 H), 2.06 (br. s, 1 H, NH) ppm. Enantiomeric excess: 85%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 39.7 min, t_R (major) = 64.1 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 4,6-Dioxo-5-phenyl-3-(*m*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4j): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 75% yield as a white solid. $[\alpha]_D^{20}$ = –98.1 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.41–7.31 (m, 3 H), 7.23–7.11 (m, 6 H), 4.57 (d, J = 8.86 Hz, 1 H), 4.12 (d, J = 6.49 Hz, 1 H), 3.87 (s, 3 H), 3.71 (t, J = 6.6 Hz, 1 H), 3.53 (t, J = 7.83 Hz, 1 H), 2.34 (s, 3 H), 2.04 (br. s, 1 H, NH) ppm. Enantiomeric excess: 93%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 17.9 min, t_R (major) = 35.1 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(2-Methoxyphenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4k): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 71% yield as a white solid. $[\alpha]_D^{20}$ = –119.5 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, J = 7.37 Hz, 1 H), 7.38–7.29 (m, 4 H), 7.11 (d, J = 7.63 Hz, 2 H), 6.96 (t, J = 7.46 Hz, 1 H), 6.88 (d, J = 8.21 Hz, 1 H), 4.73 (d, J = 7.61 Hz, 1 H), 4.14 (d, J = 6.24 Hz, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.75 (t, J = 7.78 Hz, 1 H), 3.72 (t, J = 7.90 Hz, 1 H), 2.34 (br. s, 1 H, NH) ppm. Enantiomeric excess: 87%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 21.4 min, t_R (major) = 38.8 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(2-Nitrophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4l): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 51% yield as a white solid. $[\alpha]_D^{20}$ = –1.1 (c = 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.15–7.38 (m, 3 H), 7.36–7.07 (m, 4 H), 7.05 (d, J = 6.93 Hz, 2 H), 5.10 (d, J = 8.34 Hz, 1 H), 4.16 (d, J = 6.51 Hz, 1 H), 4.06 (t, J = 8.19 Hz, 1 H), 3.87 (s, 3 H), 3.76 (t, J = 7.2 Hz, 1 H), 2.38 (br. s, 1 H, NH) ppm. Enantiomeric excess: 70%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 25.8 min, t_R (major) = 30.4 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(Naphthalen-1-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4m): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 86% yield as a white solid. $[\alpha]_D^{20}$ = –137.4 (c = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.96 (d, J = 8.26 Hz, 1 H), 7.89–7.78 (m, 3 H), 7.57–7.44 (m, 3 H), 7.32–7.27 (m, 3 H), 7.02 (d, J = 7.32 Hz, 2 H), 5.09 (d, J = 8.02 Hz, 1 H), 4.06 (d, J = 5.71 Hz, 1 H), 3.89 (s, 3 H), 3.73–3.62 (m, 2 H), 2.05 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.1, 173.1, 170.1, 133.4, 122.1, 131.5, 131.1, 129.0, 128.8, 128.6, 128.3, 126.3, 126.0, 125.6, 125.3, 123.3, 122.3, 61.4, 59.8, 52.2, 48.0, 47.9 ppm. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 25.5 min, t_R (major) = 81.3 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 3-(Furan-2-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4n): The product was obtained according to the general procedure as described above in 82% yield as a white solid. $[\alpha]_D^{20}$ = –63.0 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.45–7.40 (m, 4 H), 7.21 (d, J = 7.10 Hz, 2 H), 6.42–6.35 (m, 2 H), 4.64 (d, J = 8.77 Hz, 1 H), 4.08 (d, J = 6.99 Hz, 1 H), 3.85 (s, 3 H), 3.76 (t, J = 7.54 Hz, 1 H), 3.57 (t, J = 8.2 Hz, 1 H), 2.59 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.7, 173.8, 169.7, 149.3, 142.6, 131.6, 129.1, 128.8, 126.1, 110.5, 108.3, 62.2, 59.8, 52.5, 49.4, 49.3 ppm. Enantiomeric excess: 91%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 20.3 min, t_R (major) = 40.3 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(4-Fluorophenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5b): The product was obtained according to the general procedure as described above in 84% yield as a white solid. $[\alpha]_D^{20}$ = –97.3 (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46–7.33 (m, 5 H), 7.14–7.03 (m, 4 H), 4.62 (d, J = 8.73 Hz, 1 H), 4.16 (d, J = 6.60 Hz, 1 H), 3.87 (s, 3 H), 3.73 (t, J = 7.65 Hz, 1 H), 3.57 (t, J = 8.52 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.9, 173.5, 169.9, 161.2, 136.6, 128.5, 128.0, 127.8, 127.3, 127.0, 116.0, 64.1, 61.8, 52.3, 49.3, 48.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}FN_2NaO_4$ [M + Na] 391.1065; found 391.1081. Enantiomeric excess: 87%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 18.5 min, t_R (major) = 27.6 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(4-Chlorophenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5c): The product was obtained according to the general procedure as described above in 81% yield as a white solid. $[\alpha]_D^{20}$ = –100.7 (c = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.44–7.42 (m, 2 H), 7.39–7.32 (m, 5

H), 7.09 (d, *J* = 8.75 Hz, 2 H), 4.61 (d, *J* = 8.74 Hz, 1 H), 4.14 (d, *J* = 6.59 Hz, 1 H), 3.87 (s, 3 H), 3.72 (t, *J* = 7.58 Hz, 1 H), 3.56 (t, *J* = 8.4 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.8, 173.3, 169.9, 136.5, 134.2, 130.0, 129.2, 128.5, 127.3, 127.0, 64.1, 61.8, 52.4, 49.3, 48.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}ClN_2NaO_4$ [M + Na] 407.0769; found 407.0769. Enantiomeric excess: 92%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 18.3 min, t_R (major) = 26.3 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(4-Nitrophenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5d): The product was obtained according to the general procedure as described above in 70% yield as a white solid. $[\alpha]_D^{20}$ = –73.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.23 (d, *J* = 8.97 Hz, 2 H), 7.45-7.31 (m, 7 H), 4.64 (d, *J* = 8.85 Hz, 1 H), 4.17 (d, *J* = 6.48 Hz, 1 H), 3.92 (s, 3 H), 3.77 (t, *J* = 7.56 Hz, 1 H), 3.61 (t, *J* = 8.58 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.4, 172.9, 169.8, 146.7, 136.9, 136.4, 128.6, 126.9, 126.4, 124.9, 124.2, 64.0, 61.8, 52.3, 49.2, 48.1 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}N_3NaO_6$ [M + Na] 418.1010; found 418.1005. Enantiomeric excess: 73%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 30.6 min, t_R (major) = 41.1 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(4-Methoxyphenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5e): The product was obtained according to the general procedure as described above in 74% yield as a white solid. $[\alpha]_D^{20}$ = –96.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (d, *J* = 6.75 Hz, 2 H), 7.39–7.31 (m, 3 H), 7.04 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 4.65 (d, *J* = 8.76 Hz, 1 H), 4.19 (d, *J* = 6.69 Hz, 1 H), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.72 (t, *J* = 6.93 Hz, 1 H), 3.58 (t, *J* = 8.37 Hz, 1 H), 2.05 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.2, 173.8, 170.0, 159.2, 136.6, 128.4, 128.3, 127.2, 127.0, 124.2, 114.2, 64.1, 61.7, 55.3, 52.3, 49.3, 48.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_2NaO_5$ [M + Na] 403.1264; found 403.1246. Enantiomeric excess: 95%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 30.1 min, t_R (major) = 42.0 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 4,6-Dioxo-3-phenyl-5-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5f): The product was obtained according to the general procedure as described above in 85% yield as a white solid. $[\alpha]_D^{20}$ = –98.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.44 (d, *J* = 6.83 Hz, 2 H), 7.39–7.31 (m, 3 H), 7.18 (d, *J* = 8.13 Hz, 2 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 4.59 (d, *J* = 8.74 Hz, 1 H), 4.13 (d, *J* = 6.6 Hz, 1 H), 3.86 (s, 3 H), 3.71 (t, *J* = 7.65 Hz, 1 H), 3.54 (t, *J* = 7.65 Hz, 1 H), 2.32 (s, 3 H), 2.32 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.1, 173.6, 170.0, 138.4, 136.6, 129.5, 128.9, 128.3, 128.2, 127.0, 125.8, 64.1, 61.7, 52.2, 49.3, 48.2, 21.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_2NaO_4$ [M + Na] 387.1315; found 387.1319. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 18.8 min, t_R (major) = 28.1 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(3-Fluorophenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5g): The product was obtained according to the general procedure as described above in 87% yield as white solid. $[\alpha]_D^{20}$ = –81.8 (*c* = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45–7.31 (m, 6 H), 7.03–6.90 (m, 3 H), 4.62 (d, *J* = 8.79 Hz, 1 H), 4.15 (d, *J* = 6.54 Hz, 1 H), 3.87 (s, 3 H), 3.73 (t, *J* = 7.59 Hz, 1 H), 3.57 (t, *J* = 8.49 Hz, 1 H), 2.04 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.7, 173.2, 169.9, 162.6, 136.5, 132.6, 130.1, 130.0, 128.4, 126.9, 121.7, 115.3, 113.5, 64.0, 61.7, 52.2, 49.2, 48.1 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}FN_2NaO_4$ [M + Na] 391.1065; found 391.1065. Enantiomeric excess: 85%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 17.7 min, t_R (major) = 31.3 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(2-Fluorophenyl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5h): The product was obtained according to the general procedure as described above in 73% yield as a white solid. $[\alpha]_D^{20}$ = –87.6 (*c* = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48–7.46 (m, 2 H), 7.39–7.28 (m, 4 H), 7.19–7.07 (m, 3 H), 4.62 (d, *J* = 8.67 Hz, 1 H), 4.16 (d, *J* = 6.78 Hz, 1 H), 3.86 (s, 3 H), 3.79 (t, *J* = 7.38 Hz, 1 H), 3.63 (t, *J* = 8.37 Hz, 1 H), 2.34 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.2, 172.8, 169.9, 158.7, 136.6, 130.9, 129.1, 128.3, 127.0, 124.5, 119.4, 119.3, 116.5, 63.8, 61.6, 52.2, 49.5, 48.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}FN_2NaO_4$ [M + Na] 391.1065; found 391.1067. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 24.0 min, t_R (major) = 42.0 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 4,6-Dioxo-3-phenyl-5-(*o*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5i): The product was obtained according to the general procedure as described above in 82% yield as a white solid. $[\alpha]_D^{20}$ = –65.6 (*c* = 0.7, $CHCl_3$). For the major axial isomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48–7.43 (m, 2 H), 7.39–7.23 (m, 6 H), 7.01–6.90 (m, 1 H), 4.62 (d, *J* = 8.13 Hz, 1 H), 4.18 (d, *J* = 7.38 Hz, 1 H), 3.85 (s, 3 H), 3.78 (t, *J* = 7.44 Hz, 1 H), 3.64 (t, *J* = 8.16 Hz, 1 H), 2.30 (br. s, 1 H, NH), 2.22 (s, 3 H) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_2NaO_4$ [M + Na] 387.1315; found 387.1329. Enantiomeric excess: 82%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 15.5 min, t_R (major) = 24.4 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-(Naphthalen-1-yl)-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5j): The product was obtained according to the general procedure as described above in 66% yield as a white solid. $[\alpha]_D^{20}$ = –70.2 (*c* = 0.6, $CHCl_3$). For the major axial isomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.89–7.86 (m, 2 H), 7.49–7.18 (m, 10 H), 4.56 (d, *J* = 7.58 Hz, 1 H), 4.15 (d, *J* = 7.69 Hz, 1 H), 3.84 (s, 3 H), 3.74 (t, *J* = 7.56 Hz, 1 H), 3.63 (t, *J* = 7.99 Hz, 1 H), 2.05 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.3, 173.9, 170.0, 136.1, 134.3, 129.9, 128.5, 128.3, 128.2, 128.1, 127.1, 127.0, 126.9, 126.5, 125.7, 125.0, 122.8, 64.2, 62.1, 52.2, 49.5, 48.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{20}N_2NaO_4$ [M + Na] 423.1315; found 423.1310. Enantiomeric excess: 88%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 19.9 min, t_R (major) = 32.9 min.

(1*R*,3*S*,3a*R*,6a*S*)-Methyl 5-Methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (5k): This is a known compound.[4i] The product was obtained according to the general procedure as described above in 75% yield as a white solid. $[\alpha]_D^{20}$ = –41.8 (*c* = 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33 (m, 5 H), 4.48 (d, *J* = 8.58 Hz, 1 H), 4.06 (d, *J* = 6.78 Hz, 1 H), 3.87 (s, 3 H), 3.55 (t, *J* = 7.41 Hz, 1 H), 3.42 (t, *J* = 8.28 Hz, 1 H), 2.86 (s, 3 H), 2.05 (br. s, 1 H, NH) ppm. Enantiomeric excess: 30%, determined by HPLC (Chiralpak AS-H column; hexane/2-propanol = 50:50; 0.6 mL/min; 230 nm), t_R (minor) = 16.4 min, t_R (major) = 27.2 min.

Supporting Information (see footnote on the first page of this article): Experimental procedures, NMR spectra, and HPLC data for complexes **4a**–**n** and **5a**–**k**.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (NSFC) (grant numbers 20802075 and 21042006) and the Chinese Academy of Sciences.

[1] a) A. Bianco, M. Maggini, G. Scorrano, C. Toniolo, G. Marconi, C. Villani, M. Prato, *J. Am. Chem. Soc.* **1996**, *118*, 4072–4080; b) C. Alvarez-Ibarra, A. G. Csaky, G. A. Lopez de Silanes, M. L. Quiroga, *J. Org. Chem.* **1997**, *62*, 479–484; c) W. H. Pearson, *Pure Appl. Chem.* **2002**, *74*, 1339–1347; d) F. X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; e) W. H. Pearson, P. Stoy, *Synlett* **2003**, 903–921; f) Y. Cheng, Z. T. Huang, M. X. Wang, *Curr. Org. Chem.* **2004**, *8*, 325–351; g) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580–591; h) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 603–626.

[2] For recent reviews, see: a) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825–1872; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; d) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247–12275.

[3] For recent reviews, see: a) L. M. Harwood, R. J. Vickers, *In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds: A. Padwa, W. Pearson), John Wiley & Sons, New York, **2002**; b) C. Nájera, J. M. Sansano, *Topics Heterocyclic Chem.* (Ed.: A. Hassner) **2008**, *12*, pp. 117–146; c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902; d) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198; e) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132–3148.

[4] For selected examples, see: a) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata, M. Komatsu, *Org. Lett.* **2003**, *5*, 5043–5046; b) S. Cabrera, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394–16395; c) T. Llamas, R. G. Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 1795–1798; d) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y. D. Wu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1979–1983; e) S. Cabrera, R. G. Arrayás, B. Martín-Matute, F. P. Cossío, J. C. Carretero, *Tetrahedron* **2007**, *63*, 6587–6602; f) S. I. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747–1750; g) A. López-Pérez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085; h) J. Hernández-Toribio, R. G. Arrayás, B. Martin-Matute, J. C. Carretero, *Org. Lett.* **2009**, *11*, 393–396; i) C.-J. Wang, Z.-Y. Xue, G. Liang, Z. Lu, *Chem. Commun.* **2009**, 2905–2907; j) C.-J. Wang, G. Liang, Z.-Y. Xue, F. Gao, *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251; k) P. Silvia, T. Rubn, A. Javier, J. C. Carretero, *Org. Lett.* **2010**, *12*, 5608–5611.

[5] For selected examples, see: a) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401; b) C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175; c) T. F. Knopfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971–5973; d) W. Zeng, Y.-G. Zhou, *Org. Lett.* **2005**, *7*, 5055–5058; e) C. Alemparte, G. Blay, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 4569–4572; f) C. Nájera, M. D. G. Retamosa, J. M. Sansano, *Org. Lett.* **2007**, *9*, 4025–4028; g) W. Zeng, G.-Y. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750–751; h) C. Nájera, M. D. G. Retamosa, J. Sansano, *Angew. Chem. Int. Ed.* **2008**, *47*, 6055–6058; i) Z.-Y. Xue, T.-L. Liu, Z. Lu, H. Huang, H. Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 1727–1729.

[6] J.-W. Shi, M. X. Zhao, Z.-Y. Lei, M. Shi, *J. Org. Chem.* **2008**, *73*, 305–308.

[7] a) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236–4238; b) O. Dogan, H. Koyuncu, P. Garner, A. Bulut, W. J. Youngs, M. Panzner, *Org. Lett.* **2006**, *8*, 4687–4690.

[8] T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332.

[9] M. Martín-Rodríguez, C. Nájera, J. M. Sansano, F.-L. Wu, *Tetrahedron: Asymmetry* **2010**, *21*, 1184–1186.

[10] For selected examples, see: a) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168–5170; b) I. Ibrahem, R. Rios, J. Vesely, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 6252–6257; c) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653; d) C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417; e) Y.-H. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873–9877; f) A. Kumar, G. Gupta, S. Srivastava, *J. Comb. Chem.* **2010**, *12*, 458–462; g) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691–694; h) M. Nakano, M. Terada, *Synlett* **2009**, 1670–1674; i) W. Du, Y.-K. Liu, L. Yue, Y.-C. Chen, *Synlett* **2008**, 997–3000; j) J.-W. Xie, K. Yoshida, K. Takasu, Y. Takemoto, *Tetrahedron Lett.* **2008**, *49*, 6910–6913; k) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2007**, *46*, 7667–7670.

[11] For selected biological studies on enantioenriched-substituted succinimides, see: a) S. Ahmed, *Drug Des. Discovery* **1996**, *14*, 77–89; b) M. L. Curtin, R. B. Garland, H. R. Heyman, R. R. Frey, M. R. Michaelidies, J. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, S. K. Davidsen, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919–2923; for synthetic applications of this useful scaffold, see: c) A. R. Katritzky, J. Yao, M. Qi, Y. Chou, D. J. Sikora, S. Davis, *Heterocycles* **1998**, *48*, 2677–2691; d) R. Ballini, G. Bosica, G. Cioci, D. Fiorini, M. Petrini, *Tetrahedron* **2003**, *59*, 3603–3608.

[12] For reviews concerning bifunctional-thiourea organocatalysis, see: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427.

[13] a) J.-F. Bai, L. Peng, L.-L. Wang, X.-Y. Xu, L.-X. Wang, *Tetrahedron* **2010**, *66*, 8928–8932; b) L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2010**, *46*, 8064–8066; c) L. Peng, X.-Y. Xu, L.-L. Wang, J. Huang, J.-F. Bai, Q.-C. Huang, L.-X. Wang, *Eur. J. Org. Chem.* **2010**, 1849–1853; d) J.-F. Bai, X.-Y. Xu, Q.-C. Huang, L. Peng, L.-X. Wang, *Tetrahedron Lett.* **2010**, *51*, 2803–2805.

[14] Tertiary amine-thiourea catalysts **1c**–**f** were prepared in a similar procedure to that of **1d**, see: L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248–12249.

[15] The stereochemical assignment of the endo/exo adducts was established by NOE studies (for details see the Supporting Information).

[16] a) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata, M. Komatsu, *Org. Lett.* **2003**, *5*, 5043–5046; b) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; c) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; d) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931; e) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

Received: February 15, 2011
Published Online: June 1, 2011

