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Asymmetric Michael Addition of α-Substituted Isocyanoacetates with Maleimides Catalyzed by Chiral Tertiary Amine Thiourea

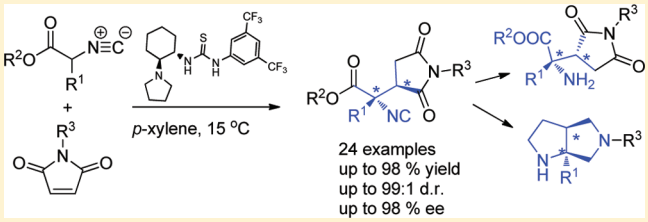
Jian-Fei Bai,[†,‡] Liang-Liang Wang,[†,‡] Lin Peng,[†] Yun-Long Guo,[†,‡] Li-Na Jia,[†,‡] Fang Tian,[†] Guang-Yun He,[†] Xiao-Ying Xu,*[,†] and Li-Xin Wang*[,†]

[†]Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

[‡]Graduate School of Chinese Academy of Sciences, Beijing, China

Supporting Information

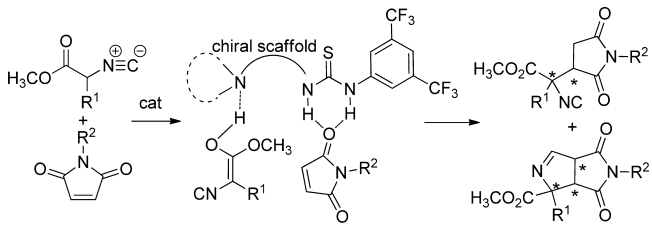
ABSTRACT: A highly diastereoselective and enantioselective Michael addition of α-substituted isocyanoacetates with maleimides catalyzed by bifunctional tertiary amine thioureas has been developed. Various chiral succinimide derivatives bearing adjacent quaternary and tertiary stereocenters were prepared in excellent yields (up to 98%), diastereoselectivities (up to 99:1), and enantioselectivities (up to 98% ee). The synthetic utility of chiral succinimide derivatives is also demonstrated in the preparation of h5-HT_{1d} receptor agonist motifs.



The enantioselective construction of adjacent quaternary and tertiary stereocenters is one of the most demanding key steps in the stereocontrolled synthesis of complex natural compounds and pharmaceuticals.[1] To date, numerous strategies have been developed.[2] A generally applied and feasible way is the conjugate addition of a prochiral trisubstituted nucleophile with α,β-substituted acceptor. Among them, α-substituted isocyanoacetate participated conjugate addition has shown a promising strategy. Isocyanoacetate derivatives are versatile and useful building blocks for the synthesis of nitrogen-containing compounds such as branched amino acids and various peptides.[3] Therefore, the development of effective catalytic systems for the asymmetric addition of α-substituted isocyanoacetate to construct adjacent quaternary and tertiary stereocenters is needed. Up to now, isocyanoacetates react with many acceptors, such as aldehydes, imines, nitroalkenes, azodicarboxylates, and α,β-unsaturated carbonyl compounds, and afford cyclic compounds in most reported cases.[4] To the best of our knowledge, the use of maleimide as an acceptor has not been reported.[5] Interestingly, both Michael addition and [3 + 2] cycloaddition reactions are possible in the reaction of isocyanoacetates and maleimides. Both reactions are straightforward methods to synthesize chiral substituted succinimides, valuable structural motifs in molecules with interesting biological activities such as branched chiral amino acids and natural products.[6] Therefore, it is highly desirable to develop catalytic asymmetric protocols using isocyanoacetates and maleimides.

Over the past years, bifunctional thiourea catalysts, powerful tools to simultaneously activate both donors and acceptors to induce high enantioselectivity and diastereoselectivity, have been investigated extensively in asymmetric catalysis.[7] On the basis of the concept of bifunctional catalysis, we envisioned that the addition of α-isocyanoacetates to maleimides may be realized in the presence of chiral tertiary amine thiourea catalysts. α-Isocyanoacetates with two electron-withdrawing substituents at the α-position (an isocyanide group and a carboxylic group) can be easily deprotonated by tertiary amine, and the maleimide may be activated by the thiourea moiety through double H-bondings (Scheme 1). Thus the synergistic

Scheme 1. Proposed Organocatalytic Reaction of α-Substituted Isocyanoacetate and Maleimides



interactions of bifunctional catalysis would ensure high stereoselectivity in the Michael addition or the [3 + 2] cycloaddition. As a part of our continuing interest in asymmetric synthesis,[8] herein we wish to report the first asymmetric Michael addition of α-substituted isocyanoacetates to maleimides catalyzed by chiral tertiary amine thioureas. Noteworthy is that the reaction affords multifunctionalized succinimides bearing both a quaternary and a tertiary

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Scheme 2. Evaluated Bifunctional Catalysts 4a−4i

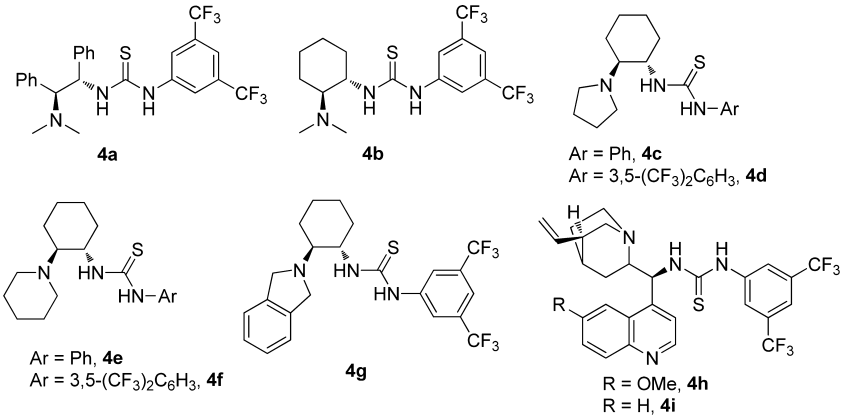
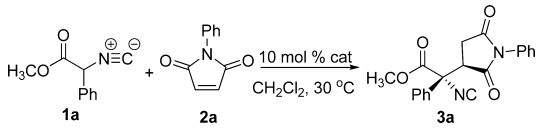


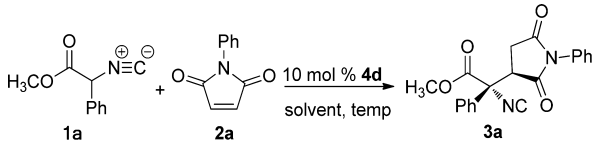
Table 1. Catalyst Screening[a]



entry	catalyst	time (h)	yield[b] (%)	d.r.[c]	ee[d] (%)
1	**4a**	54	55	99:1	25
2	**4b**	10	64	99:1	65
3	**4c**	10	78	99:1	58
4	**4d**	10	79	99:1	82
5	**4e**	10	73	99:1	45
6	**4f**	10	80	99:1	66
7	**4g**	72	trace	n.d.	n.d.
8	**4h**	20	65	99:1	70
9	**4i**	20	48	99:1	57

[a]Unless noted, all reactions were carried out with **1a** (17.5 mg, 0.10 mmol), **2a** (17.3 mg, 0.10 mmol), and **4** (10 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC and ^{1}H NMR. [d]Enantiomeric excesses were determined by chiral HPLC analysis.

Table 2. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	30	17	79	82
2	$CHCl_3$	30	17	78	76
3	$ClCH_2CH_2Cl$	30	17	76	71
4	toluene	30	17	76	78
5	*p*-xylene	30	17	84	84
6	*m*-xylene	30	17	87	80
7	mesitylene	30	17	84	81
8	chlorobenzene	30	17	83	84
9	*p*-xylene	26	18	88	92
10	*p*-xylene	15	20	93	94
11	chlorobenzene	26	18	88	86
12	chlorobenzene	0	20	89	89
13	chlorobenzene	−10	24	88	91
14	chlorobenzene	−20	60	87	93
15	chlorobenzene	−30	72	81	92

[a]Unless noted, all reactions were carried out with **1a** (17.5 mg, 0.10 mmol), **2a** (17.3 mg, 0.10 mmol), and **4d** (10 mol %) in 0.5 mL of anhydrous solvent. [b]Isolated yield. Generally, 99:1 d.r. was observed. [c]Enantiomeric excesses were determined by chiral HPLC analysis.

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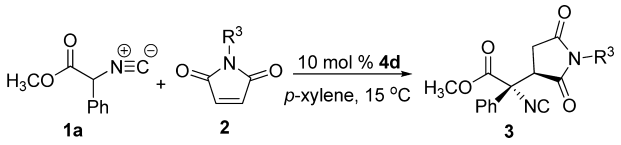
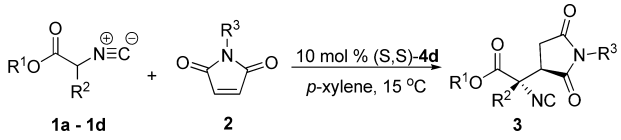
Table 3. Scope of *N*-Substituted Maleimides[a]



entry	R^3	product	yield[b] (%)	d.r.[c]	ee[d,e] (%)
1	Ph	**3a**	93	99:1	94
2	4-F-C_6H_4	**3b**	98	99:1	91
3	4-Cl-C_6H_4	**3c**	93	99:1	92
4	4-Br-C_6H_4	**3d**	95	99:1	90
5	4-NO_2-C_6H_4	**3e**	98	99:1	90
6	4-CH_3-C_6H_4	**3f**	98	97:3	90
7	4-CH_3O-C_6H_4	**3g**	97	99:1	90
8	3-F-C_6H_4	**3h**	96	98:2	98
9	3-OH-C_6H_4	**3i**	91	80:20	96
10[f]	CH_3	**3j**	74	85:15	60
11[f]	Bn	**3k**	95	85:15	85
12[f]	cyclohexyl-	**3l**	63	95:5	74
13[f]	allyl-	**3m**	95	90:10	61

[a]Unless noted, all reactions were carried out with **1a** (0.20 mmol), **2** (0.2 mmol), and **4d** (10 mol %) in 1.0 mL of *p*-xylene at 15 °C for 18 h. [b]Isolated yield. [c]Determined by chiral HPLC and ^{1}H NMR. [d]Enantiomeric excesses were determined by chiral HPLC analysis. [e]The absolute configuration was determined by single crystal X-ray analysis of **3q**. [f]The reaction time was 30 h.

Table 4. Scope of Isocyanoacetates[a]



1a: $R^1 = CH_3$, R^2 = Ph; **1b**: $R^1 = CH_3$, R^2 = Bn;
1c: $R^1 = CH_3$, $R^2 = CH_3$; **1d**: $R^1 = C_2H_5$, R^2 = Ph;

entry	1	R^3	3	time (h)	yield[b] (%)	d.r.[c]	ee[d] (%)
1	**1a**	Ph	**3a**	18	93	99:1	94
2[e]	**1b**	Ph	**3n**	72	71	55:45	58/10[f]
3[e]	**1c**	Ph	**3o**	72	65	55:45	54/16[f]
4	**1d**	Ph	**3p**	18	98	99:1	92
5	**1d**	4-Br-C_6H_4	**3q**	18	92	93:7	86
6	**1d**	CH_3	**3r**	30	76	75:25	72
7	**1d**	Bn	**3s**	30	79	70:30	77
8[g]	**1d**	4-Br-C_6H_4	**3t**	18	94	96:4	−90

[a]Unless noted, all reactions were carried out with **1** (0.20 mmol), **2** (0.20 mmol), and **4d** (10 mol %) in 1.0 mL of *p*-xylene at 15 °C for 18 h. [b]Isolated yield. [c]Determined by chiral HPLC and ^{1}HNMR. [d]Enantiomeric excesses were determined by chiral HPLC analysis. [e]20 mol % of catalyst was used. [f]ee of minor diastereomer. [g]In this case, catalyst (*R*,*R*)-**4d** was used.

stereocenter that can be easily transformed to chiral bicyclic aza compounds.

To validate our hypothesis, we selected the reaction between α-phenylisocyano acetate (**1a**) and *N*-phenylmaleimide (**2a**) in the presence of various tertiary amine-thioureas **4a**−**4i** (Scheme 2).

As shown in Table 1, catalyst **4b** with a chiral cyclohexane-1,2-diamine skeleton gave better yield and enantioselectivity than catalyst **4a** with chiral 1,2-diphenylethylene-diamine skeleton (Table 1, entry 1 vs 2). So other thiourea catalysts derived from **4b** skeleton were then synthesized and evaluated (Table 1, entries 3−7). The effect of substituents on nitrogen atoms of the catalyst was examined first. Higher enantioselectivities were observed for the cyclic substituted amines **4c**−**4f** except benzocyclic substituted **4g** (Table 1, entries 2 vs 4, 6, 7). A pyrrolidine substituted catalyst **4d** gave **3a** in 82% ee, and the corresponding piperidine substituted catalyst **4f** gave 66% ee (Table 1, entries 4 and 6). Catalyst **4g** did not give the desired adduct (Table 1, entry 7). The substitution on the thiourea moiety was also studied. A bis(trifluoromethyl)phenyl group afforded better enantioselectivity (Table 1, entries 3 vs 4, 5 vs 6), possibly because of the acidity of the N−H in the thiourea group. The use of cinchona alkaloid derived thioureas **4h** and **4i** did not provide better results in catalytic activity and enantioselectivity (Table 1, entries 8 and 9). Thus, catalyst **4d** was chosen for further optimization of solvents and reaction temperature (Table 2).

Most commonly used solvents are compatible with our asymmetric conditions and afforded good yields (65−87%) with excellent diastereoselectivities (up to 99:1) and varied enantioselectivities (Table 2, entries 1−8). When the reaction was carried out in chlorinated solvents, product **3a** was isolated in almost unchanged yields and slightly decreased enantioselectivities (Table 2, entries 1−3). Aromatic hydrocarbon

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solvents afforded good yields and enantioselectivities (76−87% yields; 78−84% ee; Table 2, entries 4−8). *p*-Xylene and chlorobenzene gave almost same results and were chosen as candidate solvents for further screening of temperature. At a lower temperature (15 °C), *p*-xylene gave the best result (93% yield and 94% ee; Table 2, entry 10) and was chosen as a suitable reaction media. On the basis of the above screening, the optimal reaction conditions, 1.0 equiv of **1a** and 1.0 equiv of **2a** in *p*-xylene with 10 mol % catalyst **4d** at 15 °C, were established.

To broaden the substrate scope, a variety of *N*-substituted maleimides were further examined, and the results were shown in Table 3, Generally, most substrates provided excellent yields and high stereoselectivities. The substitution position on the maleimides had a minor influence on the enantioselectivity. Either electron-withdrawing or electron-donating groups at *para*- or *meta*-positions afforded the desired products with excellent yields (up to 98%), diastereoselectivities (up to 99:1), and enantioselectivities (up to 98% ee) (Table 3, entries 1−9). Less reactive *N*-alkyl substitued maleimides gave moderate to good diasteroselectivites and enantioselectivities (Table 3, entries 10−13).

The substrate scope of various α-substituted isocyanoacetates was also evaluated (Table 4). It was found that the α-substituted group of isocyanoacetate was critical. When R^2 was changed from phenyl to benzyl or methyl, only moderate yields, diastereoselectivities, and enantioselectivities were obtained (Table 4, entries 2 and 3). Variation on the ester moiety was then considered. Ethyl isocyanoacetate **1d** reacted well with *N*-arylmaleimides and gave excellent results (Table 4, entries 4 and 5), whereas *N*-alkyl substituted maleimides gave only moderate yields, disastereoselectivities, and enantioselectivities (Table 4, entries 6 and 7). When the catalyst was changed from (*S*,*S*)-**4d** to (*R*,*R*)-**4d**, the corresponding (*S*,*S*)-enantiomer of **3q** was obtained with a comparable yield and selectivity (Table 4, entry 8).

To determine the absolute configuration of the products, X-ray analysis was performed on a single crystal of compound **3q**. The absolute configuration was assigned as (6*R*,7*R*).[9] On the basis of the above results and commonly accepted mechanism, we proposed a plausible transition state model as shown in Figure 1. α-Phenylisocyanoacetate (**1a**) and *N*-phenylmaleimide (**2a**) would be activated by tertiary amine and thiourea simultaneously, enolized isocyanoester attacked maleimide

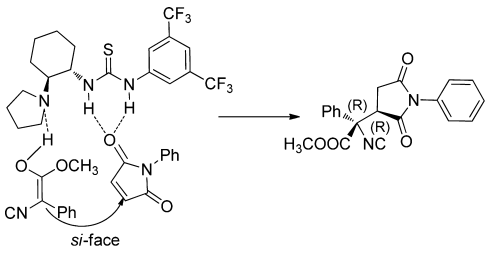
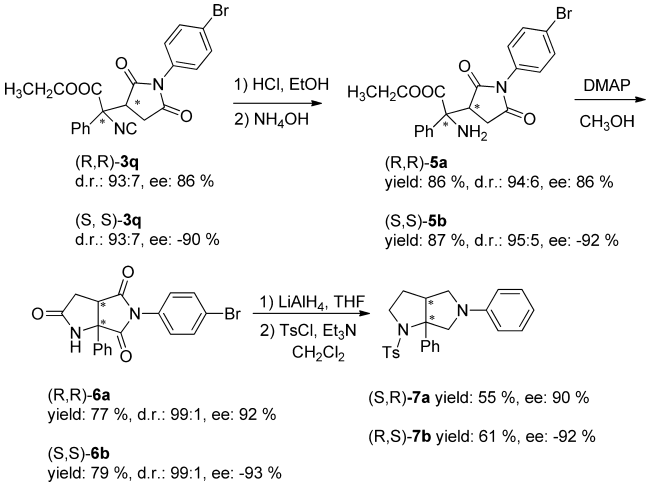


Figure 1. Proposed transition state model.

from *si*-face and the corresponding product with (*R*,*R*)-configuration was obtained.[10]

Michael adducts **3** are valuable building blocks for asymmetric synthesis, especially for the synthesis of chiral unnatural α-amino acids with a quaternary stereocenter as well as nitrogen-containing bicyclic compounds. As shown in Scheme 3, two enantiomers of compound **3q** were readily transformed to the corresponding α-amino acid derivatives **5a** and **5b** with concentrated HCl in EtOH in good yields (86 and

Scheme 3. Synthetic Utility of Adducts 3



87%).[11] Ring-opening reaction with DMAP/CH_3OH followed by cyclization led to chiral bicyclic γ-lactam derivative **6a** and **6b** in 77 and 79% yield.[12] After reduction with $LiAlH_4$ and protection using TsCl, octahydropyrrolo[3,4-b]pyrroles **7a** and **7b**, the basic unit of h5-HT_{1d} receptor agonists, were isolated in 55−61% yields and 90−92% ee.[9,13]

In conclusion, we have developed a highly diastereoselective and enantioselective Michael addition of α-substituted isocyanoacetate to maleimides catalyzed by a chiral tertiary amine thiourea. The construction of adjacent quaternary and tertiary stereocenters was possible in excellent yields (up to 98%), diastereoselectivities (up to 99:1), and enantioselectivities (up to 98% ee). After simple synthetic transformations, chiral octahydropyrrolo[3,4-b]pyrroles were successfully prepared. Further application of this reaction to other substrates and to the preparation of biologically relevant compounds are currently underway.

EXPERIMENTAL SECTION

General Procedure for Asymmetric Michael Addition of α-Substituted Isocyanoacetate and Maleimides. A mixture of α-substituted isocyanoacetate (0.20 mmol), *N*-arylmaleimides (0.20 mmol), and catalyst **4d** (0.02 mmol) was stirred in *p*-xylene (1.0 mL) at 15 °C for 18 h (monitored by TLC). After evaporation under the reduced pressure, the residue was purified through column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 3/1) to yield pure products.

*(R)-Methyl 2-((R)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3a**).* Yield 93%; white solid: $[\alpha]^{20}_D$ = −52.0 (*c* 0.56, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64−7.61 (m, 2H), 7.48−7.41 (m, 6H), 7.29 (d, *J* = 6.93 Hz, 2H), 4.41 (dd, *J* = 6.0 Hz, 9.41 Hz, 1H), 3.85 (s, 3H), 2.78 (dd, *J* = 9.45 Hz, 18.57 Hz, 1H), 2.49 (dd, *J* = 5.97 Hz, 18.57 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 172.9, 166.5, 164.5, 131.9, 131.2, 129.9, 129.5, 129.2, 129.0, 126.5, 125.4, 71.1, 54.4, 48.3, 30.6; HRMS (ESI) for $C_{20}H_{16}N_2NaO_4$ $[M + Na]^+$ calcd 371.1002, found 371.0992; IR (KBr) ν = 3480, 2135, 1783, 1750, 1716, 1267, 1041 cm^{-1}. Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 16.37 min, t_R (major) = 26.42 min.

*(R)-Methyl 2-((R)-1-(4-Fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3b**).* Yield 98%; white solid: $[\alpha]^{20}_D$ = −43.9 (*c* 0.58, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.62 (m, 2H), 7.49−7.47 (dd, *J* = 2.78 Hz, 5.0 Hz, 3H), 7.32−7.26 (m,

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2H), 7.19−7.13 (m, 2H), 4.43 (dd, J = 5.93 Hz, 9.42 Hz, 1H), 3.87 (s, 3H), 2.80 (dd, J = 9.45 Hz, 18.64 Hz, 1H), 2.51 (dd, J = 5.92 Hz, 18.62 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 172.9, 166.5, 164.5, 162.5 (J_{C-F} = 247.8 Hz), 131.8, 130.0, 129.3, 128.4, 127.0, 125.4, 116.4 (J_{C-F} = 23.0 Hz), 71.1, 54.4, 48.2, 30.6; HRMS (ESI) for $C_{20}H_{15}FN_2NaO_4$ $[M + Na]^+$ calcd 389.0908, found 389.0897; IR (KBr) ν = 3487, 2134, 1787, 1754, 1720, 1246, 1068 cm^{-1}. Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 17.45 min, t_R (major) = 24.82 min.

*(R)-Methyl 2-((R)-1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3c**).* Yield 93%; white solid: $[\alpha]^{20}_D$ = −55.0 (c 0.64, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, J = 2.37 Hz, 7.67 Hz, 2H), 7.49−7.43 (m, 5H), 7.28−7.25 (m, 2H), 4.43 (dd, J = 6.0 Hz, 9.42 Hz, 1H), 3.87 (s, 3H), 2.79 (dd, J = 9.45 Hz, 18.63 Hz, 1H), 2.50 (dd, J = 5.97 Hz, 18.63 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 172.6, 166.5, 164.5, 134.9, 131.8, 130.0, 129.6, 129.5, 129.4, 127.7, 125.3, 71.0, 54.5, 48.2, 30.6; HRMS (ESI) for $C_{20}H_{15}ClN_2NaO_4$ $[M + Na]^+$ calcd 405.0613, found 405.0603; IR (KBr) ν = 3473, 2132, 1744, 1715, 1210, 1018 cm^{-1}. Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 19.19 min, t_R (major) = 26.66 min.

*(R)-Methyl 2-((R)-1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3d**).* Yield 95%; white solid: $[\alpha]^{20}_D$ = −49 (c 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64−7.58 (m, 4H), 7.52−7.47 (m, 3H), 7.26−7.19 (m, 2H), 4.43 (dd, J = 6.05 Hz, 9.38 Hz, 1H), 3.87 (s, 3H), 2.79 (dd, J = 9.44 Hz, 18.62 Hz, 1H), 2.51 (dd, J = 5.95 Hz, 18.61 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 172.6, 166.4, 164.5, 132.4, 131.8, 130.1, 130.0, 129.5, 128.0, 125.3, 122.9, 71.1, 54.5, 48.3, 30.6; HRMS (ESI) for $C_{20}H_{15}BrN_2NaO_4$ $[M + Na]^+$ calcd 449.0107, found 449.0091; IR (KBr) ν = 3473, 2132, 1744, 1715, 1210, 1016 cm^{-1}. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 19.59 min, t_R (major) = 26.16 min.

*(R)-Methyl 2-Isocyano-2-((R)-1-(4-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**3e**).* Yield 98%; white solid: $[\alpha]^{20}_D$ = −54.3 (c 0.60, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (d, J = 8.79 Hz, 2H), 7.61−7.43 (m, 7H), 4.48 (dd, J = 6.21 Hz, 9.12 Hz, 1H), 3.89 (s, 3H), 2.85 (dd, J = 9.51 Hz, 18.74 Hz, 1H), 2.56 (dd, J = 6.0 Hz, 18.78 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 172.0, 166.3, 164.7, 147.3, 136.6, 131.6, 130.1, 129.4, 127.1, 126.8, 125.3, 71.0, 54.6, 48.4, 30.7; HRMS (ESI) for $C_{20}H_{15}N_3NaO_6$ $[M + Na]^+$ calcd 416.0859, found 416.0864; IR (KBr) ν = 3433, 2133, 1751, 1723, 1526, 1384, 1247, 1088 cm^{-1}. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AS-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 26.23 min, t_R (major) = 40.84 min.

*(R)-Methyl 2-((R)-2,5-Dioxo-1-(p-tolyl)pyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3f**).* Yield 98%; white solid: $[\alpha]^{20}_D$ = −47.9 (c 0.48, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.62 (m, 2H), 7.50−7.46 (m, 3H), 7.27 (d, J = 8.54 Hz, 2H), 7.18 (d, J = 8.33 Hz, 2H), 4.41 (dd, J = 5.93 Hz, 9.36 Hz, 1H), 3.86 (s, 3H), 2.78 (dd, J = 9.43 Hz, 18.56 Hz, 1H), 2.50 (dd, J = 5.96 Hz, 18.56 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 173.2, 166.5, 164.4, 139.2, 131.9, 129.9, 129.4, 128.5, 126.2, 125.4, 71.1, 54.4, 48.2, 30.6, 21.2; HRMS (ESI) for $C_{21}H_{19}N_2O_4$ $[M + H]^+$ calcd 363.1339, found 363.1333; IR (KBr) ν = 3485, 2134, 1785, 1754, 1715, 1247, 1040 cm^{-1}. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 14.60 min, t_R (major) = 25.80 min.

*(R)-Methyl 2-Isocyano-2-((R)-1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**3g**).* Yield 97%; white solid: $[\alpha]^{20}_D$ = −50.7 (c 0.66, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.64 (m, 2H), 7.48−7.46 (m, 3H), 7.21 (dd, J = 2.11 Hz, 6.85 Hz, 2H), 6.97 (dd, J = 2.16 Hz, 6.85 Hz, 2H), 4.41 (dd, J = 5.90 Hz, 9.39 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.78 (dd, J = 9.43 Hz, 18.56 Hz, 1H), 2.49 (dd, J = 5.89 Hz, 18.56 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 173.3, 166.5, 164.3, 159.8, 131.9, 129.9, 129.4, 127.7, 125.4, 123.7, 114.5, 71.1, 55.5, 54.5, 48.2, 30.5; HRMS (ESI) for $C_{21}H_{18}N_2NaO_5$ $[M + Na]^+$ calcd 401.1108, found 401.1094; IR (KBr) ν = 3483, 2134, 1785, 1754, 1715, 1197, 1030 cm^{-1}. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 15.58 min, t_R (major) = 27.79 min.

*(R)-Methyl 2-((R)-1-(3-Fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3h**).* Yield 96%; white solid: $[\alpha]^{20}_D$ = −50.1 (c 0.63, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.62 (m, 2H), 7.49−7.43 (m, 4H), 7.13−7.08 (m, 3H), 4.43 (dd, J = 6.0 Hz, 9.39 Hz, 1H), 3.88 (s, 3H), 2.81 (dd, J = 9.48 Hz, 18.62 Hz, 1H), 2.52 (dd, J = 6.0 Hz, 18.63 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 172.5, 166.5, 164.5, 162.6 (J_{C-F} = 246 Hz), 132.4, 131.8, 130.4 (J_{C-F} = 8.8 Hz), 129.9, 129.5, 125.4, 122.1(3.3), 116.1 (J_{C-F} = 20.7 Hz), 114.1 (J_{C-F} = 24.3 Hz), 71.1, 54.5, 48.2, 30.6; HRMS (ESI) for $C_{20}H_{15}FN_2NaO_4$ $[M + Na]^+$ calcd 389.0908, found 389.0893; IR (KBr) ν = 3482, 2135, 1787, 1748, 1716, 1268, 1042 cm^{-1}. Enantiomeric excess: 98%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 17.71 min, t_R (major) = 21.31 min.

*(R)-Methyl 2-Isocyano-2-((R)-1-methyl-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**3j**).* Yield 74%; colorless oil: $[\alpha]^{20}_D$ = −10.6 (c 0.60, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60−7.56 (m, 2H), 7.49−7.44 (m, 3H), 4.25 (dd, J = 5.97 Hz, 9.07 Hz, 1H), 3.88 (s, 3H), 3.05 (s, 3H), 2.61 (dd, J = 9.18 Hz, 18.39 Hz, 1H), 2.33 (dd, J = 5.97 Hz, 18.39 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 173.9, 166.5, 164.1, 132.0, 129.8, 129.4, 125.3, 70.5, 54.4, 48.3, 30.5, 25.1; HRMS (ESI) for $C_{15}H_{14}N_2NaO_4$ $[M + Na]^+$ calcd 309.0846, found 309.0845; IR (KBr) ν = 3473, 2136, 1781, 1749, 1706, 1258, 1052 cm^{-1}. Enantiomeric excess: 60%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 30/70, 0.4 mL/min, 220 nm), t_R (major) = 13.63 min, t_R (minor) = 14.26 min.

*(R)-Methyl 2-((R)-1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3k**).* Yield 95%; colorless oil: $[\alpha]^{20}_D$ = −9.6 (c 0.52, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (m, 2H), 7.59−7.56 (m, 3H), 7.45−7.43 (m, 2H), 7.39−7.26 (m, 3H), 4.71 (m, 2H), 4.25 (dd, J = 6.24 Hz, 9.14 Hz, 1H), 3.88 (s, 3H), 2.59 (dd, J = 9.06 Hz, 18.38 Hz, 1H), 2.34 (dd, J = 6.15 Hz, 18.38 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 173.5, 164.6, 164.5, 135.1, 132.1, 129.8, 129.4, 128.5, 127.9, 127.0, 125.3, 70.6, 53.8, 48.2, 42.8, 30.5; HRMS (ESI) for $C_{21}H_{18}N_2NaO_4$ $[M + Na]^+$ calcd 385.1159, found 385.1147; IR (KBr) ν = 3473, 2134, 1751, 1709, 1257, 1067 cm^{-1}. Enantiomeric excess: 85%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 14.05 min, t_R (major) = 15.17 min.

*(R)-Methyl 2-((R)-1-Cyclohexyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3l**).* Yield 63%; white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.56 (m, 2H), 7.46−7.35 (m, 3H), 4.18 (dd, J = 5.91 Hz, 9.31 Hz, 1H), 4.01−3.99 (m, 1H), 3.87 (s, 3H), 2.56 (dd, J = 9.42 Hz, 18.44 Hz, 1H), 2.28 (dd, J = 5.85 Hz, 18.45 Hz, 1H), 2.21−2.10 (m, 2H), 1.84−1.80 (m, 2H), 1.66−1.63 (m, 3H), 1.32−1.21 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 174.1, 166.7, 163.9, 132.1, 129.7, 129.3, 125.3, 70.6, 54.4, 52.3, 47.6, 30.3, 28.7, 28.6, 25.7; HRMS (ESI) for $C_{20}H_{22}N_2NaO_4$ $[M + Na]^+$ calcd 377.1472, found 377.1466. Enantiomeric excess: 73%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.5 mL/min, 220 nm), t_R (minor) = 13.92 min, t_R (major) = 14.75 min.

*(R)-Methyl 2-((R)-1-Allyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3m**).* Yield 95%; colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60−7.57 (m, 2H), 7.48−7.43 (m, 3H), 5.82−5.73 (m, 1H), 5.23 (m, 2H), 4.27 (dd, J = 6.12 Hz, 9.24 Hz, 1H), 4.14 (d, J = 5.82 Hz, 2H), 3.86 (s, 3H), 2.62 (dd, J = 9.27 Hz, 18.42 Hz, 1H), 2.34 (dd, J = 6.09 Hz, 18.47 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 166.5, 164.3, 161.5, 132.0, 130.1, 129.9, 129.3, 125.3, 118.8, 70.7, 59.6, 53.8, 41.4, 30.4; HRMS (ESI) for $C_{17}H_{16}N_2NaO_4$ $[M + Na]^+$ calcd 335.1002, found 335.0992; For major isomer, Enantiomeric excess: 61%, determined by HPLC (Chiralpak OD-H column, hexane/2-propanol = 85/15, 1.0 mL/min, 220 nm), t_R (major) = 13.15 min, t_R (minor) = 17.53 min.

*(S)-Methyl 2-((R)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-3-phenylpropanoate (**3n**).* Yield 71%; white solid. For major isomer, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.26 (m, 10H), 3.77 (s, 3H),

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3.72−3.66 (m, 2H), 3.31 (d, J = 6.34 Hz, 1H), 3.11−3.05 (m, 1H), 2.97−2.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 173.0, 167.1, 163.7, 132.8, 131.3, 130.2, 129.8, 129.2, 128.7, 128.4, 126.6, 69.4, 53.9, 42.6, 32.0; HRMS (ESI) for $C_{21}H_{18}N_2NaO_4$ $[M + Na]^+$ calcd 385.1159, found 385.1144. Enantiomeric excess: 58%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 85/15, 1.0 mL/min, 220 nm), t_R (major) = 19.75 min, t_R (minor) = 35.20 min.

*(S)-Methyl 2-((R)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanopropanoate (**3o**).* Yield 65%; colorless oil: For major isomer, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.42 (m, 3H), 7.29−7.28 (m, 2H), 3.90 (s, 3H), 3.63−3.60 (m, 1H), 3.12−3.06 (m, 1H), 2.92−2.86 (m, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 173.0, 167.9, 162.2, 131.2, 129.2, 129.0, 126.5, 63.9, 54.2, 47.3, 31.8, 25.2; HRMS (ESI) for $C_{15}H_{14}N_2NaO_4$ $[M + Na]^+$ calcd 309.0846, found 309.0841. Enantiomeric excess: 54%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.5 mL/min, 220 nm), t_R (major) = 11.88 min, t_R (minor) = 15.06 min.

*(R)-Ethyl 2-((R)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3p**).* Yield 98%; white solid: $[\alpha]^{20}_D$ = −45.5 (c 0.58, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66−7.63 (m, 2H), 7.50−7.39 (m, 6H), 7.32−7.26 (m, 2H), 4.45 (dd, J = 6.0 Hz, 9.35 Hz, 1H), 4.37−4.25 (m, 2H), 2.79 (dd, J = 9.44 Hz, 18.54 Hz, 1H), 2.51 (dd, J = 5.92 Hz, 18.58 Hz, 1H), 1.29 (t, J = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 173.0, 165.9, 164.2, 132.1, 131.2, 129.8, 129.4, 129.2, 129.0, 126.5, 125.4, 71.1, 64.0, 48.1, 30.7, 13.7; HRMS (ESI) for $C_{21}H_{19}N_2O_4$ $[M + H]^+$ calcd 363.1339, found 363.1329; IR (KBr) ν =3481, 2135, 1784, 1747, 1716, 1256, 1041 cm^{-1}. Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 17.64 min, t_R (major) = 24.20 min.

*(R)-Ethyl 2-((R)-1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3q**).* Yield 92%; white solid: $[\alpha]^{20}_D$ = −45.6 (c 0.63, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64−7.55 (m, 4H), 7.55−7.46 (m, 3H), 7.25−7.19 (m, 2H), 4.45 (dd, J = 5.99 Hz, 9.42 Hz, 1H), 4.38−4.25 (m, 2H), 2.79 (dd, J = 9.45 Hz, 18.63 Hz, 1H), 2.50 (dd, J = 5.96 Hz, 18.60 Hz, 1H), 1.31 (t, J = 7.11 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 172.6, 165.8, 164.2, 132.4, 131.9, 130.1, 129.8, 129.4, 128.0, 125.3, 122.9, 71.1, 64.0, 48.1, 30.6, 13.7; HRMS (ESI) for $C_{21}H_{17}BrN_2NaO_4$ $[M + Na]^+$ calcd 463.0264, found 463.0260; IR (KBr) ν = 3475, 2139, 1783, 1741, 1716, 1247, 1024 cm^{-1}. Enantiomeric excess: 86%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 22.56 min, t_R (major) = 24.01 min.

*(R)-Ethyl 2-Isocyano-2-((R)-1-methyl-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**3r**).* Yield 76%; colorless oil: $[\alpha]^{20}_D$ = −4.8 (c 0.70, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.53 (m, 2H), 7.48−7.42 (m, 3H), 4.39−4.23 (m, 3H), 2.60 (dd, J = 9.21 Hz, 18.38 Hz, 1H), 2.31 (dd, J = 6.0 Hz, 18.36 Hz, 1H), 1.31 (t, J = 7.14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 174.0, 165.9, 163.8, 132.1, 129.7, 129.3, 125.3, 70.8, 64.0, 48.2, 30.5, 25.1, 13.7; HRMS (ESI) for $C_{16}H_{16}N_2NaO_4$ $[M + Na]^+$ calcd 323.1002, found 323.1018; IR (KBr) ν = 3474, 2135, 1783, 1748, 1704, 1286, 1056 cm^{-1}. Enantiomeric excess: 72%, determined by HPLC (Chiralpak AS-H column, hexane/2-propanol = 80/20, 1.0 mL/min, 220 nm), t_R (minor) = 9.62 min, t_R (major) = 13.11 min.

*(R)-Ethyl 2-((R)-1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**3s**).* Yield 79%; colorless oil: $[\alpha]^{20}_D$ = −5.0 (c 0.79, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56−7.43 (m, 5H), 7.39−7.27 (m, 5H), 4.68 (dd, J = 8.75 Hz, 18.84 Hz, 1H), 4.37−4.25 (m, 2H), 4.37−4.23 (m, 2H), 2.57−2.55 (m, 1H), 2.33 (dd, J = 6.15 Hz, 18.41 Hz, 1H), 1.32 (t, J = 7.13 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 173.6, 165.9, 164.1, 135.1, 134.1, 132.2, 129.7, 129.3, 128.7, 128.3, 128.0, 70.8, 64.0, 48.1, 42.8, 32.2, 13.7; HRMS (ESI) for $C_{22}H_{20}N_2NaO_4$ $[M + Na]^+$ calcd 399.1315, found 399.1322; IR (KBr) ν = 3473, 2134, 1782, 1747, 1712, 1242, 1026 cm^{-1}. Enantiomeric excess: 77%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (major) = 14.89 min, t_R (minor) = 15.50 min.

Synthesis of 5 from 3q. To a solution of **3q** (0.2 mmol) in absolute ethanol (2 mL), a few drops of concentrated hydrochloric acid were added, and the reaction mixture was stirred at room temperature for 5 h. Ethanol was evaporated under reduced pressure; the residue was dissolved in water and brought to pH 9−10 by addition of NH_4OH solution, then extracted with ethyl acetate. Combined ethyl acetate extract was washed with water and brine. After evaporation under the reduced pressure, the residue was purified through column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1) to gave amino ester **5**.

*(R)-Ethyl 2-Amino-2-((R)-1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**5a**).* Yield 86%; white solid: $[\alpha]^{20}_D$ = −29.5 (c 0.52, CH_2Cl_2); ^{1}H NMR ($CHCl_3$, 300 MHz) δ 7.55 (dd, J = 7.61 Hz, 10.70 Hz, 4H), 7.43−7.37 (m, 3H), 7.19 (d, J = 8.47 Hz, 2H), 4.29−4.22 (m, 3H), 2.65 (d, J = 7.60 Hz, 2H), 2.17 (br s, NH, 2H), 1.26 (t, J = 7.11 Hz, 3H); ^{13}C NMR ($CHCl_3$, 75 MHz) δ 176.3, 174.7, 173.4, 139.3, 132.2, 130.6, 128.9, 128.6, 127.9, 125.4, 122.4, 64.2, 62.3, 48.4, 31.6, 13.9; HRMS (ESI) for $C_{20}H_{20}BrN_2O_4$ $[M + H]^+$ calcd 431.0601, found 431.0588. Enantiomeric excess: 86%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (major) = 18.50 min, t_R (minor) = 22.34 min.

Synthesis of 6 from 5. Compound **5** (0.2 mmol) was dissolved in 2 mL of methanol, and DMAP (10%) was added, and mixture stirred at room temperature for 24 h. The mixture was evaporated under a vacuum, and the residue was purified through column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 3/1) to gave **6** as a white solid.

*(3aR,6aR)-5-(4-Bromophenyl)-6a-phenyltetrahydropyrrolo[3,4-b]pyrrole-2,4,6(5H)-trione (**6a**).* Yield 77%; white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.50 (s, 1H), 7.73 (d, J = 7.61 Hz, 2H), 7.52−7.45 (m, 2H), 7.42−7.16 (m, 5H), 4.01 (d, J = 6.68 Hz, 1H), 2.90−2.81 (m, 1H), 2.74−2.73 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 175.4, 175.1, 174.3, 138.4, 131.9, 131.2, 129.4, 128.6, 128.4, 125.8, 121.8, 68.0, 48.0, 31.9; HRMS (ESI) for $C_{18}H_{13}BrN_2NaO_3$ $[M + Na]^+$ calcd 407.0002, found 406.9996; IR (KBr) ν = 3480, 3423, 1783, 1713, 1693 cm^{-1}. Enantiomeric excess: 92%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 50/50, 0.6 mL/min, 220 nm), t_R (minor) = 70.97 min, t_R (major) = 87.33 min.

Synthesis of 7 from 6. To a stirred solution of **6** (0.2 mmol) in THF (2 mL), $LiAlH_4$ (0.6 mmol) was added at 0 °C. After being stirred for 0.5 h, the mixture was heated at 70 °C for 12 h. When it cooled to 0 °C, 10% aq NaOH solution was added, and then the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed to afford the product as yellow oil. The oil (0.1 mmol) was dissolved in DCM with triethylamine (0.2 mmol), then p-toluenesulfonyl chloride (0.12 mmol) was added. After being stirred for 6 h at room temperature, the mixture was evaporated under a vacuum, and the residue was purified through column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1) to give **7** as a white solid.

*(3aS,6aR)-5,6a-Diphenyl-1-tosyloctahydropyrrolo[3,4-b]pyrrole (**7a**).* Yield 55%; white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.42 (m, 4H), 7.34−7.22 (m, 5H), 7.0 (d, J = 8.0 Hz, 2H), 6.76 (t, J = 7.22 Hz, 1H), 6.53 (d, J = 8.08 Hz, 2H), 4.36 (d, J = 11.53 Hz, 1H), 4.14 (d, J = 11.51 Hz, 1H), 3.75 (t, J = 6.90 Hz, 2H), 3.48 (t, J = 10.54 Hz, 1H), 3.0−2.93 (m, 2H), 2.29 (s, 3H), 2.07 (dd, J = 5.97 Hz, 12.98 Hz, 1H), 1.87 (dd, J = 5.12 Hz, 11.97 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.8, 142.8, 142.4, 137.1, 129.2, 129.1, 128.3, 127.2, 126.8, 125.9, 116.6, 112.1, 78.4, 57.7, 54.2, 50.8, 48.3, 27.5, 21.3; HRMS (ESI) for $C_{25}H_{27}N_2O_2S$ $[M + H]^+$ calcd 419.1788, found 419.1797. Enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol = 80/20, 1.0 mL/min, 220 nm), t_R (minor) = 11.12 min, t_R (major) = 33.73 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra and HPLC analysis spectra of all compounds and X-ray structural data (CIF) of compounds **3q**

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and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: wlxioc@cioc.ac.cn; xuxy@cioc.ac.cn.

Notes

The authors declare no competing financial interest.

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