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Organocatalytic cyclization-rearrangement cascade reaction: asymmetric construction of γ-lactams†

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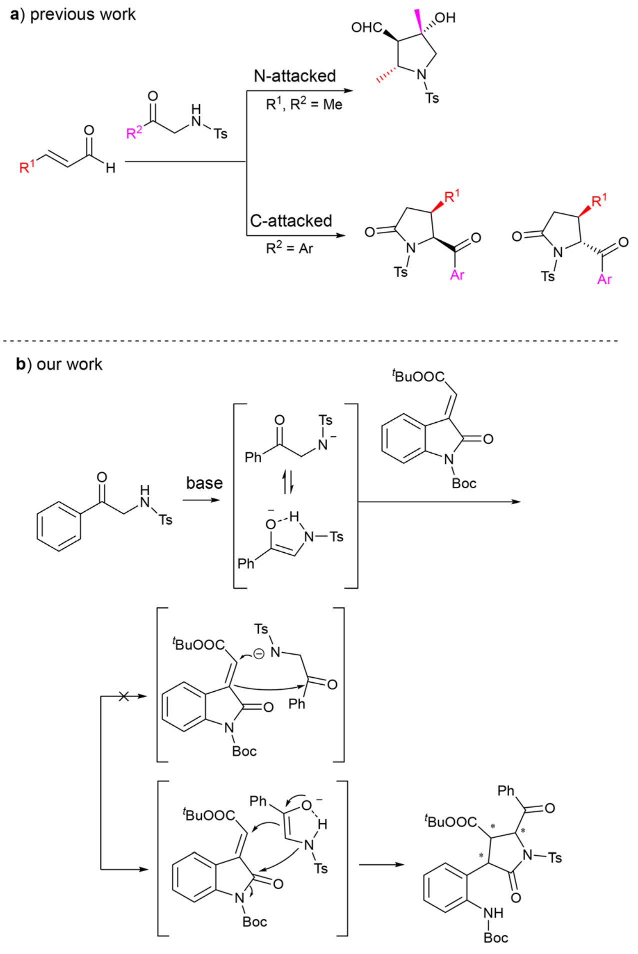
We report a chiral thiourea-catalyzed Michael/ring-reorganization cyclization of 3-methyleneoxindoles with *N*-(*p*-toluenesulfonyl)-α-amino ketones, facilitating the asymmetric synthesis of γ-lactams. This method efficiently generates a range of optically pure γ-lactams, in yields ranging from 60% to 86% and excellent stereoselectivity (up to 20 : 1 dr, >99% ee). The gram-scale experiments confirmed the scalability of the reaction without compromising the yield or stereoselectivity. Performed under mild conditions, this investigation showcases its potential applicability for synthesizing complex chiral γ-lactams with consecutive three chiral centers.

Introduction

The γ-lactam framework constitutes a pivotal structural motif in natural products and bioactive molecules, underpinning their diverse pharmacological activities including antibacterial, anticancer, and antiviral effects.[1–3] Despite its pharmaceutical relevance, the synthesis of γ-lactams bearing multiple stereocenters presents formidable challenges in stereochemical control, a critical determinant of drug efficacy and specificity.[4] This challenge highlights the central role of asymmetric synthesis in modern organic synthesis, particularly in pharmaceutical and agrochemical development.

Organocatalytic asymmetric synthesis has emerged as a vital strategy for constructing chiral γ-lactams, where the strategic selection of synthetic building blocks dictates the efficiency of stereochemical control.[5–12] Among commonly used precursors, Ts-protected α-amino ketones and α-amino esters exhibit unique reactivity profiles due to the dual activation effects of the *p*-toluenesulfonyl group.[13–20] This protecting group not only elevates the NH acidity (pK_a 10–16) to enable facile deprotonation under mild basic conditions but also creates a chemoselectivity dilemma by activating both α-carbon and nitrogen as potential nucleophilic sites, a phenomenon first systematically elucidated by Uria *et al.*[21] Uria's seminal work revealed substrate-dependent chemoselectivity through comparative studies (Scheme 1a). They



Scheme 1 α-Aminophenone for construction of nitrogen-containing heterocyclic units.

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investigated the reactions of Ts-protected α-amino ketones with α,β-unsaturated aldehydes and observed two distinct outcomes. Specifically, when Ts-protected α-aminoacetophenone was used, the product predominantly resulted from a carbon nucleophilic attack. Conversely, when Ts-protected α-aminopropiophenone reacted with α,β-unsaturated aldehydes, the product mainly arose from a nitrogen nucleophilic attack.

Based on our previous work regarding the construction of azaspirocyclic oxindoles through aza-Michael/annulation cascades of 3-methyleneoxindoles,[22–24] we sought to extend this strategy to extend this strategy to the asymmetric synthesis of nitrogen-containing heterocycles. As depicted in Scheme 1b, Ts-protected α-amino ketones can adopt two distinct tautomeric forms under basic conditions, potentially displaying different reactivities towards 3-methyleneoxindole. If the nitrogen atom initiates the reaction, an aza-Michael/aldol cascade may ensue; conversely, if the α-carbon is the initial point of attack, a Michael addition could be followed by a possible ring-opening event. Empirical data have consistently demonstrated that the latter pathway predominates in these reactions.

Results and discussion

To further optimize the conditions, we used **1a** and **2a** as substrates for screening (Table 1). Initially, we screened various catalysts (Table 1). We began by evaluating bifunctional cinchona alkaloid catalysts. As shown in Table 1, all cinchona alkaloid-based catalysts yielded the desired products with excellent stereoselectivity (99% ee, 20 : 1 dr), with the main differences being in yield. Thiourea-based catalysts performed better in terms of yield compared to squaramide-based catalysts (entry 3 *versus* entry 5). The best cinchona alkaloid catalyst was the thiourea catalyst **3e**, achieving a yield of 71%.

Next, cyclohexanediamine-based catalysts were screened to further optimize the conditions. Unfortunately, cyclohexanediamine-based catalysts generally demonstrated inferior stereoselectivity compared to cinchona alkaloid catalysts. The best cyclohexanediamine-based catalyst was **3f**, yielding the desired product with 62% yield, 8 : 1 diastereoselectivity, and 99% enantioselectivity (entry 6). Additionally, increasing the steric hindrance of cyclohexanediamine led to decreased stereoselectivity and yield, prompting us to discontinue further screening of these catalysts. Ultimately, we selected **3e** as the optimal catalyst.

After identifying the optimal catalyst, we screened for the best reaction solvent. The results indicated no differences in stereoselectivity among the solvents tested, with ethyl acetate giving the highest yield of 76%, making it the chosen solvent (entry 13). To further optimize the conditions, we examined the catalyst loading. Reducing the catalyst loading to 5 mol% and 2 mol% (entries 15 and 16) did not affect stereoselectivity but resulted in lower yields. We hypothesized that the lower catalyst concentration slowed the reaction rate. Extending the reaction time to 72 hours with a 5 mol% catalyst loading (entry 17) resulted in only a slight increase in yield by 3%. Considering all factors, we determined the conditions in entry 13 to be the optimal reaction conditions.

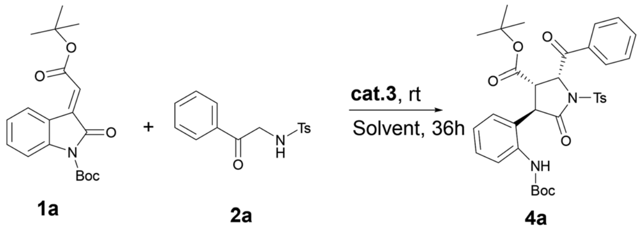
Following the determination of optimal reaction conditions, we expanded our investigation to explore the substrate scope, as delineated in Scheme 2. Initially, we focused on the impact of various substituents on the aryl ring of 3-methyleneoxindole. Overall, these substituents exhibited good stereoselectivity. However, the nitro-substituted derivative **4h** showed decreased diastereoselectivity and yield, with only a 10 : 1 dr and a 65% yield. This could be attributed to the strong hydrogen-bonding ability of the nitro group, which might interfere with the catalyst's efficiency. Similarly, the 7-methyl-substituted oxindole substrate **4k** also exhibited reduced performance. The hydrogen-bonding sites of the catalyst are typically located on the carbonyl oxygen of the protecting group Boc and the 2-oxo group of the oxindole. The 7-methyl substituent may hinder the hydrogen bonding, resulting in less efficient catalysis. The reaction with substrate **1**, containing a methyl group at the terminal position of the Michael acceptor site, was attempted but proved unsuccessful. This result highlights a clear limitation of the reaction scope, indicating that only highly activated alkylideneoxindoles with a terminal electron-withdrawing group are suitable substrates for this transformation.

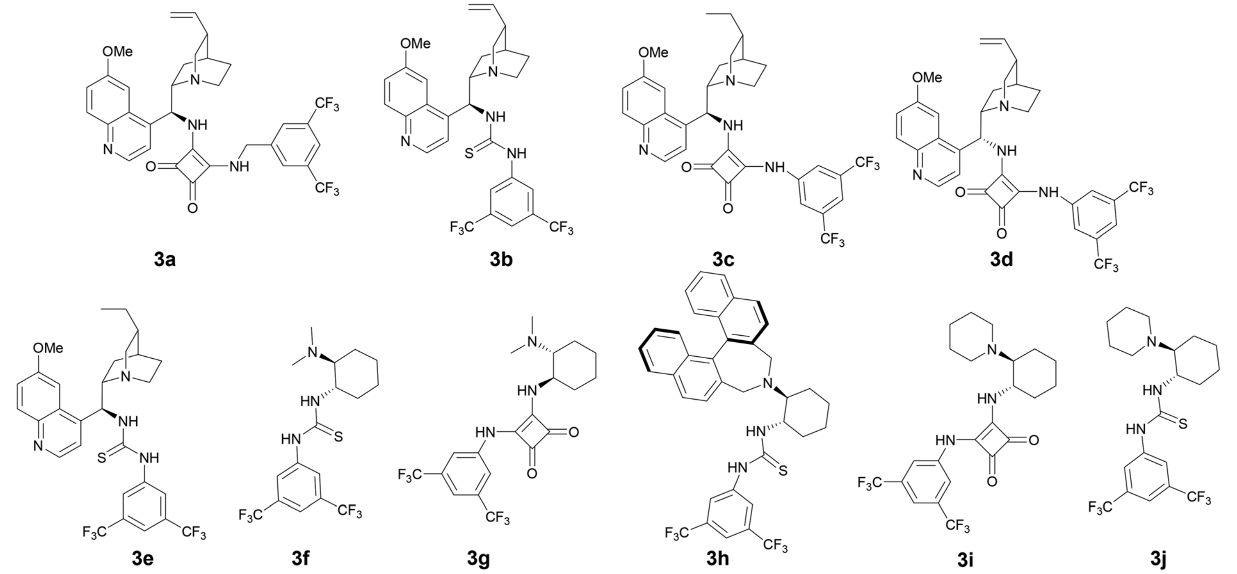
Next, we examined α-amino ketone compounds. The results showed that only the *ortho*-substituted derivative **4r** experienced reduced stereoselectivity, with a 10 : 1 dr. The other derivatives maintained excellent stereoselectivity (20 : 1 dr, 99% ee) and yielded the desired products in moderate to good yields. We also attempted the reaction with a heterocyclic α-amino ketone, **4s**, which afforded the product with a yield of 65%, a diastereoselectivity of 20 : 1, and an enantioselectivity of 99%.

To assess the practicality of the method, we conducted a gram-scale experiment, as illustrated in Scheme 2. Employing the standard conditions, we utilized the template substrates **1a** and **2a** in the reaction, yielding the product **4a** with a 70% yield, a diastereoselectivity greater than 20 : 1, and an enantioselectivity exceeding 99%. Although the isolated yield was slightly lower compared to the small-scale experiments, the excellent stereoselectivity was maintained, indicating the promising applicability of the approach. Some synthetic elaborations of **4a** were made to explore the derivatization of the compounds, including Boc removal, hydrolysis of the *tert*-butyl ester, and exhaustive reduction of the lactam to the pyrrolidine, as well as complete hydrolysis to the open-chain amino acid derivative. But unfortunately, these attempts were unsuccessful, likely due to the high sensitivity of the substrates to acidic or basic conditions.

Based on the absolute configuration of the final product (CCDC 2363697†) (Scheme 3) and the catalytic mode of the bifunctional catalyst,[25–28] we propose a plausible transition state model for this cascade reaction. Our previous research has identified that the carbonyl oxygen of the Boc group and the carbonyl oxygen of the oxindole are excellent hydrogen-bonding sites for thiourea. These interactions not only create a

Table 1 Screening reaction conditions[a]





Entry	Ratio	Cat.	Solvent	dr[b]	Yield (%)	ee[c] (%)
1	1 : 1 : 0.1	**3a**	DCM	20 : 1	54	99
2	1 : 1 : 0.1	**3b**	DCM	20 : 1	65	99
3	1 : 1 : 0.1	**3c**	DCM	20 : 1	56	99
4	1 : 1 : 0.1	**3d**	DCM	20 : 1	60	−99
5	1 : 1 : 0.1	**3e**	DCM	20 : 1	71	99
6	1 : 1 : 0.1	**3f**	DCM	8 : 1	62	99
7	1 : 1 : 0.1	**3g**	DCM	7 : 1	45	−97
8	1 : 1 : 0.1	**3h**	DCM	—	Trace	—
9	1 : 1 : 0.1	**3i**	DCM	3 : 1	35	90
10	1 : 1 : 0.1	**3j**	DCM	4 : 1	40	97
11	1 : 1 : 0.1	**3e**	$CHCl_3$	20 : 1	72	99
12	1 : 1 : 0.1	**3e**	Toluene	20 : 1	70	99
13	1 : 1 : 0.1	**3e**	EtOAc	20 : 1	76	99
14	1 : 1 : 0.1	**3e**	THF	20 : 1	42	99
15	1 : 1 : 0.05	**3e**	EtOAc	20 : 1	61	99
16	1 : 1 : 0.02	**3e**	EtOAc	20 : 1	36	99
17[d]	1 : 1 : 0.05	**3e**	EtOAc	20 : 1	64	99

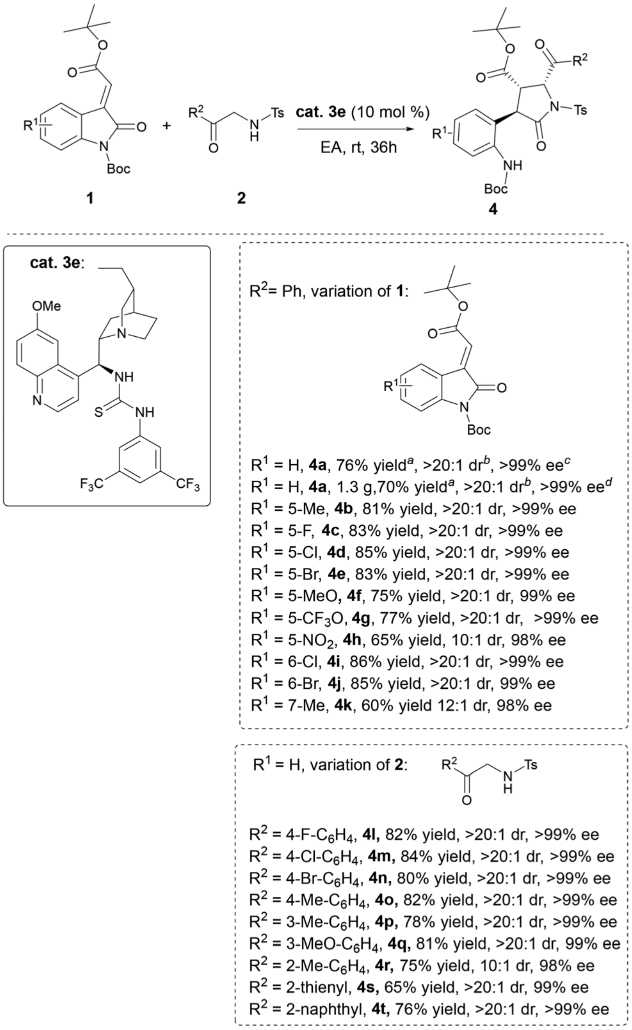
[a] Typical reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), **cat. 3** (0.02 mmol) in solvent (0.5 mL), at 25 °C for 36 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture before purification. [c] Determined by HPLC analysis. [d] Prolong the reaction time to 72 h.

chiral environment but also enhance the electron-withdrawing effect of the double carbonyls, facilitating the nucleophilic addition to the double bond of the oxindole (Scheme 3). The tertiary amine of the cinchona alkaloid catalyst polarizes the enolate's H–O bond, enabling a more favorable *Re*-face attack on the double bond of the oxindole *via* Michael addition. Upon completion of the addition, the Ts-protected amine undergoes a nucleophilic reaction with the carbonyl group of the lactam, leading to the cleavage of the C–N bond, ring-opening, and the formation of a new lactam ring, ultimately yielding the desired product **4i**.

Experimental

General information

All reagents and all solvents were obtained from commercial suppliers and used without further purification except as indicated

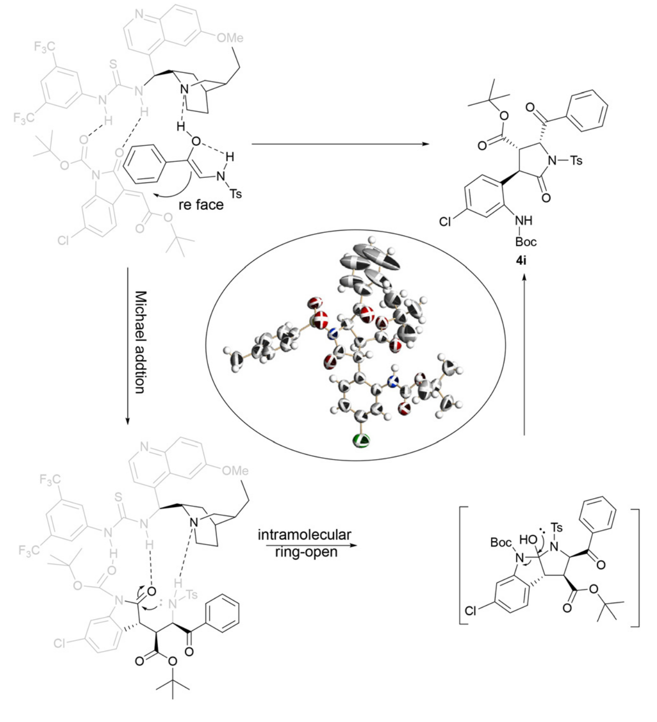


Scheme 2 Substrate applicability evaluation. Typical reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), **3e** (0.02 mmol) in EtOAc (0.5 mL), at 25 °C for 36h. ^{a} Isolated yield. ^{b} Determined by ^{1}H NMR analysis of the crude reaction mixture before purification. ^{c} Determined by HPLC analysis. ^{d} Gram-scale experiment.

below. The silica gel (300–400 mesh) was used for column chromatography and TLC inspections were on silica gel GF 254 plates (0.25 mm layer thickness). NMR spectra were all recorded on a Bruker AM400 (400 MHz) spectrometer. Chemical shifts are reported in δ ppm referenced to an internal SiMe$_4$ standard for ^{1}H NMR and chloroform-*d* (δ 77.16) for ^{13}C NMR. Enantioselectivities were determined by high-performance liquid chromatography (HPLC) with an Aglilent-1260 intelligent uv/vis detector (λ = 214 nm, 220 nm or 254 nm) and a Daicel IA or Daicel AD-H column. Optical rotations were measured in CHCl$_3$ on a Pekin-Elmer 241MC automatic polarimeter. HRESIMS were recorded on an Agilent 6210 TOF LC/MS equipped with an electrospray ionization (ESI) probe operating in positive or negative ion mode.

Typical procedure and analytical data

Synthesis of γ-lactams 3: general procedure. A solution of 3-methyleneoxindoles **1** (0.20 mmol), *N*-(*p*-toluenesulfonyl)-α-amino ketones **2** (0.2 mmol) and catalyst **3e** (10 mol%) in EtOAc (0.5 mL) was stirred at room temperature (25 °C) for 36 h. The mixture was concentrated under reduced pressure and the residue was purified *via* flash chromatograph on silica gel to give the desired product **4**.



Scheme 3 Proposed mechanism and transition state for the reaction.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4a).** Yield: 96 mg, 76%, foamy solid, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 16.1 min, ee > 99%. $[\alpha]_D^{20}$ 5.2 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.15 (d, *J* = 7.8 Hz, 2H), 7.79–7.53 (m, 6H), 7.44 (s, 1H), 7.25 (dd, *J* = 11.2, 6.7 Hz, 3H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.27 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 3.78–3.58 (m, 1H), 2.40 (s, 3H), 1.53 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 172.3, 167.8, 153.7, 145.7, 137.0, 135.6, 134.8, 133.9, 129.5, 129.2, 129.2, 129.1, 129.0, 128.9, 128.8, 128.6, 125.0, 84.1, 80.2, 56.9, 50.8, 45.8, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{38}N_2O_8S$ $[M + Na]^+$ 657.2246, found 657.2246.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-methylphenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4b).** Yield: 105 mg, 81%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 14.6 min, ee > 99%. $[\alpha]_D^{20}$ 12.0 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.21–8.10 (m, 2H), 7.74–7.68 (m, 3H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.49 (s, 1H), 7.27–7.21 (m, 2H), 7.20–7.12 (m, 1H), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.26 (d, *J* = 9.0 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 3.68 (dd, *J* = 11.4, 8.9 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H), 1.52 (s, 9H), 0.95 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 172.4, 167.8, 153.9, 145.7, 135.7, 134.8, 134.7, 134.3, 133.9, 129.4, 129.4, 129.2, 129.1, 129.1, 129.0, 128.2, 125.5, 83.9, 80.0, 57.0, 50.8, 46.0, 28.3, 27.2, 21.7, 20.9. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_8S$ [M + Na]$^+$ 671.2403, found 671.2402.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-fluorophenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4c).** Yield: 108 mg, 83%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel AD-H column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 18.5.0 min, t_{minor} = 13.0 min, ee > 99%. $[\alpha]_D^{20}$ 9.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.22–8.09 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 3H), 7.61 (t, *J* = 7.7 Hz, 3H), 7.33–7.17 (m, 3H), 7.06–6.94 (m, 1H), 6.83 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.27 (d, *J* = 8.9 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.70 (dd, *J* = 11.5, 8.8 Hz, 1H), 2.43 (s, 3H), 1.55 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.8, 167.5, 161.1, 158.6, 154.0, 145.9, 135.6, 134.9, 133.9, 133.0, 131.6, 129.5, 129.3, 129.1, 127.8, 115.7, 115.5, 84.2, 80.4, 57.0, 50.3, 46.3, 28.3, 27.2, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.5. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}FN_2O_8S$ [M + Na]$^+$ 675.2152, found 675.2152.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-chlorophenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4d).** Yield: 113 mg, 85%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 27.5 min, ee > 99%. $[\alpha]_D^{20}$ 10.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.21–8.10 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 3H), 7.63 (q, *J* = 8.9, 7.6 Hz, 3H), 7.46 (s, 1H), 7.26 (dd, *J* = 10.5, 8.2 Hz, 3H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.28 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 3.68 (dd, *J* = 11.6, 8.9 Hz, 1H), 2.44 (s, 3H), 1.54 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.6, 167.6, 153.6, 145.9, 135.9, 135.6, 134.9, 133.8, 130.3, 130.0, 129.5, 129.4, 129.2, 129.1, 128.8, 128.7, 126.4, 84.4, 80.6, 56.9, 50.7, 45.7, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}ClN_2O_8S$ [M + Na]$^+$ 691.1857, found 691.1857.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(5-bromo-2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4e).** Yield: 118 mg, 83%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 14.0 min, t_{minor} = 12.6 min, ee > 99%. $[\alpha]_D^{20}$ 14.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, *J* = 7.7 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 3H), 7.59 (t, *J* = 7.6 Hz, 3H), 7.49 (s, 1H), 7.42–7.32 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.15 (s, 1H), 6.26 (d, *J* = 8.8 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 3.72–3.56 (m, 1H), 2.41 (s, 3H), 1.51 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.6, 167.6, 153.4, 145.9, 136.4, 135.5, 134.9, 133.7, 131.6, 131.4, 130.4, 129.5, 129.3, 129.1, 129.1, 126.4, 117.5, 84.4, 80.6, 56.8, 50.7, 45.4, 28.2, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}BrN_2O_8S$ [M + Na]$^+$ 735.1352, found 735.1348.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-methoxyphenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4f).** Yield: 99 mg, 75%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 20.8 min, t_{minor} = 31.2 min, ee = 99%. $[\alpha]_D^{20}$ 11.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.20–8.07 (m, 2H), 7.73–7.68 (m, 3H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.25 (dd, *J* = 9.2, 3.0 Hz, 2H), 7.17 (dt, *J* = 8.0, 2.5 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.65 (d, *J* = 2.9 Hz, 1H), 6.23 (d, *J* = 8.9 Hz, 1H), 4.49 (t, *J* = 11.0 Hz, 1H), 3.75 (s, 4H), 2.41 (s, 3H), 1.54 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 172.3, 167.5, 157.4, 154.5, 145.7, 135.7, 134.7, 134.1, 129.7, 129.4, 129.3, 129.1, 129.0, 128.4, 127.3, 115.0, 114.1, 83.8, 80.2, 57.2, 55.5, 50.1, 47.0, 28.3, 27.3, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_9S$ [M + Na]$^+$ 687.2352, found 687.2350.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-(trifluoromethoxy)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4g).** Yield: 110 mg, 77%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 5/95, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 17.6 min, ee > 99%. $[\alpha]_D^{20}$ 16.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.23–8.08 (m, 2H), 7.74 (dt, *J* = 7.5, 2.5 Hz, 4H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.46 (s, 1H), 7.35–7.23 (m, 2H), 7.16 (dt, *J* = 9.0, 1.9 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 6.28 (d, *J* = 8.9 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 3.69 (dd, *J* = 11.6, 8.9 Hz, 1H), 2.44 (s, 3H), 1.55 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.6, 171.6, 167.4, 153.7, 146.0, 145.8, 135.9, 135.6, 134.9, 133.9, 130.5, 129.5, 129.4, 129.1, 126.7, 121.7, 121.5, 121.3, 119.1, 84.4, 80.7, 57.0, 50.2, 46.1, 28.3, 27.2, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.0. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{37}F_3N_2O_9S$ [M + Na]$^+$ 741.2070, found 741.2072.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-5-nitrophenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4h).** Yield: 88 mg, 65%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr = 10 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 27.0 min, t_{minor} = 16.5 min, ee = 98%. $[\alpha]_D^{20}$ 11.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.23–8.15 (m, 3H), 8.15–8.06 (m, 2H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.74 (dd, *J* = 7.8, 5.7 Hz, 3H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.31 (d, *J* = 8.8 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 3.75 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.43 (s, 3H), 1.53 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.2, 167.8, 152.6, 146.2, 144.1, 143.3, 135.4, 135.1, 133.7, 129.6, 129.5, 129.3, 129.2, 129.1, 127.0, 124.1, 122.6, 85.0, 81.5, 56.8, 50.5, 45.1, 28.2, 27.2, 21.8. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}N_3O_{10}S$ $[M + Na]^+$ 702.2097, found 702.2098.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-4-chlorophenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4i).** Yield: 115 mg, 86%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 17.1 min, t_{minor} = 14.5 min, ee > 99%. $[\alpha]_D^{20}$ 15.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.23–8.08 (m, 2H), 7.81 (s, 1H), 7.78–7.57 (m, 6H), 7.26 (dt, *J* = 8.4, 2.9 Hz, 2H), 7.10 (dq, *J* = 8.4, 2.2 Hz, 1H), 7.01 (dd, *J* = 8.5, 4.0 Hz, 1H), 6.28 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.54 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.63 (ddd, *J* = 11.2, 8.7, 4.1 Hz, 1H), 2.43 (s, 3H), 1.54 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.9, 167.9, 153.2, 145.9, 138.5, 135.6, 134.9, 134.3, 133.8, 129.8, 129.5, 129.3, 129.1, 129.1, 126.3, 124.8, 124.2, 84.5, 80.7, 56.8, 51.0, 45.2, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}ClN_2O_8S$ $[M + Na]^+$ 691.1857, found 691.1857.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(4-bromo-2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4j).** Yield: 121 mg, 85%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 220 nm), retention time: t_{major} = 18.2 min, t_{minor} = 15.0 min, ee = 99%. $[\alpha]_D^{20}$ 13.6 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.18–8.10 (m, 2H), 7.98–7.89 (m, 1H), 7.76–7.66 (m, 3H), 7.65–7.54 (m, 3H), 7.26–7.19 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.26 (d, *J* = 8.9 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 3.60 (dd, *J* = 11.5, 8.9 Hz, 1H), 2.41 (s, 3H), 1.52 (s, 9H), 0.95 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 171.8, 167.9, 153.2, 145.9, 138.6, 135.6, 134.9, 133.8, 130.0, 129.5, 129.3, 129.1, 129.1, 127.8, 127.2, 127.0, 122.3, 84.5, 80.7, 56.8, 50.9, 45.3, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}BrN_2O_8S$ $[M + Na]^+$ 735.1352, found 735.1348.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-benzoyl-4-(2-((*tert*-butoxycarbonyl)amino)-3-methylphenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4k).** Yield: 78 mg, 60%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr = 12 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel AD-H column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 10.0 min, t_{minor} = 8.5 min, ee = 98%. $[\alpha]_D^{20}$ 15.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.11 (d, *J* = 7.7 Hz, 2H), 7.71 (dt, *J* = 9.8, 5.0 Hz, 3H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.30–7.19 (m, 3H), 7.15 (q, *J* = 7.0, 6.5 Hz, 2H), 6.20 (d, *J* = 9.2 Hz, 2H), 4.47 (d, *J* = 11.1 Hz, 1H), 3.86 (t, *J* = 10.3 Hz, 1H), 2.42 (s, 3H), 2.28 (s, 3H), 1.64 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.9, 173.1, 167.4, 154.5, 145.5, 138.7, 135.9, 134.5, 134.4, 130.9, 129.3, 129.2, 129.1, 129.0, 129.0, 127.7, 83.2, 80.3, 57.4, 49.2, 28.2, 27.3, 21.7, 18.0. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_8S$ $[M + Na]^+$ 671.2403, found 671.2402.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(4-fluorobenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4l).** Yield: 107 mg, 82%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IB column, i-PrOH/*n*-hexane = 5/95, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 19.4 min, ee > 99%. $[\alpha]_D^{20}$ 4.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.19 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.67 (dd, *J* = 19.7, 8.0 Hz, 3H), 7.37 (s, 1H), 7.27 (dt, *J* = 12.3, 5.7 Hz, 5H), 7.17–7.01 (m, 2H), 6.21 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 3.69 (dd, *J* = 11.4, 8.8 Hz, 1H), 2.41 (s, 3H), 1.52 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 194.4, 172.2, 168.0, 167.8, 165.4, 153.7, 145.8, 137.0, 133.8, 132.3, 132.2, 129.3, 129.0, 128.9, 128.7, 125.1, 116.4, 116.2, 84.1, 80.2, 56.8, 50.7, 45.9, 28.3, 27.3, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.6. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}FN_2O_8S$ $[M + Na]^+$ 675.2152, found 675.2152.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(4-chlorobenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4m).** Yield: 112 mg, 84%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 21.6 min, ee > 99%. $[\alpha]_D^{20}$ 6.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.76–7.51 (m, 5H), 7.34 (s, 1H), 7.26 (t, *J* = 8.2 Hz, 3H), 7.17–7.02 (m, 2H), 6.19 (d, *J* = 8.9 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 3.76–3.62 (m, 1H), 2.41 (s, 3H), 1.53 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.0, 172.2, 167.8, 153.8, 145.8, 141.4, 137.0, 134.1, 133.8, 130.7, 129.4, 129.3, 129.0, 128.9, 128.7, 125.4, 125.2, 84.2, 80.3, 56.8, 50.6, 45.9, 28.3, 27.3, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}ClN_2O_8S$ $[M + Na]^+$ 691.1857, found 691.1856.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-(4-bromobenzoyl)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4n).** Yield: 114 mg, 80%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 22.7 min, ee > 99%. $[\alpha]_D^{20}$ 7.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.69 (td, *J* = 20.9, 20.4, 7.7 Hz, 5H), 7.34 (s, 1H), 7.26 (t, *J* = 8.0 Hz, 3H), 7.10 (dt, *J* = 14.9, 7.7 Hz, 2H), 6.18 (d, *J* = 8.9 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 3.78–3.60 (m, 1H), 2.41 (s, 3H), 1.52 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.3, 172.2, 167.8, 153.8, 145.9, 137.0, 134.5, 133.8, 132.4, 130.8, 130.3, 129.3, 129.0, 128.9, 128.7, 125.4, 125.2, 84.2, 80.3, 56.8, 50.6, 45.9, 28.3, 27.3, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{34}H_{37}BrN_2O_8S$ $[M + Na]^+$ 735.1352, found 735.1348.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(4-methylbenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4o).** Yield: 106 mg, 82%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 9.4 min, ee > 99%. $[\alpha]_D^{20}$ 3.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 9.0 Hz, 3H), 7.47 (s, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.25 (dd, *J* = 15.2, 5.8 Hz, 3H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.23 (d, *J* = 8.8 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 3.67 (dd, *J* = 11.4, 8.8 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H), 1.52 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.2, 172.4, 167.8, 153.7, 146.0, 145.7, 137.1, 133.9, 133.3, 129.7, 129.6, 129.2, 129.1, 128.9, 128.9, 128.5, 125.0, 84.0, 80.2, 56.8, 50.9, 45.8, 28.3, 27.2, 21.9, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_8S$ $[M + Na]^+$ 671.2403, found 671.2402.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(3-methylbenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4p).** Yield: 101 mg, 78%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IB column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 10.2 min, t_{minor} = 8.9 min, ee > 99%. $[\alpha]_D^{20}$ 8.3 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99–7.87 (m, 2H), 7.69 (dd, *J* = 23.7, 8.1 Hz, 3H), 7.48 (dt, *J* = 19.9, 6.0 Hz, 3H), 7.25 (t, *J* = 6.8 Hz, 3H), 7.10 (q, *J* = 8.6, 8.1 Hz, 2H), 6.26 (d, *J* = 8.9 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.73–3.58 (m, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 1.52 (s, 9H), 0.95 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.7, 172.3, 167.8, 153.7, 145.7, 138.9, 137.1, 135.6, 135.5, 133.9, 129.9, 129.2, 129.2, 128.9, 128.8, 128.7, 128.6, 126.7, 125.1, 125.0, 84.0, 80.2, 57.1, 50.8, 45.8, 28.3, 27.1, 21.7, 21.4. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_8S$ $[M + Na]^+$ 671.2403, found 671.2405.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(3-methoxybenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4q).** Yield: 107 mg, 81%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IB column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 13.0 min, t_{minor} = 10.6 min, ee = 99%. $[\alpha]_D^{20}$ 5.6 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.85–7.56 (m, 5H), 7.54–7.36 (m, 2H), 7.25 (t, *J* = 7.0 Hz, 4H), 7.15–7.01 (m, 2H), 6.23 (d, *J* = 8.9 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 3.89 (s, 3H), 3.69 (dd, *J* = 11.5, 8.9 Hz, 1H), 2.40 (s, 3H), 1.52 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.5, 172.3, 167.8, 160.1, 153.7, 145.7, 137.0, 136.9, 133.9, 130.0, 129.2, 129.1, 128.9, 128.8, 128.6, 125.2, 125.0, 122.2, 121.3, 113.4, 84.1, 80.2, 57.2, 55.6, 50.7, 45.8, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_9S$ $[M + Na]^+$ 687.2352, found 687.2350.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-(2-methylbenzoyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4r).** Yield: 97 mg, 75%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr = 10 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 240 nm), retention time: t_{major} = 25.8 min, t_{minor} = 21.5 min, ee = 98%. $[\alpha]_D^{20}$ 6.3 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.37–7.21 (m, 5H), 7.15–7.03 (m, 2H), 6.23 (d, *J* = 8.7 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 3.62 (dd, *J* = 12.0, 8.6 Hz, 1H), 2.51 (s, 3H), 2.42 (s, 3H), 1.51 (s, 9H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 196.5, 172.0, 167.9, 153.6, 145.7, 141.7, 137.1, 134.5, 134.0, 133.5, 132.8, 131.0, 129.3, 129.2, 128.8, 128.7, 128.6, 128.6, 126.1, 124.9, 83.8, 80.1, 67.1, 59.2, 50.9, 45.4, 28.3, 27.1, 21.8, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{40}N_2O_8S$ $[M + Na]^+$ 671.2403, found 671.2400.

***tert*-Butyl (2*R*,3*S*,4*R*)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-2-(thiophene-2-carbonyl)-1-tosylpyrrolidine-3-carboxylate (4s).** Yield: 83 mg, 65%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IB column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 254 nm), retention time: t_{major} = 16.9 min, t_{minor} = 14.3 min, ee = 99%. $[\alpha]_D^{20}$ 14.4 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.07 (d, *J* = 3.9 Hz, 1H), 7.87 (d, *J* = 4.9 Hz, 1H), 7.68 (dd, *J* = 16.4, 7.9 Hz, 3H), 7.49 (s, 1H), 7.27 (dt, *J* = 20.0, 6.1 Hz, 4H), 7.17–7.03 (m, 2H), 6.01 (d, *J* = 8.8 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 3.68 (dd, *J* = 11.4, 8.7 Hz, 1H), 2.40 (s, 3H), 1.52 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 188.1, 172.2, 167.8, 153.7, 145.8, 142.9, 137.0, 136.9, 135.3, 133.9, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 125.1, 125.1, 84.0, 80.2, 58.7, 50.9, 45.8, 28.3, 27.2, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{36}N_2O_8S_2$ $[M + H]^+$ 641.1991, found 641.1994.

***tert*-Butyl (2*R*,3*S*,4*R*)-2-(2-naphthoyl)-4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-5-oxo-1-tosylpyrrolidine-3-carboxylate (4t).** Yield: 104 mg, 76%, colorless oil, purified by chromatography on silica gel (*n*-hexane/EtOAc 4/1). dr > 20 : 1. HPLC: the ee value was determined by HPLC analysis (Chiralcel IA column, i-PrOH/*n*-hexane = 10/90, 1.0 ml min^{-1}, 240 nm), retention time: t_{major} = 11.5 min, ee > 99%. $[\alpha]_D^{20}$ 15.3 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.74 (s, 1H), 8.09 (dd, *J* = 15.1, 8.4 Hz, 2H), 7.97 (dd, *J* = 22.5, 8.4 Hz, 2H), 7.67 (dt, *J* = 24.2, 7.7 Hz, 5H), 7.47 (s, 1H), 7.31–7.18 (m, 3H), 7.17–7.07 (m, 2H), 6.45 (d, *J* = 8.9 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 3.75 (dd, *J* = 11.4, 8.8 Hz, 1H), 2.40 (s, 3H), 1.54 (s, 9H), 0.85 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 195.5, 172.3, 167.9, 153.7, 145.7, 137.1, 136.2, 133.9, 133.0, 132.4, 132.1, 130.0, 129.6, 129.2, 129.1, 129.0, 128.9, 128.8, 128.8, 128.6, 127.9, 127.3, 125.0, 124.0, 84.0, 80.2, 57.1, 50.9, 45.9, 28.3, 27.1, 21.7. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{40}N_2O_8S$ $[M + Na]^+$ 707.2403, found 707.2405.

Conclusions

In this study, we have successfully catalyzed a Michael/ring-reorganization cyclization reaction between 3-methyleneoxindoles and *N*-(*p*-toluenesulfonyl)-α-amino ketones using a thiourea-based bifunctional catalyst. This approach has yielded highly functionalized γ-lactams with good yields (up to 86%) and excellent stereoselectivity (up to 20 : 1 dr, >99% ee). The gram-scale experiments demonstrated that the scalability of the reaction does not compromise yield or stereoselectivity, indicating a promising potential for application. The reaction conditions are mild, and the substrate scope is broad, further highlighting the versatility and robustness of this catalytic system.

Data availability

The data that support the findings of this study are available on request from the corresponding author. For this article, crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number 2363697.† The ^{1}H and ^{13}C NMR spectra for all new compounds are included as part of the ESI.† Copies of the spectra can also be obtained from the authors upon request.

Conflicts of interest

The authors declare no competing financial interest.

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