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Organocatalyzed enantioselective [3+3] annulation for the direct synthesis of conformationally constrained cyclic tryptophan derivatives

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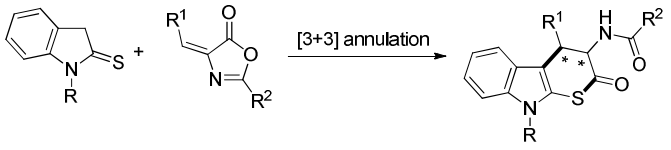
An enantioselective formal [3+3] annulation of 1-methylindoline-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones has been developed by the use of a L-*tert*-leucine-derived bifunctional tertiary amine-squaramide catalyst, which furnished a series of optically active conformationally strained β-branched cyclic tryptophan derivatives in acceptable yields with good to excellent diastereo- and enantioselectivities.

Introduction

Optically active non-proteinogenic amino acids are of great interest due to their significant biological activities, and extensive applications in organic synthesis and new drug discovery.[1] Among those valuable amino acids, tryptophan analogues are very attractive motifs owing to their wide range biological significance[2] and high versatility as important building blocks of many pharmacologically useful molecules and natural products.[3] Accordingly, considerable efforts for the development of efficient synthetic strategies towards these targets have been undertaken and many synthetic methods have been developed to approach this moiety in an asymmetric manner. However, most of the developed methods are mainly focused on the introduction of different substituents on the indole core.[4] Currently, conformational constraint has been proven to be a major approach to modify the chemical and biological properties of endogenous bioactive peptide hormones and neurotransmitters.[5] Therefore, design and synthesis of conformationally constrained amino acids provides a unique opportunity to obtain new insights into the stereochemical, conformational and topographical requirements of peptide ligand-receptor interactions and for signal transduction. With respect to the conformationally constrained β-substituted tryptophan analogues, reports for the enantioselective route to these compounds have been largely relied on the use of chiral starting materials or stoichiometric amount of chiral inducers.[6] To the best of our knowledge, only two asymmetric catalytic version appeared for the synthesis of β-substituted tryptophans. Chen et al. have achieved the synthesis of *syn*-β-substituted tryptophan derivatives in moderate diastereoselectivities (<44% dr) and good enantioselectivities (41–89% ee) via the copper catalyzed asymmetric Friedel–Crafts alkylation of indoles with nitroacrylates and the subsequent reduction reaction.[7] Hou et al. have realized the generation of *anti*-β-substituted tryptophans with improved diastereo- and enantioselectivity by the reaction of glycine derivatives with sulfonylindoles in the presence of catalyst derived from AgCl and a commercially available chiral monodentate phosphoramidite ligand.[8] Recently, organocatalyzed enantioselective tandem processes have become a powerful, fascinating, and highly efficient tool for the rapid assembly of complex structures.[9] Undoubtedly, the application of these powerful strategies to the synthesis of novel optically active conformationally strained tryptophan derivatives will be of great importance and highly desirable. Currently, indolin-2-thiones have been proven to be versatile 1,3-dinucleophiles in the organocatalyzed annulation reactions,[10] we envisioned that cyclic β-substituted tryptophans could be conveniently accessed via a formal [3+3] cyclization between indolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones (Scheme 1). As part of our continued interest in the organocatalyzed cascade reactions,[11] herein, we report an efficient and straightforward protocol to the synthesis of conformationally strained cyclic β-substituted tryptophan derivatives via bifunctional squaramide catalyzed asymmetric [3+3] cascade reaction of indolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones.

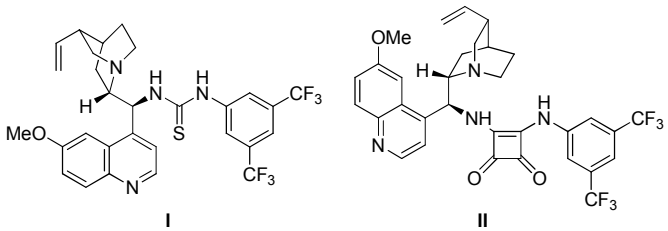


Scheme 1. Synthesis of cyclic β-substituted tryptophans via a [3+3]-annulation strategy.

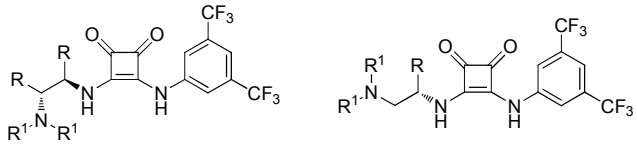
Results and discussion

We commenced our study by exposure of 1-methylindoline-2-thione (**1a**) with (*E*)-4-benzylidene-2-phenyloxazol-5(4*H*)-one (**2a**) in dichloromethane at room temperature in the presence of 10 mol% of various readily available chiral thiourea-[12] and

squaramide-based[13] bidentate hydrogen bond donor catalysts **I**–**IV** (Figure 1).



I **II**

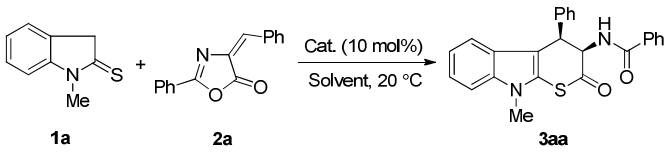


IIIa, R-R = $(CH_2)_4$, R^1 = Me
b, R = Ph, R^1-R^1 = $(CH_2)_5$

IVa, R = Bn, R^1 = Me
b, R = ^{t}Bu, R^1 = Me
c, R = ^{t}Bu, R^1-R^1 = $(CH_2)_5$

Figure 1. Screened bidentate hydrogen bond donor catalysts.

Table 1. Screening of catalysts and optimization of the reaction conditions [a]



1a **2a** **3aa**

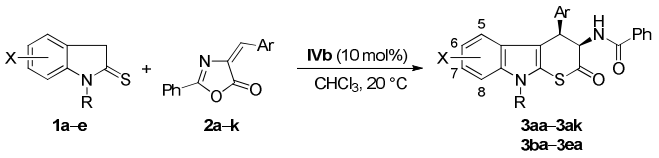
Entry	Cat.	Solvent	Time (d)	Yield (%) [b]	Dr [c]	Ee (%) [d]
1	**I**	CH_2Cl_2	3	43	>19/1	56
2	**II**	CH_2Cl_2	3	53	>19/1	64
3	**IIIa**	CH_2Cl_2	3	40	>19/1	–72
4	**IIIb**	CH_2Cl_2	3	47	>19/1	–59
5	**IVa**	CH_2Cl_2	3	52	>19/1	65
6	**IVb**	CH_2Cl_2	3	65	>19/1	91
7	**IVc**	CH_2Cl_2	3	68	>19/1	84
8	**IVb**	$CHCl_3$	3	62	>19/1	93
9	**IVb**	$ClCH_2CH_2Cl$	3	49	>19/1	92
10	**IVb**	PhCl	3	47	>19/1	92
11	**IVb**	toluene	3	48	>19/1	88
12	**IVb**	Et_2O	3	38	>19/1	27
13	**IVb**	EtOAc	3	39	>19/1	4
14	**IVb**	CH_3CN	3	35	>19/1	2
15 [e]	**IVb**	$CHCl_3$	2	57	>19/1	71
16 [f]	**IVb**	$CHCl_3$	2	60	>19/1	92
17 [g]	**IVb**	$CHCl_3$	2.5	63	>19/1	92
18	**IVb**	$CHCl_3$	4	58	>19/1	89

a. Unless otherwise specified, all reactions were carried out by using **1a** (0.22 mmol), **2a** (0.20 mmol) in the presence of 10 mol% of catalyst in 1.0 mL of solvent at 20 °C. b. Isolated yield. c. Determined by ^{1}H NMR analysis. d. Determined by HPLC analysis using a chiral stationary phase. e. The reaction was performed at 40 °C. f. 20 mol% of catalyst **IVb** was loaded. f. 1.5 equivalent of **1a** was employed. g. The reaction was performed in 2 mL of chloroform.

As shown in Table 1, all the tested catalysts, either thiourea or squaramide promoted the model reaction efficiently to generate the corresponding β-branched cyclic tryptophan derivative **3aa** in acceptable yields with excellent diastereoselectivities (Entries 1–7, >19/1 dr). With regard to the enantioselectivity, the use of quinine-derived thiourea **I** afforded the desired product **3aa** with moderate enantioselectivty (Entry 1, 56% ee). A slightly improved ee value was observed for bifunctional squaramide **II** incorporating the same diamine scaffold as **I** (Entry 2 vs. 1). Further screening of squaramide-based catalysts **IIIa,b**, and **IVa,b** that bearing different chiral diamine scaffolds revealed that squaramide **IVb**, derived from L-*tert*-leucine, was the promising catalyst for this cascade process and provided product **3aa** with an obviously enhanced ee value (Entry 6, 91% ee). No superior result was obtained by changing the substituent attached to the nitrogen atom (Entry 7).

Having identified squaramide **IVb** as the optimal catalyst for this cascade transformation, we then turned our attention to the effect of the solvent. The results listed in Table 1 (Entries 6, 8–14) clearly indicate that the reaction medium plays an important role on the reaction. In all cases, although excellent diastereoselectivity was observed, the enantioselectivity was highly dependent on the solvent employed. For example, excellent enantioselectivities were obtained by performing the reaction in chlorohydrocarbons, such as methylene chloride, chloroform, 1,2-dichloroethane and chlorobenzene (entries 6, 8–10, 91–93%). Toluene was also found to be a good solvent for this transformation, affording product **3aa** with 88% ee (Entry 11). The ee value decreased sharply when ether, ethyl acetate or acetonitrile was used as the solvent (Entries 12–14), and almost racemic **3aa** was obtained in ethyl acetate and acetonitrile (Entries 13 and 14). Chloroform proved to be the best solvent giving the highest ee value of 93% among all the tested solvents (Entry 8). Attempt to accelerate the reaction rate and improve the yield by conducting the reaction at elevated temperature failed. Raising the temperature to 40 °C indeed accelerated the reaction but led to an obvious decrease in both yield and enantiomeric excess (Entry 15). Increasing the catalyst loading (Entry 16), tuning the ratio of substrates (Entry 17) and performing the reaction in diluted concentration (Entry 18) all failed to further improve the yield and enantioselectivity of the reaction.

Table 2. Substrate scope of **IVb**-catalyzed cascade Michael/thiolactonization reaction [a]



Entry	**3** (X, R, Ar)	Time (d)	Yield (%) [b]	Dr [c]	Ee (%) [d]
1	**3aa** (H, Me, Ph)	3	62	>19/1	93
2	**3ab** (H, Me, 4-FC_6H_4)	3	57	>19/1	87
3	**3ac** (H, Me, 4-ClC_6H_4)	3	53	>19/1	81
4	**3ad** (H, Me, 3-ClC_6H_4)	3	67	>19/1	85
5	**3ae** (H, Me, 4-BrC_6H_4)	3	61	>19/1	91
6	**3af** (H, Me, 2-BrC_6H_4)	3	59	>19/1	54
7	**3ag** (H, Me, 4-$MeOC_6H_4$)	3	53	>19/1	73
8	**3ah** (H, Me, 2-$MeOC_6H_4$)	3	50	>19/1	72
9	**3ai** (H, Me, 3-MeC_6H_4)	3	57	>19/1	72
10	**3aj** (H, Me, 2-MeC_6H_4)	3	59	>19/1	70
11	**3ak** (H, Me, 2-thienyl)	3	47	>19/1	80
12	**3ba** (6-F, Me, Ph)	3	53	>19/1	75
13	**3ca** (6-Br, Me, Ph)	3	54	>19/1	84
14	**3da** (5-Me, Me, Ph)	3	43	>19/1	80
15	**3ea** (H, Bn, Ph)	4	41	>19/1	68

a. All reactions were carried out using **1a** (0.22 mmol), **2a** (0.20 mmol) in chloroform (1.0 mL) at 20 □C in the presence of 10 mol% of catalyst **IVb**. b. Isolated yield. c. Determined by 1H NMR analysis. d. Determined by HPLC analysis with a chiral stationary phase.

With the optimized reaction conditions in hand, the scope of this [3+3] cascade reaction was explored (Table 2). The reaction was found to be tolerant of both electron-deficient and electron-rich 4-arylmethylideneoxazolin-5(4*H*)-ones (**2**), delivering the desired cyclic β-substituted tryptophans in acceptable yields (50–67%) with excellent diastereoselectivities (>19/1 dr). With respect to enantioselectivity, the introduction of substituent on the benzene ring resulted in somewhat decrease in ee value. Generally, compared with the results of those substrates bearing electron-withdrawing substituent, some loss of stereocontrol was observed for electron-donating group substituted unsaturated azalactones (Entries 2–5 vs. entries 7–10). In the case of bromo-substituted azalactones, the substitution pattern demonstrated a significant impact on the stereochemical outcome of the reaction. The reaction of *para*-substituted azalactone **2e** gave the corresponding product **3ae** with 91% ee, while a sharply decreased ee value was obtained for *ortho*-substituted azalactone **2f** (Entry 5 vs. entry 6). 4-arylmethylideneoxazolin-5(4*H*)-ones **2k** bearing a heteroaromatic group was also a suitable reaction partner, generating the corresponding addition/thiolactonization product **3ak** in 47% yield with 80% ee (Entry 11). Moreover, tolerance to substitution on the indolin-2-thione **1** was also investigated. In all cases, the tandem Michael–thiolactonization reaction took place efficiently to provide the desired *syn*-β-substituted tryptophans in acceptable yields with excellent diastereo- (>19/1) and good enantioselectivities (75–84% ee) regardless of the nature of the substituents and the substitution pattern (entries 12–14). In addition, *N*-benzylindolin-2-thione **1e** can also be subject to this transformation, giving the corresponding annulation product **3ea** in 41% yield with >19/1 dr and 68% ee (Entry 15).

The relative and absolute configuration of the product **3aa** is unequivocally established as 2*R*,3*R* by X-ray analysis (Figure 2), and the remaining configurations are assumed by analogy.[14]

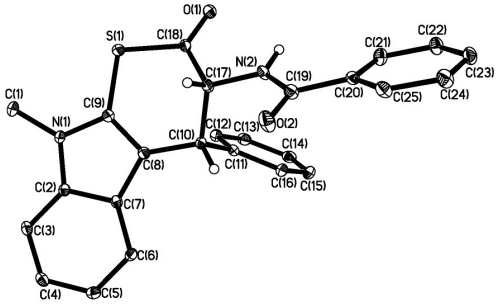
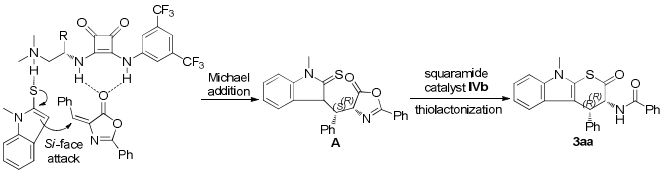


Figure 2. X-ray crystal structure of (*R*,*R*)-**3aa**. Most of the hydrogen atoms have been omitted for clarity.

To account for the observed stereochemical outcome of the reaction, a possible mechanism is proposed for this cascade transformation (Scheme 2). Unsaturated azalactone **2a** is fixed and activated by the squaramide moiety via double hydrogen bonding interactions. Then the direct approach of the thioenolate formed by deprotonating of 1-methylindolin-2-thione **1a** with the tertiary amine functionality from the *Si*-face to the double bond of unsaturated azalactone **2a** gives the Michael addition intermediate **A**. Subsequently, thiolactonization of the Michael addition product **A** with the aid of the bifunctional squaramide catalyst **IVb** generated the desired product (*R*,*R*)-**3aa**.



Scheme 2. Proposed mechanism for the [3+3] annulation.

Experimental

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired on Varian 400 MHz instrumental. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). Specific rotations were measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on a Shimadzu LC-20A instrument (chiral column; mobile phase: Hexane/*i*-PrOH). HRMS was performed on a Varian QFT-ESI instrumental. Melting points were determined on a Taike X-4 melting point apparatus. All temperatures were uncorrected. The racemic samples for HPLC analysis were prepared via triethylamine catalyzed reaction of 1-methylindolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones.

General procedure for IVb-catalyzed cascade Michael addition-thiolactonization reaction of 1-methylindolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones: A solution of squaramide catalyst **IVb** (9 mg, 0.02 mmol, 10 mol %), 1-methylindolin-2-thione (**1a**, 36 mg, 0.22 mmol) and (*E*)-4-benzylidene-2-phenyloxazol-5(4*H*)-one (**2a**, 50 mg, 0.20 mmol) in chloroform (1 mL) was stirred at 20 °C for three days. After removal of solvent under reduced pressure, the crude product purified through column chromatography on silica gel (200–300 mesh, PE/EtOAc = 8/1) to afford the desired β-branched cyclic tryptophan **3aa** (51 mg) as a white solid. The title compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS and specific rotation data. The enantiomeric excess of the pure products was determined by HPLC analysis using a chiral stationary phase.

(3*R*,4*R*)-Benzamido-9-methyl-4-phenyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3aa): White solid, m.p. 198–200 °C, 51 mg, 62% yield, $[\alpha]_D^{25}$ –105.4 (c 1.0, CH_2Cl_2), >19/1 dr, 93% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.2 Hz, 2 H), 7.38–7.52 (m, 4 H), 7.18–7.32 (m, 7 H), 7.09–7.10 (m, 1 H), 6.64 (d, *J* = 4.4 Hz, 1 H), 5.66 (s, 1 H), 5.08 (d, *J* = 3.2 Hz, 1 H), 3.73 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.7, 166.9, 138.0, 137.3, 133.7, 132.0, 128.8, 128.7, 128.5, 127.8, 127.1, 126.2, 124.1, 121.9, 120.3, 117.8, 109.3, 108.9, 62.1, 41.2, 30.4. HRMS (ESI) m/z calc'd for $C_{25}H_{21}N_2O_2S$ $[M+H]^+$: 413.1318, found 413.1318. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 20.14 (minor) and 27.71 min (major).

(3*R*,4*R*)-3-Benzamido-4-(4-fluorophenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ab): White solid, m.p. 183–185 °C, 49 mg, 57% yield, $[\alpha]_D^{25}$ –121.0 (c 1.0, CH_2Cl_2), >19/1 dr, 87% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 6.94 (t, *J* = 8.4 Hz, 2 H), 6.70 (d, *J* = 6.4 Hz, 1 H), 5.61 (t, *J* = 6.4 Hz, 1 H), 5.13 (d, *J* = 6.4 Hz, 1 H), 3.77 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.7, 166.9, 162.4 (d, *J* = 246.6 Hz), 138.1, 133.6, 133.0 (d, *J* = 3.1 Hz), 132.1, 130.2 (d, *J* = 8.1 Hz), 128.8, 127.1, 126.1, 124.0, 122.1, 120.4, 117.8, 115.7 (d, *J* = 21.4 Hz), 109.2, 109.0, 62.3, 40.2, 30.5. HRMS (ESI) m/z calc'd for $C_{25}H_{20}FN_2O_2S$ $[M+H]^+$: 431.1224, found 431.1223. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 17.97 (minor) and 24.79 min (major).

(3*R*,4*R*)-3-Benzamido-4-(4-chlorophenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ac): White solid, m.p. 188–190 °C, 47 mg, 53% yield, $[\alpha]_D^{25}$ –110.0 (c 1.0, CH_2Cl_2), >19/1 dr, 81% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.21 – 7.25 (m, 3 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 6.0 Hz, 1 H), 5.61 (t, *J* = 6.4 Hz, 1 H), 5.13 (d, *J* = 6.0 Hz, 1 H), 3.76 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.6, 166.9, 138.1, 135.8, 133.8, 133.5, 132.2, 130.0, 129.0, 128.8, 127.1, 126.1, 124.0, 122.2, 120.5, 117.7, 109.0, 108.9, 62.2, 40.4, 30.5. HRMS (ESI) m/z calc'd for $C_{25}H_{20}ClN_2O_2S$ $[M+H]^+$: 447.0929, found 447.0927. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 24.07 (minor) and 32.23 min (major).

(3*R*,4*R*)-3-Benzamido-4-(3-chlorophenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ad): White solid, m.p. 190–192 °C, 60 mg, 67% yield, $[\alpha]_D^{25}$ –193.5 (c 1.0, CH_2Cl_2), >19/1 dr, 85% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.21–7.26 (m, 3 H), 7.19 (t, *J* = 8.4 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 2 H), 6.74 (d, *J* = 6.4 Hz, 1 H), 5.63 (t, *J* = 6.4 Hz, 1 H), 5.13 (d, *J* = 6.4 Hz, 1 H), 3.77 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.5, 167.0, 139.4, 138.1, 134.7, 133.6, 132.1, 130.0, 128.8, 128.7, 128.1, 127.1, 126.9, 126.1, 124.2, 122.1, 120.5, 117.7, 109.1, 108.5, 62.0, 40.6, 30.5. HRMS (ESI) m/z calc'd for $C_{25}H_{20}ClN_2O_2S$ $[M+H]^+$: 447.0929, found 447.0925. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 14.39 (minor) and 23.40 min (major).

(3*R*,4*R*)-3-Benzamido-4-(4-bromophenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ae): White solid, m.p. 181–183 °C, 60 mg, 61% yield, $[\alpha]_D^{25}$ –71.7 (c 1.0, CH_2Cl_2), >19/1 dr, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 3 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 6.4 Hz, 1H), 5.63 (t, *J* = 6.4 Hz, 1 H), 5.13 (d, *J* = 6.4 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.5, 167.0, 138.1, 136.4, 133.5, 132.1, 131.9, 130.3, 128.8, 128.4, 127.1, 126.1, 124.0, 122.1, 120.5, 117.7, 109.0, 108.8, 62.1, 40.4, 30.5. HRMS (ESI) m/z calc'd for $C_{25}H_{20}BrN_2O_2S$ $[M+H]^+$: 491.0423, found 491.0408. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 26.45 (minor) and 32.42 min (major).

(3*R*,4*S*)-3-Benzamido-4-(2-bromophenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3af): White solid, m.p. 191–193 °C, 58 mg, 59% yield, $[\alpha]_D^{25}$ –100.8 (c 1.0, CH_2Cl_2), >19/1 dr, 53% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 6.8 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.08 (d, *J* = 7.6 Hz, 1 H), 6.45 (d, *J* = 6.8 Hz, 1 H), 5.85 (t, *J* = 6.8 Hz, 1H), 5.71 (d, *J* = 6.8 Hz, 1 H), 3.74 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.1, 167.4, 138.0, 137.9, 133.9, 133.2, 131.8, 129.9, 129.4, 128.6, 128.5, 127.2, 126.1, 125.0, 124.2, 122.1, 120.4, 117.9, 109.6, 108.9, 61.9, 40.2, 30.4. HRMS (ESI) m/z calc'd for $C_{25}H_{20}BrN_2O_2S$ $[M+H]^+$: 491.0423, found 491.0415. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 9.64 (minor) and 22.77 min (major).

(3*R*,4*R*)-3-Benzamido-4-(4-methoxyphenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ag): White solid, m.p. 180–182 °C, 47 mg, 53% yield, $[\alpha]_D^{25}$ –118.1 (c 1.0, CH_2Cl_2), >19/1 dr, 74% ee. 1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 8.4 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 2

H), 6.65 (d, *J* = 6.4 Hz, 1 H), 5.63 (t, *J* = 6.4 Hz, 1 H), 5.03 (d, *J* = 6.4 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H). 13C NMR (100.6 MHz, $CDCl_3$): δ 193.9, 166.9, 159.2, 138.1, 133.7, 132.0, 129.6, 129.3, 128.7, 127.1, 126.2, 124.0, 121.9, 120.3, 117.8, 114.2, 109.6, 108.9, 62.3, 55.2, 40.5, 30.4. HRMS (ESI) m/z calc'd for $C_{26}H_{23}N_2O_3S$ [M+H]+: 443.1424, found 443.1419. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 33.49 (minor) and 49.36 min (major).

(3*R*,4*R*)-3-Benzamido-4-(2-methoxyphenyl)-9-methyl-2-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ah): White solid, m.p. 176–178 °C, 44 mg, 50% yield, $[\alpha]_D^{25}$ –68.2 (c 1.0, CH_2Cl_2), >19/1 dr, 72% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.2 Hz, 1 H), 7.38–7.43 (m, 3 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.16–7.24 (m, 3 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 6.84 (t, *J* = 7.2 Hz, 2 H), 6.71 (d, *J* = 6.4 Hz, 1 H), 5.65 (t, *J* = 6.8 Hz, 1 H), 5.59 (d, *J* = 6.8 Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.3, 166.9, 157.1, 138.0, 134.0, 131.7, 130.1, 129.0, 128.5, 127.0, 126.3, 126.0, 125.0, 121.7, 121.2, 120.0, 117.8, 110.6, 109.0, 108.8, 61.7, 55.0, 35.2, 30.3. HRMS (ESI) m/z calc'd for $C_{26}H_{23}N_2O_3S$ $[M+H]^+$: 443.1424, found 443.1425. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 13.37 (minor) and 25.91 min (major).

(3*R*,4*R*)-3-Benzamido-9-methyl-2-oxo-4-(m-tolyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ai): White solid, m.p. 169–171 °C, 49 mg, 57% yield, $[\alpha]_D^{25}$ –168.0 (c 1.0, CH_2Cl_2), >19/1 dr, 72% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.04–7.18 (m, 5 H), 6.62 (d, *J* = 7.2 Hz, 1 H), 5.66 (t, *J* = 6.8 Hz, 1 H), 5.04 (d, *J* = 6.8 Hz, 1 H), 3.76 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.7, 166.9, 138.5, 138.1, 137.3, 133.8, 131.9, 129.2, 128.7 (3 C), 127.1, 126.2, 125.6, 124.1, 121.9, 120.3, 117.8, 109.3, 108.9, 62.0, 41.2, 30.4, 21.4. HRMS (ESI) m/z calc'd for $C_{26}H_{23}N_2O_2S$ $[M+H]^+$: 427.1475, found 427.1478. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 14.85 (minor) and 19.81 min (major).

(3*R*,4*R*)-3-Benzamido-9-methyl-2-oxo-4-(o-tolyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3aj): White solid, m.p. 169–171 °C, 50 mg, 59% yield, $[\alpha]_D^{25}$ –85.0 (c 1.0, CH_2Cl_2), >19/1 dr, 70% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 6.8 Hz, 2 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 3 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 6.8 Hz, 1 H), 7.07–7.13 (m, 3 H), 6.51 (d, *J* = 6.4 Hz, 1 H), 5.80 (t, *J* = 6.8 Hz, 1 H), 5.37 (d, *J* = 6.4 Hz, 1 H), 3.74 (s, 3 H), 2.50 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.7, 167.2, 138.0, 136.8, 136.4, 133.6, 132.0, 130.7, 128.7, 128.2, 127.6, 127.0, 126.2, 124.1, 121.9, 120.2, 117.5, 110.2, 109.0, 62.2, 37.1, 30.4, 20.0. HRMS (ESI) m/z calc'd for $C_{26}H_{23}N_2O_2S$ $[M+H]^+$: 427.1475, found 427.1475. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 8.14 (major) and 17.25 min (minor).

(3*R*,4*R*)-3-Benzamido-9-methyl-2-oxo-4-(thiophen-2-yl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ak): White solid, m.p. 185–187 °C, 39 mg, 47% yield, $[\alpha]_D^{25}$ –116.0 (c 1.0, CH_2Cl_2), >19/1 dr, 80% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 6.8 Hz, 3 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 6.8 Hz, 1 H), 6.90 (t, *J* = 4.0 Hz, 1 H), 6.83 (d, *J* = 3.2 Hz, 1 H), 5.58 (t, *J* = 6.4 Hz, 1 H), 5.38 (d, *J* = 6.4 Hz, 1 H), 3.75 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.6, 166.9, 139.9, 138.0, 133.6, 132.1, 128.7, 127.2, 127.1, 126.1, 125.9, 125.4, 123.9, 122.1, 120.5, 117.8, 109.6, 109.1, 62.0, 36.6, 30.5. HRMS (ESI) m/z calc'd for $C_{23}H_{19}N_2O_2S_2$ $[M+H]^+$: 419.0882, found 419.0880. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 25.35 (minor) and 35.23 min (major).

(3*R*,4*R*)-3-Benzamido-6-fluoro-9-methyl-2-oxo-4-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ba): White solid, m.p. 188–190°C, 46 mg, 53% yield, $[\alpha]_D^{25}$ –125.6 (c 1.0, CH_2Cl_2), >19/1 dr, 75% ee. 1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.19–7.24 (m, 6 H), 7.01 (dd, *J* = 9.2, 2.0 Hz, 1 H), 6.92 (dt, *J* = 8.8, 2.0 Hz, 1 H), 6.60 (d, *J* = 6.8 Hz, 1 H), 5.64 (t, *J* = 6.8 Hz, 1 H), 4.98 (d, *J* = 6.8 Hz, 1 H), 3.72 (s, 3 H). 13C NMR (100.6 MHz, $CDCl_3$): δ 193.3, 166.9, 158.2 (d, J = 236.8 Hz), 137.1, 134.7, 133.6, 132.0, 129.0, 128.7, 128.5, 128.0, 127.1, 126.5 (d, *J* = 10.2 Hz), 126.0, 110.2 (d, *J* = 26.4 Hz), 109.7 (d, *J* = 9.8 Hz), 109.2 (d, *J* = 4.8 Hz), 103.0 (d, *J* = 24.1 Hz), 62.0, 41.3, 30.7. HRMS (ESI) m/z calc'd for $C_{25}H_{20}FN_2O_2S$ [M+H]+: 431.1224, found 431.1221. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 22.14 (major) and 72.05 min (minor).

(3*R*,4*R*)-3-Benzamido-6-bromo-9-methyl-2-oxo-4-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ca): White solid, m.p. 220–222 °C, 53 mg, 54% yield, $[\alpha]_D^{25}$ –93.8 (c 1.0, CH_2Cl_2), >19/1 dr, 84% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.2 Hz, 2 H), 7.47–7.57 (m, 4 H), 7.10–7.29 (m, 7 H), 6.65 (d, *J* = 5.6 Hz, 1 H), 5.68 (t, *J* = 5.6 Hz, 1 H), 5.04 (d, *J* = 5.6 Hz, 1 H), 3.77 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.1, 166.9, 136.9, 136.8, 133.6, 132.1, 129.0, 128.7, 128.5, 128.1, 127.7, 127.1, 125.9, 124.8, 120.4, 113.8, 110.4, 108.9, 62.0, 41.1, 30.6. HRMS (ESI) m/z calc'd for $C_{25}H_{20}BrN_2O_2S$ $[M+H]^+$: 491.0423, found 491.0417. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 24.82 (minor) and 36.32 min (major).

(3*R*,4*R*)-3-Benzamido-6,9-dimethyl-2-oxo-4-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3da): White solid, m.p. 179–181°C, 37 mg, 43% yield, $[\alpha]_D^{25}$ –65.9 (c 1.0, CH_2Cl_2), >19/1 dr, 80% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.26 (br. s, 5 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.19 (s, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 6.8 Hz, 1 H), 5.64 (t, *J* = 6.8 Hz, 1 H), 5.07 (d, *J* = 6.8 Hz, 1 H), 3.73 (s, 3 H), 2.39 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.9, 166.9, 137.4, 136.5, 133.7, 132.0, 129.7, 128.8, 128.7, 128.6, 127.8, 127.1, 126.4, 123.9, 123.5, 117.5, 108.8, 108.7, 62.2, 41.1, 30.5, 21.3. HRMS (ESI) m/z calc'd for $C_{26}H_{23}N_2O_2S$ $[M+H]^+$: 427.1475, found 427.1474. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): Rt = 12.86 (major) and 25.11 min (minor).

(3*R*,4*R*)-3-Benzamido-9-benzyl-2-oxo-4-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (3ea): White solid, m.p. 146–148°C, 40 mg, 41% yield, $[\alpha]_D^{25}$ –65.9 (c 1.0, CH_2Cl_2), >19/1 dr, 68% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.25–7.36 (m. 9 H), 7.07–7.18 (m, 4 H), 6.84 (d, *J* = 7.2 Hz, 1 H), 5.69 (t, *J* = 6.8 Hz, 1 H), 5.33 (s, 2 H), 5.11 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.6, 166.9, 137.9, 137.2, 136.2, 133.7, 132.0, 129.0, 128.9, 128.7, 128.6, 128.0, 127.9, 127.1, 126.5, 126.4, 124.0, 122.2, 120.5, 117.9, 110.0, 109.5, 62.1, 47.8, 41.3. HRMS (ESI) m/z calc'd for $C_{31}H_{25}N_2O_2S$ $[M+H]^+$: 489.1631, found 427.1474. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm): Rt = 17.56 (major) and 46.73 min (minor).

Conclusions

In conclusion, we have developed an organocatalyzed asymmetric formal [3+3] annulation of 1-methylindolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones, which provided a convenient approach to optically active conformationally strained *syn*-β-branched cyclic tryptophan derivatives. Under the catalysis of chiral squaramide derived from L-*tert*-leucine, a wide range of substituted 1-methylindolin-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones tolerated well in this transformation to provide the corresponding biologically significant cyclic tryptophan derivatives in acceptable yield with high levels of diastereo- and enantioselectivity.

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Notes and references

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14. CCDC-1432790 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Organocatalyzed enantioselective [3+3] annulation for the direct synthesis of conformationally constrained cyclic tryptophan derivatives

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Synthesis of optically active conformationally strained β-branched cyclic tryptophan derivatives has been realized via chiral squaramide catalyzed enantioselective formal [3+3] annulation of 1-mentylindoline-2-thiones and 4-arylmethylideneoxazolin-5(4*H*)-ones.