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Enantioselective Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters catalyzed by new squaramide-linked bisoxazoline–Zn(OTf)$_2$ complexes

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ABSTRACT

Enantioselective Friedel–Crafts alkylation reactions of indoles with β,γ-unsaturated α-ketoesters catalyzed by novel chiral C_2-symmetric squaramide-linked bisoxazoline–Zn(OTf)$_2$ complexes were investigated. The corresponding indole ketoesters were obtained in good to excellent yields (up to 98%) and with high enantioselectivities (up to 94% ee). This is the first report on the use of chiral squaramide-linked bisoxazoline **SQBOX** in a catalytic enanitioselective Friedel–Crafts alkylation reaction.

1. Introduction

Many scientists have focused on the catalytic enantioselective Friedel–Crafts reaction because this reaction is a versatile and powerful carbon—carbon bond-forming method in organic synthesis.[1,2] In medicinal chemistry and complex target synthesis, the framework of indole has a structural motif of particular value.[3] Among the various types of substrates used in enantioselective Friedel–Crafts alkylation, the reactions of indoles, β,γ-unsaturated α-ketoesters are important substrates for the synthesis of enantiomerically enriched indole derivatives. The indole derivatives of these alkylation reactions can be readily functionalized into the corresponding amino acids or α-hydroxy acids,[4] and these reactions have attracted much attention over the past decade.

In recent years, there have been a few reports based on chiral metal complexes for the asymmetric Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters.[5–9] Jørgensen and co-workers reported on the first enantioselective Friedel–Crafts reaction of aromatic C—H bonds to β,γ-unsaturated α-ketoesters catalyzed by chiral bisoxazoline (BOX)–Cu(II) complexes.[5] Desimoni and co-workers reported on the asymmetric Friedel–Crafts reaction between a series of substituted indoles and β,γ-unsaturated α-ketoesters catalyzed by the pybox–Sc(OTf)$_3$ complexes, and the alkylated products were obtained with high to excellent enantioselectivities (up to 99% ee).[6] In 2010, Feng and co-workers reported on the first example of central metal controlled reversal of enantioselectivity in asymmetric Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters using the *N*,*N*′-dioxide–AgAsF$_6$ or Sm(OTf)$_3$ complexes as catalysts.[7] Thereafter, a binary chiral phosphoric acid/MgF$_2$ catalyst has been applied to the same reaction,[8] and afforded relatively lower enantioselectivities (82–92% ee) than those obtained using Lewis acid catalysts. In 2012, using heteroarylidene–tethered bisoxazoline copper complexes, Fu et al. expanded upon these asymmetric Friedel–Crafts alkylations of indoles with β,γ-unsaturated α-ketoesters to unprotected pyrroles, the 3-indolyl adducts were achieved with excellent enantioselectivities, but 2-pyrrolyl adducts were obtained in lower enantioselectivities than the indole derivatives.[9]

Although a number of methods have already been published that describe high to excellent enantioselectivities for this reaction using various catalysts, the development of inexpensive and facile synthesized ligands remains a challenge. Meanwhile, this well-established Friedel–Crafts reaction can be used as an evaluation platform for new catalysts' development in a modular manner.[10] Oxazoline is a significant type of 'privileged ligand' due to its modular nature and has been successfully applied to various catalytic asymmetric reactions.[11] The reported results have demonstrated that the linker in bioxazoline ligands may have an important influence on the catalytic performance.[2e,12] Meanwhile, squaramides have been demonstrated to be exceptionally versatile scaffolds and efficient catalysts in asymmetric organocatalysis.[13] We envisioned that the modular assembly of the oxazoline and squaramide moieties together will provide a facile method for the rapid synthesis of squaramide-linked bisoxazoline **SQBOX** ligands.

Herein we report the modular synthesis of a series of squaramide-linked bisoxazoline ligands. Their primary application in catalytic asymmetric Friedel–Crafts alkylations of indoles with β,γ-unsaturated α-ketoesters was evaluated, and the corresponding substituted 4-(indol-3-yl)-2-oxo-4-arylbutyric acid esters were obtained in good to excellent yields and with high enantioselectivities (up to 94% ee).

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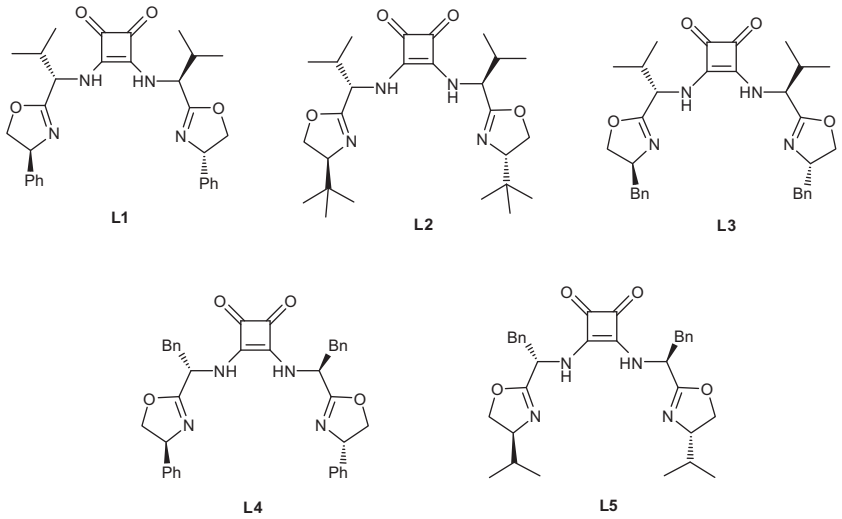
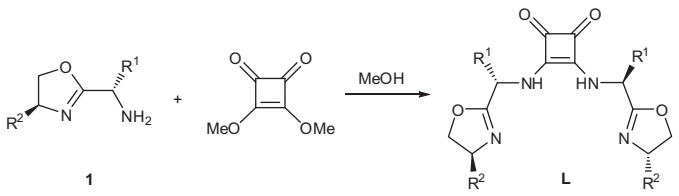


Figure 1. Squaramide-linked bisoxazoline ligands.

2. Results and discussion

Firstly, 2-(aminomethyl)oxazoline modules **1** were synthesized following the literature.[13] A small library of C_2-symmetric modular squaramide-linked bisoxazoline ligands **L1**–**L5** (Fig. 1) was then easily synthesized from the reaction of 2-(aminomethyl)oxazolines **1** and dimethyl squarate (Scheme 1). These squaramide-linked bisoxazolines were used as organocatalysts to catalyze asymmetric Friedel–Crafts alkylations of indole **2a** with α-ketoester **3a**, the corresponding product was obtained in very low yield in racemic form. Next, the catalytic performance of these squaramide-bisoxazoline ligand metal complexes in the asymmetric Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters was investigated.



Scheme 1. Modular synthesis of squaramide-linked bisoxazoline ligands.

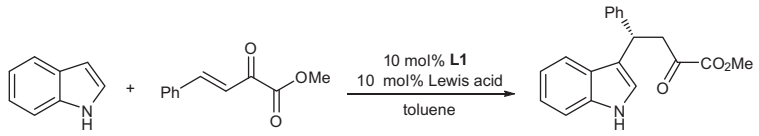
In order to optimize the reaction conditions, ligand **L1** was first chosen to explore the effect of Lewis acids at 10 mol % catalyst loading. The effect of the Lewis acid was firstly screened in the model alkylation reaction of indole **2a** with 2-oxo-4-phenyl-but-3-enoic acid methyl ester **3a** in toluene at room temperature, and the results are summarized in Table 1. According to the initial experiment, $Zn(OTf)_2$ gave the most promising results of 86% ee and 80% yield (Table 1, entry 1). In most cases, the presence of a catalytic amount of Lewis acid (10 mol %) was found to remarkably accelerate the reaction. However, the enantioselectivities varied greatly (0–86% ee) depending on the Lewis acid used. Most of the Lewis acids examined only afforded **4a** in nil or modest ee values (entries 3–18). The results also indicate that the anion in the Lewis acid plays a prominent role in the catalysis. For instance, the catalyst generated from $Zn(OTf)_2$ and ligand **L1** afforded the product **4a** with 86% ee (Table 1, entry 1), whereas changing the anion of the zinc salt to either a chloride or perchlorate anion led to an erosion in the enantioselectivity (entries 15 and 18). From the above evaluation, the **L1**–$Zn(OTf)_2$ complex was chosen as the best catalyst and employed in subsequent optimization reactions.

In order to further optimize the reaction conditions, the effect of solvents, the amount of indole, catalyst loading, and reaction temperature were then evaluated and the results are summarized in Table 2. The solvents had a significant effect on the yields and enantioselectivity. When the reaction was carried out in chloroform or acetonitrile, the product was obtained in excellent yields (97% and 99%), but the enantioselectivities were moderate (Table 2, entries 7 and 8). while other solvents such as THF, dichloromethane (DCM), ether, ethyl acetate, acetone, and xylene gave moderate yields and enantioselectivities. 1,2-Dichloroethane and toluene were more suitable for this reaction in terms of enantioselectivity, and the best results (80% yield and 86% ee) were obtained in toluene (Table 2, entry 1). In order to evaluate the influence of the mixed solvent, we tested the mixed solvent effect at different temperatures. Poor results (69% yield and 40% ee) were obtained in THF–PhMe (1:1) solvent (Table 2, entry 12). The DCM–PhMe (1:1) mixed solvent afforded good to high enantioselectivities (81–88% ee, Table 2, entries 13–15), and the best result (93% yield and 90% ee) was obtained at room temperature. When the reaction was performed in $CHCl_3$–PhMe (1:1) mixed solvent, preferable enantioselectivities (86–93% ee) were obtained (Table 2, entries 16–18); the best result (89% yield and 93% ee) was obtained at 0 °C. In general, the reaction temperature had no obvious effect on the enantioselectivities. Lowering the reaction temperature to −10 °C, led to a similar enantioselectivity (92% ee) (Table 2, entry 17), while the yield slightly decreased to 87%.

The different structures of the ligands had distinct effects on the enantioselectivity. The effect of different ligands was then evaluated in this reaction using $CHCl_3$–PhMe (1:1) mixed solvent at °C (Table 2, entries 18–22). Ligand **L2** afforded the product with very low enantioselectivity, while ligands **L3**–**L5** gave moderate to good enantioselectivities. The best result was obtained with ligand **L1**. Reducing the catalyst loading to 5 mol %, gave a similar yield (97%, Table 2, entry 23), while the enantioselectivity slightly decreased to 87% ee. When 1 equiv of indole was used, 93% ee and 48% yield were obtained (Table 2, entry 24). From the above evaluation, the optimized reaction conditions were found to be a combination of 10 mol % of **L1** with 10 mol % of $Zn(OTf)_2$, and 1.5 equiv of indole in $CHCl_3$–PhMe (1:1) (2 mL) at 0 °C.

Under the optimal reaction conditions, the substrate scope of the asymmetric Friedel–Crafts alkylation reaction of indoles with

Table 1
Screen of Lewis acid for catalytic enantioselective Friedel–Crafts reaction of indole **2a** with β,γ-unsaturated α-ketoester **3a**[a]

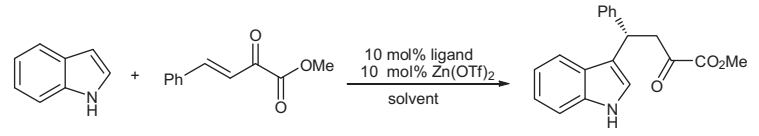


2a **3a** **4a**

Entry	Lewis acid	Yield[b] (%)	ee[c] (%)
1	$Zn(OTf)_2$	80	86
2	$La(OTf)_3$	11	68
3	$PdCl_2$	53	8
4	$Mg(OTf)_2$	78	20
5	$Pd(OAc)_2$	66	4
6	$Cu(OTf)_2$	33	3
7	$Sc(OTf)_3$	49	3
8	$CuOTf{\cdot}1/2C_6H_6$	20	1
9	AgOTf	21	4
10	$Yb(OTf)_3$	25	5
11	$In(OTf)_3$	20	2
12	LiOTf	7	0
13	Ag_2CO_3	77	20
14	$AgPF_4$	40	15
15	$ZnCl_2$	96	11
16	$Ni(ClO_4)_2{\cdot}H_2O$	66	39
17	$Pd(PPh_3)_4$	49	3
18	$Zn(ClO_4)_2{\cdot}H_2O$	43	20

[a] Unless otherwise noted, reactions were carried out with **L1** (10 mol %), Lewis acid (10 mol %), **2a** (0.3 mmol) and **3a** (0.2 mmol) in PhMe (2.0 mL) at room temperature for 4–10h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis. The absolute configuration was assigned by comparison with literature data.[5,6]

Table 2
Optimization of the reaction conditions for catalytic enantioselective Friedel–Crafts alkylation of indole **2a** with β,γ-unsaturated α-ketoester **3a**[a]



2a **3a** **4a**

Entry	Ligand	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	**L1**	PhMe	rt	80	86
2	**L1**	THF	rt	64	33
3	**L1**	DCM	rt	48	65
4	**L1**	EtOAc	rt	72	73
5	**L1**	CH_3COCH_3	rt	63	67
6	**L1**	Et_2O	rt	61	55
7	**L1**	$CHCl_3$	rt	99	77
8	**L1**	CH_3CN	rt	97	39
9	**L1**	$ClCH_2CH_2Cl$	rt	72	82
10	**L1**	Xylene	rt	66	63
11	**L1**	MeOH	rt	77	0
12	**L1**	THF/PhMe = 1:1	rt	69	40
13	**L1**	DCM/PhMe = 1:1	rt	93	88
14	**L1**	DCM/PhMe = 1:1	0	79	87
15	**L1**	DCM/PhMe = 1:1	−10	82	81
16	**L1**	$CHCl_3$/PhMe = 1:1	rt	90	86
17	**L1**	$CHCl_3$/PhMe = 1:1	−10	87	92
18	**L1**	$CHCl_3$/PhMe = 1:1	0	89	93
19	**L2**	$CHCl_3$/PhMe = 1:1	0	82	20
20	**L3**	$CHCl_3$/PhMe = 1:1	0	81	83
21	**L4**	$CHCl_3$/PhMe = 1:1	0	85	65
22	**L5**	$CHCl_3$/PhMe = 1:1	0	87	62
23[d]	**L1**	$CHCl_3$/PhMe = 1:1	0	97	87
24[e]	**L1**	$CHCl_3$/PhMe = 1:1	0	48	93

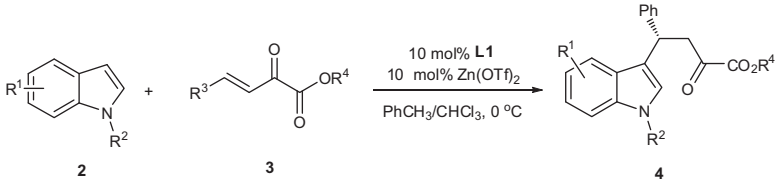
[a] Unless otherwise noted, reactions were carried out with **L1** (10 mol %), Lewis acid (10 mol %), **2a** (0.3 mmol), and **3a** (0.2 mmol) in PhMe (2.0 mL) at room temperature for 4–12h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 5 mol % ligand-Lewis acid was used.
[e] 0.2 mmol indole was used.

β,γ-unsaturated α-ketoesters was investigated further. The results are summarized in Table 3. We first studied a variety of β,γ-unsaturated α-ketoesters bearing different substituents in the benzene ring (Table 3, entries 1–9). All of these substrates reacted with the indole and afforded the corresponding products **4a**–**4i** in good to excellent yields (74–98%) and with good to high enantioselectivities (71–94% ee). The steric and electronic nature of the substituents in the benzene ring of the β,γ-unsaturated α-ketoesters, only slightly affected the yields and enantioselectivities. The strong electron-withdrawing substituent NO_2 led to a lower yield and enantioselectivity (Table 3, entries 7 and 8). The substrate scope of the reaction was further demonstrated by varying the substituent of the indoles. When various indole derivatives bearing either electron-donating or electron-withdrawing substituents at the 5-position were used, the reaction proceeded smoothly and afforded the corresponding products **4k**–**4l** in good yields and with high enantioselectivities (Table 3, entries 11–13). However, when *N*-Me indole was used, the enantioselectivity decreased to 32% ee (Table 3, entry 10). Extending the substrates to ester groups, the corresponding reactions also proceeded well and gave the alkylation products **4n**–**4q** in high yields and with high enantioselectivities (Table 3, entry 14–17). The absolute configuration of products **4** was assigned as (*S*) by comparison with previous literature reports.[5,6]

Further substrate scope with other non-indole nucleophiles was also investigated. When pyrrole was used, the product was obtained as complex mixtures. As shown in Scheme 2, when 3-methoxyphenol was used, the corresponding product **4r** was obtained with excellent enantioselectivity (95% ee) but with very lower reactivity (35% yield).

As a control experiment, (2*S*)-2-methyl-1-((4*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl)propylamine **1a** was also used as the ligand in the model reaction under the optimized reaction; **1a**–$Zn(OTf)_2$ complexes afforded the corresponding product in 37% yield and with 20% ee. This result demonstrates that the squaramide linker is crucial for generating a synergistic catalytic effect. A tentative transition state (Fig. 2) has been proposed to explain the observed stereochemical outcome. The β,γ-unsaturated α-ketoester coordinates to the zinc center in an approximately tetrahedral geometry in the **L1**–$Zn(OTf)_2$ complex, and the indole attacks the β,γ-unsaturated α-ketoesters preferably from the *Si* face, leading to predominant formation of the (*S*)-configured adduct. The high enantioselectivity comes from the well-defined squaramide-bisoxazoline chiral environment around the zinc center.

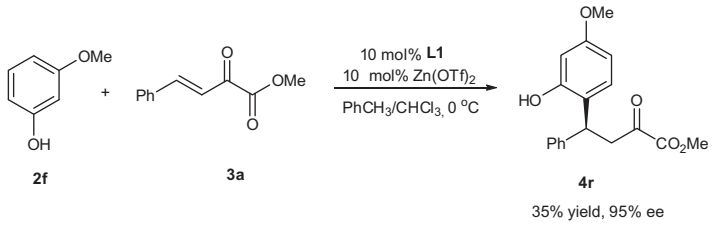
Table 3
Catalytic enantioselective Friedel–Crafts reaction of indoles **2** with β,γ-unsaturated α-ketoesters **3**[a]



2 **3** **4**

Entry	**2**	R^1	R^2	**3**	R^3	R^4	Time (h)	Product	Yield[b] (%)	ee[c] (%)
1	**2a**	H	H	**3a**	Ph	Me	4	**4a**	89	93
2	**2a**	H	H	**3b**	4-ClC_6H_4	Me	4	**4b**	98	88
3	**2a**	H	H	**3c**	4-BrC_6H_4	Me	4	**4c**	82	81
4	**2a**	H	H	**3d**	4-FC_6H_4	Me	12	**4d**	92	89
5	**2a**	H	H	**3e**	4-$MeOC_6H_4$	Me	4	**4e**	86	89
6	**2a**	H	H	**3f**	4-MeC_6H_4	Me	4	**4f**	98	91
7	**2a**	H	H	**3g**	4-$NO_2C_6H_4$	Me	12	**4g**	83	79
8	**2a**	H	H	**3h**	2-$NO_2C_6H_4$	Me	12	**4h**	74	71
9	**2a**	H	H	**3i**	3,4-$(MeO)_2C_6H_3$	Me	12	**4i**	92	89
10	**2b**	H	Me	**3a**	Ph	Me	8	**4j**	87	32
11	**2c**	5-Me	H	**3a**	Ph	Me	8	**4k**	86	91
12	**2d**	5-Cl	H	**3a**	Ph	Me	8	**4l**	87	83
13	**2e**	5-MeO	H	**3a**	Ph	Me	8	**4m**	87	94
14	**2a**	H	H	**3j**	Ph	Et	6	**4n**	83	89
15	**2a**	H	H	**3k**	Ph	Bn	6	**4o**	84	85
16	**2a**	H	H	**3l**	Ph	*i*-Pr	6	**4p**	81	86
17	**2a**	H	H	**3m**	Ph	Vinyl	6	**4q**	86	89

[a] Unless otherwise noted, reactions were carried out with **L1** (10 mol %), $Zn(OTf)_2$ (10 mol %), **2** (0.3 mmol), and **3** (0.2 mmol) in 2 mL of PhMe–$CHCl_3$ (1:1) at 0 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis, the absolute configuration was determined by comparison with literature data.[5,6]



2f **3a** **4r**
35% yield, 95% ee

Scheme 2. Further investigation of substrate scope.

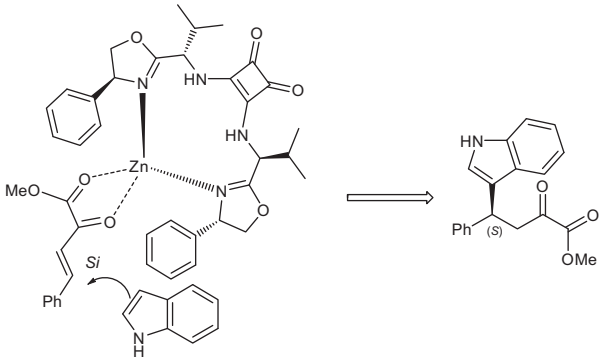


Figure 2. The proposed transition state for stereochemical control.

3. Conclusion

In conclusion, a series of novel modular C_2-symmetric squaramide-linked bisoxazoline ligands have been synthesized. These squaramide-linked bisoxazoline–Zn(OTf)$_2$ complexes have been applied to enantioselective Friedel–Crafts reactions of indoles with β,γ-unsaturated α-ketoesters, and the corresponding alkylation products were obtained in good to excellent yields (up to 98%) and with high enantioselectivities (up to 93% ee). This enantioselective protocol provides practical and efficient access to indole derivatives bearing a chiral tertiary carbon center and ketoester functional groups, which may be further transformed into types of potential chiral intermediates and functional materials. Further investigations on the applications of novel chiral C_2-symmetric squaramide-bisoxazoline ligands in other asymmetric catalytic reactions are currently in progress in our laboratory.

4. Experimental

4.1. General methods

Commercially available compounds were used without further purification. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured with an XT-4 melting point apparatus without correction. The ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz or Bruker 400 MHz spectrometer, while ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer. The high resolution mass ESI-HRMS spectra were obtained using electron spray ionization (ESI) with a Bruker APEX IV FTMS spectrometer. Optical rotations were measured on a WZZ-3 polarimeter at the indicated concentration with unit g per 100 mL. The enantiomeric excesses of the products were determined by chiral HPLC analysis using Agilent 1200 LC instrument with Daicel Chiralpak AD-H, IA, IB or AS-H column.

4.2. Materials

2-(Aminomethyl)oxazolines **1** were prepared by following a previously reported method.[14]

4.2.1. Typical procedure for the preparation of squaramide-bisoxazoline ligand

A mixture of (2*S*)-2-methyl-1-((4*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl)propylamine **1a** (479.6 mg, 2.2 mmol) and dimethyl squarate (142.0 mg, 1 mmol) in MeOH (5 mL) was stirred at room temperature for 4 h. The solvent was evaporated and the crude residue material was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to afford a white solid **L1** (380.3 mg, 74% yield). Following this typical procedure, the other following ligands **L2–5** were prepared.

4.2.2. 3,4-Bis((*S*)-1-((*S*)-4,5-dihydro-4-phenyloxazol-2-yl)-2-methylpropylamino)cyclobut-3-ene-1,2-dione L1

74% yield, mp 114–116 °C, $[\alpha]_D^{19} = -6.0$ (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15–8.02 (m, 2H, NH), 7.36–7.32 (m, 4H, ArH), 7.29–7.24 (m, 6H, ArH), 5.29–5.23 (m, 2H, CH), 4.90–4.82 (m, 2H, CH), 4.78–4.74 (m, 2H, CH), 4.17–4.04 (m, 2H, CH), 2.23–2.13 (m, 2H, CH), 0.97 (d, J = 6.8 Hz, 12H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.6, 167.3, 165.6, 142.2, 128.45, 128.40, 127.2, 126.6, 126.5, 126.4, 74.6, 68.3, 56.5, 31.9, 30.5, 18.4, 17.3 ppm. IR (KBr): *v* 3252, 3063, 3030, 2965, 2903, 2877, 1799, 1669, 1590, 1526, 1494, 1454, 1390, 1371, 1344, 1311, 1148, 1080, 987, 927, 758, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{35}N_4O_4$ $[M+H]^+$ 515.26528, found 515.26559.

4.2.3. 3,4-Bis((*S*)-1-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-2-methylpropylamino)cyclobut-3-ene-1,2-dione L2

99% yield, mp 99–102 °C, $[\alpha]_D^{19} = -71.3$ (*c* 0.085, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00–7.83 (m, 2H, NH), 4.69 (dd, J_1 = 5.8 Hz, J_2 = 9.8 Hz, 2H, CH), 4.25 (t, J = 9.6 Hz, 2H, CH), 4.11 (t, J = 8.4 Hz, 2H), 3.84 (t, J = 9.0 Hz, 2H, CH), 2.10–2.04 (m, 2H, CH), 0.91 (d, J = 6.8 Hz, 12H, CH_3), 0.81 (s, 18H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.6, 167.5, 164.2, 74.3, 68.6, 56.6, 33.2, 31.7, 25.5, 18.6, 17.2 ppm. IR (KBr): *v* 3148, 2962, 2905, 2873, 1803, 1671, 1587, 1534, 1465, 1393, 1360, 1245, 1209, 1151, 1098, 1046, 984, 929, 915, 840, 767, 739, 684 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{43}N_4O_4$ $[M+H]^+$ 475.32788, found 475.32895.

4.2.4. 3,4-Bis((*S*)-1-((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylamino)cyclobut-3-ene-1,2-dione L3

75% yield, mp 134–136 °C, $[\alpha]_D^{19} = -61.1$ (*c* 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07–7.94 (m, 2H, NH), 7.29–7.16 (m, 10H, ArH), 4.74–4.66 (m, 2H, CH), 4.47–4.28 (m, 4H, CH_2), 4.04–3.97 (m, 2H, CH), 2.94–2.72 (m, 2H, CH), 2.09–2.03 (m, 2H, CH), 0.92–0.87 (m, 12H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.4, 167.1, 164.6, 137.8, 129.3, 129.2, 129.1, 128.2, 128.1, 128.0, 126.1, 71.7, 71.6, 66.4, 66.3, 56.3, 40.7, 31.8, 18.4, 17.1 ppm. IR (KBr): *v* 3243, 3060, 3027, 2964, 2932, 2875, 1799, 1671, 1591, 1527, 1496, 1453, 1390, 1371, 1344, 1311, 1243, 1205, 1150, 1095, 1073, 1029, 985, 948, 850, 752, 701 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{32}H_{39}N_4O_4$ $[M+H]^+$ 543.29658, found 543.29622.

4.2.5. 3,4-Bis((*S*)-1-((*S*)-4,5-dihydro-4-phenyloxazol-2-yl)-2-phenylethylamino)cyclobut-3-ene-1,2-dione L4

45% yield, mp 121–124 °C, $[\alpha]_D^{19} = +19.6$ (*c* 0.105, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10–7.96 (m, 2H, NH), 7.49–6.93 (m, 20 H, ArH), 5.24–5.16 (m, 4H, CH_2), 4.74 (dd, J_1 = 9.2 Hz, J_2 = 18.4 Hz, 2H, CH_2), 4.05 (t, J = 8.4 Hz, 2H, CH), 3.26–3.07 (m, 4H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 167.3, 141.3, 135.45, 129.6, 129.4, 128.71, 128.69, 128.56, 128.48, 127.8, 127.7, 127.1, 127.0, 126.6, 126.5, 75.8, 75.7, 69.0, 53.3, 52.8, 40.2 ppm. IR (KBr): *v* 3125, 3029, 2935, 1800, 1676, 1655 1575, 1550, 1492, 1455, 1268, 1242, 1214, 1166, 1123 1080, 1029, 1001, 917, 851, 757, 739, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{38}H_{35}N_4O_4$ $[M+H]^+$ 611.26528, found 611.26486.

4.2.6. 3,4-Bis((*S*)-1-((*S*)-4,5-dihydro-4-isopropyloxazol-2-yl)-2-phenylethylamino)cyclobut-3-ene-1,2-dione L5

37% yield, mp 126–139 °C, $[\alpha]_D^{19} = -52.3$ (*c* 0.135, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, J = 6.8 Hz, 2H, NH), 7.66–6.97 (m, 10H, ArH), 5.05 (br s, 2H, CH), 4.32 (t, J = 9.2 Hz, 2H, CH), 4.03 (t, J = 7.8 Hz, 2H, CH), 3.93–3.76 (m, 2H, CH), 3.11 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 2H, CH_2), 3.01 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz,

2H, CH_2), 1.63–1.58 (m, 2H, CH), 0.86 (d, J = 6.4 Hz, 6H, CH_3), 0.79 (d, J = 6.4 Hz, 6H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.5, 166.8, 164.0, 136.0, 129.3, 128.3, 126.6, 71.2, 70.2, 52.3, 48.6, 31.9, 18.4, 18.0 ppm. IR (KBr): ν 3157, 3059, 3029, 2956, 1802, 1675, 1649, 1570, 1495, 1467, 1386, 1240, 1223, 1116, 1006, 978, 953, 914, 855, 776, 751, 726, 698 cm^{-1}. HRMS (ESI): m/z calcd for $C_{32}H_{39}N_4O_4$ $[M+H]^+$ 543.29658, found 543.29739.

4.3. General procedure for the enantioselective Friedel–Crafts alkylation reaction

A mixture of ligand **L1** (10.4 mg, 0.02 mmol), $Zn(OTf)_2$ (7.2 mg, 0.02 mmol) and β,γ-unsaturated α-ketoester **3** (0.2 mmol) in $CHCl_3$–PhMe (1:1) mixed solvent (2 mL) was stirred at room temperature for 0.5–1 h under an argon atmosphere. Next, indole **2** (0.3 mmol) was added with stirring. The reaction mixture was stirred for the indicated time and then directly purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 4:1) to give product **4**.

4.3.1. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid methyle ster 4a[9]

Compound **4a** was obtained according to the general procedure as a white solid (54.0 mg, 89% yield). Mp 99–102 °C, $[\alpha]_D^{20}$ = +26.3 (c 3.15, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 12.4 min, t_R (major) = 14.5 min, 93% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, NH), 7.41 (d, J = 8.0 Hz, 1H, ArH), 7.22–7.33 (m, 5H, ArH), 7.18–7.11 (m, 2H, ArH), 7.03–6.97 (m, 2H, ArH), 4.91 (t, J = 7.6 Hz, 1H, CH), 3.74 (s, 3H, OCH_3), 3.67 (dd, J = 17.0, 7.6 Hz, 1H, CH_2), 3.59 (dd, J_1 = 17.0 Hz, J_2 = 7.8 Hz, 1H, CH_2) ppm. IR (KBr): ν 3401, 3021, 2956, 1729, 1717, 1602, 1491, 1459, 1434, 1417, 1335, 1298, 1204, 1100, 1065, 822, 777, 759, 750, 700 cm^{-1}.

4.3.2. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-chlorophenyl)butyric acid methyl ester 4b[7]

Compound **4b** was obtained according to the general procedure as a white solid (66.9 mg, 98% yield). Mp 148–150 °C, $[\alpha]_D^{20}$ = +20.9 (c 3.35, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detected at 254 nm): t_R (minor) = 13.2 min, t_R (major) = 19.9 min, 88% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.39–7.14 (m, 7H, ArH), 7.05–6.96 (m, 2H, ArH), 4.89 (t, J = 7.4 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.66 (dd, J_1 = 17.2 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.57 (dd, J_1 = 17.2 Hz, J_2 = 8.0 Hz, 1H, CH_2) ppm. IR (KBr): ν 3364, 3061, 2956, 2876, 1746, 1638, 1547, 1489, 1458, 1437, 1418, 1399, 1338, 1285, 1255, 1235, 1219, 1091, 1071, 1015, 969, 943, 834, 820, 791, 761, 749, 727, 702, 668 cm^{-1}.

4.3.3. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-bromophenyl)butyric acid methyl ester 4c[7]

Compound **4c** was obtained according to the general procedure as a white solid (63.0 mg, 82% yield). Mp 153–154 °C, $[\alpha]_D^{20}$ = +11.9 (c 3.15, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 13.7 min, t_R (major) = 20.9 min, 81% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.39–7.32 (m, 4H, ArH), 7.21–7.14 (m, 3H, ArH), 7.03 (t, J = 7.4 Hz, 2H, ArH), 4.88 (t, J = 7.4 Hz, 1H, CH), 3.79 (s, 3H, OCH_3), 3.67 (dd, J_1 = 17.2 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.57 (dd, J_1 = 17.2 Hz, J_2 = 8.0 Hz, 1H, CH_2) ppm. IR(KBr): ν 3362, 3048, 2953, 2899, 2877, 1746, 1737, 1637, 1547, 1486, 1458, 1437, 1419, 1400, 1337, 1283, 1255, 1235, 1220, 1071, 1012, 970, 943, 831, 788, 767, 750, 725, 675 cm^{-1}.

4.3.4. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-florophenyl)butyric acid methyl ester 4d[7]

Compound **4d** was obtained according to the general procedure as a white solid (59.0 mg, 92% yield). Mp 110–113 °C, $[\alpha]_D^{20}$ = +41.7 (c 3.00, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 12.0 min, t_R (major) = 16.4 min, 89% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH), 7.39–7.26 (m, 4H, ArH), 7.17 (t, J = 7.6 Hz, 1H, ArH), 7.03–6.92 (m, 4H, ArH), 4.90 (t, J = 7.4 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.67 (dd, J_1 = 17.0 Hz, J_2 = 7.0 Hz, 1H, CH_2), 3.58 (dd, J_1 = 17.2 Hz, J_2 = 8.0 Hz, 1H, CH_2) ppm. IR (KBr): ν 3375, 3141, 2960, 2927, 2893, 1742, 1732, 1603, 1505, 1459, 1428, 1391, 1337, 1286, 1241, 1218, 1069, 1015, 962, 834, 743, 705, 677 cm^{-1}.

4.3.5. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-methoxyphenyl)butyric acid methyl ester 4e[7]

Compound **4e** was obtained according to the general procedure as a white solid (65.0 mg, 86% yield). Mp 98–103 °C, $[\alpha]_D^{20}$ = +24.1 (c 2.85, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AS-H column, *n*-hexane–2-propanol 85:15, flow rate 1.0 mL/min, detection at 230 nm): t_R (minor) = 23.5 min, t_R (major) = 29.0 min, 89% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H, NH), 7.41 (d, J = 7.6 Hz, 1H, ArH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.25–7.19 (m, 2H, ArH), 7.14 (t, J = 7.4 Hz, 1H, ArH), 7.03–6.96 (m, 2H, ArH), 6.85–6.73 (m, 2H, ArH), 4.86 (t, J = 7.2 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.67 (dd, J_1 = 17.2 Hz, J_2 = 7.2 Hz, 1H, CH_2), 3.57 (dd, J_1 = 16.8 Hz, J_2 = 8.0 Hz, 1H, CH_2) ppm. IR (KBr): ν 3366, 2949, 2832, 1747, 1737, 1611, 1510, 1460, 1398, 1338, 1289, 1247, 1174, 1072, 1038, 840, 770, 748, 706, 677 cm^{-1}.

4.3.6. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-methylphenyl)butyric acid methyl ester 4f[6]

Compound **4f** was obtained according to the general procedure as a white solid (63.0 mg, 98% yield). Mp 125–127 °C, $[\alpha]_D^{20}$ = +28.0 (c 1.20, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 13.7 min, t_R (major) = 17.2 min, 91% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H, NH), 7.42 (d, J = 7.6 Hz, 1H, ArH), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.23–7.18 (m, 2H, ArH), 7.15–7.11 (m, 1H, ArH), 7.06 (d, J = 8.0 Hz, 2H, ArH), 7.03–6.99 (m, 1H, ArH), 6.98 (d, J = 2.0 Hz, 1H, ArH), 4.87 (t, J = 7.6 Hz, 1H, CH), 3.74 (s, 3H, OCH_3), 3.67 (dd, J_1 = 17.0 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.57 (dd, J_1 = 16.8 Hz, J_2 = 8.0 Hz, 1H, CH_2), 2.27 (s, 3H, CH_3) ppm. IR (KBr): ν 3361, 3043, 3018, 2951, 2921, 2879, 1747, 1734, 1618, 1511, 1459, 1437, 1402, 1337, 1288, 1256, 1236, 1221, 1072, 973, 828, 770, 743, 724, 702, 676 cm^{-1}.

4.3.7. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(4-nitrophenyl)butyric acid methyl ester 4g[7]

Compound **4g** was obtained according to the general procedure as a white solid (58.0 mg, 83% yield). Mp 153–155 °C, $[\alpha]_D^{20}$ = +13.6 (c 1.70, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 24.9 min, t_R (major) = 32.8 min, 79% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, NH), 8.11 (d, J = 8.8 Hz, 2H, ArH), 7.50 (d, J = 8.8 Hz, 2H, ArH), 7.34 (t, J = 8.2 Hz, 2H, ArH), 7.20–7.15 (m, 1H, ArH), 7.09 (d, J = 1.6 Hz, 1H, ArH), 7.05–7.01 (m, 1H, ArH), 5.02 (t, J = 7.4 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 3.74 (dd, J_1 = 17.6, J_2 = 6.8 Hz, 1H, CH_2), 3.64 (dd, J_1 = 18.0 Hz, J_2 = 8.0 Hz, 1H, CH_2) ppm. IR (KBr): ν 3371, 3115, 3074, 2957, 2881, 1745, 1608, 1598, 1520, 1459, 1401, 1349, 1284, 1255, 1068, 947, 859, 785, 754, 716, 663 cm^{-1}.

4.3.8. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(2-nitrophenyl)butyric acid methyl ester 4h

Compound **4h** was obtained according to the general procedure as a white solid (52.0 mg, 74% yield). Mp 172–174 °C, $[\alpha]_D^{20}$ = +64.8 (*c* 1.70, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak IA column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 13.4 min, t_R (major) = 21.4 min, 71% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H, NH), 7.83–7.80 (m, 1H, ArH), 7.44–7.38 (m, 2H, ArH), 7.35–7.29 (m, 3H, ArH), 7.17–7.13 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.12 (d, J = 1.6 Hz, 1H, ArH), 7.03–6.98 (m, 1H, ArH), 5.57 (t, J = 7.4 Hz, 1H, CH), 3.829 (s, 3H, OCH_3), 3.825 (dd, J_1 = 17.4 Hz, J_2 = 8.0 Hz, 1H, CH_2), 3.56 (dd, J_1 = 17.4 Hz, J_2 = 7.0 Hz, 1H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 161.1, 149.6, 137.6, 136.5, 132.8, 130.0, 127.5, 126.2, 124.4, 122.6, 122.0, 119.9, 119.2, 116.5, 111.2, 53.1, 45.3, 32.4 ppm. IR (KBr): ν 3459, 3445, 3062, 2953, 1732, 1605, 1525, 1458, 1437, 1417, 1399, 1359, 1295, 1254, 1068, 945, 857, 790, 741, 708, 667 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{17}N_2O_5$ $[M+H]^+$ 353.11320, found 353.11338; calcd for $C_{19}H_{20}N_3O_5$ $[M+NH_4]^+$ 370.13975, found 370.13944.

4.3.9. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-(3,4-dimethoxyphenyl)butyric acid methyl ester 4i

Compound **4i** was obtained according to the general procedure as a white solid (67.0 mg, 92% yield). Mp 233–235 °C, $[\alpha]_D^{20}$ = +80.7 (*c* 3.35, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak IB column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 230 nm): t_R (minor) = 19.6 min, t_R (major) = 23.8 min, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H, NH), 7.44 (d, J = 8.0 Hz, 1H, ArH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.17–7.12 (m, 1H, ArH), 7.05–7.01 (m, 1H, ArH), 6.99 (d, J = 2.0 Hz, 1H, ArH), 6.86–6.84 (m, 2H, ArH), 6.75 (d, J = 8.8 Hz, 1H, ArH), 4.87 (t, J = 7.6 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.65 (dd, J_1 = 16.8 Hz, J_2 = 6.8 Hz, 1H, CH_2), 3.59 (dd, J_1 = 16.8 Hz, J_2 = 7.8 Hz, 1H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 161.3, 148.8, 147.6, 136.6, 135.7, 126.3, 122.2, 121.4, 119.6, 119.45, 119.35, 118.5, 111.3, 111.13, 111.09, 55.8, 52.9, 45.7, 37.5 ppm. IR (KBr): ν 3372, 2934, 2837, 1730, 1593, 1515, 1460, 1420, 1261, 1140, 1075, 1024, 857, 809, 745 m^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$ 368.14925, found 368.14927; calcd for $C_{21}H_{25}N_2O_5$ $[M+NH_4]^+$ 385.17580, found 385.17559.

4.3.10. (*S*)-4-(1-Methyl-1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester 4j[5,6]

Compound **4j** was obtained according to the general procedure as a yellow solid (64.0 mg, 87% yield). Mp 106–108 °C, $[\alpha]_D^{20}$ = +18.7 (*c* 3.20, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AS-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 230 nm): t_R (minor) = 8.7 min, t_R (major) = 10.0 -min, 32% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.33 (d, J = 7.2 Hz, 2H, ArH), 7.27–7.23 (m, 3H, ArH), 7.19–7.14 (m, 2H, ArH), 7.03–6.99 (m, 1H, ArH), 6.86 (s, 1H, ArH), 4.91 (t, J = 7.6 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, NCH_3), 3.67 (dd, J_1 = 17.2, J_2 = 7.2 Hz, 1H, CH_2), 3.59 (dd, J_1 = 17.2, J_2 = 7.8 Hz, 1H, CH_2) ppm. IR (KBr): ν 1729, 1477, 1374, 1329, 1296, 1258, 1085, 1063, 744, 703, 668 cm^{-1}.

4.3.11. (*S*)-4-(5-Methyl-1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester 4k[7]

Compound **4k** was obtained according to the general procedure as a white solid (60.0 mg, 86% yield). Mp 125–126 °C, $[\alpha]_D^{20}$ = +11.1 (*c* 3.00, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 11.0 min, t_R (major) = 14.1 min, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H, NH), 7.34–7.31 (m, 2H, ArH), 7.27–7.24 (m, 2H, ArH), 7.21–7.14 (m, 3H, ArH), 6.98–6.95 (m, 2H, ArH), 4.89 (t, J = 7.6 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.66 (dd, J_1 = 17.0 Hz, J_2 = 7.4 Hz, 1H, CH_2), 3.59 (dd, J = 17.0 Hz, J_2 = 7.8 Hz, 1H, CH_2), 2.37 (s, 3H, CH_3) ppm. IR (KBr): ν 3443, 3111, 3056, 3024, 2949, 2886, 2829, 1728, 1652, 1614, 1603, 1547, 1486, 1477, 1453, 1437, 1397, 1374, 1328, 1296, 1258, 1228, 1192, 1152, 1134, 1120, 1085, 1064, 1037, 1013, 945, 931, 915, 844, 823, 764, 744, 703, 668, 599, 567 cm^{-1}.

4.3.12. (*S*)-4-(5-Chloro-1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester 4l[6]

Compound **4l** was obtained according to the general procedure as a yellow solid (58.0 mg, 87% yield). Mp 100–102 °C, $[\alpha]_D^{20}$ = +75.0 (*c* 3.05, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak IA column, *n*-hexane–2-propanol 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 19.6 min, t_R (major) = 23.4 min, 83% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H, NH), 7.37 (d, J = 2.0 Hz, 1H, ArH), 7.30–7.24 (m, 4H, ArH), 7.21–7.16 (m, 2H, ArH), 7.08 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, ArH), 7.04 (d, J = 2.0 Hz, 1H, ArH), 4.84 (t, J = 7.6 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.65 (dd, J_1 = 17.2 Hz, J_2 = 7.6 Hz, 1H, CH_2), 3.57 (dd, J_1 = 17.2 Hz, J_2 = 7.8 Hz, 1H, CH_2) ppm. IR (KBr): ν 3348, 3021, 2954, 2894, 1741, 1614, 1494, 1464, 1437, 1418, 1395, 1303, 1279, 1237, 1101, 1069, 964, 944, 898, 863, 812, 754, 705, 687, 667 cm^{-1}.

4.3.13. (*S*)-4-(5-Methoxy-1*H*-indol-3-yl)-2-oxo-4-phenylbutyric acid methyl ester 4m[6]

Compound **4m** was obtained according to the general procedure as a yellow oil (64.0 mg, 87% yield). $[\alpha]_D^{20}$ = +96.1 (*c* 4.35, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralcel AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 15.6 min, t_R (major) = 23.2 min, 94% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, NH), 7.34–7.29 (m, 2H, ArH), 7.28–7.22 (m, 2H, ArH), 7.18–7.14 (m, 2H, ArH), 6.97 (d, J = 2.4 Hz, 1H, ArH), 6.82 (d, J = 2.4 Hz, 1H, ArH), 6.80 (dd, J_1 = 2.4, J_2 = 8.8 Hz, 1H, ArH), 4.85 (t, J = 7.4 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.67 (dd, J_1 = 17.2, J_2 = 7.2 Hz, 1H, CH_2), 3.58 (dd, J_1 = 17.2, J_2 = 7.8 Hz, 1H, CH_2) ppm. IR (KBr): ν 3365, 3081, 3038, 2996, 2837, 1745, 1711, 1627, 1580, 1483, 1455, 1443, 1396, 1303, 1287, 1240, 1207, 1174, 1099, 1069, 1039, 968, 947, 922, 847, 806, 755, 720, 709, 641,586 cm^{-1}.

4.3.14. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid ethyl ester 4n[7]

Compound **4n** was obtained according to the general procedure as a white solid (53.3 mg, 83% yield). Mp 87–89 °C, $[\alpha]_D^{20}$ = +35.4 (*c* 2.79, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm), t_R (minor) = 12.5 min, t_R (major) = 14.7 min, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, NH), 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.32 (t, J = 7.2 Hz, 3H, ArH), 7.27–7.24 (m, 2H, ArH), 7.20–7.12 (m, 2H, ArH), 7.02 (d, J = 7.4 Hz, 2H, ArH), 4.92 (t, J = 7.4 Hz, 1H, CH), 4.21 (q, J = 7.2 Hz, 2H, CH_2), 3.68 (dd, J_1 = 16.8, J_2 = 7.2 Hz, 1H, CH_2), 3.59 (dd, J_1 = 17.0, J_2 = 7.8 Hz, 1H, CH_2), 1.27 (t, J = 7.0 Hz, 3H, CH_3) ppm. IR (KBr): ν 3410, 3115, 3053, 2987, 2932, 1720, 1601, 1492, 1458, 1423, 1388, 1339, 1297, 1260, 1106, 1088, 1057, 1007, 944, 842, 827, 753, 744, 736, 704, 648 cm^{-1}.

4.3.15. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid benzyl ester 4o

Compound **4o** was obtained according to the general procedure as a white solid (64.1 mg, 84% yield). Mp 123–125 °C,

$[\alpha]_D^{20}$ = +35.1 (*c* 3.45, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 24.0 min, t_R (major) = 25.4 min, 85% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1H, NH), 7.39–7.31 (m, 10H, ArH), 7.24 (t, J = 7.2 Hz, 2H, ArH), 7.09 (t, J = 7.0 Hz, 1H, ArH), 7.03 (t, J = 7.4 Hz, 1H, ArH), 6.91 (t, J = 7.4 Hz, 1H, ArH), 5.24 (s, 2H, CH_2), 4.76 (t, J = 7.2 Hz, 1H, CH), 3.78 (dd, J_1 = 17.4, J_2 = 7.4 Hz, 1H, CH_2), 3.63 (dd, J_1 = 17.6, J_2 = 7.2 Hz, 1H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.3, 160.2, 144.3, 136.3, 134.9, 128.4, 128.34, 128.31, 128.1, 127.5, 126.1, 126.0, 122.0, 121.0, 118.5, 118.3, 117.0, 111.3, 67.1, 45.1, 37.0 ppm; IR (KBr): ν 3448, 3022, 1717, 1603, 1492, 1458, 1412, 1338, 1275, 1239, 1095, 1075, 1051, 1009, 907, 808, 768, 752, 698 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}NO_3$ $[M+H]^+$ 384.15942, found 384.15940; calcd for $C_{25}H_{25}N_2O_3$ $[M+NH_4]^+$ 401.18597, found 401.18626.

4.3.16. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid isopropyl ester 4p

Compound **4p** was obtained according to the general procedure as a white solid (54.0 mg, 81% yield). Mp 120–122 °C, $[\alpha]_D^{20}$ = +136.0 (*c* 3.40, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 8.6 min, t_R (major) = 10.3 min, 86% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H, NH), 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.33–7.23 (m, 5H, ArH), 7.19–7.12 (m, 2H, ArH), 7.04–7.00 (m, 2H, ArH), 5.07–5.00 (m, 1H, CH), 4.91 (t, J = 7.4 Hz, 1H, CH), 3.66 (dd, J_1 = 16.8, J_2 = 7.6 Hz, 1H, CH_2), 3.57 (dd, J_1 = 16.8, J_2 = 8.0 Hz, 1H, CH_2), 1.26 (d, J = 6.0 Hz, 3H, CH_3), 1.22 (d, J = 6.4 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 160.5, 143.2, 136.5, 128.5, 127.7, 126.5, 126.3, 122.1, 121.6, 119.5, 119.4, 119.3, 118.2, 111.1, 70.7, 45.6, 37.8, 21.5, 21.4 ppm. IR (KBr): ν 3410, 3115, 3053, 2987, 2932, 1720, 1601, 1492, 1458, 1423, 1388, 1339, 1297, 1260, 1106, 1088, 1057, 1007, 944, 842, 753, 744, 736, 704, 648 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.15942, found 336.15951.

4.3.17. (*S*)-4-(1*H*-Indol-3-yl)-2-oxo-4-phenylbutyric acid allyl ester 4q

Compound **4q** was obtained according to the general procedure as a yellow oil (57.3 mg, 86% yield). $[\alpha]_D^{20}$ = +34.4 (*c* 3.45, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 85:15, flow rate 1.0 mL/min, detection at 254 nm): t_R (minor) = 12.9 min, t_R (major) = 14.4 min, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H, NH), 7.42 (d, J = 8.0 Hz, 1H, ArH), 7.34–7.24 (m, 5H, ArH), 7.19–7.13 (m, 2H, ArH), 7.02 (t, J = 7.4 Hz, 2H, ArH), 5.91–5.81 (m, 1H, CH), 5.32 (d, J = 17.2 Hz, 1H, =CH_2), 5.26 (d, J = 6.4 Hz, 1H, =CH_2), 4.92 (t, J = 7.4 Hz, 1H, CH), 4.63 (d, J = 5.6 Hz, 2H, CH_2), 3.68 (dd, J_1 = 16.8, J_2 = 7.2 Hz, 1H, CH_2), 3.57 (dd, J_1 = 16.8, J_2 = 7.8 Hz, 1H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 160.5, 143.1, 136.5, 130.6, 128.5, 127.7, 126.6, 126.4, 122.2, 121.5, 119.9, 119.5, 119.2, 118.2, 111.1, 66.8, 45.7, 37.7 ppm. IR (KBr): ν 3405, 3356, 3057, 3024, 1733, 1648, 1618, 1492, 1458, 1420, 1337, 1279, 1254, 1232, 1098, 1057, 997, 938, 760, 743, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.14377, found 334.14379.

4.3.18. (*S*)-Methyl 4-(2-hydroxy-4-methoxyphenyl)-2-oxo-4-phenylbutanoate 4r[8]

Compound **4r** was obtained according to the general procedure as a yellow oil (22.0 mg, 35% yield). $[\alpha]_D^{21}$ = −2.5 (*c* 0.40, CH_2Cl_2). The ee was determined by HPLC analysis (Daicel Chiralpak AD-H column, *n*-hexane–2-propanol 90:10, flow rate 1.0 mL/min, detection at 254 nm): t_R (major) = 26.3 min, t_R (minor) = 29.6 min, 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (m, 5H, ArH), 6.89 (d, J = 8.0 Hz, 1H, ArH), 6.35 (d, J = 2.4 Hz, 1H, ArH), 6.31 (dd, J = 8.4, 2.4 Hz, 1H, ArH), 4.91 (t, J = 7.6 Hz, 1H, CH), 4.73 (s, 1H, OH), 3.81 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.61 (dd, J = 16.8, 7.6 Hz, 1H), 3.45 (dd, J = 16.8, 7.6 Hz, 1H) ppm.

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