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Copper/GanPhos-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides: An Efficient Access to Chiral Pyrrolidine Spirocycles

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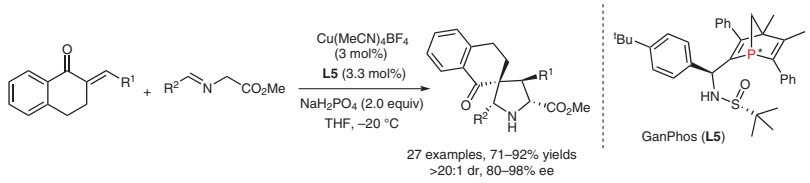

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Abstract A highly efficient copper/GanPhos-catalyzed 1,3-dipolar cycloaddition of azomethine ylides is reported. This viable transformation provides a series of optically active spiro[dihydronaphthalene-2,3′-pyrrolidine]s, bearing one spiro quaternary and three tertiary stereogenic centers, in good yields and with high ee values. This protocol features high diastereo- and enantioselectivity, broad substrate scope and mild reaction conditions.

Key words pyrrolidine spirocycles, 1,3-dipolar cycloaddition, azomethine ylides, stereogenic centers, copper, GanPhos

Optically active pyrrolidine derivatives bearing spirocyclic skeletons are frequently found in pharmaceuticals, natural alkaloids, and as fascinating building blocks in organic synthesis.[1] For example, compound **A** demonstrates potent anticonvulsant activity,[2] tetracyclic pyrrolidines **B** are a class of steroidal alkaloids that contain the key BCDE ring system of (+)-conessine,[3] whilst compound **C** exhibits antimicrobial activity (Figure 1).[4] The abundant applications of pyrrolidines in organic synthesis, the pharmaceutical industry, and in peptide chemistry, have promoted the development of efficient routes for the stereoselective construction of diverse pyrrolidine spirocycles.

The metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides[5] with activated olefins has become a very useful and atom-economical strategy for the enantioselective synthesis of pyrrolidines since Grigg's pioneering work.[6] The steric and electronic properties of metal catalysts can usually be primarily affected by ligands that coordinate to the metal center.[7] In this regard, numerous structurally diverse ligands including Fesulphos,[8] Biphamphos,[9] MingPhos,[10] Deng's N,O ligands[11] and so on[12] have been developed, affording excellent results in 1,3-dipolar

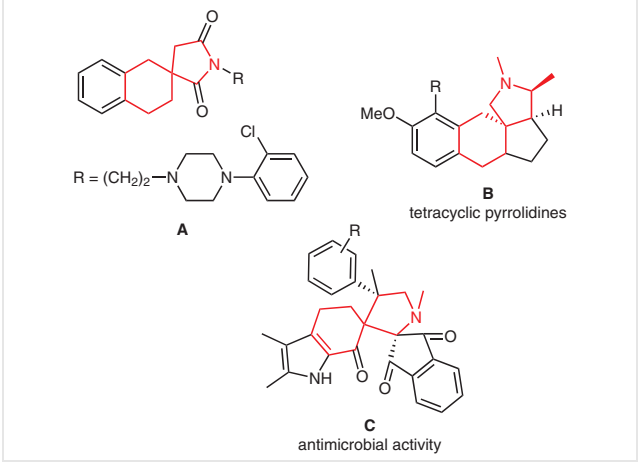

Figure 1 Selected bioactive natural products and synthetic drugs containing pyrrolidine spirocycles

cycloadditions of azomethine ylides and activated alkenes. However, this type of [3+2] cycloaddition for the precise synthesis of the polysubstituted pyrrolidines bearing spiro[naphthalene-2,3′-pyrrolidin]-1-one motifs is an important yet underdeveloped area.

Recently, we developed novel P-stereogenic phosphine ligands, bearing a flexible 1-phosphanorbornediene moiety, named GanPhos, which exhibited good stereoselectivities in metal-catalyzed asymmetric 1,3-dipolar cycloadditions.[13] Encouraged by these achievements, we envisioned that easily available (*E*)-2-arylidene-3,4-dihydronaphthalen-1(2*H*)-ones could be utilized to enable facile access to enantioenriched spiro[naphthalene-2,3′-pyrrolidin]-1-one derivatives. Herein, we report the first Lewis acid catalyzed highly enantioselective construction of spiro[dihydronaphthalene-2,3′-pyrrolidine] derivatives containing spiro

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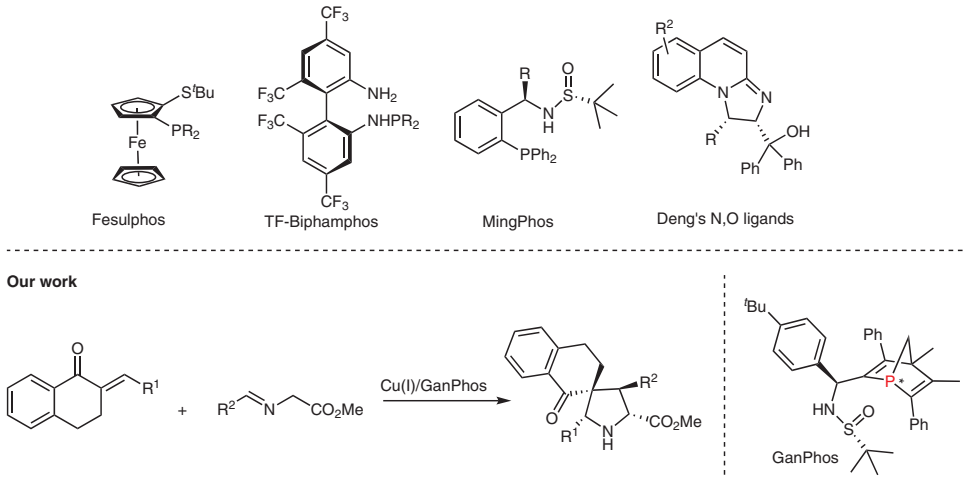


Scheme 1 Examples of privileged ligands utilized for the 1,3-dipolar cycloadditions of azomethine ylides

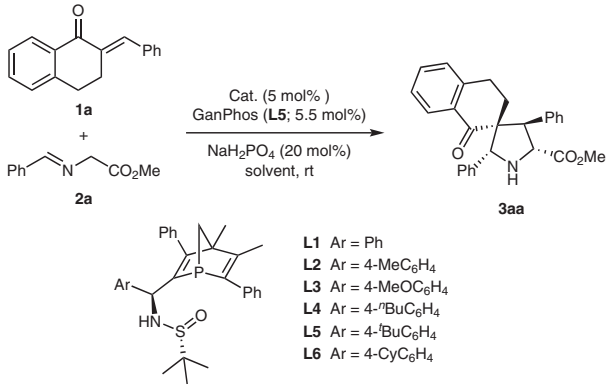
quaternary stereogenic centers via Cu(I)/Ganphos-catalyzed 1,3-dipolar cycloaddition with azomethine ylides (Scheme 1).

With this background in mind, and in continuation of our efforts on cycloaddition reactions, we initially optimized the reaction conditions (Table 1).[14] (*E*)-2-Benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**1a**) and aldimino ester **2a** were chosen as the model substrates to examine the [3+2] cycloaddition. Screening of solvents and bases at room temperature revealed that THF as the solvent and NaH_2PO_4 as the base were the best choices (see Table S1 in the Supporting Information). Gratifyingly, the reaction was complete in 12 hours when using a catalytic amount of $Cu(CH_3CN)_4BF_4$/GanPhos (**L5**) as the catalyst system at room temperature in THF, affording the desired adduct **3aa** in 80% yield, excellent diastereoselectivity (dr > 20:1) and high enantioselectivity (84% ee) (Table 1, entry 1). Encouraged by this result, we then tested the effects of different metal salts, and found that $Cu(CH_3CN)_4BF_4$ was the best catalyst leading to the highest asymmetric induction (Table 1, entries 1–6). Next, various P-stereogenic ligands (**L1**–**L6**), as reported by our group,[13] were screened with $Cu(CH_3CN)_4BF_4$ as the metal catalyst to compare their catalytic activity, with the combination of $Cu(CH_3CN)_4BF_4$/GanPhos (**L5**) exhibiting the best asymmetric induction ability (Table 1, entries 1 vs 7–11). Examination of the catalyst loading showed that the use of $Cu(CH_3CN)_4BF_4$ (3 mol%) led to slightly elevated ee values (Table 1, entries 1 vs 12 and 13). Reducing the reaction temperature from room temperature to –20 °C led to completion of the reaction with an excellent enantioselectivity of 92% ee (Table 1, entries 13 and 14 vs 15). Therefore, the optimized reaction conditions were as follows: $Cu(CH_3CN)_4BF_4$ (3 mol%)/GanPhos (**L5**) (3.3 mol%), NaH_2PO_4 (20 mol%), THF, –20 °C (see Table 1, entry 15).

With optimized reaction conditions in hand, we next turned our attention to explore the scope with respect to various (*E*)-2-arylidene-3,4-dihydronaphthalen-1(2*H*)-ones **1** in reactions with aldimino ester **2a**. As summarized in Table 2, the experimental results showed that a wide range of dipolarophiles **1** bearing electron-neutral, electron-rich, or electron-deficient groups on the phenyl ring reacted with aldimino ester **2a** to afford the corresponding products **3** in good yields, enantioselectivities and diastereoselectivities (Table 2, entries 1–10). The dipolarophile **1** bearing 2-Br and 4-F groups on the phenyl ring also reacted smoothly to produce the desired adduct **3ka** in 91% yield and 90% ee (Table 2, entry 11). Noticeably, almost the same high levels of yields and enantioselectivities were achieved when dipolarophiles **1** bearing 1-naphthyl and heteroaromatic (2-furyl, 2-thiophenyl, 3-thiophenyl) groups were used in this reaction, and the desired spirocyclic adducts **3la**–**oa** were obtained in 78–88% yields and 90–97% ee (Table 2, entries 12–15). Also, the dipolarophile **1p** bearing an alkyl substituent (a cyclohexyl group) gave chiral pyrroloindoline **3pa** with satisfactory enantioselectivity (Table 2, entry 16).

Next, various aldimino esters were investigated under the optimized experimental conditions to test the scope of this asymmetric 1,3-dipolar cycloaddition reaction, and representative results are summarized in Table 3. The electronic properties of the aromatic substituents influenced the enantioselectivity, with electron-donating (3-Me, 3-MeO, and 4-MeO) groups typically resulting in lower enantioselectivities compared to electron-withdrawing substituents (2-F, 3-F, 2-Cl, 3-Cl, 4-Cl, 4-Br and 3-CF_3) (Table 3, entries 1–10). Remarkably, an aliphatic aldimino ester

Table 1 Optimization of the Reaction Conditions[a]

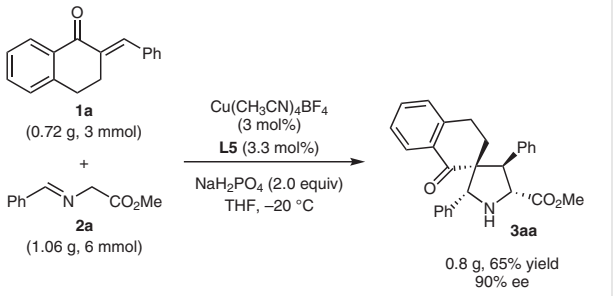


Entry	Catalyst	Ligand	Yield (%)[b]	ee (%)[c]
1	$Cu(CH_3CN)_4BF_4$	**L5**	80	84
2	$Cu(CH_3CN)_4PF_6$	**L5**	99	71
3	$Cu(OTf)_2$	**L5**	89	73
4	AgOAc	**L5**	99	63
5	AgOTf	**L5**	43	73
6	$AgNTf_2$	**L5**	70	82
7	$Cu(CH_3CN)_4BF_4$	**L1**	84	66
8	$Cu(CH_3CN)_4BF_4$	**L2**	65	30
9	$Cu(CH_3CN)_4BF_4$	**L3**	77	35
10	$Cu(CH_3CN)_4BF_4$	**L4**	54	62
11	$Cu(CH_3CN)_4BF_4$	**L6**	39	82
12[d]	$Cu(CH_3CN)_4BF_4$	**L5**	64	86
13[e]	$Cu(CH_3CN)_4BF_4$	**L5**	77	86
14[e,f]	$Cu(CH_3CN)_4BF_4$	**L5**	75	90
15[e,g]	$Cu(CH_3CN)_4BF_4$	**L5**	73	92

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), GanPhos (6 mol%), NaH_2PO_4 (20 mol%), rt, 12 h.
[b] Isolated yield of **3aa**. The diastereomeric ratio (d.r.) was >20:1.
[c] The ee value was determined by HPLC analysis on a chiral stationary phase.
[d] $Cu(CH_3CN)_4BF_4$ (2.5 mol%) and GanPhos (2.75 mol%) were used.
[e] $Cu(CH_3CN)_4BF_4$ (3 mol%) and GanPhos (3.3 mol%) were used.
[f] Reaction temperature: 0 °C.
[g] Reaction temperature: –20 °C.

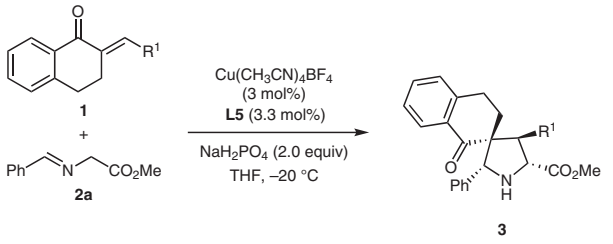
participated in the [3+2] cycloaddition to afford the corresponding product **3al** in 83% yield and 80% ee (Table 3, entry 11). The structures and stereochemistries of products **3** were characterized by a combination of NMR, HPLC, HRMS, and single-crystal X-ray analysis (**3oa**) (see the Supporting Information).[15]

To explore the synthetic potential of this reaction, a large-scale synthesis of **3aa** was carried out. When (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**1a**) and aldimino ester **2a** were used in the presence of $Cu(CH_3CN)_4BF_4$ (3 mol%)/GanPhos (**L5**) (3.3 mol%) in THF at –20 °C, the reaction proceeded smoothly to afford the desired adduct **3aa** in 65% yield and 90% ee (Scheme 2).



Scheme 2 A gram-scale preparation of adduct **3aa**

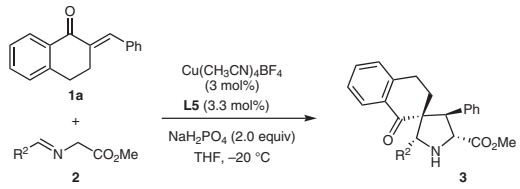
Table 2 Substrate Scope of Various (*E*)-2-Arylidene-3,4-dihydronaphthalen-1(2*H*)-ones **1**[a]



Entry	R^1	Yield (%)[b]	ee (%)[c]
1	Ph (**1a**)	73 (**3aa**)	92
2	2-MeC_6H_4 (**1b**)	75 (**3ba**)	87
3	3-MeC_6H_4 (**1c**)	72 (**3ca**)	91
4	4-MeC_6H_4 (**1d**)	79 (**3da**)	83
5	3-FC_6H_4 (**1e**)	74 (**3ea**)	93
6	4-FC_6H_4 (**1f**)	81 (**3fa**)	90
7	2-ClC_6H_4 (**1g**)	73 (**3ga**)	88
8	2-BrC_6H_4 (**1h**)	77 (**3ha**)	87
9	3-BrC_6H_4 (**1i**)	92 (**3ia**)	93
10	4-BrC_6H_4 (**1j**)	87 (**3ja**)	87
11	2-Br-4-FC_6H_3 (**1k**)	91 (**3ka**)	90
12	1-naphthyl (**1l**)	85 (**3la**)	90
13	2-furyl (**1m**)	78 (**3ma**)	97
14	2-thiophenyl (**1n**)	88 (**3na**)	94
15	3-thiophenyl (**1o**)	79 (**3oa**)	97
16	Cy (**1p**)	74 (**3pa**)	90

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Cu(CH_3CN)_4BF_4$ (3 mol%), GanPhos (3.3 mol%), NaH_2PO_4 (20 mol%), –20 °C, 12 h.
[b] Isolated yield of **3**. The diastereomeric ratio (d.r.) was >20:1.
[c] The ee value was determined by HPLC analysis on a chiral stationary phase.

Table 3 Substrates Scope of Various Aldimino Esters[a]



Entry	R^2	Yield (%)[b]	ee (%)[c]
1	3-MeC_6H_4 (**2b**)	85 (**3ab**)	80
2	3-MeOC_6H_4 (**2c**)	79 (**3ac**)	83
3	4-MeOC_6H_4 (**2d**)	83 (**3ad**)	85
4	2-FC_6H_4 (**2e**)	90 (**3ae**)	96
5	3-FC_6H_4 (**2f**)	71 (**3af**)	98
6	2-ClC_6H_4 (**2g**)	90 (**3ag**)	83
7	3-ClC_6H_4 (**2h**)	83 (**3ah**)	94
8	4-ClC_6H_4 (**2i**)	84 (**3ai**)	83
9	4-BrC_6H_4 (**2j**)	75 (**3aj**)	91
10	3-F_3C-C_6H_4 (**2k**)	83 (**3ak**)	83
11	Cy (**2l**)	83 (**3al**)	80

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Cu(CH_3CN)_4BF_4$ (3 mol%), GanPhos (3.3 mol%), NaH_2PO_4 (20 mol%), –20 °C, 12 h.
[b] Isolated yield of **3**. The diastereomeric ratio (d.r.) was >20:1.
[c] The ee value was determined by HPLC analysis on a chiral stationary phase.

According to previous literature,[16] a reaction pathway has been proposed (Scheme 3). The P-stereogenic ligand and in situ formed azomethine ylide coordinate to the Cu(I) center, leading to a tetracoordinated species, which facilitated the deprotonation by NaH_2PO_4 to generate the well-organized, enantioenriched, N-metalated azomethine ylide **A**. Conjugate addition of the enolate to (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**1a**) gave the zwitterionic intermediate **C**. Subsequent intramolecular cyclization then produced the intermediate **D**. Finally, protonation gave the product **3aa** and regenerated the catalyst.

In summary, we have accomplished a highly effective, diastereo- and enantioselective 1,3-dipolar cycloaddition using 2-arylidene-3,4-dihydronaphthalen-1(2*H*)-ones and aldimino esters. This methodology provides efficient and economic access to a series of optically active spiro[dihydronaphthalene-2,3′-pyrrolidine]s, bearing one spiro quaternary and three tertiary stereogenic centers, in good yields and with high ee values. Remarkably, an aliphatic aldimino ester also participated in the [3+2] cycloaddition to afford the corresponding product **3al** in high yield and enantioselectivity. Further studies on the exploration of other types of catalytic asymmetric transformations are under way in our laboratory.

All reactions were performed under nitrogen using solvents dried by standard methods. All commercially available reagents were used without further purification. All known compounds were synthesized according to literature procedures.[17] Qingdao Ocean silica gel (200–300 mesh) was used for chromatographic separations. Melting points were recorded using a SGW X-4B apparatus (heating rate: 4 °C/min) and are uncorrected. NMR spectra were obtained using a Bruker AV300 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from TMS as the internal standard. HRMS spectra were obtained on an Agilent 1290-6540 UHPLC Q-Tof HR-MS spectrometer. X-ray crystallographic analyses were performed on an Oxford Diffraction Gemini E diffractometer. Enantiomeric excesses were determined by chiral HPLC analysis using Chiralcel IA/AD columns and by comparison with authentic racemates. Chiral HPLC analyses were recorded on Thermoscientific Dionex Ultimate 3000 and Agilent Technologies 1260 Infinity instruments.

1,3-Dipolar [3+2] Cycloaddition; General Procedure

GanPhos (**L5**) (6.0 mg, 0.0066 mmol, 3.3 mol%) and $Cu(CH_3CN)_4BF_4$ (3.14 mg, 0.006 mmol, 3 mol%) were dissolved in THF (2.0 mL) in a Schlenk tube under N_2. After stirring at room temperature for 1 h, 2-alkylidene-cycloketone **1** (0.2 mmol) and aldimino ester **2** (0.4 mmol) were added, followed by NaH_2PO_4 (48 mg, 0.4 mmol). The resulting mixture was then stirred at –20 °C until the 2-alkylidene-cycloketone had been totally consumed. The reaction mixture was directly purified by flash column chromatography (petroleum ether/ethyl acetate, 5:1) to afford the corresponding product **3**.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-2′,4′-diphenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3aa)

Yield: 60.2 mg (73%); white solid; mp 194–195 °C; $[\alpha]_D$ +69 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70–1.80 (m, 1 H), 1.90–1.98 (m, 1 H), 2.23 (s, 1 H), 2.70–2.78 (m, 1 H), 3.07–3.18 (m, 1 H), 3.77 (s, 3 H), 4.37 (d, *J* = 8.8 Hz, 1 H), 4.55 (d, *J* = 8.8 Hz, 1 H), 4.64 (s, 1 H), 6.96 (d, *J* = 7.8 Hz, 1 H), 7.05–7.10 (m, 4 H), 7.16–7.19 (m, 2 H), 7.24–7.27 (m, 2 H), 7.32–7.38 (m, 4 H), 7.61–7.64 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.4, 30.6, 52.4, 55.5, 61.4, 64.3, 71.0, 126.3, 127.1, 127.5, 127.8, 127.95, 128.01, 128.28, 129.31, 132.9, 132.9, 138.2, 139.3, 142.0, 173.9, 198.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}NO_3$: 412.1907; found: 412.1908.

HPLC: 92% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 21.12 and 25.01 min.

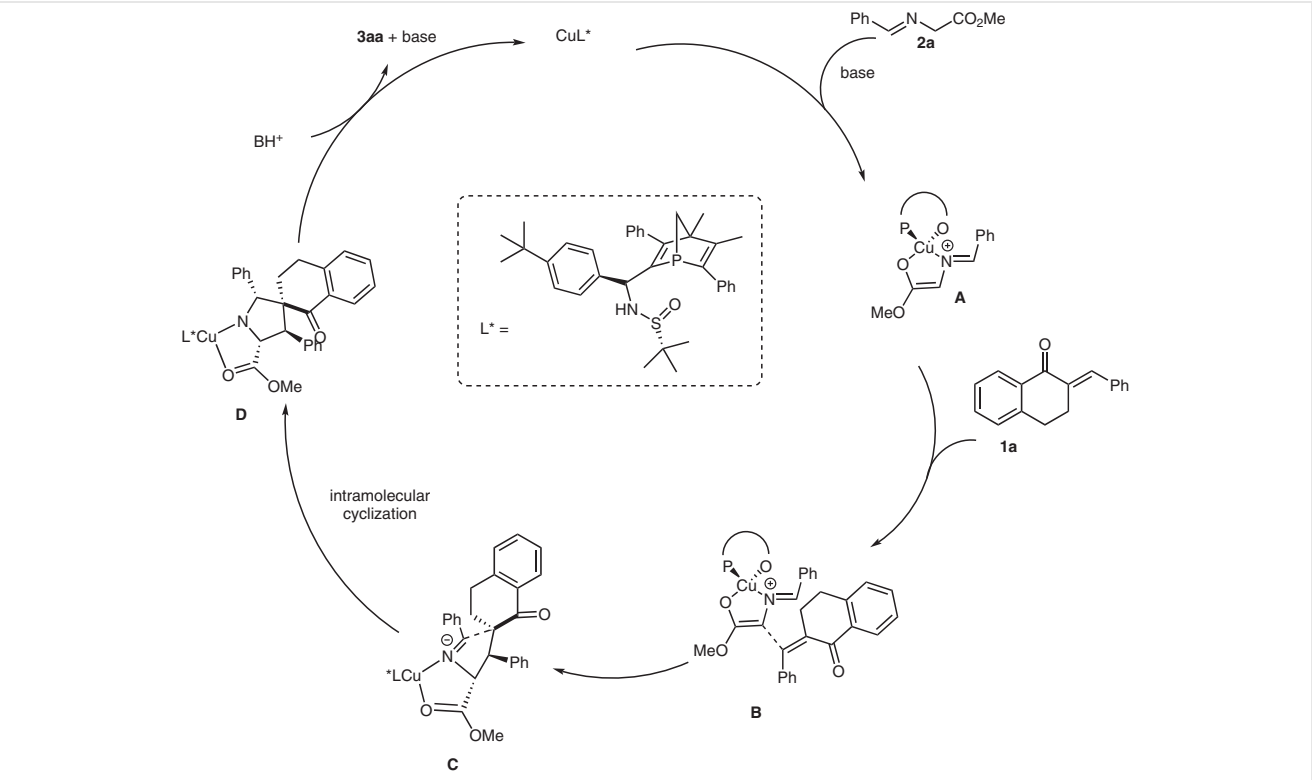
Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-2′-phenyl-4′-(*o*-tolyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ba)

Yield: 63.9 mg (75%); white solid; mp 141–142 °C; $[\alpha]_D$ +80 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74–1.81 (m, 2 H), 2.27 (s, 3 H), 2.43–2.52 (m, 1 H), 2.76–2.87 (m, 1 H), 3.15 (s, 1 H), 3.85 (s, 3 H), 4.28 (d, *J* = 5.9 Hz, 1 H), 4.55 (s, 1 H), 4.65 (d, *J* = 5.9 Hz, 1 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 7.04–7.15 (m, 4 H), 7.18–7.25 (m, 4 H), 7.28–7.34 (m, 2 H), 7.50–7.53 (m, 1 H), 7.85–7.88 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 20.7, 25.7, 31.0, 52.4, 52.6, 60.2, 67.5, 74.6, 126.3, 126.9, 127.5, 127.9, 127.97, 128.03, 128.3, 128.4, 130.7, 132.7, 133.1, 137.3, 137.9, 139.0, 142.6, 174.0, 200.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{28}NO_3$: 426.2064; found: 426.2065.



Scheme 3 A proposed reaction mechanism

HPLC: 87% ee (Chiralpak IA-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 11.35 and 12.47 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-2′-phenyl-4′-(*m*-tolyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ca)

Yield: 61.4 mg (72%); white solid; mp 144–145 °C; $[\alpha]_D$ +103 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.82 (m, 1 H), 1.88–1.95 (m, 1 H), 2.34 (s, 3 H), 2.70–2.76 (m, 1 H), 3.04–3.15 (m, 2 H), 3.78 (s, 3 H), 4.49 (d, *J* = 8.4 Hz, 1 H), 4.61 (s, 1 H), 6.95 (d, *J* = 7.7 Hz, 1 H), 7.05–7.07 (m, 4 H), 7.16–7.27 (m, 7 H), 7.65 (d, *J* = 7.9 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 21.5, 25.4, 30.6, 52.4, 55.7, 61.2, 64.5, 71.2, 126.2, 126.3, 127.5, 127.82, 127.84, 127.9, 128.0, 128.1, 130.2, 132.9, 133.0, 137.9, 138.3, 139.2, 142.1, 173.9, 198.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{28}NO_3$: 426.2064; found: 426.2065.

HPLC: 91% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 13.28 and 13.36 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-2′-phenyl-4′-(*p*-tolyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3da)

Yield: 67.3 mg (79%); white solid; mp 76–77 °C; $[\alpha]_D$ +107 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73–1.98 (m, 2 H), 2.32 (s, 3 H), 2.71–2.98 (m, 2 H), 3.06–3.18 (m, 1 H), 3.76 (s, 3 H), 4.36 (d, *J* = 8.8 Hz, 1 H), 4.54 (d, *J* = 8.8 Hz, 1 H), 4.63 (s, 1 H), 6.96 (d, *J* = 7.6 Hz, 1 H), 7.04–7.14 (m, 6 H), 7.17–7.20 (m, 2 H), 7.24–7.27 (m, 3 H), 7.64 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 21.1, 25.4, 30.5, 52.4, 55.2, 61.4, 64.3, 70.9, 126.3, 127.5, 127.8, 127.95, 127.98, 128.1, 129.0, 129.2, 132.9, 133.0, 135.1, 136.6, 139.5, 142.1, 174.0, 198.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{28}NO_3$: 426.2064; found: 426.2066.

HPLC: 83% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 25.66 and 34.45 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(3-Fluorophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ea)

Yield: 63.7 mg (74%); white solid; mp 145–146 °C; $[\alpha]_D$ +77 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69–1.80 (m, 1 H), 1.94–2.01 (m, 1 H), 2.72–2.82 (m, 2 H), 3.13–3.24 (m, 1 H), 3.77 (s, 3 H), 4.33 (d, *J* = 9.0 Hz, 1 H), 4.55 (d, *J* = 9.0 Hz, 1 H), 4.65 (s, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 7.05–7.15 (m, 6 H), 7.22–7.36 (m, 5 H), 7.57–7.61 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.5, 52.5, 54.7, 61.4, 63.8, 70.5, 127.3, 127.6, 127.9, 128.0, 128.1, 129.4, 129.5, 132.8, 133.1, 134.2, 139.2, 140.1, 141.9, 173.5, 197.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}FNO_3$: 430.1813; found: 430.1814.

HPLC: 93% ee (Chiralpak IA-H, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 26.10 and 27.59 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(4-Fluorophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3fa)

Yield: 69.7 mg (81%); white solid; mp 143–144 °C; $[\alpha]_D$ +83 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.78 (m, 1 H), 1.96–2.00 (m, 1 H), 2.77–2.91 (m, 2 H), 3.15–3.26 (m, 1 H), 3.76 (s, 3 H), 4.32 (d, *J* = 9.4 Hz, 1 H), 4.56–4.65 (m, 2 H), 6.97–7.15 (m, 8 H), 7.25–7.35 (m, 4 H), 7.58 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3 (s), 30.4, 52.4, 54.3, 61.5, 63.8, 70.2, 115.1 (d, *J* = 21.1 Hz), 126.4, 127.5, 127.8, 127.9, 128.0, 128.1, 130.8 (d, *J* = 7.8 Hz), 132.9, 133.0, 133.4 (d, *J* = 3.3 Hz), 139.6, 141.9, 161.9 (d, *J* = 245.7 Hz), 173.7, 198.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}FNO_3$: 430.1813; found: 430.1815.

HPLC: 90% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 22.71 and 31.04 min.

Methyl (2*R*,2′*R*,4′*S*,5′*R*)-4′-(2-Chlorophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ga)

Yield: 65.1 mg (73%); white solid; mp 88–89 °C; $[\alpha]_D$ +47 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59–1.63 (m, 1 H), 1.90–2.04 (m, 1 H), 2.42–2.59 (m, 1 H), 2.68– 2.79 (m, 1 H), 3.16 (s, 1 H), 3.90 (s, 3 H), 4.24 (d, *J* = 4.1 Hz, 1 H), 4.48 (s, 1 H), 4.93 (d, *J* = 4.5 Hz, 1 H), 6.78 (d, *J* = 7.4 Hz, 1 H), 7.01–7.03 (m, 2 H), 7.09–7.25 (m, 4 H), 7.27–7.28 (m, 1 H), 7.37–7.42 (m, 3 H), 7.63–7.65 (m, 1 H), 7.90–7.92 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.7, 30.3, 52.6, 53.6, 59.8, 67.2, 74.8, 126.3, 127.4, 127.9, 128.0, 128.2, 128.4, 128.5, 129.6, 129.8, 132.7, 133.0, 135.1, 137.5, 139.1, 142.6, 174.0, 200.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}ClNO_3$: 446.1517; found: 446.1519.

HPLC: 88% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 18.00 and 26.54 min.

Methyl (2*R*,2′*R*,4′*S*,5′*R*)-4′-(2-Bromophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ha)

Yield: 75.5 mg (77%); white solid; mp 92–93 °C; $[\alpha]_D$ +73 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57–1.61 (m, 1 H), 1.94–2.04 (m, 1 H), 2.43–2.52 (m, 1 H), 2.67–2.78 (m, 1 H), 3.22 (s, 1 H), 3.93 (s, 3 H), 4.21 (d, *J* = 4.0 Hz, 1 H), 4.48 (s, 1 H), 4.92 (d, *J* = 4.3 Hz, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 7.02–7.04 (m, 3 H), 7.11–7.26 (m, 4 H), 7.27–7.28 (m, 1 H), 7.43–7.47 (m, 1 H), 7.60–7.65 (m, 2 H), 7.91–7.93 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.7, 30.5, 52.6, 56.4, 59.7, 67.7, 74.9, 126.3, 126.5, 127.4, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 129.6, 132.7, 133.0, 133.2, 137.5, 141.0, 142.6, 174.0, 200.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}BrNO_3$: 490.1012; found: 490.1013.

HPLC: 87% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 18.08 and 25.16 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(3-Bromophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ia)

Yield: 90.2 mg (92%); white solid; mp 76–77 °C; $[\alpha]_D$ +61 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.79 (m, 1 H), 1.93–2.00 (m, 1 H), 2.74–2.81 (m, 2 H), 3.12–3.23 (m, 1 H), 3.76 (s, 3 H), 4.32 (d, *J* = 9.1 Hz, 1 H), 4.54 (d, *J* = 9.1 Hz, 1 H), 4.64 (s, 1 H), 6.96–6.99 (m, 1 H), 7.04–7.08 (m, 4 H), 7.13–7.20 (m, 3 H), 7.24–7.27 (m, 1 H), 7.29–7.31 (m, 1 H), 7.36–7.39 (m, 1 H), 7.52–7.60 (m, 2 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.5, 52.5, 54.7, 61.4, 63.8, 70.5, 122.5, 126.4, 127.6, 127.9, 128.0, 128.06, 128.08, 129.8, 130.3, 132.3, 132.8, 133.1, 139.3, 140.5, 141.9, 173.6, 197.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}BrNO_3$: 490.1012; found: 490.1014.

HPLC: 93% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 13.25 and 23.55 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(4-Bromophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ja)

Yield: 85.7 mg (87%); white solid; mp 123–124 °C; $[\alpha]_D$ +54 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.77 (m, 1 H), 1.94–2.00 (m, 1 H), 2.75–2.83 (m, 2 H), 3.16–3.26 (m, 1 H), 3.75 (s, 3 H), 4.32 (d, *J* = 9.5 Hz, 1 H), 4.55 (d, *J* = 9.5 Hz, 1 H), 4.64 (s, 1 H), 6.98–7.16 (m, 7 H), 7.22–7.28 (m, 3 H), 7.42–7.44 (m, 2 H), 7.56–7.58 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.4, 52.5, 54.4, 61.5, 63.6, 70.2, 121.1, 126.4, 127.6, 127.9, 128.0, 128.1, 131.1, 131.4, 132.8, 133.1, 136.8, 139.5, 141.9, 173.6, 197.8).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}BrNO_3$: 490.1012; found: 490.1012.

HPLC: 87% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 26.96 and 24.65 min.

Methyl (2*R*,2′*R*,4′*S*,5′*R*)-4′-(2-Bromo-4-fluorophenyl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ka)

Yield: 91.5 mg (90%); white solid; mp124–125 °C; $[\alpha]_D$ +90 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57–1.62 (m, 1 H), 1.91–2.01 (m, 1 H), 2.45–2.53 (m, 1 H), 2.70–2.80 (m, 1 H), 3.20 (s, 1 H), 3.93 (s, 3 H), 4.14 (d, *J* = 4.2 Hz, 1 H), 4.45 (s, 1 H), 4.88 (d, *J* = 4.4 Hz, 1 H), 6.78–6.81 (m, 1 H), 7.02–7.04 (m, 3 H), 7.10–7.27 (m, 5 H), 7.34–7.38 (m, 1 H), 7.59–7.64 (m, 1 H), 7.89–7.92 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 30.6, 52.7, 55.6, 59.6, 67.8, 74.8, 115.3 (d, *J* = 20.9 Hz), 120.2 (d, *J* = 23.9 Hz), 126.4, 127.4, 127.9, 128.0, 128.2, 128.4, 130.4 (d, *J* = 8.7 Hz), 132.7, 133.1, 137.0 (d, *J* = 3.6 Hz), 137.4, 142.5, 161.1 (d, *J* = 251.0 Hz), 173.9, 200.3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{24}BrFNO_3$: 508.0918; found: 508.0920.

HPLC: 90% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 21.43 and 44.18 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(Naphthalen-1-yl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3la)

Yield: 78.6 mg (85%); white solid; mp 101–102 °C; $[\alpha]_D$ +53 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.71 (m, 2 H), 2.31–2.37 (m, 1 H), 2.74–2.85 (m, 1 H), 3.05 (s, 1 H), 3.83 (s, 3 H), 4.50 (d, *J* = 5.7 Hz, 1 H), 4.62 (s, 1 H), 5.40 (d, *J* = 5.6 Hz, 1 H), 6.74 (d, *J* = 7.3 Hz, 1 H), 7.04–7.18 (m, 5 H), 7.27–7.31 (m, 2 H), 7.45–7.48 (m, 2 H), 7.58–7.63 (m, 1 H), 7.77–7.94 (m, 4 H), 8.11–8.14 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.6, 31.1, 51.2, 52.5, 60.5, 67.3, 74.6, 124.0, 125.4, 125.7, 125.9, 126.3, 126.5, 127.5, 127.8, 127.9, 128.0, 128.1, 128.5, 128.9, 132.90, 132.94, 133.0, 133.9, 136.9, 138.0, 142.6, 174.2, 200.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{28}NO_3$: 462.2064; found: 462.2066.

HPLC: 90% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 20.14 and 29.91 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-(Furan-2-yl)-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ma)

Yield: 62.7 mg (78%); white solid; mp 175–176 °C; $[\alpha]_D$ +87 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96–2.05 (m, 1 H), 2.37–2.45 (m, 1 H), 2.66–2.82 (m, 2 H), 3.14–3.19 (m, 1 H), 3.41 (s, 3 H), 4.18 (s, 1 H), 4.35 (d, *J* = 11.0 Hz, 1 H), 4.63 (d, *J* = 11.0 Hz, 1 H), 5.99–6.18 (m, 2 H), 7.19–7.34 (m, 6 H), 7.45–7.54 (m, 3 H), 8.06 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.4, 29.7, 49.7, 52.5, 61.6, 62.9, 71.0, 108.6, 110.3, 126.4, 127.5, 127.87, 127.90, 127.95, 128.1, 132.9, 133.1, 138.8, 142.1, 142.4, 152.5, 173.4, 198.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_4$: 402.1700; found: 402.1701.

HPLC: 97% ee (Chiralpak IA-H, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 31.01 and 33.11 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-2′-phenyl-4′-(thiophen-2-yl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3na)

Yield: 73.6 mg (88%); white solid; mp 160–161 °C; $[\alpha]_D$ +83 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01–2.11 (m, 1 H), 2.30–2.35 (m, 1 H), 2.82–2.88 (m, 2 H), 3.24–3.34 (m, 1 H), 3.42 (s, 3 H), 4.25 (s, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 4.73 (d, *J* = 11.3 Hz, 1 H), 6.78–6.82 (m, 2 H), 7.06 (d, *J* = 4.5 Hz, 1 H), 7.20–7.27 (m, 2 H), 7.32–7.37 (m, 3 H), 7.45–7.50 (m, 1 H), 7.62–7.65 (m, 2 H), 8.07 (d, *J* = 7.6 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.2, 29.5, 51.9, 53.5, 61.7, 66.6, 66.7, 124.2, 126.4, 126.7, 126.8, 127.7, 127.9, 128.1, 128.6, 128.7, 132.6, 133.5, 139.0, 139.8, 143.3, 172.9, 197.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_3S$: 418.1471; found: 418.1473.

HPLC: 94% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 36.92 and 38.10 min.

Methyl (2*R*,2′*R*,4′*S*,5′*R*)-1-Oxo-2′-phenyl-4′-(thiophen-3-yl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3oa)

Yield: 66.1 mg (79%); white solid; mp 170–171 °C; $[\alpha]_D$ +71 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.83 (m, 1 H), 1.98–2.05 (m, 1 H), 2.62–2.88 (m, 2 H), 3.19–3.30 (m, 1 H), 3.78 (s, 3 H), 4.32 (d, *J* = 9.8 Hz, 1 H), 4.67–4.71 (m, 2 H), 7.03–7.14 (m, 8 H), 7.17–7.18 (m, 1 H), 7.23–7.31 (m, 2 H), 7.55–7.58 (m, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 29.8, 50.4, 52.5, 61.6, 63.9, 69.3, 122.8, 125.2, 126.4, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 133.0, 138.0, 139.9, 142.0, 173.9, 197.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{24}NO_3S$: 418.1471; found: 418.1472.

HPLC: 97% ee (Chiralpak IA-H, *n*-hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 31.01 and 33.11 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-4′-Cyclohexyl-1-oxo-2′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3pa)

Yield: 61.9 mg (74%); white solid; mp 133–134 °C; $[\alpha]_D$ +60 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.57–0.80 (m, 2 H), 0.84–1.03 (m, 3 H), 1.21–1.45 (m, 6 H), 2.34–2.42 (m, 3 H), 3.02–3.07 (m, 1 H), 3.19–3.25 (m, 1 H), 3.30–3.34 (m, 1 H), 3.38 (s, 3 H), 4.06–4.12 (m, 2 H), 7.29–7.42 (m, 5 H), 7.51 (t, *J* = 7.1 Hz, 1 H), 7.65 (d, *J* = 7.3 Hz, 2 H), 8.06 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 26.1, 26.22, 26.24, 26.5, 32.6, 33.7, 34.1, 39.8, 52.2, 60.8, 61.9, 65.2, 76.4, 126.4, 126.6, 128.1, 128.2, 133.2, 134.0, 137.3, 142.9, 176.1, 200.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{32}NO_3$: 418.2377; found: 418.2378.

HPLC: 90% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 16.58 and 18.52 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-4′-phenyl-2′-(*m*-tolyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ab)

Yield: 72.5 mg (85%); white solid; mp 149–150 °C; $[\alpha]_D$ +107 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69–1.79 (m, 1 H), 1.88–1.95 (m, 1 H), 2.12 (s, 3 H), 2.68–2.92 (m, 2 H), 3.06–3.16 (m, 1 H), 3.76 (s, 3 H), 4.37 (d, *J* = 8.7 Hz, 1 H), 4.54 (d, *J* = 8.7 Hz, 1 H), 4.59 (s, 1 H), 6.85–7.10 (m, 6 H), 7.23–7.38 (m, 6 H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 21.2, 25.4, 30.5, 52.4, 55.5, 61.3, 64.3, 71.0, 125.1, 126.2, 127.0, 127.4, 127.9, 128.0, 128.3, 128.5, 128.7, 129.3, 132.9, 133.2, 137.5, 138.3, 139.1, 142.1, 173.9, 198.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064; found: 426.2066.

HPLC: 80% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 16.15 and 24.62 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(3-Methoxyphenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ac)

Yield: 69.9 mg (79%); white solid; mp 157–158 °C; $[\alpha]_D$ +57 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.80 (m, 1 H), 1.94–1.98 (m, 1 H), 2.73–3.21 (m, 3 H), 3.63 (s, 3 H), 3.76 (s, 3 H), 4.39 (d, *J* = 8.6 Hz, 1 H), 4.54–4.63 (m, 2 H), 6.61–6.80 (m, 3 H), 7.00–7.13 (m, 3 H), 7.27–7.35 (m, 6 H), 7.67 (d, *J* = 7.4 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.4, 30.4, 52.4, 55.1, 55.2, 61.5, 64.1, 70.6, 113.1, 114.0, 120.3, 126.4, 127.1, 127.5, 128.1, 128.3, 129.0, 129.4, 133.0, 133.1, 138.0, 141.2, 142.1, 159.1, 174.0, 198.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{28}NO_4$: 442.2013; found: 442.2016.

HPLC: 83% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 44.72 and 57.05 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(4-Methoxyphenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ad)

Yield: 73.4 mg (83%); white solid; mp 160–161 °C; $[\alpha]_D$ +66 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.78 (m, 1 H), 1.87–1.94 (m, 1 H), 2.56–2.76 (m, 2 H), 3.04–3.15 (m, 1 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 4.34 (d, *J* = 8.7 Hz, 1 H), 4.50–4.59 (m, 2 H), 6.58–6.61 (m, 2 H), 6.96 (d, *J* = 7.6 Hz, 1 H), 7.10–7.06 (m, 3 H), 7.24–7.36 (m, 6 H), 7.66 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.4, 30.6, 52.4, 55.1, 55.6, 61.1, 64.2, 70.5, 113.3, 126.3, 127.0, 128.0, 128.3, 129.1, 129.3, 131.3, 132.9, 138.3, 142.1, 159.0, 174.0, 198.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{28}NO_4$: 442.2013; found: 442.2014.

HPLC: 85% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 42.61 and 49.11 min.

Methyl (2*R*,2′*S*,4′*R*,5′*R*)-2′-(2-Fluorophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ae)

Yield: 77.4 mg (90%); white solid; mp 158–159 °C; $[\alpha]_D$ +48 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70–1.81 (m, 1 H), 1.97–2.02 (m, 1 H), 2.62–2.77 (m, 2 H), 3.15–3.25 (m, 1 H), 3.74 (s, 3 H), 4.40 (d, *J* = 9.5 Hz, 1 H), 4.59 (d, *J* = 9.5 Hz, 1 H), 5.09 (s, 1 H), 6.65–6.72 (m, 1 H), 6.99–7.08 (m, 4 H), 7.23–7.35 (m, 6 H), 7.47–7.53 (m, 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2, 52.4, 55.2, 61.2, 61.3, 61.7, 63.6, 114.7 (d, *J* = 22.9 Hz), 124.2 (d, *J* = 3.4 Hz), 126.2, 126.9 (d, *J* = 12.0 Hz), 127.1, 127.4, 128.1, 128.3, 129.1 (d, *J* = 8.8 Hz), 129.35, 129.44 (d, *J* = 3.2 Hz), 132.6, 133.0, 137.6, 142.7, 159.9 (d, *J* = 245.7 Hz), 173.8, 198.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}FNO_3$: 430.1813; found: 430.1814.

HPLC: 96% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 21.18 and 28.47 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(3-Fluorophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3af)

Yield: 61.1 mg (71%); white solid; mp 153–154 °C; $[\alpha]_D$ +79 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.83 (m, 1 H), 1.93–2.00 (m, 1 H), 2.65 (s, 1 H), 2.74–2.83 (m, 1 H), 3.07–3.23 (m, 1 H), 3.76 (s, 3 H), 4.39 (d, *J* = 8.6 Hz, 1 H), 4.56 (d, *J* = 9.1 Hz, 1 H), 4.64 (s, 1 H), 6.73–6.79 (m, 1 H), 6.91–7.13 (m, 5 H), 7.24–7.36 (m, 6 H), 7.65 (d, *J* = 7.3 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.2, 52.4, 54.8, 61.4, 63.9, 69.8, 114.6 (d, *J* = 21.4 Hz), 115.1 (d, *J* = 22.4 Hz), 123.6 (d, *J* = 2.3 Hz), 126.5, 127.2, 127.6, 128.2, 128.3, 129.36, 129.47 (d, *J* = 8.5 Hz), 133.2, 137.7, 141.9, 142.5 (dd, *J* = 6.6, 1.9 Hz), 173.8, 175.1 (d, *J* = 12.2 Hz), 197.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}FNO_3$: 430.1813; found: 430.1815.

HPLC: 98% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 23.73 and 25.80 min.

Methyl (2*R*,2′*S*,4′*R*,5′*R*)-2′-(2-Chlorophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ag)

Yield: 80.3 mg (90%); white solid; mp 145–146 °C; $[\alpha]_D$ +59 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76–1.86 (m, 1 H), 1.98–2.05 (m, 1 H), 2.71–2.80 (m, 1 H), 2.92 (s, 1 H), 3.23–3.34 (m, 1 H), 3.76 (s, 3 H), 4.44 (d, *J* = 9.2 Hz, 1 H), 4.58 (d, *J* = 9.2 Hz, 1 H), 5.30 (s, 1 H), 6.97–7.06 (m, 3 H), 7.09–7.27 (m, 3 H), 7.24–7.26 (m, 1 H), 7.29–7.36 (m, 4 H), 7.57–7.67 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 30.1, 52.4, 55.4, 61.9, 63.8, 64.8, 126.3, 126.9, 127.1, 127.4, 128.1, 128.3, 128.7, 129.1, 129.4, 130.0, 132.7, 133.1, 133.3, 137.5, 137.7, 143.0, 174.0, 198.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}ClNO_3$: 446.1517; found: 446.1518.

HPLC: 83% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 23.01 and 33.40 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(3-Chlorophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ah)

Yield: 74.1 mg (83%); white solid; mp 146–147 °C; $[\alpha]_D$ +101 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.82 (m, 1 H), 1.94–1.98 (m, 1 H), 2.68 (s, 1 H), 2.76–2.82 (m, 1 H), 3.05–3.17 (m, 1 H), 3.77 (s, 3 H), 4.39 (d, *J* = 9.0 Hz, 1 H), 4.54–4.61 (m, 2 H), 7.00–7.04 (m, 3 H), 7.09–7.15 (m, 3 H), 7.27–7.36 (m, 6 H), 7.65 (d, *J* = 7.6 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.1, 52.4, 54.6, 61.4, 63.9, 69.6, 126.1, 126.6, 127.2, 127.6, 127.8, 128.2, 128.3, 129.2, 129.4, 132.9, 133.2, 133.7, 137.7, 141.8, 142.0, 173.8, 197.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}ClNO_3$: 446.1517; found: 446.1520.

HPLC: 94% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 20.29 and 26.45 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(4-Chlorophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ai)

Yield: 74.9 mg (84%); white solid; mp 149–150 °C; $[\alpha]_D$ +94 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71–1.81 (m, 1 H), 1.92–1.99 (m, 1 H), 2.73–2.87 (m, 2 H), 3.04–3.15 (m, 1 H), 3.75 (s, 3 H), 4.38 (d, *J* = 9.0 Hz, 1 H), 4.54 (d, *J* = 9.0 Hz, 1 H), 4.62 (s, 1 H), 6.98–7.13 (m, 6 H), 7.24–7.35 (m, 6 H), 7.64 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.2, 52.4, 54.9, 61.3, 63.9, 69.8, 126.6, 127.2, 127.6, 128.1, 128.2, 128.3, 129.3, 132.8, 133.2, 133.4, 137.7, 138.3, 141.9, 173.9, 198.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}ClNO_3$: 446.1517; found: 446.1518.

HPLC: 83% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 34.96 and 42.47 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-(4-Bromophenyl)-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3aj)

Yield: 73.5 mg (75%); white solid; mp 148–149 °C; $[\alpha]_D$ +79 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71–1.82 (m, 1 H), 1.93–1.98 (m, 1 H), 2.59–2.88 (m, 2 H), 3.04–3.15 (m, 1 H), 3.75 (s, 3 H), 4.37–4.40 (m, 1 H), 4.53–4.61 (m, 2 H), 6.99–7.14 (m, 4 H), 7.19–7.35 (m, 8 H), 7.64 (d, *J* = 7.7 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.3, 30.2, 52.4, 54.9, 61.3, 63.9, 69.7, 121.7, 126.6, 127.2, 127.6, 128.2, 128.3, 129.3, 129.7, 131.0, 132.8, 133.3, 137.7, 138.7, 141.9, 173.9, 198.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{25}BrNO_3$: 490.1012; found: 490.1013.

HPLC: 91% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 23.87 and 32.29 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-1-Oxo-4′-phenyl-2′-[4-(trifluoromethyl)phenyl]-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3ak)

Yield: 79.7 mg (83%); white solid; mp 165–166 °C; $[\alpha]_D$ +113 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73–1.83 (m, 1 H), 2.01–2.06 (m, 1 H), 2.80–3.19 (m, 3 H), 3.77 (s, 3 H), 4.42 (d, *J* = 9.2 Hz, 1 H), 4.60 (d, *J* = 9.2 Hz, 1 H), 4.71 (s, 1 H), 6.99–7.11 (m, 2 H), 7.22–7.34 (m, 8 H), 7.49–7.59 (m, 3 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.2, 20.0, 52.4, 54.2, 61.4, 63.7, 69.4, 124.5 (d, *J* = 3.7 Hz), 124.9 (d, *J* = 3.9 Hz), 126.6, 127.2, 127.5, 128.2, 128.3, 128.5, 129.4, 131.2, 132.8, 133.3, 137.4, 141.1, 141.6, 173.8, 197.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{25}F_3NO_3$: 480.1781; found: 480.1783.

HPLC: 83% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 25.05 and 27.44 min.

Methyl (2*R*,2′*R*,4′*R*,5′*R*)-2′-Cyclohexyl-1-oxo-4′-phenyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidine]-5′-carboxylate (3al)

Yield: 69.4 mg (83%); white solid; mp 134–135 °C; $[\alpha]_D$ +44 (*c* 0.1, CH_2Cl_2, 21 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.13 (m, 3 H), 1.39–1.55 (m, 5 H), 1.66–1.79 (m, 3 H), 1.86–1.98 (m, 2 H), 2.41–2.55 (m, 2 H), 2.70–2.81 (m, 1 H), 3.13 (d, *J* = 5.0 Hz, 1 H), 3.63 (s, 3 H), 4.14 (dd, *J* = 30.6, 9.9 Hz, 2 H), 7.07–7.09 (m, 1 H), 7.15–7.24 (m, 4 H), 7.27–7.31 (m, 2 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 8.02 (d, *J* = 7.3 Hz, 1 H).

^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.4, 26.15, 26.21, 26.5, 29.0, 31.5, 33.3, 39.9, 52.1, 58.5, 59.5, 64.0, 74.8, 126.8, 127.1, 127.5, 128.2, 128.4, 129.1, 133.29, 133.32, 137.9, 142.9, 173.2, 200.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{31}NO_3$: 418.2377; found: 418.2379.

HPLC: 80% ee (Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm); t_R = 8.90 and 21.16 min.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706599.

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