Asymmetric Synthesis of Five-Membered Spiropyrazolones via N-Heterocyclic Carbene (NHC)-Catalyzed [3+2] Annulations

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Abstract A new synthetic strategy for the asymmetric synthesis of five-membered spiropyrazolones via N-heterocyclic carbene-catalyzed [3+2] annulations employing enals and unsaturated pyrazolones as substrates has been developed. The new protocol allows the flexible variation of all four substituents of the pharmaceutically important spiropyrazolones in moderate to very good yields and in most cases with excellent diastereoselectivities and good to excellent enantioselectivities.

Key words asymmetric synthesis, spiropyrazolone, N-heterocyclic carbene, organocatalysis, [3+2] cycloaddition

Since the first enantioselective carbon–carbon bond formations catalyzed by N-heterocyclic carbenes (NHCs) in the case of the benzoin condensation reported by Sheehan and Hunnemann in 1966,^{1a} and the first enantioselective Stetter reaction developed by our group in the late eighties,^{1b,c} the field of asymmetric NHC-organocatalysis² has grown rapidly being now an important chapter of Lewis-base organocatalysis.

In recent years, pyrazolones and related derivatives turned out to display a wide range of biological and pharmaceutical activities,³ especially the spiropyrazolone derivatives. For example, spiropyrazolone **A** shows anticancer activity,^{4a} whereas spiro compounds **B** and **C** possess phosphodiesterase inhibitor activity (Figure 1).^{4b,c} Many organocatalytic asymmetric methods have been developed for the asymmetric synthesis of this important heterocyclic core structure, owing to the wide existence of the pyrazolone scaffold in related bioactive compounds.⁵ Recently, NHCs have also been employed for the asymmetric synthesis of spiropyrazolone derivatives. In this context, Biju's group reported a formal [3+3] annulation reaction of α,β -unsaturat-

ed aldehydes with α -arylidene-pyrazolinones under oxidative NHC catalysis (Scheme 1, a).⁶ Very recently, our group has developed an asymmetric multicomponent one-pot synthesis of spiropyrazolones using NHC organocatalysis (Scheme 1, b).⁷ Based on our previous work, herein we report a new strategy for the asymmetric synthesis of spiropyrazolones using unsaturated pyrazolones and enals as substrates via an NHC-catalyzed [3+2] annulation reaction. This new protocol allows the flexible variation of all four substituents R^1 – R^4 (Scheme 1, c).

Figure 1 Selected pharmaceutically active spiropyrazolones

We started our studies with the unsaturated pyrazolone **1a** and cinnamaldehyde (**2a**) as test substrates in dichloromethane at room temperature (Table 1). Initially, we obtained the spiropyrazolone product **3a** in 45% yield with excellent diastereoselectivity when the achiral pre-catalyst **4a** was employed. A series of chiral NHC pre-catalysts (Table 1, entries 2–6) was screened encouraged by the initial result and showed that the pre-catalyst **4b** was the best one. The optimization studies of the bases (entries 7–13) revealed that Cs_2CO_3 gave the product **3a** with the improved ee of 94% but with a 1:1 diastereomeric ratio (entry 7). When DMAP was employed as base (entry 11), the ee value was virtually the same (93%), but the reaction occurred with excellent diastereoselectivity in moderate yield. Using **4b** as catalyst and DMAP as base, different solvents were screened and it turned out that DCE provided the desired

product **3a** in very good yield (71%), as well as with excellent diastereoselectivity (dr >20:1) and enantiomeric excess of 93% ee (entry 18).

With the optimized reaction conditions in hand, the scope of the reaction substrates was investigated. First, a variety of enals were tested and the unsubstituted cinnamaldehyde worked very well under the standard conditions giving the product **3a**. When enals with electron-donating and electron-withdrawing groups at the *para*-position were used, the spirocyclopentane pyrazolones **3b** and **c** were obtained in moderate to good yields and with very good diastereo- and enantioselectivities. Other enal derivatives, bearing a 2-furyl and 1-propenyl group as R^4 were also tolerated and gave the desired products **3d** and **e** in moderate to good yields and with very good to excellent ee and dr values (Scheme 2).

The relative and absolute configuration of the spiro-pyrazolone **3p** was determined by X-ray crystal structure analysis (Figure 2),⁸ and the configuration of all other products **3** was assigned accordingly.

Subsequently, the variation of the unsaturated pyrazolones **1** was investigated. Substitution at the *ortho*-position as well as *para*-position of the phenyl ring of R^1 resulted in the smooth conversion to the spiro-pyrazolones **3f,g** in good yields and with excellent ee and dr. Moreover, instead of the phenyl ring, the indole group, 2-furyl group, and a 1-propenyl group furnished the desired products **3h-j** in good yields and with very good to excellent ee values. The substrate scope was further evaluated by screening different substituents R^2 and R^3 . Various pyrazolones with aliphatic R^2 -substituents afforded the corresponding spiro-pyrazolone products **3k-m** in good yields and with enantioselectivities under virtually complete diastereoselectivities (dr ≥ 20:1). This was also true for the variation of the N-substituent R^3 (**3n-q**). Only in the case of R^2 = Me and R^3 = *p*-chlorophenyl, a lower yield and stereoselectivity was observed (Scheme 3).

Table 1 Optimization of the Reaction Conditions^a

Entry	4	Solvent	Base	Yield (%) ^b	dr ^c	ee (%) ^d
1	4a	CH ₂ Cl ₂	DBU	45	>20:1	–
2	4b	CH ₂ Cl ₂	DBU	49	5:1	92
3	4c	CH ₂ Cl ₂	DBU	42	1:1	93
4	4d	CH ₂ Cl ₂	DBU	23	>20:1	90
5	4e	CH ₂ Cl ₂	DBU	27	>20:1	88
6	4f	CH ₂ Cl ₂	DBU	15	>20:1	86
7	4b	CH ₂ Cl ₂	Cs ₂ CO ₃	45	1:1	94
8	4b	CH ₂ Cl ₂	K ₃ PO ₄	24	>20:1	92
9	4b	CH ₂ Cl ₂	KOt-Bu	11	>20:1	93
10	4b	CH ₂ Cl ₂	KOAc	42	>20:1	92
11	4b	CH ₂ Cl ₂	DMAP	51	>20:1	93
12	4b	CH ₂ Cl ₂	DABCO	39	1:2	89
13	4b	CH ₂ Cl ₂	DIPEA	20	5:1	93
14	4b	EtOAc	DMAP	51	>20:1	88
15	4b	THF	DMAP	54	>20:1	85
16	4b	toluene	DMAP	44	>20:1	90
17	4b	1,4-dioxane	DMAP	71	>20:1	85
18	4b	DCE	DMAP	71	>20:1	93
19	4b	MeCN	DMAP	57	>20:1	89

^a Reaction conditions: **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), **4** (0.04 mmol, 10 mol%), base (0.4 mmol, 1.0 equiv), solvent (2 mL) at r.t. for 12 h.

^b Yield **3a** after column chromatography.

^c The dr values were determined by ¹H NMR analysis of the crude reaction mixture.

^d The ee values were determined by HPLC on a chiral stationary phase.

Scheme 2 Substrate scope of the spiropyrazolones (variation of the enals)

A plausible catalytic cycle of the NHC-catalyzed [3+2] annulation of enals and unsaturated pyrazolones is depicted in Scheme 4. First, the deprotonation of the pre-catalyst with DMAP generates the free NHC-catalyst, which reacts with the enals **2** to form the Breslow intermediate **I**. This homoenolate equivalent then undergoes a Michael addition with the pyrazolones **1** to afford the acyl azolium intermediate **II**, which cyclizes to the spiropyrazolone product **3** and returns the catalyst (Scheme 4).

In summary, the asymmetric NHC-catalyzed [3+2] annulation of enals and unsaturated pyrazolones affords the corresponding spirocyclopentane pyrazolones in moderate to very good yields (up to 86%), in most cases with excellent diastereoselectivities (dr >20:1) and very good to excellent enantioselectivities (up to 95% ee) with broad substrate scope. The new variant allows the flexible variation of all four substituents as well.

Figure 2 X-ray crystal structure of the spiropyrazolone **3p**

Unless otherwise noted, all commercially available compounds were used without further purification. Anhyd CH_2Cl_2 was purified by distillation over CaH_2 . The products were purified by column chroma-

Scheme 3 Extended substrate scope of the spiropyrazolones

Scheme 4 Proposed catalytic cycle of the asymmetric spiropyrazolone synthesis

tography on Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). For TLC analysis, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm). Optical rotation values were measured on a PerkinElmer 241 polarimeter. High-resolution mass spectra (HRMS) were acquired on a ThermoFisher Scientific LTQ-Orbitrap XL. IR spectra (cm^{-1}) were taken on a PerkinElmer Spectrum 100 FT-IR Spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded at r.t. on Inova 400 or Agilent VNMRs 600 spectrometers. Chemical shifts (δ) are given in ppm relative to solvent residual peak (CDCl_3 , $\delta = 7.26$) as external standard. Standard abbreviations for denoting multiplicities were used. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases [Daicel IC, Daicel AD, Daicel IA, Merck (S,S)-Whelk 01]. The melting point was obtained with a LLG MPM-H2 apparatus. The carbene catalysts **4a–f**,⁹ the unsaturated pyrazolones¹⁰ and the corresponding cinnamaldehydes¹¹ were prepared according to literature procedure. The racemic samples of the spiropyrazolones **3** were prepared by using the racemic pre-catalyst **4a** with DMAP.

Spiropyrazolones; General Procedure

A dried and argon-filled Schlenk tube was charged with the unsaturated pyrazolone **1** (0.4 mmol, 1.0 equiv) and triazolium salt **4b** (0.04 mmol, 10 mol%) in anhydrous 1,2-dichloroethane (2 mL). Subsequently, the α,β -unsaturated aldehyde **2** (0.8 mmol, 2.0 equiv) and DMAP (0.4 mmol, 1.0 equiv) were introduced. The resulting mixture was stirred at r.t. for 12 h, and the reaction was completed as monitored by TLC. After purification by column chromatography on silica gel (pentane/EtOAc, 15:1), the desired spiropyrrolone **3** were obtained as yellow oils (**3a–o,q,r**) or as a colorless solid (**3p**).

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-2,8-diphenyl-9-[(*E*)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (**3a**)

Yield: 131 mg (71%); yellow oil.

The analytical and spectroscopic data were in accordance with the previously reported values.⁷

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-8-(4-methoxyphenyl)-2-phenyl-9-[(*E*)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (**3b**)

Compound **3b** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 134 mg (68%); yellow oil; $[\alpha]_{\text{D}}^{27} +264.6$ ($c = 0.5$, CHCl_3).

HPLC: Chiralpak IB, *n*-heptane/*i*-PrOH (9:1), 1.0 mL/min, t_{R} (minor) = 5.16 min, t_{R} (major) = 7.23 min; $T = 30^\circ\text{C}$; 95% ee.

IR (ATR): 3363, 2969, 2320, 1740, 1607, 1496, 1367, 1220, 1035, 948, 852, 746, 682 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.89$ (dd, $J = 8.9, 1.1$ Hz, 2 H, ArH), 7.40 (dd, $J = 8.6, 7.3$ Hz, 2 H, ArH), 7.26 (d, $J = 8.6$ Hz, 2 H, ArH), 7.23–7.16 (m, 6 H, ArH), 6.91 (d, $J = 8.7$ Hz, 2 H, ArH), 6.20–6.19 (m, 2 H, CH=CH), 4.30 (td, $J = 11.7, 8.4$ Hz, 1 H, CHCH=CH), 3.87–3.83 (m, 1 H, CHCH₂), 3.80 (s, 3 H, OCH₃), 3.17 (dd, $J = 19.3, 8.4$ Hz, 1 H, CHHCO), 2.82 (dd, $J = 19.3, 12.2$ Hz, 1 H, CHHCH), 1.40 [s, 9 H, C(CH₃)₃].

^{13}C NMR (150 MHz, CDCl_3): $\delta = 205.6, 168.5, 165.8, 158.7, 137.6, 136.2, 135.0, 131.8, 128.8$ (2 C), 128.4 (2 C), 127.8, 126.4 (2 C), 125.4, 123.9, 119.3 (2 C), 114.3 (2 C), 75.7, 55.5, 55.3, 46.0, 43.8, 36.3, 29.5 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₂H₃₃N₂O₃: 493.2485; found: 493.2480.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-8-(4-chlorophenyl)-2-phenyl-9-[(*E*)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (**3c**)

Compound **3c** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 115 mg (58%); yellow oil; $[\alpha]_{\text{D}}^{27} +263.3$ ($c = 0.5$, CHCl_3).

HPLC: Chiralpak IB, *n*-heptane/EtOH (9:1), 1.0 mL/min, t_{R} (minor) = 4.34 min, t_{R} (major) = 5.12 min; $T = 30^\circ\text{C}$; 94% ee.

IR (ATR): 3461, 2966, 2320, 1742, 1596, 1490, 1369, 1297, 1203, 1088, 960, 826, 749, 686 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): δ (major) = 7.89 (dd, $J = 8.8, 1.2$ Hz, 2 H, ArH), 7.41 (dd, $J = 8.7, 7.4$ Hz, 2 H, ArH), 7.36–7.34 (m, 3 H, ArH), 7.28–7.26 (m, 2 H, ArH), 7.22–7.19 (m, 3 H, ArH), 7.19–7.16 (m, 2 H, ArH), 6.19–6.18 (m, 2 H, CH=CH), 4.34 (td, $J = 11.7, 8.4$ Hz, 1 H, CHCH=CH), 3.85–3.82 (m, 1 H, CHCH₂), 3.18 (dd, $J = 19.2, 8.4$ Hz, 1 H, CHHCO), 2.81 (dd, $J = 19.2, 12.1$ Hz, 1 H, CHHCH), 1.39 [s, 9 H, C(CH₃)₃].

^{13}C NMR (150 MHz, CDCl_3): δ (major) = 204.9, 168.4, 165.6, 138.4, 135.9, 135.3, 133.1, 130.2, 129.2, 129.1 (2 C), 128.9, 128.8, 128.7, 128.5, 128.0, 126.5, 126.4, 125.5, 123.4, 120.8, 119.3 (2 C), 75.6, 55.4, 45.6, 43.9, 36.3, 29.5 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₁H₃₀ClN₂O₂: 497.1990; found: 497.1981.

(5S,8S,9R)-4-(tert-Butyl)-8-(furan-2-yl)-2-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3d)

Compound **3d** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 101 mg (56%); pale yellow oil; [α]_D²⁷ +290.8 (*c* = 0.5, CHCl₃).

HPLC: Chiralpak IB, *n*-heptane/EtOH (9:1), 1.0 mL/min, *t*_R (minor) = 10.65 min, *t*_R (major) = 8.73 min; *T* = 30 °C; 91% ee.

IR (ATR): 3458, 2970, 2328, 1739, 1366, 1216, 1095, 906, 752, 687 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.88–7.86 (m, 2 H, ArH), 7.42–7.38 (m, 3 H, ArH), 7.25–7.18 (m, 6 H, ArH), 6.31–6.28 (m, 2 H, ArH), 6.22–6.18 (m, 2 H, CH=CH), 4.39 (td, *J* = 11.4, 8.4 Hz, 1 H, CHCH=CH), 4.01 (dd, *J* = 11.2, 8.3 Hz, 1 H, CHCH₂), 3.08 (dd, *J* = 19.2, 8.4 Hz, 1 H, CHHCO), 2.99 (dd, *J* = 19.2, 11.7 Hz, 1 H, CHHCH), 1.37 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): δ (major) = 204.7, 168.4, 165.8, 152.4, 142.0, 137.6, 136.2, 135.1, 128.8 (2 C), 128.5 (2 C), 127.9, 126.4 (2 C), 125.4, 123.7, 119.2 (2 C), 110.4, 107.8, 75.2, 52.4, 42.9, 38.4, 36.3, 29.4 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₉H₂₉N₂O₃: 453.2172; found: 453.2161.

(5S,8R,9R)-4-(tert-Butyl)-2-phenyl-8-[(E)-prop-1-en-1-yl]-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3e)

Compound **3e** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 77 mg (45%); pale yellow oil; [α]_D²⁷ +282.8 (*c* = 0.5, CHCl₃).

HPLC: Chiralpak AD, *n*-heptane/*i*-PrOH (97:3), 1.0 mL/min, *t*_R (minor) = 10.56 min, *t*_R (major) = 9.29 min; *T* = 30 °C; 86% ee.

IR (ATR): 3370, 2967, 2318, 1696, 1598, 1491, 1369, 1296, 1201, 1088, 961, 825, 749, 686 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.87–7.85 (m, 2 H, ArH), 7.39–7.37 (m, 2 H, ArH), 7.30–7.17 (m, 6 H, ArH), 6.48 (d, *J* = 15.9 Hz, 1 H, ArH), 6.21 (dd, *J* = 15.9, 8.6 Hz, 1 H, ArH), 5.64–5.60 (m, 1 H, CH=CHPh), 5.44–5.40 (m, 1 H, CHCH=CH), 3.71 (td, *J* = 11.5, 5.8 Hz, 1 H, CHCH=CH), 3.48 (dd, *J* = 11.5, 8.6 Hz, 1 H, CHCH₂), 2.92 (dd, *J* = 19.0, 8.6 Hz, 1 H, CHHCO), 2.48 (dd, *J* = 19.0, 11.5 Hz, 1 H, CHHCH), 1.72–1.70 (m, 3 H, CH₃), 1.33 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): δ = 205.9, 168.5, 165.8, 134.9, 130.4, 128.7 (2 C), 128.5 (2 C), 128.4 (2 C), 127.8, 126.5 (2 C), 125.3, 124.4, 119.2 (2 C), 75.3, 53.9, 44.3, 41.7, 36.3, 29.4 (3 C), 18.0.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₈H₃₁N₂O₂: 427.2380; found: 427.2378.

(5S,8S,9R)-4-(tert-Butyl)-9-[(E)-4-methoxystyryl]-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3f)

Compound **3f** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 108 mg (55%); yellow oil; [α]_D²⁷ +260.4 (*c* = 0.5, CHCl₃).

HPLC: Chiralpak AD, *n*-heptane/*i*-PrOH (97:3), 1.0 mL/min, *t*_R (minor) = 24.64 min, *t*_R (major) = 20.12 min; *T* = 30 °C; 95% ee.

IR (ATR): 3454, 2930, 2320, 1740, 1598, 1493, 1368, 1223, 1117, 958, 752, 688 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.87 (dd, *J* = 8.7, 1.2 Hz, 2 H, ArH), 7.40–7.31 (m, 6 H, ArH), 7.28–7.25 (m, 1 H, ArH), 7.21–7.18 (m, 1 H, ArH), 7.08 (d, *J* = 8.8 Hz, 2 H, ArH), 6.73 (d, *J* = 8.8 Hz, 2 H, ArH), 6.11 (d, *J* = 15.8 Hz, 1 H, CH=CHPh), 6.04 (dd, *J* = 15.9 Hz, 8.2, 1 H,

CHCH=CH), 4.31 (td, *J* = 11.7, 8.4 Hz, 1 H, CHCH=CH), 3.88 (d, *J* = 8.1 Hz, 1 H, CHCH₂), 3.74 (s, 3 H, OCH₃), 3.17 (dd, *J* = 19.3, 8.4 Hz, 1 H, CHHCHO), 2.84 (dd, *J* = 19.3, 12.1 Hz, 1 H, CHHCH), 1.38 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): δ = 205.7, 168.6, 165.8, 159.4, 140.0, 137.6, 134.4, 129.0 (2 C), 128.9, 128.8, 128.7, 127.6 (2 C), 127.5 (2 C), 127.3, 125.4, 121.4, 119.3 (2 C), 113.8 (2 C), 75.8, 55.4, 55.3, 45.9, 44.5, 36.3, 29.5 (3 C).

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₂H₃₃N₂O₃: 493.2485; found: 493.2479.

(5S,8S,9R)-4-(tert-Butyl)-9-[(E)-2-methoxystyryl]-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3g)

Compound **3g** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 158 mg (80%); pale yellow oil; [α]_D²⁷ +257.7 (*c* = 6.2, CHCl₃).

HPLC: Chiralpak IA, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, *t*_R (minor) = 9.74 min, *t*_R (major) = 11.34 min; *T* = 30 °C; 92% ee.

IR (ATR): 3483, 2964, 2304, 2079, 1969, 1879, 1748, 1689, 1594, 1468, 1367, 1296, 1244, 1191, 1122, 1031, 958, 841, 751, 686 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 7.92 (d, *J* = 8.6 Hz, 2 H, ArH), 7.44–7.35 (m, 6 H, ArH), 7.31–7.26 (m, 1 H, ArH), 7.22–7.18 (m, 2 H, ArH), 7.15 (t, *J* = 7.8 Hz, 1 H, ArH), 6.81 (t, *J* = 10.9 Hz, 1 H, ArH), 6.74 (d, *J* = 8.2 Hz, 1 H, ArH), 6.53 (d, *J* = 16.1 Hz, 1 H, CH=CHPh), 6.22–6.16 (m, 1 H, CHCH=CH), 4.41–4.33 (m, 1 H, CHCH=CH), 3.98–3.91 (m, 1 H, CHCH₂), 3.59 (s, 3 H, OCH₃), 3.20 (dd, *J* = 19.3, 8.4 Hz, 1 H, CHHCO), 2.87 (dd, *J* = 19.3, 12.1 Hz, 1 H, CHHCH), 1.42 [s, 9 H, C(CH₃)₃].

¹³C NMR (151 MHz, CDCl₃): δ = 205.8, 168.6, 165.9, 156.6, 140.1, 137.7, 130.0, 128.9 (2 C), 128.8 (2 C), 127.6 (2 C), 127.3 (2 C), 126.9, 125.5, 125.3, 124.2, 120.5, 119.2 (2 C), 110.9, 75.8, 55.7, 55.3, 46.1, 44.4, 36.3, 29.6 (3 C).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₃₂H₃₂N₂O₃Na: 515.2305; found: 515.2296.

(5S,8S,9R)-9-[(E)-2-(1H-Indol-2-yl)vinyl]-4-(tert-butyl)-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3h)

Compound **3h** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 96 mg (48%); pale yellow oil; [α]_D²⁷ +292.7 (*c* = 0.5, CHCl₃).

HPLC: Chiralpak IC, *n*-heptane/EtOH (97:3), 1.0 mL/min, *t*_R (minor) = 7.06 min, *t*_R (major) = 5.07 min; *T* = 30 °C; 87% ee.

IR (ATR): 3352, 2323, 2096, 1727, 1644, 1370, 1279, 1218, 1116, 681 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 8.16 (br s, 1 H, NH), 7.93–7.90 (m, 2 H, ArH), 7.47–7.46 (m, 1 H, ArH), 7.41–7.36 (m, 4 H, ArH), 7.34–7.32 (m, 2 H, ArH), 7.30–7.27 (m, 1 H, ArH), 7.23–7.19 (m, 2 H, ArH), 7.13–7.11 (m, 1 H, ArH), 7.04–7.01 (m, 1 H, ArH), 6.28 (dd, *J* = 2.1, 1.0 Hz, 1 H, ArH), 6.21 (d, *J* = 16.1 Hz, 1 H, CH=CHPh), 6.06–6.02 (m, 1 H, CHCH=CH), 4.34 (td, *J* = 11.7, 8.5 Hz, 1 H, CHCH=CH), 3.93 (dd, *J* = 11.2, 8.7 Hz, 1 H, CHCH₂), 3.20 (dd, *J* = 19.4, 8.5 Hz, 1 H, CHHCO), 2.89 (dd, *J* = 19.4, 12.1 Hz, 1 H, CHHCH), 1.41 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): δ = 205.1, 168.6, 165.9, 139.6, 137.5, 136.7, 134.5, 129.0 (2 C), 128.9 (2 C), 128.3 (2 C), 127.5 (2 C), 125.8, 125.6, 123.0, 121.7, 120.6, 120.1, 119.3 (2 C), 110.7, 103.9, 75.8, 55.4, 45.8, 44.8, 36.4, 29.5 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₃H₃₂N₃O₂: 502.2489; found: 502.2482.

(5S,8S,9R)-4-(tert-Butyl)-9-[(E)-2-(furan-2-yl)vinyl]-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3i)

Compound **3i** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 92 mg (51%); yellow oil; $[\alpha]_D^{27} +356.5$ ($c = 0.5$, CHCl₃).

HPLC: Chiralpak IA, *n*-heptane/EtOH (97:3), 1.0 mL/min, t_R (minor) = 15.28 min, t_R (major) = 14.11 min; $T = 30^\circ\text{C}$; 94% ee.

IR (ATR): 3461, 2964, 2331, 1743, 1597, 1490, 1368, 1211, 1113, 952, 749, 689 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 7.90\text{--}7.88$ (m, 2 H, ArH), 7.42–7.27 (m, 7 H, ArH), 7.23–7.19 (m, 2 H, ArH), 6.25 (dd, $J = 3.3$, 1.8 Hz, 1 H, ArH), 6.14 (dd, $J = 15.9$, 8.5 Hz, 1 H, CH=CHPh), 6.05 (d, $J = 3.3$ Hz, 1 H, ArH), 5.98 (d, $J = 15.9$ Hz, 1 H, CHCH=CH), 4.33 (td, $J = 11.7$, 8.5 Hz, 1 H, CHCH=CH), 3.86 (dd, $J = 11.3$, 8.5 Hz, 1 H, CHCH₂), 3.18 (dd, $J = 19.3$, 8.4 Hz, 1 H, CHHCO), 2.83 (dd, $J = 19.3$, 12.1 Hz, 1 H, CHHCH), 1.38 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): $\delta = 205.4$, 168.3, 165.6, 151.5, 142.1, 139.9, 137.6, 128.9 (2 C), 128.8, 127.5 (2 C), 127.4 (2 C), 125.4, 122.9, 122.1, 119.3 (2 C), 111.1, 108.3, 75.6, 55.0, 46.0, 44.4, 36.3, 29.5 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₉H₂₉N₂O₃: 453.2172; found: 453.2171.

(5S,8S,9R)-4-(tert-Butyl)-9-[(1E,3E)-penta-1,3-dien-1-yl]-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3j)

Compound **3j** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 103 mg (60%); pale yellow oil; $[\alpha]_D^{27} +279.6$ ($c = 3.2$, CHCl₃).

HPLC: Chiralcel OJ, *n*-heptane/EtOH (97:3), 0.7 mL/min, t_R (minor) = 7.54 min, t_R (major) = 10.64 min; $T = 30^\circ\text{C}$; 90% ee.

IR (ATR): 3482, 2967, 2297, 2061, 1952, 1748, 1694, 1595, 1493, 1368, 1294, 1198, 1124, 1061, 986, 941, 849, 754, 687 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ (major) = 7.88 (d, $J = 8.5$ Hz, 2 H, ArH), 7.43–7.35 (m, 4 H, ArH), 7.33–7.26 (m, 3 H, ArH), 7.22–7.18 (m, 1 H, ArH), 5.87–5.74 (m, 2 H, CHCH=CH), 5.54–5.41 (m, 2 H, CH=CHCH₃), 4.27–4.19 (m, 1 H, CHCH=CH), 3.74 (dd, $J = 11.7$, 8.5 Hz, 1 H, CHCH₂), 3.13 (dd, $J = 19.3$, 8.5 Hz, 1 H, CHHCO), 2.78 (dd, $J = 19.3$, 11.7 Hz, 1 H, CHHCH), 1.62 (d, $J = 7.3$ Hz, 3 H, CH=CHCH₃), 1.35 [s, 9 H, C(CH₃)₃].

¹³C NMR (150 MHz, CDCl₃): δ (major) = 205.7, 168.5, 165.8, 140.1, 137.7, 135.3, 130.6, 130.2, 128.8 (2 C), 128.5, 127.5 (2 C), 127.2 (2 C), 125.3, 124.0, 119.2 (2 C), 75.7, 54.9, 46.1, 44.4, 36.2, 29.5 (3 C), 17.9.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₈H₃₁N₂O₂: 427.2380; found: 427.2379.

(5S,8S,9R)-4-Methyl-2,8-diphenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3k)

Compound **3k** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 77 mg (71%); pale yellow oil; $[\alpha]_D^{20} +54.5$ ($c = 1.7$, CHCl₃).

HPLC: Chiralpak AS, *n*-heptane/*i*-PrOH (9:1), 1.0 mL/min, t_R (minor) = 6.20 min, t_R (major) = 8.29 min; $T = 30^\circ\text{C}$; 85% ee.

IR (ATR): 3437, 3030, 2927, 2847, 2635, 2324, 2101, 1894, 1712, 1594, 1495, 1450, 1368, 1304, 1222, 1076, 1020, 897, 838, 754, 694 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 7.82$ (d, $J = 8.7$ Hz, 2 H, ArH), 7.40–7.36 (m, 2 H, ArH), 7.36–7.30 (m, 4 H, ArH), 7.28–7.26 (m, 1 H, ArH), 7.22–7.18 (m, 3 H, ArH), 7.18–7.14 (m, 3 H, ArH), 6.26–6.21 (m, 1 H,

CH=CHPh), 6.17–6.13 (m, 1 H, CHCH=CH), 4.37 (td, $J = 11.2$, 9.0 Hz, 1 H, CHCH=CH), 3.46 (dd, $J = 11.2$, 8.5 Hz, 1 H, CHCH₂), 3.27 (dd, $J = 19.6$, 9.0 Hz, 1 H, CHHCO), 2.72 (dd, $J = 19.6$, 11.2 Hz, 1 H, CHHCH), 2.19 (s, 3 H, CH₃).

¹³C NMR (151 MHz, CDCl₃): $\delta = 205.0$, 167.9, 157.2, 139.8, 137.4, 135.9, 135.1, 128.9 (2 C), 128.8 (2 C), 128.5 (2 C), 128.0 (2 C), 127.4 (2 C), 126.5 (2 C), 125.5, 123.3, 119.3 (2 C), 75.7, 55.7, 46.0, 43.7, 14.4.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₈H₂₅N₂O₂: 421.1911; found: 421.1914.

(5S,8S,9R)-4-Ethyl-2,8-diphenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3l)

Compound **3l** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 76 mg (44%); yellow oil; $[\alpha]_D^{20} +99.4$ ($c = 2.5$, CHCl₃).

HPLC: Chiralpak IB, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, t_R (minor) = 10.02 min, t_R (major) = 9.31 min; $T = 30^\circ\text{C}$; 86% ee.

IR (ATR): 3440, 3031, 2925, 2647, 2321, 2098, 1992, 1887, 1694, 1595, 1494, 1455, 1350, 1227, 1137, 1061, 961, 901, 834, 751, 691 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 7.86$ (d, $J = 7.8$ Hz, 2 H, ArH), 7.39 (t, $J = 8.0$ Hz, 2 H, ArH), 7.37–7.34 (m, 2 H, ArH), 7.33–7.30 (m, 2 H, ArH), 7.28–7.24 (m, 2 H, ArH), 7.22–7.19 (m, 2 H, ArH), 7.19–7.14 (m, 3 H, ArH), 6.24–6.14 (m, 2 H, CH=CH), 4.36 (td, $J = 20.2$, 11.3 Hz, 1 H, CHCH=CH), 3.49 (dd, $J = 11.3$, 8.1 Hz, 1 H, CHCH₂), 3.25 (dd, $J = 19.6$, 8.8 Hz, 1 H, CHHCO), 2.73 (dd, $J = 19.6$, 11.3 Hz, 1 H, CHHCH), 2.59–2.44 (m, 2 H, CH₂CH₃), 1.34 (t, $J = 7.4$ Hz, 3 H, CH₂CH₃).

¹³C NMR (151 MHz, CDCl₃): $\delta = 205.2$, 168.1, 161.0, 139.8, 137.6, 135.9, 135.0, 128.9 (2 C), 128.8 (2 C), 128.5 (2 C), 127.9 (2 C), 127.4 (2 C), 126.5 (2 C), 125.5, 123.4, 119.3 (2 C), 75.6, 55.6, 46.1, 43.8, 22.2, 9.6.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₉H₂₇N₂O₂: 435.2067; found: 435.2065.

(5S,8S,9R)-4-Isopropyl-2,8-diphenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3m)

Compound **3m** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 90 mg (50%); yellow oil; $[\alpha]_D^{20} +188.9$ ($c = 2.7$, CHCl₃).

HPLC: Chiralpak IB, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, t_R (minor) = 8.73 min, t_R (major) = 7.92 min; $T = 30^\circ\text{C}$; 80% ee.

IR (ATR): 3031, 2971, 2324, 2098, 1953, 1880, 1748, 1691, 1596, 1494, 1455, 1345, 1240, 1130, 1065, 963, 905, 837, 749, 689 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 7.86$ (d, $J = 7.7$ Hz, 2 H, ArH), 7.41–7.37 (m, 2 H, ArH), 7.37–7.34 (m, 2 H, ArH), 7.34–7.31 (m, 2 H, ArH), 7.28–7.26 (m, 1 H, ArH), 7.22–7.18 (m, 3 H, ArH), 7.18–7.14 (m, 3 H, ArH), 6.23–6.15 (m, 2 H, CH=CH), 4.33 (td, $J = 11.6$, 8.5 Hz, 1 H, CHCH=CH), 3.57 (dd, $J = 11.4$, 6.5 Hz, 1 H, CHCH₂), 3.22 (dd, $J = 19.4$, 8.5 Hz, 1 H, CHHCO), 2.82–2.74 (m, 2 H, CHHCH), 1.36 (d, $J = 6.9$ Hz, 3 H, CCH₃), 1.31 (d, $J = 6.9$ Hz, 3 H, CCH₃).

¹³C NMR (151 MHz, CDCl₃): $\delta = 205.1$, 168.2, 164.1, 139.7, 137.6, 136.0, 135.0, 128.9 (2 C), 128.8 (2 C), 128.5 (2 C), 127.9 (2 C), 127.4 (2 C), 126.4 (2 C), 125.4, 123.7, 119.3 (2 C), 75.6, 55.3, 46.2, 44.2, 29.3, 21.3, 19.8.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₀H₂₉N₂O₂: 449.2224; found: 449.2229.

(5S,8S,9R)-2-(4-Bromophenyl)-4-(tert-butyl)-8-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3n)

Compound **3n** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 138 mg (64%); pale yellow oil; $[\alpha]_D^{20} +270.5$ ($c = 1.3$, CHCl_3).

HPLC: Chiralpak IB, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, t_R (minor) = 7.84 min, t_R (major) = 7.06 min; $T = 30^\circ\text{C}$; 88% ee.

IR (ATR): 3476, 2966, 2319, 2072, 1899, 1691, 1597, 1482, 1367, 1293, 1199, 1126, 1059, 963, 824, 731 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.80$ (d, $J = 8.9$ Hz, 2 H, ArH), 7.52–7.48 (m, 2 H, ArH), 7.39–7.34 (m, 2 H, ArH), 7.34–7.31 (m, 2 H, ArH), 7.29–7.26 (m, 1 H, ArH), 7.23–7.15 (m, 3 H, ArH), 7.15–7.12 (m, 2 H, ArH), 6.17–6.15 (m, 2 H, CH=CH), 4.30 (td, $J = 11.7$, 8.4 Hz, 1 H, CHCH=CH), 3.92–3.87 (m, 1 H, CHCH₂), 3.18 (dd, $J = 19.3$, 8.4 Hz, 1 H, CHHCO), 2.86 (dd, $J = 19.3$, 12.1 Hz, 1 H, CHHCH), 1.38 [s, 9H, C(CH₃)₃].

^{13}C NMR (151 MHz, CDCl_3): $\delta = 205.3$, 168.4, 166.2, 139.7, 136.6, 136.1, 135.1, 131.8 (2 C), 129.0 (2 C), 128.5 (2 C), 127.9 (2 C), 127.5 (2 C), 127.4 (2 C), 126.4 (2 C), 123.5, 120.6, 118.3, 75.7, 55.3, 45.9, 44.5, 36.4, 29.5.

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₃₁H₂₉BrN₂O₂Na: 563.1305; found: 563.1305.

(5S,8S,9R)-4-(tert-Butyl)-2-(4-methoxyphenyl)-8-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3o)

Compound **3o** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 170 mg (86%); pale yellow oil; $[\alpha]_D^{20} +299.6$ ($c = 5.2$, CHCl_3).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (9:1), 1.0 mL/min, t_R (minor) = 4.11 min, t_R (major) = 5.17 min; $T = 30^\circ\text{C}$; 92% ee.

IR (ATR): 3489, 3027, 2966, 2305, 2059, 1957, 1880, 1749, 1688, 1596, 1508, 1455, 1371, 1296, 1246, 1182, 1131, 1062, 1030, 950, 831, 749, 695, 662 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.75$ (d, $J = 9.0$ Hz, 2 H, ArH), 7.39–7.35 (m, 2 H, ArH), 7.35–7.32 (m, 2 H, ArH), 7.29–7.27 (m, 1 H, ArH), 7.23–7.19 (m, 2 H, ArH), 7.19–7.14 (m, 3 H, ArH), 6.94–6.91 (m, 2 H), 6.23–6.15 (m, 2 H, CH=CH), 4.34 (td, $J = 11.7$, 8.5 Hz, 1 H, CHCH=CH), 3.90 (dd, $J = 11.3$, 7.3 Hz, 1 H, CHCH₂), 3.82 (s, 3 H, OCH₃), 3.18 (dd, $J = 19.3$, 8.5 Hz, 1 H, CHHCO), 2.86 (dd, $J = 19.3$, 12.1 Hz, 1 H, CHHCH), 1.38 [s, 9 H, C(CH₃)₃].

^{13}C NMR (151 MHz, CDCl_3): $\delta = 205.7$, 168.1, 165.7, 157.3, 139.9, 136.2, 134.9, 130.9, 128.9 (2 C), 128.5, 127.8 (2 C), 127.5, 127.4 (2 C), 126.4 (2 C), 123.9, 121.2 (2 C), 114.0 (2 C), 75.5, 55.5, 55.3, 45.9, 44.5, 36.3, 29.5 (3 C).

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₂H₃₃N₂O₃: 493.2486; found: 493.2476.

(5S,8S,9R)-2-Benzyl-4-(tert-butyl)-8-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3p)

Compound **3p** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 108 mg (57%); colorless solid; mp 122–124 $^\circ\text{C}$; $[\alpha]_D^{20} +151.5$ ($c = 6.4$, CHCl_3).

HPLC: Chiralpak IC; *n*-heptane/*i*-PrOH 9:1, 0.5 mL/min, $t_R = 7.24$ min (major), $t_R = 20.72$ min (minor); $T = 30^\circ\text{C}$; 85% ee.

IR (ATR): 3368, 2967, 2322, 2079, 1963, 1888, 1744, 1690, 1592, 1492, 1455, 1367, 1271, 1186, 1140, 1113, 1067, 1029, 963, 904, 849, 747, 695 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.38$ –7.34 (m, 2 H, ArH), 7.34–7.31 (m, 2 H, ArH), 7.29–7.26 (m, 1 H, ArH), 7.25–7.22 (m, 2 H, ArH), 7.22–7.19 (m, 2 H, ArH), 7.19–7.16 (m, 1 H, ArH), 7.14–7.09 (m, 4 H, ArH), 6.18–6.10 (m, 2 H, CH=CH), 4.97 (d, $J = 15.5$ Hz, 1 H, CHHN), 4.76 (d, $J = 15.5$ Hz, 1 H, CHHP), 4.31 (dd, $J = 20.2$, 11.4 Hz, 1 H, CHCH=CH), 3.86 (dd, $J = 11.1$, 7.0 Hz, 1 H, CHCH₂), 3.15 (dd, $J = 19.1$, 8.3 Hz, 1 H, CHHCO), 2.83 (dd, $J = 19.1$, 12.2 Hz, 1 H, CHHCH), 1.31 [s, 9 H, C(CH₃)₃].

^{13}C NMR (151 MHz, CDCl_3): $\delta = 206.2$, 170.1, 165.5, 140.0, 136.2, 136.2, 134.8 (2 C), 128.9 (2 C), 128.5 (2 C), 128.4 (2 C), 127.8 (2 C), 127.5 (2 C), 127.3 (2 C), 126.4 (2 C), 124.2, 74.3, 54.9, 47.9, 46.1, 44.3, 36.1, 29.6 (3 C).

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₃₂H₃₂N₂O₂Na: 499.2356; found: 499.2346.

(5S,8S,9R)-4-(tert-Butyl)-2-(2,6-dimethylphenyl)-8-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3q)

Compound **3q** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 116 mg (59%); yellow oil; $[\alpha]_D^{20} +148.7$ ($c = 4.4$, CHCl_3).

HPLC: Chiralpak IA, *n*-heptane/EtOH (7:3), 0.5 mL/min, t_R (minor) = 10.74 min, t_R (major) = 12.35 min; $T = 30^\circ\text{C}$; 85% ee.

IR (ATR): 3812, 3460, 3091, 2971, 2323, 2058, 1898, 1739, 1595, 1469, 1369, 1294, 1225, 1035, 961, 801, 729 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.38$ –7.31 (m, 4 H, ArH), 7.28–7.26 (m, 1 H, ArH), 7.26–7.23 (m, 2 H, ArH), 7.22–7.19 (m, 3 H, ArH), 7.18 (d, $J = 7.5$ Hz, 1 H, ArH), 7.12 (d, $J = 7.5$ Hz, 1 H, ArH), 7.04 (d, $J = 7.5$ Hz, 1 H, ArH), 6.36–6.25 (m, 2 H, CH=CH), 4.34 (td, $J = 11.8$, 8.3 Hz, 1 H, CHCH=CH), 3.94 (dd, $J = 11.2$, 8.3 Hz, 1 H, CHCH₂), 3.18 (dd, $J = 19.1$, 8.3 Hz, 1 H, CHHCO), 2.87 (dd, $J = 19.1$, 12.3 Hz, 1 H, CHHCH), 2.24 (s, 3 H, ArCH₃), 2.02 (s, 3 H, ArCH₃), 1.38 [s, 9 H, C(CH₃)₃].

^{13}C NMR (151 MHz, CDCl_3): $\delta = 206.0$, 169.0, 166.2, 139.9, 137.3, 135.0, 129.2, 129.0 (2 C), 128.5 (2 C), 128.4, 128.2 (2 C), 127.9 (2 C), 127.4 (2 C), 127.3 (2 C), 126.3 (2 C), 124.5, 74.4, 54.9, 46.1, 44.4, 36.3, 29.7 (3 C), 18.3, 18.1.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₃₃H₃₅N₂O₂: 491.2693; found: 491.2693.

(5S,8S,9R)-2-(4-Chlorophenyl)-4-methyl-8-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3r)

Compound **3r** was isolated after flash chromatography (*n*-pentane/EtOAc, 20:1); yield: 93 mg (46%); yellow oil; $[\alpha]_D^{20} +57.0$ ($c = 2.2$, CHCl_3).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, t_R (minor) = 4.98 min, t_R (major) = 4.52 min; $T = 30^\circ\text{C}$; 70% ee.

IR (ATR): 3452, 3023, 2928, 2649, 2322, 2105, 1989, 1907, 1725, 1591, 1492, 1365, 1298, 1219, 1087, 1010, 896, 827, 754, 696 cm^{-1} .

^1H NMR (600 MHz, CDCl_3): $\delta = 7.80$ (d, $J = 9.0$ Hz, 2 H, ArH), 7.37–7.33 (m, 4 H, ArH), 7.33–7.30 (m, 2 H, ArH), 7.28–7.26 (m, 1 H, ArH), 7.23–7.19 (m, 2 H, ArH), 7.19–7.13 (m, 3 H, ArH), 6.23 (d, $J = 15.8$ Hz, 1 H, CH=CHPh), 6.13 (dd, $J = 15.8$, 8.6 Hz, 1 H, CHCH=CH), 4.35 (td, $J = 11.3$, 9.0 Hz, 1 H, CHCH=CH), 3.46 (dd, $J = 11.4$, 8.6 Hz, 1 H, CHCH₂), 3.27 (dd, $J = 19.7$, 9.0 Hz, 1 H, CHHCO), 2.72 (dd, $J = 19.7$, 11.2 Hz, 1 H, CHHCH), 2.19 (s, 3 H, CH₃).

^{13}C NMR (151 MHz, CDCl_3): $\delta = 204.8$, 167.9, 157.5, 139.6, 136.0, 135.8, 135.2, 130.6, 128.9 (2 C), 128.8 (2 C), 128.5, 128.1, 127.5 (2 C), 127.4 (2 C), 126.5 (2 C), 123.1, 120.2 (2 C), 75.7, 55.7, 46.0, 43.7, 14.4.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₂₈H₂₄ClN₂O₂: 455.1521; found: 455.1524.

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0036-1588381>.

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