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 carbine, 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,\(^{1bc}\) the field of asymmetric NHC-organocatalysis\(^2\) 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).\(^{4bc}\) 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 \(\alpha,\beta\)-unsaturated aldehydes with \(\alpha\)-arylidenepyrazolinones 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).

We started our studies with the unsaturated pyrazolone 1\(a\) and cinnamaldehyde (2\(a\)) as test substrates in dichloromethane at room temperature (Table 1). Initially, we obtained the spiropyrazolone product 3\(a\) in 45% yield with excellent diasteroselectivity when the achiral pre-catalyst 4\(a\) 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 4\(b\) was the best one. The optimization studies of the bases (entries 7–13) revealed that Cs\(\text{2CO}_3\) gave the product 3\(a\) 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 4\(b\) 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 R4 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 spiropyrazolone 3p was determined by X-ray crystal structure analysis (Figure 2), 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 R1 resulted in the smooth conversion to the spiropyrazolones 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-prope- nyl 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 R2 and R3. Various pyrazolones with aliphatic R2-substituents afforded the corresponding spiropyrazolone 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 R3 (3n-q). Only in the case of R2 = Me and R3 = p-chlorophenyl, a lower yield and stereoselectivity was observed (Scheme 3).
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.

Unless otherwise noted, all commercially available compounds were used without further purification. Anhyd CH₂Cl₂ was purified by distillation over CaH₂. The products were purified by column chroma-
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 spirocyclopentane pyrazolones 3 were obtained as yellow oils (3a–o,q,r) or as a colorless solid (3p).

**Scheme 4** Proposed catalytic cycle of the asymmetric spiropyrazolone synthesis

**Synthesis**
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(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]₂⁰+290.8 (c = 0.5, CHCl₃).

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

IR (ATR): 3458, 2970, 2328, 1739, 1366, 1216, 1205, 906, 752, 687 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 7.88–7.85 (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 (dd, 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, CHCH₃), 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 C_{26}H_{28}O_{3}N: 214.2171; found: 214.2168.

(5S,8S,9R)-4-(tert-Butyl)-2-phenyl-[{(E)-prop-1-en-1-yl}-9-[(R)-4-methoxystyryl]-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: 77 mg (45%); pale yellow oil; [α]₂⁰+282.8 (c = 0.5, CHCl₃).

HPLC: Chiralpak AD, n-heptane/PrOH (97:3), 1.0 mL/min, tₚ (minor) = 10.56 min, tₚ (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, 6 H, CH=CHPh), 5.44–5.40 (m, 4 H, CH=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, CHCH₃), 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 (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 + Na]⁺ calcd for C_{32}H_{32}N_{2}O_{3}Na: 515.2305; found: 515.2296.

(5S,8S,9R)-9-[(E)-2-[(1H-indol-2-yl)vinyl]-4-(tert-buty1)-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]₂⁰+292.7 (c = 0.5, CHCl₃).

HPLC: Chiralpak IC, n-heptane/EtOH (97:3), 1.0 mL/min, tₚ (minor) = 7.06 min, tₚ (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, CH=CHCH=CH), 4.34 (td, J = 11.7, 8.5 Hz, 1 H, CHCH=CH), 3.93 (dd, J = 11.2, 8.1 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, CHCH₃), 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, 125.3, 120.3, 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 C_{33}H_{32}N_{2}O₂: 502.2489; found: 502.2482.
(5S,5S,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%); pale yellow oil; [α]D 20 +356.5 (c = 0.5, CHCl3).

HPLC: Chiralpak IA, n-heptane/EtOH (97:3), 1.0 mL/min, tR (minor) = 15.28 min, tR (major) = 14.11 min; T = 30 °C; 94% ee.

IR (ATR): 3482, 2967, 2297, 2061, 1952, 1748, 1694, 1595, 1493, 1368, 749, 689 cm−1.

1H NMR (600 MHz, CDCl3): δ = 7.90–7.88 (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 (dd, J = 3.3 Hz, 1 H, ArH), 5.98 (dd, J = 15.9 Hz, 1 H, CH=CH(CH3)), 4.33 (td, J = 11.7, 8.5 Hz, 1 H, CH=CH(CH3)), 3.86 (dd, J = 11.3, 8.5 Hz, 1 H, CH2CH2), 3.18 (dd, J = 19.3, 8.4 Hz, 1 H, CH=CHCO), 2.83 (dd, J = 19.3, 12.1 Hz, 1 H, CH=CH2), 1.38 [s, 9 H, (C(CH3))3].

13C NMR (150 MHz, CDCl3): δ = 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, 75.5, 55.0, 46.0, 44.4, 36.3, 29.5 (3 C).


(5S,5S,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; [α]D 20 +279.6 (c = 3.2, CHCl3).

HPLC: Chiralcel OJ, n-heptane/EtOH (97:3), 0.7 mL/min, tR (minor) = 7.54 min, tR (major) = 10.64 min; T = 30 °C; 90% ee.

IR (ATR): 3440, 3021, 2952, 2647, 2098, 1992, 1887, 1694, 1595, 1494, 1455, 1350, 1227, 1137, 1061, 961, 834, 751, 691 cm−1.

1H NMR (600 MHz, CDCl3): δ = 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 (dd, J = 20.2, 11.3 Hz, 1 H, CH=CH=CH=), 3.49 (dd, J = 11.3, 8.1 Hz, 1 H, CH2CH2), 3.25 (dd, J = 19.6, 8.8 Hz, 1 H, CH=CHCO), 2.73 (dd, J = 19.6, 11.3 Hz, 1 H, CH=CH2), 2.59–2.44 (m, 2 H, CH2CH2), 1.34 (t, J = 7.4 Hz, 3 H, CH3CH2).

13C NMR (151 MHz, CDCl3): δ = 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, 124.3, 119.3 (2 C), 75.5, 55.6, 46.1, 43.8, 22.9, 9.6.


(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%); pale yellow oil; [α]D 20 +188.9 (c = 2.7, CHCl3).

HPLC: Chiralpak IB, n-heptane/PrOH (9:1), 0.7 mL/min, tR (minor) = 8.73 min, tR (major) = 9.72 min; T = 30 °C; 80% ee.


1H NMR (600 MHz, CDCl3): δ = 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, CH=CH=CH=), 3.37 [d, J = 14.4, 6.5 Hz, 1 H, CH2CH2], 3.22 (dd, J = 19.4, 8.5 Hz, 1 H, CH=CHCO), 2.82–2.74 (m, 2 H, CH2CH2), 1.36 (d, J = 6.9 Hz, 3 H, CH3CH2), 1.31 (d, J = 6.9 Hz, 3 H, CH3).

13C NMR (151 MHz, CDCl3): δ = 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.

(5S,8S,R)-2-(4-Bromophenyl)-4-(tert-buty1)-8-phenyl-9-[(E)-styryl]-2,3-diaza­spirol[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; [α]20D +151.5 (c = 5.2, CHCl3).

HPLC: Chiralpak IA, n-heptane/i-PrOH (9:1), 0.5 mL/min, tR (minor) = 10.74 min, tR (major) = 12.35 min; T = 30 °C; 85% ee.

IR (ATR): 3476, 2966, 2319, 2072, 1899, 1691, 1597, 1264, 1237, 1175, 1059, 963, 824, 731 cm−1.


(5S,8S,R)-4-(tert-Butyl)-2-(4-methoxyphenyl)-8-phenyl-9-[(E)-styryl]-2,3-diaza­spirol[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; [α]20D +148.7 (c = 4.4, CHCl3).

HPLC: Chiralpak IA, n-heptane/EOH (7:3), 0.5 mL/min, tR (minor) = 10.40 min, tR (major) = 12.37 min; T = 30 °C; 92% ee.

IR (ATR): 3476, 2966, 2319, 2072, 1899, 1759, 1595, 1469, 1369, 1294, 1225, 1035, 961, 801, 729 cm−1.

1H NMR (600 MHz, CDCl3): δ = 7.28–7.27 (m, 2 H, ArH), 7.22–7.19 (m, 3 H, ArH), 7.19–7.16 (m, 1 H, ArH), 7.14–7.11 (m, 4 H, ArH), 6.23–6.15 (m, 2 H, CH=CH), 3.93–3.86 (m, 2 H, OCH2CH3).

13C NMR (151 MHz, CDCl3): δ = 126.7, 123.7, 121.2 (2 C), 114.0, 112.8 (2 C), 112.7 (2 C), 127.4 (2 C), 127.2 (2 C), 126.3 (2 C), 124.5, 74.4, 46.1, 44.4, 36.3, 29.7 (3 C).


(5S,8S,R)-2-Benzyl-4-(tert-buty1)-8-phenyl-9-[(E)-styryl]-2,3-diaza­spirol[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; [α]20D +299.6 (c = 5.2, CHCl3).

HPLC: Chiralpak IA, n-heptane/EOH (7:3), 0.5 mL/min, tR (minor) = 10.40 min, tR (major) = 12.37 min; T = 30 °C; 70% ee.

IR (ATR): 3476, 2966, 2319, 2072, 1899, 1759, 1595, 1469, 1369, 1294, 1225, 1035, 961, 801, 729 cm−1.

1H NMR (600 MHz, CDCl3): δ = 7.28–7.27 (m, 2 H, ArH), 7.22–7.19 (m, 3 H, ArH), 7.19–7.16 (m, 1 H, ArH), 7.14–7.11 (m, 4 H, ArH), 6.23–6.15 (m, 2 H, CH=CH), 3.93–3.86 (m, 2 H, OCH2CH3).

13C NMR (151 MHz, CDCl3): δ = 126.7, 123.7, 121.2 (2 C), 114.0, 112.8 (2 C), 112.7 (2 C), 127.4 (2 C), 127.2 (2 C), 126.3 (2 C), 124.5, 74.4, 46.1, 44.4, 36.3, 29.7 (3 C).

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Supporting Information

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References


(8) CCDC 1516205 contains the supplementary crystallographic data of spiropyrozolone 3p. The data can be obtained free of charge at www.ccdc.cam.ac.uk/structures.

