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

Sun Li\textsuperscript{a}
Lei Wang\textsuperscript{a}
Pankaj Chauhan\textsuperscript{a}
Anssi Peuronen\textsuperscript{b}
Kari Rissanen\textsuperscript{b}
Dieter Enders*\textsuperscript{a}

\textsuperscript{a} Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
\textsuperscript{b} Department of Chemistry, Nanoscience Center, University of Jyväskylä, 40014 JYU, Finland

Enders@rwth-aachen.de

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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,\textsuperscript{1a} and the first enantioselective Stetter reaction developed by our group in the late eighties,\textsuperscript{1b,c} the field of asymmetric NHC-organocatalysis\textsuperscript{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,\textsuperscript{3} especially the spiropyrazolone derivatives. For example, spiropyrazolone A shows anticancer activity,\textsuperscript{4a} whereas spiro compounds B and C possess phosphodiesterase inhibitor activity (Figure 1).\textsuperscript{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.\textsuperscript{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-unsaturated aldehydes with α-arylidenepyrazolinones under oxidative NHC catalysis (Scheme 1, a).\textsuperscript{6} Very recently, our group has developed an asymmetric multicomponent one-pot synthesis of spiropyrazolones using NHC organocatalysis (Scheme 1, b).\textsuperscript{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\textsuperscript{1}–R\textsuperscript{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\textsubscript{2}CO\textsubscript{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 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 otho-position as well as para-position of the phenyl ring of R^1 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-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 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 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).
A plausible catalytic cycle of the NHC-catalyzed [3+2] annihilation 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 to form the Breslow intermediate. This homoenolate equivalent then undergoes a Michael addition with the pyrazolones to afford the acyl azolium intermediate, which cyclizes to the spiropyrazolone product and returns the catalyst (Scheme 4).

In summary, the asymmetric NHC-catalyzed [3+2] annihilation of enals and unsaturated pyrazolones affords the corresponding spirocyclpentane 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.
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 spiropyrrolpentane pyrazolones $3$ were obtained as yellow oils ($3a$-$o,q,r$) or as a colorless solid ($3p$).

(55,85,9R)-4-(tert-Butyl)-2,8-diphenyl-9-[(E)-styryl]-2,3-di-azaspiro[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.$^7$

(55,85,9R)-4-(tert-Butyl)-8-(4-methoxyphenyl)-2-phenyl-9-[(E)-styryl]-2,3-di-azaspiro[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; $\left[\alpha\right]_D^{27} +264.6\ (c = 0.5, \text{CHCl}_3)$.

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

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

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.89 (dd, $J = 8.9, 1.1\ \text{Hz}, 2\ H,\text{ArH})$, 7.40 (dd, $J = 8.6, 7.3\ \text{Hz}, 2\ H,\text{ArH})$, 7.26 (dd, $J = 8.6\ \text{Hz}, 2\ H,\text{ArH})$, 7.23–7.16 (m, 6 H, ArH), 6.91 (dd, $J = 8.7\ \text{Hz}, 2\ H,\text{ArH})$, 6.20–6.19 (m, 2 H, CH=CH$^\text{H}$), 4.30 (td, $J = 11.7, 8.4\ \text{Hz}, 1\ H,\text{CHCH}_2$), 3.87–3.83 (m, 1 H, CH$_2$CH$_2$), 3.80 (s, 3 H, OCH$_3$), 3.17 (dd, $J = 19.3, 8.4\ \text{Hz}, 1\ H,\text{CHICO})$, 2.82 (dd, $J = 19.3, 12.2\ \text{Hz}, 1\ H,\text{CHFCH})$, 1.40 (s, 9 H, C(CH$_3$)$_3$).

$^{13}$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 (EST$^+$): $m/z$ [M + H$^+$] calcd for C$_{32}$H$_{33}$N$_2$O$_3$: 493.2485; found: 493.2480.

(55,85,9R)-4-(tert-Butyl)-8-(4-chlorophenyl)-2-phenyl-9-[(E)-styryl]-2,3-di-azaspiro[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; $\left[\alpha\right]_D^{27} +27+263.3\ (c = 0.5, \text{CHCl}_3)$.

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

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

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.89 (dd, $J = 8.8, 1.2\ \text{Hz}, 2\ H,\text{ArH})$, 7.40 (dd, $J = 8.7, 7.4\ \text{Hz}, 2\ H,\text{ArH})$, 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$^\text{H}$), 4.34 (td, $J = 11.7, 8.4\ \text{Hz}, 1\ H,\text{CHCH}_2$), 3.85–3.82 (m, 1 H, CH$_2$CH$_2$), 3.18 (dd, $J = 19.2, 8.4\ \text{Hz}, 1\ H,\text{CHICO})$, 2.81 (dd, $J = 19.2, 12.1\ \text{Hz}, 1\ H,\text{CHFCH})$, 1.40 (s, 9 H, C(CH$_3$)$_3$).

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 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).


(558,589R)-4-(tert-Buty1)-8-((furan-2-yl)-2-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3d) was isolated after flash chromatography (n-pentane/EtOAc, 20:1); yield: 101 mg (55%); pale yellow oil; [α]₂⁰⁺ = 270.0 (c = 0.5, CHCl₃).

HPLC: Chiralpak IA, n-heptane/i-PrOH (97:3), 0.7 mL/min; T = 30 °C; 86% ee.


(558,589R)-4-(tert-Buty1)-8-((furan-2-yl)-2-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3e)


(558,589R)-4-(tert-Buty1)-8-((furan-2-yl)-2-phenyl-9-[(E)-styryl]-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3f)


(558,589R)-4-(tert-Buty1)-9-[(E)-2-(1H-indol-2-yl)vinyl]-4-((E)-methoxystyryl)-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3g)


(558,589R)-4-(tert-Buty1)-9-[(E)-2-(1H-indol-2-yl)vinyl]-4-((E)-methoxystyryl)-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (3h)

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₆H₂₉N₃O₂: 400.1790; found: 400.1790.

Compound 3i was isolated after flash chromatography (n-pentane/EtOAc, 20:1); yield: 92 mg (51%); yellow oil; [\text{\alpha}]_D^{20} +99.4 (c = 2.5, CHCl_3).

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\text{[M + H]}^+ \text{ for C}_{29}H_{27}N_2O_2: 435.2067; \text{found: 435.2065.}
\]

Compound 3j was isolated after flash chromatography (n-pentane/EtOAc, 20:1); yield: 76 mg (44%); yellow oil; [\text{\alpha}]_D^{20} +188.9 (c = 2.7, CHCl_3).

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\text{[M + H]}^+ \text{ for C}_{28}H_{25}N_2O_2: 421.1911; \text{found: 421.1914.}
\]
**化合物** azaspiro[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]D20 +270.5 (c = 1.3, CHCl3).

HPLC: Chiralpak IB, n-heptane/i-PrOH (9:1); 0.7 ml/min, tₘ (minor) = 7.84 min, tₘ (major) = 7.06 min; T = 30 °C; 88% ee.

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

1H NMR (600 MHz, CDCl3): δ = 7.40 (m, 2 H, ArH), 7.39–7.34 (m, 2H, 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 (dd, J = 11.7, 8.4 Hz, 1 H, CH=CH=CH), 3.92–3.87 (m, 1 H, CH2CH2), 3.18 (dd, J = 19.3, 8.4 Hz, 1 H, CHCH=CH).

13C NMR (151 MHz, CDCl3): δ = 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.


**化合物** tert-butyl-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: 170 mg (86%); pale yellow oil; [α]D20 +299.6 (c = 5.2, CHCl3).

HPLC: Chiralpak IC, n-heptane/i-PrOH (9:1); 1.0 ml/min, tₘ (minor) = 4.11 min, tₘ (major) = 5.17 min; T = 30 °C; 99% ee.

IR (ATR): 3489, 3027, 2966, 2305, 2059, 1957, 1780, 1749, 1688, 1596, 1508, 1455, 1371, 1296, 1246, 1182, 1131, 1062, 1030, 950, 831, 749, 695, 662 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 7.39–7.34 (m, 2 H, ArH), 7.32–7.27 (2 H, ArH), 7.20–7.16 (1 H, ArH), 6.95–6.91 (2 H, ArH), 6.27–6.25 (1 H, CH=CH), 4.34 (dd, J = 11.7, 8.4 Hz, 1 H, CH=CH=CH), 3.60 (dd, J = 11.3, 7.3 Hz, 1 H, CH2CH2), 3.82 (s, 3 H, OCH3), 3.14 (dd, J = 19.3, 8.5 Hz, 1 H, CHCH=CH).

13C NMR (151 MHz, CDCl3): δ = 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]+ calc'd for C32H35N2O3: 491.2693; found: 491.2693.

**化合物** 2-Benzyl-4-(tert-butyl)-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: 93 mg (46%); yellow oil; [α]D20 +57.0 (c = 2.2, CHCl3).

HPLC: Chiralpak IC, n-heptane/i-PrOH (9:1); 0.7 ml/min, tₘ (minor) = 4.98 min, tₘ (major) = 4.52 min; T = 30 °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, CDCl3): δ = 7.38–7.34 (m, 2 H, ArH), 7.28–7.26 (m, 1 H, ArH), 7.26–7.23 (2 H, ArH), 7.22–7.19 (m, 2 H, ArH), 7.19–7.16 (1 H, ArH), 7.14–7.09 (m, 4 H, ArH), 6.18–6.10 (m, 2 H, CH=CH), 4.97 (dd, J = 15.5 Hz, 1 H, CHNH), 4.76 (dd, J = 15.5 Hz, 1 H, CHCH=CH), 4.31 (dd, J = 20.2, 11.4 Hz, 1 H, CH=CH=CH), 3.86 (dd, J = 11.1, 7.0 Hz, 1 H, CHCH=CH), 3.15 (dd, J = 19.1, 8.3 Hz, 1 H, CHCH=CH).

13C NMR (151 MHz, CDCl3): δ = 206.2, 170.1, 165.5, 140.0, 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), 1264 (2 C), 124.2, 74.3, 54.9, 47.9, 46.1, 44.3, 36.1, 29.3 (6 C).

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Supporting Information

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

References


(2) For selected reviews, see: (a) Sheehan, J.; Hunnemann, D. H.


(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.

