Stereoselective Epoxide Generation with Cyclic Rhodium Carbenoids: A New Access to Spiro-indolooxiranes

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This paper is dedicated with best wishes to Professor Goverdhan Mehta on the occasion of his 60th birthday.

Abstract: The reaction of cyclic diazoamides with aryl aldehydes catalyzed by rhodium(II) acetate leads to intermolecular stereoselective epoxide ring formation. A series of spiro-indolooxiranes has been synthesized following the described method in a facile manner. The use of aryl dialdehydes in the course of reaction of cyclic diazoamide resulted the formation of bis-spiro-indolooxiranes

Key words: carbenoids, diazo ketones, oxiranes, rhodium(II) acetate, spiro compounds

Diazo moiety has become a key component in a number of synthetic transformations since from the first recorded synthesis of α-diazo carbonyl compound by Curtius[1] in 1883. The emergence of diazo carbonyl compounds as useful precursors in organic synthesis can be traced to their ready participation in cyclopropanation, insertion reactions and ylide formation upon exposure to transition metal catalysts.[2] The metal-carbenoid generated transient ylides can undergo 1,3-dipolar cycloaddition reaction with a range of dipolarophiles, rearrangement reactions or cyclization to three-membered ring (aziridine or epoxide formation). The cyclization of transition metal generated carbonyl ylides, in principle, can deliver the oxirane ring systems. However, the literature reports[2,3] on carbonyl ylides are dominated by 1,3-dipolar cycloaddition reactions rather than the formation of the oxirane ring system. Originally, Huisgen reported[4] that the formation of 7% oxirane in the reaction between dimethyl diazomalonate and benzaldehyde catalyzed by $Cu(acac)_2$. But the formation of oxirane was not observed when the reaction was catalyzed by $Rh_2(OAc)_4$. The rhodium(II)-catalyzed decomposition of ethyl diazoacetate in the presence of aldehydes furnished dioxolanes (by means of 1,3-dipolar cycloaddition of the carbonyl ylide intermediate with a second equivalent of aldehyde) and did not produce oxiranes.[5]

Despite the commonality and selectivity (vide infra) of rhodium(II) acetate catalyzed reactions of diazo carbonyl compounds, they were not found to produce the oxirane ring systems until the recent report by Doyle[6] and followed by Davies.[7] In an alternative route, Aggarwal delineated a useful method[8] for the formation of oxirane by intercepting the metal carbene with alkyl sulfide. Recently, we have been extensively involved in developing new synthetic strategies[9] using diazo carbonyl compounds. The reactivity of cyclic diazo ketones and amides was studied with olefins and heteroaromatic dipolarophiles to furnish cyclopropanation,[10] C-H insertion[11] or cycloadducts[12] via 1,3-dipolar cycloaddition reactions. To the best of our knowledge, only simple acyclic diazo carbonyl compounds have been used in the epoxide generation, which mainly led to the benzylidene or methylidene transfer. Continuing our interest in the reactions of cyclic diazoamides[10,11] and motivated by the recent reports,[6,7] we herein delineate the rhodium(II) acetate catalyzed reaction of cyclic diazoamides with aryl aldehydes that leads to the stereoselective construction of spirocyclic oxiranes.

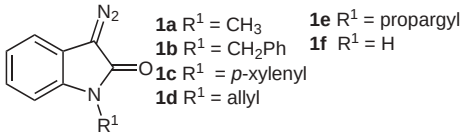

Figure 1

Initially, we planned to study the reactions of cyclic diazoamides **1** (Figure 1) with aldehydes in the presence of rhodium(II) acetate catalyst. The required N-substituted 3-diazooxindoles (**1a**–**e**) were assembled by N-alkylation of 3-diazooxindole[13] (**1f**) using methyl iodide, benzyl bromide, *p*-xylenyl bromide, allyl bromide or propargyl bromide in the presence of sodium hydride/DMF in 80% to 95% yield. Subsequently, we studied the rhodium(II) acetate catalyzed reactions of cyclic diazoamide **1a** with benzaldehyde in the presence of a catalytic amount of rhodium(II) acetate under reflux conditions to afford the spiro-indolooxirane **3a** in 57% yield (Scheme 1). The ^1H NMR spectrum of **3a** revealed the presence of two singlets at δ = 3.08 and 4.64 ppm for *N*-methyl and OCH protons, respectively. Furthermore, ^{13}C and DEPT experiments disclosed the presence of characteristic quaternary carbon at δ = 62.5 ppm and a CH signal at 68.1 ppm, which unequivocally confirms the formation of the spiro-oxirane ring system. All other data were in good agreement with the assigned structure. The reaction of other diazoamides **1b**–**e** with benzaldehyde also produced the spiro-oxiranes in moderate to good yields. We further car-

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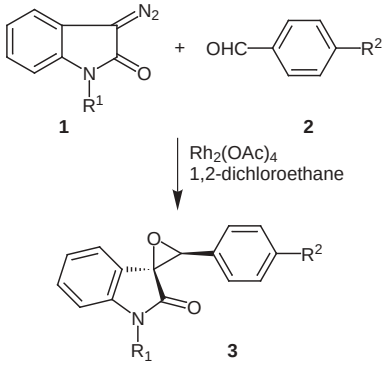
ried out the similar reactions with 4-methoxy benzaldehyde to furnish the spiro-indolooxiranes in good yield and the results are described in Table 1. Interestingly, spiro-indolooxirane derivatives have use as anticonvulsants, diuretics, sedatives, sleep potentiators and also show transaminase inhibiting activity.[14,15]



Scheme 1

Table 1 Synthesis of Spiro-indolooxiranes

Entry	R^1	R^2	Yield (%) of **3**[a]
a	CH_3	H	57
b	CH_2Ph	H	64
c	4-$CH_3C_6H_4CH_2$	H	65
d	Allyl	H	61
e	Propargyl	H	55
f	CH_3	OCH_3	64
g	CH_2Ph	OCH_3	84
h	4-$CH_3C_6H_4CH_2$	OCH_3	81
i	Allyl	OCH_3	77
j	Propargyl	OCH_3	73

[a] Yields are unoptimized and refer to isolated and chromatographically pure compounds **3**.

The stereochemistry of spiro-indolooxiranes was determined as *Z* based on the single crystal X-ray analysis[16,17] of the representative product **3g** (Figure 3).

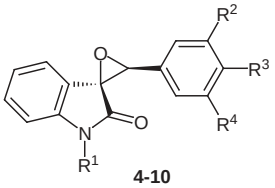


Figure 2

To generalize the intermolecular spiro-oxirane formation, we have carried out the reactions with more substituted aromatic aldehydes to furnish the respective spiro-indolooxiranes (Figure 2) as single diastereomer in very good yields and the results are given in Table 2. The reaction did not work in the presence of electron withdrawing substituents such as nitro-group.

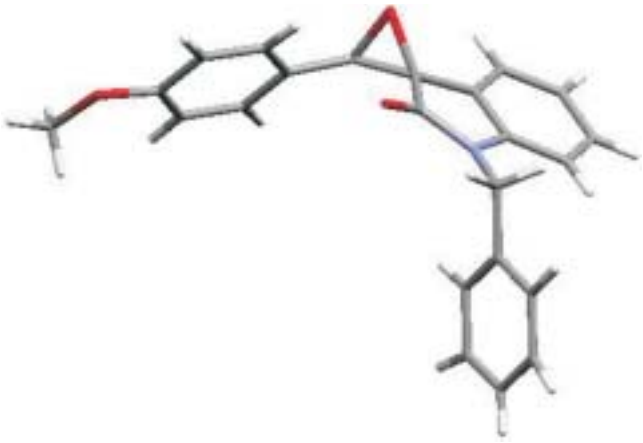


Figure 3

Table 2 Synthesis of Spiro-indolooxiranes

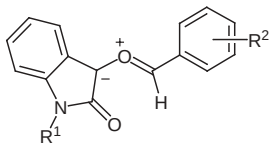
Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
4	CH_3	H	OCH_3	OCH_3	65
5	CH_2Ph	H	OCH_3	OCH_3	82
6	4-$CH_3C_6H_4CH_2$	H	OCH_3	OCH_3	81
7	Allyl	H	OCH_3	OCH_3	73
8	Propargyl	H	OCH_3	OCH_3	63
9	CH_2Ph	OCH_3	OCH_3	OCH_3	82
10	Propargyl	OCH_3	OCH_3	OCH_3	80

[a] Yields are unoptimized and refer to isolated and chromatographically pure compounds **4**–**10**.

Mechanistically, we propose the formation of carbonyl ylide **11** (Figure 4) as a reactive intermediate. The subsequent selective cyclization of this intermediate **11** leads to the formation of single isomer with *Z*-stereochemistry. Interestingly, the reaction was repeated in the presence of two equivalents of aldehyde to provide the spiro-oxirane system without forming the dioxolane system. Importantly, the conformation of ylides **11** may be favorable over the 1,3-dipolar cycloaddition due to the faster ring closure, with a second equivalent of aldehyde to produce the dioxolane system.

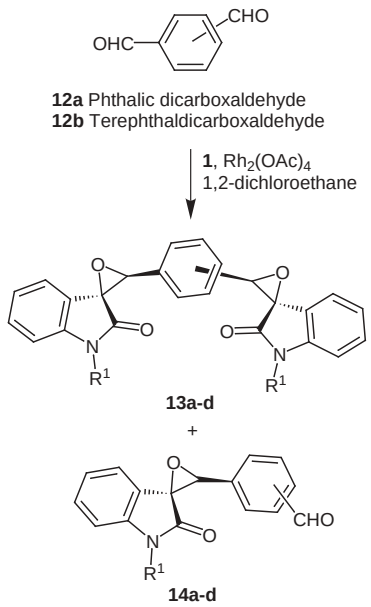
To advance this process further, we considered the formation of the bis-spiro-indolooxirane ring system using dialdehydes. To this end, phthalic dicarboxaldehyde was chosen as the prototypical substrate and the rhodium(II) acetate catalyzed reaction carried out using 2.5 equiva-

lents of cyclic diazoamide **1b**. Column chromatographic purification of the reaction mixture afforded two products **13a** and **14a** in 27% and 6% yields, respectively. Spectroscopic analysis clearly revealed the formation of compound **13a**, a bis-oxirane system, with minor amounts of mono-oxirane compound **14a**. The stereochemistry of the bis-oxiranes is tentatively assigned based on the above studies. This process forms an interesting example in which the bis-oxirane ring system is synthesized from the diazo carbonyl compound. The free aldehyde group present in the mono-epoxide **14a** can also be further functionalized to obtain dissymmetric bis-oxirane ring systems.



11

Figure 4



Scheme 2

Table 3 Synthesis of Bis-spiro-indolooxiranes

Entry	Dialdehyde	R^1	Yield of **13** (%)[a]	Yield of **14** (%)[a]
a	**12a**	CH_2Ph	27	6
b	**12a**	Allyl	37	11
c	**12b**	CH_3	31	5
d	**12b**	CH_2Ph	35	7

[a] Yields are unoptimized and refer to isolated and chromatographically pure compounds **13** and **14**.

The bis-oxirane formations were further generalized using aromatic dialdehydes (**12a**,**b**) to deliver the corresponding bis- as well as mono-epoxides (**13b**–**d** and **14b**–**d**, Scheme 2, Table 3).

In conclusion, we have demonstrated the novel stereoselective synthesis of mono- and bis-spiro-indolooxiranes using cyclic rhodium carbenoids generated from the cyclic diazoamides with various aromatic aldehydes and dialdehydes. The scope and further applications of this theoretically interesting transformation towards the strained ring system are currently under active investigation in our laboratory and will be disclosed in due course.

Typical Procedure for the Synthesis of Spiro-oxiranes: An oven-dried 50 mL flask was charged with aldehyde (1.2 mmol) and rhodium(II) acetate in a freshly distilled dry 1,2-dichloroethane (5 mL) under nitrogen atmosphere. A dry 1,2-dichloroethane (15 mL) solution of cyclic diazoamide (1.0 mmol) was added dropwise to the above reaction mixture at 60 °C for the period of 1 h and followed by TLC. After completion of the reaction, the solvent was concentrated under reduced pressure and the reaction mixture purified by chromatography using the flash silica-gel column (hexane/EtOAc 75:25) to afford the pure spiro-indolooxiranes. All new compounds exhibited spectral data consistent with their structures. Selected spectral data:

3′-Phenyl-1-methylspiro[indole-3,2′-oxiran]-2(1*H*)-one (3a): Yellow solid; mp 112–114 °C (hexane/EtOAc). IR (KBr): 3067, 2929, 1720, 1617, 1494, 1470, 1453, 1373, 1345, 1246, 1217, 1111, 1027, 893, 742 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.08 (s, 3 H, N-CH_3), 4.64 (s, 1 H, OCH), 6.83 (d, 1 H, *J* = 7.7 Hz, ArH), 7.04–7.18 (m, 3 H, ArH), 7.27–7.46 (m, 4 H, ArH), 7.56–7.68 (1 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.0 (N-CH_3), 62.5 (*quat-C*), 68.1 (OCH), 109.2 (CH), 122.2 (CH), 123.2 (CH), 128.0 (CH), 128.3 (CH), 129.3 (CH), 130.8 (CH), 131.4 (*quat-C*), 132.4 (*quat-C*), 145.2 (*quat-C*), 174.3 (*quat-C*). MS (EI): *m/z* (%) = 251 (100) [M^+], 223 (53), 194 (38), 165 (9), 117 (24), 105 (36), 90 (37), 77 (32). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.26; H, 5.17; N, 5.62.

3′-(4-Methoxyphenyl)-1-benzylspiro[indole-3,2′-oxiran]-2(1*H*)-one (3g): Colorless solid; mp 148–150 °C (hexane/EtOAc). IR (KBr): 3027, 2935, 1732, 1614, 1515, 1465, 1360, 1246, 1173, 1035, 754 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 4.64 (s, 1 H, OCH), 4.73 (d, B part of AB-system, 1 H, *J* = 15.8 Hz, NCH_2), 4.89 (d, A part of AB-system, 1 H, *J* = 15.8 Hz, NCH_2), 6.75 (d, 1 H, *J* = 7.7 Hz, ArH), 6.91 (d, 2 H, *J* = 8.0 Hz, ArH), 7.04 (t, 1 H, *J* = 7.7 Hz, ArH), 7.07–7.24 (m, 5 H, ArH), 7.57 (d, 2 H, *J* = 8.0 Hz, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.6 (N-CH_2), 55.8 (OCH_3), 62.6 (*quat-C*), 68.5 (OCH), 110.2 (CH), 113.8 (CH), 114.5 (*quat-C*), 122.2 (CH), 123.2 (CH), 124.3 (*quat-C*), 128.0 (CH), 128.3 (CH), 129.3 (CH), 129.4 (CH), 130.5 (CH), 136.2 (*quat-C*), 144.2 (*quat-C*), 160.2 (*quat-C*), 170.8 (*quat-C*). MS (EI): *m/z* (%) = 357 (2) [M^+], 307 (15), 238 (10), 167 (7), 130 (20), 120 (24), 102 (20), 91 (100), 65 (15), 51 (20); Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.02; H, 5.41; N, 3.95.

3′-(3,4,5-Trimethoxyphenyl)-1-(prop-2-ynyl)spiro[ind ole-3,2′-oxiran]-2(1*H*)-one (10): Orange solid; mp 144–146 °C (hexane/EtOAc). IR (KBr): 3281, 1732, 1692, 1591, 1466, 1422, 1266, 1129, 1007, 739 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.25 (s, 1 H, CCH), 3.86 (s, 3 H, OCH_3), 3.88 (s, 6 H, OCH_3), 4.46 (s, 2 H, N-CH_2), 4.60 (s, 1 H, OCH), 6.88 (s, 2 H, ArH), 7.11–7.22 (m, 3 H, ArH), 7.42 (t, 1 H, *J* = 7.4 Hz, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 30.1 (N-CH_2), 56.7 (OCH_3), 56.9 (OCH_3), 62.9 (*quat-C*), 68.8 (OCH), 73.3 (*quat-C*), 77.1 (CH), 105.5 (CH), 107.4 (CH), 110.3 (CH), 122.3 (CH), 123.7 (CH), 124.1 (*quat-C*), 127.4 (*quat-C*),

130.8 (CH), 143.2 (*quat-C*), 153.4 (*quat-C*), 169.7 (*quat-C*). MS (EI): *m/z* (%) = 366 (26) [M + 1], 365 (100) [M^+], 337 (26), 322 (91), 298 (21), 165 (38), 150 (26), 102 (26); Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.28; H, 5.30; N, 3.41.

1,4-Di(1-benzylspiro[indole-3,2′-oxiran]-2(1*H*)-one-3′-yl)benzene (13d): Colorless solid; mp 168–170 °C (hexane/EtOAc). IR (KBr): 3056, 2928, 1730, 1615, 1468, 1359, 1265, 1180 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.76 (s, 2 H, OCH), 4.77 (d, B part of AB-system, 2 H, *J* = 15.7 Hz, NCH_2), 5.00 (d, A part of AB-system, 2 H, *J* = 15.7 Hz, NCH_2), 6.78 (d, 2 H, *J* = 7.7 Hz, ArH), 7.07 (t, 2 H, *J* = 7.7 Hz, ArH), 7.22–7.27 (m, 14 H, ArH), 7.68 (s, 4 H, ArH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.9 (N-CH_2), 62.7 (*quat-C*), 68.4 (OCH), 110.4 (CH), 122.4 (CH), 123.4 (CH), 124.2 (*quat-C*), 127.7 (CH), 128.2 (CH), 128.4 (CH), 129.5 (CH), 130.8 (CH), 133.1 (*quat-C*), 136.2 (*quat-C*), 144.4 (*quat-C*), 170.7 (*quat-C*). MS (EI): *m/z* (%) = 576 (4) [M^+], 444 (6), 355 (9), 237 (9), 223 (13), 146 (16), 91 (100); Anal. Calcd for $C_{38}H_{28}N_2O_4$: C, 79.15; H, 4.89; N, 4.86. Found: C, 79.39; H, 4.95; N, 4.81.

3′-(4-Formylphenyl)-1-benzylspiro[indole-3,2′-oxiran]-2(1*H*)-one (14d): Colorless solid; mp 108–110 °C (hexane/EtOAc). IR (KBr): 2924, 1727, 1694, 1611, 1491, 1468, 1361, 1303, 1178, 1001, 746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.76 (s, 1 H, OCH), 4.80 (d, B part of AB-system, 1 H, *J* = 12.7 Hz, NCH_2), 4.95 (d, A part of AB-system, 1 H, *J* = 12.7 Hz, NCH_2), 6.81 (d, 1 H, *J* = 7.6 Hz, ArH), 7.09 (t, 1 H, *J* = 7.3 Hz, ArH), 7.17–7.32 (m, 6 H, ArH), 7.66–7.69 (m, 1 H, ArH), 7.79 (d, 2 H, *J* = 8.1 Hz, ArH), 7.91 (d, 2 H, *J* = 8.0 Hz, ArH), 10.01 (s, 1 H, CHO). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.6 (N-CH_2), 65.3 (*quat-C*), 67.3 (OCH), 110.5 (CH), 122.5 (CH), 123.5 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.4 (CH), 129.7 (CH), 130.4 (*quat-C*), 130.7 (CH), 131.1 (CH), 135.9 (*quat-C*), 138.9 (*quat-C*), 140.6 (*quat-C*), 144.4 (*quat-C*), 192.4 (CHO). MS (EI): *m/z* (%) = 356 (9) [M + 1], 355 (30 [M^+], 236 (23), 220 (11), 208 (24), 165 (8), 134 (16), 102 (15), 91 (100); Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.95; H, 4.89; N, 3.91.

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(16) Crystal data for compound **3g:** Colorless rectangular crystal. $C_{23}H_{19}NO_3$, *M* = 357.39, 0.50 × 0.08 × 0.05 mm^3, triclinic, space group p-1 with *a* = 5.9327(13) Å, *b* = 10.800(2) Å, *c* = 14.812(3) Å, *α* = 90.925(4)°, *β* = 94.846(4)°, *γ* = 101.966(4)°, *V* = 924.6(4) $Å^3$, *T* = 293(2) K, R_1 = 0.0496, wR_2 = 0.1204 on observed data, z = 2, D_{calcd} = 1.284 g cm^{-3}, *F*(000) = 376, Absorption coefficient = 0.085 mm^{-1}, *λ* = 0.71073 Å, 3567 reflections were collected on a smart apex ccd single crystal CCD diffractometer, 2632 observed reflections [I 2σ (I)]. The largest difference peak and hole = 0.234 and –0.246*e* $Å^{-3}$, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software.
(17) Crystallographic data for **3g** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no CCDC-222010. Copies of the data can be obtained free of charge on application to 12, Union Road, Cambridge CB2 1EZ, UK. [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].