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Demonstration of 14–20-membered intramolecular carbonyl ylides: diastereoselective synthesis of macrocycles incorporating spiro-indolooxiranes

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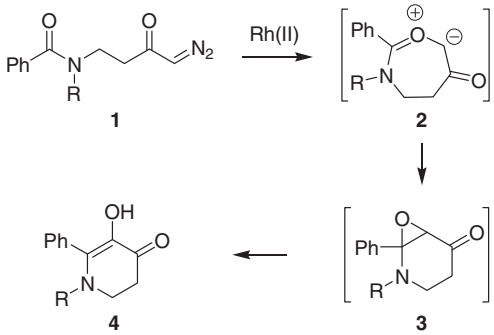
ABSTRACT

A range of macrocycles (13–19-membered) possessing spiro-indolooxirane unit were synthesized with complete diastereoselectivity in good yield by the rhodium(II) acetate catalyzed reaction of substituted cyclic diazoamides in dry dichloromethane. The reaction proceeds via the formation of the corresponding macrocyclic carbonyl ylide followed by a con-rotatory electrocyclization process.

The reaction of diazocarbonyl compounds with rhodium(II) carboxylate is a well illustrated method to produce rhodium carbenoids, which experience an array of reactions, such as cyclopropanation, C–H or heteroatom-H insertion, and ylide formation.[1] The metal-carbenoid generated transient ylides can undergo 1,3-dipolar cycloaddition reaction with a range of dipolarophiles,[2] rearrangement reactions,[2c] or cyclization to three-membered ring (aziridine or epoxide formation). However, the 1,3-dipolar cycloaddition reactions of carbonyl ylides are well-known rather than their electrocyclization. Three-membered heterocyclic rings provide an uncommon combination of reactivity, synthetic flexibility, and atom economy.[3] An oxirane was formed[4] in only 7% yield, when the reaction of dimethyl diazomalonate with benzaldehyde was performed at 125 °C in the presence of 1 mol % of $Cu(acac)_2$, but there was no formation of oxirane when the reaction was catalyzed by $Rh_2(OAc)_4$. The metal-catalyzed decomposition of ethyl diazoacetate in the presence of aldehydes does not effectively produce oxiranes.[5] Instead, dioxolanes are formed, whereby, the intermediate ylide undergoes a 1,3-diploar cycloaddition with a second equivalent of aldehyde. Diazocarbonyl compounds were not found to produce the oxirane ring system via intermolecular carbonyl ylides until Doyle[6] and Davies[7] groups reported stereospecific epoxide formation from rhodium acetate catalyzed diazo decomposition of aryldiazoacetate with aryl aldehydes or ketones. We have also reported[8] the stereoselective process to synthesize spiro-indolooxiranes from cyclic diazoamides in an intermolecular manner.

The intramolecular carbonyl ylide **2**, derived from diazo ketone **1**, in the presence of Rh(II)-catalyst afforded[9] oxirane **3** as a transient intermediate to furnish dihydropyridone **4** (Scheme 1). The fused oxirane ring system was an isolated example reported during the synthesis of komaroviquinone[10] skeleton via intramolecular carbonyl ylide. To the best of our knowledge, only five to seven-membered[2b] and a lonely example[11] for 10-membered intramolecular carbonyl ylides are available in the literature. Many naturally existing macrocycles possessing oxirane unit were known to have biological activity, for example, laulimalide,[12] radicicol,[13] maytansinoid,[14] macrocyclic trichothecenes.[15] In continuation of our



Scheme 1. Synthesis of dihydropyridone **4**.

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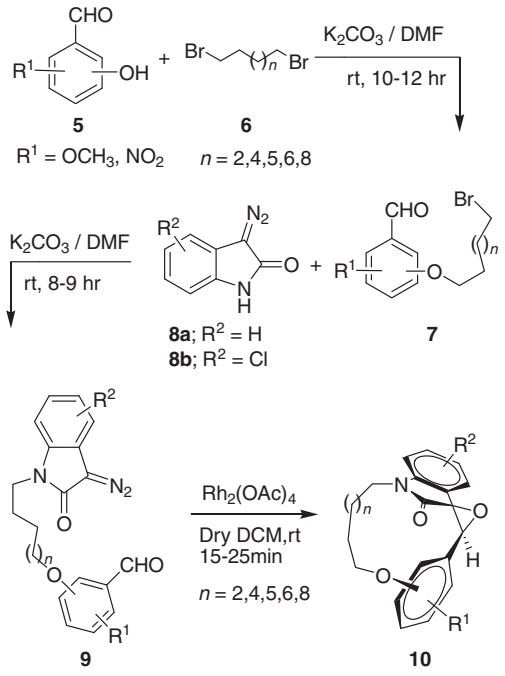


Scheme 2. Synthesis of macrocyclic spiro-oxiranes.

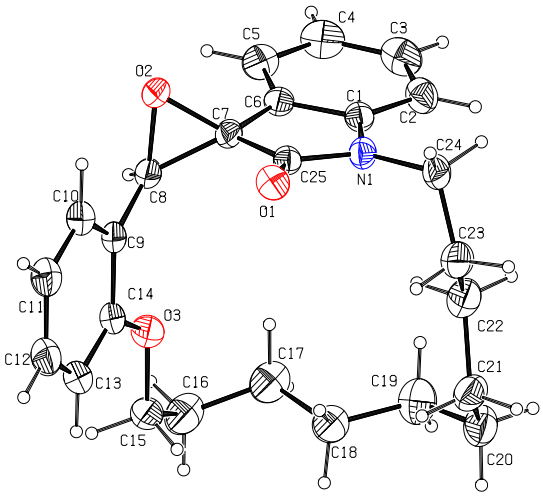


Figure 1. ORTEP view macrocycle **10d**.

interest in developing new synthetic strategies[16] utilizing carbonyl ylides, we herein demonstrate rhodium(II) acetate catalyzed generation of 14–20-membered intramolecular carbonyl ylides and their electrocyclization to afford the macrocycles incorporating spiro-indolooxiranes in good yield with complete diastereoselectivity.

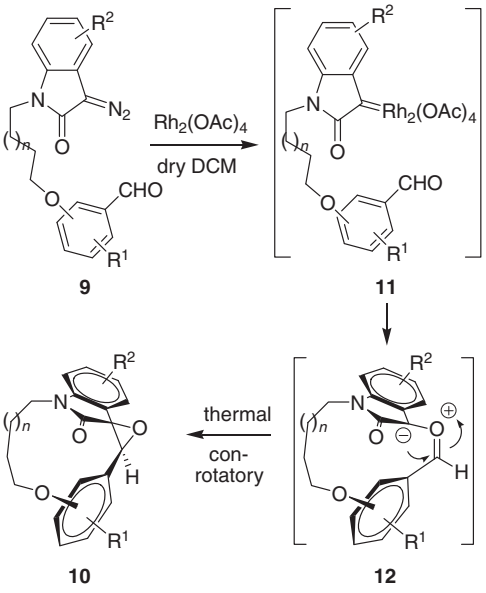
In order to demonstrate the macrocyclic carbonyl ylides, the required substituted cyclic diazoamides **9a–j** were assembled by O-alkylation of hydroxybenzaldehydes **5** using dibromoalkanes **6** in the presence of potassium carbonate/DMF to afford[17] the corresponding bromobenzaldehydes **7** in 80–85% yield. Subsequent N-alkylation of 3-diazooxiindoles **8a,b** using bromobenzaldehydes **7** in the presence of potassium carbonate/DMF afforded the substituted diazoamides **9a–j** in very good yield (Scheme 2).

Our aim is to demonstrate macrocyclic carbonyl ylides from diazoamides **9** in the presence of a metal catalyst. Toward this,

Table 1
Synthesis of macrocyclic spiro-oxiranes **10**

Entry	Aldehyde **5**	*n*	R^2	Yield of **9**[a] (%)	Yield of **10**[a] (%)
1	2-Hydroxybenzaldehyde	2	H	90 (**9a**)	60 (**10a**)
2	2-Hydroxybenzaldehyde	4	H	86 (**9b**)	63 (**10b**)
3	2-Hydroxybenzaldehyde	5	H	88 (**9c**)	67 (**10c**)
4	2-Hydroxybenzaldehyde	6	H	85 (**9d**)	70 (**10d**)
5	2-Hydroxybenzaldehyde	8	H	81 (**9e**)	59 (**10e**)
6	2-Hydroxy-4-methoxy benzaldehyde	6	H	89 (**9f**)	71 (**10f**)
7	2-Hydroxy-3-nitro benzaldehyde	6	H	82 (**9g**)	67 (**10g**)
8	2-Hydroxybenzaldehyde	6	Cl	83 (**9h**)	68 (**10h**)
9	3-Hydroxybenzaldehyde	4	H	84 (**9i**)	62 (**10i**)
10	3-Hydroxybenzaldehyde	6	H	82 (**9j**)	69 (**10j**)

[a] Yields are unoptimized and refer to isolated yields.

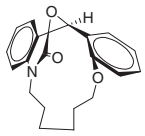
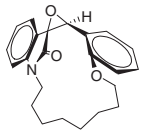
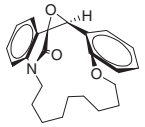
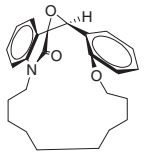
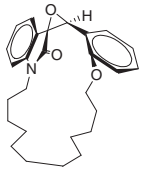
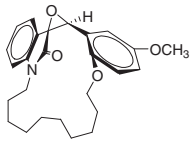
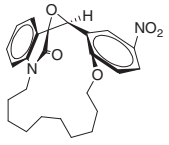
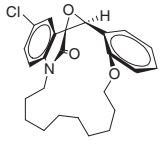
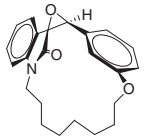
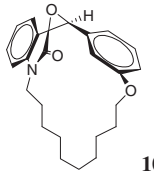


Scheme 3. Plausible mechanism.

the substituted cyclic diazoamide **9a**[18] in the presence of 1.3 mol % of rhodium(II) acetate under argon atmosphere afforded the 14-membered intramolecular macrocyclic carbonyl ylide and its subsequent electrocyclization producing macrocycle **10a**[19] in 60% yield as a single isomer (Scheme 2, Table 1) based on the crude NMR spectrum. The ^{1}H NMR spectrum of **10a** revealed the presence of one singlet at $\delta = 4.51$ ppm for OCH proton. Furthermore, ^{13}C and DEPT-135 experiments disclosed the presence of characteristic quaternary carbon at $\delta = 61.31$ ppm and a CH signal at 64.04 ppm, which unequivocally confirms the formation of the spiro-oxirane ring unit. All other signals in ^{13}C spectrum are due to six CH_2 carbons and eight CH carbons present with the assigned structure. Next, the reaction of cyclic diazoamides **9b–e** were carried out under similar reaction conditions to generate the corresponding 16–18 and 20-membered macrocyclic carbonyl ylides and their subsequent electrocyclic ring closure afforded the corresponding macrocycles **10b–e** in good yield as a single isomer (Table 2). The yield of the macrocyclic compounds **10b–e** is comparable with **10a** even though there is an increase in size of the macrocyclic core. The structure and stereochemistry of the representative macrocycle **10d** were confirmed based on the single crystal X-ray analysis (Fig. 1).

The reaction of cyclic diazoamides having electron-donating or electron-withdrawing substituent was planned. The reactions of cyclic diazoamides having substituents on both benzaldehyde

Table 2
Synthesis of macrocyclic spiro-oxiranes **10**

Entry	Macrocycles **10**	Size of the carbonyl ylide **12**	Size of the macrocycles **10**
1	 **10a**	14	13
2	 **10b**	16	15
3	 **10c**	17	16
4	 **10d**	18	17
5	 **10e**	20	19
6	 **10f**	18	17
7	 **10g**	18	17
8	 **10h**	18	17
9	 **10i**	17	16
10	 **10j**	19	18

9f,g and oxindole part **9h** were performed under similar reaction conditions to furnish macrocycles **10f–h** in good yield. The reaction of *ortho*- or *meta*-substituted aromatic aldehydes tethered on cyclic diazoamides **9** yielded the corresponding macrocycles **10** in good yield. However, *para*-substituted aromatic aldehydes tethered on cyclic diazoamides **9** did not yield the product.

We have studied the synthesis of macrocycles based on the spacer length, and it plays an important role to form intramolecular carbonyl ylides. It was found that the 14-membered intramolecular carbonyl ylide is not favorable to produce the corresponding macrocycles, whereas the 13-membered or lesser did not afford the product.

Mechanistically, we propose that the electron-deficient carbenoid carbon of rhodium(II) carbenoids **11** reacts with the remotely placed oxygen atom of the aromatic aldehyde functionality affording the interesting 14 and 16–20-membered intramolecular carbonyl ylides **12** (Scheme 3). Then, the reaction is assumed to proceed with stereospecific thermal con-rotatory electrocyclization of **12** to yield the observed macrocyclic epoxide **10** as a single diastereoisomer. Interestingly, the formation of the carbonyl ylides proceeds in an intramolecular manner and no products were observed[8] due to an intermolecular pathway.

In conclusion, we have demonstrated for the first time the generation of 14–20-membered intramolecular carbonyl ylides from cyclic diazoamides in the presence of rhodium(II) acetate as catalyst. The subsequent electrocyclization of macrocyclic carbonyl ylides furnished the 13–19-membered macrocycles incorporating spiro-indolooxirane units with complete diastereoselectivity.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, proton and carbon spectra of all new compounds and X-ray crystallographic data (CCDC-799942) for **10d**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.052.

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18. *Diazoamide* ***9a***: 3-diazo-1,3-dihydro-2*H*-indol-2-one (**8a**) (1.5 g, 9.43 mmol) and potassium carbonate (3.26 g, 23.57 mmol) were taken in dry DMF under an argon atmosphere and stirred for 5 min. 2-(6-Bromohexyloxy) benzaldehyde (3.2 g, 11.32 mmol) and a catalytic amount of tetrabutylammonium iodide were then added. The reaction mixture was allowed to stir for 9 h to obtain **9a** (90%) as a red liquid based on the general procedure. IR (neat): ν_{max} 2927, 2849, 1723, 1669, 1473, 1449, 1419, 1217, 1139, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.33–1.37 (m, 2H, CH_2), 1.38–1.46 (m, 2H, CH_2), 1.61–1.67 (m, 2H, CH_2), 1.70–1.77 (m, 2H, CH_2), 3.72–3.76 (t, 2H, *J* = 7.2 Hz, N–CH_2), 3.93–3.96 (t, 2H, *J* = 6.4 Hz, OCH_2), 6.83–7.10 (m, 6H, ArH), 7.39–7.43 (m, 1H, ArH), 7.70–7.72 (dd, 1H, J_1 = 7.6, J_2 = 1.2 Hz, ArH), 10.38 (s, 1H, OCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.70 (CH_2), 26.48 (CH_2), 27.92 (CH_2), 28.90 (CH_2), 40.43 (CH_2), 68.23 (CH_2), 108.81 (=CH), 112.50 (=CH), 116.68 (quat-C), 118.40 (=CH), 120.41 (=CH), 121.88 (=CH), 124.75 (quat-C), 125.40 (=CH), 128.03 (=CH), 133.71 (quat-C), 135.91 (quat-C), 161.39 (quat-C), 166.66 (quat-C), 189.58 (CHO); HRMS (ESI) calcd for $C_{21}H_{21}N_3NaO_3$ $[M+Na]^+$ 386.1519; found, 386.1509.
19. *Macrocycle* **10a**: a solution of aldehyde substituted diazoamide **9a** (100 mg, 1.0 mmol) and rhodium(II) acetate (1.6 mg, 1.3 mol %) in dichloromethane (15 mL) was stirred at room temperature for 25 min. The reaction mixture was concentrated under reduced pressure and purified on silica (hexane/EtOAc, 65:35) to afford **10a** in 60% yield. Colorless solid; mp 150–152 °C; IR (neat): ν_{max} 2922, 2851, 1728, 1617, 1487, 1467, 1361, 1235, 1178, 900, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.96–1.05 (m, 1H, CH_2), 1.18–1.25 (m, 2H, CH_2), 1.47–1.61 (m, 3H, CH_2), 1.61–1.70 (m, 1H, CH_2), 1.75–1.83 (m, 1H, CH_2), 3.29–3.33 (m, 1H, N–CH_2), 3.88 (t, 2H, *J* = 4.8 Hz, OCH_2), 4.19 (td, 1H, J_1 = 14 Hz, J_2 = 4.8 Hz, N–CH_2), 4.51 (s, 1H, OCH), 6.74 (d, 1H, *J* = 8.0 Hz, ArH), 6.86 (d, 1H, *J* = 7.6 Hz, ArH), 6.96 (t, 1H, *J* = 8.0 Hz, ArH), 7.04 (t, 1H, *J* = 7.6 Hz, ArH), 7.16 (d, 1H, *J* = 8.0 Hz, ArH), 7.22–7.26 (m, 1H, ArH), 7.30 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz, ArH), 7.54 (d, 1H, *J* = 7.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.40 (CH_2), 24.72 (CH_2), 24.83 (CH_2), 27.37 (CH_2), 39.92 (CH_2), 61.31 (quat-C), 64.04 (CH, observed in DEPT-90 NMR) 64.79 (CH_2), 109.21 (=CH), 110.55 (=CH), 120.45 (=CH), 121.88 (=CH), 122.06 (quat-C), 122.37 (=CH), 123.58 (quat-C), 129.03 (=CH), 129.45 (=CH), 129.90 (=CH), 143.89 (quat-C), 155.35 (quat-C), 170.46 (quat-C); HRMS (ESI) calcd for $C_{21}H_{21}NNaO_3$ $[M+Na]^+$ 358.1423; found, 358.1413.