Synthetic Methods

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Macrocyclization of Oxetane Building Blocks with Diazocarbonyl Derivatives under Rhodium(II) Catalysis**

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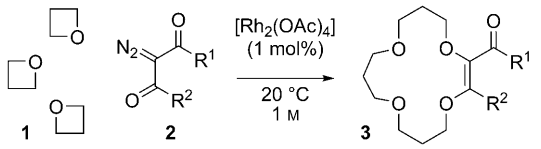
Oxetanes, which are four-membered-ring cyclic ethers of type **1**, are important building blocks in medicinal and natural product chemistry.[1] Oxetanes are useful reagents that undergo ring-opening[2] or ring-expansion[3] reactions because of a large ring strain (ca. 25 kcal mol^{-1})[4] and a high nucleophilicity of the O atom.[5] These derivatives react readily in the presence of Brønsted or Lewis acids to promote polymerization reactions.[6] Macrocyclizations, which, in principle, can be also afforded in these reactions, are rare.[7] In this context, we report the unusual Rh^{II}-catalyzed condensation of oxetanes **1** and α-diazocarbonyls **2** that yields exclusively a rare type of functionalized 15-membered macrocycle **3** [Eq. (1)]. Interestingly, three oxetanes and one metal carbenoid intermediate condense in a one-pot process, and this under high concentration conditions (1M) and yields up to 84%.

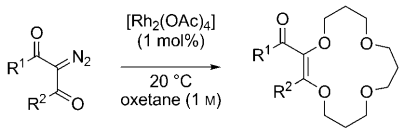


1 2 3 (1)

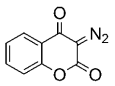
Previously, it has been shown that macrocycles can be generated from oxonium ylides.[8] These intermediates are readily prepared by reactions of ethers and α-diazocarbonyls under photoirradiation, electrophilic activation, or metal catalysis.[7,9] For instance, 18-membered macrocycles were recently prepared in a single step by the condensation of two α-diazo-β-ketoesters and two cyclic ethers (1,4-dioxane, tetrahydropyrane) in the presence of [$Rh_2(OAc)_4$] or [$Rh_2(Oct)_4$].[9d] A dimerization under high concentration of two oxonium ylide intermediates was postulated to explain the reactivity. We wondered what the outcome would be of the reaction using more reactive cyclic ethers, particularly oxetanes.

Methyldiazoacetoacetate **2a** (R^1 = OMe, R^2 = Me; Table 1, entry 1) was added at 20°C to a solution of [$Rh_2(OAc)_4$] (1.0 mol%) in oxetane **1** (used as solvent).[10] The reaction was performed under high concentration (1M of **2a**)

Table 1: Substrate scope.



2a-k **3a-k**

Entry[a]	2	R^1	R^2	Product	Yield [%][b]
1	**2a**	MeO	Me	**3a**	60
2	**2b**	EtO	Me	**3b**	66
3	**2c**	*t*BuO	Me	**3c**	55
4	**2d**	$PhCH_2CH_2O$	Me	**3d**	75
5	**2e**	$CH_2{=}CHCH_2O$	Me	**3e**	84
6	**2f**	EtO	Et	**3f**	81
7	**2g**	EtO	Pr	**3g**	60
8	**2h**	EtO	Ph	**3h**	84
9	**2i**	EtO	*i*Pr	**3i**	80
10	**2j**			**3j**	59
11	**2k**	Me	Me	**3k**	70

[a] Reaction conditions: **2a–k** (1 equiv, 1M in oxetane),[11] [$Rh_2(OAc)_4$] (1 mol%), 20°C. [b] Yield of isolated product after column chromatography on neutral alumina.

and reached completion in less than four hours.[11] The single product **3a** was observed in the crude reaction mixture. NMR spectroscopic analysis indicated the formation of an original 15-membered macrocyclic structure composed of one fragment derived from **2a** and three propyloxy units; this kind of 15-C-4 polyether macrocycle is rare in the literature.[12] This result was confirmed by mass spectrometry ([M+H$^+$] = 289.2, ESI) and later by X-ray diffraction analysis (see below). No significant difference was noticed when employing [$Rh_2(Oct)_4$] instead of [$Rh_2(OAc)_4$]; the moderate yield of 60% (isolated) is due to the sensitivity of **3a** to the chromatographic purification conditions (Al_2O_3, pH 6.5 to 7.5).[13] Only polymerization reactions were observed when various copper or CpRu (Cp = C_5H_5) salts were used in place of the rhodium(II) catalysts.[14]

This novel reaction was extended to other α-diazo-β-ketoesters (Table 1). First, substrates with different ester groups were utilized (**2b–2e**, R^1 = EtO, *t*BuO, $PhCH_2CH_2O$,

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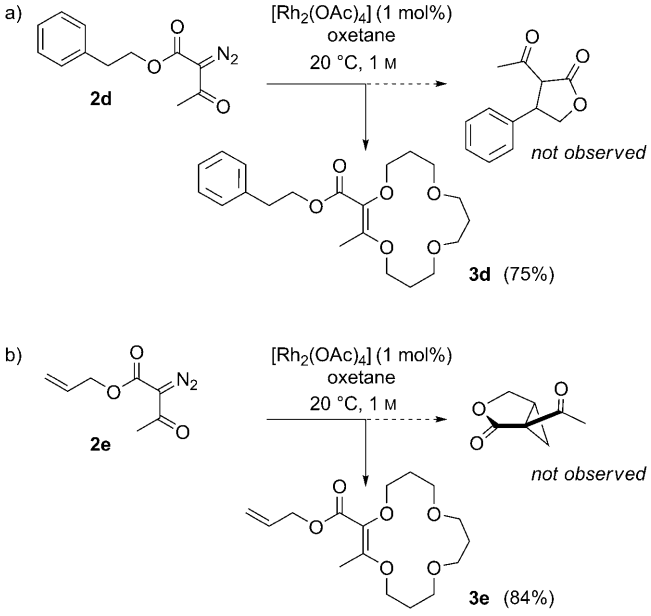
CH_2=$CHCH_2O$; entries 2–5) and all reactions proceeded smoothly indicating a general lack of steric influence from substituents. Remarkably, the homobenzylic **2d** and allylic **2e** afforded the corresponding macrocycles **3d** and **3e** as single products (75 and 84% respectively; Scheme 1). Classical adducts of intramolecular C–H insertion[15] or cyclopropanation[16,17] reactions are totally absent from the crude reaction mixtures. Clearly, under these reaction conditions, the intermolecular macrocyclization pathway is preferred.



Scheme 1. Competitive reactions. a) Macrocyclization vs. C-H insertion. b) macrocyclization vs. cyclopropanation.

Next, the nature of the ketone substituent was varied. Again, little steric effect was noticed. Diazoketoesters **2f–2i** (R^2 = Et, Pr, Ph, *i*Pr; R^1 = OEt) reacted with **1** and the corresponding macrocycles were obtained in moderate to good yields (60 to 84%; Table 1, entries 6–9). The product **3h** was found to be moderately soluble in *n*-heptane and a slow diffusion of this solvent into a CH_2Cl_2 solution of **3h** afforded X-ray quality crystals. A structural analysis was performed and confirmed unambiguously the chemical nature of the macrocyclic structure (Figure 1). Noticeably, compounds **3h** (R^2 = Ph) and **3i** (R^2 = *i*Pr) are obtained in good yields whereas little or no amount of 18-membered macrocycles were obtained when substrates **2h** and **2i** were reacted in 1,4-dioxane as solvent.[9d] Two other substrates were tested. Diazocoumarin **2j**, known to react differently in such macrocyclic reactions,[9c] yielded the expected product **3j** (59%, entry 10). Reactive diazodiketone **2k** afforded also **3k** in good yield (70%, entry 11).

The procedure was extended to commercially available or readily prepared[3e,18] 3,3′-dimethyl and 3,3′-diethyl oxetanes. Using **2a** as the substrate, the macrocyclization reactions proceeded as foreseen to afford compounds **4** and **5**, respectively, although with slightly lower rates (Figure 2).

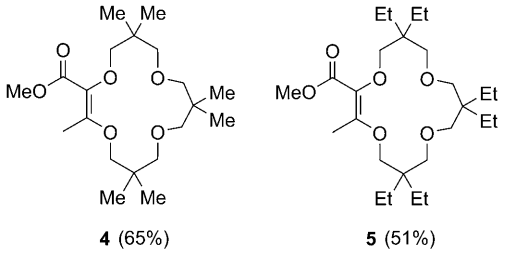


Figure 2. Alkyl-substituted 15-membered macrocyles.

One mechanistic rational is described in Scheme 2. It involves the generation of electrophilic metal carbenoids of type **6**. Addition of an oxetane to this moiety results in the formation of an oxonium ylide of type **7**. This highly reactive (ring-strained) intermediate reacts then with the best nucleophile in the medium, the oxetane itself,[5a] thus promoting the synthesis of **8** and what would normally be the first step of a polymerization. However, under the present situation, intermediate **8** reacts with a single molecule of oxetane to generate **9**, which is trapped intramolecularly by the oxygen atom of the "rhodium enolate" to form the final product.

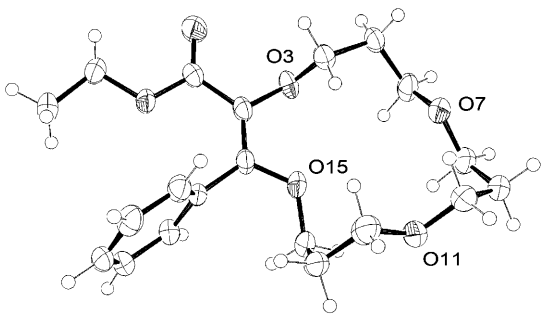
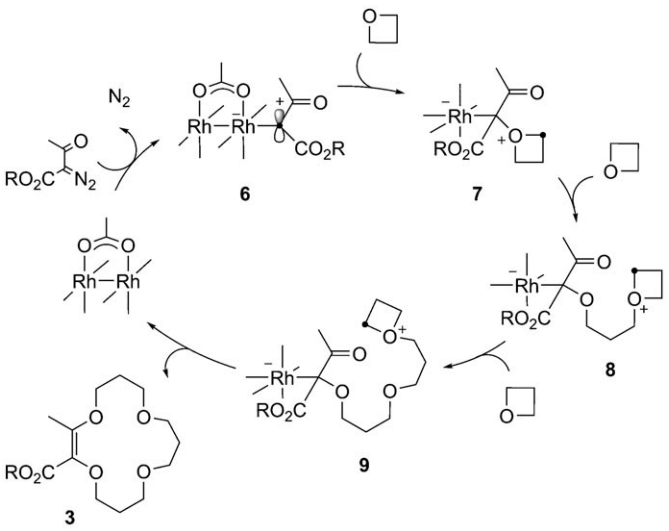


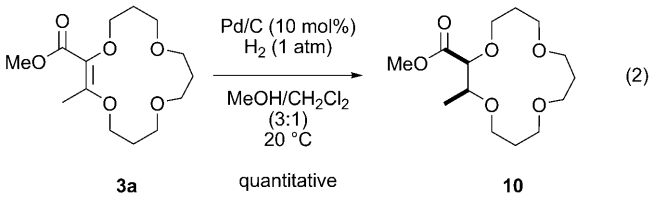
Figure 1. ORTEP view of the crystal structure of **3h**. Thermal ellipsoids are drawn at 50% probability.



Scheme 2. Mechanistic rational. The electrophilic sites are indicated by dots.

Several elements can be considered to rationalize this pathway and the exclusive formation of the 15-membered rings. First, as each nucleophilic addition on oxonium ions **7**, **8**, and **9** should proceed through an S_N2-like transition state, 180° bond angles are necessary between the entering and internal leaving groups.[19] As a consequence, compound **7** cannot undergo intramolecular 5- or 7-*endo*-tet cyclization reactions.[20] For compound **8**, the situation is different. Previous studies have shown evidence that S_N2 transition states may be achieved in nine-membered rings.[19,21] However, in the present case, the 9-*endo*-tet pathway competes with the intermolecular nucleophilic attack from the oxetane; the conjunction of high nucleophilicity of the cyclic ether[5b] and of a probable transannular strain within **8** renders the bimolecular process more likely. Then, at the next stage, the resulting intermediate **9** can readily achieve, with minimal strain, the 180° bond angle necessary to form the 15-membered ring by O alkylation. This endocyclic reaction is now faster than the bimolecular reaction,[22] and consequently precludes further chain growth.

Finally, the hydrogenation of the tetrasubstituted double bond was performed under classical heterogeneous conditions (Pd/C 10%, 1 atm of H_2, 20°C) to afford, using **3a** as the substrate, the corresponding 15-C-4 analogue **10** in quantitative yield as a single stereoisomer having a *cis* configuration [Eq. (2)].[23]



3a quantitative **10** (2)

Herein, we have presented the one-step synthesis of unsaturated macrocycles through a novel one-pot procedure. The process is general. It occurs under high concentration and mild reaction conditions, and a priori without template effects. This procedure can be applied to a large variety of diazo derivatives and oxetanes. This represents a new methodology to obtain functionalized 15-C-4 analogues.

Experimental Section

Representative procedure: A 10 mM blue solution of $[Rh_2(OAc)_4]$ (3.2 μmol, 1.4 mg) in oxetane (0.32 mL) was added in one portion to the diazo compound **2a** (0.32 mmol, 45 mg) that was contained in a 1 mL screw-cap vial equipped with a magnetic stirring bar. The vial was then flushed with argon and capped. The reaction was stirred at 20°C and monitored by thin-layer chromatography (Al_2O_3). After completion (4 h), the solvent was removed under reduced pressure. The desired product **3a** was obtained after a rapid chromatographic purification (5 × 1 cm, neutral Al_2O_3, *n*-pentane/Et_2O 95:5→80:20) as a colorless oil (55 mg, 60%).

CCDC 818723 (**3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[13] Care should be taken to use neutral alumina instead of silica gel for the purification as unsaturated derivatives of type **3** are sensitive to acids.
[14] Cu(OTf), $Cu(OTf)_2$, and $[Cu(NCCH_3)_4][BF_4]$ and different complexes made of $[CpRu(NCCH_3)_3][PF_6]$ and diimine ligands were used. For use of these later complexes as diazo decomposition catalysts, see M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* **2011**, *13*, 1394 – 1397.
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[22] Interestingly, literature precedents on the photochemical decomposition of diazo derivatives in oxetane medium also indicate the preferred formation of 15-membered macrocycles albeit in lower yields. See Ref. [7].
[23] The 6.6 Hz value for the $^3J_{H,H}$ coupling constant occurring between the protons α to the ester and methyl groups is consistent with a *cis* and not a *trans* configuration of product **10**.

