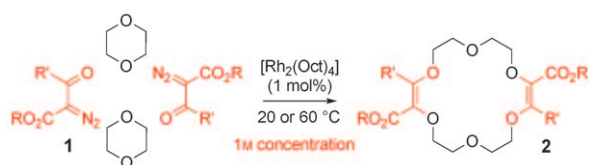


Rhodium(II)-Catalyzed One-Pot Four-Component Synthesis of Functionalized Polyether Macrocycles at High Concentration**

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The transition-metal-catalyzed decomposition of diazo compounds is a powerful method for the generation of electrophilic metal carbenes.^[1,2] These intermediates undergo many synthetic transformations, including cyclopropanation, dimerization, insertion, dipolar addition, ylide generation, and rearrangement reactions.^[3,4] The reported combination of these reactions with polyether-macrocyclic synthesis offers an interesting alternative to classical procedures for the synthesis of this important class of substrates.^[5,6] In this context, we report the rhodium(II)-catalyzed regioselective condensation of two α -diazo- β -ketoesters **1** and two cyclic ethers to yield functionalized 16- to 18-membered macrocycles such as **2** (Scheme 1). Against conventional wisdom, the process couples four separate components in one reaction vessel^[7] under conditions of high concentration (≥ 1 M) in yields up to 75 %.



Scheme 1. High-concentration one-pot condensation of two α -diazo- β -ketoesters **1** and two cyclic ethers (1,4-dioxane used as the solvent).

Acceptor/acceptor-substituted diazo compounds are among the most stable diazo reagents, in particular those derived from β -ketoesters.^[2,4] They are readily prepared by using diazo-transfer reagents, such as *p*-acetamidobenzene-sulfonyl azide (*p*-ABSA).^[8] In our case, methyl diazoacetate (**1a**; R,R' = Me in Scheme 1) was simply treated at 60 °C with Rh₂(OAc)₄ (0.5 mol %) in 1,4-dioxane (**3**). The

reaction was over in less than 20 minutes. The precipitate that formed upon cooling of the crude mixture to 20 °C was filtered. A single compound, **2a**, was observed in the solid fraction by NMR spectroscopy; this novel derivative was also the major component of the mother liquor. The two fractions were combined, and **2a** was isolated in pure form in 45 % yield by flash chromatography on neutral Al₂O₃. NMR spectroscopic analysis indicated that **2a** was a polyether adduct formed by the ring opening of 1,4-dioxane.^[9] The ¹H NMR spectrum indicated a 1:1 ratio of a component derived from **1a** and a component derived from 1,4-dioxane (**3**) in the product. This observation pointed first to the formation of a nine-membered-ring compound.^[9] However, mass spectrometry indicated clearly that the molecule had twice the mass ($[M+H]^+ = 405.5$, ESI) expected for such a compound. Only an 18-membered macrocyclic structure of type **2** that included two fragments derived from **1a** and two from **3** connected in an alternating manner fitted the data. Furthermore, the reaction was completely regio- and stereo-selective: all alkene bonds had a *Z* configuration. We investigated the reaction further by optimizing the reaction conditions and using other α -diazo- β -ketoesters as substrates (**1b–i**;^[5,10,11] Table 1).

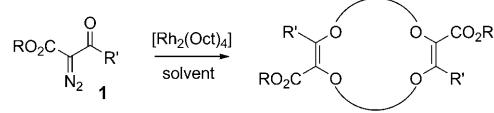
The reaction was found to be general in terms of the catalyst class. Under the same reaction conditions, [Rh₂(esp)₂]^[12] and [Rh₂(Oct)₄] (0.5 mol %) performed equally well to give macrocycle **2a** in 49 and 51 % yield, respectively (**1a**: 1 M in 1,4-dioxane, 60 °C). The use of [Rh₂(tfa)₄] led to a lower yield (23 %; tfa = trifluoroacetate).^[13] The catalyst loading was first optimized with [Rh₂(OAc)₄]. The reaction proceeded with only 0.05 or 0.1 mol % of the catalyst, but a sharp decrease in yield was observed (15 and 17 %, respectively). When the amount of the catalyst was increased from 0.5 to 1 mol %, the yield improved slightly (50 %), but Rh₂(OAc)₄ tended to precipitate with the product. With the more soluble catalyst [Rh₂(Oct)₄], reactions were performed with 1, 2, and 5 mol % of the catalyst (**1a**: 1 M in 1,4-dioxane) to afford **2a** in 54, 58, and 42 % yield, respectively. We found that it was generally more practical to use this lipophilic catalyst, which was selected for the remainder of the study. The catalyst loading was set to 1 mol %. We also investigated concentration effects. When we carried out the reaction at 2.0, 0.5, and 0.05 M concentrations of **1a**, **2a** was formed in 54, 37, and 18 % yield, respectively. Surprisingly, as the concentration was increased, the formation of **2a** became more efficient.^[14] Finally, we noticed that macrocycle **2a** was slightly sensitive to the chromatographic purification conditions. When the reaction was carried out on a larger scale (7.0 mmol), and **2a** was isolated by precipitation/filtration, the product was obtained in higher yield (75 %; Table 1, entry 2).

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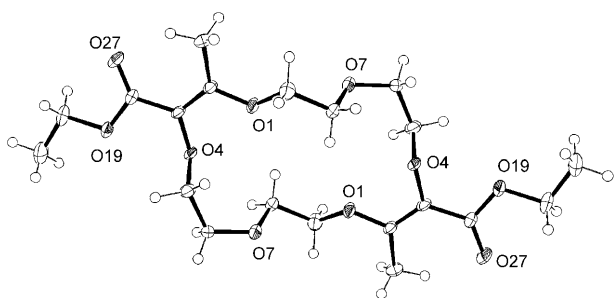
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201003559>.

Table 1: Substrate scope.^[a]


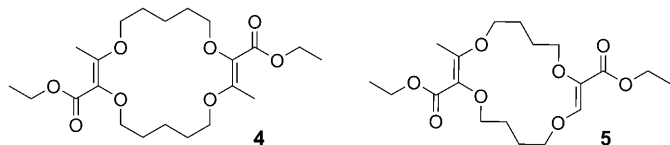
Entry	1	R	R'	Solvent	Product	Method	Yield [%] ^[b]
1	1a	Me	Me	3	2a	A	54
2 ^[c]	1a	Me	Me	3	2a	B	75
3	1b	Et	Me	3	2b	A	48
4	1b	Et	Me	THP	4	A	31
5	1b	Et	Me	THF	5	A	43
6	1c	PhCH ₂ CH ₂	Me	3	2c	B	62
7	1d	allyl	Me	3	2d	B	47
8	1e	PhCH=CH ₂	Me	3	2e	B	51
9	1f	Et	Et	3	2f	B	48
10	1g	Et	nPr	3	2g	B	58
11 ^[d]	1h	Et	Ph	3	2h	A	14
12	1i	Et	iPr	3	2i	A or B	0

[a] Method A: **1** (0.64 mmol, 1 M in the solvent), [Rh₂(Oct)₄] (1 mol %), 60 °C, 20 min, argon atmosphere; method B: **1** (0.64 mmol, 1 M in the solvent), [Rh₂(Oct)₄] (1 mol %), 20 °C, 12 h, argon atmosphere. [b] Yield of the isolated product after chromatography. [c] The reaction was carried out on a 7.0 mmol scale (with respect to **1a**); Rh₂(OAc)₄ was used instead of [Rh₂(Oct)₄]; **2a** was isolated by filtration. [d] The product **2h** was isolated by precipitation and filtration.

The procedure was extended to other α -diazo- β -ketoesters and cyclic ethers. The reaction of ethyl-substituted **1b** (R = Et, R' = Me) in 1,4-dioxane proceeded to afford **2b** (48%; Table 1, entry 3). The product was found to be moderately soluble in acetonitrile; slow crystallization from that solvent afforded crystals suitable for X-ray crystallography. Structural analysis showed that **2b** adopts a rather rigid rectangular geometry enforced by the presence of the two constraining double bonds (Figure 1).

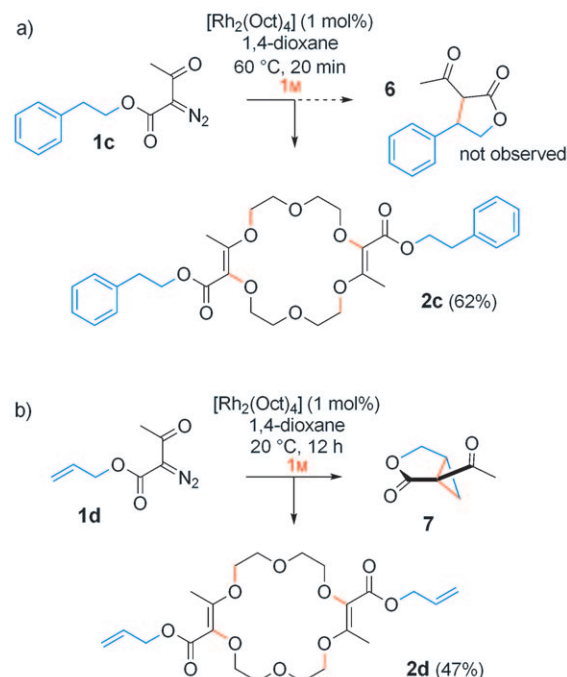
**Figure 1.** ORTEP view of the crystal structure of **2b**. The thermal ellipsoids are drawn at 50% probability.

The procedure was also tested with **1b** in the solvents tetrahydro-2H-pyran (THP) and tetrahydrofuran (THF). The 18- and 16-membered macrocycles **4** and **5** were obtained in



moderate yields (31 and 43 %, respectively; Table 1, entries 4 and 5). Compound **5** was also found to crystallize from an acetonitrile/pentane mixture. Its structure is analogous to that of **2b** (see the Supporting Information for the results of X-ray diffraction analysis of **5**). Three other substrates, **1c**, **1d**, and **1e**, were also tested in 1,4-dioxane. The reactions afforded **2c**, **2d**, and **2e** in 62, 47, and 51 % yield, respectively (Table 1, entries 6–8).

These results are interesting, as **1c** is known to react in benzene at reflux in the presence of Rh₂(OAc)₄ to yield γ -lactone **6** (Scheme 2a) in excellent yield (86 %).^[15] However,

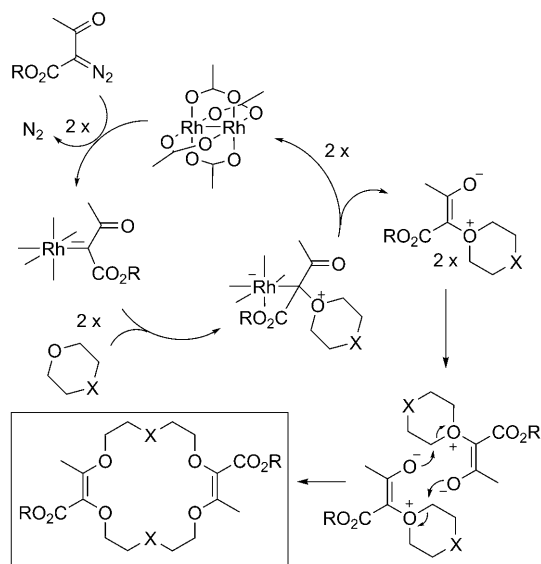
**Scheme 2.** Competitive reactions: a) macrocyclization versus C–H insertion; b) macrocyclization versus cyclopropanation.

we did not observe this product of an intramolecular reaction in the NMR spectrum of the crude reaction mixture; thus, selectivity in favor of the macrocyclization was strong. In the case of **1d**, **2d** (47%) was found to be present in the crude mixture along with the “expected” bicyclic lactone **7** (1.2:1 ratio; Scheme 2b).^[16,17] In the reaction of **1e** (R = PhCH=CH₂, R' = Me), macrocycle **2e** (51 %) was also found to predominate.^[11,18] These three examples show that the “intermolecular” cyclization procedure competes effectively with traditional intramolecular reactions.

Steric hindrance tends to affect the reaction, as shown with substrates **1f–i**, which contain larger substituents next to the keto group (R' = Et, nPr, Ph, iPr; R = Me). Under the standard conditions (60 °C, 20 min), the macrocycles were obtained in poor yield, if at all. Reactions of these sensitive substrates were performed at room temperature (20 °C). Longer reaction times (12 h) were necessary, but macrocycles

2f and **2g** were now isolated in good yields (48 and 58%, respectively; Table 1, entries 9 and 10).

One plausible speculative mechanism is outlined in Scheme 3. It involves the generation of electrophilic metal carbenoids and the addition of the cyclic ethers to these intermediates.^[19] Stabilized oxonium ylides result.^[20] Interest-



Scheme 3. Proposed mechanism involving the synchronous “concerted” dimerization of the oxonium ylide intermediate. R = alkyl, X = O, CH₂.

ingly, these intermediates do not undergo 1,4-H⁺ shifts.^[21] Possibly, in a single elemental step, two such ylide intermediates generate the macrocycle in two synchronous intermolecular nucleophilic attacks of the O enolate of each moiety onto the oxonium electrophilic α carbon atom of the other (Scheme 3).^[21,22] This last step, which rationalizes the regioselectivity, may also explain an interesting aspect of this reaction: that is, the more efficient formation of the macrocycles at high concentration. The reaction conditions (≥ 1 M) favor the encounter of high-energy reactive intermediates (such as ylides), which, under classical dilute conditions, would have a lower probability of reaction with one another. Kinetic or thermodynamic template effects were expected to have little influence on the reaction. This assumption was briefly tested by adding KPF₆ (0.5 equiv) to the α -diazo- β -ketoester **1a** in 1,4-dioxane. The reaction rate remained the same, and the yield decreased owing to the formation of novel by-products.^[23]

In conclusion, we have described novel reactivity in the rhodium(II)-catalyzed decomposition of diazo compounds. To our knowledge, this one-step synthesis of functionalized polyether macrocycles 1) at high concentration (≥ 1 M), 2) under nontemplated conditions, 3) from two classes of readily available building blocks, and 4) through primarily intermolecular connections is the first of its kind.

Experimental Section

Representative procedure: In a 2 mL screw-cap vial equipped with a magnetic stirring bar, a 10 mM solution of [Rh₂(Oct)₄] in 1,4-dioxane (or another solvent; 0.64 mL) was added in one portion to **1c** (148.8 mg, 0.64 mmol). The vial was flushed with argon and capped. The reaction mixture was stirred at 60 °C, and the reaction was monitored by thin-layer chromatography. After completion, the solution was cooled to 20 °C, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (neutral Al₂O₃) gave **2c** as a white solid (117 mg, 62%).

CCDC 774656 (**2b**) and 774840 (**5**) contain 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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