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Synthetic Methodology

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

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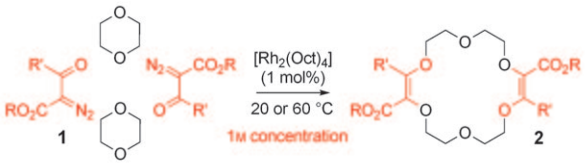
The transition-metal-catalyzed decomposition of diazo compounds is a powerful method for the generation of electrophilic metal carbenes.[1,2] These intermediates undergo many synthetic transformations, including cyclopropanation, dimerization, insertion, dipolar addition, ylide generation, and rearrangement reactions.[3,4] The reported combination of these reactions with polyether-macrocycle 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*-acetamidobenzenesulfonyl azide (*p*-ABSA).[8] In our case, methyl diazoacetoacetate (**1a**; R,R′ = Me in Scheme 1) was simply treated at 60 °C with $Rh_2(OAc)_4$ (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 $Al_2O_3$. NMR spectroscopic analysis indicated that **2a** was a polyether adduct formed by the ring opening of 1,4-dioxane.[9] The $^1$H 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 stereoselective: 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, $[Rh_2(esp)_2]$[12] and $[Rh_2(Oct)_4]$ (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 $[Rh_2(tfa)_4]$ led to a lower yield (23%; tfa = trifluoroacetate).[13] The catalyst loading was first optimized with $[Rh_2(OAc)_4]$. 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 $Rh_2(OAc)_4$ tended to precipitate with the product. With the more soluble catalyst $[Rh_2(Oct)_4]$, 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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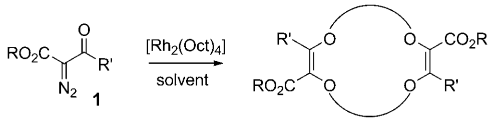
***Table 1:*** Substrate scope.[a]



| 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** | $PhCH_2CH_2$ | 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 | *n*Pr | **3** | **2g** | B | 58 |
| 11[d] | **1h** | Et | Ph | **3** | **2h** | A | 14 |
| 12 | **1i** | Et | *i*Pr | **3** | **2i** | A or B | 0 |

[a] Method A: **1** (0.64 mmol, 1 M in the solvent), $[Rh_2(Oct)_4]$ (1 mol%), 60 °C, 20 min, argon atmosphere; method B: **1** (0.64 mmol, 1 M in the solvent), $[Rh_2(Oct)_4]$ (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**); $Rh_2(OAc)_4$ was used instead of $[Rh_2(Oct)_4]$; **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).

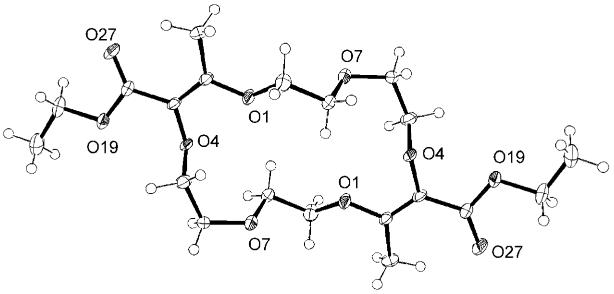
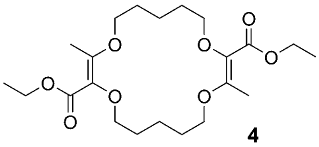
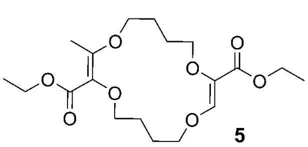


***Figure 1.*** ORTEP view of the crystal structure of **2b**. The thermal ellipsoids are drawn at 50% probability.

The procedure was also tested with **1b** in the solvents tetrahydro-2*H*-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).

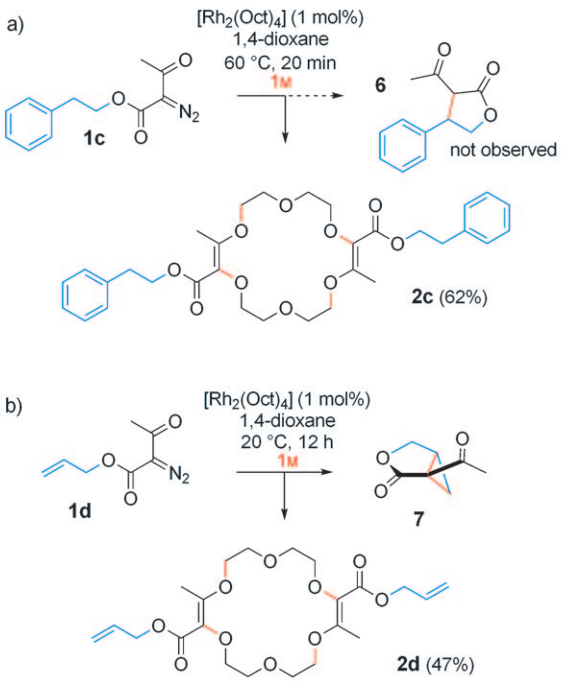


**4**



**5**

These results are interesting, as **1c** is known to react in benzene at reflux in the presence of $Rh_2(OAc)_4$ to yield γ-lactone **6** (Scheme 2a) in excellent yield (86%).[15] However, 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 = $PhCH{=}CH_2$, 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.

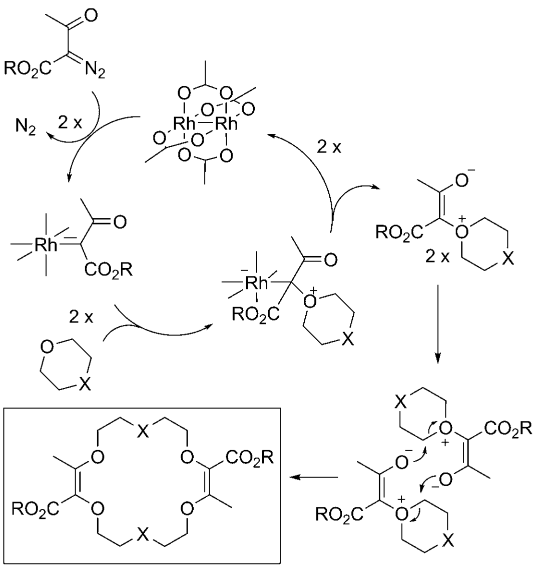


***Scheme 2.*** Competitive reactions: a) macrocyclization versus C–H insertion; b) macrocyclization versus cyclopropanation.

Steric hindrance tends to affect the reaction, as shown with substrates **1f–i**, which contain larger substituents next to the keto group (R′ = Et, *n*Pr, Ph, *i*Pr; 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] Interestingly, these intermediates do not to 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 (≥ 1M) 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 $KPF_6$ (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]



*Scheme 3.* Proposed mechanism involving the synchronous "concerted" dimerization of the oxonium ylide intermediate. R = alkyl, X = O, $CH_2$.

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 (≥ 1M), 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 $[Rh_2(Oct)_4]$ 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 $Al_2O_3$) 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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[7] Traditionally, in multicomponent reactions, three or more different starting materials form a product in convergent reactions, in which all or most of the atoms contribute to the newly formed product. Precisely such a process occurs in the described reaction, with the exception that the four components include only two different compounds.

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[13] $[Rh_2(tpa)_4]$ was found not to be soluble in 1,4-dioxane under these conditions (tpa = triphenylacetate).

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[16] Compound **7** has been described previously: L. L. Welbes, T. W. Lyons, K. A. Cychosz, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837.

[17] The reaction with **1d** is better performed at 20°C. At 60°C, a 2:3 ratio between **2d** and **7** was observed.

[18] The reaction of **1e** is also better performed at 20°C. When it was carried out at 60°C, **2e** was isolated in considerably lower yield (8%).

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[22] These nucleophilic attacks may also occur in a stepwise manner to give the product through a domino-like reaction.

[23] This lack of a template effect is also consistent with the X-ray structural analysis of **2b**. The absence of a lumen inside the macrocycle and the distribution of the oxygen atoms on both faces of the macrocycle render any binding event unlikely.