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One-Step Synthesis of Diaza Macrocycles by Rh(II)-Catalyzed [3+6+3+6] Condensations of Morpholines and α-Diazo-β-ketoesters

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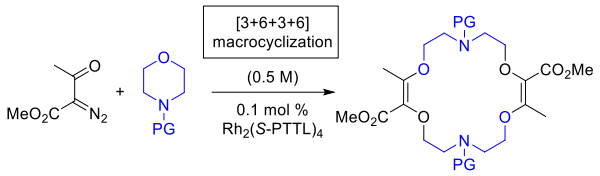
Supporting Information Placeholder



Selective formation of oxonium ylides from morpholines and α-diazo-β-ketoesters was achieved. This was applied to the high-concentration (0.5 M) dirhodium-catalyzed (0.1 mol %) [3+6+3+6] synthesis of 18-membered ring diaza macrocycles (46-72%). Late-stage functionalization of these derivatives is demonstrated. Mechanistic evidences for a novel (undesired) diazo decomposition pathway is also reported.

Decompositions of diazo compounds in presence of oxygen, nitrogen, sulfur or phosphorus *Lewis* bases is a recognized strategy to generate the corresponding ylides efficiently.[1] In the case of oxonium ylides, diazo reagents decomposed by photochemical or metal-catalyzed conditions[2] are known to react with cyclic ethers such as epoxides,[3] oxetanes,[4] THF,[5] THP,[6] 1,3- and 1,4-dioxanes,[7] or oxepane,[8] and the subsequent intermediates are used in a large panel of reactions. Morpholines, and other N-containing cyclic ethers, are however rarely utilized for the formation of oxonium ylides. Amines, with their higher nucleophilicity,[9] compete effectively for the carbenes leading to a preferred formation of the nitrogen ylides instead. For instance, preferred insertion on the N-atom occurs when 2-phenyloxazolidines are treated with methyldiazoacetate under copper catalysis (Figure **1**, top).[9e] Herein, exclusive formation of oxonium ylide intermediates is reported using morpholines carrying electron-withdrawing (EWG) or sterically hindered groups on the N-atom. These groups that reduces the overall nucleophilicity by electronic or steric reasons, do not prevent reactions with α-diazo-β-ketoesters **1**. Under Rh(II)-catalysis (0.1 mol %), 18-membered ring diaza macrocycles are afforded in one-pot in good yields (46-72%). Mechanistically, it is shown that a lowering of the catalyst loading is necessary to favor the [3+6+3+6] macrocyclization over a deleterious diazo decomposition pathway which is being characterized for the first time. Late-stage functionalization of the resulting macrocycles is also demonstrated.

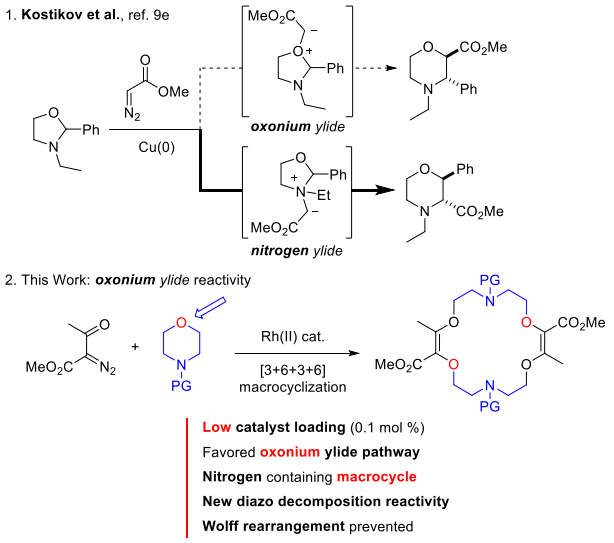


Figure 1. Competitive formation of oxonium *vs* nitrogen ylide (top) and [3+6+3+6] macrocyclization through favored oxonium ylide (bottom).

Previously, it was shown that cyclic ethers like THF, THP, 1,4-dioxane or oxepane react with α-diazo-β-ketoesters **1** to generate in one-pot 16- to 20-membered unsaturated heterocycles in [3+X+3+X] macrocyclizations (X=5 to 7).[7b, 8, 10] Morpholine substrates, despite the importance of polyazamacrocycles in fundamental and applied chemistry,[11] were not studied to avoid the predicted competition between oxygen and nitrogen ylide reactivity. However,

with recent studies revealing key mechanistic aspects of these macrocyclizations and more active catalysts (Figure **2A**),[12] it was decided to tackle the challenge. Care was taken nevertheless to use morpholines **2a**-**2h** protected on the N-atom with electron-withdrawing or sterically-demanding substituents (Figure **2B**).

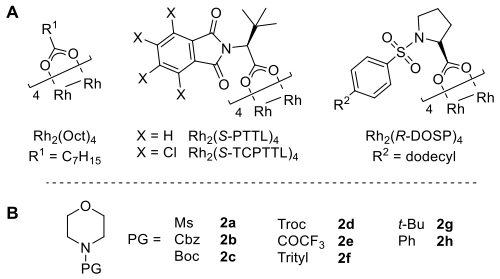
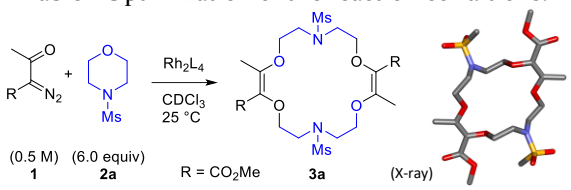


Figure 2. Selected catalysts (**A**) and morpholine substrates (**B**). (Ms: mesyl; Cbz: carboxybenzyl; Boc: *t*-butyloxycarbonyl; Troc: 2,2,2-trichloroethoxycarbonyl; trityl: triphenylmethyl)

The macrocyclization was first attempted with methyl α-diazo-β-ketoester **1** (0.35 mmol, 50 mg) and *N*-mesyl morpholine **2a** (6 equiv) using previously reported conditions (25 °C, 0.5 M of **1**, $CDCl_3$ as solvent) and $Rh_2(Oct)_4$ as catalyst (1.0 mol %).[6, 12,13] To our satisfaction, macrocycle **3a** was obtained in 26% yield after 3 hours of reaction (Table 1, entry 1). Its structure was confirmed by NMR spectroscopic analyses and X-ray diffraction analysis (Table 1). Using Hashimoto-Ikegami catalysts, Rh_2(*S*-PPTL)$_4$ and Rh_2(*S*-TCPPTL)$_4$, yields increased and decreased to 36% and 7% respectively (entries 2 and 3); the stronger *Lewis* acidic nature of polychlorinated complex being possibly detrimental. Interestingly and of importance for the study, it was noticed that a reduction in catalyst loading from 1.0 mol % to 0.1 mol % was strongly beneficial. In fact, with the same three catalysts but at 1 mol ‰ level, quite higher yields were obtained (entries 4-6); Rh_2(*S*-PPTL)$_4$ remaining the most active complex (63% yield of **3a**).[14] The reason for the higher outcome at lower catalyst loading will be later explained. Additional reduction to 0.01 mol % of Rh(II) did not induce further improvements as **3a** was isolated in 53% and 44% with Rh_2(*S*-PPTL)$_4$ and Rh_2(*S*-TCPPTL)$_4$ respectively (entries 7-8). At this lower concentration (0.1 mol %), Davies' Rh_2(*R*-DOSP)$_4$ was also tested and provided **3a** in 47% yield (entry 9). Conditions highlighted in entry 5 were thus selected for the remainder of the study increasing however the scale of the reaction to 1.41 mmol (200 mg) of α-diazo-β-ketoester **1**.

Table 1 Optimization of the reaction conditions.

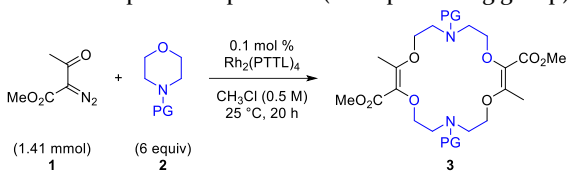


entry	Rh_2L_4	loading (mol %)	time (h)	yield (%)[a]
1	$Rh_2(Oct)_4$	1.0	3	26
2	Rh_2(*S*-PPTL)$_4$	1.0	3	36 (39)[b]
3	Rh_2(*S*-TCPPTL)$_4$	1.0	3	7
4	$Rh_2(Oct)_4$	0.1	24	43 (42)[b]
5	Rh_2(*S*-PPTL)$_4$	0.1	14	63 (61)[b]
6	Rh_2(*S*-TCPPTL)$_4$	0.1	14	35 (31)[b]
7	Rh_2(*S*-PPTL)$_4$	0.01	46	53
8	Rh_2(*S*-TCPPTL)$_4$	0.01	60	44
9	Rh_2(*R*-DOSP)$_4$	0.1	40	47

[a] ^{1}H NMR yield using 1,4-bis(trimethylsilyl)benzene as external standard; [b] isolated yield. Stick view of the crystal structure of **3a**; hydrogen atoms are removed for clarity.

The results are reported in Table 2. *N*-mesyl protected macrocycle **3a** was obtained in exactly the same isolated yield on larger scale (61%, entry 1). The corresponding Cbz, Boc and Troc *N*-macrocyclic structures **3b**, **3c** and **3d** were successfully isolated in 72%, 70% and 74% yields respectively (entries 2-4). A slightly lower yield was obtained with *N*-trifluoroacetamide protecting group as macrocycle **3e** was formed in 55% yield (entry 5). As it could be expected, ^{1}H and ^{13}C NMR characterization of products **3b** to **3e** required the use of higher temperatures (70-120 °C in DMSO-d_6); broad or split signals being observed at room temperature due to the relatively slow rotation (NMR time scale) of the amide and carbamate groups.[15] Satisfactorily, with sterically-demanding *N*-trityl morpholine, **3f** was formed in 46% yield (entry 6). Not surprisingly, when other electron-rich nitrogen substituents were tested, such as tert-butyl and phenyl groups (substrates **2g** and **2h**),[16] none of the corresponding macrocycles were generated; these "protecting" groups being not sufficiently bulky to shield the reactivity (lone pair) of the nitrogen atom. Finally, it is worth mentioning that yields of **3c** and **3e** remained essentially constant on even larger scale of diazo reagent (1.0 gram, 7 mmol).

Table 2. Scope of morpholines (PG = protecting group).



entry	morpholine	macrocycle	yield (%)
1	**2a** (*N*-Ms)	**3a**	61
2	**2b** (*N*-Cbz)	**3b**	72
3	**2c** (*N*-Boc)	**3c**	70 (69)[a]
4	**2d** (*N*-Troc)	**3d**	74
5	**2e** (*N*-$COCF_3$)	**3e**	55 (49)[a]
6	**2f** (*N*-Trityl)	**3f**	46
7	**2g** (*N*-*t*-Bu)	**3g**	-[b]
8	**2h** (*N*-Ph)	**3h**	-[b]

[a] 7 mmol scale (1.0 g of α-diazo-β-ketoester). [b] Formation of macrocycles **3** not observed.

With diaza macrocyclic structures **3a**-**3f** in hand, removal of the nitrogen protecting groups was pursued. In view of the sensitivity of the unsaturated macrocycles to acidic conditions, care was taken to select primarily **3a**, **3b** and **3e** as substrates (Figure **3**). Trifluoroacetamide deprotection of **3e** was achieved by addition of an excess of $NaBH_4$ leading to **4** in 92% yield. The benzyl carbamate group of **3e** was simply removed by hydrogenolysis; the use of Pd/C (10% w/w) leading to a clean deprotection of the nitrogen atoms (94% yield) without reducing the double bonds. However, with more active $Pd(OH)_2/C$ (50% w/w), saturated derivatives **5** and **6** can be isolated in good yields and diastereoselectivity (>12:1).[17] The relative configurations of the generated stereocenters are unknown but the presence of local symmetry in the ^{1}H NMR spectra and the probable syn additions of H_2 led us to propose the following stereochemistry for **5** (chiral, racemic) and **6** (*meso*, achiral).

Furthermore, care was also taken to derive compounds of type **3** into functional bisamides **7**, **8** or **9** by double tandem amidation plus olefin transposition.[18] This type of biaryl derivatives can be applied in fields as varied as pH-independent nanosensors, heteroditopic salt receptors, ratiometric luminescent or reversible chiroptical switches;[8, 19] these previous examples lacking however nitrogen atoms within the macrocyclic core. Satisfactorily, by mixing **3a** with an excess of 3,5-bis(trifluoromethyl)aniline and *t*-BuOK, compound **7a** was obtained in one step (77%, Figure **4**). The structure of **7a** was confirmed by X-ray diffraction (Figure **S2**). This compound was further hydrogenated (Pd/C, 10% w/w)[19a] to afford saturated derivative **8** in 79% yield as a 9:1 mixture of diastereoisomers.[20] With **3e**, as it could be expected, deprotection of the trifluoroacetamide groups occurred during the (highly basic) amidation/transposition reaction. The resulting macrocycle **7e** was highly polar and difficult to isolate. It was then engaged directly in a reductive amination protocol with an excess of propanal and $NaBH(OAc)_3$to afford **9** in a combined 73% yield for two successive steps (Figure **4**).[21]

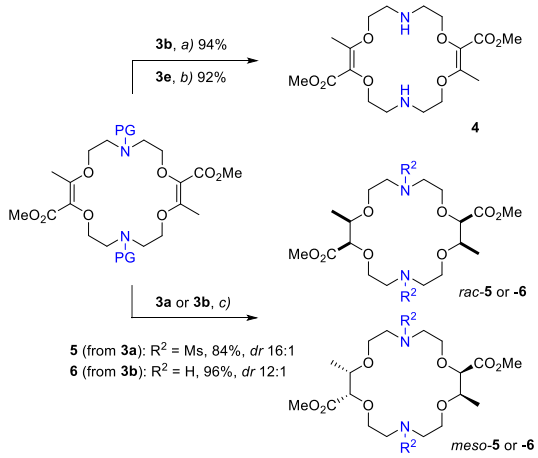


Figure 3. Reactivity of diaza macrocycles **3a**, **3b** or **3e**: *a*) H_2 (1 atm.), Pd/C (10% w/w), CH_2Cl_2/MeOH (1:1), 25 °C, 2 h; *b*) $NaBH_4$ (5 equiv), CH_2Cl_2/MeOH (1:1), 25 °C, 1 h; *c*) H_2 (1 atm.), $Pd(OH)_2/C$ (50% w/w), MeOH, 25 °C, 4 h.

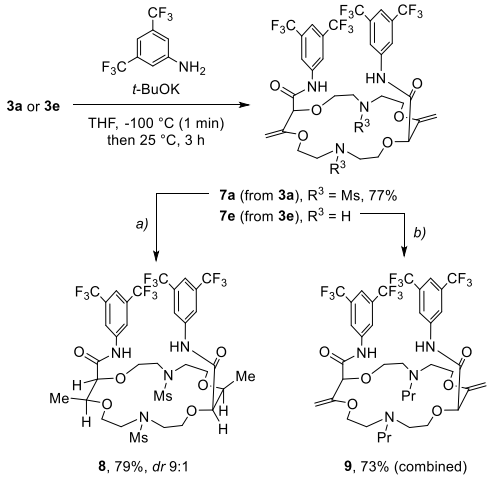
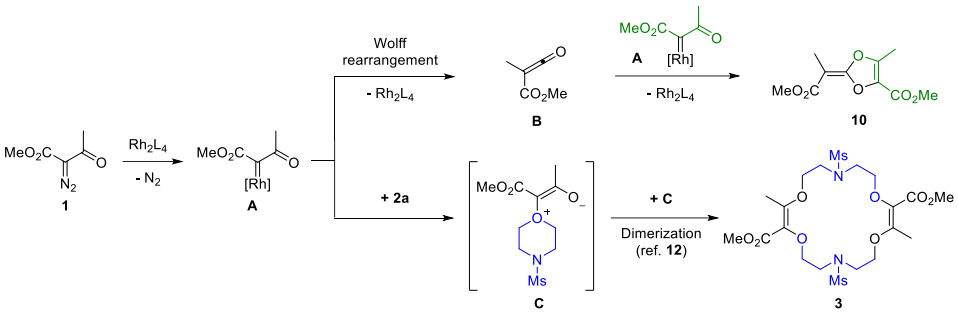


Figure 4. Derivatisation of **3a** and **3e**. *a)* H_2 (1 atm.), Pd/C (10% w/w), THF, 25 °C, 2 h; *b*) propanal (8 equiv). $NaBH(OAC)_3$ (10 equiv), 1,2-dichloroethane, 25 °C, 2 h.

Finally, care was taken to rationalize the observed improvement of reaction yields upon the reduction of catalysts loading from 1.0 to 0.1 mol %. Crude reaction mixtures of **1** and **2a** were analyzed by GC-MS and, along with macrocycle **3a**, a major by-product **10** was evidenced (Figures S5-S8). With a mass of 228 (twice that of the carbene derived from **1**), and a $C_{10}H_{12}O_6$ composition determined by HRMS, **10** was clearly the result of an unidentified decomposition pathway of diazo **1**.[22] Importantly, it was possible to observe by-product **10** upon the addition of diazo **1** to a solution of $Rh_2(Oct)_4$ (1 mol %) in CH_2Cl_2 at -78 °C. After stirring (5 h) at that temperature, a slow warm up to 25 °C and an additional stirring (20 h), compound **10** was isolated (12%) as a mixture of geometrical isomers as determined by

^{1}H and ^{13}C NMR spectroscopy. Compound **10** was found to be unstable in solution, yet fairly crystalline. X-ray structural analysis afforded good indications on the chemical structure of it; the quality of the structural model being however not enough for it to be reported. **10** is comprised of a dioxolene ring fused with an α,β-unsaturated ester moiety. Its formation is rationalized by a Wolff rearrangement of metal carbene **A** to form ketene **B**, which reacts with a second molecule of **A** to yield **10** (Scheme **1**).[23] Considering that both steps **A**→**B** and **B**→**10** involve metal carbenes **A**, and that the second one is rate-determining, then the rate law for the formation of **10** is 2nd order in dirhodium catalyst. Decreasing the amount of catalyst hence disfavors the formation of **10**. Intermediate **A** has also a higher probability of reaction with morpholine **2a** giving rise to ylide intermediate **C** and then to macrocycle **3a**.[12] The experimental results in Table **1** fit nicely this hypothesis and the observation of a higher yield of macrocycles upon a decrease of catalyst loading.

Scheme 1. Proposed pathways for the formation of by-product **10** or diaza macrocycle **3**.



In conclusion, through a careful selection of nitrogen protecting groups and reaction conditions, an efficient dirhodium-catalyzed synthesis of diaza-polyether macrocycles has been achieved by condensation of N-protected morpholines with α-diazo-β-ketoesters. Exclusive formation of the oxonium ylide pathway is observed. The diaza-polyether macrocycles are generated in good yields (46-72%). Derivatization of the macrocycles leads to highly functionalized scaffolds in high yields, in a few steps only from simple reagents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental conditions, full characterizations, ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of all new compounds, GC-MS traces (PDF); X-ray files (cif).

Accession Codes

CCDC 1881855 and 181856 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no conflict of interest.

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(13) Contrary to classical macrocyclization procedures, a relatively high concentration is required (0.5-1.0 M) to favor the rate-determining 2nd-order dimerization of intermediates **C**; see Scheme 1 and references 6, 7b and 12.

(14) With the benzyl α-diazo-β-ketoester, a much lower yield of the corresponding macrocycle was obtained (12%, see ESI); further studies were all performed in the methyl ester series.

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(16) More morpholine substrates were tested with no success. These moieties are detailed in Scheme S1 (ESI).

(17) Hydrogenolysis and hydrogenation conditions were screened and are reported in Table S2.

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(20) In analogy to previously reported derivatives (see reference 19a), an all-*cis* configuration is assumed for the major diastereoisomer.

(21) Abdel-Magid, A. F.; Mehrman, S. J., *Org. Process Res. Dev.* **2006**, *10*, 971-1031.

(22) This undesired reactivity is less present when 1,4-dioxane is used as cyclic ether (see ref. 12). With substrates **2a-2f** that include strong electron-withdrawing substituents, the oxygen atoms of the corresponding morpholines are most probably less basic/nucleophilic than that of 1,4-dioxane. As a consequence, reaction **A**→**C** is slower than usual and the formation of **10** becomes kinetically competitive at higher concentration of Rh_2L_4.

(23) The pathway from **B** plus **A** to **10** probably involves a ketene-ylide intermediate.