

## Configurational Lability of Imino-Substituted *Ethano Tröger* Bases. Insight on the Racemization Mechanism

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### Abstract

Polycyclic indoline-benzodiazepines are afforded in one step by the reaction of Tröger bases with N-sulfonyl-1,2,3-triazoles under Rh(II) catalysis. After  $\alpha$ -imino carbene formation, the process involves a cascade of [1,2]-Stevens rearrangement, Friedel-Crafts, Grob fragmentation, and amination reactions. It is highly diastereoselective (d.r. >49:1, four stereocenters incl. two bridgehead N-atoms). However and in contrast with other reported carbene additions to these moieties, full racemization occurs when enantiopure Tröger bases are used as substrates. To pinpoint the origin of this unexpected behavior, a key elemental step of the mechanism was evaluated and tested. Interestingly, it is not only the initial ring-opening but also the latter reversible Mannich reaction of the imino-substituted ethano Tröger base intermediate that is responsible for the loss of enantiospecificity.

### Reference

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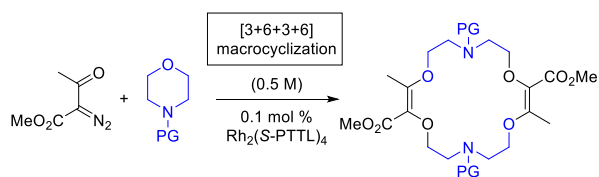
# One-Step Synthesis of Diaza Macrocycles by Rh(II)-Catalyzed [3+6+3+6] Condensations of Morpholines and $\alpha$ -Diazo- $\beta$ -ketoesters

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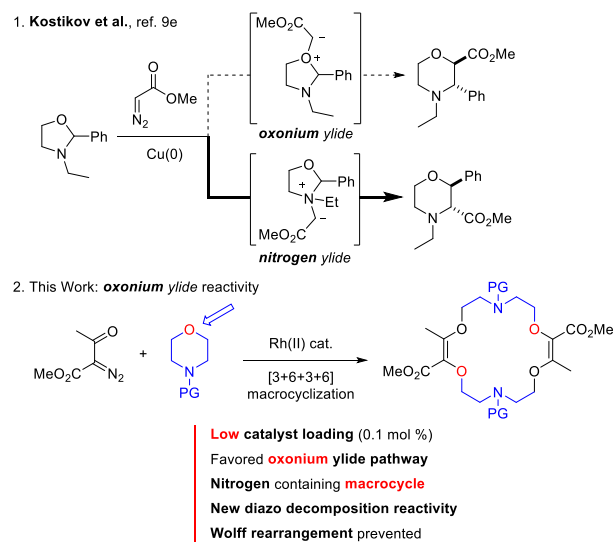
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Supporting Information Placeholder



Selective formation of oxonium ylides from morpholines and  $\alpha$ -diazo- $\beta$ -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.

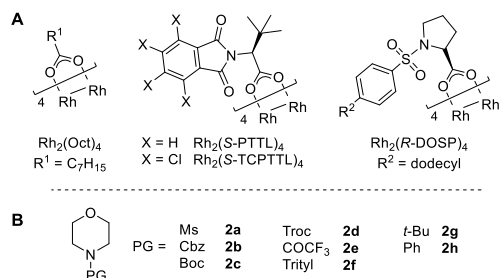
Decompositions of diazo compounds in presence of oxygen, nitrogen, sulfur or phosphorus Lewis bases is a recognized strategy to generate the corresponding ylides efficiently.<sup>1</sup> In the case of oxonium ylides, diazo reagents decomposed by photochemical or metal-catalyzed conditions<sup>2</sup> are known to react with cyclic ethers such as epoxides,<sup>3</sup> oxetanes,<sup>4</sup> THF,<sup>5</sup> THP,<sup>6</sup> 1,3- and 1,4-dioxanes,<sup>7</sup> or oxepane,<sup>8</sup> 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,<sup>9</sup> 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).<sup>9e</sup> 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  $\alpha$ -diazo- $\beta$ -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  $\alpha$ -diazo- $\beta$ -ketoesters **1** to generate in one-pot 16- to 20-membered unsaturated heterocycles in [3+X+3+X] macrocyclizations (X=5 to 7).<sup>7b, 8, 10</sup> Morpholine substrates, despite the importance of polyazamacrocycles in fundamental and applied chemistry,<sup>11</sup> were not studied to avoid the predicted competition between oxygen and nitrogen ylide reactivity. However,

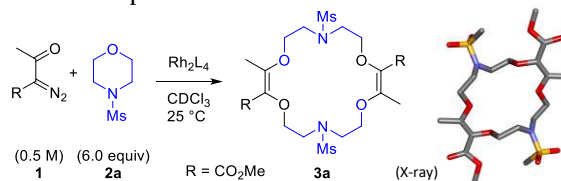
with recent studies revealing key mechanistic aspects of these macrocyclizations and more active catalysts (Figure 2A),<sup>12</sup> it was decided to tackle the challenge. Care was taken nevertheless to use morpholines **2a-2h** protected on the N-atom with electron-withdrawing or sterically-demanding 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  $\alpha$ -diazo- $\beta$ -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<sub>3</sub> as solvent) and Rh<sub>2</sub>(Oct)<sub>4</sub> as catalyst (1.0 mol %).<sup>6, 12, 13</sup> 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<sub>2</sub>(S-PPTL)<sub>4</sub> and Rh<sub>2</sub>(S-TCPPTL)<sub>4</sub>, 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<sub>2</sub>(S-PPTL)<sub>4</sub> remaining the most active complex (63% yield of **3a**).<sup>14</sup> 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<sub>2</sub>(S-PPTL)<sub>4</sub> and Rh<sub>2</sub>(S-TCPPTL)<sub>4</sub> respectively (entries 7-8). At this lower concentration (0.1 mol %), Davies' Rh<sub>2</sub>(R-DOSP)<sub>4</sub> 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  $\alpha$ -diazo- $\beta$ -ketoester **1**.

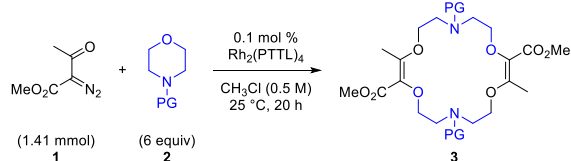
Table 1 Optimization of the reaction conditions.



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

[a] <sup>1</sup>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, <sup>1</sup>H and <sup>13</sup>C NMR characterization of products **3b** to **3e** required the use of higher temperatures (70-120 °C in DMSO-*d*<sub>6</sub>); broad or split signals being observed at room temperature due to the relatively slow rotation (NMR time scale) of the amide and carbamate groups.<sup>15</sup> 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**),<sup>16</sup> 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).

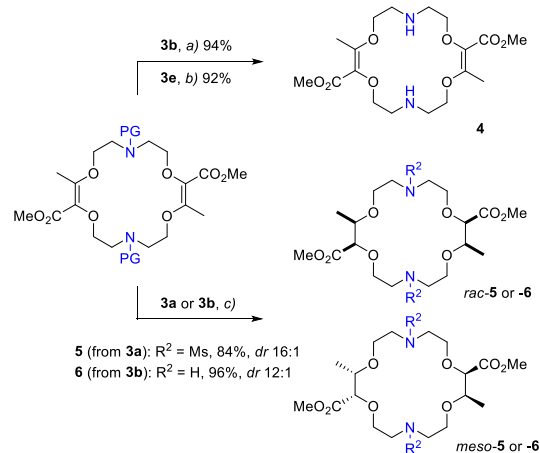
entry	morpholine	macrocycle	yield (%)
1	<b>2a</b> ( <i>N</i> -Ms)	<b>3a</b>	61
2	<b>2b</b> ( <i>N</i> -Cbz)	<b>3b</b>	72
3	<b>2c</b> ( <i>N</i> -Boc)	<b>3c</b>	70 (69) <sup>[a]</sup>
4	<b>2d</b> ( <i>N</i> -Troc)	<b>3d</b>	74
5	<b>2e</b> ( <i>N</i> -COCF <sub>3</sub> )	<b>3e</b>	55 (49) <sup>[a]</sup>
6	<b>2f</b> ( <i>N</i> -Trityl)	<b>3f</b>	46
7	<b>2g</b> ( <i>N</i> - <i>t</i> -Bu)	<b>3g</b>	– <sup>[b]</sup>
8	<b>2h</b> ( <i>N</i> -Ph)	<b>3h</b>	– <sup>[b]</sup>

[a] 7 mmol scale (1.0 g of  $\alpha$ -diazo- $\beta$ -ketoester). [b] Formation of macrocycles **3** not observed.

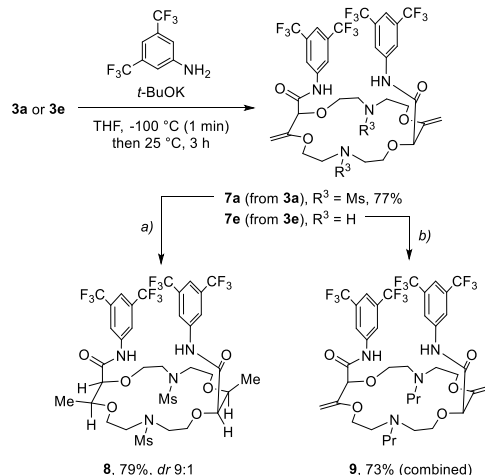
With diaza macrocyclic structures **3a–3f** in hand, removal of the nitrogen protecting groups was pursued. In view of the sensitivity of the unsaturated macrocycles to acidic conditions, care was taken to select primarily **3a**, **3b** and **3e** as substrates (Figure 3). Trifluoroacetamide deprotection of **3e** was achieved by addition of an excess of NaBH<sub>4</sub> 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)<sub>2</sub>/C (50% w/w), saturated derivatives **5** and **6** can be isolated in good yields and diastereoselectivity (>12:1).<sup>17</sup> The relative configurations of the generated stereocenters are unknown but the presence of local symmetry in the <sup>1</sup>H NMR spectra and the probable syn additions of H<sub>2</sub> 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.<sup>18</sup> 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,<sup>8, 19</sup> 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)<sup>19a</sup> to afford saturated derivative **8** in 79% yield as a 9:1 mixture of diastereoisomers.<sup>20</sup> 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)<sub>3</sub> to afford **9** in a combined 73% yield for two successive steps (Figure 4).<sup>21</sup>



**Figure 3.** Reactivity of diaza macrocycles **3a**, **3b** or **3e**: a) H<sub>2</sub> (1 atm.), Pd/C (10% w/w), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), 25 °C, 2 h; b) NaBH<sub>4</sub> (5 equiv), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), 25 °C, 1 h; c) H<sub>2</sub> (1 atm.), Pd(OH)<sub>2</sub>/C (50% w/w), MeOH, 25 °C, 4 h.

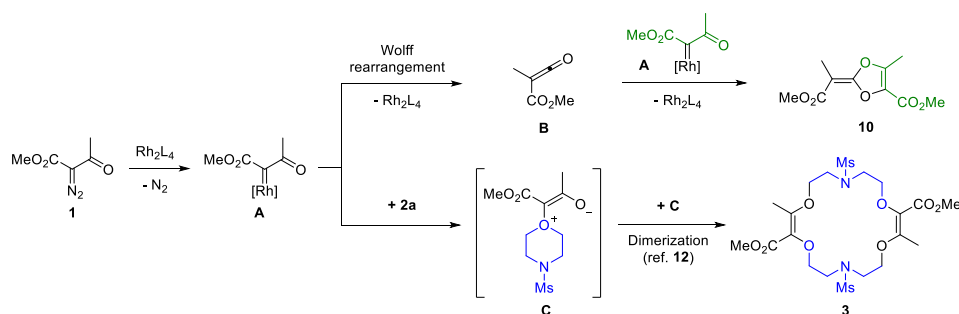


**Figure 4.** Derivatization of **3a** and **3e**. a) H<sub>2</sub> (1 atm.), Pd/C (10% w/w), THF, 25 °C, 2 h; b) propanal (8 equiv), NaBH(OAc)<sub>3</sub> (10 equiv), 1,2-dichloroethane, 25 °C, 2 h.

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<sub>10</sub>H<sub>12</sub>O<sub>6</sub> composition determined by HRMS, **10** was clearly the result of an unidentified decomposition pathway of diazo **1**.<sup>22</sup> Importantly, it was possible to observe by-product **10** upon the addition of diazo **1** to a solution of Rh<sub>2</sub>(Oct)<sub>4</sub> (1 mol %) in CH<sub>2</sub>Cl<sub>2</sub> 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

$^1\text{H}$  and  $^{13}\text{C}$  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  $\alpha,\beta$ -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).<sup>23</sup> Considering that both steps **A**→**B** and **B**→**10** involve metal carbenes **A**, and that the second one is rate-determining, then

**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  $\alpha$ -diazo- $\beta$ -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,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and  $^{19}\text{F}$  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](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto: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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the rate law for the formation of **10** is 2<sup>nd</sup> 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**.<sup>12</sup> 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.

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### Author Contributions

||These authors contributed equally.

### 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 2<sup>nd</sup>-order dimerization of intermediates **C**; see Scheme 1 and references 6, 7b and 12.
- (14) With the benzyl  $\alpha$ -diazo- $\beta$ -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).
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- (20) In analogy to previously reported derivatives (see reference 19a), an all-*cis* configuration is assumed for the major diastereoisomer.
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- (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<sub>2</sub>L<sub>4</sub>.
- (23) The pathway from **B** plus **A** to **10** probably involves a ketene-ylide intermediate.

