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# Catalytic Intramolecular Addition of Metal Carbenes to Remote Furans

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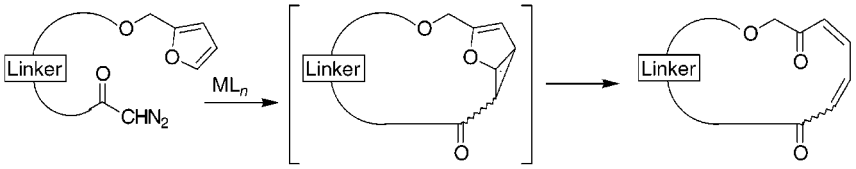
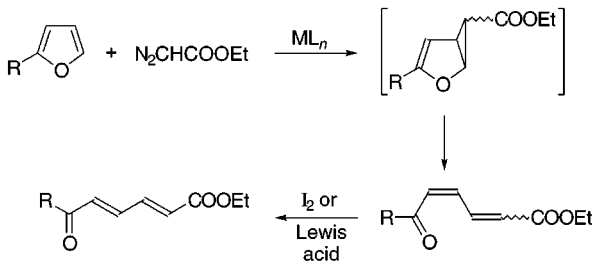
## ABSTRACT




**Diazo esters and diazo ketones linked to a furan undergo catalytic intramolecular addition of an intermediate metal carbene to the remote furan to form diendiones with ring sizes up to 17. Regioselectivity is catalyst dependent with addition to either the more or less substituted double bond. The high product yields and absence of need for high dilution suggest that this methodology is general for macrocycle preparations.**

Transition metal catalyzed addition of carbene intermediates to furans via diazocarbonyl compounds is now well established.[1] In intermolecular reactions with diazo esters, addition occurs onto the less substituted double bond to produce a labile, but generally detectable, cyclopropane intermediate which rearranges to ring-opened products in which a diene is located between two carbonyl groups (Scheme 1).[2] An alternative mechanism involving electrophilic aromatic addition to the furan to form a zwitterionic intermediate is also possible, and probably operative, with select diazocarbonyl compounds;[1] the outcome is the same, but the framework for stereocontrolled ring opening is absent. In any case, the net result is a four-carbon homologation of a carbene intermediate to a highly functionalized product.

**Scheme 1**




Similar addition occurs with diazo ketones,[3] but in these cases the intermediate addition product has not been detected. There have been a few examples of intramolecular addition[4] but here also, ring opening of the presumed initially formed addition product directs the formation of the observed product. Dirhodium(II) acetate has been the catalyst of choice for these reactions.

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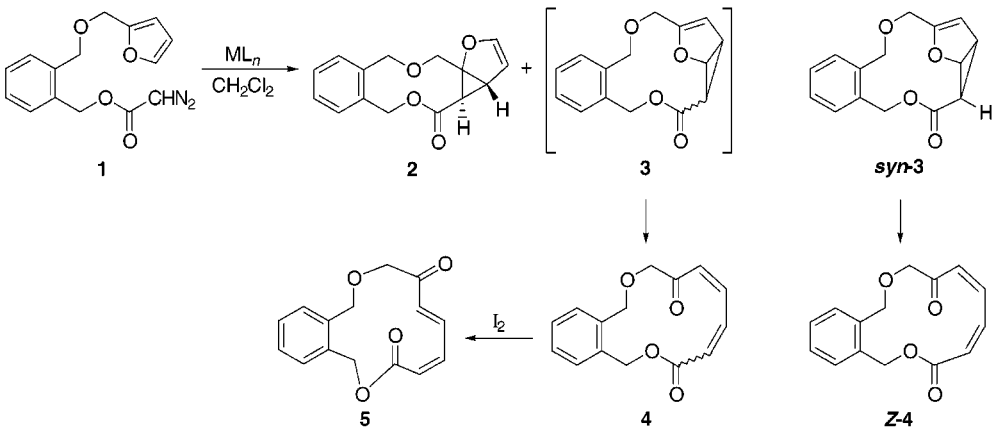
**Scheme 2**




We have previously reported investigations of intramolecular addition reactions of diazocarbonyl compounds to alkenes,[5,6] alkynes,[7] and benzene derivatives[8] that have resulted in the formation of macrocyclic esters and ketones. We now report results from addition to tethered furans that document their facility as well as their catalyst-dependent regio- and stereocontrol and that suggest this process as an exceptional methodology for macrocyclization.

We have used the benzenedimethanol tether to link the diazocarbonyl carbene source to the reacting functional group,[5−8] and we did so this time. The synthesis of these compounds involved leaving group displacement on the monoprotected benzenedimethyl mesylate by the sodium salt of furfuryl alcohol and subsequent preparation of the diazocarbonyl compound, withthese steps occuring in moderate to high yield. Diazo decomposition of **1** with $Rh_2(OAc)_4$ produced three products (**2** and *Z*-**4**/*E*-**4**, Table 1), two of which were formally derived from the *syn* and *anti* isomers of **3** (Scheme 2). Each product was isolated as a chromatographically pure material and fully characterized.

**Table 1.** Products from Catalytic Diazo Decomposition of **1**[a]

| | | rel yield, % | | |
|---|---|---|---|---|
| catalyst | isolated yield, %[b] | **2** | **4** | **4** (*Z*/*E*)[c] |
| $Rh_2(OAc)_4$ | 62 | 19 | 81 | 86/14 |
| $Rh_2(cap)_4$ | 40 | 0 | 100 | 70/30 |
| $Rh_2(pfb)_4$ | 67 | 48 | 52 | 72/28 |
| $Cu(MeCN)_4PF_6$ | 73 | 45 | 55 | 87/13 |

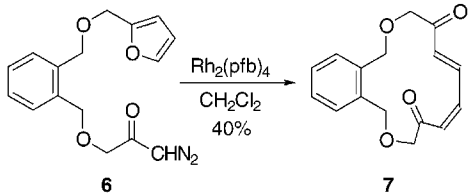
[a] Reactions performed in refluxing dichloromethane; diazo ester was added to catalyst (1.0 mol %) solution via a syringe pump. [b] Yield of purified product after chromatographic purification. [c] Refers to the olefin geometry at the α,β-position.

The influence of catalyst on regioselectivity and diastereoselectivity was determined, and as can be seen from the data in Table 1, changing the ligand on $Rh_2(OAc)_4$ to caprolactamate (cap)[9] allowed exclusively the production of **4**.

Use of $Cu(MeCN)_4PF_6$[8] gave virtually the same results as $Rh_2(pfb)_4$ (pfb = perfluorobutyrate).[10] In one case the reaction mixture was worked up immediately after addition, and *syn*-**3** was detected in the reaction mixture; as expected in a symmetry-controlled process, *syn*-**3** formed *Z*-**4** exclusively. Treatment of the mixture of *Z*-**4** and *E*-**4** with 1 mol % of $I_2$ caused the immediate conversion of *Z*-**4** to **5** and a much slower isomerization of *E*-**4**, first to *Z*-**4**, and then to **5** quantitatively. Addition product **2** was stable to ring opening even in the presence of a stoichiometric amount of $I_2$ at room temperature (16 h). Computational analysis[11] showed *E*-**4** to be less stable than *Z*-**4** and that **5** was more stable than either isomer of **4**.

Dienes *Z*-**4** and *E*-**4** are consistent with the formation of *syn*-**3** and *anti*-**3**, respectively, with *syn*-**3** favored over *anti*-**3** by at least 70:30 (Table 1). However, the exclusive formation of **7** suggests that only *syn* addition occurs with **6**.

In a like manner, diazo ketone **6** was treated with $Rh_2(pfb)_4$ at room temperature, and following chromatographic purification, only **7** (eq 1) was formed (40% yield).




(1)

The presumed cyclopropane precursor was not observed, nor was the product, like **2**, from addition to the 2,3-position of the furan ring. Their absence is consistent with results from intermolecular reactions with diazo ketones.[3] Although these results were not optimized, they demonstrate, as did comparable aromatic cycloaddition reactions,[8] inherent selectivity differences between diazoacetates and diazo ketones.

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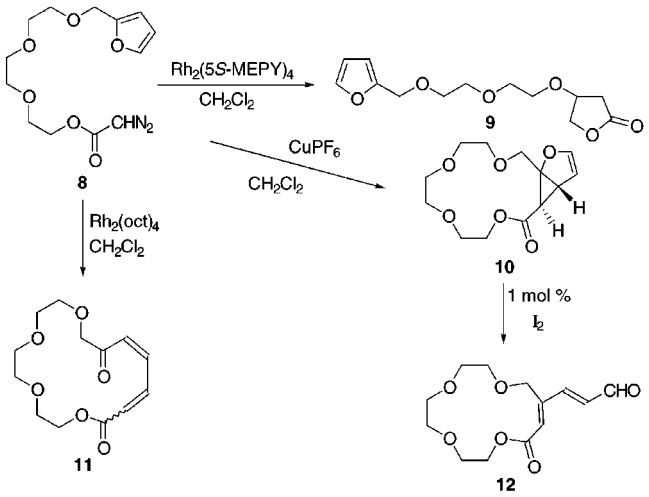
The extent to which this macrocyclization process can be used for the preparation of large-ring esters can be seen in results from diazo decomposition of the diazoacetate **8** derived from triethylene glycol (Scheme 3).

**Scheme 3**



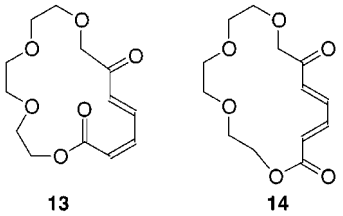

Catalysis by $Rh_2(cap)_4$ gave only the product from C-H insertion (**9**) whereas use of $Cu(MeCN)_4PF_6$ gave mainly **10** and dirhodium(II) octanoate, $Rh_2(oct)_4$, and $Rh_2(OAc)_4$ gave mainly ring-opened products **11** (Table 2).

**Table 2.** Products from Catalytic Diazo Decomposition of **8**[a]

| | | rel yield, % | | | |
|---|---|---|---|---|---|
| catalyst | isolated yield,%[b] | **9** | **10** | **11** | **11** (*Z*/*E*) |
| $Rh_2(cap)_4$ | | 100 | 0 | 0 | |
| $Rh_2(oct)_4$ | 58 | 0 | 16 | 84 | 36/64[b] |
| $Rh_2(OAc)_4$ | 50 | 0 | 20 | 80 | 18/82[b] |
| $Rh_2(pfb)_4$ | 33 | 0 | 32 | 68 | 18/82 |
| $Cu(CH_3CN)_4PF_6$ | 65 | 0 | 82[c] | 18 | 17/83 |

[a] Reactions performed in refluxing dichloromethane; diazo ester was added to catalyst (1.0 mol %) solution via syringe pump. [b] Product *E*-**11** was isolated in 30% yield. [c] Product **10** was isolated in 55% yield.

The product from *anti* addition, *E*-**11**, was favored over the product from *syn* addition, *Z*-**11**, in this case. Furthermore, **10** was converted to **12** by treatment with 1 mol % of $I_2$ in chloroform (4 h), and **11** was isomerized to **13** quantitatively, but in this case conversion of *E*-**11** to **13** occurred through the *trans*,*trans*-isomer **14** rather than via *Z*-**11**.




That $Rh_2(cap)_4$ promoted exclusive formation of **9** is consistent with its overall reduced electrophilic character of dirhodium(II) carboxamidates compared to carboxylates.[12] However, the disparity in product formation between dirhodium(II) and copper(I) was unexpected, especially in view of results from diazo decomposition of **1** (Table 1). Preliminary results with the next higher glycol homologue of **8**—the one that would form the 21-membered homologue of **11** and the 17-membered homologue of **12**—show similar selectivity with dirhodium(II) and copper(I) catalysts, suggesting a generality that may be related to copper(I) coordination with the ether framework.

In summary, catalytic metal carbene addition to remote furans appears to be a general and highly versatile methodology for the synthesis of macrocyclic lactones and ketones. These reactions occur in high yield without the need for high dilution methods. Further extensions and applications are under active investigation.

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**Supporting Information Available:** Experimental and spectral data that include the synthesis and reactions of diazo compounds and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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