

# Synthesis of Cyclic Ethers from Copper Carbenoids by Formation and Rearrangement of Oxonium Ylides<sup>1</sup>

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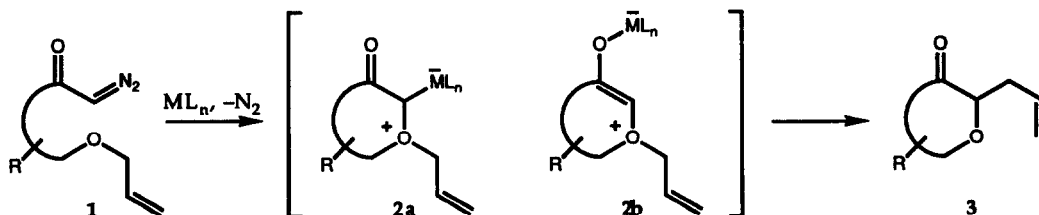
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**Abstract:** Copper carbenoids undergo efficient intramolecular insertion into allyl ethers, and the resulting ylide-type species rearrange to furnish cyclic ethers (ring sizes 6–8) in high yield. Copper(II) hexafluoroacetylacetonate is an extremely efficient catalyst for this reaction, and use of this complex minimises competing C–H insertion.

Cyclic ethers are found as sub-units in many biologically important and structurally complex natural products. Consequently, the development of new, efficient, and general methods for the synthesis of these compounds continues to be an important objective.<sup>2</sup>

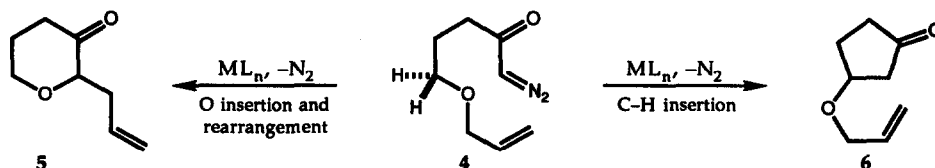
We recently reported that 2,5-dialkyl tetrahydrofuran-3-ones can be prepared in good yield and with high levels of diastereocontrol,<sup>3</sup> by intramolecular insertion of allyl ethers into copper carbenoids, generated from  $\alpha$ -diazo carbonyl compounds such as 1, and rearrangement of the resulting oxonium ylide-type species (Scheme 1).<sup>4,5</sup> Our results suggested that rearrangement takes place directly from a metal-bound ylide equivalent, in which the metal is attached to carbon (2a) or oxygen (2b), rather than by [2,3]-sigmatropic rearrangement of a free oxonium ylide.



Scheme 1

We have recently investigated the insertion and ylide rearrangement reaction as a general method for the synthesis of cyclic ethers with ring sizes 6–8, and we present the results of this work herein.

Initial studies were directed towards the synthesis of the tetrahydropyran-3-one **5** by oxygen insertion of metal carbenoids derived from the precursor  $\alpha$ -diazo ketone **4**, and rearrangement of the resulting ylide-type species (Scheme 2). The  $\text{Rh}_2(\text{OAc})_4$ -catalysed cyclisation of **4** has been investigated by Pirrung and Johnson previously,<sup>6,7</sup> and Pirrung reported that the reaction afforded only a low yield of **5** along with a significant amount of the C–H insertion product **6**. We were concerned that competing C–H insertions of metal carbenoids might be a general problem during the formation of cyclic ethers with ring sizes greater than five, because of the propensity of C–H bonds proximate to ether oxygens to insert into rhodium-carbenoids.<sup>8</sup>



Scheme 2

As expected,  $\text{Rh}_2(\text{OAc})_4$ -catalysed cyclisation reactions of **4** (entries 1–4, Table) afforded modest yields of the tetrahydropyran-3-one **5** along with significant amounts of the C–H insertion product **6**.<sup>9</sup> The relative amounts of **5** and **6** produced were found to be solvent and temperature dependent. When the reaction was performed in  $\text{CH}_2\text{Cl}_2$  at room temperature (entry 1), we obtained yields of **5** and **6** that were consistent with those of Pirrung.<sup>7</sup> However, by using THF as the solvent and increasing the reaction temperature, we were able to obtain a reasonable yield of pyran-3-one **5** at the expense of the C–H insertion product **6** (entry 4).

Entry	Catalyst <sup>a</sup>	Solvent	Temperature	Yield <b>5</b> , % <sup>b</sup>	Yield <b>6</b> , % <sup>b</sup>
1	$\text{Rh}_2(\text{OAc})_4$	$\text{CH}_2\text{Cl}_2$	RT	37	22
2	$\text{Rh}_2(\text{OAc})_4$	$\text{CH}_2\text{Cl}_2$	Reflux	41	18
3	$\text{Rh}_2(\text{OAc})_4$	$\text{C}_6\text{H}_6$	RT	15	18
4	$\text{Rh}_2(\text{OAc})_4$	THF	Reflux	58	12
5	$\text{Cu}(\text{acac})_2$	THF	Reflux	60	12
6	$\text{Cu}(\text{acac})_2$	$\text{CH}_2\text{Cl}_2$	Reflux	61	12
7	$\text{Cu}(\text{tfacac})_2$	$\text{CH}_2\text{Cl}_2$	Reflux	78	0
8	$\text{Cu}(\text{hfacac})_2$	$\text{CH}_2\text{Cl}_2$	Reflux	83	0

<sup>a</sup> Reactions were performed on a 1 mmol scale in the presence of 2 mol% of catalyst.  $\text{Cu}(\text{tfacac})_2$  = copper(II) trifluoroacetylacetonate,  $\text{Cu}(\text{hfacac})_2$  = copper(II) hexafluoroacetylacetonate.

<sup>b</sup> Isolated yield of product.

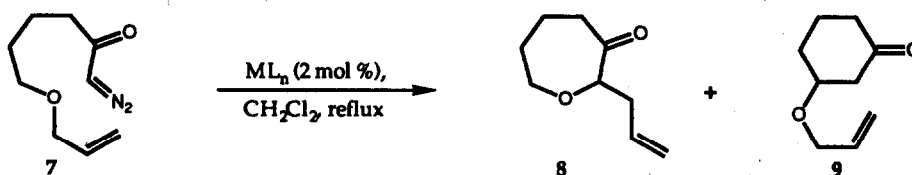
Table

Because of the apparent limitations of  $\text{Rh}_2(\text{OAc})_4$  as a catalyst for the reaction, we turned our attention to the use of copper catalysts. When  $\text{Cu}(\text{acac})_2$  was employed as the catalyst, only a marginal improvement in the yield of pyran-3-one **5** was observed, and a significant amount of C–H insertion product **6** was produced (entries 5 and 6, Table). In an attempt to suppress C–H insertion, we investigated the effect of altering the electron demand of the catalyst ligand.

Copper(II) trifluoroacetylacetonate [Cu(tfacac)<sub>2</sub>] and copper(II) hexafluoroacetylacetonate [Cu(hfacac)<sub>2</sub>] were selected as catalysts so that the electron demand of the ligand could be increased without changing the type of ligand,<sup>10,11</sup> and hence the results could be compared with those from the Cu(acac)<sub>2</sub>-catalysed reaction.<sup>12</sup> Both Cu(tfacac)<sub>2</sub> and Cu(hfacac)<sub>2</sub> proved to be extremely efficient catalysts for the reaction, and high yields of **5** were obtained without the formation of cyclopentanone **6** (entries 7 and 8). Good yields were obtained when CH<sub>2</sub>Cl<sub>2</sub> was used as the solvent, and performing the reaction in other solvents gave less satisfactory results.

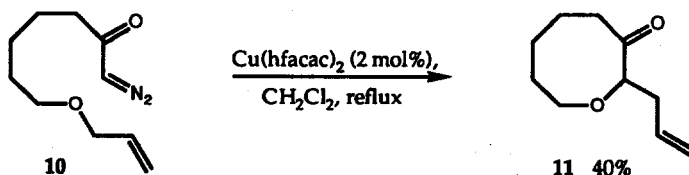
The successful cyclisation of **4** to the tetrahydropyran-3-one **5** encouraged us to apply the reaction to the synthesis of larger oxacycles. Medium-ring ethers were particularly attractive targets due to the common occurrence of these systems in marine natural products, and the paucity of general and high yielding methods for their synthesis.<sup>13</sup>

The Rh<sub>2</sub>(OAc)<sub>4</sub>-catalysed cyclisation of allyl ether **7** was investigated first (CH<sub>2</sub>Cl<sub>2</sub> at reflux), but this reaction failed to give any of the desired oxepan-3-one **8** (Scheme 3).<sup>14</sup> When Cu(acac)<sub>2</sub> was used as the catalyst under optimum conditions (CH<sub>2</sub>Cl<sub>2</sub> at reflux), **8** was obtained in only 18% yield along with a large amount of the C–H insertion product **9** (61% yield). The yield of oxepan-3-one **8** was increased to 38% by using Cu(tfacac)<sub>2</sub> as the catalyst in CH<sub>2</sub>Cl<sub>2</sub> at reflux, but cyclohexanone **9** (isolated in 41% yield) was still the predominant product. Satisfactory results were achieved when Cu(hfacac)<sub>2</sub> was used as the catalyst and the reaction was performed in CH<sub>2</sub>Cl<sub>2</sub> at reflux. Under these conditions, **7** cyclised to oxepan-3-one **8** in 76% yield and the yield of **9** was reduced to 3%.



Scheme 3

Finally, the synthesis of oxocan-3-one **11** from the  $\alpha$ -diazo ketone **10** was examined (Scheme 4).<sup>14</sup> Cyclisation of **10** in the presence of Rh<sub>2</sub>(OAc)<sub>4</sub>, Cu(acac)<sub>2</sub>, or Cu(tfacac)<sub>2</sub>, did not afford the desired oxocan-3-one **11**, but instead gave complex mixtures of unidentified products. However, by using Cu(hfacac)<sub>2</sub> as the catalyst and performing the reaction in CH<sub>2</sub>Cl<sub>2</sub> at reflux, a 40% yield of the required cyclic ether **11** was obtained.



Scheme 4

It is clear from our results that intramolecular tandem oxygen insertion and ylide rearrangement reactions of copper carbenoids are of general use for the synthesis of cyclic ethers, but that the success of the reaction depends on the nature of the copper catalyst and the reaction conditions employed. The direct and efficient synthesis of medium-sized cyclic ethers from acyclic precursors is remarkable and noteworthy.

The role of the catalyst in these reactions is unclear, but increasing the electron demand of the catalyst ligands could promote the reaction in several ways. Although oxygen insertion will be more rapid, due to the increased electrophilicity of the intermediate carbenoid species, we

believe that the high yields of cyclic ethers obtained from the  $\text{Cu}(\text{hfacac})_2$ -catalysed reactions result from stabilisation of the metal-bound ylide intermediates, which suppresses reformation of the original carbenoid species,<sup>15</sup> or reduction in the energy difference between the metal-bound ylide-species and the transition states for rearrangement.

Further work is in progress in order to clarify the role of the catalyst in these reactions, and to apply the method to the synthesis of natural product targets.

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#### References and Notes

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9.  $\text{Rh}_2(\text{OAc})_4$ -catalysed cyclisation reactions of 4 were performed in  $\text{CH}_2\text{Cl}_2$ ,  $\text{C}_6\text{H}_6$ , THF and dioxane at room temperature and reflux. Only a representative selection of the results is shown in the Table.
10.  $\text{Cu}(\text{tfacac})_2$  and  $\text{Cu}(\text{hfacac})_2$  were purchased from Aldrich Chemical Company and used without further purification.
11.  $\text{Cu}(\text{hfacac})_2$  has been used to catalyse the formation of ylides of S, Te, As, Sb, Bi from diazo compounds: Glidewell, C.; Lloyd, D.; Metcalfe, S. *Synthesis*, 1988, 319.
12.  $\text{Cu}(\text{OTf})_2$  was also employed as a catalyst for the reaction, but yields of 5 were generally inferior to those obtained when  $\text{Cu}(\text{acac})_2$  was used.
13. Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc. Perkin Trans I*, 1992, 83 and references therein.
14. All new compounds exhibited satisfactory spectroscopic and either microanalytical, or mass spectrometry data.
15. There is evidence that formation of oxonium ylides by insertion of ethers into rhodium-carbenoids is reversible: Pirrung, M. C.; Brown, W. L.; Rege, S.; Loughton, P. J. *Am. Chem. Soc.*, 1991, 113, 8561.

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