A novel approach to the construction of medium-ring carbocycles utilising the rearrangement of oxonium ylides generated from metal carbenoids

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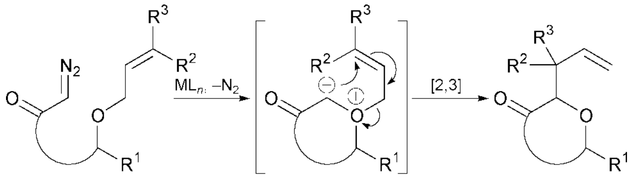
Medium-ring carbocycles have been prepared by intramolecular reactions of metal carbenoids with tethered α-vinyl methyl ethers and subsequent [2,3] rearrangement of the presumed cyclic oxonium ylide intermediates.

Natural products containing medium-ring carbocycles continue to be important targets because of the synthetic challenges that they present and the potent biological activity they frequently possess.[1] As a consequence, the discovery of new reactions which permit the implementation of novel strategies for medium-ring construction continues to be an important endeavour in organic synthesis.[2]

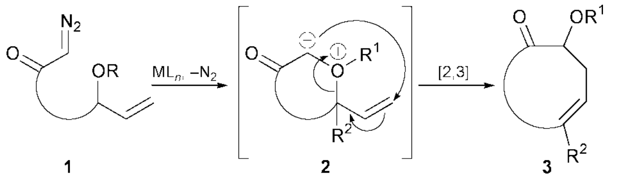
Recently, several research groups, including our own, have shown that cyclic ethers can be prepared by rearrangement of the putative oxonium ylides generated by *intramolecular* reaction of ethers with metal carbenoids derived from diazocarbonyl compounds.[3–11] When allylic ethers are employed as substrates, an apparent [2,3] rearrangement occurs to give the corresponding cyclic ether.[4–6,8,9] In the case of acetals and non-allylic ethers, ylide generation is usually followed by a [1,2] rearrangement,[6,7,8c,10] which is generally efficient when the migrating group is benzylic.[6,7]

The substrates used in our previous studies possess an allylic ether group pendant to the main carbon chain (Scheme 1).[4] In these cases, oxonium ylide formation results in ring closure and subsequent rearrangement delivers the cyclic ether with preservation of ring size.



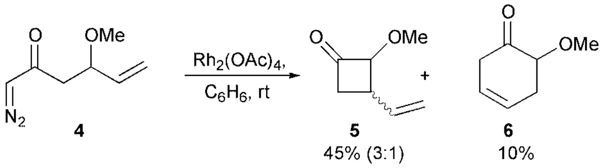
Scheme 1

It occurred to us that it might be possible to broaden the scope of the tandem ylide generation and rearrangement reaction to the preparation of carbocycles, by employing substrates in which the unsaturated group is incorporated into the main chain (Scheme 2). For example, the carbenoid derived from the diazoketone **1** should undergo intramolecular cyclisation to give the cyclic ylide **2** and subsequent [2,3] rearrangement would then deliver the carbocycle **3**. During the rearrangement process, the ring size would be increased by one and the ether substituent would be positioned outside the ring.



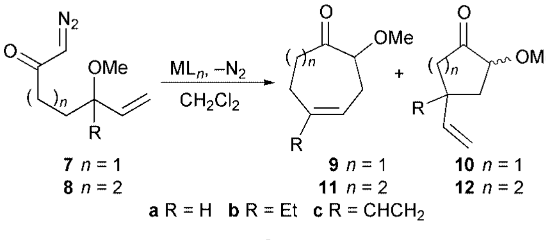
Scheme 2

There are few literature precedents for catalytic oxonium ylide generation and rearrangement using systems of the type shown in Scheme 2. In fact, the only example comes from Johnson's original studies on the generation of oxonium ylides by intramolecular reaction of metal carbenoids with ethers (Scheme 3).[6] In this case however, treatment of the diazoketone **4** with rhodium(II) acetate afforded mainly the cyclobutanone **5**, resulting from [1,2] rearrangement with ring contraction, and only a small amount of the [2,3] rearrangement product **6** was isolated (Scheme 3).[6]



Scheme 3

Although the literature precedent above did not bode well for the development of a general reaction of the type outlined in Scheme 2, we explored the construction of cycloheptenones and cyclooctenones by an analogous ylide formation and rearrangement process (Scheme 4, Table 1). The cyclisation reaction of the diazoketone **7a** was investigated first, and treatment of this precursor with rhodium(II) acetate delivered the required cycloheptenone **9a** in 39% yield. The copper(II) hexafluoroacetylacetonate mediated reaction was also performed with the expectation that it would deliver a higher yield of the required product. However, the yield of cycloheptenone **9a** was



Scheme 4

Table 1 Metal-mediated ylide formation and rearrangement

Precursor	Catalyst ML_n	Temp. (°C)[a]	Product and yield (%)
7a	$Rh_2(OAc)_4$	Rt	**9a** 39[b]
7a	$Cu(hfacac)_2$	Reflux	**9a** 11[b]
7b	$Rh_2(OAc)_4$	Rt	**9b** 49 **10b** 16 (~1:1)
7b	$Cu(hfacac)_2$	Reflux	**9b** 15[b]
7c	$Rh_2(OAc)_4$	Rt	**9c** 63 **10c** 11
7c	$Cu(hfacac)_2$	Reflux	**9c** 46[b]
8b	$Rh_2(OAc)_4$	Rt	**11b** 8 **12b** 22 (~2:1)
8c	$Rh_2(OAc)_4$	Rt	**11c** 26 **12c** 9

[a] Reactions performed in DCM at rt or reflux. [b] Traces of the corresponding [1,2] rearrangement products were formed.

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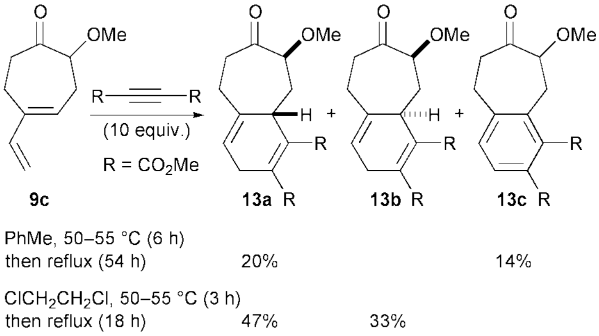
substantially lower than that obtained from the corresponding rhodium carbenoid.† This result was surprising because we have found that copper-catalysed oxonium ylide generation and rearrangement is more efficient than the corresponding rhodium-catalysed process in most cases.[4,7]

It seemed likely that the modest yield of the ketone **9a** was due to the relatively low rate of [2,3] rearrangement as a consequence of vinyl group adopting an equatorial position in the lowest energy conformation of the cyclic oxonium ylide. We reasoned that introduction of another substituent adjacent to the ether should help populate the conformer in which the vinyl group is disposed to participate in the rearrangement reaction. In order to explore this possibility, the substrates **7b** and **7c** were prepared. Higher product yields were obtained from the rhodium- and copper-catalysed cyclisation reactions of the ethyl-substituted diazoketone **7b** (Table 1). The yields were increased further when an additional vinyl substituent was present; treatment of the substrate **7c** with rhodium(II) acetate afforded the expected product **9c** in a yield of 63% and the corresponding copper-catalysed reaction delivered the same product in 46% yield.

The construction of cyclooctenones by oxonium ylide formation and rearrangement was also explored. As expected, treatment of the substrates **8b** and **8c** with rhodium(II) acetate afforded the desired products **11b** and **11c** in much lower yields (8 and 26% respectively) than had been obtained from reactions of the homologues **7b** and **7c** (Table 1). In the case of the diazoketone **8b**, the major product **12b** was that arising from [1,2] rearrangement of the intermediate ylide. The divinyl substrate **8c** underwent cyclisation and [2,3] rearrangement in a higher yield (26%) than the diazoketone **8b**, and a small amount of the corresponding [1,2] rearrangement product **12c** (8%) was also isolated.

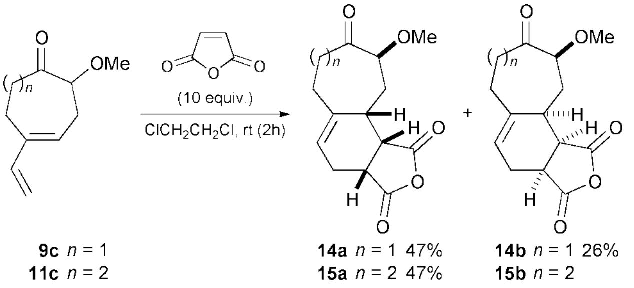
The divinyl susbtrates **7c** and **8c** underwent the most efficient cyclisations in each series and the products from these reactions are synthetically useful because they are amenable to further elaboration as Diels–Alder substrates. The Diels–Alder reactions of the dienes **9c** and **11c** were investigated (Scheme 5). Treatment of the diene **9c** with DMAD in toluene at reflux afforded the 1,4-diene **13a**‡ in 20% yield along with the aromatised product **13c** in 14% yield. When the reaction was performed in 1,2-dichloroethane at reflux, the isomers **13a**‡ and **13b**‡ were obtained in yields of 47 and 33% respectively, without formation of the aromatised product **13c**.



Scheme 5

The Diels–Alder reactions of **9c** and **11c** with the reactive dipolarophile maleic anhydride were also explored (Scheme 6). Cycloaddition of the diene **9c** with maleic anhydride afforded two cycloadducts. The major adduct was the tricyclic compound **14a**‡ produced by *endo* addition of the dipolarophile. The available data suggests that the minor isomer is the product **14b** resulting from *endo* addition of the other face of diene by analogy with the reaction of the same diene with DMAD (Scheme 5). In the case of the diene **11c**, Diels–Alder reaction with maleic anhydride delivered **15a** as a single isolable product in 47% yield.‡

Finally, the oxonium ylide formation and rearrangement reaction and Diels–Alder reaction were performed in a one-pot fashion. Thus, addition of the diazoketone **7c** to a solution of rhodium(II) acetate (1 mol%) and DMAD (10 equiv.) in 1,2-dichloroethane at reflux provided the isomers **13a** and **13b** in a combined and unoptimised yield of 34%.



Scheme 6

In summary, we have shown that it is possible to construct medium-ring carbocycles by rearrangement of oxonium ylides generated by intramolecular reaction of metal carbenoids with allylic ethers (Scheme 2). We have also shown that the diene products resulting from this reaction undergo Diels–Alder addition, and that the two reactions can be coupled to give a one-pot reaction.

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Notes and references

† Carbenoids were also generated using $Rh_2(O_2CCF_3)$, $Rh_2(NHCOCF_3)$, and $Rh_2(O_2CC_3F_7)$, but they generally gave inferior yields of the cycloheptenone **9a**.

‡ The structure and relative stereochemistry were confirmed by X-ray crystallography.

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