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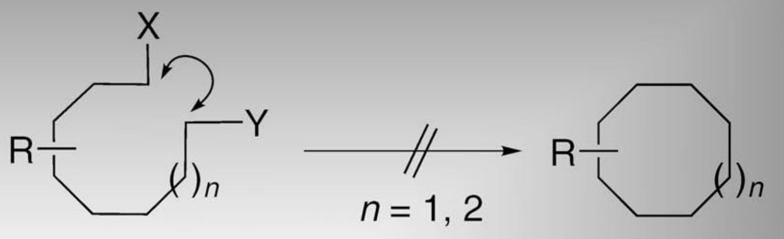

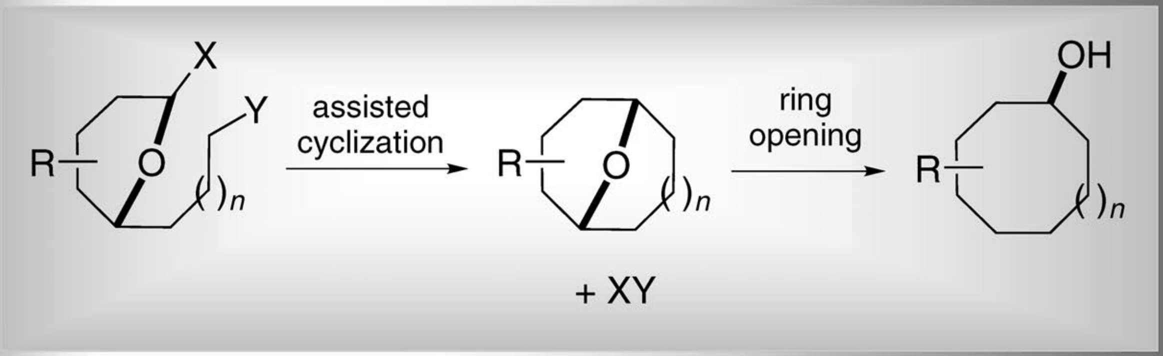

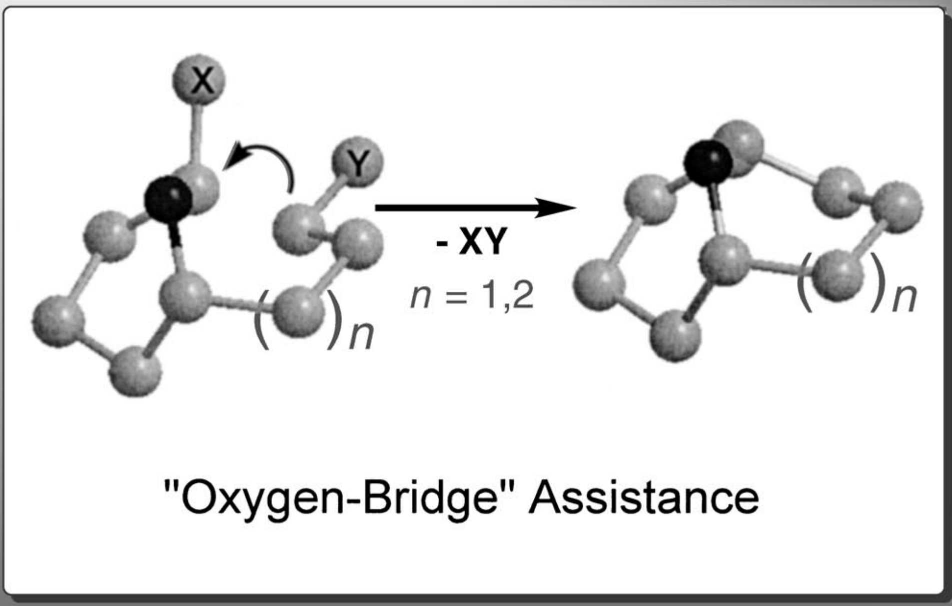

The Oxygen-Bridge Templating Approach to Eight- and Nine-Membered Carbocycles: Recent Developments Based on Catalytic Reactions

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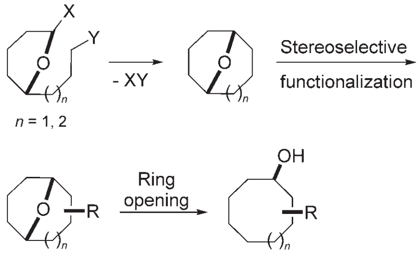
Abstract: Recent developments concerning metal-catalyzed reactions have led to the implementation of new, rapid, and practical routes to eight- and nine-membered carbocycles based on an oxygen-bridge templated cyclization.

Keywords: carbocycles · cyclization · oxygen-bridged carbocycles · synthetic methods

Introduction

The development of practical and stereoselective approaches to medium-sized carbocycles, in particular to eight- and nine-membered rings, continues to be an important synthetic challenge owing to the well-known difficulties associated with their construction by direct cyclization routes.[1,2] Even the powerful ring-closing metathesis technology fails to give rings of these sizes, unless the substrates are conformationally predisposed to undergo the cyclization reaction.[3] An appealing synthetic alternative consists of the temporary creation of an internal oxygen tether in the precursor that could provide for low-energy cyclization pathways through six- or seven-membered transition structures. The oxygen atom of the tether could also facilitate the cyclization by triggering the reactivity of the bridgehead carbon atom (Scheme 1). An additional bonus of the strategy arises from the possibility of stereoselectively manipulating the resulting oxabicyclic products prior to unmasking the carbocycle by cleavage of the oxygen bridge.[4]



Scheme 1. Oxygen-bridge templating approach for the construction of eight- and nine-membered carbocycles.

It is remarkable that although there have been numerous reports on the preparation of a variety of oxygen-bridged medium-sized rings using this templating strategy, the approach has not been specifically considered as a formal alternative to synthesize this type of rings. Recent achievements, which involve the use of metal-catalyzed reactions to assemble the required intermediates, have provided fresh impetus to this templating strategy and led to some of the most practical and rapid approaches to medium-sized carbocycles.

Discussion

The origin of this approach for the construction of eight-membered carbocycles can be traced to the late 1970s when Kagan[5] and Jung[6] reported preliminary and serendipitous findings on the autocondensation of phenylacetaldehyde under acidic conditions to give oxa-bridged dibenzocyclooctenes. One decade later, Harmata described an alternative and more controlled way of making this type of product based on an intramolecular Lewis acid induced Friedel–Crafts reaction (Scheme 2a).[7] In 1999, Mikami and coworkers reported a related process involving the use of a trisubstituted alkene instead of the aryl group as the nucleophilic component in the cyclization. The reaction, which is promoted by solid acids such as montmorillonite K10, proceeds through a (2,5)-oxonium–ene mechanism and provides

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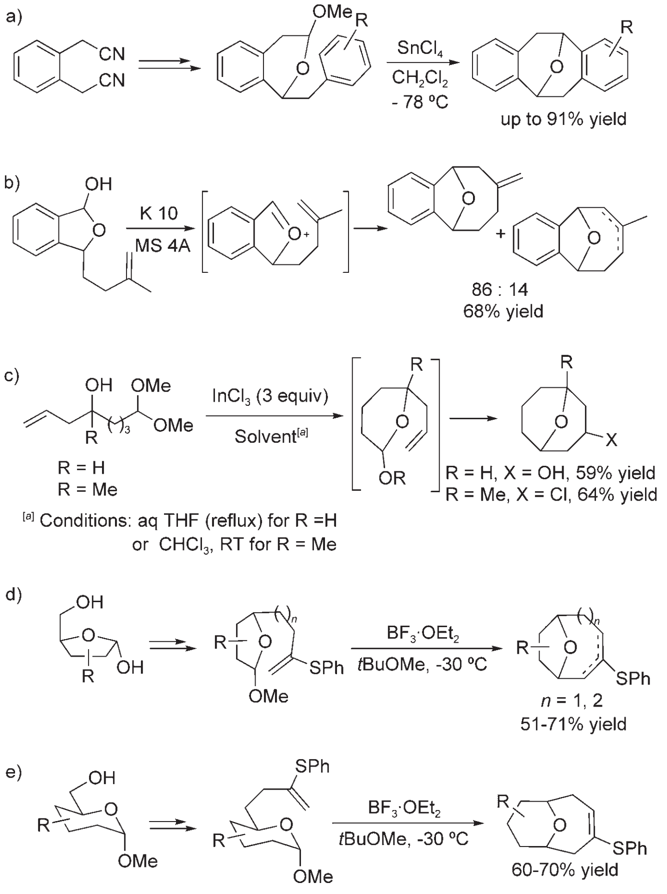
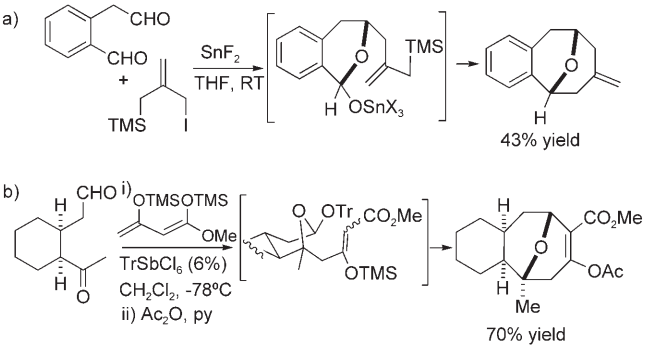


Scheme 2. Some selected approaches to oxa-bridged medium-sized carbocycles involving a Lewis acid induced alkene–acetal cyclization.

mixtures of *exo*- and *endo*-cyclic oxygen-bridged cyclooctenes (Scheme 2b).[8] In 2002, Cho and co-workers reported an alternative procedure to assemble simple 9-oxabicyclo[3.3.1]nonane systems from 5-hydroxyoct-7-enals, based on a Prins-type cyclization induced by $InCl_3$.[9] The process, which requires over-stoichiometric amounts of the Lewis acid reagent, must involve the formation of mixed acetal intermediates, and provides the products in moderate yields (Scheme 2c).

In 2003 Sasmal and Maier reported related cyclizations promoted by $BF_3{\cdot}OEt_2$ (2 equiv), although in these cases the precursors were prepared from pyranosides and furanosides in a multistep sequence. As shown in Scheme 2d and e, the authors used vinyl sulfides as nucleophilic agents for the cyclization reactions.[10]

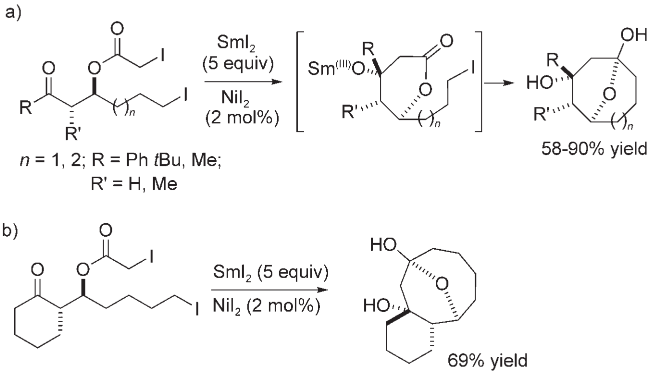
An alternative and more in-depth study on the use of oxygen-bridge templating strategies to make medium-sized carbocycles was carried out by Molander and co-workers.[11] This group established a variety of elegant [*N*+3] annulation routes to different types of products containing seven- and eight-membered carbocycles (Scheme 3).[12] Their initial studies involved the use of trimethylenemethane dianion equivalents generated from 3-iodo-2-[(trimethylsilyl)methyl]propene and stannous fluoride (Scheme 3a). The reaction of these dinucleophilic systems with dialdehydes or ketoaldehydes provided the corresponding bicyclic systems with high diastereoselectivity.[12a] Other three-carbon components employed by this group are bis(trimethylsilyl)enol ethers (Scheme 3b), which behave as synthetic equivalents of β-carbonyl dianions. The differential reactivity of the two nucleophilic centers of the three-carbon unit is translated into high regioselectivity in the annulation processes with 1,4- or 1,5-ketoaldehydes. The mechanism of the process involves the initial formation of a bicyclic oxocarbenium ion intermediate from the 1,4- or 1,5-dicarbonyl substrates, which undergoes a nucleophilic attack by the bis(trimethylsilyl)enol ether to provide a neutral acetal intermediate (depicted in Scheme 3b). Ring closure via a second cyclic oxocarbenium ion generates the final oxacycle.[12b]



Scheme 3. Molander [*N*+3] annulation routes to oxa-bridged medium-sized carbocycles ($TrSbCl_6$ = trityl hexachloroantimonate).

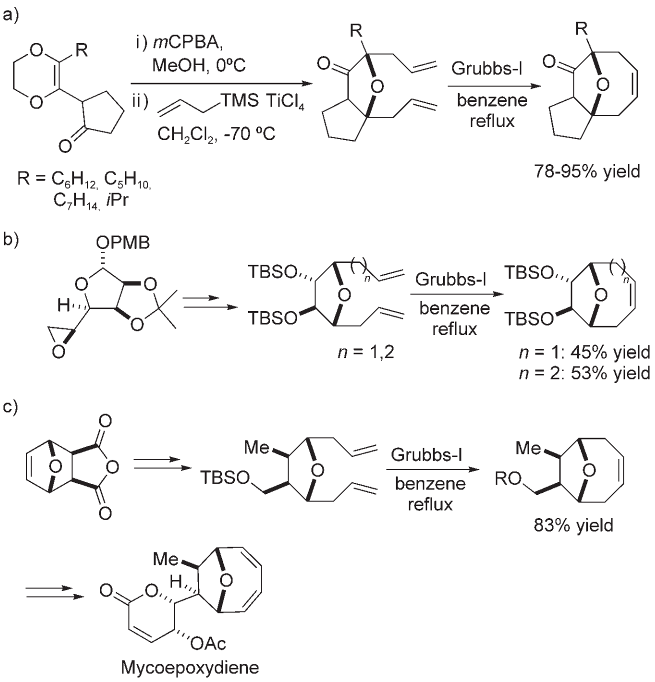
More recently, the authors described another approach to make cyclooctanoids and cyclononanoids, also based on an oxa-bridging concept.[13] The overall process consists of a SmI_2-induced domino reaction involving a Reformatsky reaction and a subsequent nucleophilic acyl substitution (Scheme 4a and b). The products are obtained with excellent yields under mild conditions and, in most cases, as single diastereoisomers.

As mentioned in the introduction, the assembly of medium-sized carbocycles by ring-closing metathesis (RCM) requires the precursors to be somewhat pre-organized so



Scheme 4. Approach of Molander to make oxa-bridged cyclooctanoids and cyclononanoids based on the use of SmI_2.

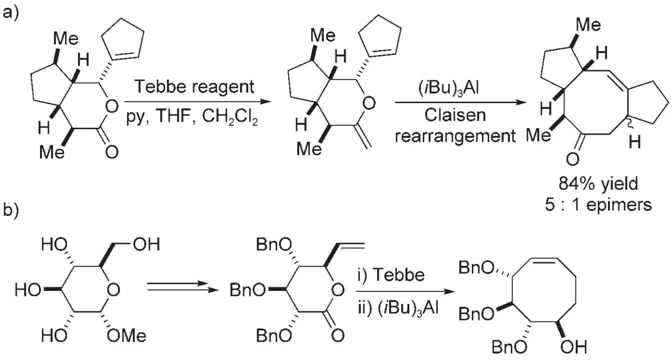
that the entropic cost of the process is not too high. The groups of Hanna,[14] Armas and García Tellado,[15] and Tadano[16] independently demonstrated that it is possible to make oxa-bridged eight-membered carbocyclic systems by RCM of dienyl precursors containing a suitable 1,5-oxygen bridge (Scheme 5). Using this strategy Tadano and co-workers prepared the core of Mycoepoxydiene, a fungal metabolite isolated from the fermentation of a fungus in 1999 (Scheme 5c). The synthesis of the required 2,5-diallyl tetrahydrofuran precursor involved nine steps from the Diels–Alder adduct of furan and maleic anhydride. The oxygen bridge assists the metathesis reaction by conformationally orienting the *syn*-2,5-diallyl systems. Undoubtedly, the requirement of a *cis*-configuration for the dienyl tethers in the precursors represents a significant drawback of the approach, since the assembly of precursors with such stereochemistry may not be straightforward.



Scheme 5. Ring-closing metathesis approaches for the construction of oxygen-bridged eight-membered skeletons.

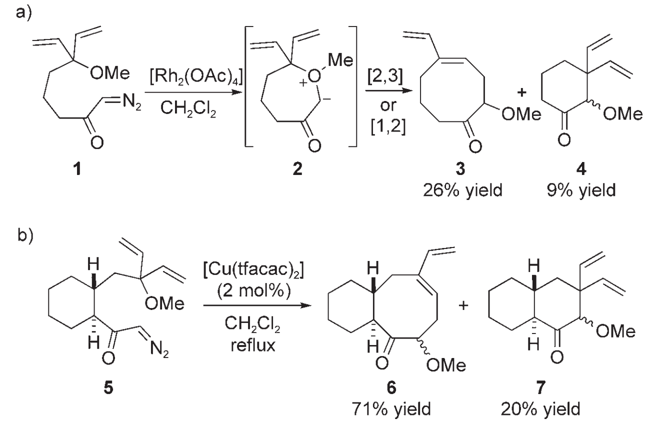
Another interesting approach to highly substituted cyclooctanes, which involves oxygen-bridged transition structures, has been pioneered by Paquette et al. and is based on a Claisen rearrangement of 2-methylen-6-vinyl tetrahydropyrans (Scheme 6a).[17] The process was elegantly extended in recent years to cyclooctanoid carbasugars by other authors such as Sinaÿ[18] and Thiem.[19] The required substrates can be readily assembled from appropriately protected carbohydrate precursors as exemplified in Scheme 6b.[18a]

Overall, the above results demonstrate the potential of the oxygen-bridging strategy to prepare eight- and nine-membered carbocycles. However, the requirement of quite elaborate and functionalized precursors and/or the need for stoichiometric amounts of the reagents in key steps represent substantial limitations for these methods in terms of atom efficiency and practicality. Therefore, the use of catalytic reactions to prepare the corresponding precursors and/or to promote the cyclization reaction would be desirable.



Scheme 6. Approaches to eight-membered carbocycles based on Claisen rearrangement of 2-methylen-6-vinyl tetrahydropyrans.

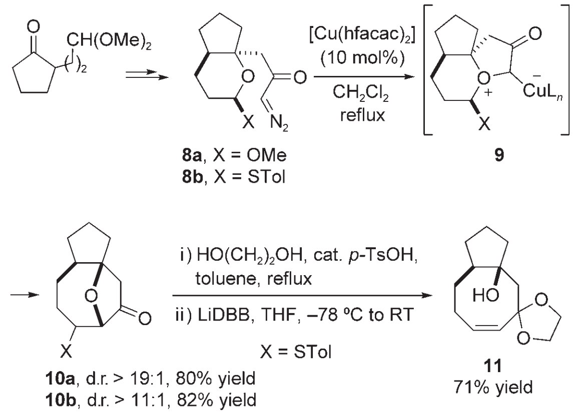
Recent developments based on catalytic reactions: In recent years, several reports on new versions of the strategy, most of which are based on the use of catalytic processes, have been published. For example, the group of Clark demonstrated in 2001 that cyclic oxonium ylides, generated by reaction of acyclic diazoketones with a metal catalyst, can undergo a [2,3]-rearrangement to deliver eight-membered carbocycles.[20] Although the major reaction pathway when diazoketone **1** is treated with rhodium(II) acetate was the desired [2,3]-rearrangement of the intermediate oxonium ylide (**2**) to give the cyclooctane **3**, there is a competing [1,2]-rearrangement to give **4** (Scheme 7a). Overall the efficiency of the process is rather low. However, in a very recent report,[21] the same group disclosed an improvement in the strategy based on the use of diazoketones containing a cyclohexane unit that conformationally assists the intramolec-



Scheme 7. Approaches to oxa-bridged medium-sized carbocycles based on rearrangements of oxonium ylides (tfacac = trifluoroacetylacetonate).

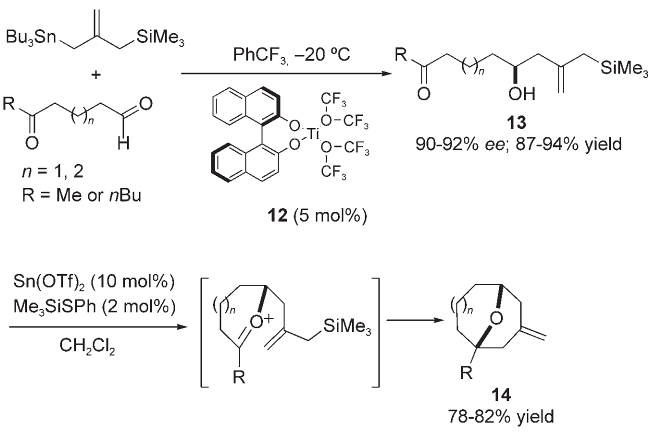
ular rearrangement. An additional factor that increases the efficiency of the process derives from the use of [Cu(tfacac)$_2$] (tfacac = trifluoroacetylacetonate) instead of Rh(OAc)$_2$ to generate the carbenoid species. Thus, the reaction of diazoketone **5** with [Cu(tfacac)$_2$] (2 mol %) afforded the desired 6,8-bicyclic structure (**6**) in good yield, although the formation of the 6,6-bicyclic structure due to the competing Stevens [1,2]-shift could not be completely suppressed (Scheme 7 b).

In the period between these two articles by Clark, West and co-workers reported an alternative method to assemble cyclooctanoid systems which was also based on the catalytic generation of an oxonium ylide that subsequently undergoes a Stevens [1,2]-rearrangement[22] (Scheme 8). These authors showed that treatment of α-diazoketones **8** with catalytic amounts of [Cu(hfacac)$_2$] (hfacac = hexafluoroacetylacetonate) provides the oxabicycles **10** through a [1,2]-shift of the five-membered oxonium ylide intermediate (**9**). The major isomer, which is obtained with high diastereoselectivity, results from a [1,2]-rearrangement with retention of configuration. Importantly, the thioaryl group present in the product serves to direct the rearrangement as well as to trigger the subsequent cleavage of the bridging ether by using electron transfer reductive conditions.



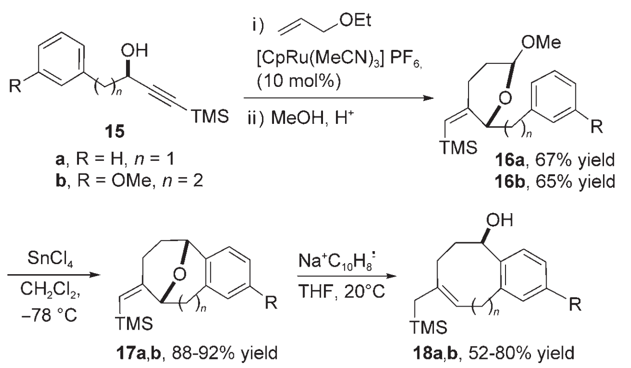
Scheme 8. Heteroatom-assisted [1,2]-shift of oxonium ylides (hfacac = hexafluoroacetylacetonate; LiDBB = lithium di-*tert*-butylbiphenyl).

In 2002 Yu and co-workers described a very efficient method to prepare oxygen-bridged medium-sized carbocycles based on a Lewis acid catalyzed intramolecular allylsilane addition to a carbonium cation generated from a 1,5- or 1,6-hydroxyketone derivative (**13**; Scheme 9).[23] Importantly, these precursors can be assembled in an enantioselective manner by means of a chemo- and enantioselective allylic-transfer reaction catalyzed by the binol–Ti^{IV} complex **12** (binol = 1,1′-binaphthalene-2,2′-diol). Although the authors did not try to elaborate the oxacyclic adducts (**14**), the presence of allylic protons in the carbon adjacent to the fusion positions augurs well for the stereoselective manipulation of the carbocycle as well as for cleavage of the oxygen bridge.



Scheme 9. Approach by Yu and co-workers[23] to oxa-bridged medium-sized carbocycles.

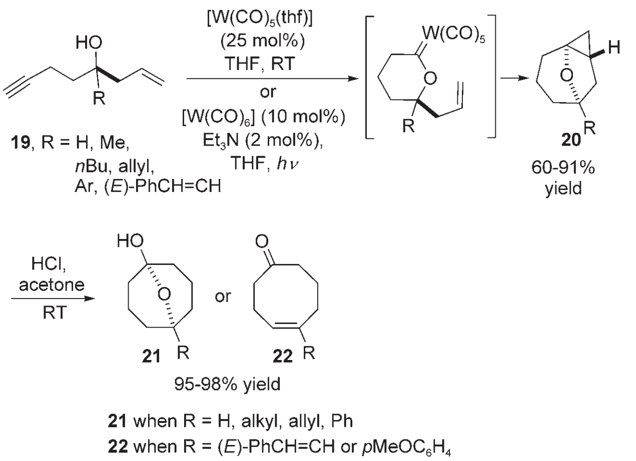
Also in 2002, we reported a practical approach to eight- and nine-membered carbocycles from readily accessible 1-alkyn-3-ols.[24] The assembly of the medium-sized ring relies on an oxygen-templated Prins-like carbocyclization. An important advantage of this method arises from the fact that the required mixed acetal precursors (**16**) can be readily assembled by means of a very practical catalytic transformation; namely, a regio- and chemoselective Ru-catalyzed C–C coupling of 1-trimethylsilyl-1-alkyn-3-ols (**15**) and commercially available allyl ethyl ether (Scheme 10).



Scheme 10. Strategy for the assembly of medium-sized carbocycles by Mascareñas' group.

Importantly, the exocyclic double bond present in the resulting adducts, functionality created in the Ru-catalyzed reaction, allowed for facile reductive opening of the oxygen bridge to unmask the embedded eight- and nine-membered carbocycles. Since the approach involves the use of chiral alkynols, an asymmetric version based on the generation of these precursors by means of a Ru-catalyzed enantioselective hydrogen-transfer reaction has also been developed.[25]

Finally, two recent communications by Barluenga and coworkers have provided new and relevant momentum to the medium-sized carbocycle assembly strategy. Both reports are based on the use of modern metal-catalyzed isomerizations of γ- and δ-alkynols. In the first article,[26] the group discloses a practical and short route to construct cyclooctanoid systems from oct-1-en-7-yn-4-ols by using a tandem tungsten-catalyzed cycloisomerization/cyclopropanation sequence (Scheme 11). Subsequent ring-fragmentation of the resulting bicarbocycles leads to the desired cyclooctanoids.



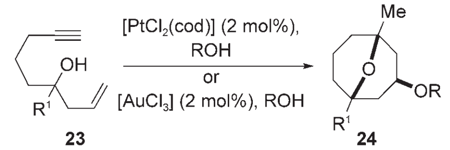
Scheme 11. Tandem cycloisomerization/cyclopropanation route to eight-membered carbocycles.

According to the authors, the transformation can be accomplished either by preforming the catalytic complex $[W(CO)_5(thf)]$ (25 mol %), or by the in situ generation of the active catalyst upon irradiation of a solution of $[W(CO)_6]$ (10 mol %) in THF in the presence of Et_3N (2 mol %). Both methods provided comparable results, although the latter is more convenient for practical reasons. The final transformation of the tricyclic structures **20** into the eight-membered carbocycles was achieved by simple treatment with HCl in acetone at room temperature. The formation of the lactols **21** or the dehydrated cyclooctanoids **22** depends on the nature of the substituent at the bridgehead carbon.

In a new tour de force, the same authors developed a related, but even more straightforward and practical version of the methodology that allows 1,6-oxygen-bridged cyclooctanoids **24** to be obtained from simple enynols.[27] The process involves the coupling, in a tandem sequence, of a metal-catalyzed 6-exo-cycloisomerization of 5-hexynol derivatives (**23**) and a Prins-type cyclization of the resulting cyclic enol ethers. After testing several metals, it was found that gold and platinum complexes were capable of catalyzing the transformation. Thus, treatment of substrates **23a–j** with 2 mol % of $[PtCl_2(cod)]$, $PtCl_4$, or $AuCl_3$ at 65–80 °C in an alcoholic solution (i.e., MeOH, EtOH, *i*PrOH, *n*PrOH) provided the corresponding eight-membered oxygen-bridge carbocycles **24** in excellent yields (88–96 %; Table 1).

Labeling studies by using deuterated solvents or a substrate deuterated at the alkyne terminus led the authors to propose the mechanism outlined in Figure 1. Coordination of the gold or platinum complexes to the triple bond of the starting alkynol is followed by intramolecular addition of the hydroxyl group to the internal carbon of the triple bond. Migration of the hydrogen atom from the oxygen to the metal and subsequent reductive elimination would regenerate the catalytic species, while forming the enol ether required for the following intramolecular Prins-type cyclization.

Table 1. Pt- or Au-catalyzed tandem 6-*exo*-cycloisomerization/Prins-type cyclization (selected examples).



23/24	R^1	R	Catalyst	Yield [%]
a	allyl	Et	$[PtCl_2(cod)]$	92
b	allyl	Pr	$[AuCl_3]$	94
c	Me	Me	$[PtCl_2(cod)]$	94
d	Me	Et	$[AuCl_3]$	96
e	Bu	Me	$[PtCl_2(cod)]$	92
f	*i*Pr	Me	$[PtCl_2(cod)]$	92
g	*i*Pr	Et	$[AuCl_3]$	88
h	*t*Bu	Me	$[PtCl_2(cod)]$	90
i	*t*Bu	Et	$[AuCl_3]$	91
j	H	Me	$PtCl_4$	88

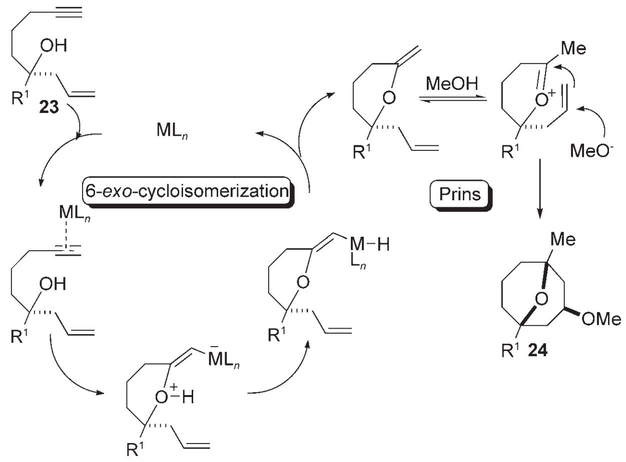


Figure 1. Proposed mechanism for the Pt- or Au-catalyzed tandem formation of oxygen-bridged eight-membered carbocycles.

Conclusion

In summary, the combination of modern transition-metal-catalyzed reactions with oxygen-bridge templated carbocyclization processes has led to the development of several powerful and practical methods to construct eight- and nine-membered carbocycles. The ready availability of the substrates, simplicity of the protocols, and atom-efficiency of the transformations allows these approaches to be ranked among the best to make medium-sized carbocycles in a truly practical and rapid manner.

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[1] a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95; b) L. Mandolini, *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

[2] For reviews on the synthesis of medium-sized rings, see: a) N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757–5821; b) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881–930; c) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007. For a Highlight on metal-catalyzed cycloaddition approaches, see: M. Murakami, *Angew. Chem.* **2003**, *115*, 742–744; *Angew. Chem. Int. Ed.* **2003**, *42*, 718–720.

[3] For a recent minireview on the construction of carbocyclic eight-membered rings by ring closing metathesis, see: A. Michaut, J. Rodriguez, *Angew. Chem.* **2006**, *118*, 5870–5881; *Angew. Chem. Int. Ed.* **2006**, *45*, 5740–5750.

[4] For selected approaches to open the oxygen bridge of oxacyclic compounds, see: a) G. A. Molander, P. R. Eastwood, *J. Org. Chem.* **1995**, *60*, 4559–4565; b) M. Harmata, S. Elahmad, C. L. Barnes, *J. Org. Chem.* **1994**, *59*, 1241–1242; c) H. Ohmura, K. Mikami, *Tetrahedron Lett.* **2001**, *42*, 6859–6863; d) M. E. Jung, S. J. Miller, *J. Am. Chem. Soc.* **1981**, *103*, 1984–1992.

[5] J. Kagan, S.-A. Chen, D. A. , Jr., Agdeppa, W. H. Watson, V. Zabel, *Tetrahedron Lett.* **1977**, *18*, 4469–4470.

[6] M. E. Jung, A. B. Mossman, M. A. Lyster, *J. Org. Chem.* **1978**, *43*, 3698–3701.

[7] a) M. Harmata, T. Murray, *J. Org. Chem.* **1989**, *54*, 3761–3763; b) M. Harmata, C. L. Barnes, *Tetrahedron Lett.* **1990**, *31*, 1825–1828.

[8] a) H. Ohmura, Smyth, G. D.; K. Mikami, *J. Org. Chem.* **1999**, *64*, 6056–6059; b) K. Mikami, H. Ohmura, M. Yamanaka, *J. Org. Chem.* **2003**, *68*, 1081–1088; c) H. Ohmura, K. Mikami, *Tetrahedron Lett.* **2001**, *42*, 6859–6863.

[9] Y. S. Cho, H. Y. Kim, J. H: Cha, A. N. Pae, H. Y. Koh, J. H. Choi, M. H. Chang, *Org. Lett.* **2002**, *4*, 2025–2028.

[10] P. K. Sasmal, M. E. Maier, *J. Org. Chem.* **2003**, *68*, 824–831.

[11] G. A. Molander, *Acc. Chem. Res.* **1998**, *31*, 603–609, and references therein.

[12] a) G. A. Molander, D. C. Schubert, *J. Am. Chem. Soc.* **1987**, *109*, 6877–6878; b) G. A. Molander, K. O. Cameron, *J. Org. Chem.* **1993**, *58*, 5931–5943.

[13] a) G. A. Molander, G. A. Brown, I. Storch de Gracia, *J. Org. Chem.* **2002**, *67*, 3459–3463; b) G. A. Molander, C. Köllner, *J. Org. Chem.* **2000**, *65*, 8333–8339.

[14] I. Hanna, V. Michaut, *Org. Lett.* **2000**, *2*, 1141–1143.

[15] P. de Armas, F. García-Tellado, J. J. Marrero-Tellado, *Eur. J. Org. Chem.* **2001**, 4423–4429.

[16] K. Takao, G. Watanabe, H. Yasui, K. Tadano, *Org. Lett.* **2002**, *4*, 2941–2943.

[17] a) C. M. G. Philippo, N. H. Vo, L. A. Paquette, *J. Am. Chem. Soc.* **1991**, *113*, 2762–2764; b) D. Friedrich, L. A. Paquette, *J. Org. Chem.* **1991**, *56*, 3831–3840; c) L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841–3849.

[18] a) M. Sollogoub, J.-M. Mallet, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 370–372; *Angew. Chem. Int. Ed.* **2000**, *39*, 362–364; b) W. Wang, Y. Zhang, M. Sollogoub, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 2588–2590; *Angew. Chem. Int. Ed.* **2000**, *39*, 2466–2467; c) W. Wang, Y. Zhang, H. Zhou, Y. Blériot, P. Sinaÿ, *Eur. J. Org. Chem.***2001**, 1053–1059; d) P. A. V. van Hooft, G. A. van der Marel, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron Lett.* **2001**, *42*, 1769–1772.

[19] a) S. Jürs, B. Werschkun, T. Thiem, *Eur. J. Org. Chem.* **2006**, 4451–4462; b) B. Werschkum, J. Thiem, *Angew. Chem.* **1997**, *109*, 2905–2906; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2793–2794.

[20] J. S. Clark, A. L. Bate, T. Grinter, *Chem. Commun.* **2001**, 459–460.

[21] J. S. Clark, S. B. Walls, C. Wilson, S. P. East, M. J. Drysdale, *Eur. J. Org. Chem.* **2006**, 323–327.

[22] a) F. P. Marmsäter, G. K. Murphy, F. G. West, *J. Am. Chem. Soc.* **2003**, *125*, 14724–14725; b) G. K. Murphy, F. G. West, *Org. Lett.* **2005**, *7*, 1801–1904.

[23] C-M. Yu, J-Y. Lee, B. So, J. Hong, *Angew. Chem.* **2002**, *114*, 169–171; *Angew. Chem. Int. Ed.* **2002**, *41*, 161–163.

[24] F. López, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2002**, *124*, 4218–4219.

[25] F. López, L. Castedo, J. L. Mascareñas, *Org. Lett.* **2005**, *7*, 287–290.

[26] a) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2005**, *117*, 128–130; *Angew. Chem. Int. Ed.* **2005**, *44*, 126–128; b) for a previous example based on the stoichiometric use of ketone enolates and alkenyl Fischer carbene complexes to generate tricyclic structures such as **20**, see: J. Barluenga, A. Diéguez, F. Rodíguez, J. Flórez, F. J. Fañanás, *J. Am. Chem. Soc.* **2002**, *124*, 9056–9057; c) for experimental and theoretical studies on these cyclizations, see: J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, T. Sordo, P. Campomanes, *Chem. Eur. J.* **2005**, *11*, 5735–5741.

[27] J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2006**, *118*, 2145–2147; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091–2093.