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Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation

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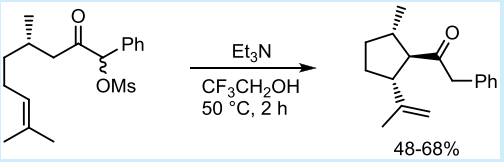
Supporting Information

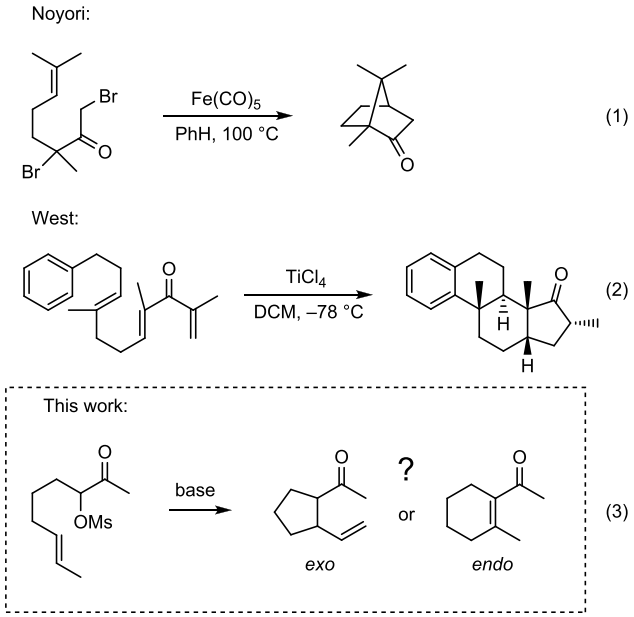
ABSTRACT: Unsaturated oxyallyl cations with a suitably positioned alkene bond undergo 5-*exo*-cyclization with the formation of vinylcyclopentane derivatives. Alkyne analogues provide allenes. The reaction proceeds with a moderate to excellent level of stereoselectivity and allows for asymmetric induction in the reaction with chiral substrate.



Reactive intermediates are the cornerstones of chemical reactivity. Depending on the reaction conditions, these species can (more or less selectively) pursue one of many available pathways within a rich mechanistic manifold, resulting in a number of synthetically useful reactions that surpasses by far the number of known reactive intermediates (radicals, diradicals, carbenes, carbocations, carbanions, and their heteroatom analogues). However, to the best of our knowledge, oxyallyl cations have found limited synthetic application,[1] which includes the Favorskii rearrangement,[2] [4 + 3] cycloadditions,[3] and intermolecular reactions with nucleophiles;[4] this last reaction can be combined with a second bond-forming reaction to give products of a formal [3 + 2] cycloaddition.[5] Apart from [4 + 3] cycloadditions and few isolated examples of reductive [3 + 2] cycloadditions of dihaloketones, intramolecular reactions of oxyallyl cations have not been systematically investigated.[6] We set out to explore in more detail cyclization reactions of these species.

Intermolecular reactions of oxyallyl cations with nucleophiles (including alkenes) work well only with strongly activated ones.[4,7] We presumed that the oxyallyl cation should undergo cyclization with suitably positioned, unactivated alkene, where the spatial proximity would compensate for the lack of electronic activation. Scarce literature data inferred the feasibility of this conception. Thus, Noyori reported iron carbonyl-induced reductive cyclization of dihaloketones into camphor derivatives, which probably proceeds as a stepwise [3 + 2] cycloaddition (Scheme 1, example 1).[8] West accomplished the intramolecular olefin trapping in the interrupted Nazarov cyclization[9] of polyunsaturated substrates (Scheme 1, example 2).[10] However, dihaloketones used in the first example may not always be readily accessible; in addition, several structurally related precursors failed to cyclize. In its turn, the Nazarov reaction requires specific precursor structure. We endeavored to explore a cyclization of oxyallyl cations generated by a more general method, from readily accessible precursors, such as hydroxyketone derivatives (Scheme 1, example 3).[4] We surmised that unsaturated oxyallyl cations should undergo cyclization, which may proceed with 5-*exo*- or 6-*endo*-selectivity. In addition to these two most probable reaction pathways, formal [3 + 2] cycloaddition with the formation of bicyclic, carbocyclic product, and/or [3 + 2] cycloaddition with the formation of bicyclic, heterocyclic product, could also be envisaged.[11]

Scheme 1. Previous Reports of Oxyallyl Cation Cyclization and This Work



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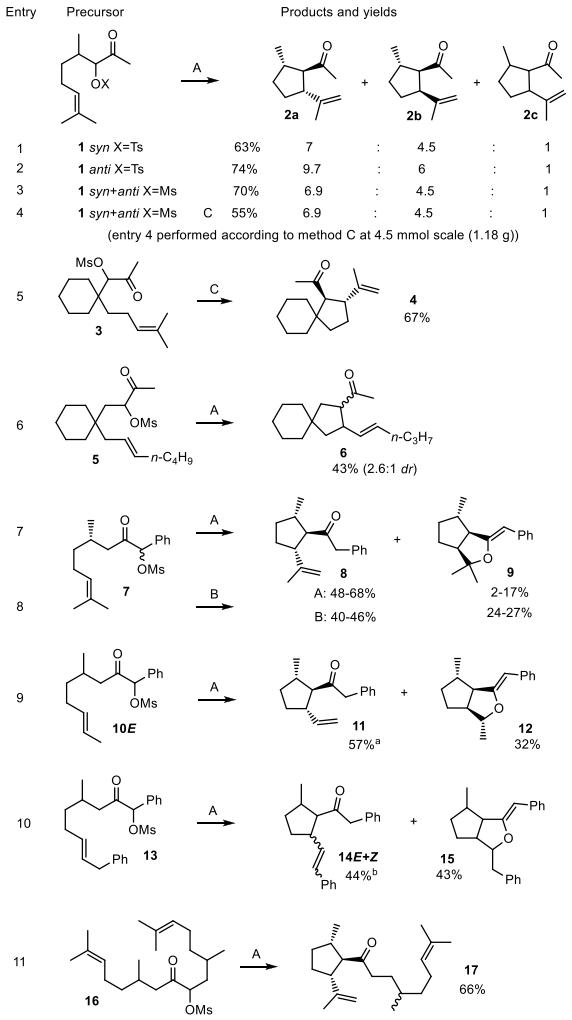
In the first experiment, tosylate **1***syn*[12] was treated with triethylamine in trifluoroethanol. To our delight, the product of the reaction was vinylcyclopentane derivative **2**, i.e., the product of 5-*exo*-cyclization, which was isolated in 63% yield as a mixture of three diastereoisomers (Scheme 2, entry 1).

Scheme 2. Cyclizations of Oxyallyl Cations: Reactions of All-Carbon, Acyclic Alkene Precursors[a]



[a]Reagents and conditions: Method A, Et_3N, TFE, 45 °C; Method B, Et_3N, SiO_2, DCM, rt; Method C, Et_3N, $LiClO_4$, PhMe, 60 °C; (a) dr = 5:1; only the major isomer is represented; (b) isolated as a mixture of geometrical isomers in a ratio **14***E*:**14***Z* = 5.2:1.

Stereoisomeric precursor **1***anti* (X = Ts) gave a similar result (74%; entry 2), indicating that the product distribution does not depend on the stereochemistry of the nucleofuge-bound carbon atom. Therefore, the next experiment was performed with a stereoisomeric mixture of mesylates **1***syn*+*anti* to obtain product **2** in 70% yield, with similar dr (entry 3).[13] The reaction was also performed in toluene, in the presence of $LiClO_4$, on a gram scale, with comparable results (entry 4). Cyclohexane-derived precursor **3** gave spiro product **4** as a single diastereoisomer (67%; entry 5). However, in the reaction with structurally related substrate **5**, spirobicyclic product **6** was obtained as a mixture of diastereoisomers (dr = 2.6:1; entry 6). The example represented in entry 7 is important for several reasons: although the product of 5-*exo*-cyclization (**8**) was accompanied by the [3 + 2] heterocycloadduct (**9**), the former was obtained as a single diastereoisomer (out of four possible), indicating the complete transfer of the stereochemical information in the transition state, from the single stereogenic center (in the precursor **7**) to the two newly created stereocenters (in the product **8**). Again, the configuration of the mesyloxy-bearing carbon atom is irrelevant for the stereochemical outcome of the reaction; this fact has mechanistic implications (vide infra), but it also allows for flexibility in the preparation of the precursors. Also of note is the translocation of the reaction center: the cyclization occurs at the α-position of ketone **7**, although the leaving group is in the α'-position; this is a useful feature of oxyallyl cation cyclization that contributes positively to the synthetic applicability. The cyclization of substrate **7** with a defined absolute configuration at the methyl-bearing carbon atom produced optically pure ketone **8** (entry 8). Substrates with terminal alkene do not react; however, a single (*E*)-configured methyl (entry 9) or methylene substituent (entries 6 and 10) is sufficient for the cyclization to occur; no cyclization was observed with the (*Z*)-configured precursor. This observation is relevant for establishing the reaction mechanism (vide infra). We have not observed other cyclization modes apart from 5-*exo*. Substrate **16** that contains both Δ^5 and Δ^6 alkene bonds (with respect to the reaction center) affords exclusively cyclopentane derivative **17** (entry 11).

Heteroatom can be present in the chain when heterocyclic derivatives are obtained (Scheme 3, entries 1−3). A couple of cyclic precursors have also been submitted to the cyclization conditions, aiming to obtain bi- or polycyclic products. Cyclohexanone-derived precursor **25** afforded tricyclic derivative **26**, which is structurally quite similar to the product obtained by West in the interrupted Nazarov cyclization (entry 3);[10a] the important difference, however, is that Nazarov-type products inevitably contain cyclopentane as the core structure, whereas the generation of oxyallyl cation from α-mesyloxy ketone is not limited by such a constraint. Transannular cyclization of **27** stereoselectively produced (*E*)-configured, *trans*-condensed bicyclo[7.3.0]dodec-7-en-2-one **28** (entry 4). Cyclization of alkynes proceeds as well: thus, ynone **29** afforded allene derivative **30** (67%, entry 5), which could be isomerized into dienone **31**. The cyclization/isomerization tandem occurred spontaneously with the oxygen-containing analogue **32** (entry 6). It is of note that in all examples cyclopentane derivatives were obtained exclusively; this is in contrast to the scarce literature examples of related systems,[10,14] where transient oxyallyl cationic species afforded six-membered rings—the expected regiochemical outcome of cationic polyene cyclizations.

Some side reactions have been observed, as well. These include the Favorskii rearrangement (Scheme 4, example 1), cheletropic elimination of carbon monoxide (example 2),[15] formation of trifluoroethoxy acetals from the starting mesyloxyketone, and the unexpected intramolecular attack of an oxygen nucleophile to the oxyallyl cation with the tetrahydrofuran ring closure (example 3). The Favorskii rearrangement and the acetal formation can be suppressed by performing the reaction in toluene in the presence of lithium perchlorate. This procedure improved the yield in entry 2 (Scheme 3) from 25% to 40%.

As for the mechanism of the reaction, two pathways can be envisaged: concerted and stepwise. For the related intermolecular ene reaction of allylic cations with isobutylene, Noyori

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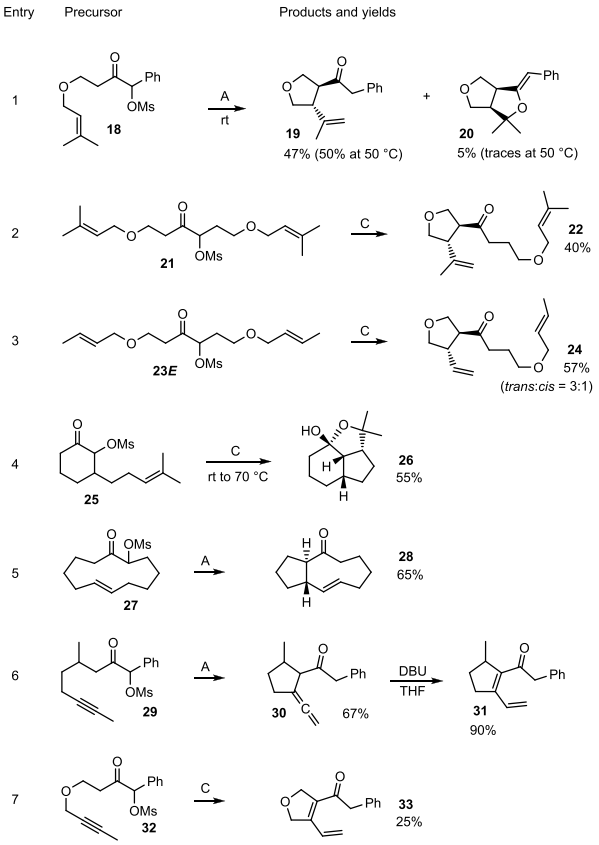
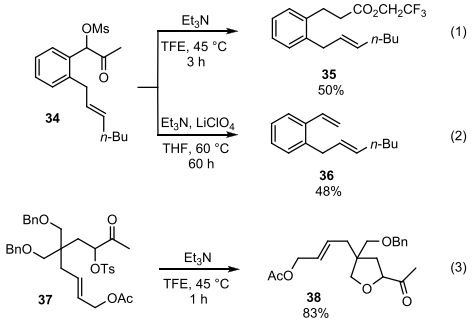
Scheme 3. Cyclizations of Oxyallyl Cations: Reactions of Heteroatom-Containing Presursors, Cyclic Precursors, and Alkynes[a]



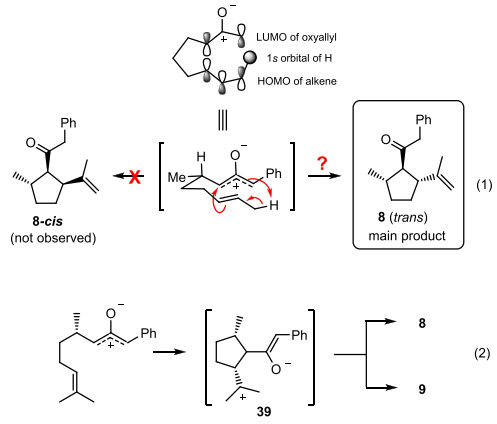
[a]Reagents and conditions: Method A, Et_3N, TFE, 45 °C; Method C, Et_3N, $LiClO_4$, PhMe, 60 °C.

Scheme 4. Side Reactions



proposed a concerted mechanism.[16] An intramolecular variant of this mechanistic possibility is represented in Scheme 5 (eq 1). The pericyclic reaction would be expected to produce predominantly (if not exclusively) the *cis*-configured product **8**-*cis*.[17] However, in all of our experiments *trans*-configured products were favored, or even obtained exclusively, such as **8**, whose relative configuration was unambiguously established by a NOESY experiment.[18] Therefore, the stereochemical outcome of the cyclization does not support the concerted mechanism. The second possibility would be a stepwise mechanism where the reaction proceeds via a cationic intermediate **39** (Scheme 5, eq 2), which can further undergo either a proton elimination (with the formation of the vinylcyclopentane-type product, e.g., **8**) or intramolecular

Scheme 5. Proposed Reaction Mechanism



attack of the enolate oxygen (which produces dihydrofuran-type product, e.g., **9**). In this mechanistic scenario, the formation of *endo*-products would also be expected, at least with compounds **10** or **23**. However, the *exo*-products were exclusively formed in all cases. Also, it is not clear why *E*-isomers of **10** and **23** cyclize, whereas the *Z*-isomers do not. In addition, Noyori has provided evidence which, apparently, rules out the intermediacy of carbocationic intermediate of type **39** in the intermolecular reaction.[16] Preliminary modeling of the transition state at DFT/BLYP/TZ2P level of theory failed to explain the experimental results and additional calculations, and experiments are needed to clarify this issue.

To summarize, a stereoselective cyclization of oxyallyl cations was developed which proceeds with the translocation of the reactive center and affords unsaturated cyclopentane derivatives in moderate to good yields. Studies toward the application of this method in the synthesis of natural products are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03791.

Experimental procedures, spectral data and copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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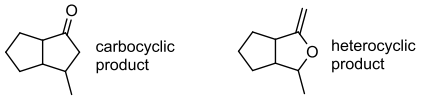

(12) The assignation of *syn* and *anti* stereochemistry to the diastereoisomers of **1** is tentative.

(13) The diastereoisomeric ratio of **2a**, **2b**, and **2c** apparently does not depend on the reaction time. The reaction was performed several times with monitoring by GC: the initial dr (i.e., after 1 h) did not change after up to 48 h (see the Supporting Information for details).

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(17) Alternatively, the proton transfer could occur from carbon to oxygen, with the same stereochemical outcome. We thank the Reviewer for this suggestion.

(18) In the representation of transition state in Scheme 5, one of two methyl groups at the alkene bond is omitted for clarity. Detailed NOESY analyses are provided for compounds **2**, **4**, **8**, and **28**. See the Supporting Information for details.

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