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Catalytic Rearrangement of 2-Alkoxy Diallyl Alcohols: Access to Polysubstituted Cyclopentenones

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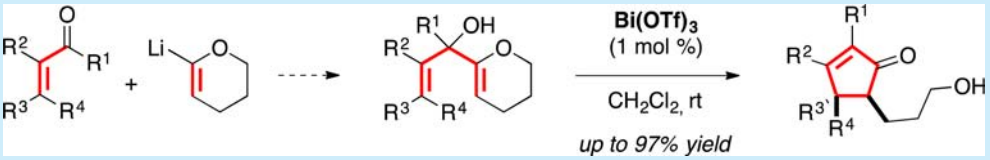
Supporting Information

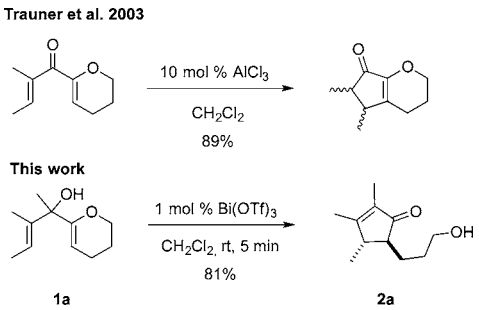


ABSTRACT: A catalytic rearrangement of diallyl alcohols comprising a cyclic enol ether has been developed using very mild conditions. Bismuth(III) triflate was found to be a very active catalyst for the ring rearrangement of a range of tertiary allylic alcohols to efficiently afford polysubstituted cyclopentenones with a high degree of diastereoselectivity.

Nature's ability to produce complex molecular architectures with manifold functions in diverse biological processes is still fascinating organic chemists. The assembly of (poly)cyclic scaffolds within a target molecule often represents a synthetic challenge. In this context, cycloisomerizations have emerged as a particularly efficient, atom economic tool, allowing a rapid increase in skeletal complexity starting from relatively simple precursors.[1] Cyclopentenones are very useful building blocks for the synthesis of polysubstituted five-membered carbocyles that can be found in many natural products.[2] The classical Nazarov reaction has been studied extensively and established as a powerful tool for the synthesis of cyclopentenones via Brønsted or Lewis acid promoted cyclization of divinyl ketones.[3] These electrocyclizations offer a straightforward way to form new carbon−carbon bonds in a highly regio- and stereoselective manner by simple orbital reorganization. Modifications of both substrates and cyclization conditions have led to several versatile and efficient variants for the preparation of compounds containing five-membered carbocycles.[4] However, the use of the corresponding alcohols in Nazarov-type electrocyclizations remains quite unexplored to date and only a few examples have been reported.[5] All of them usually require multiple stabilizing substituents in the α-position as well as on the diallyl scaffold or with one of the allylic double bonds being part of an aromatic system itself. Furthermore, the Lewis or Brønsted acid is mostly employed in stoichiometric or overstoichiometric amounts.[6]

In 2003, Trauner and Frontier reported simultaneously efficient Nazarov cyclizations of 2-alkoxy-1,4-pentadien-3-ones using $AlCl_3$ and $Cu(OTf)_2$, respectively, as the Lewis acid catalyst, thereby demonstrating an activating effect of the 2-alkoxy group.[7]

We recently reported a bismuth(III) triflate mediated cationic-type cycloisomerization of allene-enol ether substrates toward functionalized cyclopentenes.[8] In this and related examples reported in the literature, mostly concerning semipinacol rearrangements,[9] the electrophilic activation of the enol ether is the initial step of the transformation. In contrast with these results, we have now found that the diallyl alcohol **1a** undergoes an interesting rearrangement when subjected to 1 mol % of bismuth(III) triflate. Cyclopentenone **2a** is obtained in high yield and diastereoselectivity under very mild conditions.[10]



The cyclization of diallyl alcohol **1a** served as a model reaction for a screening of Lewis and Brønsted acids with catalyst loadings of 1−5 mol % (Table 1).

Among the catalysts tested, $Bi(OTf)_3$ gave the best results in terms of yield and product selectivity (entry 1). Full conversion of **1a** was reached after only 5 min at room temperature, and the product was isolated in 81% yield. Other metal triflates tested required longer reaction times and gave lower yields (entries 2−5), indicating the influence of the metal cation on the activity of the catalyst. Slower reaction rates gave rise to side reactions, such as hydrolysis of the enol ether. The less reactive bismuth tosylate $Bi(OTs)_3$ afforded **2a** after 4.5 h in 40% yield, but the catalyst loading had to be increased to 5% to ensure complete conversion of the starting material (entry 6). Bismuth(III) chloride showed catalytic activity similar to that

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Table 1. Screening of Catalysts for the Rearrangement of 1a

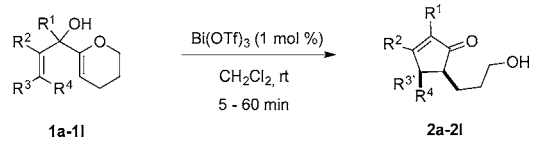
entry	catalyst (mol %)[a]	time (min)[b]	yield of **2a** (%)[c]
1	$Bi(OTf)_3$ (1)	5	81
2	$Al(OTf)_3$ (1)	10	71
3	$In(OTf)_3$ (1)	15	63
4	$Sc(OTf)_3$ (1)	45	58
5	$Cu(OTf)_2$ (1)	120	45
6	$Bi(OTs)_3$ (5)	270	40
7	$BiCl_3$ (5)	240	52
8	TfOH (1)	5	62

[a]General screening procedure: the catalyst was added to a solution of **1a** in anhydrous CH_2Cl_2 (0.1 M) at room temperature. [b]Time until complete conversion of **1a** (TLC). [c]Isolated yields.

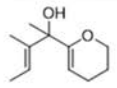
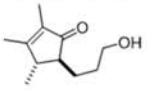
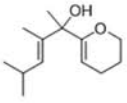
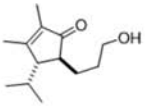
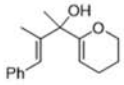
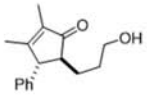
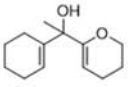
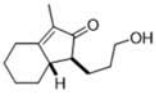
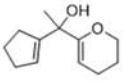
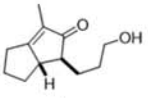
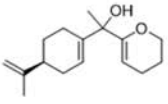
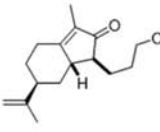
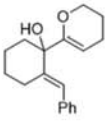
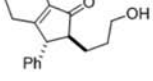
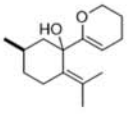
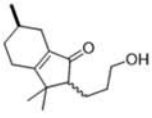
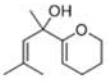
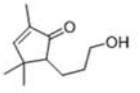
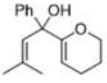
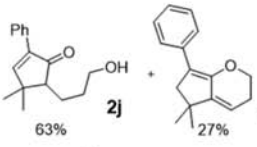
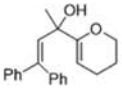
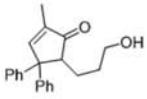
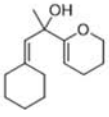
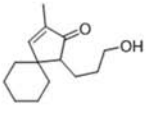
of the tosylate, yielding the product in 52% yield after 4 h (entry 7). Triflic acid also catalyzed the reaction and afforded the product in 62% yield,[11] alongside some nonidentified oligomeric material. $Bi(OTf)_3$ was shown to be the most suitable catalyst for this cycloisomerization.[12,13] In addition, it is commercially available, inexpensive, nontoxic, and easier to handle than the corrosive triflic acid.

These advantages prompted us to further explore the scope of this new $Bi(OTf)_3$-catalyzed cycloisomerization process. A range of tertiary diallyl alcohols **1a**−**1l** were tested and readily afforded the corresponding cyclopentenones **2a**−**2l** in good to excellent yields (Table 2). The starting alcohols were generally synthesized in one step from the corresponding ketones and lithiated dihydropyran using an alkyllithium (see Supporting Information).[14] A series of substrates with R^4 = H were tested (entries 1−7). Model substrate **1a** gave cyclopentenone **2a** in 81% yield and with a *trans*:*cis* diastereomeric ratio of 19:1 (entry 1). Increasing the steric bulk of R^3 by introducing an isopropyl substituent led to an even higher *trans*-selectivity, and **2b** was obtained in 71% yield with a *dr* > 99:1 (entry 2). Alcohol **1c**, bearing a phenyl group, afforded similar results (entry 3). For the substrates **1d**−**1f**, where the double bond was part of a ring (entries 4−6), the corresponding bicyclic products **2d**−**2f** were isolated with the expected *trans*-configuration. Compounds **1d** and **1e** afforded bicyclic alcohols **2d** and **2e** in 87% and 83% yield, respectively, with complete stereocontrol (entries 4 and 5). For alcohol **1f**, containing an (*S*)-limonene core, a small influence of the stereogenic center could be observed and two diastereoisomers were obtained in a 1.9:1 ratio (entry 6). Here again, only the *trans*-configuration between the propanol substituent and the cyclohexane ring was observed. To increase the structural diversity of the products formed by this transformation, diallyl alcohol **1g**, featuring an exocyclic trisubstituted double bond, was synthesized and afforded **2g** in 85% yield with a clean *trans*-selectivity, the double bond being located at the fused ring junction (entry 7). The substitution pattern of the olefinic double bond was further modified, moving the C2-substituent to C3 (R^2 = H, R^3 and R^4 ≠ H, entries 8−12). These modifications did not have any influence on the reaction outcome and the products were obtained in comparably high yields. Alcohol **1h** was synthesized from pulegone and cleanly afforded bicyclic **2h** in 97% yield as a 1:1 mixture of diastereoisomers (entry 8). Prenyl derivative **1i** led to cyclopentenone **2i** in 84% yield (entry 9). Replacing the methyl substituent at the C1-position by a phenyl group in **1j** had an interesting effect (entry 10): the expected cyclopentenone **2j** was formed in 63% yield alongside with 27% of dihydropyran-fused cyclopentene **3**.

Table 2. Scope of the $Bi(OTf)_3$-Catalyzed Rearrangement



1a-1l **2a-2l**

entry	substrate		product		yield (%)[a]
1		**1a**		**2a**	81[b]
2		**1b**		**2b**	71
3		**1c**		**2c**	74
4		**1d**		**2d**	83
5		**1e**		**2e**	83
6		**1f**		**2f**	88[c]
7		**1g**		**2g**	85
8		**1h**		**2h**	97[d]
9		**1i**		**2i**	84
10		**1j**		**2j** (63%) + **3** (27%)	90
11		**1k**		**2k**	87
12		**1l**		**2l**	80

[a]Isolated overall yields. [b]Obtained as a 19:1 mixture of two diastereomers. [c]Obtained as a 1.9:1 mixture of two diastereomers. [d]Obtained as a 1:1 mixture of two diastereomers.

Substrate **1k**, bearing two phenyl groups at the C3 position, was also converted into **2k** in 87% yield (entry 11).

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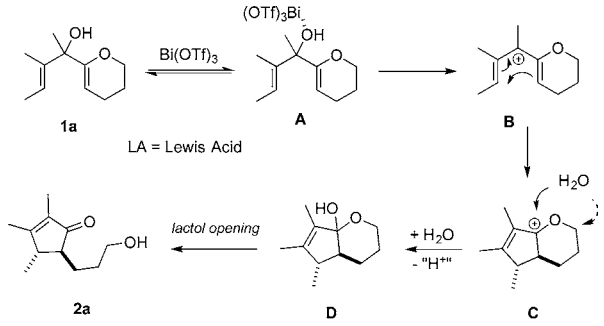
Cyclohexylidene derivative **1l** gave the expected spirobicycle **2l** in 80% yield (entry 12).

The cyclopentenone rings of compounds **2** were formed between the termini of the two double bonds present in diallyl alcohols of type **1**; the propanol substituent was found stereoselectively in a *trans*-configuration with respect to the vicinal substituent. To explain the formation of **2**, the allylic alcohol of **1** is activated preferentially by the Lewis acid which promotes the formation of pentadienyl-type carbocation **B** (Scheme 1).

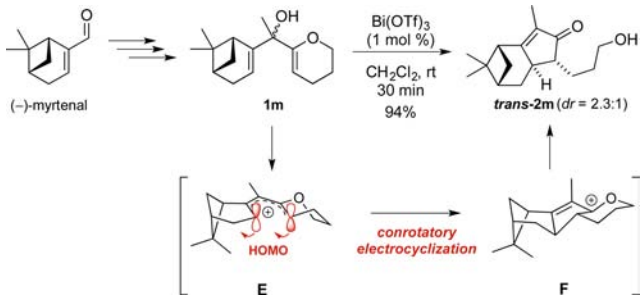
Scheme 1. Proposed Mechanism for the Formation of Cyclopentenone 2a



A 4π-electrocyclic ring closure of the alkoxypentadienyl cation system[15] then affords oxonium ion **C** which is intercepted by the previously expelled water (or metal hydroxide) to furnish the highly substituted lactol **D**. The lactol opens leading to the more stable cyclopentenones **2**.[16] Direct formation of **2a** from cationic intermediate **C** by a S_N2 mechanism is unlikely as suggested by ^{18}O-labeling experiments (see Supporting Information). During this completely atom economic process, one C−C bond is formed through a pericyclic reaction while a C−O bond is broken with a formal migration of a water molecule. For the particular case of **1j**, formation of compound **3** could be the result of proton elimination from the oxonium ion of type **C**, followed by a double-bond isomerization. Elimination would be enhanced in the presence of an aromatic substituent, since an extended conjugated π-system is formed.

The high diastereoselectivity observed in these reactions could be explained by a stereospecific conrotatory 4π-electrocyclization of a pentadienyl carbocation. To confirm this hypothesis, the substrate **1m**, containing a chiral α-pinene core, was synthesized starting from (−)-myrtenal (Scheme 2). The two diastereoisomers of **1m** could be separated to some extent. When the mixture of isomers (ca. 5:1) was subjected to

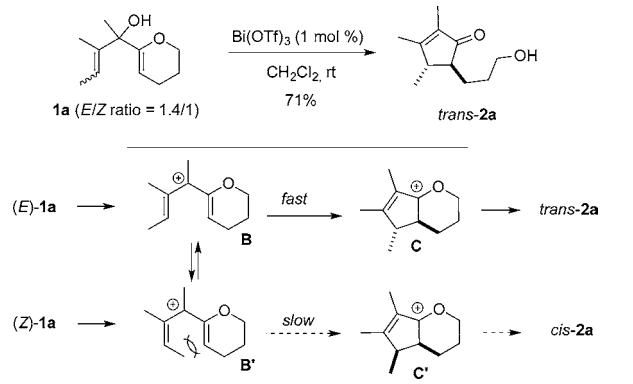
Scheme 2. Proposed 4π-Electrocyclization of a Transient Pentadienyl Carbocation



1 mol % of $Bi(OTf)_3$, the cyclization led to two *trans*-isomers (*trans*-**2m**) in 94% yield with a diastereomeric ratio of 2.3:1. This is indicative of a completely stereoselective cyclization of the diene unit, in which the chiral core had only a small influence on the reaction outcome (torquoselectivity). Interestingly, subjecting a single diastereoisomer of **1m** to identical conditions gave the same results, confirming the formation of a transient planar carbocation of type **E** with a cyclic array of π-electrons, resulting in a complete loss of the stereochemical information at the C1 carbon of **1m**.

Additionally, the reaction performed on a mixture of (*E*)- and (*Z*)-isomers of **1a** exclusively led to cyclopentenone *trans*-**2a** (Scheme 3). The same behavior has been reported for the

Scheme 3. Cyclization of an (*E*)/(*Z*) Mixture of 1a



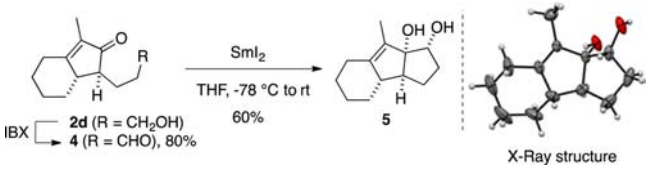
Nazarov electrocyclization of divinyl ketones bearing one internal substituent which usually cyclizes to give the *trans* isomer.[17] An acid-catalyzed isomerization of the substrate prior to cyclization has been invoked. Therefore, we can speculate that isomerization of a pentadienyl cation intermediate **B′** into **B** occurs, as the planar conformation required for cyclization of **B′** suffers from strong steric hindrance.

The possibility that the final product epimerizes under the Lewis acidic conditions has been considered but ruled out by some isotope labeling experiments. Indeed, no deuterium incorporation was observed in the final product **2a** when the reaction with **1a** was conducted in the presence of 3 equiv of D_2O, which precludes epimerization through the keto−enol tautomeric equilibrium (see Supporting Information).

Finally, we wished to take advantage of the presence of the alcohol function within the side chain for the selective construction of polycyclic scaffolds. Therefore, the tricyclic structure **5** was obtained through a samarium(II) iodide mediated pinacolic coupling from the corresponding aldehyde **4** (Scheme 4).[18] X-ray structure of **5** was obtained confirming the stereochemistry (CCDC 1450023).

In conclusion, we have shown that 2-alkoxy diallyl alcohols undergo an electrocyclic rearrangement to form the corresponding cyclopentenones with good to excellent yields using

Scheme 4. Further Transformation from Alcohol 2d



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only 1 mol % of bismuth(III) triflate as the catalyst. Preliminary evidence for a cationic conrotatory 4π-electrocyclization mechanism has been stated, explaining the high *trans*-selectivity of the process. This methodology allows for the straightforward and stereocontrolled assembly of polycylic structures as well as for synthesis of cyclopentanoid derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00270.

Experimental details, characterization data for the products, copies of NMR spectra (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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