Organic LETTERS

Cycloisomerization of Allene–Enol Ethers under Bi(OTf)$_3$ Catalysis

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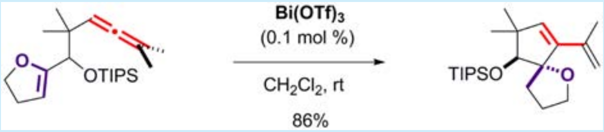
Ⓢ *Supporting Information*

ABSTRACT: The cycloisomerization of allene–enol ethers under Bi(OTf)$_3$ catalysis was developed as a novel "atom-economic" tool for accessing interesting functionalized cyclopentene rings. Bi(OTf)$_3$ was shown to promote selectively the activation of the enol ether moiety of the substrate. This catalytic methodology was further extended to the synthesis of dihydrofuran and oxaspirocycle derivatives.

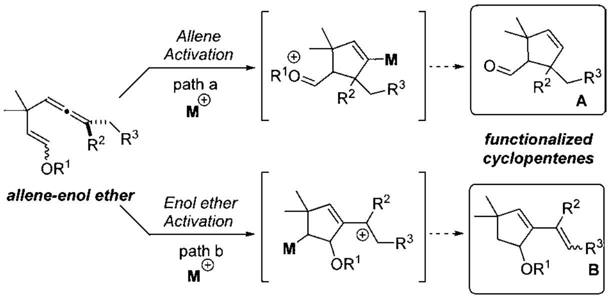


Metal-catalyzed cycloisomerization reactions have emerged as powerful tools to rapidly generate molecular complexity via the construction of carbon–carbon and carbon–heteroatom bonds. For the past two decades, reports on cycloisomerization reactions have primarily focused on noble metal-based catalysis (Au, Pd, Pt, Rh).[1] Beyond this, the development of new efficient carbocyclization reactions using relatively inexpensive, nontoxic, and easily reusable catalysts with low loading is of significant interest.

A variety of novel catalyzed cycloisomerization reactions employing ene–allenes as starting substrates have been reported in the past few years.[1b] However, although enol ethers and silyl enol ethers have been used in cyclization reactions with alkyne partners,[2] few reports can be found on unactivated allenes.[2b,3] Most of these studies involve either allene amides or allene carbamates and deal with metal-catalyzed cycloadditions,[4] [2 + 2]-photocycloadditions,[5] and Claisen rearrangements.[6]

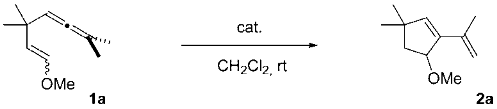
We have previously shown that, by means of Bi(III)-based catalysis, allenes could act as electrophilic partners in hydroarylation reactions[7] and also as nucleophiles, as in the cycloisomerization of γ-allenic ketones.[8] As do allenes, enol ethers can also exhibit electrophilic/nucleophilic behaviors. We were thus interested in studying the reactivity of readily available 1,4-enol ether–allenes under metal triflate catalysis (Scheme 1).[9] Indeed, we envisaged two divergent cyclization pathways resulting from the chemoselective activation of these difunctional substrates. Activation of the allene moiety would induce a nucleophilic attack of the enol ether to form cyclopentene carbaldehyde derivatives of type **A** (Scheme1, path a). In contrast, the activation of the enol ether moiety of the molecule, with subsequent nucleophilic attack of the allene, would lead to alkoxy cyclopentenes of type **B** (Scheme1, path b). Both pathways seem to be likely to occur, and in both cases, these would give access to interesting functionalized cyclopentene derivatives.

Scheme 1. Possible Reactivity of Allene–Enol Ether Substrates under Lewis Acid Activation



Initially, we investigated this reactivity on the model allene–enol ether **1a** as a mixture of (E)- and (Z)- isomers under metal triflate catalysis. This substrate was readily synthesized from 2-methylbut-3-yn-2-ol via a Claisen rearrangement followed by a Wittig reaction. A range of metal triflate catalysts were screened for their catalytic activity in the cycloisomerization of **1a** (Table 1). While the conversion of **1a** was found to be very low with Fe(OTf)$_3$ and Cu(OTf)$_2$ in dichloromethane (Table 1, entries 4 and 5), a good yield of methoxy(propenyl)cyclopentene **2a**

Table 1. Screening of Metal Triflate Catalysts



entry[a]	catalyst (mol %)	time	yield[b] (%)
1	Al(OTf)$_3$ (2)	18 h	82
2	In(OTf)$_3$ (0.5)	20 min	81
3	Bi(OTf)$_3$ (0.5)	4 min	84
4	Cu(OTf)$_2$ (2)	24 h	0
5	Fe(OTf)$_3$ (2)	24 h	0
6	**Bi(OTf)$_3$ (0.1)**	20 min	**88**
7[c]	Bi(OTf)$_3$ (0.1)	16 h	89
8	TfOH (0.1)	20 min	78

[a] General screening procedure: To a solution of enol ether **1a** in CH$_2$Cl$_2$ (0.2 M) was added the catalyst (0.1–2 mol %). [b] GC yields. [c] The reaction was conducted in toluene.

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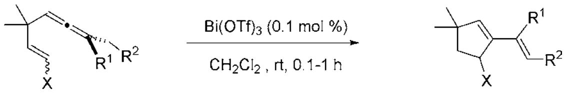
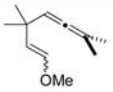
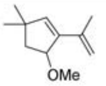
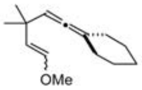
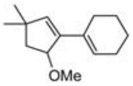
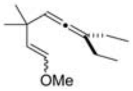
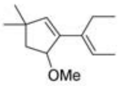
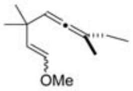
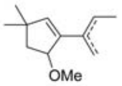
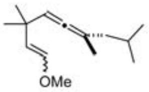
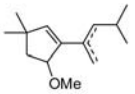
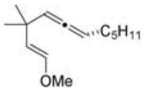
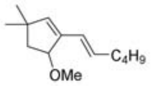
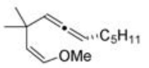
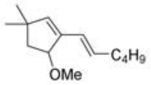
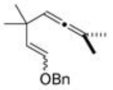
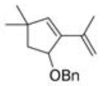
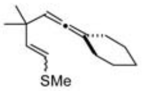
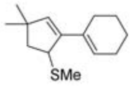
(cyclopentene of type **B**) was obtained using 2 mol % of Al(OTf)$_3$ (Table 1, entry 1). In addition, when a very low catalytic loading of In(OTf)$_3$ or Bi(OTf)$_3$ was used, **1a** was converted to **2a** with similar efficiencies and much shorter reaction times (Table 1, entries 2 and 3). With Bi(OTf)$_3$, the catalytic loading could be further lowered to 0.1 mol %. Indeed, the reaction proceeded in 20 min and the yield of **2a** was improved to 88% (Table 1, entry 6). Furthermore, this reaction could be efficiently performed in toluene despite the much longer reaction time (Table 1, entry 7). Triflic acid also catalyzed this reaction, although the yield was reduced (Table 1, entry 8). Therefore, the relatively inexpensive and easy to use Bi(OTf)$_3$[10] was selected as the best catalyst for this novel catalytic cycloisomerization reaction. With a low catalytic loading of 0.1 mol %, the reaction proceeded in dichloromethane at room temperature in 20 min to afford **2a** in 88% yield.

Table 2. Bi(OTf)$_3$-Catalyzed Cycloisomerization of Allene–Enol (Thio)ether Derivatives



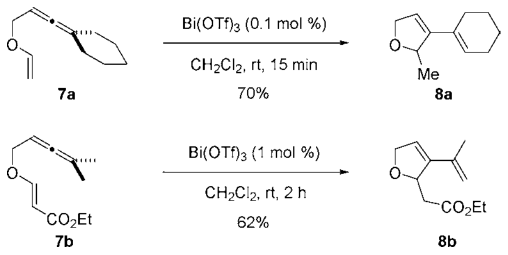
entry[a]	substrate[b]	product	yield (%)[c]
1	 OMe **1a**	 OMe **2a**	75
2	 OMe **1b**	 OMe **2b**	82[d]
3	 OMe **1c**	 OMe **2c**	65
4	 OMe **1d**	 OMe **2d**	71[e]
5	 OMe **1e**	 OMe **2e**	77[f]
6	 C$_5$H$_{11}$, OMe **(*E*)-1f**	 C$_4$H$_9$, OMe **2f**	71
7	 C$_5$H$_{11}$, OMe **(*Z*)-1f**	 C$_4$H$_9$, OMe **2f**	67
8	 OBn **3**	 OBn **4**	81
9[g]	 SMe **5**	 SMe **6**	85

[a] General procedure: to a solution of enol ether in CH$_2$Cl$_2$ (0.2 M) at rt was added Bi(OTf)$_3$ (0.1 mol %). [b] *E*/*Z* ratio range from 1/0.5 to 1/1. [c] Isolated yields. [d] The reaction was carried out on a gram scale. [e] A 5/1 ratio of isomers was obtained. [f] A 2/1 ratio of isomers was obtained. [g] The reaction was conducted in nitromethane with 5 mol % of catalyst for 16 h.

These initial results prompted us to further explore the scope of this reaction. Thus, under the optimized catalytic conditions, allene–enol ether **1b**, with a cyclohexylidene moiety, could be converted to bicylic diene **2b** in an isolated yield of 82% (Table 2, entry 2). The cycloisomerization of the acyclic allenic substrate **1c**, bearing a *gem*-diethyl group at the terminal carbon of the allene, allowed us to gain insight into the diastereoselectivity of the process. In the presence of a catalytic amount of Bi(OTf)$_3$, the reaction proved to be highly diastereoselective, with the exclusive formation of the cyclopentene product **2c** displaying the *E*-configuration for the newly formed double bond (Table 2, entry 3). Furthermore, the cycloisomerizations of the nonsymmetrically trisubstituted substrates **1d** and **1e** were also efficient and led to the dienes **2d** and **2e**, respectively, as mixtures of two isomers. Although no regioselectivity was observed in these transformations, the *E*-diastereoselectivity was still excellent (Table 2, entries 4 and 5). This methodology could also be extended to the cycloisomerization of isomerically pure 1,3-disubstituted allenes (*E*)-**1f** and (*Z*)-**1f** to furnish dienic product **2f** as a single stereoisomer in good yields (Table 2, entries 6 and 7). Interestingly, this reaction was not restricted to only methoxymethylidene derivatives. Indeed, the benzyloxy analogue **3** was successfully cyclized to the corresponding cyclopentene **4** (Table 2, entry 8). Although thio enol ethers are less reactive than their related oxygenated homologues, we were able to isolate the sulfide derivative **6** in 85% yield from the cycloisomerization of the allenic thioether **5**. In this case, the catalytic loading was increased to 5 mol % (Table 2, entry 9).

We sought to expand the scope of this cyclization to the synthesis of other five-membered rings. Allenic substrates **7a** and **7b** possess an enol ether function in which the oxygen atom was directly linked to the tether. Both **7a** and the less activated enol ether **7b** were prone to cyclization, affording the expected functionalized 2,5-dihydrofurans **8a** and **8b**, respectively (Scheme 2).

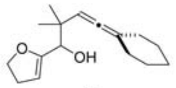
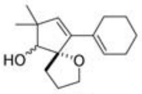
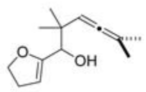
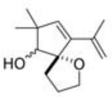
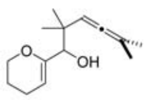
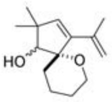
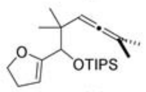
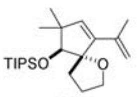
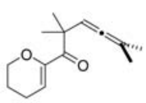
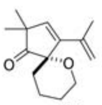
Scheme 2. Bi(OTf)$_3$-Catalyzed Synthesis of Dihydrofuran Derivatives



Increased molecular complexity resulted when cyclic enol ethers, such as dihydrofuran or dihydropyan derivatives, bearing additional hydroxy substituents, were employed. The allenic alcohol substrates **9a–c** were converted into the oxaspirocyles **10a–c** using only 0.1 mol % of Bi(OTf)$_3$ (Table 3, entries 1–3).

Despite the presence of an alcohol at a sensitive allylic position, no elimination was detected under these conditions. Moreover,

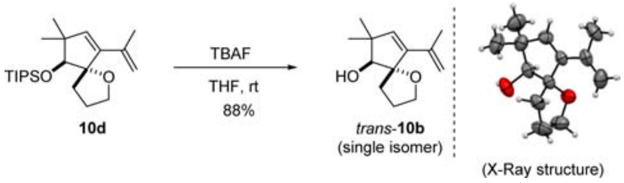
Table 3. $Bi(OTf)_3$-Catalyzed Synthesis of Oxaspirocycles

entry[a]	substrate	product	time (h)	yield (%)[b]
1	 **9a**	 **10a**	0.5	90[c]
2	 **9b**	 **10b**	0.25	73[c] (65)[d]
3	 **9c**	 **10c**	0.25	71[c]
4	 **9d**	 **10d**	0.5	86
5[e]	 **11**	 **12**	1.5	74

[a] General procedure: to a solution of enol ether in CH_2Cl_2 (0.1 M) at rt was added $Bi(OTf)_3$ (0.1 mol %). [b] Isolated yields. [c] A mixture of two diastereosiomers was obtained. [d] 0.3 mol % of triflic acid was used. The same dr was observed. [e] 1 mol % of $Bi(OTf)_3$ was used.

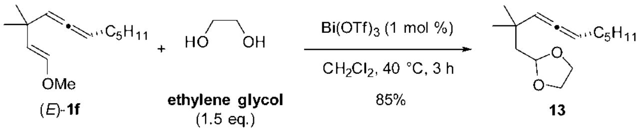
no addition of the alcohol on the allene function was observed as could be possibly expected.[11] With free alcohols as starting substrates, the relative configuration of the two contiguous stereogenic centers could not be controlled during this process. However, an excellent diastereoselectivity resulted in the case of the TIPS-protected alcohol **9d** (Table 3, entry 4, TIPS = triisopropylsilyl). Spirocyclic ether **10d** was obtained in 86% yield as a single isomer with the two oxygen atoms in a *trans*-configuration. The structure of the alcohol *trans*-**10b**, resulting from the deprotection of **10d** with TBAF, was confirmed by X-ray crystallography (Scheme 3).[12] Interestingly, the ketone−enol ether derivative **11** could also be efficiently cyclized under the same reaction conditions to afford compound **12** in 74% yield (Table 3, entry 5).

Scheme 3. Deprotection of 10d and Crystal Structure of the Alcohol *trans*-10b



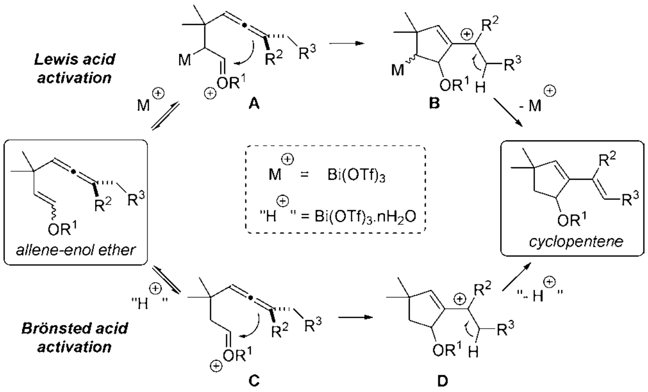
From a mechanistic point of view, the active catalytic species involved in these cycloisomerizations preferentially activates the enol ether part of the substrates. To attest to this chemoselectivity, the cyclization of (*E*)-**1f** could be interrupted by conducting the reaction in the presence of an exogeneous nucleophile such as ethylene glycol (Scheme 4). The allene−acetal **13** was obtained as the sole reaction product in 85% yield.

Scheme 4. $Bi(OTf)_3$-Catalyzed Formation of Acetal 13



Two different possibilities can be proposed for this cyclopentene synthesis that follows activation of the enol ether moiety (e.g., path b of Scheme 1). This activation can be initiated either by coordination of bismuth(III) (Lewis acid activation) or by protonation (Brönsted acid activation), to generate the reactive oxonium species of type **A** or **C**, respectively (Scheme 5).

Scheme 5. Proposed Mechanisms for the Cycloisomerization of Allene−Enol Ether Substrates



Electrophilic activation through π-complexation has already been proven in the case of $BiBr_3$[13] and suggested for the hydroamination of dienes with $Bi(OTf)_3$.[14] However, the possibility that this salt acts, in fact, as a Brönsted acid source seems more likely. The acid species would be generated either by hydrolysis or hydration of the triflate salt.[15] The hydrolysis would liberate triflic acid and therefore $Bi(OTf)_3$ would serve as a reservoir of superacid.[15c] The other possibility would involve an acidic hydrated metal species which could act as a Lewis acid-assisted Brønsted Acid (LBA)-type catalyst.[16] Even though the proper role of $Bi(OTf)_3$ is not precisely defined so far, some recent calculations[15a,b] suggest that hydration of triflate salts is energetically favored over the hydrolysis. Therefore, a LBA-type mechanism should be more appropriated. The oxonium intermediates **A** or **C** could then undergo a 5-*exo*-*dig* cyclization involving the nucleophilic attack of the central allenic carbon to afford the allylic carbocations of type **B** and **D**, respectively. Dienic products would then be obtained after a diastereoselective proton elimination and, in the case of the metallic activation pathway (intermediate **B**), a subsequent protodemetalation.

In summary, we have shown that substrates presenting both an unactivated allene and an enol ether moiety could be efficiently cyclized in the presence of a very low catalytic loading of $Bi(OTf)_3$, a relatively inexpensive and easily reusable catalyst.[7] Functionalized alkoxycyclopentenes and 2,5-dihydrofurans have been cleanly obtained from 1,4-enol ether−allenes. More complex oxaspirocyclic ether derivatives have also been synthesized from 1,5-enol ether−allenes featuring a dihydrofuran or a dihydropyran ring. The cyclization proved to be highly diastereoselective when the corresponding TIPS-protected alcohol was used. All these cycloisomerization reactions proceed through a nucleophilic attack of the allene onto the activated enol ether.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data for the products, copies of NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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