

Catalytic formation of C–O bonds by alkene activation: Lewis acid-cycloisomerisation of olefinic alcohols

Lydie Coulombel,^a Isabelle Favier^a and Elisabet Duñach^{*ab}

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Tin(IV) trifluoromethanesulfonate has been found to be an excellent catalyst for the cycloisomerisation of non-activated and differently substituted olefinic alcohols to cyclic ethers.

The tetrahydrofuran and tetrahydropyran rings are very important structural moieties, which are present in a large variety of natural products such as polyether antibiotics.¹ They are also found as perfuming or flavouring ingredients in foodstuffs.² The intramolecular hydroalkoxylation reaction, the addition of alcohols onto carbon–carbon multiple bonds, provides an efficient and direct access to this class of heterocycles.³ Although this reaction is known to be effected in the presence of over-stoichiometric amounts of protic acids, only a few protic acid-catalysed cyclisations have been reported.^{4,5} The use of Lewis acids as catalysts for the activation of alkenes, involving the formation of new C–O bonds, has not yet been reported. To our knowledge, a single example describes the use of Lewis acids to effect the cycloisomerisation of unsaturated alcohols, though in stoichiometric amounts.⁶ Lewis acid catalysis in non protic media is of increasing interest for organic transformations and allows enantioselective cycloisomerisation by the introduction of chiral ligands on the metal centre.

Recent attention has been devoted to the concept of enhancement of the electrophilic alkene activation by increasing the net positive charge in transition-metal complexes.⁷ In this context, the trifluoromethanesulfonate group constitutes one of the most electron-withdrawing ligands and confers high activity to the corresponding Lewis acid metal salts.⁸

Herein, we report the novel use of metallic trifluoromethanesulfonates, and more particularly the use of tin(IV) trifluoromethanesulfonate, as the catalyst in the cycloisomerisation of non-activated unsaturated alcohols to the corresponding cyclic ethers in non protic media.

We prepared Sn(OTf)₄ (not commercially available) as well as other metallic triflates using an electrochemical procedure, similar to that recently reported for the preparation of metallic bis(trifluoromethanesulfonyl)imide salts.⁹ In contrast to the usual methods of metallic triflate preparation, from the corresponding oxides and triflic acid, that afford hydrated triflate salts,¹⁰ the electrochemical method led to the formation of anhydrous metallic triflates.¹¹

The possibilities of Lewis-acid catalysed cycloisomerisation of unsaturated alcohols were first examined for the cyclisation of the model substrate **1a** (Table 1, entry 1) in the presence of different metallic triflates. The reactivities of Al(OTf)₃, Ni(OTf)₂, Zn(OTf)₂,

Sm(OTf)₃ and Sn(OTf)₄, used in a 5 mol% ratio with respect to **1a**, were examined in refluxing acetonitrile. The most efficient catalyst was Sn(OTf)₄, which led quantitatively and selectively to the corresponding tetrahydropyran **2a** in 0.5 h. The reaction was regioselective and only the 6-membered ring **2a** was formed, without the presence of the isomeric 5-membered ring ether.

Different solvents such as dichloromethane, acetonitrile, dichloroethane and nitromethane were tested for the cyclisation of both **1a** and **1e** (*cis* isomer) using Sn(OTf)₄ (5 mol%) (For **1e** see Table 1, entry 5). Whereas **1a** led quantitatively to **2a** in all the solvents tested, no products were formed with **1e** in refluxing dichloromethane after 24 h; a 10% conversion of **1e** with the formation of cyclic ether **2e** was obtained in refluxing acetonitrile, and in refluxing dichloroethane 23% conversion of **1e** was attained. In contrast, in refluxing nitromethane, the reaction of **1e** was more efficient and afforded 73% conversion after 1.5 hours with the formation of the cyclised 5-membered ring ether **2e**, obtained in 90% yield and with 92% regioselectivity.

We extended the cyclisation to other olefinic alcohols by using a catalytic amount of Sn(OTf)₄ (5 mol%) in refluxing nitromethane (Table 1). The reactivity of γ,δ -unsaturated alcohols possessing a trisubstituted double bond such as in compounds **1a** or **1b**, afforded exclusively one product, the corresponding substituted tetrahydropyrans **2a** or **2b**, respectively (entries 1–2). In contrast, the methylene disubstituted olefinic alcohol **1c** led exclusively to the substituted tetrahydrofuran **2c** (entry 3). It is worth noting that the cyclisation took place exclusively at the more substituted carbon atom of the double bond.

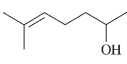

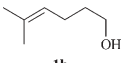

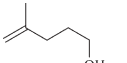

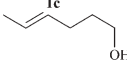

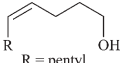

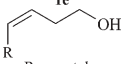

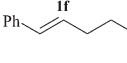

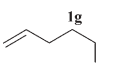

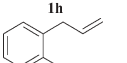

With alcohols bearing a terminal or an internal disubstituted double bond, the catalytic cyclisation was efficient only in refluxing CH₃NO₂. In the case of the cycloisomerisation of disubstituted γ,δ -unsaturated alcohols *trans*-**1d** or *cis*-**1e** (entries 4–5), the corresponding tetrahydrofurans **2d** and **2e** were regioselectively formed. In both cases, tetrahydrofuran/tetrahydropyran selectivity was 92:8. In the case of the *cis*- β,γ -unsaturated alcohol **1f** (entry 6), the cyclisation led exclusively to the 5-membered ring **2f**, the 4-membered ring not being detected.

Under the same conditions, the cyclisation of *trans*-5-phenyl-4-penten-1-ol **1g** afforded the corresponding tetrahydropyran isomer **2g** as the only isolated compound (entry 7). The isolated yield was in this case lower, certainly due to some partial polymerisation of the styrenic moiety.

Terminal olefinic alcohols such as **1h** or **1i** (entries 8 and 9) could also be cyclised, though with incomplete conversions; the 5-membered cyclic ethers **2h** and **2i** were the only products obtained in quantitative yields according to GC analysis. Interestingly, the cycloisomerisation with catalytic amounts of

*dunach@unice.fr

Table 1 Cycloisomerisation of unsaturated alcohols catalysed by Sn(OTf)₄ (5 mol%)¹²

Entry	Unsaturated alcohol	Time	Conversion (%)	Major product	Yield/converted 1 (%) ^d
1		10 min	100		>98
2		1 h	100		>98
3		15 min	100		>98
4		5 h	78		88 ^b
5		1.5 h	73		90 ^b
6		1 h	73		>98
7		1 h	90		77
8		1 h	44		>98
9		7 h	40		>98

^a Yields presented were determined by GC analysis and, in some cases with an internal standard. Isolated yields for products **2e–2g** and **2i** were in the range of 60–77% and for compounds **2a–2d** and **2h** in the range of 34–70%, due to their high volatility. ^b In both entries 4 and 5, the regioselectivity of 5- versus 6-membered rings was 92:8.

tin(IV) triflate could also be run with terminal non-activated olefinic alcohols, indicating a high activity of the catalyst in the activation of both the hydroxyl group and the C–C double bond.

The cyclisation of **1a** could also be carried out in the absence of solvent using 1 mol% of Sn(OTf)₄ at 80 °C; the cyclic ether **2a** was obtained quantitatively after 2 h. The same reaction in the absence of solvent could also be run using only 0.1 mol% of Sn(OTf)₄ with a quantitative formation of **2a** after 10 h.

Our results indicate that the reactivity order in the cycloisomerisation with Sn(OTf)₄ is: trisubstituted olefins \cong 1,1-disubstituted > 1,2-disubstituted > monosubstituted. We can also conclude that for β,γ -unsaturated alcohols the reaction was regioselective affording exclusively the 5-membered ring ethers. In the case of γ,δ -unsaturated alcohols, the cyclic ethers followed the Markovnikov's rule, with the attack of the hydroxyl group on the more substituted olefinic carbon. For 1,2-disubstituted γ,δ -unsaturated alcohols, the 5-membered ring ethers were regioselectively favoured over the tetrahydropyran structures, except for the cycloisomerisation of phenyl-substituted **1g**. In the case of **1g**, we observed the selective formation of the 6-membered ring ether, due to the stabilisation by the phenyl substituent.

In order to better determine the role of Sn(OTf)₄ as the catalyst for alkene activation, the possibility of catalysis participation by protons present in the medium was examined. The cyclisation of **1a** catalysed by 5% molar of trifluoromethanesulfonic acid also afforded **2a** quantitatively. In contrast, the reaction of **1a** with TfOH (5 mol%) in the presence of a hindered-base, such as

2,6-lutidine (5 mol%), led to no conversion after 24 h. We then studied the cyclisation of **1a** in the presence of Sn(OTf)₄ and the base (**1a**:Sn(OTf)₄:base molar ratio of 20:1:1). The result of the cycloisomerisation was similar to that in entry 1 (Table 1), with a quantitative formation of **2a**, indicating that protons were not involved in the catalytic activity. The role of water was also examined, in view of a partial hydrolysis of the metallic triflate. The cyclisation of **1a** in the presence of Sn(OTf)₄ and water (**1a**:Sn(OTf)₄:H₂O molar ratios of 20:1:1 and 20:1:10) afforded the same results as those given for **1a** in Table 1. The presence of water had a very low influence on the activity of tin(IV) triflate. These sets of experiments indicate that tin(IV) triflate plays an active role as the catalyst in the intramolecular hydroalkoxylation of unsaturated olefins.

The reported cycloisomerisation of unsaturated alcohols constitutes the first example of such a reaction using a catalytic amount of a strong Lewis acid. Our results also suggest that tin(IV) triflate is able to coordinate and efficiently activate not only the –OH group, but also the double bond of the substrate, by enhancing the electrophilic character of the C–C double bond and by favouring the intramolecular nucleophilic addition of the alcohol group. The high electrophilicity of the metal centre of tin(IV) triflate should considerably contribute to the alkene activation.

In conclusion, Sn(OTf)₄ was shown to be an effective catalyst for the cycloisomerisation of differently substituted unsaturated alcohols leading to the corresponding cyclic ethers regioselectively

and quantitatively. Tetrahydrofuran and tetrahydropyran structures were formed according to the structure and the substitution of the starting alcohols **1** with 0.1 to 5 mol% of the catalyst. This reaction could also be run efficiently in the absence of solvent using a low catalyst ratio (0.1 mol%). Moreover, the development of new catalysts for the hydroalkoxylation reaction constitutes a novel example of atom economy in cyclisation processes.

Lydie Coulombel,^a Isabelle Favier^a and Elisabet Duñach^{*ab}

^aLaboratoire Arômes, Synthèses et Interactions, Université de

Nice-Sophia Antipolis, Parc Valrose, 06108 Nice cedex 2, FRANCE

^bLaboratoire de Chimie Bio-Organique, CNRS, UMR 6001; Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice cedex 2, FRANCE. E-mail: dunach@unice.fr

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- 11 The electrochemical preparation of Sn(OTf)₄ was carried out in a one-compartment cell, in nitromethane as the solvent, at room temperature in the presence of triflic acid. The anodic material consisted of a rod of tin and the cathode was of stainless steel. The reaction was stopped after the passage of 1 F per mol of acid. After evaporation of the solvent and washing of the powder, Sn(OTf)₄ was obtained in 76% yield, coordinated to 1.4 solvent molecules, according to NMR data and elemental analysis.
- 12 General Lewis acid-catalysed cyclisation procedure: a mixture of unsaturated alcohol (1 mmol) and Sn(OTf)₄ (0.05 mmol) in distilled nitromethane (5 ml) was stirred at reflux for 10 min to 7 h, depending on the unsaturated alcohol. The progress of the reaction was monitored by GC analysis, with classical work-up. The known products **2a–2i** were analysed by ¹H and ¹³C-NMR and mass spectrometry and the data compared to those described in the literature.