CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200501478

Aluminium(III) Trifluoromethanesulfonate as an Efficient Catalyst for the Intramolecular Hydroalkoxylation of Unactivated Olefins: Experimental and Theoretical Approaches

Lydie Coulombel,[a] Michel Rajzmann,[b] Jean-Marc Pons,*[b] Sandra Olivero,[a] and Elisabet Duñach*[a]

Abstract: The Al(OTf)$_3$-catalyzed cycloisomerization of unactivated unsaturated alcohols was studied from experimental and theoretical points of view. A series of cyclic ethers was obtained in excellent yields and regioselectivities. This catalyst system provides one of the most straightforward routes to cyclic ethers with Markovnikov-type regioselectivity under mild conditions. Theoretical and NMR studies were carried out in order to better determine the mechanism of this reaction. The NMR studies were in agreement with preferential complexation of Al(OTf)$_3$ to the oxygen atom of the unsaturated alcohol, but did not exclude complexation to the double bond of the alcohol. Theoretical calculations indicated strong acidification of the hydroxyl proton when Al(OTf)$_3$ was complexed to the alcohol oxygen atom. A plausible catalytic cycle for the Al(OTf)$_3$-catalyzed intramolecular hydroalkoxylation of unactivated olefins is proposed.

Keywords: aluminum • cyclization • Lewis acids • oxygen heterocycles • reaction mechanisms

Introduction

Saturated oxygen heterocycles are important core structures which are frequently found in polyether antibiotics and other biologically active natural products.[1] Great interest is focused on the development of new and efficient methods for the synthesis of cyclic ethers. One of the most appealing approaches to these heterocycles is intramolecular hydroalkoxylation, in which the cyclic ether is formed by addition of an alcohol to an olefin.[2] Although this reaction is known to be catalyzed by Brønsted acids in superstoichiometric amounts, we recently reported the use of tin(IV) triflate as catalyst for the hydroalkoxylation of unactivated alkenes.[3] Indeed, the highly Lewis acidic character of this catalyst is due to the strongly electron withdrawing trifluoromethanesulfonate group.[4]

The use of transition-metal catalysis for selective hydroalkoxylation of unsaturated hydrocarbons[5] has been reported in the cases of C≡C[6] and activated C=C bonds such as allenes,[7] 1,3-dienes[8] and Michael acceptors.[9] Ce^{III}/NaI,[10] Ru^{III}/Ag^{I}[11] and Au^{I}/Ag^{I} systems,[12] as well as Pt^{II} complexes in the presence of phosphine ligands,[13] have recently been used as catalysts for the intramolecular hydroalkoxylation of unactivated γ- and δ-hydroxy alkenes to form cyclic ethers.

Herein we report that aluminium(III) trifluoromethanesulfonate is an efficient catalyst for the highly regioselective intramolecular hydroalkoxylation of unactivated olefins to afford the corresponding cyclic ethers in excellent yields. Our study includes experimental results and some mechanistic considerations based on NMR experiments and semiempirical calculations. The use of Al^{III} compounds for the intramolecular cyclization of alcohols has only been reported with superstoichiometric amounts of AlCl$_3$.[14]

Results and Discussion

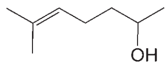
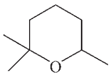
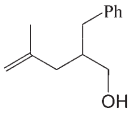
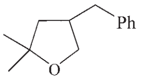
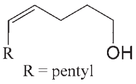
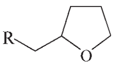
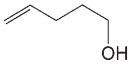
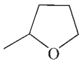
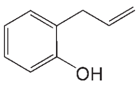
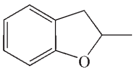
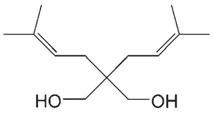
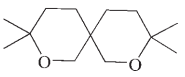
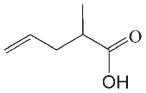
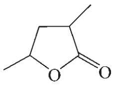
Cycloisomerization of unsaturated alcohols catalyzed by Al(OTf)$_3$: Aluminium(III) triflate, which is commercially available, was investigated as catalyst for the intramolecular hy-

---

[a] Dr. L. Coulombel, Dr. S. Olivero, Dr. E. Duñach
Laboratoire de Chimie des Molécules Bioactives et des Arômes
UMR-CNRS 6001, Université de Nice-Sophia Antipolis
Parc Valrose, 06108 Nice Cedex 2 (France)
Fax: (+33) 492-076-125
E-mail: dunach@unice.fr

[b] Dr. M. Rajzmann, Prof. J.-M. Pons
Laboratoire SYMBIO, UMR-CNRS 6178
Faculté des Sciences et Techniques, Université Paul Cézanne
Boîte D12, 13397 Marseille Cedex 20 (France)
Fax: (+33) 491-288-841
E-mail: jean-marc.pons@univ.u-3mrs.fr

Table 1. Hydroalkoxylation of γ,δ-unsaturated alcohols catalyzed by $Al(OTf)_3$ (5 mol %).

Entry	Unsaturated alcohol	Conditions	Major product	Yield of isolated product [%]	Regioselectivity five- vs six-membered cyclic ether
1	 **1a**	CH_2Cl_2, 40 °C, 1 h	 **3a**	93	0:100
2	 **1b**	CH_2Cl_2, 40 °C, 1 h	 **2b**	88	100:0
3	 R = pentyl **1c**	CH_3NO_2, 101 °C, 1.5 h	 **2c**	88	92:8
4	 **1d**	CH_3NO_2, 101 °C, 1 h	 **2d**	87	100:0
5	 **1e**	CH_3NO_2, 101 °C, 3 h	 **2e**	>93	100:0
6	 **1f**	$ClCH_2CH_2Cl$, 84 °C, 0.5 h	 **3f**	91	0:100
7	 **1g**	CH_3NO_2, 101 °C, 1.5 h	 **2g**	88	100:0[a]

[a] *cis*/*trans* ratio of **2g** was 60:40, as calculated by GC and as determined by NOESY NMR experiments.

droalkoxylation of unactivated olefins. The influence of the solvent (e.g., dichloromethane, acetonitrile, dichloroethane and nitromethane) on the cycloisomerization of two model substrates **1a** and **1c** was first examined in the presence of $Al(OTf)_3$ (5 mol %). Whereas unsaturated alcohol **1a** led quantitatively to tetrahydropyran **3a** in all solvents tested, no reaction occurred with **1c** in refluxing dichloromethane, and only 10 % conversion of **1c** was reached in refluxing acetonitrile after 22 h. However, cyclization of **1c** was efficient in refluxing nitromethane and afforded the corresponding tetrahydrofuran **2c** after 1.5 h with 92 % regioselectivity.

The cyclization of differently substituted olefinic alcohols was examined by using a catalytic amount of $Al(OTf)_3$ (5 mol %). The required solvent and reaction temperature was dependent on the double-bond substitution of the olefin (Table 1). For each substrate the solvent was chosen according to its boiling point. However, the solubility of $Al(OTf)_3$ was much higher in nitromethane.

As shown in Table 1, the hydroalkoxylation of an unsaturated alcohol with a trisubstituted double bond, such as **1a** (entry 1), led exclusively to formation of the corresponding tetrahydropyran **3a**, the result of cyclization at the more substituted carbon atom of the double bond in a Markovnikov-type addition. No five-membered cyclic ether was observed.

Cycloisomerization of alcohol **1b** (entry 2) bearing a 1,1-disubstituted double bond gave the five-membered cyclic ether **2b** as the only product in 88 % yield, regiospecifically. In both cases, the reaction was complete in refluxing dichloromethane after 1 h.

In the case of alcohol **1c**, with an internal disubstituted *Z* double bond (entry 3), cyclization was successfully carried out in refluxing nitromethane and afforded the five-membered cyclic ether as the major compound. The selectivity for five-versus six-membered cyclic ether was 92:8.

The $Al(OTf)_3$ catalyst system was also applied to the intramolecular hydroalkoxylation of terminal, unactivated olefins such as **1d** or **1e** (entries 4 and 5). For both substrates, the reaction took place at the more substituted olefinic carbon atom and led exclusively to the corresponding tetrahydrofurans **2d** and **2e**.

The $Al(OTf)_3$-catalyzed hydroalkoxylation was also efficiently applied to the synthesis of spirobicyclic ether **3f**, starting from the corresponding doubly unsaturated diol **1f** (entry 6). Bis-tetrahydropyran **3f** was obtained with complete regioselectivity in quantitative yield.

As an extension of the reaction, the preparation of γ-lactone **2g** from the corresponding γ,δ-unsaturated carboxylic acid **1g** (entry 7) was carried out under the same catalytic conditions, with 100 % regioselectivity in favour of the γ-lactone.

The reaction rates observed for the cycloisomerization of γ,δ-unsaturated alcohols in the presence of $Al(OTf)_3$ allowed the following reactivity order to be established: trisubstituted ≈ 1,1-disubstituted > 1,2-disubstituted > monosubstituted olefins.

The hydroalkoxylation of olefins was very dependent on the nature of the catalyst. To highlight the influence of the counterion on reactivity and selectivity of cycloisomerization, we examined the cyclization of substrate (*Z*)-4-decenol (**1c**) in the presence of several aluminum(III) compounds as catalysts.

Kinetics of the reaction are shown in Figure 1 for $Al(OTf)_3$, $AlBr_3$, $AlCl_3$ and $Al(O\textit{i}Pr)_3$. After 1.5 h in refluxing nitromethane, the reaction of decenol **1c** with 5 mol % of

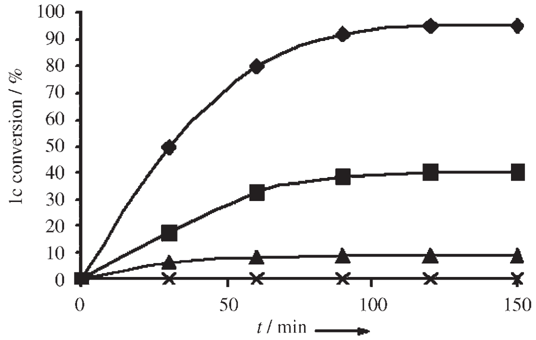
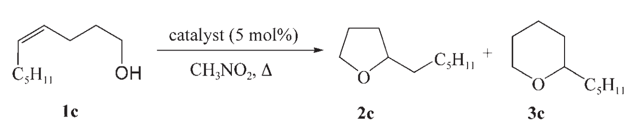


Figure 1. Kinetics of the hydroalkoxylation of (*Z*)-4-decenol (**1c**) catalyzed by aluminium compounds (5 mol %) in refluxing nitromethane (*n*-undecane used as internal standard); ◆: $Al(OTf)_3$, ■: $AlCl_3$, ▲: $AlBr_3$, ×: $Al(O\textit{i}Pr)_3$.

$AlCl_3$ gave a mixture of tetrahydrofuran **2c** and tetrahydropyran **3c** (Scheme 1) with less than 10 % conversion. With $AlBr_3$ the conversion reached up to 40 % in favour of **2c**, but no further evolution of the reaction mixture was observed. No reaction occurred with $Al(O\textit{i}Pr)_3$. The same reaction with 5 mol % of $Al(OTf)_3$ took place quantitatively after 1.5 h. The Lewis acidity of the catalyst strongly determines the reactivity and the selectivity.



Scheme 1.

Mechanistic studies on the $Al(OTf)_3$-catalyzed hydroalkoxylation of olefins: In protic acidic media, the mechanism of the cycloisomerization of unsaturated alcohols is a well-known process.[15] It generally involves initial protonation of the double bond with intermediate formation of the more substituted carbocation. Subsequent attack of the hydroxyl group on the more substituted carbon atom of the double bond forms the ether with Markovnikov-type regioselectivity. The mechanism of this reaction in the presence of Lewis acids has not been yet reported.

In a recent example with Pt^{II} in the presence of phosphine ligands for the hydroalkoxylation of unactivated olefins,[13] the observed regioselectivity was similar to that found with $Al(OTf)_3$ (Markovnikov-type addition). The proposed mechanism involved platinum(II) complexation to the olefin, followed by outer-sphere attack of the pendant hydroxyl group.

To better determine the role of Al^{III} Lewis acid as catalyst for the hydroalkoxylation reaction, the cyclization of substrate **1a** was examined in the presence of an added base or water, and the results were compared to the use of TfOH with or without an added base. The results are summarized in Table 2.

Table 2. Cyclization of **1a** in the presence of 5 mol % of $Al(OTf)_3$ or TfOH and an additive in refluxing dichloromethane.

Entry	Catalyst (5 mol %)	Additive	*t* [h]	Conversion of **1a** [%][a]	Yield of isolated **3a** [%]
1	$Al(OTf)_3$	–	1	100	93
2	$Al(OTf)_3$	2,6-lutidine (5 mol %)	1	100	92
3	TfOH	–	0.5	100	90
4	TfOH	2,6-lutidine (5 mol %)	24	< 5	–
5	$Al(OTf)_3$	H_2O (5 mol %)	1	100	92
6	$Al(OTf)_3$	H_2O (50 mol %)	1	98	90

[a] Conversions calculated by GC with *n*-undecane as internal standard.

In the presence of 2,6-lutidine as a hindered base ($Al(OTf)_3$/base 1:1), the $Al(OTf)_3$-catalyzed hydroalkoxylation of heptenol **1a** was similar to that obtained without added base (cf. entries 1 and 2). This result indicates that the hindered base does not inhibit cyclization, and proton capture by the base is not directly involved in the reaction.

The cycloisomerization of **1a** could also be run with 5 mol % of TfOH and afforded the corresponding tetrahydropyran **3a** quantitatively (entry 3). However, the reaction of **1a** with 5 mol % of TfOH and a hindered base as additive (5 mol %) gave a very low conversion of **1a** (< 5 %) after 24 h (entry 4).

These observations clearly indicate that when $Al(OTf)_3$ is involved, the reaction is indeed induced by the Lewis acid and not by triflic acid, which could result from the reaction between $Al(OTf)_3$ and the alcohol.

The influence of water on the $Al(OTf)_3$-catalyzed cycloisomerization of **1a** was examined with a view to partial hydrolysis of the catalyst. Interestingly, as shown in Table 2 (entries 5 and 6), similar results were obtained with or without added water, that is, the presence of water has minor influence on the catalytic activity of $Al(OTf)_3$. All these experiments indicate that $Al(OTf)_3$ is an active species in the intramolecular hydroalkoxylation of unactivated olefins, and its catalytic activity is similar to that of a superacid.

The $Al(OTf)_3$-catalyzed hydroalkoxylation (Table 1) exhibits Markovnikov-type regioselectivity, as is observed for the same reaction in protic acidic media. This suggests that the mechanism of Lewis acid catalyzed hydroalkoxylation of double bonds should involve cationic-type intermediates.

In the hydroalkoxylation of olefins catalyzed by $Al(OTf)_3$, which is a strong Lewis acid, it is assumed that the aluminium atom should preferentially coordinate to the hydroxyl group. However, we were interested to determine whether coordination to both the hydroxyl oxygen atom and the C–C double bond of the unsaturated alcohol could be considered.

To investigate this possibility, we carried out ^1H and ^{13}C NMR studies on the complexation of $Al(OTf)_3$ to alcohol **1c**. NMR experiments can highlight complex formation and have previously been used, for example, to evaluate the complexation between Ag^+ and alkynes.[16]

Several NMR experiments with decenol **1c** were carried out in CD_3NO_2 at room temperature with tetramethylsilane (TMS) as internal standard in the presence of 6 equiv $Al(OTf)_3$. At the concentrations used, $Al(OTf)_3$ was not soluble in $CDCl_3$ or CD_2Cl_2.

The ^1H NMR experiments were carried out with **1c** and $Al(OTf)_3$. A shift of the signal corresponding to protons H^1 of almost 0.1 ppm ($\Delta\delta = +0.092$ ppm, see Figure 2 for numbering) indicates, as expected, complexation of Al^{III} to the hydroxyl oxygen atom of decenol **1c**. A very small variation of the chemical shift of the ethylenic protons H^4 and H^5 ($\Delta\delta = +0.009$ ppm) does not allow complexation of the double bond to be concluded.

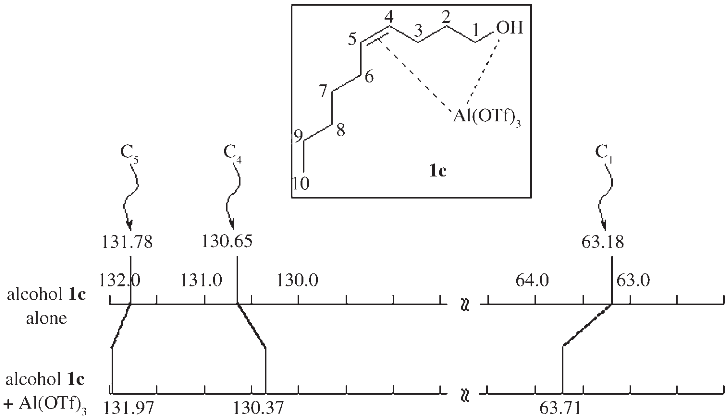


Figure 2. ^{13}C NMR chemical shifts [ppm vs TMS] of alcohol **1c** alone and complexed to $Al(OTf)_3$ for characteristic carbon atoms C^1, C^4 and C^5 in CD_3NO_2 at 20 °C. $[\mathbf{1c}] = 0.03$ M and $[Al(OTf)_3] = 0.18$ M.

The same trend, but more pronounced, was observed in ^{13}C NMR experiments (Figure 2). The complexation of $Al(OTf)_3$ to the double bond and to the oxygen atom of decenol **1c** was shown by slight shifts of $\Delta\delta = +0.19$ and -0.28 ppm for the signals corresponding to ethylenic carbon atoms C^5 and C^4, respectively, and a larger shift of $\Delta\delta = +0.53$ ppm for C^1 bearing the hydroxyl group.

The NMR studies are in agreement with preferential complexation of $Al(OTf)_3$ to the hydroxyl oxygen atom of **1c**, but do not exclude some complexation with the isolated C–C double bond.

Our results suggest that in the $Al(OTf)_3$-catalyzed hydroalkoxylation of unactivated olefins, structures **A** and **B** could both be considered as intermediate species leading to the cyclic ethers (Figure 3).

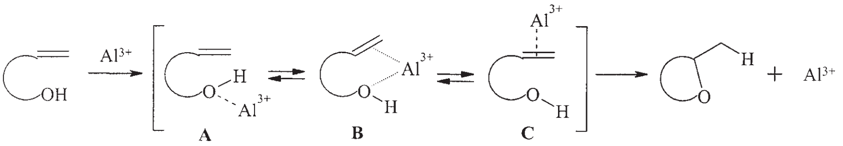
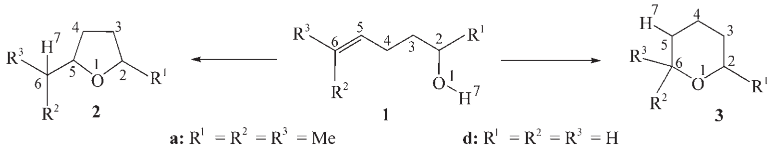


Figure 3. Possible Al^{III} coordination modes to an unsaturated alcohol.

Theoretical Studies

Methodology: All calculations reported in this work were performed with the semiempirical AM1 method[17] available in the AMPAC program.[18] Geometries of stationary points were determined by minimization of energy with respect to all geometric parameters. Transition states were located by the chain method[19] and characterized by one, and only one, negative eigenvalue of the Hessian matrix. Finally, the transitions states found were shown to belong to the studied reaction by intrinsic reaction coordinate (IRC). The AM1 method was chosen mainly for three reasons: 1) its reliability compared to ab initio calculations for reactions involving Lewis acids and our experience in the field,[20] 2) the reasonably short calculation times, which enabled us to perform IRC on each transition state, and 3) the possibility to tackle the real molecules and therefore compare calculations to experiments.

Calculations were run on unsaturated alcohols **1a** and **1d**, with the following goals (Scheme 2): 1) Understanding the action of the Lewis acid and the importance of its nature; 2) Understanding the selectivity for five versus six-membered cyclization on going from **1** to **2** or **3**, respectively.



Scheme 2.

Calculations involved only one alcohol molecule, since preliminary studies showed that the introduction of a second one had very little influence on the activation energies of the uncatalyzed or $Al(OTf)_3$-catalyzed reactions leading from alcohol **1d** to tetrahydrofuran **2d**.[21] Moreover, kinetic data indicated a first-order reaction with respect to the alcohol.

Cyclization of 4-penten-1-ol (1d): Calculations were first run on the cyclization of pentenol **1d** in the absence of Lewis acid, considering both the formation of tetrahydrofuran **2d** (Table 3, entry 1) and tetrahydropyran **3d** (Table 3, entry 2). As shown by the energies of their transition states, the competition should be in favour of the five-membered cyclic molecule **2d**, but in both cases, the activation energies are important (>60 $kcal\,mol^{-1}$). The process is a concerted

Table 3. Energies [kcal mol^{-1}] for alcohols **1a** and **1d**, complexes **A**, **A′** and **C**, transition states **TS1**–**TS12** and ethers **2a**,**d** and **3a**,**d**.

Entry	Starting material	Lewis acid	SM energy	Complex type	Complex	Complex energy	TS	TS energy	E_a	Product	Product energy
1	**1d**		−52.2				**TS1**	+9.7	+61.9	**2d**	−62.8
2	**1d**						**TS2**	+19.4	+71.6	**3d**	−64.3
3	**1d**	$AlCl_3$	−192.5	O		−199.1	**TS3**	−140.4	+58.7	**2d**-$AlCl_3$	−208.9
4	**1d**	$AlCl_3$		C=C		−196.6	**TS4**	−137.8	+58.8	**2d**-$AlCl_3$	
5	**1d**	$AlCl_3$		O		−200.5	**TS5**	−129.2	+71.3	**3d**-$AlCl_3$	−212.8
6	**1d**	$AlCl_3$		C=C		−196.9	**TS6**	−128.1	+68.8	**3d**-$AlCl_3$	
7	**1d**	$Al(OTf)_3$	−891.0	O	**A**	−904.8	**TS7**	−877.6	+27.2	**2d**-$Al(OTf)_3$	−913.7
8	**1d**	$Al(OTf)_3$		C=C	**C**	−901.6	**TS8**	−845.1	+56.5	**2d**-$Al(OTf)_3$	
9	**1d**	$Al(OTf)_3$		O	**A**	−905.3	**TS9**	−875.2	+30.1	**3d**-$Al(OTf)_3$	−915.6
10	**1d**	$Al(OTf)_3$		C=C	**C**	−901.6	**TS10**	−834.1	+67.5	**3d**-$Al(OTf)_3$	
11a	**1a**	$Al(OTf)_3$	−910.5	O	**A′**	−927.6	**TS11a**	−904.0	+23.6	**2a**-$Al(OTf)_3$	−928.0
11b	**1a**	$Al(OTf)_3$		O			**TS11b**	−895.8	+31.8	**2a**-$Al(OTf)_3$	
12a	**1a**	$Al(OTf)_3$		O			**TS12a**	−904.0	+23.6	**3a**-$Al(OTf)_3$	−923.2
12b	**1a**	$Al(OTf)_3$		O			**TS12b**	−907.8	+19.8	**3a**-$Al(OTf)_3$	

mechanism. These results are consistent with the experimental observation that neither of these two ethers is formed from **1d** in the absence of catalyst.

We then involved $AlCl_3$ in the calculations with **1d** (Table 3, entries 3–6) and four different approaches were investigated: complexation of $AlCl_3$ to the oxygen atom of the alcohol, as in intermediate **A** of Figure 3 (entries 3 and 5) or to the C−C double bond, as in structure **C** of Figure 3 (entries 4 and 6). In both cases, the five- versus six-membered competition leading to **2d** and **3d**, respectively, was considered.[22]

The calculations indicated that the introduction of $AlCl_3$ as catalyst has a very small influence on the activation energy of the reaction. In all four cases, the reaction remains concerted and involves a single transition state. The activation energies involved are still in favour of formation of tetrahydrofuran **2d** (entry 3), as illustrated in Figure 4. The introduction of $AlCl_3$ as Lewis acid catalyst is not efficient for the cyclization reaction, in agreement with the experimental results shown in Figure 1.

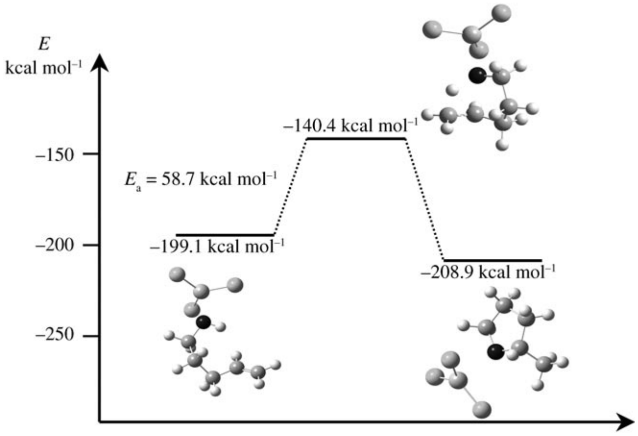


Figure 4. $AlCl_3$-catalyzed cycloisomerization of 4-penten-1-ol (**1d**) to 2-methyltetrahydrofuran **2d** by Al^{III} complexation to the oxygen atom of **1d**.

The results of introducing $Al(OTf)_3$ in the calculations with alcohol **1d**, following the same approach as described for $AlCl_3$, are reported in entries 7–10 of Table 3.

Figure 5 presents the energies and geometries for the less demanding cyclization process corresponding to entry 7.

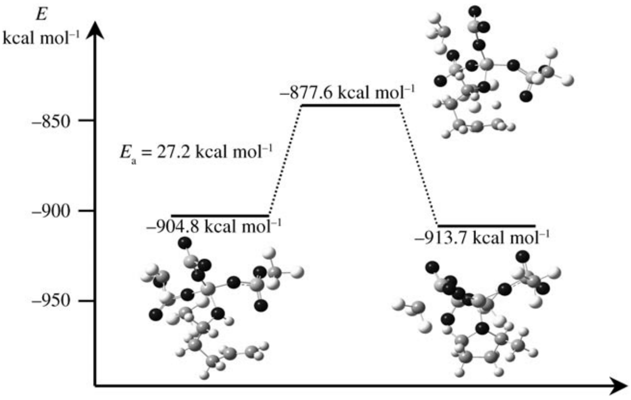


Figure 5. $Al(OTf)_3$-catalyzed cycloisomerization of 4-penten-1-ol (**1d**) to 2-methyltetrahydrofuran **2d** by complexation to the oxygen atom.

Apparently, complexation of $Al(OTf)_3$ to the oxygen atom of alcohol **1d** allows the reactions towards tetrahydrofuran **2d** and tetrahydropyran **3d** to still proceed in a concerted manner, with much smaller activation energies of 27.2 kcal mol^{-1} (entry 7) and 30.1 kcal mol^{-1} (entry 9), respectively. These data compare with 61.9 and 70.9 kcal mol^{-1} for the calculations without catalyst (entries 1 and 2), and 58.7 and 71.3 kcal mol^{-1} with $AlCl_3$ (entries 3 and 5).

On the other hand, complexation of $Al(OTf)_3$ to the C−C double bond of alcohol **1d** (entries 8 and 10) shows high activation energies, similar to those calculated for the uncatalyzed (entries 1 and 2) and $AlCl_3$-catalyzed reactions (entries 4 and 6).

Calculations on the more favoured O complexation indicated that the competition is in favour of formation of the five-membered cyclic ether **2d**. A difference of around 3 kcal mol^{-1} (entries 7 and 9) was found between the transition-state energies leading to **2d** and **3d**. The strong reduction of the activation energy of the process leading to tetrahydrofuran **2d** (entry 7) as compared to the formation of tetrahydropyran **3d** (entry 9) is in complete agreement with the experimental results, in which exclusive formation of product **2d** was observed (Table 1, entry 4).

A reaction path involving alkoxyalumination was also investigated. The addition of the RO–$Al(OTf)_2$ group to the C=C bond with formation of an $R'Al(OTf)_2$ intermediate and subsequent protonation of this organometallic compound (with concomitant regeneration of the $Al(OTf)_3$ catalyst) by triflic acid was considered. Although the first step leading to the five-membered cyclic intermediate requires only 18.4 kcal mol^{-1}, the protonation step requires a much higher activation energy ($E_a = 54.5$ kcal mol^{-1}). Such a mechanism was therefore unlikely to occur and was not further investigated.

Cyclization of 6-methyl-5-hepten-2-ol (1a): Experimental results indicated that the use of $Al(OTf)_3$ was necessary for the efficient and catalytic cycloisomerization of unsaturated alcohols. Calculations with **1d** were in agreement with a much higher efficiency of $Al(OTf)_3$ as compared to $AlCl_3$, which indicates a much lower activation energy for the cyclization (Table 3, entry 7). The lowest transition-state energy was found for $Al(OTf)_3$ complexed to **1d** through its oxygen atom. Accordingly, for the next calculations concerning the cyclization of **1a**, we only used $Al(OTf)_3$, and we investigated the competition between five- (**2a**) and six-membered ring formation (**3a**) with $Al(OTf)_3$ complexed to the oxygen atom of **1a**, as in intermediate **A** of Figure 3 (Table 3, entries 11 and 12).

For formation of both five- and six-membered cyclic ethers, the calculated reaction mechanism becomes stepwise and involves two transition states **TS11a** and **TS11b** from **1a** leading to tetrahydrofuran **2a**, and **TS12a** and **TS12b** leading to tetrahydropyran **3a** (Figure 6). The activation energies found for the cyclization of **1a** with $Al(OTf)_3$ are in agreement with those listed in entries 7 and 9 for **1d**, and are in the range of 19.8–31.8 kcal mol^{-1} (entries 11a, 11b and 12a, 12b). Moreover, **TS11a** and **TS12a** are quasi-equivalent and both involve an interesting lengthening of the O^1–H^7 bond and an interaction between H^7 and C^5 (Table 4, entries 8 and 10; numbering shown in Scheme 2).

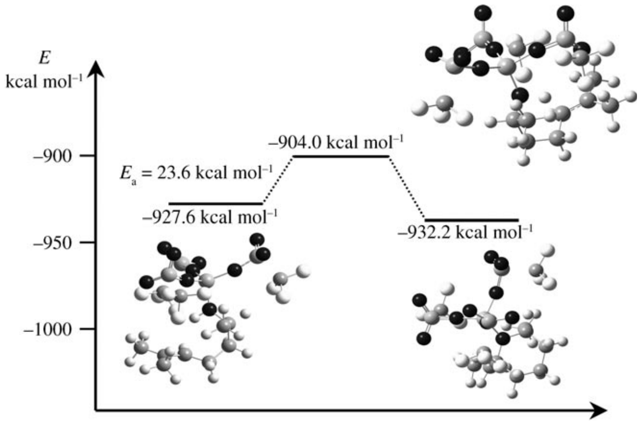


Figure 6. $Al(OTf)_3$-catalyzed cycloisomerization of 6-methyl-5-hepten-2-ol (**1a**) to 2,2,6-trimethyltetrahydropyran (**3a**) through **TS12a** (note that **TS12b**, with lower energy than **TS12a** and close to **TS12a**, is not shown in this figure).

Data on the bond lengths and partial charges of the different complexes and transition states are presented in Table 4.

The energy difference between the two reaction paths leading to **2a** (**TS11a** and **TS11b**) or **3a** (**TS12a** and **TS12b**) is in favour of the cyclization steps leading to the six-membered **3a**. The charge distribution on C^5 and C^6 in **TS12b** (Table 4, entry 11) induces the transfer of H^7 to C^5 in **TS12b**, as well as O^1 transfer to C^6.

Calculated data are clearly in agreement with the experimental results. Indeed, the activation energy required to selectively form tetrahydropyran **3a** from **1a**—the first step is clearly rate-determining, since the second has a relative activation energy of –3.8 kcal mol^{-1} and involves only minor re-

Table 4. Main distances and partial charges of alcohols **1a** and **1d**, complexes **A** and **A′** and transition states **TS7**, **TS9**, **TS11a**, **TS11b**, **TS12a** and **TS12b** (see also Table 3).

Entry	Structures	Distances [Å]						Partial charges [e]			
		O^1–C^5	O^1–C^6	O^1–H^7	C^5–C^6	C^5–H^7	C^6–H^7	δC^5	δC^6	δO^1	δH^7
1	**1d**	3.360	4.350	0.965	1.331	2.650	3.557	–0.173	–0.213	–0.330	0.199
2	complex **A** (**1d**+$AlCl_3$ on O_1)	3.240	4.213	0.969	1.331	2.560	3.391	–0.187	–0.202	–0.320	0.231
3	complex **A** (**1d**+$Al(OTf)_3$ on O_1)	3.087	3.598	0.985	1.332	2.340	2.686	–0.225	–0.196	–0.332	0.322
4	**TS7**	2.835	2.719	1.495	1.381	1.923	1.323	+0.141	–0.347	–0.543	+0.398
5	**TS9**	2.702	2.434	2.337	1.421	1.174	1.990	–0.259	+0.299	–0.568	+0.283
6	**1a**	3.062	4.147	0.966	1.343	2.484	3.381	–0.198	–0.111	–0.327	0.202
7	complex **A′** (**1a**+$Al(OTf)_3$ on O_1)	3.043	3.751	0.984	1.344	2.262	2.872	–0.254	–0.063	–0.327	0.319
8	**TS11a**	2.613	3.502	1.446	1.403	1.298	2.112	–0.347	+0.235	–0.511	+0.369
9	**TS11b**	2.619	3.296	1.993	1.399	1.511	1.392	–0.008	+0.027	–0.557	+0.335
10	**TS12a**	2.611	3.510	1.446	1.403	1.295	2.116	–0.348	+0.235	–0.508	+0.367
11	**TS12b**	2.647	2.044	2.816	1.483	1.129	2.142	–0.214	+0.364	–0.516	+0.150

arrangements--is more than 8 kcal$\,$mol^{-1} lower than the activation energy necessary for the formation of tetrahydrofuran **2a** (Table 3, cf. entries 11b and 12a). The calculations for the cyclization of **1a** to **3a** are presented in Figure 6.

On the other hand, comparing the cyclization of substrates **1d** and **1a**, the activation energy leading to tetrahydropyran **3a** (Table 3, entry 12a: 23.6 kcal$\,$mol^{-1}) is lower than that leading to tetrahydrofuran **2d** (Table 3, entry 7: 27.2 kcal mol^{-1}). These results are also in agreement with the experimental results of Table 1: cyclization of **1a** can take place at much lower temperature than cyclization of **1d** (Table 1, entries 1 and 4).

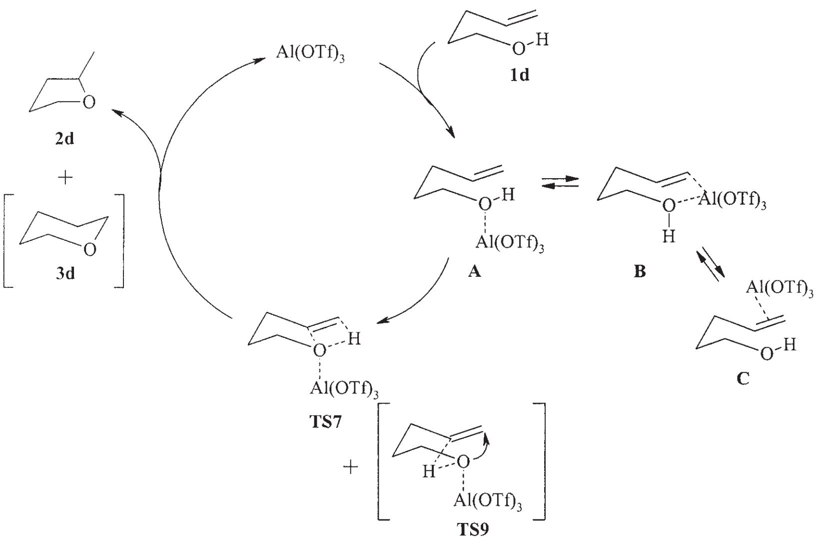


Figure 7. Proposed mechanism for the concerted and regioselective Al(OTf)$_3$-catalyzed cycloisomerization of 4-penten-1-ol (**1d**) to 2-methyltetrahydrofuran (**2d**).

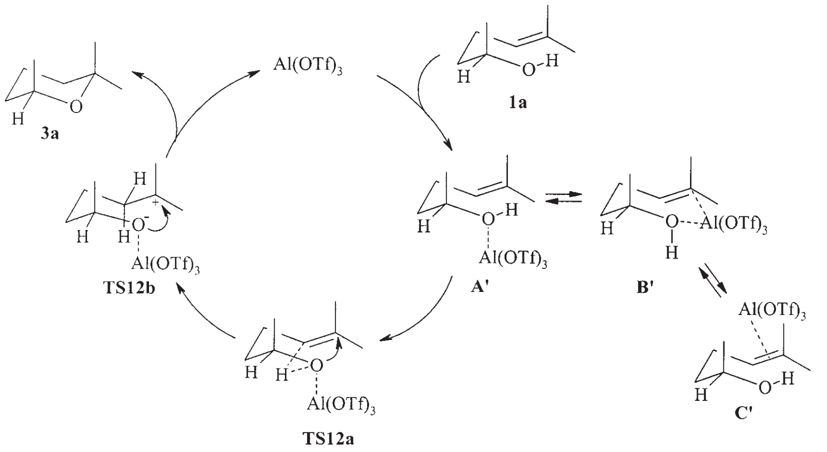


Figure 8. Proposed mechanism for the stepwise Al(OTf)$_3$-catalyzed cycloisomerization of 6-methyl-5-hepten-2-ol (**1a**) to 2,2,6-trimethyltetrahydropyran (**3a**).

Discussion

Proposed catalytic cycle: Based on our catalytic reaction and on semiempirical calculations, we can propose a different mechanism for the Al(OTf)$_3$-catalyzed cycloisomerization of each of the unsaturated alcohols **1a** and **1d** (Figures 7 and 8).

Theoretical and experimental studies indicate that $AlCl_3$ is not active enough to efficiently effect the cyclization of **1a** or **1d**, as opposed to Al(OTf)$_3$. Reaction paths involving the coordination of Al(OTf)$_3$ to the C$-$C double bond, as in structure **C**, are energetically much more demanding than those involving O complexation, as in structure **A** (Figure 3). Therefore, the catalytic cycles for the cycloisomerization of **1a** and **1d** will only be proposed for Al(OTf)$_3$ complexed to the oxygen atom of the alcohols.

In the case of pentenol **1d**, theoretical calculations provided a plausible cyclization mechanism involving a single transition state. We can thus consider a concerted mechanism with a catalytic cycle (Figure 7). In the first step, coordination of the catalyst to the oxygen atom of the unsaturated alcohol gives intermediate complex **A**. This intermediate may be in equilibrium with chelate **B** in which the catalyst is coordinated both to the C=C bond and to the oxygen atom of **1d**, as suggested by NMR data. Complex **C**, involving a complexation only to the double bond of **1d**, could also be considered. However, theoretical calculations are clearly in favour of intermediate **A** as the reactive complex, since it leads to more stable transitions states **TS7** and **TS9** (Figure 7 and Table 3, entries 7 and 9).

The theoretical data on the cyclization of **1d** towards five-membered cyclic ether **2d** indicate that the O^1$-$H^7 bond length in **1d** (0.965 Å) is larger in complex **A** (0.985 Å) and further increases in transition state **TS7** (1.495 Å), as shown in Table 4 (entries 1, 3 and 4).

On the other hand, the partial charge on H^7 of the hydroxyl group in **1d** (+0.199) increases to +0.322 in complex **A** and to at most +0.398 in transition state **TS7**. As a consequence, oxygen atom O^1 becomes more negatively charged (from -0.330 in **1d** to -0.543 in **TS7**). These data are indicative of a strong increase in the acidity of the OH group on going from **1d** to **TS7**.

Elongation of the C^5–C^6 bond in transition state **TS7** is also observed with greater electrophilic character on C^5 as compared to C^6. In **TS7**, the C^6–H^7 distance (1.323 Å) is shorter than the C^5–H^7 distance (1.923 Å), and this indicates approach of O–H to the double bond, selectively favouring formation of five-membered cyclic ether **2d**.

For the less favoured cycloisomerization of **1d** to tetrahydropyran derivative **3d** via **TS9**, the same general tendencies were observed concerning elongation of the O^1–H^7 and C^5–C^6 bonds. The charges on O^1, H^7, C^5 and C^6 in transition state **TS9** are compatible with cyclization to **3d** (Table 4, entry 5). The C^5–H^7 distance is shorter than the C^6–H^7 distance (not shown), and the O–C^5 distance is shorter than the O–C^6 distance, that is, formation of the six-membered cyclic ether **3d** is favoured.

According to the calculated activation energies for formation of **2d** (27.1 $kcal\,mol^{-1}$, Figure 5) and **3d** (30.1 $kcal\,mol^{-1}$, Table 3, entry 9), the theoretical ratio **2d/3d** as predicted by the Arrhenius equation at 374.15 K (experimental temperature of 101 °C) is of 98.8/1.2. This ratio is in good agreement with the experimental data of 100/0 (Table 1, entry 4).

Theoretical studies allow a slightly different catalytic cycle for the cycloisomerization of alcohol **1a** with $Al(OTf)_3$ to be proposed, considering the complexation of Al^{III} to the oxygen atom of the substrate. The mechanism involves a nonconcerted pathway with two more favoured transition states **TS12a** and **TS12b** (Table 3, entries 11, 12; Figure 8). Cyclization of **1a** was examined towards the formation of the corresponding tetrahydrofuran and tetrahydropyran derivatives **2a** and **3a**. Semiempirical calculations are clearly in favour of formation of tetrahydropyran **3a**. Since transition states **TS11a** and **TS12a** have the same energy and are structurally very close, the selected pathway arises from the energy difference between transition states **TS11b** and **TS12b**. Indeed, while **TS11b** is 8.2 $kcal\,mol^{-1}$ higher in energy than **TS11a**, **TS12b** is 3.8 $kcal\,mol^{-1}$ lower in energy than **TS12a**.

The theoretical selectivity of **3a** versus **2a** calculated by the Arrhenius equation at 313.15 K (40 °C) is strongly in favour of six-membered cyclic ether **3a**, with a **3a/2a** ratio of $>99.99/<0.01$. This ratio is also in excellent agreement with experiment, in which tetrahydropyran **3a** was exclusively obtained (Table 1, entry 1). Therefore, only the mechanism for the cycloisomerization of **1a** towards the six-membered cyclic ether **3a** is presented in Figure 8.

Accordingly, the first step of the catalytic cycle involves, as in Figure 8, complexation of the catalyst to the oxygen atom of **1a** to form intermediate complex **A′**. Complexes **B′** and **C′**, in equilibrium with **A′**, can also be considered, although theoretical calculations clearly point to complex **A′** as the reactive intermediate.

In the first transition state **TS12a**, an increase in the the O^1–H^7 distance of 0.48 Å was calculated compared with **1a**, together with an increase of the positive charge on the hydroxyl hydrogen atom from +0.202 to +0.367 (Table 4, entries 6 and 10). These data suggest the generation of a more acidic hydroxyl proton. In **TS12a**, the C^5–H^7 distance is shorter than the C^6–H^7 distance, and the charge at C^5 is much more negative than at C^6, so that selective protonation of the double bond at C^5 is expected. In the second transition state **TS12b**, the O^1–C^6 distance (2.044 Å) is shorter than the O^1–C^5 distance (2.647 Å; Table 4, entry 11). Bond formation of the oxygen atom with C^6 leads to **3a** with recycling of $Al(OTf)_3$ in the catalytic cycle.

The combination of Brønsted and Lewis acids has been a particularly useful tool for explaining several examples of asymmetric catalysis.[23] The design of such "combined acid systems", which can be classified as Brønsted acid assisted Lewis acids (BLA), Lewis acid assisted Lewis acids (LLA), Lewis acid assisted Brønsted acids (LBA) and Brønsted acid assisted Brønsted acid (BBA), enhance acidity by associative interaction and provide more organized structures that lead to more effective asymmetric environments. For example, the combination of $SnCl_4$ with an optically active binaphthol derivative increased the acidity of the OH proton in enantioselective protonation and enantioselective polyene cyclization.[24]

To explain the high catalytic activity of $Al(OTf)_3$ in the cycloisomerization of unsaturated alcohols, we propose a Lewis acid assisted Brønsted acid situation (LBA) in which the Lewis acid $Al(OTf)_3$ strongly enhances the Brønsted acidity of the hydroxyl protons of unsaturated alcohols.

Conclusion

In summary, we have demonstrated, for the first time, the catalytic efficiency of aluminum(III) trifluoromethanesulfonate for the efficient, regioselective and atom-economic cycloisomerization of unactivated unsaturated alcohols. Substituted tetrahydrofurans and tetrahydropyrans were selectively and quantitatively obtained from γ,δ-unsaturated alcohols, depending on the substitution of the double bond, with Markovnikov-type selectivity.

The experimental results obtained in the presence of a hindered base or water indicate that no inhibition is exhibited by these additives. $Al(OTf)_3$ plays a particularly active role as the catalyst in the intramolecular hydroalkoxylation of unactivated olefins.

Theoretical and NMR complexation studies show that O complexation to unsaturated alcohols **1a** and **1d** of $Al(OTf)_3$ is stronger and more efficient than complexation with the double bond. Theoretical calculations indicated lengthening of the O–H bond in the transition states when $Al(OTf)_3$ was complexed to the oxygen atom of the unsaturated alcohols. This interesting feature is an example of the enhancement of the "acidity" of the hydroxyl hydrogen atom by substrate coordination with a Lewis superacid. The cycloisomerization of unsaturated alcohols catalyzed by $Al(OTf)_3$ can be considered as an example of the concept of Lewis acid assisted Brønsted acid (LBA).[23]

The proposed mechanistic cycles for the cycloisomerization of alcohols **1a** and **1d** involve the formation of a complex between the oxygen atom of the unsaturated alcohol and $Al(OTf)_3$ with an increase in the acidity of the hydroxyl proton in the first step. This proposed mechanism is different from that recently proposed for platinum-catalyzed cycloisomerization of unsaturated alcohols, in which coordination of platinum(II) to the double bond was proposed in the first step.[13] Our studies constitute the first example of cycloisomerization of unsaturated alcohols catalyzed by an Al-centred Lewis acid, and include a mechanistic investigation which supports the increased acidity of the hydroxyl proton as the key to activating unactivated double bonds.

Experimental Section

Materials and methods: Reagents were obtained from Alfa Aeser and Aldrich, and were used without further purification. Aluminum(III) trifluoromethanesulfonate is commercially available, but it can also be easily prepared by electrosynthesis from triflic acid and an aluminium rod.[25] ^1H and ^{13}C NMR studies were carried out with a Bruker Avance 500 operating at 500 MHz (^1H). ^1H and ^{13}C NMR spectra of cyclic ethers were run with a Bruker AC 200 operating at 200 MHz (^1H). GC analyses were performed with a Varian CP 3380.

General procedure for $Al(OTf)_3$-catalyzed hydroalkoxylation of unsaturated alcohols: A mixture of unsaturated alcohol (1 mmol) and $Al(OTf)_3$ (23.7 mg, 0.05 mmol) in distilled nitromethane or dichloromethane (5 mL) was stirred at reflux for 0.5–3 h. The progress of the reaction was monitored by GC analysis. The reaction mixture was quenched with HCl (1 M) and extracted with Et_2O. The organic layer was washed with HCl (0.1 M), dried with $MgSO_4$ and the solvent was evaporated. The products were purified by silica-gel column chromatography with pentane/diethyl ether 95:5 as eluent and analyzed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, with comparison to data for reported compounds. The regioselectivities **2**:**3** were calculated by GC and NMR analysis.

For the kinetic studies shown in Figure 1, the reactions were followed by GC with *n*-undecane as internal standard. Reactions were repeated twice with an estimated error of 3%. The ratio of **1c** to undecane was 2:1. The GC response factor of **1c** to undecane (relative areas for a 1:1 molar ratio and a typical FID detection) was 1.95, and that of **2c** to undecane was 1.02. Kinetic data for the cycloisomerization of **1c** with $Al(OTf)_3$ (Figure 1) indicated a first-order reaction with respect to **1c** with a rate constant of $k=7\times10^{-4}\,s^{-1}$ ($R^2=0.987$).

2,2,6-Trimethyltetrahydropyran (3a):[26] ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.7$ (dqd, $J=12.3$, 6.2, 2.0 Hz, 1H; CH), 1.7–1.3 (m, 6H; $(CH_2)_3$), 1.21 (s, 3H; CH_3), 1.19 (s, 3H; CH_3), 1.1 ppm (d, $J=6.2$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=72.0$, 66.7, 36.4, 33.8, 32.4, 23.1, 22.4, 20.5 ppm; MS (70 eV, EI): m/z (%): 128 (0.7) $[M]^+$, 113 (69) $[M-CH_3]^+$, 110 (1) $[M-H_2O]^+$, 95 (9), 59 (100) $[C_3H_7O]^+$.

4-Benzyl-2,2-dimethyltetrahydrofuran (2b):[27] ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.4$–7.1 (m, 5H; ArH), 3.9 (dd, $J=8.4$, 6.7 Hz, 1H; C*H*HO), 3.5 (dd, $J=8.4$, 7.8 Hz, 1H; CH*H*O), 2.7–2.5 (m, 1H; CH, CH_2Ph), 1.9 (dd, $J=12.3$, 6.9 Hz, 1H; C*H*HC$(CH_3)_2$), 1.5 (dd, $J=12.3$, 8.3 Hz, 1H; CH*H*C$(CH_3)_2$), 1.3 (s, 3H; CH_3), 1.2 ppm (s, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=141.3$, 129.0, 128.8, 126.4, 81.3, 72.6, 45.6, 42.1, 39.9, 29.4, 28.6 ppm; MS (70 eV, EI): m/z (%): 190 (2) $[M]^+$, 175 (44) $[M-CH_3]^+$, 157 (20), 134 (8) $[M-C_4H_8]^+$, 117 (22) $[CH(CH_2)_2Ph]^+$, 104 (10) $[CHCH_2Ph]^+$, 91 (66) $[CH_2Ph]^+$, 77 (5) $[Ph]^+$, 43(100) $[C_3H_7]^+$.

2-Hexyltetrahydrofuran (2c):[28] ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.9$–3.6 (m, 3H; CH, CH_2), 1.9–1.7 (m, 3H; C*H*HCH(C_6H_{13}), CH_2), 1.5–1.1 (m, 11H; CH*H*CH(C_6H_{13}), $(CH_2)_5$), 0.8 ppm (t, $J=6,8$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=79.9$, 68.0, 36.2, 32.2, 31.8, 29.8, 26.8, 26.1, 23.0, 14.5 ppm; MS (70 eV, EI): m/z (%): 156 (0.2) $[M]^+$, 138 (2) $[M-H_2O]^+$, 71 (100) $[M-C_6H_{13}]^+$, 43 (34) $[C_3H_7]^+$.

2-Methyltetrahydrofuran (2d):[29] ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.0$–3.8 (m, 3H; CH, C*H*H), 3.7 (ddd, $J=8.1$, 7.7, 6.4 Hz, 1H; CH*H*), 2.1–1.8 (m, 3H; C*H*HCHCH$_3$, CH_2), 1.5–1.3 (m, 1H; CH*H*CHCH$_3$), 1.2 ppm (d, $J=6.1$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=75.3$, 67.7, 33.1, 25.9, 21.0 ppm.

2-Methyl-2,3-dihydrobenzofuran (2e):[30] ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.2$–7.0 (m, 2H; ArH), 6.8–6.6 (m, 2H; ArH), 4.8 (ddq, $J=8.8$, 7.7, 6.3 Hz, 1H; CHOR), 3.2 (dd, $J=15.4$, 8.8 Hz, 1H; C*H*H), 2.7 (dd, $J=15.4$, 7.7, 1H; CH*H*), 1.4 ppm (d, $J=6.3$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=159.2$, 128.4, 127.3, 125.8, 120.1, 109.2, 79.1, 37.0, 22.2 ppm; MS (70 eV, EI): m/z (%): 134 (100) $[M]^+$, 133 (43) $[M-H]^+$, 119 (61) $[M-CH_3]^+$, 105 (24) $[M-C_2H_5]^+$, 91 (78) $[M-C_3H_7]^+$, 77 (24) $[Ph]^+$, 51 (22).

3,3,9,9-Tetramethyl-2,8-dioxaspiro[5.5]undecane (3f):[31] ^1H NMR (200 MHz, $CDCl_3$): $\delta=3.45$ (d, $J=12.0$ Hz, 2H; C*H*HOR), 3.35 (d, $J=12.0$ Hz, 2H; CH*H*OR), 1.7–1.5 (m, 2H; C*H*HC$(CH_3)_2$), 1.4 (dd, $J=6.3$, 5.6 Hz, 4H; CH_2), 1.35–1.25 (m, 2H; C*H*HC$(CH_3)_2$), 1.12 (s, 6H; CH_3), 1.10 ppm (s, 6H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=71.9$, 67.6, 32.2, 31.7, 28.2, 27.3, 25.9 ppm. MS (70 eV, EI): m/z (%): 212 (0.4) $[M]^+$, 197 (80) $[M-CH_3]^+$, 179 (4) $[M-CH_5O]^+$, 138 (54), 109 (87), 67 (100).

***trans*-3,5-Dimethyldihydrofuran-2-one (2g) (*cis*/*trans* 60:40)**:[32] ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.6$ (qt, $J=6.4$, 5.2 Hz, 1H; CHOR), 2.8–2.5 (m, 1H; C*H*CH$_3$), 2.0–1.8 (m, 2H; CH_2), 1.3 (d, $J=6.4$ Hz, 3H; CH_3), 1.2 ppm (d, $J=7.3$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=180.4$, 75.0, 37.4, 34.4, 21.4, 16.1 ppm; MS (70 eV, EI): m/z (%): 114 (0.9) $[M]^+$, 99 (5) $[M-CH_3]^+$, 55 (73), 45 (14), 44 (10), 43 (63), 42 (100), 41 (66).

***cis*-3,5-Dimethyldihydrofuran-2-one (2g) (*cis*/*trans* 60:40)**:[32] ^1H NMR (200 MHz, $CDCl_3$): $\delta=4.4$ (qt, $J=6.1$, 5.2 Hz, 1H; CHOR), 2.8–2.5 (m, 1H; C*H*CH$_3$), 2.4 (ddd, $J=12.0$, 8.4, 5.2 Hz, 1H; C*H*HCH(CH_3)O), 1.4 (ddd, $J=12.0$, 11.8, 10.4 Hz, 1H; CH*H*CH(CH_3)O), 1.3 (d, $J=6.1$ Hz, 3H; CH_3), 1.2 ppm (d, $J=6,8$ Hz, 3H; CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta=180.0$, 75.3, 39.5, 36.8, 21.3, 15.5 ppm; MS (70 eV, EI): m/z (%): 114 (1.3) $[M]^+$, 99 (8) $[M-CH_3]^+$, 55 (67), 45 (14), 44 (11), 43 (67), 42 (100), 41 (69).

---

[1] a) G. Cardillo, M. Orena, *Tetrahedron* **1990**, *46*, 3321–3408; b) P. A. Bartlett, *Tetrahedron* **1980**, *36*, 2–72; c) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309–3362; d) H. Kotsubi, *Synlett* **1992**, 97–106; e) M. C. Elliot, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1291–1318; f) M. C. Elliot, E. Williams, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2303–2340.

[2] K. Tani, Y. Katoaka, *Catalytic Heterofunctionalization* (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, Weinheim, **2001**, p. 171.

[3] L. Coulombel, I. Favier, E. Duñach, *Chem. Commun.* **2005**, *17*, 2286–2288.

[4] D. D. DesMarteau, *Science* **2000**, *289*, 72–73.

[5] For recent reviews, see a) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198; b) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; c) J. Muzart, *Tetrahedron* **2005**, *61*, 5955–6008.

[6] a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159; b) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, T. Sordo, P. Campomanes, *Chem. Eur. J.* **2005**, *11*, 5735–5741.

[7] A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538.

[8] a) P. W. Jolly, N. Kokel, *Synthesis* **1990**, 771–773; b) M. Utsunomiya, M. Kawatsura, J. F. Hartwig, *Angew. Chem.* **2003**, *115*, 6045–6048; *Angew. Chem. Int. Ed.* **2003**, *42*, 5865–5868.

[9] a) T. Hosokawa, T. Shinohara, T. Ooka, S.-I. Murahashi, *Chem. Lett.* **1989**, 2001–2004; b) S. Ganguly, D. M. , Roundhill, *Organometallics* **1993**, *12*, 4825–4832; c) K. J. Miller, T. T. Kitagawa, M. M. Abu-Omar, *Organometallics* **2001**, *20*, 4403–4412.

[10] E. Marotta, E. Foresti, T. Marcelli, F. Peri, P. Righi, N. Scardovi, G. Rosini, *Org. Lett.* **2002**, *4*, 4451–4453.

[11] a) K. Hori, H. Kitagawa, A. Miyoshi, T. Ohta, I. Furukawa, *Chem. Lett.* **1998**, *11*, 1083–1084; b) Y. Oe, T. Otha, Y. Ito, *Chem. Commun.* **2004**, 1620–1621; c) Y. Oe, T. Otha, Y. Ito, *Synlett* **2005**, *1*, 179–198.

[12] a) C.-G. Yang, N. W. Reich, Z. Shi, C. He, *Org. Lett.* **2005**, *7*, 4553–4556; b) C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2005**, *127*, 6966–6967.

[13] H. Qian, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 9536–9537.

[14] M. L. Mihailovic, Z. Petrovic, A. Teodorovic, S. Konstantinovic, V. Andrejevic, *C.R. Acad. Sci. Paris* **1989**, *308*, 29–32.

[15] J. A. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, 3rd ed., Wiley Interscience, New York, **1985**, pp. 634–636.

[16] a) T. C. Wabnitz, J-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484–493.

[17] M. J. S. Dewar, E. G. Zoebish, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

[18] All calculations were performed with AMPAC 8.16, Semichem, Inc., PO Box 1649, Shawnee, KS 66222, USA.

[19] D. A. Liotard, *Int. J. Quantum Chem.* **1992**, *44*, 723–741.

[20] J.-M. Pons, M. Oblin, A. Pommier, M. Rajzmann, D. Liotard, *J. Am. Chem. Soc.* **1997**, *119*, 3333–3338.

[21] The introduction of a second molecule of alcohol **1d** slightly increased the activation energies: from 61.9 to 64.7 kcal mol^{-1} in the case of the uncatalyzed reaction, and from 27.2 to 28.7 kcal mol^{-1} in the case of the $Al(OTf)_3$-catalyzed reaction.

[22] Since NMR experiments indicated a certain complexation of the C–C double bond with $Al(OTf)_3$ (as in complex **B**, Figure 3), we also examined the possibility of a reaction path starting from a chelate in which the aluminium atom of the catalyst would be complexed both to the oxygen atom and the C–C double bond of the starting molecule. In order to do so, we assumed dismutation of $Al(OTf)_3$ and concomitant formation of $Al(OTf)_2^+$. The formation of such a chelate (**1d**-$Al(OTf)_2^+$) is indeed exothermic, but we were not able to find an original reaction path leading to tetrahydrofuran **2d** with a comparable or even lower activation energy than that found starting from the O complex (Table 3, entries 7 and 9). Indeed, if the reaction is to proceed, the chelate must be cleaved, and due to the relative strengths of complexation (π complexation vs O complexation), the Lewis acid remains on the oxygen atom. From these results, we propose to explain the NMR chemical shifts observed for the ethylenic carbon atoms either as resulting from the formation of this chelate **B** or from the C=C complex **C**. Both complexes can not lead to the product of the reaction, but since their formation is reversible, they can exist and therefore be observed by spectroscopy.

[23] H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958–1977; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924–1942.

[24] H. Ishibashi, K. Ishihara, H. Yamamoto, *Chem. Rec.* **2002**, *2*, 177–188.

[25] a) E. Dunach, I. Favier, D. Hebrault, J-R. Desmurs (Rhodia Chimie), FR 2818994, **2000**; [*Chem. Abstr.* **2002**, *137*, 239065]; b) I. Favier, E. Dunach, *Tetrahedron Lett.* **2003**, *44*, 2031–2032.

[26] G. Carr, D. Whittaker, *J. Chem. Soc. Perkin Trans. 2* **1989**, 359–366.

[27] J. Diab, M. Abou-Assali, C. Gervais, D. Anker, *Tetrahedron Lett.* **1985**, *26*, 1501–1502.

[28] J. Kula, T. B. Quang, M. Sikora, *Tetrahedron: Asymmetry* **2000**, *11*, 943–950.

[29] Data compared to commercial sample.

[30] V. H. Grant, B. Liu, *Tetrahedron Lett.* **2005**, *46*, 1237–1239.

[31] B. K. Wasson, J. M. Parker, US 3099662, **1963** [*Chem. Abstr.* **1963**, *60*, 9784].

[32] J. L. Garcia Gutierrez, F. Jimenez-Cruz, N. R. Espinosa, *Tetrahedron Lett.* **2005**, *46*, 803–805.

Received: November 29, 2005
Revised: March 2, 2006