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Bi(OTf)₃-catalysed intramolecular cyclisation of unsaturated acetals†

Raphaël Saget,[ab] Piotr Jaunky[*b] and Elisabet Duñach [iD] [*a]

A series of highly functionalized carbocycles was efficiently prepared *via* the selective cyclisation of unsaturated acetals and ketals in the presence of only 1 mol% of Bi(III) or Fe(III) triflates as the catalysts at room temperature, with yields ranging from 60 to 90%. With Bi(OTf)₃ catalysis, α,β-unsaturated ether carbocycles are formed selectively, whereas with the Fe(OTf)₃ system, a cycloisomerisation to carbocyclic diethers is mainly obtained. This acetal/olefin cyclisation could be run at a multi-gram scale and compound **2c** could be obtained on a 300 gram-scale with a yield of 69% after precipitation in hexane.

Introduction

In the context of C–C bond formation catalysed by Lewis acids, several fundamental processes have found important applications, namely the Friedel–Crafts arylations,[1] aldol-type condensations,[2] diene cyclisations,[3] carbonyl-ene or Prins reactions,[4] among others. Although the carbonyl-ene reaction is well documented, both under stoichiometric and catalytic conditions,[5] related enol ether–olefin[6] or acetal–olefin cyclisations have been much less developed.

Among acetal–olefin coupling reactions, the Hosomi–Sakurai reaction involves the Lewis acid promoted allylation of an acetal with an allylsilane (generally allyltrimethylsilane) for the synthesis of homoallyl ethers,[7] including several interesting examples in the field of glycochemistry.[8] This process takes advantage of the nucleophilic activation of the allyl group by the β-stabilisation effect of the silicon atom. Besides the Hosomi–Sakurai allylation, examples of acetal-ene reactions involving non-activated double bonds are scarce. Coupling reactions have been reported under stoichiometric or over-stoichiometric amounts of Lewis acids such as TiCl₄,[9] SnCl₄,[10,11] SnCl₂ [12] or EtAlCl₂.[13] To our knowledge, only two examples using PtCl₂ or FeCl₃ refer to catalytic processes.[14,15]

Interested by the catalytic activation of olefins by strong Lewis acids such as metallic triflates,[16,17] we present here our results on novel aspects of the cyclisation of acetals and ketals bearing differently substituted olefins on the side-chain.

Results and discussion

We observed that in the presence of a low amount of a metal triflate, generally 1 mol%, the model unsaturated acetal **1a** could undergo a selective cyclisation. Compound **1a** was prepared *via* allylation of dimethyl malonate and further alkylation by 2-bromoacetaldehyde dimethyl acetal. Its catalytic reaction in the presence of a Lewis acid afforded the highly functionalised carbocycles **2a** and/or **3a** (Scheme 1).

Acetal **1a** was chosen for the optimisation of the cyclisation conditions. Table 1 summarises the results of the effect of several parameters. A first reaction was carried out using 1 mol% of Al(OTf)₃ in nitromethane at room temperature (entry 1). The reaction was followed by GC and the complete conversion of **1a** was reached after 3 h. Compounds **2a** and **3a** were formed as the main products in 75% combined yield in a 39 : 61 ratio, respectively. Unsaturated ether **2a** was issued from a cyclisation involving the loss of methanol, whereas dimethoxy derivative **3a** involves a cycloisomerisation process.

The same reaction with Cu(OTf)₂ as the catalyst led to a complete conversion within 0.5 h, with a cyclisation yield of 69% and a ratio **2a** : **3a** of 41 : 59 (entry 2). No reaction occurred with Mg(OTf)₂ (entry 3) and starting **1a** could be recovered. With Fe(OTf)₃ and Bi(OTf)₃ at 1 mol% (entries 4 and 5), the conversion of **1a** was complete in less than 10 min with cyclisation yields of 77–81% and isomer ratios of 40 : 60 and 42 : 58, respectively.

These different catalysts were also tested in 1,2-dichloroethane (DCE) at room temperature. Al(OTf)₃ and Cu(OTf)₂ reacted smoothly in 1–3 h (entries 6 and 7). The most active catalysts resulted to be Bi(OTf)₃ and Fe(OTf)₃ (entries 8 and 9), both affording selectivities towards **2a** in the range of 73–78%. Interestingly, in DCE the selectivity **2a** : **3a** was reversed as compared to that obtained in nitromethane.

The reaction catalysed by Bi(OTf)₃ in DCE was slightly more efficient as compared to Fe(OTf)₃ and led to a higher selectivity towards **2a**. Similar results were obtained with Bi(OTf)₃ in

ᵃInstitut de Chimie de Nice, Université Cote d'Azur, CNRS, Parc Valrose, 06108 Nice cedex 2, France. E-mail: dunach@unice.fr; Web: http://web.univ-cotedazur.fr/labs/icn/fr

ᵇV. MANE Fils, Centre de Recherche en Chimie Organique, 620 Route de Grasse, Le Bar-sur-Loup, 06620, France. E-mail: piotr.jaunky@mane.com; Web: https://www.mane.com/
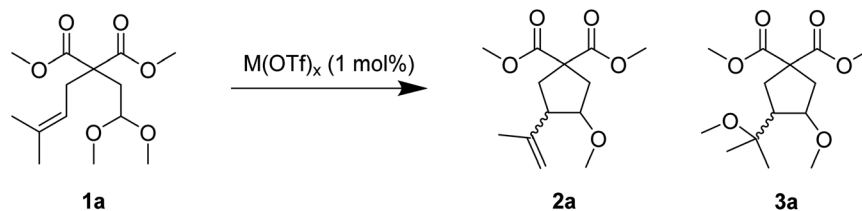
Scheme 1 Intramolecular cyclisation of unsaturated acetals catalysed by metal triflates at 1 mol%.

dichloromethane (DCM) as the solvent within 10 min reaction at 20 °C, with a selectivity of 89% for **2a** (entry 10). The cyclisation of **1a** was also possible with Bi(OTf)$_3$ in toluene and resulted in 72% of **2a** : **3a** with a ratio of 87 : 13 after 3 h at room temperature (entry 11).

At 0 °C, Bi(OTf)$_3$ (1 mol%) led to a 85% conversion of **1a** after 7 h, with a cyclisation yield of only 39% (entry 12). The cyclisation was also efficient with only 0.1 mol% of Bi(OTf)$_3$ at room temperature, with a selectivity **2a** : **3a** of 87 : 13, but it was only completed after 6 h, with some product degradation (entry 13). In some cases, diene **4a**, issued from methanol elimination from **2a** (and/or **3a**) was also formed in low yields (see Scheme 2). Possibly, the polymerisation of the 1,3-diene **4a** accounts for this product degradation.

The Lewis superacid character imparted by the triflate ligands was crucial for an efficient catalytic activity, since both BiCl$_3$ and BiBr$_3$, under the conditions of entry 10, failed to give any conversion of **1a**.

For comparison, we also tested the use of triflic acid (HOTf) as the catalyst. At 1 mol% in nitromethane, **1a** afforded 76% of **2a** : **3a** with a ratio of 37 : 63 after 1 h at room temperature. This result indicated a relatively efficient protic acid cyclisation, although other protic acids (*e.g. p*-toluenesulfonic acid) afforded poor results. We continued the study with metal triflates as the catalysts, HOTf being toxic and its handling as a fuming compound being much less convenient.[18]

The results of Table 1 indicate a strong influence of the nature of the solvent in the outcome of the cyclisation. In a polar solvent such as nitromethane, the formation of **3a** was favoured (entries 1, 2, 4 and 5), whereas in less polar solvents such as toluene or chlorinated solvents, compound **2a** was formed with a higher selectivity (entries 6–13). Moreover, the several catalysts tested presented a strong difference in activity. Whereas in nitromethane, the complete conversion of **1a** was reached in 10 min with Bi(OTf)$_3$ and Fe(OTf)$_3$, it needed 0.5 h with Cu(OTf)$_2$ and 3 h with Al(OTf)$_3$. No reaction of **1a** with Mg(OTf)$_2$ could be observed after 6 h.

For comparison, cyclisations of **1a** with the reported PtCl$_2$ or FeCl$_3$ catalytic systems under the conditions of entry 10 were carried out. Whereas with FeCl$_3$ no reaction occurred, in the presence of the PtCl$_2$/AgOTf catalytic system, a conversion of 33% was obtained after 10 min with a yield of **2a** of 13%; however, the reaction did not go to completion and the yield of **2a** was of 37% after 8 h.

Concerning the cyclisation of **1a** to **2a**, the most efficient system was obtained with 1 mol% of Bi(OTf)$_3$ in dichloromethane at room temperature, with a selectivity for **2a** of 89% (entry 10). Under these conditions, **2a** was formed in a *cis/trans* ratio of 15/85, as shown by NOE-NMR analysis.

Concerning the formation of **3a**, we chose to further explore Fe(OTf)$_3$ as the catalytic system. The best selectivities obtained in nitromethane were in the range of 60% (Table 1). In order to enhance the selectivity towards **3a**, some cyclisations of **1a** were run with 1 mol% of Fe(OTf)$_3$ with added methanol. As depicted in Table 2, the addition of 2 or 4 equiv. of MeOH led to enhanced selectivities for **3a**, up to 87% (entries 2 and 3). It is to note that using methanol as the solvent did not allow any cyclisation, possibly due to the deactivation of the catalyst (entry 4).

Table 1 Influence of reaction parameters in the cyclisation of **1a**[a]

Entry	Catalyst (1 mol%)	Solvent	Reaction time (h)	Yield of cyclisation (%)	Selectivity **2a** : **3a**
1	Al(OTf)$_3$	MeNO$_2$	3	75	39 : 61
2	Cu(OTf)$_2$	MeNO$_2$	0.5	69	41 : 59
3	Mg(OTf)$_2$	MeNO$_2$	6	—	—
4	Fe(OTf)$_3$	MeNO$_2$	0.17	81	40 : 60
5	Bi(OTf)$_3$	MeNO$_2$	0.17	77	42 : 58
6	Al(OTf)$_3$	DCE	1	63	66 : 34
7	Cu(OTf)$_2$	DCE	3	61	69 : 31
8	Bi(OTf)$_3$	DCE	0.17	69	78 : 22
9	Fe(OTf)$_3$	DCE	0.5	64	73 : 27
10	Bi(OTf)$_3$	CH$_2$Cl$_2$	0.17	68	89 : 11
11	Bi(OTf)$_3$	Toluene	3	72	87 : 13
12[b]	Bi(OTf)$_3$	CH$_2$Cl$_2$	7	39	86 : 14
13[c]	Bi(OTf)$_3$	CH$_2$Cl$_2$	6	66	87 : 13

[a] General reaction conditions: **1a** (0.5 mmol) in the corresponding solvent (5 mL) with the added catalyst (1 mol% unless otherwise stated) was stirred at 20 °C (unless otherwise stated). Reactions were followed by GC with 1,4-dichlorobenzene as the internal standard and stopped after complete consumption. [b] The reaction was run at 0 °C. [c] The cyclisation was carried out with 0.1 mol% of catalyst at 20 °C.
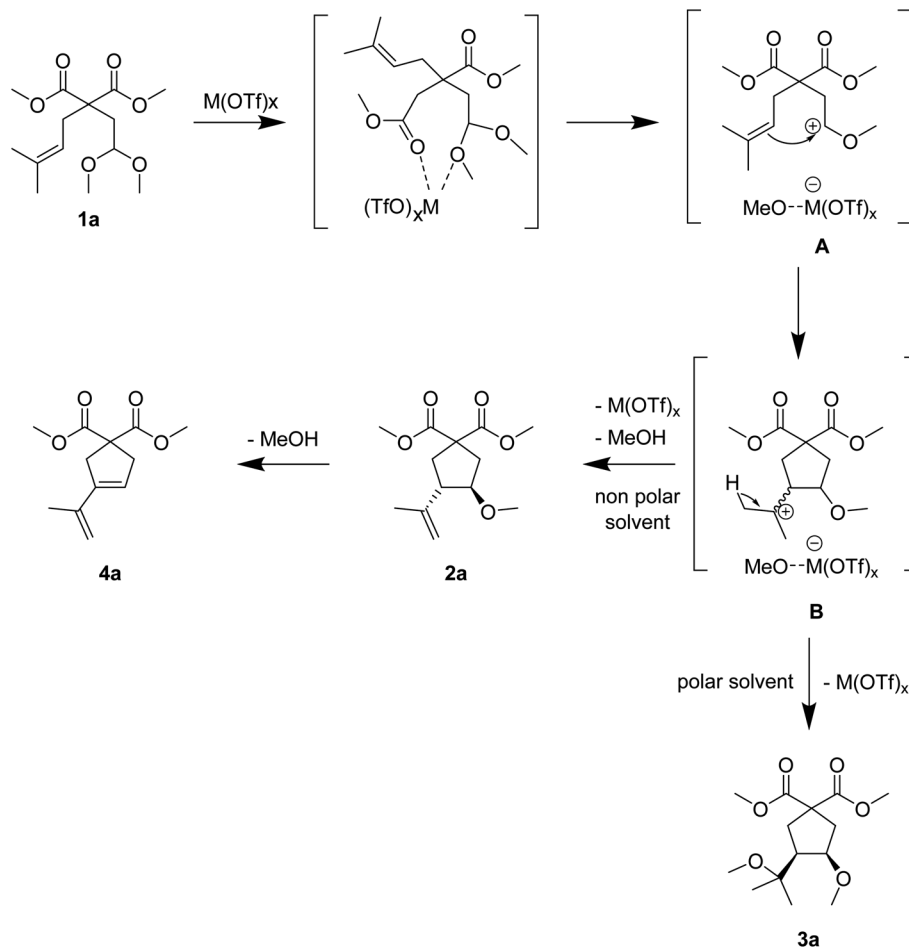
Scheme 2 Proposed cyclisation mechanism of unsaturated acetal **1a** with a metal triflate.

Interestingly, for this novel acetal–olefin coupling, the experimental conditions can be tuned in order to direct the cyclisation of **1a** either towards **2a** or towards **3a**, both catalytic systems affording chemoselectivities in the range of 80–90%.

In a first set of experiments, the cyclisation was extended to other substrates of type **1** using 1 mol% of Bi(OTf)₃ in dichloromethane at room temperature (Table 3). The cyclisation of acetal **1b** afforded the six-membered ring carbocycle **2b** in 60% yield with a *cis/trans* ratio of 70 : 30 (entry 2). The ratio **2b** : **3b** was 95 : 5. Unsaturated ketals reacted also efficiently. Thus, the ketal **1c** gave access to **2c** in 81% yield (entry 3). The

Table 2 Cycloisomerisation of **1a** to **3a** with Fe(OTf)₃ in MeNO₂: influence of MeOH[a]

Entry	MeOH	Cyclisation yield (%)	Selectivity **2a** : **3a**
1	—	81	40 : 60
2	2 equiv.	92	15 : 85
3	4 equiv.	84	13 : 87
4[b]	Solvent	—	—

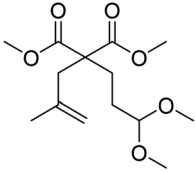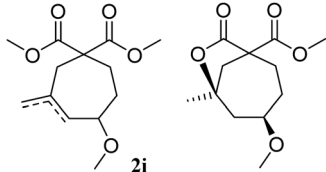[a] General reaction conditions: **1a** (0.5 mmol) in nitromethane (5 mL) with 1 mol% of Fe(OTf)₃ and MeOH (0–4 equiv.) were stirred at 20 °C. Reactions were followed by GC with 1,4-dichlorobenzene as the internal standard and stopped after complete consumption of **1a**. [b] Only MeOH (5 mL) was used as solvent.

cis/trans ratio in this case was 70/30. Isolated **2c** could be crystallised in hexane and the X-ray analysis confirmed its *cis*-stereochemistry, in agreement with 2D-NMR.[19]

The 2,2-disubstituted olefin **1d** afforded **2d** in 75% yield, a ratio of 80/20 was found for the position of the double bond (entry 4).

The more hindered diisopropyl malonate **1e** reacted efficiently affording **2e** in 70% yield, with a *cis/trans* ratio of 10/90 (entry 5).

The cinnamyl acetal derivatives **1f** and **1g** (entries 6 and 7) gave the 5- and 6-membered rings **3f** and **3g**, in 85 and 91% yield, respectively. In these cases, the corresponding mono-methoxylated carbocycle **2** was not formed, and the cycloisomerisation compounds **3f** and **3g** were obtained chemospecifically. Analogous unsaturated ketal **1h** reacted similarly and afforded **3h** in 80% yield (entry 8). For **3f** and **3g**, the major isomer presented a *trans*-stereochemistry with selectivities of 65–70%. The main isomer of **3h** was a *cis* carbocycle with a selectivity of 65%.

The possibility of preparing 7-membered rings was tested with substrate **1i**, which afforded 19% of the expected **2i**, together with 49% of an unexpected cyclisation compound **5i**. The formation of lactone **5i** can be explained by the further transformation of **2i**, involving the cyclisation of one of the ester groups on the tertiary position of the double bond. This type of ester/olefin cyclisation to lactones has already been observed in related Lewis acid-catalysed reactions.[3,20]

Table 3 Cyclisation of unsaturated acetals 1 catalysed by Bi(OTf)$_3$ (1 mol%) at 20 °C[a]

Entry	Reaction time	Substrate	Main product	Yield	Ratio cis/trans
1	10 min	1a	2a	60%	15/85
2	10 min	1b	2b	60%	70/30
3	10 min	1c	2c	81%	70/30
4[b]	10 min	1d	2d	75%	—
5	10 min	1e	2e	70%	10/90
6	20 min	1f	3f	85%	30/70
7	20 min	1g	3g	91%	35/65
8	20 min	1h	3h	80%	65/35

Table 3 (Contd.)

Entry	Reaction time	Substrate	Main product	Yield	Ratio cis/trans
9[c]	24 h	1i	2i, 5i	2i: 19% 5i: 49%	— 60/40

[a] General reaction conditions: **1** (6.9–20.8 mmol) in CH_2Cl_2 (69–104 mL) with $Bi(OTf)_3$ (1 mol%) was stirred at 20 °C. Reactions were followed by GC with 1,4-dichlorobenzene as the internal standard and stopped after complete consumption of the starting material. Cyclised compounds were purified by column chromatography on silica-gel with cyclohexane/ethyl acetate mixtures as the eluents. [b] For **2d**, the ratio of α,β- versus β,γ-double bond was 20 : 80. [c] No reaction occurred in CH_2Cl_2 and $MeNO_2$ was used as the solvent. For **2i**, the ratio terminal versus internal olefin was 56/44.

Noteworthy, this acetal/olefin cyclisation could be run at a multi-gram scale. Moreover, cyclohexane derivative **2c** could be obtained on a 300 gram-scale with 69% yield after precipitation in hexane.

Concerning the stereoselectivity in these reactions with $Bi(OTf)_3$ as the catalyst in dichloromethane, we can observe that whereas the cis-isomer was favoured in six-membered ring carbocycles **2b** and **2c**, the five-membered rings **2a** and **2e** gave mainly the trans-isomer. The cinnamyl-derived **3f** and **3g** afforded the trans-isomers preferentially, both for 5 or 6-membered rings, whereas the more hindered **3h** led to a preferential cis-stereoselectivity. In order to better understand the differences in selectivity, theoretical DFT calculations were carried out comparing the relative energies of **1a**, **1b** and **2a**, **2b** on their cis/trans forms, as well as the energies of their carbocation intermediates (see above, Mechanistic considerations). The calculated data indicated a very small energy difference (less than 4.5 kJ mol^{-1}) between cis/trans in both 5 or 6-membered rings. Again, a very small difference in the activation energy for the cyclisation of the corresponding cations (less than 8.5 kJ mol^{-1}) was obtained (see the ESI† for details). This small energy differences may explain the results obtained for the reaction selectivity. In the related literature on glycosylation reactions with several nucleophiles, it has already been observed that small changes in the nature of the nucleophiles could reverse the stereochemical outcome of the reactions.[8]

Examples of the cycloisomerisation of **1** to **3** using $Fe(OTf)_3$ as the catalyst at 1 mol% in nitromethane, in the presence of 2 equiv. of methanol are presented in Table 4.

With $Fe(OTf)_3$ catalysis, compound **3a** was obtained from **1a** after 10 minutes at room temperature, with a yield of 78%. The cis/trans ratio for **3a** was of 60/40, according to NOE analysis (entry 1). The prenyl derivative **1b** gave the 6-membered ring **3b** with a moderate yield of 51%, and a cis/trans ratio of 83/17 (entry 2). The analogous diisopropyl malonate **3e** was obtained with 72% yield and a cis/trans selectivity of 65/35 (entry 3). The 7-membered ring **3i** was obtained with 64% yield and a cis/trans ratio of 84/16 (entry 4).

In the examples developed with $Fe(OTf)_3$ catalysis in nitromethane, all the compounds were selective towards the cis-isomer.

When comparing the selectivities with both $Bi(OTf)_3$ and $Fe(OTf)_3$ systems for the same starting substrates, differences appear in the cases of the major products for the reactions of **1a** and **1e**. Here again, the literature indicates in related examples that the nature of the solvent (CH_2Cl_2 and nitromethane) as well as the nature of the catalyst could strongly influence the isomer ratios.[21]

Mechanistic considerations

The acetal–olefin cyclisation of malonate derivatives of type **1** was catalysed by $Bi(OTf)_3$ in dichloromethane to afford generally monomethylated derivatives **2**. In addition, **1** could also afford dimethoxy-substituted carbocycles of type **3** with $Fe(OTf)_3$/MeOH catalytic system in nitromethane. A common first part of the mechanism is proposed to proceed through the initial activation of the acetal group by the highly electrophilic Lewis acid. As depicted in Scheme 2 in the case of **1a**, the activation of the acetal is followed by the formation of an intermediate carbocation **A**, by loss of one methoxy group.[22] Follows the intramolecular nucleophilic addition of the double bond generating intermediate carbocation **B**. The ring-closing step (C–C bond formation) is controlled by the stability of **B**, and the ring size depends on the olefin substitution. Intermediate **B** may react according to the nature of the solvent: in a polar solvent such as nitromethane, we suggest that the MeO$^-$ group eliminated in the first step stays coordinated to the Bi(III) centre and can therefore attack on carbocation **B**, leading to the formation of **3a**. In less polar solvents such as DCE or DCM, intermediate **B** mainly evolves through a selective proton elimination to **2a**. The cyclised compound **2a** can also form diene **4a**, observed as a by-product, via further methanol elimination. In polar solvents, the ion-pair in intermediates **A** and **B** should be better stabilised as compared to their stabilisation in less polar ones. In the case of the reactivity of cinnamyl derivatives such as **1f**–**1h**, the higher stabilisation of intermediates **B** due to the resonance effect of the phenyl group may facilitate the attack of the methoxy group, to selectively form compounds **3**.

Table 4 Cyclisation of unsaturated acetals catalysed by Fe(OTf)$_3$ (1 mol%) in nitromethane[a]

| Entry	Reaction time	Substrate	Product	Yield	Ratio cis/trans
1	10 min	**1a**	**3a**	78%	60/40
2	1 h	**1b**	**3b**	51%	83/17
3	10 min	**1e**	**3e**	72%	65/35
4	2 h	**1i**	**3i**	64%	84/16

[a] General reaction conditions: **1** (8.7–10.4 mmol) in MeNO$_2$ (100–150 mL) with Fe(OTf)$_3$ (1 mol%) and 2 equiv. of MeOH were stirred at 20 °C. Reactions were followed by GC with 1,4-dichlorobenzene as the internal standard and stopped after complete consumption of the starting material. Compounds **3** were purified by column chromatography on silica-gel with cyclohexane/ethyl acetate mixtures as the eluents.

This process can be mechanistically related to the carbonyl-ene cyclisation of unsaturated aldehydes, which leads to the corresponding homoallylic alcohols.[4] However, the carbonyl-ene reaction has only been efficiently developed with unsaturated aldehydes and presents a very low interest with unsaturated ketones, due to low yields and reaction reversibility.[23]

Scheme 3 illustrates the comparison between the reactivity of the carbonyl-ene and the ketal-ene processes with the same catalytic system. Whereas ketone **6** reacted with 1 mol% of Bi(OTf)$_3$ in dichloromethane to give alcohol **7** in 23% yield after 48 h at room temperature, the corresponding ketal **1c** afforded the analogous **2c** with a yield of 81% in only 10 min at the same temperature. The results indicated that the ketal activation was highly facilitated and that the cyclisation of **1c** to **2c** was much more efficient than the cyclisation of ketone **6** to alcohol **7**.

DFT calculations on the relative energy of the formation of the carbocation intermediates of type **A** from acetals (and ketals) and the analogous carbocations issued from carbonyl compounds were carried out (Scheme 2). In order to simplify the calculations, the Lewis acid was replaced by a proton and

the substituents of the acetal and the carbonyl compounds by methyl or ethyl groups. The results indicated a much higher stabilisation of intermediates **A** for acetals of ketals as compared to analogous carbonyl compound intermediates, in agreement with the experimental results (Scheme 3). Thus, whereas the addition of a proton to an aldehyde or ketone led to a stabilisation of −11 and −30 kJ mol^{-1}, respectively, the proton addition to the corresponding dimethyl acetal or ketal gave stabilisation energies of −101 and −150 kJ mol^{-1}, respectively. The formation of methanol in the case of acetal/ketal protonation may partly explain this efficient stabilisation. The simulation of the cyclisation of **1a** to **2a** by a proton gave an activation energy of 63–69 kJ mol^{-1}. Experimentally, with Bi(OTf)$_3$ as the catalyst, the activation energy for the cyclisation of **1a** was evaluated to be of 151 kJ mol^{-1} after kinetic data of reactions run at 0, 10 and 20 °C. An important energy difference was found in this case for the DFT process calculated for a proton cyclisation as compared to the experimental data in which the cyclisation is run with Bi(OTf)$_3$, a much more bulky Lewis acid catalyst. Details of these calculations are to be found in the ESI.†
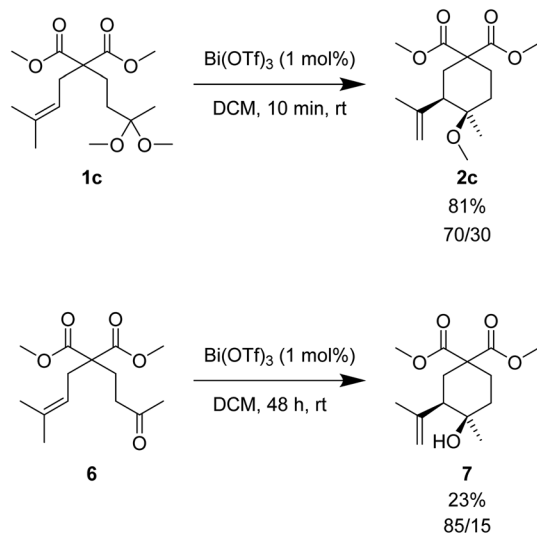
Scheme 3 Comparison between the reactivity of ketal **1c** and the corresponding ene-reaction with ketone **6**.

Conclusions

In conclusion, an efficient and highly catalytic intramolecular acetal–olefin cyclisation of compounds of type **1** was developed, by using only 1 mol% of $Bi(OTf)_3$ in low polarity solvents such as dichloromethane. The coupling reaction selectively afforded α,β-unsaturated ethers of type **2**. Bismuth(III) triflate resulted to be a powerful catalyst: the activation of the acetal group takes place readily and the reactions were generally completed in 10–20 min at room temperature. The present transformation provides a simple and selective procedure to access highly functionalised carbocycles in good yields.

By adapting the reaction conditions, carbocyclic diethers of type **3** could also be prepared in a cycloisomerisation process, in particular by using a 1 mol% $Fe(OTf)_3$-based catalytic system in polar aprotic solvents such as nitromethane, under very mild conditions.

Cycloisomerisations leading to 5-, 6-, and also 7-membered ring highly substituted carbocycles were obtained.

Experimental section

General cyclisation procedure: the unsaturated acetal **1** (1 equiv.) was added to the appropriate solvent (DCM, DCE or $MeNO_2$, 0.1 M). $Bi(OTf)_3$ or $Fe(OTf)_3$ (0.01 equiv.) were added to the solution and the mixture was stirred at room temperature. After full conversion of **1**, the reaction was quenched with neutral activated aluminum oxide. The solution was then filtered off and the solvent removed under reduced pressure. The oily residue was purified by flash-chromatography through silica-gel with cyclohexane/AcOEt mixtures as the eluents or by distillation. See the ESI† for further details.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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