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# C-O and C-C bond formation in the cyclisation of *gem*-(dialkoxymethyl)-1,6-dienes catalysed by tin(IV) triflimidate at room temperature

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# ABSTRACT

We described herein a  $Sn(NTf_2)_4$ -catalysed cyclisation of *gem*-(dialkoxymethyl)-1,6-dienes and derivatives where cyclohexane or tetrahydrofuran rings are formed following either a 6-*enexo-endo*-trig process or a 5-*exo*-trig process, respectively, depending on substitution patterns. The latter process features an unusual dealkylative ether cyclisation, triggered by the strong Lewis acid character of the tin(IV) triflimidate catalyst.

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Lewis superacids such as metal triflates and triflimidates have been widely used in the recent years in catalytic transformations where electrophilic activation is required<sup>1</sup> with salts derived from indium, <sup>2</sup> rare earth metals,<sup>3</sup> or bismuth, <sup>4,5</sup> for example. We have been interested in the preparation of metal triflates and triflimidates<sup>6,7</sup> and their use in homogeneous catalysis, in various interand intramolecular C–O, C–S and C–C bonds formation processes.<sup>8</sup> In particular, we have described a cycloisomerisation reaction of 1,6-dienes catalysed by Sn(NTf<sub>2</sub>)<sub>4</sub> (Scheme 1),<sup>9</sup> showing an unusual preference for 6-*enexo-endo*-trig cyclisation, while transition metals typically exhibit 5-*endo*-trig and 5-*exo*-trig cyclisation modes.<sup>10–12</sup>

Of concern in the 1,6-diene transformation was the role of side groups on the tether, the best results being obtained with a *gem*diester moiety at the homoallylic position. Should these groups influence the course of the reaction by a Thorpe–Ingold effect or by a stabilisation of intermediate species by coordination? In this Letter we report our results on the cyclisation of a series of *gem*-(dialkoxymethyl)-1,6-dienes catalysed by  $Sn(NTf_2)_4$  where we show that in the absence of the carbonyl function, replaced by a methylene, the cycloisomerisation to 6-membered carbocycles is in competition with an unusual dealkylative cyclisation to cyclic ethers. We initially performed a screening of catalysts and conditions on model substrate **1a**. A striking difference with the

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cycloisomerisation of *gem*-diester-1,6-dienes was the formation of two isomers, **1b** and **1c**, differing by the final position of the double bond.

Nitromethane as the solvent allowed the best results as compared to dichloroethane or toluene, which gave almost no conversion at room temperature. The results of the catalyst screening are summarised in Table 1. We identified that  $Sn(NTf_2)_4$  could be used at 5 mol % in CH<sub>3</sub>NO<sub>2</sub> at 25 °C to obtain the cyclisation of **1a** into **1b** + **1c** in 86% yield, in a 1:1.7 ratio, respectively.

We further examined the effect of structural changes on the cyclisation reaction (Table 2). Exchange of the methoxy groups into ethoxy (**2a**) or acetoxy (**3a**) did not alter the reaction outcome and the C–C cyclised products **2b/2c** and **3b/3c** were obtained in 74% and 82% yields, respectively (entries 2, 3). However, the selectivity between isopropenyl cyclohexane **3b** and isopropyl cyclohexene **3c** was modified. The presence of two acetoxy groups strongly favoured the formation of **3b**, in a 10:1 ratio with **3c**.

We examined the reactivity of **4a**, the monoester analogue of **1a**, which could be a probe to evaluate the importance of a





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## Table 1

Screening of catalyst and conditions in the cyclisation of 1a

![](_page_1_Figure_3.jpeg)

Entry <sup>a</sup>	Catalyst, x mol % <sup>b</sup>	T (°C), time	Conversion	( <b>1b</b> + <b>1c</b> ) yield <sup>c</sup>	1b:1c
1	$Zn(NTf_2)_2$ , 10	25, 24 h	<5%	_	_
2	Bi(NTf <sub>2</sub> ) <sub>3</sub> , 10	25, 24 h	10%	5%	N.D.
3	$In(NTf_2)_3, 10$	25, 24 h	20%	10%	1:1.2
4	Sn(NTf <sub>2</sub> ) <sub>4</sub> , 10	25, 20 h	100%	71%	1:2.3
5	Sn(NTf <sub>2</sub> ) <sub>4</sub> , 5	25, 24 h	100%	86%	1:1.7
6	Sn(NTf <sub>2</sub> ) <sub>4</sub> , 3	25, 24 h	90%	77%	1:1.6
7	$Sn(NTf_2)_4$ , 1	25, 24 h	76%	68%	1:1.3
8	$Sn(NTf_2)_4$ , 5	40, 18 h	100%	73%	1:2.4

<sup>a</sup> Conditions: **1a** (0.5 mmol), in anhydrous CH<sub>3</sub>NO<sub>2</sub> (0.5 M).

<sup>b</sup> Catalysts solvated with DMSO molecules, see Ref. <sup>7</sup>.

<sup>c</sup> GC-FID yields determined by internal standard method.

Table 2					
C–C and C–O bonds formation	in the cyclisation	of gem-(dialkox	vmethyl)-1,6	-dienes 1	la-10a

![](_page_1_Figure_9.jpeg)

(continued on next page)

Table 2 (continued)

![](_page_2_Figure_3.jpeg)

<sup>a</sup> Conditions: Substrate (0.5 mmol) and 5 mol % Sn(NTf<sub>2</sub>)<sub>4</sub> in anhydrous CH<sub>3</sub>NO<sub>2</sub> (0.5 M) at 25 °C.

<sup>b</sup> GC-FID yields determined by internal standard method. Products were isolated and characterised by <sup>1</sup>H and <sup>13</sup>C NMR, MS and compared with literature data or authentic samples.

<sup>c</sup> Along with elimination products.

<sup>d</sup> Conversion 100% (66% after 48 h).

Thorpe–Ingold effect in this cyclisation. The C–C cycloisomerisation was not affected and **4b/4c** was obtained in 80% yield, as a 5:3 mixture (entry 4).

The access to fused bicyclic compounds was envisaged through the cyclisation of **5a**, but a complex mixture of isomerised products was obtained (entry 5). By changing the prenyl side chain(s) for one or two methallyl side chain(s), a significant shift of reactivity was observed towards C-O cyclisation. In particular, methallylprenyl substrate **6a** afforded the monocyclic ether **6d** in 39% yield (entry 6). Ether **6d** was presumably formed by dealkylative alkoxylation of the methallyl moiety, triggered by  $Sn(NTf_2)_4$ . A similar reaction was reported to occur with stoichiometric TfOH in the dealkylative lactonisation of related gem-diester substrates.<sup>13</sup> Bismethallyl substrate 7a afforded the cyclic ether 7d in 53% yield after 72 h (entry 7). TMS-protected derivative 8a was cleanly and rapidly converted into the spirocyclic diether 8e in 96% yield, after a Sn(NTf<sub>2</sub>)<sub>4</sub>-catalysed desilylation/C–O cycloisomerisation (entry 8). The same product was obtained in 66% yield when cyclic ketal **9a** was used as the substrate (entry 9). The preference for C–O versus C–C cyclisation was confirmed when using **10a** as the starting material. The substrate bearing a free hydroxyl group and two prenyl moieties afforded the cyclic ether 10d in 100% yield after 3 h at room temperature in the presence of  $Sn(NTf_2)_4$  (entry 10).<sup>14</sup>

The dealkylation reaction observed is rather surprising since such reaction usually takes place in the presence of stoichiometric Lewis acids, including metal chlorides or boron-derivatives.<sup>15</sup> Under our conditions, dealkylation could become the main reaction (Table 2, entries 6, 7). This divergence between (C-C) and (C-O) bond-forming cyclisations, comparing the fate of 1a, 5a and 6a for example, appeared to us as a consequence of the combined electronic effects of substituents on the double bonds and size of the ring to be formed. In the case of **1a**, one double bond acts as an electrophile and undergoes the nucleophilic attack of either an oxygen atom of the functional groups in a (C-O)-6-endo-trig process, or a carbon atom of the other double bond in a (C-C)-6enexo-endo-trig process. As a consequence of the trisubstitution, the double bond is nucleophilic enough and the (C-C)-6enexo-endo-trig process is favoured, ring size being identical in both processes. For 6a, the competition is between a (C-C)-5enexo-exo-trig, a (C-C)-7-enendo-endo-trig, a (C-O)-6-endo-trig and a (C-O)-5-exo-trig, and we observed that the 5-membered ring ether formation was favoured, showing that when 5-membered rings could be formed, the ether formation is favoured to the detriment of the cyclopentane, which suffers from destabilising eclipsing interactions (Scheme 2).

In the case of 7a, the disubstituted double bond is not nucleophilic enough to enter into a (C-C)-6-enendo-exo-trig process, in competition with a (C-O)-5-exo-trig process, which is favoured. Comparing these reactions with the previously reported cycloisomerisation of 1,6-dienes bearing a gem-diester moiety<sup>9</sup> instead of the gem-(dialkoxymethyl), it seems that the overall efficiency of the process is improved with gem-(dialkoxymethyl) substrates, efficiently converted at room temperature while gem-diester substrates sometimes required heating. The selectivity is however attained with diester substrates, as depicted in Scheme 1, affording one single product. In contrast with the C-O type cyclisation presented here, with gem-diester substrates the C-C process is highly favoured. It is frequent to invoke that the ester groups could be involved in Thorpe-Ingold effects or in the stabilisation of cationic intermediates, but these two features are also possible with gem-(dialkoxymethyl) substrates. The attack of olefin could also be anchimerically-assisted by one ester group, thereby favouring the C-C bond forming process.

The variation of the  $\mathbf{b/c}$  ratio from 7:1 to 1:2.4 depending on the substrate and the reaction conditions suggested an additional

![](_page_2_Figure_14.jpeg)

Scheme 2. Proposed rationale for the cyclisation of 1a and 6a.

![](_page_3_Figure_1.jpeg)

Scheme 3. Access to 1b via reduction and methylation of the gem-diester containing cyclised product.

isomerisation reaction. This was tested with a sample of pure **1b**, prepared from the cyclisation of the gem-diester analogue of **1a** affording selectively the desired cyclised compounds further reduced by LiAlH<sub>4</sub> and methylated (Scheme 1+Scheme 3, 61%, three steps).

When **1b** was submitted to the reaction conditions of Table 2, **1c** was slowly formed and the ratio **1b/1c** was of 7:3 after 6 h; 1:1 after 24 h and 3:7 after 48 h. The phenomenon could not be observed beyond 120 h because degradation occurred (6% after 24 h and 10% after 48 h). This set of data clearly indicates that 1b could be converted into **1c**, which is the thermodynamic product.

As the question frequently appears in Lewis acid-catalysed processes,<sup>16,17</sup> we investigated the hypothesis of protons as the active catalytic species. Various Bronsted acids (AcOH, H<sub>3</sub>PO<sub>4</sub>, TfOH, Tf<sub>2</sub>NH at a loading of 5 mol %) were used under our conditions (0.5 M in CH<sub>3</sub>NO<sub>2</sub> at rt). After 24 h, the weak acids AcOH and H<sub>3</sub>PO<sub>4</sub> showed no conversion of **1a**. After 18 h, TfOH and Tf<sub>2</sub>NH both led to 100% conversion, however the cumulated yields of (1b + 1c) were of 62% and 58%, respectively, significantly lower than the 86% obtained with  $Sn(NTf_2)_4$ . The controversy in metallic triflate catalysis is based on the hypothesis of a slow hydrolysis of the triflate salt by trace amounts of water. In our case, a triflimidate salt is used, and the conjugate acid, the triflimide Tf<sub>2</sub>NH, is not considered a Bronsted superacid. The catalyst was prepared as a solvate with DMSO molecules, thereby limiting the quantity of water in the reaction medium, after drying of the solvent used by conventional procedures.<sup>18</sup> Under our conditions, it is however possible to have a discrete number of water molecules coordinated to the metal centre therefore affording a hybrid Lewis assisted Bronsted acid (LBA)<sup>19</sup> catalyst rather than hydrolysing the catalyst to triflimide HNTf<sub>2</sub>. Regardless of the exact nature of the active species, the best experimental results were obtained using Sn(NTf<sub>2</sub>)<sub>4</sub>.<sup>20</sup>

In summary, we described here a Sn(NTf<sub>2</sub>)<sub>4</sub>-catalysed cyclisation reaction of gem-(dialkoxymethyl)-1,6-dienes where cyclohexane derivatives could be formed following a 6-enexo-endo-trig process or tetrahydrofuran derivatives following a 5-exo-trig process, depending on the substitution pattern of the double bonds. The latter process featured an unusual dealkylative ether cyclisation, probably triggered by the strong Lewis acid character of the tin(IV) triflimide salt.

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- 20. Typical experiment: Cyclisation of 1a. Sn(NTf<sub>2</sub>)<sub>4</sub>·6DMSO (0.015 mmol, 26 mg) was introduced under a nitrogen atmosphere in a Schlenk tube closed with a septum. Nitromethane (0.5 mL), previously dried over CaCl<sub>2</sub>, was added with a syringe and the mixture stirred at room temperature until dissolution of the catalyst. Diene 1a (0.3 mmol, 72 mg) in nitromethane (0.1 mL) was added to the solution with a syringe. The reaction progress was monitored by GC-FID analysis. After completion, the reaction mixture was filtrated over a pad of silica gel and eluted with diethylether (10 mL). After solvent removal, the crude mixture was submitted to column chromatography over silica gel with a gradient Et<sub>2</sub>O/pentane 1:9 to 1:1 as eluent to afford the mixture 1b + 1c as a colourless oil. Spectral data for 1b: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz, 20 °C): 4.76 (s, 1H); 4.55 (s, 1H); 3.27 (s, 2H); 3.26 (s, 6H); 3.08 (s, 2H); 1.90 (m, 1H); 1.65 (s, 3H); 1.55–1.00 (m, 6H); 0.82 & 0.78 (s, 3H & s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz, 20 °C): 146.3; 111.6; 79.1; 71.7; 58.4; 47.4; 36.7; 32.7; 38.1; 30.6; 24.4; 30.2; 22.9; 19.2. MS (EI, 70 eV): 240(0) [M<sup>+</sup>], 208(74), 193(5), 176(5), 163(100), 133(16), 121(30), 107(96), 93(76), 79(58), 71(65). Spectral data for 1c: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz, 20 °C): 5.20 (s, 1H); 3.27 (s, 6H); 3.25-3.00 (m, 4H); 2.24 (hept, *J* = 6.8 Hz, 1H); 1.75–1.05 (m, 4H); 0.93 (d, *J* = 6.8 Hz, 6H); 0.93 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz, 20 °C): 153.5; 119.9; 75.4; 58.4; 39.6; 34.4; 22.8; 34.3; 26.9; 26.8; 24.2. MS (EI, 70 eV): 240(1) [M<sup>+</sup>], 208(1), 195(100), 163(24), 133(20), 121(92), 111(23), 107(87), 93(87), 79(32), 69(22). HRMS calcd for  $C_{15}H_{28}O_2$  [M]<sup>•+</sup> 240.2089, found: 240.2091,  $\Delta = 0.83$  ppm. HRMS calcd for  $C_{15}H_{27}O_2$  [M–H]<sup>•</sup> 239.2011, found: 239.2009,  $\Delta = 0.84$  ppm.