

# Novel Catalytic Tandem Isomerisation/Cyclisation Reaction of $\alpha$ -Methallyloxy Carboxylic Acids

Xavier Chaminade,<sup>[a]</sup> Lydie Coulombel,<sup>[a]</sup> Sandra Olivero,<sup>[a]</sup> and Elisabet Dunach<sup>\*[a]</sup>

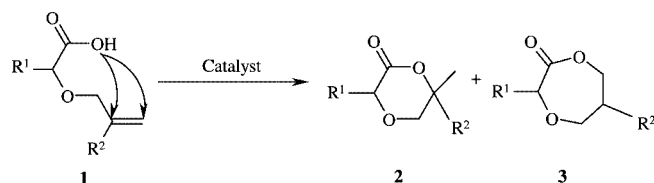
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A new tandem isomerisation/cyclisation of  $\alpha$ -methallyloxy carboxylic acids leading to substituted 1,3-dioxolan-4-ones in 60–70 % yields was catalysed by  $\text{Cu}(\text{OTf})_2$  or  $\text{Al}(\text{OTf})_3$ . Extension to the synthesis of oxathiolanones and oxathianones is also described.

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Transition metal catalysed cycloisomerisation of unsaturated hydrocarbons is an attractive and atom-economical route for the preparation of carbo- and heterocycles.<sup>[1]</sup> This reaction has been successfully applied to the cyclisation of enyne and diyne derivatives.<sup>[2]</sup> The catalytic cycloisomerisation of olefinic alcohols has recently been reported by the use of transition-metal complexes<sup>[3–7]</sup> and constitutes a novel and alternative method for the construction of oxygenated heterocycles. The novel use of tin(IV) triflate as a Lewis super-acid for cycloisomerisation of non-activated olefinic alcohols,<sup>[8]</sup> prompted us to examine other Lewis acid catalysed cyclisation processes under aprotic conditions.

Here we present a new reaction based on the Lewis acid catalysed tandem isomerisation/cyclisation of  $\alpha$ -allyloxy carboxylic acids of type **1**, in order to obtain the corresponding six- and/or seven-membered ring oxygenated heterocycles **2** and **3**, respectively, according to Scheme 1.



Scheme 1. Expected reactivity of  $\alpha$ -methallyloxy carboxylic acids in the presence of a Lewis acid catalyst.

Some dioxanone **2** and dioxepanone **3** derived heterocycles have been isolated from natural sources<sup>[9]</sup> and present biological activities. These heterocycles may also have some potential interest in flavour and fragrance chemistry.<sup>[10]</sup>

[a] Laboratoire de Chimie des Molécules Bioactives et des Arômes, CNRS, UMR 6001, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice cedex 2, France  
E-mail: dunach@unice.fr

Preliminary cyclisation studies were carried out with model substrate **1a** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{Me}$ , Table 1). Its intramolecular cyclisation was examined with several Lewis acids derived from triflates, such as  $\text{Co}(\text{OTf})_2$ ,  $\text{Cu}(\text{OTf})_2$ ,

Table 1. Cycloisomerisation of  $\alpha$ -methallyloxy carboxylic acids **1a–1f** ( $\text{R}^2 = \text{Me}$ ) using copper(II) triflate (5 mol-%) as the catalyst in refluxing 1,2-dichloroethane.

Entry	$\text{R}^1$	Reaction time	Products	Isolated yield of <b>4</b> (cis/trans) <sup>[a]</sup>
1	Ph <b>1a</b>	0.5 h		69% (58:42)
2	H <b>1b</b>	0.5 h		65%
3	Me <b>1c</b>	0.5 h		70% (71:29)
4	Et <b>1d</b>	0.8 h		70% (68:32)
5	Bu <b>1e</b>	0.5 h		64% (67:33)
6	$\text{C}_{12}\text{H}_{25}$ <b>1f</b>	0.8 h		62% (67:33)

[a] See ref.<sup>[15]</sup>

$\text{Zn}(\text{OTf})_2$ ,  $\text{Al}(\text{OTf})_3$  and  $\text{Sc}(\text{OTf})_3$ . The most efficient and selective catalytic systems were copper(II) and aluminium(III) triflates, used in a 5 mol-% ratio with respect to **1a** in refluxing 1,2-dichloroethane.  $\text{Cu}(\text{OTf})_2$  presented a higher catalytic activity and the complete conversion of **1a** was attained after 0.5 h. In contrast, the reaction of **1a** with  $\text{Al}(\text{OTf})_3$  was completed after 2.5 h. The cyclisation of **1a** with  $\text{Cu}(\text{OTf})_2$  could also be run in refluxing nitromethane, but no conversion was observed in refluxing dichloromethane after 24 h.

With copper(II) triflate, the reaction of **1a** afforded a quantitative cyclisation, with a mixture of two compounds. The expected dioxanone **2a** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{Me}$ ), formed as the minor product in 28% yield, and the unexpected dioxolanone **4a**, obtained in 68% yield and a *cis/trans* ratio of 58:42 (Scheme 2). The rearrangement leading to **4a** was also observed with other triflate-based catalytic systems and no conditions were found leading to dioxepanone **3a**.

The formation of the five-membered heterocycle **4** can be explained by a first  $\text{Cu}^{\text{II}}$ -catalysed isomerisation of the double bond to form the enol ether intermediate **5** before the cyclisation/hydrocarboxylation occurs (Scheme 2). The double-bond isomerisation of allylic ethers to the corresponding enol ethers has already been described with other transition metal complexes.<sup>[11,12]</sup> However, to the best of our knowledge, no example of a tandem isomerisation/cyclisation process has yet been reported.

The  $\text{Cu}^{\text{II}}$  triflate catalyses the double-bond isomerisation of **1** to **5**, the double bond in **5** being more stable due to its higher substitution and to the conjugation with the  $\alpha$ -oxygen atom. Moreover, the  $\text{Cu}^{\text{II}}$  Lewis acid coordinates to the carboxylate group of **1** (and **5**) and enhances the acidity of the carboxylic acid, allowing its addition to the double bond of intermediate **5**. The cyclisation of the carboxylate group of **5** by a hydrocarboxylation of the double bond can then occur both on the most substituted olefinic carbon atom to form the 1,3-dioxanone **2** or on the carbon atom  $\alpha$  to the oxygen atom to form the corresponding 1,3-dioxolanone **4**. Whereas the formation of **2** can be explained by the stabilisation of the tertiary carbocation intermediate, the formation of **4** is favoured by the stabilisation of the carbocation intermediate by the  $\alpha$ -oxygen atom.

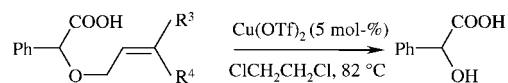
The nature of the catalyst, and in particular that of the triflate anion was essential for the success of the reaction. No cyclisation occurred in the presence of  $\text{CuCl}_2$  or  $\text{AlCl}_3$ . The particular Lewis acidity of  $\text{Cu}^{\text{II}}$  triflate enhanced the double-bond isomerisation as well as its regioselective hydrocarboxylation.

In order to extend the scope of this tandem isomerisation/cyclisation process to the synthesis of other 1,3-dioxolan-4-ones, the influence of other  $\text{R}^1$  substituents in substrates **1**, with  $\text{R}^2 = \text{Me}$ , was first examined. The results obtained for the  $\text{Cu}(\text{OTf})_2$ -catalysed cycloisomerisation are presented in Table 1.

All the substrates **1a–1f** led to quantitative cyclisation yields and the corresponding dioxolanones **4a–4f** were obtained as the major products in 62–70% yields. Whatever the nature of the  $\text{R}^1$  substituent, the isomerisation/cyclisation process occurred selectively. The *cis* isomer of dioxolanones **4** was always favoured. The *cis/trans* assignments were determined by NOESY-NMR experiments on isolated compounds.

Cycloisomerisations with  $\text{Al}(\text{OTf})_3$  occurred at a lower rate than with  $\text{Cu}(\text{OTf})_2$ . For **1a**, dioxolanone **4a** was obtained in 70% yield and a *cis/trans* ratio of 61:39. The cyclisation of **1e** occurred in 1.5 h [to be compared to 0.5 h with  $\text{Cu}(\text{OTf})_2$  under the same conditions], affording 77% of **4e** (*cis/trans* = 75:25). It was also checked in reactions with **1b**, **1c** and **1e** that there was no additional isomerisation from **2** to **4** after 24 h.

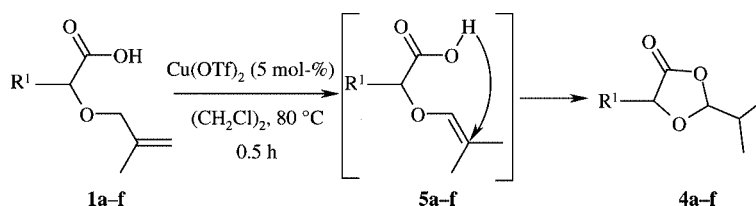
We further extended the cyclisation process to other substrates using differently substituted olefins. In the reaction with the non-substituted allyl ether derivative **1g** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ), no conversion took place in refluxing 1,2-dichloroethane after 24 h with either copper or aluminium triflates. In the case of prenyl, crotyl or cinnamyl ether derivatives of mandelic acid (**1h**, **1i**, **1j**, respectively, Scheme 3), with both catalysts the starting compound was consumed but no cyclisation occurred. The main reaction product was mandelic acid, obtained almost quantitatively and issued from the cleavage of the carbon–oxygen bond of the allylic moiety of substrates **1i–1j**.



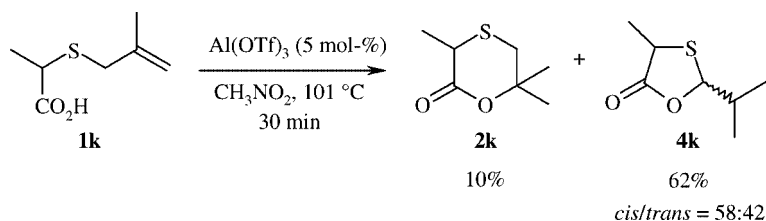
Scheme 3. Catalytic C–O cleavage of allyloxy carboxylic acids **1h** ( $\text{R}^3 = \text{R}^4 = \text{Me}$ ), **1i** ( $\text{R}^3 = \text{Me}$ ,  $\text{R}^4 = \text{H}$ ) and **1j** ( $\text{R}^3 = \text{Ph}$ ,  $\text{R}^4 = \text{H}$ ).

The catalytic and selective cleavage of the allyl–oxygen bond of allyl ethers **1h–1j** using metal triflates constitutes an alternative method of deprotection of these derivatives.<sup>[11,13,14]</sup>

Our experiments pointed out an important difference in reactivity between the behaviour of the methallyl group and that of other differently substituted or non-substituted al-



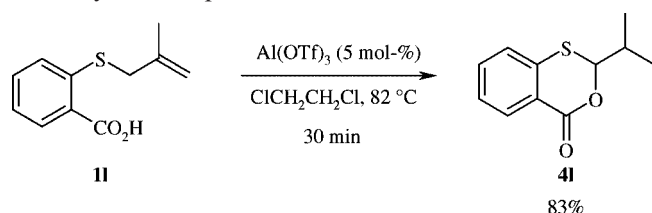
Scheme 2. Copper(II) triflate catalysed cycloaddition reaction of **1a–1f** involving double-bond isomerisation.

Scheme 4. Aluminium(III)-catalysed tandem isomerisation/cyclisation of thioallyl derivative **1k**.

lylic ether double bonds. The results seem to indicate that the isomerisation of the double bond constitutes a key step for the success of the tandem isomerisation/cyclisation reaction leading to dioxolanones. In the case of the methallyl group, the isomerisation of **1a–1f** to an enol ether **5** (Scheme 2) is being highly favoured, affording a trisubstituted double bond  $\alpha$  to the oxygen atom. In the case of the prenyl (**1h**), crotyl (**1i**) or cinnamyl (**1j**) derivatives, the double-bond isomerisation is less favoured and the cleavage of the C–O bond is then facilitated by the Lewis acid through the formation of a more stable allylic cation intermediate (Scheme 3).

We also examined the reactivity of two analogous thiomethallyl derivatives **1k** and **1l**. With these substrates, the best cyclisation results were obtained using  $\text{Al(OTf)}_3$  as the catalyst. The cycloisomerisation of thiolactic acid derivative **1k** (Scheme 4) occurred with a 65% conversion in refluxing nitromethane after 0.5 h. As with the analogous ether derivative **1c**, the methallyl sulfide **1k** underwent a tandem isomerisation/cyclisation process, affording 2-isopropyl-4-methyl-1-oxa-3-thiolan-5-one (**4k**) in 62% yield.

The  $\text{Al(OTf)}_3$ -catalysed reaction of thiobenzoic acid derivative **1l** afforded exclusively the six-membered ring **4l** in 83% isolated yield (Scheme 5). The formation of benzoxathianone **4l** can also be explained by a tandem isomerisation/cyclisation process.

Scheme 5. Isomerisation/cyclisation reaction of thiobenzoic acid derivative **1l** catalysed by  $\text{Al(OTf)}_3$ .

An additional example of isomerisation/cyclisation was further examined by considering the reverse intramolecular reaction: the possibility of cyclisation between an  $\alpha$ -hydroxy

function and the methallyl ester **1m** of L-lactic acid (Scheme 6). In this case, we expected the addition of the O–H group of the alcohol across the double bond to form a six-membered heterocycle. With  $\text{Al(OTf)}_3$ , **1m** led exclusively to the five-membered ring compound **4m** in a 38% yield by isomerisation of the double bond of the allylic ester to a vinyl carboxylate intermediate **5m** and selective intramolecular addition. The formation of **4m** indicated that with the Lewis acid, the alcohol function was also able to add to the double bond in the absence of a protic catalyst.

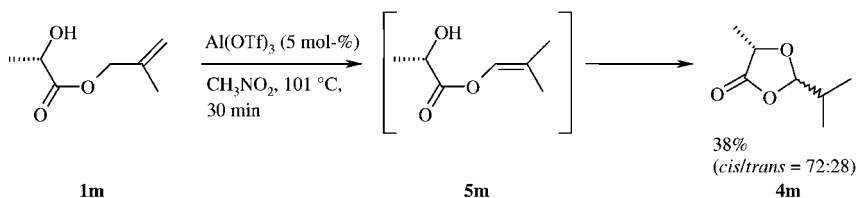
The use of copper(II) triflate instead of aluminium(III) triflate led to similar results. The cyclisation of **1m** with  $\text{Cu(OTf)}_2$  occurred in 2 h and formed **4m** in 39% yield with a *cis/trans* ratio of 73:27.

The present work constitutes the first example of a tandem isomerisation/cyclisation process and constitutes also the first example of direct and catalytic preparation of dioxolanones and their sulfur analogues. It is also a novel example of catalytic “super” Lewis acid reactivity.

In conclusion, copper(II) and aluminium(III) triflates were shown to be efficient catalysts for the isomerisation/cyclisation of  $\alpha$ -methallyloxy carboxylic acids. The tandem reaction was carried out efficiently and allowed the formation of 2,5-disubstituted 1,3-dioxolan-4-ones in yields of 60–70%. The same isomerisation/cyclisation reaction was extended to  $\alpha$ -thiomethallyloxy carboxylic acids for the synthesis of oxathiolanones and oxathianones. The tandem process also occurred with  $\alpha$ -hydroxy methallyl esters. Other allylic ethers underwent allylic deprotection. The simplicity of the catalytic system, the use of commercially available  $\text{Cu}^{\text{II}}$  or  $\text{Al}^{\text{III}}$  triflates without the need of ligand and the relative mild reaction conditions are to be emphasised.

## Acknowledgments

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Scheme 6. Tandem isomerisation/cyclisation of the methallyl ester of L-lactic acid catalysed by  $\text{Al(OTf)}_3$ .

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- [15] General procedure for catalytic tandem isomerisation/cyclisation of **1a–f**: Substrate **1** (1 mmol) was added to a refluxing dry 1,2-dichloroethane solution (15 mL) of copper(II) or aluminium(III) triflate (5 mol-%, 0.05 mmol) under an inert gas and the reaction was monitored by GC analysis of aliquots. After complete conversion, the reaction mixture was treated with saturated NaHCO<sub>3</sub> solution and extracted with 3 × 30 mL of Et<sub>2</sub>O. The organic layer was dried with MgSO<sub>4</sub> and the solvent evaporated under vacuum. The *cis/trans* ratio of compounds **4** was determined by <sup>1</sup>H NMR and GC. The dioxolanones were purified and separated by column chromatography on silica gel using hexane/diethyl ether mixtures as the eluents. The products were analysed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and mass spectrometry. Compounds **4a**,<sup>[16]</sup> **4b**<sup>[17]</sup> and **4c**<sup>[18]</sup> are known.
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