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Tin(IV) triflimidate-catalyzed cyclization of epoxy esters to functionalized δ-hydroxy-γ-lactones

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ABSTRACT

In the presence of 5 mol % of tin(IV) triflimidate, a cyclization reaction of epoxyesters to δ-hydroxy-γ-lactones proceeding in 46–98% yields without additives, ligands, or co-catalysts was observed. The cyclization to five-membered rings is greatly favored compared to the possible six-membered rings formation and is probably under the control of a Thorpe–Ingold type effect.

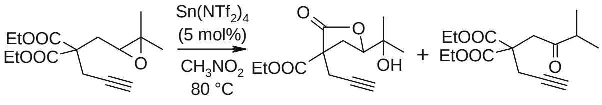
Metal-based catalytic reactions involving functionalized compounds have provided the organic chemist with a wide collection of efficient, selective, atom-economical, and creative methods to form new bonds and molecules.[1–3] Among these methodologies, cycloisomerization of functionalized substrates has been developed, based on ring-closure processes involving the metal-based electrophilic activation of unsaturated compounds (alkynes, allenes, alkenes, as well as carbonyl compounds) to allow the attack of a remote nucleophile (e.g., alcohols, amides, sulfonamides, thiols, carboxylic acids, active methylene, and electrons-rich arenes).[4–13] In many instances, the creation of new functionalities on the product results in new opportunities of reaction within the same molecule in cascade reactions of high synthetic efficiency.[14–17]

We have developed cycloisomerization reactions based on the electrophilic activation of electron-rich olefins by metallic triflates and triflimidates in intramolecular hydroalkoxylation,[18,19] hydrocarboxylation,[20] hydro-thiolation,[21] hydrooxyamination,[22] and 1,6-dienes cycloisomerization.[23] We have been lately interested in using strong Lewis acids such as $Sn(NTf_2)_4$ as catalyst to activate triple bonds and allow the nucleophilic addition of a remote epoxide function. The challenging metal triflimidate activation of a triple bond was recently reported by Nakamura with $In(NTf_2)_3$, which was able to catalyze a cyclization reaction through the addition of the active methylene of a β-ketoester to a terminal alkyne (Conia-ene reaction).[24] In our case however, we also had to bypass the innate propensity of epoxides to isomerize into carbonyl compounds. Recent reactions on similar substrates were described, for example, in Au^I-catalyzed tandem epoxide ring-opening/hydroalkoxylation reactions of epoxy alkynes[25,26] and in Au^I- and Au^{III}-catalyzed synthesis of functionalized furans,[27–29] acylindenes,[30] spiropyranones,[31] and divinylketones[32] from epoxy propargyl derivatives.

When epoxypropargyl ester **1a** was heated at 80 °C in nitromethane in the presence of 5 mol % $Sn(NTf_2)_4 \cdot 6DMSO$,[33] the starting material was totally consumed in favor of the formation of the corresponding δ-hydroxy-γ-lactone **2a** in 70% yield as a 3/1 mixture of 2 diastereomers, leaving unchanged the propargyl side chain (Scheme 1). As a side product, the isopropylketone **3a** resulting from the epoxide isomerization was formed in 30% yield.

In a previous work of Baltas and co-workers, a cyclization reaction of γ,δ-epoxy-β-hydroxyesters promoted by excess $ZnCl_2$ was described to lead to mixtures of γ- and δ-lactone derivatives, with a selectivity strongly influenced by the presence of a hydroxyl group at carbon atom β.[34] In these reactions, *tert*-butyl esters, leading to the release of the stable *tert*-butyl cation, were used and 4 equiv of Lewis acid were needed to overcome the intrinsically weak nucleophilicity of the ester function. In particular, while compounds with free alcohol at C-β were cyclized to δ-lactone derivatives with more than 95% selectivity, the protection of the hydroxyl group by TBDMS or TBDPS resulted in a spectacular inversion of the selectivity in favor of the γ-lactone derivatives. Conversely, Ti(III)-catalyzed radical cyclizations of epoxy alkenes proceed selectively by ring-closure with attack of the most substituted carbon atom.[35] In our case with **1a** and in the presence of 5 mol % of tin(IV) catalyst, the cyclization proceeded exclusively to δ-hydroxy-γ-lactone **2a** through the 5-*exo*-tet nucleophilic attack of one ester group.

The δ-hydroxy-γ-lactone motif is the core structure of bioactive natural products such as (±)-muricatacin and has been the focus of



1a

2a, 70%, dr 3/1

3a, 30%

Scheme 1.

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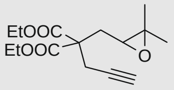
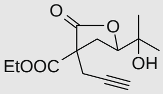
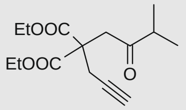
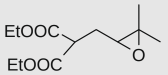
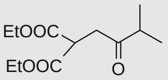
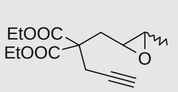
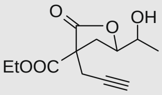
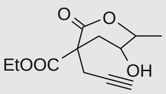
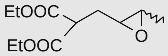
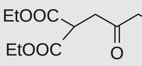
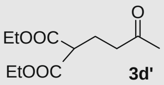
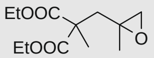
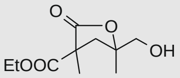
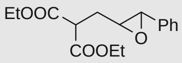
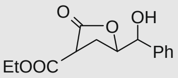
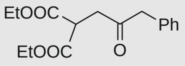
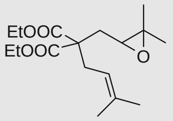
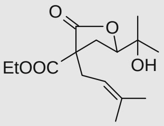
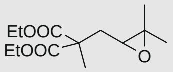
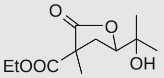
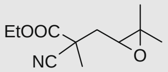
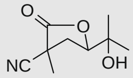
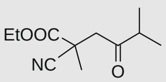
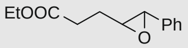
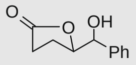
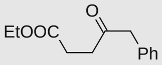
recent research.[36–39] We thus examined the behavior of epoxyesters **1a–j**, displaying various substitution patterns, in the presence of 5 mol % of tin(IV) triflimidate (Table 1). Taking into account the lack of reactivity of the alkyne moiety, we engaged compound **1b** in the reaction (entry 2). However, in the absence of the side chain, the cyclization was not observed and ketone **3b** was quantitatively formed through epoxide isomerization. Product **3b** was also obtained in 100% yield when the reaction was performed in toluene or acetonitrile (entries 3 and 4). The reaction of entry 2 was repeated in the presence of 10 mol % of 1-hexyne as ligand

Table 1
Reaction of γ,δ-epoxyesters **1a–j** catalyzed by tin(IV) triflimidate (5 mol %)

Entry[a]	Substrate	Solvent/*T*/time	Products, yields[b]
1[c]	 **1a**	CH_3NO_2/80 °C/6 h	**2a**, 70% dr=1/3  +  **3a**, 30%
2	 **1b**	CH_3NO_2/80 °C/2 h	 **3b**, 100%
3		Toluene/80 °C/2 h	
4		CH_3CN/80 °C/2 h	
5	 **1c**	CH_3NO_2/80 °C/24 h	 +  **2c**, 72% **2c'**, 28% Mixture of 4 diastereomers of **2c** and 4 diastereomers of **2c'**
6	 **1d**	CH_3NO_2/80 °C/3 h	 **3d** +  **3d'** Complexe mixture of products including **3d** and **3d'**
7	 **1e**	CH_3NO_2/80 °C/7 h	**2e**, 65% dr 3/2 
8	 **1f**	CH_3NO_2/80 °C/4.5 h	**2f**, 46% dr=n.d.  +  **3f**, 54%
9	 **1g**	CH_3NO_2/60 °C/3 h	**2g**, 85% dr=2/1 
10	 **1h**	CH_3NO_2/80 °C/7 h	**2h**, 98% dr=1/1 
11	 **1i**	CH_3NO_2/60 °C/5 h	**2i**, 45% 1 diastereoisomer  +  **3i**, 55%
12	 **1j**	CH_3NO_2/60 °C/7 h	**2j**, 73% 1 diastereoisomer  +  **3j**, 27%

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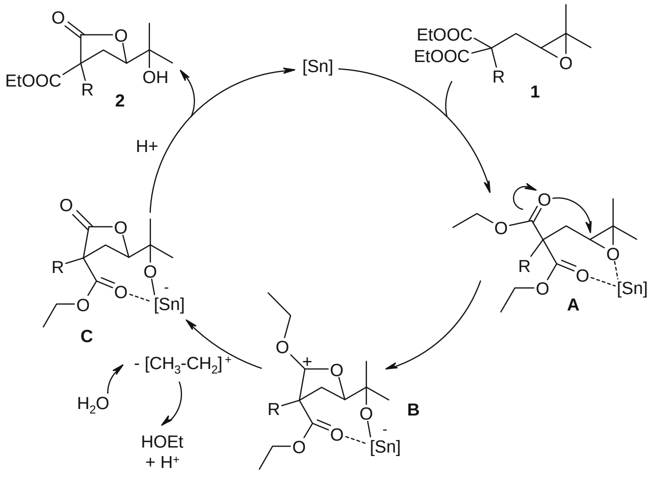
[a] Reactions were performed in 1 mL of anhydrous and degassed solvent on 0.5 mmol of substrate in the presence of 0.025 mmol $Sn(NTf_2)_4·6DMSO$ prepared following a procedure previously described.[33]

[b] Isolated yields.

[c] Taken from Scheme 1.

but again, ketone **3b** was obtained quantitatively (not shown). With substrate **1c**, compared to substrate **1a**, the only change of methyl group for a hydrogen atom on the oxirane significantly altered the regioselectivity of the reaction yielding a 7/3 mixture of diastereoisomers of γ- and δ-lactones **2c** and **2c′** almost quantitatively (entry 5). The decrease in steric hindrance at carbon atom δ in that particular case probably allowed the nucleophilic attack of one ester group, disfavored in the case of **1a**. Substrate **1d** did not cyclize under our conditions (entry 6) and the isomerization of the epoxide to both possible carbonyl compounds **3d** and **3d′** occurred, within a complex mixture of unidentified products. In that case, the lower substitution of the oxirane ring and the absence of substituent at carbon atom α resulted in a decrease in the overall efficiency of the reaction. Taking into account the results of entries 2–4,6, it appeared more plausible that rather than a coordination of the electron-rich alkyne moiety to the metal during the cyclization, the presence of a quaternary carbon atom at position α, putting the substrate into a more favorable conformation for cyclization in a Thorpe–Ingold type effect,[40] could explain our results. Thus, substrate **1e**, with a methyl substituent at carbon atom α, cyclized to δ-hydroxy-γ-lactone **2e** in 65% yield as a 3/2 mixture of diastereoisomers (entry 7).

The case of compound **1f** offered another example of competition cyclization/isomerization with the formation of the δ-hydroxy-γ-lactone **2f** in a moderate 46% yield, the main product being ketone **3f** formed in 53% yield (entry 8). Compound **1g** bearing a prenyl side chain selectively cyclized to δ-hydroxy-γ-lactone **2g** in 85% yield (dr = 2/1, entry 9). During the process, the question of whether or not **2g** could then cyclize again through a Sn(IV)-catalyzed intramolecular hydroalkoxylation[18] was of concern, but no eight-membered product was observed. The best result was undoubtedly obtained with substrate **1h** bearing a methyl group at carbon atom α for optimal conformational control during cyclization, and the δ-hydroxy-γ-lactone **2h** was obtained in 98% yield (dr = 1/1, entry 10) in sharp contrast with what was observed with substrate **1b** (entry 2). Substrate **1i** cyclized to δ-hydroxy-γ-lactone **2i** in 45% yield, with isomerized ketone **3i** (55%, entry 11). This result suggests that the presence of two ester groups is important to achieve good yields of cyclized product. Finally, substrate **1j** without substituent at the α position nor additional ester function led to a mixture of δ-hydroxy-γ-lactone **2j** and ketone **3j** in 73% and 27% yields, respectively. As for **1f**, the presence of a phenyl group was beneficial to the cyclization process even without quaternary carbon atom at α position. It is worth noting than only one single diastereomer was obtained for δ-hydroxy-γ-lactones **2i** and **2j**.[41]



Scheme 2.

In terms of mechanism, we hypothesize that, following the formation of the starting complex **A**, the reaction could start with an ester group attacking the epoxide on the opposite side at the less substituted position to form intermediate **B** (Scheme 2). Intermediate **B** would further dealkylate to yield **C**, in a process similar to the dealkylative lactonization recently described in TfOH-mediated reactions, and maybe favored by the involvement of a water molecule.[42] Protonolysis of the tin alcoholate would then lead to **2** and the recovery of the catalyst. The putative seven-membered ring chelate **A** allows to explain why a less strained five-membered ring-closure with the attack of the less substituted oxirane atom is observed while Lewis acid epoxide ring-opening usually proceeds through the attack of the most substituted carbon atom, where more stable carbocations could be formed.

In summary, we have described a novel tin(IV) triflimidate-catalyzed (5 mol %) cyclization reaction involving the ring-opening of epoxides by readily available ethyl ester groups to δ-hydroxy-γ-lactones in 46–98% yields.[43] We suggest that the reaction is under the control of steric hindrance and conformation through a Thorpe–Ingold type effect.

Acknowledgments

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43. *Representative procedure*: Cyclization of **1a** to **2a**. To a solution of **1a** (0.5 mmol, 141 mg) in degassed anhydrous nitromethane (1 mL), Sn(NTf$_2$)$_4$·6DMSO (0.025 mmol, 43 mg) was added and the mixture was stirred at 80 °C under a nitrogen atmosphere. After completion, the reaction mixture was purified by flash chromatography over silica gel (eluent: petroleum ether/diethyl ether, 100/0 to 95/5) yielding **2a** as a colorless oil (89 mg, 70% yield, 1:3 mixture of 2 diastereomers). ^{1}H NMR (200 MHz, CDCl$_3$, 20 °C): δ ppm 4.42–4.36 (m, 1H); 4.22–4.14 (m, 2H); 2.86–2.78 (m, 2H); 2.65–2.30 (m, 2H); 2.06–1.97 (m, 1H); 1.37–1.11 (m, 9H). ^{13}C NMR (50 MHz, CDCl$_3$, 20 °C): δ ppm, major diastereomer: 172.7 ($C{=}O$); 169.1 ($C{=}O$); 84.4 (CH); 84.3 (CH); 71.9 ($>C<$); 71.6 ($>C<$); 62.7 (CH$_2$); 55.5 ($>C<$); 32.1 (CH$_2$); 26.8 (CH$_3$); 24.0 (CH$_2$); 23.8 (CH$_3$); 14.0 (CH$_3$). MS (EI, 70 eV): major diastereomer 254(0) [M$^{+\cdot}$], 236(1), 209(3), 197(11), 180(3), 163(14), 151(30), 139(13), 123(26), 111(35), 105(39), 93(63), 79(41), 58(100). Minor diastereomer 254(1) [M$^{\cdot}$], 236(2), 207(2), 197(21), 179(2), 163(15), 151(50), 139(15), 123(29), 111(34), 105(44), 93(99), 79(52), 58(100). HRMS (*m*/*z*): [MNa]+ calculated for $C_{13}H_{18}O_5Na$, 277.10464; found 277.10446.