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## Tin(IV) triflimidate-catalyzed cyclization of epoxy esters to functionalized $\delta$ -hydroxy- $\gamma$ -lactones

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ARTICLE INFO	ABSTRACT
Article history: Received 6 February 2009 Revised 9 March 2009 Accepted 10 March 2009 Available online 14 March 2009	In the presence of 5 mol % of tin(IV) triflimidate, a cyclization reaction of epoxyesters to $\delta$ -hydroxy- $\gamma$ -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.<sup>1–3</sup> 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).<sup>4–13</sup> 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.<sup>14–17</sup>

We have developed cycloisomerization reactions based on the electrophilic activation of electron-rich olefins by metallic triflates and triflimidates in intramolecular hydroalkoxylation,<sup>18,19</sup> hydrocarboxylation,<sup>20</sup> hydro-thiolation,<sup>21</sup> hydrooxyamination,<sup>22</sup> and 1,6-dienes cycloisomerization.<sup>23</sup> 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<sub>2</sub>)<sub>3</sub>, which was able to catalyze a cyclization reaction through the addition of the active methylene of a  $\beta$ -ketoester to a terminal alkyne (Coniaene reaction).<sup>24</sup> 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<sup>1</sup>-catalyzed tandem epoxide ring-opening/hydroalkoxylation reactions of epoxy alkynes<sup>25,26</sup> and in Au<sup>II</sup> and Au<sup>III</sup>-catalyzed synthesis of functionalized furans,<sup>27-29</sup> acylindenes,<sup>30</sup> spiropyranones,<sup>31</sup> and divinylketones<sup>32</sup> from epoxy propargyl derivatives.

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In a previous work of Baltas and co-workers, a cyclization reaction of  $\gamma_1\delta$ -epoxy- $\beta$ -hydroxyesters promoted by excess ZnCl<sub>2</sub> was described to lead to mixtures of  $\gamma$ - and  $\delta$ -lactone derivatives, with a selectivity strongly influenced by the presence of a hydroxyl group at carbon atom  $\beta$ .<sup>34</sup> 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- $\beta$  were cyclized to  $\delta$ -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  $\gamma$ -lactone derivatives. Conversely, Ti(III)-catalyzed radical cyclizations of epoxy alkenes proceed selectively by ring-closure with attack of the most substituted carbon atom.<sup>35</sup> In our case with **1a** and in the presence of 5 mol % of tin(IV) catalyst, the cyclization proceeded exclusively to  $\delta$ -hydroxy- $\gamma$ -lactone **2a** through the 5-*exo*-tet nucleophilic attack of one ester group.

The  $\delta$ -hydroxy- $\gamma$ -lactone motif is the core structure of bioactive natural products such as (±)-muricatacin and has been the focus of





When epoxypropargyl ester **1a** was heated at 80 °C in nitromethane in the presence of 5 mol % Sn(NTf<sub>2</sub>)<sub>4</sub>·6DMSO,<sup>33</sup> the starting material was totally consumed in favor of the formation of the corresponding  $\delta$ -hydroxy- $\gamma$ -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.

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  $\gamma$ , $\delta$ -epoxyesters **1a-j** catalyzed by tin(IV) triflimidate (5 mol %)



<sup>a</sup> 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<sub>2</sub>)<sub>4</sub>·6DMSO prepared following a procedure previously described.<sup>33</sup>

<sup>b</sup> Isolated yields.

<sup>c</sup> 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  $\gamma$ - and  $\delta$ -lactones **2c** and **2c**' almost quantitatively (entry 5). The decrease in steric hindrance at carbon atom  $\delta$  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  $\alpha$  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  $\alpha$ , putting the substrate into a more favorable conformation for cyclization in a Thorpe-Ingold type effect,<sup>40</sup> could explain our results. Thus, substrate **1e**, with a methyl substituent at carbon atom  $\alpha$ , cyclized to  $\delta$ -hydroxy- $\gamma$ -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  $\delta$ -hydroxy- $\gamma$ -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  $\delta$ -hydroxy- $\gamma$ -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<sup>18</sup> 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  $\alpha$  for optimal conformational control during cyclization, and the  $\delta$ -hydroxy- $\gamma$ -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  $\delta$ -hydroxy- $\gamma$ -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  $\alpha$  position nor additional ester function led to a mixture of  $\delta$ -hydroxy- $\gamma$ -lactone **2***j* and ketone **3***j* 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  $\alpha$  position. It is worth noting than only one single diastereomer was obtained for  $\delta$ -hydroxy- $\gamma$ -lactones **2i** and 2j.41



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.<sup>42</sup> 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  $\delta$ -hydroxy- $\gamma$ lactones in 46–98% yields.<sup>43</sup> We suggest that the reaction is under the control of steric hindrance and conformation through a Thorpe–Ingold type effect.

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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<sub>2</sub>)<sub>4</sub>·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). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, 20 °C):  $\delta$  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). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>, 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<sub>2</sub>); 55.5 (⊃C⊂); 32.1 (CH<sub>2</sub>); 26.8 (CH<sub>3</sub>); 24.0 (CH<sub>2</sub>); 23.8 (CH<sub>3</sub>); 14.0 (CH<sub>3</sub>). MS (EI, 70 eV): major diastereomer 254(0) [M<sup>+</sup>], 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<sup>-</sup>], 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 C13H18O5Na, 277.10464; found 277.10446.