

Radical reactions of epoxy esters induced by titanocene chloride

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Abstract—The reductive radical cyclizations of several epoxy esters have been achieved using titanocene chloride. The tether length from the initial radical to the carbonyl acceptor is the key of the reactions. We obtained products from radical cyclization onto carbonyl formate and products from formate and hydrogen elimination. The stereochemical outcome of the 5-*exo* radical cyclization of two diastereomers is reported. A radical cascade cyclization of an unsaturated epoxy formate is also described.

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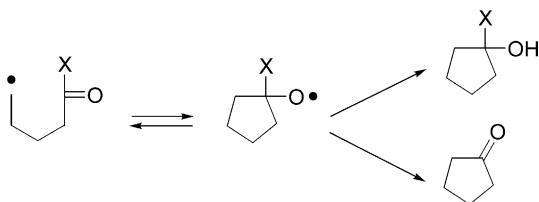
The addition of alkyl radicals to carbonyl groups is difficult owing to its reversibility.¹ The synthesis of cyclic compounds through this route has been limited by the high rate of cyclic alkoxy radical fragmentation.² However, in the case of aldehydes and ketones (Scheme 1, X = H, alkyl) this problem has been resolved by generating the radicals from epoxides with titanocene chloride³ (Cp₂TiCl) and trapping the alkoxy radicals rapidly with Ti(III).^{3a} In this way, we have been able to obtain cyclic compounds ranging from cyclopropanols to cyclohexanols in high yields.^{3a}

Additionally, only a few acid derivatives, such as thioesters, selenoesters or acyl germanes, are effective in radical cyclizations to afford cyclic ketones by using highly efficient radical leaving groups (Scheme 1, X = SPh, SePh, GePh₃).¹ Because of this limitation, the synthesis of cycloalkanones has been achieved through indirect ways, using alkynes, oxime ethers, and nitriles as radical acceptors.¹ In this context, our group has recently

described an efficient method for obtaining products ranging from cyclobutanones to cycloheptanones, in a good yield, through the reaction of epoxy nitriles with titanocene chloride.⁴

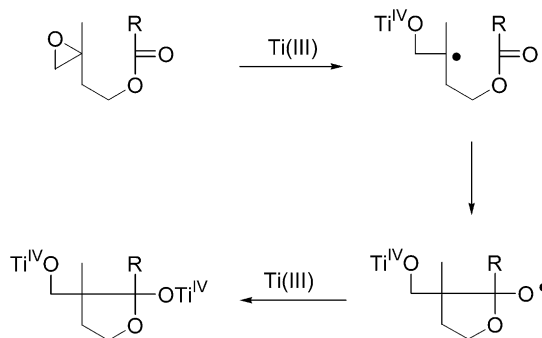
It has been stated that, ‘unfortunately the readily available carboxylic esters are inert to alkyl radical additions’.^{1,5} Taking this challenge as a final point, we began a search for the intramolecular radical addition to carboxylic esters, using epoxy esters as substrates and Cp₂TiCl as a radical-generating agent and an efficient reductant of alkoxy radicals (Scheme 2).

The present study was limited to esters in which the ether-type oxygen is situated between the initial radical and the carbonyl acceptor (*endo*). Previous experiments with epoxy esters, in which the ether-type oxygen was *exo* with respect to the initial radical and the carbonyl acceptor, afforded negative results.^{3a}



Scheme 1.

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Scheme 2.

The investigation was initiated with three epoxyesters derived from geraniol.⁶ We selected trisubstituted epoxides in order to ensure the regioselective formation of the tertiary radical.^{3,7} We chose epoxy esters that differed in the nature of the group bonded to the carbonyl (CH₃ donor, CF₃ acceptor, and H small atom) to see their influence on the radical acceptor. The reaction of epoxy acetate **1** with Ti(III) exclusively gave the unsaturated hydroxy ester **1a**, which arises from the homolytic cleavage of oxirane followed by a selective β -hydrogen elimination.^{3a} The same reaction happened with trifluoroacetate **2** (Scheme 3).

Fortunately, epoxy formate **3** gave both cyclic and acyclic products, in a 5:1 ratio (76%). The former major product **3b** was constituted by a 2:1 mixture of two diastereomeric hydroxy hemiacetals, resulting from the radical cyclization onto the carbonyl formate. The latter minor product **3a** was formed by a selective β -hydrogen elimination from the initial radical.

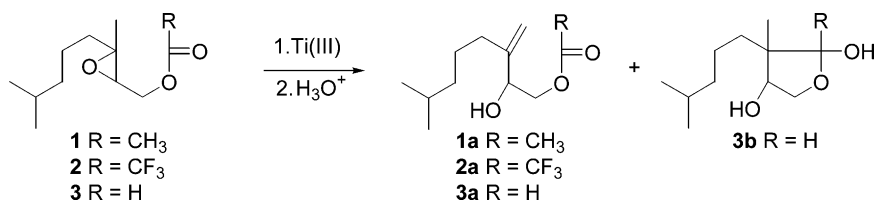
Our next experiment was a similar 5-*exo* radical cyclization onto the formate carbonyl with an epoxy ester derivative of β -cyclogeraniol.⁸ The reaction of **4** with Ti(III) afforded bicyclic and monocyclic products in a 3:1 ratio (88%). The major bicyclic product,

the result of a radical cyclization, was a mixture of two diastereomers **4a** and **4b**, in a 2:1 ratio (Scheme 4).

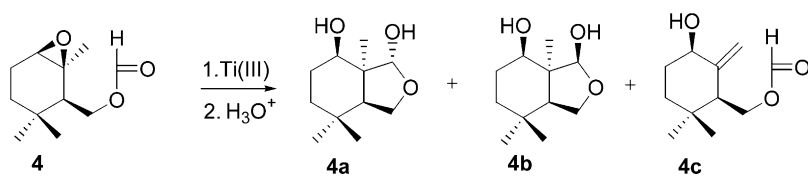
This success encouraged us to attempt the 6-*exo* radical cyclization onto the formate carbonyl with epoxy ester **5**. Treatment with Ti(III) gave cyclic and acyclic products in a 3:2 ratio (90%). A mixture of four diastereomers constituted the cyclic hemiacetal **5a** (Scheme 5).

In order to obtain hemiacetals with a four membered ring through a 4-*exo* radical cyclization process onto the carbonyl, as we have done previously with aldehydes,^{3a} we attempted the reaction of epoxy formate **6** with Ti(III). Surprisingly, from this reaction we obtained only the allylic alcohol **6a**, in a good yield (71%) (Scheme 6).

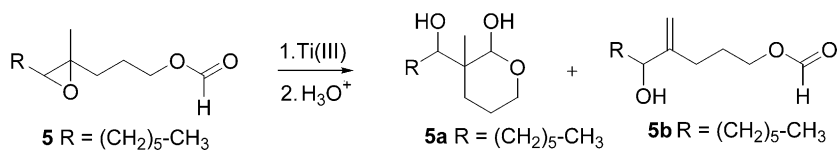
This result could be explained in terms of a homolytic cleavage of the oxirane induced by Ti(III), followed by the elimination of the formate anion. The fragmentation could be either homolytic, or heterolytic via two electron reduction of the epoxide.⁹ The reaction deserves further study. While epoxy formate **6** gave only one product with Ti(III), allylic alcohol **6a**, epoxy trifluoroacetate **7** gave the β -hydrogen elimination product **7a** plus allylic



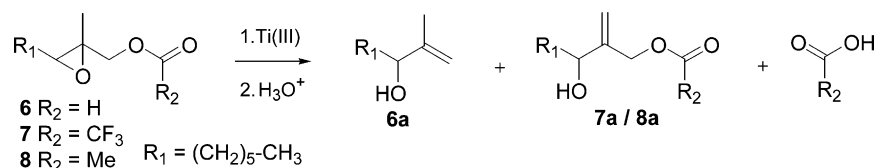
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

alcohol **6a** in a 2:3 ratio; the epoxy acetate analog **8** gave **8a** and **6a** in a 3:1 ratio.

The next trial was the 7-*exo* radical cyclization, which we achieved with epoxy nitriles in a previous work.⁴ The reaction of epoxy formate **9** with Ti(III) only afforded products from the deoxygenation, **9a**, and the β -hydrogen elimination, **9b** in a 1:2 ratio (79%) (Scheme 7).

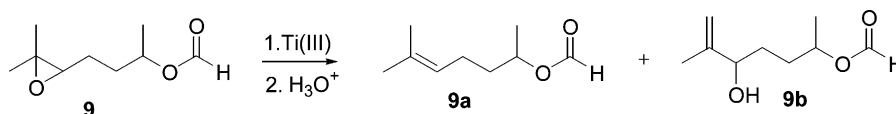
The reactivity of 1,2-disubstituted epoxides with Ti(III) differs from that of trisubstituted epoxides in the lack of regioselectivity of the initial homolytic cleavage (mainly for similar substituents) and in the reduction rate of the initial radical with Ti(III), which is higher for secondary radicals.^{3b} In this context, we tackled the reaction of epoxy ester **10** with Ti(III). Two products were obtained: the unsaturated formate **10a** (*E* + *Z* isomers) (44%), and allylic alcohol **10b** (30%). The former, **10a**, arose from the reduction of radicals A or B with Ti(III) followed by further elimination of [TiCp₂Cl]₂O, and the latter, **10b**, was due to the ultimate elimination of the formate from radical A. After treatment with Ti(III), the analogous epoxy acetate **11** gave only the deoxygenation product **11a** (Scheme 8).

To study the stereoselectivity of the 5-*exo* radical cyclization onto formates we compared two epoxy formates

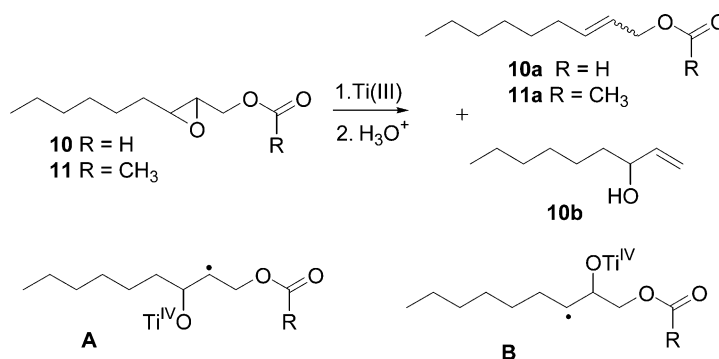
derivatives from *tert*-butylcyclohexane. It has been stated that the stereochemistry of a reaction that occurs at an alkyl radical center cannot be dictated by the stereogenicity of the pro-radical center because stereoisomeric precursors generate the same radical.¹⁰ To test this hypothesis we addressed the reaction of diastereomers **12** and **13**¹¹ with Ti(III). Surprisingly, we obtained the 5-*exo* radical cyclization products **12a/b**¹² in a 75% yield from epoxide **12** with the oxirane C–O equatorial, and only reduction product **13a** from epoxide **13** with the oxirane having the C–O axial. This result evidently does not fit in with the above postulate (Scheme 9).

Finally, we tackled an intramolecular radical cascade reaction with epoxy formate **14** using the oxirane as the initiator and the formate as the final captor. The slow addition of titanocene chloride to epoxy formate **14** gave three products: the bicyclic hemiacetal **14a** (25%), the unsaturated alcohol **14b** (11%), and the hydroxy formate **14c** (43%). The former, **14a**, is the result of two 5-*exo* radical cyclizations (Scheme 10).

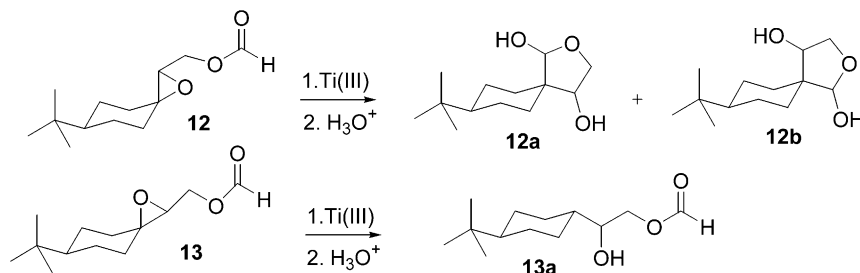
The second one, **14b**, must arise from a 5-*exo* radical cyclization followed by 1,5-hydrogen abstraction, carbon dioxide elimination and finally β -hydrogen elimination, while **14c** was a product from epoxide reduction. When the reaction was carried out by the inverse addi-



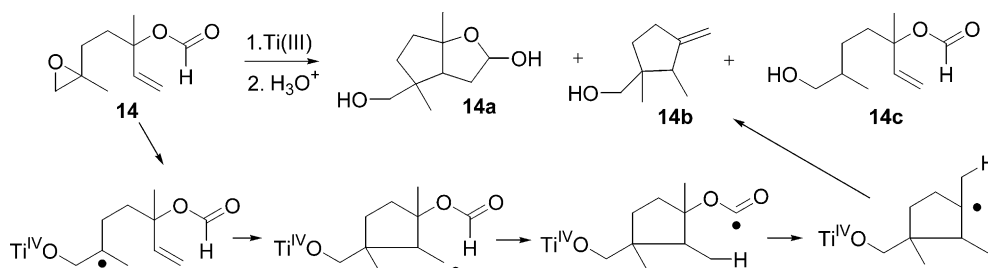
Scheme 7.



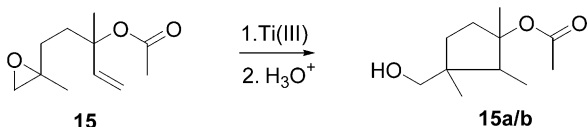
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

tion of epoxy formate to titanocene chloride, only **14b** (52%) and **14c** (19%) were obtained.

The analogous epoxyacetate **15** by reaction with Ti(III) only gave a mixture of hydroxyacetate diastereomers **15ab** (92%, Scheme 11) from the 5-*exo* cyclization onto the C=C double bond.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.08.124](https://doi.org/10.1016/j.tetlet.2006.08.124).

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