

Green Reductive Regioselective Opening of Epoxides: A Green Chemistry Laboratory Experiment

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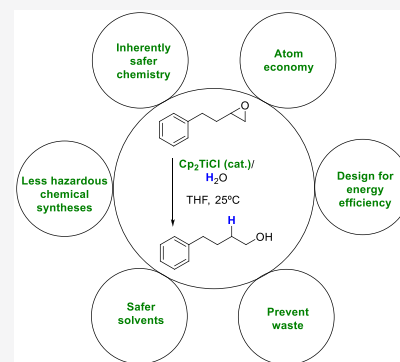
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ABSTRACT: Green chemistry is finding its place as one of the most essential study topics in the curriculum of future chemists and chemical engineers. Experiments that meet green chemistry principles contribute to make the laboratory a safer working place, generate less waste, and allow students to increase their knowledge in new environmentally friendly chemical methodologies. The work reported here focuses on the reductive opening of epoxides to afford the less substituted alcohols, which can be carried out at room temperature under catalytic conditions and using water as a hydrogen atom source. The results of this work, as well as a procedure which allows the initiation of students in the application of green chemistry techniques through a particular example, are reported. This laboratory practice can be used to teach organic and radical chemistry, green chemistry principles, and product analysis (thin layer chromatography, flash chromatography, ^1H NMR spectroscopy, and IR spectroscopy).

KEYWORDS: green chemistry, reductive opening of epoxides, laboratory instruction, titanocene



INTRODUCTION

The main goal of Green Chemistry is the reduction of the use of reagents and chemical protocols that lead to the production of toxic or dangerous substances.¹ The incorporation of teaching green chemistry in the chemistry and chemical engineering curriculum is progressively increasing and so are the educational resources available on this subject.² Normally, in a typical green chemistry and chemical engineering laboratory experiment, the lecturer suggests the students to perform a reaction that has been reported to incorporate several green principles.^{2k} Each experiment should illustrate green principles and strategies,¹ teaching students to consider the environmental impact of their work. Students are expected to understand how the transformation of conventional chemical techniques into green ones is carried out.

The reductive opening of epoxides to obtain alcohols, which has been widely included in the curriculum, is conventionally performed using stoichiometric amounts of metal hydride reducing agents such as NaBH_4 and LiAlH_4 and, more recently, by selective hydroboration.³ Both methodologies originate the more substituted alcohol or mixtures of both of them and are reactions which students seldom carry out in the laboratory because the first procedure uses a stoichiometric amount of highly flammable reagents and the second requires handling diborane, which is pyrophoric in air. On the other hand, reduction with H_2 under homogeneous catalytic conditions can represent a valuable alternative for the reductive ring opening of epoxides.⁴ However, this alternative also has several issues, such as poor regioselectivity and the use of highly flammable H_2 , noble metals, and expensive ligands.

Although some efforts have been made to improve the reductive ring opening of epoxides by homogeneous catalysis,^{4d–f} the above-mentioned considerations offer an opportunity for the development of a greener strategy for the synthesis of less substituted alcohols, which is suitable for an undergraduate laboratory. Therefore, we report herein a green, simple, and clean synthesis of less substituted alcohols through homolytic oxirane opening catalyzed by Cp_2TiCl using water as the hydrogen atom source.

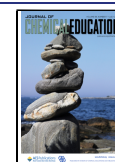
Cp_2TiCl -Catalyzed Synthesis of Less Substituted Alcohols

Among the different methodologies reported in the literature on the opening of oxirane rings to form the less substituted alcohols,⁵ regioselective reduction of epoxides catalyzed by Cp_2TiCl , using water as hydrogen atom donor,⁶ is among the safest and most environmentally friendly procedures. Recently, Cp_2TiCl has been considered as a new green chemistry reagent able to catalyze important transformations in organic chemistry.⁷ This applicable version could be completed successfully in a teaching laboratory during four sessions over 2 weeks using epoxides as the starting material. This chemical strategy was devised to illustrate the main concepts of green chemistry.

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Process of Greening the Reaction

Cp_2TiCl has recently been considered a green chemistry reagent.⁷ Therefore, the radical oxirane opening catalyzed by Cp_2TiCl , using water as hydrogen atom donor, can be used as a good example of a green chemical process. Cp_2TiCl is a single electron transfer (SET) system generated from “relatively innocuous materials” such as Mn and Cp_2TiCl_2 (Figure 1). In tetrahydrofuran (THF) solution, the reduction

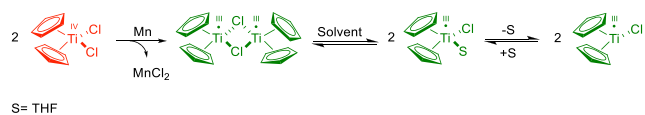


Figure 1. Preparation of the dimer of Cp_2TiCl from Cp_2TiCl_2 and its equilibrium with monomeric species.

of Cp_2TiCl_2 (red-orange color) gives Cp_2TiCl (dark green color), which is in an equilibrium between dinuclear and mononuclear species (Figure 1).

Although Cp_2TiCl_2 is not a “renewable feedstock”,⁸ it is derived from titanium, one of the safest and most abundant transition metals on Earth.⁹ A breakthrough in the use of this SET reagent in the reductive opening of epoxides was the development of a reductive “catalytic” cycle. So, in order to obtain the less substituted alcohol, the radical oxirane opening was carried out using the catalytic cycle procedure described by Gansäuer et al.¹⁰ (Figure 2), but using water as hydrogen

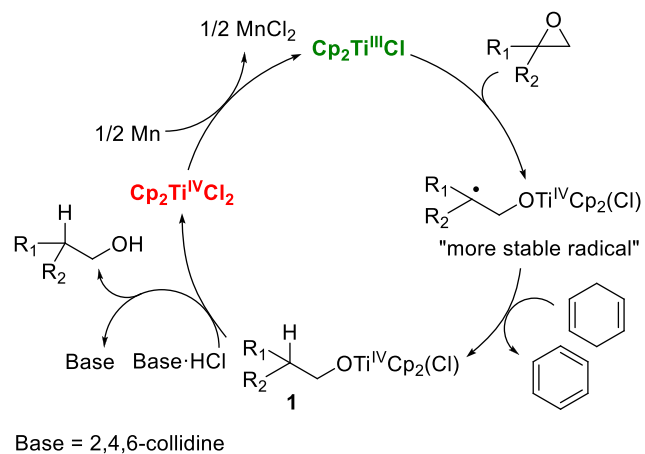


Figure 2. Epoxide opening with catalytic Cp_2TiCl .⁹

atom donor. This catalytic cycle allows the regeneration of Cp_2TiCl_2 from the titanium(IV)-alkoxy species **1**, formed after radical cleavage of the C–O bond of the oxirane and addition of a hydrogen atom. Collidine hydrochloride can be used to dissociate the Ti–O bond, protonate the alkoxy product, and regenerate Cp_2TiCl_2 . The amount of Cp_2TiCl used in these experiments is usually 20 mol %. This catalytic cycle is shown in Figure 2.

Therefore, this procedure for generating the less substituted alcohols from epoxides minimizes “waste generation”, which increases the number of chemical reactions considered as environmentally sustainable. Although the reducing metal (Mn) is used as an overstoichiometric reagent, the excess can be recovered by filtration. In addition, it was reported that 2,4,6-collidine, which is also used in this catalytic reaction, can be recovered by acid–base extraction during the reaction

workup.^{10b} Another principle to be considered in green chemistry is the use of “safer solvents”. In this context, tetrahydrofuran, the solvent used to generate Cp_2TiCl from Cp_2TiCl_2 and Mn, appears in the pharmaceutical industry guidelines for solvents,¹¹ listed as a usable solvent, because its dangerous impact is minimal. The second area of improvement is the use of water as the hydrogen atom source, avoiding the use of conventional hydrogen atom donors such as Bu_3SnH , cyclohexa-1,4-diene, or *tert*-butylthiol, which are expensive, toxic, and/or foul smelling. Under these conditions, the carbon radical generated by the homolytic epoxide opening is reduced using water as a hydrogen atom source in a process catalyzed by Cp_2TiCl .^{6,12} This reduction proceeds via hydrogen atom transfer (HAT) from a titanocene(III) aqua complex to the carbon radical. This HAT is possible by activation of water with Cp_2TiCl . The propensity of water to act as a HAT reagent could be explained by the weakening of the bond dissociation energy of the O–H bond in almost 60 kcal/mol in the presence of Cp_2TiCl . Initially, the aqua complex **2** was proposed as a HAT reagent (pathway A, Figure 3).⁶ However,

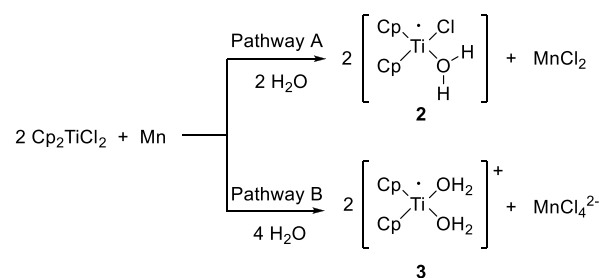


Figure 3. Reported Cp_2TiCl aqua complexes.

after more extension and refinement of theoretical calculations, electroparamagnetic resonance techniques, and cyclic voltammetry studies, Gansäuer et al.^{12b} reported that the aqua complex **3** is the active HAT reagent (pathway B, Figure 3).¹²

In addition, due to the mild reaction conditions (room temperature and atmospheric pressure), it is also a good example of an energy-efficient process. Finally, this reaction incorporates the principle “less hazardous chemical synthesis” by replacing reagents that are pyrophoric in air. The prevailing idea is that it is always better to avoid the formation of waste products than having to treat and eliminate them and, at the same time, that with the use of safer chemical processes, it is easier to minimize risks for the environment. Although the principle “atom economy” is somewhat verified as Cp_2TiCl is used in catalytic quantities and therefore few atoms are wasted and the rest of the reagents can be easily recovered by filtration or simple acid–base extraction, it would be desirable to perform a quantitative analysis of this principle, which will be addressed in the future.

When evaluating the whole process, students should understand that 6 of the 12 principles of green chemistry have been taken into account. This evaluation process of the green chemistry principles allows students to deduce that there is no reaction that fulfills all of them. However, this fact should be considered to be a positive reality in their educational process, as it allows them to analyze the different features of green chemistry before undertaking any specific reaction.

EXPERIMENTAL OVERVIEW

The regioselective opening of epoxides catalyzed by Cp_2TiCl to form the less substituted alcohols was tested over an academic year by eight students (grouped in pairs) as part of the organic chemistry laboratory course during 2 weeks of the second term. The first session (2 h) included the concepts of green chemistry principles and a comparison between the standard reductive opening of epoxides using metal hydride reducing reagents and Cp_2TiCl -catalyzed regioselective reductive epoxide opening using water as the hydrogen atom donor, with special emphasis on the verification of green chemistry principles. In the second session, the synthesis of alcohol **5** (Figure 4) was addressed from the available 2-(2-phenylethyl)-

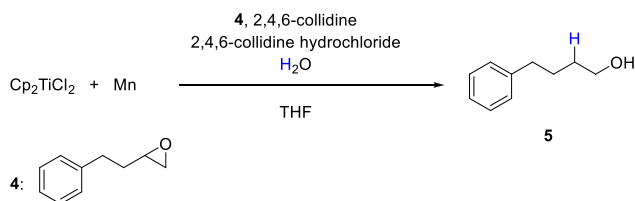


Figure 4. Reductive opening of oxirane **4** catalyzed by $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$.

oxirane (**4**), Cp_2TiCl (cat.), and water. The reaction was catalyzed by Cp_2TiCl and was run using THF as solvent at room temperature. Water is used as a hydrogen atom source, whereas 2,4,6-collidine hydrochloride allows the regeneration of the initial titanium complex (Cp_2TiCl_2). After 48 h, the reaction was quenched in the third session (3 h). Alcohol **5** was isolated by flash chromatography on silica gel. Finally, in the fourth session (1 h), the students ran a TLC of the isolated product, using a standard for identification purposes. The remaining time was used for a discussion of the ^1H NMR and IR spectra of compound **5**, which was handed to the students by the lecturer.

LEARNING OBJECTIVES

This synthetic exercise can be used as a launch pad for the discussion of multiple aspects related to radical chemistry, reaction mechanisms, manipulation of reagents and inert atmosphere, green chemistry principles, and characterization of organic compounds. The main learning objectives are listed below:

- Describing the main procedures for the reductive opening of epoxides.
- Describing Cp_2TiCl as a single electron transfer reagent that fulfills many of the green chemistry principles.
- Applying the use of a vacuum line to obtain an inert atmosphere.
- Qualitatively observing evidence of the generation of Cp_2TiCl (based on color change).
- Qualitatively interpreting the TLC.
- Applying the use of flash chromatography to the purification of organic compounds.
- Interpreting ^1H NMR and IR spectra.

HAZARDS

A well-ventilated hood is used in all experiments. Safety measures for students include wearing goggles and gloves. Both the epoxide (starting material) and the alcohol (reaction product) are flammable and can be irritants. Tetrahydrofuran

is a flammable solvent and a potential peroxide generator. Cp_2TiCl_2 is toxic by inhalation and is an irritant to the skin and mucous membranes. Mn is a flammable solid. Cp_2TiCl causes skin irritation and serious eye irritation. 2,4,6-Collidine is flammable and harmful if swallowed, and the vapor might cause serious eye, respiratory, and skin irritation. 2,4,6-Collidine·HCl is harmful if swallowed. KHSO_4 might cause skin burns, eye damage, and respiratory irritation. Pentane and ethyl acetate are highly flammable liquids, which might cause skin and eye irritation. Deuteriochloroform is harmful if swallowed; the vapor might cause serious eye, respiratory, and skin irritation, and it is a possible carcinogen.

EXPERIMENT

In the second session (2 h), the group of eight students was split into pairs. Each pair of students carried out the homolytic opening of epoxide **4** reported in Figure 4. Deoxygenated THF (20 mL) was added to a mixture of commercial Cp_2TiCl_2 (49.8 mg, 0.2 mmol) and manganese dust (439.5 mg, 8 mmol) under an argon atmosphere, and the suspension was vigorously stirred at room temperature until the students observed the color of the solution change from orange to dark green (after about 15 min). Then a deoxygenated solution of epoxide **4** (148.2 mg, 1 mmol), water (144 mg, 8 mmol), 2,4,6-collidine (484.7 mg, 4 mmol), and 2,4,6-collidine hydrochloride (630.5 mg, 4 mmol) in THF (5 mL) was added under argon to the green solution. When this suspension was added, the students observed a color change to dark blue. The reaction was stirred at room temperature for 48 h. In the third session (after 48 h), the reaction was quenched with a saturated solution of KHSO_4 (3×20 mL) and extracted with EtOAc (3×15 mL). The organic layer was washed with brine (3×20 mL) and dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel using 95:5 mixture of pentane and ethyl acetate as eluent to afford the less substituted alcohol (student report yields 40–62%). The formation of the desired product and its purity was confirmed running a TLC analysis using **5** as a standard.

RESULTS AND DISCUSSION

In the first session, after analyzing the most common methodologies for the reductive opening of epoxides, students should be able to deduce which of them (reductive opening epoxides by metal hydride reagents or by Cp_2TiCl using water as the hydrogen atom donor) possess more principles of green chemistry. Students are made aware of the need of the development of environmentally sustainable chemical procedures. Before starting the second session, the lecturer can guide the students on the stability of the different radicals (primary, secondary, and tertiary), a knowledge previously acquired in organic chemistry courses. This comment will help students to predict the regioselectivity of the radical opening of epoxides generating the less substituted alcohols.

The experiment allows students to work under anhydrous reaction conditions, becoming familiar with the operation of the vacuum line. This experiment was performed by eight chemical engineering students grouped in pairs. The best yield obtained was 62% (after flash chromatography). Finally, in the last session, the students also get the chance to interpret the ^1H NMR spectra of alcohol **5** and check the key resonances (see Supporting Information) that corroborate the presence of the OH group in the obtained product. The formation of the less

substituted alcohol can be clearly deduced from the ^1H NMR spectra by observation of the chemical shift and multiplicity pattern of the signal at 3.68 ppm and its integral ($\delta = 3.68$ ppm, t, $J = 6.6$ Hz, 3H). Furthermore, this functional group (OH) can be easily identified by IR spectroscopy (see [Supporting Information](#)), as alcohol **5** shows a very characteristic O–H bond infrared absorption ($\sim 3332\text{ cm}^{-1}$). The result obtained showed this reaction to be regioselective, producing only the less substituted alcohol. This result is explained by the fact that the first intermediate formed in the Ti-catalyzed oxirane ring opening is the most substituted radical, which subsequently suffers hydrogen transfer from water in a process also catalyzed by Cp_2TiCl , leading to intermediate **1**. It has been proven that coordination of Cp_2TiCl to water produces a weakening of the O–H bond dissociation energy and acts as a useful hydrogen atom source.^{6,12}

ASSESSMENT

In the first session, students were introduced to the 12 principles of green chemistry, which provided them the necessary background to evaluate the preparation of alcohol **5**. Students were prompted to specify in their lab reports the green chemistry principles that were particularly verified in this chemical process, stating their reasons (see [Supporting Information](#)). All students correctly detected that the principles of catalysis and energy efficiency were verified in this synthesis, as substoichiometric amounts of titanocene(III) were used, and the reaction proceeded at room temperature. The use of safer solvent and less hazardous chemical synthesis was also addressed by most of them, but only a few were able to mention that this synthesis minimizes waste generation, as excess manganese could be recovered by simple filtration, and the collidine used in the reaction could be recovered in the reaction workup by simple acid–base extraction. The atom economy principle was also mentioned, although some of them had a bit of confusion between this concept and the reaction yield or the amounts of reagents and reactants. The students were also asked about general concepts, both experimental and theoretical, of radical chemistry mediated by Cp_2TiCl (see [Supporting Information](#)). Most students were able to respond successfully based on the concepts developed during the first session.

In the fourth session, ^1H NMR and IR spectra of epoxide **4** and alcohol **5** were handed to the students in order to assign the signals due to each hydrogen and the absorption bands. Comparison between the ^1H NMR and IR spectra of **4** with the spectra of alcohol **5** to distinguish the characteristic signals of the synthesized alcohol **5** was suggested. Students were prompted to fill in a data sheet with the spectroscopic properties of alcohol **5** and committed to assign all of the proton signals in ^1H NMR spectra and absorption bands in the IR spectra (see [Supporting Information](#)). Most of them had no problem with this assignment, as all of them were already familiar with those techniques.

CONCLUSIONS

The radical opening of epoxides catalyzed by Cp_2TiCl and using water as a H atom donor is a good reaction to illustrate the principles of green chemistry. Also, the chemistry laboratory experiment described herein allowed the students an opportunity to carry out a reaction under an anhydrous atmosphere and assess the regiochemistry of the radical

opening of epoxides using Cp_2TiCl and water as the H atom donor. The students addressed the regiochemistry of the reaction based on electronic and steric mechanistic interpretations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00409>.

Temporal development of the practice, prelaboratory assignment, instructor's note, and student handout ([PDF](#))

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Notes

The authors declare no competing financial interest.

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