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Electrochemically induced titanocene-mediated reductive opening of epoxides

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A new method for chemo- and regioselective electrochemical reductive opening of epoxides yielding primary alcohols with titanocene dichloride as a catalyst has been elaborated.

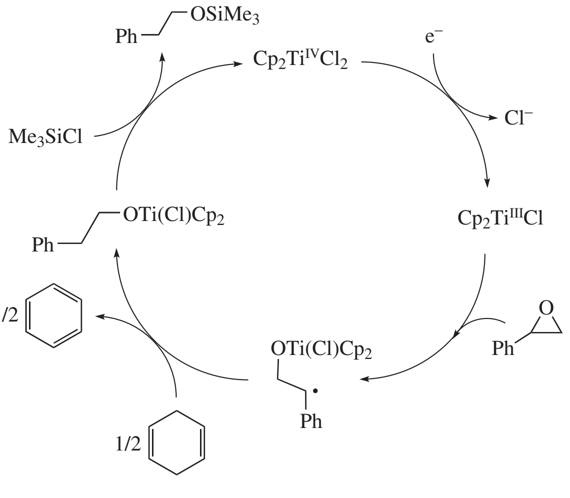
Epoxides are used in organic synthesis since they can undergo selective nucleophilic substitution;[1] two-electron reduction of epoxides to carbanionic species allows reactions with electrophiles to occur; epoxides also provide an excellent source of functionalized radicals.[2,3] As compared to reactions involving polar intermediates, free radical-mediated reactions are usually performed under mild conditions and possess high functional group tolerance.[4] The regio- and stereochemistry of homolytic epoxide opening is guided by the relative stability of the intermediate radicals and it usually differs from the case of S_N2 openings.

Paramagnetic metal complexes are often used as radical initiators, with bis(cyclopentadienyl)titanium(III)chloride being the most popular reagent. It was applied for selective reduction of α,β-epoxy ketones to β-hydroxy ketones,[5] deoxygenation of epoxides,[4,6] epoxy olefin and epoxy alkyne cyclization,[7,8] reduction of epoxides and their intermolecular addition to double bonds.[4]

$Cp_2Ti^{III}Cl$ is easily generated from the stable titanocene dichloride using various chemical reductants, *i.e.*, metals (Mn, Mg, Zn, Al, *etc.*) or organometallic complexes (RMgX, RLi).[9] The application of electrochemical techniques allows one to avoid the usage of these ecotoxicants. Moreover, it gives one a possibility not only to generate short-lived organometallic species (in particular, during the catalytic cycle) but also to monitor the reactivity and the concentration of reagents during the reaction course, thus clarifying the mechanism and kinetics of the process.

Surprisingly, there are still only few works where electrochemical electron transfer is used to generate $Cp_2Ti^{III}Cl$ species or other Ti^{III} complexes which are further involved in a catalytic process. The publications to be quoted in this context describe the indirect reduction of nitroarenes to the corresponding amines in a biphasic (protic-organic) media by the hydrolyzed titanocene complex,[10–12] a pinacol coupling of aldehydes[13] and reductive dehalogenation of organic halides.[14–17] Recently, a detailed investigation of the mechanism and kinetics of titanocene-mediated epoxide opening was published.[18] It also includes voltammetric investigation of Ti^{III} species involved in the process. However, in preparative experiments electron transfer was provided by the use of zinc metal rather than electrochemistry. Here we report electrochemically reduced titanocene dichloride as a catalyst for reductive opening of epoxides yielding alcohols and demonstrate that electrochemical protocol is applicable even to the epoxides with easily reducible functional groups such as NO_2, which is incompatible with activation with organometallic compounds.

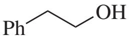
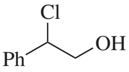
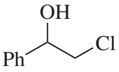
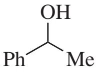
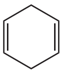
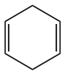
For investigation, two epoxides were chosen: styrene and 4-nitrostyrene oxides. The optimization of the reaction conditions was carried out at the unsubstituted substrate. The electrocatalytic reaction was performed in a two-compartment H-type electrochemical cell in THF containing 0.15 M Bu_4NBF_4 in a potentiostatic mode at a potential of the Cp_2TiCl_2 reduction (–0.85 V *vs.* Ag/AgCl/KCl). Graphite tissue ('Ural', Russia) with the surface area of 12 $m^2\ g^{-1}$ was used as a working electrode. The amount of the electricity passed through the solution was 10.6 C per 0.1 mmol of epoxide, which corresponds to one-electron reduction. The current density value during the electrolysis fell from 1.7 to 0.15 mA cm^{-2} (as calculated respectively to geometrical surface area of the electrode).



Scheme 1

In the electrocatalytic process thus formed Ti^{III} species react with epoxide [it should be mentioned that the direct electrochemical reduction of styrene oxide occurs at much more cathodic potential (–1.3 V *vs.* Ag/AgCl/KCl)] yielding the intermediate regioselective formation of the secondary radical of benzylic type (Scheme 1). The regioselectivity is controlled by the radical stability, as well as by steric interactions between the epoxide and cyclopentadienyl ligands.[18,19] To prevent side reactions involving the benzylic radical and paramagnetic Ti^{III} species, H-atom donor should be added to the reaction mixture. Two additives were tested, triphenylmethane and 1,4-cyclohexadiene, with the latter turning out to be more efficient (Table 1). Thus, as it was demonstrated,[18] at the first reaction step the epoxide is converted into titanocene alkoxide. To perform the reaction in a catalytic mode, the regeneration of the catalyst is necessary and it requires Ti–O bond cleavage. The first reagent which was tested was collidine hydrochloride. It was shown[19] that it was efficient in Ti–O bond cleavage and, at the same time, did not initiate the epoxide opening. However, the

Table 1 The optimization of reaction conditions for the electrocatalytic styrene oxide opening (C = 10 mmol dm^{-3}, 3 mmol dm^{-3} Cp_2TiCl_2, E = –0.85 V *vs.* Ag/AgCl/KCl, $C_{\text{H-donor}}$ = 15 mmol dm^{-3}, C_{Me_3SiCl} = 15 mmol dm^{-3}).

Reagent for Ti–O bond cleavage	H-donor	Reaction products, yield (%)			
					
Collidine hydrochloride	Ph_3CH	4	28	45	0
		12	24	44	0
Me_3SiCl	Ph_3CH	23	42	21	0
		75	14	3	0

GCMS analysis of the reaction solutions obtained in the electrolysis of a mixture of styrene oxide and Cp_2TiCl_2 in the presence of collidine hydrochloride revealed the formation of isomeric chlorohydrins which are the products of the oxirane ring opening with chloride anions (Table 1). The control experiments showed that peak potential value for collidine hydrochloride reduction is about –1.2 V *vs.* Ag/AgCl/KCl but at an applied potential of –0.85 V a partial reduction of the protons in collidine hydrochloride occurs leading to the formation of some amount of chloride anions. As it was already mentioned, the electrolysis was performed in a two-compartment cell and the anodic oxidation of chloride ions did not decrease their concentration in the cathodic compartment. This enforced us to turn to trimethylsilane as the reagent for Ti–O bond cleavage. The control experiments revealed that it did not open oxirane ring under the reaction conditions (contrary to Me_3SiBr which gave bromohydrins). The silylated alcohol formed at the final reaction step can be easily converted to the corresponding primary alcohol by the treatment with the 2 M HCl or KF. The optimization of the reaction conditions allowed us to obtain 2-phenylethanol in 75% yield (Table 1). The regioselectivity of the reaction was proved using GCMS analysis: two isomeric phenylethanols can be distinguished by their characteristic fragmentations in mass spectra which are available in 'Wiley275' database.

It was of interest to investigate the applicability of the proposed electrocatalytic ring opening to the substrates with easily reducible functional groups, *e.g.*, 4-nitrostyrene oxide. Electrochemical reduction of nitro group in this compound occurs at a potential of about 200 mV more cathodic as compared to the potential of titanocene dichloride reduction (–1.05 V) and it constrains us to be especially careful in the installation of the electrolysis potential value. To prevent the direct reduction of nitro group at the electrode, the electrolysis was performed at a potential of –0.75 V which is a little less below the peak potential value for Cp_2TiCl_2. The reaction protocol was the same as that used for unsubstituted styrene oxide, KF was used for Si–O bond cleavage. As a result, 2-(4-nitrophenyl)ethanol was obtained in 81% yield.

Thus, it was demonstrated that potentiostatic electrolysis at a potential of Cp_2TiCl_2 electroreduction can be considered as a convenient method for the electrocatalytic reductive opening of the oxirane ring yielding primary alcohols. The regioselectivity of the process is the opposite to that of S_N2 reactions and it is determined by the stability of intermediate radical species and steric interactions. The main advantage of the electrochemical approach is a possibility of a precise adjustment of a reaction potential value which allows one to avoid side reactions involving easily reducible functional groups. This makes the approach applicable to the substrates for which activation with organometallic compounds is not valid.

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