

# Erbium Triflate a Very Powerful Catalyst

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**Abstract:** Recently, erbium triflate has found to have a wide application in organic synthesis. Owing to its high oxophilicity, it has been used for reactions involving epoxide ring with applications both in laboratory and industrial organic chemistry. Moreover, it easily catalyzes the Ferrier rearrangement of glycols, the cleavage of protecting groups, the synthesis of imines and Diels Alder reactions.

**Keywords:** Erbium triflate, Lewis acid, Epoxide, Ferrier rearrangement, Catalyst.

## 1. INTRODUCTION

Mosander discovered erbium in 1843, separating from gadolinite three fractions, which he called yttria, erbia and terbia (all for Ytterby, a town in Sweden). Erbium ranks 43<sup>rd</sup> in natural abundance among the elements in the earth's crust [1].

Only ion-exchange production techniques, developed in the late 20th century, have greatly brought down the cost of production of all rare-earth metals and their chemical compounds. For this reason, papers about their employment in organic synthesis started to appear in the chemical literature, only recently [2].

The lanthanoid family possesses the interesting feature of a regular variation of many properties along the series with a discontinuity between Eu and Gd, the so-called 'gadolinium break', which reflects the stability of the 4f<sup>7</sup> configuration of Gd<sup>3+</sup> ion.

Lanthanide salts are used as Lewis acids (LA) in organic chemistry, because of their stability, especially in water as compared to more traditional catalysts, but, chiefly, all the lanthanide compounds are of low to moderate toxicity, although their toxicity has not been investigated in detail [3]. Therefore, lanthanide salts assumed a great importance in green chemistry.

Recently, the relative Lewis acidity of rare earth metal triflates was evaluated from their competitive ligand dissociation from complexes, using tandem mass spectrometry. In these studies erbium (III) resulted as one of the most active lanthanoid (III) derivatives [4].

Lewis acid strength was also evaluated in correlation with hydrolysis constants ( $pK_h$ ) and water exchange rate constant (WERC). In particular, metal compounds which have  $pK_h$  values from 4.3 to 10.08 and WERC greater than  $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ , showed the higher acid power [5]. Actually erbium(III), that has  $pK_h = 7.9$  and  $\text{WERC} = 1.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ , perfectly fits Kobayashi's parameters.

Finally, Lewis acidity of lanthanoid ions has been related to the principal properties, (PPs) that are intrinsic properties representative of experimentally observable macroscopic descriptors, by predicting the reaction yields of a model LA-catalyzed reaction. Also, these measures are in agreement with the other ones in evaluating the high ability of erbium ion as LA [6].

Despite these findings, the Lewis acid power of erbium salts has not been exploited until the last five years, when literature suddenly increased.

An objection commonly raised about  $\text{Er}(\text{OTf})_3$  catalyzed reaction is, which true species (Brønsted or Lewis) performs the catalysis. In fact, although its water solution is only weakly acidic, nevertheless, adventitious TfOH released from the hydrolysis of  $\text{Er}(\text{OTf})_3$

or remained from its preparation could be present in the salt. However, the observation that TfOH does not catalyze most of the below-described reactions as effectively as  $\text{Er}(\text{OTf})_3$ , suggests that the Lewis acidic erbium ion is more likely involved than simple proton.

## 2. EPOXIDE RING OPENING

The capability of erbium to coordinate the oxygen atom of the three-membered epoxy ring prompted chemists to explore reactions involving epoxides, which can be catalyzed by erbium(III) triflate. Two main lines of research were followed: our research group developed Lewis acid catalyzed epoxide reaction, Garcia's group, instead, studied the use of erbium (III) triflate as an initiator for low curing temperature epoxy powder coatings.

### 2.1. Lewis Acid Catalyzed Organic Reactions

The rearrangement of epoxides (1) to carbonyl compounds (3) is, for example, a useful synthetic transformation with high atom economy. It would be a good example of green chemistry, if the reaction conditions require no purification processes, and use an easily recoverable, non-toxic catalyst. During our studies on cerium salts, [7] we found that epoxide rearrangement was not successfully exploited by cerium triflate. On the other hand, erbium triflate does it in very high yields (ranging from 82 % to almost quantitative) in the presence of only 1 mol % of catalyst in dichloromethane, at room temperature [8]. Rearrangements of alkyl epoxides are more difficult than aryl ones, so refluxing temperatures are necessary for the reaction to occur. Finally, the advantages of  $\text{Er}(\text{OTf})_3$  include the regioselectivity, the broad applicability, and easy recoverability over 90%.

Product distribution on limonene oxide supports a probable mechanism involving coordination of the Lewis acid to the oxygen atom, releasing of the torsional energy through the formation of the most stable carbocation, and finally, rearrangement of the substituents according to their migratory aptitude (Scheme 1).

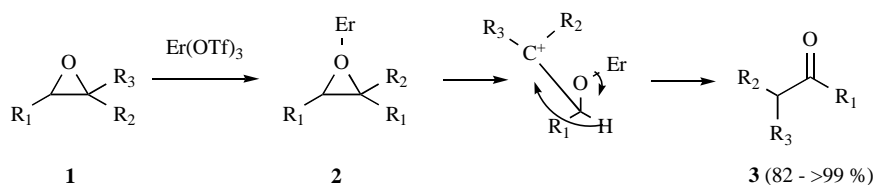
Butene oxides give unexpectedly yields near to 50 %, accounting 2-ethyl-2,4,5-trimethyl-1,3-dioxolane for the other 50 %. This result shows the ability of  $\text{Er}(\text{OTf})_3$  to stereoselectively convert epoxides into protected diols in a one-step procedure.

Actually, when erbium triflate is added to a solution of epoxide in acetone, acetonides (4) are easily recovered in very good yields (77 %-almost quantitative) (Scheme 2) [9].

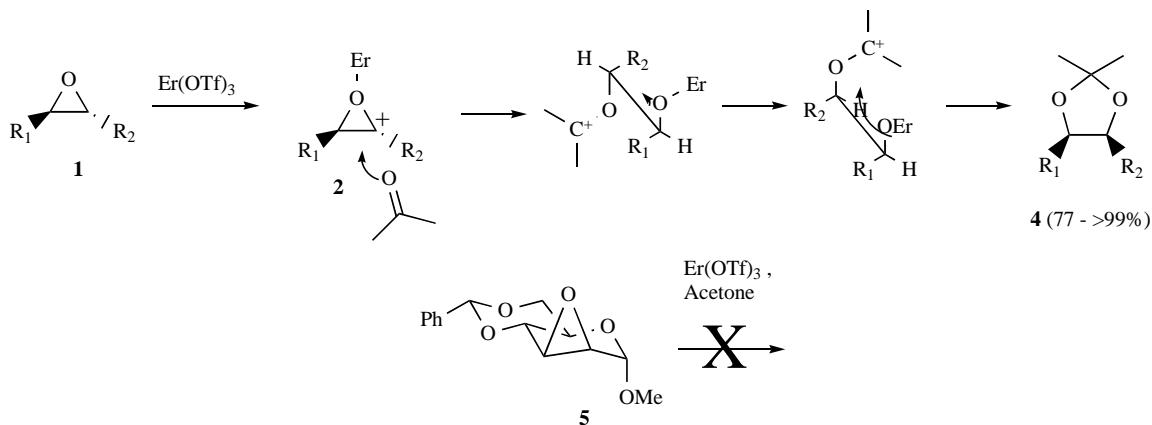
The catalyst amount is critical: aromatic epoxides need only 0.1 mol % to avoid rearrangement, whereas for aliphatic epoxides, where the rearrangement process is slower, 1 mol % of catalyst gives the best results. The reaction can be extended to other ketones, but the reactions are considerably slower. The presence of benzyl, phenyloxy and propargyloxy groups on the epoxide ring drastically decreases yields (29-44 %).

Evidence of the preferential coordination of the erbium cation at the epoxide oxygen rather than carbonyl oxygen atom arises from

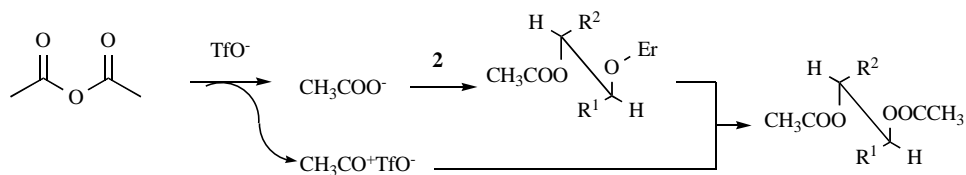
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Scheme 1.



Scheme 2.

Table 1. Synthesis of 1,2-Diacetates from Epoxides and Acetic Anhydride under Er(OTf)<sub>3</sub> Catalysis

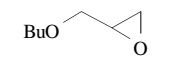
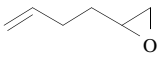
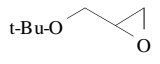
Epoxide	Time (h)	Yield (%) <sup>a</sup>
	0.25	97
	3	93
	1	>99
	5	60 <sup>b</sup>
	1	>99
	1	91
	6	73

<sup>a</sup> Isolated yields.<sup>b</sup> Peracetylated product.

the complete unreactivity of methyl 2,3-anhydro-4,6-*O*-benzylidene- $\alpha$ -D-allopyranoside (**5**), whose epoxide oxygen is crowded.

Among epoxide transformations, the direct conversion into 1,2-diacetates is a very important, but scarcely studied, reaction. Actually, the reaction can be carried out in the presence of 0.1% mol of

**Table 2. Reaction of Epoxides with Amines under Er(OTf)<sub>3</sub> Catalysis at 60 °C in Deionized Water**

Epoxide	Amine	t (h)	Yield (%) <sup>a</sup>
Cyclohexene oxide	Piperidine	2	>99
	Butylamine	5	80
	Pyrrolidine	2	>99
	Morpholine	2	>99
	Cyclohexylamine	4	93
	Benzylamine	2	>99
	Aniline	8	95
	p-Toluidine	8	92
	m-Toluidine	8	92
	o-Toluidine	8	90
	p-Anisidine	8	90
	4-Aminophenol	8	92
	4-Chloroaniline	8	95
	4-Bromoaniline	8	92
4-Nitroaniline	8	90	
Stilbene oxide	Aniline	8	78
1-Hexene oxide		8	87 (100:0)
		p-Toluidine	8
8			92 (100:0)
	Aniline	8	82 (100:0)
Epichloridrine		8	90 (100:0) <sup>b</sup>
		8	87 (100:0)
Styrene oxide	Piperidine	2	>99 (100:0)
	Butylamine	2.5	93 (90:10)
	Pyrrolidine	2	97 (90:10)
	Morpholine	2	95 (96:4)
	Benzylamine	2.5	90 (75:25)
	Aniline	8	95 (15:85)
	p-Toluidine	8	93 (10:90)
	m-Toluidine	6	93 (12:88)
	o-Toluidine	6	92 (10:90)
	p-Anisidine	6	94 (12:88)
	4-Aminophenol	6	93 (13:87)
	4-Chloroaniline	8	94 (5:95)
	4-Bromoaniline	8	92 (18:92)
	4-Nitroaniline	8	88 (7:93)

<sup>a</sup> Isolated yields. In parentheses unsubstituted/substituted position ratio.<sup>b</sup> No product arising from S<sub>N</sub>2 on chlorine was detected.

erbium(III) triflate as catalyst, by mixing together the epoxide and acetic anhydride. Since the only by-product is acetic acid from the excess of anhydride, these conditions are also environmentally benign. The results are collected in Table 1. All reactions proceeded in good to very high yields, with the formation of only one diastereoisomer with the two acetoxy groups anti each other [10].

Aromatic epoxides cannot be converted into 1,2-diacetoxy, but better into 1,1-diacetoxy derivatives, owing to the competitive above-described rearrangement. Moreover, competitive experiments with other nucleophiles, such as alcohol and amines, show that under these reaction conditions they prefer epoxide addition rather than acylation reaction. This evidence once more demon-

strates, that the preferential coordination site is the epoxide oxygen atom. Then, the activated epoxide ring is opened from the opposite side by acetate ion, whereas the addition of acilium triflate completes the reaction [11].

The features of the reaction allowed to synthetically exploit the catalytic power of erbium salt, both in the synthesis of 1,1-diacetoxy derivatives from aldehydes (see section 4.2) and in the addition of nucleophiles to epoxides [12].

The reaction is carried out in water as the solvent, since it is the most 'green' solvent available and also a simple, efficient and robust system for the reuse of the catalyst. In fact, after the completion of reaction, the aqueous mixture is extracted with organic solvent, the products are separated, fresh substrate is added to the aqueous layer, and the process is repeated with comparable activity. Some aliphatic amines react at room temperature in the presence of 1 mol % of catalyst, but the most general results have been obtained with 5 mol % of catalyst at 60 °C (Table 2).

The reaction rate of aminolysis in water depends on the structure of the epoxide and on the nucleophilicity of the amine. The less substituted carbon of aliphatic oxiranes is always regioselectively attacked and no nucleophilic displacement of leaving groups present on the epoxide was ever observed. On the other hand, unsymmetrical aromatic epoxides gave the major product with the opposite regiochemistry, since electronic factors prevail over steric ones.

All the procedures presented in this section are very simple and use a low toxicity and low cost catalyst, mild reaction conditions, short times and excellent stereo-, regio- and chemoselectivity.

## 2.2. As Curing Agent in Epoxy Resins

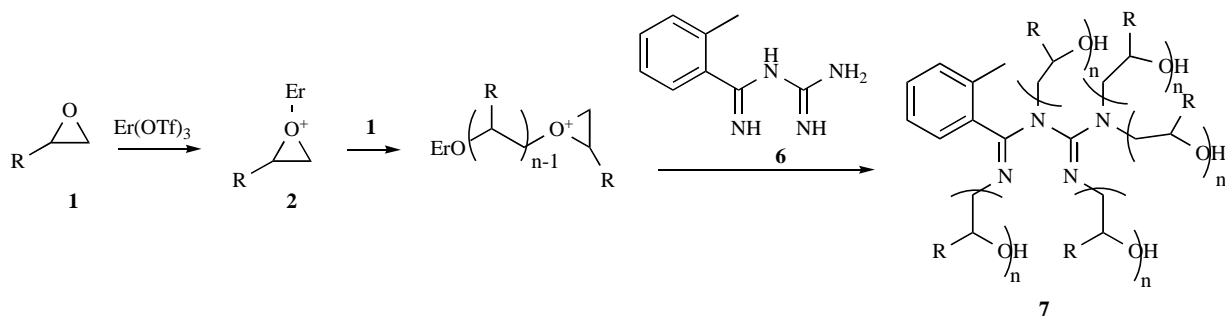
Powder coatings are currently the fastest growing section of industrial paints, because of their favorable environmental attributes (less than 4% of volatile organic contents) and performance advantages [13]. However, classical powder coatings cannot be applied on thermo-sensible substrates like wood or plastic, owing to the high curing temperature (higher than 170 °C). For this reason, the formulation of new epoxy powder coatings capable to cross-link at lower temperatures has become one of the main lines of research.

The use of Lewis acid, particularly lanthanide triflates as catalysts, has given very good results in accelerating the curing reaction between epoxy and *o*-tolybiguanide (TBG, **6**) by the promotion of the polymerization oxirane/NH of the TBG (Scheme 3) [14].

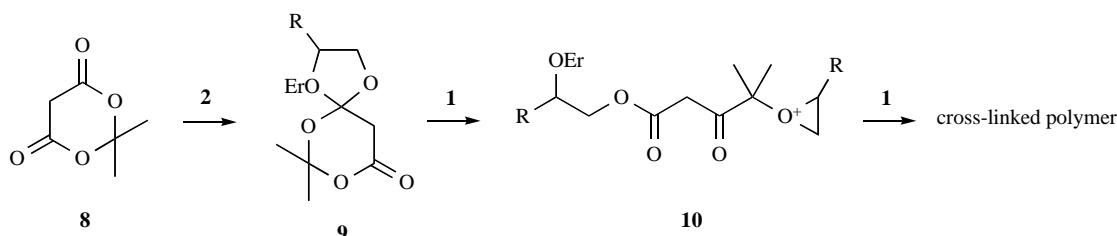
In particular, erbium(III) triflate (1 phr = parts of initiator per hundred of resin, w/w) reduced the curing time and/or temperature (for a curing temperature of 130 °C, about 45% reduction in curing time is obtained with respect to a system without catalyst) on a solid bisphenol-A based epoxy resin of medium molecular weight [15]. When increasing the content of Er(OTf)<sub>3</sub>, there was a reduction of the adherence and an augmentation of the cross-linking. When initiator content reaches 2 phr, an increase in porosity was observed because there was no sinterization, so showing very bad anticorrosive properties [16]. The reduction of the adhesion was probably due to the decrease of the number of hydroxyl groups by the curing mechanism or shrinkage of the system.

In order to overcome these drawbacks, a newly formulated system using Meldrum acid (**8**) as a cross-linking copolymer has given very good kinetic properties, lowering temperatures and times needed to cure the formulations (Scheme 4). Under industrial conditions, where the curing time must be between 20 to 25 min, a system using Meldrum acid 5 phr/erbium triflate 0.5 phr reduces the curing temperature to 110 °C. The use of the Meldrum acid gave rise to a less cross-linked network, but, at the same time, with lower shrinkage and very good anticorrosive behavior [17].

These promising results could open the door of industrial use of erbium(III) triflate, since its low toxicity increases the favorable environmental attributes of powder coatings for paints.



Scheme 3.



Scheme 4.

### 3. FERRIER REARRANGEMENT

Pseudoglycals are 2,3-unsaturated glycosides, generally accessed via acid-mediated allylic rearrangement of glycals, otherwise known as the Ferrier rearrangement. A lot of methodologies already exist to accomplish the synthesis of *C*-glycosides by means of Ferrier rearrangement, but many of them have limitations in terms of stringent reaction conditions, demanding workup, reaction time and amount of catalyst; some others were tested in only limited examples by using expensive or commercially unavailable reagents [18].

The use of  $\text{Er}(\text{OTf})_3$  as the catalyst for the Ferrier rearrangement presents several advantages, which include high product yields, cleaner reaction profiles, short reaction times, and mild reaction conditions. In Table 3, some representative examples referred to glucal are collected, but the reaction can be extended to other 2,3-unsaturated sugars.

*C*-glycosides can be obtained in  $\text{CH}_2\text{Cl}_2$  at room temperature in the presence of 3-10 mol % of erbium(III) trifluoromethanesulfonate for about five minutes [19].

*N*-glycosides can be prepared in very satisfactory yields by Ferrier rearrangement, carrying out the reaction in anhydrous acetonitrile with 10 mol % of  $\text{Er}(\text{OTf})_3$  at 50 °C [20].

Finally, the glycosylation with primary, secondary, benzyl, allyl, and propargyl alcohols and ethanethiol proceeds smoothly at room temperature in nitromethane and 5 mol % of  $\text{Er}(\text{OTf})_3$  to afford the corresponding *O*- and *S*-glycosides [21]. The Ferrier rearrangement with phenols and thiophenol is not as easy, but 80% yield of the product can be obtained, when the amount of the catalyst was improved to 10 mol % and temperature was raised to 50 °C.

The stereoselectivity of these reactions is excellent, and the observed predominant formation of either  $\alpha$ -isomer or  $\beta$ -isomer in gluco and galacto series and in the deoxygluco series respectively, may be easily explained, if cation **12** is the key step of the reaction (Scheme 5). In fact, after the formation of **12**, the nucleophile attacks from the side of the molecule providing maximum continuous overlap of the orbitals. In the hexopyranosides derivatives, all cationic intermediates should take a conformation with C6 in pseudo-equatorial orientation, independent of the 4-AcO-group position. Then, the less hindered face of the C-1–O  $\pi$ -orbital of *D*-gluco and galacto series orients the incoming nucleophile to form a bond always in the  $\alpha$ -axial position.

This method offers several advantages such as mild reaction conditions, high yields of glycosides, wide range of applicability, recoverability, and reusability of the catalyst, which make  $\text{Er}(\text{OTf})_3$  a very powerful Lewis acid catalyst in the Ferrier rearrangement.

### 4. PROTECTION AND DEPROTECTION METHODS

#### 4.1. Cleavage of 1,3-Dioxolanes

Acetals and ketals are frequently used to protect both carbonyl function and diols during complex synthetic pathways. A wide variety of methods using Lewis acids have been developed for their deprotection in mild conditions [22].

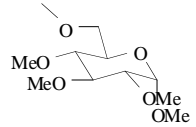
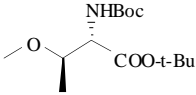
Among them,  $\text{Er}(\text{OTf})_3$  revealed to be a very useful catalyst for this purpose. Moreover, it represents an improvement with respect to the use of  $\text{Ce}(\text{OTf})_3$  that we recently reported [7b]. In fact, amounts of  $\text{Er}(\text{OTf})_3$  6-50 times smaller than  $\text{Ce}(\text{OTf})_3$  are sufficient to hydrolyze the same substrates. Dialkyl acetals and ketals derived from aromatic as well as aliphatic carbonyl compounds undergo smooth deprotection (yields ranging from 90 % to almost quantitative) at room temperature in nitromethane saturated with water in the presence of 1 mol % of catalyst [23].

Cyclic acetals and ketals require prolonged reaction times to be quantitatively deprotected. In particular, the cleavage of cyclic acetals and ketals of aromatic carbonyl compounds strongly depends on the electronic demand of the aromatic ring. Weak electron-withdrawing substituents need higher amount of  $\text{Er}(\text{OTf})_3$  (5 mol %), whereas with strong ones no cleavage was observed. This deprotection method is compatible with other protecting groups such as acetyl, benzyl, *p*-methoxybenzyl, and *t*-butyldimethylsilyl ones.

Nevertheless, two classical cyclic dioxolanes (benzylidene and isopropylidene acetals) are easily cleft by erbium(III) triflate by modifying the reaction conditions.

For the cleavage of benzylidene acetals, acetonitrile and 5.0 mol % of catalyst at room temperature are the best reaction conditions. [24] Many protected carbohydrate derivatives are smoothly cleft in 55-95 % yield. Only 3,4-*O*-benzylidene-*D*-ribonic- $\delta$ -lactone (the only product whose deprotected form is soluble in the reaction mixture) furnishes a very scarce yield of deprotected product (14 %). This evidence suggests that an equilibrium between protected-deprotected products is very likely established. However, the use of

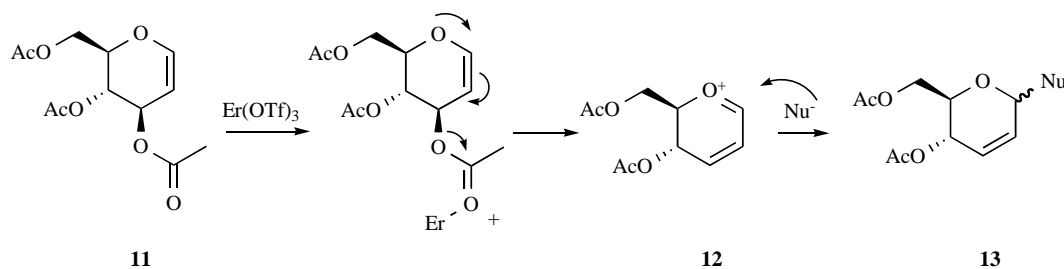
Table 3. Glycosidation of Glucal (11) Using Er(OTf)<sub>3</sub> as the Catalyst<sup>a</sup>.

Nu in 13	T (h)	Yield (%) <sup>b</sup>	α:β
Allyl	7	95	92:8
CN	6	95	60:40
CH <sub>3</sub> C≡C	20	82	100:0
PhC≡C	21	75	100:0
Thymine	7	64	70:30
Uracyl	10	55	75:25
Cytosine	10	45	71:29
Adenine	8	60	65:35
n-Butoxy	2	95	98:2
Octoxy	0.25	83	100:0
Allyloxy	2.5	85	90:10
Propargyloxy	0.33	80	68:32
Isopropoxy	0.33	88	77:23
3-Bromopropoxy	0.17	75	100:0
Cyclohexanoxo	0.17	78	100:0
Benzoyloxy	0.17	90	100:0
	24	70	85:15
	0.5	79	100:0
4-Methoxyphenoxy	24	80	90:10
Phenoxy	24	77	80:20
4-Nitrophenoxy	24	78	85:15
Ethylthio	1.5	85	90:10
Phenylthio	0.2	90	98:2

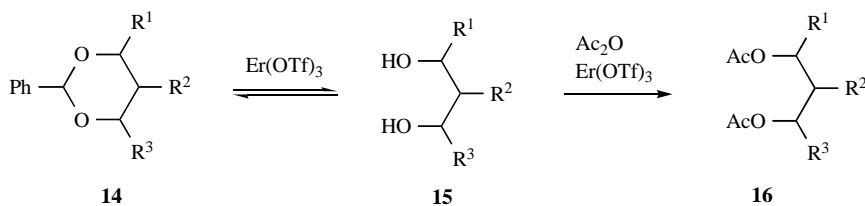
<sup>a</sup> For catalyst amounts see text and/or ref. [19-21].<sup>b</sup> Isolated yields.

acetic anhydride as solvent shifts the equilibrium towards peracetylated products, that are obtained in almost quantitative yields and very short reaction times (Scheme 6).

As expected, the oxirane ring does not stand the reaction conditions, being more labile than the benzylidene group (see section 2).



Scheme 5.



Scheme 6.

Cleavage of isopropylidene protecting group can be often very difficult in tricky substrates. While Er(OTf)<sub>3</sub> is unable to cleave acetonides under conventional heating system, extremely fast and complete removal is obtained in Er(OTf)<sub>3</sub> microwave-assisted deprotection [25]. Obstinate acetonides of nucleosides and carbohydrates and multifunctional substrates are cleft in high yields (higher than 78%) and in very efficient way. Actually the MW-assisted Er(OTf)<sub>3</sub> catalyzed isopropylidene cleavage protocol can be considered as a tangible improvement with respect to the other existing mild methods, moreover, the process can really be considered 'green' since all reactions run smoothly in very short time, and almost under neutral conditions in pure water.

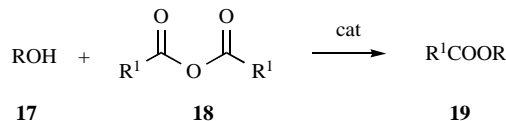
#### 4.2. Acylation

As dioxolanes are one of the most important and widely used protection methods to preserve 1,2-diols or carbonyl compounds, acylation is for the hydroxy function. Many methods are going on to appear in literature, but it is over the aim of this account [22].

In our previous work, we proposed the use of Ce(OTf)<sub>3</sub> as a mild Lewis acid catalyst in acetylation reactions [7c], but we found that Er(OTf)<sub>3</sub> is ten-fold more efficient under dry conditions, since 0.1 mol % was sufficient to replicate the results obtained with 1.0 mol % of cerium salt. Phenols, primary, secondary, and tertiary alcohols undergo smooth acetylation with almost quantitative yields. Dehydration (except for the heavy sterically hindered 2-phenylisopropanol) in the aliphatic series, products arising from Fries rearrangement in the aromatic one, and rearrangement with allylic and propargyl substrates have never been observed. The reaction tolerates the presence of various functionalities on the substrates and optically active compounds are acylated without any loss of optical purity, but the acid sensitive *t*-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) protective groups do not survive and both the functions are replaced by the acetyl group (Table 4) [26].

Conversely from cerium triflate, the reaction can be extended to anhydrides, other than acetic, without any evident differences of reactivity. Only benzoylation results relatively slower and better results are reached when the reaction temperature, the anhydride and catalyst amount are increased.

Also, ErCl<sub>3</sub> has been tested in the acylation reaction. Higher catalyst amounts and temperatures are necessary to obtain the same results (Table 4) [27]. However, the lower cost and toxicity of this salt counterbalance the higher charged amounts, so this protocol represents an improvement with respect to erbium triflate. Moreo-

Table 4. Comparison Among Some Representative Examples of Acylation of Alcohols Catalyzed by Ce(OTf)<sub>3</sub>, Er(OTf)<sub>3</sub> and ErCl<sub>3</sub>

Alcohol	R <sup>1</sup>	Yield (Time) <sup>a</sup>			
		Ce(OTf) <sub>3</sub> (1 mol %), Anhydride (1.5 equiv), r.t., dry MeCN (2.0 mL)	Er(OTf) <sub>3</sub> (0.1 mol %), Anhydride (1.5 equiv), r.t., dry MeCN (2.0 mL)	ErCl <sub>3</sub> (5 mol %), Anhydride (1.5 equiv), 50 °C, neat	
Octanol		a. q. (1 h)	a. q. (20 min)	a. q. (1.5 h)	
		0 (1.1 h) <sup>b</sup>	n. r.	a. q. (6 h) <sup>c</sup>	
Cholesterol		93 (5 h)	a. q. (2 h)	a. q. (6 h)	
Glucose <sup>d</sup>		a. q. (2.5 h)	a. q. (100 min) <sup>e,f</sup>	a. q. (6 h)	
HO(CH <sub>2</sub> ) <sub>4</sub> OTBDMS <sup>d</sup>	Me	a. q. (4 h)	a. q. (20 min)	a. q. (12 min)	
HO(CH <sub>2</sub> ) <sub>4</sub> OTHP <sup>d</sup>		a. q. (4 h)	a. q. (30 min)	a. q. (12 min)	
Crotyl alcohol		a. q. (2.5 h)	a. q. (30 min)	n. r.	
Propargyl alcohol		a. q. (1 h)	a. q. (30 min)	a. q. (1.2 h)	
Phenol		a. q. (2.5 h)	n. r.	a. q. (1.2 h)	
4-NO <sub>2</sub> phenol		a. q. (12 min)	a. q. (25 min)	a. q. (12 min)	
4-MeOphenol		a. q. (30 min)	a. q. (20 min)	n. r.	
Menthol			a. q. (0.5 h)	a. q. (50 min)	a. q. (6 h)
		Et	n. r.	a. q. (30 min) <sup>f</sup>	a. q. (4 h) <sup>e</sup>
		<i>t</i> -Bu	n. r.	a. q. (35 min) <sup>f</sup>	a. q. (6 h) <sup>e</sup>
	CF <sub>3</sub>	n. r.	a. q. (3 h) <sup>f</sup>	a. q. (4 h) <sup>e</sup>	
	Ph	n. r.	a. q. (100 min) <sup>f,g</sup>	n. r.	

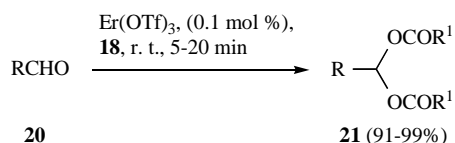
<sup>a</sup> Isolated product; a.q.=almost quantitative; n. r. = not reported; <sup>b</sup> R<sup>2</sup>= Me, only alkene from elimination; <sup>c</sup> R<sup>2</sup>= H; <sup>d</sup> Peracetylated product; <sup>e</sup> Anhydride as solvent; <sup>f</sup> 0.5 mol % of catalyst; <sup>g</sup> 50 °C.

ver it is worth noting that 2-phenylpropan-2-ol does not dehydrate with this catalyst conversely from erbium and cerium triflate.

The erbium salt/acyl anhydrides protocol can be considered as an improvement with respect to the other existing methods, which involve the use of triflate derivatives. Erbium salts are used in really catalytic amounts in the presence of a very low excess of acyl anhydride. Most of the reactions run smoothly at room temperature, the catalysts can be almost quantitatively recovered and they are the first Lewis acid catalysts with such a wide applicability.

Acylals (geminal diacetates) or gem-bis(acyloxy)alkanes (**21**) have been considered to be important protecting groups in organic synthesis, as alternatives to acetals for protection of aldehydes (**20**), owing to their stability towards aqueous acids and bases [22].

In the section 2.1, we have already reported that in the aromatic series, epoxide rearrangement is faster than ring opening by acetate ion, but under those conditions rearrangement is followed by formation of acylal. This evidence allowed setting up a general synthesis of acylals starting from aldehydes (Scheme 7) [28].



Scheme 7.

The reaction completes in few minutes and smoothly affords the corresponding acylals **21** in excellent yields (always over 91%) with 0.1 mol % of erbium(III) triflate in solvent free conditions at

ambient temperature, with many different anhydrides and both on aliphatic and aromatic aldehydes. Only dimethylaminobenzaldehyde remains unaffected, while benzoic anhydride needs longer reaction times.

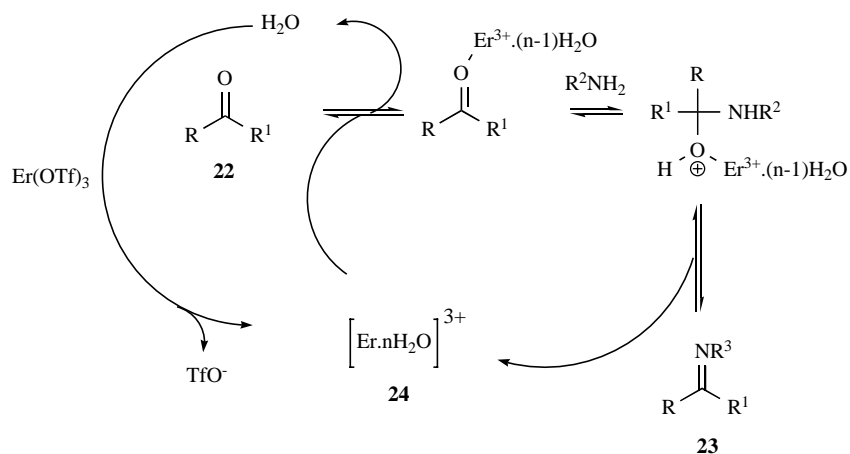
Moreover, erbium is revealed as the most efficient among the known catalysts, since it is the one that is able to give acylals of anhydrides other than acetic.

## 5. MISCELLANEOUS

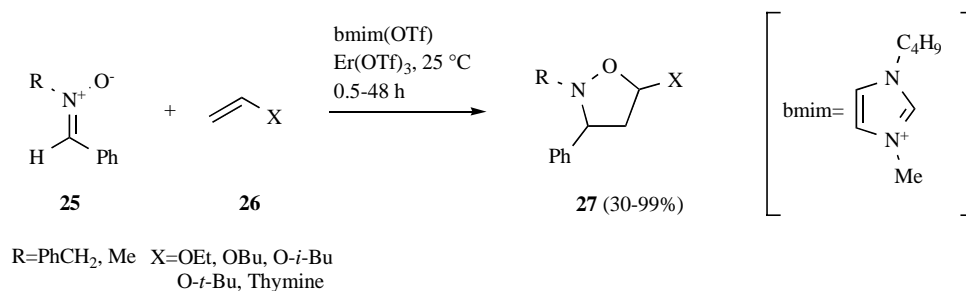
Other reactions are catalyzed by Er(OTf)<sub>3</sub> but cannot be classified into the previous sections; therefore they will be collected here.

For example, Er(OTf)<sub>3</sub> catalyzes a good method for the synthesis of imines and enamines. The yields are very interesting considering that it is a well-known equilibrium reaction: 67-98 % for aldimines, 50-68 % for ketimines and 70 % - almost quantitative for enamines. This protocol shows some important advantages: use of non-anhydrous conditions, non-sophisticated equipment, a negligible release into the environment, and low costs [29].

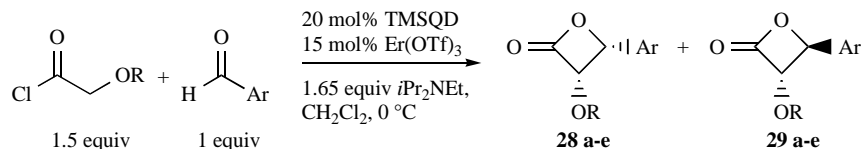
However, the most interesting feature of the reaction is the role of water. In fact, attempts to increase yields by removing water are unsuccessful. Moreover, imine synthesis is much slower in anhydrous conditions, which appears to be a contradiction. A tentative explanation of this behavior may be attributed to the role of erbium in sequestering the water, formed during the reaction. In particular only hydrated cations should be able to act as Lewis acids. If water is scavenged, cations cannot be dissociated from the counter ion and catalysis does not occur, so the reaction rate is lowered. Therefore, a very subtle equilibrium between these two opposite needs



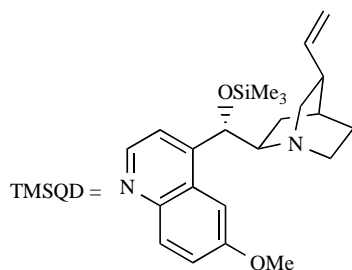
Scheme 8.



Scheme 9.



a: R=Ph, Ar=Ph; b R=Ph, Ar=4-NO<sub>2</sub>Ph; c R=Ph, Ar=4-BrPh; d R=Ph, Ar=3-ClPh; e R=CH<sub>2</sub>Ph, Ar=4-CNPh



Scheme 10.

must occur: there must be enough water present to partially hydrate the cation to exploit catalysis, but not too much to reverse the equilibrium back towards the reagents (Scheme 8).

Erbium triflate has also been tested among all the lanthanide as additive (5 mol %) for indium-mediated Barbier-type reaction of difluoropropargyl bromide with benzaldehyde in aqueous media. However, the corresponding europium salt gives the best results [30].

Moreover, the Friedel-Crafts acylation of activated aromatic substrates can be exploited. In particular, heptanoic acid can acylate *p*-xylene in 66% yield, at 250 °C for 12 h in sealed tube in the presence of 15 mol % of Er(OTf)<sub>3</sub>. Hexanoic acid gives much lower yields, so erbium was abandoned in favor of Bi(NTf<sub>2</sub>)<sub>3</sub> [31].

Finally Er(OTf)<sub>3</sub> has been used as the catalyst for 1,3-dipolar cycloadditions of nitrones with alkenes to afford the corresponding isoxazolidines in ionic liquids (*N*-benzyl-*N'*-methylimidazolium triflate) (Scheme 9) [32].

In particular, a ratio nitrone/alkene/Er(OTf)<sub>3</sub> of 1:20:0.2 gives an almost complete conversion to the cycloadduct in 3 h at room temperature. Compared to conventional conditions [33], the cycloaddition reactions performed in ionic liquids are much faster and selective. Isolation of the cycloadduct is simple and straightforward. It is noteworthy that the reaction occurs also with the vinyl nucleobases although in moderate yield, leading to isoxazolidinyl nucleosides of pharmaceutical importance.

Asymmetric catalysis with cinchona alkaloids recently encountered wide application. Numerous reports have described the ability of the alkaloids to determine nucleophile facial selectivity [34]; and

a number of Lewis acids are compatible with cinchona alkaloid-catalyzed reactions of ketenes with imine [35] and aldehydes [36].

For example, the combination of a chiral nucleophile (cinchona alkaloid) and an achiral Lewis acid (metal triflate) catalyzes the asymmetric condensation of acid chlorides with aromatic aldehydes [37]. The efficiency and diastereoselectivity of the reaction depends highly on the size of the Lewis acid. The use of triflates of the smaller lanthanides, such as ytterbium and erbium, gives the highest selectivity for the *cis*-isomer, while the use of either larger or smaller metals, such as gadolinium or scandium, leads to relatively larger proportions of the *trans*-isomer. In particular, Er(OTf)<sub>3</sub> produced the highest yield of product **28a** (89% with >99% *ee*). (Scheme 10).

Other electron-withdrawing group-substituted benzaldehydes also yield the *cis*- $\beta$ -lactones in high diastereo- and enantioselectivities, as does benzaldehyde itself, still in high yields and >99% *ee*.

## 6. CONCLUSION

The literature on erbium(III) triflate as Lewis acid catalyst in many organic reactions appeared in last five years demonstrates the usefulness of this salt and its synthetic potentiality. The epoxide reactivity shows the most interesting results both in classical and industrial organic chemistry, but also the Lewis acid catalysis in the protection/deprotection chemistry also appears to be full of developing prospects. Finally, the low-impact on the environment of erbium increases the importance of these protocols.

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