KATHOLIEKE
UNIVERSITEIT
LEUVEN

Faculteit Wetenschappen
Departement Chemie
Moleculair Design en Synthese
Laboratorium voor Coördinatiechemie

Lanthanide-mediated organic synthesis: lanthanide(III) compounds as Lewis acid catalysts and cerium(IV) compounds as reagents for reactions in ionic liquids

Proefschrift ingediend voor het behalen van de graad van
Doctor in de Wetenschappen

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Leuven, 2007

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Wettelijk depot D/2007/10.705/53
ISBN 978-90-8649-131-5

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Voorwoord

Nu u dit boekje in handen hebt zit mijn doctoraat er op. Alvorens een nieuwe weg in te slaan kijk ik nog even achterom naar de voorbije doctoraatsjaren die voor mij een verrijkende periode waren. Onderzoek verrichten is niet altijd zo eenvoudig. Af en toe zou je de moed verliezen als iets na veel proberen niet loopt zoals je verwacht. Maar uiteindelijk maken onverwachte resultaten het scheikundig onderzoek toch ook heel boeiend. Het doet mij nu enorm veel plezier om het resultaat van een viertal jaar geboeid en volhardend werken gebundeld te zien. Maar dit werk zou echter niet tot stand gekomen zijn zonder de bijdrage van heel wat mensen. Ik wil alvast iedereen die mij de voorbije jaren op de een of andere manier heeft bijgestaan heel hartelijk bedanken.

In het bijzonder prof. C. Görller-Walrand voor de mogelijkheid om een boeiende wetenschappelijke periode in het labo coördinatiechemie te beleven. Mijn promotor Prof. Koen Binnemans en co-promotor Dr. Tanja Parac-Vogt verdienen een groot dank-je-wel voor de wetenschappelijke ondersteuning. Bij jullie kon ik steeds terecht voor de bespreking van onderzoeksresultaten en jullie bezorgden mij vaak ook een vloed aan nieuwe inspiratie en ideeën. En Tanja, je deed me vaak ook beseffen dat het als wetenschapper toch ook niet zo boeiend zou zijn als alles onmiddellijk zou lukken zoals je verwacht. “Why make things simple if it can be difficult?” zou je kunnen zeggen.

De electrochemische experimenten werden uitgevoerd in samenwerking met Prof. Jan Fransaer en Stijn Schaltin van het departement metaalkunde en toegepaste materiaalkunde (MTM). Bedankt voor de tijd die jullie namen voor mijn experimenten en om mij in te wijden in de praktische aspecten van electrochemie.

Last year I also got the opportunity to work some weeks on *in-situ* infrared spectroscopy in the lab of Prof. István Horváth in Budapest. Thanks especially to Hasan for the practical support. Besides the many hours I spent in the lab, I look back on an agreeable stay in Budapest.

De voorbije jaren kreeg ik ook de hoede over enkele thesisstudenten. Danzhao wil ik bedanken voor haar bijdrage omtrent het gebruik van Lewiszuur-surfactant-gecombineerde katalysatoren en Michaël voor een deel van de experimenten omtrent de acylering van alcoholen.

Petra, Leen, Dirk en Paul wil ik bedanken voor het uitvoeren van CHN- en massa-analyses, en ook voor hun praktische ondersteuning in het labo. Karel dank ik voor de begeleiding bij NMR-experimenten. Dank ook aan Sabina en Prof. Dirk De Vos van het centrum voor oppervlaktechemie en katalyse voor het uitvoeren van GC-MS analyses. Daarnaast wil ik mijn appreciatie uitdrukken aan Rita voor het regelen van tal van administratieve zaken die de dagelijkse werking eenvoudiger maken. De KULeuven wil ik bedanken voor de financiële ondersteuning met een doctoraatsbeurs.

Ook wil ik zeker de post-docs en alle COC-collega's van de voorbije jaren bedanken. Naast de wetenschappelijke medewerking zorgden jullie voor een aangename sfeer in het labo. Bedankt ook aan de organische groep binnen Moleculair Design en Synthese.

Verder wil ik mijn familie en vrienden bedanken die het leven naast de chemie boeiend houden en bij wie ik steeds terecht kan voor een babbel of om plezier te maken.

En tenslotte wil ik mijn naaste familie bedanken. Koen, Liesbeth, Jonah en Margot voor de fijne momenten en begrip voor mijn gebetenheid de afgelopen jaren. In het bijzonder ook mama voor het vertrouwen dat ze me geeft in alles wat ik doe. ’t Was niet altijd makkelijk na de dood van papa maar tijdens mijn studies en doctoraat was je er steeds voor mij. Papa kon dit spijtig genoeg niet meer meemaken maar ik voelde steeds zijn steun. Ik wil deze verhandeling dan ook in het bijzonder aan hem opdragen.

Karen Deleersnyder
Leuven, oktober 2007

Contents

List of abbreviations

GC	Gas chromatography
FID	Flame ionization detector
NMR	Nuclear magnetic resonance
FTIR	Fourier transform infrared
MS	Mass spectrometry
OTf	Trifluoromethanesulfonate (triflate), $CF_3SO_3^-$
OMs	Methanesulfonate (mesylate), $CH_3SO_3^-$
TOS	*p*-Toluenesulfonate (tosylate)
3-NBSA	3-Nitrobenzenesulfonate, *m*-nitrobenzenesulfonate
4-NBSA	4-Nitrobenzenesulfonate, *p*-nitrobenzenesulfonate (nosylate)
2,4-NBSA	2,4-Dinitrobenzenesulfonate
DOS	Dodecylsulfate
LA	Lewis acid
LASC	Lewis acid-surfactant-combined catalyst
CAS	Cerium(IV) ammonium sulfate
CAN	Cerium(IV) ammonium nitrate, ammonium hexanitratocerate(IV)
IL	Ionic liquid
emim	1-Ethyl-3-methylimidazolium
bmim	1-Butyl-3-methylimidazolium
chol	Choline
NTf_2	Bis(trifluoromethylsulfonyl)imide
CV	Cyclic voltammetry

Introduction

Organic synthesis of bulk and fine chemicals has been dominated by the search for improvements in reaction yield and purity, but recently, scientist are becoming aware of the malignant effects on the environment of many well-known procedures. Therefore, a new challenge in organic synthesis is the development of economically efficient procedures that are as harmless as possible to humans and the environment.

A first point of attention is an appropriate choice of the reaction solvent and in this study greener solvents such as water, ionic liquids and rather unhazardous organic solvents are investigated. Furthermore, this study focuses on the use of lanthanide-mediated organic reactions. Lanthanides exhibit unique physical and chemical properties which differ from those of main group elements and d-block transition elements and their low toxicity and availability at a moderate price makes these elements attractive for organic synthesis.

From an economical and environmental viewpoint it is also desirable to produce a minimal amount of waste during the reaction and work-up procedure. Therefore, reactions in which usually stoichiometric amounts of catalyst are required should be reinvestigated in the presence of a reusable catalyst. The first part of this PhD study is dedicated to the use of lanthanide(III) compounds as strong Lewis acid catalysts for various organic reactions. During the last decade, scandium(III) and lanthanide(III) triflates have been widely studied for numerous organic reactions to overcome the drawbacks of conventional Lewis acids. However, the disadvantages of triflate salts include their high cost and the fact that one needs to handle the corrosive triflic acid for their preparation. Therefore, we investigate the use of lanthanide(III) salts of less corrosive and much cheaper aromatic sulfonic acids, such as *p*-toluenesulfonic acid and nitrobenzenesulfonic acids, as new Lewis acid catalysts for a variety of reactions. In addition, *Lewis acid-surfactant-combined catalysts* (LASCs) are studied for reactions in water.

Furthermore, an enormous interest has arisen in the use of ionic liquids as ‘green solvents’. The second part of this PhD study is dedicated to the use of cerium(IV) compounds as reagents for reactions in ionic liquids.

Outline

In *Chapter 1*, a literature overview is given on the principles of green chemistry, some important properties of lanthanides and the widespread application of lanthanide compounds in organic synthesis.

Chapter 2 contains information on the experimental techniques used during this PhD.

In *Chapter 3*, the use of lanthanide(III) tosylates and nitrobenzenesulfonates as new, inexpensive and reusable Lewis acid catalysts is investigated for a variety of reactions: nitration of aromatic compounds, the acylation of alcohols and the synthesis of calix[4]resorcinarenes.

In order to perform Lewis acid-catalyzed reactions in pure water, Lewis acid-surfactant-combined catalysts (LASCs) have been developed. *Chapter 4* presents our results of the LASC catalyzed allylation of aldehydes with tetraallyltin.

Finally, tetravalent cerium is also a good alternative to the heavy metals as oxidizing agent. In *Chapter 5*, the application of cerium(IV) compounds in ionic liquids is studied for oxidation and nitration reactions. In addition, the electrochemical oxidation of cerium(III) to cerium(IV) is studied in ionic liquids.

Chapter 1. Literature overview

1.1. Introduction

Organic chemists are constantly developing more successful methods to prepare useful fine and bulk chemicals. Nowadays their strategies are not only influenced by economical aspects, expressed in improvement of reaction yield and purity, but the environmental aspect is gaining more importance as well. As the minimization of using hazardous reagents and solvents is one of the main reasons why this study concerning lanthanide-promoted organic synthesis was performed, this chapter will start with a brief introduction describing the principles of performing more environmentally-friendly chemistry with a focus on some alternative solvents for organic synthesis.

1.2. Green chemistry

1.2.1. Basic principles of green chemistry

In the early 1990s the term *Green Chemistry* was introduced and defined as *"the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances"*.[1] As the terminology "green chemistry" may have some political connotation the term *sustainable chemistry* is very often used instead. The latter can be defined as "*chemistry for a sustainable environment*" which may sound as a less focused description of the subject.[2] Both expressions are generally accepted and throughout this work the term green chemistry will be used taking distance from any political connotation.

Since all substances and all activity have some impact just by their being, nothing is completely benign. Consequently, what is being discussed when the term green chemistry is used is simply an ideal. Striving to make chemistry more benign wherever possible is merely a goal. Chemists working toward this goal have made dramatic advances in technologies that not only address issues of environmental and health impacts but do so in a manner that satisfies the economic criteria that are crucial to having these technologies incorporated into widespread use.[3] The twelve principles of green chemistry, as articulated by Anastas et al.[1] are summarized in Table 1.1, and guide chemists towards more environmentally benign organic synthesis.

Table 1.1 The twelve principles of green chemistry[1]

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

In order to measure the "green" character of a reaction, a few simple parameters have been proposed. The *E-factor* and *atom economy* are useful tools for rapid evaluation of the amount of waste generated. The concept of atom economy was defined by Trost as the ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all substances produced in the stoichiometric equation for the reaction involved.[4] The ideal situation is obtained if a synthetic transformation can achieve 100% yield of product combined with 100% atom economy. As defined by Sheldon, the environmental factor (E-factor) is given by the ratio of the amount of side-products (waste) to the amount of product.[5]

$$\text{E-factor} = \frac{\text{amount of waste}}{\text{amount of product}} \qquad (1.1)$$

The E-factors of chemical processes increase dramatically on going downstream from bulk to fine chemicals and pharmaceuticals, mainly owing to the use of stoichiometric methods (Table 1.2).[6] For example, processes employing mineral acids (H_2SO_4, HCl, …) or Lewis acids ($AlCl_3$, $ZnCl_2$, …) in stoichiometric amounts, represent a major source of inorganic waste that cannot easily be recycled.[7] The key to waste minimization in fine chemicals manufacture is the widespread substitution of classical organic synthesis employing stoichiometric amounts of inorganic reagents with cleaner, catalytic alternatives.[2] The most obvious contribution of catalysis to green chemistry originates from the fundamental principle that a catalyst decreases the activation energy of the reaction and hence the amount of energy required is reduced. Furthermore, the specificity of a catalyst reduces the amount of undesired by-products, thereby reducing waste generated and separation needs. In conclusion, catalytic procedures have been effectively implemented to accomplish several of the green chemistry principles simultaneously.[8]

Table 1.2 Relative efficiencies of different chemical manufacturing sectors.[6]

Industry sector	Product tonnage	E-factor
Oil refining	10^6-10^8	< 0.1
Bulk chemicals	10^4-10^6	1-5
Fine chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25-100

1.2.2. Environmentally benign solvents for organic synthesis

A significant approach towards reduction of hazardous compounds is effected by the appropriate choice of solvent. Many volatile organic solvents contribute not only to air and water pollution but cause also harm to humans. They are harmful to humans not only because of exposure during the production process of a compound, but residual amounts of solvent are often incorporated in the final reaction product because solvents are not always completely removed by practical manufacturing techniques. These residual amounts of solvents are especially of importance in the production of pharmaceutical products. Therefore, the U.S. Food and Drug Administration has published a recommendation to industry concerning the use of organic solvents in drug manufacturing.[9] By risk assessment they have classificated residual solvents into three categories. The classification of some frequently and formerly used solvents in organic synthesis is summarized according to these recommendations in Table 1.3. Class 1 solvents, such as known human carcinogens, strongly suspected human carcinogens and environmentally hazardous solvents, are to be avoided unless their use can be justified for a specific goal in a risk-benefit assessment. Class 2 includes solvents that are recommended to be limited in order to protect patients from potential adverse effects. They contain nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity and solvents suspected of other significant but reversible toxicities. Class 3 solvents are solvents with low toxicity and lower risk to human health and ideally they should replace class 1 and 2 solvents where possible.

Table 1.3 Classification of some frequently used solvents based on risk assessment of the U.S. Food and Drug Administration.[9]

Class 1	Class 2	Class 3
benzene	acetonitrile	acetic acid
carbon tetrachloride	chloroform	acetone
1,2-dichloroethane	dichloromethane	dimethyl sulfoxide
	methanol	ethanol
	nitromethane	ethyl acetate
	tetrahydrofuran	diethyl ether
	toluene	heptane

Nowadays the choice of solvents is not only dominated by risk to humans but solvents with deleterious environmental effects should also be avoided. While halogenated solvents for example are suspected human carcinogens, chlorofluorocarbons are known to deplete the stratospheric ozone layer.[8] Recently, perfluorocarbon fluids (fluorous solvents) have also been studied as alternative solvents,[10] but their widespread use is limited. Not only are they very expensive but they also have high global warming potentials and extremely long atmospheric lifetimes and hence they belong to the greenhouse gases that are controlled in the Kyoto Protocol.[11,12] Therefore, when a solvent is needed, benign solvents, such as water, supercritical carbon dioxide, ionic liquids or class 3 solvents are preferred. On the other hand, for some applications solvent-free organic synthesis is also useful.[13,14] Furthermore, one should also consider separation techniques at the end of the process for suitable choice of solvent. Because part of this research was performed in water and ionic liquids, the advantages of both solvents will be discussed in the next pages.

1.2.3. Advantages of water as reaction solvent

Water is the most abundant and available resource on earth. It is a cheap, non toxic and environmentally friendly solvent. Some other relevant advantages of performing organic reactions in an aqueous reaction medium are listed below.

- control of pH is possible
- inflammable and anhydrous solvents are not needed
- generation of volatile organic compounds is avoided
- reactions in aqueous medium are generally carried out under conventional conditions of temperature and pressure
- possibility of using additives such as surfactants
- possibility of isolating products by decanting or filtration

Nevertheless, for a long time organic chemists have undervalued water as a reaction medium due to two main reasons: the low solubility of organic compounds in water and the instability of many intermediates and catalysts in water.[15] As will be discussed later, the problem of low solubility of some organic compounds in water can be solved using surfactants. And recently, much research has been done on water-stable Lewis acid catalysts. One strategy to prepare water-tolerant Lewis acids is to attach ionic or polar substituents to known ligands. Sulfonation is the method most widely used for making organic ligands water-soluble. The use of water as reaction solvent has been considered meaningful since Breslow and coworkers around 1980 observed that some Diels-Alder reactions were strongly accelerated when carried out in water compared to the reactions in organic solvents.[16] Some years later, the aqueous medium has shown beneficial effects on the diastereoselectivity of the reaction. Breslow's work was the first to show quantitatively the beneficial effects of water on the reactivity and selectivity of an organic reactions, and so stimulated further research in this area.[15,17] A decade ago, the first comprehensive review on carbon-carbon bond formations in aqueous media was reported,[18] and since then water has found widespread applications as a reaction medium.[19,20,21] In conclusion, the use of water as a reaction medium can lead to surprisingly beneficial effects on reaction rate, product yield, and regio-, diastereo- and enantioselectivity.[22,23] However, appropriate disposal of the produced aqueous waste streams should also be considered.

1.2.4. Ionic liquids

Ionic liquids (ILs) are liquids that are composed entirely of ions. According to current convention, a salt melting below 100 °C is recognized as an ionic liquid.[24] While ionic liquids are only recently discovered as new green solvents, ionic liquids underwent a long development which has its orgin in higher temperature molten salts. One of the main advantages to use molten salts as reaction media is their great thermal, chemical and electrochemical stability. But their high melting temperature, 800 °C for example for sodium chloride and 335 °C for the alkali halide eutectic mixture LiCl-KCl, results in serious material incompatibilities. The first ionic liquid was discovered in the mid-nineteenth century when chemists performed $AlCl_3$-catalyzed Friedel-Crafts alkylations. During the course of the reaction a red oil was formed which was later identified as a stable intermediate comprised of a carbocation and the heptachlorodialuminate anion.[25] The first room-temperature ionic liquid, $[EtNH_3][NO_3]$, was discovered in the beginning of the twentieth century,[26] but ionic liquids only became attractive at the end of the twentieth century with the discovery of binary ionic liquids made from mixtures of aluminum(III) chloride and *N*-alkylpyridinium or 1,3-dialkylimidazolium chloride,[27,28] which were primarily used as electrolytes in batteries. Besides, other organic liquid salts, including many quaternary ammonium salts, are reported in the early literature but as they are very viscous oils they were not studied in depth beyond their initial identification. The chloroaluminate salts are of limited applicability because both the starting materials and the ionic liquid products are moisture sensitive. Tetrachloroaluminate hydrolyzes in the presence of atmospheric moisture to form HCl. In order to be useful as a reaction solvent, water-stable ionic liquids have been designed using water-stable anions. Some commonly used cations and anions for ionic liquids are presented in Figure 1.1.

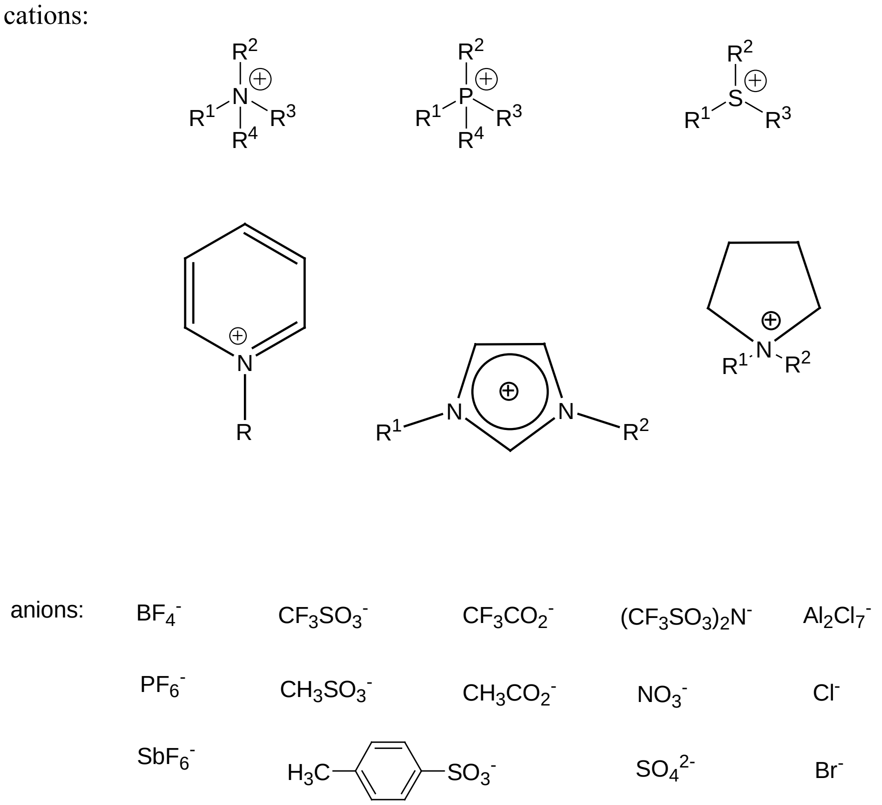


Figure 1.1 Some frequently used cations and anions in ionic liquids.

Ionic liquids generally consist of a salt where one or both the ions are large, and the cation is preferably unsymmetrical. These factors tend to reduce the lattice energy of the crystalline form of the salt, and hence lower the melting point.[29] The melting point is also influenced by the nature of the anion. Lower melting points are for example observed with triflate anions compared to chloride anions.[30]

Room temperature ionic liquids have several characteristic properties which make them attractive media for homogeneous catalysis in organic synthesis:[30,24]

- Ionic liquids involving fully quaternized nitrogen cations are non-flammable and have essentially no vapour pressure. This permits a range of separation techniques such as destillation or sublimation of products and byproducts.
- Ionic liquids avoid the production of volatile organic compounds.
- Ionic liquids generally have reasonable thermal stability.
- Ionic liquids are able to dissolve a wide range of organic, inorganic and organometallic compounds.
- Many ionic liquids have a wide liquid range of about 300 °C with a melting point around room temperature.
- Ionic liquids have high conductivity.
- The solubility of gases is generally good.
- Ionic liquids are immiscible with some organic solvents such as alkanes, and hence they can be used in two-phase systems.
- Polarity and hydrophilicity or hydrophobicity can be readily adjusted by a suitable choice of cation and anion.
- Ionic liquids can be designed to be greener solvents.

In conclusion, properties such as melting point, viscosity, density and hydrophobicity can be varied by simple changes to the structure of the ions. As ionic liquids can be designed to possess a particular set of solvent properties they are also called “designer solvents”.[29] One should be aware of the fact that not all ionic liquids are green solvents. Hexafluorophosphate ionic liquids for example are easily hydrolyzed by absorption of water from the atmosphere leading to volatiles such as hydrogen fluoride.[31] However, ionic liquids can at least be designed to be greener alternative solvents. An additional reason why ionic liquids are studied as reaction solvents is the possibility of easy product separation and recycling of the solvent/catalyst system. An excellent overview on the properties and the applications of ionic liquids is given by Wasserscheid and Welton.[32] Furthermore, good review articles on the use of ionic liquids as solvent in organic synthesis and catalysis are available by several authors, including Sheldon,[30] Zhao,[33] Olivier-Bourbigou,[34] Gordon,[35] Welton,[36] and Wasserscheid.[37]

1.3. General properties of lanthanides

1.3.1. Introduction

The *lanthanides*, abbreviated as Ln, are strictly defined as the 14 elements following lanthanum, but more commonly lanthanum is also included. The lanthanides, indicated in olive green in Figure 1.2, belong to the third group and the sixth period of the periodic table and have atom numbers from 57 (lanthanum) to 71 (lutetium). Scandium and yttrium, which lie just above the lanthanides and have similar characteristics as the lanthanides, are frequently studied together with the lanthanides. The lanthanides together with scandium and yttrium are defined as *rare earths*. However, especially in the field of catalysis, the term lanthanides is also used for scandium and yttrium.

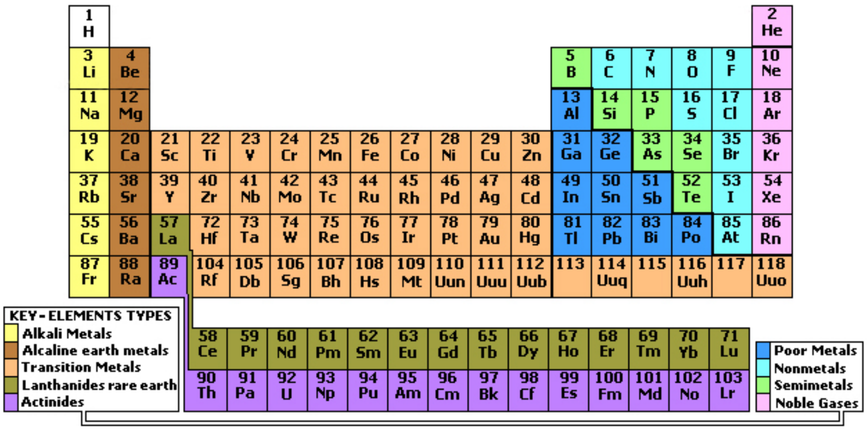


Figure 1.2 Position of the lanthanides in the periodic system

1.3.2. Occurrence

The lanthanides belong to the group of rare earths. However, this term is somewhat misleading since they are not really rare. Cerium for example, which is the most abundant lanthanide, is more abundant than cobalt, tin and zinc; and thulium, which is the least abundant, occurs in similar quantities to mercury and is more abundant than silver. The lanthanides appear in more than hundred minerals but due to their lithophilic character they tend to stay spread in the rocks. Therefore only a few ores are suitable for industrial production. The most important ores are monazite and bastnaesite, but xenotime and loparite can also be used. All lanthanide metals, except promethium which is radioactive and does not occur naturally, are nowadays produced on an industrial scale and they are commercially available as oxides, chlorides, nitrates or in pure form. Their costs are strongly dependant on their natural abundance, the required purity and the market demand. In general, the elements with an even atom number occur in higher amounts, which makes them cheaper.

1.3.3. Electronic configuration

The lanthanides are also named f-block elements due to the presence of 4f-electrons (only lanthanum does not contain 4f-electrons). They exhibit the extended Xe-core electronic configuration $[Xe]4f^n$ (n= 1–14) and their 4f shell is well-shielded by the $5s^2$ and $5p^6$ orbitals. Some characteristic data of the lanthanides are summarized in Table 1.4.

Table 1.4 Some characteristics of the lanthanides.

Element		Z	M_w (g/mol)	Electronic configuration	Atomic radius Ln (Å)
scandium	Sc	21	44.956	$(Ar)3d^1 4s^2$	1.64
yttrium	Y	39	88.9	$(Kr)4d^1 5s^2$	1.80
lanthanum	La	57	138.91	$(Xe)5d^1 6s^2$	1.88
cerium	Ce	58	140.12	$(Xe)4f^2 5d^0 6s^2$	1.82
praseodymium	Pr	59	140.91	$(Xe)4f^3 5d^0 6s^2$	1.82
neodymium	Nd	60	144.24	$(Xe)4f^4 5d^0 6s^2$	1.82
promethium	Pm	61	145.0	$(Xe)4f^5 5d^0 6s^2$	1.81
samarium	Sm	62	150.35	$(Xe)4f^6 5d^0 6s^2$	1.80
europium	Eu	63	151.96	$(Xe)4f^7 5d^0 6s^2$	2.04
gadolinium	Gd	64	157.25	$(Xe)4f^7 5d^1 6s^2$	1.80
terbium	Tb	65	158.924	$(Xe)4f^9 5d^0 6s^2$	1.78
dysprosium	Dy	66	162.5	$(Xe)4f^{10} 5d^0 6s^2$	1.77
holmium	Ho	67	164.93	$(Xe)4f^{11} 5d^0 6s^2$	1.77
erbium	Er	68	167.26	$(Xe)4f^{12} 5d^0 6s^2$	1.76
thulium	Tm	69	168.93	$(Xe)4f^{13} 5d^0 6s^2$	1.75
ytterbium	Yb	70	173.04	$(Xe)4f^{14} 5d^0 6s^2$	1.94
lutetium	Lu	71	174.97	$(Xe)4f^{14} 5d^1 6s^2$	1.73

1.3.4. Oxidation states

The most stable oxidation state for the lanthanides is Ln^{3+}. The existence of the trivalent oxidation state for lanthanides is due to the combination of a low ionization energy and a high solvation energy rather than to the formation of a specific electronic configuration. On the other hand, the +2 and +4 oxidation states are only formed by elements that can attain empty, half-filled or filled 4f shells. Among dipositive lanthanides, Eu^{2+} (f^7, half-filled) and Yb^{2+} (f^{14}, filled) are the most stable although they gradually react with water. Sm^{2+} (f^6, nearly half-filled) is relatively unstable and exhibits strong reducing power. Tm^{2+} (f^{13}, nearly filled) is an extremely unstable species. Among tetrapositive lanthanides, Ce^{4+} (f^0, empty) is the most stable but Pr^{4+} (f^1, nearly empty) and Tb^{4+} (f^7, half-filled) also exist in solid state compounds. The redox properties depend on electronic factors such as the stability of the $4f^N$ configuration, but they are also effected by the medium and ligands attached to the element.

1.3.5. Atomic and ionic radius

As can be seen in Table 1.4, the atomic radius increases from scandium over yttrium to lanthanum. Similarly there is an increase in ionic radius in the sequence $Sc^{3+} < Y^{3+} < La^{3+}$. The increase in atomic or ionic radius by filling a higher shell is much bigger than the decrease in radius by the increasing nuclear charge. However, the increase in effective nuclear charge is responsible for the gradual decrease of the atomic and ionic radius within the lanthanide series. As the lanthanides are situated between lanthanum and hafnium in the periodic system and the atomic radius decreases within the lanthanide series, the atomic radius of hafnium is comparable to that of zirconium, which is the element situated above hafnium in the periodic system. Furthermore, the ionic radius of holmium(III) is almost identical to that of yttrium(III). This phenomenon is known as the *lanthanide contraction*. The relatively large ionic radius of the lanthanides allows the coordination of up to 12 ligands in the first coordination sphere. The possibility of high coordination numbers results in new structural and reactivity patterns unprecedented in main group and d-transition metal chemistry. The lanthanides in the beginning of the series, whose ionic radii are largest, have most frequently coordination number nine while the smaller lanthanides at the end of the series have coordination number eight.

1.3.6. Toxicity

Lanthanide salts are known to have a low acute and chronic toxicity.[38] Chlorides, nitrates and citrates of the lanthanide series have almost the same level of toxicity as sodium chloride. Some oral LD_{50} values for rats are summarized in Table 1.5. The LD_{50} value (abbreviation for lethal dose, 50%) of a toxic substance is the dose required to kill half the members of a tested population. These data indicate that lanthanides are orally less toxic than most transition metals.

Table 1.5 Oral, rat LD_{50} values (from material safety data sheets)[39]

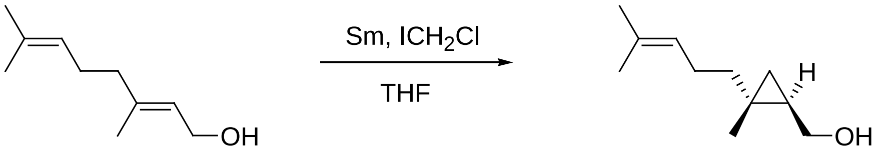
compound	LD_{50} (mg/kg)
NaCl	3000
$LaCl_3$	4200
$FeCl_3$	450
$CoCl_2$	80
$NiCl_2$	681
$CuCl_2$	584
$HgCl_2$	1

1.4. Lanthanide-mediated organic reactions

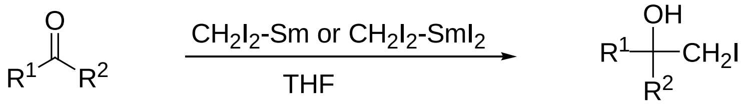
During the last decades, the chemistry of lanthanides and their use in organic synthesis has developed rapidly. Lanthanide elements exhibit unique physical and chemical properties which differ from those of main group elements and d-block transition elements. Furthermore, their low toxicity and availability at a moderate price makes these elements attractive for use in organic synthesis. The occurrence of divalent, trivalent and tetravalent lanthanides ions makes them suitable for many organic reactions. The trivalent lanthanides, which are in the most common oxidation state for lanthanides, have found widespread use in carbon-carbon forming reactions and functional group transformation whereby the trivalent state of the lanthanide is preserved. As some lanthanides are capable of forming relatively stable divalent states, they can be used for the reduction of organic functional groups and for reductive coupling reactions with formation of the more stable trivalent lanthanide ion. Since cerium occurs both as tripositive and tetrapositive cation, tetravalent cerium is a good alternative to the heavy metals as oxidizing agent. The lanthanides in pure form as ingots or as powder are also utilized for the reduction of organic functional group or carbon-carbon bond-forming reactions. In the next pages a brief literature overview on the use of metallic, divalent, trivalent and tetravalent lanthanides in organic synthesis is given. Because lanthanide reagents have proven to be useful in many diverse reactions, this overview is not exclusive but only gives an impression of the widespread application of lanthanide compounds in organic synthesis and several comprehensive reviews have been written by Kagan,[40] Kobayashi,[41] Imamoto,[42] Steel,[43] and Molander.[44]

1.4.1. Metallic lanthanides

Metallic cerium, which is the cheapest of all rare-earth metals, is potentially useful for reducing organic functional groups. The reducing ability of cerium is greatly enhanced by pretreatment with mercury(II) chloride or iodine, which removes the surface oxide coating. A number of organic compounds, such as organic halides, ketones, imines, are reductively coupled by this activated cerium.[45] Metallic samarium, europium and ytterbium, which are capable of forming a relatively stable divalent state, also promote unique functional group transformations. Of these three metals, samarium is currently the most synthetically useful. Samarium metal reacts with diiodomethane or chloroiodomethane in THF to generate the divalent samarium species ICH_2SmI and $ClCH_2SmI$. In addition to the enhanced chemoselectivity, high diastereoselectivity is observed in samarium-promoted cyclopropanation reactions (Scheme 1.1).[46] Furthermore, nucleophilic iodomethylation of carbonyl compounds, which is known to be difficult with most organometallic compounds, could be achieved by using samarium metal or samarium(II) iodide (Scheme 1.2).[47,48] Ytterbium metal dissolved in liquid ammonia also represents a useful reducing agent which resembles the Birch reaction using alkali metal.[49] In addition, lanthanide intermetallics (alloys), such as $LaNi_5$, $PrCo_5$ and $SmCo_5$, absorb large quantities of hydrogen rapidly and reversibly and hence they are shown to be efficient for the hydrogenation of unsaturated organic compounds.[50]



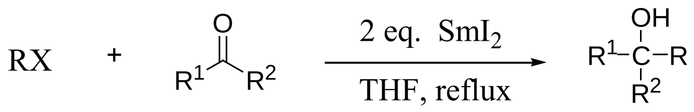
Scheme 1.1



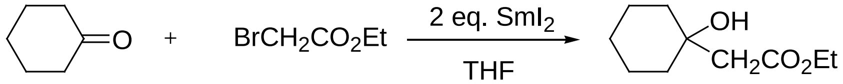
Scheme 1.2

1.4.2. Divalent lanthanides

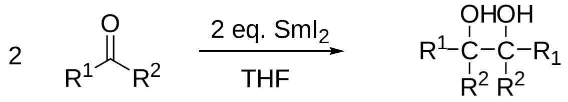
Compounds of divalent europium, samarium and ytterbium are relatively stable. From the reduction potential of the Ln^{3+}/Ln^{2+} redox couple in water, which changes in the following order: Eu(II) < Yb(II) < Sm(II), it can be predicted that samarium(II) compounds are capable of reducing organic functional groups more easily than divalent ytterbium and europium compounds are. In addition, samarium is the cheapest of these lanthanides and consequently divalent samarium compounds, as for example samarium(II) iodide, dicyclopentadienylsamarium(II) and bis(pentamethylcyclopentadienyl)samarium(II), have found widespread use as reducing agents.[42] Of these compounds samarium(II) iodide, SmI_2, is most frequently used for the reduction of numerous organic compounds with THF as the solvent. Organic halides for example are reduced by SmI_2 to alkanes and carbonyl compounds are reduced to alcohols in the presence of a proton source.[51,52] Furthermore, SmI_2 can be used for the reduction of various carbonyl compounds in strongly basic or acidic medium.[53] Besides the application as reducing agent, SmI_2 is also known to promote carbon-carbon bond-forming reactions such as Barbier-type (Scheme 1.3) and Reformatsky-type reactions (Scheme 1.4).[54] In addition, SmI_2 also promotes reductive coupling reactions such as the pinacol coupling. In the absence of a proton source carbonyl compounds undergo reductive dimerization to pinacols (Scheme 1.5).[55]



Scheme 1.3



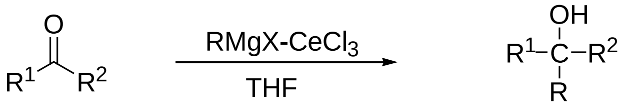
Scheme 1.4



Scheme 1.5

1.4.3. Trivalent lanthanides

As the trivalent state is the most common oxidation state for the lanthanides, trivalent lanthanide compounds are very often used in organic synthesis. Various trivalent salts are available at moderate prices which allows their use in stoichiometric amounts. Grignard-like reactions with trivalent organolanthanides have been reported by Evans.[56] In particular, organocerium compounds have been studied in carbonyl addition reactions.[57,58] Furthermore, addition of $CeCl_3$ to Grignard reagents significantly reduces the production of side-products in Grignard reactions (Scheme 1.6).[59] Trivalent cerium salts are also added to reducing agents to increase selectivity. Luche reported that selective reduction of ketones is obtained using $NaBH_4$-$CeCl_3$.[60] Comparably, the $LiAlH_4$-$CeCl_3$ system is efficient for the reduction of organic halides.[61]



Scheme 1.6

Furthermore, various trivalent lanthanide compounds have been known a long time as Lewis acid catalysts for many organic reactions. As most of our research deals with the application of some new Lewis acid lanthanide salts, a separate section concerning lanthanide(III) compounds as Lewis acid catalysts in organic synthesis will be presented later.

1.4.4. Tetravalent lanthanides

Among the existing tetravalent lanthanides, cerium(IV) is the most stable and many cerium(IV) compounds have been isolated. Several cerium(IV) compounds are commercially available at moderate prices and of these ammonium hexanitratocerate(IV), $(NH_4)_2[Ce(NO_3)_6]$, also known as cerium(IV) ammonium nitrate or CAN for short is most frequently used. However, the use of CAN somethimes results in a complex mixture of reaction products. Therefore a range of other cerium(IV) salts – as for example ammonium cerium(IV) sulfate (CAS), cerium(IV) sulfate tetrahydrate, cerium(IV) trifluoroacetate, cerium(IV) perchlorate, cerium(IV) methanesulfonate and cerium(IV) triflate – have been developed and studied as alternatives for CAN. Since part of this research work deals with the use of cerium(IV) compounds in organic synthesis, an extended section on the application of cerium(IV) is found at the end of this chapter.

1.5. Lanthanide(III) compounds as Lewis acid catalysts

1.5.1. Lewis acid concept

The Brønsted-Lowry theory of acids and bases focuses on the transfer of a proton between species. However, this concept does not take in account large number of substances which show similar features but in which no protons are transferred. A more general view on acidity was introduced by G.N. Lewis. A Lewis acid (LA) is defined as a substance that acts as an electron pair acceptor while a Lewis base is a substance that acts as an electron pair donor.[62]

For evaluation of the Lewis acid and base strengths, Pearson introduced a classification of substances into ‘hard’ and ‘soft’ acids and bases (HSAB classification).[63] The two classes are identified empirically by the opposite order of strengths with which they form complexes with halide ion bases (as measured by the formation constant, K_f, of the complex).

- Hard acids bind in the order: $I^- < Br^- < Cl^- < F^-$
- Soft acids bind in the order: $F^- < Cl^- < Br^- < I^-$

Generally, hard acids tend to bind to hard bases and soft acids tend to bind to soft bases. The bonding between hard acids and bases can be described in terms of ionic interactions, while the interaction between soft acids and bases has a more pronounced covalent character.[62]

1.5.2. Lewis acidity of lanthanides

According to Pearson's HSAB classification, trivalent lanthanides are considered to be hard acids. Consequently, lanthanide(III) species have strong affinity toward hard bases such as oxygen donor ligands. This strong oxophilicity is one of the most important characteristic features of lanthanide(III) compounds making them suitable as Lewis acid catalysts.[42]

Recently, the relative Lewis acidity of rare-earth metals has been evaluated using tandem mass spectrometry based on competitive ligand dissociation from complexes $M(OTf)_3(L)_4$ (L = hexamethylphosphoramide, triethylphosphine oxide, trimethyl phosphate, N,N'-dimethylpropyleneurea, or dimethyl sulfoxide).[64] This analysis proves that the Lewis acidity increases within the lanthanide series with the highest acidity for ytterbium(III) and scandium(III) complexes. These results are in accordance to the extraordinary catalytic activity of scandium(III) and ytterbium(III) in most Lewis acid-catalyzed reactions. The higher Lewis acidity of scandium(III) and the lanthanides at the end of the series can be attribuated to their smaller ionic radii.[65] The decrease of ionic radius should more properly be expressed as an increase of the charge-to-size ratio, Z/r. The higher this ratio, the stronger the Lewis acidity of the cation as it becomes more polarizing. However, the analysis by tandem mass spectrometry also shows that the Lewis acidity of ytterbium(III) is stronger than that of lutetium(III) although the ionic radius of lutetium(III) is smaller. This may originate from the incomplete number of electrons in the 4f orbitals of ytterbium. This incompletely filled shell has a tendency to become a filled shell which renders the ytterbium(III) ion more electron-attractive than the lutetium(III) ion.

In the beginning of this research project only lanthanides were used but later experiments were performed with some transition metals as well for comparison. In Table 1.6 ionic radii and charge-to-size ratio (Z/r) are given for the trivalent lanthanide ions and some transition metal ions. The ionic radii reported in different studies differ a little bit depending on the method used for determination. In this study values are based on experimental crystal structure determinations and are taken from the CRC Handbook of Chemistry and Physics.[66]

Table 1.6 Ionic radii, based on the coordination number (CN) that applies to the metals M used in this study, and charge-to-size ratio of lanthanides and some other metals.[59]

M	La^{3+}	Ce^{3+}	Pr^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}	Tb^{3+}
CN	8	8	8	8	8	8	8	8
r (Å)	1.16	1.14	1.13	1.12	1.08	1.07	1.05	1.04
Z/r (Å)	2.59	2.63	2.65	2.68	2.78	2.80	2.86	2.88
M	Dy^{3+}	Ho^{3+}	Er^{3+}	Tm^{3+}	Yb^{3+}	Lu^{3+}	Y^{3+}	Sc^{3+}
CN	8	8	8	8	8	8	8	6
r (Å)	1.03	1.02	1.00	0.99	0.99	0.97	1.02	0.75
Z/r (Å)	2.91	2.94	3.00	3.03	3.03	3.09	2.94	4
M	Na^{+}	Ni^{2+}	Co^{2+}	Cu^{2+}	Fe^{3+}			
CN	4	6	6	6	6			
r (Å)	0.99	0.69	0.65	0.73	0.55			
Z/r (Å)	1.01	2.90	3.08	2.74	5.45			

1.5.3. Lewis acids in organic synthesis

Lewis acid-catalyzed reactions are of great interest because of their unique selectivities and mild reaction conditions used.[67,68] Traditionally, Lewis acids such as $AlCl_3$, $ZnCl_2$, BF_3, $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, … are used in organic synthesis. However, these Lewis acids have some serious drawbacks. First of all, they are moisture sensitive and in the presence of even a small amount of water they easily decompose or deactivate since they preferentially react with the hard base water instead of with the substrate. Therefore, it has generally been accepted that Lewis acid catalysis needs to be done under completely anhydrous conditions. Moreover, these conventionally used Lewis acids are often required in more than stoichiometric amounts and they cannot be recovered and reused. Consequently, the work-up after performing reactions with conventional Lewis acids produces a large amount of waste, which may bring some severe environmental problems. In conclusion, using the conventional Lewis acids can not be considered as performing really catalytic chemistry but should better be regarded as Lewis acid promoted organic synthesis.

Alternatively, several trivalent lanthanide complexes - as for example lanthanide(III) trihalide, perchlorate, alcoholate, carboxylate, β-diketonate and cyclopentadienyl complexes – have been already known as Lewis acidic catalysts for more than twenty years. Although the lanthanide complex is sometimes required in stoichiometric amounts it can in principle be fully recovered. Moreover, in many cases the reaction is truly catalytic with respect to the amount of lanthanide used. These lanthanide compounds are efficient chemo- and stereoselective catalysts for a widespread series of reactions including Diels-Alder reactions, aldol condensations, olefin polymerization, and bromination of aromatic compounds.[40,41,42] Among the above mentioned lanthanide(III) salts, the simple lanthanide trihalides are often used but in many applications they are only active in their anhydrous form, which is not easily obtained.

In 1991, the first report on water-compatible Lewis acids, lanthanide triflates [$Ln(OTf)_3$], appeared by the group of Kobayashi.[69] These compounds had been described earlier in the literature but their use in organic synthesis was limited. Since this first report, the lanthanide(III) triflates have been widely used as good alternative catalysts for numerous organic reactions.[70] Among the triflate salts especially scandium(III) triflate has been extensively studied.[71] The rare-earth triflates can be prepared in aqueous medium and they are more soluble in water than in organic solvents. Furthermore, they are only required in small catalytic amounts and they can be recycled and reused without loss of efficiency and selectivity, avoiding the acidic waste drain produced when using the traditional Lewis acids or mineral acids. Moreover, they can be used in the presence of coordinating solvents like THF, DMSO, DMF, MeCN, and most remarkably, they are not decomposed or deactivated by water. The application of some frequently used lanthanide(III) compounds as Lewis acid catalysts is discussed in more detail in the following section.

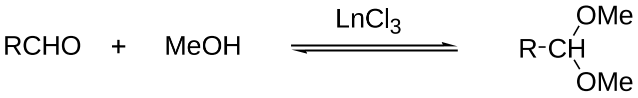
1.5.4. Lanthanide trihalides

Lanthanide trihalides can catalyze a variety of organic reactions. Friedel-Crafts alkylations for example, are efficiently catalyzed by an anhydrous lanthanide trihalide (Scheme 1.7)[72] and anhydrous ytterbium(III) chloride is used to promote the allylation of aldehydes with allyltrimethylsilane,[73] and Diels-Alder reactions.[74]

$$\mathrm{ArH} + \underset{\mathrm{X{=}\ Cl,\ Br}}{\mathrm{RX}} \xrightarrow{\mathrm{LnCl_3}} \mathrm{ArR} + \mathrm{HX}$$

Scheme 1.7

Of all lanthanide trihalides, cerium trichloride heptahydrate has been most often used as an effective Lewis acid, mainly in combination with sodium iodide.[75] Very recently, the use of erbium(III) chloride has been reported for the acylation of various alcohols with acetic anhydride. Catalytic amounts (5 mol%) of $ErCl_3$ were sufficient and the catalyst can be easily recycled and reused without significant loss of activity. Because the reaction is significantly faster when the catalyst is dried before use, the absence of water seems to be essential.[76] As can be seen from these examples, lanthanide trihalides are often required to be completely anhydrous in order to be active. However, they are not so straightforward to dry because deactivation occurs during heating above 90 °C due to the generation of hydrochloric acid and the corresponding oxychlorides.[65] Furthermore, lanthanide trihalides are difficult to solubilize in many organic solvents. An example in which lanthanide chloride hydrates are used is the acetalization of aldehydes.[77] When one equivalent of lanthanide chloride hydrate is added to an aldehyde in methanol, the aldehyde-acetal equilibrium is almost immediately reached (Scheme 1.8).



Scheme 1.8

1.5.5. Perfluorinated rare-earth metal salts in fluorous phase

To overcome the drawbacks of traditionnally used Lewis acids, perfluorinated rare-earth metal salts, such as $Ln(OSO_2C_8F_{17})_3$, were investigated in fluorous solvents. Especially the perfluoroalkanes have some unique properties which make them suitable for use in organic synthesis. Their limited miscibility with conventional organic solvents resulted in the investigation in fluorous biphase catalysis.[78,79,80] The reaction system is biphasic consisting of the fluorous solvent which contains the fluorinated catalyst and a second phase, that may be any organic or non-organic solvent with limited solubility in the fluorous phase, containing the reagents.[6] With some fluorous biphasic systems a monophasic system is obtained upon heating above a certain temperature which allows efficient homogeneous catalysis. Cooling down results again in two phases and consequently the products are easily obtained from the hydrocarbon phase while the fluorous solvent containing the fluorinated catalyst can be reused. Perfluorinated rare-earth metal salts give moderate yields in the nitration reactions of aromatics in fluorous solvents, such as perfluorodecalin.[10] The reaction products are extracted with dichloromethane and the fluorous solvent, which still contains the perfluorinated rare-earth catalyst, is used in a subsequent reaction. However, fluorous solvents are very expensive and from environmentally viewpoint, the use of fluorous compounds on an industrial scale can be questionned.

1.5.6. Lanthanide(III) triflates

In the last decade, extensive research has been performed on the use of lanthanide(III) trifluoromethanesulfonates as new Lewis acid catalysts. Lanthanide(III) trifluoromethanesulfonates, abbreviated as lanthanide(III) triflates are prepared by reaction of the corresponding metal oxide or chloride with aqueous trifluoromethanesulfonic acid.[81] Anhydrous samples can be obtained after drying at elevated temperature under high vacuum. The lanthanide(III) triflates can also be prepared by the reaction of an aqueous solution of the corresponding metal halide with silver triflate. After slow evaporation of the aqueous solution at room temperature, large needle-like crystals are deposited. The crystal structures of the nonahydrates of the rare-earth trifluoromethanesulfonates, $[M(OH_2)_9][CF_3SO_3]_3$ (M = La-Lu, Y, Sc) belong to space group $P6_3/m$ (hexagonal) with cell dimensions $a \approx 13.7$ Å, $c \approx 7.5$ Å and $Z = 2$, with the coordination around the rare-earth atom being a tricapped trigonal prism. The crystal structures indicate that nine molecules of water are found in the first coordination sphere of the lanthanide. This $[M(OH_2)_9]^{3+}$ cations (M = La-Lu, Y) are linked through hydrogen bonding to the three $[F_3CSO_3]^-$ anions (Figure 1.3).[82,83]

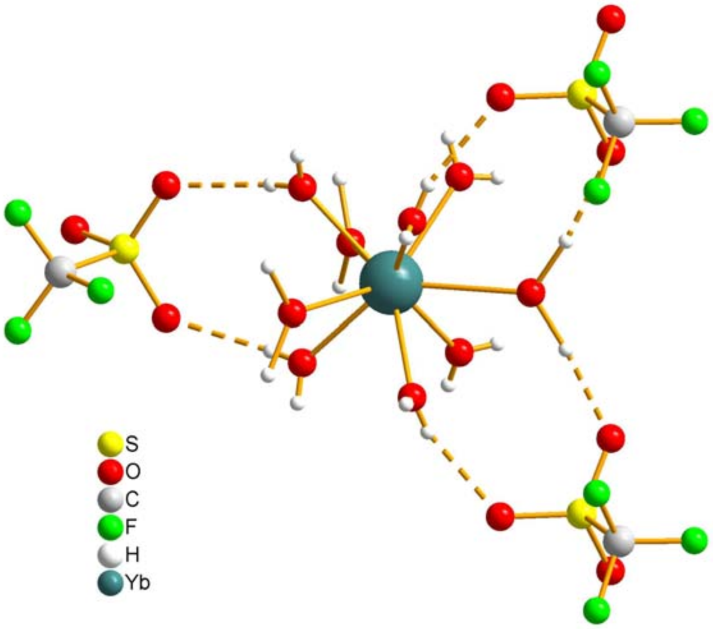
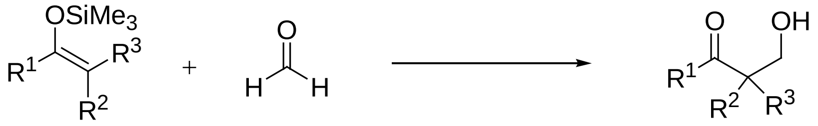


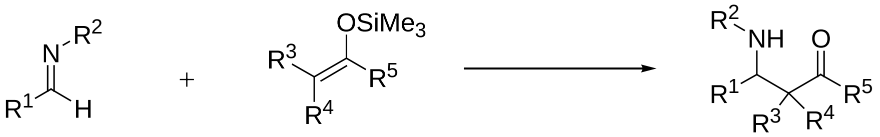
Figure 1.3 Molecular structure of $Yb(OTf)_3 \cdot 9H_2O$ [82]

Not only lanthanide triflates but also scandium and yttrium triflates were shown to be water-compatible Lewis acids. A catalytic amount of these rare-earth metal triflates [$RE(OTf)_3$] is sufficient to perform a number of synthetically useful reactions such as aldol condensations (Scheme 1.9), allylation reactions, Mannich-type reactions between an aldimine and a trimethylsilyl enolate (Scheme 1.10), Diels-Alder reactions, Friedel-Crafts acylation and alkylation, aromatic nitrations, among others.[70]

From the structure of the lanthanide(III) triflates it is clear that the triflate counterion is only a spectator ion. As the Lewis acidity of lanthanides increases from lanthanum to ytterbium the observed catalytic activity also increases from lanthanum(III) to ytterbium(III) triflate.



Scheme 1.9



Scheme 1.10

One of the main disadvantages of the lanthanide(III) triflates is the fact that one needs to handle the expensive and corrosive triflic acid for their preparation and hence lanthanide(III) triflates are also rather expensive compounds. Furthermore, lanthanide(III) triflate catalyzed reactions are often performed in harmful organic solvents. If one wants to carry out these lanthanide(III) triflate catalyzed reactions in water, an organic co-solvent is needed to solubilize the reagents.

1.5.7. Lewis acid catalysis in micellar systems

Aldol reactions of silyl enol ethers with aldehydes, for example, are successfully carried out in THF-water or toluene-ethanol-water mixtures in the presence of a catalytic amount of lanthanide triflate,[84,85] but lower yields are obtained in pure water.[86] Although several organic reactions in micelles were reported, the group of Kobayashi was the first to describe Lewis acid catalysis in micelles by using lanthanide triflates in the presence of surfactants, such as sodium dodecylsulfate (SDS). Mukaiyama aldol and Mannich-type reactions could be performed well in water without the use of any organic co-solvent when using 5-10 mol% lanthanide triflate and 20 mol% sodium dodecylsulfate.[87, 88]

The basic principles of surfactants and micellar chemistry are reviewed by Goodling and van Stam.[89,90] Ionic surfactants, such as for example sodium dodecylsulfate, are amphiphilic substances consisting of a hydrophylic charged head-group and a hydrophobic hydrocarbon tail. At a certain surfactant concentration, known as the critical micelle concentration, surfactants which have a long hydrocarbon chain will form a macroscopic phase separation or micelles. Micelle formation is not a macroscopic phase separation, but the formation of a thermodynamically stable, microheterogeneous supramolecular system, with surfactant molecules aggregated in micelles dissolved in the aqueous bulk. Normal micelles are those occuring in aqueous solution in which the surfactant molecules orient themselves into spherical or elliptical structures with their hydrophobic tails oriented toward the center and their hydrophilic heads oriented toward the surrounding water. Cabane showed in an NMR study that the micelles formed by the well-known surfactant sodium dodecylsulfate (SDS) have about 1/3 of their surface covered by the hydrophilic head-groups, and the remaining 2/3 of the surface covered by hydrocarbon tails.[91] A schematic structure of an ionic surfactant and the micelle it forms is shown in Figure 1.4, where it can be seen that the surface is composed of ionic head-groups, hydrophobic hydrocarbon tails and counterions. Because the nonpolar regions of micelles are able to solubilize nonpolar organic materials,[92] organic reactions can proceed in micelles. Therefore, by using surfactants, the problem of low solubility of organic substrates in water may be overcome.

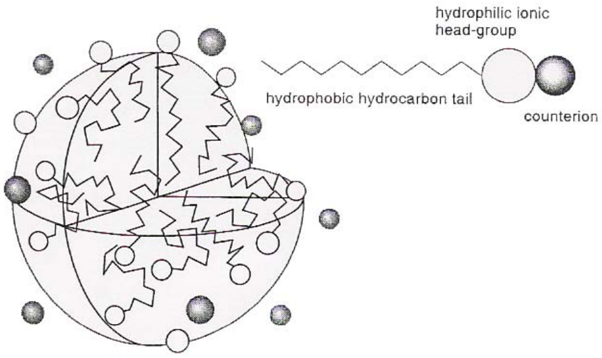
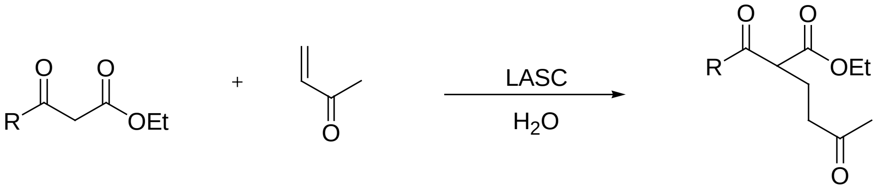


Figure 1.4 Schematic structure of an ionic surfactant molecule and the micelle it forms.[90]

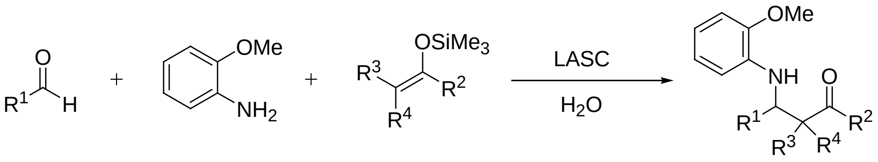
1.5.8. Lewis acid-surfactant-combined catalysts (LASCs)

As described above, scandium(III) triflate can be used as an efficient catalyst in pure water if some surfactant is added. But as scandium(III) triflate is water-soluble, Kobayashi and coworkers reported that the concentration of scandium triflate in the hydrophobic reaction field is low. To increase the scandium content, they designed the Lewis acid-surfactant combined catalyst scandium trisdodecylsulfate (STDS).[93] This new type of catalyst is thus composed of a water-stable cationic Lewis acid and an anionic surfactant as the counter ion. These systems act both as a catalyst to activate the substrate molecules and as a surfactant to form stable colloidal dispersion systems with organic substates in water. The colloidal particles formed by mixing a scandium-based LASC with an organic substrate in water have extensively been studied by the group of Kobayashi.[94] LASCs, such as scandium(III) dodecylsulfonate and scandium(III) dodecylsulfate for example, have a low solubility in water. However, when they are mixed with organic substrates, a white turbid mixture is formed through colloid formation. The average size of the colloidal particles formed by scandium(III) dodecylsulfonate in the presence of benzaldehyde, determined by dynamic light scattering, is proved to be 1.1 μm in diameter and light microscopic observations revealed their spherical shape. The shape and size of the colloidal particles is also confirmed by transmission electron microscopy and atomic force microscopy.

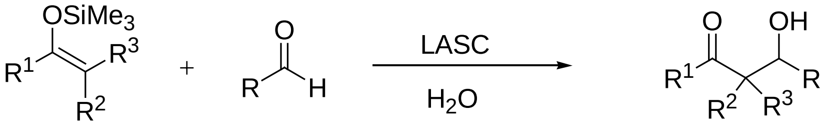
The use of scandium trisdodecylsulfate and scandium trisdodecylsulfonate has been studied in various reaction systems. In the presence of a catalytic amount of scandium trisdodecylsulfate, reactions of different β-ketoesters with enones proceeded smoothly in pure water to afford the corresponding Michael adducts in high yields (Scheme 1.11).[95] Three-component Mannich-type reactions of aldehydes, amines and silyl enolates are also efficiently catalyzed by scandium trisdodecylsulfate in water (Scheme 1.12).[96] The LASCs made with scandium have also been investigated for Mukaiyama aldol (Scheme 1.13),[93,97] and allylation reactions,[94] but the use of cheaper lanthanides and transition metals has been limited to the Mukaiyama aldol reaction.[98] Surprisingly, LASCs are poor catalysts for Diels-Alder reactions of dienophiles which are generally subject to Lewis acid catalysis in organic synthesis.[99]



Scheme 1.11



Scheme 1.12



Scheme 1.13

In addition, the use of scandium(III) dodecylsulfate for aldol reactions is investigated in different solvents by the group of Kobayashi but the best yields were obtained using water as the solvent.[100] This advantageous effect of water is attributed to the following factors: (1) hydrophobic interactions in water to concentrate the catalyst and the substrates; (2) aggregation of the substrates through hydrophobic interactions, which squeeze water molecules out of the organic substrate phase, leading to a decrease of the rate of hydrolysis of the organic substrates, such as silyl enol ether; (3) hydration of the metal cation and the counteranion by water molecules to form highly Lewis acidic species such as $[M(H_2O)_x]^{n+}$; (4) rapid hydrolysis of the initially formed metal aldolate to secure fast catalytic turnover.

1.6. Cerium(IV)-mediated reactions

1.6.1. Redox properties of cerium(IV)

Cerium is the most abundant rare-earth element and hence it is the cheapest of all rare earths. Furthermore, cerium is the only rare-earth element which has a stable tetravalent oxidation state in solution. To understand the redox properties of cerium it is important to have a look at its electronic configuration. The electronic configuration of cerium in the ground state is $[Xe]4f^2 5d^0 6s^2$. Hence, the Ce^{3+} ion has the electronic configuration $[Xe]4f^1$, while Ce^{4+} has the electronic configuration $[Xe]f^0$, which is the same as for the noble gas xenon. The ability of tetravalent cerium originates thus from the enhanced stability of the vacant f-shell.

In acidic medium, cerium(IV) is a very strong one-electron oxidant and its half-reaction is:

$$Ce^{4+} + e^- \rightleftharpoons Ce^{3+}$$

Cerium(IV) is called an oxidizing agent or an oxidant since it has a strong affinity for electrons and tends to remove them from other species. On the other hand, cerium(III) is the reducing agent or reductant which readily donates electrons to another species. The terms *cerous* and *ceric* are regularly used, respectively for cerium(III) and cerium(IV).

An extensive review on the applications of tetravalent cerium compounds was written by Binnemans.[101] This review also presents a detailed literature overview on the redox properties of cerium(IV). After the first study on the redox potential of the Ce^{4+}/Ce^{3+} couple in sulfuric acid by Kunz in 1931, the redox potential of this couple was also reported in other acids and these studies showed that the redox potential strongly depends on the nature and the concentration of the acid. Redox potentials for the Ce^{4+}/Ce^{3+} couple in different acids (measured versus normal hydrogen electrode) are summarized in Table 1.7. The large reduction potential of tetravalent cerium makes cerium(IV) compounds superior oxidizing agents compared to other metal ions.

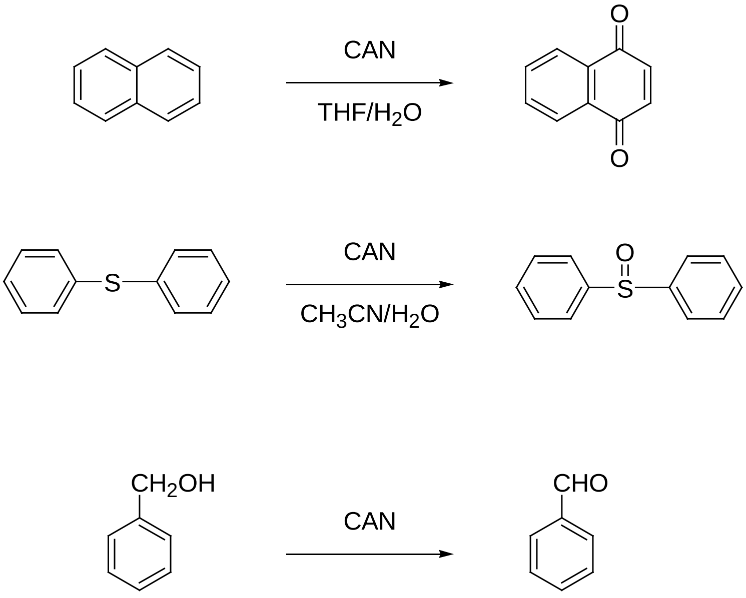
Table 1.7 Redox potentials of the Ce^{4+}/Ce^{3+} couple.[101]

Acidic solution	Redox potential
1M HCl	+ 1.28
1M H_2SO_4	+ 1.44
1M HNO_3	+ 1.61
1M $HClO_4$	+ 1.70
8M $HClO_4$	+ 1.87

As the reduction of Ce^{4+} to Ce^{3+} proceeds cleanly in acidic solution, the Ce^{4+}/Ce^{3+} redox couple is frequently used for redox titrations. Titrimetric methods based on cerium(IV) are also known as cerimetry or cerate oxidimetry. Most often, acidic cerium(IV) sulfate solutions are used as standard solutions and experimental procedures for cerimetric titration of various metal ions are described in the work of Kolthoff on volumetric analysis and in Vogel’s textbook of quantitative inorganic analysis.[102, 103] In the past, cerimetry has also been applied for the determination of organic compounds. And for the moment, cerimetry is still used for the determination of hydrogen peroxide.

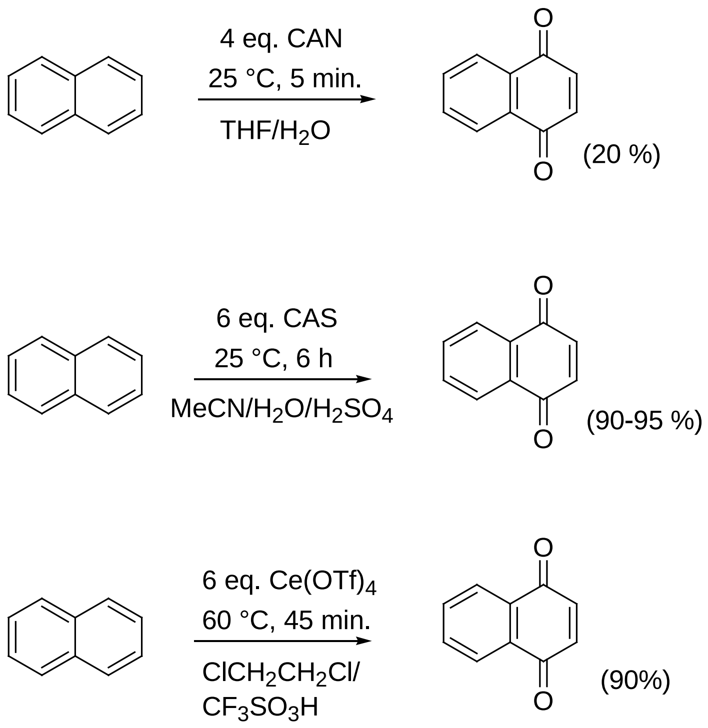
1.6.2. Cerium(IV)-mediated oxidation reactions

Oxidation reactions are very important in organic synthesis in order to prepare various useful compounds. Aldehydes for example are used in perfumes or as intermediates for pharmaceuticals, and naphthoquinones are important intermediates for organic dyes. Cerium(IV) compounds have been reported in the oxidation of a wide range of organic functional groups including hydrocarbons, nitrogen and sulfur functionalities, carbonyl compounds, alcohols and phenols (Scheme 1.14).[42,101,104]



Scheme 1.14

While symmetrical aromatics such as naphthalene and anthracene are converted to their corresponding quinones by cerium(IV) ammonium nitrate (CAN) in aqueous THF, asymmetric aromatics are converted into many products.[42] As nitration of the aromatic ring can also occur with CAN, cerium(IV) ammonium sulfate (CAS) dissolved in a mixture of acetonitrile and 4M aqueous sulfuric acid[105] and cerium(IV) triflate in a mixture of 1,2-dichloroethane and 3M triflic acid[106] are often used (Scheme 1.15). In these oxidation reactions water is needed as the source of oxygen and stoichiometric studies indicated that six equivalents of cerium(IV) salt are required to oxidize one equivalent of naphthalene to 1,4-naphthoquinone.[107] Quinones can also be obtained from CAN mediated oxidation of hydroquinones and catechols, although the reaction conditions are critical to avoid over-oxidation.[104]



Scheme 1.15

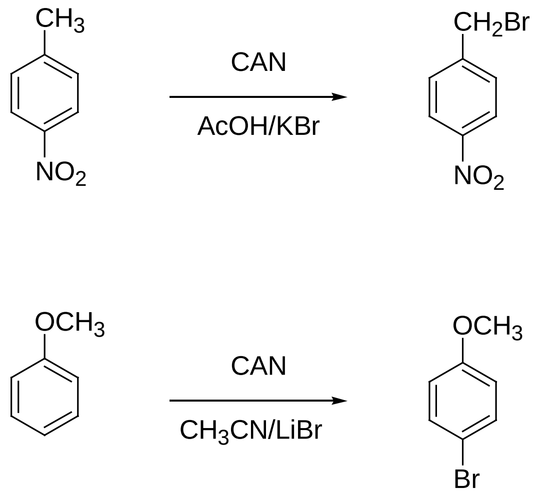
The use of cerium(IV) triflate for the oxidation of substituted alkylbenzenes and alcohols with cerium(IV) triflate has been reported by Imamoto.[108] Laali and coworkers also reported that cerium(IV) triflate has a superior chemoselectivity towards benzylic oxidation compared to CAN.[109] In acetonitrile, highest amounts of benzylic carbonyl compounds are obtained when using cerium(IV) triflate hydrates, whereas significant amounts of the benzylic alcohols are formed when using the anhydrous cerium(IV) triflate. Moreover, in the presence of a cerium(IV) salt alcohols can undergo either direct oxidation, fragmentation or both processes depending on the structure of the alcohol.[110] Benzylic and allylic alcohols are easier to oxidize than simple secondary alcohols and simple primary alcohols generally resist oxidation by cerium(IV) compounds. On the other hand, tertiary alcohols and vicinal diols undergo oxidative cleavage.[42] Cerium(IV)-mediated oxidation of benzylic alcohols is usually performed in water, aqueous acetic acid or acetonitrile but recently the first report on CAN and cerium(IV) triflate mediated oxidation of benzylic alcohols in an ionic liquid appeared by Mehdi and coworkers.[111]

However, as cerium(IV) is a one-electron oxidant, more than stoichiometric amounts of the cerium(IV) reagent are required to perform oxidation reactions. Therefore, much research has been done on indirect and catalytic reactions with cerium(IV) reagents. CAN can be used catalytically in oxidations in combination with a bromate ion as the co-oxidant. Benzylic alcohols for example are oxidized to the corresponding aldehydes in the presence of CAN and sodium bromate.[112] Furthermore, Ganin reported the oxidation of alkyl aromatics in the presence of CAN and potassium bromate.[113,114] The resulting cerium(III) ion after reduction by the alkylbenzene is reoxidized by the bromate ion. On the other hand, Christoffers reported that the α-hydroxylation of β-dicarbonyl compounds with oxygen proceeds smoothly when catalytic amounts of cerium(III) chloride heptahydrate are used.[115] In addition, cerium(III) acetate has been reported in combination with sodium bromide and hydrogen peroxide for the selective oxidation of toluenes into benzaldehydes although the reaction mechanism is not yet very clear.[116] Another way to obtain an industrially more attractive system is the reoxidation of the cerium(III), that is formed during oxidation reactions of organic compounds, into cerium(IV) which can then be used in subsequent reactions. Cerium(III) can be oxidized to cerium(IV) electrolytically or by the use of strong oxidizing agents, such as silver(II) oxide.[101] But when metal-containing oxidizing agents are used, the cerium solution gets contaminated by other metal ions. On the other hand, the usefulness of electrolytical oxidation of cerium(III) to cerium(IV) has for a long time been limited by the anions used with cerium(IV). Cerium chlorides, nitrates, perchlorates and sulfates for example have limited applicability due to their instability toward oxidation or limited solubility of the cerium salt. Significant improvements were obtained when the group of Kreh reported that cerium(III) and cerium(IV) have a high solubility in aqueous methanesulfonic acid.[117] The solubility of cerium(IV) in aqueous methanesulfonic acid is lower than the solubility of cerium(III) and the solubility of cerium(III) and cerium(IV) depends strongly on the concentration of methanesulfonic acid. With increasing methanesulfonic acid concentration the solubility of cerium(IV) increases whereas the solubility of cerium(III) decreases. The more expensive trifluoromethanesulfonic acid (triflic acid) is also used instead of methanesulfonic acid. Consequently, highly acidic cerium salt solutions of methanesulfonate and trifluoromethanesulfonate exhibit the desired combination of properties (such as stability, solubility, reactivity, capability to achieve high current density, capability of repeated cycling between cerous and ceric) for electrolytical oxidation of cerium(III) to cerium(IV).[118,119,120] For example, Kreh and coworkers reported the electrolytical preparation of cerium(IV) methanesulfonate and cerium(IV) trifluoromethanesulfonate in acidic solution starting from cerium(III) carbonate.[106,121] To a stirred suspension of cerium(III) carbonate in water is added dropwise an excess of methanesulfonic acid or trifluoromethanesulfonic acid resulting in an acidic solution of the cerium(III) salt. This acidic solution of cerium(III) salt is introduced into the anolyte compartment of an electrolytic cell where it is oxidized to the cerium(IV) salt. The anolyte is separated from the catholyte by a perfluorinated ion exchange membrane (Nafion membrane), and the catholyte compartment is filled with a 6M solution of the respective acid causing reduction of protons to hydrogen gas. The acidic cerium(IV) solution obtained in this way has shown to be useful for the oxidation of various aromatic compounds and the resulting cerium(III) could then again be reoxidized and successfully used in oxidation reactions. This cyclic process involving electrochemical generation of a redox agent and the use of the agent to effect a chemical reactions is known as mediated or indirect electrosynthesis. Electrosynthesis (electrochemical synthesis) offers several advantages: toxic reagents can be avoided, less waste is produced, it is applicable to a wide range of substrates and it is often a very selective method. Electrons are also relatively cheap reagents and the conditions in electrochemical processes are close to ambient temperature and pressure.[101] Besides ceric trifluoromethanesulfonate and ceric methanesulfonate, Purgato reported the use of ceric *p*-toluenesulfonate for the electrocatalytic oxidation of alcohols, diols and arenes.[122] Although most electrochemical processes are performed with divided cells, an undivided cell can also be used in multiphase systems.[123] By proper choice of organic phase and phase catalyst, cerium(IV) is immediately after its formation transferred from the aqueous phase to the organic phase so that it is protected from cathodic reduction, whereas cerium(III) returns to the aqueous phase for reoxidation.

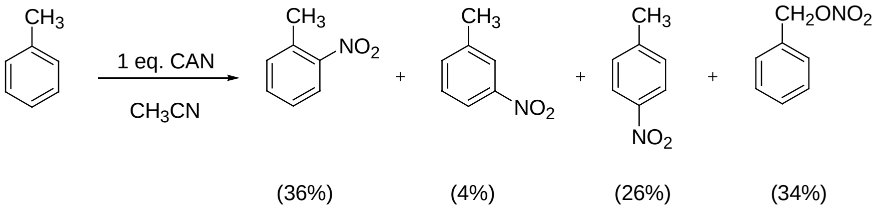
In the above mentioned examples of electrochemical oxidation, cerium(III) is oxidized to cerium(IV) in the anolyte compartment and in the catholyte compartment protons of the acid solution are reduced. Instead of reducing protons at the cathode it would be advantageous to produce simultaneously with the regenerated cerium(IV) another redox mediator in the reduced form. This reduced mediator could then perform reductive electrochemical reactions. Harrison developed an electrolytic system in which there is a simultaneous reduction of tetravalent titanium and oxidation of trivalent cerium.[124] A methanesulfonic acid solution containing tetravalent titanium and trivalent cerium is used as the electrolyte solution for both the anolyte and the catholyte. In this way, the rates of transfer of cerium(III) and water to the catholyte and methanesulfonic anion to the anolyte are counteracted by physical transfer from the respective reservoirs of anolyte to catholyte and catholyte to anolyte. Briefly, at the anode trivalent cerium is oxidized to tetravalent cerium, a powerful oxidizing agent for organic compounds. On the other hand, at the cathode tetravalent titanium is reduced to trivalent titanium, a powerful reducing agent used for reduction of organic compounds such as ketones and nitro-groups. After performing oxido-reduction reactions tetravalent titanium and trivalent cerium are obtained which are then again recycled in the electrolytic cell.

1.6.3. Other CAN-mediated reactions

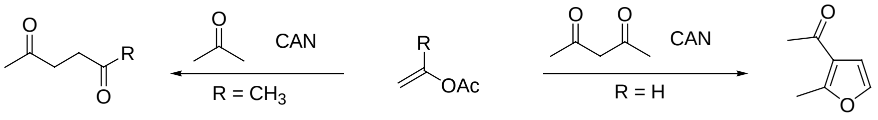
Furthermore, CAN is also used in carbon-carbon and carbon-heteroatom bond (C-S, C-N, C-Se, C-Br, C-I) forming reactions and several reviews discussing these topics are written by Nair and coworkers.[125,126,127] Most carbon-heteroatom bond forming reactions involve oxidative addition of heteroatom-centered radicals, formed by oxidation of anions by CAN, to alkenes or alkynes. Halogenation of aromatic compounds for example is performed with KBr in acetic acid or LiBr in acetonitrile in the presence of CAN (Scheme 1.16), and CAN is also used as a nitrating agent for aromatic nitrations (Scheme 1.17). An example of the use of CAN in carbon-carbon bond forming reactions is the formation of furan derivatives or 1,4-diketones by the oxidative addition to olefins of radicals generated from 1,3-dicarbonyl compounds and ketones, respectively (Scheme 1.18).[128,129] In addition, CAN also mediates the esterification of carboxylic acids and alcohols. This reaction proceeds probably through coordination of the carboxylic oxygen to cerium(IV) followed by nucleophilic attack by the alcohol.[130] Furhermore, CAN is also a mild reagent for deprotection of acetals.[131] And as mentioned earlier, it is sometimes possible to use CAN in catalytic amounts. In the electrophilic substitution reaction of indoles with carbonyl compounds for example, CAN serves as a Lewis acid catalyst instead of as a single-electron oxidant.[132]



Scheme 1.16



Scheme 1.17



Scheme 1.18

Chapter 2. Instrumentation

2.1 Gas chromatography (GC)
2.2 Nuclear magnetic resonance spectroscopy (NMR)
2.3 Infrared spectroscopy (IR)
2.4 Mass spectrometry (MS)
2.5 GC-MS
2.6 Elemental analysis
2.7 Karl Fischer titrator

2.1. Gas chromatography (GC)

2.1.1. Specifications of the GC equipment

GC analyses were performed on a ThermoFinnigan Trace GC equipped with a FID detector (Flame Ionisation Detector). The parameters used are summarized below.

Injector:
Temperature: 230 °C
Injection mode: splitless
Split flow: 60 mL/min.
Injection of about 1,5µL of the diluted reaction mixture.

Carrier gas (helium): constant pressure of 60 kPa

Capillary column:
Stationary phase: Crossbond 5% diphenyl - 95% dimethylsiloxane
  length: 15 m
  internal diameter: 0.32 mm
  film thickness: 0.25 µm

Detector:
Temperature: 250 °C
Compressed air: 350 mL/min
Hydrogen gas: 35 mL/min

Column oven: In all GC-measurements throughout this study the temperature of the column oven was gradually increased to obtain faster elution. The specific heating programs developed for different reaction mixtures are described in the experimental section.

2.1.2. Data processing

Retention times and integrated peak areas were obtained by using the software package ChromCard. As a FID-detector is mass-sensitive, the integrated peak areas of a chromatogram are proportional to the mass of the organic compounds present in the reaction mixture. Since no detector responds equally to different compounds, a "response factor" must be calculated for each compound with a particular detector. The response of a compound i is compared with the response of a reference material r. The respons factor (RF) is then calculated according to equation 2.1:

$$\mathrm{RF_i} = \frac{A_i / m_i}{A_r / m_r} \qquad (2.1)$$

where A_i and A_r are the integrated peak areas of compound i and the reference compound r, and m_i and m_r are their respective masses.

2.1.3. Calculation of the conversion

The conversion is the molar percentage of a substrate that is converted into one or more reaction products. When an internal standard was required during this work, dodecane was added after the reaction. The response factor of each product was calculated with the internal standard as reference compound and by dividing the peak area of the product by this response factor a corrected peak area is obtained. The amount of product formed during the reaction can be calculated by comparing the corrected peak area of the product and the peak area of the internal standard, which is representative for the known amount of internal standard that was added after reaction.

In the cases when only one product is formed during the reaction or if the reaction was not complete, the use of an internal standard could be avoided since the conversion can also be determined by comparing the peak areas of the reaction products to the peak area of the starting product (substrate). The response factor of the products is then calculated with the substrate as a reference and the yield of the reaction is given by equation 2.2:

$$\text{Conversion (\%)} = \frac{\sum_i A_i / RF_i}{A_s + \sum_i A_i / RF_i} * 100$$

(2.2)

where A_i and A_s are the integrated peak areas of the reaction products i and the substrate s, and RF_i the response factor of the reaction products compared to the substrate.

2.1.4. Calculation of the product distribution

The product distribution is given by the selectivity toward each reaction product. The selectivity toward a reaction product is defined by the ratio of the molar amount of this compound to the total molar amount of formed products and represented by equation 2.3:

$$\text{Selectivity for product i} = \frac{A_i / RF_i}{\sum_i A_i / RF_i} * 100 \qquad (2.3)$$

where A_i represents the integrated peak areas of the reaction products i, and RF_i the response factor of the reaction products compared to the substrate. Equation 2-3 is only valid if all reaction products are visible on the chromatogram.

2.2. Nuclear magnetic resonance spectroscopy (NMR)

Characterization of organic compounds has been done by combination of ^{1}H NMR, ^{13}C NMR, DEPT and COSY spectra. The recorded DEPT (*distortionless enhancement by polarization transfer*) spectra show only signals for carbon atoms bound to H-atoms and from the spectrum one can distinguish CH_2 groups (negatively phased) from CH and CH_3 groups (positively phased). COSY (*homonuclear shift correlation spectroscopy*) combines two ^{1}H NMR spectra and the contour plot gives information on which protons are binded to adjacent carbon atoms. Proton and COSY spectra were recorded on a Bruker Avance 300 spectrometer, operating at 300 MHz for ^{1}H whereas carbon-13 and DEPT spectra were recorded on a Bruker AMX 400 spectrometer, operating at 100 MHz for ^{13}C .

2.3. Infrared spectroscopy (IR)

FTIR spectra of solid compounds were recorded on a Bruker IFS-66 spectrometer, using the KBr pellet method. *In-situ* infrared spectra of reaction mixtures were obtained using a ReactIR 1000 IR spectrometer (Applied Systems Inc., Mettler Toledo).

2.4. Mass spectrometry (MS)

Mass spectra were recorded on a Thermo Electron mass spectrometer, type LCQ, with an electrospray ionization source (ESI).

2.5. GC-MS

Analyses were performed on a GC-MS of Agilent. The 6980N Network GC system contains a HP-5MS (5% diphenyl - 95% dimethylsiloxane) capillary column and is coupled to a 5973 Network Mass Selective Detector.

2.6. Elemental analysis

CHN Elemental analyses (Carbon – Hydrogen – Nitrogen) were performed on a CE Instruments EA-1110 elemental analyzer.

2.7. Karl Fischer titrator

The water content of the ionic liquids was determined by a Mettler Toledo Coulometric Karl Fischer Titrator, model DL39.

Chapter 3. Lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed reactions

3.1. Introduction

Lanthanide complexes have in recent years attracted considerable attention as reagents for a variety of organic reactions. Among them, the lanthanide salts of triflic acid, lanthanide(III) triflates, have been particularly successfully applied as catalyst for a large number of organic transformations.[70] In this chapter, the use of some new water-tolerable Lewis acid catalysts, lanthanide(III) salts of *p*-toluenesulfonic acid and different nitrobenzenesulfonic acids, is investigated for several organic reactions. So far, the complexes of lanthanides with aromatic sulfonic acids have not been explored as catalysts in organic reactions. First, the preparation and characterization of these complexes will be discussed. Afterwards, results of the lanthanide(III) tosylate catalyzed nitration of aromatic compounds and acylation of alcohols is reported. Finally, the formation of calix[4]resorcinarenes is reported catalyzed by lanthanide(III) tosylates and nitrobenzenesulfonates.

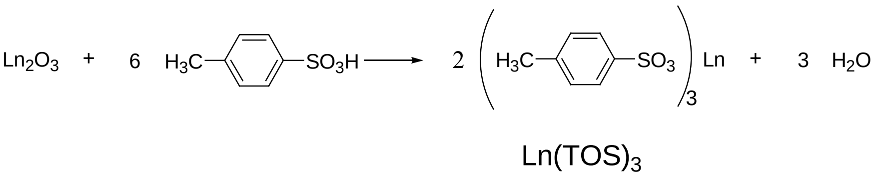
3.2. Lanthanide(III) salts of *p*-toluenesulfonic acid and nitrobenzenesulfonic acids

3.2.1. Introduction

To the best of our knowledge, lanthanide(III) salts of nitrobenzenesulfonic acids are virtually unexplored compounds and no literature data about chemical and structural properties of these reagents were available before the exploration of this topic in our research group. On the other hand, structural data on lanthanide(III) *p*-toluenesulfonates have already been published and these will be discussed later. Because benzenesulfonic acids are frequently used in cation exchange resins in order to separate different lanthanides, Nakani and coworkers have studied the behaviour of lanthanide(III) *p*-toluenesulfonates in solution long ago.[133]

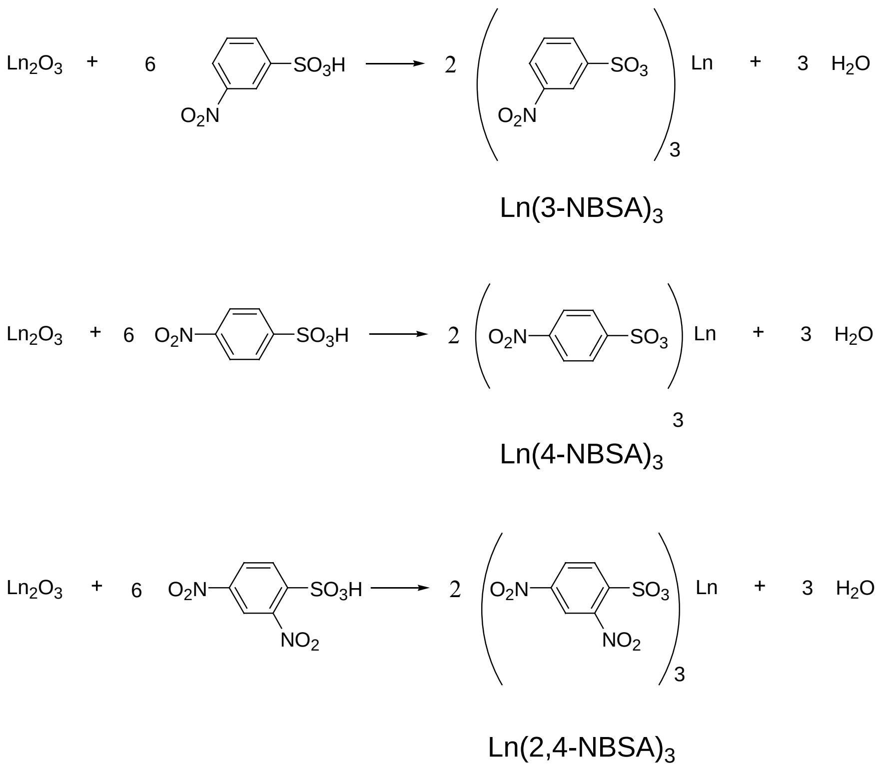
3.2.2. Synthesis and characterization

Lanthanide(III) salts of *p*-toluenesulfonic acid were prepared by reaction of *p*-toluenesulfonic acid with the corresponding lanthanide(III) oxide (Scheme 3.1).[133]



Scheme 3.1

Similarly, lanthanide(III) salts of 3-nitrobenzenesulfonic acid (*m*-nitrobenzenesulfonic acid), 4-nitrobenzenesulfonic acid (*p*-nitrobenzenesulfonic acid) and 2,4-dinitrobenzenesulfonic acid were also prepared by reaction of the respective acid with the corresponding lanthanide(III) oxide (Scheme 3.2). Notice that lanthanide(III) *p*-toluenesulfonates are also named lanthanide(III) tosylates, and similarly, lanthanide(III) *p*-nitrobenzenesulfonates are often named lanthanide(III) nosylates. Besides lanthanide(III) tosylates, many transition metal tosylates and some alkali metal tosylates have been described.[134] In this study, some experiments with iron(III) and copper(II) tosylates were also performed for comparison. Iron(III) tosylate is commercially available at relatively low price, whereas copper(II) tosylate was synthesized from copper(II) oxide and *p*-toluenesulfonic acid.



$Ln(3\text{-}NBSA)_3$

$Ln(4\text{-}NBSA)_3$

$Ln(2,4\text{-}NBSA)_3$

Scheme 3.2

All aromatic acids are commercially available at moderate price. Furthermore *p*-nitrobenzenesulfonic acid was also prepared very cheaply in a one-step procedure from sulfanilic acid.[135] A stirred mixture of sulfanilic acid, *p*-$H_2NC_6H_4SO_3H$ (20.7 g), glacial acetic acid (163 mL) and 30% H_2O_2 was heated for one hour at 70-80 °C while an additional 50 mL of 30% H_2O_2 was added. After addition of all hydrogen peroxide heating and stirring were continued for 2.25 hours. The obtained solution was evaporated to dryness and dried at 60-70 °C in vacuum resulting in pure p-$O_2NC_6H_4SO_3H{\cdot}H_2O$. The NMR-spectrum of the synthesized *p*-nitrobenzenesulfonic acid was identical to that of the purchased product.

CHN-analysis: p-$O_2NC_6H_4SO_3H \cdot 2H_2O$, Calcd. (found): C, 30.12 (30.06); H, 3.79 (3.93); N, 5.85 (5.84) %.

Procedure for the synthesis of Ln(TOS)$_3$ and Ln(NBSA)$_3$ complexes:
The lanthanide(III) salts were synthesized by reaction of 1.1 equivalent of the corresponding lanthanide(III) oxide, and six equivalents of *p*-toluenesulfonic acid in water. After stirring the solution in boiling water for 30 minutes to 1 hour, the excess of oxide was removed by filtration. The filtered solution was evaporated to dryness and the resulting solid was dried in a vacuum oven at 50 °C over night. Yields were usually >98%. The lanthanide(III) nitrobenzenesulfonates were prepared in a similar way from the respective nitrobenzenesulfonic acid.

Elemental analysis results: La(TOS)$_3$•3H$_2$O, ($C_{21}H_{27}S_3O_{12}La$) Calcd. (found): C, 35.70 (35.68); H, 3.85 (3.76) %. Nd(TOS)$_3$•2H$_2$O, ($C_{21}H_{25}S_3O_{11}Nd$) Calcd. (found): C, 36.47 (36.76); H, 3.65 (3.36) %. Sm(TOS)$_3$•3H$_2$O, ($C_{21}H_{27}S_3O_{12}Sm$) Calcd. (found): C, 35.05 (34.79); H, 3.78 (3.73) %. Eu(*TOS*)$_3$•3H$_2$O, ($C_{21}H_{27}S_3O_{12}Eu$) Calcd. (found): C, 35.00 (35.35); H, 3.78 (3.74)%. Gd(TOS)$_3$•3H$_2$O, ($C_{21}H_{27}S_3O_{12}Gd$) Calcd. (found): C, 34.76 (34.60); H, 3.75 (3.70)%. Dy(TOS)$_3$•2H$_2$O, ($C_{21}H_{25}S_3O_{11}Dy$) Calcd. (found): C, 35.34 (35.54); H, 3.53 (3.30) %. Ho(TOS)$_3$•3H$_2$O, ($C_{21}H_{27}S_3O_{12}Ho$) Calcd. (found): C, 34.43 (34.45); H, 3.72 (3.62)%. Er(TOS)$_3$•2H$_2$O, ($C_{21}H_{25}S_3O_{11}Er$) Calcd. (found): C, 35.25 (35.50); H, 3.52 (3.87) %. Tm(TOS)$_3$•2H$_2$O, ($C_{21}H_{25}S_3O_{11}Tm$) Calcd. (found): C, 35.10 (35.13); H, 3.51 (3.30) %. Yb(TOS)$_3$•H$_2$O, ($C_{21}H_{23}S_3O_{10}Yb$) Calcd. (found): C, 35.75 (35.63); H, 3.29 (3.69) %. Y(TOS)$_3$•H$_2$O, ($C_{21}H_{23}S_3O_{10}Y$) Calcd. (found): C, 40.65 (40.56); H, 3.74 (4.08) %. Cu(TOS)$_2$•H$_2$O, ($C_{14}H_{16}S_2O_7Cu$) Calcd. (found): C, 39.66 (39.71); H, 3.88 (4.78) %. Yb(3-NBSA)$_3$•2H$_2$O, ($C_{18}H_{16}S_3O_{17}N_3Yb$) Calcd. (found): C, 26.51 (26.47); H, 1.98 (2.06) N, 5.15 (5.41) %. Yb(4-NBSA)$_3$•3H$_2$O, ($C_{18}H_{18}S_3O_{18}N_3Yb$) Calcd. (found): C, 25.94 (25.57); H, 2.18 (2.34) N, 5.04 (5.52) %. Yb(2,4-NBSA)$_3$•4H$_2$O, ($C_{18}H_{17}S_3O_{25}N_6Yb$) Calcd. (found): C, 21.91 (21.52); H, 1.74 (1.65) N, 8.52 (8.57) %.

The elemental analysis results of the investigated complexes indicated that upon drying the crystalline solid at 50 °C *in vacuo*, some water molecules of crystallization are lost, but that the complexes still contain one to four molecules of water. Consequently, infrared spectral data of the complexes showed strong and broad absorption in the region between 3200 and 3600 cm^{-1}, corresponding to the –OH stretching of water molecules. Anhydrous complexes can be obtained after drying at 160 to 200 °C in vacuum. Since the coordination number of the trivalent lanthanide ion is commonly 8 or 9, it can be assumed that upon removal of the hydrated water molecules from the crystal, the coordination mode of the sulfonate anions changes so that they act as multidentate ligands forming more metal-oxygen bonds in order to replace the removed water oxygen atoms from the first coordination sphere of the lanthanide(III) ion. The absence of traces of free acid in these complexes was proved by infrared and NMR analyses. The infrared spectra of lanthanide(III) complexes showed that the broad infrared absorption band between 2400 and 3100 cm^{-1}, typical for the OH stretching mode of protonated benzenesulfonic acid,[136] was absent in all cases. In addition, comparison of the ^1H NMR spectra in deuterated dimethyl sulfoxide (DMSO) of lanthanide(III) tosylate and *p*-toluenesulfonic acid also confirmed the absence of free acid in the lanthanide complex. Similar experiments with nitrobenzenesulfonic acid confirmed the absence of free acid in the lanthanide complexes of nitrobenzenesulfonic acid. The aqueous solution of lanthanide(III) complexes always had a close-to-neutral pH (pH ≈ 6), which further confirms the absence of free *p*-toluenesulfonic or nitrobenzenesulfonic acid in the isolated lanthanide(III) salts.

3.2.3. Crystal structures

Structural data on lanthanide(III) tosylates have been published in literature and these indicated a break from purely aqua-ligand nine-coordination to mixed aqua-anion eight-coordination across the series.[137] This striking difference compared to the isomorphous series of nonahydrate lanthanide(III) triflates can be explained in view of the fact that tosylate is a superior coordinating agent compared to triflate.[138] Single-crystal X-ray determination of lanthanide(III) tosylates, crystallized from water, revealed that the early lanthanide(III) tosylates [Ln = La, Ce, Nd] are monoclinic tridecahydrates belonging to space group C2/c with cell dimensions $a \approx 32$ Å, $b \approx 7.2$ Å, $c \approx 35$ Å, $\beta \approx 115°$ and $Z = 8$.[137] The cation is a tricapped trigonal prismatic nonaaqualanthanide(III) species, $[M(OH_2)_9]^{3+}$, with three tosylate counter ions and four lattice water molecules per asymmetric unit. The tosylate counterions are hydrogen bonded to the water molecules in the first coordination sphere of the lanthanide (Figure 3.1)

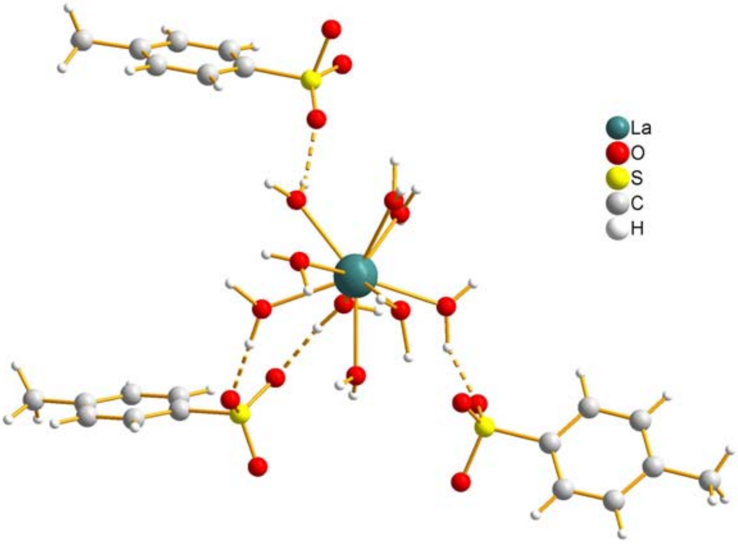


Figure 3.1 Molecular structure of La(TOS)$_3$[137]

On the other hand, in the lanthanide(III) tosylates from the end of the lanthanide series (Sm - Lu) and yttrium(III) tosylate, the first coordination sphere around the metal atom is occupied by two tosylate anions and six water molecules, while the third tosylate anion appears in the second coordination sphere.[139,140] These rare-earth tosylates [Ln = Sm, Eu, Gd, Tb, Dy, Ho, Er, Yb, Lu, Y] are monoclinic salts belonging to space group $P2_1/n$ with cell dimensions $a \approx 25$ Å, $b \approx 7.5$ Å, $c \approx 18$ Å, $\beta \approx 99°$ and $Z = 4$. The rare-earth atom of these complexes is octa-ligated in a square-antiprismatic geometry in which two monodentate sulfonate and six water oxygen atoms are ligated as depicted in Figure 3.2. The third sulfonate ion is not coordinated to the metal atom but bridged by hydrogen bondings to the coordinated water molecules.

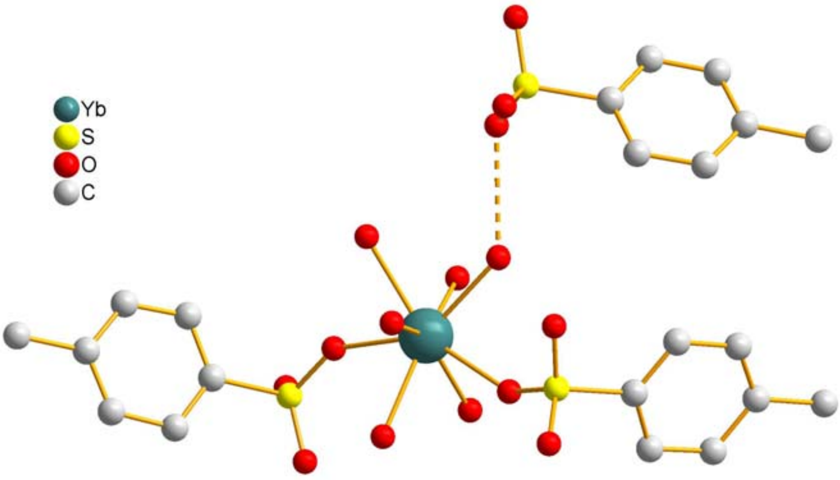


Figure 3.2 Molecular structure of Yb(TOS)$_3$ [139]

Similarly, scandium(III) tosylate is monoclinic with as space group $P2_1/a$ and $Z = 4$ (cell constants are $a = 23.67$ Å; $b = 15.79$ Å; $c = 7.75$ Å; $\beta = 92.86°$). The scandium atom is hexa-coordinated in an octahedral geometry, in which two monodentate sulfonate oxygen atoms and four water oxygen atoms are ligated.

Structural studies on copper(II) tosylate revealed that this complex crystallizes with six molecules of water in the first coordination sphere and the tosylate anions are hydrogen bonded to these water molecules (Figure 3.3).[141] Copper(II) tosylate is a monoclinic salt belonging to space group $P2_1/c$ and cell constants are: $a = 5.85$ Å, $b = 25.71$ Å, $c = 7.35$ Å, $\beta = 105.4°$, $Z = 2$. To the best of our knowledge, the crystal structure of iron(III) tosylate is not known, but studies on iron(II) tosylate indicate that three tosylate ions bind to iron(II) in a bidentate fashion. Comparison of infrared spectra of iron(II) tosylate and iron(III) tosylate, implied that iron(III) is also six-coordinated by three tosylate anions.[142]

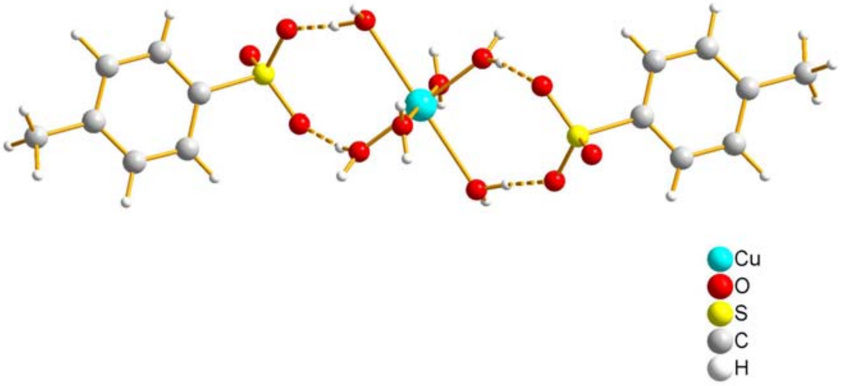


Figure 3.3 Molecular structure of Cu(TOS)$_2$ [141]

In the case of the rare-earth salts of nitrobenzenesulfonic acids only few crystal structures are reported. Tateyama reported the crystal structure of a linear polymeric scandium(III) complex of *m*-nitrobenzenesulfonic acid: $[Sc_2(OH)_2(O_2NC_6H_4SO_3)_4(H_2O)_2]_n$,[143] and more recently, the crystal structure of ytterbium(III) *m*-nitrobenzenesulfonate has been published by our group.[144] Analogous to $Yb(TOS)_3$, the coordination environment around the ytterbium(III) in $Yb(3\text{-}NBSA)_3•6H_2O$ is occupied by oxygen atoms of two 3-nitrobenzenesulfonate anions and six oxygen atoms from water molecules (Figure 3.4). The coordination polyhedron around ytterbium(III) can be described as a slightly distorted quadratic antiprism and the third 3-nitrobenzenesulfonate anion forms hydrogen bonds with two of the coordinated water molecules. Ytterbium(III) 3-nitrobenzenesulfonate is a monoclinic salt belonging to space group C2/c and the cell constants are: a = 56.55 Å, b = 7.624 Å, c = 14.158 Å, β = 93.28°, Z = 8.

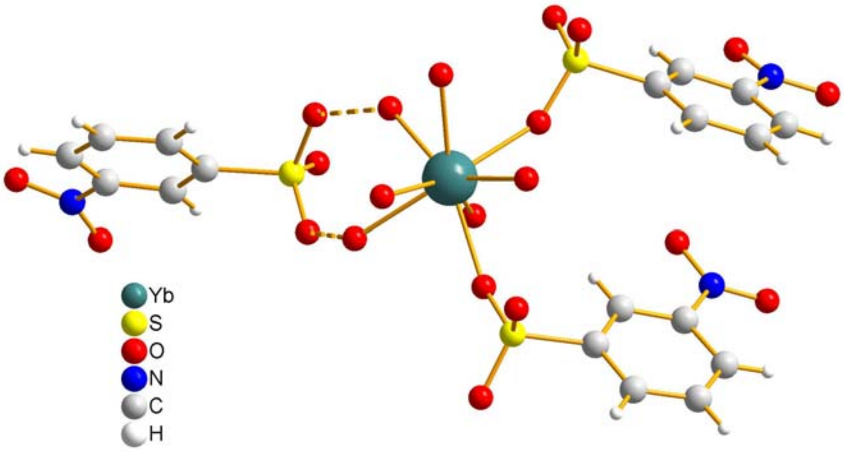


Figure 3.4 Molecular structure of $Yb(4\text{-}NBSA)_3•6H_2O$[144]

3.2.4. Discussion

Crystal structure determinations of lanthanide(III) tosylates and nitrobenzenesulfonates showed striking differences along the lanthanide series in the solid state. However, throughout this study lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed reactions were always performed in a solvent. Therefore it is of crucial importance to know whether these structural differences are preserved in the reaction solvent used in the study. In water for example, proton resonances of the ligands showed the same chemical shifts as in the fully dissociated acids, implying that there is no binding of the ligand to the lanthanide(III) ion and that the ligands become spectator ions. However, solution studies of $Ln(TOS)_3$ complexes have indicated that the solid-state structure is preserved in solutions of noncoordinating or weakly coordinating solvents.[133]

In conclusion, lanthanide(III) complexes of *p*-toluenesulfonic acid and various nitrobenzenesulfonic acids are easily prepared and the next sections report their application as new Lewis acid catalysts for various organic reactions: aromatic nitration, acylation of alcohols and the formation of calix[4]resorcinarenes.

3.3. Nitration of aromatic compounds

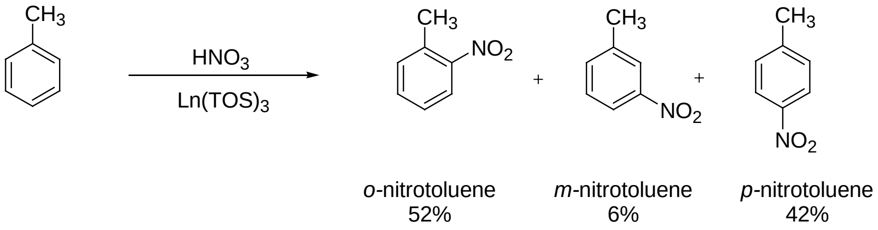
3.3.1. Introduction

Aromatic nitro compounds are widely utilized for the synthesis of a great variety of materials such as dyes, plastics and pharmaceuticals. Therefore, the nitration of aromatic compounds is one of the most important and extensively studied organic reactions.[145,146] The classical nitration procedure requires the use of a potent mixture of concentrated nitric and sulfuric acid, yielding large amounts of waste of inorganic acids, which are environmentally unfriendly and expensive to dispose. In addition, the synthetic procedure is not very selective and often leads to overnitration or to oxidized by-products. Several nitration procedures in ionic liquids have also been described.[147] Alternatively, the use of strong Lewis acids, such as boron trifluoride, in combination with nitric acid has been reported.[148] However, conventional Lewis acids are required in stoichiometric quantities and they are destroyed in the work-up procedure causing large amounts of strongly acidic by-products. The use of lanthanide reagents for the aromatic nitration has already been reported more than twenty years ago, but stoichiometric quantities of lanthanide(III) nitrates were used for the selective nitration of phenols.[149] On the other hand, Waller and coworkers reported the use of hafnium(IV), zirconium(IV), scandium(III), and lanthanide(III) triflates, $[Ln(OTf)_3]$, as efficient catalysts for the nitration of a range of simple aromatic compounds in 1,2-dichloroethane as the solvent.[150,151,152] The group of Waller claims that the extreme acidity of triflic acid is necessary to increase the polarizing power of the metal ion, which plays a crucial role in the formation of the de facto nitrating agent NO_2^+. The lanthanide(III) triflate catalyzed nitration requires only one equivalent of nitric acid and catalytic quantities of scandium(III) or lanthanide(III) triflates. Although these catalysts can readily be recycled and reused, the preparation of lanthanide(III) triflates requires the rather expensive triflic acid which makes the lanthanide(III) triflates high-priced catalysts. In addition, the strong acidity and corrosivity of the triflic acid used for the preparation of the triflates often poses problems in practical handling. An alternative method avoiding the use of chlorinated solvents is developed employing perfluorinated lanthanide salts $[Ln(OSO_2C_8F_{17})_3]$ as the catalyst, and various fluorous compounds as the solvents.[10] Although the procedure was devoid of chlorinated solvents and required very small catalyst loading (0.05 mol%) for achieving moderate to good yields (40–60%) of nitrated toluene, the method is still unlikely to be utilized on a large industrial scale as the fluorinated solvents are much more expensive than most of the conventional solvents, and in addition, their large global warming potential could pose serious environmental problems.[11,12]

So far, the complexes of lanthanides with aromatic sulfonic acids have not been explored as catalysts in organic reactions. The advantages of aromatic sulfonic acids over triflic acid, which include much cheaper costs and easier handling, prompted our research group to explore lanthanide complexes of various aromatic sulfonic acids. This study on the atom economic nitration of aromatic compounds only concerns the possible use of lanthanide(III) tosylates, $Ln(TOS)_3$. Reaction conditions for the lanthanide(III) tosylate-catalyzed nitration of toluene and naphthalene were optimized and the nitration of various other simple aromatic compounds was reported. In addition, different solvents were studied in order to avoid the use of chlorinated organic solvents. Simultaneously, Parac-Vogt and coworkers from our research group screened the use of lanthanide complexes of benzene sulfonic acid, $Ln(BSA)_3$, 2-naphthalenesulfonic acid, $Ln(NSA)_3$, and different nitrobenzenesulfonic acids, $Ln(NBSA)_3$, for the nitration of various aromatic compounds.[153,154,144]

3.3.2. General procedure for the lanthanide-catalyzed nitration of aromatic compounds

To a solution of toluene (240 µL, 3 mmol) in 5 mL of 1,2-dichloroethane was added a catalytic amount of lanthanide(III) tosylate (10 mol%, 0.3 mmol) and one equivalent of nitric acid (67%, d = 1.41 g/cm^3, 200 µL, 3.0 mmol). The mixture was stirred and heated at reflux temperature (84 °C). After a given period of time the solution was cooled and extracted with water. The yellow organic phase was dried with $MgSO_4$, evaporated and analyzed by ^{1}H NMR. Afterwards, the organic phase was diluted in acetone and GC-analysis was performed using the following temperature program: elution at 50 °C for 2 minutes, followed by ramping at 20 °C/min to 123 °C, at 1 °C/min to 126 °C, at 20 °C/min to 200 °C and maintaining this final temperature for 3 minutes. In the GC-analysis no peak could be observed for toluene because the peak corresponding to toluene could not be resolved from the acetone solvent peak. Hence, the reaction yield could not be determined from GC-analysis but was determined by ^{1}H NMR. The nitration reaction of toluene in the presence of 10 mol% of lanthanide(III) tosylate yielded three isomers: *o*-nitrotoluene, *m*-nitrotoluene and *p*-nitrotoluene (Scheme 3.3).



Scheme 3.3

As can be seen from Figure 3.5, only the amount of *o*-nitrotoluene could be determined from the ^{1}H NMR spectrum, because the methyl peaks of *m*-nitrotoluene and *p*-nitrotoluene coincide. Therefore, the isomer distribution of the nitrotoluene isomers was determined by GC-analysis. The ratio of *ortho:meta:para* nitrotoluene was in all reactions around 52:6:42, which is consistent with a direct electrophilic attack by the nitronium ion, NO_2^+.

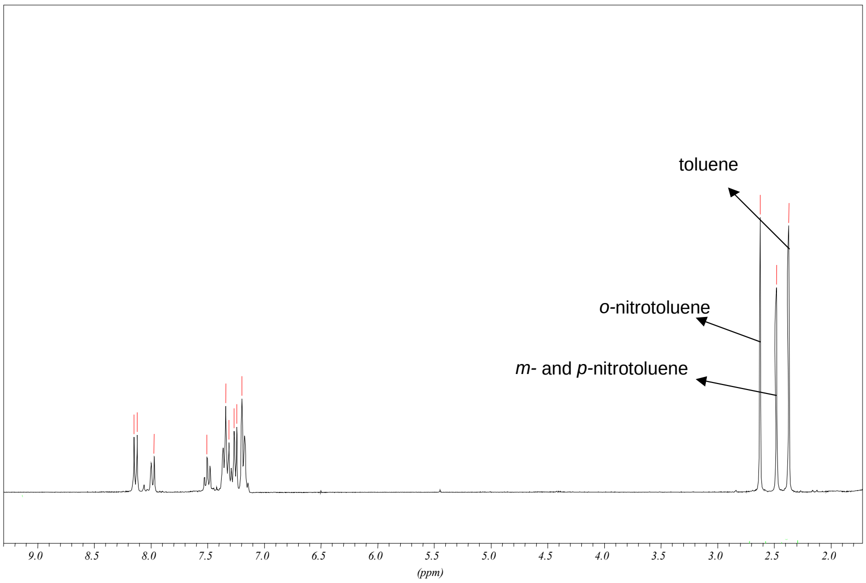
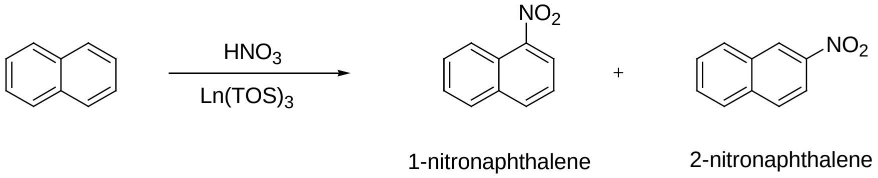


Figure 3.5 ^{1}H NMR spectrum of the nitration reaction of toluene

On the other hand, for the nitration reaction of naphthalene and other aromatic compounds with a rather high boiling point, GC-analysis resulted not only in the isomer distribution of the products but the reaction yield could also been easily calculated from the peak areas as explained in Chapter 2. The nitration of naphthalene always resulted in a mixture of 1-nitronaphthalene and 2-nitronaphthalene with a ratio of 1-nitronaphthalene to 2-nitronaphthalene of around 9 to 1 (Scheme 3.4). The 1-nitronaphthalene is preferably formed because the arenium ion formed by electrophilic attack at C-1 is relatively stable. The aromaticity of one ring is kept and the positive charge on the other ring is delocalized by allylic resonance. In the formation of 2-nitronaphthalene the aromaticity is broken by benzylic resonance to stabilize the arenium intermediate.[155]



Scheme 3.4

3.3.3. Effect of the reaction solvent

As the nitration of aromatic compounds is usually reported in halogenated solvents such as 1,2-dichloroethane, the possible use of lanthanide(III) tosylates was first explored in halogenated solvents and the obtained results were compared with the literature. Afterwards, lanthanide(III) tosylate catalyzed aromatic nitration reactions in non-halogenated solvents were explored.

While the nitration of aromatic compounds did not succeed in chloroform and dichloromethane, in 1,2-dichloroethane complete conversion of toluene was obtained after 19 hours in the presence of 10 mol% of $Yb(TOS)_3$. On the other hand, the blank reaction resulted only in 60 to 70% of conversion. Nonetheless, it is important to take in account that the reactions in different solvents were always performed at the reflux temperature of that solvent (84 °C for 1,2-dichloroethane, 61 °C for chloroform, and 40 °C for dichloromethane). Therefore, the fact that the reaction did not succeed in chloroform and dichloromethane can maybe also be due to the lower reaction temperature.

As the nitration reaction of naphthalene is the easiest one to study with GC-analysis, optimization of the reaction conditions was examined for this substrate. A mixture of HNO_3 and naphthalene was refluxed during 6 hours in 1,2-dichloroethane. In the presence of 10 mol% of $Yb(TOS)_3$, naphthalene was completely converted into nitronaphthalenes. Since naphthalene is a very reactive substrate, the reaction time and reaction temperature could be reduced. As can be seen in Table 3.1 the yield decreased only slightly with decreasing reaction temperature and at lower temperatures, the reaction became a bit more selective towards the formation of 1-nitronaphthalene.

Table 3.1 Screening of different reaction temperatures for the nitration of naphthalene.[a]

Temperature	Conversion (%)	Isomer distribution (%)	
		1-NO_2	2-NO_2
reflux (84°C)	>99	94	6
50°C	96	96	4
room temperature	74	97	3

[a] 10 mol% $Yb(TOS)_3$, 5 mL 1,2-dichloroethane, 6 hours

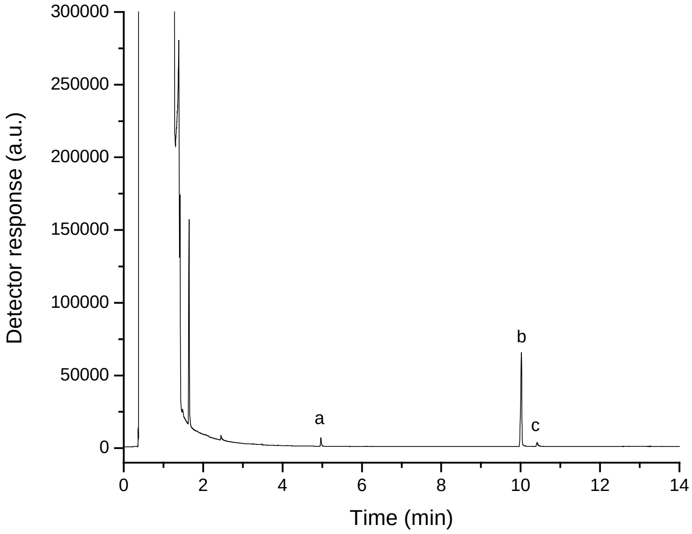
Besides the reaction temperature, the reaction time could be significantly decreased for the nitration reaction of naphthalene. After 1 hour of reaction at 60 °C in the presence of $Yb(TOS)_3$, 87% of nitronaphthalenes was formed (96% 1-NO_2; 4% 2-NO_2). However, under these reaction conditions the blank reaction also resulted in 84% conversion (96% 1-NO_2; 4% 2-NO_2). This implies that the reaction of naphthalene proceeds very well in 1,2-dichloroethane and does not require a catalyst under these reaction conditions.

As mentioned earlier, the use of chlorinated solvents, and especially 1,2-dichloroethane, should be avoided and hence the nitration of aromatic compounds was also studied in less harmful solvents. The reaction of naphthalene with HNO_3 in ethanol did not proceed after 18 hours of reflux, both in the absence and presence of the catalyst $Yb(TOS)_3$. On the other hand, when this $Yb(TOS)_3$-catalyzed reaction was performed in heptane, complete conversion of naphthalene was obtained (94% 1-NO_2; 6% 2-NO_2). The following experiments were all done in heptane at reflux temperature (98 °C).

3.3.4. Effect of the reaction time and the reaction temperature

The $Yb(TOS)_3$-catalyzed nitration of naphthalene does not require long reaction times in heptane. After 1 hour of reaction in the presence of 10 mol% of $Yb(TOS)_3$, 96% conversion was obtained (94% 1-NO_2; 6% 2-NO_2). As the blank reaction only results in 55% of conversion under these conditions (92% 1-NO_2; 8% 2-NO_2), ytterbium(III) tosylate has an important effect on the reaction yield (see Figure 3.6).

On the other hand, the nitration of toluene proceeded much slower. In heptane, the reaction of toluene with nitric acid lead to complete conversion after 18 hours refluxing in the presence of 10 mol% of $Yb(TOS)_3$. At 60°C this reaction resulted in 57% of nitrotoluene in the presence of catalyst, while only 24% was obtained for the blank reaction.



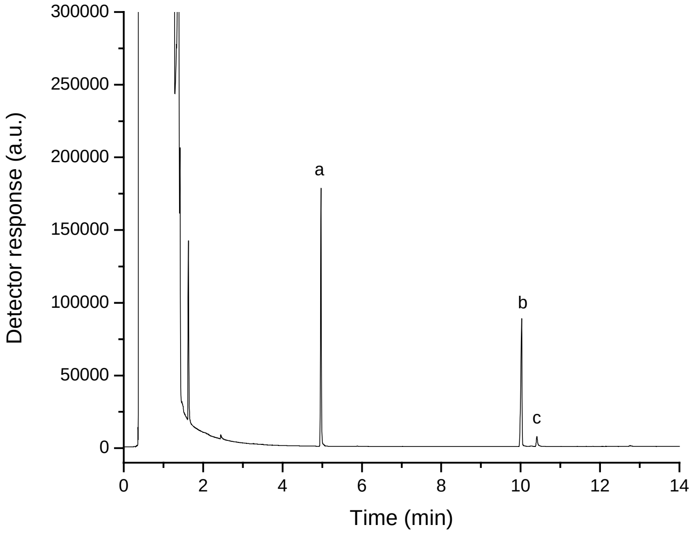


Figure 3.6 Chromatogram recorded after 1 hour of reaction of naphthalene with nitric acid in heptane. Top: in the presence of 10 mol% of Yb(TOS)$_3$ nearly all naphthalene (a) was converted into 1-nitronaphthalene (b) and 2-nitronaphthalene (c); Below: in the absence of a catalyst, significant amounts of naphthalene were unreacted.

3.3.5. Effect of the amount of catalyst

As can be seen from Figure 3.7, only moderate improvements are obtained in the nitration of naphthalene and toluene in heptane when increasing the catalyst loading from 1 mol% to 10 mol%, but rather low conversion was obtained when using less than 1 mol%. The catalyst loading has no significant effect on the isomer distribution of the obtained nitronaphthalenes (each time around 93% 1-NO_2 and 7% 2-NO_2) and nitrotoluenes (52% *ortho,* 6% *meta,* 42% *para*). In addition, the result obtained with 10 mol% of $Yb(TOS)_3$ showed that the conversion of naphthalene is much lower after 30 minutes compared to complete conversion after 1 hour under the same reaction conditions.

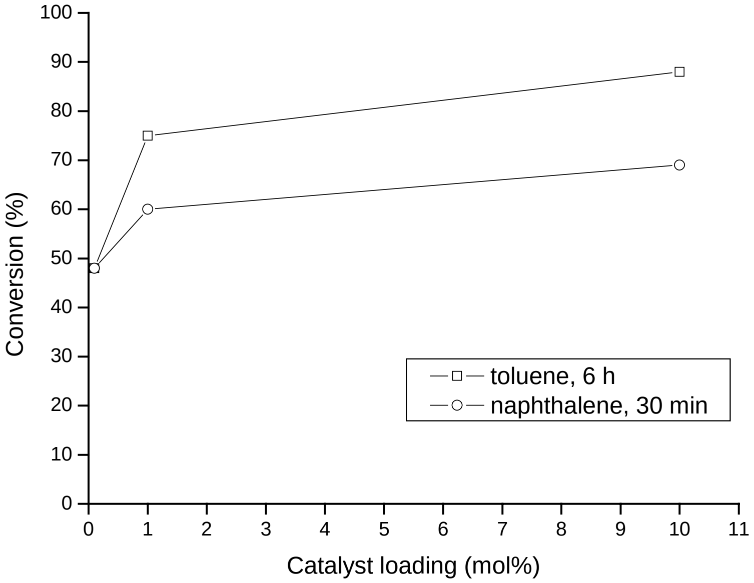


Figure 3.7 Effect of the amount of $Yb(TOS)_3$ on the nitration of toluene and naphthalene in refluxing heptane. Reactions with toluene were analyzed after 6 hours whereas the reactions with naphthalene were analyzed after 30 minutes.

3.3.6. Recovery and reuse of lanthanide(III) tosylates

In order to develop a real catalytic system the possibility to recover and reuse lanthanide(III) tosylates was studied. Figure 3.8 shows the work-up procedure of the reaction mixture for recovery of lanthanide(III) tosylates. An extraction with water separates the products (in the heptane phase) from the catalyst (in the aqueous phase). Afterwards, Ln(TOS)_3, was recoverd by evaporating the water from the aqueous phase. NMR-analysis of the recovered La(TOS)_3 indicated that the catalyst did not change during the reaction. ^{1}H NMR (300 MHz, CDCl_3, δ ppm): 2.21 (s, 3H, CH_3); 7.18 (d, 2H, H_{aryl}); 7.52 (d, 2H, H_{aryl}).

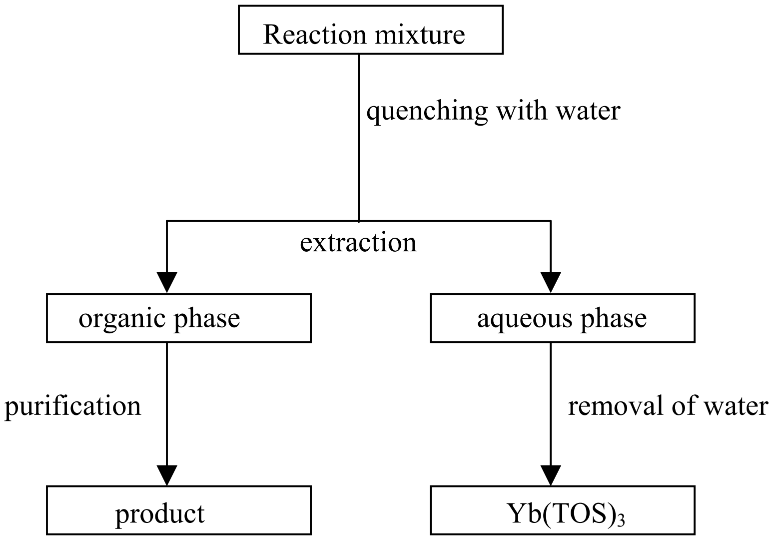


Figure 3.8 Work-up procedure of the reaction mixture for recovery of lanthanide(III) tosylates.

3.3.7. Nitration of various aromatic compounds

The nitration of various aromatic compounds was performed in heptane in the presence of 10 mol% of Yb(TOS)$_3$ and the results after 18 hours of reflux are summarized in Table 3.2. Good conversions were obtained for aromatic compounds with alkyl or aryl substituents which are electron-rich compounds, whereas the nitration of aromatic compounds with electron-withdrawing groups was not very effective.

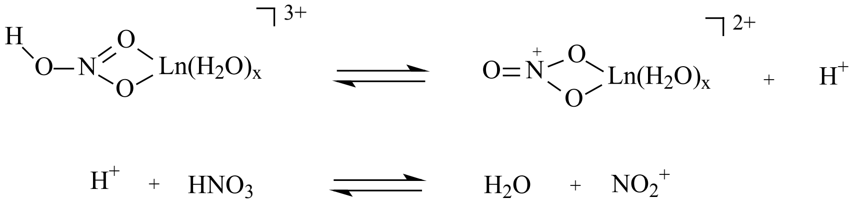
Table 3.2 Nitration of various aromatic compounds.[a]

Arene	Conversion (%)	Isomer distribution (%)		
Ph-CH_3	>99	ortho: 56	meta: 5	para: 39
Ph-Ph	50[b]	-	-	-
Ph-Br	9[c]	-	-	-
Ph-NO_2	0	-	-	-
m-xylene	68[c]	4-NO_2: -		2-NO_2: -
naphthalene	>99	1-NO_2: 94		2-NO_2: 6

[a] 5 mL of heptane, 18 hours, 10 mol% Yb(TOS)$_3$; [b] isolated yield, isomer distribution was not determined; [c] conversions were calculated from GC-measurements without correction with response factors, isomer distribution was not determined.

3.3.8. Mechanism

The nitration of toluene always resulted in the same isomer distribution regardless of the reaction time and the catalyst used. The ratio of *ortho:meta:para* nitrotoluene was in all reactions around 52:6:42, which is consistent with a direct electrophilic attack by the nitronium ion, NO_2^+. The nitronium ion was also indicated as de facto nitrating agent in Ln(OTf)$_3$ catalyzed nitration of aromatic compounds.[151] The postulated mechanism (Scheme 3.5) involves binding of nitric acid to the lanthanide via displacement of water ligands upon which the strong polarization due to the metal results in proton liberation. Reaction of the proton with another molecule of nitric acid liberates NO_2^+ in the classical manner. Waller and coworkers reported that the role of the lanthanide(III) ion in fact can be seen as the accentuation of the Brønsted acidity of nitric acid via a Lewis acid-Lewis base interaction between the tripositive lanthanide cation and nitrate anion and hence the term *Lewis-assisted Brønsted acidity* is used to describe this phenomenon. The observed increase in reactivity of the lanthanide(III) triflates along the lanthanide series can be explained in view of this mechanism. Because the smaller lanthanides are more polarizing than the larger lanthanide ions they will bind nitrate more strongly and hence liberation of protons necessary to produce the nitronium ion is facilitated. Waller also suggested that the triflate counterion is crucial for the catalytic activity since it is the conjugate base of an extremely strong acid allowing that nitric acid is preferentially protonated which can lead to production of nitronium ion. However, our results have shown that the conjugate bases of aromatic sulfonic acids, which are about 10^6 times much weaker acid than the triflic acid, can also fulfil the role played by the triflate counterions.



Scheme 3.5

It is likely that a similar mechanism applies for the nitration catalyzed by the lanthanide(III) compounds investigated in our research group (tosylates and nitrobenzenesulfonates) since they differ from $Ln(OTf)_3$ only in the nature of the counterion. Indeed, under various reaction conditions an increase in reactivity was observed along the lanthanide series in the nitration of naphthalene and toluene with lanthanide(III) tosylates (Table 3.3). Surprisingly, when lanthanide(III) nitrobenzenesulfonates were used for the nitration of aromatic compounds, an opposite trend along the lanthanide series was observed.[144] It has been demonstrated that in weakly coordinating solvents lanthanide(III) nitrobenzenesulfonates at the end of the lanthanide series retain their two anion ligands in the first coordination sphere which induces sterical hindrance for the coordination of the nitric acid, while lanthanide(III) nitrobenzenesulfonates at the beginning of the lanthanide series possess no sterical hindrance as they only contain water molecules in their first coordination sphere.

Table 3.3 Comparison of $La(TOS)_3$ and $Yb(TOS)_3$ for the nitration of naphthalene and toluene under various reaction conditions.[a]

substrate	time (h)	solvent	Conversion (%)	
			La	Yb
naphthalene	0.5	heptane	42	69
naphthalene	0.5	1,2-dichloroethane	21	53
toluene	1	1,2-dichloroethane	28	64

[a] 5 mL of solvent, reflux temperature, 10 mol% of $Ln(TOS)_3$

From these results we can conclude that the solid state structures of the lanthanide(III) tosylates at the end of the series are not preserved under these reaction conditions. If the two tosylate anions would be present in the first coordination sphere, the resulting sterical hindrance in $Yb(TOS)_3$ would lead to lower reactivity than in the case of $La(TOS)_3$.

3.3.9. Discussion

This study shows that lanthanide(III) tosylates are efficient catalysts for the nitration of various aromatic compounds. However, similarly to the procedure with lanthanide(III) triflates, very electron poor aromatics such as nitrotoluene can not be nitrated by the use of lanthanide(III) tosylates. Anyway, in 1,2-dichloroethane the results obtained with lanthanide(III) tosylates are as good as the ones reported for lanthanide(III) triflates,[150] although aromatic sulfonic acids are about 10^6 times weaker acids than triflic acid. Hence, the extreme acidity and corrosivity of triflic acid, required for the preparation of lanthanide(III) triflates, can be avoided by the use of lanthanide(III) tosylates as alternative catalysts. In addition, nitration of various aromatic compounds was also successful if heptane is used as the reaction solvent. This is important since nitroaromatic compounds are also used in manufacturing of pharmaceuticals. According to the classification of residual solvents by the U.S. Food and Drug Administration (see chapter 1), 1,2-dichloroethane belongs to the class 1 solvents, which are to be avoided in the synthesis of pharmaceuticals. On the other hand, heptane belongs to the class 3 solvents, which are less toxic solvents with lower risks to human health. Furthermore, there is also a demand to replace chlorinated solvents from an environmental point of view. Moreover, the yields obtained in heptane are at least as good as the ones obtained with perfluorinated lanthanide salts in fluorous solvents,[10] with the additional advantage of a less hazardous and environmentally more benign solvent. Furthermore, lanthanide(III) tosylates are only required in small amounts, and they are recycled and reused without loss in efficiency and selectivity. Nonetheless, the evaporation of water to recover the catalyst is a rather energy consuming process. In conclusion, the use of lanthanide(III) tosylates for the atom economic nitration of aromatic compounds, with water as the only side-product, is an important contribution towards green chemistry.

3.4. Acylation of alcohols

3.4.1. Introduction

The acetylation (or in general the acylation) of hydroxyl groups is one of the most frequently used procedures in organic chemistry.[156] Acetylation of alcohols is frequently performed with acid anhydride,[157] or acetyl chloride,[158] in the presence of a basic catalyst such as triethylamine, pyridine, 4-dialkylaminopyridines,[159,160,161] 4-pyrrolidinopyridine, or *N,N,N',N'*-tetramethylethylenediamine.[162] Alternatively, various Lewis acid catalysts including zinc chloride,[163] magnesium bromide,[164,165] indium(III) chloride,[166] tantalum(V) chloride,[167] titanium(IV) chloride tris(trifluoromethanesulfonate),[168] diorganotin dichloride,[169] could be applied. An alternative approach is the use of ionic liquids as medium for Lewis acid-catalyzed acetylation.[170,171,172]

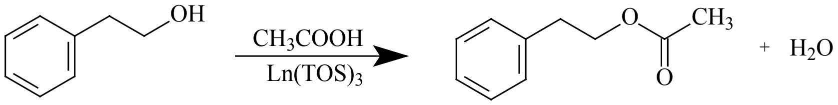
In recent years, various trifluoromethanesulfonate salts, so-called triflates, such as scandium(III) triflate,[173,174,175] lanthanum(III) triflate,[173] cerium(III) triflate,[176] erbium(III) triflate,[177] ytterbium(III) triflate,[173] copper(II) triflate,[178,179] indium(III) triflate,[180] bismuth(III) triflate,[181,182,183] have been described as efficient catalysts for the acetylation of various alcohols in the presence of acetic acid, acetic anhydride, or acetyl chloride. An important property of triflate catalysts is their compatibility with water and other protic solvents. After work-up, the catalysts can be recycled and reused without significant loss of activity. Since our studies on the nitration of aromatic compounds revealed that lanthanide(III) tosylates were as efficient as their triflate analogues, we exploited the advantages of lanthanide(III) tosylates, which include much cheaper costs and easier handling, to further explore lanthanide(III) tosylates as catalysts for other types of organic reactions as for example the esterification of alcohols. In addition, most of the mentioned procedures in literature use an anhydride or acetyl chloride as the acylating agent but from an economical point of view it is advantageous to use a carboxylic acid as the acylating agent. First of all, both the acid anhydride and the acyl chloride are prepared from the corresponding carboxylic acid, and consequently they are significantly more expensive than the corresponding carboxylic acid. In addition, the use of anhydrides is inherently wasteful since half of every acid anhydride molecule is lost as a carboxylic acid and the use of acyl chlorides releases hydrogen chloride. Therefore we decided to study the lanthanide(III) tosylate catalyzed reaction of various alcohols with carboxylic acids. The acid-catalyzed reaction of an alcohol and a carboxylic acid to form an ester is also known as the Fischer-esterification.

3.4.2. General procedure for the lanthanide-catalyzed acylation of alcohols

To a solution of the respective lanthanide(III) catalyst (5 mol%, 0.05 mmol) in glacial acetic acid (2 mL) was added the alcohol (1 mmol). The mixture was stirred and heated at reflux (118 °C). After a given period of time the solution was cooled and diluted with water and dichloromethane. The organic phase was dried with $MgSO_4$, the solvent was evaporated and the residue was analysed by ^1H NMR or gas chromatography. Samples for GC-analysis were diluted with acetone and the following temperature program was used: elution at 50 °C for 2 minutes, followed by ramping at 20 °C/min to 200 °C and maintaining this final temperature for 3 minutes.

3.4.3. Screening of various lanthanide(III) tosylates

In order to optimize the rate of the acylation reaction, a range of lanthanide(III) tosylates were examined as potential catalysts. The reaction we chose for the initial screening of the catalytic activity of the lanthanide(III) tosylates was acetylation of phenethyl alcohol (2-phenylethanol) using acetic acid as the solvent (Scheme 3.6). The use of acetic acid rather than acetyl chloride or acetic anhydride is both economically and environmentally beneficial. Moreover, in the esterification of an alcohol with a carboxylic acid the only side-product formed is water.



Scheme 3.6

As can be seen from Figure 3.9, all complexes exhibited catalytic activity, but noticeable differences in reactivity were observed. While lanthanum(III) tosylate gave only 26% conversion of phenethyl alcohol to phenethyl acetate after 18 hours of reaction at 50 °C, ytterbium(III) tosylate and erbium(III) tosylate yielded quantitative conversion under the same conditions. Apart from some scattered data points, there is a clear inverse correlation between the ionic radii of the lanthanide(III) ion and the yield of acetylation reaction. Previous studies involving reactions catalyzed by lanthanide(III) triflates have revealed a similar trend.[70] The smaller ionic radius of trivalent lanthanide ion leads to the greater charge-to-size ratio, Z/r, which in turn results in greater polarizing power of the lanthanide(III) center.

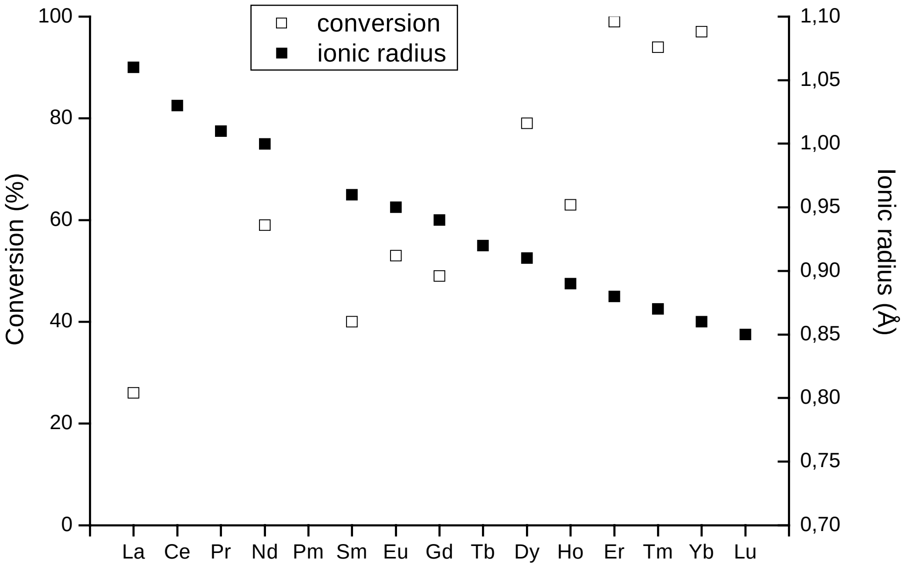


Figure 3.9 Effect of the lanthanide(III) ion in the tosylate salt on the catalyzed conversion of phenethyl alcohol to phenethyl acetate in the presence of acetic acid. The ionic radii of the lanthanide(III) ions are shown for the sake of comparison.

3.4.4. Influence of reaction time, temperature and catalyst loading on the extent of acetylation

In order to further optimize the catalytic reaction, we first examined effects of temperature and the reaction time on the acetylation reaction. Since the screening of the series of lanthanide(III) catalysts revealed that ytterbium(III) tosylate was the most effective, all further acetylation experiments were performed with this catalyst. As can be seen from Table 3.4, acetylation of phenethyl alcohol was rather slow at room temperature, most likely due to the low solubility of the catalysts in acetic acid solution. Upon increasing the temperature to 50 °C, nearly quantitative conversion was achieved within 18 hours. The fastest reaction was obtained under reflux conditions, in which case acetylation was essentially complete in the time taken to bring the reaction mixture to reflux.

Table 3.4 Effects of temperature and reaction time on the acetylation of phenethyl alcohol with acetic acid in the presence of ytterbium(III) tosylate.[a]

$Yb(TOS)_3$ (mol%)	time (h)	temperature (°C)	conversion (%)
5	24	room temp.	35
0	24	room temp.	3
5	18	50	97
0	18	50	23
5	1	80	64
0	1	80	5
5	0.5	reflux	>98
0	0.5	reflux	39

[a] 1 mmol of phenethyl alcohol in 2 mL of acetic acid.

The acetylation reaction in the presence and in the absence of the catalyst was followed as a function of the time, and the results shown in Figure 3.10 are consistent with the pseudo-first order kinetics (rate constant of 3.0×10^{-3} min^{-1}), in which one of the reactants (acetic acid) is present in large excess. Fitting of the data revealed that the catalyzed reaction was at least an order of magnitude faster than the reaction run in the absence of the catalyst. In addition, different amounts of catalyst were tested in order to know the optimal catalyst amount required. As can be seen from Figure 3.11, complete acetylation of phenethyl alcohol is already obtained after 30 minutes of reflux with 2 mol% of ytterbium(III) tosylate. Furthermore, a catalyst loading of as less as 0.1 mol% resulted already in 73% of conversion.

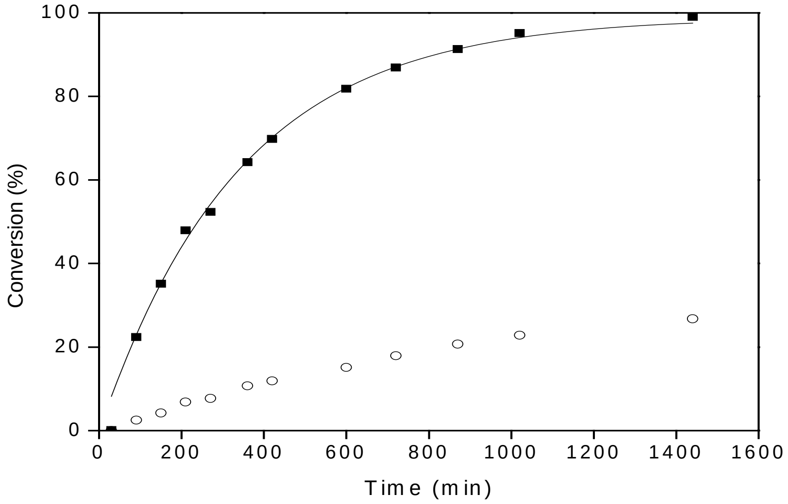


Figure 3.10 Conversion of phenethyl alcohol to phenethyl acetate in the presence of 5 mol% of Yb(TOS)$_3$ (black squares) and in the absence of the catalyst (open circles).

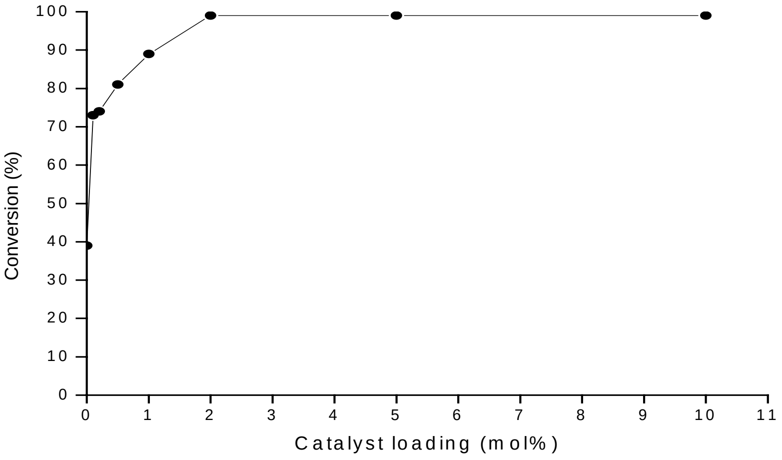


Figure 3.11 Effect of the ytterbium(III) tosylate loading on the acetylation of phenethyl alcohol with acetic acid (30 minutes of refluxing).

3.4.5. Recovery and reuse of the Yb(TOS)$_3$ catalyst

Upon quenching the reaction by addition of dichloromethane and water, the catalysts could be easily recovered from the aqueous phase by evaporating the solvent under reduced pressure. The FT-IR spectra of the recycled catalysts were identical to the spectra of freshly prepared Yb(TOS)$_3$. In addition, in the experiments performed with diamagnetic La(TOS)$_3$, the ^{1}H NMR spectrum of the recovered catalyst was identical to the spectrum of the freshly prepared La(TOS)$_3$. The recovered catalysts were shown to be active for further acetylation reaction with no apparent change in selectivity or in efficiency (Table 3.5). Because the catalyst was shown to be effective for acetylation at a loading of only 2 mol%, it is not surprising that even after some loss of the catalyst during recycling, the reaction goes to completion.

Table 3.5 Recovery and reuse of ytterbium(III) tosylate for the acetylation of phenethyl alcohol[a]

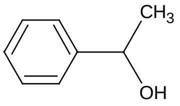
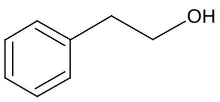
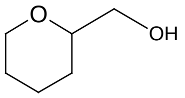
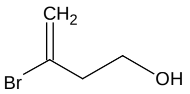
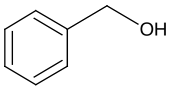
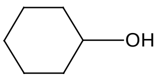
Run	Conversion (%)	Recovery of catalyst (%)
1	>98	91
2	>98	84
3	>98	71

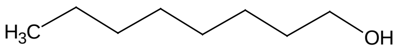
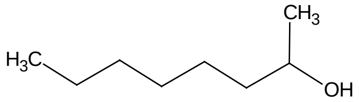
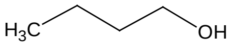
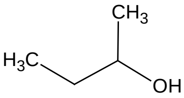
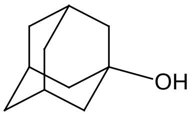
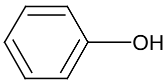
[a] 1 mmol of phenethyl alcohol in 2 mL of acetic acid, refluxing for 30 minutes, with 5 mol% of Yb(TOS)$_3$ in the first run.

3.4.6. Acetylation of various alcohols

The applicability of the acetylation reaction catalyzed by Yb(TOS)$_3$ was tested for different alcohols as the substrate. All acetylation reactions were performed with acetic acid acting as a substrate and as a solvent. The reactions of an alcohol with acetic acid where performed at reflux temperature, in the presence of 5 mol% of the catalyst. As can be seen from Table 2, the acetylation of primary alcohols proceeded quantitatively after 30 minutes. As expected, the acetylation of secondary and tertiary alcohols was slower, and required longer reaction times for completion. It is also noteworthy mentioning that no elimination products were observed.

Table 3.6 Acetylation of various alcohols with acetic acid.[a]

Alcohol	$Yb(TOS)_3$ (mol%)	Conversion (%)
	5	>98
	0	26
	5	>98
	0	39
	5	>98
	0	35
	5	>98
	0	28
	5	94
	0	42
	5	51
	0	14

	5 0	>98 33
	5 0	62 12
	5 0	95 37
	5 0	74[b] 29[b]
	5 0	76[c] 4[c]
	5 0	43[c] 2[c]

[a] 1 mmol of alcohol in 2 mL of acetic acid, refluxing for 30 minutes; [b] refluxing for 1h; [c] refluxing for 18h.

3.4.7. Acylation with various carboxylic acids

Besides acetylation in acetic acid solutions, acylation of phenethyl alcohol in other carboxylic acid solutions as for example propionic acid and cyclohexane carboxylic acid was also efficiently catalyzed by $Yb(TOS)_3$. Acylation with propionic acid and cyclohexane carboxylic acid was somewhat slower and was completed within one or two hours (Table 3.7).

Table 3.7 Acylation of phenethyl alcohol with various carboxylic acids.[a]

Acid	$Yb(TOS)_3$ (mol%)	Conversion (%)	
		50 °C, 18 h	120 °C, 30 min
Acetic acid	5	>98	>98
	0	23	39
Propionic acid	5	67	86
	0	11	20
Cyclohexane carboxylic acid	5	49	59
	0	9	12

[a] 1 mmol of phenethyl alcohol in 2 mL of acid;

3.4.8. Postulated mechanism for the $Yb(TOS)_3$ catalyzed acylation

As mentioned earlier the crystal structures of the lanthanide(III) tosylates indicate a break from purely aqua-ligand nine-coordination to mixed aqua-anion eight-coordination across the series.[137] In strongly coordinating solvents, such as water, the structures of all lanthanide(III) tosylates are the same since the coordinating solvent replaces the tosylate ligands from the inner coordination sphere. In order to have an idea of the structures of $Ln(TOS)_3$ complexes in acetic acid solutions we recorded a proton NMR spectrum of $Eu(TOS)_3$ in deuterated acetic acid solution. The X-ray single crystal structures of $Eu(TOS)_3$ shows that this complex is isostructural to $Yb(TOS)_3$ so that the coordination environment around the europium(III) is occupied by two oxygen atoms from the sulfonate group of TOS and six oxygen atoms from water molecules.[140] If this structure is preserved in solution, the two sulfonate ligands which are bound to europium(III) will exhibit a large paramagnetic shift, while the third ligand will appear at the same chemical shifts as the fully dissociated sulfonic acid. However, in acetic acid solution, only one set of proton resonances appeared in the region between 6.8 and 7.2 ppm, which is typical for the fully dissociated *p*-toluenesulfonic acid (Figure 4). The ^{1}H NMR spectrum was taken in the large proton resonance range (from –30 to +30 ppm), and the presence of paramagnetically shifted protons was not detected. This indicates that in acetic acid solution the tosylate ligands are removed to the second coordination sphere, and that the first coordination sphere around europium(III) is occupied by acetic acid ligands. It is reasonable to assume that other $Ln(TOS)_3$ complexes also undergo this ligand substitution upon being dissolved in acetic acid.

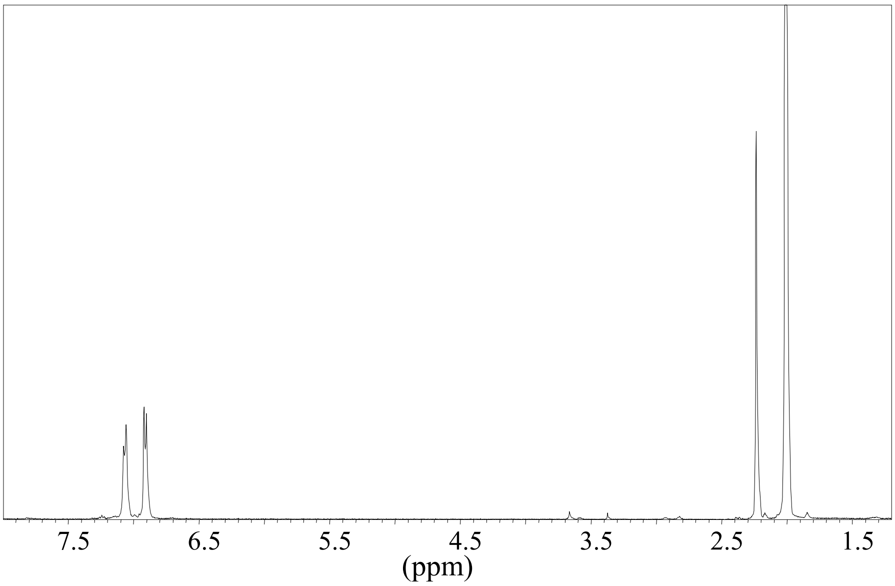
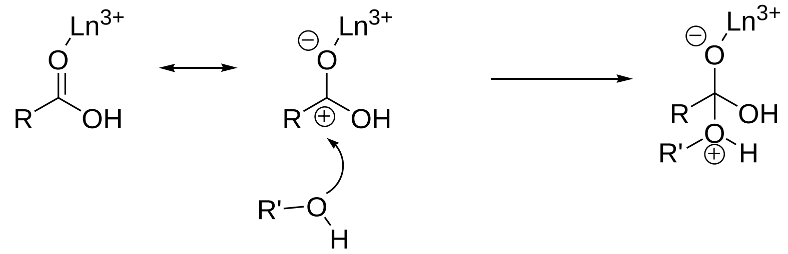


Figure 3.12 Proton NMR spectrum of $Eu(TOS)_3$ in acetic acid-d_3 solution at 80 °C. The large peak at 2.08 ppm belongs to the acetic acid-d_3 solvent.

Since the acylation experiments have shown that there is a correlation between the charge-to-size ratio, (Z/r) and the catalytic activity, there is obviously an interplay between the lanthanide(III) ion and acetic acid where an increasing electrostatic interaction leads to greater reactivity.

The mechanism can be postulated as depicted in Scheme 3.7. Upon displacement of TOS and water molecules from the inner coordination sphere by acetic acid, the resulting strong polarization due to the lanthanide(III) ion results in polarisation of the carbonyl group. This polarization increases the electrophilicity of the carbonyl carbon, making it more susceptible for the nucleophilic attack by the oxygen atom of the alcohol. By this way an oxonium ion is formed which further reacts in classical manner to produce an ester. Thus the experimentally observed correlation between the increasing charge-to-size ratios and the extent of esterification can be rationalized by noting that the nucleophilic attack of the alcohol becomes more facile as the metal becomes more polarizing.



Scheme 3.7

3.4.9. Discussion

Lanthanide(III) complexes of *p*-toluenesulfonic acid, Ln(TOS)$_3$, were prepared, characterized and examined as catalysts for the acetylation of various alcohols in acetic acid solution. Examination of a series of Ln(TOS)$_3$ catalysts in the acetylation of phenethyl alcohol revealed that there is a clear correlation between the ionic radius of the lanthanide(III) ion and the yield of reaction, with the heavier lanthanides being more effective. In the presence of 5 mol% of Yb(TOS)$_3$, quantitative conversion of phenethyl alcohol to phenethyl acetate was achieved within 18 hours at 50 °C. Faster reaction was obtained under reflux conditions, in which case acetylation was complete within 30 minutes and in the presence of only 2 mol% of the Yb(TOS)$_3$ catalyst. The Yb(TOS)$_3$ catalyst was effective for acetylation of a range of primary, secondary and tertiary alcohols. The acetylation of secondary and tertiary alcohols required longer reaction times for completion, but proceeded without formation of elimination adducts. The Yb(TOS)$_3$ catalyst was also effective for acylation of phenethyl alcohol with propionic acid and cyclohexane carboxylic acid. The catalysts could be recovered and reused for further acetylation with no apparent change in selectivity or efficiency. Despite the fact that the acidity of *p*-toluenesulfonic acid is about 10^6 times weaker than that of triflic acid, its complexes with lanthanide(III) ions are strong Lewis acids which are able to catalyze the acylation of alcohols with comparable efficiency. Moreover, from an economical and environmental point of view the use of carboxylic acid as the acylation agent is prefered compared to the majority of procedures found in literature which use an acid anhydride or acyl chloride.

More recently, after publication of our results on the lanthanide(III) tosylate catalyzed acylation of alcohols, other interesting procedures have also been reported for acylation reactions. Erbium(III) chloride for example was used in the acylation of various alcohols with acid anhydrides.[76] The reactions could be performed in the presence of 5 mol% of anhydrous ErCl$_3$ and the catalyst could be recycled and reused without significant loss of activity. However, reaction was significantly faster when the catalyst is dried prior to use and hence the absence of water seems to be essential in this procedure. Cobalt(II) chloride hexahydrate has also been reported as catalyst for the acetylation of alcohols with acetic acid.[184] Reactions have been performed in the presence of 5 mol% of CoCl$_2$·6H$_2$O and recovery and reuse of the catalyst was demonstrated. Copper(II) sulfate pentahydrate has also been used in catalytic amounts for the acetylation of various alcohols with acetic anhydride. In addition, acylation of alcohols with acetic anhydride and acetic acid has been reported with catalytic amounts of perchlorate salts of various transition metals.[185,186] However, perchlorate salts are not recommended for safety reasons as they can cause explosive reactions with organic compounds. These recent research results prompted us to reinvestigate our model system, namely the acetylation of phenethyl alcohol with acetic acid, in the presence of various lanthanide salts. The use of catalytic amounts of lanthanide(III) chlorides [Ln = Ce, Dy, Er] has already been reported for the selective monoacylation of symmetric 1,2-diols with acetic acid anhydrides,[187] and a range of transition metal chlorides has been tested for the acylation of 2-methoxynaphthalene with acyl chlorides.[188] Moreover, the acetylation of various alcohols with acetic acid was performed efficiently with 5 mol% of anhydrous iron(III) chloride.[189] As it is known that the lanthanides, and especially the ones at the end of the lanthanide series, are stronger Lewis acids than most transition metals one can expect improved results when using lanthanide(III) salts. Furthermore, it is interesting to examine the effect of the counterion on the extent of acetylation. And finally, it is also worth to investigate the recovery and reuse of various lanthanide(III) salts.

3.4.10. Use of other Lewis acid catalysts

Because our research group has already explored lanthanide(III) salts of other aromatic sulfonic acids, the acetylation of phenethyl alcohol in the presence of ytterbium(III) nosylate was investigated. As can be deduced from Table 3.8, ytterbium(III) tosylate turned out to be a superior catalyst compared to ytterbium(III) nosylate, under various reaction conditions.

Table 3.8 Comparison of the effect of ytterbium(III) 4-nitrobenzenesulfonate and ytterbium(III) tosylate on the acetylation of phenethyl alcohol.[a]

catalyst	conversion (%)	
	24 hours, rt	30 min, reflux
none	3	39
Yb(TOS)$_3$	35	>98
Yb(4-NBSA)$_3$	25	96

[a] 1 mmol phenethyl alcohol in 2 mL of acetic acid, 5 mol% of catalyst.

Besides lanthanide salts of aromatic sulfonic acids, simple lanthanide trichloride hydrates and salts of some transition metals were also tested in this reaction and these results are summarized in Figure 3.13. When reactions were performed for 18 hours at 50 °C, the variation in catalytic activity within the lanthanide series is smaller in the case of lanthanide(III) chlorides compared to lanthanide(III) tosylates. Under these reaction conditions, Yb(TOS)$_3$ is a superior catalyst compared to YbCl$_3$ whereas LaCl$_3$ is a better catalyst than La(TOS)$_3$. In addition, high conversion was obtained using iron(III) salts, which can probably be explained by the high Lewis acidity of trivalent iron due to a high charge-to-size ratio. Although iron(III) chloride is also a good oxidizing agent,[190] no oxidation products were observed under our reaction conditions. Furthermore, the reaction solution is acidic enough to prevent hydrolysis of iron(III) chloride under these reaction conditions.

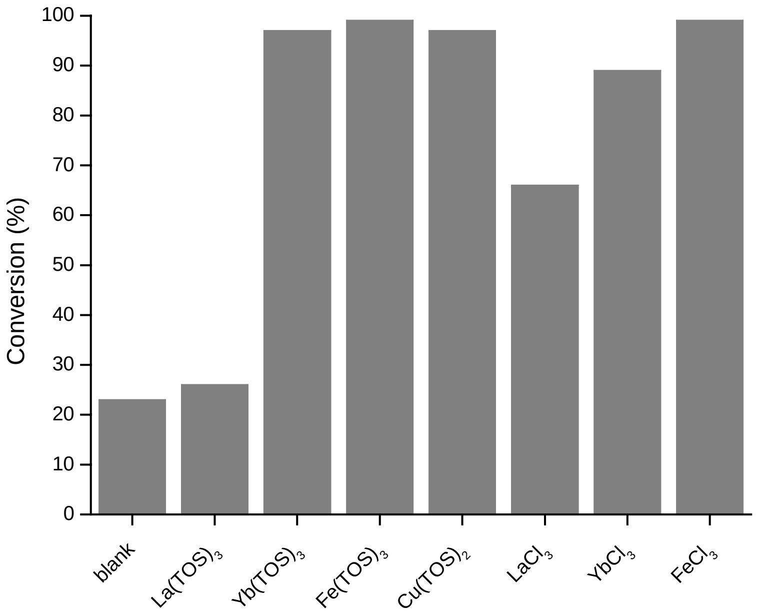


Figure 3.13 Comparison of Lewis acid catalysts on the acetylation of phenethyl alcohol in acetic acid. Reactions were performed for 18 hours at 50 °C and all catalysts were used in their hydrated form.

Evidently the reaction time could strongly be decreased when increasing the reaction temperature and similar experiments were performed for 30 minutes at reflux temperature (Figure 3.14). From Figure 3.14 can be seen that Yb(TOS)$_3$ is indeed a superior catalyst compared to YbCl$_3$. Moreover, at higher temperature, La(TOS)$_3$ is also a better catalyst than LaCl$_3$. In order to investigate the effect of the anion on the catalyst efficiency, lanthanum(III) nitrate, La(NO$_3$)$_3$•6H$_2$O, and lanthanum(III) sulfate, La$_2$(SO$_4$)$_3$•6H$_2$O, were also included in this study. Figure 3.14 shows that the catalyst activity decreases in the following order: tosylate > chloride > nitrate > sulfate. Furthermore, all investigated lanthanide(III) and iron(III) catalysts could be recovered and reused with nearly no decrease in efficiency. After extraction of the reaction mixture, the aqueous phase was evaporated under vacuum. The resulting solid compound, the respective lanthanide(III) or iron(III) catalyst, could then directly be reused for further reaction. It is also important to point out that all reactions were performed with the catalyst in the hydrated form. Consequently, depending on the reaction conditions, high conversions could be obtained with lanthanide(III) and iron(III) chlorides without extensive drying of the catalyst prior to use. Furthermore, lanthanide(III) and iron(III) salts are superior catalyst for the acetylation of phenethyl alcohol compared to recently investigated cobalt(II) chloride hexahydrate.[184] In conclusion, good catalytic activity was observed using 5 mol% of lanthanide(III) and iron(III) tosylates and chloride hydrates.

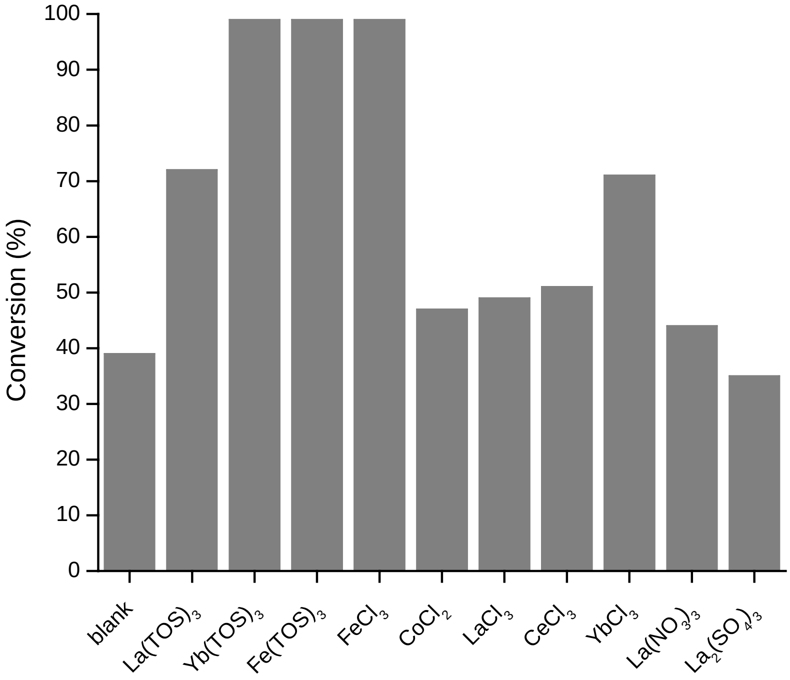


Figure 3.14 Comparison of Lewis acid catalysts on the acetylation of phenethyl alcohol in acetic acid. Reactions were performed for 30 minutes at reflux temperature and all catalysts were used in their hydrated form.

3.5. Formation of calix[4] resorcinarenes

3.5.1. Introduction

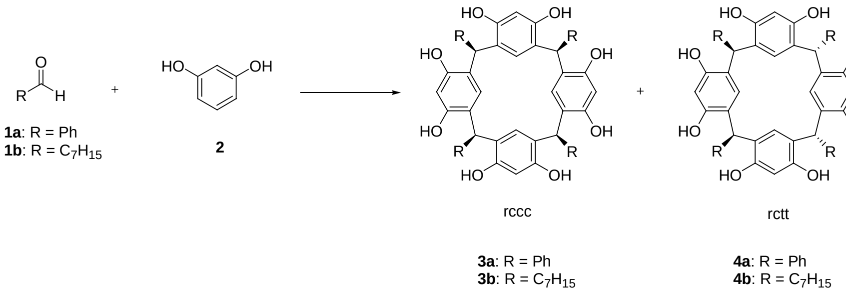
Adolf von Baeyer reported already in 1872 that the addition of concentrated sulfuric acid to a mixture of benzaldehyde and resorcinol gave a red-colored product.[191] In 1968, Erdtman finally proved the cyclic tetrameric structure of these condensation products by single crystal X-ray diffraction analysis.[192] As the official IUPAC name of this type of compounds is very complicated, they are commonly called *calixarenes*, referring to the resemblance of the shape of one of the conformers to a type of Greek vase called a calix crater.[193] Calix[4]resorcinarenes (resorcinarenes), the resorcinol-derived calixarenes, are versatile host compounds for ions, sugars and organic molecules. Therefore they serve as starting materials for a variety of cavitands and other macrocyclic host compounds.[194,195,196] They have also found application as stationary phases in HPLC.[197] Furthermore, they can exhibit liquid-crystalline behavior by appropriate choice of the R groups on the resorcinarene.[198,199,200] Resorcinarenes are traditionnally prepared by the mineral-acid catalyzed condensation of resorcinol with an aliphatic or aromatic aldehyde.[201,202] However, this synthetic procedure requires the use of large quantities of acid, leading to excessive waste streams that are environmentally unfriendly and expensive to deal with. A solvent-free synthesis of resorcinarenes using *p*-toluenesulfonic acid as the catalyst has also been reported.[203] In addition, some conventional Lewis acids like $BF_3{\cdot}OEt_2$, $AlCl_3$ and $SnCl_4$ have been used in the synthesis of aromatic aldehyde-derived resorcinarenes.[204,205] Although these Lewis acids are usually efficient catalysts, they have several drawbacks: they need to be used in stoichiometric amounts, they are easily deactivated by water and they cannot be recycled or reused. More recently, trifluoromethanesulfonate salts, the so-called triflates, such as ytterbium(III) triflate[206] and bismuth(III) triflate[207], have been described as efficient catalysts for the synthesis of calix[4] resorcinarenes. We examined lanthanide(III) salts of less corrosive aromatic sulfonic acids, such as *p*-toluenesulfonic acid and nitrobenzenesulfonic acids as catalysts for the formation reaction of calix[4]resorcinarenes.

3.5.2. General procedure for the lanthanide-catalyzed formation of calix[4] resorcinarenes

To a stirred solution of the nonahydrated lanthanide(III) catalyst (5 mol%, 0.318 mmol) in absolute ethanol (10 mL) was added the resorcinol (6.36 mmol, 699 mg) and benzaldehyde (6.36 mmol, 645 μL). This solution was heated till just beneath the reflux temperature. After a given period of time the solution was cooled and poured into distilled water (20 mL). The precipitated resorcinarene was filtered on a dry weighed crucible and washed with water (3 x 10 mL). After drying the resorcinarene to constant weight (after about 48 hours in a vacuum oven at 90 °C) the crucible was weighed again giving the amount of formed resorcinarene. To obtain the isomer distribution, a small amount of resorcinarene was dissolved in deuterated DMSO and a ^1H NMR spectrum was recorded. The ratio was obtained by integration of the signals at $\delta = 5.64$ (4H, benzylic hydrogens of *rccc*-isomer) versus the signals at $\delta = 5.54$ (4H, benzylic hydrogens of *rctt*-isomer) and $\delta = 5.57$ (2H, *ortho* to OH in *rctt*-isomer). Electron spray ionization mass spectrometry was performed to prove the tetrameric structure: m/e (ESI^+) = 793 $(M+1)^+$, 1608 $(2M+Na+1)^+$. CHN-analysis was performed after drying the calix[4]resorcinarene for 48 hours at 50 °C in a vacuum oven: $C_{52}H_{40}O_8 \bullet 3H_2O$ Calcd. (found): C, 73.74 (73.89); H, 5.47 (5.56) %. The procedures for the reactions with octanal were identical with the only difference that these reactions were performed at reflux temperature. CHN-analysis was also performed after drying the calix[4]resorcinarene for 48 hours at 50 °C in a vacuum oven: $C_{56}H_{80}O_8 \cdot 3H_2O$ Calcd. (found): C, 71.91 (71.51); H, 9.27 (9.35) %.

3.5.3. Formation of resorcinarenes

The formation of calix[4]resorcinarenes through lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed condensation of resorcinol with benzaldehyde and octanal was investigated (Scheme 3.8). During this reaction, only the tetrameric resorcinarene and water are formed. The tetrameric nature of the compounds was confirmed by mass-spectrometric analysis. Of the four diastereoisomers that could form, we observed the all-*cis* (*rccc*) isomer **(3a)** and the *cis-trans-trans* (*rctt*) isomer **(4a)** in the reactions with benzaldehyde, with a relative ratio depending on the reaction conditions used. Only in the case of short reaction times (4 hours or less) or low catalyst concentration (0.1 mol%), a small amount of a third product is formed. Based on the NMR data this product is likely one of the other possible isomers, however the exact structure of the product was not further investigated. In the lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed reactions with octanal only the all-*cis* isomer **(3b)** is formed, although after short reaction times a small amount of a less thermodynamically stable isomer could also be detected. The configuration of the isomers has previously been determined by X-ray diffraction analysis and our NMR spectra are in agreement with the literature data.[196,208] Although the use of an inert atmosphere is frequently recommended for the formation of resorcinarenes, our experiments indicate that there is no difference in yields or isomer distribution in the reactions performed under argon, nitrogen or air. Therefore, the reactions can be performed in a simple reflux setup, open to the air.



Scheme 3.8

3.5.4. Influence of the lanthanide ion

In order to find the most suitable lanthanide(III) ion for the calix[4] resorcinarene formation, a range of lanthanide(III) tosylates were examined as potential catalysts. As can be seen in Table 3.9, only small differences in yield and isomer distribution are observed for the reaction with benzaldehyde using different lanthanide(III) tosylates. While 93% of resorcinarene is formed after 24 hours by using 5 mol% of $Yb(TOS)_3$, 84% of resorcinarene is formed when using $La(TOS)_3$. In contrast, surprisingly large differences are observed for the reaction with octanal. The use of $Yb(TOS)_3$ leads to 92% of resorcinarene, while only 11% of the product is formed with $La(TOS)_3$ as the catalyst. This trend over the lanthanide series is consistent with the previous section involving lanthanide(III) tosylates in the acetylation of alcohols. As mentioned earlier, the solid-state structure of lanthanide(III) tosylates, which shows clear structural differences across the lanthanide(III) series, is not preserved in strongly-coordinating solvents. Ethanol coordinates strongly enough to the lanthanide ion to displace the tosylate ligands to the second coordination sphere, so that the first coordination sphere around the lanthanide(III) is occupied by ethanol molecules only. In this case, a smaller ionic radius of trivalent lanthanide ion leads to a larger charge-to-size ratio, Z/r, which in turn results in a stronger polarizing power of the lanthanide(III) center, a stronger Lewis acidity and hence higher reaction yields.

Table 3.9 Effect of the lanthanide(III) ion on the formation of calix[4]resorcinarenes.[a]

Ln-ion	benzaldehyde		octanal
	yield (%)	*rccc* : *rctt* (%)	yield (%)
La	84	38 : 62	11
Gd	81	36 : 64	30
Yb	93	42 : 58	92
Y	84	33 : 67	75

[a] 5 mol% of lanthanide(III) *p*-toluenesulfonate, after 24 hours, at reflux temperature.

3.5.5. Influence of the reaction time

Since the screening of the different lanthanide(III) tosylates revealed that the ytterbium(III) complexes are the most powerful catalysts in the lanthanide(III) series, ytterbium(III) nitrobenzenesulfonates were examined as catalysts for the formation of resorcinarenes with benzaldehyde or octanal. When performing the condensation reaction of resorcinol with octanal in the presence of 2 mol% of ytterbium(III) tosylate or nosylate (abbreviation for 4-nitrobenzenesulfonate), the yields are 93 to 95%, respectively, after 24 hours. The yields and isomer distributions in the reaction of benzaldehyde using ytterbium(III) 3-nitrobenzenesulfonate [$Yb(3\text{-}NBSA)_3$], ytterbium(III) 4-nitrobenzenesulfonate [$Yb(4\text{-}NBSA)_3$] and ytterbium(III) 2,4-dinitrobenzenesulfonate [$Yb(2,4\text{-}NBSA)_3$] are summarized in Table 3.10. Only minor differences in total yield are observed for the different catalysts.

Table 3.10 Effect of the counterion (tosylate or nitrobenzenesulfonate) in function of time on the ytterbium(III) catalyzed formation of resorcinarenes with benzaldehyde. [a]

	% yield (*rccc*:*rctt*)			
time (h)	TOS	3-NBSA	4-NBSA	2,4-NBSA
4	90 (32:68)	80 (40:60)	68 (46:54)	86 (40:60)
24	93 (42:58)	87 (45:55)	>98 (61:39)	92 (45:55)
48	95 (51:49)	89 (47:53)	>98 (73:27)	>98 (57:43)
96	96 (64:36)	90 (64:36)	>98 (86:14)	>98 (70:30)
216	96 (86:14)	95 (65:35)	>98 (96:4)	>98 (72:28)

[a] 5 mol% of Yb-catalyst, at reflux temperature; TOS = *p*-toluenesulfonate, 3-NBSA = 3-nitrobenzenesulfonate, 4-NBSA = 4-nitrobenzenesulfonate, 2,4-NBSA = 2,4-dinitrobenzenesulfonate.

As can be seen in Table 3.10 and Figure 3.15, after a certain time the largest amount of *rccc*-isomer is formed when using Yb(4-NBSA)$_3$. Furthermore, the amount of *rccc*-isomer can be increased by increasing the reaction time. This is consistent with the previous findings in which Yb(OTf)$_3$ was used as the catalyst,[206] although this latter catalyst resulted in a higher extent of *rccc*-isomer.

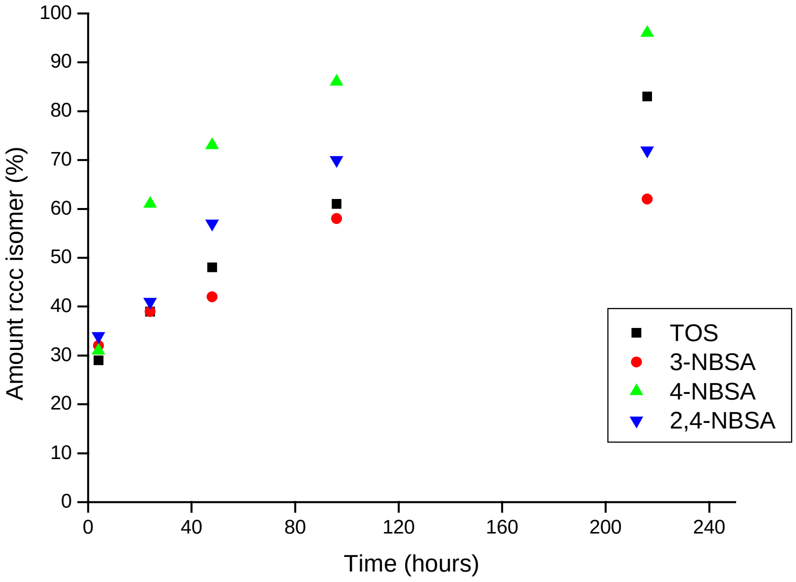


Figure 3.15 Amount of rccc (all-cis) isomer as a function of time and counterion for the formation of benzaldehyde-based resorcinarenes with ytterbium(III) catalysts.

3.5.6. Effects of temperature and catalyst loading on the extent of resorcinarene formation

The influence of temperature was studied for the reactions with benzaldehyde and octanal. For the reaction with octanal we could not isolate any resorcinarene when the reaction was performed at room temperature or at 50 °C. However, the reaction with benzaldehyde resulted in resorcinarene formation at room temperature, although with lower yields and less *rccc*-isomer formed. Reaction for 48 hours at room temperature leads to 80% of yield with 36% of *rccc*-isomer. In order to further optimize the reaction conditions, we also studied the effect of the catalyst amount on both condensation reactions. As can be seen from Table 3.11, good yields are achieved by using only 0.1 mol% $Yb(TOS)_3$.

Table 3.11 The effect of the ytterbium(III) tosylate loading on the formation of resorcinarenes with benzaldehyde and octanal.[a]

catalyst load (mol%)	benzaldehyde		octanal
	yield (%)	*rccc*:*rctt* (%)	yield (%)
None	2	n.d.	0
0.1	71	32 : 68	84
1	88	33 : 67	86
2	88	34 : 66	92
5	93	42 : 58	92

[a] after 24 hours, at reflux temperature

However, in the reaction of benzaldehyde a small amount of a third isomer was formed when less than 0.1 mol% of $Yb(TOS)_3$ was used. For the condensation with benzaldehyde, an increase to 5 mol% of $Yb(TOS)_3$ resulted also in a larger amount of *rccc*-isomer, but in this case the total yield and amount of *rccc*-isomer are almost not improved when increasing the catalyst load to 10 mol%. Furthermore, in the reaction of octanal with resorcinol, 84% of resorcinarene was formed after 24 hours by using 0.1 mol% of $Yb(TOS)_3$ while no resorcinarene could be isolated without using a catalyst. The use of higher catalytic amounts lead to a slight increase in yield: 92% by using 5 mol% under the same reaction conditions.

3.5.7. Recovery and reuse of the lanthanide(III) catalyst

After quenching the reaction mixture with water, the resorcinarene was filtered off and washed with water. The catalysts could be easily recovered from the filtrate as mentioned earlier by evaporating the water under reduced pressure. The ^{1}H NMR spectrum of the recovered Yb(TOS)$_3$ showed a very small amount of impurity compared to the spectrum of the freshly prepared Yb(TOS)$_3$. But as can be seen in Table 3.12, the presence of this impurity - a few percent of unreacted resorcinol and octanal - had no negative influence on the reactivity of the catalyst in the subsequent runs. Due to this small amount of impurity the weight of the recovered catalyst was somewhat higher than the weight of catalyst used in the first run. In combination with the small catalyst loading required for quantitative reaction, we can conclude that this condensation reaction, catalyzed by lanthanide(III) tosylates and various nitrobenzenesulfonates, is a real catalytic system.

Table 3.12 Recovery and reuse of ytterbium(III) tosylate after the reaction of resorcinol with octanal. [a]

Run	% yield	% recovered Yb(TOS)$_3$
1	95	>98
2	96	>98
3	94	>98

[a] after 24 hours, at reflux temperature, the recovered amount of catalyst is each time compared to the initial 5 mol% of Yb(TOS)$_3$ used in the first run.

3.5.8. Influence of the reaction solvent

Besides ethanol some other solvents were also tested for the condensation reaction of resorcinol with benzaldehyde and octanal. Reactions were always performed at their respective reflux temperatures: dichloromethane (40 °C), tetrahydrofuran (67 °C) and methanol (65 °C). In the Yb(TOS)$_3$ catalyzed reaction of resorcinol with octanal no reasonable amount of calix[4]resorcinarene was formed in either dichloromethane, tetrahydrofuran and methanol. This is not that unexpected because experiments on different temperatures revealed that this reaction requires rather high temperatures. The $Yb(TOS)_3$ catalyzed reaction of resorcinol with benzaldehyde on the other hand resulted after 48 hours in 28 % of calixarene in dichloromethane, 7% in tetrahydrofuran, 81% in methanol compared to 88% in ethanol. The lower reflux temperature of methanol probably accounts for the somewhat lower yield that is obtained. In summary, the reaction proceeds much better in solvents like methanol and ethanol compared to dichloromethane and this indicates that the alcohol plays an important role in the Lewis acid-catalyzed formation of calix[4]resorcinarenes.

3.5.9. Postulated mechanism for the lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed formation of calix[4]resorcinarenes

Barrett and coworkers proposed in their study on $Yb(OTf)_3$-catalyzed formation of resorcinarenes that once the resorcinarene is formed, it (reversibly) binds to $Yb(OTf)_3$, thus generating a complex which liberates triflic acid, or is itself acidic enough to promote protodealkylation and hence isomerization.[206] Although the above work clearly demonstrates the Brønsted acid-catalyzed nature of the isomerization of resorcinarenes, it is not clear how the initial resorcinol-aldehyde bond formation is initiated.

We performed *in-situ* infrared experiments to gain more insight into the initial interactions between the aldehyde and $Yb(TOS)_3$. Octanal could be monitored following the carbonyl absorption band at 1721 cm^{-1}. Unfortunately, it was not possible to follow the formation of resorcinarene with *in-situ* infrared spectroscopy, since the vibration bands of the C-C bonds in the resorcinarene, such as for example the band at 1603 cm^{-1}, fall in the same region as the vibration bands of the C-C bonds in resorcinol, leading to strong overlapping. Figure 3.16 shows the most interesting part of recorded *in-situ* infrared spectra, which shows the step-by-step addition of octanal, Yb(TOS)$_3$ and resorcinol to an ethanolic solution. The changes in infrared absorption are also clearly shown in Figure 3.17 presenting the quick profile of the peaks at 1721 cm^{-1} (vibration of C=O in octanal, red line), 1603 cm^{-1} (C-C vibrational modes in resorcinol and resorcinarene, blue line) and 1011 cm^{-1} (vibrations of C-O in the acetal, brown line).

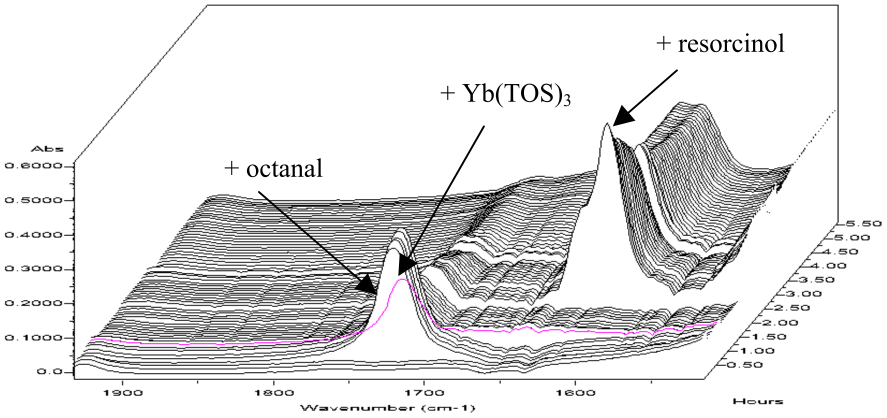


Figure 3.16 In-situ infrared spectra of the Yb(TOS)$_3$-catalyzed reaction of octanal and resorcinol in the presence of an excess of ethanol. Only the part giving information on the initial interaction of Yb(TOS)$_3$ is depicted. At the addition of the first portion of Yb(TOS)$_3$ catalyst (pink line), an immediate decrease in absorbance of the C=O absorption of octanal (1721 cm^{-1}) is observed.

By addition of 5 mol% of Yb(TOS)$_3$ - in three portions after 40, 55 and 70 minutes - the intensity of the carbonyl absorption band of octanal at 1721 cm^{-1} strongly decreased. This can not originate from a full coordination of ytterbium to octanal since Yb(TOS)$_3$ was present in only 5 mol%. Rather, Yb(TOS)$_3$-catalyzed acetal formation can be expected (Scheme 3.9, step A). The ability of Sc(OTf)$_3$ to catalyze the acetal formation at an early reaction stage has been described in the Friedel-Crafts alkylation of aromatics with arenecarbaldehydes in the presence of 1,3-propanediol.[209] Since the lanthanide(III) tosylates have similar catalytic properties as triflate salts, it can be expected that tosylates also can catalyze the acetal formation in the presence of an excess of ethanol. Furthermore, a new absorption band that appeared at 1011 cm^{-1}, is consistent with the C-O single bond absorption characteristic for acetals. The intensity of this absorption band increases upon addition of $Yb(TOS)_3$, consistent with the $Yb(TOS)_3$ catalyzed formation of the acetal.

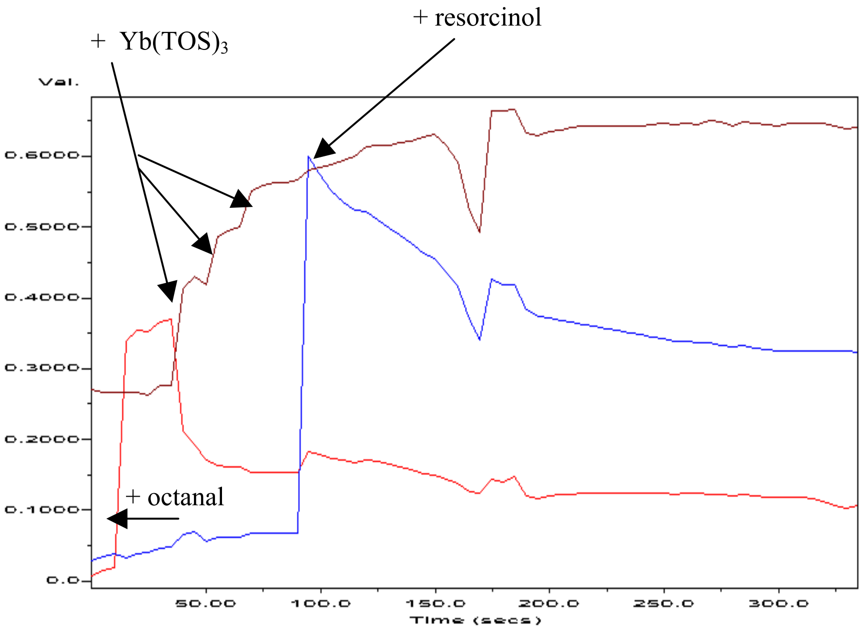
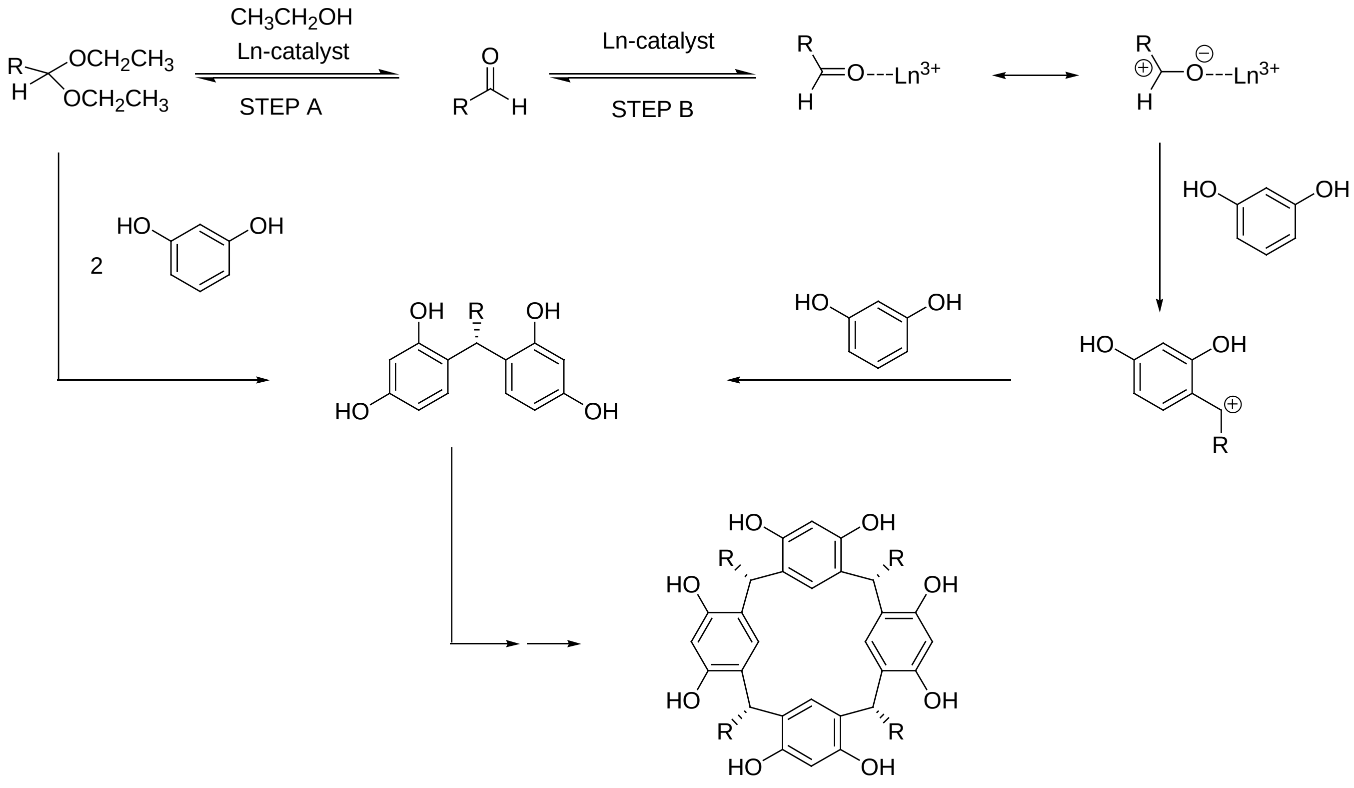


Figure 3.17 Peak profile of the peaks at 1721 (vibrations of C=O in octanal, red line), 1603 (C-C vibrational modes in resorcinol, resorcinarene, blue line) and 1011 (vibrations of C-O in formed acetal, brown line) in the $Yb(TOS)_3$-catalyzed reaction of octanal and resorcinol in an excess of ethanol. The artefacts around 175 minutes are due to the presence of a bubble around the probe because one is working around reflux temperature.

The catalytic reaction was also followed by proton NMR spectroscopy in deuterated ethanol at 65 °C (Figure 3.18). Addition of octanal to an ethanolic solution of resorcinol resulted in formation of a small peak around 4.5 ppm, consistent with acetal formation (Scheme 3.9, step A). Upon addition of 5 mol% $Yb(TOS)_3$ the proton signal of the aldehyde group nearly completely disappeared while the signal around 4.5 ppm that can be attributed to the CH-proton of the acetal strongly increases. Furthermore, peaks of the remaining octanal are broadened upon addition of $Yb(TOS)_3$, which indicates coordination of the carbonyl group to paramagnetic ytterbium(III) ion (Scheme 3.9, step B). Unfortunately, it was not possible to follow the disappearance of the acetal peak as the reaction proceeded, due to overlap with the peak of water that is formed in the course of reaction. The spectrum shown in Figure 3c corresponds to the reaction mixture after 11 hours of reaction. As it can be seen in the aromatic NMR region at this stage of the reaction several calixarene isomers are formed, however after 24 hours of reaction only the all-*cis* isomer is present in solution.



Scheme 3.9

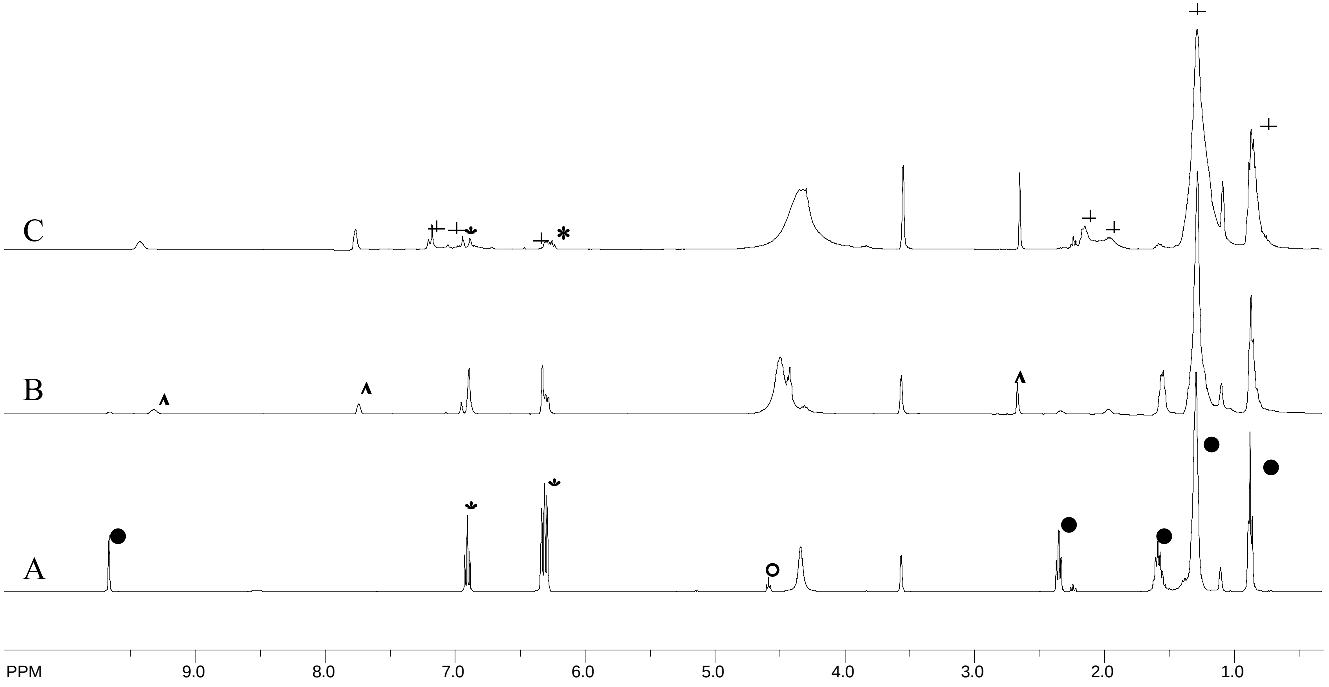


Figure 3.18 Proton NMR spectra of formation of calix[4]resorcinarenes at 65 °C. The peaks at 1.11, 3.57 and 4.40 ppm are due to ethanol and water (A): resorcinol (stars) and octanal (black circles) in CD_3CD_2OD result in formation of small amount of acetal (white circles), (B) after addition of 5 mol% $Yb(TOS)_3$ (white triangles) more acetal is produced and, (C): after 11 hours of reaction different isomers of calix[4]resorcinarene are present in the solution (plus signs).

In summary, the *in-situ* infrared and proton NMR measurements established that lanthanide(III) tosylates and nosylates catalyze acetal formation in the reaction between the aldehyde and ethanol. Once the acetal is formed, the reaction proceeds similarly to the build-up sequence postulated by Weinelt and Schneider for the acid-catalyzed condensation reaction between resorcinol and acetaldehyde in methanol/HCl.[210] The acid-catalyzed condensation has frequently been interpreted in terms of cationic intermediates and electrophilic aromatic substitution,[193] but our experiments indicate that the lanthanide(III) catalyst is responsible for more than simple coordination to the aldehyde. In fact, if ethanol is used as a solvent, the lanthanide ion plays a dual role (Scheme 3.9). Most of the octanal is conversed to the acetal by lanthanide-catalyzed acetal formation and the remaining octanal coordinates to the lanthanide ion to form a cationic electrophilic species which attacks the resorcinol to form the calix[4]resorcinarene.

It is reasonable to assume that once some calix[4]resorcinarene is formed, it binds to the lanthanide(III) tosylate or nitrobenzenesulfonate in a way similar as proposed in the study on $Yb(OTf)_3$-catalyzed formation of resorcinarenes. Barrett and coworkers suggest that this complex liberates the associated acid, or is itself acidic enough to promote protodealkylation and hence isomerization.[206] In order to determine whether the complex itself or the liberated acid catalyzes the isomerization, the following experiment was performed. Benzaldehyde-derived calix[4]resorcinarene (1g) with a known isomer distribution was left to react with the respective catalyst in 10 mL of ethanol just beneath the reflux temperature. After 120 hours, the calix[4]resorcinarene was isolated in the usual way and the isomer distribution was determined from the ^1H NMR spectrum. As can be seen in Table 3.13, the degree of isomerization strongly depends on the counter ion. If the lanthanide-resorcinarene complex would itself promote protodealkylation we expect no difference between the various counter ions. Moreover, during this experiment a clear descrease in pH was noticed. Thus, we can assume that the liberated acid catalyzes the isomerization and hence the extent of isomerization depends on the acidity of the respective sulfonic acid formed. Since *p*-toluenesulfonic acid (pK_A = -6.56),[211] *p*-nitrobenzenesulfonic acid (pK_A = -7.23) and *m*-nitrobenzenesulfonic acid (pK_A = -7.25)[212] are much weaker acids than triflic acid (pK_A < - 12),[213] they do not really catalyze the isomerization of the all-*cis* isomer (*rccc*) to the *cis-trans-trans* isomer (*rctt*).

Table 3.13 Influence of the tosylate and nitrobenzenesulfonate counter ion on the isomerization of cis-trans-trans calix[4]resorcinarene (rctt), formed from benzaldehyde and resorcinol, to all-cis calix[4]resorcinarene (rccc).[a]

catalyst	*rccc*: *rctt*	pK_A of the acid
$Yb(TOS)_3$	45 : 55	- 6.56
$Yb(3\text{-}NBSA)_3$	55 : 45	- 7.25
$Yb(4\text{-}NBSA)_3$	55 : 45	- 7.23
$Yb(2,4\text{-}NBSA)_3$	54 : 46	N.A.
$Er(OTf)_3$	71 : 29	≤- 12

[a] 1g of benzaldehyde-based calix[4]resorcinarene (44% *rccc*, 56% *rctt*), 10 mol% of hydrated lanthanide catalyst, 10 mL of ethanol, 120 hours, reflux temperature.

As shown in Table 3.10 and Figure 3.15, the smallest amounts of rccc isomer was formed when using $Yb(3\text{-}NBSA)_3$ or $Yb(2,4\text{-}NBSA)_3$. The lower efficiency of these two catalysts may be contributed to the steric effect of the substituents on the aromatic ring which may form more crowded environment around the lanthanide(III) ion. As the latter experiments indicate that calixarene formation results in a lanthanide-calixarene complex with concomitant liberation of the associated Brönsted acid, it is evident that further formation of calixarene can also occur autocatalytically by this liberated acid. For comparison, the reaction between benzaldehyde and resorcinol was also carried out in the presence of 5 mol% of *p*-toluenesulfonic acid monohydrate and after 24 hours of reflux in ethanol nearly complete conversion was obtained (83% *rccc*-isomer and 17% *rctt*-isomer).

3.5.10. Use of other acidic catalysts

Since copper(II) complexes with some sulfate ligands are also known to be good Lewis acid catalysts (see chapter 4), we set out to test the activity of tosylates of transition metals, iron(III) and copper(II), as catalysts for the formation of calixarenes. Iron(III) tosylate is commercially available at relative low price and copper(II) tosylate was prepared following the procedure applied for the synthesis of lanthanide(III) tosylates. The reactions of resorcinol with octanal and benzaldehyde catalyzed by 5 mol% $Cu(TOS)_2$ and $Fe(TOS)_3$ are shown in Table 3.14.

Table 3.14 The effect of the metal ion and its counterion on the formation of calix[4]resorcinarene.[a]

Catalyst	benzaldehyde		octanal
	yield (%)	*rccc* : *rctt* (%)	yield (%)
$La(TOS)_3$	84	38 : 62	11
$Cu(TOS)_3$	91	48 : 52	93
$Fe(TOS)_3$	95	73 : 27	96
$Yb(TOS)_3$	93	42 : 58	95
$Yb(3\text{-}NBSA)_3$	87	45 : 55	91
$Yb(4\text{-}NBSA)_3$	>98	61 : 39	96
$Yb(2,4\text{-}NBSA)_3$	>98	57 : 43	96
HCl[b]	> 98 / 81[c]	100 : 0 / 60 : 40[c]	95

[a] 5 mol% of catalyst, after 24 hours, at reflux temperature; [b] equimolar amount of HCl; [c] after 1 hour.

In all cases nearly quantitative conversion was obtained after 24 hours of reaction. Furthermore, a remarkably high amount of all-*cis* isomer was formed in the reaction with iron(III) tosylate. As a comparison, the reported reaction with 8 mol% of ytterbium(III) triflate achieves around 46% of all-*cis* isomer after 48 hours of reaction. This exceptionnally high amount of all-*cis* isomer can probably be explained by the strong Lewis acidity of iron(III) that results from its high charge-to-size ratio. Moreover, in the reaction of resorcinol with octanal the initial reaction rates are higher with copper(II) and iron(III) tosylate compared to lanthanide(III) tosylates. By using copper(II) and iron(III) tosylate 91 to 94% of resorcinarene was formed after 6 hours of reaction while in the case of ytterbium(III) tosylate 18 hours of reaction was necessary to obtain the same yield. Moreover, these catalysts can also be recovered and reused.

In addition, the reaction yields obtained by using transition metal and lanthanide tosylates were compared with those when traditional mineral acid such as HCl was used. Nowadays the mineral acid HCl is used in equimolar amounts to promote the formation of resorcinarenes. We compared our results to the ones obtained in the reaction of resorcinol with benzaldehyde or octanal in the presence of 500μL of 37% HCl, which corresponds almost to an equimolar amount compared to the other reactants. As can be seen in Table 3.14, the reactions promoted by HCl are faster and in the reaction with benzaldehyde more all-*cis* isomer is formed. On the other hand, tosylate complexes of transition metals and lanthanides are beneficial for several reasons: they are not required in stoichiometric amounts but catalytic amounts as small as 0.1 mol% are sufficient, they can be recovered and reused several times without loss of activity and hence they limit the consumption of strong acids.

Chloride salts of aluminum(III) and tin(IV) have also been reported as catalysts for calix[4]resorcinarene formation, however, dry diethyl ether and up to 50 mol% of catalyst were required for efficient reaction.[204,205] To the best of our knowledge lanthanide trihalides have never been explored as catalysts for this reaction. As our studies on metal tosylates revealed that iron(III) tosylate also possesses strong Lewis acid activity, iron(III) chloride hexahydrate was also included in this study. Interestingly, catalytic amounts of lanthanide(III) chloride hydrates are sufficient to obtain large amounts of resorcinarenes. After 24 hours of reflux the reaction of resorcinol and benzaldehyde with 5 mol% of $LaCl_3{\cdot}7H_2O$ yielded 84% of resorcinarene with the following isomer distribution: 38% *rccc* (**3a**) and 62% *rctt* (**4a**). These results compare very well to the results obtained with the lanthanide(III) tosylate catalysts. On the other hand, a remarkably higher amount of the octanal-derived calixarene was formed when lanthanum(III) chloride (94%) was used instead of lanthanum(III) tosylate (11%), although a mixture of isomers is obtained in the case of lanthanum(III) chloride. This results prompted us to further investigate the use of lanthanide(III) and iron(III) chloride hydrates in the condensation reaction of resorcinol with octanal and these results are presented in Figure 3.19 and Table 3.15.

After 24 hours, all chloride salts resulted in high amounts of calix[4]resorcinarenes but differences in isomer composition were noticed. The portion of *rccc* isomer increases slightly along the lanthanide series and if iron(III) chloride hexahydrate is used nearly only the all-*cis* isomer (**3b**) was formed. After prolonged reaction times of several days, the pure all-*cis* isomer was also obtained using lanthanide(III) chlorides. On the other hand, shortening the reaction time allows to examine the effect of the metal ion on the reaction yields. After 4 hours of heating at reflux temperature, a noticeable increase in yield was observed along the lanthanide series, which can be explained by the increase in Lewis acidity along the lanthanide series. At this point of reaction the isomer distribution was nearly identical for all lanthanides. Similarly to our previous study with iron(III) tosylate, high initial reaction rates were observed by using iron(III) chloride hexahydrate. Furthermore, after 4 hours of refluxing with iron(III) chloride hexahydrate a much higher amount of all-*cis* isomer **3b** was formed compared to the reactions with lanthanide(III) chlorides. Various isomers of the octanal-derived calixarene can thus be obtained depending on the reaction conditions, but the reaction conditions can be tuned in such way to obtain only the all-*cis* isomer **3b**.

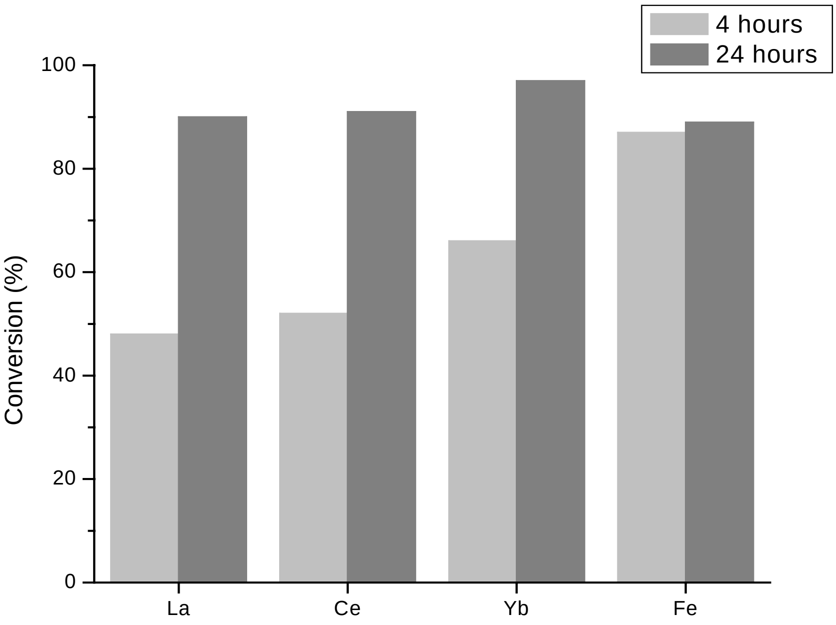


Figure 3.19 Influence of the trivalent metal ion of the chloride salt on the condensation reaction of resorcinol with octanal.

Table 3.15 The influence of the metal ion on the formation of calix[4]resorcinarenes.[a]

catalyst	time (hours)	octanal	
		yield (%)	*rccc* : *rctt* (%)
$LaCl_3 \cdot 7H_2O$	4	48	58 : 42
$CeCl_3 \cdot 7H_2O$	4	52	57 : 43
$YbCl_3 \cdot 6H_2O$	4	66	58 : 42
$FeCl_3 \cdot 6H_2O$	4	87	81 : 19
$LaCl_3 \cdot 7H_2O$	24	94	60 : 40
$CeCl_3 \cdot 7H_2O$	24	91	61 : 39
$YbCl_3 \cdot 6H_2O$	24	97	70 : 30
$FeCl_3 \cdot 6H_2O$	24	89	93 : 7

[a] 5 mol% of catalyst, at reflux temperature

When technical grade ethanol was used as the reaction solvent instead of absolute ethanol, the reaction yields and isomer distribution remained the same in the case of lanthanide(III) chloride hydrates and iron(III) chloride hexahydrate. Moreover, the lanthanide(III) chloride and iron(III) chloride could be recovered and reused with no apparent difference in efficiency and selectivity which demonstrates that they act in a real catalytic system. For example, the reaction of resorcinol with octanal in the presence of 5 mol% of cerium(III) chloride heptahydrate for example yielded 91% of resorcinarene in the first run and after complete recovery of the catalyst by evaporation of the filtrate, a 90% yield was obtained in the second run. The isomer distributions of *rccc* and *rctt* isomer were identical in both runs (see Table 3.16). It is important to notice that under these reaction conditions a small amount of the iron(III) chloride is hydrolized but most of the iron(III) chloride could be recovered and reused for subsequent reactions.

Table 3.16 Recovery and reuse of cerium(III) chloride after the reaction of resorcinol with octanal.[a]

Run	yield (%)	*rccc* : *rctt* (%)	% recovered $CeCl_3$
1	91	61 : 39	> 98
2	90	60 : 40	n.d.

[a] 24 hours, at reflux temperature, 5 mol% of $CeCl_3 \cdot 7H_2O$ used in the first run.

Our study on lanthanide(III) tosylate catalyzed formation of calix[4]resorcinarenes revealed that this reaction occurs both through direct coordination of the lanthanide cation to the aldehyde and lanthanide catalyzed acetal formation with ethanol. Since the acetal formation with stoichiometric amounts of lanthanide chloride hydrates is reported,[77] we can assume that the lanthanide(III) and iron(III) chloride catalyzed formation of calixarenes in ethanol most likely also occurs through the formation of an acetal intermediate.

3.5.11. Discussion

In this study we demonstrated that lanthanide(III) tosylates and lanthanide(III) nitrobenzenesulfonates can be used as efficient, inexpensive, recyclable, and environmentally friendly catalysts for the synthesis of calix[4]resorcinarenes. In addition, we established that copper(II) and iron(III) complexes of *p*-toluenesulfonic acid also efficiently catalyze the formation of calixarenes. Moreover, in the reactions with benzaldehyde, the amount of each isomer can be tuned not only by variation of the reaction time but also by appropriate choice of the metal ion. Although *p*-toluenesulfonic and nitrobenzenesulfonic acids are about 10^6 times weaker than triflic acid, these lanthanide salts are capable of catalyzing the formation of calix[4]resorcinarenes as efficient as lanthanide(III) and bismuth(III) triflates. Furthermore, the initial formation of acetals as key intermediates has been confirmed. The use of *p*-toluenesulfonic acid and nitrobenzenesulfonic acids over triflic acid for the preparation of lanthanide(III) catalysts is both environmentally and economically advantageous. These catalysts can easily be recovered and reused several times without loss of efficiency. Moreover, resorcinarene formation with benzaldehyde and octanal also proceeds in the presence of small amounts of lanthanide(III) and iron(III) chloride hydrates. Various isomers can be obtained depending on the reaction conditions but the reaction conditions can be tuned in order that only the all-*cis* isomer is obtained. It is important to point out that the hydrate forms of the catalysts are very efficient in this reaction and that there is thus no need to work with anhydrous salts or anhydrous solvents. In conclusion, besides metal salts of triflic and aromatic sulfonic acids, catalytic amounts of metal chloride hydrates are also powerful for the Lewis acidic catalyzed formation of calix[4]resorcinarenes.

3.6. Conclusions

In this chapter the use of lanthanide(III) salts of various aromatic sulfonic acids as efficient alternative Lewis acid catalysts has been demonstrated. In contrast to many classical Lewis acids nowadays used in organic synthesis, lanthanide(III) tosylates and nitrobenzenesulfonates are only required in small amounts and in addition they are easily recovered and reused without loss in efficiency and selectivity. Moreover, the presence of water in the reaction system does not pose problems as these catalysts are water-stable and even hydrated lanthanide salts were suitable. These properties have also been demonstrated for the well-studied lanthanide(III) triflates but lanthanide(III) triflates are not the ideal alternative catalysts. One of the main disadvantages of the lanthanide(III) triflates is the fact that one needs to handle the expensive and corrosive triflic acid for their preparation and hence lanthanide(III) triflates are also rather expensive compounds. Lanthanide(III) tosylates and nitrobenzenesulfonates are prepared from the non-corrosive and cheaper corresponding acids. Consequently these unexplored Lewis acids are both environmentally and economically advantageous. Despite the fact that the acidity of *p*-toluenesulfonic acid and nitrobenzenesulfonic acids is about 10^6 times weaker than that of triflic acid, its complexes with lanthanide(III) ions are strong Lewis acids which are able to catalyze various reactions, as for example the nitration of aromatic compounds, the acylation of various alcohols and the formation of calix[4]resorcinarenes.

Due to its extraordinary high charge-to-size ratio, commercially available iron(III) tosylate was also an effective and recyclable catalyst. At the end of our study, we have shown that lanthanide(III) chloride hydrates are also rather efficient catalysts for some organic reactions. They were only required in catalytic amounts and they were reusable. However, the widespread use of these catalysts for other reactions will probably be limited by solubility problems. Comparison of ytterbium(III) tosylate and ytterbium(III) chloride showed that ytterbium(III) tosylate is the most active catalyst. Finally, this work is also a contribution towards green chemistry. Besides the use of efficient catalysts attention was also paid to replace solvents that are hazardous to humans and environment. Furthermore, the formation of less waste was promoted and substrates were chosen to make the reaction as atom efficient as possible.

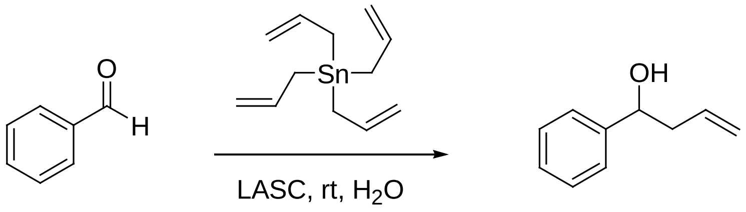
Chapter 4. Reactions with Lewis acid-surfactant-combined catalysts in water

4.1. Introduction

The Lewis acid-catalyzed allylation of aldehydes using allylstannanes or silanes is a versatile synthetic tool.[214,215] Allylation of a carbonyl group introduces simultaneously a hydroxyl group and a double carbon-carbon bond into the product. Various kinds of Lewis acid promoted reactions have been developed and versatile roles of Lewis acids in the reactions of allylic tin compounds were studied.[216] Strictly anhydrous conditions are required when typical Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$ are used. Recently, the use of lanthanide(III) triflates as Lewis acids is introduced by Kobayashi and coworkers. These lanthanide(III) triflate catalyzed reactions are often performed in pure organic solvents, such as dichloromethane or acetonitrile.[217,218] Improved reaction yields are obtained when benzoic acid,[219,220,221] HCl,[222] or acetic anhydride[223] are added to Lewis acid-catalyzed systems in acetonitrile or tetrahydrofuran. If reactions are performed in water, an organic solvent is desired to solubilize the substrates.[224,225] A solvent-free procedure was also described but after completion of reaction, solvents are needed to extract the products.[226] The allylation of aldehydes and ketones was also reported with silica- and alumina-supported Lewis acid catalysts.[221,227,228] The allylation of aldehydes has been performed in ionic liquids as well.[229,230,231] There are also reports of water or methanol promoted allylations, without the use of a catalyst.[232,233,234,235] To overcome the solubility problems in water, a surfactant such as sodium dodecylsulfate can be added to perform the allylation reaction in a micellar environment.[236] More recently, Kobayashi and coworkers simplified the $Ln(OTf)_3$/SDS system by introducing Lewis acid-surfactant-combined catalysts (LASCs). Although the use of Lewis acid-surfactant combined catalysts for organic synthesis in water was extensively studied for aldol reactions by the group of Kobayashi, they only briefly reported the allylation of aldehydes with scandium(III) dodecylsulfate.[94] They performed the reaction of tetraallyltin with benzaldehyde in the presence of 10 mol% of scandium(III) dodecylsulfate which gave 82% of isolated product after stirring for 10 hours at room temperature.[94] The LASC was found to form rapidly stable colloidal dispersions in the presence of reaction substrates in water. A Brønsted acid can be added to this system to shorten the reaction period.[237]

A number of allyl organometallic compounds with group 14 elements have been investigated as the allyl source. Akiyama reported the use of tetraallylgermane,[238] but allyltin and allylsilicon reagents have been mostly used for the mild conversion of aldehydes and ketones to versatile homoallylic alcohol intermediates. In particular allyltributyltin has been frequently used as the allyl source. However, from an atom efficient viewpoint tetraallyltin is preferable since one mole of tetraallyltin provides four allyl groups and hence reacts with 4 moles of aldehyde.

To the best of our knowledge, the use of LASCs in the allylation of aldehydes with tetraallyltin is limited to scandium(III) dodecylsulfate. This prompted us to perform a profound study on this reaction system by using cheaper lanthanides and transition metals as the Lewis acid in the LASCs. In this chapter, the Lewis acid-surfactant-combined-catalyzed allylation of benzaldehyde with tetraallyltin is presented in water (Scheme 4.1).



Scheme 4.1

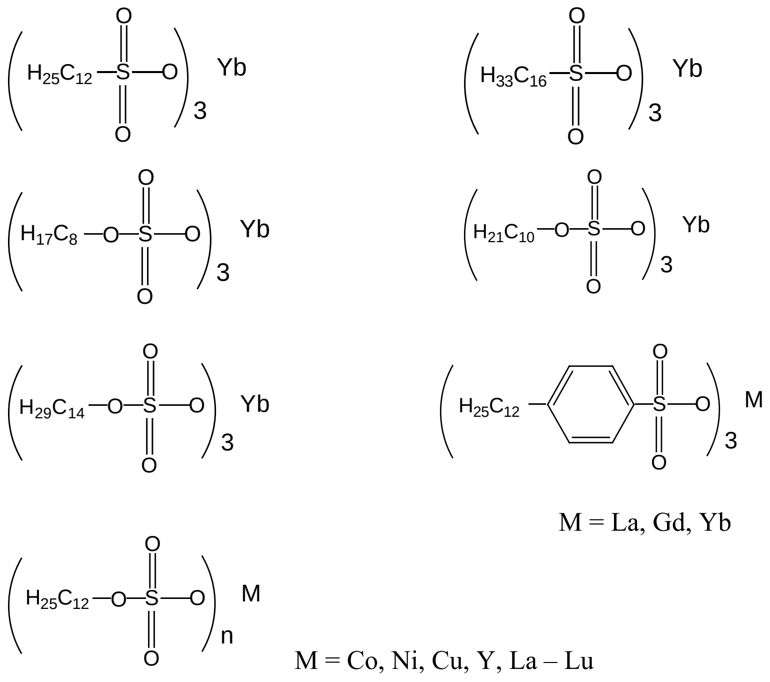
4.2. Synthesis and characterization of Lewis acid-surfactant-combined catalysts

4.2.1. Introduction

A series of divalent transition metal and trivalent lanthanide alkylsulfonates and alkylsulfates were synthesized, characterized and used as catalysts for the allylation reaction of benzaldehyde. These Lewis acid-surfactant-combined complexes (LASCs) were prepared as described in literature by a metathesis reaction between sodium dodecylsulfate (NaDOS) and the corresponding metal chloride or lanthanide chloride,[98,239] although for some complexes small adjustments to the known procedures were required. (Scheme 4.2) The prepared complexes are shown in Scheme 4.3.

$$\mathrm{MCl_n} \;+\; n\ \mathrm{Na(OSO_3C_{12}H_{25})} \rightarrow \mathrm{M(OSO_3C_{12}H_{25})_n} + \; n\ \mathrm{NaCl}$$

Scheme 4.2



Scheme 4.3

4.2.2. Synthesis of transition metal(II) dodecylsulfates

Sodium dodecylsulfate (2.07 g, 7.19 mmol) was dissolved in water (70 mL) at 70 °C. To this was added a solution of $CuCl_2 \cdot 2H_2O$ (0.613 g, 3.60 mmol) in water (1 mL) at the same temperature. The mixture was cooled to room temperature and left in the fridge during several days. The resulting precipitate was filtered on a crucible, washed thoroughly with water and dried in a vacuum oven at 50 °C overnight to afford the pure $Cu(OSO_3C_{12}H_{25})_2$. After leaving the mixture for two weeks in the fridge around 60% of $Cu(OSO_3C_{12}H_{25})_2$ was obtained. The complexes with cobalt and nickel were also prepared in this way.

Elemental analysis results:

$Cu(OSO_3C_{12}H_{25})_2{\bullet}3H_2O$, ($C_{24}H_{56}S_2O_{11}Cu$) Calcd. (found): C, 44.45 (44.00); H, 8.70 (8.07) %. $Ni(OSO_3C_{12}H_{25})_2{\bullet}2H_2O$, ($C_{24}H_{54}S_2O_{10}Ni$) Calcd. (found): C, 46.08 (46.01); H, 8.70 (9.51) %. $Co(OSO_3C_{12}H_{25})_2{\bullet}H_2O$, ($C_{24}H_{52}S_2O_9Co$) Calcd. (found): C, 48.88 (48.42); H, 8.54 (8.19) %.

4.2.3. Synthesis of lanthanide(III) dodecylsulfates

To a stirred aqueous solution (50 mL) of sodium dodecylsulfate (6 mmol, 1.73 g), a solution of $YbCl_3{\cdot}6H_2O$ (2 mmol, 0.77 g) in water (20 mL) was added dropwise at room temperature. The solution was left to stir for about 1 hour. The precipitate was then filtered on a crucible, washed thoroughly with water and dried in a vacuum oven at 50 °C over night to afford the pure $Yb(OSO_3C_{12}H_{25})_3$. The other lanthanide(III) dodecylsulfates were prepared in an analogous manner by using the corresponding lanthanide(III) chloride. Yields from 95% to 99% were obtained.

Elemental analysis results:

$Y(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}Y$) Calcd. (found): C, 46.94 (47.16); H, 8.64 (9.14) %. $La(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}La$) Calcd. (found): C, 44.52 (44.75); H, 8.14 (8.02) %. $Ce(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}Ce$) Calcd. (found): C, 44.47 (44.62); H, 8.19 (8.70) %. $Pr(OSO_3C_{12}H_{25})_3{\bullet}H_2O$, ($C_{36}H_{77}S_3O_{13}Pr$) Calcd. (found): C, 45.27 (45.36); H, 8.13 (8.54) %. $Nd(OSO_3C_{12}H_{25})_3{\bullet}_3 3H_2O$, ($C_{36}H_{81}S_3O_{15}Nd$) Calcd. (found): C, 43.48 (43.81); H, 8.21 (8.24) %. $Sm(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}Sm$) Calcd. (found): C, 44.00 (44.28); H, 8.10 (8.25) %. $Eu(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}Eu$) Calcd. (found): C, 43.93 (44.15); H, 8.09 (8.23) %. $Gd(OSO_3C_{12}H_{25})_3{\bullet}2H_2O$, ($C_{36}H_{79}S_3O_{14}Gd$) Calcd. (found): C, 43.70 (43.73); H, 8.05 (8.38) %.

$Tb(OSO_3C_{12}H_{25})_3{\cdot}2H_2O$, ($C_{36}H_{79}S_3O_{14}Tb$) Calcd. (found): C, 43.63 (43.84); H, 8.09 (8.58) %. $Dy(OSO_3C_{12}H_{25})_3{\cdot}2H_2O$, ($C_{36}H_{79}S_3O_{14}Dy$) Calcd. (found): C, 43.47 (43.53); H, 8.00 (8.57) %. $Ho(OSO_3C_{12}H_{25})_3{\cdot}2H_2O$, ($C_{36}H_{79}S_3O_{14}Ho$) Calcd. (found): C, 43.36 (43.14); H, 7.99 (8.02) %. $Er(OSO_3C_{12}H_{25})_3{\cdot}H_2O$, ($C_{36}H_{77}S_3O_{13}Er$) Calcd. (found): C, 44.06 (43.90); H, 7.91 (7.85) %. $Tm(OSO_3C_{12}H_{25})_3{\cdot}H_2O$, ($C_{36}H_{77}S_3O_{13}Tm$) Calcd. (found): C, 43.98 (43.94); H, 7.89 (8.48) %. $Yb(OSO_3C_{12}H_{25})_3{\cdot}H_2O$, ($C_{36}H_{77}S_3O_{13}Yb$) Calcd. (found): C, 43.80 (44.01); H, 7.86 (8.31) %. $Lu(OSO_3C_{12}H_{25})_3{\cdot}2H_2O$, ($C_{36}H_{79}S_3O_{14}Lu$) Calcd. (found): C, 42.93 (42.93); H, 7.91 (8.50) %.

4.2.4. Synthesis of ytterbium(III) alkylsulfates

To study the influence of the alkyl chain on the catalytic activity we also wanted to prepare ytterbium(III) octylsulfate, decylsulfate and tetradecylsulfate. No information on ytterbium(III) octylsulfate was found in literature. Although various methods were tried, we were not able to synthesize ytterbium(III) octylsulfate. After mixing sodium octylsulfate and ytterbium chloride no precipitation was formed and if the water of this solution was removed by evaporation, the resulting powder was contaminated by ytterbium chloride and sodium octylsulfate residues. The reason might be that the hydrophobic C_8 alkyl chain is too short, so that the driving force for solution of the headgroup ($-OSO_3-$) in aqueous media is strong enough to dissolve the whole molecule. The shorter the hydrophobic hydrocarbon tail of an anionic surfactant is, the higher is its solubility in water. This also explains why sodium tetradecylsulfate dissolves more difficultly in water than sodium dodecylsulfate. Therefore, during the preparation of ytterbium(III) tetradecylsulfate, the sodium tetradecylsulfate solution was heated up to 60 – 70 °C to solubilize the surfactant. After dissolution of the sodium tetradecylsulfate, the ytterbium chloride solution was added dropwise and the procedure for ytterbium(III) dodecylsulfate was further followed. The synthesis of ytterbium(III) decylsulfate was similar to the one for ytterbium(III) dodecylsulfate but after mixing sodium decylsulfate and ytterbium chloride the resulting white precipitate had to be filtrated immediately and washed with a very small amount of water since the complex re-dissolves easily in the aqueous solution.

Elemental analysis results:
$Yb(OSO_3C_{10}H_{21})_3{\bullet}3H_2O$, ($C_{30}H_{69}S_3O_{15}Yb$) Calcd. (found): C, 38.36 (38.02); H, 7.41 (7.75) %. $Yb(OSO_3C_{14}H_{29})_3{\bullet}2H_2O$, ($C_{42}H_{91}S_3O_{14}Yb$) Calcd. (found): C, 46.31 (46.48); H, 8.42 (8.75) %.

4.2.5. Synthesis of ytterbium(III) alkylsulfonates and arylsulfonates

Sulfonates dissolve less easily in water than sulfates because of their less polar headgroup. Therefore, in the synthesis of $Yb(O_3SC_{12}H_{25})_3$ and $Yb(O_3SC_{16}H_{33})_3$ the sodium salt had to be dissolved in water at 50 °C before adding the ytterbium(III) chloride. Then the mixture was cooled to room temperature and the resulting precipitate was filtered.

The synthesis of lanthanide(III) 4-alkylbenzenesulfonates was similar to the synthesis of ytterbium(III) dodecylsulfate but after mixing sodium 4-alkylbenzenesulfonate and ytterbium(III) chloride the resulting white precipitate had to be filtrated immediately and washed with a very small amount of water since the complex re-dissolves easily in the aqueous solution.

Elemental analysis results:
$Yb(O_3SC_{12}H_{25})_3{\cdot}2H_2O$, ($C_{36}H_{79}S_3O_{11}Yb$) Calcd. (found): C, 45.17 (45.59); H, 8.32 (8.85) %. $Yb(O_3SC_{16}H_{33})_3{\cdot}H_2O$, ($C_{48}H_{101}S_3O_{10}Yb$) Calcd. (found): C, 52.05 (51.98); H, 9.19 (9.35) %. $La(O_3SC_6H_4C_{12}H_{25})_3{\cdot}H_2O$, ($C_{54}H_{89}S_3O_{10}La$) Calcd. (found): C, 57.23 (57.44); H, 7.91 (7.56) %. $Gd(O_3SC_6H_4C_{12}H_{25})_3{\cdot}H_2O$, ($C_{54}H_{89}S_3O_{10}Gd$) Calcd. (found): C, 56.31 (56.52); H, 7.78 (7.27) %. $Yb(O_3SC_6H_4C_{12}H_{25})_3{\cdot}4H_2O$, ($C_{54}H_{95}S_3O_{13}Yb$) Calcd. (found): C, 53.09 (53.10); H, 7.84 (7.92) %.

4.2.6. Discussion

The complexes were characterized by elemental analysis, which indicated that upon drying the crystalline solid at 50 °C in vacuo, some water of crystallization is lost, but the complexes still contain about one to three molecules of water. As the coordination number of lanthanides is in general high (commonly eight or nine), it is likely that upon removal of hydrated water molecules from the crystal, the sulfate anions move and act as multidentate ligands forming more metal-oxygen bonds to replace the removed water oxygen atoms. Proton NMR spectra of the paramagnetic $Eu(DOS)_3$ and the diamagnetic $Y(DOS)_3$ complexes in deuterated water solutions were nearly identical, implying that dodecylsulfate counter ions are essentially spectator ions located in the outer sphere, and that the first coordination sphere around the lanthanide(III) ion is occupied by water molecules.

4.3. Allylation of aldehydes with Lewis acid-surfactant-combined catalysts

4.3.1. General procedure for the allylation of benzaldehyde

To a solution of the respective Lewis acid surfactant catalyst (10 mol%, 0.025 mmol) in water (1.5 mL) was added benzaldehyde (0.25 mmol; 25µL) and tetraallyltin (0.075 mmol; 18µL). The mixture was stirred at room temperature. After a given period of time the reaction mixture was extracted with ethyl acetate. The organic phase was diluted in acetone and analyzed by gas chromatography to obtain the yield of the reaction. The analyses were performed using the following temperature program: elution at 50 °C for 2 minutes, followed by ramping at 20 °C/min to 250 °C and maintaining this final temperature for 3 minutes.

When the reaction mixture was prepared in deuterated water solutions, the reaction progress could be conveniently monitored by proton NMR spectroscopy. As Figure 4.1 shows, in the presence of diamagnetic $Y(DOS)_3$ catalyst, peaks which can be assigned to benzaldehyde and tetraallyltin were observed in the beginning of the reaction. Interestingly, the proton NMR resonances of tetraallyltin are slightly shifted (upfield) compared to proton NMR resonances in pure water, which is probably due to the hydrophobic interactions with the alkyl chains of dodecylsulfate anions. After 24 hours of reaction at room temperature, the resonances corresponding to the starting products disappeared, while new resonances corresponding to the final reaction product, 1-phenyl-3-buten-1-ol, could be detected in the proton NMR spectrum.

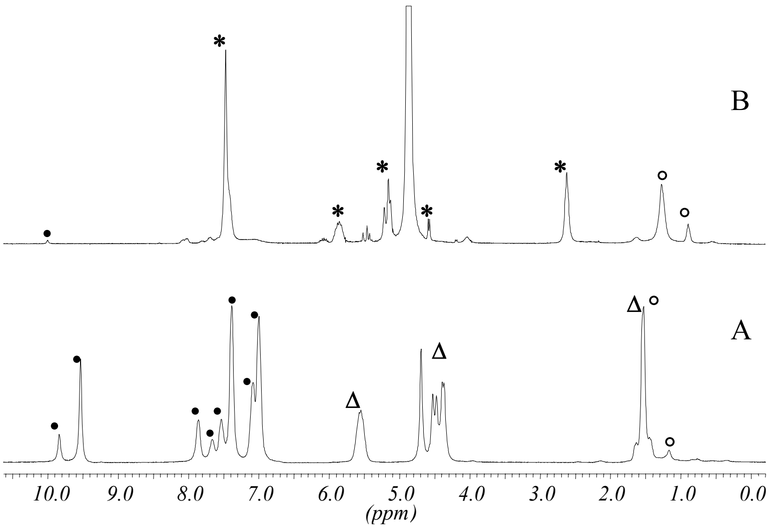


Figure 4.1 Proton NMR spectrum of solutions in D_2O *containing (A): benzaldehyde (black circles), 0.3 equivalents of tetraallyltin (white triangles) and 10 mol% of* $Y(DOS)_3$ *(white circles) upon mixing, (B): the product of the reaction 1-phenyl-3-buten-1-ol (stars) formed after 24 hours of reaction.*

4.3.2. Effect of the amount of allylating agent

Because tetraallyltin contains four allyl groups, in theory every molecule of tetraallyltin should react with four molecules of benzaldehyde, resulting in an atom-economic reaction. However, as Figure 4.2 shows, the allylation of benzaldehyde performed with 0.25 equivalents of tetraallyltin does not result in quantitative yields even after prolonged reaction times. When the experiments were performed with 0.3 equivalents of tetraallyltin it was noticed that this small excess of tetraallyltin results in a rather large increase in the reaction yields. From Figure 4.3 can be seen that using 0.3 equivalents of tetraallyltin instead of 0.25 under the same conditions resulted in the increase of 1-phenyl-3-buten-1-ol yield from 73% to 90%. Therefore, we always used 0.3 equivalent of tetraallyltin in further experiments.

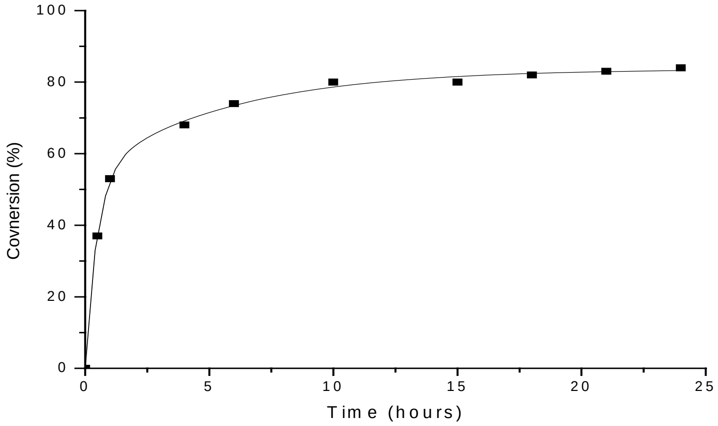


Figure 4.2 Conversion of 1 equivalent benzaldehyde to 1-phenyl-3-buten-1-ol in the presence of 0.25 equivalents of tetraallyltin and 10 mol% of Yb(DOS)$_3$ at room temperature, followed as a function of time.

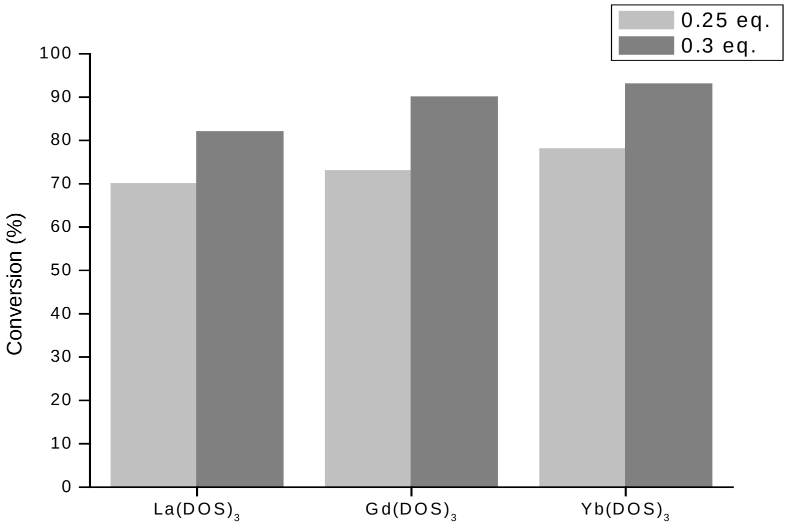


Figure 4.3 Effect of the amount of tetraallyltin on the conversion of benzaldehyde to 1-phenyl-3-buten-1-ol, with 10 mol% of Ln(DOS)$_3$, 6 hours, room temperature.

4.3.3. Screening of transition metal(II) and lanthanide(III) dodecylsulfates

In order to test the efficiency of the catalysts, the yields of 1-phenyl-3-buten-1-ol were measured after four hours of reaction time at room temperature. As can be seen in Figure 4.4, the allylation reaction performed in the absence of any catalyst (blank reaction) resulted in low yields. In contrast to ytterbium(III) tosylate, Yb(TOS)$_3$, all metal dodecylsulfate complexes exhibited catalytic activity, but noticeable differences in the reactivity were observed. While nickel(II) dodecylsulfate gave only 53% conversion to 1-phenyl-3-buten-1-ol, copper(II) dodecylsulfate yielded 93% conversion under the same conditions. The yields in the presence of Ln(DOS)$_3$ (Ln = La, Gd, Yb) catalysts were somewhat smaller. However, after six hours of reaction time (Figure 4.5) the efficiency of Yb(DOS)$_3$ was comparable to the efficiency of Cu(DOS)$_2$, as seen by 95 vs. 97% reaction yield respectively. Previous studies involving LASCs have suggested that they act both as a catalyst which activates the substrate molecules and as a surfactant forming micelles in which the reactants are dissolved. Our results shown in Figure 4.5 are consistent with these findings. Low yields obtained with the strong Lewis acid ytterbium(III) tosylate, which can not form micellar systems, imply that formation of a hydrophobic reaction medium facilitates the allylation reaction. Similarly, low yields obtained in the presence of sodium dodecylsulfate, which forms micelles in solution, but acts as a weak Lewis acid suggest that merely presence of a micellar system is not sufficient for the efficient allylation of benzaldehyde.

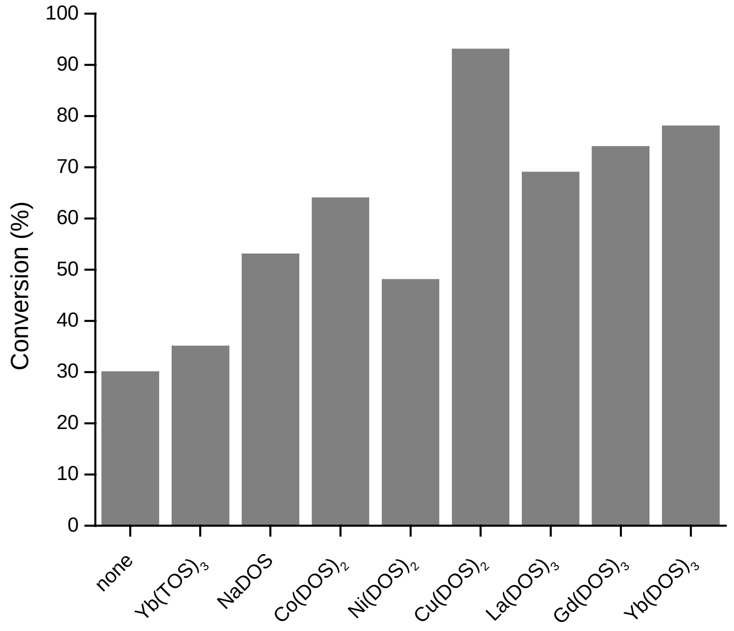


Figure 4.4 Screening of different catalysts in the reaction of benzaldehyde with 0.3 equivalents of tetraallyltin and 10 mol% of catalyst after 4 hours at room temperature.

The metal ion has an important role in the catalytic activity and, as can be seen in Figure 4.5, the yields of reaction depend on the nature of the metal ion used in the LASC. The differences in Lewis acidity between the metal cations can be expressed by the hydrolysis constants (K_h) and exchange rate constants for substitution of inner-sphere water ligands, expressed as water exchange rate constant (WERC).[240,241,242] Kobayashi and co-workers have suggested that metals should have a pK_h in the range from about 4 to 10 and WERC values greater than 3.2×10^6 $M^{-1}s^{-1}$ in order to be effective catalysts in aldol reactions.[100] When pK_h values are larger than 10, cations are generally difficult to hydrolyze which decreases their Lewis acidity. On the other hand, when pK_h values are less than 4, cations are easily hydrolyzed and oxonium ions are formed. However, under these conditions some organic substrates may be rapidly decomposed. As the aldehyde must coordinate to the metal cation to get activated, large WERC values are needed for effective reaction in aqueous medium.

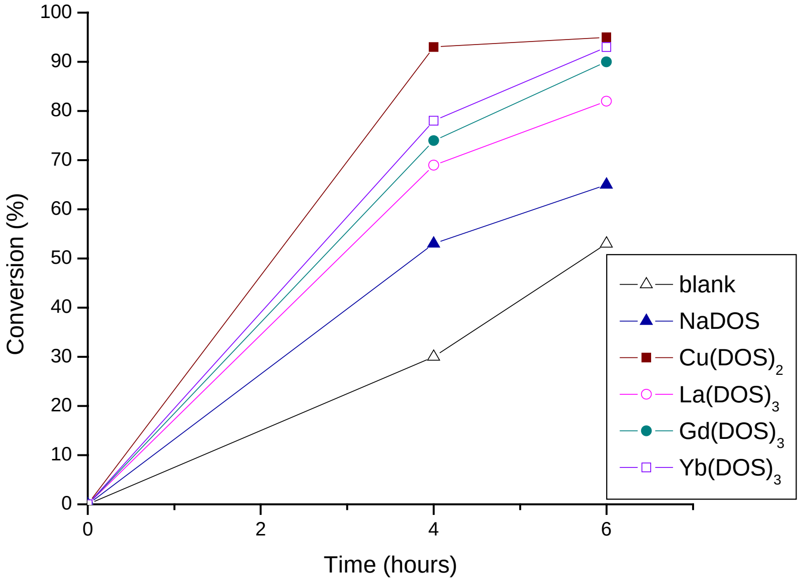


Figure 4.5 Influence of the nature of the metal ion in the dodecylsulfate complex on the extent of benzaldehyde conversion to 1-phenyl-3-buten-1-ol. The reaction was performed in the presence of 0.3 equivalents of tetraallyltin and 10 mol% of M(DOS)$_x$ at room temperature.

The low WERC values for Co^{2+} (2×10^5 $M^{-1}s^{-1}$) and Ni^{2+} (2.7×10^4 $M^{-1}s^{-1}$) explain their low Lewis acidic activity for the allylation of benzaldehyde in water. In contrary, Na^+ has a fast WERC (1.9×10^8 $M^{-1}s^{-1}$) but its pK_h value is too large (14.18), resulting in inefficient hydrolysis and low Lewis acidity. Inspection of pK_h and WERC values for copper(II) and lanthanide(III) shows that they are in the optimal range (pK_h values from 7.5 to 8.5, and the WERC values from 6×10^7 $M^{-1}s^{-1}$ to 7×10^8 $M^{-1}s^{-1}$).

Hence, low conversion of benzaldehyde to 1-phenyl-3-buten-1-ol in the presence of sodium, nickel(II) or cobalt(II) dodecylsulfate compared to a lanthanide(III) and copper(II) dodecylsulfate, can be explained either in terms of the high hydrolysis constants or low WERC values resulting in inefficient substitution of inner-sphere water ligands by benzaldehyde. Although the hydrolysis constants and WERC values of Cu^{2+} and Ln^{3+} are in the same range, the catalytic activity of Cu^{2+} was higher than that of Ln^{3+} in the initial stages of reaction. These differences are probably due to different molar ratios of the metal cations to dodecylsulfate anions. Highly charged metal cations, which form salts of low cation-to-anion ratios, should attenuate the headgroup repulsion of the anionic surfactant. As a result, the packing of the headgroups becomes tight which can reduce the probability of benzaldehyde to coordinate to the metal cation, resulting in the lower catalytic activity.[98]

4.3.4. Influence of the lanthanide(III) cation

As can be seen from Figure 4.6, apart from some anomalous results a small increase in reaction yield with decreasing ionic radius of the lanthanide(III) ion was observed. Reactions were at least three times performed and identical results were obtained validating the anomalous trend. Previous studies involving reactions catalyzed by lanthanide(III) tosylates revealed a similar trend.[243] Our NMR results suggest that in strongly coordinating solvents such as water, the first coordination sphere of all lanthanide(III) dodecylsulfates will be the same, since the coordinating solvent replaces DOS ligand to form strong Lewis acid species such as $[Ln(H_2O)_n]^{3+}$ (n = 8-9). The smaller ionic radius of trivalent lanthanide ion leads to a greater charge to size ratio (Z/r), which in turn results in greater polarizing power of the lanthanide(III) center. This polarization increases the electrophilicity of the carbonyl carbon, making this bond more susceptible to nucleophilic attack by tetraallyltin.

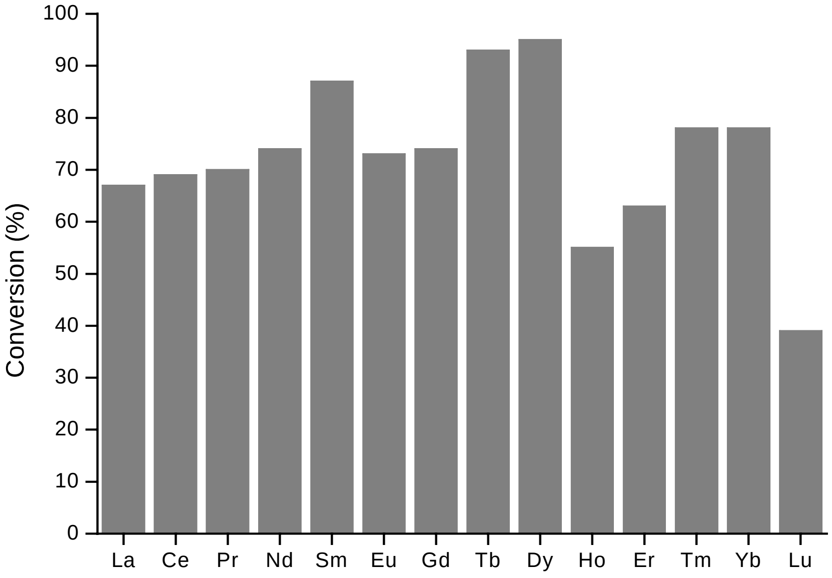


Figure 4.6 Influence of the nature of the lanthanide ion in the dodecylsulfate complex on the extent of benzaldehyde conversion to 1-phenyl-3-buten-1-ol. The reaction was performed in the presence of 0.3 equivalents of tetraallyltin and 10 mol% of Ln(DOS)$_3$ at room temperature.

4.3.5. Effect of the amount of catalyst on the extent of allylation

The effect of catalyst concentration on the reaction yields was examined by varying the concentration of the catalyst from 1 to 50 mol%. The results presented in Figure 4.7 show that when 20 mol% of Yb(DOS)$_3$ catalyst was used instead of 10 mol%, the yield of 1-phenyl-3-buten-1-ol increased from 78 to 92%. On the other hand, increasing the catalyst concentration from 20 mol% to 50 mol% resulted in an increase from 92 to 98%.

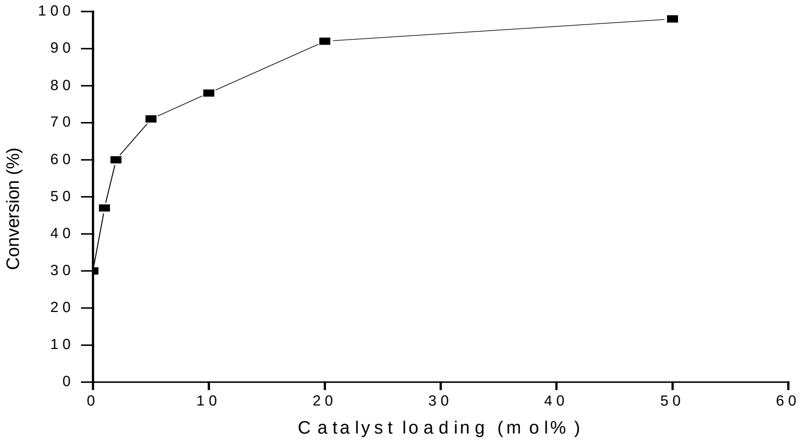


Figure 4.7 Effect of the ytterbium(III) dodecylsulfate loading on the allylation of benzaldehyde in the presence of 0.3 equivalents of tetraallyltin, after 4 hours at room temperature.

4.3.6. Effect of different surfactant anions on the catalysts efficiency

In order to examine the importance of the surfactant anions for the efficiency of LASC catalyst, ytterbium(III) complexes containing alkylsulfate and alkylsulfonate anions with different alkyl chain length were prepared and used as catalysts in the allylation of benzaldehyde. The results shown in Table 4.1 indicate that the ytterbium(III) alkylsulfates are more efficient catalysts than the corresponding ytterbium(III) alkylsulfonates, with the highest yield achieved by using ytterbium(III) dodecylsulfate. This trend is similar to the trend observed for aldol reactions catalyzed by scandium(III) alkylsulfates and scandium(III) alkylsulfonates.[93] The mixtures of Lewis acid-surfactant-combined catalyst and the organic substrates form dispersions, and the particle size and stability of these dispersions depend on the size and the nature of the surfactant anions. Higher yields of benzaldehyde allylation in the presence of ytterbium(III) alkylsulfate compared to the yields obtained with ytterbium(III) alkylsulfonate suggest that a better hydrophobic reaction field is formed in the presence of the former catalyst. This prompted us to explore the lanthanide(III) 4-alkylbenzenesulfonate catalysts for the allylation of benzaldehyde. Within four hours, $Ln(C_{12}H_{25}C_6H_4SO_3)_3$ (Ln = La, Gd, Yb) catalysts effected benzaldehyde conversion of ca. 50-55 %, compared to ca. 35% yields obtained with $Ln(C_{12}H_{25}SO_3)_3$ under the same conditions. This finding can be attributed to the π-π interaction between the molecules of the surfactant containing the aromatic group and benzaldehyde, which may lead to the stabilization of the substrates in the hydrophobic cavities.[244]

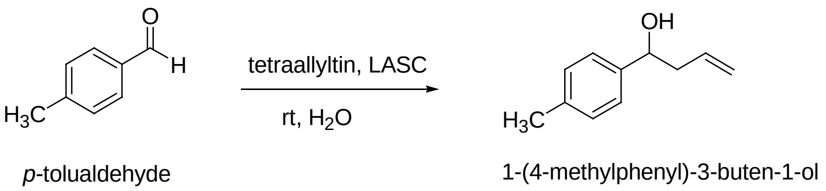
Table 4.1 Effects of the alkyl chain length in ytterbium(III) alkylsulfate and ytterbium(III) alkylsulfonate on the allylation of benzaldehyde.[a]

	Conversion (%)	
R	$Yb(OSO_3R)_3$	$Yb(OSO_2R)_3$
$C_{10}H_{21}$	64	n.d.
$C_{12}H_{25}$	78	38
$C_{14}H_{29}$	74	n.d.
$C_{16}H_{33}$	n.d.	37

[a] 4 hours at room temperature, 10 mol% of catalyst

4.3.7. Allylation of other aldehydes

The use of Lewis acid-surfactant-combined catalysts for the allylation of aldehydes is not restricted to the allylation of benzaldehyde. In this study the use of the less active *p*-tolualdehyde and *p*-anisaldehyde is also included. The allylation of *p*-tolualdehyde is very similar to that of benzaldehyde and 1-(4-methylphenyl)-3-buten-1-ol is formed (Scheme 4.4).



Scheme 4.4

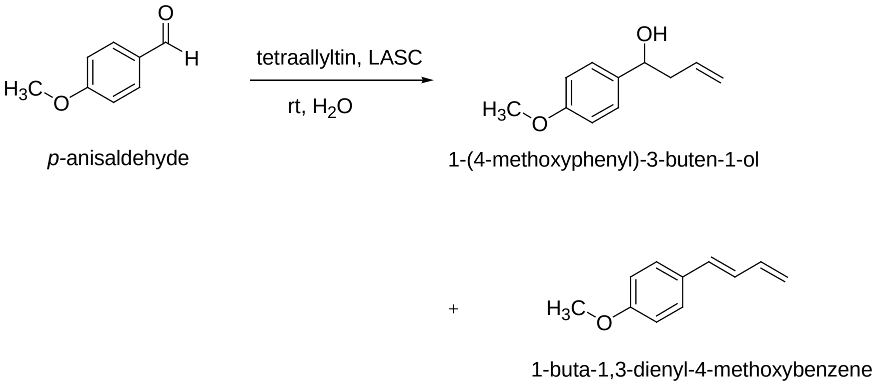
As can been seen from Table 4.2, the conversion of p-tolualdehyde into 1-(4-methylphenyl)-3-buten-1-ol increases from lanthanum to ytterbium. And similarly as in the reaction with benzaldehyde, after a short reaction time the highest conversion is obtained with copper(II) dodecylsulfate. However, after 24 hours of reaction complete conversion is also obtained with ytterbium(III) dodecylsulfate.

Table 4.2 Influence of the metal ion on the allylation of p-tolualdehyde.[a]

LASC	Conversion (%)
SDS	34
La(DOS)$_3$	56
Yb(DOS)$_3$	81
Cu(DOS)$_2$	>99

[a] 4 hours at room temperature, 10 mol% of catalyst

On the other hand, in the reaction with *p*-anisaldehyde, 1-(4-methoxyphenyl)-3-buten-1-ol and 1-buta-1,3-dienyl-4-methoxybenzene are detected (Scheme 4.5). The formation of 1-buta-1,3-dienyl-4-methoxybenzene was confirmed by GC-MS analysis and the mass spectrum was in accordance with the one found in literature.[245]



Scheme 4.5

The amount of 1-buta-1,3-dienyl-4-methoxybenzene increases with the reaction time and after 24 hours of reaction in the presence of 10 mol% of ytterbium(III) dodecylsulfate only 4% of 1-(4-methoxyphenyl)-3-buten-1-ol is left. As can be seen from Table 4.3, the effect of the metal ion is likewise to the reactions with benzaldehyde and *p*-tolualdehyde.

Table 4.3 Influence of the metal ion on the allylation of p-anisaldehyde.[a]

LASC	Conversion (%)	1-(4-methoxyphenyl)-3-buten-1-ol (%)
SDS	16	20
La(DOS)$_3$	75	55
Yb(DOS)$_3$	>99	77
Cu(DOS)$_2$	>99	60

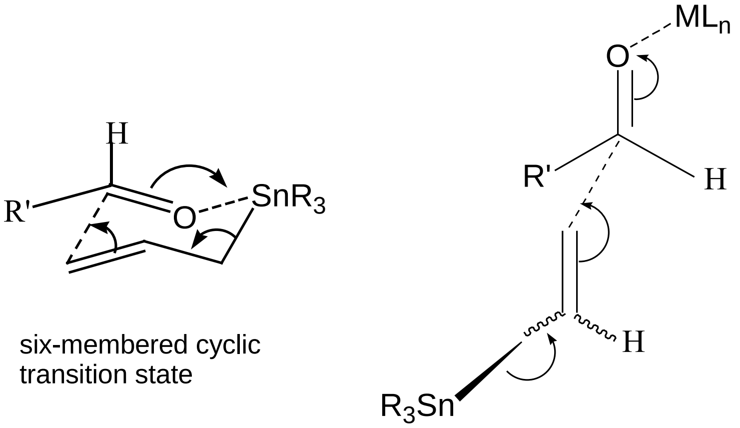
[a] 4 hours at room temperature, 10 mol% of catalyst

In conclusion, the allylation of tetraallyltin with benzaldehyde, *p*-tolualdehyde and *p*-anisaldehyde proceeds very well in the presence of 10 mol% of Lewis acid-surfactant-combined catalyst in water. Although *p*-tolualdehyde and *p*-anisaldehyde are normally less active aldehydes than benzaldehyde, complete conversion of *p*-tolualdehyde into 1-(4-methylphenyl)3-buten-1-ol is obtained after four hours when using copper(II) dodecylsulfate. 1-(4-methoxyphenyl)-3-buten-1-ol can also be obtained in relatively high amount when using ytterbium(III) dodecylsulfate if the reaction time is limited to avoid further conversion into 1-buta-1,3-dienyl-4-methoxybenzene.

4.3.8. Mechanism

As the obtained results are similar to those for Lewis acid-surfactant combined aldol condensation reactions in water, the reaction mechanism for LASC catalyzed allylation can be assumed to be similar to that of LASC catalyzed aldol reaction in water as postulated by Kobayashi and coworkers.[94] In the presence of organic substrates, an aldehyde and tetraallytin in our study, LASC molecules form stable colloidal particles in which the surfactant moiety of the LASCs surrounds the organic substrates. Furthermore, when the LASC is added to water it dissociates into the metal cation and the surfactant anion, and hydration of the metal occurs immediately to form a highly Lewis acidic species, $[M(H_2O)_n]^{x+}$. The countercations are attracted to the surface of the particles through electrostatic interactions between the anionic surfactant molecules and the cation. Although the metal cation is hydrated by several water molecules, these can readily be replaced by the aldehyde. Hence the aldehyde moves from the organic phase to the interface to coordinate to the cations. At this stage, the aldehyde is more reactive towards nucleophilic substances, such as tetraallyltin. From this mechanism, it is evident that the Lewis acidity of the metal cation strongly depends on the hydrolysis constants (K_h) and the exchange rate constants for substitution of inner-sphere water ligands by aldehyde molecules, expressed as water exchange rate constant (WERC).

The interactions between an aldehyde and tetraallyltin were extensively studied in the absence and presence of a Lewis acid catalyst.[216] In the absence of a catalyst, a six-membered cyclic transition state is formed and the tetraallyltin acts not only as the substrate but also as the Lewis acid. However, when a Lewis acid is present and coordinates with the carbonyl group, the reaction proceeds via an alternative pathway: an acyclic antiperiplanar and *anti*-S_E'-path is generally accepted. Both transition states are shown in Scheme 4.6 (R represents an allylic group and ML_n represents the metal complex). In the absence of a Lewis acid catalyst, the reaction shows diasterioselectivity, *syn* or *anti*, depending on the geometry of the reagent, Z or E, respectively. In the presence of a Lewis acid catalyst both Z and E tin compounds lead exclusive to the *syn* isomer.



six-membered cyclic transition state

antiperiplanar, *anti*-S_E' transition state

Scheme 4.6

4.3.9. Discussion

The results in this study indicate that the use of LASCs in water is powerful for the allylation of aldehydes. The LASC acts both as a catalyst to activate the aldehyde molecules, and is responsible for the formation of a hydrophobic unit in water which solubilizes organic substrates. This allows the use of water as the reaction medium, which is both economically and environmentally beneficial. There is no need for addition of organic co-solvents or Brønsted acids in this reaction system. However, as these reactions were performed on a small scale, ethyl acetate was necessary to extract the products from the reaction mixture. In order to apply the LASC system to large-scale synthesis, a workup procedure without using any organic solvents would be more desirable. Kobayashi reported centrifugation of the reaction mixture after performing LASC-catalyzed aldol reactions whereby the product is separated without using any organic solvent and in addition the LASC is recovered for further use.[94] After centrifugation the colloidal mixture becomes a tri-phasic system in which the LASC is deposited between a transparent water phase and an organic product phase. This procedure enables, on a large scale, recovery and reuse of LASCs and the separation of the organic products without using organic solvents. Although the use of organic solvents is unnecessary and the catalyst can be recovered, one can still question if this process fully meets the objectives of green chemistry because hazardous organometallic compounds such as tetraallyltin are required. However, to the best of our knowledge completely non-hazardous alternatives are not available for these kind of allylation reactions. Very often allyltributyltin, which is somewhat less toxic than tetraallyltin, is used in allylation reactions. But in these reactions one equivalent of allyltributyl is required for the allylation of one equivalent of aldehyde whereas the allylation using tetraallyltin only requires one fourth equivalent of organometallic compound. Hence, the use of tetraallyltin better satisfies the principle of atom efficiency.

Furthermore, it is reported that the resultant inorganic stannane salts are easily isolated following freeze drying of the aqueous phase.[235] Hence, the use of water also improves the isolation of the environmentally unfriendly tin containing byproducts.

4.4. Conclusions

In conclusion, we have shown that the allylation of aldehydes can be achieved in high yields in pure water by using several Lewis acid-surfactant combined catalysts (LASCs). Both the cation and the anion have a strong influence on the reactivity of the LASC. Variation of the anion showed that better results are obtained in the order alkylsulfates > arylsulfonates > alkylsulfonates with the highest conversions when using lanthanide(III) or copper(II) dodecylsulfate catalysts. Complete conversion is already obtained after four hours when using copper(II) dodecylsulfate, whereas the use of lanthanide(III) requires a few hours more to lead to complete conversion. Efficient catalysis by LASCs is not restricted to the allylation of benzaldehyde. While good conversions into the homoallylic alcohol are obtained for benzaldehyde and *p*-tolualdehyde, the homoallylic alcohol formed from *p*-anisaldehyde is dehydrated resulting in 1-buta-1,3-dienyl-4-methoxybenzene. Although conversions from benzaldehyde and *p*-tolualdehyde into the homoallyl alcohol are reported rather than isolated yields, it is evident from this study that fast conversion occurs at room temperature when using LASCs in water. The ability of these metal complexes to form stable dispersion systems in water and also to act as a catalyst activating the substrate molecules allows the use of water as the reaction medium, which is both economically and environmentally beneficial.

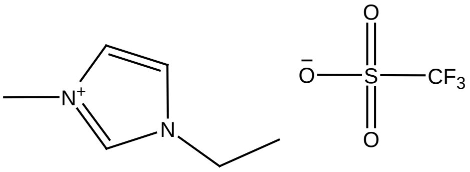
Chapter 5. Cerium(IV)-mediated reactions in ionic liquids

5.1. Introduction

Tetrahydrofuran, acetonitrile, dichloromethane and methanol are the most common solvents for oxidation reactions with ammonium hexanitratocerate (IV) (CAN). Nevertheless, these polar solvents are not suitable for the oxidation of some non-polar substrates. Bar reported that the range of possible substrates for oxidation reactions with CAN in dichloromethane is extended by addition of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4].[246] Mehdi and coworkers recently reported cerium(IV)-mediated organic reactions in an ionic liquid without the addition of any other solvent.[111] In this study the solubility of various cerium(IV) salts in imidazolium-based ionic liquids has been tested in order to obtain a homogeneous reaction system. Among the tested ionic liquids and cerium(IV) salts, the best solubility was found for CAN and cerium(IV) trifluoromethanesulfonate (commercially available as the hydrate $Ce(OTf)_4{\cdot}xH_2O$ with $x = 9$), in 1-ethyl-3-methylimidazolium triflate and 1-hexyl-3-methylimidazolium triflate. Based on these results we decided to further explore the use of CAN and $Ce(OTf)_4{\cdot}xH_2O$ in 1-ethyl-3-methylimidazolium triflate. The next section describes the most important properties of 1-ethyl-3-methylimidazolium triflate. Afterwards, the oxidation of naphthalene and 2-methylnaphthalene with $Ce(OTf)_4{\cdot}xH_2O$ and CAN will be discussed. However, as cerium(IV) is a one-electron oxidant, 6 equivalents of the cerium(IV) salt are required. Therefore, it is desirable to recover and reuse the cerium(IV) salt for subsequent oxidation reactions. The last section of this chapter discusses the electrochemical oxidation of cerium(III) to cerium(IV) in the ionic liquid.

5.2. Properties of 1-ethyl-3-methylimidazolium triflate

The ionic liquid used during this work is 1-ethyl-3-methylimidazolium triflate, abbreviated as [emim][OTf] or [C_2mim][OTf], (Scheme 5.1). This can be prepared from 1-ethylimidazole and methyl triflate.[247] The 1-ethyl-3-methylimidazolium triflate ionic liquid used in this study was purchased from IoLiTec as a red colored liquid and used without further treatment. Colored impurities are often present in ionic liquids in trace amounts and they cannot be detected by NMR nor identified by UV/VIS spectroscopy. Indeed, the proton NMR spectrum of [emim][OTf] we recorded showed no additional peaks but was identical to the predicted one. The chemical nature of the colored impurities is still not very clear, but it is probably a mixture of traces of compounds originating from the starting materials, oxidation products, and thermal degradation products of the starting materials.[32] Special precautions can be taken to obtain colorless ionic liquids but this is only required for UV/VIS experiments.



Scheme 5.1

Various properties of [emim][OTf] have been described by Bonhôte and coworkers and are summarized in Table 5.1.[247] Ionic liquids generally have higher viscosity than conventional organic solvents. Among the ionic liquids, the ones with perfluorinated anions have lower viscosity because strong delocalization of the negative charge weakens hydrogen bonding with the cation, and the viscosity increases as the perfluorinated chain of the anion becomes longer due to van der Waals interactions. The viscosity is also influenced by the structure of the cation. Alkyl chain lengthening or fluorination makes the salt more viscous due to increased van der Waals interactions. Furthermore, [emim][OTf] is hydrophilic and very well miscible with water.

Table 5.1 Properties of 1-ethyl-3-methylimidazolium triflate, [emim][OTf] [247]

Melting point	-9 °C
Thermal stability	up to 400 °C
Dynamic viscosity at 20 °C	45 cP
Ionic conductivity at 20 °C	8.6 mS cm^{-1}
Molar conductivity at 20 °C	1.61 $cm^2\ \Omega^{-1}\ mol^{-1}$
Density at 20 °C	1.39 g/cm^{-3}
Refractive index at 20 °C	1.4332

5.3. CAN-mediated reactions of naphthalene and 2-methylnaphthalene: nitration versus oxidation

5.3.1. Introduction

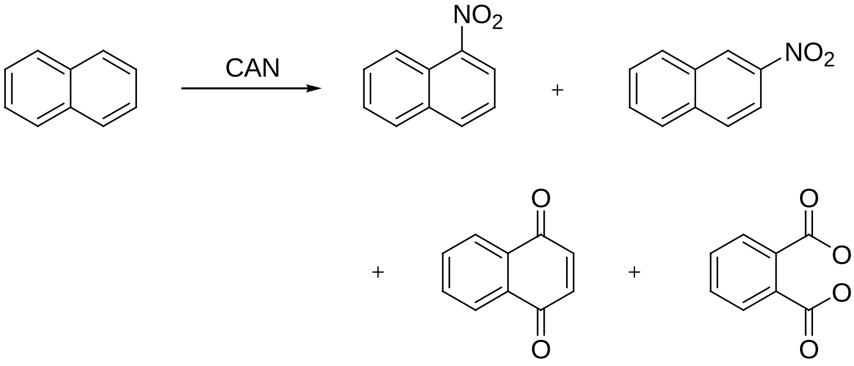
Naphthalene is a high-volume commercial product and is used to prepare many intermediates for the synthesis of dyes, medicines, pesticides, stabilizers and polymers.[248] A useful product derived from 2-methylnaphthalene by oxidation is 2-methyl-1,4-naphthoquinone, which is better known as menadione or vitamin K_3. It is used as a supplement for the vitamins K_1 and K_2 in animal feed and it is also a synthetic intermediate of vitamin K. Vitamin K_3 is produced on an industrial scale by oxidation of 2-methylnaphthalene with stoichiometric amounts of chromium(VI) oxide in sulfuric acid.[249] Other procedures to obtain menadione use catalytic amounts of metal derivatives in combination with strong oxidizing agents such as hydrogen peroxide and periodic acid.[250,251] Oxidation of 2-methylnaphthalene has also been reported without metal catalyst but such procedures require potent mixtures of strong acids. In this study, cerium(IV)-mediated oxidation of naphthalene and 2-methylnaphthalene in [emim][OTf] is investigated.

Furthermore, when CAN is used as the oxidizing agent, competition with aromatic nitration can be expected. Nitration of naphthalene derivatives has been reported with CAN suspended in dichloromethane in the presence of two equivalents of sulfuric acid.[252] CAN-mediated nitration of naphthalene has also been reported in acetonitrile.[253] This study revealed that under the same reaction conditions naphthalene and anisole are more reactive towards CAN than towards nitric acid, while similar reactivities were observed for the CAN and nitric acid mediated nitration of toluene. In ionic liquid medium aromatic nitration has been reported with nitric acid,[254,255] and some other nitrating agents.[147, 256] To the best of our knowledge, nitration reactions with CAN have not been performed in ionic liquids yet. Therefore, we combined the use of ammonium hexanitratocerate(IV) and ionic liquids as green solvents for oxidation and nitration of naphthalene and 2-methylnaphthalene.

5.3.2. General procedure for the CAN-mediated reaction of naphthalene and 2-methylnaphthalene

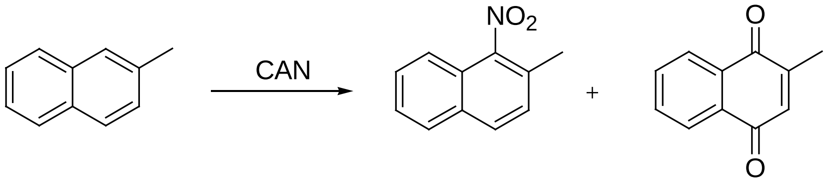
To a solution of CAN (1 mmol, 548 mg or 6 mmol, 3.288 g) in 1-ethyl-3-methylimidazolium triflate, [emim][OTf] (5 g, 3.6 mL) was added naphthalene (1 mmol, 128 mg) or 2-methylnaphthalene (1 mmol, 142 mg) and eventually some water (36 µL, 1 mL or 5 mL). At room temperature 6 mmol of CAN was not completely dissolved in 5 g of [emim][OTf], but a clear solution was obtained upon heating. The mixture was stirred and heated in an oil bath adjusted to 100 °C. After a given period of time the solution was cooled and extracted with toluene (5 X 5 mL). The organic phase was dried with $MgSO_4$, which also removes traces of ionic liquid that would contaminate the GC-apparatus. The resulting sample was diluted with acetone and GC-analysis was performed using the following temperature program: elution at 60 °C for 4 minutes, followed by ramping at 20 °C/min to 250 °C and maintaining this final temperature for 3 minutes.

As mentioned in Chapter 3, the nitration of naphthalene results in the formation of two isomers: 2-nitronaphthalene and 1-nitronaphthalene. On the other hand, formation of 1,4-naphthoquinone is expected under conditions suitable for oxidation. The oxidation of naphthalene derivatives into 1,4-naphthoquinones requires an oxygen source. Moreover, oxidation of an arene into a naphthoquinone requires six equivalents of cerium(IV) salt, as cerium(IV) is a one-electron oxidant, whereas nitration can be accomplished with only one equivalent of CAN as the nitrating agent. Depending on the reaction conditions, a small amount of naphthalene can be overoxidized to phthalic acid (Scheme 5.2). All compounds formed during the CAN-mediated reaction of naphthalene in [emim][OTf] were identified by GC-MS analysis.



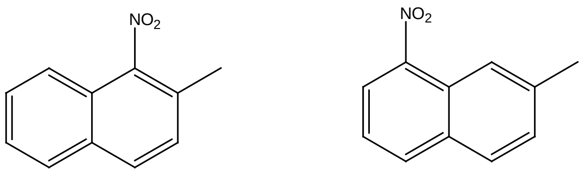
Scheme 5.2

In the CAN-mediated reactions of 2-methylnaphthalene in [emim][OTf] only 2-methyl-1,4-naphthoquinone was observed as the oxidation product, and no oxidation of the methyl group was observed. Moreover, depending on the reaction conditions various nitrated 2-methylnaphthalenes were obtained. Among these isomers, 1-nitro-2-methylnaphthalene was always formed as the major product (Scheme 5.3).



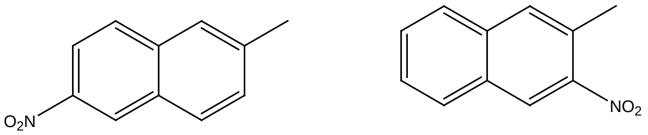
Scheme 5.3

This is in agreement with various other nitration procedures of 2-methylnaphthalene using nitric acid, wherein 2-methyl-1-nitronaphthalene is formed in the largest quantity (50-60%) among the six occuring nitrated isomers (Figure 5.1).[257] The other isomers were formed in the following order: 8-nitro > 4-nitro > 5-nitro > 6-nitro > 3-nitro (in trace amounts). Unfortunately, the other isomers formed during the CAN-mediated reaction in [emim][OTf] could not be identified by GC-MS analysis. These peaks could not completely be resolved for identification and consequently the integration of the peaks is not that accurate so that the amount of these isomers should be seen as an estimation. Probably, we can assume that the isomer distribution is similar to that of other procedures and that in our reactions also 7-methyl-1-nitronaphthalene (nitro function at position 8 if methyl group is counted as position 2), 3-methyl-1-nitronaphthalene (nitro function at position 4 if methyl group is counted as position 2) and 6-methyl-1-nitronaphthalene (nitro function at position 5 if methyl group is counted as position 2) are formed in detectable amounts.



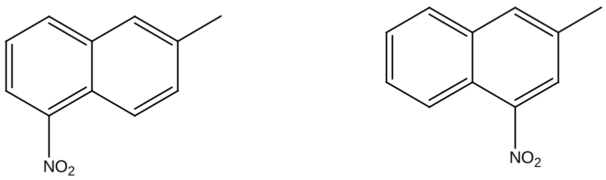
2-Methyl-1-nitro-naphthalene

7-Methyl-1-nitro-naphthalene



2-Methyl-6-nitro-naphthalene

2-Methyl-3-nitro-naphthalene



6-Methyl-1-nitro-naphthalene

3-Methyl-1-nitro-naphthalene

Figure 5.1 Different isomers formed upon nitration of 2-methylnaphthalene.

5.3.3. Oxidation versus nitration

As can be seen from Table 5.2, the extent of oxidation and nitration depends on the amount of CAN used and the presence of water in the ionic liquid. While the presence of water is necessary to obtain oxidation of naphthalene, it has a strong retarding effect on the nitration reaction (entry 2-3). Initially, the ionic liquid [emim][OTf] contained 0.05 mass% of water as determined with a Karl Fischer titrator. After drying the ionic liquid at 80 °C under vacuum or freeze-drying for several hours still 0.03

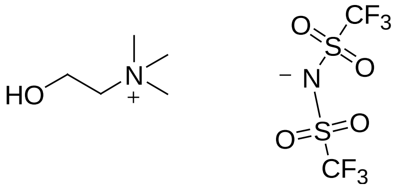
mass% of water was present in the ionic liquid. Consequently, we were not able to make this hydrophilic ionic liquid completely free of water. This explains why we always noticed trace amounts of oxidation products under conditions where complete nitration would be expected (entries 1-2). However, the amount of side-products could be reduced by increasing the reaction temperature. While still 7% of oxidation products (1,4-naphthoquinone and phthalic acid) were observed in the nitration reaction of naphthalene at 100 °C, only 2% of oxidation products were detected when performing the same reaction at 150 or 180 °C. In addition, complete conversion was already obtained after 1 hour using these higher reaction temperatures. Furthermore, entries 3, 4, 6 and 7 show the necessity of adding water to obtain a reasonable amount of 1,4-naphthoquinone. More than the theoretically necessary amount of water is desired for the formation of 1,4-naphthoquinone. The CAN-mediated reaction of naphthalene was also performed with compressed air as the oxygen source. When compressed air was bubbled through the reaction mixture, 78% of the naphthalene was nitrated while only 11% of 1,4-naphthoquinone and 11% of phthalic acid was formed. Hence, the oxidation of naphthalene towards 1,4-naphthoquinone proceeds better in the presence of water.

CAN-mediated reactions of naphthalene were also tested in the cheaper ionic liquids 1-ethyl-3-methylimidazolium methanesulfonate, [emim][OMs], and choline bis(trifluoromethylsulfonyl)imide, [chol][NTf$_2$] (Scheme 5.4). The reaction as in entry 4 for example was performed in [chol][NTf$_2$] but this resulted in a lower amount of 1,4-naphthoquinone (15%). On the other hand, the reaction as in entry 7 resulted in 66% of conversion in the ionic liquid [emim][OMs], which is comparable to the reaction in [emim][OTf]. The product distribution was also very similar: 77% of 1,4-naphthoquinone and 23% of nitronaphthalene isomers.

Table 5.2 CAN-mediated reaction of naphthalene in [emim][OTf] . [a]

Entry	CAN (eq.)	added amount of H_2O (mL)	Time (min.)	Conversion (%)	Product distribution (%)b[d]			
					1-nitro	2-nitro	NQ	PA
1	1	0	180	88	89	7	2	2
2	1	0	60	52	86	7	4	3
3	1	1	60	7	16	0	84	0
4	6	1	60	>98	62	5	32	1
5	6	0	30	>98	79	4	6	11
6	6	1	30	96	46	3	50	1
7	6	5	30	68	21	1	78	0

[a] 1 mmol of naphthalene in 5 g of [emim][OTf], oil bath adjusted to 100 °C; [b] 1-nitro: 1-nitronaphthalene, 2-nitro: 2-nitronaphthalene, NQ: 1,4-naphthoquinone, PA: phthalic acid.



Scheme 5.4

Table 5.3 shows that similar trends were observed for the CAN-mediated reaction of 2-methylnaphthalene. Moreover, the proton NMR spectrum of the ionic liquid recovered after the reaction showed no difference with the initial ionic liquid which indicates that the imidazolium cation is not nitrated in the presence of CAN under these reaction conditions.

Table 5.3 CAN-mediated reaction of 2-methylnaphthalene in [emim][OTf].[a]

CAN (eq.)	added H_2O (mL)	Time (h)	Yield (%)	Product distribution (%)[b]				
				NQ	1-nitro	8-nitro	4-nitro	5-nitro
1	0	1	>98	14	40	19	17	10
6	1	1	>98	54	30	8	5	3
6	1	5	>98	53	34	7	4	2

[a] 1 mmol of 2-methylnaphthalene in 5 g of [emim][OTf], oil bath adjusted to 100 °C; [b] NQ: 2-methyl-1,4-naphthoquinone, 1-nitro: 2-methyl-1-nitronaphthalene, 8-nitro: 7-methyl-1-nitronaphthalene, 4-nitro: 3-methyl-1-nitronaphthalene, 5-nitro: 6-methyl-1-nitronaphthalene.

5.3.4. Comparison of various nitration procedures

As seen from the previous results, naphthalene and 2-methylnaphthalene can efficiently be nitrated in [emim][OTf] in the presence of 1 equivalent of CAN as the nitrating agent. The nitration of naphthalene in [emim][OTf] was evaluated by comparison with the procedures in 1,2-dichloroethane and heptane as described in Chapter 3. The results are summarized in Table 5.4 and the isomer distribution was almost the same in all reactions (92 to 96% of 1-nitronaphthalene).

Table 5.4 Comparison of various procedures for the nitration of naphthalene.

Solvent [a]	Nitrating system	Time (h)	T (°C)	Conversion (%)
1,2-dichloroethane	1 eq. HNO_3 (65%)	1	Reflux (84°C)	84
1,2-dichloroethane	1 eq. HNO_3 (65%) + 10 mol% $Yb(TOS)_3$	1	Reflux (84°C)	87
heptane	1 eq. HNO_3 (65%)	1	Reflux (98 °C)	55
heptane	1 eq. HNO_3 (65%) + 10 mol% $Yb(TOS)_3$	1	Reflux (98 °C)	96
[emim][OTf]	1 eq. HNO_3 (65%) + 10 mol% $Yb(TOS)_3$	1	100 °C	15
[emim][OTf]	1 eq. HNO_3 (65%) + 10 mol% $Ce(OTf)_4$	1	100 °C	54
[emim][OTf]	1 eq. CAN	1	100 °C	52
[emim][OTf]	1 eq. CAN	3	100 °C	88
[chol][NTf_2]	1 eq. HNO_3 (65%) + 10 mol% $Yb(TOS)_3$	1	100 °C	78
[chol][NTf_2]	1 eq. CAN	1	100 °C	45

[a] 5 mL of 1,2-dichloroethane or heptane, 5 g of [emim][OTf] or [chol][NTf_2]

The highest extent of nitration is obtained in 1,2-dichloroethane, in which case a catalyst like Yb(TOS)$_3$ is unnecessary. But according to the classification of residual solvents by the U.S. Food and Drug Administration (see Chapter 1), 1,2-dichloroethane should be avoided and replaced by less hazardous solvents such as heptane or ionic liquids. Besides [emim][OTf], choline bis(trifluoromethylsulfonyl)imide, [chol][NTf$_2$], was also tested for this reaction. After 1 hour of reaction at 100 °C in the presence of 1 equivalent of nitric acid and 10 mol% of Yb(TOS)$_3$, 78% of nitronaphthalene was formed in [chol][NTf$_2$] compared to 15% in [emim][OTf]. Nonetheless, the ytterbium(III) tosylate catalyzed nitration with nitric acid is more efficient in heptane (96%) than in the tested ionic liquids [emim][OTf] and [chol][NTf$_2$]. From this results it is clear that [chol][NTf$_2$] is a better solvent than [emim][OTf] for the ytterbium(III) tosylate catalyzed nitration of naphthalene, whereas the nitration with CAN gave poor yields in [chol][NTf$_2$] due to the low solubility of CAN in this ionic liquid.

5.4. Cerium(IV) triflate-mediated oxidation of naphthalene and 2-methylnaphthalene

In order to obtain solely oxidation of naphthalene and 2-methylnaphthalene, reactions with Ce(OTf)$_4$·xH$_2$O instead of CAN were also studied. CHN-analysis revealed that the commercially available cerium(IV) trifluoromethanesulfonate (Aldrich) is nonahydrated. As mentioned earlier, six equivalents of Ce(OTf)$_4$·xH$_2$O are required for the oxidation of naphthalene. However, such a large amount of Ce(OTf)$_4$·xH$_2$O did not dissolve in [emim][OTf]. Therefore, reactions were performed with 1 equivalent of Ce(OTf)$_4$·xH$_2$O in order to see of some amount of 1,4-naphthoquinone could be obtained. But reaction of naphthalene in 5 g of [emim][OTf] and 1 mL of water in the presence of 1 equivalent of Ce(OTf)$_4$·xH$_2$O did not proceed. During this reaction the naphthalene did not dissolve very well and after a while it was accumulated at the entrance of the reflux cooler. Lowering of the temperature to 80 °C, to avoid refluxing of the water, gave also no reaction. Moreover, addition of 1 equivalent of nitric acid resulted neither in reaction.

5.5. Electrochemical regeneration of cerium(IV) in [emim][OTf]

5.5.1. Introduction

Electrochemical oxidation of cerium(III) to cerium(IV) and subsequent reuse in oxidation reactions has been reported by Kreh and coworkers in acidic solutions.[121] In continuation on the work in our research group on cerium(IV)-mediated oxidation reactions in ionic liquids (see previous section and work of Mehdi and coworkers),[111] investigation on the electrochemical regeneration of cerium(IV) in the ionic liquid is now reported. If cerium(IV) can also be regenerated directly in the ionic liquid, the use of ionic liquids is more beneficial than the use of acidic solutions.

Electrochemical experiments were performed galvanostatically in a two-compartment cell (Figure 5.2). The compartments are separated by a glass frit whose pore sizes are in the range 10−20 µm. A platinum wire was immersed in both compartments to perform the electrolysis. The compartments were filled with 5 mL of the respective solutions. First, the electrochemical oxidation of cerium(III) to cerium(IV) was reproduced in acidic solutions using our setup. Afterwards oxidation of cerium(III) to cerium(IV) in [emim][OTf] was studied with cyclic voltammetry, and finally electrolysis of the cerium salt in the ionic liquid was investigated.

Figure 5.2 Two-compartment cell.

5.5.2. Electrochemical oxidation of cerium(III) to cerium(IV) in acidic solution

Solutions of cerium(III) methanesulfonate and cerium(III) trifluoromethanesulfonate in the corresponding free acid were prepared according to the procedure reported by Kreh and coworkers.[121] To a stirred suspension of cerium(III) carbonate (13.25 g) in 40 mL of water, methanesulfonic acid (60 g; 40.5 mL) was added dropwise resulting in CO_2-evolution (Scheme 5.5).

$$Ce_2(CO_3)_3 + 6\ CH_3SO_3H \longrightarrow 2\ Ce(CH_3SO_3)_3 + 3\ CO_2 + 3\ H_2O$$

Scheme 5.5

This resulted in a solution of 0.72 M cerium(III) methanesulfonate in 5.64 M methanesulfonic acid. A turbid solution was obtained as cerium(III) was not completely soluble in this solution, which is in accordance with solubility studies.[117] A less concentrated solution of cerium(III) methanesulfonate in methanesulfonic acid was also prepared. This turbid solution of 0.41 M cerium(III) methanesulfonate in 4.21 M methanesulfonic acid was introduced in the anolyte compartment of the two-compartment cell, whereas the catholyte was filled with 6 M methanesulfonic acid. During electrolysis, the initially very pale yellow solution in the anolyte became darker yellow but remained turbid.

A solution of 0.857 M cerium(III) trifluoromethanesulfonate in 2.25 M trifluoromethanesulfonic acid was prepared following the same procedure. Again a turbid solution was obtained. In order to try to dissolve the cerium(III) trifluoromethanesulfonate completely, more water was added to the solution resulting in a solution of 0.353 M cerium(III) trifluoromethanesulfonate in 0.926 M trifluoromethanesulfonic acid. This solution was introduced in the anolyte compartment and 6 M triflic acid was used as the catholyte. The initially milky turbid solution became yellow during electrolysis. The catholyte solution on the other hand changed from yellow to colorless. After electrolysis, the amount of cerium(IV) present in the anolyte solution was determined from titration with Mohr's salt, $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$, as titrant and ferroin as indicator, which is in fact the tris(1,10-phenanthroline)iron(II) complex, $[Fe(phen)_3]^{2+}$. The results are summarized in Table 5.5. This titration revealed that 64% of cerium(III) was oxidized to cerium(IV). The experiment was repeated at 50 °C but then somewhat less conversion was obtained (51%). This is probably due to a higher amount of diffusion of cerium from the anolyte to the catholyte compartment.

A solution of $Ce(OTf)_3$ was also tested in a mixture of ionic liquid [emim][OTf] and water, acidified to prevent hydrolysis of cerium. $Ce(OTf)_3$ as above prepared in a triflic acid solution was isolated. The elemental analysis was in accordance with the calculated percentages taking in account hydrated water molecules. CHN-analysis: $Ce(OTf)_3 \cdot 9H_2O$ Calcd. (found): C, 4.81 (4.77); H, 2.42 (2.30) %. $Ce(OTf)_3$ (4.2 mmol) was dissolved in a mixture of [emim][OTf] (10 mL), water (2 mL) and triflic acid (1 mL). The resulting solution contained 0.323 M $Ce(OTf)_3$ and 0.462 M triflic acid in ionic liquid and water (5 to 1 mixture). During electrolysis the catholyte solution remained yellow. The anolyte solution, initially a cloudy red solution since the ionic liquid colors red from some small impurities, changed into a milky colored cloudy solution. After electrolysis at room temperature or 50 °C no Ce^{4+} was present in the solution. The previous results are summarized in Table 5.5.

Table 5.5 Electrolysis of $Ce(OTf)_3$ in acidic solution and in [emim][OTf].[a]

anolyte solution	temperature (°C)	conversion (%)
0.353 M $Ce(OTf)_3$ in 0.926 M TfOH	20	64
0.353 M $Ce(OTf)_3$ in 0.926 M TfOH	50	51
0.323 M $Ce(OTf)_3$; 0.462 M triflic acid; 10 mL IL – 2 mL water	20	0
0.323 M $Ce(OTf)_3$; 0.462 M triflic acid; 10 mL IL – 2 mL water	50	0

[a] 6 M triflic acid as catholyte solution

In conclusion, electrochemical oxidation of cerium(III) to cerium(IV) was reproduced in acidic solutions but lower conversion efficiency was obtained compared to the experiments performed by Kreh, which is probably due to differences in the used experimental setup. Because the exact size of the platinum wire used as the working electrode in our experiments is not known, comparison of the current density used in literature experiments and our experiments was not possible. Furthermore, no conversion was obtained in the cerium solutions in a mixture of ionic liquid and water. In the experiments containing IL no color change was observed in the anolyte and catholyte solution. On the other hand, in the experiments in aqueous solution the catholyte solutions changes from yellow to colorless. This is strange because the reaction in the catholyte is expected to be the same in all experiments.

5.5.3. Cyclic voltammetry of solutions of CAN in [emim][OTf]

In order to test the possibility of electrolytical oxidation of cerium(III) to cerium(IV) in [emim][OTf], cyclic voltammetry (CV) was used. Note that Mehdi reported already the observation of anodic oxidation peaks in preliminary cyclic voltammetry,[111] but this was now studied more extensively. A first series of experiments was performed with platinum wires as the working electrode, the counter electrode and the pseudo-reference electrode. The electrochemical window of the ionic liquid, [emim][OTf], was measured and turned out to be around 4V as reported in literature.[247] In the case of ionic liquids, the potential window depends on the resistance of the cation to reduction and the resistance of the anion to oxidation. The CV of the pure IL showed a small additional reduction peak, which is probably due to the coloring impurity in the IL.

Experiments were performed with CAN, $(NH_4)_2[Ce(NO_3)_6]$, because of its higher solubility in [emim][OTf] compared to $Ce(OTf)_4$. Cyclic voltammograms of solutions of 0.1 M, 0.2 M and 0.3 M of CAN in [emim][OTf] were measured and the peak currents at the oxidation and reduction increased linearly with increasing concentration. In order to have more precise information on the position of the potential window and the oxidation and reduction peak, experiments were performed using a reference electrode based on the ferrocene redox couple Fc/Fc$^+$ in [emim][OTf]. Calibration of this reference electrode in a solution of ferrocene in [emim][OTf] revealed a deviation of + 30 mV and the ferrocene reference electrode is + 400 mV compared to the standard hydrogen electrode (SHE). Hence, potentials measured versus the ferrocene reference electrode can be converted to potentials measured versus SHE by adding 430 mV to the potential. With this reference electrode, a solution of 0.3 M CAN in [emim][OTf] was measured. The working electrode used during this experiment has a surface of 0.2 mm^2. As can be seen in Figure 5.3, the reduction of cerium(IV) to cerium(III) occurs around 0.6 V (1.03 V versus SHE) and oxidation occurs around 0.9 V (1.33 V versus SHE).

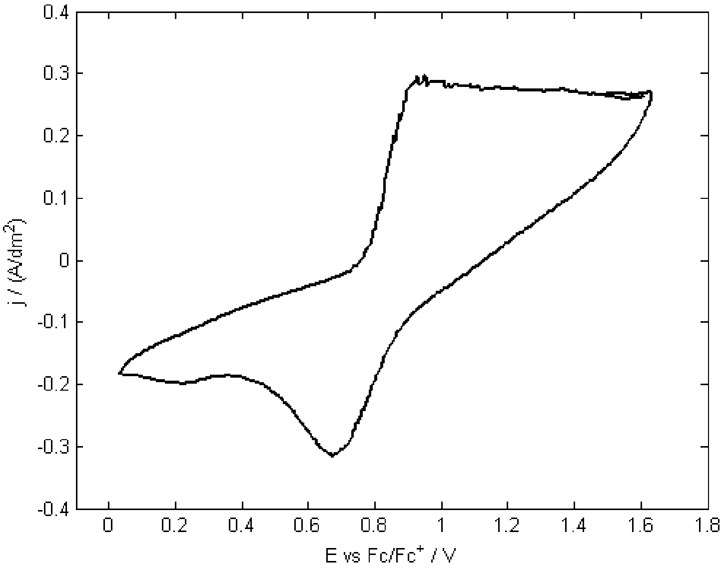


Figure 5.3 Cyclic voltammogram of a solution of 0.3 M CAN in [emim][OTf], measured at room temperature using a Pt working and Fc/Fc$^+$ reference electrode.

Strangely, after oxidation of cerium the current did not return towards zero. As the potential window of the pure ionic liquid showed that the ionic liquid is stable at this potential, this remaining current should originate from the addition of CAN, $(NH_4)_2[Ce(NO_3)_6]$. In order to exclude the oxidation of cerium(III), a solution of ammonium nitrate in [emim][OTf] was also examined. A solution of 0.1 M NH_4NO_3 in [emim][OTf] was prepared but NH_4NO_3 dissolved only partially in the ionic liquid. The CV of NH_4NO_3 in [emim][OTf] showed a somewhat higher current around 1.6 V compared to the CV of the pure ionic liquid. As the conductivity of both samples was nearly the same, this small difference in current does not originate from a difference in conductivity, but it can indicate that the ammonium ions are also partially oxidized. However, the oxidation of ammonium is not that likely under these conditions and maybe the fact that the current does not decrease to zero can be attribuated to the presence of water in the mixture. Further experiments in which the effect of water on the redox properties of cerium in [emim][OTf] was examined, indead indicated that the remaining water is decomposed at this potential.

5.5.4. Electrochemical oxidation of cerium(III) to cerium(IV) in [emim][OTf] after performing oxidation reactions

The cyclic voltammetry study of the previous section indicates that it should be possible to reoxidize cerium(III) to cerium(IV) directly in the ionic liquid [emim][OTf]. Hence, the ionic liquid phase obtained after the CAN-mediated oxidation reaction of benzyl alcohol to benzaldehyde was investigated for reoxidation of the cerium salt and reuse for further oxidation reactions. A mixture of 1 equivalent of benzyl alcohol and 2 equivalents of CAN in [emim][OTf] was heated and stirred in an oil bath at 100 °C during 6 hours under nitrogen atmosphere. Afterwards, the solution was extracted with toluene and the organic phase was analyzed with GC using dodecane as an internal standard. Almost complete conversion of benzyl alcohol into benzaldehyde was observed (95%), besides traces of benzyl alcohol and benzoic acid. Consequently, the resulting ionic liquid phase contained almost only cerium(III) salt. This ionic liquid phase was then evaporated under reduced pressure to remove traces of toluene. The resulting solution was introduced in the anolyte of the two-compartment cell. The catholyte was filled with pure ionic liquid to prevent contamination by an aqueous solution. During electrolysis for several hours the color of the solution changed from pale yellow to yellow-orange, which indicates that cerium(III) is oxidized to cerium(IV). During the subsequent reaction with benzyl alcohol the solution became yellow already after a short time. After 6 hours, the reaction mixture was extracted with toluene and the organic phase was analyzed with GC using dodecane as the internal standard. In this second run, 72% of benzyl alcohol was oxidized to benzaldehyde. Furthermore, the final ionic liquid phase was pale yellow to colorless. These experiments indicate that the cerium(III) that is obtained after the oxidation reaction was partially reoxidized to cerium(IV) directly in the ionic liquid, which makes it possible to reuse this ionic liquid mixture for subsequent oxidation reactions. However, complete conversion could not be obtained in the second run because some cerium was lost during the reoxidation due to diffusion of cerium from the anolyte to the catholyte.

5.6. Conclusions

Depending on the reaction conditions, the outcome of the CAN-mediated reaction of naphthalene and 2-methylnaphthalene in [emim][OTf] could be directed towards nitration or oxidation. In summary, the highest amount of 1,4-naphthoquinone was obtained when naphthalene (1 mmol, 128 mg) was left to react with six equivalents of CAN (6 mmol, 3.288 g) in the presence of 5 mL of water. On the other hand, almost exclusively nitration was obtained in the reaction with one equivalent of CAN at high temperature (> 100 °C) if no oxygen source was present. Furthermore, oxidation of naphthalene and 2-methylnaphthalene with $Ce(OTf)_4{\cdot}xH_2O$ was not successful.

However, as cerium(IV) is a one-electron oxidant several equivalents of the cerium(IV) salt are required in the investigated oxidation reactions. Therefore, recovery and reuse of the cerium salt was also studied. The redox properties of cerium in [emim][OTf] were studied with cyclic voltammetry. In addition, our experiments proved that the cerium(III) salt that was obtained after oxidation reactions could to a large extent be reoxidized to cerium(IV) directly in the ionic liquid and this cerium(IV)-containing ionic liquid could then be reused for subsequent oxidation reactions. To the best of our knowledge this is the first proof of principle that a cerium(IV)-containing ionic liquid can be reused for several oxidation reactions by electrochemical reoxidation of the cerium(III), that was formed during the oxidation reaction of an arene, directly in the ionic liquid.

General conclusions

In this PhD project, new procedures were investigated for various important organic reactions. Nowadays, organic procedures should not only result in high reaction yields and purity but moreover they should be designed to be environmentally friendly as well. Therefore, a proper choice of catalyst and solvent is an important aspect. In this study, greener solvents such as ionic liquids (chapter 5), water (chapter 4) and rather unhazardous organic solvents (chapter 3) were used. Moreover, this PhD research was focused on the use of lanthanide complexes in catalysis. The optimal reaction conditions as well as the role of the lanthanide ion in the reaction mechanism were investigated. Besides cerium(IV)-mediated reactions in ionic liquids (chapter 5), the use of lanthanide(III) compounds as strong Lewis acids was examined for the catalysis of various organic reactions (chapters 3 and 4).

Currently, acid-catalyzed organic synthesis is mostly performed using mineral acids or Lewis acids such as $AlCl_3$, $ZnCl_2$, BF_3, $TiCl_4$, $SnCl_4$, $BF_3 \cdot OEt_2$, … However, these conventional Lewis acids are often required in stoichiometric amounts and are not stable in the presence of water. In addition, large amounts of waste are formed during the work-up procedure as these Lewis acids can not be recovered and reused. Hence, new procedures in which less waste is produced are desired. During the last decade, lanthanide(III) triflates have been widely studied for numerous organic reactions to overcome the drawbacks of conventional Lewis acids. However, the disadvantages of triflate salts include their high cost and the fact that one needs to handle the corrosive triflic acid for their preparation. Based on the work of the groups of Kobayashi and Braddock concerning lanthanide(III) triflates, we investigated the use of lanthanide(III) salts of less corrosive and much cheaper aromatic sulfonic acids, such as *p*-toluenesulfonic acid and nitrobenzenesulfonic acids, as new Lewis acid catalysts. Lanthanide(III) tosylates and nitrobenzenesulfonates are straightforwardly prepared from the respective lanthanide(III) oxide and sulfonic acid. From the results presented in chapter 3, it can be seen that these complexes efficiently catalyze a variety of reactions like the nitration of aromatic compounds, the acylation of alcohols and the synthesis of calix[4]resorcinarenes. Complete conversion can already be obtained with only a few mol% of catalyst and moreover these catalysts are easily recovered and reused without loss in efficiency and selectivity. The presence of water in the reaction system does not deactivate the catalyst and even hydrated lanthanide(III) salts are effective. Besides trivalent lanthanides, commercially available iron(III) tosylate was also found to be an effective and recyclable catalyst. In addition, we have shown that lanthanide(III) chloride hydrates were also rather efficient catalysts for the acylation of alcohols and the formation of calix[4]resorcinarenes. Although lanthanide(III) chloride hydrates were also reusable and only required in catalytic amounts, their widespread use will probably be limited by solubility problems. Moreover, comparison of ytterbium(III) tosylate and ytterbium(III) chloride showed that ytterbium(III) tosylate is a somewhat superior catalyst. Additionally, hazardous solvents were avoided where possible. The nitration of aromatics for example could be performed in heptane, which is a less hazardous reaction solvent than the 1,2-dichloroethane nowadays used for this reaction. The results presented in chapter 3 demonstrated the efficiency of lanthanide(III) tosylates and nitrobenzenesulfonates as catalysts for various reactions and hence it is worth to extend the use of these catalysts for other Lewis acid-catalyzed reactions. In my opinion, the lanthanide(III) tosylates and nitrobenzenesulfonates form a really good alternative for the Lewis acids nowadays used.

Kobayashi and coworkers also reported that lanthanide(III) triflates can be used to perform reactions in water if a water-soluble organic solvent is added to solubilize the organic reagents. To overcome this solubility problem an anionic surfactant can be added to the Lewis acid. This lead to the development of *Lewis acid-surfactant combined catalysts* (LASCs). The use of LASCs has extensively been studied for some reactions as for example the aldol reaction but remained largely unexplored for reactions as for example the allylation of aldehydes. Our results in chapter 4 proved that lanthanide(III) and copper(II) surfactant-combined catalysts could efficiently be used in the allylation of benzaldehyde with tetraallyltin in water. Due to the formation of micelles the reaction could be achieved in the absence of organic solvents. Our results indicated that both the cation and the anion have a strong influence on the reactivity of the LASC. Variation of the anion showed that better results were obtained in the order alkylsulfates > arylsulfonates > alkylsulfonates with the highest conversions when using lanthanide(III) or copper(II) dodecylsulfate catalysts. Complete conversion was already obtained at room temperature after a few hours when using a few mol% of copper(II) dodecylsulfate, whereas the use of lanthanide(III) dodecylsulfate required a few hours more. Lewis acid-surfactant-combined catalysts act both as a catalyst activating the substrate molecules and as a surfactant forming micelles. Consequently, they allow the use of water as the reaction medium, which is both economically and environmentally beneficial. In order to extend the use of water as a reaction solvent, it is of interest to explore these Lewis acid-surfactant combined catalysts for other reactions.

In the last decades an enormous interest has arisen in the use of ionic liquids as ‘green solvents’. Based on the research performed in our group by Mehdi, cerium(IV)-mediated reactions in ionic liquids were further explored (chapter 5). The use of CAN, $(NH_4)_2Ce(NO_3)_6$, was studied for the oxidation and nitration of naphthalene and 2-methylnaphthalene in 1-

ethyl-3-methylimidazolium triflate, [emim][OTf]. Depending on the reaction conditions, the outcome of these CAN-mediated reactions could be directed towards nitration or oxidation. However, stoichiometric amounts of the cerium salt were required for these oxidation reactions. In order to obtain an attractive procedure, reuse of the cerium-containing ionic liquid is desirable. Our experiments proved that the cerium(III) salt, obtained after the oxidation reaction of benzyl alcohol to benzaldehyde, could to a large extent be reoxidized to cerium(IV) directly in the ionic liquid and this cerium(IV)-containing ionic liquid could then be reused for subsequent oxidation reactions. To the best of our knowledge this is the first proof of principle that a cerium(IV)-containing ionic liquid could be reused for several oxidation reactions by electrochemical reoxidation of the cerium(III) salt. As mentioned before it would be profitable to produce simultaneously with the regenerated cerium(IV) an other redox mediator in the reduced form. A next step would thus be the development of a process in which in the ionic liquid simultaneously trivalent cerium is oxidized and an other redox mediator, as for example titanium(IV), is reduced, analogue to the system developed by Harrison in acidic solution. As there is already a huge amount of ionic liquids known, a more profound study on the requirements of an ionic liquid in order to be an effective reaction solvent for cerium-mediated reactions can be interesting. Furthermore, an exploration of other cerium-mediated oxidation reactions in ionic liquids, in which the cerium salt can be recovered and reused directly in the ionic liquid, is worth to investigate.

Samenvatting

Tijdens dit doctoraatsproject werden nieuwe procedures onderzocht voor verscheidene belangrijke organische reacties. Tegenwoordig wordt van organische procedures niet enkel een hoog rendement en zuiverheid verwacht, maar ze worden ook verondersteld milieuvriendelijker te zijn. Om dit te bereiken speelt de keuze van katalysator en solvent een belangrijke rol. Gedurende deze studie werden milieuvriendelijkere solventen zoals ionische vloeistoffen (hoofdstuk 5), water (hoofdstuk 4) en eerder onschadelijke organische solventen (hoofdstuk 3) gebruikt. Daarenboven was dit doctoraatsonderzoek vooral gericht op het gebruik van lanthanideverbindingen in katalyse. Zowel de optimale reactieomstandigheden als de rol van het lanthanide-ion in het reactiemechanisme werden onderzocht. Naast het gebruik van vierwaardig cerium in reacties in ionische vloeistoffen (hoofdstuk 5) werd ook het gebruik van lanthanide(III)verbindingen als sterke Lewiszuren bestudeerd in uiteenlopende reacties (hoofdstukken 3 en 4).

Momenteel worden zuurgekatalyseerde organische reacties vooral uitgevoerd met minerale zuren of Lewiszuren zoals bijvoorbeeld $AlCl_3$, $ZnCl_2$, BF_3, $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, … Deze conventionele Lewiszuren zijn echter vaak vereist in stoechiometrische hoeveelheden en zijn niet stabiel in de aanwezigheid van water. Bovendien wordt er gedurende de opwerking een grote hoeveelheid afval gevormd doordat deze Lewiszuren niet teruggewonnen en herbruikt kunnen worden. Vandaar dat nieuwe procedures die minder afval produceren gewenst zijn. Gedurende de laatste decennia werden lanthanide(III)triflaten voor tal van organische reacties bestudeerd als alternatief voor de conventionele Lewiszuren. Triflaten hebben echter ook enkele belangrijke nadelen zoals bijvoorbeeld hun hoge kostprijs en het feit dat het erg corrosieve trifluormethaansulfonzuur vereist is voor hun bereiding. Gebaseerd op het werk van de onderzoeksgroepen van Kobayashi en Braddock omtrent lanthanide(III)triflaten, onderzochten we het gebruik van lanthanide(III)zouten van niet-corrosieve en veel goedkopere aromatische sulfonzuren, zoals *p*-tolueensulfonzuur en nitrobenzeensulfonzuren, als nieuwe Lewiszuren. Lanthanide(III)tosylaten en -nitrobenzeensulfonaten worden eenvoudig bereid uit hun respectievelijke lanthanide(III)oxide en aromatisch sulfonzuur. Uit de resultaten in hoofdstuk 3 blijkt dat deze complexen efficiënte katalysatoren zijn voor tal van reacties zoals bijvoorbeeld de nitrering van aromatische verbindingen, de acylering van alcoholen en de synthese van calix[4]resorcinarenen. Volledige omzetting kan al bereikt worden met slechts enkele mol% katalysator en bovendien kunnen deze katalysatoren eenvoudig teruggewonnen en herbruikt worden. De aanwezigheid van water in het reactiesysteem deactiveert de katalysator niet en zelfs gehydrateerde lanthanide(III)zouten zijn katalytisch actief. Naast driewaardige lanthaniden bleek ook het commercieel beschikbare ijzer(III)tosylaat een efficiënte en herbruikbare katalysator te zijn. Bovendien bleek uit ons onderzoek dat gehydrateerde lanthanide(III)chloriden ook behoorlijk efficiënte katalysatoren zijn voor de acylering van alcoholen en de vorming van calix[4]resorcinarenen. Alhoewel gehydrateerde lanthanide(III)chloriden ook herbruikbaar zijn en slechts in katalytische hoeveelheden vereist zijn, wordt hun algemeen gebruik toch wat begrensd door hun beperkte oplosbaarheid in heel wat organische solventen. Uit vergelijking van ytterbium(III)tosylaat en ytterbium(III)chloride blijkt echter ook dat ytterbium(III)tosylaat een enigszins betere katalysator is. Bovendien werden schadelijke solventen vermeden waar mogelijk. De nitrering van aromaten bijvoorbeeld kon uitgevoerd worden in heptaan, een minder schadelijk reactiesolvent dan het 1,2-dichloorethaan dat vandaag de dag voor deze reactie gebruikt wordt. De resultaten uit hoofdstuk 3 tonen dus aan dat lanthanide(III)tosylaten en nitrobenzeensulfonaten efficiënte katalysatoren zijn voor verscheidene reacties en het loont dus de moeite het gebruik van deze katalysatoren ook te onderzoeken voor andere Lewiszuur gekatalyseerde reacties. Mijns inziens vormen de lanthanide(III)tosylaten en lanthanide(III)nitrobenzeensulfonaten een goed alternatief voor de tegenwoordig gebruikte Lewiszuren.

Kobayashi en medewerkers rapporteerden ook dat lanthanide(III)triflaten gebruikt kunnen worden voor reacties in water indien een wateroplosbaar organisch solvent toegevoegd wordt om de reagentia op te lossen. Om dit oplosbaarheidsprobleem te vermijden kan ook een anionisch surfactant toegevoegd worden. Dit leidde tot de ontwikkeling van Lewiszuur-surfactant-gecombineerde katalysatoren (LASCs). Het gebruik van LASCs is uitgebreid beschreven voor enkele reacties zoals de aldolreactie maar werd niet uitvoerig onderzocht voor andere reacties zoals bijvoorbeeld de allylering van aldehyden. Onze resultaten uit hoofdstuk 4 tonen aan dat lanthanide(III)- en koper(II)surfactant-gecombineerde katalysatoren efficiënt zijn voor de allyleringsreactie van benzaldehyde met tetraallyltin in water. Door de vorming van micellen kan deze reactie uitgevoerd worden in de afwezigheid van organische solventen. Uit onze experimenten bleek dat zowel het anion als het kation een sterke invloed hebben op de reactiviteit van het LASC. Variatie van het anion toonde aan dat betere resultaten bekomen werden in de volgorde alkylsulfaten > arylsulfonaten > alkylsulfonaten, waarbij de hoogste omzetting bekomen werd bij het gebruik van lanthanide(III)- of koper(II)dodecylsulfaten. Volledige omzetting werd reeds na enkele uren bekomen bij reactie op kamertemperatuur in de aanwezigheid van enkele mol% koper(II)dodecylsulfaat, terwijl in het geval van lanthanide(III)dodecylsulfaten een iets langere reactietijd vereist was. Lewiszuur-surfactant-gecombineerde katalysatoren gedragen zich zowel als katalysator om de substraatmoleculen te activeren en als surfactanten die micellen vormen. Hierdoor kunnen organische solventen vervangen worden door water wat economisch voordeliger is en ook beter is voor het milieu. Om het gebruik van water als reactiesolvent uit te breiden, lijkt het mij interessant om het gebruik van deze Lewiszuur-surfactant-gecombineerde katalysatoren verder te bestuderen voor andere reacties.

In de laatste decennia is een enorme interesse ontstaan in het gebruik van ionische vloeistoffen als ‘groene solventen’. Gebaseerd op het onderzoek verricht in onze groep door Mehdi, werd het gebruik van cerium(IV) voor reacties in ionische vloeistoffen verder onderzocht (hoofdstuk 5). Het gebruik van CAN, $(NH_4)_2Ce(NO_3)_6$, werd bestudeerd voor de oxidatie en nitrering van naftaleen en 2-methylnaftaleen in 1-ethyl-3-methylimidazoliumtriflaat, [emim][OTf]. Afhankelijk van de reactieomstandigheden kan het resultaat van deze reactie beïnvloed worden in de richting van nitrering of oxidatie. Voor deze oxidatiereacties is echter een stoechiometrische hoeveelheid ceriumzout vereist. Om een aantrekkelijke procedure te bekomen is het hergebruik van de ceriumhoudende ionische vloeistof dus gewenst. Onze experimenten bewezen dat het driewaardig ceriumzout, bekomen na de oxidatiereactie van benzylalcohol tot benzaldehyde, grotendeels terug geoxideerd kon worden in de ionische vloeistof en deze cerium(IV)houdende ionische vloeistof kon dan gebruikt worden voor verdere oxidatiereacties. Voor zover we weten is dit het eerste bewijs dat een cerium(IV)houdende ionische vloeistof herbruikt kan worden voor oxidatiereacties na elektrochemische reoxidatie van het cerium(III) zout in de ionische vloeistof. Zoals reeds eerder vermeld zou het rendabeler zijn als gelijktijdig met het regenereren van cerium(IV) een andere redox-mediator in zijn gereduceerde vorm bekomen wordt. Een volgende stap is dus het ontwikkelen van een procédé waarbij in de ionische vloeistof gelijktijdig driewaardig cerium geoxideerd wordt en een andere redox-mediator, zoals bijvoorbeeld titanium(IV), gereduceerd wordt naar analogie van het systeem ontwikkeld door Harrison in zuur milieu. Aangezien er momenteel al een enorme hoeveelheid ionische vloeistoffen gekend zijn, kan het interessant zijn om een grondige studie uit te voeren naar de vereisten waaraan een ionische vloeistof moet voldoen om een efficiënt reactiesolvent te zijn voor reacties met cerium. Bovendien lijkt de uitbreiding naar andere oxidatiereacties met cerium, waarbij het ceriumzout in de ionische vloeistof teruggewonnen en herbruikt kan worden, mij de moeite waard om te onderzoeken.

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List of publications

- **“Lanthanide(III) complexes of aromatic sulfonic acids as catalysts for the nitration of toluene”**
  T.N. Parac-Vogt, K. Deleersnyder, K. Binnemans, *J. Alloys. Compd.* **2004,** 374, 46-49.

- **“Lanthanide(III) tosylates as new acylation catalysts”**
  T.N. Parac-Vogt, K. Deleersnyder, K. Binnemans, *Eur. J. Org. Chem.* **2005***, 9,* 1810-1815.

- **“Lanthanide-surfactant-combined catalysts for the allylation of benzaldehyde with tetraallyltin in aqueous solutions”**
  K. Deleersnyder, D. Shi, K. Binnemans, T.N. Parac-Vogt, *J. Alloys. Compd.* **2007**, doi:10.1016/j.jallcom.2007.04.161.

- **“Lanthanide(III) nitrobenzenesulfonates and *p*-toluenesulfonate complexes of lanthanide(III), iron(III), and copper(II) as novel catalysts for the formation of calix[4]resorcinarene”**
  K. Deleersnyder, H. Mehdi, I.T. Horváth, K. Binnemans, T.N. Parac-Vogt, *Tetrahedron* **2007**, *63*, 9063-9070.

- **“Lanthanide(III) and iron(III) chloride catalyzed formation of calix[4]resorcinarenes”**
  K. Deleersnyder, K. Binnemans, T.N. Parac-Vogt, submitted.

Attended conferences

- 7th Junior Conference of Chemistry in Flanders (VJC), 16 April 2004, Ghent (Belgium). Poster: "Lanthanide(III) tosylaten als Lewiszure katalysatoren voor de directe acetylering van alchoholen met azijnzuur".

- 8th Summer School on Green Chemistry, 5-11 September 2005, Venice (Italy). Poster: "Lanthanide(III) and copper(II) surfactant combined catalysts for the efficient allylation of benzaldehyde in water".

- CERC3 Young Chemists Workshop "Lanthanide-mediated organic reactions", 8-11 February 2006, Knokke (Belgium).

- 8th Junior Conference of Chemistry in Flanders (VJC), 7 April 2006, Leuven (Belgium). Lecture: "Lanthanide(III) tosylaten en nosylaten als Lewiszure katalysatoren voor milieuvriendelijke organische reacties".

- 6th International Conference on f-elements, 4-9 September 2006, Wroclaw (Poland). Poster: "Lanthanide(III) tosylates and nosylates as novel Lewis acid catalysts for environmentally friendly organic reactions".

- Workshop "Lewis acidity in catalysis", 7-8 December 2006, Leuven (Belgium). Poster: "Lanthanide(III) tosylates and nosylates as novel Lewis acid catalysts for environmentally friendly organic reactions"