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The Direct Synthesis of 2-Oxazolines from Carboxylic Esters Using Lanthanide Chloride as Catalyst

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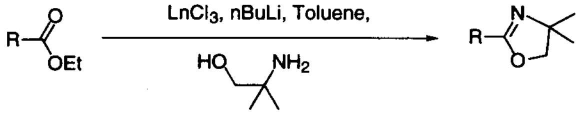
Abstract: Using catalytic amounts of lanthanide III (Ln = La, Sm) chlorides and amino alkoxides as reagents, an one-pot direct synthesis for 2-oxazolines, in good yield, from carboxylic esters has been developed. © 1997 Elsevier Science Ltd.

The use of lanthanide(III) compounds as catalysts or promoters in organic synthesis is a topic of extreme interest in the recent literature[1]. Lanthanide additives or complexes can enhance the reactivity and selectivity for numerous types of reactions: reduction, carbon-carbon bond formation, aldol condensations, cycloadditions, ring opening and polymerization to name just a few. Although lanthanide triflates, alkoxides and amides have been extensively used, the use of lanthanide amino alkoxide complexes as reagents has yet to be reported. Here we wish to report our preliminary investigation concerning the synthesis of 2-oxazolines from carboxylic esters and lanthanide 2-amino alkoxide complexes that were prepared *in situ* using an amino alcohol and lanthanide chlorides.

2-Oxazoline compounds have various synthetic uses in modern organic synthesis[2]. 2-Oxazolines are efficient directors for ortho-metalation, nucleophilic substitution, addition to aromatic systems, lateral metalation in heteroaromatic systems[3], for metalation, pericyclic reactions, and conjugate addition in aliphatic oxazolines. Oxazolines are used as a protecting group for carboxylic acids resisting nuleophiles, bases, and radicals[4]. Chiral bis-oxazolines are excellent ligands for catalytic asymmetric synthesis[5].

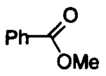
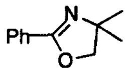
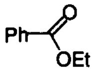
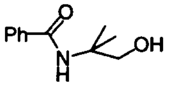
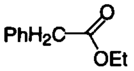
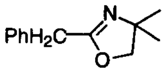
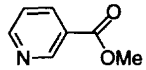
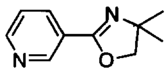
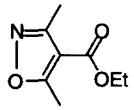
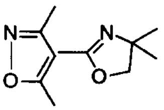
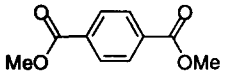
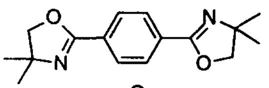
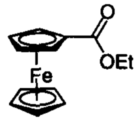
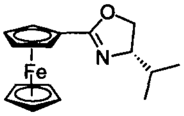
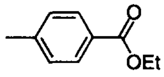
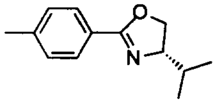
We have found that 2-amino-2-methylpropoxide, which was easily prepared *in situ* from 2-amino-2-methyl-1-propanol and n-butyllithium, complexed with a 5-10% molar equivalent of anhydrous lanthanide chloride suspension in toluene and reacted with different carboxylic esters to produce 2-oxazolines (Table). The product was isolated in up to 82% yield depending on the ester used. Lanthanum or samarium trichlorides effected good yields of oxazoline formation. However, with lanthanum triflate the reaction stopped at the corresponding amide intermediate. The reaction procedure is straight forward and product recovery is conveniently achieved using aqueous extraction.

Although there are several different synthetic methods for oxazolines, general and direct routes from carboxylic derivatives, especially from carboxylic esters are not common[2], this new method will have a valuable synthetic application for the synthesis of 2-oxazolines directly from carboxylic esters in consideration its simplicity applicability and efficiency, which could make this new protocol to be largely preferred to other ones previously described: Compared with the traditional four-step and three-intermediate route from esters to 2-oxazolines, this conversion is more direct and efficient (for example: Entry 6 the best literature yield was 55%[6]); compared with Vorbruggen's recent excellent one-pot method from carboxylic acids[7], our route is very facile, suitable for the oxazoline synthesis directly from carboxylic ester as starting compounds, and has comparable yields.



Further studies defining the full scope and limitations of this method are currently under investigation.

Table. Summary of Lanthanide Catalyzed Reactions of Esters with Amino Alkoxides

Entry	Substrate	$LnCl_3$ Equivalent	Product	Isolated yield, %
1		0.10 $LaCl_3$		81.8
2		0.050 $LaCl_3$		79.4
3		0.050 $LaTf_3$		0(100)*
4		0.050 $LaCl_3$		75.4
5		0.10 $LaCl_3$		64.1
6		0.10 $SmCl_3$		82
7		0.20 $LaCl_3$		44
8		0.10 $SmCl_3$		52
9		0.10 $SmCl_3$		54 (40)*

* Isolated yield of corresponding amide.

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7. Vorbruggen H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.
8. *Typical experimental procedure:* To a flask charged with anhydrous lanthanum chloride (0.2 mmol) was added 20 ml dry toluene and 2-amino-2-methyl-1-propanol (5 mmol), then nBuLi (1.99 M in pentane, 4.4 mmol) was added to this suspension at 0°C. After the reaction was stirred at 0°C for 15 minutes, the flask was warmed to reflux (100°C). Carboxylic ester (2 mmol) was added and the reaction mixture was refluxed for an additional 12 hours. The suspension was cooled to room temperature, after filteration and washing with chloroform (3 x 15mL), extractive isolation gave the desired product in very pure form. Further purification can be carried out with kugelrohr distillation or flash chromatography (silica gel; EtOAc: Hexane).
9. The rotation data for Entry 8: Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S., *J. Org. Chem.* **1996**, *61*, 4937.

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