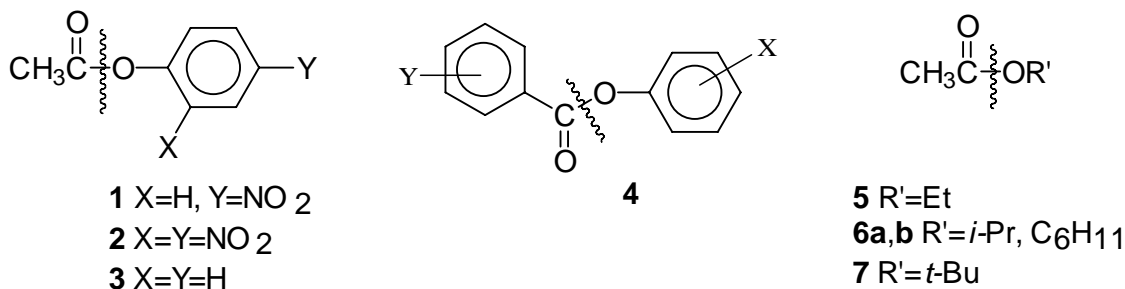
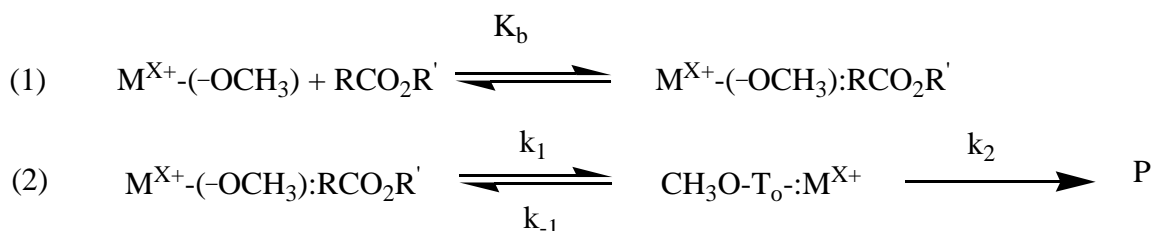


Chiral Resolution of Esters and Lactones

In this project we are interested in creating metal-ion catalysts to promote the enantioselective/enantiospecific cleavage of esters via a metal-catalyzed transesterification. As we have shown that La^{3+} , Eu^{3+} and a Zn^{2+} -complex¹ can promote the transesterification of a variety of esters such as:



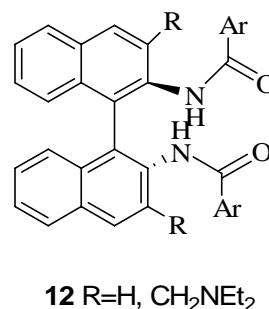
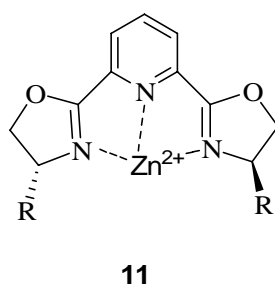
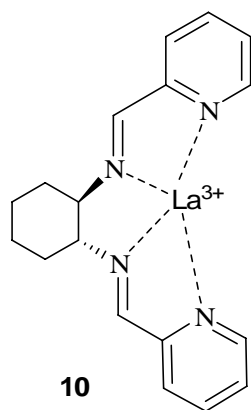
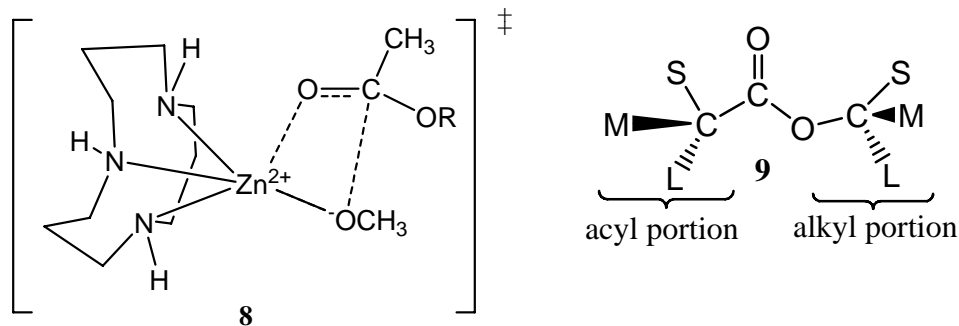
Through detailed mechanistic evaluation^{1c} we showed that the mechanism for the process involves a binding step for the association of the metal catalyst and the substrate, followed by an intracomplex delivery of the metal-coordinated methoxide to the C=O unit of the coordinated ester to give a tetrahedral intermediate. For some leaving groups



(poor ones whose conjugate acids have high pK_a values in methanol), breakdown of the tetrahedral intermediate is rate limiting, while for good leaving groups (whose pK_a in methanol is low) formation of the tetrahedral intermediate is rate limiting.

These reactions are very efficient. For example, a 1 molar solution of ethyl acetate (**5**) in methanol at 25 °C in the presence of 2 mM of La^{3+} ion and 2 mM of added NaOCH_3 decomposes with a half time of about 7 minutes, affording at least a million-fold acceleration over the reaction at neutral pH in the absence of catalyst. Interestingly, the active form of the La^{3+} catalyst is $\text{La}^{3+}_2(\text{OCH}_3)_2$, while the active form of the Zn^{2+} -complex is the 1,5,9-triazacyclododecane: $\text{Zn}^{2+}(\text{OCH}_3)$ form, shown in **8** as the presumed transition state in promoting the transesterification reaction.^{1c}

The next facet of this research is to determine whether the La^{3+} or Zn^{2+} catalysts, if bound to ligands that are chiral, can select a single enantiomer of an ester (**9**) and perform a 'chiral kinetic resolution' by selectively reacting with it. Such esters can be chiral in either the acyl or alkyl portion. Ligands **10-12**, for example, should bind the metal ions tightly under the catalytic conditions, and may provide the correct chiral environment for the reaction to proceed. After synthesis and characterization of the metal complexes, we will look at the ability of their methoxy complexes to promote the transesterification in methanol, and various solvents containing lesser amounts of methanol. In addition, we will look at the ring opening reactions of chiral lactones to see if the catalysts can select one of the enantiomers preferentially.



1 (a) Alexei A. Neverov, Todd McDonald, Graham Gibson, and R.S. Brown “Ln^{x+} Catalyzed Transesterifications. Million-Fold Acceleration of Transacylation from Esters to Methanol Promoted by La³⁺.” *Can. J. Chem.* **2001**, 79, 1704-1710.

(b) Alexei A. Neverov, Graham Gibson and R. S. Brown. “Europium Ion Catalyzed Methanolysis of Esters at Neutral pH and Ambient Temperature. Catalytic Involvement of $\text{Eu}^{3+}(\text{CH}_3\text{O})(\text{CH}_3\text{OH})_x$.” *Inorg. Chem.* **2003**, 42, 228-234.

(c) Alexei A. Neverov, N. E. Sunderland and R. Stan. Brown “Metal Ion Promoted Transesterifications of Carboxylate Esters. A Structure/Activity Study of the Efficacy of Zn²⁺ and La³⁺ to Catalyze the Methanolysis of Some Aryl and Aliphatic Esters.” *Org. Biomol. Chem.*, **2005**, 3, 65 - 72.