

March 2002 CUME

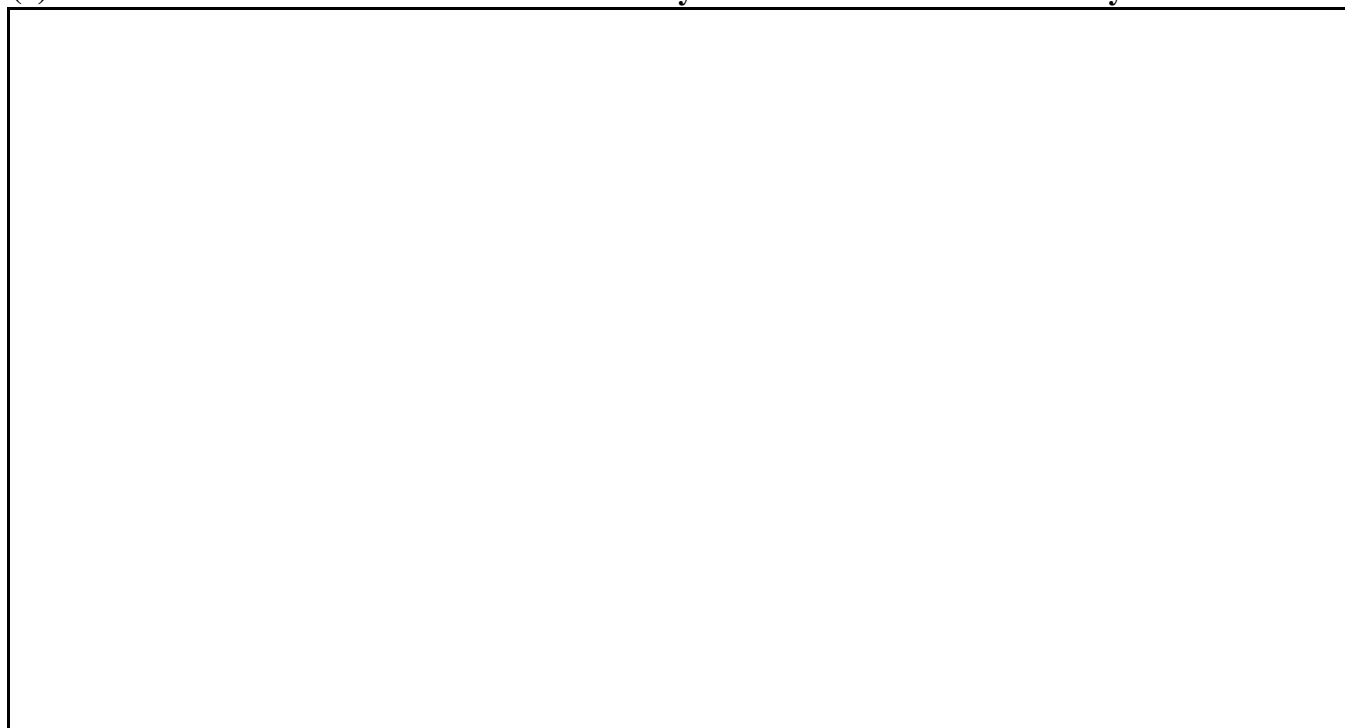
Organic Chemistry

Department of Chemistry
University of Missouri—Columbia
Saturday, March 2nd, 2002
Dr. Rainer Glaser

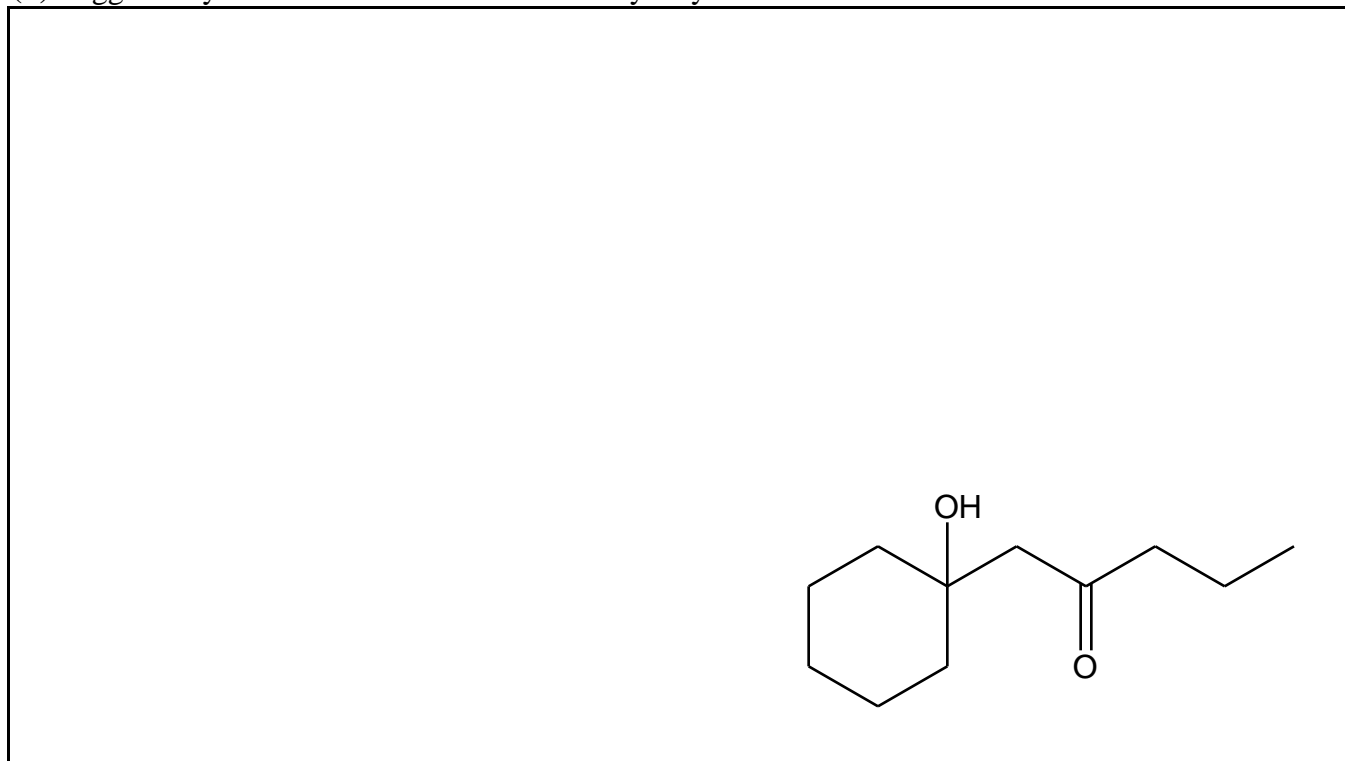
Announced Reading: "Aldol Addition Reactions"

Question 1. Warm-up. (20 points)

(a) Provide a detailed mechanism for the **base-catalyzed aldol reaction of acetaldehyde.**



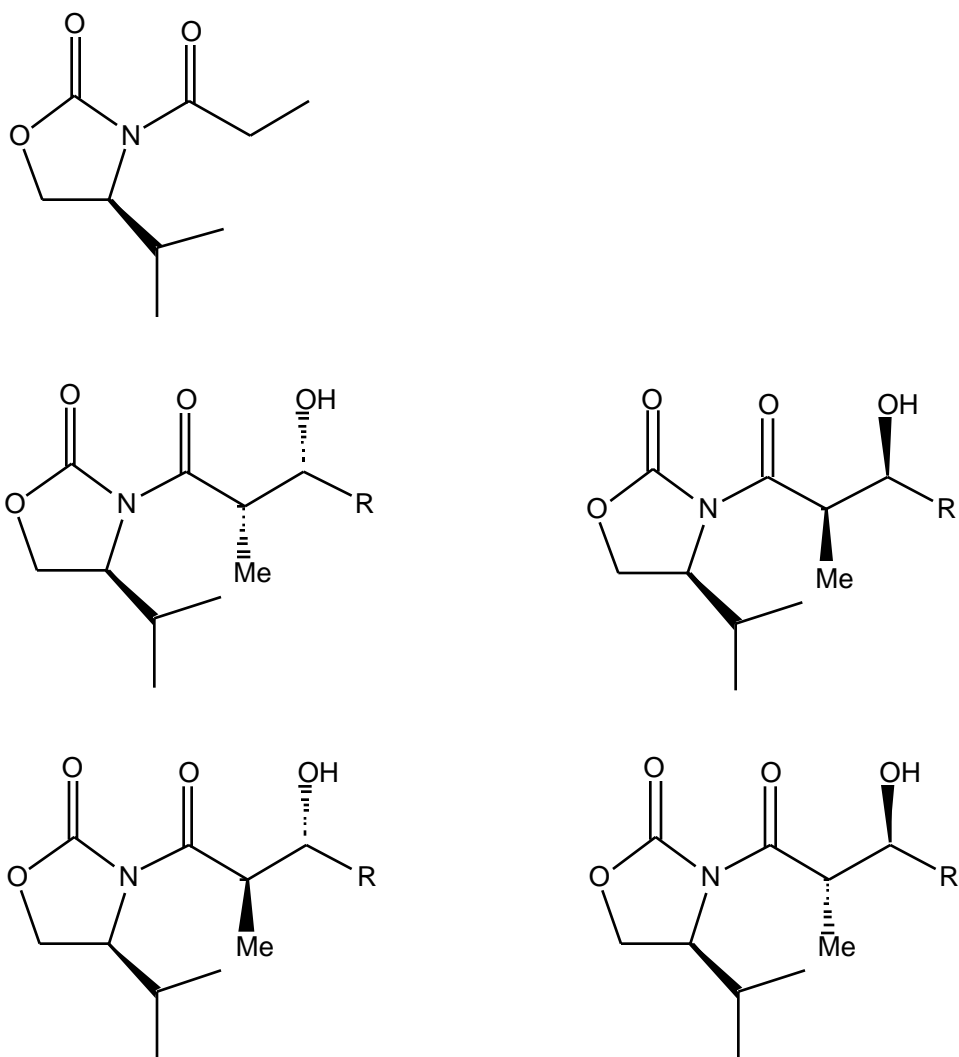
(b) Suggest a synthesis of the molecule shown by way of a **crossed aldol addition reaction.**



Question 2. Stereoselective Evans Reactions. (20 points)

The review article by Palomo et al. (*Chem. Eur. J.* **2002**, 8, 37-44) discusses directed aldol reactions under stoichiometric conditions and starts with a classical example by Evans. Prototype chiral auxiliaries useful in aldol reactions are the α -amino acid derived oxazolidinone-2-ones.

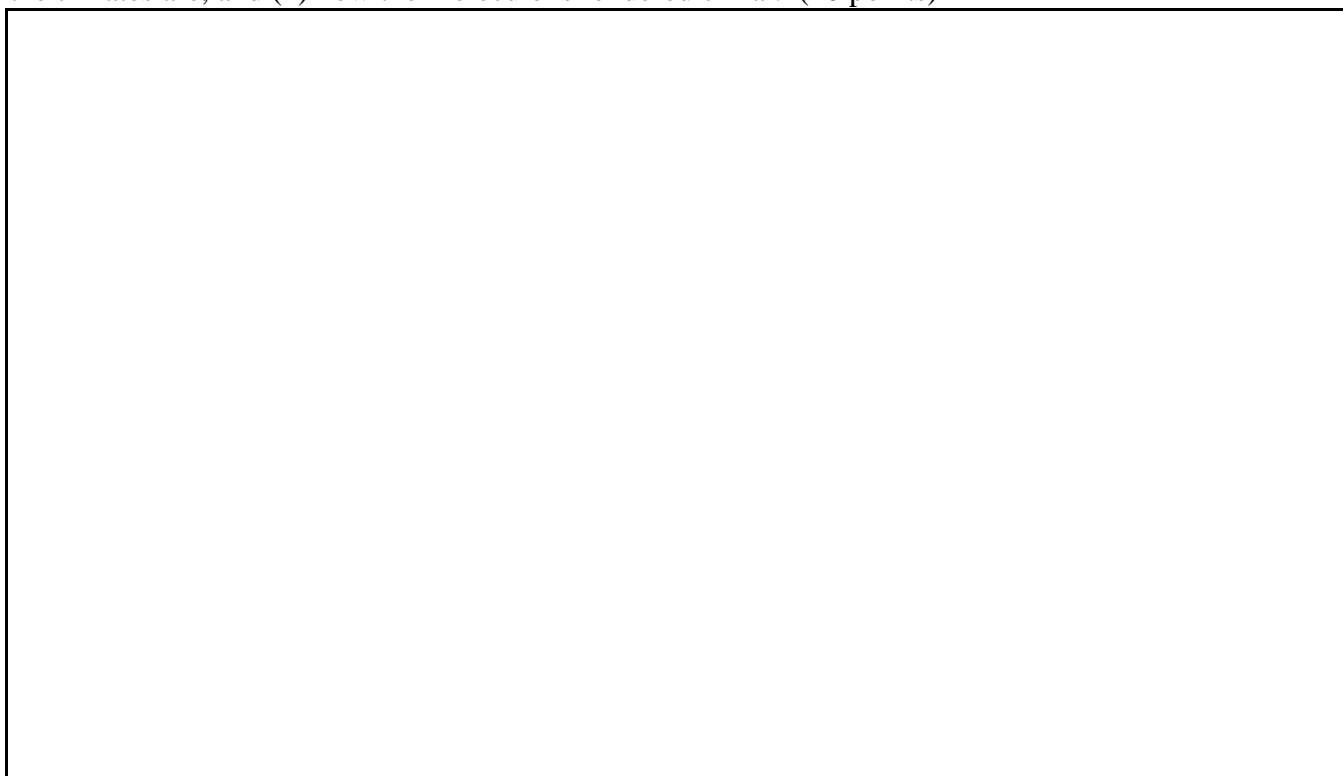
Boron-mediated aldol reactions of *N*-acyl 2-oxazolidinone and aldehydes—using Bu_2BOTf , $i\text{Pr}_2\text{EtN}$, CH_2Cl_2 in step 1 and RCHO in step 2—gives ONE of the four products shown. Circle those products which are “syn” and draw a square around those products that are “anti”. Mark the one major product of the Evans synthesis as “major”. For just one of the four products—the one at the bottom right—provide the *R/S* labels for all chiral centers. Indicate any pairs of enantiomers by drawing a double-sided arrow between the enantiomers and mark the arrow by “E”. Indicate which products come from the *Z*-enolate by adding the label “Z” to that product.



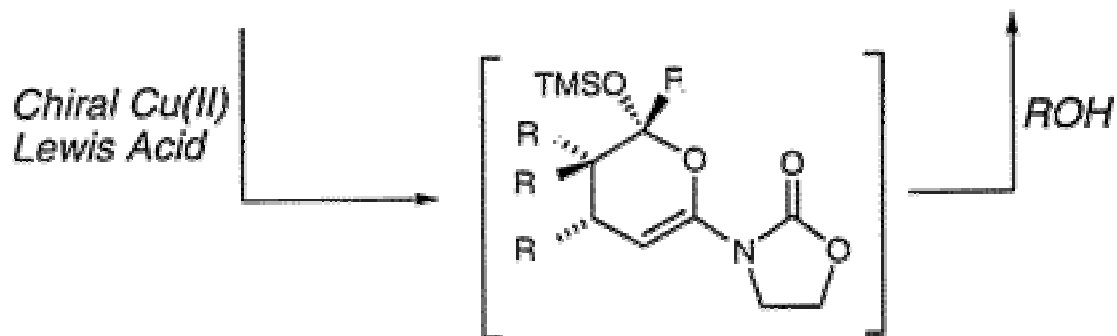
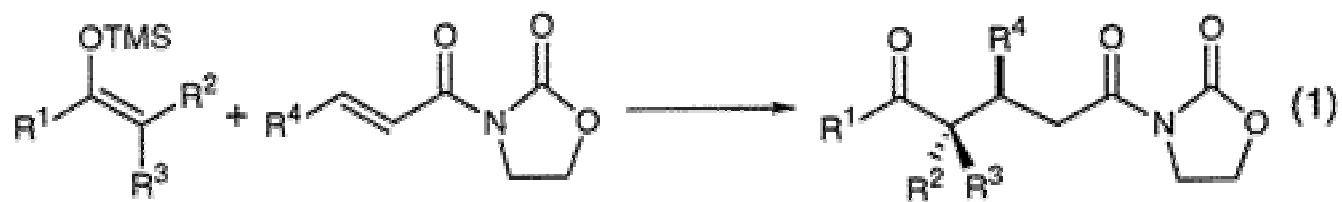
Question 3. Enantioselective Mukaiyama Reaction. (30 points)

The review article by Palomo *et al.* (*Chem. Eur. J.* **2002**, 8, 37-44) discusses directed catalytic aldol additions reactions with preformed enolates and cites examples from the group of Mukaiyama. Mukaiyama developed catalysts that allow for the enantioselective reaction of an aldehyde and an enolsilane. The enolsilane is preformed from the respective ketone. The review specifically mentioned “Sn(II) bisoxazoline triflates” as Mukaiyama catalysts.

(a) Recall as best as you can the structure of a “Sn(II) bisoxazoline triflate”. Your answer should show (1) the backbone of the bisoxazoline, (2) how the Sn(II) ion coordinates to the bisoxazoline, (3) where the triflates are, and (4) how the molecule is rendered chiral. (10 points)

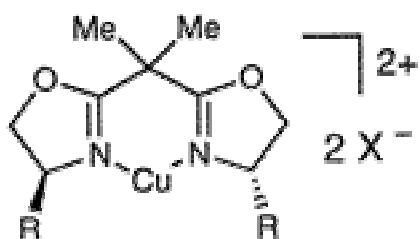


(b) Concerning a very closely related reaction, Evans *et al.* (*J. Am. Chem. Soc.* **2001**, 123, 4480 -4491) recently described “Enantioselective and Diastereoselective Mukaiyama-Michael Reactions Catalyzed by Bis(oxazoline) Copper(II) Complexes” and the paper starts as follows: “In 1974, Mukaiyama and co-workers reported the first examples of Lewis acid-catalyzed Michael reactions between enolsilanes and , -unsaturated carbonyl acceptors. ... This report describes the utilization of chiral copper Lewis acid **1a** to catalyze the addition of enolsilanes to substituted acryloyl oxazolidinones (eq 1) based on the proposed activated substrate-catalyst complex **A**. We have found that the reaction proceeds through a dihydropyran intermediate, which is subsequently hydrolyzed by an alcoholic additive.”



Predict the stereochemistry of the reaction by labeling the R groups (R1, R2, R3, etc) in the dihydropyran structure shown. (10 points)





1, X = SbF₆; 2, X = OTf

a: R = *t*-Bu; b: R = *i*-Pr;

c: R = Ph; d: R = Bn;

The copper complex is thought to complex the acryloyl oxazolidinones. As best as you can, draw the structure of the aggregate **A** formed between the copper complex and the acryloyl oxazolidinones. What atoms coordinate to Cu(II)? What is the coordination number around Cu(II)? What is the coordination geometry around Cu(II). (10 points)

Question 4. Direct Catalytic Aldol Reaction With Shibasaki Catalyst. (30 points)

The review article by Palomo *et al.* (*Chem. Eur. J.* **2002**, 8, 37-44) discusses direct catalytic aldol additions and cites examples from the group of Shibasaki. Shibasaki developed so-called **LLB** catalysts which allow for the enantioselective aldol reaction between methyl ketones and aldehydes.

(a) Mukaiyama-type Reactions



(b) Direct Reactions

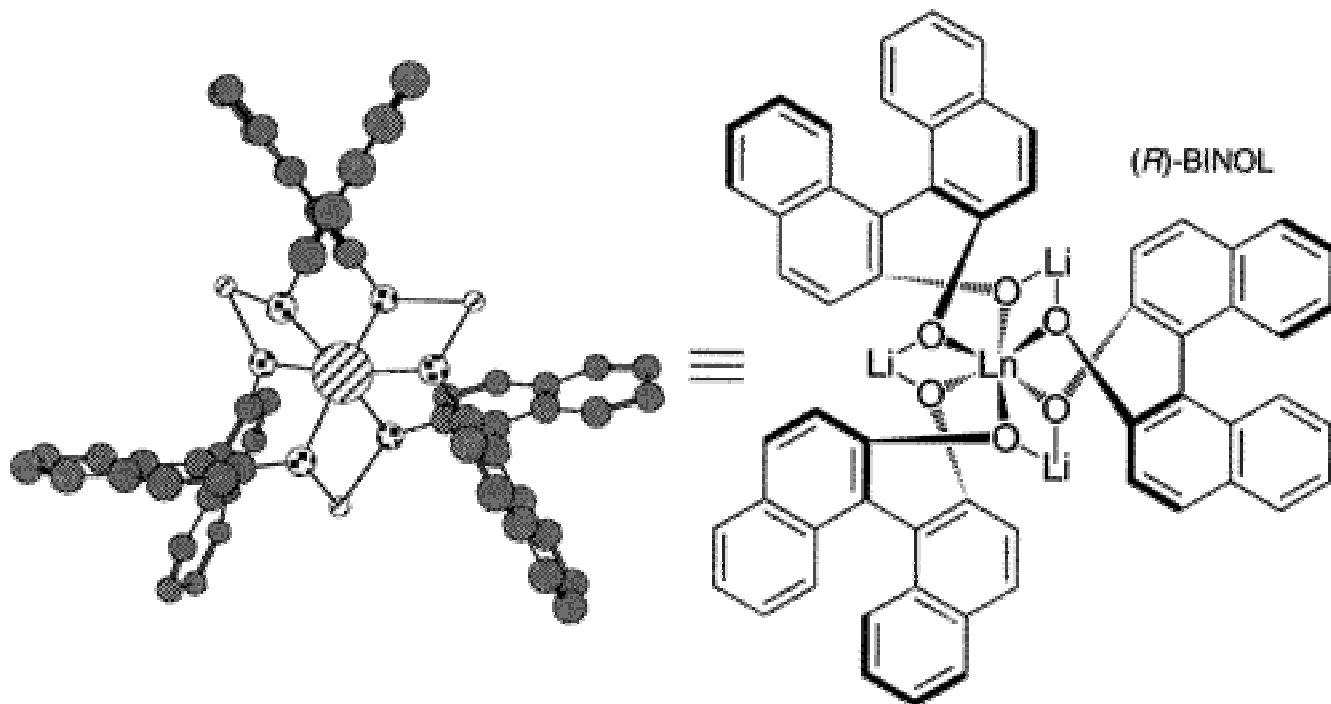


Figure 4.1. The structure of the LLB catalyst is as shown. Figures taken from Shibasaki, M. *et al.* *J. Am. Chem. Soc.* **1999**, 121, 4168 -4178.

(a) Why is the catalyst called (*R*)-LLB? What does the first “L” stand for? What does the second “L” stand for? What does the “B” stand for? Explain why the catalyst shown has *R*-configuration. (18 p.)

(b) Briefly explain the concept behind the use of the Shibasaki (*R*)-LLB catalyst. Your answer should address which part of the LLB catalyst functions as a Lewis acid and which part functions as a Bronsted base. And you should state why these Lewis acid and Bronsted base functionalities are needed. (12 p.)