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Enzyme models and organometallic chemistry

Richard M. Kellogg

Department of Organic Chemistry, University of Groningen
Nijenborgh 16, 9747 AG Groningen, The Netherlands

Abstract. This lecture deals with some of the activities within our group in recent years in the areas of macrocycles, thiacrown ethers, and amino acids as ligands. Macrocycles activated by a metal are used as mimics of some aspects of alcohol dehydrogenase. Metal complexes of thiacrown ethers are employed in catalytic enantioselective synthesis of carbon-carbon bonds. Aminophosphines derived from natural and unnatural amino acids are employed as ligands for nickel and palladium in catalytic enantioselective synthesis.

INTRODUCTION

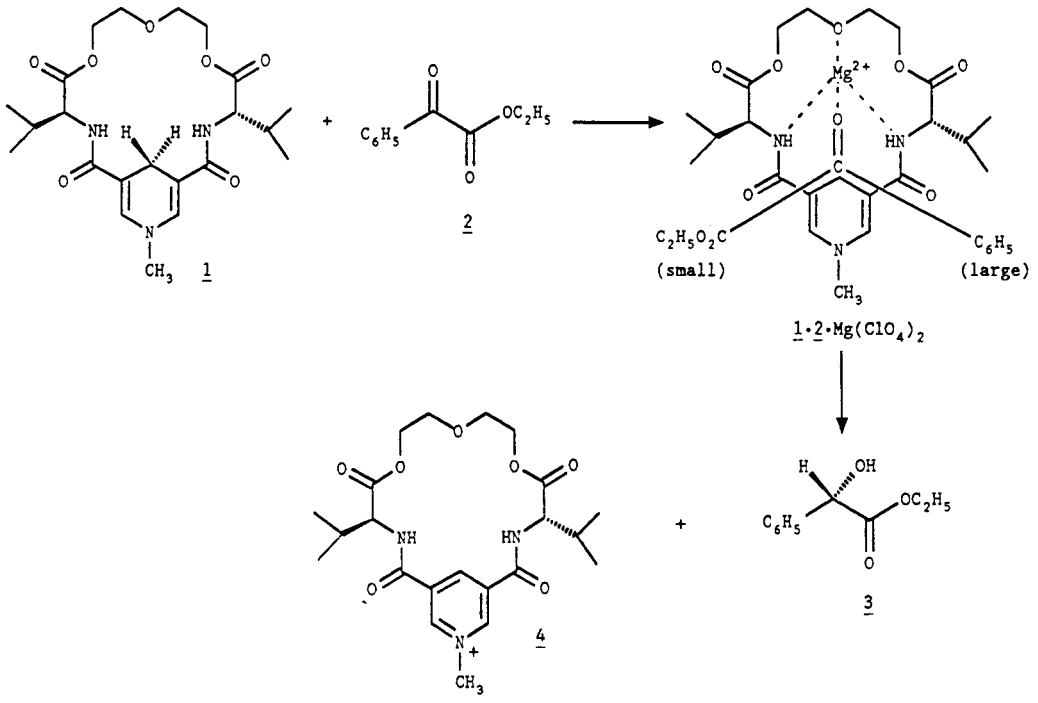
The use of molecules provided by Nature to carry out new chemistry is intrinsic to chemistry. The opportunities to do this have been enormously expanded by our increased knowledge of the structures of many biological systems and by our much better (but still primitive) ability to synthesize compounds and to understand their reactivity. One (of many possible) attractive ideas is to reconstruct an enzyme active site complete with the functional groups known to be involved in catalysis. If this could be done without immense synthetic effort a new route to the design of synthetic catalysts might be at hand. In actual practice direct reconstruction is usually too challenging. **Principles** are used rather than faithful **mimicking**. Some of the principles that may be used are **proximity** in order to enhance **effective molarities**, proper **orientation** of reactants (stereoelectronic control), restriction of **conformational flexibility**, and **mimicking** of structural elements known to be involved in catalysis by enzymes.

Our own efforts in this area have involved the use of macrocycles to position functional groups for reaction and to restrict conformational mobility, the synthesis of metal (zinc and cobalt) complexes that contain some elements of the active site of alcohol dehydrogenase, and the use of biological molecules to create a chiral nonracemic environment in which a catalytic reaction can take place. Several aspects of these efforts will be presented briefly in this chapter.

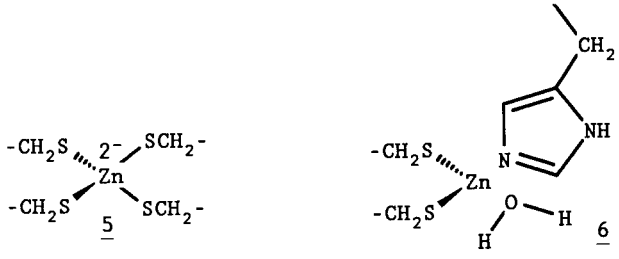
MACROCYCLES/ENZYME MIMICES

Our first experiences in this area were with macrocycles like 1;[1] the idea was to form a ternary complex [**1.2**.$Mg(ClO_4)_2$] as illustrated in Scheme 1 in which the stereoelectronic requirements for hydride transfer were met. In practice a slightly altered complex is formed. These results have been discussed in detail.[1] This work is cited here to illustrate a shortcoming; namely the lack of any **catalytic** reactivity. In the hope of finding a solution to this problem we were led not only to NADH/NAD+, the coenzyme components of alcohol dehydrogenase, but also the peptide component, the structure of which is now known.[2]

Scheme 1

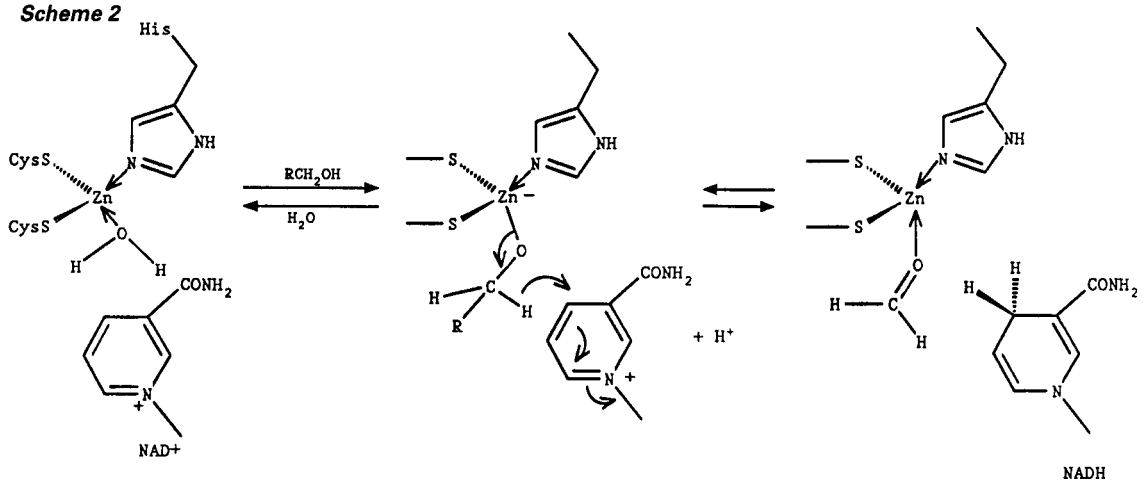


Liver alcohol dehydrogenase (LAD) from, for example, the horse is a large, 80,000 Da, enzyme, which occurs as a dimer. Each monomer contains two zinc atoms both in the +2 oxidation state. One, coordinated to four cysteines (5), fulfils apparently only a structural role. The other (6), coordinated to two cysteines, an imidazole from



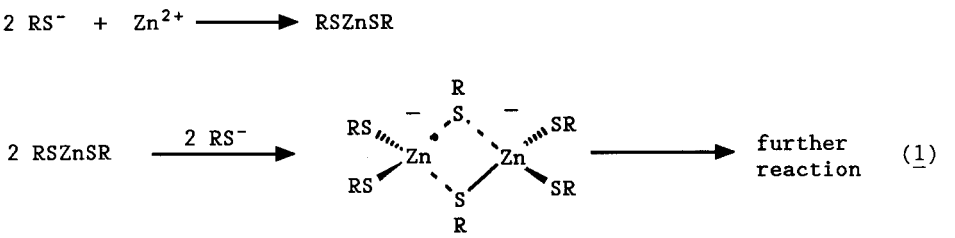
histidine, and a water molecule (or substrate molecule), is present at the active site and is clearly involved in the catalytic process, which is shown in broad detail in Scheme 2.

Scheme 2



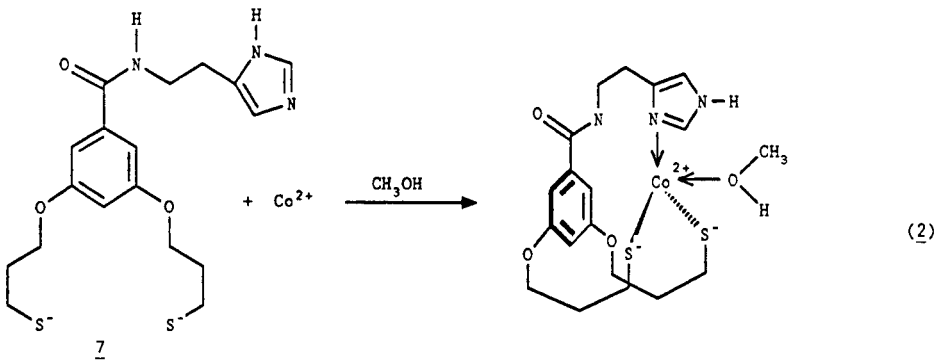
This scheme is intended to illustrate general structural features and the direction of electron flow; the degree of (de)protonation of alcohol and carbonyl components when attached to the zinc ion may in practice differ from this illustration.

This type of coordination turns out to be quite rare. There is thus little structural analogy to draw on in order to understand the workings of the zinc as component of the catalytic unit. The chief reason for the lack of structural analogs is that thiolate (as well as alkyl, alkoxy, nitrile, etc) has a strong tendency to bridge two zinc ions (eq. 1).



Attempts to prepare monomeric complexes for investigation of the chemistry of zinc thiolates depend on the use of **steric hindrance** to prevent self association; the challenge will be to find a balance between adequate steric hindrance and still sufficient accessibility to allow reaction to take place.

Two types of molecules have been prepared, **7** and **8** (eqs 2,3).[3]



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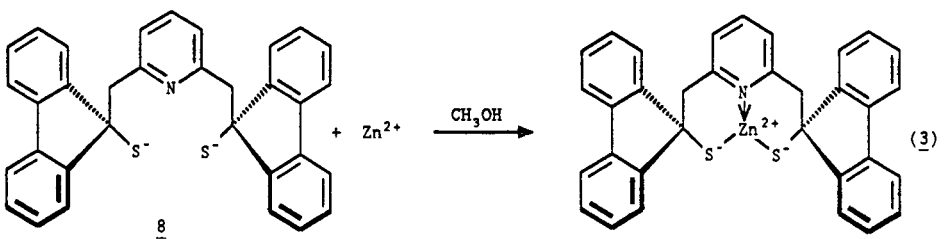
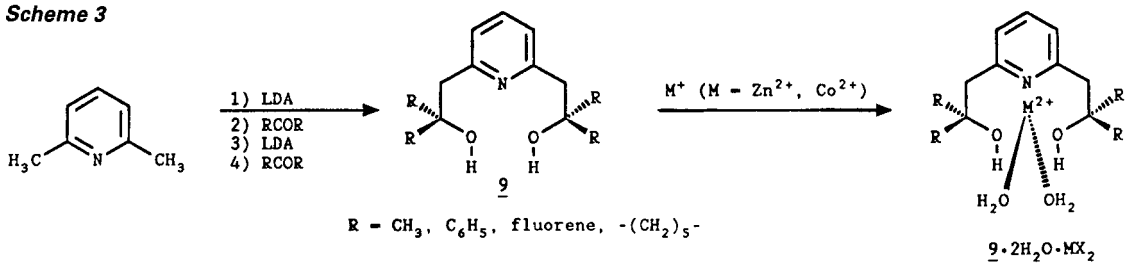


8

The chemistry of both has been described. Compound **7**, which is the structurally more accurate mimic, is not sufficiently hindered to prevent oligimerization of zinc. The cobalt complex is well behaved, however, and mimics rather well both structural features and reactivity of cobalt containing LAD. Ligand **8** is very hindered and forms unambiguously monomeric zinc thiolates. The steric hindrance is so great, however, that access by any other molecule is effectively prevented; no catalytic activity is observed.

Scheme 3

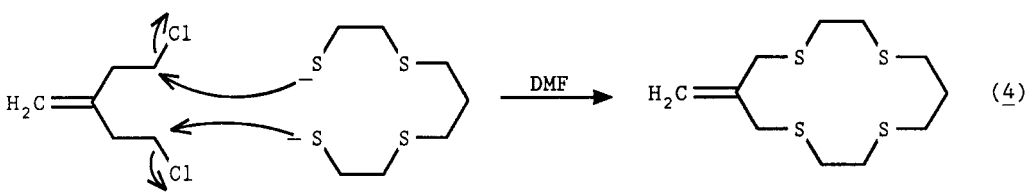


The ligand system embodied in 7 is quite interesting. The alcohol derivatives (**9**) are readily prepared as shown in Scheme 3.

These form monomeric complexes with various metals including zinc ions. Considerable variation can be achieved in the ligands, and it is possible to carry out chemistry on the metal complexes obtained.[4]

THIACROWN ETHERS

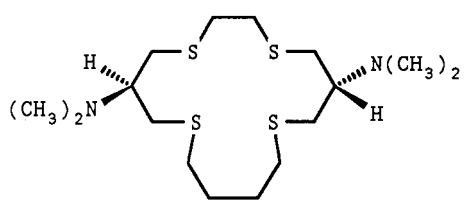
Applications of biomolecules and bioprinciples in the design of synthetic molecules, in particular catalysts, have revolved for a good deal around the use of macrocycles. Some very nice opportunities to use macrocycles in a new guise are opened by turning to "thiacrown ethers". In this case the usual oxa or aza linkages have been replaced by sulfide. The chemistry of this area has been much slower in developing than that of the oxa and aza crown ethers because of the synthetic problems involved in preparing such compounds. In particular the templated syntheses so successful with "crown ethers" have been of little use for the preparation of thia crown ethers. We have observed that the use of dimethyl formamide (DMF) as solvent together with the cesium salts of thiolates as illustrated for the specific synthesis of **10** (eq. 4) has led to remarkable improvement in yields.[5] In some but not all cases potassium or sodium can replace cesium; however difficult cyclizations, in our hands at least, require the use of cesium.



(4)

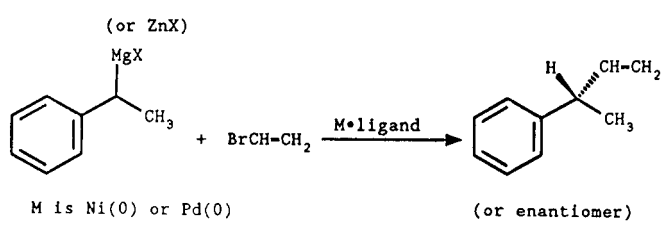
10

These "thiacrown ethers" are well suited for the complexation of various transition metals. Some time ago ligand **11** was prepared and was shown to be effective in the illustrated cross coupling affording an enantiomeric excess of 46% in the cross coupling product (Scheme 4).[6] Although the result was promising it suffered from the fact that too little was known about the coordination chemistry of **11** to allow detailed postulations of how the reaction in fact proceeded and to draw testable conclusions from those postulations.

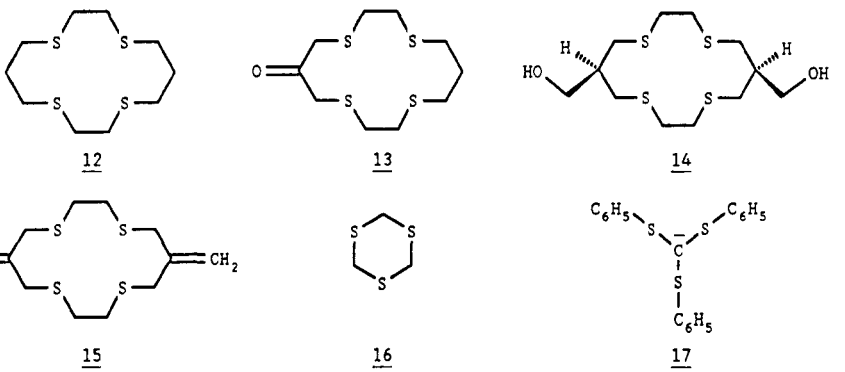


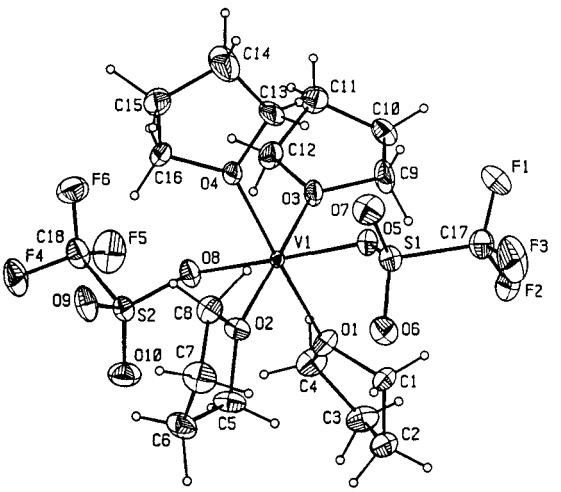
11

Scheme 4



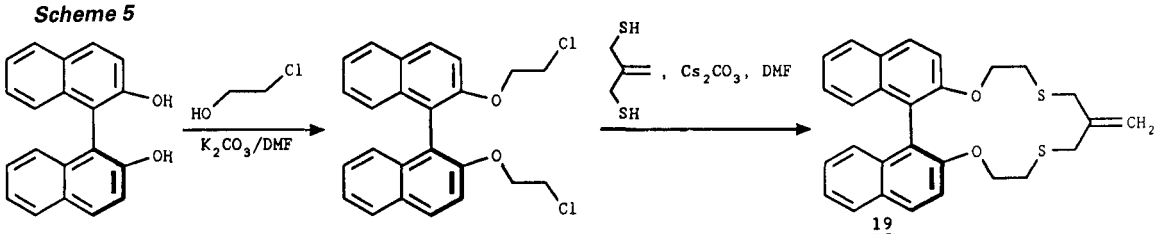
Because the amount of information on metal complexes of thia crown ethers is limited (see, for an excellent survey of the existing knowledge, Cooper[7]) we have embarked on a broad program of structural investigation of complexes of thia crown ethers and related compounds. Macrocycles **12-15** are some of the structures being used for complexations with metal ions including Zn^{2+}, Ag^{+}, Hg^{2+}, and V^{3+}.[8] Structure **16** has been used with success as a "model crown" and **17** shows promise as a unique new ligand.[8] Vanadium complex **18** has been characterized[9] and has proven to be a very good precursor of various thia crown complexes.





This synthetic work has led to a new generation of optically active thiacrown ethers derived from optically active bis-naphthol (compound **11** is derived from the amino acid cysteine; it has been our experience that the synthesis of thiacrown ethers containing also amino functionality is a serious problem because some of the intermediates are powerful vesicants). In Scheme 5 the synthesis of a bis-naphthol derived optically active thiacrown ether (**19**) is illustrated.[9] Application in, for example, cross coupling reactions like that shown in Scheme 4 is currently being explored.

Scheme 5

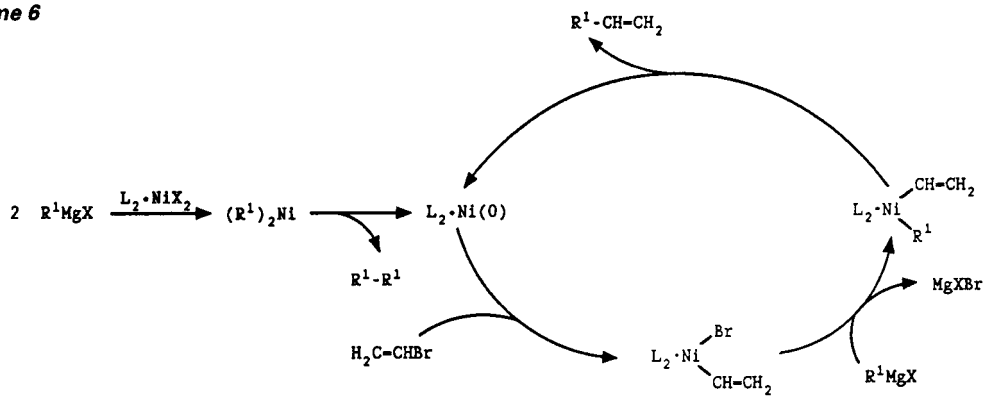


LIGANDS FROM AMINO ACIDS

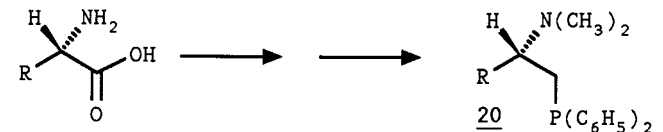
Some transition metals have enzyme-like character in their behaviour although direct structural analogy with any enzyme not present. An excellent example is the Ti^{+4}-tartrate complex that with tert-butyl hydroxide epoxidizes allylic alcohols with dramatically good enantioselectivities.[10] Reactants and substrates are brought into proximity in a complex, reaction takes place in nonracemic surroundings, and the product(s) is(are) released to regenerate the catalyst that reacts again.

The cross coupling reaction promoted by nickel or palladium has already been mentioned in Scheme 4. This reaction has similar enzyme-like characteristics in that via oxidative addition/reductive elimination (Scheme 6) a means is provided to introduce a substrate molecule (vinyl bromide), a second carbanionic reactant via substitution on the complex, and to eliminate the product in a coupling reaction (reductive elimination).[11] L_2 is a bidentate organic ligand.

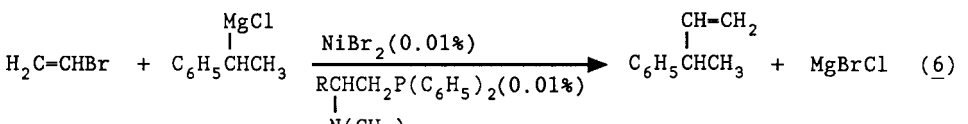
Scheme 6



Kumada and Hayashi showed that various aminophosphines derived from amino acids (eq. 5) are excellent as the bidentate organic ligands required for this reaction.[12] We have shown that tridentate aminophosphine ligands can be particularly effective.[13] The increasing trend in enantiomeric excesses on progressing from ligands derived from alanine to cysteine to methionine to homomethionine is shown in eq. 6.



R = aryl, alkyl (5)

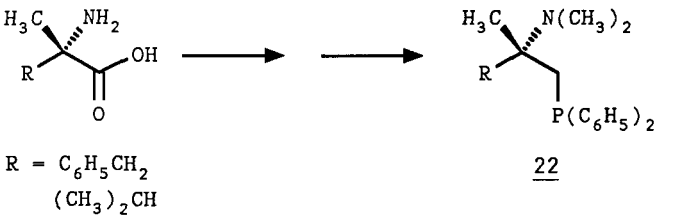


(6)

R	enantiomeric excess
CH_3	20%
CH_3SCH_2	38%
$CH_3S(CH_2)_2$	65%
$CH_3S(CH_2)_3$	90%

The rigidity of the complex leading to the coupling reaction is presumed to be increased by tridentate coordination and that this enhanced rigidity is the reason for the more faithful transfer of chirality from the ligand to cross coupling product.

Recent work has made a number of new, unnatural amino acids available in optically pure form and in sufficient quantities to carry out further reactions. It has proven possible to prepare aminophosphines (22) from α-alkylated amino acids like (21) as shown in eq. 7. It was by no means clear that this would be possible for the final step in the synthesis requires nucleophilic substitution by diphenylphosphide adjacent to a quaternary center.



(7)

R = $C_6H_5CH_2$, $(CH_3)_2CH$

22

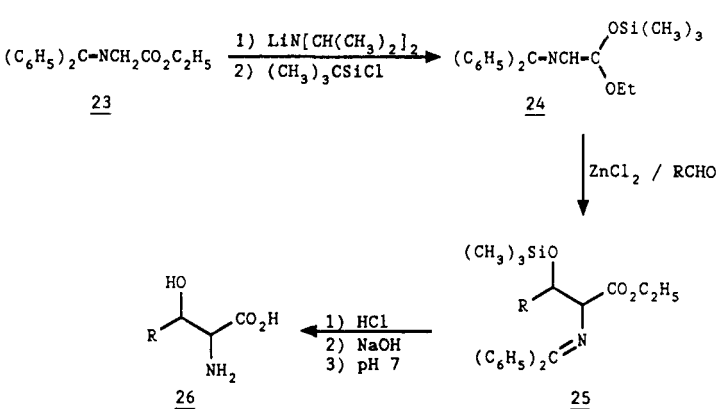
Tentative results with ligands (22) indicate that good enantiomeric excesses can be obtained. This is apparently the result of enhanced rigidity in the ligand allowing a better degree of recognition of the chirality about the ligand.[14]

Various other parameters are also very important in this reaction. The use of salt free magnesium and zinc reagents has also a profound effect. The sense of enantioselection is changed on use of zinc instead of magnesium reagents. The reasons for this are unclear.

β-HYDROXY AMINO ACIDS

On occasion preparation of potential ligands requires extra synthetic effort. The most frequent barrier encountered is that Nature does not supply enough structural variation. We were particularly interested in obtaining ß-hydroxy-α-amino acids for further conversions into ligands. A means of doing this is illustrated in Scheme 7. The Schiff base (23) of glycine ester is converted to highly unstable ketene acetal (24), which used *in situ* in the presence of LiCl condenses with various aldehydes in the presence of $ZnCl_2$ affords 25, which occurs as *syn* and *anti* diastereomers. The $ZnCl_2$ plays a pivotal role in directing the stereochemistry as illustrated with the selected examples in Scheme 7. A catalytic amount directs the reaction in the direction of formation of *syn*-25. In this case $ZnCl_2$ is probably present as Li_2ZnCl_4, owing to the excess LiCl. With stoichiometric amounts of $ZnCl_2$ the reaction is directed towards *anti*-25. This profound effect of $ZnCl_2$ indicates a change in mechanism dictated by the form in which the zinc halide is present.[15]

Scheme 7



23 → 24 → 25 → 26

R	$ZnCl_2$(%)	syn : anti (25)
$(CH_3)_3C$	5	92 : 8
$(CH_3)_3C$	100	23 : 77
C_6H_5	5	96 : 4
C_6H_5	100	61 : 39
2-thienyl	5	89 : 11
2-thienyl	100	28 : 72

CONCLUSION

Organic, molecular inorganic, and biochemistry blend together in many aspects to allow the testing of ideas, and design of new types of chemistry. This must surely broaden chemistry, which is our ultimate goal.

Acknowledgements. The names of the co-workers who have carried out the work done by my group are given in the references. I am extremely grateful to these ambitious, good humored, and capable young colleagues.

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