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Tin(II) compounds as synthetic control elements in organic synthesis

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Abstract - Based on the concept of "Synthetic Control", various diastereo- and enantioselective synthetic reactions are exploited by the utilization of characteristic properties of tin(II) compounds.

1 INTRODUCTION

In the field of organic chemistry, tin(II) compounds have long been known as reductants of aromatic nitro compounds to the corresponding aromatic amino compounds. However, other possibilities of applying tin(II) compounds to synthetic organic reactions, especially carbon-carbon bond forming reactions had not been explored until tin(II) fluoride was employed in 1979 as a reductant of several α-halocarbonyl compounds and allylic halide to generate reactive tin(IV) species, which further react with aldehyde to form a new carbon-carbon bond (Ref. 1).

During these investigations, we became interested in the following characteristic properties of tin(II) compounds; 1) tin(II) species, having vacant d orbitals in low energy levels, can accept up to 4 ligands to work well as metal template, and 2) tin(II) species form tight complexes with amines, especially with diamines.

Recently, we have been working to explore new possibilities in synthetic reactions based on the concept of "Synthetic Control", that is, utilization of common metal chelate for inter- or intramolecular interactions leading to highly selective or entropically advantageous reactions.

Thus, the exploration of highly diastereo- and enantioselective synthetic reactions was studied by utilizing these characteristic properties of tin(II) compounds. Recent results based on this concept are described in this article.

2 TIN(II) ENOLATE MEDIATED ALDOL REACTION

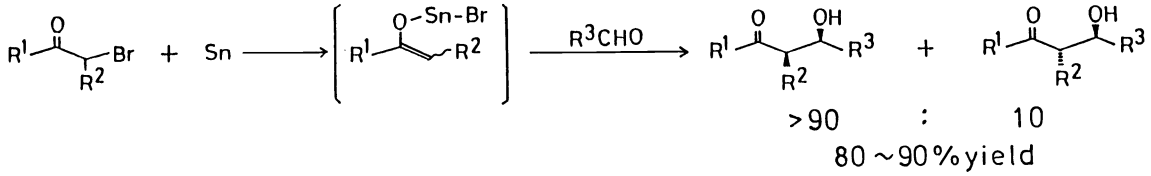
Aldol reaction is one of the most fundamental carbon-carbon bond forming reactions, and has attracted much attention as a useful method for the stereoselective synthesis of various polyoxygenated natural products such as macrolides and carbohydrates, where the control of regio- and stereochemistry is the subject of intense study. And it soon became clear that, also in this case, the concept of "Synthetic Control" is a highly effective approach for these purposes. Thus, metal enolate mediated aldol-type reactions have become known to provide very useful tools for regio- and stereocontrolled carbon-carbon bond formation via intermolecular metal chelation (Ref. 2).

Over the past decade we have explored the following two types of aldol reactions. [1] The titanium tetrachloride promoted aldol reaction, which realized the use of silyl enol ethers as an easily accessible, isolatable enolate precursor, allows the use of carbonyl compound equivalents, such as ketals and acetals, as efficient acceptors for silyl enol ethers. The mildness of reaction conditions permits the presence of base-sensitive functionalities which could not survive lithiated derivative mediated methods (Ref. 3). And, more recently, we have succeeded in developing a more efficient catalytic system employing trityl perchlorate as an effective promotor of the above mentioned reaction (Ref. 4). [2] The vinyloxyborane mediated aldol reaction was found to proceed under very mild and essentially neutral conditions to afford aldols in excellent yields (Ref. 5). Moreover, we introduced, in 1976, the use of dialkylboryl trifluoromethanesulfonate

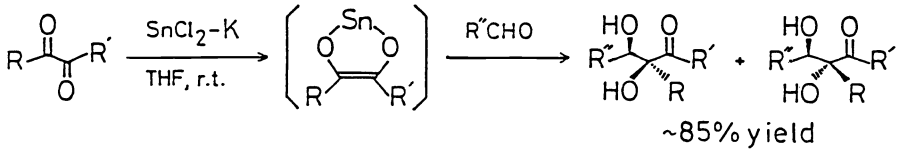
(dialkylboryl triflate), and the treatment of ketones with dialkylboryl triflate in the presence of tertiary amine gave rise to a versatile method for the generation of vinyloxyboranes from parent carbonyl compounds (Ref. 6).

Although these reactions have found wide applications in the stereoselective construction of acyclic precursors, there still remain several problems such as the method for the generation of the enolate and the reactivity of the enolate. To overcome these problems, we continued our efforts to explore a new metal enolate mediated reaction, and finally arrived at the chemistry of the tin(II) enolate.

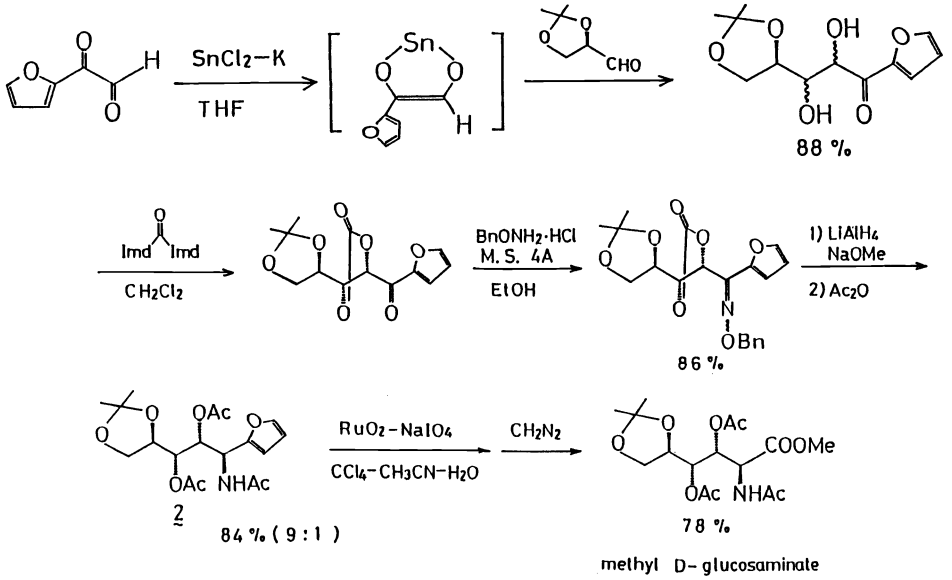
The chemistry of tin(II) enolate was developed in our laboratory by employing the reducing ability of metallic tin. Thus, tin(II) enolates are found to be generated by the oxidative addition of α-bromoketones to metallic tin, and smoothly react with aldehydes regiospecifically with high syn-selectivity (Ref. 7).



α,β-Dihydroxyketones are obtained by the reaction of α-dicarbonyl compounds and aldehydes in the presence of activated tin, prepared from $SnCl_2$ and K, via tin(II) enediolate (Ref. 8).

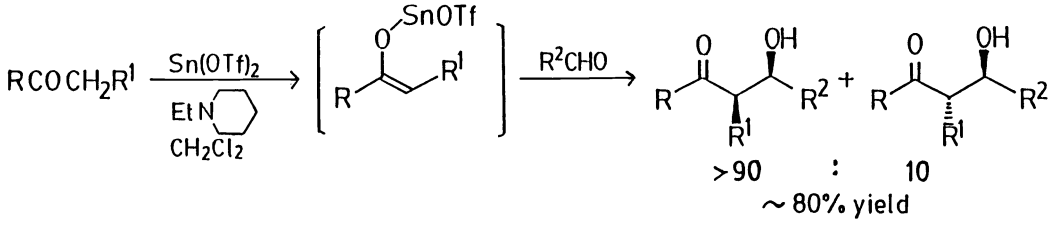


Similarly, smooth reaction takes place, when furylglyoxal is employed as α-dicarbonyl compound, and this reaction was applied to the synthesis of methyl D-glucosaminate (Ref. 9).

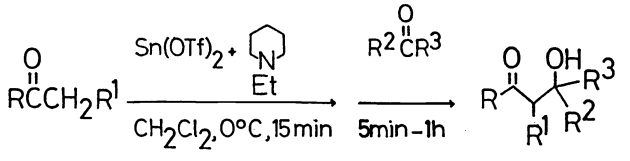


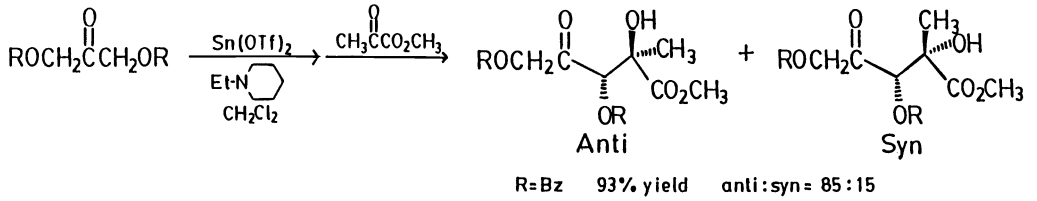
Recently, it was found that tin(II) enolate can be more conveniently prepared from the parent carbonyl compound by employing tin(II) trifluoromethanesulfonate(triflate).

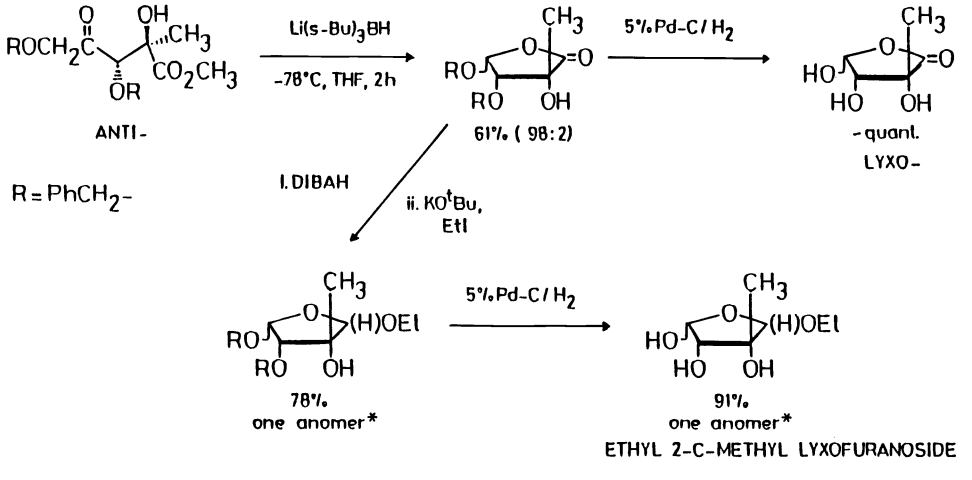
The generation of tin(II) enolates is successfully carried out by treatment of tin(II) triflate, prepared according to literature method (Ref. 10), with ketones in the presence of tertiary amine. The examination of various reaction conditions revealed that, in this reaction, the choice of the tertiary amine is crucial. For example, pyridine or DBU which can coordinate strongly to divalent tin failed to generate the intermediate enolate, while N-ethylpiperidine gave excellent results. These divalent tin enolates undergo aldol reactions to give β-hydroxy ketones in good yields, under extremely mild conditions where good to excellent syn selectivity is observed (Ref. 11).



Interestingly, the present tin(II) enolate also displays enhanced reactivity toward ketones, and a facile method for the directed aldol reaction between two different ketones is realized by using tin(II) enolates prepared from tin(II) triflate and ketones. Examination of the diastereoselectivity in this reaction revealed that when an aromatic ketone is chosen as the acceptor carbonyl compound, enhanced anti-selectivity is observed. Boron enolates, versatile metal enolates, display poor reactivity toward ketones and more nucleophilic lithium enolates react with less hindered ketones in moderate yield. Considering the reactivities of those enolates, we would like to point out here the high reactivity of tin(II) enolate (Ref. 12).

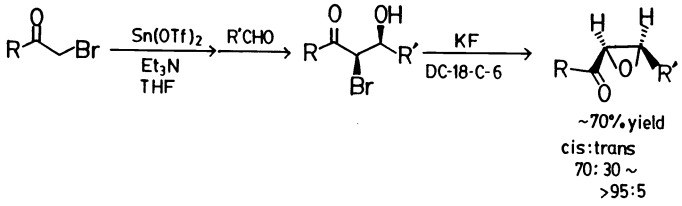




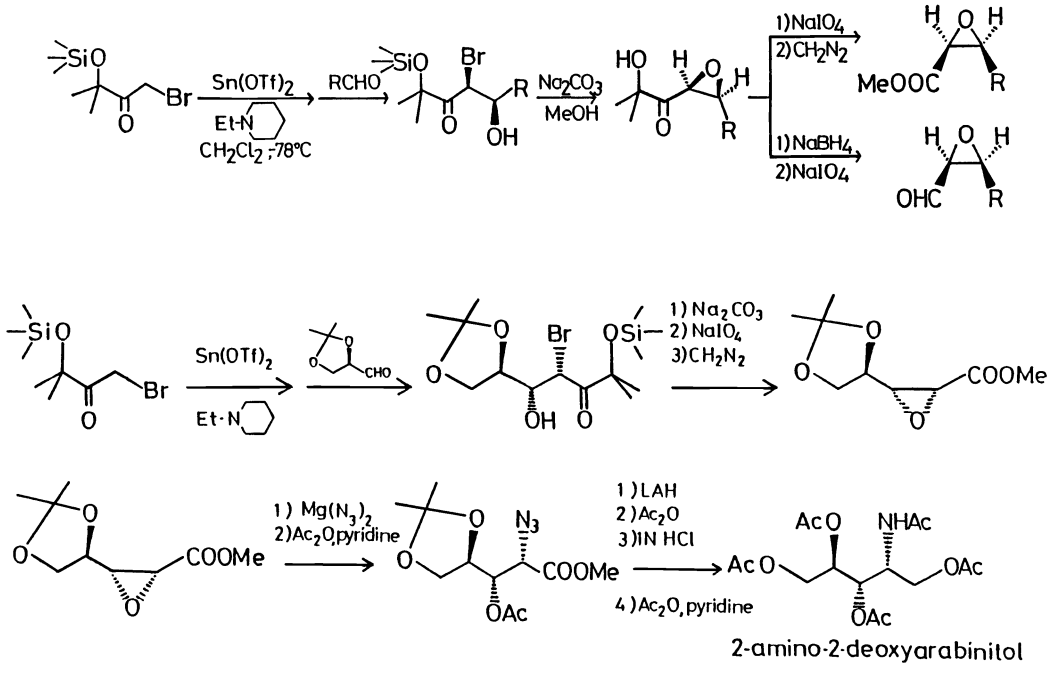


A branched-chain sugar, ethyl 2-C-methyl-DL-lyxofuranoside, is synthesized stereoselectively by application of this reaction, starting from 1,3-dihydroxy-2-propanone derivative and methyl pyruvate as shown above (Ref. 13).

A convenient method for the stereoselective synthesis of cis-β-substituted-α,β-epoxyketone is established by applying this tin(II) triflate mediated cross aldol reaction to the reaction between α-bromoketone and aldehydes. The preferentially formed adduct, syn-α-bromo-β-hydroxyketone, is converted to cis-α,β-epoxyketone, with minimum amount of isomerization to trans isomer, via intramolecular S_N2-type ring closure to oxirane by the action of potassium fluoride-dicyclohexyl-18-crown-6 on aldol (Ref. 14).

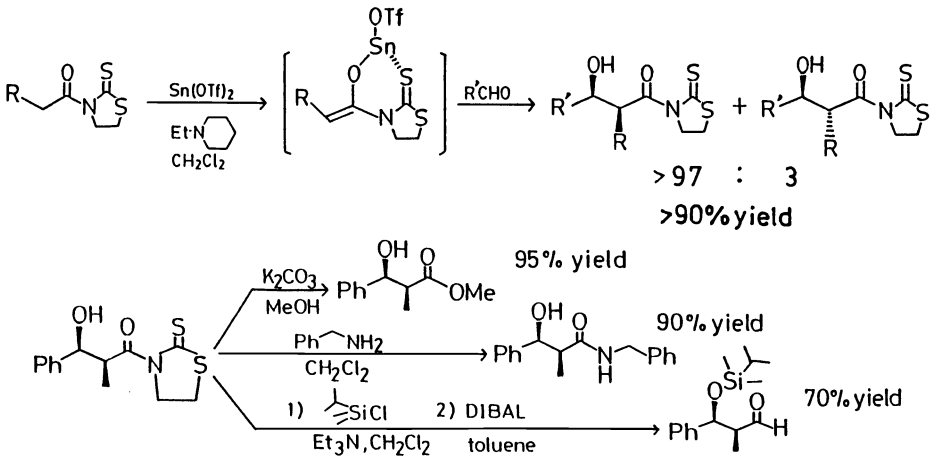


As an extention of this reaction, various cis-α,β-epoxy esters and cis-α,β-epoxy aldehydes are obtained with high stereoselectivity by using α-bromo-α'-silyloxyketone as a starting carbonyl compound. And this reaction is employed for the stereoselective synthesis of 2-amino-2-deoxy-D-arabinitol (Ref. 15).

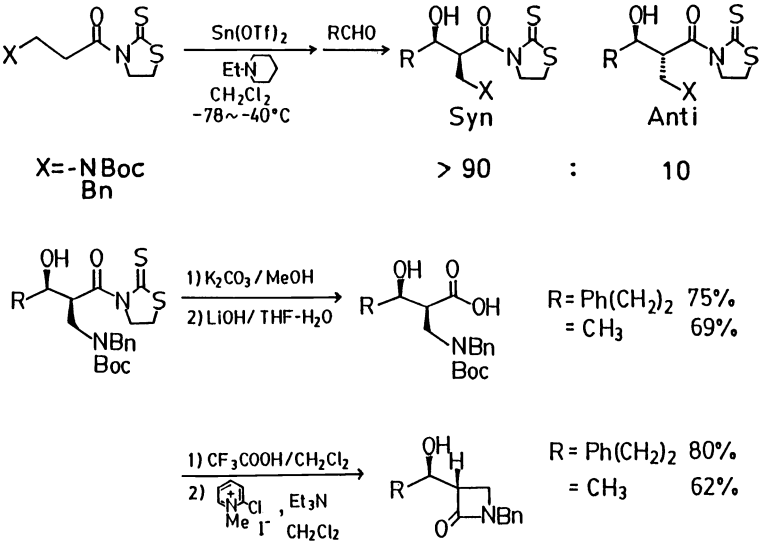


β-Hydroxy aldehydes and β-hydroxy carboxylic acid derivatives are very useful synthetic building blocks, in particular, β-hydroxy aldehydes are utilized for the construction of a variety of polyoxygenated natural products.

3-Acylthiazolidine-2-thiones, prepared from acyl chlorides and thiazolidine-2-thione or from carboxylic acids and thiazolidine-2-thione by DCC or pyridinium salts as condensation reagents (Ref. 16), undergo a similar aldol type reaction to give β-hydroxy carbonyl compounds in excellent yields with high syn selectivity. This type of crossed coupling products are very versatile synthetic materials and can be transformed into esters, amides, aldehydes, and diols in good yields respectively (Ref. 17).



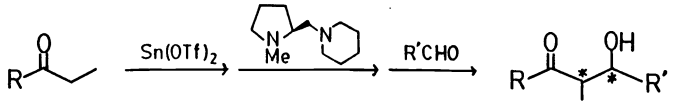
Further, enolate formation from 3-acylthiazolidine-2-thione bearing hetero atoms on β-carbon of acyl group takes place without the β-elimination of hetero substituent, and the poly-functionalized adducts are obtained by successive treatment with aldehydes. These adducts are found to be cyclized to the corresponding β-lactams by treatment with 2-chloro-1-methylpyridinium iodide via the corresponding acids (Ref. 18).



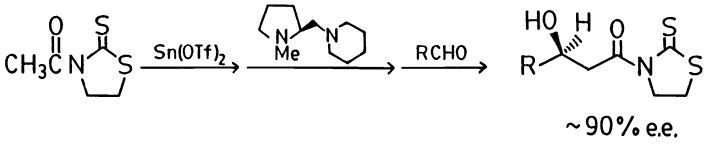
Recent development in the field of stereoselective aldol reactions has resulted in the exploitation of the asymmetric version of this reaction, and several successful methods have been reported using chiral carbonyl compounds as one of the component compounds or by using chiral boron triflate as a generator of boron enolate (Ref. 19). However, the efficiency of these reactions is greatly diminished by the necessity of tedious procedures for the attachment and removal of the chiral sources. Thus, development of a highly enantioselective aldol reaction between two achiral carbonyl compounds utilizing chiral chelating agents is strongly desirable, though the influence of such chiral addends in the aldol reaction has not met with much success.

At this point, we considered the application of tin(II) enolates to a chiral chelate type asymmetric aldol reaction based on the consideration that suitable ligands should be able to coordinate to the tin(II) metal center having vacant d orbitals. Since we have demonstrated that chiral diamines derived from (S)-proline are efficient ligands in several asymmetric reactions (Ref. 20), we directed our efforts to the examination of an enantioselective aldol reaction via divalent tin-chiral diamine complex, generated in situ from tin(II) enolate and chiral diamine derived from (S)-proline.

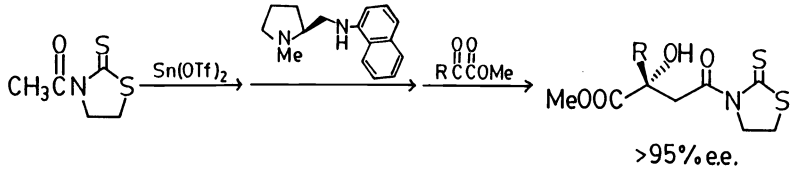
A highly enantioselective cross aldol reaction between aromatic ketones and aldehydes is accomplished by using a diamine having a piperidine side chain after various examinations of the reaction conditions and the structure of the diamine. This is the first example of the formation of cross aldol in high optical purity starting from two achiral carbonyl compounds employing chiral diamines as chelating agents (Ref. 21).



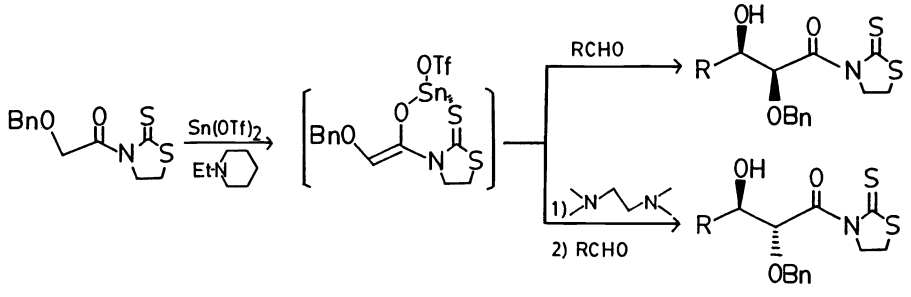
This asymmetric aldol reaction is next extended to the aldol type reaction of 3-acetylthiazolidine-2-thione with various achiral aldehydes via tin(II) enolate using chiral diamine as a ligand and the corresponding aldol adduct is obtained with high optical purity. As described before, the adduct is easily converted to β-hydroxy aldehyde or β-hydroxy carboxylic acid derivatives, and thus this method constitutes a useful method for the preparation of a variety of optically active compounds (Ref. 22).



Further, a highly enantioselective synthesis of 2-substituted malates is achieved by application of this reaction. The tin(II) enolate of 3-acetylthiazolidine-2-thione reacts with various 2-ketoesters to afford the corresponding aldol-type products, generally in greater than 95% e.e. (Ref. 23).



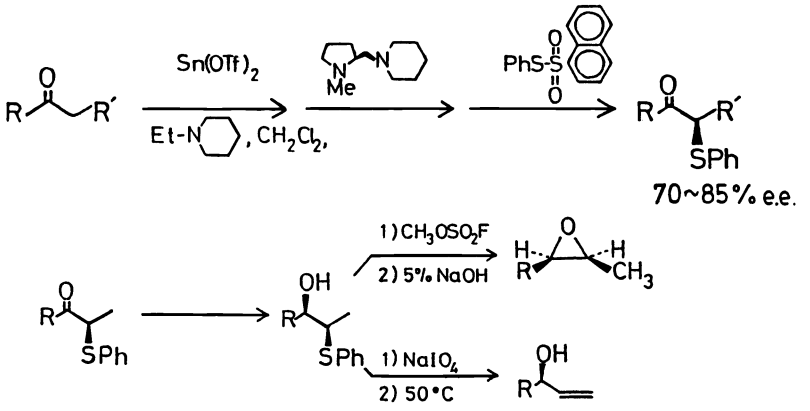
Moreover, it was observed that in the reaction of 3-(2-benzyloxyacetyl)-thiazolidine-2-thione with aldehyde, reversal of relative stereochemistry is attainable commencing from the same reactants. That is, in the absence of diamine, the α-benzyloxy adduct is predominantly of syn-stereochemistry, while, in the presence of diamine (TMEDA), anti-product prevails. Furthermore, by employing the chiral diamine, up to 94% e.e. is observed in the anti-adduct (Ref. 24).



It should be noted that in the tin(II) triflate mediated aldol reactions, both relative and absolute stereocontrol can be achieved utilizing non-bonded interaction between tin(II) enolate and various diamines.

The reaction of tin(II) enolate with various electrophiles in the presence of

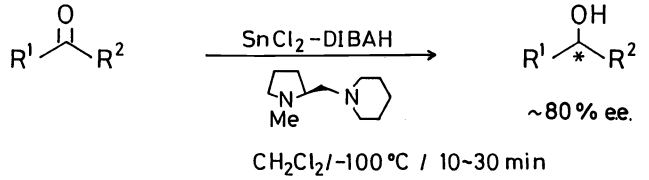
chiral diamine was further examined, and it was found that sulfenylation of ketone proceeds smoothly to afford the α-thioketone in high optical purity. And the product can be easily converted to the corresponding optically active epoxide or allylic alcohol.



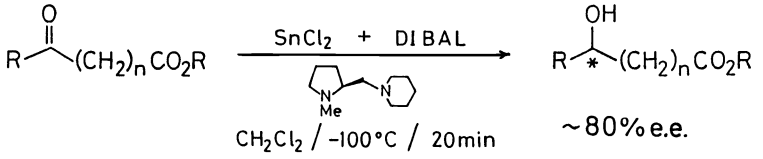
3 ASYMMETRIC REDUCTION

The asymmetric reduction of prochiral ketones has been the subject of extensive work during the past decade, and various chiral hydride reagents such as lithium aluminum hydride partially decomposed by optically active alcohols or amines, and chiral boron reagents have been developed. High enantioselectivities have been achieved in the asymmetric reductions of aryl alkyl ketones and α,β-unsaturated ketones, however, relatively low optical induction is obtained in the reduction of aliphatic ketones. And recently Alpine-Borane and NB-Enantride have emerged to be available for the asymmetric reduction of aliphatic ketones. In almost all of the asymmetric reductions mentioned above, chirality has been induced by chiral auxiliaries that are covalently bonded to the reducing agents (Ref. 25).

Bearing in mind that tin(II) compounds have strong interaction with chiral diamines, we next tried to explore a novel reducing system including tin(II) species to develop a ligand controlled (that is, chiral auxiliaries are not covalently bonded to the metal center) asymmetric reduction of various carbonyl compounds. After examination of the combination of tin(II) salts and reducing agents, it was finally found that a new chiral reducing agent, prepared by the treatment of a mixture of tin(II) chloride and a chiral diamine derived from (S)-proline with diisobutylaluminum hydride, is effective for asymmetric reduction of prochiral ketones. And higher enantioselectivity is realized in the case of aliphatic ketones compared to the conventional methods (Ref. 26).

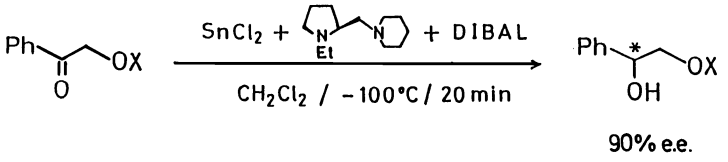


According to this procedure, various optically active hydroxy esters are obtained in high optical purities by the asymmetric reduction of the corresponding keto esters (Ref. 27).



The present asymmetric reduction, which is well controlled by the use of the bidentate chiral diamine as a ligand, is found to be applicable to the

asymmetric reduction of α-alkoxy ketones. Also, according to the similar procedure, chiral glycerol derivative is obtained from dihydroxyacetone derivative by differentiating the protective groups of the two hydroxy functions.



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