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METAL ENOLATES IN ORGANIC SYNTHESIS

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Abstract - Metal enolates play an important role in organic synthesis and in particular metal enolate mediated aldol type reactions provide very useful synthetic tools in stereoselective and asymmetric carbon-carbon bond formations. Three types of metal enolate mediated aldol reactions developed in our laboratory are discussed.

During the past decade, generations and reactions of various metal enolates have been extensively studied and successful applications to the controlled formation of carbon-carbon bonds have been realized under mild conditions. Besides the well-studied aldol reaction based on lithium enolates, very versatile regio- and stereoselective carbon-carbon bond forming reactions have been established by the use of silyl enol ethers-Lewis acids, vinyloxyboranes, and stannous enolates (Ref. 1). In this article, the chemistry of these three types of aldol reactions is discussed. They are:

1. The titanium tetrachloride promoted aldol reaction of silyl enol ethers.
2. Vinyloxyborane mediated aldol reaction.
3. The stannous enolate mediated aldol reaction.

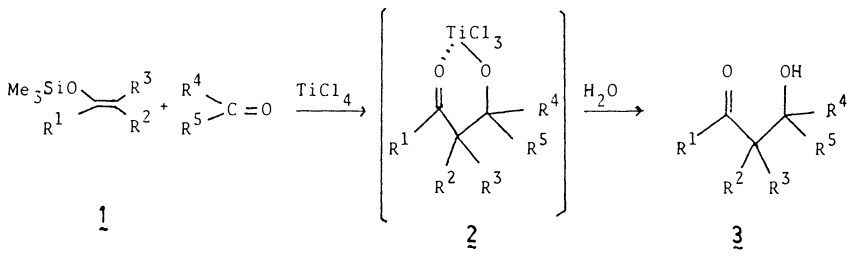
1. THE TITANIUM TETRACHLORIDE PROMOTED ALDOL REACTION (Ref. 2)

Aldol reaction has long been recognized as one of the most useful synthetic tools and the reaction is usually carried out under basic conditions. However, under classical aldol reaction conditions in which basic media are employed, dimers, polymers, self-condensation products, or α,β-unsaturated carbonyl compounds are invariably formed as by-products. Useful synthetic methods have been developed recently to alleviate those difficulties, especially under basic conditions, the lithio derivative mediated method offers one of the solutions to those problems (Refs. 1,3). On the other hand, there appeared no practical procedure for cross aldol reaction carried out under acidic conditions.

Enol ethers react with acetals or ketals by the promotion of Lewis acids to give aldol-type adducts. However, acid catalyzed reactions are often accompanied with undesirable side reactions, when stoichiometric amounts of carbonyl compounds and enol ethers are employed (Ref. 4).

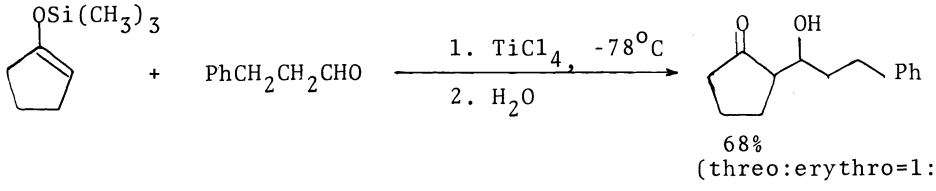
The use of stoichiometric amounts of titanium tetrachloride, trimethylsilyl enol ether, and a carbonyl compound is a great advance in directed aldol reaction. Powerful activation of carbonyl groups by $TiCl_4$ enables the nucleophilic attack by trimethylsilyl enol ethers to form trimethylsilyl chloride and the titanium salt of the aldol-type product. In this case, undesirable dissociation of the adduct is inhibited by the formation of a stable titanium chelate, hydrolysis of which yields the desired β-hydroxy ketone (Ref. 5).

This type of reaction is also promoted by various other Lewis acids such as $SnCl_4$, $BF_3 \cdot OEt_2$, $AlCl_3$, and so on. Among these acids, titanium tetrachloride was found to be superior to the other Lewis acids with respect to yields. The reaction proceeds with retention of the regiochemical integrity of the starting silyl enol ethers to afford the corresponding aldol regiospecifically. Starting enol ether compounds, silyl enol ethers, can be conveniently prepared regioselectively under either kinetically or thermodynamically controlled conditions.



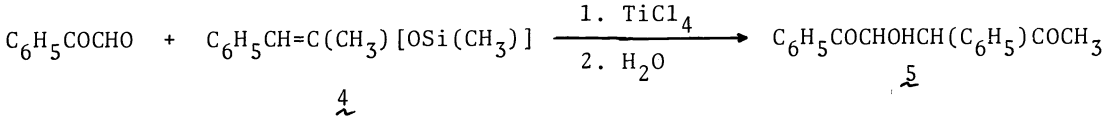
Enol ethers derived from ketones or aldehydes react with aldehydes at -78°C, whereas elevated temperatures are required for ketones.

Although precise examination of the stereochemistry of the aldol products has not been done, this $TiCl_4$ promoted reaction usually gives a mixture of *threo* and *erythro* isomers in comparable amounts.

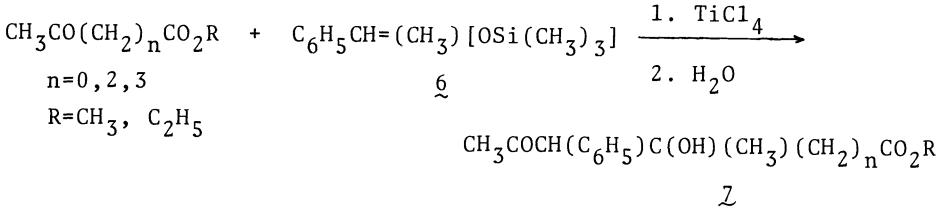


68%
(threo:erythro=1:1)

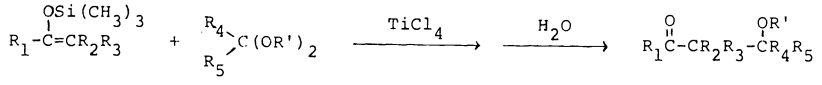
Chemoselectivity is observed with acceptors having two different kinds of carbonly functions such as aldehyde and ketone or ester in the same molecule. Treatment of phenylglyoxal with enol ether 4 at -78°C affords the α-hydroxy-γ-diketone 5 (Ref. 5a).



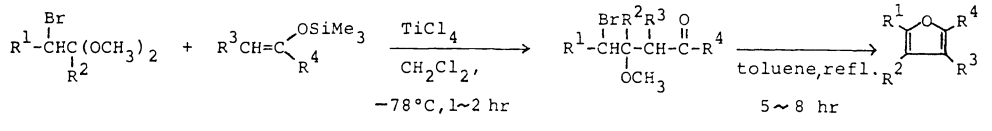
The reaction of ketoesters other than β-ketoesters with the enol ether 6 gives hydroxyketoesters 7 as sole products (Refs. 5d,e).



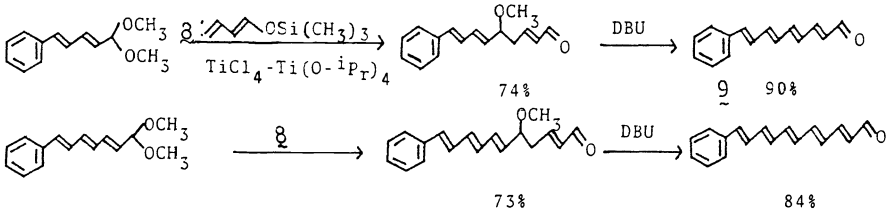
The advantage of using acetals or ketals instead of aldehydes or ketones is that they act only as electrophiles and probably coordinate with Lewis acids more strongly than the parent carbonyl compounds. Trimethylsilyl enol ethers react readily with acetals or ketals at -78°C in the presence of titanium tetrachloride to afford β-alkoxy carbonyl compounds in high yields (Ref. 6).



Various substituted furanes are readily prepared by application of the $TiCl_4$-promoted reaction of α-halo acetals with silyl enol ethers (Ref. 7).



δ-Alkoxy α,β-unsaturated aldehydes such as 9 are valuable synthetic intermediates because of their polyfunctionality. Reaction of acetals and the dienoxysilane 8 in the presence of $TiCl_4$ alone gives only polymers. However, the desired aldehyde 9 is obtained in good yield by treating acetal and the silane 8 at -40°C in the co-existence of $TiCl_4$ and $Ti(O-<)_4$ (Ref. 8).

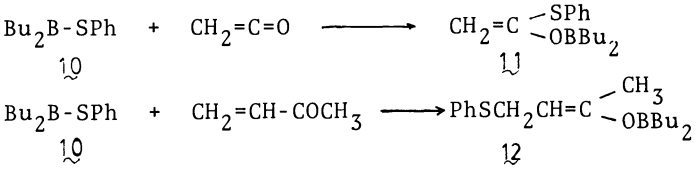


This method has been used successfully in the synthesis of natural products such as vitamin A, variotin and hypacrone (Ref. 9).

Thus the titanium tetrachloride promoted aldol reaction offers a very valuable approach to aldol adducts under mild conditions. In particular, it has realized the utility of silyl enol ethers as isolable and useful enolate equivalents and the acidic medium permits the use of base sensitive functional groups in aldol type reactions which do not survive lithiated derivative mediated methods.

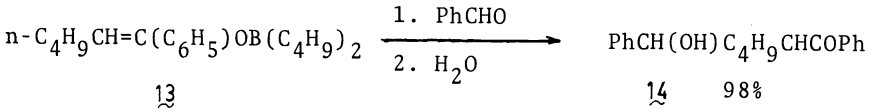
2. VIYNLOXYBORANE MEDIATED ALDOL REACTION

Ten years ago we found that the vinyloxyborane derivative 11 was formed in reaction of phenyl di-*n*-butylthioboronite 10with ketone. Similarly, vinyloxyborane 12 was prepared by the reaction of methyl vinyl ketone with phenyl di-*n*-butylthioboronite (Ref. 10).

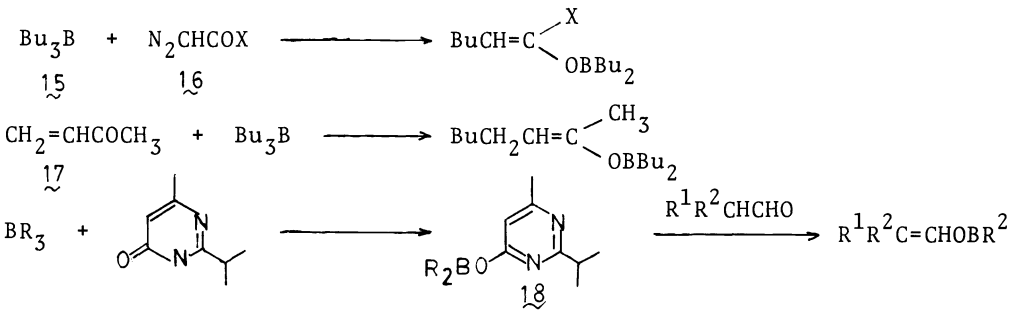


We have pointed out as a first example that these vinyloxyboranes are highly useful synthetic intermediates to react with various carbonyl compounds to afford β-hydroxycarbonyl compounds in excellent yields under essentially neutral conditions (Ref. 11).

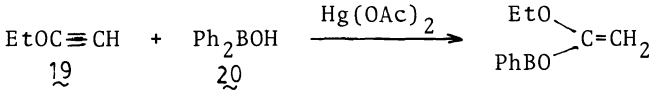
For example, treatment of vinyloxyborane 13 with benzaldehyde at room temperature for 10 minutes gives crossed aldol 14 in 98% yield. This method is a typical example of an aldol reaction carried out under neutral conditions (Ref. 10).



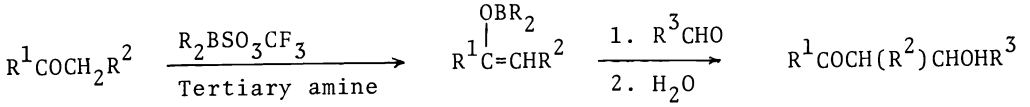
Alternatively, it had been known at that time that vinyloxyboranes could be prepared by reaction of a diazoketone 16 with a trialkylborane 15 (Ref. 11), or by the 1,4-addition of an alkylborane to an α,β-unsaturated ketone 15 (Ref. 12). The reaction of enolizable aldehydes with a 4-dialkylboryloxy-2-isopropyl-6-methylpyrimidine 18 also gives vinyloxyboranes (Ref. 13).



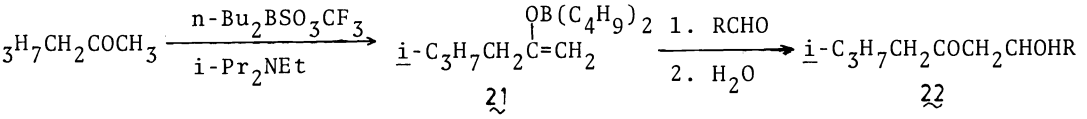
More recently, it was found that a boron enolate of an ester was generated by treatment of ethoxyacetylene 19 with mercury(II) acetate and diphenylboronic acid 20 (Ref. 14).



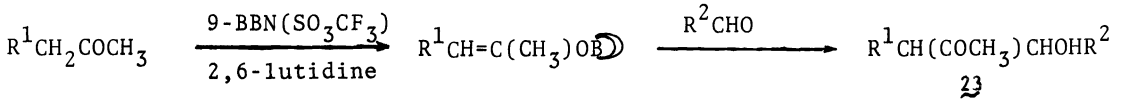
A convenient method for generation of vinyloxyboranes from a wide variety of enolizable ketones has been reported. Dialkylboryl trifluomethanesulfonate (R_2BOTf) reacts with ketones in the presence of a tertiary amine to produce vinyloxyboranes. The vinyloxyboranes thus generated react with aldehydes to give crossed aldols in high yields (Ref. 15).



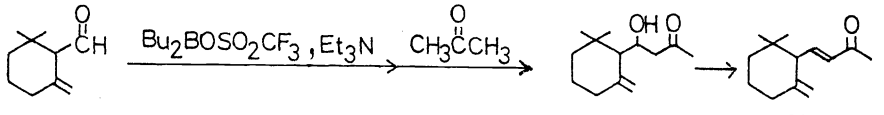
Regioselective generation of vinyloxyborane is readily controlled by a suitable combination of reagents. For example, the reaction of 4-methyl-2-pentanone with dibutylboryl trifluoromethanesulfonate and diisopropylethylamine produces the kinetically controlled vinyloxyborane 21 which then reacts with an aldehyde to afford the β-hydroxyketone 22 (Ref. 15d).



In contrast, the thermodynamically stable vinyloxyborane is generated by the reaction of the ketone and 9-borabicyclo [3.3.1]-9-nonanyl trifluoromethanesulfonate (9-BBN-triflate) in the presence of 2,6-lutidine at -78°C for 3 hours. Subsequent reaction with an aldehyde gives the corresponding aldol 23 (Ref. 15a).

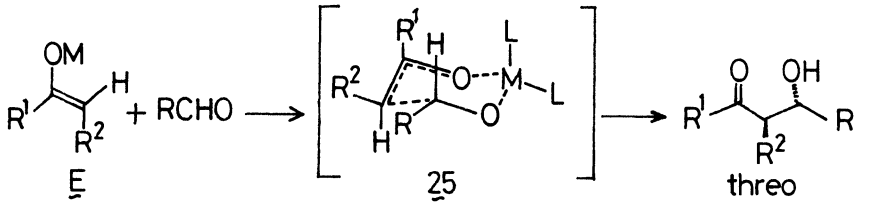


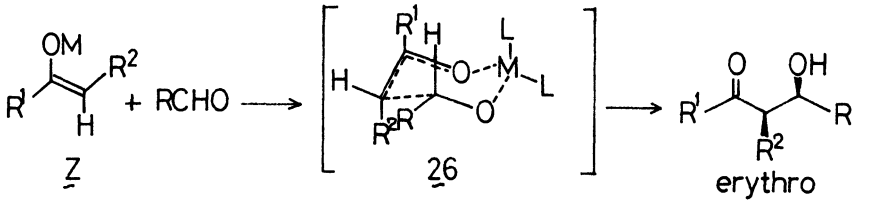
This reaction proceeds under very mild conditions without causing isomerization of double bond of β,γ-unsaturated aldehydes. Thus γ-ionon is synthesized without any contanination with isomeric α- and β-ionones by a cross aldol reaction of vinyloxyborane with γ-citral (Ref. 16).



The most important stereochemical question in the directed aldol reaction concerns the formation of *threo* and/or *erythro* isomers of aldols or ketols. Consequently, extensive stereochemical studies on the geometry of enolate species, the nature of the metal, kinetic vs. thermodynamic control, and steric effects have been carried out.

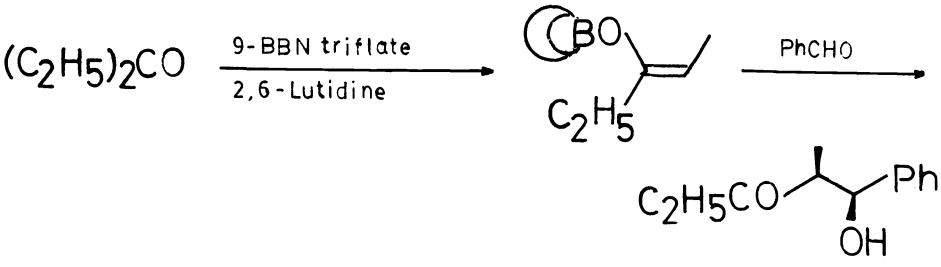
Under kinetically controlled conditions the formation of stereoisomers is dependent on the geometry of the starting enolate. In general, the (*Z*)-enolate gives the *erythro* isomer and the (*E*)-enolate gives the *threo* isomer.





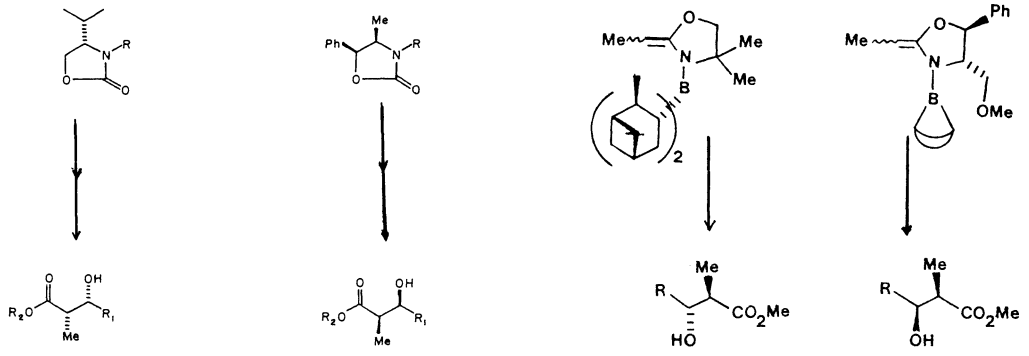
The carbonyl component approaches the enolate perpendicularly, and the reaction proceeds via a pericyclic process.

Dialkylboron enolates have relatively short metal-ligand and metal-oxygen bonds, which is suited for maximizing 1,3-diaxial R-L interactions in the transition states. Thus facilitating the formation of more stable transition states 25 and 26 where R occupies a pseudoequatorial position, the vinyloxyboranes undergo stereoselective aldol reaction (Ref. 11b). The vinyloxyborane generated in situ from 3-pentanone and 9-borabicyclo [3.3.1]-9-nonyl-trifluoromethanesulfonate (9-BBN triflate) by the action of 2,6-lutidine reacts with benzaldehyde in a complete stereoselective manner, giving *erythro* aldol 27, almost exclusively (Ref. 15a).



Further study of stereodefined vinyloxyborane condensation reactions by D. A. Evans and S. Masamune revealed that the (*Z*)–isomers react with various aldehydes to yield predominantly the *erythro* aldols, whereas the (*E*)–isomers react somewhat less stereoselectively to give *threo* aldols as the major products. In some cases the preparation of either (*E*)-vinyloxyborane or (*Z*)-vinyloxyborane in a highly stereoselective manner can be achieved starting from the same ketone, resulting in a stereoselective synthesis of either *erythro* and *threo* aldol (Refs. 17, 15b,c,f).

Furthermore, Evans (Ref. 18) and Meyers (Ref. 19) recently showed enantioselective aldol reactions using chiral boron enolates.



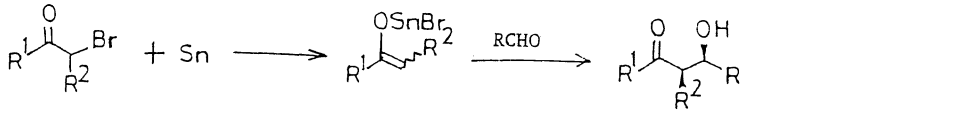
Vinyloxyboranes prepared under very mild conditions allow aldol type reactions essentially under neutral conditions. Acyclic stereoselection which is a challenge among many organic chemists has been achieved by employing vinyloxyborane mediated aldol reaction. This method is applied extensively to the synthesis of natural products.

3. THE STANNOUS ENOLATE MEDIATED ALDOL REACTION

The chemistry of tin(IV) enolates has been studied recently and several interesting features of these species have been explored (Ref. 20), whereas tin(II) analogues (stannous enolates) are relatively unkown species in synthetic organic chemistry in part for lack of general preparation methods.

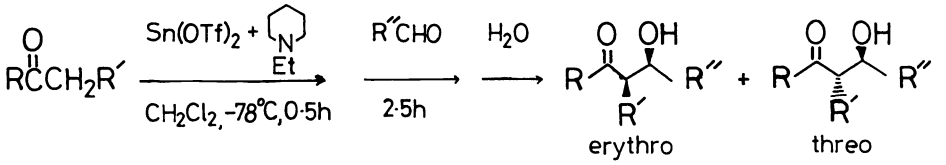
Recently we found that stannous(II) enolates could be prepared in situ by the oxidation addition of α-bromoketones to metallic tin (Ref. 21).

It was reported that the enolate was regioselectively generated by the coupled attack of dialkylaluminum chloride and zinc on α-bromoketone and that the aldol is produced in a regioselective manner, however, diastereoselectivity is generally low. Stannous enolates generated from α-bromoketones and Sn(0) react with aldehydes in a highly regioselective manner with high *erythro* selectivity (Ref. 21c).



63-99% (erythro:threo=90:10-94:6)

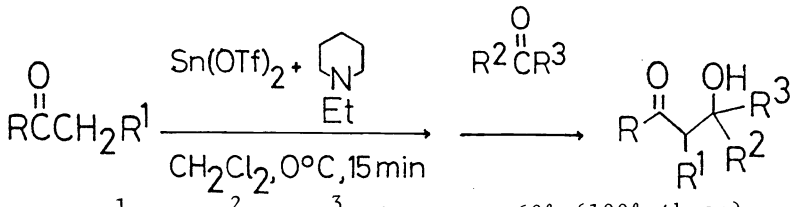
More conveniently, stannous enolates can be generated by the reaction of ketones and $Sn(OTf)_2$ in the presence of a tertiary amine. In this reaction, the choice of the tertiary amine is crucial. For example, pyridine, or DBU which can coordinate strongly to divalent tin failed to promote the reaction, while N-ethylpiperidine gave an excellent result. These divalent tin enolates undergo aldol reactions to give β-hydroxy ketones in good yields, under extremely mild conditions where good to excellent *erythro* selectivity is observed (Ref. 22).



71-86% (erythro:threo=86:14->95:5)

Moreover, the stannous enolates generated by the above procedure are highly reactive and can react even with ketones to give ketone-ketone cross coupling products in good yields (Ref. 23).

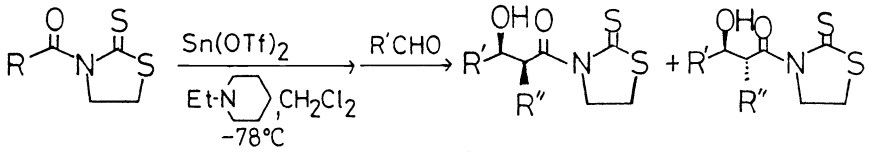
Boron enolates, which are very versatile metal enolates display poor reactivity toward ketones and more nucleophilic lithium enolates react with less hindered ketones in moderate yield. Considering the reactivities of those enolates, we would like to emphasize the high reactivity of stannous enolates. Also noteworthy is the fact that employment of aromatic ketones as acceptor enhances *threo* selectivity.



R=Ph, R^1=CH_3, R^2=Ph, R^3=CH_3 60% (100% threo)

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 undergo a similar aldol type reaction to give β-hydroxy carbonyl compounds in excellent yields with high *erythro* selectivity. This type of crossed coupling products are very versatile synthetic materials and can be transformed into esters, amides, aldehydes, diols, respectively in good yields (Ref. 24).



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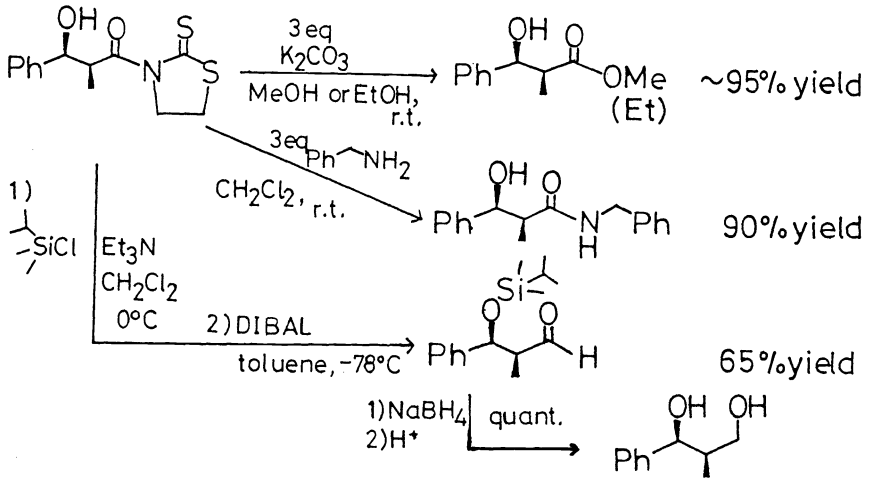
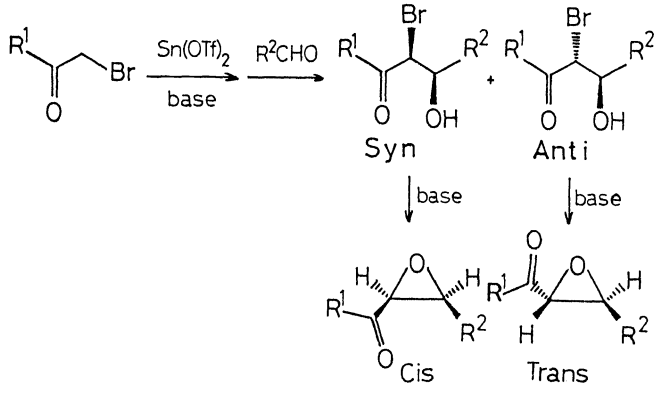
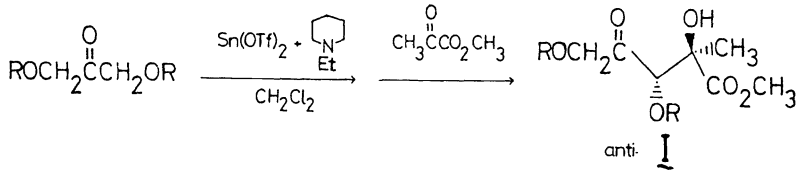
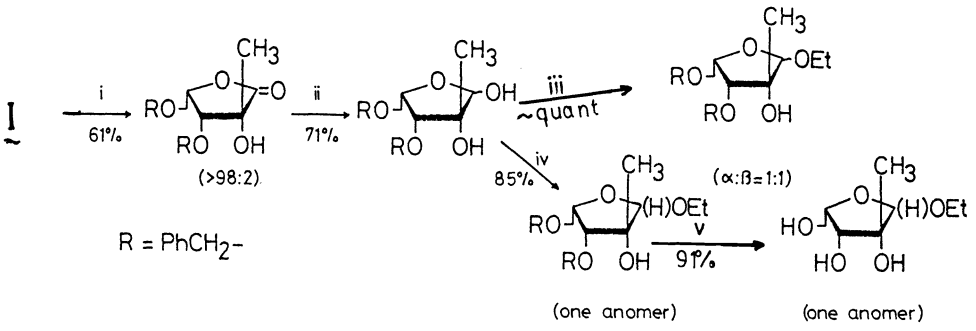


Trans-α,β-epoxyketones are usually prepared by hydrogen peroxide epoxidation of α,β-unsaturated ketones, whereas *cis*-isomers cannot easily be prepared. The mildness of the present aldol reaction provides a stereoselective synthesis of *cis*-β-substituted-α,β-epoxyketones. Aldol reaction between an α-bromoketone and an aldehyde followed by KF-dicyclohexyl-18-crown-6 tretment gave *cis*-epoxyketones stereoselectively (Ref. 25).



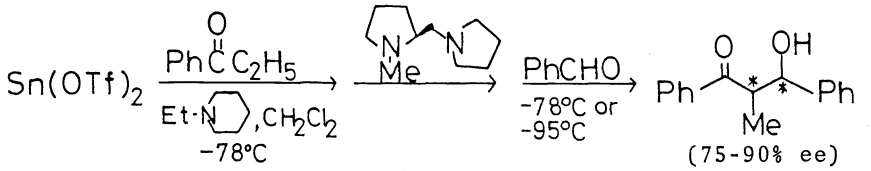
A facile synthesis of the branched chain sugar, 2-C-methyl-DL-lyxofuranoside has been achieved by using the tin(II) enolate of 1,3-dihydroxy-2-propanone derivative and methyl pyruvate (Ref. 26).



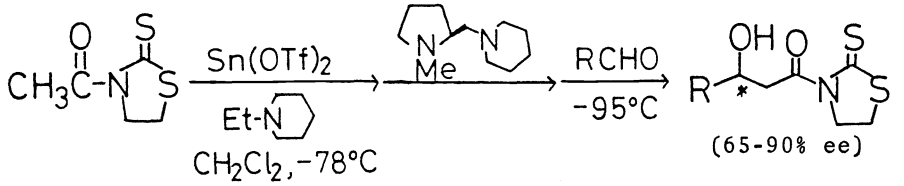


(i) Li(*s*-Bu)$_3$BH (ii) Dibal (iii) EtOH/H$^+$ (iv) KO^{t}Bu, excess EtI (v) H_2/5%Pd-C

Although several asymmetric aldol reactions have been reported recently, chiral auxiliary groups are usually attached to the ketone equivalent molecules in these reactions. No example existed so far in aldol type reaction where two achiral carbonyl compounds are used for constructing a chiral molecule with the aid of a ligand. Based on the considerations that divalent tin having vacant d orbitals, is capable of accepting a bidentate ligand coupled with the fact that (*S*)-proline derived chiral diamines are efficient ligands in certain asymmetric reactions, enantioselective aldol reaction via divalent tin enolates with chiral diamines was explored. A highly enantioselective cross aldol reaction between aromatic ketones or 3-acetylthiazolidine-2-thione and various aldehydes has been achieved, in which chiral diamines derived from (*S*)-proline worked very effectively as ligands. This is a first example for the formation of cross aldol in high optical purity starting from two achiral carbonyl compounds employing chiral diamines as chelating agents (Refs. 27,28).



(Sn(OTf)$_2$:N-ethylpiperidine:propiophenone:chiral diamine:benzaldehyde =1.0:1.15:0.8:1.2:1.2)



Sn(OTf)$_2$:N-ethylpiperidine:chiral diamine:3-acetylthiazolidine-2-thione:aldehyde =1.0:1.2:1.2:0.85:1.15.

These compounds derived from 3-acetylthiazolidine-2-thione are very versatile chiral materials, capable of being transformed into various synthetic intermediates as demonstrated before (Ref. 28). Thus the characteristic features of tin(II) enolates enable the stereoselective synthesis of aldol products even from two different ketones. Combination of Sn(OTf)$_2$ and N-ethylpiperidine provides an easy approach to tin(II) enolates, whereas tin(IV) enolates have been prepared through relatively laborious multi step procedures. Enantioselective aldol reaction effected by chiral diamines also enhances the utility of tin(II) enolate as versatile synthetic intermediate. It is highly expected that tin(II) enolates will find useful applications in organic synthesis.

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