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Author's Review

Recent Advances in Cross Aldol Reactions

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The aldol reaction plays an important role in organic synthesis and provides very useful synthetic tools for stereoselective and asymmetric carbon-carbon bond formations. Four types of aldol reactions developed in our laboratory are discussed.

INTRODUCTION

The aldol reaction, classically carried out in protic solvents with a base or acid as catalyst, is one of the most useful and versatile methods for carbon-carbon bond-formation. The scope of the aldol reaction has been extended by the introduction of lithium, magnesium and zinc enolate mediated methods. Besides these enolate species, silyl enol ethers, vinyloxyboranes, and stannous enolates have broadened the utility of the aldol type reaction for the construction of carbon skeltons of various naturally occurring materials in a stereo- and enantioselective manner.[1]

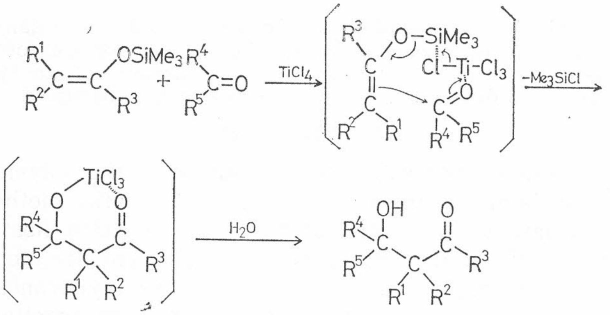
In this review, four types of metal enolate mediated aldol reactions developed in our laboratory, *i. e.* titanium tetrachloride promoted aldol reaction of silyl enol ethers, vinyloxyborane mediated aldol reaction, and stannous enolate mediated aldol reaction, trityl perchlorate catalyzed aldol reaction of silyl enol ethers, are discussed.

1. THE TITANIUM TETRACHLORIDE PROMOTED ALDOL REACTION[2]

The aldol reaction is one of the most useful synthetic tools especially in forming carbon-carbon bonds. However, conventional methods, in which a base or acid is employed as promoter in a protic solvent, have serious synthetic limitations because of the difficulties in directing the crosscoupling; the reaction is often accompanied by undesirable side reactions, such as self-condensation and polycondensation. In addition, the aldols are easily dehydrated and the resulting unsaturated carbonyl compounds may undergo the Michael addition with enolates to give a complex reaction mixture. In order to alleviate these difficulties, various metal enolate mediated aldol reactions have been developed. The reaction of carbonyl compounds with lithium enolates or lithio derivatives of imines offers one of the typical methods for the preparation of cross aldols, though under strongly basic conditions.[3] Use of magnesium, aluminum or zinc enolate permits rather mild reaction conditions in similar reactions.

On the other hand, a clean aldol reaction is achieved by using stoichiometric amounts of titanium tetrachloride as promoter in the reaction of silyl enol ethers, isolable enolates, with carbonyl compounds. The powerful activation of a carbonyl group by titanium tetrachloride provides the driving force for this reaction. 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.[5]

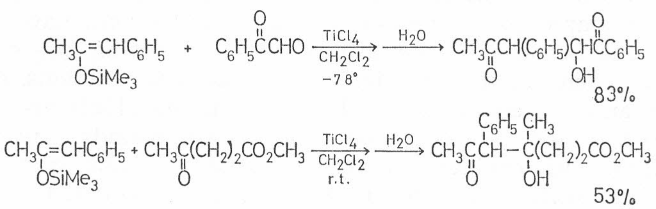
This type of reaction is also promoted by various other Lewis acids, such as $SnCl_4$, $BF_3 \cdot OEt_2$, $AlCl_3$, and so on. Titanium tetrachloride was found to be superior to the other Lewis acids with respect to yields of aldol products. The reaction proceeds with retention of the regiochemical 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.



The enol ethers react with aldehydes at —78 °C, whereas elevated temperatures are required for ketones.

Precise examination of the stereochemistry of aldol products was not performed when we developed this type of reaction. Recent studies on the stereochemical aspects of the titanium tetrachloride-silyl enol ether mediated aldol reaction in which trichlorotitanium enolates are involved have revealed many interesting features.[6]

Chemoselectivity is observed with acceptors having two different kinds of carbonyl functions, such as aldehyde and ketone (or ester) in the same molecule.[5a,b,c]

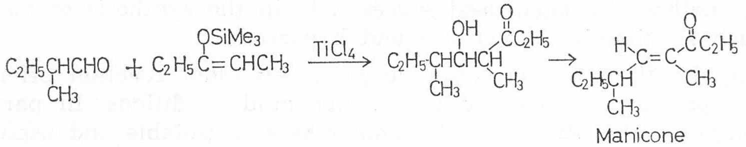


$$\underset{OSiMe_3}{CH_3C}{=}CHC_6H_5 + C_6H_5\overset{O}{\overset{\|}{C}}CHO \xrightarrow[CH_2Cl_2,\ -78°]{TiCl_4} \xrightarrow{H_2O} CH_3\underset{O}{\underset{\|}{C}}CH(C_6H_5)\underset{OH}{CH}\overset{O}{\overset{\|}{C}}C_6H_5 \quad 83\%$$

$$\underset{OSiMe_3}{CH_3C}{=}CHC_6H_5 + CH_3\underset{O}{\underset{\|}{C}}(CH_2)_2CO_2CH_3 \xrightarrow[CH_2Cl_2,\ r.t.]{TiCl_4} \xrightarrow{H_2O} CH_3\underset{O}{\underset{\|}{C}}\overset{C_6H_5}{CH}-\overset{CH_3}{\underset{OH}{C}}(CH_2)_2CO_2CH_3 \quad 53\%$$

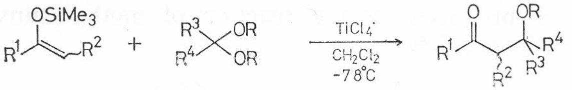
Chiral aldehydes may be used as the acceptor of silyl enol ethers without affecting the chiral centers.

The reactions of (+)-1-methylbutanal with 2-trimethylsiloxy-2-butene proceed quite smoothly at —78 °C without racemization of the aldehyde to give a diastereometic mixture of aldol products, which in turn is dehydrated to give optically pure (+)-manicone, an alarm pheromone.[7]



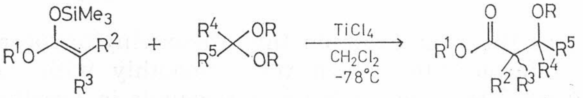
Manicone
(Alarm pheromone)

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.[8]



$R^1=CH_3$, $R^2=Ph$, $R^3=PhCH_2CH_2$, $R^4=H$. 98 %

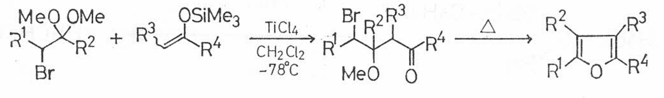
$R^1=CH_3$, $R^2=Ph$, $R^3=R^4=-(CH_2)_5-$ 91 %



$R^1=CH_3$, $R^2=PhCH_2$, $R^3=H$, $R^4=Ph$, $R^5=H$ quant.

$R^1=R^2=R^3=CH_3$, $R^4=PhCH_2$, $R^5=CH_3$ 94 %

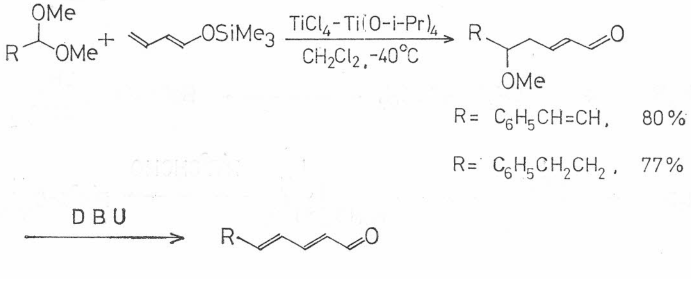
Various substituted furans are readily prepared by the application of the $TiCl_4$ promoted reaction of α-halo acetals with silyl enol ethers.[9]



$R^1=C_2H_5$, $R^2=H$, $R^3=Ph$, $R^4=CH_3$ 82 %

$R^1=R^2=-(CH_2)_4-$, $R^3=H$, $R^4=Ph$ 76 %

δ-Alkoxy α,β-unsaturated aldehydes are valuable synthetic intermediates because of their polyfunctionalities. Reaction of acetals and the dienoxysilane in the presence of $TiCl_4$ alone resulted in the formation of polymeric substances. However, the desired aldehyde is obtained in good yield by treating acetal and dienoxysilane at —40 °C with the co-existence of $TiCl_4$ and Ti(O — <)$_4$.[10]



R= $C_6H_5CH=CH$, 80%

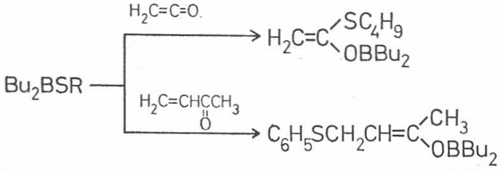
R= $C_6H_5CH_2CH_2$, 77%

This method has been used successfully in the synthesis of natural products such as vitamin A, variotin and hypacrone.[11]

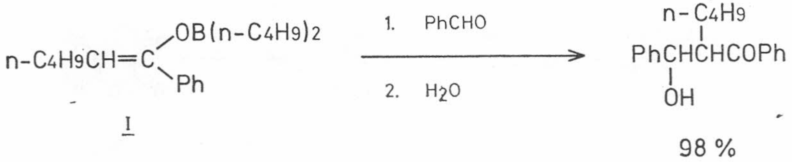
Thus, the titanium tetrachloride promoted aldol reaction offers a very valuable approach to aldol adducts under mild conditions. In particular, it has highlighted the utility of silyl enol ethers as isolable and useful enolate equivalents, and permits the use of base sensitive functional groups in aldol-type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

2. THE VINYLOXYBORANE MEDIATED ALDOL REACTION

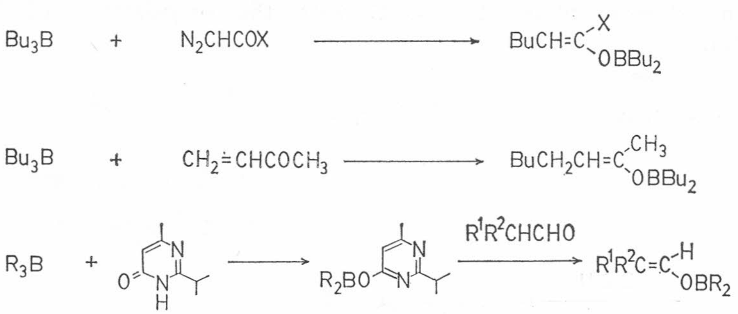
In 1973, we found that vinyloxyborane derivative was formed in situ by the reaction of phenyl di-*n*-butylthioboronite with ketene. Similarly, vinyloxyborane was prepared by the reaction of methyl vinyl ketone with phenyl di-*n*-butylthioboronite.[12]



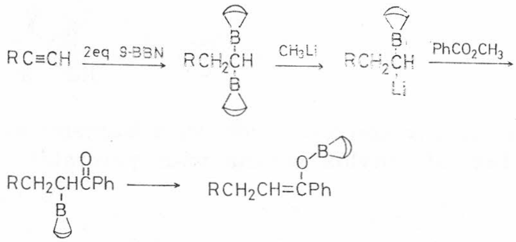
We reported as the first example that these vinyloxyboranes are highly useful synthetic intermediates which react smoothly with various carbonyl compounds to afford β-hydroxy carbonyl compounds in excellent yields under essentially neutral conditions.[12] For example, treatment of vinyloxyborane (*I*) with benzaldehyde at room temperature for 10 min gives the cross aldol in 98% yield. This method is a typical example of an aldol reaction carried out under neutral conditions.



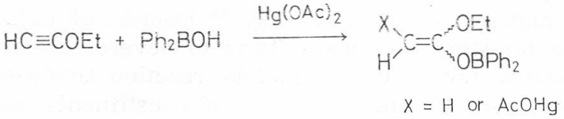
Alternatively, it was known at that time that vinyloxyboranes could be generated by reaction of a diazoketone with a trialkylborane,[13] or by the 1,4-addition of an alkylborane to an α,β-unsaturated ketone.[14] The reaction of enolizable aldehydes with 4-dialkylboryloxy-2-isopropyl-6-methylpyrimidine also gives vinyloxyboranes.[15]



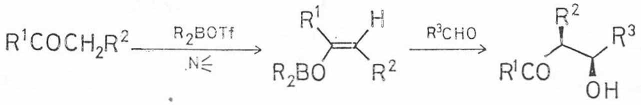
Recently, it was found that vinyloxyboranes are generated starting from acetylenic compounds. Thus, phenyl-substituted boron enolates are generated by the action of boron-stabilized carbanions with methyl benzoate.[16]



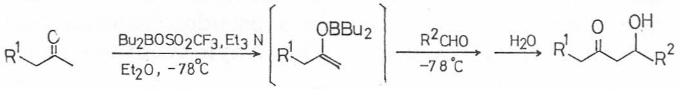
In addition, a boron enolate of an ester is generated by treatment of ethoxyacetylene with mercury(II) acetate and diphenylborinic acid.[17]



A convenient and useful method for the generation of vinyloxyboranes from a wide variety of enolizable ketones was explored in 1976. Dialkylboryl trifluoromethanesulfonate (R_2BOTf) enolizes ketones in the presence of a tertiary amine to produce vinyloxyboranes, which in turn react with aldehydes to give cross aldols in high yields.[18]



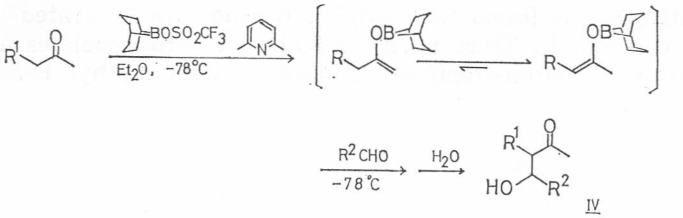
Regioselective generation of a vinyloxyborane is readily controlled by a suitable choice of substituents of boron triflate and a tertiary amine. For example, the reaction of 4-methyl-2-pentanone with dibutylboryl trifluoromethanesulfonate and diisopropylethylamine produces the kinetically controlled vinyloxyborane (*II*) which then reacts with an aldehyde to afford the β-hydroxyketone (*III*).[18d]



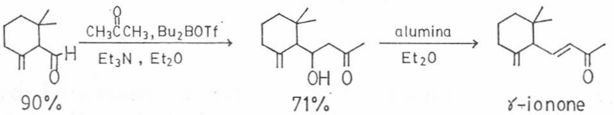
II III

In contrast, the thermodynamically stable vinyloxyborane is generated by treatment of a ketone with 9-borabicyclo[3.3.1]-9-nonanyl trifluoromethanesulfonate (9-BBN triflate) in the presence of 2,6-lutidine at —78 °C for 3 h. Subsequent reaction with an aldehyde gives the corresponding aldol (*IV*).[18a]

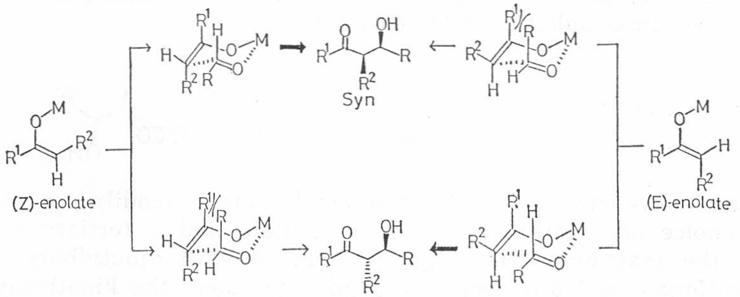
This reaction proceeds under very mild conditions without causing isomerization of the double bond of β,γ-unsaturated aldehydes. Thus, γ-ionon



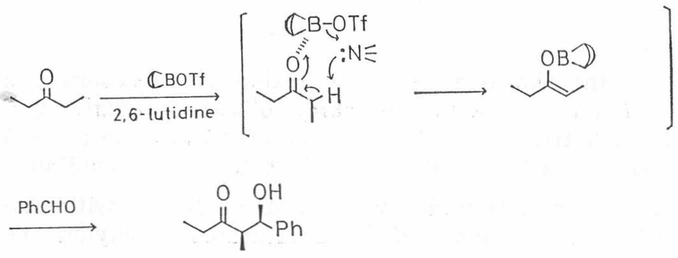
is synthesized without any contamination with isomeric α- and β-ionones by a cross aldol reaction of vinyloxyborane with γ-citral.[19]



The most important stereochemical problem in the directed aldol reaction concerns the formation of *anti* and/or *syn*[20] isomers of aldols. Consequently, extensive studies on stereochemical effects of several variables, such as the geometry of enolates, the nature of metals, reaction conditions under kinetic or thermodynamic control, and bulkiness of substituents, have been carried out in the last decade. Under kinetically controlled conditions the formation of stereoisomers is dependent on the geometry of the starting enolate. In general, the (Z)-enolate gives the *syn* isomer and the (E)-enolate gives the *anti* isomer *via* a pericyclic process.



Dialkylboron enolates have relatively short metal-ligand and metal-oxygen bonds, which is suitable for maximizing 1,3-diaxial R—L interactions in the transition states. Thus, vinyloxyboranes facilitate the formation of more stable transition states, where R occupies a pseudoequatorial position leading to the stereoselective aldol reaction.[18b] The vinyloxyborane generated *in situ*



from 3-pentanone and 9-BBN triflate by the action of 2,6-lutidine reacts with benzaldehyde in a completely stereoselective manner, giving syn aldol almost exclusively.[18]

Further study of stereodefined vinyloxyborane condensation reactions by D. A. Evans and S. Masume revealed that the (Z)-isomers react with various aldehydes to yield predominantly *syn* aldos, whereas the (E)-isomers react somewhat less stereoselectively to give *anti* 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 *syn* or *anti* aldol.[18b,c,f,21] In contrast, it was recently reported that alkenyloxy dialkoxyboranes afford *syn* aldol adducts regardless of their enolate geometry.[22]

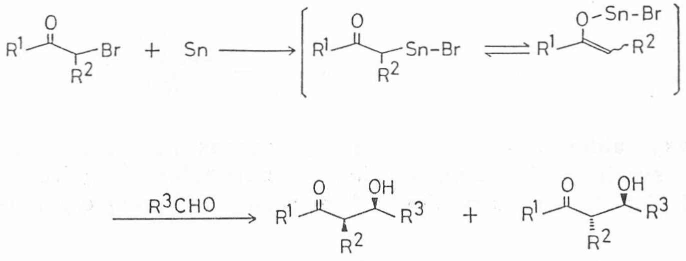
Furthermore, Evans[23] and Meyers[24] showed enantioselective aldol reactions using chiral boron enolates.

Acyclic stereoselection, which has been a challenge to many organic chemists, is achieved on the basis of vinyloxyborane mediated aldol reaction. This method is extensively applied to the synthesis of various natural products because of its high reactivity under neutral conditions and fairly good stereoselectivity.

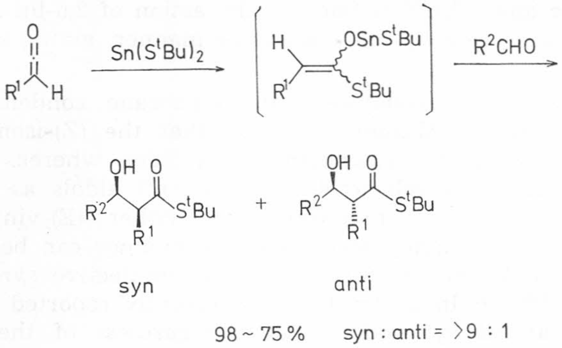
3. THE STANNOUS ENOLATE MEDIATED ALDOL REACTION

The chemistry of tin(IV) enolates has been studied recently and several interesting features of these species have been explored,[25] where tin(II) analogues (stannous enolates) are a relatively unknown species in synthetic organic chemistry, in part due to lack of general preparative methods.

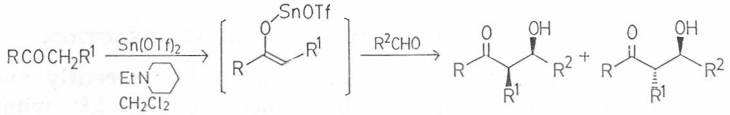
Recently it was found that stannous(II) enolates could be prepared *in situ* by the oxidative addition of — bromoketones to metallic tin.[26] It is known that the enolate is regioselectively generated by the coupled attack of dialkylaluminum chloride and zinc on α-bromoketones and the aldol is produced in a regioselective manner; however, diasteroselectivity is generally low.[27] Stannous enolates generated from α-bromoketones and Sn(0) react with aldehydes in a highly regioselective manner with high *syn* selectivity.



In addition, stannous enolates of thioesters are generated by treatment of ketene with stannous thiolates. The reaction of stannous enolates thus formed with aldehydes leads to stereoselective preparation of *syn*- β-hydroxy thioesters.

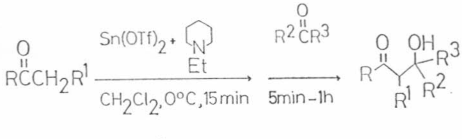


More conveniently, stannous enolates can be generated by reaction of ketones and $Sn(OTf)_2$ in the presence of a tertiary amine. In this reaction, the choice of the tertiary amine is crucial; for example, pyridine, or DBU which can coordinate strongly to divalent tin, failed to promote the reaction, while N-ethylpiperidine gave excellent results. These divalent tin enolates undergo aldol reactions to give β-hydroxy ketones in good yields under extremely mild conditions, with good to excellent *syn* selectivity.[28]



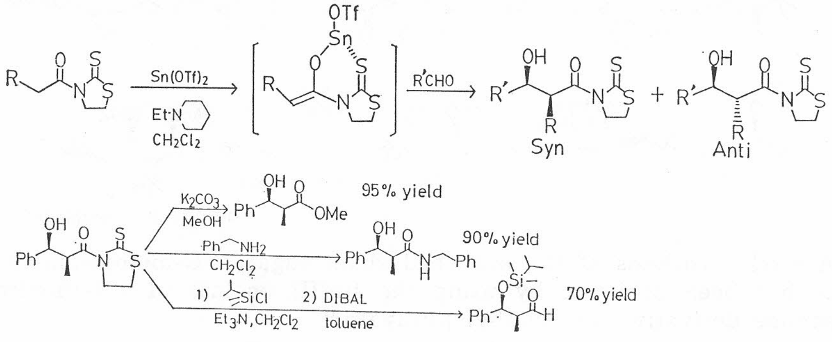
Moreover, the stannous enolates generated by the above procedure are highly reactive and can react even with ketones to give ketone-ketone cross coupling products in good yields.[29]

Boron enolates, which are very versatile metal enolates, display poor reactivity toward ketones, whereas more nucleophilic lithium enolates can react with lesshindered ketones in moderate yields. Considering the reactivities of these enolates, we would like to emphasize the high reactivity of stannous enolates. Also noteworthy is the fact that employment of aromatic ketones enhances *anti* selectivity.

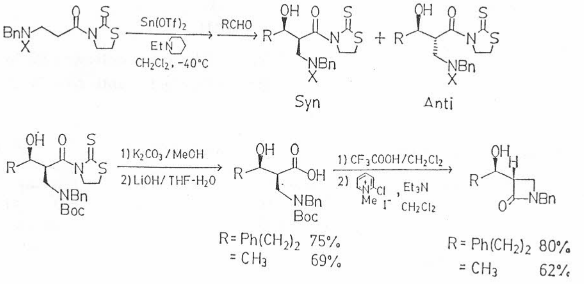


β-Hydroxy aldehydes and β-hydroxy carboxylic acid derivatives are very useful synthetic building blocks; in particular, β-hydroxy aldehydes are utilized for the construction of a series of polyoxygenated natural products.

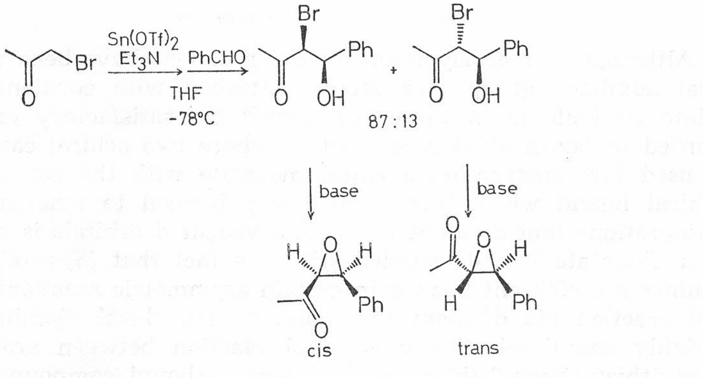
3-Acylthiazolidine-2-thiones, easily prepared from acyl chlorides and thiazolidine-2-thione or from carboxylic acids and thiazolidine-2-thione using DCC or pyridinium salts as condensation reagents, undergo a similar aldol-type reaction to give-β-hydroxy carbonyl compounds in excellent yieds with high *syn* selectivity. This type of crossed coupling product comprises very versatile synthetic intermediates and can be transformed into esters, amides, aldehydes, and diols in good yields.[30]



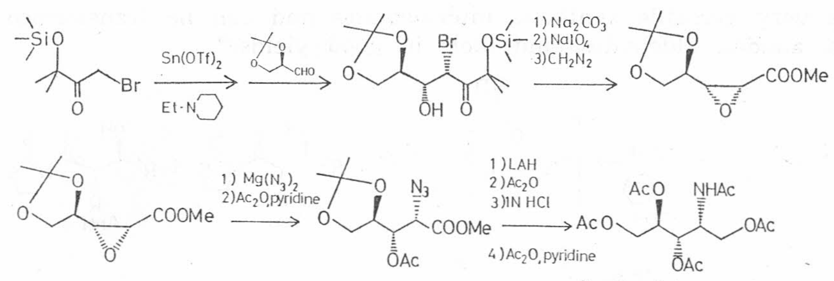
This reaction is also successfully applied to the stereoselective synthesis of β-lactam derivatives.[31]



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*-α,β-epoxyketones. Aldol reaction between an α-bromoketone and an aldehyde, followed by base treatment, gave *cis*-expoxyketones stereoselectively.[32]

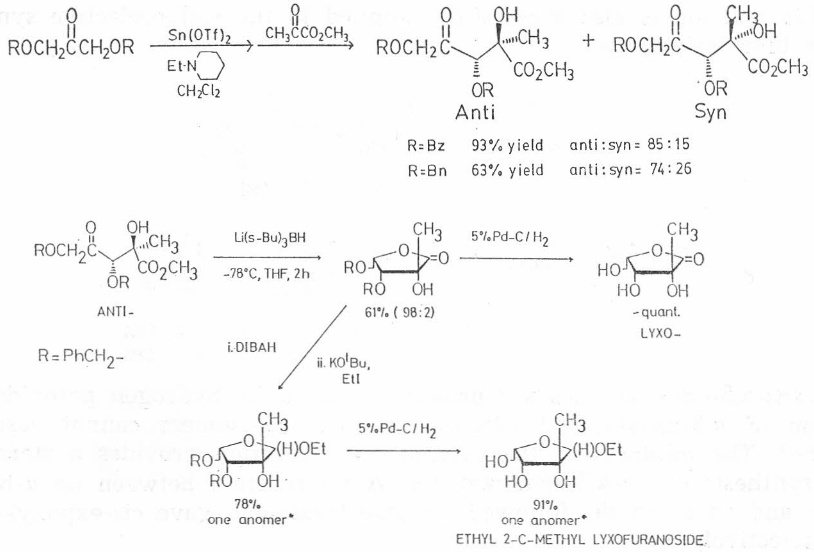


2-Amino-2-deoxy-D-arabinitol was synthesized *via* the *cis*-epoxyketone prepared, as mentioned above, from 2,3-*O*-isopropylidene-D-glyceraldehyde.[33]



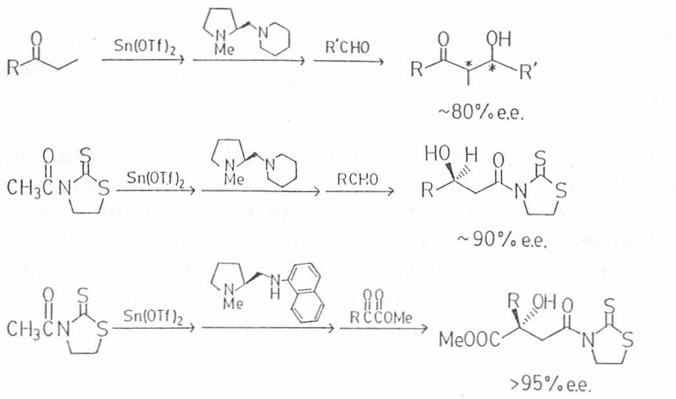
2-amino-2-deoxyarabinitol

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.[34]

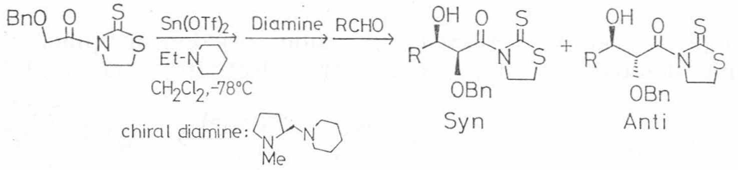


* Anomeric center configuration not determined

Although several asymmetric aldol reactions have been reported recently, chiral auxiliary groups are usually attached with covalent bonds to metal enolate equivalents in these reactions.[35] No satisfactory example has been recorded so far in aldol-type reaction where two achiral carbonyl compounds are used for constructing a chiral molecule with the aid of coordination of a chiral ligand which is not covalently bonded to reactants. 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 carbonyl compounds has been achieved, in which chiral diamines derived from (*S*)-proline act very effectively as ligands.[36] This is the first example of formation of cross aldol products in high optical purity starting from two achiral carbonyl compounds employing chiral diamines as chelating agents on the intermediate enolates.



These compounds derived from 3-acetylthiazolidine-2-thione are very versatile chiral materials, capable of being transformed into various synthetic intermediates, as demonstrated before.[30] Furthermore, in the stannous enolate mediated aldol-type reaction of 3-(2-benzyloxyacetyl)thiazolidine-2-thione, the stereochemical course of the reaction is dramatically altered by the addition of TMEDA as a ligand. High asymmetric induction is also achieved by the addition of the chiral diamine derived from L-proline.[37]

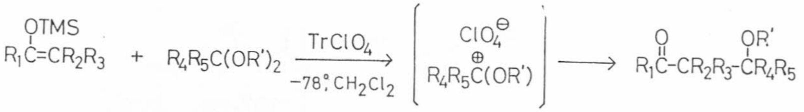


RCHO	Diamine	Yield(%)	Syn : Anti	Optical Purity(%ee)
Ph⌒CHO	——	62	75 : 25	——
	TMEDA	70	14 : 86	——
	chiral diamine	81	13 : 87	94

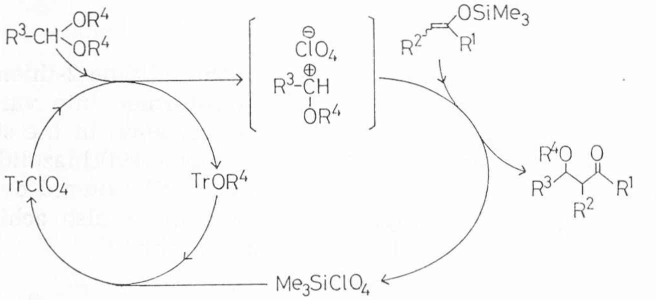
Combination of Sn(OTf)$_2$ and *N*-ethylpiperidine provides an easy approach to tin(II) enolates, whereas tin(IV) enolates have been prepared through relatively laborious multi-step procedures. Tin(II) enolates thus formed enable the stereoselective synthesis of aldol products even from two different ketones. Enantioselective aldol reactions effected by chiral diamines also enhance the utility of tin(II) enolates, which will find useful applications in organic synthesis.

4. THE TRITYL PERCHLORATE CATALYZED ALDOL REACTION

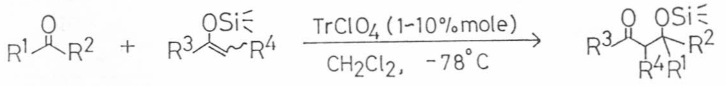
Recently we have also found that trityl perchlorate promotes the reaction of 1-*O*-acyl sugars with various nucleophiles, which indicates that trityl perchlorate effectively activates acyloxy group on the anomeric center.[38] On the assumption that trityl perchlorate could also activate alkoxy group on the acetal carbon, the aldol reaction of silyl enol ethers with acetals was examined using trityl perchlorate as catalyst and the corresponding aldols were obtained in good yields with *syn* selectivity.[39]



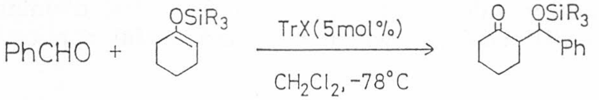
It is noteworthy that the reaction proceeds by the catalytic use of trityl perchlorate, whereas the aforementioned titanium tetrachloride promoted aldol reaction, the first example of the reaction of silyl enol ethers with acetals, requires stoichiometric amounts of $TiCl_4$ as a promotor. The catalytic cycle is achieved *via* regeneration of trityl perchlorate by the reaction of two initial products, trityl ether and silyl perchlorate, as shown in the following scheme.



Trityl perchlorate also promotes the aldol reaction of trimethylsilyl enol ethers with aldehydes, though the diastereoselectivity is not high.[40]



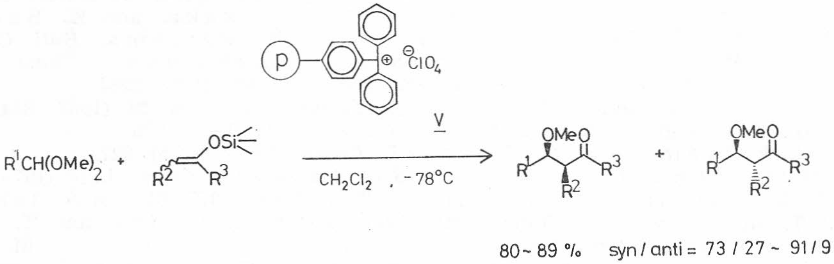
The aldol reaction is similarly catalyzed by other trityl salts, such as TrOTf, $TrPF_6$, $TrSnCl_5$, and $TrSbCl_6$. It was found that both the counter anions of trityl salts and the substituents on silicon of silyl enol ether play a significant role in the diastereoselectivity of the produced aldol. By the appropriate choice of the counter anion and the substituents of silyl group *syn* or *anti* aldol is preferentially obtained.[41] Therefore, the present reaction provides a useful method for the preparation of *anti* aldol, which has been rather difficult to obtaine by the hitherto known methods.

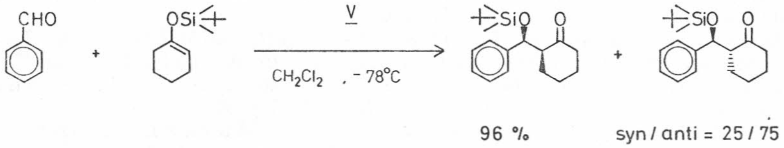


TrX	SiR_3	Yield/%	Syn:Anti
TrOTf	$SiPhMe_2$	79	78 : 22
$TrSbCl_6$	Si^tBuMe_2	92	18 : 82

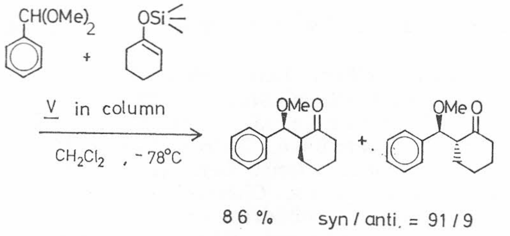
Trityl salts catalyzed aldol reaction has the advantages of a short reaction time, mild reaction conditions, and the catalytic use of TrX enabling the simplicity of the procedure. Furthermore, *anti* or *syn* aldol is preferentially prepared by the choice of the counter anion and the substituents of silyl group.

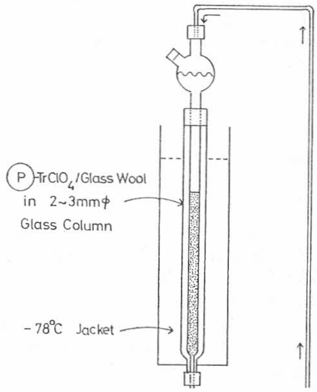
Another characteristic point of trityl salts, compared with other metallic Lewis acids such as $TiCl_4$, BF_3, and $SnCl_4$, is that modification of the aromatic ring leads to an immobilized catalyst. Polymer supported trityl perchlorate (*V*), prepared by treating trityl alcohol attached to polystyrene with perchloric acid in acetic anhydride, successfully catalyzed the aldol reaction to give the desired products in good yields.





Furthermore, the aldol product is obtained in high yield with good diastereoselectivity by recycling the solution of the silyl enol ether and an acetal (or aldehyde) through the column packed with polymer supported trityl perchlorate.[41] This method makes it possible both to separate the aldol product from the reaction system by a simple procedure, *i. e.* only by suction of the solution with a syringe after recycling the solution of reactants a few times, and to re-use the catalyst.





It is expected that the trityl perchlorate catalyzed aldol reaction will find useful applications in organic synthesis.

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POVZETEK

Novosti na področju mešanih aldolnih kondenzacij

Teruki Mukaiyama in Masahiro Murakami

Reakcije aldolne vrste igrajo pomembno vlogo v organski sintezi in predstavljajo zelo uporabljivo sintezno metodo za stereoselektiven in asimetričen način nastanka vezi ogljik-ogljik. Opisane so štiri vrste aldolnih reakcij, ki smo jih razvili v naših laboratorijih.