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Organic Synthesis in Japan: From Natural Products to Synthetic Control

TERUAKI MUKAIYAMA

Organic chemistry in present day Japan, which has developed from early interest in natural products chemistry, now includes total synthesis, physical organic chemistry, synthetic methods, and organometallic chemistry. In this article, the current state of Japanese organic chemistry is briefly reviewed and a representative aspect of today's organic chemistry—exploration of new synthetic methodology—is discussed.

JAPAN IS A LEADING NATION IN THE FIELD OF ORGANIC chemistry, and Japanese chemists have made important contributions to the recent growth of this subject. Initially, the chemistry of natural products was their main area of interest. At present there are major schools of research in total synthesis, physical organic chemistry, synthetic methods, and organometallic chemistry, and, in this article, I take the opportunity to introduce the work of some of these prominent research chemists.

Nozoe has been one of the leading figures in the development of Japanese natural products chemistry. Among his achievements, the most significant is the elucidation of the chemistry of the troponoid system. This work originated from his studies on hinokitiol [2-hydroxy-4-isopropyl-2,4,6,-cycloheptatrien-1-one], which he isolated from a natural source in 1935. His experiments led him to recognize the aromatic properties of the novel seven-membered ring independently of Dewar's tropolone hypothesis. He later synthesized tropolones and a wide variety of other nonbenzenoid aromatics, such as S- and N-analogs of tropolones; heptafulvenes; cyclic, cross-conjugated quinarenes; azulenes; and heterocyclic compounds annulated to the tropylium system. He also studied the physical and chemical properties of these diverse systems and thus established the chemistry of nonbenzenoid aromatic compounds as a new field in organic chemistry (*1*).

The development of physical organic chemistry has contributed to the basic understanding of reaction pathways. For example, Fukui has developed a theoretical approach to predict the reactivity of the organic molecule, which has proved useful for designing reaction sequences. Also well known in the field of physical organic chemistry are: Oki, for the isolation of rotational isomers and studies of their reactivity; Sakurai, for his interest in theory (chemical bonding and bond interactions) and new synthetic methods of organosilicon compounds; Misumi, for the synthesis of layered aromatic com-

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pounds and for model studies of charge-transfer and exciplex interactions of aromatic molecules; and Iwamura, for the molecular design and mechanistic studies of organic molecules in the triplet and higher-spin ground states. Tabushi is doing research in a new area of bioorganic chemistry that he established, the preparation and study of artificial enzymes and cells.

Natural Products Chemistry

By the early 1960's several Japanese chemists had made great progress and earned worldwide recognition in the field of natural products chemistry. Hirata's work on the isolation and structure determination of toxic compounds of marine origin, such as tetrodotoxin and palytoxin, exemplifies the high standards achieved by Japanese natural products chemists. Palytoxin is an extraordinarily large molecule ($C_{129}H_{223}N_3O_{54}$) with no repeating subunits such as amino acids or sugars. Because it is also unstable, noncrystalline, and insoluble in organic solvents, the isolation and structure determination of the toxin could not be carried out by standard methods but required novel techniques. Using such techniques, Hirata and his colleagues determined the planar structure of palytoxin and, in part, its stereochemistry (*2*). The latter was established completely in 1982 in collaboration with Kishi, who has contributed to the field of total syntheses of complex natural products (*3*).

The novel methodology devised in the course of structure determination of natural products has wide applicability. Goto, one of Hirata's students, has applied these techniques to the elucidation of various problems. He is interested in color chemistry, and his earlier work was concerned with the mechanism of the luminescence of luciferin. More recently, he has focused on the anthocyanin pigments, which play an important role in color variations of flowers, fruits, and autumn leaves. These pigments are unstable to hydration in aqueous solutions of *p*H 4 to 7, but are stable in petals and show a variety of colors. He has proposed that these observations are due to various types of stacking of anthocyanidin itself, and also to stacking between anthocyanidin and flavone. When stacked in a helix, anthocyanidin diglucosides are stabilized by a hydrophobic interaction between their aromatic nuclei. This stacking also caused color changes. This explanation was also applied to the copigmentation between anthocyanin and flavone (*4*). Using a variety of analytical methods, Nakanishi is also clarifying natural phenomena such as reception of light and carcinogenic processes (*5*).

Synthetic Chemistry

With the development of new analytical methods, and particularly with the introduction of x-ray analysis, the methodology and the objectives of natural products chemistry have changed dramatically. The structure of a compound can usually be determined now with only a minute amount (<1 milligram) of sample, and this fact has increased the extent of natural products research. Synthesis can often clarify the stereochemical details of a natural product and sometimes an abundant supply of a naturally occurring structure becomes available only through synthesis. Furthermore, synthesis can be used to help clarify the structure-activity relations between bioactive molecules.

Mori, one of the leading Japanese chemists in this area, has been concerned with this interface between natural products chemistry and synthetic chemistry. His group has worked on the synthesis of phytohormones, such as the gibberellins and brassinosteroids, insect hormones, pheromones, and microbial growth regulators. His studies in pheromone synthesis have clarified relations between the stereochemistry of pheromones and their biological activity (*6*).

The above-mentioned relations are subtle, and in many cases a slight change in stereochemistry results in a dramatic change in activity. Therefore, to synthesize bioactive molecules efficiently, it is desirable to develop reactions with a high degree of stereo-control (diastereo- and enantioselectivity). These high selectivities are achieved in nature by the action of enzymes. Ohno has used a combination of these enzymatic reactions and of more traditional organic reactions in natural products synthesis. Starting from symmetrical diesters, he has synthesized chiral half-esters of high optical purity by asymmetrical hydrolysis with pig liver esterase. These half-esters have been converted chemically into biologically active natural products such as carbapenems, nucleosides, and aminocyclitols (*7*).

Another approach to the synthesis of optically active compounds is nonenzymatic asymmetric synthesis. Highly efficient asymmetric reactions, based on the use of ingeniously designed substrates, have been developed. For these to be really useful in an industrial process, however, it is necessary that the chiral inducing agent be present in only catalytic amounts. One of the most successful examples is the Rh-chiral phosphine ligand-catalyzed isomerization of allylic amines to chiral enamines (*8*) developed in the laboratories of Otsuka and Noyori (*8*). This reaction is used by a Japanese perfume company as a key step in the preparation of *l*-menthol. Noyori is also interested in developing new reagents and with Suzuki has developed a widely applicable method for the stereoselective synthesis of prostaglandins (*9*).

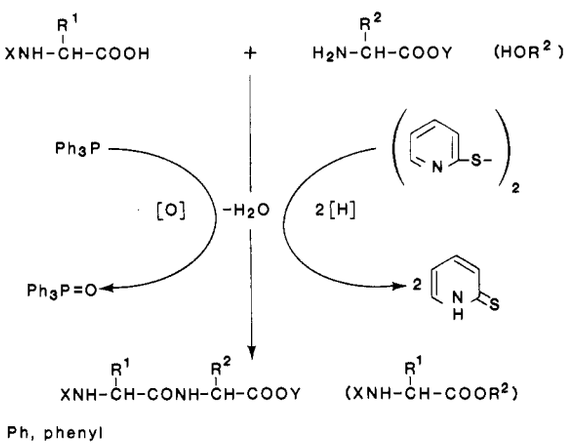
Another characteristic of enzymatic processes is the mildness of the reaction conditions used. The reactions usually proceed smoothly under neutral conditions at room temperature, and for the synthesis of complex natural products containing many labile functional groups it is desirable to develop similarly mild organic reactions. One approach to this problem is to use the characteristics of transition-metal complexes to achieve selective transformations. This is an active field of research in Japan, and many new synthetic methods have been developed. For example, Tsuji, who discovered the reaction of π-allylpalladium complexes with carbonucleophiles, has done pioneering work on palladium-catalyzed synthetic reactions. Recently, he has greatly expanded the use of β-keto esters in organic synthesis by the application of π-allylpalladium chemistry. He has discovered four palladium-catalyzed transformations of allyl β-ketocarboxylates: allylation, formation of enones, formation of exomethylene ketones, and formation of alkyl ketones. All these reactions proceed under mild conditions and are notable for not requiring any added acid or base (*10*). Negishi has also made an important contribution to the construction of cyclic compounds by the use of transition metals (*11*).

Transition metal chemistry has found extensive application in the development of useful synthetic reactions. Nozaki has studied various metal species and has developed unique reactions based on their characteristic properties (*12*). Also, Yamamoto, using novel aluminum reagents, has contributed much to the regio- and stereoselective synthesis of various chiral compounds (*13*). Kumada, using silicon reagents, has provided still other techniques for organic synthesis (*14*). The main efforts of leading Japanese organic chemists are now devoted to the development of mild and selective synthetic reactions.

Biologically active compounds, which have both many labile functional groups and numerous chiral centers, have attracted the attention of organic chemists. The synthesis of these complex and fragile natural products has required the exploitation of highly selective reactions that proceed under mild conditions. As an example of these research programs, I describe below some of the new synthetic methods that are being developed in my laboratory.

During the 1960's and the 1970's, two new types of dehydration-

condensation reactions were developed, the oxidation-reduction condensations (*15*) and those performed by the onium salts of azaaromatics (*16*). The former reaction is a conceptionally new type of condensation reaction that proceeds through elimination of 2[H] and [O] (Scheme 1) by coupled use of weak reductants and oxidants without any acid or base. Because of mildness and efficiency, these reactions have found extensive use in the synthesis of products such as heterocycles, polypeptides, nucleotides, and macrolides.



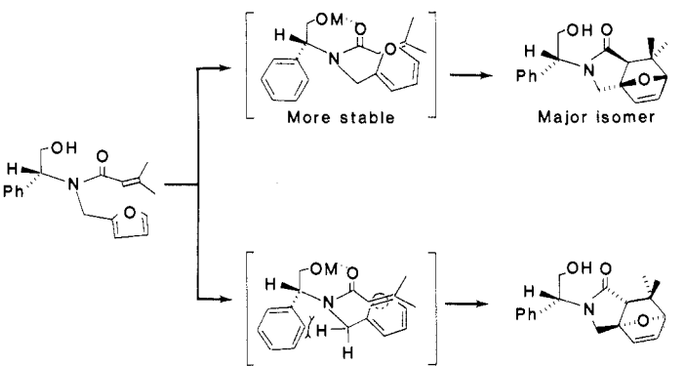
Scheme 1

Subsequently, we focused our attention on the development of new and highly efficient synthetic reactions based entirely on chemical methods to realize both mild reaction conditions and high selectivity comparable with those of biological reactions. Our goals were to develop (i) reactions that proceed under mild conditions with high efficiency so that they can be applied to multistep syntheses, (ii) control of both the relative and the absolute stereochemistry of the products to yield only the desired stereoisomer, and (iii) reactions that could ultimately be made catalytic so that cost-effective large-scale production of material can be achieved. For the achievement of these new reactions, synthetic control, that is, utilization of common metals for inter- or intramolecular chelations leading to highly selective or entropically advantageous reactions, was chosen as the basic concept and this has proved to be an effective approach. In the rest of this article, I describe our recent results based on this concept, asymmetric synthesis and metal enolate–mediated aldol reactions.

The concept of synthetic control is typically exemplified by an asymmetric intramolecular Diels-Alder reaction. This reaction is useful for the stereoselective construction of polycyclic compounds and is often used in natural products synthesis (*17*). However, there are still some limitations on the structure of the dienes and dienophiles that can be used. For example, the Diels-Alder reaction between a furan derivative and β,β-dimethylacrylic acid derivatives proceeds with difficulty because of steric hindrance, even in the intramolecular reaction.

The chiral β,β-dimethylacryloyl amide derived from L-phenylglycinol was chosen as the substrate, and the reactivity and stereoselectivity of the reaction were examined. Our basic ideas for controlling the reaction are: (i) The intramolecular coordination of an alkoxymetal salt to the carbonyl oxygen would fix the conformation of the molecule so that the diene and the dienophile are in close proximity, an entropically advantageous condition. (ii) By fixing the conformation of the molecule, the chirality in the connecting side chain is effectively transmitted to the reaction site.

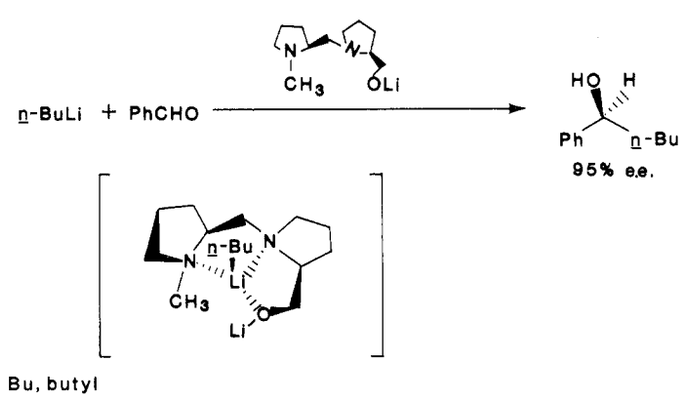
These expectations are realized by the use of magnesium salts. Thus, when a toluene solution of the substrate was refluxed for 50 hours, equal amounts of two diastereomeric cycloadducts were formed in low yield. On the other hand, one diastereomer was obtained stereoselectively in high yield when a toluene solution of the magnesium salt of the substrate was refluxed for 7 hours.



Scheme 2

These results indicate that entropically advantageous conditions and a chiral environment can be generated by the coordination of a magnesium salt to the carbonyl oxygen (*18*).

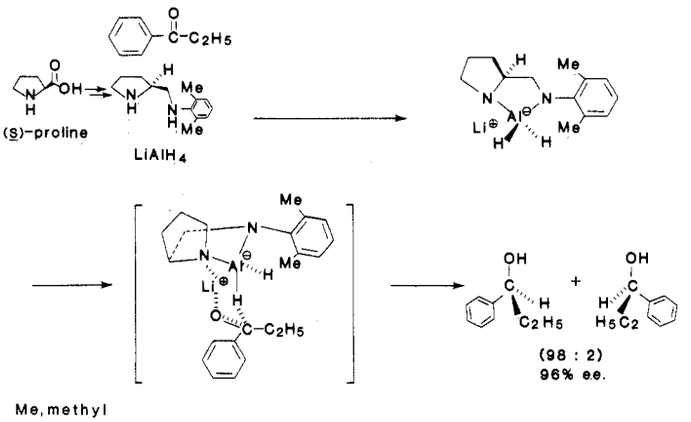
Asymmetric addition of an organometallic reagent to an aldehyde is a fundamental method for preparing optically active secondary alcohols (*19*). When we began our study in 1977, several ligands such as (−)-sparteine, (−)-*N*-methylephedrine, D-glucofuranose, and tartaric acid derivatives had already been used to investigate the enantioselective addition of alkyllithiums or Grignard reagents to carbonyls: however, the best results with these methods were at most 40% enantiomeric excess (e.e.). At this point we set out to design new efficient ligands. The basic concept was that a chiral diamine or chiral diaminoalcohol, derived from an easily available amino acid, could interact with organometallic reagents to form tight complexes in which the chiral environment generated could be transferred to the reaction sites. After examining various ligands, we found that chiral diaminoalcohols derived from (*S*)-proline are effective for the asymmetric addition of *n*-butyllithium to benzaldehyde, and (*S*)-1-phenyl-2-pentanol was obtained in 95% optical purity (Scheme 3). This is still the highest value obtained for this type of reaction. Control experiments showed that two pyrrolidine moieties and the lithiated hydroxymethyl group are essential for the asymmetric induction, and it is assumed that a rigid complex is formed by coordination of the oxygen and two nitrogen atoms to the alkylmetal, providing an effective chiral environment for asymmetric induction (*20*).



Scheme 3

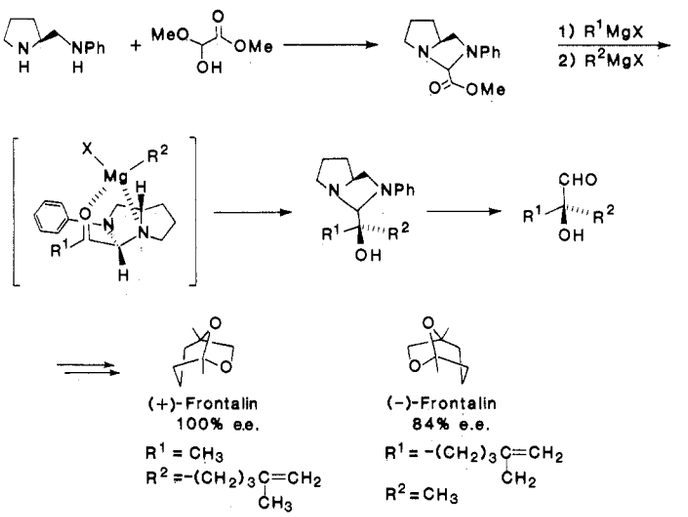
The basic concept of using (*S*)-proline–derived chiral diamine derivatives for effective asymmetric induction has been extended to various types of reactions. One example is the asymmetric reduction

of prochiral ketones, which is another useful method for preparing optically active secondary alcohols (Scheme 4). The chiral reducing agent was prepared from an (*S*)-proline–derived bidentate diamine and $LiAlH_4$ and was used to reduce aromatic ketones. In this case, very high optical yield (≥95% e.e.) could be achieved (*21*).



Scheme 4

Another example is the reactions of aminals, obtained from the diamine and the appropriate aldehydes, with organometallic reagents to afford functionalized aldehyde in high optical purity (Scheme 5). This high selectivity is due to the fixed *cis*-fused five-membered bicyclic structure and strong affinity of the organometallic reagent for the nitrogen atoms of the aminal (*22*).



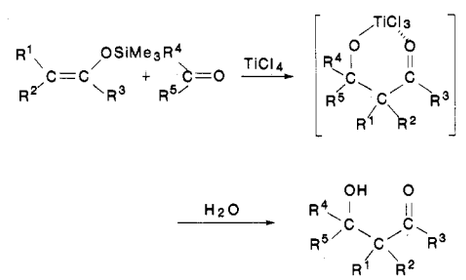
Scheme 5

The aldol reaction, one of the most fundamental carbon-carbon bond-forming reactions, is 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 crucial (*23*). Here, too, the concept of synthetic control is highly effective, and metal enolate–mediated aldol reactions provide useful regio- and stereocontrolled carbon-carbon bond formation by intermolecular metal chelation.

Until the middle of the 1960's, the aldol reaction was usually carried out under basic conditions in protic solvents. Although this reaction was widely used as a basic carbon-carbon bond-forming reaction, the conventional method had synthetic limitations because of side reactions and the difficulty of directing the coupling. In practice, when two different carbonyl compounds are used in such a cross-coupling, the reaction is often accompanied by undesirable side reactions, such as self-condensation and dehydration, and also by the formation of undesired combinations of carbonyl compounds.

Around 1970, several new methods for the directed coupling of two different carbonyl compounds were developed, giving the desired crossed aldol products. Among them, generation of the lithium enolate of a carbonyl compound by treatment with lithium dialkylamide, followed by the addition of a second carbonyl compound, is the most general and widely used method. However, this reaction is carried out under strongly basic reaction conditions and, therefore, undesired side reactions occur in some cases.

To overcome these difficulties, we initiated studies on a new directed aldol reaction, which led to the discovery of $TiCl_4$ as a promoter (*24*). This reaction is carried out in the presence of stoichiometric amounts of $TiCl_4$ as a Lewis acid, trimethylsilyl enol ethers as enolate equivalents, and acetals or carbonyl compounds as acceptors. Powerful activation of the acceptor molecules by $TiCl_4$ makes possible nucleophilic attack by trimethylsilyl enol ethers, forming 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, which is easily hydrolyzed with water to yield the desired β-hydroxy ketone. The reaction (Scheme 6) proceeds with retention of the regiochemical integrity of the starting silyl enol ethers, yielding the corresponding aldol regiospecifically. In particular, it has made it possible to use silyl enol ethers as isolatable and useful enolate equivalents; the acidic medium permits the presence of base-sensitive functional groups in this aldol-type reaction that would not survive the lithium enolate–mediated method. This $TiCl_4$-activated aldol reaction has found extensive use in synthetic organic chemistry, and a variety of related reactions have been developed by other organic chemists, based on the original idea of effective activation of the electrophile with Lewis acids.



Scheme 6

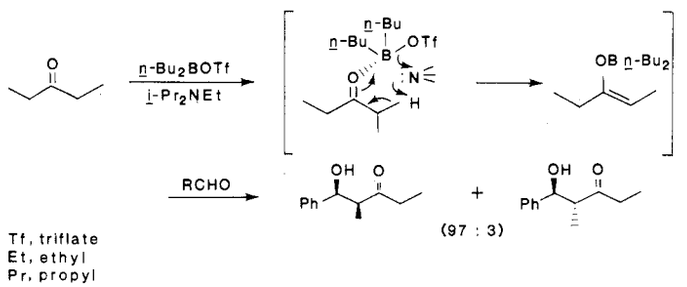
In 1973, another useful metal enolate–mediated aldol reaction that proceeds under essentially neutral conditions was explored. Vinyloxyborane (boron enolate), generated by the addition of phenyl di-*n*-butylthioboronite to ketene or to α,β-unsaturated ketone, undergoes a clean reaction with aldehyde to produce an excellent yield of β-hydroxy carbonyl compounds under neutral conditions (*25*).

As a result of our attempts to generate this boron enolate directly from the parent carbonyl compounds, we have developed a new aldol reagent, dialkylboryl triflate. In the presence of a tertiary amine, this compound reacts with ketones, generating the boron enolates, which react with aldehydes to give high yields of the crossed aldols (*26*).

More importantly, the regioselective generation of vinyloxyboranes is readily achieved by a suitable combination of reagents. Thus, the kinetic enolate is generated by the reaction of a ketone with dibutylboryl triflate in the presence of diisopropylethylamine, whereas the thermodynamic enolate is generated by the reaction of a

ketone with 9-borabicyclo[3,3,1]-9-nonanyl triflate in the presence of 2,6-lutidine.

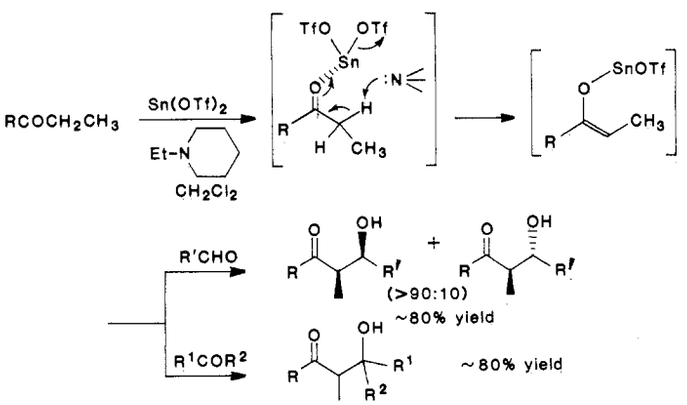
Dialkylboron enolates have relatively short metal-ligand and metal-oxygen bonds, which are suited for maximizing 1,3-diaxial interactions in the transition state. By making use of these characteristics, Masamune and others have applied this reaction to diastereo- and enantioselective aldol reactions, and have used them as one of the standard methods in the stereoselective synthesis of polyoxygenated natural products (*27*).



Scheme 7

Although the vinyloxyborane-mediated aldol reaction has proved to be a useful synthetic reaction, several problems cannot be overcome by this method. During the course of our investigations on synthetic reactions promoted by tin(II) species, we became interested in some of their characteristic properties. Tin(II) species, having vacant *d* orbitals in low energy levels, can accept up to four ligands and should work well as metal templates; furthermore, tin(II) species form tight complexes with amines, especially diamines. The characteristics of tin(II) compounds should provide synthetic control leading to highly diastereo- and enantioselective synthetic reactions.

Tin(II) enolates can be generated by treatment of tin(II) triflate with ketones in the presence of *N*-ethylpiperidine (Scheme 8). These tin(II) enolates undergo aldol reactions to give good yields of β-hydroxy ketones under extremely mild conditions, and good to excellent *syn* selectivity is observed. Moreover, the tin(II) enolates generated by this procedure are highly reactive, and can react even with ketones to give ketone-ketone cross-coupling products in good yields. Boron enolates, which are otherwise versatile, display extremely low reactivity toward ketones, and the more nucleophilic lithium enolates react with less hindered ketones in only moderate yield.



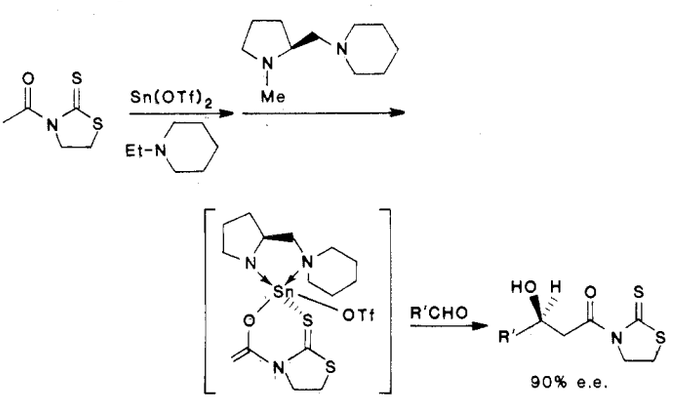
Scheme 8

By applying this tin(II) enolate–mediated aldol reaction to different substrates, we have produced polyoxygenated compounds such as *cis*-α,β-epoxy esters and aldehydes, β-hydroxycarboxylic acid derivatives, and β-hydroxyaldehydes with high stereoselectivity; stereoselective total syntheses of natural products such as carbohydrates and β-lactams have also been achieved (*28*). The most notable property of the tin(II) enolate–mediated aldol reaction is that the absolute and relative stereochemistry of the product can be controlled by the coordination of a diamine to the tin(II) metal center.

Recent development of the stereoselective aldol reactions resulted in the achievement of the asymmetric version of this reaction, and several successful methods to achieve this have been reported. These were based on the use of either chiral carbonyl compounds as one of the components or a chiral boron triflate as a generator of the boron enolate. However, the efficiency of these reactions is greatly diminished by the tedious procedures for attaching and removing the chiral auxiliaries to the reacting species. Thus, development of a highly enantioselective aldol reaction mediated by chiral ligands was desirable, although the influence of such chiral addends in the aldol reaction had not previously met with much success (*29*).

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, we directed our efforts to examining an enantioselective aldol reaction by a divalent tin–chiral diamine complex, generated in situ from a tin(II) enolate and a chiral diamine derived from (*S*)-proline.

In this way, a highly enantioselective cross aldol reaction between aromatic ketones or 3-acetylthiazolidine-2-thione and various aldehydes or α-ketoesters has been achieved (Scheme 9). In this case chiral diamines derived from (*S*)-proline worked effectively as ligands. Thus, we have been able to demonstrate the formation of cross aldol products in high optical purity from two achiral carbonyl compounds by using chiral diamines as ligands to form intermediate chelate complexes (*28*).



Scheme 9

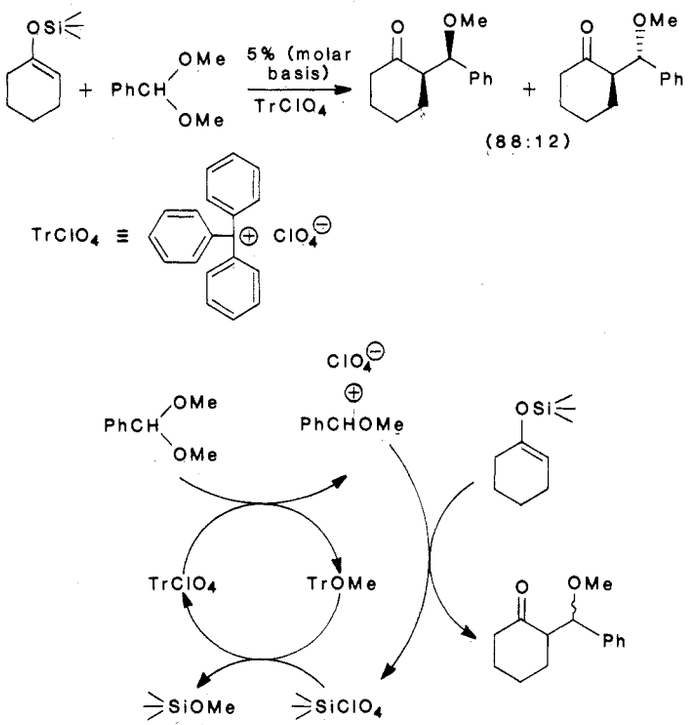
Moreover, in the reaction of 3-(2-benzyloxyacetyl)thiazolidine-2-thione with an aldehyde, the relative stereochemistry can be controlled to give either the *syn* or the *anti* isomer from the same reactants. That is, in the absence of diamine the α-benzyloxy adduct is predominantly of *syn*-stereochemistry, whereas in the presence of diamine the *anti* product prevails. Furthermore, by using a chiral diamine, it is possible to produce very high asymmetric induction in the *anti* product (*30*).

The coordinating interaction between tin(II) compounds and diamines has found wide application in other synthetic organic reactions. For example, a new chiral reducing agent has been produced by the treatment of a mixture of tin(II) chloride and a chiral diamine with diisobutylaluminum hydride. This reagent is effective for the asymmetric reduction of prochiral ketones, and higher enantioselectivity is realized in the case of aliphatic ketones

than can be achieved by conventional methods (*31*). In these reactions, a chiral environment is formed as with most enzymes by using coordinating ligands that are not covalently bound. Although stoichiometric amounts of chiral material are still necessary to induce asymmetry during reaction, these diamines can be easily obtained from natural amino acids and can be recovered for reuse. Further development of other highly selective synthetic reactions by manipulating the unique characteristics of individual metals can be expected.

A primary characteristic of an enzymatic reaction is that it proceeds catalytically. The realization of catalytic synthetic reactions forming complex carbon-carbon bonds is desirable in view of their simplicity and economy. Our most recent discoveries show that high efficiency, comparable to those of the enzymatic reactions, can in fact be achieved.

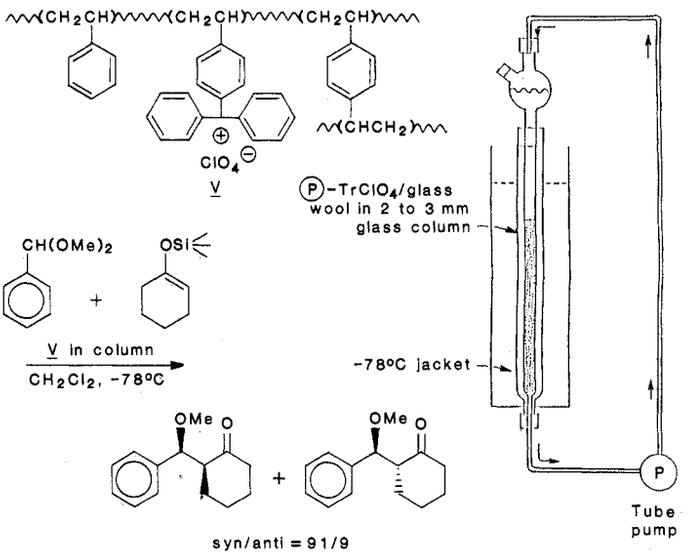
We have recently found that catalytic amounts of triphenylmethylium (trityl) reagents, exemplified by trityl perchlorate, can activate acetals and carbonyls effectively and promote their reaction with silyl enol ethers, giving the corresponding aldols cleanly in good yields (Scheme 10). The reaction requires only a catalytic amount of trityl perchlorate, whereas the aforementioned $TiCl_4$-promoted aldol reaction, the first example of the reaction of silyl enol ethers with acetals, requires stoichiometric amounts of promoter. The catalytic cycle is achieved by the regeneration of trityl perchlorate from the reaction of two of the initial products, trityl ether and silyl perchlorate (*32*).



Scheme 10

The aldol reaction is similarly catalyzed by other trityl salts, such as TrOTf, $TrPF_6$, $TrSnCl_5$, and $TrSbCl_6$, and both the counter-ions of the trityl salts and the substituents on the silicon of the silyl enol ether play a significant role in determining the diastereoselectivity of the reaction. By the appropriate choice of these factors, *syn* or *anti* aldol can be obtained preferentially starting from the same reactants (*33*).

Another characteristic of trityl salts compared with other metallic Lewis acids is that modification of the aromatic ring can lead to an immobilized catalyst. Polymer-supported trityl perchlorate can be prepared by treating trityl alcohol attached to polystyrene with perchloric acid in acetic anhydride; by just passing a solution of a silyl enol ether and an acetal through a column packed with this polymer, the aldol product is obtained in high yield with good diastereoselectivity within a short reaction time (Scheme 11). This method makes it possible to separate the aldol product from the reaction system by an exceptionally simple procedure similar to that of immobilized enzyme reactions and also makes it easy to reuse the catalyst (*34*).

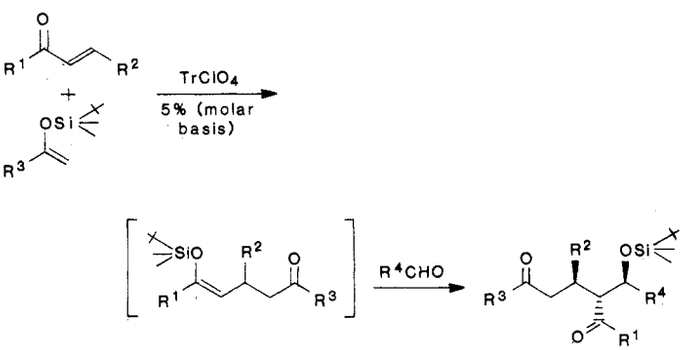


Scheme 11

The Michael reaction is another fundamental carbon-carbon bond-forming reaction. However, its synthetic use has been limited essentially to the addition of stabilized carbanions such as those derived from malonates, and the reaction with simple unstabilized enolates is often complicated by side reactions due to the high basicity of the enolates.

In 1976, we showed that $TiCl_4$ effectively promotes the Michael addition of silyl enol ethers to α,β-unsaturated ketones. Though a stoichiometric amount of $TiCl_4$ is neccesary to activate the carbonyls, this was the first example of the conjugate addition of silyl enol ethers to α,β-unsaturated ketones carried out under acidic conditions (*35*).

While investigating the chemistry of triphenylmethylium derivatives, we found that a catalytic amount of $TrClO_4$ effectively promotes the same reaction with high stereoselectivity different from the conventional base-promoted Michael reaction. Under appropriate quenching conditions, a 1,5-dicarbonyl compound or intermediate silyl enol ether can be isolated. The intermediate enol ether can be used in the aldol reaction, which makes possible a three-component condensation reaction in one operation (*36*).



Scheme 12

Although work on the trityl group is preliminary, it has already demonstrated wide applicability and high selectivity. We expect that reactions comparable to those of enzymatic systems will be achieved by modifying the catalyst.

Conclusions

Organic chemistry has developed to the extent that it is possible, by a combination of experimental and computing methods, to design molecules having specific functions that can store information. To construct these useful molecules, it will be necessary to develop efficient synthetic reactions based on new and novel concepts. For this purpose, the use of computers will be helpful; however, organic chemistry remains essentially an experimental science, and human intuition and observation based on experiments will continue to be essential to its development.

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Recent Earthquake Prediction Research in Japan

KIYOO MOGI

Japan has experienced many major earthquake disasters in the past. Early in this century research began that was aimed at predicting the occurrence of earthquakes, and in 1965 an earthquake prediction program was started as a national project. In 1978 a program for constant monitoring and assessment was formally inaugurated with the goal of forecasting the major earthquake that is expected to occur in the near future in the Tokai district of central Honshu Island. The issue of predicting the anticipated Tokai earthquake is discussed in this article as well as the results of research on major recent earthquakes in Japan—the Izu earthquakes (1978 and 1980) and the Japan Sea earthquake (1983).

IN RECENT YEARS A SPATE OF SERIOUS EARTHQUAKE DISASTERS has occurred in Japan and around the world. Major earthquakes that occur without warning can take the lives of many people and destroy cities in a matter of minutes. People living in countries subject to major earthquakes look forward to the day when it will be possible to predict when and where major earthquakes will occur, so that damage can be minimized. Located in the circum-Pacific seismic belt, Japan is one of the most earthquake-prone countries in the world. This fact has led to great interest in earthquake prediction ever since seismological studies were begun in Japan a century ago. Omori (*1*), Imamura (*2*), and other Japanese seismologists carried out pioneering research on the periodicity of great earthquakes and on seismic gaps and other subjects. Their research was limited, owing to the level of observations and the inadequacy of data in those days; however, their work contained the beginnings of the important methods used in earthquake prediction today.

Earthquakes occur when stress that has been applied to the earth's crust reaches a limit and a sudden fracture (the sudden slip of a fault) occurs at part of the earth's crust. In general, brittle materials fracture suddenly, and it is difficult to predict this fracture accurately. Earthquakes take place at intervals of 100 or more years, but

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