

Mukaiyama Aldol Reaction

The Mukaiyama Aldol Reaction: 40 Years of Continuous Development

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Dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction

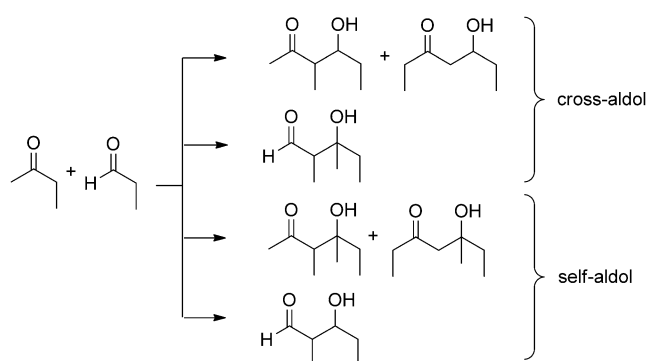
aldol reaction · history of science · silyl enol ether · stereoselectivity · synthetic methods

A directed cross-aldol reaction of silyl enol ethers with carbonyl compounds, such as aldehydes and ketones, promoted by a Lewis acid, a reaction which is now widely known as the Mukaiyama aldol reaction. It was first reported in 1973, and this year marks the 40th anniversary. The directed cross-aldol reactions mediated by boron enolates and tin(II) enolates also emerged from the Mukaiyama laboratory. These directed cross-aldol reactions have become invaluable tools for the construction of stereochemically complex molecules from two carbonyl compounds. This Minireview provides a succinct historical overview of their discoveries and the early stages of their development.

1. Introduction

An aldol reaction forms β -hydroxy carbonyl compounds from two carbonyl compounds through making a carbon–carbon bond, thereby potentially creating two new stereogenic centers to increase structural complexity.^[1] The resulting β -hydroxy carbonyl skeletons are found in many important synthetic targets, including natural products. For example, the major carbon chain of polyketides such as macrolides is derived from β -hydroxy carbonyl units. Their biosynthetic pathway consists of two steps, that is, the Claisen condensation reaction extending carbon chains and the subsequent reduction to create stereocenters therein. Because an aldol reaction does the two jobs simultaneously to give β -hydroxy carbonyl compounds, it is efficient to utilize an aldol reaction in chemical syntheses of such compounds. However, conventional aldol reactions use a Brønsted base or an acid as the promoter in protic solvents, and consequently, suffer from the occurrence of undesired side reactions including dehydration, self-condensation, and polycondensation. Furthermore, regiochemical issues impose a serious limitation on the conven-

tional methods. An aldol reaction of 2-butanone with propionaldehyde can be a typical example. Both 2-butanone and propionaldehyde act as the nucleophile at their α -carbon atoms as well as the electrophile at their carbonyl carbon atoms. Consequently, four reaction modes are possible when they are subjected to conventional conditions for an aldol reaction (Scheme 1): nucleophilic addition of 2-butanone to



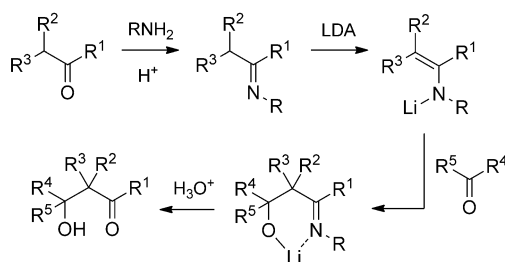
Scheme 1. Cross-aldol, self-aldol, and directed cross-aldol reactions.

propionaldehyde, propionaldehyde to 2-butanone, 2-butanone to 2-butanone, and propionaldehyde to propionaldehyde. The former two modes are called cross-aldol reactions and the latter two are self-aldol reactions. When one of the two cross-aldol reactions selectively occurs, it is called either a directed or controlled cross-aldol reaction. Further complication accompanies the case where 2-butanone is a nucleophilic partner. This substrate can add either at its methylene

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α -carbon atom or at its methyl α -carbon atom. Ultimately, it is necessary to control the relative and absolute stereochemistries of the newly formed two stereocenters. Therefore, it was a significant challenge to selectively synthesize one desired stereodefined aldol product out of the many possible alternative aldol products. These situations lead to a strong demand to develop a convenient, efficient, and controlled method for directed cross-aldol reactions.

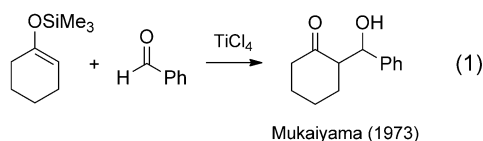
In 1963, an lithium enolate-based method for a directed cross-aldol reaction was reported by G. Wittig et al. (Scheme 2).^[2] An aldehyde is transformed into an imine, which is then deprotonated by LDA. The resulting lithium



Scheme 2. G. Wittig's method for a directed cross-aldol reaction (1963). LDA = lithium diisopropylamide.

enamide adds to an aldehyde and subsequent hydrolysis gives rise to a β -hydroxy aldehyde. Wittig's method solved the problems of self-coupling, polymerization, and regiochemistry. However, it suffered from strongly basic reaction conditions and the requisite introduction and removal of the imino group under acidic conditions.

In 1973, Mukaiyama et al. reported a ground breaking aldol reaction^[3] using silyl enol ethers (SEE),^[4] which reacted with aldehydes in the presence of the Lewis acid titanium tetrachloride [Eq. (1)].^[5] Interestingly enough, it was also 1973 when House et al. first reported a directed cross-aldol reaction via lithium enolates.^[6] Although the two aldol reactions developed by Mukaiyama and House in the same



Mukaiyama (1973)

year are contrasting in terms of the reaction conditions, one proceeding under acidic conditions and the other under basic conditions, their impact to the synthetic community was immense and the significantly increased utility of aldol reactions became widely recognized. In particular, the Mukaiyama aldol reaction provided a leading example in which aldehydes (or ketones) are activated by a Lewis acid in the presence of a carbon nucleophile. Activation of a carbonyl group by a Lewis acid facilitates attack of a nucleophile and thus a carbon–carbon bond is formed under acidic conditions. The Mukaiyama aldol reaction induced the development of a variety of carbon–carbon bond-forming reactions of this type, such as the Sakurai–Hosomi allylation reaction^[7] and hetero-Diels–Alder reactions of Danishefsky's diene.^[8] It also spearheaded the rise of chemistry based on chiral Lewis acids in the field of asymmetric synthesis.

In addition to the Mukaiyama aldol reaction of SEEs, he also developed directed cross-aldol reactions mediated by boron enolates^[9] and tin(II) enolates.^[10] These aldol reactions which emerged from the Mukaiyama laboratory have had an immense impact on the progress in the field of stereoselective construction of acyclic polyoxygenated carbon frameworks. This Minireview portrays the early stages of their developments from a historical viewpoint (Figure 1). There are excellent reviews available for comprehensive coverage of the advances in aldol chemistry.^[1,11]

2. Cross-Aldol Reaction with Silyl Enol Ethers

2.1. Discovery and Development of the Cross-Aldol Reaction with SEEs

Mukaiyama discovered the boron-mediated aldol reaction in the early 1970s (see Section 3.1).^[12] At that time, he was also developing new organic reactions using titanium(IV) chloride, which is a metallic Lewis acid but still easy to distill.^[13] It was not a coincidence for him to get the idea to use titanium(IV) chloride as the promoter of aldol reactions. He conceived that the coordination of the carbonyl oxygen atom of an aldehyde (or a ketone) to Lewis-acidic titanium(IV) chloride would make the carbonyl carbon atom more electrophilic so that it would react with a weak carbon nucleophile. He turned his attention to SEEs, which would potentially act as enolate anion equivalents. They are prepared from ketones through enolization/silylation and as they are far more stable



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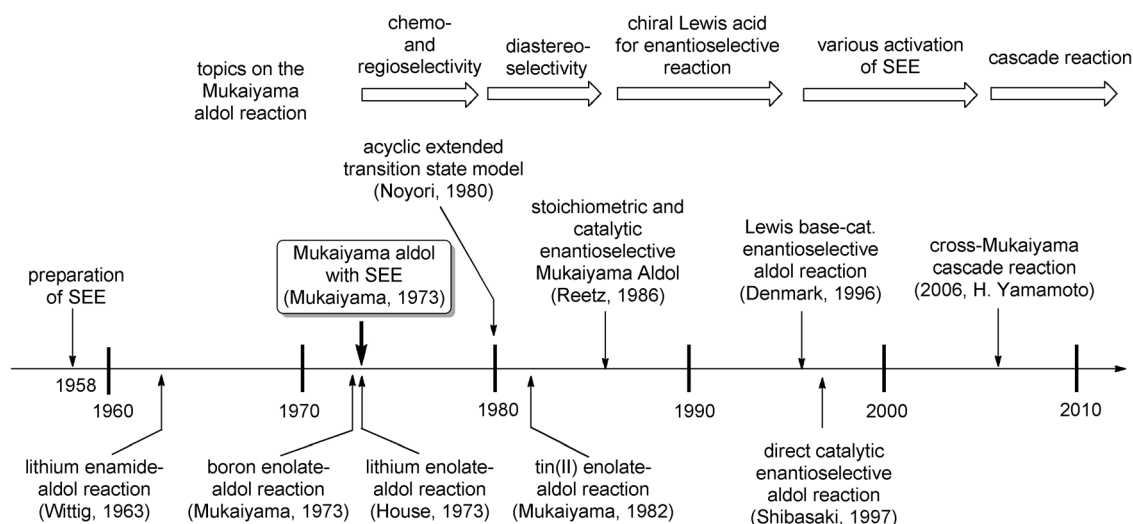
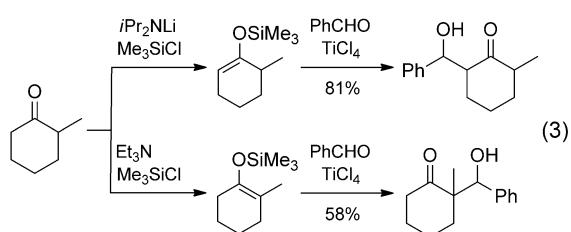
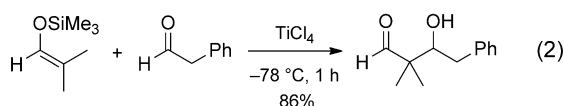


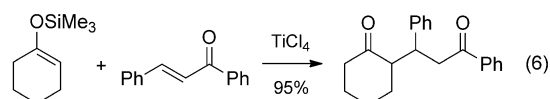
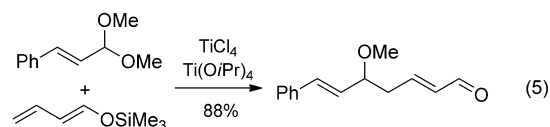
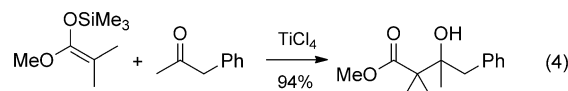
Figure 1. The history of the Mukaiyama aldol reaction.

than other metal enolates like lithium enolates, they could be isolated by distillation or even by chromatography. Nevertheless, they are significantly more nucleophilic than ordinary alkyl enol ethers. At that time, the use of SEEs in organic chemistry was still in its infancy. For example, Stork and Hudrlik utilized them as the precursor of lithium enolates.^[14] A direct reaction with electrophiles like sulfonyl chloride was reported by Murai et al.^[15] Mukaiyama reacted an SEE with an aldehyde in the presence of titanium(IV) chloride and a directed cross-aldol product was obtained in good yield [Eq. (2)].^[3,16] Since SEEs can be regioselectively prepared from ketones, the Mukaiyama aldol reaction also solved the problem of regiochemistry [Eq. (3)].^[16]



Mukaiyama also developed various related reactions forming carbon–carbon bonds.^[17] Replacement of SEEs with silyl ketene acetals (SKAs), which were prepared from carboxylic esters, produced β -hydroxy esters [Eq. (4)].^[17a] The vinylogous aldol reaction was developed by the use of silyl dienol ethers [Eq. (5)].^[17b] Conjugate 1,4-addition of SEEs to enones was also successfully catalyzed by titanium tetrachloride [Eq. (6)].^[17c] This transformation is often referred to as the Mukaiyama–Michael reaction because it forms the same products that are traditionally made by the

addition of metal enolates to α,β -unsaturated carbonyl compounds.



The Mukaiyama aldol reaction was extensively investigated by other research groups to reveal its various features such as diastereoselectivity, competency of other Lewis acids, the effect of substituents on the silyl group, etc.^[18] Induction of chirality at newly formed stereogenic centers was studied in the middle of the 1980s mostly by employing either chiral SEEs^[19] or chiral aldehydes. The Mukaiyama aldol reaction proceeded even with the use of a catalytic amount of Lewis acid, which made the reaction conditions tolerant of a wide variety of functional groups. The high functional-group tolerance was crucial for application in the synthesis of complex natural products. The catalytic Mukaiyama aldol reaction also triggered the development of catalytic enantioselective reactions, which were hardly possible with chiral-auxiliary-based and chiral metal enolate-based asymmetric syntheses.

2.2. The Reaction Mechanism of the Mukaiyama Aldol Reaction

Variations of the Mukaiyama aldol reaction are so diverse that it is difficult to explain the mechanism with a single model. Shown in Figure 2 is an extended open transition-state model, initially proposed by Noyori and co-workers.^[20] It has

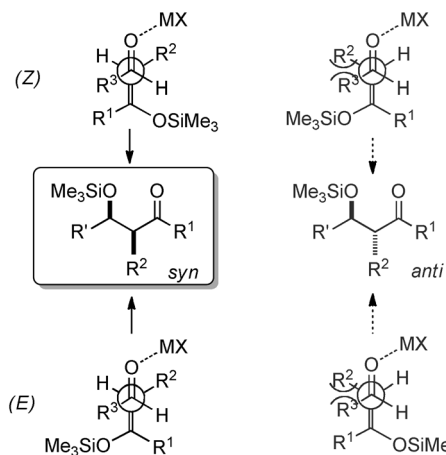


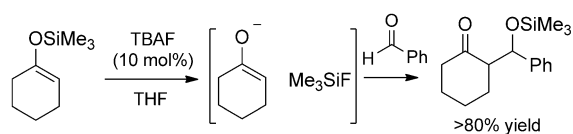
Figure 2. Open transition-state models for the Mukaiyama aldol reaction.

gained wide acceptance,^[21] whereas cyclic closed transition-state models have been also postulated to explain the stereochemical outcome.^[19a,22] Dipolar, inductive, and steric effects should be taken into consideration when interpreting the *syn/anti* diastereoselection observed. A detailed mechanism has been under experimental and theoretical investigation.^[23]

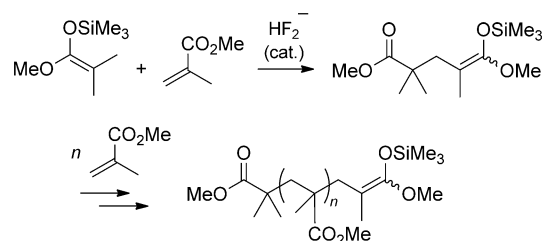
2.3. Fluoride-Catalyzed Aldol Reaction of SEEs

In 1977, Noyori, Kuwajima, and co-workers reported that a fluoride effectively catalyzed the aldol reaction of SEEs with aldehydes.^[24a] Tetrabutylammonium fluoride (TBAF)^[24a,b] and, later, tris(diethylamino)sulfonium (TAS) difluorotrimethylsilicate^[24c] were found to be suitable fluoride sources (Scheme 3). A naked enolate anion was generated by the action of a fluoride anion on SEE and it reacted with an aldehyde to form an aldolate anion, which was rapidly trapped with SEE to give a silylated aldol. The *syn* diastereomers were selectively produced regardless of the double bond geometry of the SEEs.

The fluoride-catalyzed Mukaiyama–Michael reaction found a valuable application in polymer chemistry. Group-



Scheme 3. Fluoride-catalyzed aldol reaction of SEE with aldehyde (Noyori and Kuwajima, 1977).

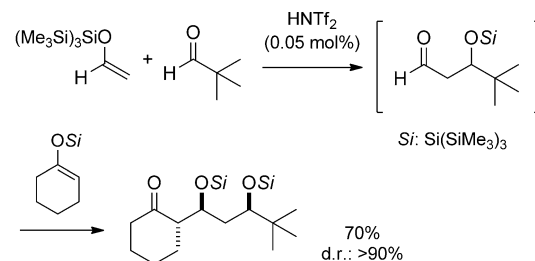


Scheme 4. Group-transfer polymerization (Webster, 1983).

transfer polymerization of α,β -unsaturated carbonyl compounds was successfully initiated by the action of a bifluoride ion on SKA to afford the corresponding polyesters (Scheme 4).^[25]

2.4. Sequential Aldol Reaction

An interesting example of a sequential Mukaiyama aldol reaction was developed by Yamamoto and co-workers in 2006.^[26] The Mukaiyama aldol reaction of a tris(trimethylsilyl)silyl (supersilyl) enol ether, derived from an aldehyde, with another aldehyde proceeded in the presence of an extremely small amount (0.05 mol %) of HNTf₂ and the produced aldol was successively subjected to a second Mukaiyama aldol reaction in one pot (Scheme 5). The success of this sequential process is ascribed to the steric bulkiness of the tris(trimethylsilyl)silyl group and the low catalyst loading of HNTf₂.

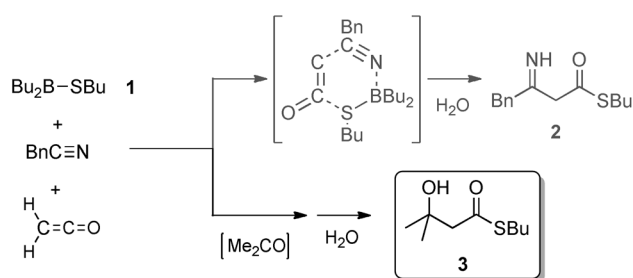


Scheme 5. Sequential aldol reaction (Yamamoto, 2006).

3. Boron-Mediated Aldol Reaction

3.1. Discovery of Boron-Mediated Aldol Reaction

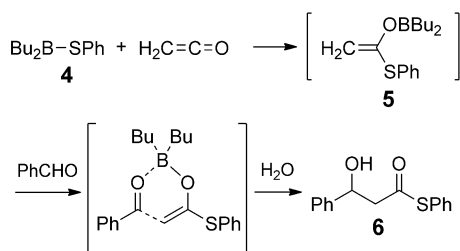
The Mukaiyama laboratory in the early 1970s was focused on the concept of “elements in combination.” The combined use of silicon and titanium was a typical example. He was also interested in compounds which have a σ bond between two elements of different characters. Thioboronites (e.g., **1**) with a boron–sulfur bond were among them, and the reaction of a ketene generated by thermal cracking of acetone, phenylacetonitrile, and the dibutylthioboronite **1** was examined to obtain the 3-imino thioester **2**^[27] (Scheme 6). Much to his surprise, the reaction afforded the β -hydroxyalkanethioate **3**.



Scheme 6. Unexpected formation of the β -hydroxyalkanothioate **3** by a reaction of a ketene, the thioester **1**, and acetone (Mukaiyama, 1971).

He suggested that acetone remained with the distilled ketene to be incorporated in the final product **3**.^[28]

Then, a reaction of a ketene with **1** was carried out in the presence of aldehydes other than acetone. The corresponding β -hydroxy thioesters were produced,^[29] thus suggesting the involvement of an enolate-type nucleophile derived from a thioester. The reaction was examined from the mechanistic viewpoint, and it was proved that the boron enolate **5** was initially generated as the key intermediate by the addition of the thioester **4** to a ketene, and that **5** added to an aldehyde to produce **6** (Scheme 7).^[12] Thus, the boron-mediated aldol reaction was unexpectedly found in the



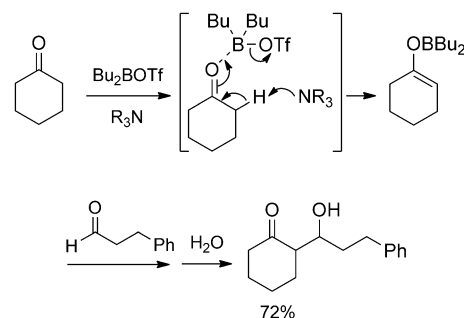
Scheme 7. The first example of a boron-mediated aldol reaction to give the β -hydroxy thioester **6** via the boron enolate **5**, which is generated from the thioester **4** and a ketene (Mukaiyama, 1973).

Mukaiyama laboratory. The finding that the addition of the nucleophile to a ketene was induced by coordination to Lewis-acidic boron contained an important underlying concept, which later led to the development of the titanium-tetrachloride-mediated Mukaiyama aldol reaction.

3.2. Direct Generation of Boron Enolates from Carbonyl Compounds

Although several methods to generate boron enolates were known at that time, those procedures were too complicated for practical use in organic synthesis.^[30] The identification of boron enolates as the key intermediate led Mukaiyama to search for a more convenient method of direct generation of these intermediates from ketones, hopefully under less basic conditions than those using LDA, to expand the synthetic utility. Intensive work was continued in his

laboratory for a few years and a breakthrough emerged in 1976. The idea was that introduction of an electron-withdrawing group onto boron would increase its Lewis acidity and facilitate coordination of a carbonyl group. Coordination of a ketone to a Lewis-acidic boron atom would also increase the acidity of the α proton so that even a weak base such as a tertiary amine would be able to abstract the α proton. Deprotonation would induce enolization to generate a boron enolate with the electron-withdrawing group acting as an excellent leaving group. At that time, super acids were gaining attention of the synthetic community and trifluoromethanesulfonic acid (TfOH) had just become available from a commercial source in Japan. The trifluoromethanesulfonyl group was chosen as the leaving group. When tributylborane and TfOH were mixed, evolution of gaseous butane was observed. Simple distillation furnished dibutylboron triflate. Finally, it was found that treatment of ketones with dibutylboron triflate in the presence of an amine such as *N,N*-diisopropylethylamine generated boron enolates (Scheme 8).^[31] A directed cross-aldol reaction took place



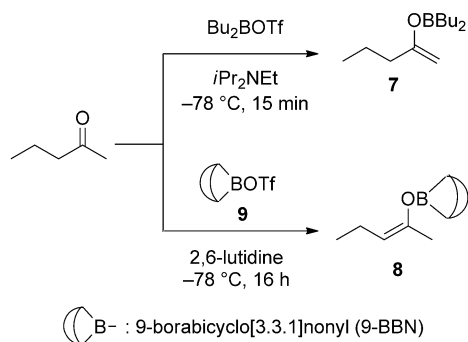
Scheme 8. Mukaiyama's original method for the generation of boron enolates from ketones using boron triflates and amines, with successive aldol reaction (1976).

upon addition of aldehydes to give β -hydroxyalkanoes. Thus, it became possible to generate boron enolates directly from ketones under conditions which were mild enough to be applied to the synthesis of complex molecules possessing base- or acid-labile functionalities.

The regiochemical issue in generation of boron enolates was also addressed by his laboratory. The kinetic boron enolate **7** was selectively generated from 2-pentanone when treated with dibutylboron triflate and *N,N*-diisopropylethylamine at -78°C for a short period of time.^[31a] In contrast, the thermodynamic enolate **8** was predominantly generated when treated with the 9-BBNOTf (**9**) and 2,6-lutidine at -78°C for a longer period of time (Scheme 9).^[31b] The regiochemical integrity was retained in the subsequent aldol reaction with aldehydes.

3.3. Stereoselective Boron-Mediated Aldol Reaction

Spectroscopic instruments for structural determination, such as NMR instruments, were significantly improved in the 1970s in response to advances in electronics and computer



Scheme 9. Regioselective generation of boron enolates (Mukaiyama, 1976, 1977).

technology. This ignited dramatic progress with regard to stereochemistry in the field of organic chemistry, which heavily depended on the ease and ability of structural determination. The important stereochemical aspect of specificity between the geometry of boron enolates and the configuration of the aldol products was initially put forward by Fenzl and Köster.^[32] *E*- and *Z*-boron enolates were generated from 3-pentanone at 85–110 °C using diethylboryl pivalate and triethylborane, with the latter acting as a base. They reacted with benzaldehyde to give *anti*- and *syn*-aldol adducts, respectively.

Mukaiyama's report on the boron-mediated aldol reaction in 1976 was immediately followed by intensive studies on the stereochemistry of this process. The groups of Masamune and Evans independently examined various combinations of boron triflates and amines to find that *E*-boron enolates were selectively generated when sterically hindered dicyclopentylboryl triflate and *N,N*-diisopropylethylamine were used at 0 °C. In contrast, the use of the sterically less hindered 9-BBN triflate led to the generation of the *Z* isomer (Figure 3).^[33] The accessibility of boron enolates with control of the double bond geometry provided a major advantage over conventional methods. Furthermore, the aldol reaction of stereoselectively prepared boron enolates exhibited higher diastereoselectivity than that of lithium enolates.^[33a] Although both aldol reactions proceed via a chairlike six-membered transition state, the one with chelation to boron is more compact and rigid than that with chelation to lithium because B–O bonds are stronger and shorter than Li–O bonds.

With the regiochemical and stereochemical issues settled, the boron-mediated aldol reaction provided one of the most general and reliable methods for the stereoselective synthesis of acyclic polyoxygenated compounds.

4. Tin(II) Enolate-Mediated Aldol Reaction

Divalent tin(II) compounds had received far less attention than tetravalent tin(IV) compounds in organic synthesis before Mukaiyama initiated his study on the use of tin(II) compounds for organic synthesis in 1980. He developed a tin(II) chloride-promoted reaction of allyl iodide with carbonyl compounds to give homoallylic alcohols.^[34] At that

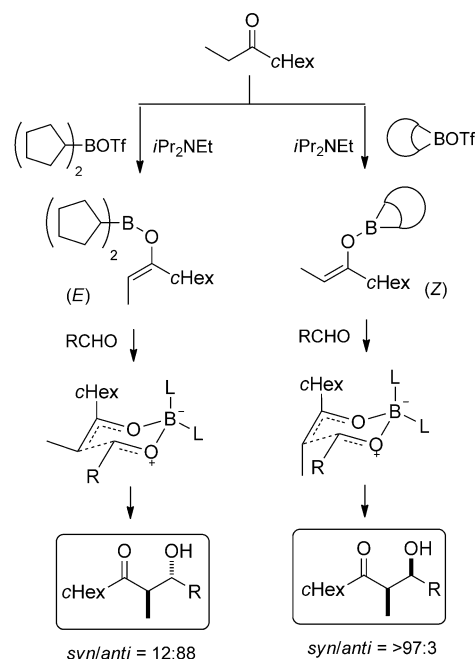
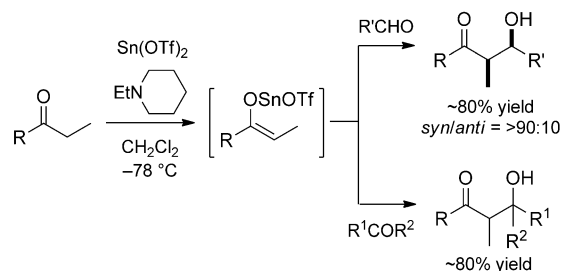


Figure 3. Stereoselective aldol reaction via *E*- and *Z*-boron enolates (Masamune and Evans, 1979).

time, it was already widely recognized that silicon- and boron-mediated aldol reactions, which Mukaiyama first discovered, were powerful synthetic tools. One limitation of the boron-mediated aldol reaction was that boron enolates had poor reactivity toward ketones. Then, he had an idea to use tin(II) compounds for aldol reactions, and again triflate attracted his attention. In 1982, he reported that a directed cross-aldol reaction between ketones and aldehydes was successfully mediated by $\text{Sn}(\text{OTf})_2$ (Scheme 10).^[35] The enhanced Lewis



Scheme 10. Cross-aldol reaction via a tin(II) enolate (Mukaiyama, 1982).

acidity of $\text{Sn}(\text{OTf})_2$ caused enolization of a ketone with assistance of a tertiary amine like *N*-ethylpiperidine. An aldol reaction proceeded under considerably mild reaction conditions, and good to excellent *syn* selectivity was observed.

During the examination of the impact of the structure of the base, it was found that a self-aldol reaction of the starting ketone proceeded when *N*-methylmorpholine was employed, thus suggesting the high reactivity of the tin(II) enolate.

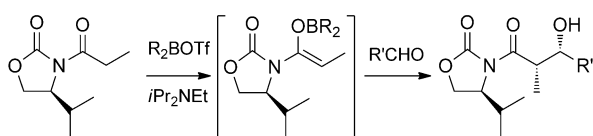
Later, the cross-aldol reaction between two ketones was successfully achieved.^[36]

5. Expansion of the Aldol Reactions Mukaiyama Developed into Asymmetric Synthesis

It is an essential issue to control the absolute stereochemistry when new stereocenters arise during carbon–carbon bond formation in the construction of carbon frameworks. Since the aldol reactions Mukaiyama developed were so powerful, much effort was then focused on the expansion into asymmetric reactions.^[37]

5.1. Diastereoselective and Enantioselective Asymmetric Boron-Mediated Aldol Reaction

Evans et al. developed a diastereoselective asymmetric boron-mediated aldol reaction by introducing chiral auxiliaries onto a carboxylic acid in 1981.^[38] A boron enolate generated from a chiral oxazolidinone derivative, dialkylboron triflate, and diisopropylethylamine reacted with aldehydes to afford the corresponding *syn*-aldol adduct with excellent level of chiral induction on the newly formed stereogenic centers (Scheme 11). This diastereoselective method proved to be highly general and reliable, thus leading to a number of applications to asymmetric synthesis of natural products and bioactive molecules.^[39]



Scheme 11. Evans' asymmetric boron aldol reaction (1981).

The groups of Masamune, Paterson, and Corey independently developed boron triflate (or bromide) with chiral auxiliaries (Figure 4), which afforded aldol products with good to high enantioselectivities.^[40]

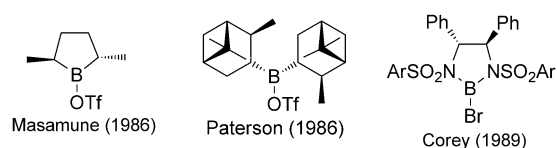
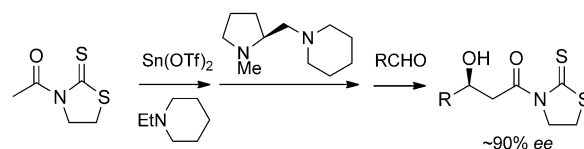


Figure 4. Boron triflates and bromide with chiral auxiliaries.

5.2. Enantioselective Aldol Reaction via Tin(II) enolates

Mukaiyama developed an enantioselective aldol reaction utilizing chiral chelating diamines in the tin(II)-enolate-mediated aldol reaction. Divalent tin(II) has several vacant d orbitals, which allow coordination of an aldehyde in addition to a diamine. He found that coordination of a chiral



Scheme 12. Enantioselective aldol reaction via a tin(II) enolate (Mukaiyama, 1982).

diamine derived from (*S*)-proline to a tin(II) enolate effected a highly enantioselective aldol reaction between two achiral carbonyl compounds (Scheme 12).^[41] Whereas the diastereoselective method using oxazolidinone derivatives developed by Evans gave unsatisfactory results with acetic acid derivatives, the tin(II) enolate/chiral diamine protocol exhibited high enantioselectivities when *N*-acetylthiazolidinethione was employed as the substrate.

5.3. Enantioselective Mukaiyama Aldol Reaction

In 1986, Reetz et al. reported the first example of the enantioselective version of a Mukaiyama aldol reaction of SEEs using chiral Lewis acids (Figure 5).^[42] Whereas enantioselectivities observed with a catalytic amount of chiral Lewis acids were low to moderate, these results disclosed a great potential of chiral Lewis acids for asymmetric synthesis.

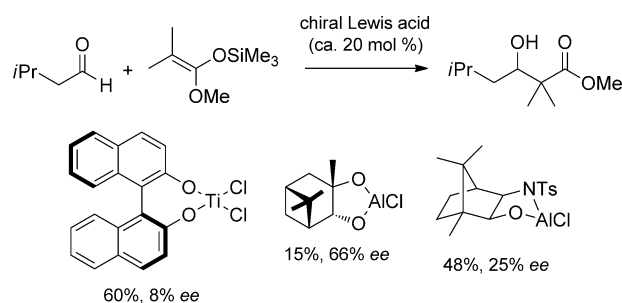


Figure 5. Enantioselective Mukaiyama aldol reaction with chiral Lewis acids (Reetz, 1986).

Mukaiyama developed an enantioselective Mukaiyama aldol reaction of SKAs in 1989 (Figure 6).^[43] Excellent enantioselectivities of over 98 % *ee* were observed when the tin(II)/chiral diamine **10** species was used together with a tin(IV) compound. The *syn*-aldol adducts were produced with almost perfect control of stereochemistry from *E* SKAs derived from thioesters of propionic acid. He proposed simultaneous double activation of an aldehyde as well as an SKA. The chiral diamine **10** coordinated to tin(II) activates the aldehyde as a Lewis acid and the ligand on tin(IV) activates the SKA as a Lewis base.

Mukaiyama further extended the enantioselective aldol reaction mentioned above to a catalytic reaction in 1990 (Figure 7).^[44] The tin(II) atom activating an aldehyde stayed on the oxygen atom of the produced aldolate **11** and Me₃SiOTf was released. Me₃SiOTf can also promote an

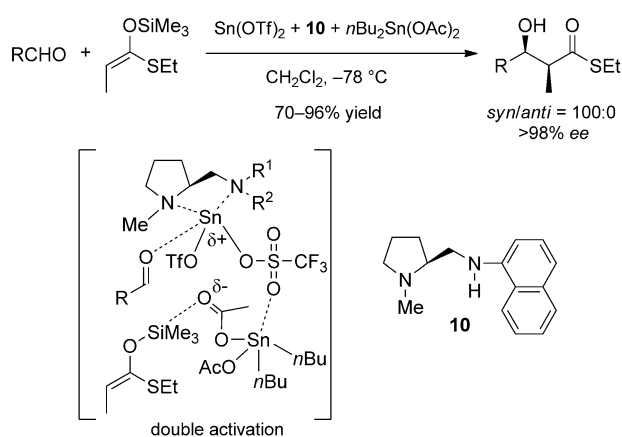


Figure 6. Highly enantioselective Mukaiyama aldol reaction with tin(II) chiral Lewis acid (Mukaiyama, 1989).

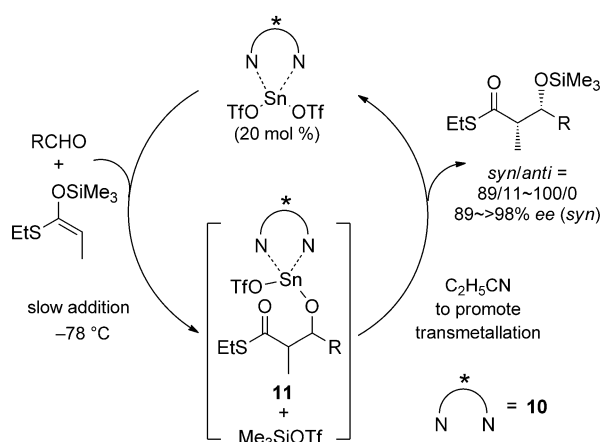


Figure 7. Catalytic enantioselective Mukaiyama aldol reaction (Mukaiyama, 1990).

undesirable background aldol reaction. Nonetheless, the exchange of the tin(II) atom to silicon was fast enough in a propionitrile solvent to suppress the background reaction by slow addition of substrates.

The catalytic asymmetric Mukaiyama aldol reactions were an active area of research through the 1990s as shown in Figure 8.^[45] Excellent enantioselectivities have been observed with chiral Lewis acids involving titanium,^[46] boron,^[47] copper,^[48] and others^[49].

6. Conclusion

Mukaiyama discovered the three important directed cross-aldol reactions, that is, those employing SEEs, boron enolates, and tin(II) enolates. These aldol reactions evoked a dramatic change in stereoselective construction of acyclic molecules, and have now become indispensable tools in organic synthesis. The increasing number of applications of these aldol reactions to the synthesis of complex natural products clearly suggests the immensity of the influence of

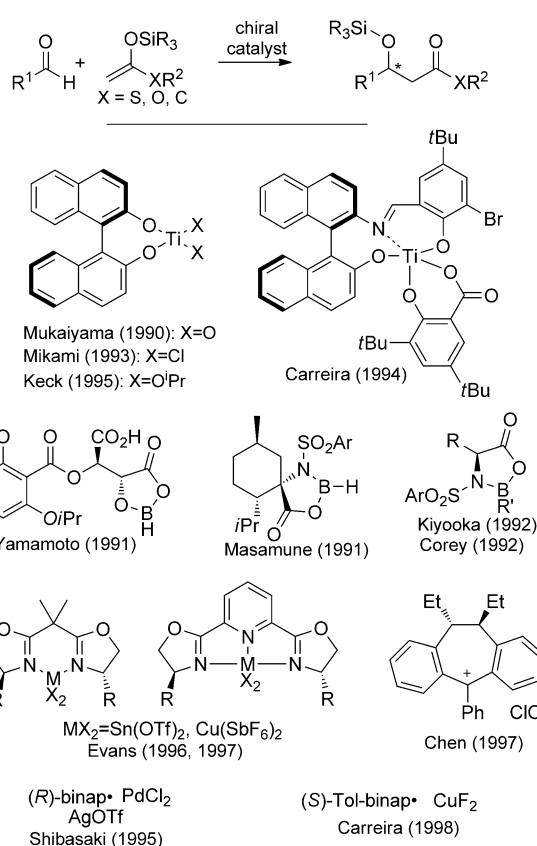


Figure 8. Chiral catalysts for catalytic enantioselective Mukaiyama aldol reaction (1990–1998). binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl.

these reactions he developed.^[39] On the basis of the milestones Mukaiyama established, development will continue, thus leading to more ideal aldol reactions such as direct aldol reactions,^[50] and organocatalyzed aldol reactions.^[51]

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