Personal Account

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Asymmetric Mukaiyama Aldol Reactions Using Chiral Diamine–Coordinated Sn(II) Triflate: Development and Application to Natural Product Synthesis

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

ABSTRACT: In 1989, the asymmetric Mukaiyama aldol reaction mediated by a Lewis acid consisting of a chiral diamine and Sn(II) triflate was reported. The asymmetric Mukaiyama aldol reaction is now widely used as a versatile tool for the construction of highly advanced, multifunctionalized molecules. In this Personal Account, the history of the development of this powerful methodology and the application of the asymmetric Mukaiyama aldol reaction in the synthesis of natural products are reviewed. **DOI 10.1002/tcr.201300022**

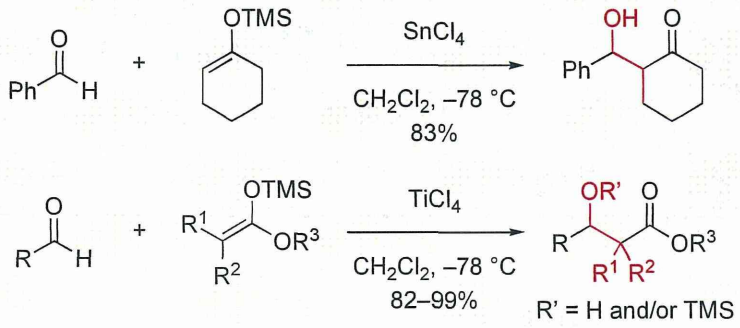
Keywords: asymmetric synthesis, chiral diamines, ketene silyl acetals, Mukaiyama aldol reaction, tin

1. Introduction

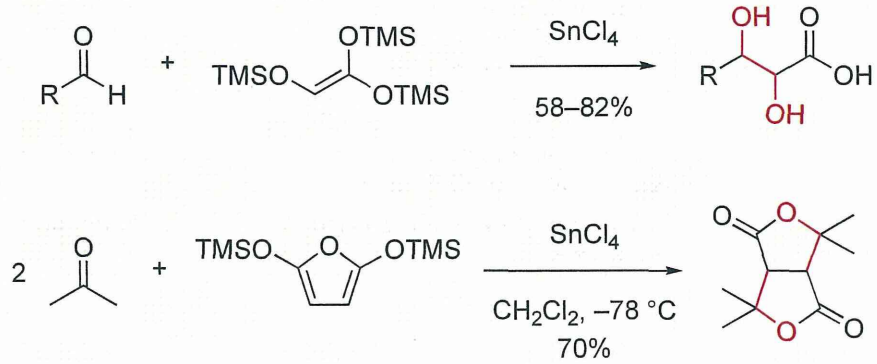
In 1973, Mukaiyama and Narasaka developed an acid-catalyzed aldol reaction of silyl enolates with electrophiles.[1–3] They showed that Lewis acids such as $TiCl_4$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, and $ZnCl_2$ are quite effective at promoting the reaction of enol silyl ethers (ESEs) and carbonyl compounds to afford β-hydroxy ketones (Scheme 1, upper equation).[1b] The synthetic utility of ketene silyl acetals (KSAs) in the new aldol reaction was subsequently reported in 1975;[1c] the corresponding β-hydroxy- and β-siloxycarboxylic esters were obtained in good combined yields using $TiCl_4$ (Scheme 1, lower equation).

Although it was reported that $TiCl_4$ appears to be superior to other Lewis acids with regard to yields, $SnCl_4$ has also been used as a popular reagent because of its mild activity and good chelation ability. For example, Wissner applied the $SnCl_4$-mediated aldol reaction of tris(trimethylsiloxy)ethene with several aldehydes to the synthesis of α,β-dihydroxycarboxylic acids (Scheme 2, upper equation).[4] Moreover, Ricci and Taddei prepared a bicyclic γ-lactone in good yield via the aldol addition of 2,5-disiloxyfuran to two molar equivalents of acetone using $SnCl_4$ (Scheme 2, lower equation).[5]

The diastereoselective addition of ESEs and KSAs to aldehydes using $SnCl_4$ was systematically studied by Heathcock, Reetz, and Gennari to produce various synthetic intermediates. As shown in Schemes 3–5, Heathcock and Reetz independently examined the



Scheme 1. Mukaiyama aldol reactions of silyl enolates with carbonyl compounds.



Scheme 2. $SnCl_4$-mediated Mukaiyama aldol reactions of silyl enolates with carbonyl compounds.

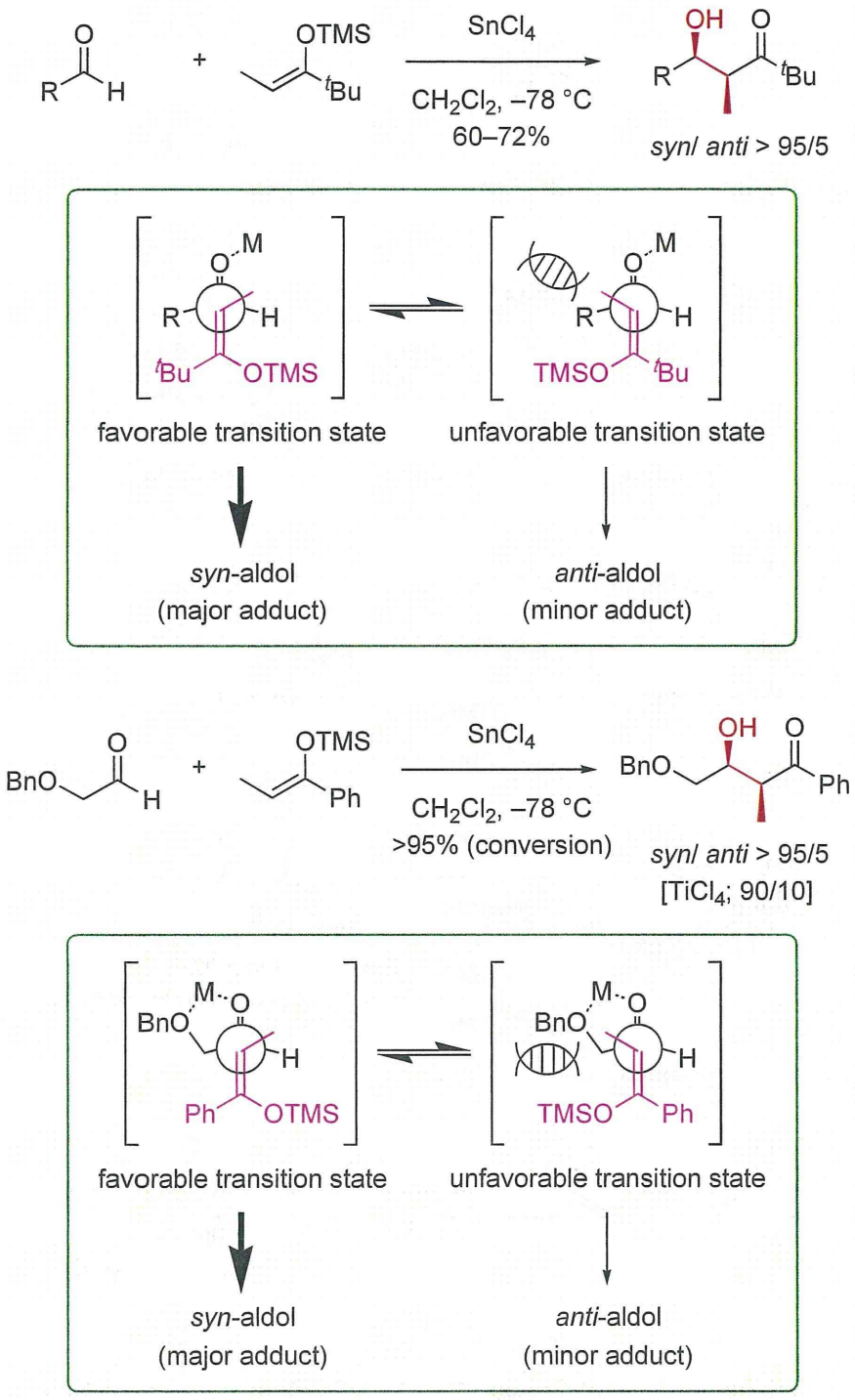
stereoselectivity of the Mukaiyama aldol reaction of ESEs with many types of aldehydes promoted by $SnCl_4$.[6,7] These results are summarized as follows:

1) Good 2,3-*syn* diastereoselection was observed in the reaction between achiral aldehydes and ESEs derived from ethyl ketones (Scheme 3). In these reactions (case 1), the open-chain model for the transition state was proposed to afford the corresponding *syn*-aldol adducts with high diastereoselectivities.
2) High 3,4-*syn* asymmetric induction was observed in the reaction between α-heteroatom-substituted aliphatic aldehydes and ESEs derived from methyl ketones (Scheme 4).
3) Good 2,3-*syn* and high 3,4-*syn* asymmetric induction was observed in the reaction between α-heteroatom-substituted aliphatic aldehydes and ESEs derived from ethyl ketones (Scheme 5).

Isamu Shiina was born in Tokyo in 1967. He completed his BSc and MSc at Tokyo University of Science (TUS), and he joined the group of Prof. Teruaki Mukaiyama at TUS as an Assistant Professor in 1992. After receiving his PhD from the University of Tokyo (UT) in 1997, he was promoted to Lecturer at the TUS, and then appointed to an Associate Professor (2003) and a Full Professor (2008). He has received the Chemical Society of Japan (CSJ) Award for Young Chemists (1997), the Banyu Young Chemist Award (2006), and the CSJ Award for Creative Work (2013). His research interests include the development of useful synthetic methods and the total synthesis of natural products.

The observed excellent 3,4-*syn* stereoselectivity for the α-branched aldehyde, in which the α-heteroatom can easily coordinate to Lewis acids (cases 2 and 3), was explained by the formation of a Lewis acid–aldehyde complex (so-called chelation model, see Scheme 6). However, good stereoselectivity was not attained when KSAs were employed, even in the reaction with 2-benzyloxypropanal, except for the cases using tetrasubstituted KSAs (Scheme 7).

Gennari further studied the Mukaiyama aldol addition of KSAs to aldehydes and found that *S*-^{t}Bu propanethioate and ethanethioate are quite suitable precursors for the required



Scheme 3. Diastereoselective Mukaiyama aldol reactions of ESEs with carbonyl compounds (for 2,3-*syn* diastereoselection).

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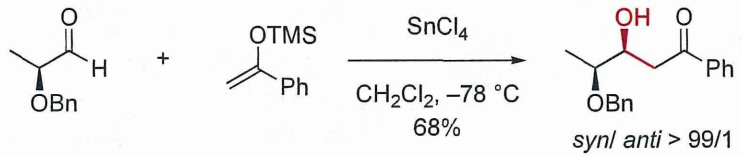
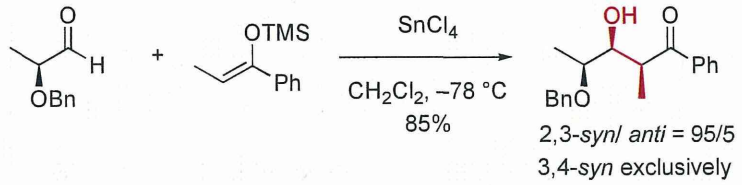
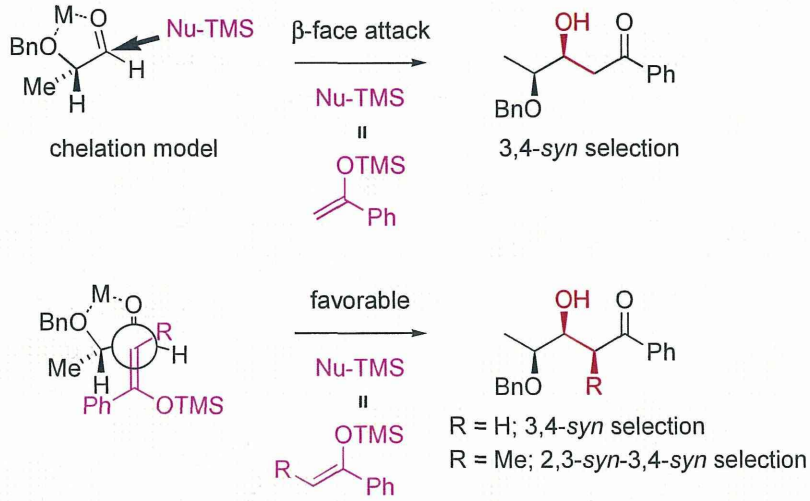


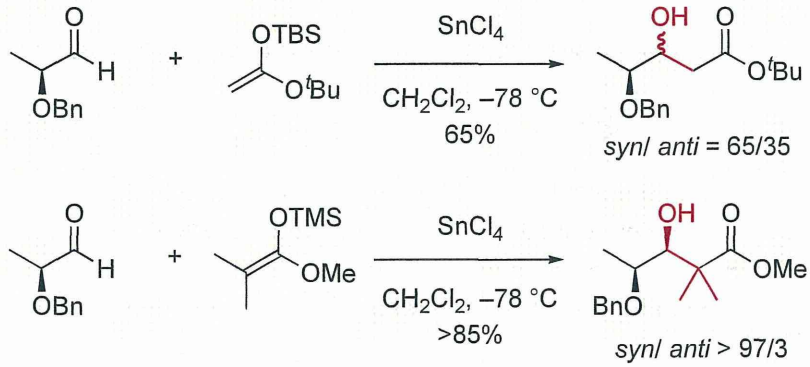
Scheme 4. Diastereoselective Mukaiyama aldol reaction of an ESE with 2-benzyloxypropanal (for 3,4-*syn* asymmetric induction).



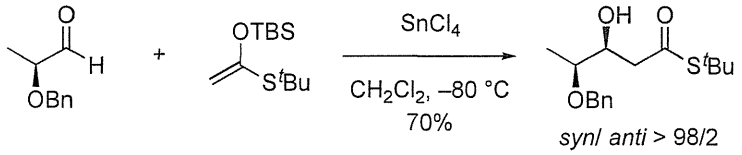
Scheme 5. Diastereoselective Mukaiyama aldol reaction of an ESE with 2-benzyloxypropanal (for 2,3-*syn* and 3,4-*syn* asymmetric induction).



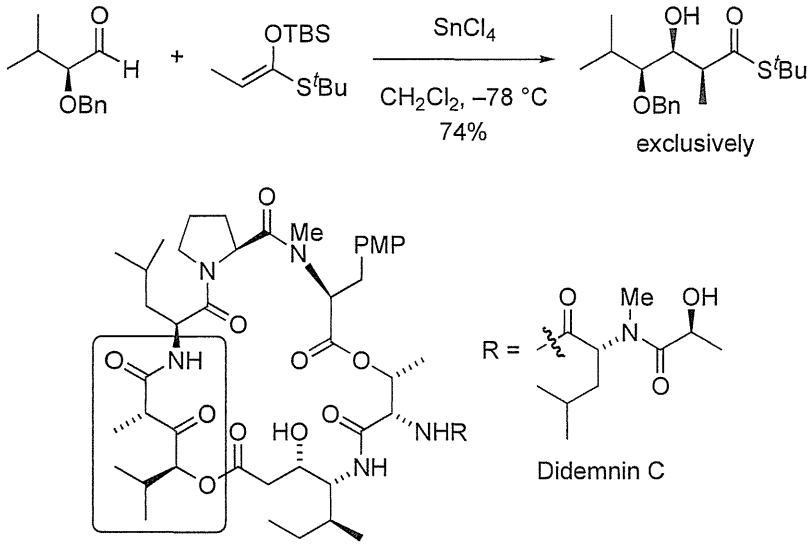
Scheme 6. Chelation model for producing 3,4-*syn*-aldols.



Scheme 7. Diastereoselectivity in the Mukaiyama aldol reaction of KSAs with 2-benzyloxypropanal (for 3,4-*syn* asymmetric induction).



Scheme 8. Diastereoselective Mukaiyama aldol reaction of KSAs with 2-benzyloxypropanal (for 3,4-*syn* asymmetric induction).



Scheme 9. Diastereoselective Mukaiyama aldol reaction of KSAs with 2-benzyloxy-3-methylbutanal for the total synthesis of didemnin C.

KSAs in this stereoselective reaction.[8] For example, a KSA derived from *S*-^{t}Bu ethanethioate gave the 3,4-*syn*-adduct preferentially in good yield (Scheme 8).

The high 3,4-*syn* asymmetric induction via chelation control using $SnCl_4$ is very effective for the construction of natural complex molecules, such as oligopeptides, oligosugars, and polyoxyamides. Joullié obtained a 2,3-*syn*-3,4-*syn*-thioester via the reaction of a KSA derived from *S*-^{t}Bu propanethioate with an α-alkoxy aldehyde (Scheme 9).[9] The prepared intermediate was successfully converted to the macrocyclic peptides didemnins A, B, and C in 1990.

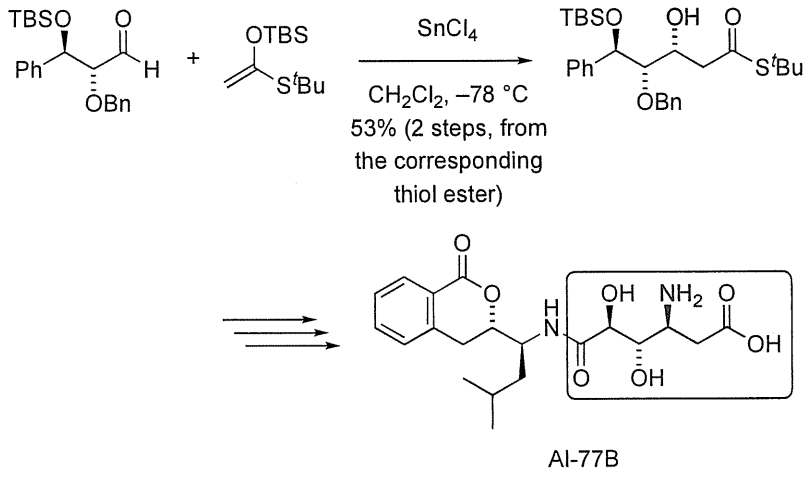
Mukai and Hanaoka, meanwhile, reported the total synthesis of AI-77B, in which they successfully utilized the stereoselective direct aldol reaction of a KSA derived from *S*-^{t}Bu ethanethioate with an α-alkoxy aldehyde (Scheme 10).[10]

Following the successful development of stannic-mediated aldol reactions of ESEs and KSAs with carbonyl compounds, which were generally used as powerful tools for the stereoselective synthesis of natural compounds, further advanced methods using Sn(II) triflate (trifluoromethanesulfonate)–promoted Mukaiyama aldol reactions of silyl enolates with carbonyl compounds have been explored during the last two decades.

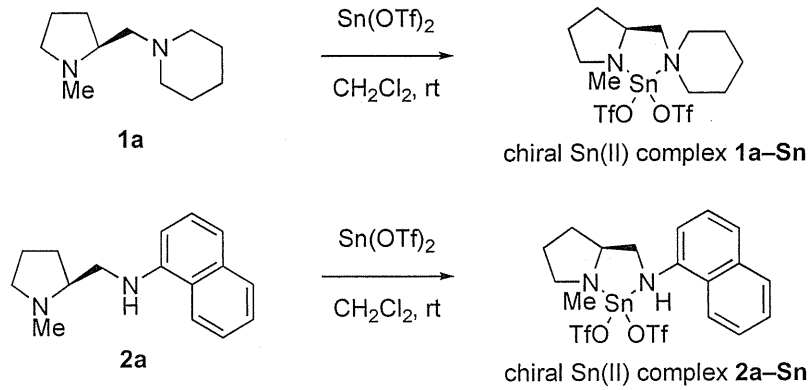
The current account first presents aldol and related addition reactions promoted by the chiral diamine–Sn(OTf)$_2$ complex for the preparation of various optically active β-hydroxy carbonyl units (aldols). A universal synthetic strategy for the preparation of optically active polyoxy compounds, including a number of chiral monosaccharides, using asymmetric Mukaiyama aldol reactions is then reviewed. Finally, recent applications of these reactions to the highly enantioselective synthesis of biologically active natural products will be described.

2. Chiral Diamine–Sn(OTf)$_2$ Complex–Mediated Aldol Reactions

The enantioselective aldol reaction is one of the most powerful tools for the construction of new carbon–carbon bonds with control of the absolute configurations of the stereogenic centers, and the utility of this reaction has been demonstrated



Scheme 10. Diastereoselective Mukaiyama aldol reaction of KSAs with 2-benzyloxy-3-(*t*-butyldimethylsiloxy)-3-phenylpropanal for the total synthesis of AI-77B.



Scheme 11. Chiral Sn(II) Lewis acids generated from Sn(OTf)$_2$ with diamines.

by its numerous applications in the synthesis of natural products, such as macrolide and polyether antibiotics and carbohydrates. In most early asymmetric aldol reactions, chiral auxiliary groups were typically attached to the reacting ketone-equivalent molecules. Until the early 1980s, there was no example of an aldol-type reaction in which two achiral carbonyl compounds were used to form a chiral molecule with the aid of a chiral ligand.

Chiral auxiliaries derived from (*S*)-proline have been particularly attractive, because they possess conformationally rigid pyrrolidine rings. Notably, chiral diamines derived from (*S*)-proline have been successfully used for the creation of efficient chiral environments; nearly all of the main group and transition metals with vacant d orbitals are capable of accepting a bidentate ligand. Intermediates derived from such bidentate chiral ligands and Sn(OTf)$_2$ are composed of a conformationally restricted *cis*-fused five-membered ring chelate and afford optically active organic compounds via reaction with appropriate substrates.

2.1. Formation of Chiral Diamine–Sn(OTf)$_2$ Complexes

Chiral Sn(II) Lewis acids prepared in situ via the coordination of chiral pyrrolidine derivatives to Sn(OTf)$_2$ were developed by Mukaiyama and Kobayashi in 1989 for the promotion of the asymmetric aldol reaction of ESEs or KSAs with carbonyl compounds. Prior to this study, the successful use of chiral Lewis acids had been reported for the Diels–Alder and related reactions in the late 1980s. The chiral Lewis acids used in these reactions consisted of rather strong and hard acidic metals such as aluminum and titanium.[11]

Chiral Sn(II) Lewis acids, which are prepared in situ via the chelation of chiral diamines to Sn(OTf)$_2$ (Scheme 11), on

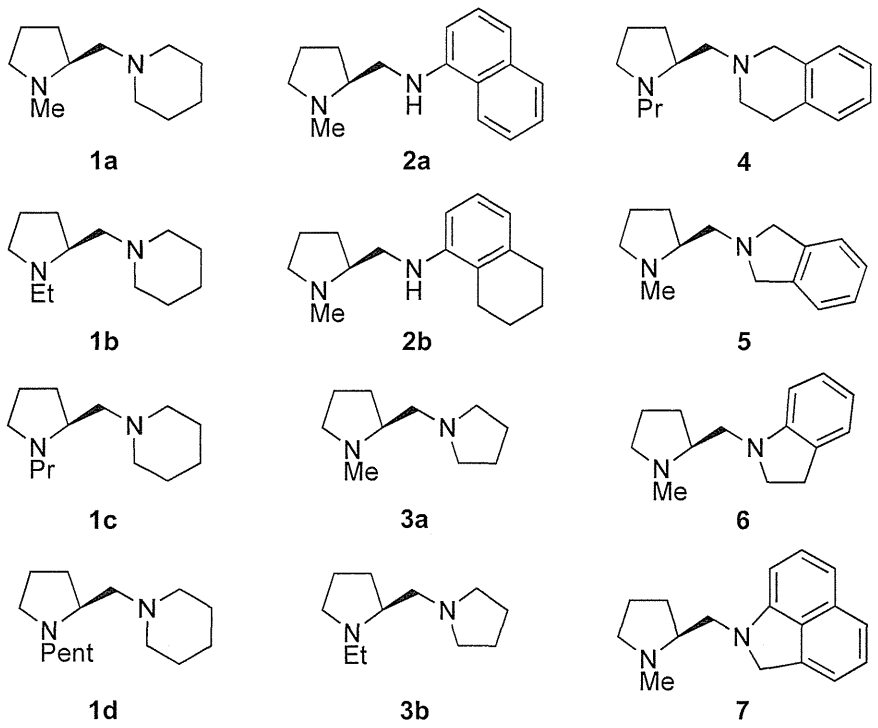
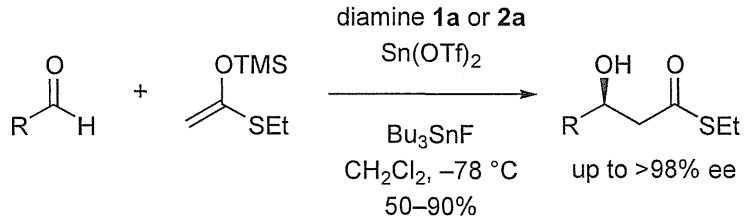


Fig. 1. Useful chiral diamines for asymmetric aldol reactions.



Scheme 12. Enantioselective Mukaiyama aldol reaction of KSA with achiral aldehydes for the preparation of chiral β-hydroxy thioesters.

the other hand, are soft Lewis acids that have one vacant d orbital for coordination to the oxygen of the carbonyl group of an aldehyde to create the favorable asymmetric environment.

Based on this consideration, various efficient asymmetric aldol reactions between achiral silyl enolates and achiral carbonyl compounds have been developed. Some of the chiral diamines used in the asymmetric aldol reaction of KSAs with carbonyl compounds promoted by $Sn(OTf)_2$ are shown in Figure 1.

2.2. Asymmetric Aldol Reaction of Silyl Enolates

The asymmetric aldol reaction of a KSA derived from *S*-Et ethanethioate with achiral aldehydes was first achieved with high ee values by using 1.0 equivalent of $Sn(OTf)_2$ coordinated with 1.2 equivalents of a chiral diamine (**1a** or **2a**) in the presence of 1.1 equivalents of Bu_3SnF (Scheme 12).[12]

The complex consisting of $Sn(OTf)_2$ and **2a** is quite effective in the reaction of the KSA generated from *S*-Et

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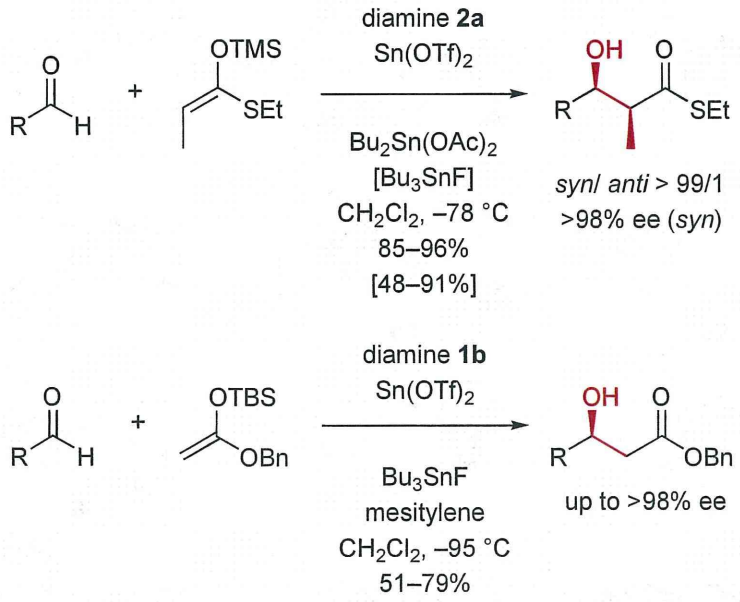
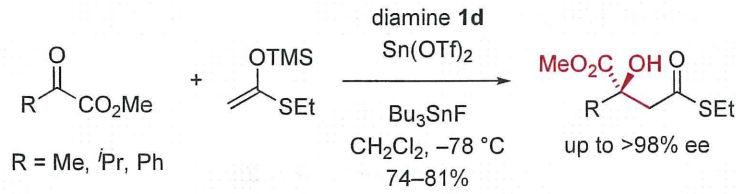


Scheme 13. Enantioselective Mukaiyama aldol reactions of KSAs with achiral aldehydes for the preparation of chiral β-hydroxy thioesters and esters.



Scheme 14. Enantioselective Mukaiyama aldol reaction of KSAs with achiral α-ketoesters for the preparation of chiral 2-substituted malates.

propanethioate with aldehydes to afford the corresponding *syn*-aldol adducts with excellent diastereo- and enantioselectivities (Scheme 13, upper equation).[12b,13] Furthermore, the highly enantioselective aldol reaction of the KSA of benzyl acetate with achiral aldehydes was carried out using the Lewis acid formed from $Sn(OTf)_2$ with **1b** (Scheme 13, lower equation).[14]

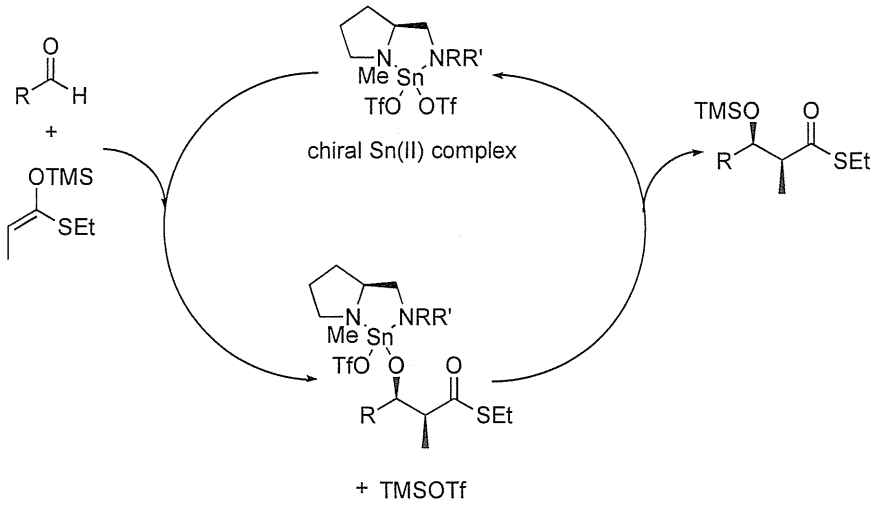
In the presence of the chiral diamine **1d**, $Sn(OTf)_2$, and Bu_3SnF, the KSA derived from *S*-Et ethanethioate reacts with α-ketoesters to afford the corresponding aldol-type adducts, 2-substituted malates, in good yields with excellent ee values (Scheme 14).[15]

2.3. Catalytic Asymmetric Aldol Reaction

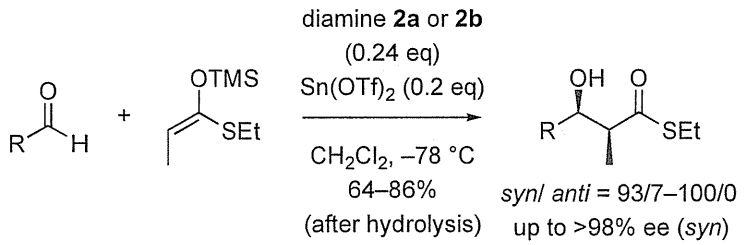
Catalytic asymmetric synthesis is an extremely desirable method for the production of optically active compounds from achiral substrates. If a catalytic system for the asymmetric aldol reaction is developed using a small amount of a chiral source, substantial amounts of optically active compounds can be synthesized in a convenient and rational manner. In the reactions described above, the chiral diamine–$Sn(OTf)_2$ complex promoter has mild acidity for accelerating the asymmetric aldol reaction of KSAs with aldehydes; however, a stoichiometric amount is required.

Therefore, based on a mechanistic examination of the stoichiometric asymmetric aldol reaction, Mukaiyama and Kobayashi considered the possibility of using a catalytic amount of the chiral diamine–$Sn(OTf)_2$ complex. They made several key observations:

1) The reaction first produces Sn(II) alkoxides and TMSOTf (Scheme 15).
2) If the substrates (KSA and aldehyde) are rapidly added to a solution of the chiral diamine–$Sn(OTf)_2$ complex, the initially formed TMSOTf promotes achiral addition to produce



Scheme 15. Catalytic cycle of the enantioselective Mukaiyama aldol reaction using chiral Sn(II) Lewis acids.



Scheme 16. Catalytic enantioselective Mukaiyama aldol reaction of KSAs with achiral aldehydes for the preparation of chiral β-hydroxy thioesters.

the racemic aldol product from the remainder of the starting materials.

3) If the substrates are slowly added to a solution of the chiral diamine–$Sn(OTf)_2$ complex according to the reaction rate of the KSA with the aldehyde, transmetalation from Sn(II) of the formed Sn(II) alkoxide to Si takes place via a sequential reaction with TMSOTf in situ.

In fact, after conducting a careful examination of the reaction conditions, an optically active trimethylsilyl ether of an aldol adduct was obtained in the reaction of the KSA derived from *S*-Et propanethioate with aldehydes via the slow addition of a mixture of the substrates to a solution including a catalytic amount of the chiral diamine–$Sn(OTf)_2$ complex (Scheme 16).[16]

The rate of this transmetalation is affected by the reaction conditions, and particularly, by the choice of solvent. Propionitrile was found to be a suitable reaction medium for the catalytic process, and various optically active aldol adducts were prepared with high ee values when solutions of an aldehyde and a KSA derived from *S*-Et propane- or ethanethioate were added to the catalyst consisting of a chiral diamine and $Sn(OTf)_2$ in propionitrile (Scheme 17).[16,17]

A novel combined catalyst generated from SnO and TMSOTf was also developed for the catalytic synthesis of the desired compounds (Scheme 18, upper equation).[18] Although the exact structure of this complex is unclear, SnO interacts with TMSOTf to form an acidic species that functions as the chiral catalyst in this reaction. Furthermore, Kobayashi employed SnO as an effective additive for the aldol reaction of KSAs with aldehydes promoted by chiral diamine–$Sn(OTf)_2$ complexes; that is, the optically active aldol adducts were synthesized with high stereoselectivity using a chiral diamine–$Sn(OTf)_2$–SnO complex (Scheme 18, lower equation).[19]

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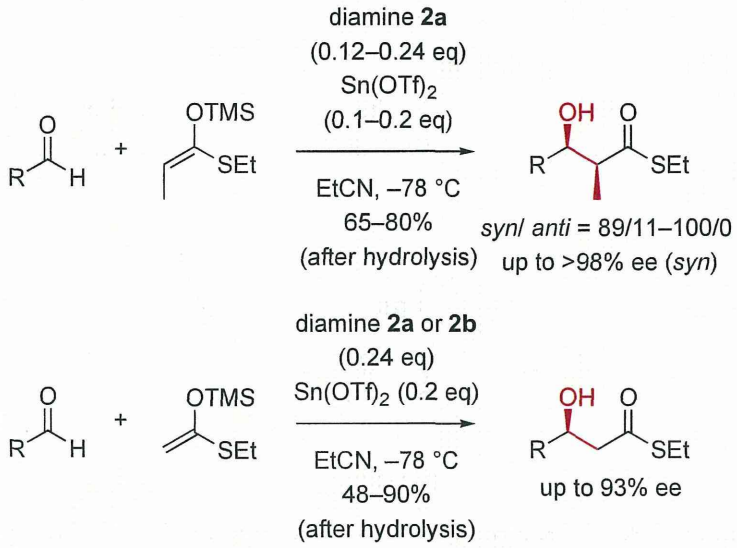
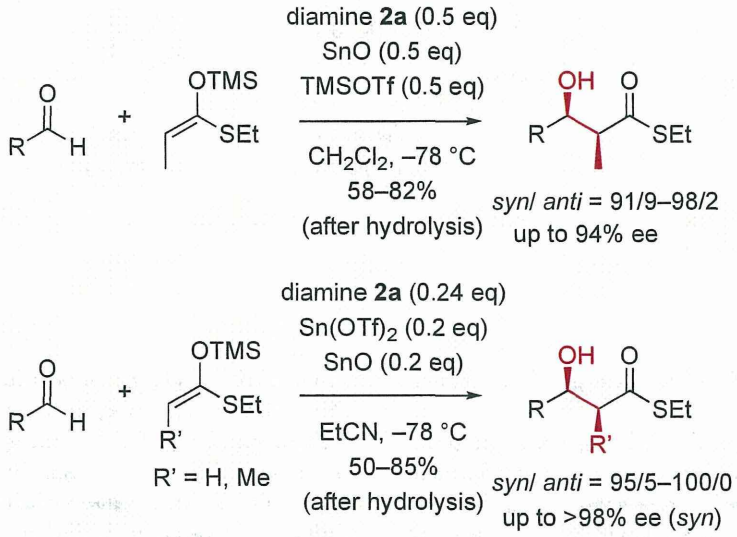


Scheme 17. Catalytic enantioselective Mukaiyama aldol reactions of KSAs with achiral aldehydes in propionitrile for the preparation of chiral β-hydroxy thioesters.

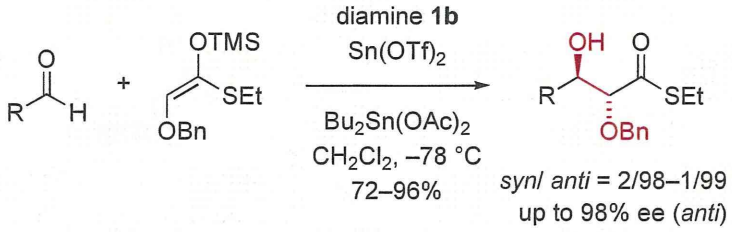


Scheme 18. Catalytic enantioselective Mukaiyama aldol reactions of KSAs with achiral aldehydes for the preparation of chiral β-hydroxy thioesters.

2.4. Asymmetric Synthesis of *syn*- and *anti*-1,2-Diol Units

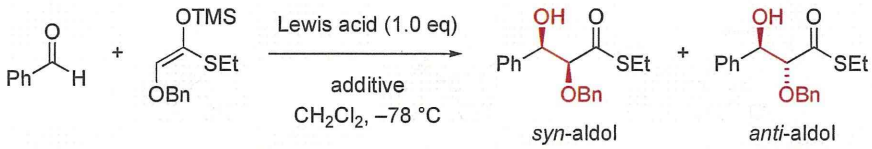
Optically active 1,2-diol units are often observed in natural products such as carbohydrates, macrolides, and polyethers. Several excellent methods for the asymmetric dihydroxylation of olefins using OsO_4 with chiral ligands have been developed that provide optically active 1,2-diol units with high enantioselectivity. However, some problems still remain, most notably the preparation of the optically active *anti*-1,2-diols.

The asymmetric aldol reaction of a KSA derived from an α-benzyloxy thioester with aldehydes developed in 1990 by Mukaiyama, Kobayashi, Uchiro, and Shiina addresses this



Scheme 19. Enantioselective synthesis of *anti*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSA with achiral aldehydes.

Table 1. Diastereoselectivity of the Mukaiyama aldol reaction of the KSA derived from α-benzyloxy thioester with benzaldehyde.



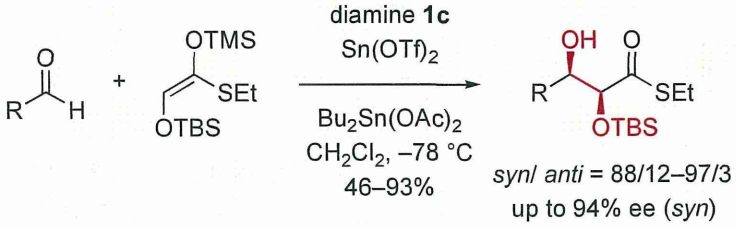
Entry	Lewis acid	Diamine	Additive	Yield	*synlanti*	ee of aldol
1	BF_3 OEt_2	none	none	36	61/39	–
2	$TiCl_4$	none	none	61	50/50	–
3	$Sn(OTf)_2$	$(PhNHCH_2)_2$	none	79	21/79	–
4	$Sn(OTf)_2$	**1b**	$Bu_2Sn(OAc)_2$	96	1/99	96% (*anti*)

issue. In this reaction, two functionalities are simultaneously introduced with stereoselective carbon–carbon bond formation using a chiral Sn(II) Lewis acid. Various optically active *anti*-α,β-dihydroxy thioester derivatives were obtained in good yields with excellent diastereo- and enantioselectivities using 1.2 equivalents of the chiral diamine **1b**, 1.0 equivalent of $Sn(OTf)_2$, and 1.1 equivalents of $Bu_2Sn(OAc)_2$ (Scheme 19).[20] Based on this aldol methodology, two different oxygenated groups can be stereoselectively introduced at the α- and β-positions during carbon–carbon bond formation.

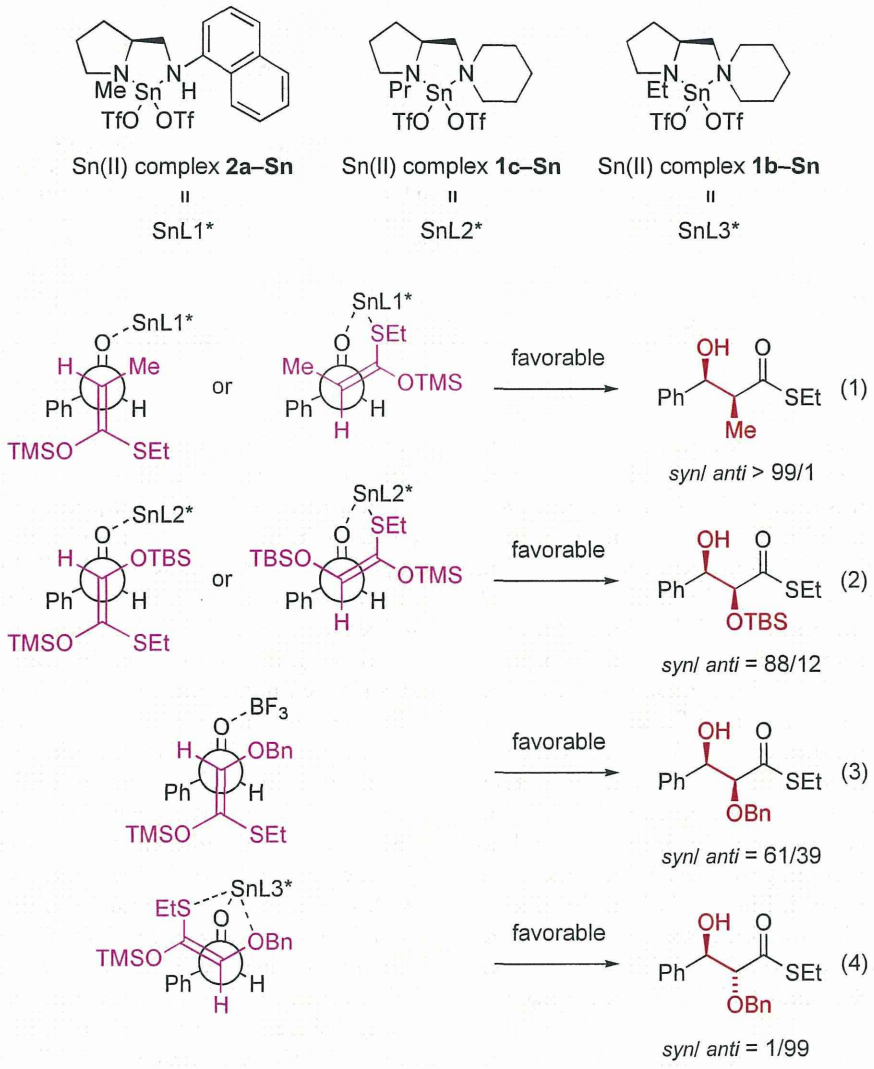
As shown in Table 1, several typical Lewis acids, such as $BF_3{\cdot}OEt_2$ and $TiCl_4$, were also used in the aldol reaction of the KSA derived from α-benzyloxy thioester with benzaldehyde; however, *syn* selectivity was observed in the $BF_3{\cdot}OEt_2$–mediated reaction (entry 1) and nonselective addition of the KSA to benzaldehyde proceeded in the $TiCl_4$-mediated aldol reaction (entry 2). On the other hand, the Mukaiyama aldol reaction with the chiral or achiral diamine–$Sn(OTf)_2$ complex afforded the corresponding *anti*-aldol preferentially (entries 3 and 4).

In 1991, it was surprisingly found that several *syn*-aldol adducts were obtained under the same reaction conditions (chiral diamine **1b**, $Sn(OTf)_2$, and $Bu_2Sn(OAc)_2$) using a KSA possessing a *t*-butyldimethylsiloxy group at the C2 position and achiral aldehydes. The reaction proceeds smoothly to afford the corresponding *syn*-α,β-dihydroxy thioester derivatives in high yields with good stereoselectivities. When the chiral diamine **1c**, which is similar to **1b** but with a propyl group on the nitrogen of the pyrrolidine ring, was used, the ee increased up to 94% (Scheme 20).[20b,21] It is thus possible to control the diastereoselectivity using the KSA derived from α-hydroxy thioester derivatives by selecting the appropriate protecting group for the hydroxyl substituent of the KSA. In this manner, both diastereomers of the optically active α,β-dihydroxy thioester derivatives can be synthesized.

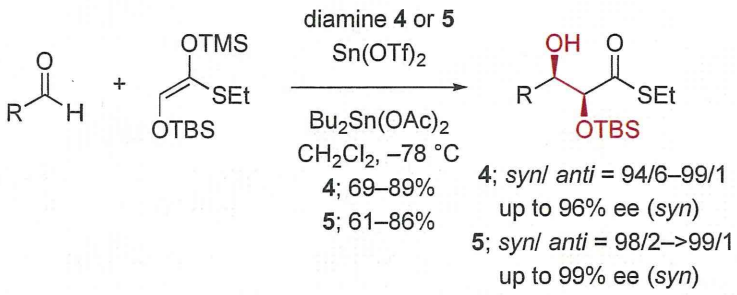
Scheme 21 represents the diastereoselectivities of the Mukaiyama aldol reaction of several KSAs derived from *S*-Et propanethioate, *S*-Et (*t*-butyldimethylsiloxy)ethanethioate, and *S*-Et benzyloxyethanethioate with benzaldehyde. In the presence of the Sn(II) complex with a chiral diamine, the KSA derived from *S*-Et propanethioate ((*Z*)-1-ethylthio-1-trimethylsiloxy-1-propene) reacts with benzaldehyde to afford the corresponding *syn*-aldol adduct exclusively (equation 1). In this reaction, the open-chain model for transition structure (antiperiplanar-type) or cyclic transition structure (synclinal-type) was plausibly assumed to afford the corresponding *syn*-aldol adduct. Based on this hypothesis for the preferable formation of the *syn*-aldol adduct, we supposed that the KSA derived from *S*-Et (*t*-butyldimethylsiloxy)ethanethioate ((*Z*)-2-(*t*-butyldimethylsiloxy)-1-ethylthio-1-(trimethylsiloxy)ethene)



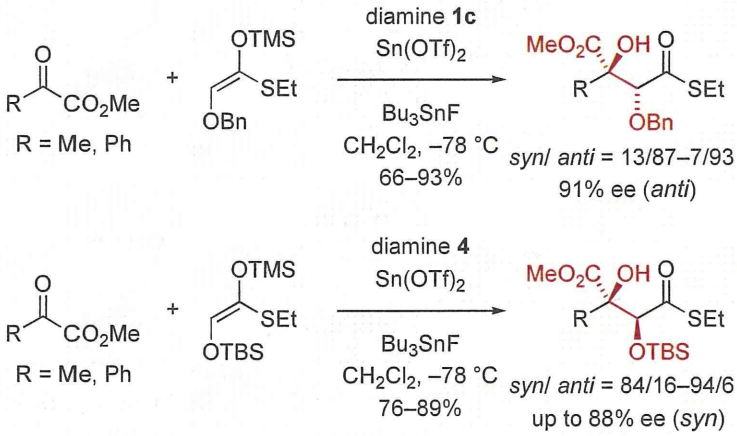
Scheme 20. Enantioselective synthesis of *syn*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.



Scheme 21. Diastereoselectivities of the Mukaiyama aldol reaction of several KSAs derived from thioesters with benzaldehyde.



Scheme 22. Enantioselective synthesis of *syn*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.



Scheme 23. Enantioselective synthesis of *syn*- and *anti*-α,β-dihydroxy-β-substituted thioester derivatives using the asymmetric Mukaiyama aldol reaction of KSAs with achiral α-ketoesters.

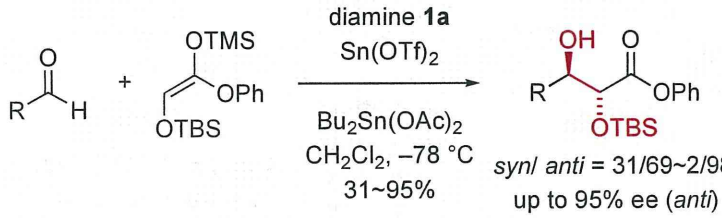
also attacks this aldehyde via the open-chain or cyclic transition state to provide the *syn*-diol unit (equation 2). On the other hand, in the reaction of the KSA derived from *S*-Et benzyloxyethanethioate ((*Z*)-2-benzyloxy-1-ethylthio-1-(trimethylsiloxy)ethene) with benzaldehyde, preference is given to the coordination of both the oxygen of the benzyloxy group and the sulfur of the ethylthio group to Sn(II). The reaction would proceed only via a cyclic transition state to afford the *anti*-diol unit with high diastereoselectivity (equation 4). When using $BF_3{\cdot}OEt_2$ as a Lewis acid for the reaction of (*Z*)-2-benzyloxy-1-ethylthio-1-(trimethylsiloxy)ethene with benzaldehyde, the opposite stereoselectivity was observed (Table 1, entry 1), because the aldol reaction took place through the open-chain model for the nonchelated transition state (equation 3).

In these reactions, the diastereoselectivities are controlled by the coordination ability of the oxygen of the α-alkoxy or α-siloxy parts of the KSAs to Sn(II). When the oxygen can easily coordinate to Sn(II), *anti*-aldols are obtained. However, when this coordination is sterically forbidden, *syn*-aldols are produced. These phenomena are useful in predicting the stereochemical course of the present asymmetric aldol reaction.

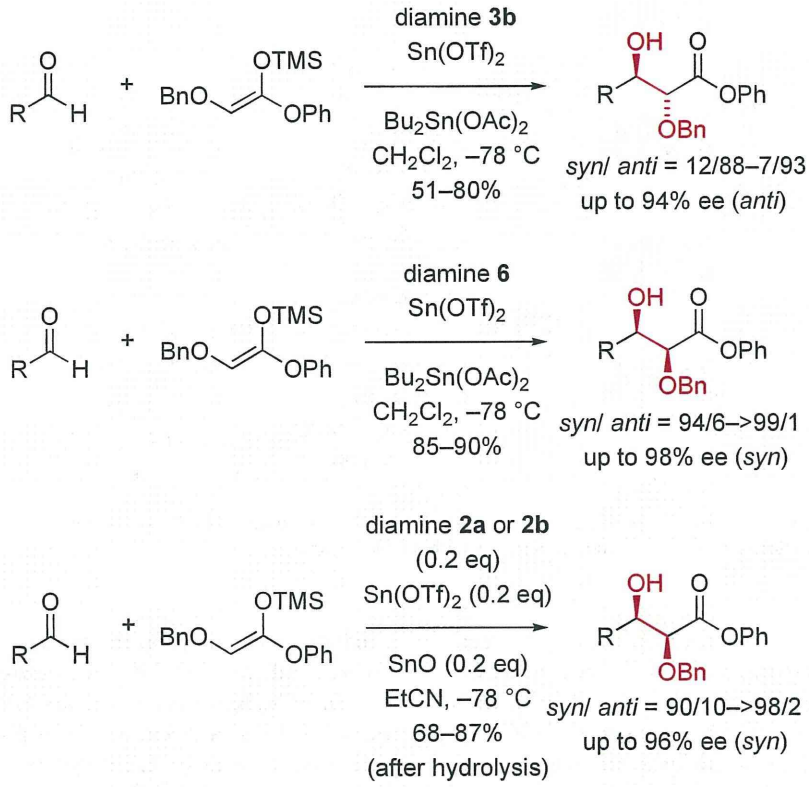
In 1994, Kobayashi introduced several new types of chiral diamines, such as **4** and **5**, which provide higher selectivity in the synthesis of *syn*-α,β-dihydroxy thioester derivatives, as shown in Scheme 22.[22,23]

The diastereo- and enantioselective synthesis of both stereoisomers of α,β-dihydroxy-β-methyl or α,β-dihydroxy-β-phenyl thioester derivatives can also be achieved by reacting KSAs possessing benzyloxy or *t*-butyldimethylsiloxy groups at the C2 position with α-ketoesters in the presence of a Sn(II) Lewis acid and either chiral diamine **1c** or **4** (Scheme 23).[22,24]

It should also be noted that KSAs derived from phenyl esters have the unique ability to promote remarkable stereoselectivity in asymmetric aldol reactions using chiral diamine–$Sn(OTf)_2$ complexes.[25–27] For instance, Kobayashi found that the (*E*)-KSA derived from phenyl (*t*-butyldimethylsiloxy)acetate reacts with aldehydes to afford the corresponding *anti*-1,2-diol derivatives with high diastereo- and enantioselectivities when promoted by a Sn(II) Lewis acid and chiral diamine **1a** (Scheme 24).[27]



Scheme 24. Enantioselective synthesis of *anti*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

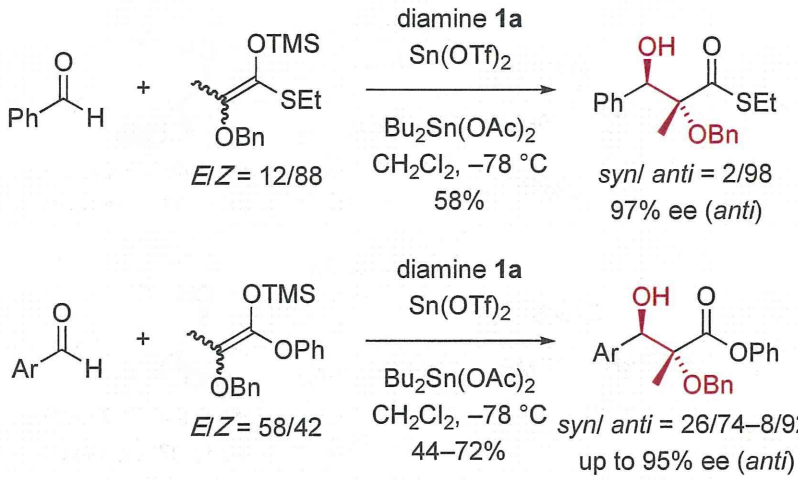


Scheme 25. Enantioselective synthesis of *syn*- and *anti*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

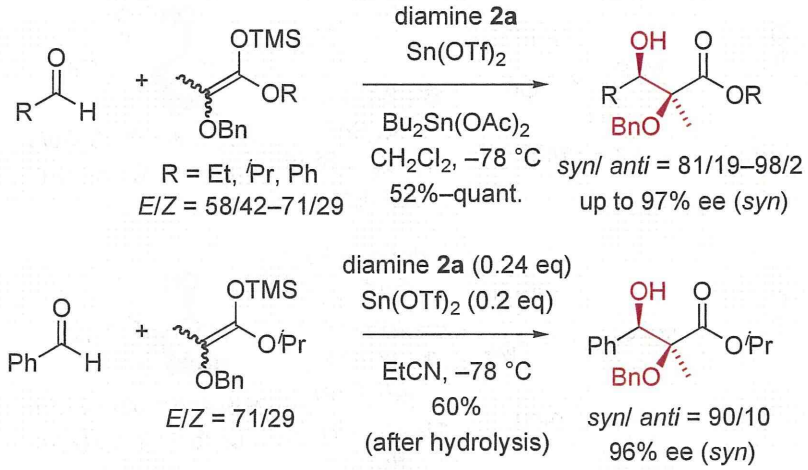
Furthermore, the reaction of the (*Z*)-KSA derived from phenyl benzyloxyacetate with aldehydes using chiral diamine **3b** also preferentially provides optically active *anti*-1,2-aldols (Scheme 25, top equation). Interestingly, the corresponding *syn*-aldol products were formed when the reaction was carried out in the presence of chiral diamine **6** (Scheme 25, middle equation).[28] The latter reaction was also accelerated in the presence of a catalytic amount of chiral diamine **2a** or **2b** according to the conditions employed by Kobayashi (with SnO) (Scheme 25, bottom equation).[29]

2.5. Construction of Quaternary Stereogenic Centers Using the Mukaiyama Aldol Reaction

This asymmetrical aldol reaction can also be applied to the construction of quaternary stereogenic centers within the 1,2-diol units. For example, in the presence of a promoter consisting of the chiral diamine **1a**, $Sn(OTf)_2$, and $Bu_2Sn(OAc)_2$, various optically active *anti*-α,β-dihydroxy-α-methyl thioester and phenyl ester derivatives were synthesized in good yields with high stereoselectivities (Scheme 26).[25,26]



Scheme 26. Enantioselective synthesis of *anti*-α,β-dihydroxy-α-methyl thioester and phenyl ester derivatives using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

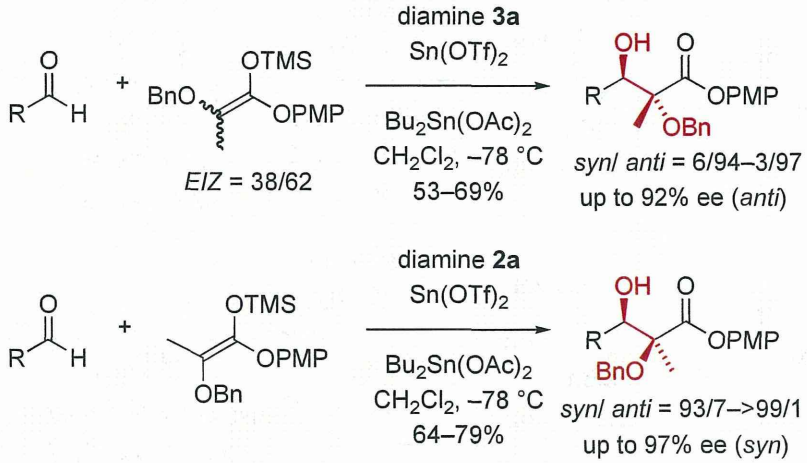


Scheme 27. Enantioselective synthesis of *syn*-α,β-dihydroxy-α-methyl ester derivatives using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

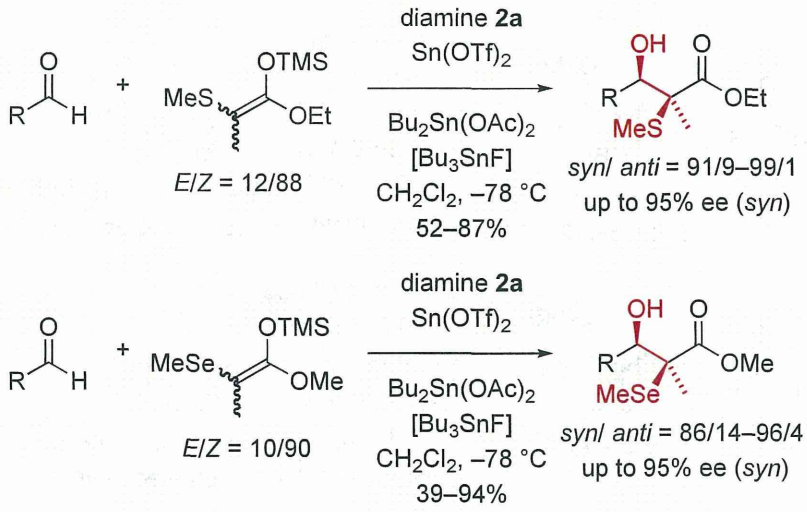
In another interesting example, *syn*-α,β-dihydroxy-α-methyl ester derivatives were produced from similar KSAs using a stoichiometric or catalytic amount of chiral catalyst containing diamine **2a**, as shown in Scheme 27.[26]

Similarly, it was found that the KSA (*E*/*Z* = 38/62) derived from *p*-methoxyphenyl 2-benzyloxypropanoate reacts with aldehydes in the presence of a Sn(II) catalyst including diamine **3a** to give the corresponding *anti*-aldol units (Scheme 28, upper equation), whereas the asymmetric aldol reaction of the (*E*)-KSA derived from *p*-methoxyphenyl 2-benzyloxypropanoate with various aldehydes promoted by $Sn(OTf)_2$ coordinated by chiral diamine **2a** afforded the stereoisomeric *syn*-compounds with high ee values (Scheme 28, lower equation).[30]

Furthermore, tetrasubstituted KSAs bearing alkylthio or alkylseleno groups also react with aldehydes to preferentially produce *syn*-aldol compounds (Scheme 29).[31,32] These compounds were used as synthetic intermediates for *anti*-β-hydroxy-α-methyl units in the total synthesis of octalactins A and B described in a later section (Section 3.8).



Scheme 28. Enantioselective synthesis of *syn*- and *anti*-α,β-dihydroxy-α-methyl ester derivatives using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.



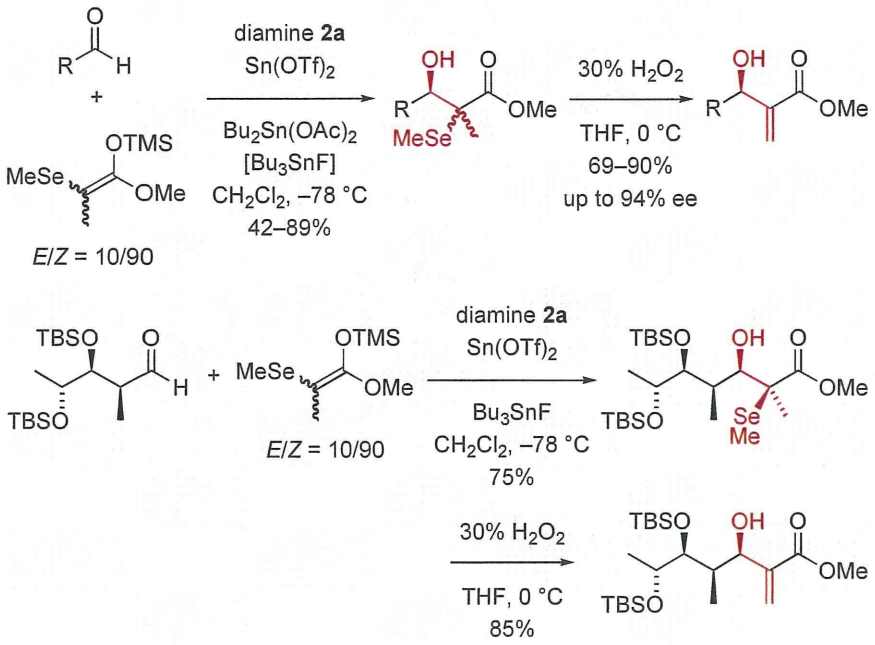
Scheme 29. Enantioselective synthesis of *syn*-α-alkylthio-β-hydroxy-α-methyl ester and *syn*-α-alkylseleno-β-hydroxy-α-methyl ester derivatives using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

2.6. Enantioselective Synthesis of Chiral α-Methylene-β-Hydroxy Esters Using the Asymmetric Mukaiyama Aldol Reaction

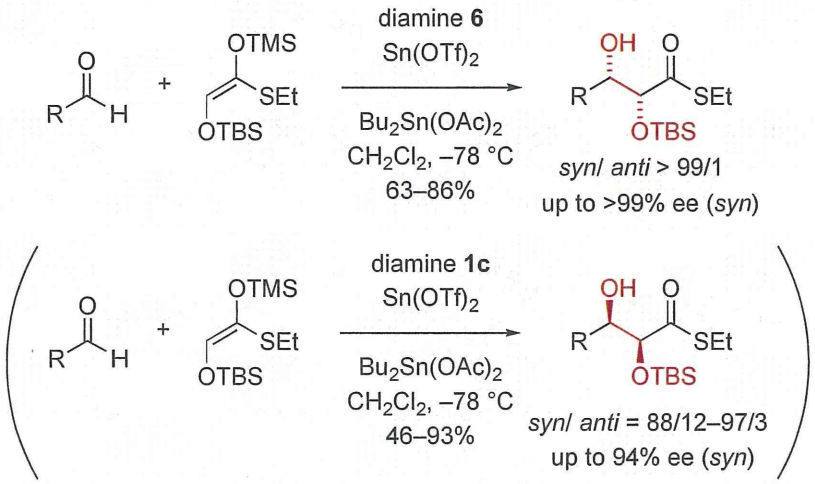
Shiina further developed a method for the synthesis of optically active α-methylene-β-hydroxy esters using a combination of the asymmetric aldol reaction of a tetrasubstituted KSA including an alkylseleno group with aldehydes and subsequent facile oxidative deselenization (Scheme 30, upper equation).[32] This protocol provides another method for the production of chiral Morita–Baylis–Hillman (MBH) adducts with high ee values, and the wide substrate scope of this reaction enables its application to the synthesis of many types of α-methylene-β-hydroxy esters bearing aromatic, aliphatic, and alkenyl substituents at the β-position (Scheme 30, lower equation).[33]

2.7. Enantioselective Synthesis of Both Enantiomers of Aldol Adducts Using Similar Diamines Derived from L-Proline

In 1994, Kobayashi reported remarkable results regarding the synthesis of optically active aldol compounds using new chiral



Scheme 30. Enantioselective synthesis of α-methylene-β-hydroxy esters (MBH adducts) using the asymmetric Mukaiyama aldol reaction of KSAs with achiral and chiral aldehydes.



Scheme 31. Enantioselective synthesis of both enantiomers of *syn*-1,2-diol units using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

diamine–$Sn(OTf)_2$ complex promoters. Namely, the reaction of the KSA derived from *S*-Et (*t*-butyldimethylsiloxy) ethanethioate with aldehydes using chiral diamine **6** mainly yielded the *syn*-(2*R*,3*S*) compounds (Scheme 31),[23,34] which are optical antipodes of the aldol adducts (*syn*-(2*S*,3*R*)) prepared via the reaction using chiral diamine **1c** (see Scheme 20).[20b,21] Furthermore, optically active *syn*-(2*R*,3*R*) aldols were prepared from propanoic acid derivatives using a Sn(II) complex with chiral diamine **7** (Scheme 32),[35] whereas *syn*-(2*S*,3*S*) aldols were produced when using chiral diamine **2a** in

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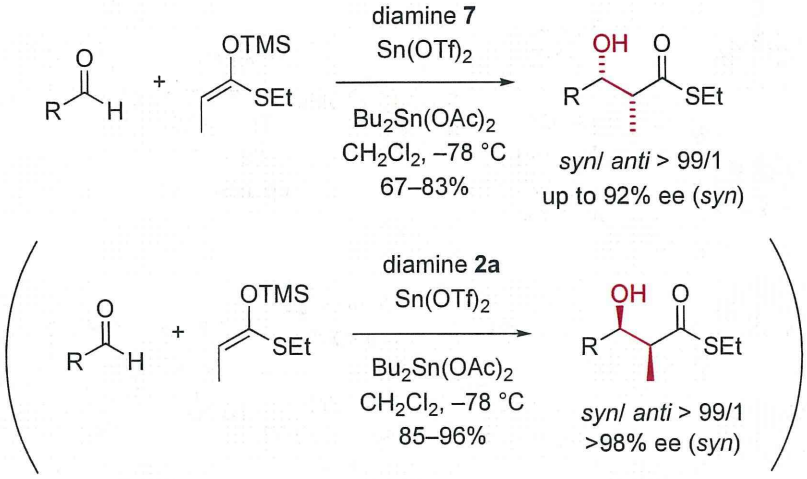
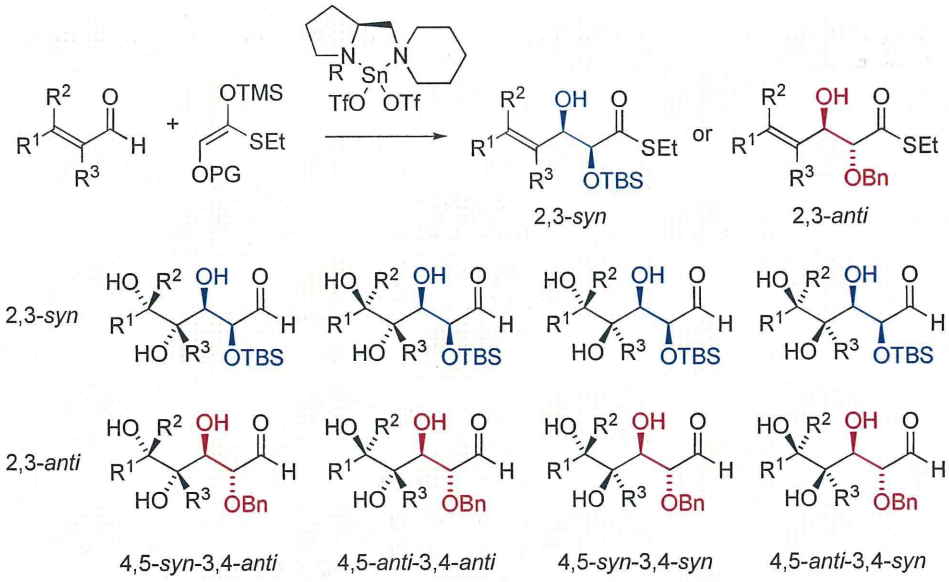


Scheme 32. Enantioselective synthesis of both enantiomers of *syn*-β-hydroxy-α-methyl esters using the asymmetric Mukaiyama aldol reaction of KSAs with achiral aldehydes.

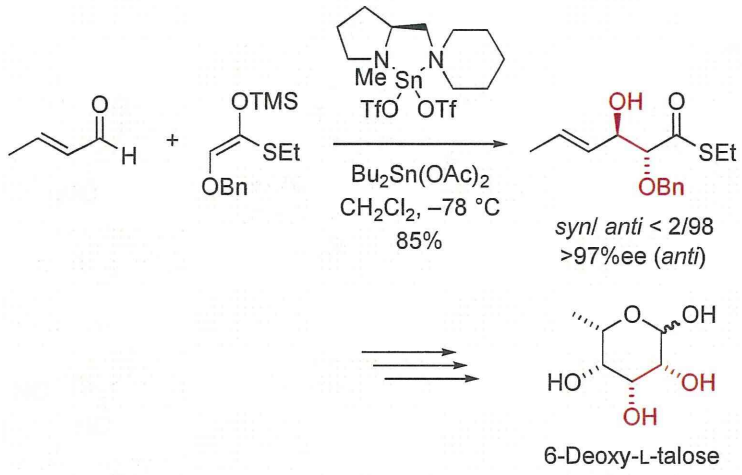


Scheme 33. Synthesis of various monosaccharides via the asymmetric aldol reaction.

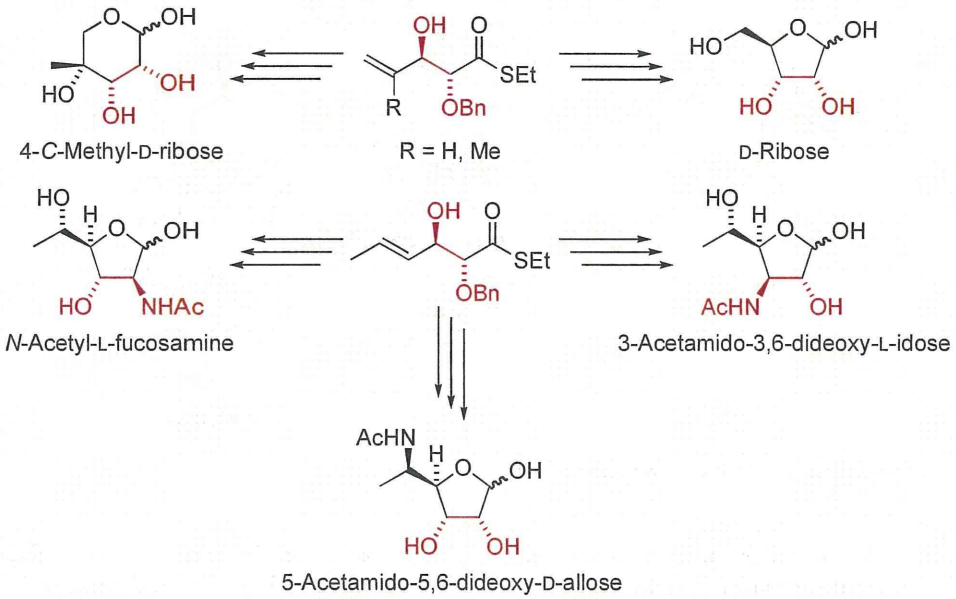
the same reaction (see Scheme 13, upper equation).[12b,13] All of the chiral diamines **1c**, **2a**, **6**, and **7** were prepared starting from L-proline and have the same absolute configuration at the C2 position. Therefore, the effective switching of the enantiofacial selectivity of the aldol reaction using only one chiral source was achieved in the above-described experiments.

3. Asymmetric Total Syntheses of Complex Molecules Using Chiral Diamine–Sn(OTf)$_2$ Catalysts

Enantioselective aldol reactions are powerful tools for the stereoselective synthesis of complex molecules, and particularly for the construction of optically active 1,2-diol units found in



Scheme 34. Synthesis of 6-deoxy-L-talose.



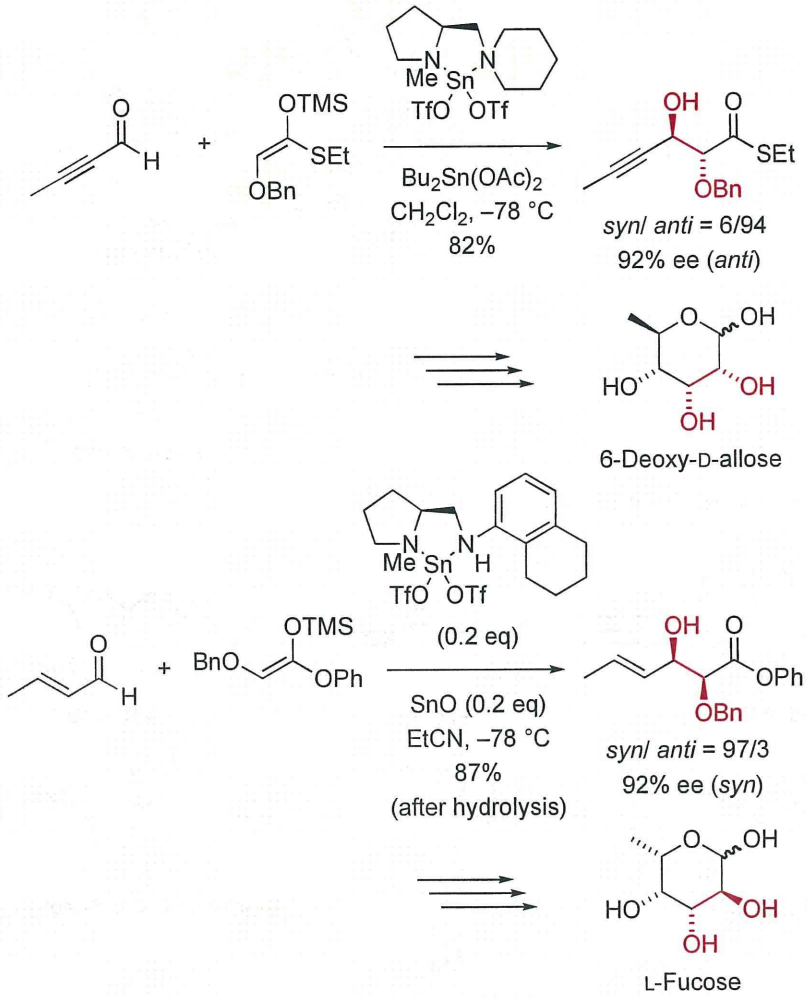
Scheme 35. Synthesis of D-ribose, 4-*C*-methyl-D-ribose, and several amino sugars.

the carbon backbones of target compounds. Recent progress in this area is discussed below, including successful methods for the stereoselective synthesis of natural and unnatural polyoxy compounds.

3.1. Monosaccharides

In the last several decades, great advances have been made in the chemical synthesis of monosaccharides based on the stereoselective addition reactions of 2,3-*O*-isopropylidene-D- or L-glyceraldehyde and 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose with enolate components or allyl nucleophiles, and many examples of the effective synthesis of both natural and unnatural sugar forms have been demonstrated.[36] In these syntheses, the glyceraldehyde and threose derivatives are typically prepared from natural chiral pool substances such as mannitol and tartaric acid, respectively.

On the other hand, a general method for the synthesis of various sugars starting from both achiral KSAs and α,β-unsaturated aldehydes has also been developed in 1990, as



Scheme 36. Synthesis of 6-deoxy-D-allose and L-fucose.

shown in Scheme 33. Chiral induction can be accomplished with an asymmetric aldol reaction using a complex consisting of $Sn(OTf)_2$ and an appropriate chiral diamine. The successive dihydroxylation or epoxidation of the double bond in the aldol adducts afforded several tetrahydroxy thioester derivatives, which are useful precursors for the synthesis of various monosaccharides, including rare sugars.

As an example, the synthesis of 6-deoxy-L-talose is shown in Scheme 34.[37] The asymmetric aldol reaction between crotonaldehyde and the KSA of α-benzyloxy thioester was carried out in the presence of $Sn(OTf)_2$, chiral diamine **1a**, and $Bu_2Sn(OAc)_2$, and the corresponding aldol adduct was obtained in 85% yield with >97% ee. The dihydroxylation of this chiral synthon followed by the successive reduction of the resultant lactone and the deprotection of the benzyl group gave the desired 6-deoxy-L-talose in good yield.

According to this universal methodology, several monosaccharides, including branched and amino sugars, were synthesized as shown in Scheme 35 (D-ribose and 4-*C*-methyl-D-ribose (1990),[37] *N*-acetyl-L-fucosamine, 3-acetamido-3,6-dideoxy-L-idose, and 5-acetamido-5,6-dideoxy-D-allose (1993)).[38]

Scheme 36 shows the syntheses of two stereoisomers of 6-deoxy-L-talose from the corresponding intermediates generated via asymmetric aldol reaction (6-deoxy-D-allose (1992)[39] and L-fucose (1993)).[29]

Furthermore, several 2-branched saccharide acid γ-lactones, 2-*C*-methyl-D- or L-threono-1,4-lactones and 2-*C*-methyl-D-erythrono-1,4-lactone, were effectively prepared according to the present strategy by the enantioselective construction of quaternary stereogenic centers developed in the former section (Scheme 37 and Scheme 38).[22,25,26]

