

Iron- and Bismuth-Catalyzed Asymmetric Mukaiyama Aldol Reactions in Aqueous Media

Taku Kitanosono,^[a] Thierry Ollevier,^[b] and Shū Kobayashi*^[a]

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

Abstract: We have developed asymmetric Mukaiyama aldol reactions of silicon enolates with aldehydes catalyzed by chiral Fe(II) and Bi(III) complexes. Although previous reactions often required relatively harsh conditions, such as strictly anhydrous conditions, very low temperature (–78 °C), etc., the present reactions proceeded in the presence of water at 0 °C. To find appropriate chiral water-compatible Lewis acids for the Mukaiyama aldol reactions, many Lewis acids combined with chiral bipyridine **L1**, which was already found

to be a suitable chiral ligand in aqueous media, were screened. Three types of chiral catalysts consisting of Fe(II) or Bi(III), **L1**, and an additive have been discovered, and a wide variety of substrates (silicon enolates and aldehydes) reacted to afford the desired aldols in high yields with high diastereo- and enantioselectivities by appropriate selection of one of the three sets of catalytic systems. Mechanistic studies have elucidated the coordination environments around Fe(II) and Bi(III), and the effect of additives in the chiral catalysts. It is noted that both Brønsted

acids and bases worked as efficient additives in Fe(II)-catalyzed reactions. The assumed catalytic cycle and transition states have shown the important roles of water for efficient asymmetric Mukaiyama aldol reactions in aqueous media on the basis of the broadly applicable and versatile catalytic systems.

Keywords: iron • bismuth • aldol reaction • asymmetric catalysis • C–C coupling

Introduction

In 1973, Mukaiyama et al. reported TiCl₄-mediated aldol reactions of silicon enolates (silyl enol ethers) with aldehydes.^[1] In contrast to classical aldol reactions carried out under basic conditions, which led to side reactions such as isomerization (racemization), retroreactions, overreactions, self-condensations of aldehydes, etc.,^[2] this aldol reaction provided the desired cross-aldol adducts in high yields and has been regarded as one of the most reliable carbon–carbon bond-forming reactions in organic synthesis; namely, the “Mukaiyama aldol reaction,” which has been applied to syntheses of many natural products, pharmaceuticals, agricultural

chemicals, functionalized materials, etc.

Catalytic asymmetric variants of the Mukaiyama aldol reaction were initiated by a report on chiral tin(II) Lewis acid-catalyzed reactions in 1990,^[3] and chiral boron,^[4] chiral titanium,^[5] and chiral zirconium^[6] Lewis acids followed. Since then, many chiral Lewis acids have been developed to target asymmetric Mukaiyama aldol reactions.^[7] On the other hand, for catalytic asymmetric aldol reactions, direct-type aldol reactions, in which the reactions were not via silicon enolates but ketones or equivalents, reacted as nucleophiles with aldehydes directly.^[8] While silicon enolates have to be prepared (isolated) from ketones using stoichiometric amounts of bases and silicon sources in Mukaiyama aldol reactions, direct-type reactions gave aldol adducts directly.^[9] Therefore, from an atom economical point of view, the latter has an advantage. At the present stage, however, nucleophiles that can be used in direct-type aldol reactions are limited to ketones and aldehydes; and furthermore, there are few examples among them using aromatic ketones or acyclic ketones.^[10] Thus, the applicable substrates are limited in direct-type aldol reactions.^[11] Silicon enolates that can be applied to the Mukaiyama aldol reaction are derived not only from ketones and aldehydes but also from esters, amides, lactones, lactams, enones, unsaturated esters, unsaturated amides, and others. Therefore, from the standpoint of substrate generality, the Mukaiyama aldol reaction still has an advantage over the direct-type aldol reaction.

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As mentioned above, while catalytic asymmetric Mukaiyama aldol reactions have been reported since 1990,^[3] relatively harsh conditions, such as strictly anhydrous conditions, very low temperature ($-78\text{ }^{\circ}\text{C}$), etc., have been required in many cases, substrates have been limited, and there is room for improvement as a practical asymmetric synthesis. To address these issues, we have developed catalytic asymmetric reactions that can be carried out in the presence of water under mild conditions. In this report, we describe catalytic asymmetric Mukaiyama aldol reactions that can be applied to a wide scope of substrates, in aqueous solutions at $0\text{ }^{\circ}\text{C}$.

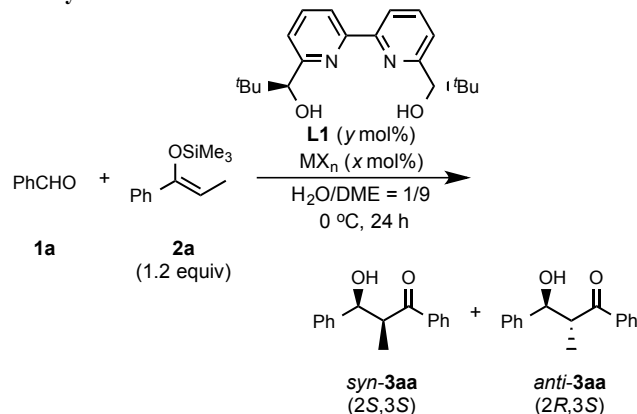
Results and Discussion

1. Evaluation of Lewis Acids with a Chiral 2,2'-Bipyridine Ligand. To attain catalytic asymmetric Mukaiyama aldol reactions in aqueous solutions,^[12] development of water-compatible Lewis acids^[13] is required. We have already discovered a series of water-compatible Lewis acids and found suitable factors including hydrolysis constant and water-exchange rate constant^[14] for estimating their catalytic activities, by which these Lewis acids were systematically classified.^[15] We have also clarified that while conventional monodentate, bidentate, and sometimes tridentate ligands have been used in asymmetric catalysis in organic solvents, tetradentate or higher multidentate ligands are effective for creating chiral water-compatible Lewis acids.^{[16],[17]} Among them, optically active bipyridine ligand **L1**^[18] developed by Bolm was found to be a particularly excellent ligand.^[19] In 2004, the first use of **L1** in aqueous solvents combined with Sc(III) as a chiral water-compatible Lewis acid was reported in asymmetric hydroxymethylation of silicon enolates.^[20] After this report, Bi(III)-**L1**,^{[21],[22]} Cu(II)-**L1**,^{[22],[23]} Zn(II)-**L1**,^{[22],[22b],[24]} etc. were shown to be effective chiral Lewis acids in aqueous solvents, and enantioselective hydroxymethylation reactions,^{[20],[21],[25]} ring-opening reactions of *meso*-epoxides,^{[22],[23],[26],[27]} Nazarov cyclizations,^[28] α -alkyl- or α -chloroallylation of aldehyde,^[24] etc. have been developed.

To find the best chiral Lewis acid catalyst in the Mukaiyama aldol reaction based on this background, we first examined the reaction of benzaldehyde **1** with propiophenone-derived silicon enolate **2a** in the presence of 10 mol% of Lewis acid and 12 mol% of **L1** (System A) or in the presence of 3 mol% of Lewis acid and 9 mol% of **L1** (System B) in aqueous media. The screening data are summarized in Tables S-1a and 1b (see Supporting Information). Previous studies exploring organic reactions in water proved that the generation of naked metal cations is crucial for attainment of high Lewis acidity in an aqueous environment. Therefore, metal trifluoromethanesulfonates (triflates) or metal perchlorates were chosen as Lewis acids. From the screening data, selected examples are shown in Table 1. Relatively high enantioselectivities were obtained by using Al(III), Sc(III), Fe(II), Cu(II), Cd(II), Sn(II), Yb(III), Lu(III), Hg(II), Pb(II), and Bi(III).^[29] However, the yields were low using Al(III) and Cu(II) in both System A and B. As for Cd(II) and Pb(II), relatively high enantioselectivities were observed for only minor diastereomers. While System A gave higher enantioselectivities for Yb(III) and Hg(II), System B showed higher enantioselectivities for Sc(III), Fe(II), and Sn(II). Both System A and B showed high enantioselectivities for Lu(III) and Bi(III). Among them, it is noted that Bi(III) showed very high selectivities (*syn/anti* = $>99/<1$, 91% enantiomeric excess (ee) (*syn*)) in System B. Moreover, while no reaction occurred using Fe(II) in System A, an outstanding level of product yield and promising selectivity (70%

yield, diastereoselectivity ratio (dr) 97/3, 75% ee (*syn*)) were obtained in System B. Regarding ionic radii of various six-coordinated metal cations (Table S-2), these results have shown that chiral 2,2'-bipyridine **L1** formed complexes with a wide variety of metal cations; ionic radii of those cations have a minimum of 53.5 pm (Al(III)) and a maximum of 119 pm (Pb(II)).

Table 1. Evaluation of Lewis Acid Catalysis in the Asymmetric Mukaiyama Aldol Reaction.



Entry	Metal Salt	<i>x/y</i>	Yield (%) ^a	Dr (<i>syn/anti</i>) ^b	Ee (%) ^c
1	Al(OTf) ₃	10/12	4	61/39	-51/3
2		3/9	5	73/27	-7/1
3	Sc(OTf) ₃	10/12	52	64/36	24/1
4		3/9	23	80/20	59/4
5	Fe(OTf) ₂	10/12	NR	—	—
6		3/9	70	97/3	75/43
7	Cu(OTf) ₂	10/12	8	82/18	-41/4
8		3/9	5	88/12	-57/0
9	Cd(OTf) ₂	10/12	11	89/11	3/13
10		3/9	36	88/12	-32/66
11	Sn(OTf) ₂	10/12	14	84/16	1/22
12		3/9	5	85/15	75/6
13	Yb(OTf) ₃	10/12	66	79/21	60/23
14		3/9	63	76/24	38/28
15	Lu(OTf) ₃	10/12	55	79/21	62/6
16		3/9	19	81/19	53/9
17	Hg(OTf) ₂	10/12	27	98/2	66/77
18		3/9	2	49/51	-5/4
19	Pb(ClO ₄) ₂	10/12	28	89/11	-32/78
20		3/9	22	90/10	-1/25
21	Bi(OTf) ₃	10/12	10	95/5	69/17
22		3/9	17	$>99/<1$	91/31

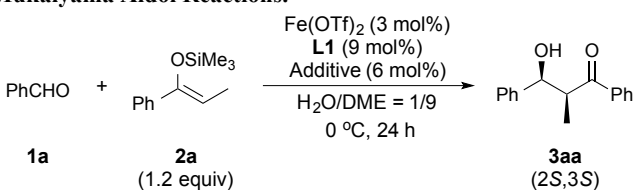
^a Yield of isolated product. ^b Determined by ¹H NMR analysis. ^c Determined by HPLC analysis. Minus value shows reverse enantioselectivity.

2. Identification of Optimal Conditions and Catalysts. In addition to Sc(III) and Bi(III) catalyses developed hitherto in enantioselective hydroxymethylation, Fe(II) catalysis seemed to be a promising candidate.

Several additives were examined in the presence of 3 mol% of Fe(OTf)₂ and 9 mol% of **L1** (Table 2). The amount of additive was set to 6 mol%. Acetic acid and benzoic acid were found to be effective additives for Lewis acid catalysis (entries 2, 6). Strong acids such as TfOH or *p*-toluenesulfonic acid (TsOH), however, impeded the function of the catalyst that operated the precise stereocontrol (entries 3, 5). It is interesting that a significant enhancement of enantioselectivity was also observed in the presence of a Brønsted base (entries 7, 8). To gain more insight into the

interaction between Fe(II) and an additive, several pyridine derivatives were examined. Slowing down of the reaction rate and a higher level of enantioselectivity were brought about in the presence of a less hindered base, especially α -substituted pyridines (entries 9, 10). Coordinative substituents should also be avoided to obtain higher selectivity (entries 11, 12). 2,6-Lutidine used as an additive afforded the aldol adduct in a high enantiomeric manner (entry 13). On the other hand, enantioselectivity of the desired aldol adduct was unaffected by the use of strongly hindered bases (entries 14–16). An interesting influence on enantioselectivity was observed when using imidazole and *N*-methylimidazole, presumably because of competitive coordination to Fe(II) with the chiral ligand (entries 17, 18). Such unprecedented assistance of these additives in Lewis acid catalysis intrigued us, whether they are Brønsted acids or bases. Regardless of their nature, all additives exhibited the best performance when employed at 6 mol%, twice the amount of Fe(OTf)₂.

Table 2. Effect of Additives in Chiral Fe(II)-Catalyzed Mukaiyama Aldol Reactions.



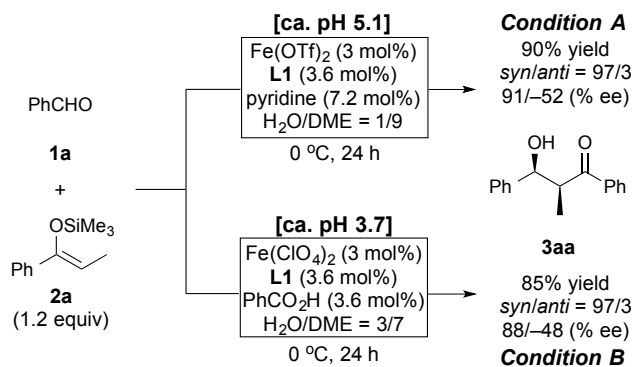
Entry	Additive	Yield (%) ^a	Dr (<i>syn/anti</i>) ^b	Ee (%) ^c
1	–	70	97/3	75/43
2	AcOH	70	98/2	89/13
3	TfOH	21	98/2	25/6
4	PhOH	37	98/2	83/0
5	TsOH	13	98/2	15/12
6	PhCO ₂ H	71	97/3	88/16
7	2,2'-Bipyridyl	76	97/3	86/26
8	R = H	68	97/3	91/–48
9	R = Me	27	97/3	93/–9
10	R = Et	31	97/3	92/–33
11	R = CH ₂ OH	46	95/5	7/7
12	R = OMe	60	98/2	77/14
13	2,6-Lutidine	18	98/2	91/19
14	2,6-Diphenylpyridine	58	97/3	76/39
15	R = H	69	97/3	77/38
16	R = Me	67	98/2	77/28
17	Imidazole	7	85/15	0/0
18	<i>N</i> -Me-Imidazole	26	97/3	73/–31

^a Yield of isolated product. ^b Determined by ¹H NMR analysis.

^c Determined by HPLC analysis.

Intensive investigations on the optimization of the reaction conditions (Table S-3) led to the discovery of two distinct catalytic systems, respectively including a Brønsted base (pyridine, defined as **Condition A**) and an acid (benzoic acid, defined as **Condition B**)^[30] (Scheme 1). These additives, in spite of their antithetic nature, could assist Lewis-acid catalysis exerted by a chiral Fe(II) complex formed with **L1** to afford the product in a higher enantioselective manner in an aqueous environment, which shows that this powerful assistance cannot be explained by the adjustment of the pH value in the reaction solution.

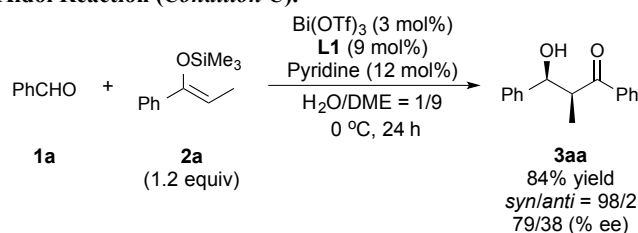
Scheme 1. The Optimal Conditions for the Fe(II)-Catalyzed Mukaiyama Aldol Reaction.



The acidity of these ternary catalytic solutions was manifested by the statistically robust measurement of pH value in these catalytic systems. The Pourbaix diagram, calculated from the redox potentials of various iron species and water using the Nernst equation and hydrolysis constants (Figure S-1), shows that Fe(II) is clearly the active species in these catalytic systems. Indeed, Fe(III) exhibited inferior performance in Table S-1b.

The superb performance of Bi(III) catalysis exhibited in asymmetric hydroxymethylation^[21] also led us to harbor expectations about the further evolution of this catalytic system to enlarge the substrate generality.^[31] Furthermore, the availability of bismuth because of its affordability, abundance, and ubiquity is comparable to that of iron. The reaction proceeded smoothly in the presence of a Brønsted base to afford the product with the same level of enantioselectivity. The best performance was displayed when 12 mol% of pyridine was added to 3 mol% of a chiral Bi(III) complex formed with threefold excess of **L1** (Scheme 2).

Scheme 2. The Conditions for the Bi(III)-Catalyzed Mukaiyama Aldol Reaction (Condition C).

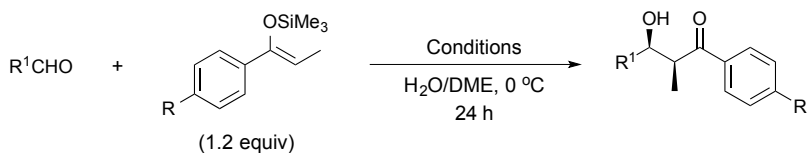


3. Substrate Generality. The substrate generality was evaluated under the optimized reaction conditions. The intriguing assistance by two distinct additives suggested the possibility that the careful selection of additives could enlarge the substrate generality. Based on such a perspective, a general tendency was investigated with regard to the correlation between an effective additive and a substrate (Table 3). It was found that the pyridine additive was more effective in the Mukaiyama aldol reaction of **1a** with **2a** (entry 1). Electronic effects resulting from the substituents on the aromatic ring of **2a** were surveyed. An electron-donating group (OMe) (**2b**) resulted in a definite drop in the reaction rate. Extending the reaction time allowed almost complete consumption of an aldehyde to afford the product **3ab** with excellent diastereo- and enantioselectivities in the presence of pyridine. However, the reaction hardly proceeded when benzoic acid was employed as the additive (entry 2). An electron-donating group on the aromatic ring might contribute to the stabilization of the O–Si bond of the silicon enolate, thus slowing the rate of hydrolysis after the nucleophilic attack. The substitution with an electron-withdrawing group led to an imperceptible decrease in the reaction rate. Addition of pyridine affected the enantioselectivity of the product, irrespective of the substituent on the aromatic ring (entries 1–3). However, the reaction of 4-

fluorobenzaldehyde **1d** or 1-naphthaldehyde **1f** proceeded in a higher enantioselective manner when benzoic acid was used as an additive (entries 4, 5). The optimal conditions could be applied to aliphatic aldehydes, which are often poor electrophiles for Lewis acid-mediated asymmetric processes because of both electronic and steric difficulties in enantiofacial differentiation. It is interesting that the reaction of **1h** and **1n** proceeded very smoothly to afford the desired products in high yields with high selectivities when pyridine was used as an additive (entries 6, 7). It was also confirmed that the

use of Fe(II) perchlorate instead of triflate, changing the water-dimethoxyethane (DME) ratio to 3/7, and the use of benzoic acid instead of pyridine retarded the catalytic turnover. On the other hand, the use of benzoic acid as an additive showed superior performance in the reaction of thiophenecarboxaldehyde **1i** and α,β -unsaturated aldehydes **1l** and **1m** (entries 7–9). Based on these tendencies, we continued to examine the substrate generality of aldehydes and silicon enolates.

Table 3. Effect of Additives on Substrate Scope.

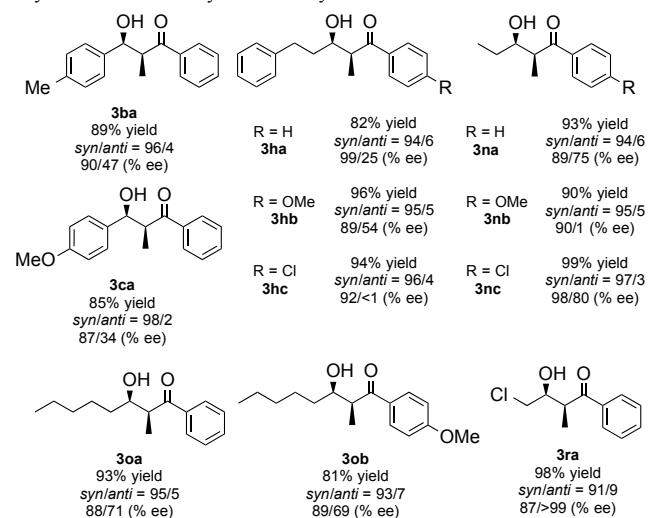
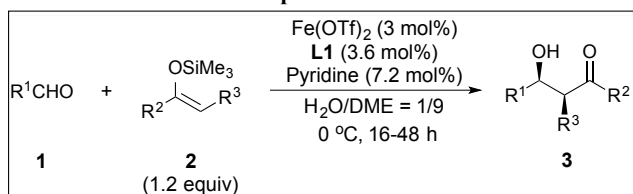


Entry	R ¹	Silicon Enolate R		Condition ^a	Yield (%) ^b	Dr (syn/anti) ^c	Ee (%) ^d	
1	Ph	1a	H	2a	A	90 (3aa)	97/3	91/52
					B	85	97/3	88/48
2	Ph	1a	OMe	2b	A ^e	91 (3ab)	97/3	85/21
					B	6	>99/<1	49/nd
3	Ph	1a	Cl	2c	A ^f	87 (3ac)	93/7	89/66
					B	70	95/5	65/40
4	4-FC ₆ H ₄	1d	H	2a	A	76 (3da)	92/8	65/33
					B	99	96/4	89/39
5	Naphthyl	1f	H	2a	A	55 (3fa)	98/2	88/82
					B	Quant.	96/4	91/40
6	PhCH ₂ CH ₂	1h	H	2a	A	82 (3ha)	94/6	99/25
					B	75	94/6	96/25
7	2-C ₄ H ₃ S	1i	H	2a	A	1 (3ia)	–	–
					B	70	98/2	91/31
8	CH ₂ =CH	1l	H	2a	A ^e	41 (3la)	86/14	75/28
					B ^e	54	95/5	75/30
9	PhCH ₂ =CH	1m	H	2a	A	82 (3ma)	88/12	84/61
					B ^f	94	88/12	95/73
10	CH ₃ CH ₂	1n	H	2a	A	93 (3na)	94/6	90/75
					B	71	87/13	66/37

^a Condition A: Fe(OTf)₂ (3 mol%), **L1** (3.6 mol%), Pyridine (7.2 mol%), H₂O/DME = 1/9. Condition B: Fe(ClO₄)₂ (3 mol%), **L1** (3.6 mol%), PhCO₂H (3.6 mol%), H₂O/DME = 3/7. ^b Yield of isolated product. ^c Determined by ¹H NMR analysis. ^d Determined by HPLC analysis. ^e For 48 h. ^f For 36 h.

Condition A. It was found that the pyridine additive was generally more effective in the Mukaiyama aldol reaction. Condition A was thus set as the standard condition in the initial substrate survey (Scheme 3). The addition of pyridine affected the enantioselectivity of the product, irrespective of the substituents on the aromatic ring in silicon enolates. Not only aliphatic aldehydes (**1h**, **1n**, **1o**, and **1r**) but also aromatic aldehydes bearing electron-donating groups (**1b** and **1c**) reacted with silicon enolates in a highly stereoselective manner.

Scheme 3. Substrate Scope – Condition A.

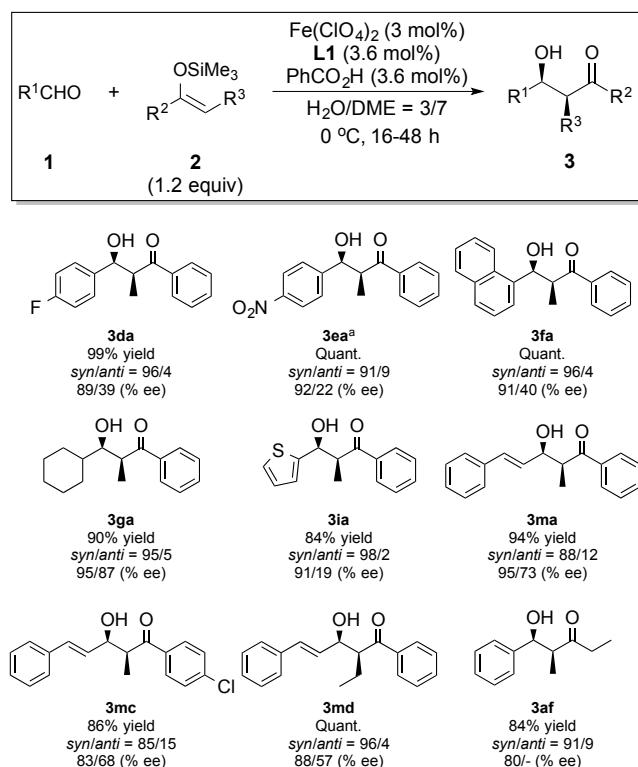


^a DTBP (3 equiv) was added.

Condition B. When benzoic acid was employed as an additive, a superior effect was obtained in the reactions of electron-deficient aromatic aldehydes (**1d**, **1e**, **1f**), secondary aliphatic aldehyde **1g**, thiophenecarboxaldehyde **1i**, and α,β -unsaturated aldehyde **1m** (Scheme 4). Introduction of an electron-withdrawing (chloro) group on the aromatic ring in the silicon enolate led to a slightly lower but satisfactory level of selectivity in high yield (**3mc**). The combination

of Fe(II) and benzoic acid could also be applied to the reaction of **1a** with the silicon enolate derived from 3-pentanone (**2f**).^[32]

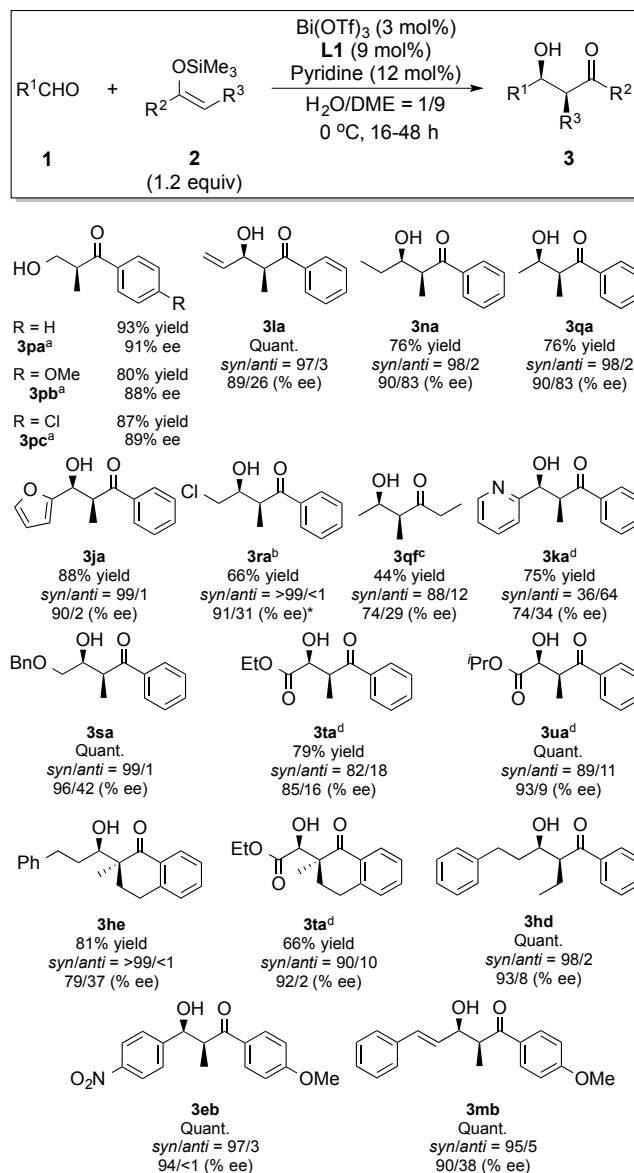
Scheme 4. Substrate Scope – Condition B.



^a Fe(ClO₄)₂ (3 mol%), L1 (9 mol%), PhCO₂H (3.6 mol%).

Condition C. Chiral Bi(III) catalyst (defined as **Condition C**) was also found to be an attractive choice as an alternative toolbox for asymmetric Mukaiyama aldol reactions (Scheme 5). In a previous report on Bi(III)-catalyzed asymmetric hydroxymethylation,^[21] 2,2'-bipyridyl was selected as an effective additive. In that system, only a trace amount of product was obtained using Bi(OTf)₃ without L1, presumably because of the rapid decomposition of silicon enolates promoted by TfOH generated readily from Bi(OTf)₃ in water. Water-soluble aldehydes such as aqueous formaldehyde **1p**, acrolein **1l**, etc., reacted with silicon enolates to afford the corresponding aldol adducts in high yields with high enantioselectivities. The aldol reaction of acetaldehyde **1q** is regarded as difficult because acetaldehyde has high reactivity as both a nucleophile and an electrophile, causing a self-aldol reaction. Therefore, until recently, no asymmetric reactions using acetaldehyde have been reported.^[33] The chiral Bi(III) complex catalyzed the reaction of **1q** with **2a** to afford the desired product in good yield with high diastereo- and enantioselectivities. The Bi(III) complex was also applicable to the reactions of aldehydes bearing functional groups (**1j**, **1k**, **1s**, **1t**, and **1u**). It is noteworthy that asymmetric quaternary carbons were constructed with high selectivities. Silicon enolate **2b** bearing an electron-donating group was not applicable to **Condition B**, whereas the chiral Bi(III) complex catalyzed the reactions with **2b** in high yields with high selectivities.

Scheme 5. Substrate Scope – Condition C.

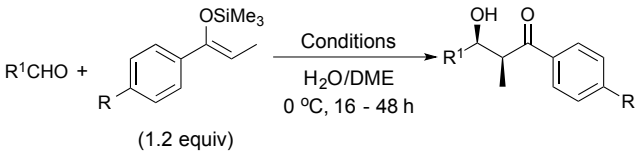


^a Bi(OTf)₃ (1 mol%), L1 (3 mol%), 2,2'-bipyridyl (5 mol%), in H₂O/DME = 1/4. See ref. [21]. ^b DTBP (3 equiv.) was added. ^c Sc(OTf)₃ (10 mol%), L1 (12 mol%). ^d Without pyridine.

The effect of choice of ternary catalytic systems and the substituent effects obtained are summarized in Table 4. It is noted that introduction of electron-withdrawing groups on the aromatic ring in the structure of benzaldehyde preferred **Condition B** as the best condition. In contrast, electron-donating aromatic aldehydes preferred **Condition A**, indicating that the difference between pyridine and benzoic acid as the additive may lie in electronic effects through coordination with Fe(II). The substituents on the aromatic ring in the structure of the propiophenone-derived silicon enolates affected neither reactivity nor selectivity, except for **Condition B**. The reaction with butyrophenone-derived silicon enolate, which led to a significant loss in enantioselectivity in the presence of a chiral gallium catalyst with a Trost-type ligand,^[34] also led to an excellent result. Introduction of a methoxy group on the aromatic ring of the silicon enolate led to a significant drop in both reactivity and stereoselectivity under **Condition B**, whereas the reaction proceeded quantitatively to afford the product with excellent selectivities under **Condition C** (e.g., **3eb**, **3mb**). In addition, **Condition C** was effective for the reaction of less bulky aldehydes, including water-soluble aldehydes as well as aldehydes

that can chelate with metals. Stereoselective construction of asymmetric quaternary carbons was also displayed.

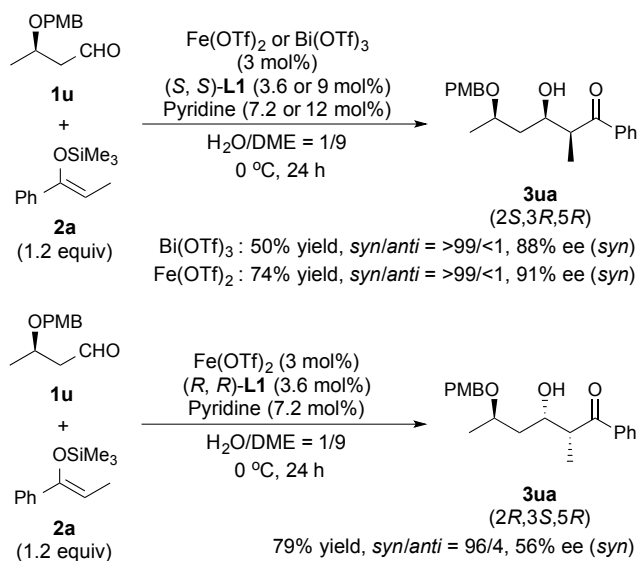
Table 4. Tendency on Correlation among Aldehydes, Aromatic Ketone-Derived Silicon Enolates, and Catalytic Systems.



R	Aldehyde (R ¹ CHO)		
	More Bulky	Electron-rich	Electron-poor
H	Condition A	Condition B	Condition C
OMe (ED)	Condition A	Condition C	Condition C
Cl (EW)	Condition A	Condition B	Condition C

The reaction of a chiral β -alkoxy aldehyde bearing potential directing ability was surveyed to offer a rationale for the stereocontrol (Scheme 6). Exposure of aldehyde **1u** and silicon enolate **2a** to the chiral Bi(III) complex formed with (*S,S*)-**L1** exhibited exclusive diastereofacial preference with high enantioselectivity. The use of Fe(II) instead of Bi(III) improved the reactivity with a high level of stereoselection. In contrast, the “mismatched” case using (*R,R*)-**L1** resulted in lower enantioselectivity, albeit the same level of yield and *syn*-selectivity because of the chelation.

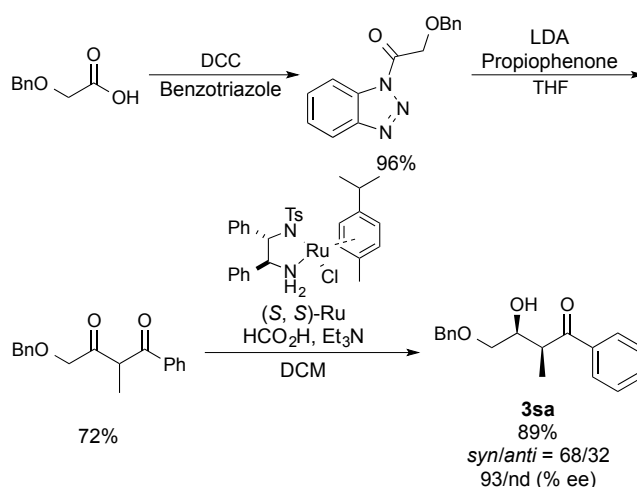
Scheme 6. Match/Mismatch Effect.



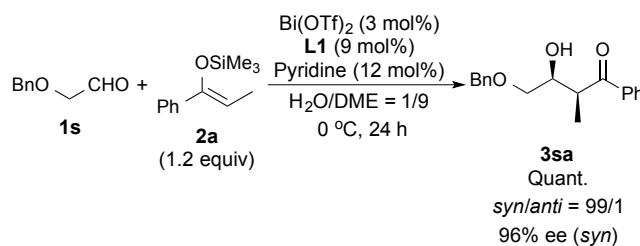
The Mukaiyama aldol reaction of benzyloxyacetaldehyde with **2a** was then carried out using the optimal catalytic systems. The desired aldol adduct is known to be a key intermediate in the total synthesis of various natural compounds. For instance, the total synthesis of bafilomycin A₁, an inhibitor of vacuolar H⁺-ATPase *in vitro*, entailed three steps to control the stereogenic centers.^[35] In the conventional method (Scheme 7), 2-(benzyloxy)acetic acid was treated with benzotriazole in the presence of DCC. The lithium enolate of propiophenone was then added to afford the desired diketone, which was reduced under asymmetric transfer hydrogenation conditions with a chiral ruthenium complex to afford the desired β -hydroxyketone with a dr of 68/32 in a total 62% yield (three steps). The major isomer was formed with an ee of 93%. On the other hand, in the Mukaiyama aldol reaction, employment of the chiral Bi(III) catalyst (3 mol%) led to the best result; the reaction

proceeded quantitatively with excellent diastereo- and enantioselectivities (Scheme 8). The utility of this aldol process is obvious, even considering the preparation of the silicon enolate and chiral 2,2'-bipyridine **L1**.^[36]

Scheme 7. Conventional Synthesis of β -Hydroxyketone.^[35]



Scheme 8. Bismuth-Mediated Synthetic Methodology for β -Hydroxyketone.

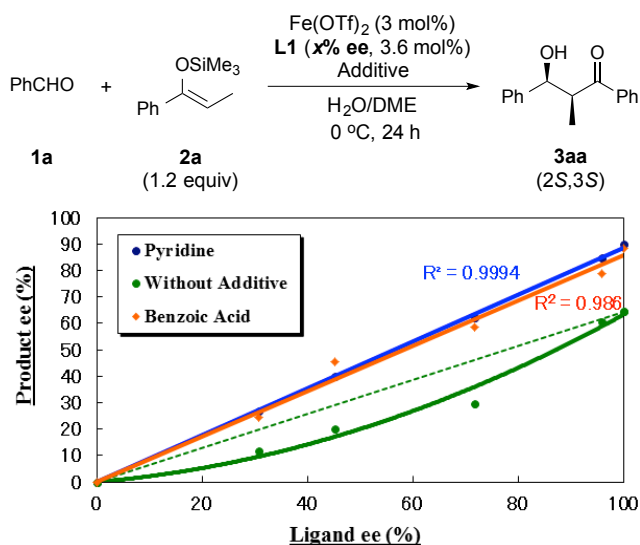


4. Reaction Mechanism.

4.1. Coordination Environments around the Metals. The complex formed with Fe(II) salt and **L1**, reported in 2012,^[30] adopts a pentagonal bipyramidal structure, where the tetradentate ligand occupies four of the equatorial sites. It resembles that of the corresponding Sc(III) and Bi(III) complexes (For X-ray structures, see Figure S-2). Several examples^[37] of a hepta-coordination mode of Fe(II) ion were reported, and X-ray crystals of three kinds of Fe(II)-**L1** complexes^[38] were obtained, all showing hepta-coordination. Thermogravimetric analyses implied that the chiral complex could behave in a hepta-coordination fashion under the reaction conditions.^[39] Apical binding of an aldehyde is favored because of its lower basicity and its ability to form stereoelectronically favored hydrogen bonding with the alcohol moieties of **L1** and the relatively greater trans effect of the pyridine ligand.^[40] The dependence on the choice of an additive on the electronic nature of the aldehydes indicates the coordination of an additive to the Fe(II) center. On the other hand, the behavior of Bi(III) as a naked cation is inferred from the fact that 2,6-di-*tert*-pyridine, a proton scavenger, could be an efficient additive. To obtain fundamental insights into the catalyst structure, a model reaction of **1a** with **2a** was carried out in the presence of enantiomerically impure 2,2'-bipyridine **L1**, and the results are shown in Figure 1. While negative nonlinear effects were observed in the absence of additive, the nonlinearity disappeared in the presence of additive. Since subtle erosion of enantioselectivity in product **3aa** was observed in the absence of additive, the observations may be rationalized by the changes in the catalyst structure from a dimeric or oligomeric form without the additive to a monomeric form with the additive, which might be an actual

catalytic species that resulted in high enantioselectivity and reactivity.

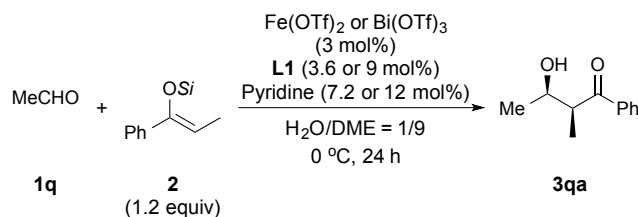
Figure 1. Nonlinear Experiments.



2.4.2. Effect of Additives. To gain insight into the catalyst structures, the reaction solution was directly subjected to several spectrometric investigations. The chiral Fe(II) complex formed with **L1** did not give rise to massive changes in the NMR analysis, in contradiction to chiral Sc(III) and Bi(III) complexes. Likewise, changes using an additive were not observed through NMR or UV-vis analyses. Meanwhile, ESI-MS experiments could shed light on the differences (Figure S-3). In the absence of an additive, two types of mono-Fe(II) complexes, $[\text{Fe}^{\text{II}}(\text{L1})(\text{OTf})(\text{DME})]^+$ and $[\text{Fe}^{\text{II}}(\text{L1})(\text{OTf})]^+$ were observed. One is coordinated by a DME molecule, and the other is not. Some amounts of an Fe(II) complex composed of two molecules of the chiral ligand were also identified. When pyridine was used as the additive, the triflate anion was not identified as a counter anion. Instead of triflate, the formation of hydroxide $[\text{Fe}^{\text{II}}(\text{L1})(\text{OH})]^+$ was verified. The major peak corresponded to Fe(II) benzoate complex $[\text{Fe}^{\text{II}}(\text{L1})(\text{O}_2\text{CPh})]^+$ formed with **L1**. The surroundings around Bi(III), known to be dependent upon the metal-to-ligand ratio, were also proved to be a naked cation without any ligand, as mentioned above (Figure S-3).^[20b]

Because of the ability of silicon atoms to adopt higher coordination states, promoting the Mukaiyama aldol reaction under basic conditions is known to be possible.^[41] In that sense, an additive can function as a Lewis base in our catalytic systems. To examine whether a nucleophilic attack takes place at silicon or not, the Mukaiyama aldol reaction using dimethylsilyl enol ether was carried out (Table 5). Throughout the enhancement of the reaction rate, an almost quantitative amount of the product was obtained under **Condition A**, while it also led to a significant drop in selectivity. In the case of the chiral Bi(III) catalyst, it was found that the enantioselectivity remained definitely at the same level; however, the reactivity was not enhanced at all. These results imply some involvement of silicon enolate activation by a Lewis base in the Fe(II)-catalyzed mechanism and no or very little involvement in the Bi(III)-catalyzed mechanism. In the latter case, the pyridine additive is assumed to be swamped with the elimination of in situ-generated triflic acid.

Table 5. Effect of Silicon Enolate.

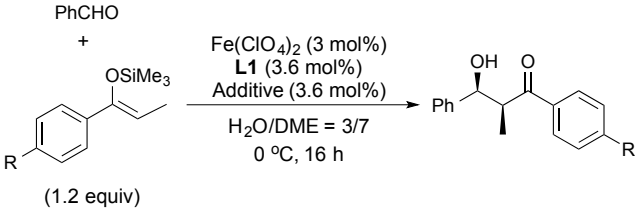


	<i>Si</i> = SiMe ₃	<i>Si</i> = SiMe ₂ H
Condition A [Fe(OTf) ₂]	72% yield <i>syn/anti</i> = 93/7 74% ee (<i>syn</i>)	95% yield <i>syn/anti</i> = 84/16 28% ee (<i>syn</i>)
Condition C [Bi(OTf) ₃]	76% yield <i>syn/anti</i> = 98/2 90% ee (<i>syn</i>)	70% yield <i>syn/anti</i> = 96/4 90% ee (<i>syn</i>)

As for the role of benzoate anion as a Lewis base, the electronic effect on the additive was investigated (Table 6). When 4-methoxybenzoic acid was used as the additive, the reaction proceeded smoothly to provide almost the same results as those using benzoic acid. In contrast, in the case of 4-nitrobenzoic acid, both the reaction yield and the enantioselectivity suffered from a significant drop. The enantioselectivity of the *syn* isomer was almost the same level as that in the absence of any additive. As mentioned above, the substituents on the aromatic ring in the structure of silicon enolates significantly affected the reactivity and the selectivity. Similarly, Mukaiyama et al. reported that 10 mol% of metal carboxylate could function as a Lewis base catalyst to mediate the reaction between benzaldehyde and a ketene silyl acetal at -45 °C in DMF/H₂O = 50/1.^[42] They assumed that the role of the carboxylate in the catalytic cycle was the formation of a lithium aldolate via a hexa-coordinated hypervalent silicate, which underwent rapid hydrolysis and subsequent neutralization to regenerate the lithium acetate catalyst. The dependence of reactivity on the electrophilicity of aldehydes supports their hypothesis in accord with the results shown in Table 6.

Ligand field theory is helpful for deepening our understanding of the effect of additives. The donation of electrons by σ -donor ligands to *d* orbitals and some weak bonding and antibonding interactions with *s* and *p* orbitals of Fe(II) is plausible. Compared with nonbonding orbitals consisting of *d*_{xz} and *d*_{yz}, the antibonding orbitals between 4*s*, 4*p*, *d*_{xy}, and *d*_{x²-y²}, and between 4*s*, 4*p*_z, and *d*_{z²} become destabilized. When pyridine was used as an additive, the OH ligand at an equatorial position or pyridine at an apical position makes the former bonding orbital unstable and the latter stable. The consequent spin transition in the HOMO orbital overcomes the deactivation by the coordination of a Lewis base,^[43] and the lower HOMO destabilizes the π^* orbital of aldehydes. Given the intriguing equilibrium shift observed in the case of Sc-**L1** complex,^[44] the stabilization of the pentagonal bipyramidal structure even in an aqueous environment is expected. In contrast, bidentate coordination of benzoate anion to iron makes the latter unstable. The resultant HOMO-LUMO gaps between aldehydes and silicon enolates correspond to the experimental tendencies shown in Table 4. The strength of interactions between iron and both substrates governs the stereoselectivities on the assumption of some interaction between iron and the π -orbital of silicon enolates.^[45]

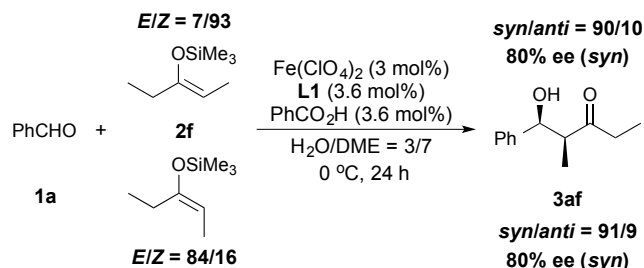
Thus, there are two functions for the additives in the Fe(II) complexes: coordination to Fe(II) ion and coordination to the silicon of silicon enolates for activation.^[46] Two kinds of additives can regulate the balance between the two interactions to afford the desired aldol adducts in high yields with high diastereo- and enantioselectivities. On the other hand, Lewis base additive is consumed for scavenging in situ-formed TfOH in the case of the Bi(III) complex.

Table 6. Effect of Silicon Enolate.


Entry	R	Additive	Yield (%) ^a	Dr (<i>syn/anti</i>) ^b	Ee (%) ^c
1	H	–	70	97/3	75/43
2	H	PhCO ₂ H	85	97/3	88/48
3	H	PhCO ₂ K	NR	–	–
4	H	4-MeOC ₆ H ₄ CO ₂ H	80	97/3	84/43
5	H	4-NO ₂ C ₆ H ₄ CO ₂ H	52	96/4	73/47
6	MeO	PhCO ₂ H	6	97/3	49/nd
7	Cl	PhCO ₂ H	70	93/7	65/40

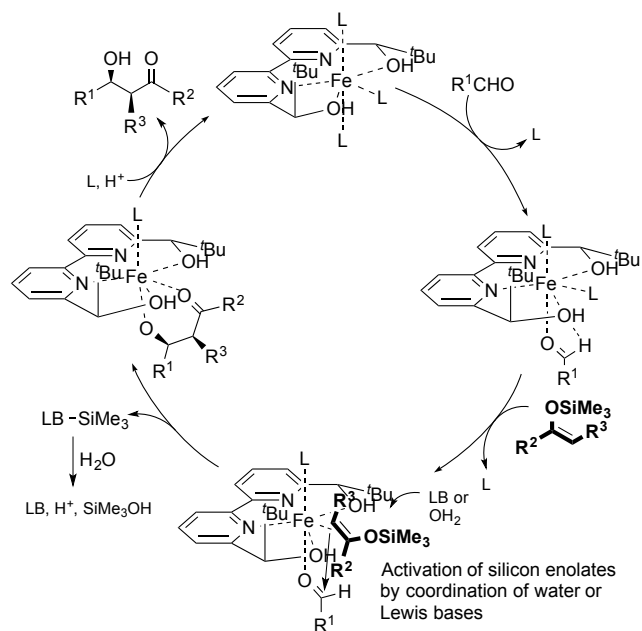
2.4.3. Reaction Pathways and Transition States. Three different mechanisms have been proposed for Mukaiyama aldol reactions: (1) Zimmerman–Traxler’s six-membered model;^[47] (2) the acyclic open transition state model, which involves antiperiplanar orientation of enolates and carbonyls;^[48] and (3) the transmetalation model, which involves transmetalation of the silicon of silicon enolates to the second metal of Lewis acids. An initial mechanistic hypothesis in Mukaiyama’s landmark report in 1973 involved the formation of titanium enolate via transmetalation.^[11] Although the resulting titanium enolate was believed to react with an aldehyde to afford a stable titanium aldolate with *anti*-selectivity, no structural evidence could be supplied at that time. After that, the application of an INEPT (insensitive nuclei enhanced by polarization transfer) ²⁹Si NMR study was emphatic in disproving the transmetalation.^[49] Nevertheless, the reactions of preisolated titanium enolates with aldehydes were amazingly *syn*-selective.^[50] On the other hand, the closed transition state hypothesis was underscored by computational chemistry, and a six-membered transition state model that does not involve transmetalation was also proposed.^[51] To date, the actual mechanism has not been determined conclusively.

While all of these mechanistic works have been carried out in organic solvents, the kinetics for a hydroxymethylation reaction using aqueous formaldehyde with **2a** in the presence of Sc-**L1** complex was examined in 2011.^[52] In consequence, a first-order dependence of both **2a** and the chiral catalyst was recorded, which ruled out the possibility of the transmetalation mechanism. The acyclic open transition state model is more suitable when the reaction is performed in an aqueous environment, because water can disturb a weak interaction between metals and the oxygen atom of silicon enolates. A direct comparison on the effect of enolate geometry was conducted using (*E*)- and (*Z*)-silyl enolates derived from 3-pentanone under the Fe(II)-catalyzed conditions (Scheme 9). It was found that both (*E*)- and (*Z*)-enolates gave *syn*-aldol adducts, which also supports the acyclic open transition state model. The independence of stereochemistry from enolate geometry was also confirmed in the case of the chiral Bi(III) complex (**Condition C**).

Scheme 9. Correlation between Stereochemical Outcome and Enolate Geometry.

A plausible catalytic cycle for this Mukaiyama aldol reaction in aqueous media is shown in Scheme 10. An aldehyde coordinates to the pentagonal bipyramidal Fe(II) consisting of Fe(II), **L1**, and an additive in the axial position. One of the ligands, pyridine, benzoic acid, or water, may be replaced by the aldehyde. Water coordinated with Fe(II) is willing to exchange and may help the replacement. One face of the aldehyde is shielded by the *t*-butyl group of **L1**.^[53] A silicon enolate then attacks the aldehyde via an antiperiplanar acyclic transition state. Water also plays a key role here to coordinate to the silicon of the silicon enolate to assist the reaction. The additive, pyridine or benzoic acid, is also suggested to play the same role (**Condition A**, **Condition B**). In the Bi(III)-catalyzed reaction (**Condition C**), it was shown that the coordination of pyridine to the silicon atom was not significant; however, water coordination was assumed to be crucial there. Carbon–carbon bond formation then occurred with high diastereo- and enantioselectivities, and the resulting Fe(II) alkoxide reacts with water to afford the desired aldol adduct along with regeneration of the Fe(II) catalyst. The silicon moiety is quenched with water to decrease Lewis acidity (Me₃Si–O–SiMe₃) to prevent undesired Si-catalyzed achiral pathways, which often reduce diastereo- and enantioselectivities in asymmetric Mukaiyama aldol reactions. It is noted that here water also plays an important role.^[54] In our reaction systems, water is a *sine qua non* for in situ generation of active species in the presence of pyridine or benzoic acid. Indeed, the reaction in DME in the absence of water did not lead to the formation of the desired aldol adduct.^[55] The higher the ratio of water to DME, the lower the reaction yield and the higher the observed diastereo- and enantioselectivity. The amount of water governs the stereochemical outcomes as well as the consequent catalytic turnover, although water is prone to destabilize silicon enolates through hydrolysis of metal complexes.^[56]

Scheme 10. Plausible Catalytic Cycle.



Conclusion

We have developed Fe(II)- and Bi(III)-catalyzed asymmetric Mukaiyama aldol reactions of silicon enolates with aldehydes. Three kinds of novel ternary catalytic systems consisting of Fe(II) or Bi(III), chiral bipyridine **L1**, and an additive have been exploited. While previous reactions often required relatively harsh conditions, such as strictly anhydrous conditions, very low temperature ($-78\text{ }^{\circ}\text{C}$), etc., the present reactions proceeded in the presence of water at $0\text{ }^{\circ}\text{C}$. A wide variety of silicon enolates and aldehydes reacted under these conditions to afford the desired aldol products in high yields with high diastereo- and enantioselectivities. The superiority of this methodology over conventional reactions has also been proved by high catalytic activity, simplicity of experimental procedures, wide substrate range including aqueous aldehydes that have been regarded to be difficult to govern the stereochemistry. Coordination environments around Fe(II) and Bi(III) and the effect of additives in the chiral catalysts have been elucidated by mechanistic studies. It is noted that both Brønsted acids and bases worked as efficient additives in Fe(II)-catalyzed reactions. The assumed catalytic cycle and transition states have clarified the important roles of water, a) producing the active metal complexes with high water-exchange rate constant (3.2×10^6) to activate substrates effectively and to catalyze the reaction via acyclic transition states, b) facilitating the catalytic turnover with simultaneous desilylation as direct access to aldol adducts or facile recovery of active metal complexes, and c) stabilizing rigid transition states composed of metal complexes and reactants through entropy-driven aggregation derived from its highest cohesive energy density (ced).^[57] Forty years after the discovery of the Mukaiyama aldol reaction, we have established a definitive catalytic asymmetric variant using Fe(II) and Bi(III) with chiral bipyridine **L1** in aqueous media.

Experimental Section

Typical Experimental Procedure for Mukaiyama Aldol Reaction of Silyl Enol Ethers with Various Aldehydes (Table 3, entry 1):

A mixture of $\text{Fe}(\text{OTf})_2$ (3.2 mg, 0.009 mmol), chiral 2,2'-bipyridine ligand (3.5 mg, 0.0108 mmol) and pyridine (1.6 mg, 0.0216 mmol) in 0.65 mL of degassed DME was stirred at room temperature for 30 min. The catalyst solution was then cooled at $0\text{ }^{\circ}\text{C}$ for 30 min and 70 μL of water was added. To the mixture were aldehyde **1a** and silyl enol ether **2a** added successfully. After stirred for 24 h at room temperature, the reaction mixture was quenched with satd. aqueous NaHCO_3 and brine. The aqueous layer was extracted with dichloromethane (three times), and the combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (elution: $^n\text{hexane}/\text{AcOEt} = 3/1$) to give the corresponding aldol **3aa** (64.0 mg, 90% yield) as colorless oil

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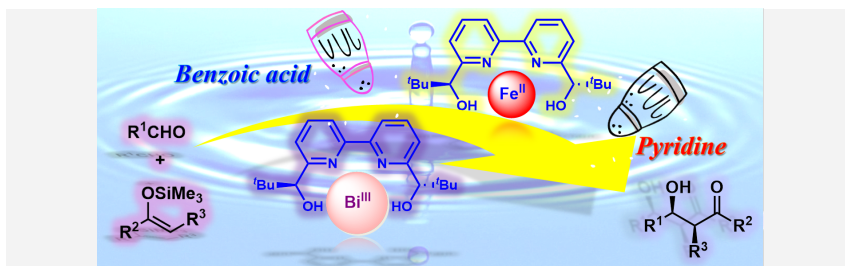
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Iron- and Bismuth-Catalyzed Asymmetric Mukaiyama Aldol Reactions in Aqueous Media



The ternary catalytic systems comprising the chiral ligand, metal salt (Fe^{II} or Bi^{III}) and an additive could enlarge the substrate generality complementarily as the foremost and distinguished catalyst for asymmetric Mukaiyama aldol reactions. A facile synthesis of chiral ligand can underscore its versatility.

The superiority of our methodology is also proved by the catalytic activity, simplicity of the experimental procedure, overwhelmingly wide substrate range covering even aqueous aldehydes which has been regarded to be difficult to govern the stereoselectivities.