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

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

Dedicated to Professor Teruaki Mukaiyama on the occasion 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 temperatures (−78 °C), etc., the reactions reported herein proceeded in the presence of water at 0 °C. To find appropriate chiral water-compatible Lewis acids for the Mukaiyama aldol reaction, many Lewis acids were screened in combination with chiral bipyridine **L1**, which had previously been found to be a suitable chiral ligand in aqueous media. Three types of chiral catalysts that consisted of a Fe^{II} or Bi^{III} metal salt, a chiral ligand (**L1**), and an additive have been discovered and a wide variety of substrates (silicon enolates and aldehydes) reacted to afford the desired aldol products in high yields with high diastereo- and enantioselectivities through an appropriate selection of one of the three catalytic systems. Mechanistic studies elucidated the coordination environments around the Fe^{II} and Bi^{III} centers and the effect of additives on the chiral catalysis. Notably, both Brønsted acids and bases worked as efficient additives in the Fe^{II}-catalyzed reactions. The assumed catalytic cycle and transition states indicated important roles of water in these efficient asymmetric Mukaiyama aldol reactions in aqueous media with the broadly applicable and versatile catalytic systems.

Keywords: aldol reaction · asymmetric catalysis · bismuth · C−C coupling · iron

Introduction

In 1973, Mukaiyama et al. reported a $TiCl_4$-mediated aldol reaction of silicon enolates (silyl enol ethers) with aldehydes.[1] In contrast to classical aldol reactions, which were carried out under basic conditions and led to various side reactions, such as isomerization (racemization), retro-reactions, over-reactions, and self-condensation of the aldehyde,[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." Indeed, this reaction has been applied to the syntheses of many natural products, pharmaceuticals, agricultural chemicals, functionalized materials, etc.

Catalytic asymmetric variants on the Mukaiyama aldol reaction were initiated in 1990 by using a chiral Sn^{II} Lewis acid catalyst[3] and the application of chiral boron,[4] titanium,[5] and zirconium[6] Lewis acids soon followed thereafter. Since then, many chiral Lewis acids have been developed for asymmetric Mukaiyama aldol reactions.[7] On the other hand, "direct-type aldol reactions" have been reported, in which the reactions did not proceed through a silicon enolate but rather through a ketone or a synthetic equivalent, which reacted as a nucleophile directly with the aldehyde.[8] Thus, whereas silicon enolates have to be prepared (isolated) from ketones by using stoichiometric amounts of the base and silicon source in Mukaiyama aldol reactions, direct-type reactions give the aldol adducts directly.[9] Therefore, from an atom-economical point of view, the latter process has an advantage. However, at this stage, nucleophiles that can be used in direct-type aldol reactions are limited to ketones and aldehydes; furthermore, there are few examples of such reactions with aromatic ketones or acyclic ketones.[10] Thus, the applicable substrates for direct-type aldol reactions are limited,[11] whereas silicon enolates that can be applied to the Mukaiyama aldol reaction are not only derived from ketones and aldehydes, but also from esters, amides, lactones, lactams, enones, unsaturated esters, unsaturated amides, and others. Therefore, from the standpoint of

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[a] T. Kitanosono, Prof. Dr. S. Kobayashi
Department of Chemistry, School of Science
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-0634
E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp

[b] Prof. Dr. T. Ollevier
Département de chimie
Université Laval
1045 avenue de la Médecine
Québec, G1V 0A6 (Canada)

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substrate scope, the Mukaiyama aldol reaction still has an advantage over the direct-type aldol reaction.

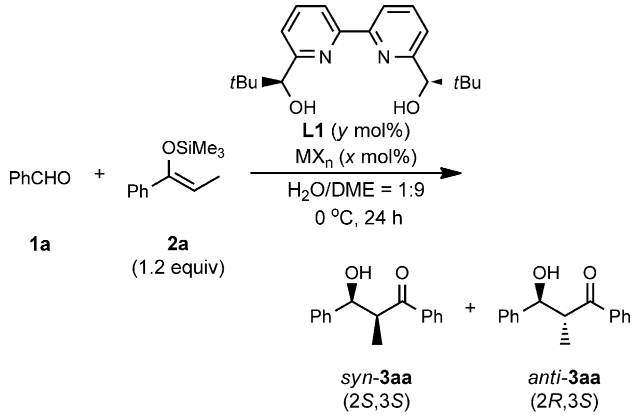
As mentioned above, although catalytic asymmetric Mukaiyama aldol reactions have been known since 1990,[3] relatively harsh conditions, such as strictly anhydrous conditions, very low temperatures (−78 °C), etc., have been required in many cases, the substrates that are tolerated have been limited, and there remains great 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. Herein, we describe catalytic asymmetric Mukaiyama aldol reactions that can be applied to a wide range of substrates in aqueous solutions at 0 °C.

Results and Discussion

Evaluation of the Lewis Acids with a Chiral 2,2′-Bipyridine Ligand

To perform catalytic asymmetric Mukaiyama aldol reactions in aqueous solution,[12] the development of water-compatible Lewis acids[13] is required. We have previously reported a series of water-compatible Lewis acids and determined suitable factors, including the hydrolysis constant and water-exchange rate constant,[14] for estimating their catalytic activities, by which these Lewis acids were systematically classified.[15] We also clarified that, whereas 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] as developed by Bolm et al., was found to be a particularly excellent ligand.[19] The first use of ligand **L1**, combined with Sc^{III} as a chiral water-compatible Lewis acid, in aqueous solvents was reported in 2004 in the asymmetric hydroxymethylation of silicon enolates.[20] Since that report, Bi^{III}/**L1**,[21,22] Cu^{II}/**L1**,[22,23] and Zn^{II}/**L1**[,22b,24] systems were shown to be effective chiral Lewis acids for enantioselective hydroxymethylation reactions,[20,21,25] ring-opening reactions of *meso*-epoxides,[22,23,26,27] Nazarov cyclization reactions,[28] and α-alkyl- or α-chloroallylation reactions of aldehydes[24] in aqueous solvents.

Table 1. Evaluation of Lewis acid catalysts in the asymmetric Mukaiyama aldol reaction.



Entry	System	Metal salt	x/y	Yield [%][a]	d.r. (*syn*/*anti*)[b]	*ee* [%][c]
1	A	Al(OTf)$_3$	10/12	4	61:39	−51/3
2	B		3/9	5	73:27	−7/1
3	A	Sc(OTf)$_3$	10/12	52	64:36	24/1
4	B		3/9	23	80:20	59/4
5	A	Fe(OTf)$_2$	10/12	NR	--	--
6	B		3/9	70	97:3	75/43
7	A	Cu(OTf)$_2$	10/12	8	82:18	−41/4
8	B		3/9	5	88:12	−57/0
9	A	Cd(OTf)$_2$	10/12	11	89:11	3/13
10	B		3/9	36	88:12	−32/66
11	A	Sn(OTf)$_2$	10/12	14	84:16	1/22
12	B		3/9	5	85:15	75/6
13	A	Yb(OTf)$_3$	10/12	66	79:21	60/23
14	B		3/9	63	76:24	38/28
15	A	Lu(OTf)$_3$	10/12	55	79:21	62/6
16	B		3/9	19	81:19	53/9
17	A	Hg(OTf)$_2$	10/12	27	98:2	66/77
18	B		3/9	2	49:51	−5/4
19	A	Pb(ClO$_4$)$_2$	10/12	28	89:11	−32/78
20	B		3/9	22	90:10	−1/25
21	A	Bi(OTf)$_3$	10/12	10	95:5	69/17
22	B		3/9	17	$>99:<1$	91/31

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis; minus values indicate opposite enantioselectivity. NR = no reaction.

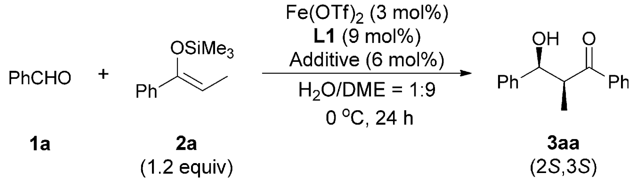
In this context, to find the best chiral Lewis acid catalyst for the Mukaiyama aldol reaction, we first examined the reaction of benzaldehyde **1** with propiophenone-derived silicon enolate **2a** in the presence of 10 mol % of the Lewis acid and 12 mol % of compound **L1** (system A) or in the presence of 3 mol % of the Lewis acid and 9 mol % of compound **L1** (system B) in aqueous media. The data are summarized in the Supporting Information, Tables S1 a, b (see the Supporting Information). Previous studies on organic reactions in water showed that the generation of naked metal cations was crucial for attaining high Lewis acidity in an aqueous environment. Therefore, metal trifluoromethanesulfonates (triflates) or metal perchlorates were chosen as Lewis acids. 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 by using Al^{III} and Cu^{II} in both systems A and B. For Cd^{II} and Pb^{II}, relatively high enantioselectivities were only observed for the minor diastereomers. Whereas 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}. Notably, Bi^{III} showed very high selectivities (*syn*/*anti* = $>99:<1$, 91 % *ee* (*syn*)) in system B. Moreover, whereas no reaction occurred by using Fe^{II} in system A, outstanding yield and promising selectivity (70 % yield, d.r. 97:3, 75 % *ee* (*syn*)) were obtained with system B. Regarding the ionic radii of various six-coordinate metal cations (see the Supporting Information, Table S2), these results showed that chiral 2,2′-bipyridine **L1** formed complexes with a wide variety of metal cations; the ionic radii of the cations were within the range 53.5 (Al^{III}) to 119 pm (Pb^{II}).

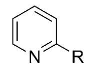
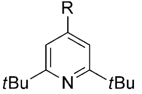
Identification of Optimal Conditions and Catalysts

In addition to the hitherto developed Sc^{III} and Bi^{III} catalysis for enantioselective hydroxymethylation reactions, Fe^{II} catalysis also seemed to be a promising candidate.

Several additives were examined in the presence of 3 mol % of $Fe(OTf)_2$ and 9 mol % of compound **L1** (Table 2); the amount of additive was set at 6 mol %. Acetic acid and benzoic acid were found to be effective additives for Lewis acid catalysis (Table 2, entries 2 and 6). However, strong acids, such as TfOH and *p*-toluenesulfonic acid (TsOH), impeded the function of the catalyst in exerting precise stereocontrol (Table 2, entries 3 and 5). Interestingly, a significant enhancement in enantioselectivity was also observed in the presence of a Brønsted base (Table 2, entries 7 and 8). To gain more insight into the interactions between Fe^{II} and an additive, several pyridine derivatives were examined. Slowing 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 (Table 2, entries 9 and 10). Coordinative substituents should also be avoided to obtain higher selectivities (Table 2, entries 11 and 12). The use of 2,6-lutidine as an additive afforded the aldol adduct with high enantiomeric purity (Table 2, entry 13). On the other hand, the enantioselectivity of the desired aldol adduct was unaffected by the use of strongly hindered bases (Table 2, entries 14–16). An interesting influence on enantioselectivity was observed when using imidazole and *N*-methylimidazole, presumably because of competitive coordination with the chiral ligand onto Fe^{II} (Table 2, entries 17 and 18). Such unprecedented assistance of these additives in Lewis acid catalysis, whether Brønsted acids or bases, intrigued us; regardless of their nature, all of the additives exhibited the best performance when employed at 6 mol %, twice the amount of $Fe(OTf)_2$.

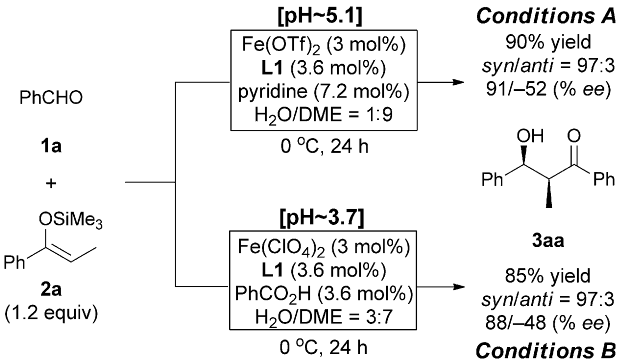
Table 2. Effect of additives in chiral-Fe^{II}-catalyzed Mukaiyama aldol reactions.



Entry	Additive	Yield [%][a]	d.r. (*syn*/*anti*)[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	$PhCO_2H$	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_2OH	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	*N*-Me-imidazole	26	97:3	73/−31

[a] Yield of the isolated product. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis. Ac = acetyl, Ts = 4-toluenesulfonyl.

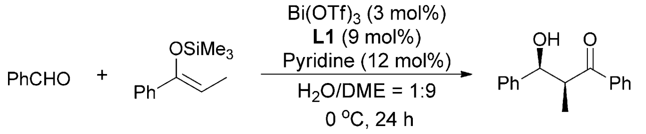
Intensive optimization of the reaction conditions (see the Supporting Information, Table S3) led to the discovery of two distinct catalytic systems that included a Brønsted base (pyridine, defined as "conditions A") or acid (benzoic acid, defined as "conditions B";[30] Scheme 1). In spite of their opposing natures, these additives assisted the Lewis acid catalysis of a chiral Fe^{II}/**L1** complex to afford the product in a highly enantioselective manner in an aqueous environment, which showed that this powerful assistance could not be explained by the adjustment of the pH value in the reaction solution.



Scheme 1. 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, as calculated from the redox potentials of various iron species and water by using the Nernst equation and hydrolysis constants (see the Supporting Information, Figure S1), shows that Fe^{II} is clearly the active species in these catalytic systems. Indeed, Fe^{III} exhibited inferior performance (see the Supporting Information, Table S1 b).

The superb performance of Bi^{III} catalysis in asymmetric hydroxymethylation reactions[21] led us to harbor expectations about the further evolution of this catalytic system to broaden the substrate scope.[31] Furthermore, the availability of bismuth, because of its affordability, abundance, and ubiquity, was 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 that was formed with threefold excess of compound **L1** (Scheme 2).



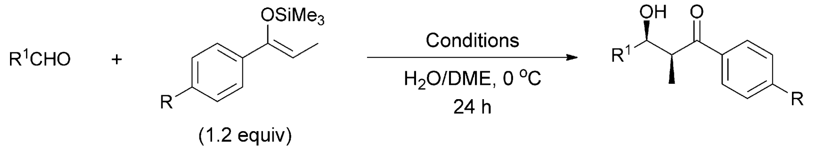
1a **2a** (1.2 equiv) **3aa** 84% yield *syn*/*anti* = 98:2 79/38 (% *ee*)

Scheme 2. Conditions for the Bi^{III}-catalyzed Mukaiyama aldol reaction (conditions C).

Substrate Scope

The substrate scope was evaluated under the optimized reaction conditions. The intriguing assistance of two distinct additives suggested the possibility that the careful selection of an additive could broaden the substrate scope. Based on such a perspective, the correlation between various substrates and their effective additives was investigated (Table 3). We found that the pyridine additive was more effective in the Mukaiyama aldol reaction of compound **1a** with compound **2a** (Table 3, entry 1). Electronic effects that resulted from the substituents on the aromatic ring of compound **2a** were surveyed. An electron-donating group (OMe, **2b**) resulted in a definite drop in the reaction rate. Prolonging the reaction time allowed the 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 an additive (Table 3, entry 2). An electron-donating group on the aromatic ring might contribute to stabilization of the O–Si bond of the silicon enolate, thus slowing the rate of hydrolysis after the nucleophilic attack. Substitution with an electron-withdrawing group led to an imperceptible decrease in the reaction rate. The addition of pyridine affected the enantioselectivity of the product, irrespective of the substituents on the aromatic ring (Table 3, entries 1–3). However, the reactions of 4-fluorobenzaldehyde (**1d**) and 1-naphthaldehyde (**1f**) proceeded in a highly enantioselective manner with benzoic acid as an additive (Table 3, entries 4 and 5). The optimal conditions could also be applied to aliphatic aldehydes, which are often poor electrophiles for Lewis-acid-mediated asymmetric processes because of both electronic and steric difficulties in the enantiofacial discrimination. Interestingly, the reactions of compounds **1h** and **1n** proceeded very smoothly to afford the desired products in high yields with high selectivities with pyridine as an additive (Table 3, entries 6 and 7). Moreover, 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 reactions of thiophenecarboxaldehyde (**1i**) and α,β-unsaturated aldehydes **1l** and **1m** (Table 3, entries 7–9). Based on these tendencies, we continued to examine the substrate scope of the aldehyde and silicon enolate.

Table 3. Effect of additives on the substrate scope.

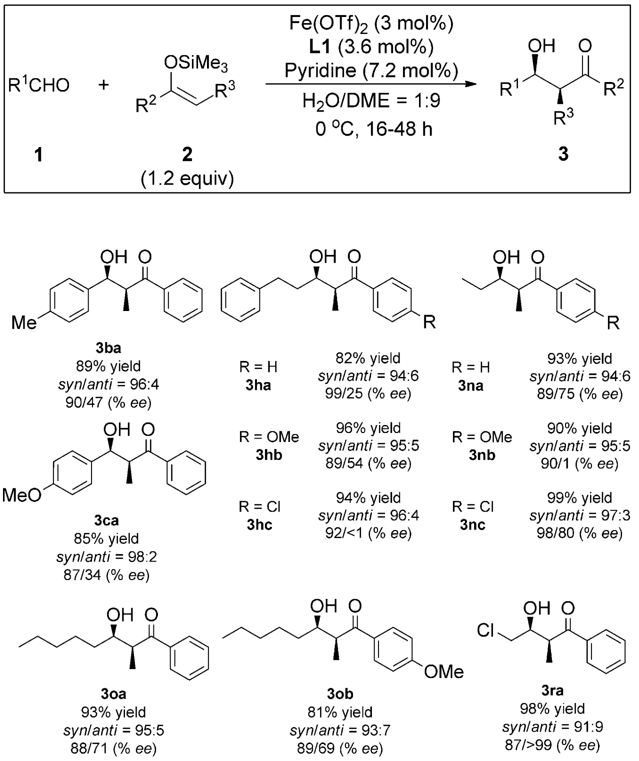


Entry	R^1		Silicon enolate R		Conditions[a]	Yield [%][b]	d.r. (*syn*/*anti*)[c]	*ee* [%][d]
1	Ph	**1a**	H	**2a**	A	90 (**3aa**)	97:3	91/52
					B	85	97:3	88/48
2	Ph	**1a**	OMe	**2b**	A[e]	91 (**3ab**)	97:3	85/21
					B	6	>99:<1	49/nd
3	Ph	**1a**	Cl	**2c**	A[f]	87 (**3ac**)	93:7	89/66
					B	70	95:5	65/40
4	4-FC_6H_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	quantitative	96:4	91/40
6	$PhCH_2CH_2$	**1h**	H	**2a**	A	82 (**3ha**)	94:6	99/25
					B	75	94:6	96/25
7	2-C_4H_3S	**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_3CH_2	**1n**	H	**2a**	A	93 (**3na**)	94:6	90/75
					B	71	87:13	66/37

[a] Conditions A: $Fe(OTf)_2$ (3 mol %), **L1** (3.6 mol %), pyridine (7.2 mol %), water/DME (1:9). Conditions B: $Fe(ClO_4)_2$ (3 mol %), **L1** (3.6 mol %), $PhCO_2H$ (3.6 mol %), water/DME (3:7). [b] Yield of the isolated product. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis. [e] For 48 h. [f] For 36 h. nd = not determined.

Conditions A

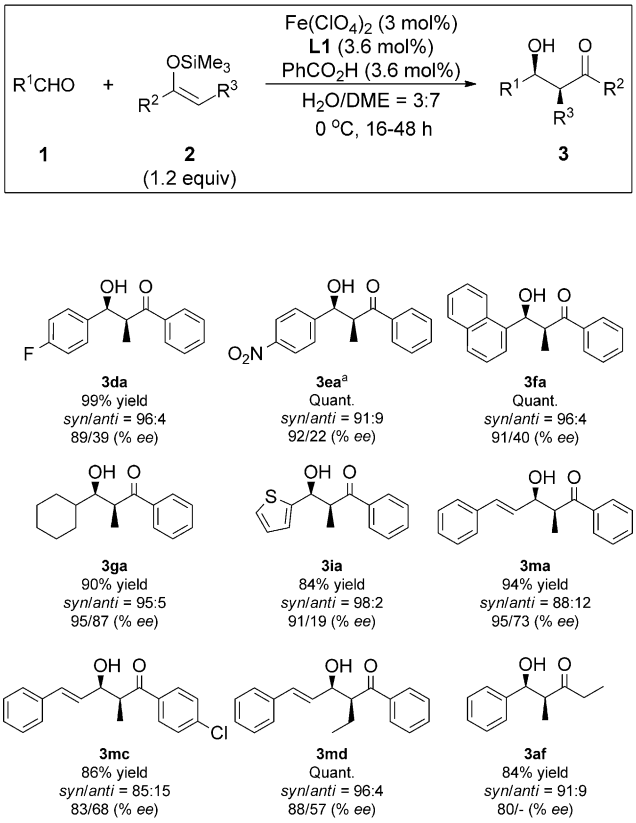
We found that pyridine was generally the most effective as an additive in the Mukaiyama aldol reaction. Thus, conditions A were used as the standard conditions for an initial substrate screen (Scheme 3). The addition of pyridine improved the enantioselectivity of the product, irrespective of the substituents on the aromatic ring in the silicon enolate. Not only aliphatic aldehydes (**1h**, **1n**, **1o**, and **1r**) but also aromatic aldehydes that contained electron-donating groups (**1b** and **1c**) reacted with the silicon enolates in a highly stereoselective manner.



Scheme 3. Substrate scope, conditions A. [a] 2,6-di-*tert*-butylpyridine (DTBP, 3 equiv) was added.

Conditions B

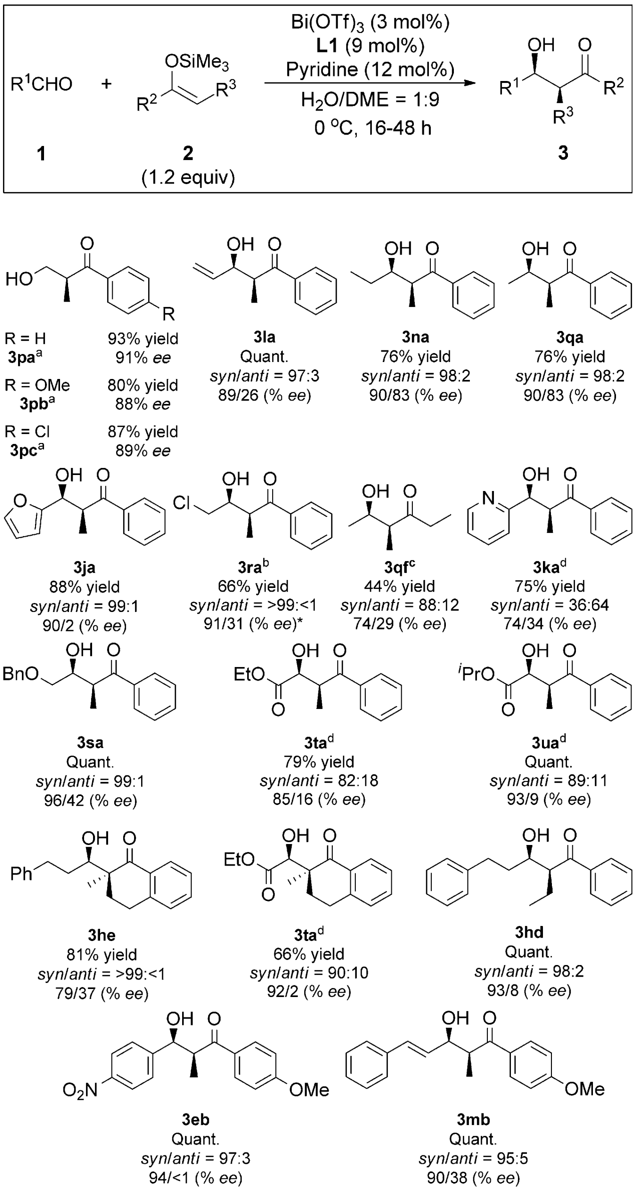
When benzoic acid was employed as an additive, a superior effect was obtained in the reactions of electron-deficient aromatic aldehydes (**1d**, **1e**, **1f**), secondary aliphatic aldehyde **1g**, thiophenecarboxaldehyde (**1i**), and α,β-unsaturated aldehyde **1m** (Scheme 4). The introduction of an electron-withdrawing (chloro) group onto 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 compound **1a** with the silicon enolate that was derived from 3-pentanone (**2f**).[32]



Scheme 4. Substrate scope, conditions B. [a] $Fe(ClO_4)_2$ (3 mol %), **L1** (9 mol %), and $PhCO_2H$ (3.6 mol %).

Conditions C

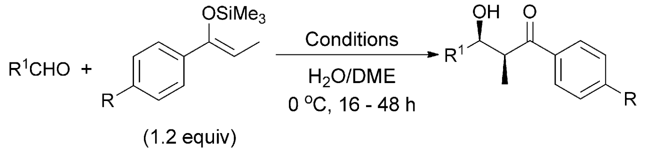
A chiral Bi^{III} catalyst (defined as conditions C) was also found to be attractive as an alternative system for asymmetric Mukaiyama aldol reactions (Scheme 5). In a previous report on Bi^{III}-catalyzed asymmetric hydroxymethylation reactions,[21] 2,2′-bipyridyl was selected as an effective additive. In that system, only trace amounts of the product were obtained by using $Bi(OTf)_3$ without compound **L1**, presumably because of the rapid decomposition of the silicon enolate as promoted by TfOH that was readily generated from $Bi(OTf)_3$ in water. Water-soluble aldehydes, such as aqueous formaldehyde (**1p**), and acrolein (**1l**), reacted with silicon enolates to afford their corresponding aldol adducts in high yields with high enantioselectivities. The aldol reaction of acetaldehyde (**1q**) is regarded to be difficult because acetaldehyde is highly reactive as both a nucleophile and an electrophile, thus causing a self-aldol reaction. Therefore, until recently, no asymmetric reactions by using acetaldehyde have been reported.[33] The chiral Bi^{III} complex catalyzed the reaction of compound **1q** with compound **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 that contained various functional groups (**1j**, **1k**, **1s**, **1t**, and **1u**). Notably, asymmetric quaternary carbon atoms were constructed with high selectivities. Silicon enolate **2b**, which contained an electron-donating



Scheme 5. Substrate scope, conditions C. [a] $Bi(OTf)_3$ (1 mol %), **L1** (3 mol %), 2,2′-bipyridyl (5 mol %), in water/DME (1:4). See Ref. [21]. [b] DTBP (3 equiv) was added. [c] $Sc(OTf)_3$ (10 mol %), **L1** (12 mol %). [d] Without pyridine. Tf = trifluoromethanesulfonyl.

group, was not applicable to conditions B, whereas the chiral Bi^{III} complex catalyzed the reactions with compound **2b** in high yields with high selectivities.

Table 4. Correlation between the properties of the aldehydes and aromatic ketone-derived silicon enolates and the most-effective catalytic systems.



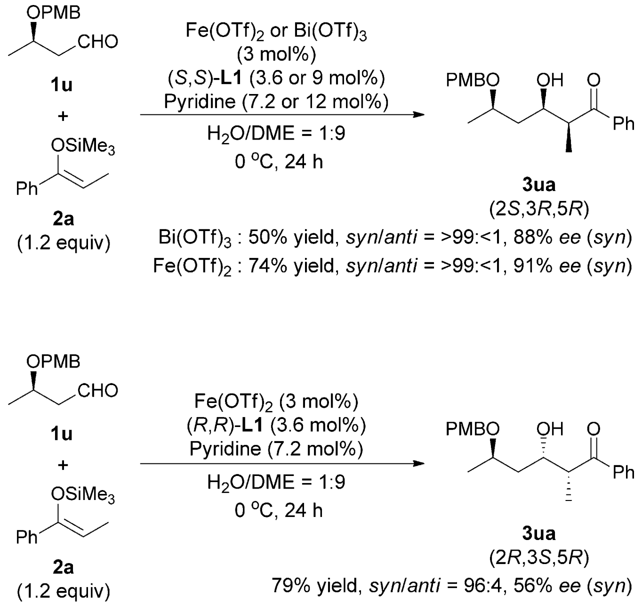
R[a]	Aldehyde (R^1CHO)		
	More bulky		Sterically small, chelate-type
	Electron-rich	Electron-poor	
H	conditions A	conditions B	conditions C
OMe (ED)	conditions A	conditions C	conditions C
Cl (EW)	condition A	conditions B	conditions C

[a] ED = electron donating, EW = electron withdrawing.

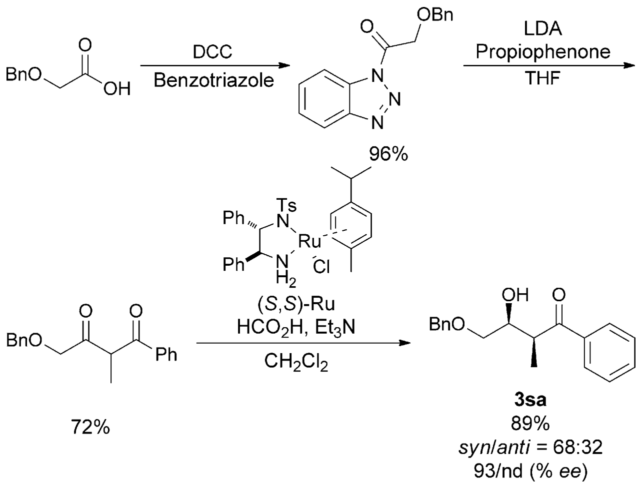
The effect of the choice of ternary catalytic system and substituent effects on this reaction are summarized in Table 4. Notably, the introduction of electron-withdrawing groups on the aromatic ring of benzaldehyde preferred conditions B. In contrast, electron-donating aromatic aldehydes preferred conditions A, thus indicating that the difference between pyridine and benzoic acid as the additive may lie in electronic effects through coordination to Fe^{II}. The substituents on the aromatic ring in the structure of the propiophenone-derived silicon enolates affected neither the reactivity nor selectivity, except for conditions 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. The introduction of a methoxy group onto the aromatic ring of the silicon enolate led to a significant drop in both reactivity and stereoselectivity under conditions B, whereas the reaction proceeded quantitatively to afford the product with excellent selectivities under conditions C (e.g., **3eb** and **3mb**). In addition, conditions C were effective for the reactions of less-bulky aldehydes, including water-soluble aldehydes and aldehydes that could chelate to the metal atoms. The stereoselective construction of asymmetric quaternary carbons was also observed.

The reaction of a chiral β-alkoxy aldehyde that contained potential directing ability was surveyed to offer a rationale for the stereocontrol (Scheme 6). The exposure of aldehyde **1u** and silicon enolate **2a** to the chiral Bi^{III} complex 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 with (*R*,*R*)-**L1** resulted in lower enantioselectivity, albeit the same level of yield and *syn*-selectivity because of the chelation.

Then, the Mukaiyama aldol reaction of benzyloxyacetaldehyde with compound **2a** was carried out by 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 A_1, an in vitro inhibitor of vacuolar H^+-ATPase, 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. Then, the lithium enolate of propiophenone was 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 d.r. of 68:32 in a total 62 % yield (three steps). The major isomer was formed with 93 % *ee*. On the other hand, in the



Scheme 6. Match/mismatch effect.



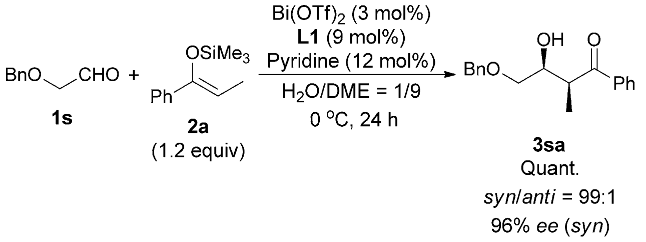
Scheme 7. Conventional synthesis of a β-hydroxyketone.[35] DCC = *N,N'*-dicyclohexylcarbodiimide, LDA = lithium diisopropylamide, Bn = benzyl.

Mukaiyama aldol reaction, the employment of a 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]

Reaction Mechanism

Coordination Environment around the Metal Centers

The complex between an Fe^{II} salt and ligand **L1**, first reported in 2012,[30] adopts a pentagonal bipyramidal structure, in which the tetradentate ligand occupies four of the equatorial sites. This structure resembles that of the corresponding Sc^{III} and Bi^{III} complexes (for the X-ray structures, see the Supporting Information, Figure S2). Several examples[37] of a heptacoordination mode of the Fe^{II} ion have been reported and X-ray crystals of three types of Fe^{II}/**L1** complexes[38] have been obtained, all of which showed heptacoordination. Thermogravimetric analysis implied that the chiral complex could behave in a heptacoordinated 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 interactions with the alcohol moieties of ligand **L1** and the relatively greater *trans*-effect of the pyridine ligand.[40] The dependence of the choice of 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 some fundamental insight into the catalyst structure, a model reaction between compounds **1a** with **2a** was carried out in the presence of enantiomerically impure 2,2'-bipyridine **L1** (Figure 1). Whereas negative nonlinear effects were observed in the absence of an additive, the nonlinearity disappeared in the presence of an additive. Because subtle erosion of the enantioselectivity in product **3aa** was observed in



Scheme 8. Bismuth-mediated synthesis of a β-hydroxyketone.

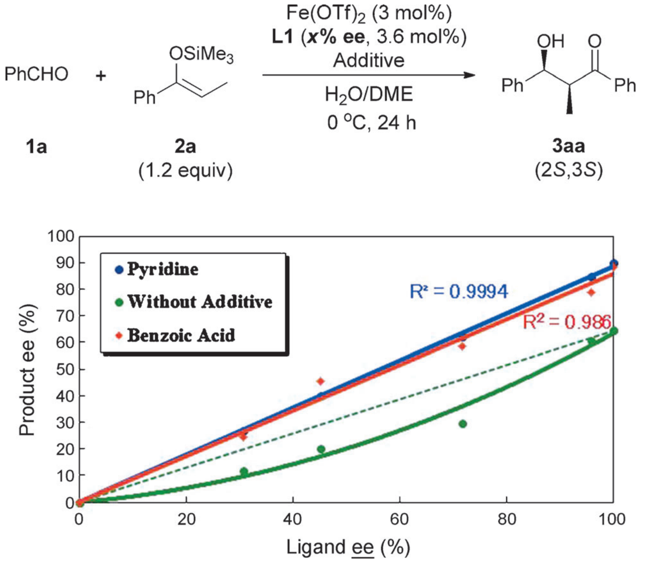


Figure 1. Nonlinear experiments.

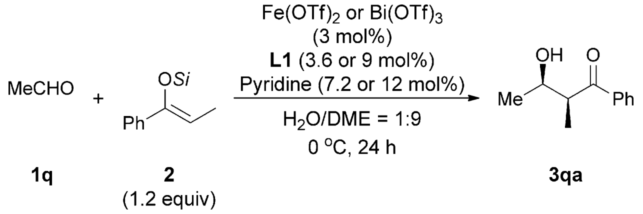
the absence of an additive, the observations may be rationalized by the changes in the catalyst structure from a dimeric or oligomeric form without the additive into a monomeric form with the additive, which might be an actual catalytic species that resulted in high enantioselectivity and reactivity.

Effect of Additives

To gain some insight into the structures the catalysts, the reaction solution was directly subjected to spectrometric investigation. The chiral Fe^{II} complex with ligand **L1** did not give rise to massive changes in the NMR analysis, unlike the chiral Sc^{III} and Bi^{III} complexes. Likewise, on using an additive, no changes were observed in the NMR or UV/Vis analyses. ESI-MS experiments could shed some light on the differences (see the Supporting Information, Figure S3). In the absence of an additive, two types of mono-Fe^{II} complexes, that is, $[Fe^{II}(\mathbf{L1})(OTf)(DME)]^+$ and $[Fe^{II}(\mathbf{L1})(OTf)]^+$, were observed; one was coordinated by a DME molecule, whereas the other was not. Some amounts of an Fe^{II} complex that was 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 counteranion. Instead of a triflate, the formation of a hydroxide complex, $[Fe^{II}(\mathbf{L1})(OH)]^+$, was verified. The major peak corresponded to a Fe^{II}/benzoate complex with ligand **L1**, $[Fe^{II}(\mathbf{L1})(O_2CPh)]^+$. The environment around Bi^{III}, which is known to be dependent upon the metal-to-ligand ratio, were also found to be a naked cation without any ligand, as mentioned above (see the Supporting Information, Figure S3).[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. Thus, to examine whether a nucleophilic attack takes place at the silicon atom or not, a Mukaiyama aldol reaction by 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 conditions A, although it also led to a significant drop in selectivity. In the case of the chiral Bi^{III} catalyst, we found that the enantioselectivity remained 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.

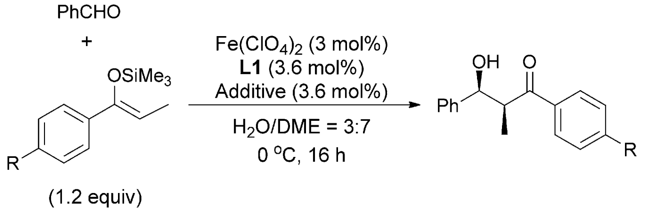
Table 5. Effect of the silicon enolate.



Conditions	*Si* = SiMe$_3$			*Si* = SiMe$_2$H		
	Yield [%]	*syn*/*anti*	*ee* [%]	Yield [%]	*syn*/*anti*	*ee* [%]
A	72	93:7	74 (*syn*)	95	84:16	28 (*syn*)
C	76	98:2	90 (*syn*)	70	96:4	90 (*syn*)

To determine the role of the 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 with benzoic acid. In contrast, in the case of 4-nitrobenzoic acid, both the reaction yield and enantioselectivity suffered from a significant drop. The enantioselectivity of the *syn* isomer was almost the same 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 selectivity. Similarly, Mukaiyama et al. reported that 10 mol% of a metal carboxylate could function as a Lewis basic catalyst to mediate the reaction between benzaldehyde and a silyl ketene acetal at −45 °C in DMF/water (50:1).[42] They assumed that the role of the carboxylate in the catalytic cycle was the formation of a lithium aldolate through a hexacoordinated hypervalent silicate, which underwent rapid hydrolysis and subsequent neutralization to regenerate the lithium acetate catalyst. The dependence of reactivity on the electrophilicity of the aldehyde supports their hypothesis, in accord with the results shown in Table 6.

Table 6. Effect of the silicon enolate.



Entry	R	Additive	Yield [%][a]	d.r. (*syn*/*anti*)[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

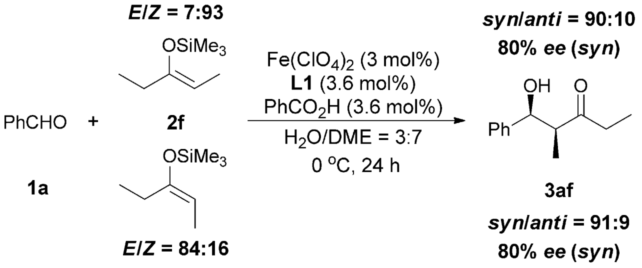
Ligand field theory is helpful for deepening our understanding of the effect of additives. The donation of electrons by σ-donor ligands to *d* orbitals and some weak bonding and antibonding interactions with *s* and *p* orbitals of Fe^{II} are plausible. Compared with nonbonding orbitals that consist of d_{xz} and d_{yz} orbitals, the antibonding orbitals between 4*s*, 4*p*, d_{xy}, and $d_{x^2-y^2}$ and between 4*s*, 4p_z, and d_{z^2} become destabilized. When pyridine was used as an additive, the OH ligand in an equatorial position or pyridine in an apical position made the former bonding orbital unstable and the latter stable. The consequent spin transition in the HOMO orbital overcame the deactivation by the coordination of a Lewis base[43] and the lower HOMO destabilized the π* orbital of aldehyde. Given the intriguing observed equilibrium shift in the Sc/**L1** complex,[44] stabilization of the pentagonal bipyramidal structure, even in an aqueous environment, was expected. In contrast, the bidentate coordination of a benzoate anion to the iron atom made the latter unstable. The resultant HOMO–LUMO gaps between the aldehyde and the silicon enolate correspond to the experimental trends as shown in Table 4. The strength of the interactions between the iron center and both substrates governs the stereoselectivities, on the assumption of some interactions between the iron atom and the π-orbital of the silicon enolate.[45]

Thus, there are two functions for the additive in the Fe^{II} complexes: 1) Coordination to the Fe^{II} ion and 2) coordination to the silicon atom of the silicon enolate 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, a Lewis base additive is consumed by scavenging the in situ formed TfOH in the case of the Bi^{III} complex.

Reaction Pathways and Transition States

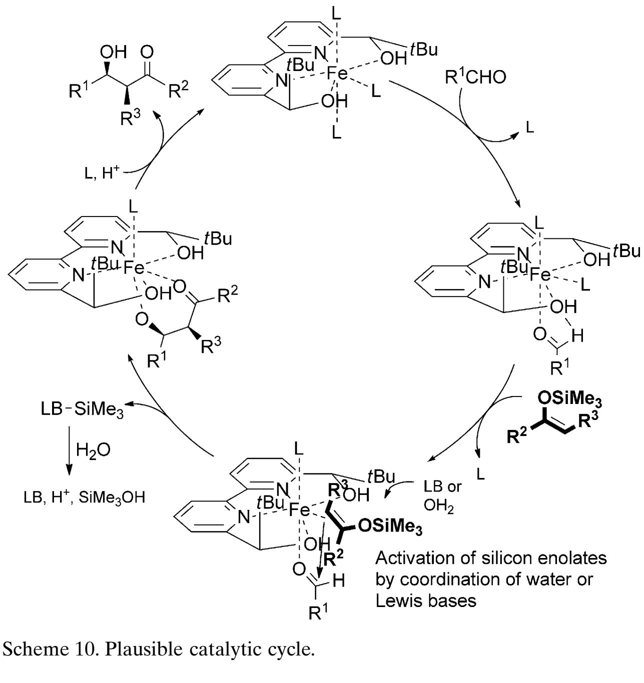
Three different mechanisms have been proposed for Mukaiyama aldol reactions: 1) The Zimmerman–Traxler six-membered model;[47] 2) the acyclic open-transition-state model, which involves an antiperiplanar orientation of the enolate and carbonyl compounds;[48] and 3) the transmetalation model, which involves transmetalation of the silicon atom of the silicon enolate to the second metal of the Lewis acid. An initial mechanistic hypothesis in Mukaiyama's landmark report in 1973 involved the formation of a titanium enolate through transmetalation.[1] 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. Since then, an INEPT (insensitive nuclei enhanced by polarization transfer) ^{29}Si NMR study was emphatic in disproving the operation of a transmetalation pathway.[49] Nevertheless, the reactions of pre-isolated 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 did not involve transmetalation was also proposed.[51] To date, the actual mechanism has not yet been conclusively determined.

Whereas all of these mechanistic investigations were carried out in organic solvents, the kinetics of a hydroxymethylation reaction between aqueous formaldehyde and compound **2a** in the presence of a Sc/**L1** complex was reported in 2011.[52] In consequence, a first-order dependence of both compound **2a** and the chiral catalyst was observed, which ruled out the possibility of a 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 the metal and the oxygen atom of the silicon enolate. A direct comparison of the effect of enolate geometry was conducted by using (*E*)- and (*Z*)-silicon enolates that were derived from 3-pentanone under the Fe^{II}-catalyzed conditions (Scheme 9). We found that both (*E*)- and (*Z*)-enolates gave *syn*-aldol adducts, which also supported the acyclic open-transition-state model. The independence of stereochemistry from enolate geometry was also confirmed for the chiral Bi^{III} complex (conditions C).



Scheme 9. Correlation between the stereochemical outcome and the enolate geometry.

A plausible catalytic cycle for this Mukaiyama aldol reaction in aqueous media is shown in Scheme 10. First, the aldehyde coordinates to the pentagonal bipyramidal Fe^{II} complex, which consists of the Fe^{II} atom, ligand **L1**, and an additive in the axial position. One of the ligands, that is, pyridine, benzoic acid, or water, may be replaced by the aldehyde. Water that is coordinated to the Fe^{II} center is disposed to exchange and may facilitate the replacement. One face of



Scheme 10. Plausible catalytic cycle.

the aldehyde is shielded by the *tert*-butyl group of ligand **L1**.[53] Then, a silicon enolate attacks the aldehyde through an antiperiplanar acyclic transition state. Water also plays a key role in coordinating to the silicon atom of the silicon enolate to assist the reaction. The additive, that is, pyridine or benzoic acid, is also though to play the same role (conditions A/B). In the Bi^{III}-catalyzed reaction (conditions C), the coordination of pyridine to the silicon atom was not significant; however, water coordination was assumed to be crucial in that case. Then, carbon–carbon bond formation occurs with high diastereo- and enantioselectivities and the resulting Fe^{II}/alkoxide complex 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 the Lewis acidity ($Me_3Si{-}O{-}SiMe_3$) and prevent undesired achiral Si-catalyzed pathways, which often decrease the diastereo- and enantioselectivities in asymmetric Mukaiyama aldol reactions. Notably, water also plays an important role.[54] In our reaction systems, water is essential for the 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 water/DME ratio, the lower the yield and the higher the observed diastereo- and enantioselectivities. The amount of water governed the stereochemical outcome, as well as the consequential catalytic turnover, although water is prone to destabilize silicon enolates through hydrolysis of the metal complexes.[56]

Conclusions

We have developed Fe^{II}- and Bi^{III}-catalyzed asymmetric Mukaiyama aldol reactions of silicon enolates with aldehydes. Three kinds of new ternary catalytic systems, which consisted of a Fe^{II} or Bi^{III} metal salt, chiral bipyridine ligand **L1**, and an additive, have been exploited. Whilst previous reactions often required relatively harsh conditions, such as strictly anhydrous conditions, very low temperatures (−78 °C), etc., the reactions reported herein proceeded in the presence of water at 0 °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 method over conventional reactions has also been confirmed by the high catalytic activity, the simplicity of the experimental procedure, and broad substrate range, including aqueous aldehydes, for which the stereochemistry of the reaction has been regarded to be difficult to govern. The coordination environments around the Fe^{II} and Bi^{III} atoms and the effect of additives on the chiral catalysts have been elucidated by mechanistic studies. Notably, both Brønsted acids and bases worked as efficient additives in the Fe^{II}-catalyzed reactions. The assumed catalytic cycle and transition states clarified the important roles of water in:[57] 1) producing the active metal complexes with a high water-exchange rate constant (3.2×10^6) to effectively activate the substrates and to catalyze the reactions through acyclic transition states; 2) facilitating the catalytic turnover with simultaneous desilylation to provide direct access to the aldol adducts or facile recovery of the active metal complexes; and 3) stabilizing rigid transition states that were composed of the metal complexes and the reactants through entropy-driven aggregation that was derived from its highest cohesive energy density (ced).[58] 40 Years after the discovery of the Mukaiyama aldol reaction, we have established a definitive catalytic asymmetric variant by using Fe^{II} and Bi^{III} salts with chiral bipyridine ligand **L1** in aqueous media.

Experimental Section

Typical Procedure for the Mukaiyama Aldol Reaction between a Silyl Enol Ether and an Aldehyde (Table 3, entry 1)

A mixture of $Fe(OTf)_2$ (3.2 mg, 0.009 mmol), the chiral 2,2′-bipyridine ligand (3.5 mg, 0.0108 mmol), and pyridine (1.6 mg, 0.0216 mmol) in degassed DME (0.65 mL) was stirred at RT for 30 min. Then, the catalyst solution was cooled at 0 °C for 30 min and water (70 μL) was added. To the mixture were successively added aldehyde **1a** and silyl enol ether **2a**. After stirring for 24 h at RT, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and washed with brine. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layer was 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 (*n*-hexane/EtOAc, 3:1) to give the corresponding aldol (**3aa**, 64.0 mg, 90 % yield) as a colorless oil.

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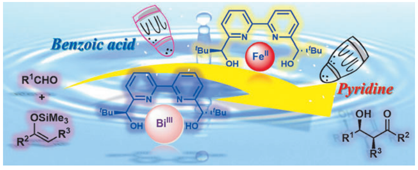
Bi^{III}Fe^{II} Clyro: Ternary catalytic systems that comprise a chiral ligand, a (Fe^{II} or Bi^{III}) metal salt, and an additive broaden the scope for the asymmetric Mukaiyama aldol reaction. The facile synthesis of the ligand underscores its versatility.



Aldol Reaction

*Taku Kitanosono, Thierry Ollevier, Shū Kobayashi** ________ ■■■■–■■■■

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