Siloxy Esters as Traceless Activator of Carboxylic Acids: Boron-Catalyzed Chemoselective Asymmetric Aldol Reaction

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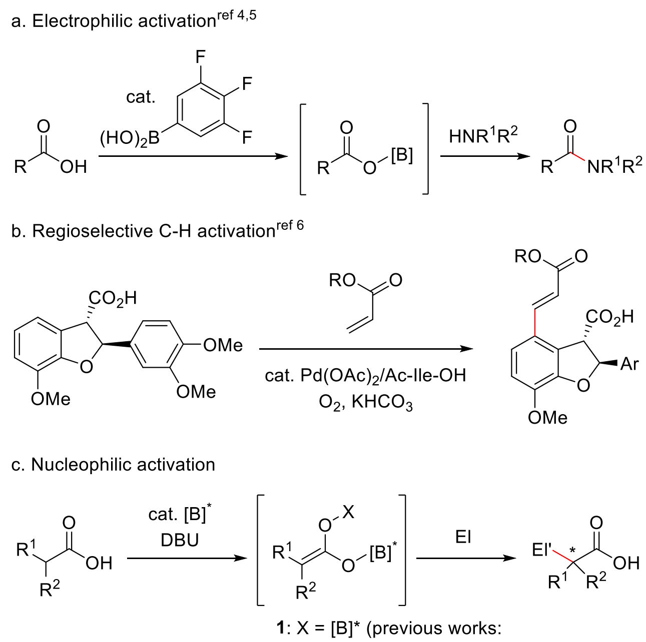
ABSTRACT: The catalytic asymmetric aldol reaction of carboxylic acids is among the most useful reactions for the synthesis of biologically active compounds and pharmaceuticals. Despite the existence of many prominent reports, no general method is available to incorporate the aldol motif into complex carboxylic acids and their derivatives at late stages. Chemoselective catalytic asymmetric aldol reaction of multifunctional carboxylic acids is difficult to achieve, due to the high basicity required for enolization and the poisonous chelation of β-hydroxy acid products to Lewis acid catalysts. Herein, we identified that pre-conversion of carboxylic acids to siloxy esters facilitated the boron-catalyzed direct aldol reaction, leading to the development of carboxylic acid-selective, catalytic asymmetric aldol reaction applicable to multifunctional substrates. The asymmetric boron catalyst stereodivergently controlled the products' stereochemistry depending on the catalyst's chirality, not on the stereochemical bias of substrates. Computational studies rationalized the mechanism of the catalytic cycle and the stereoselectivity, and proposed Si/B enediolates as the active species for the asymmetric aldol reaction. The silyl ester formation facilitated both enolization and catalyst turnover through acidifying the α-proton of substrates and attenuating poisonous Lewis bases to the boron catalyst.

INTRODUCTION

The carboxyl group is a common functional group existing in a wide range of organic molecules, especially in biologically active natural products and pharmaceuticals: e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)[1] and antibiotics.[2] Therefore, catalytic, chemoselective, and asymmetric C–C bond-formation of carboxylic acids containing multiple functional groups is useful in complex molecule synthesis and late-stage structural diversifications of drug leads for optimizing their pharmaceutical properties.[3]

Due to the high acidity of carboxylic acids compared to other common functional groups, chemoselective recognition and activation of carboxylic acids is possible through reversible catalyst–substrate covalent bond- or salt-formation. Yamamoto reported a pioneering example of boronic acid-catalyzed electrophilic activation of carboxylic acids in the presence of amines for amidation (Scheme 1a).[4,5] Electron-withdrawing arylboronic acids chemoselectively formed acyloxyboron intermediates with substrate carboxylic acids to enhance their electrophilicity. Yu reported site-selective, palladium-catalyzed C–H bond functionalizations of carboxylic acids at distal positions (β- or farther positions) to the carboxyl group and their applications to natural product synthesis (Scheme 1b).[6] The carboxylate group worked as a directing group of the palladium catalyst by coordination, realizing highly practical site-selective C–H functionalizations. Our group reported chiral boronate-catalyzed nucleophilic activation of carboxylic acids through enolization, enabling chemoselective and asymmetric Mannich reaction and α-allylation of carboxylic acids (Scheme 1c).[7,8] Chiral diboron enediolate **1**[9] was proposed as the active species for those reactions. Due to the high oxophilicity of the boron catalyst, however, this enolization method was not effective in

Scheme 1. Catalytic Chemoselective Activation of Carboxylic Acids



1: X = [B]* (previous works: El = imine, allyl[ref 7])
2: X = [Si] (this work: El = aldehyde)

promoting a catalytic asymmetric aldol reaction of carboxylic acids,[10] another fundamental and synthetically useful C–C bond-forming reaction.[11–14] Here we found that *in-situ* pre-conversion of carboxylic acids to siloxy esters dramatically facilitated the boron-catalyzed, carboxylic acid-selective asymmetric aldol reaction. The siloxy group worked as a traceless activator, allowing for the direct use of carboxyl group-containing multifunctional drugs and natural products themselves as substrates of catalytic asymmetric aldol reactions.[15] We propose Si/B enediolates **2** as the active species for this reaction. Since the boron catalyst did not promote aldol reactions of simple esters (e.g. *t*Bu ester), the reactivity is unique to siloxy esters.

RESULTS AND DISCUSSION

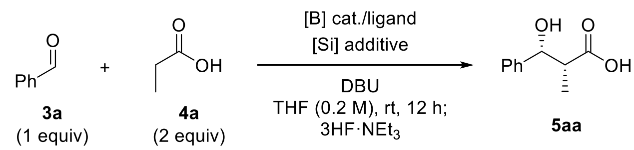
We began optimization of the reaction between benzaldehyde (**3a**) and propionic acid (**4a**) using a chiral boron catalyst generated from either $BH_3{\bullet}SMe_2$ or $(AcO)_4B_2O$ with ligand **L1**[7,10] (Table 1). In the absence of any additives, the yield of product **5aa** was up to the loading amount of the boron catalyst (entries 1 and 2). We attributed the lack of catalyst turnover to the high stability of the catalytically inactive boron aldolate intermediate **6**. To facilitate catalyst turnover, we added silylating reagents.[13a] Although using $BH_3{\bullet}SMe_2$ as a boron source did not produce **5aa** in the presence of Me_3SiCl (entry 3), $(AcO)_4B_2O$ afforded the product in 42% yield (entry 4). Treatment of **4a** with Me_3SiCl prior to the aldol reaction further improved the yield to 48% (entry 5). NMR studies revealed that **4a** was converted to its silyl ester by this treatment.[16] Screening silylating reagents led us to identify $(EtO)_3SiCl$ as the optimum additive regarding product yield, affording **5aa** in 92% yield with 13/1 dr, but with only 3% ee (entry 6). The selectivity slightly improved to 15/1 dr and 6% ee in THF, despite yield lowered to 71% (entry 7). No reaction proceeded in the absence of the boron catalyst (entry 8).

To improve enantioselectivity, we next studied valine-derived ligands with various *N*-aryl sulfonyl groups. Enantioselectivity increased according to the number of fluorine substituents on the aryl group of ligands **L1**–**L4**,[7b,10a,17] but diastereoselectivity decreased accordingly (entries 7 and 9–11). To optimize the electronic properties of the sulfonyl group, we substituted the 4-fluorine atom of **L4** with an electron-donating MeO (**L5**: entry 12) or Me_2N (**L6**: entry 13) group: using **L6** afforded balanced dr and ee (entry 13). Finally, reducing the amount of DBU to 3.5 equiv and concentration to 0.1 M afforded **5aa** in 69% yield with 16/1 dr and 86% ee (entry 14).

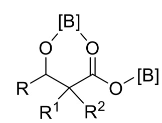
We then examined the substrate scope under the optimized conditions (Table 2). The scope of carboxylic acids was first investigated using benzaldehyde (**3a**). 3-Phenylpropionic acid (**4b**) furnished **5ab** in high yield and stereoselectivities (89%, >20/1 dr, 90% ee). The amount of boron catalyst could be reduced to 8 mol % without significant erosion in reactivity and selectivity (76%, 19/1 dr, 89% ee). The reaction was applicable on a gram scale (64%, >20/1 dr, 90% ee). Carboxylic acids containing potentially reactive functional groups such as unsaturated C–C bonds, halogens, and a hydroxy group were investigated (**4c**–**4k**). In all cases, the reaction proceeded smoothly with high diastereo- and enantioselectivity (**5ac**–**5ak**). The reaction was chemoselective at the α-position of the carboxyl group in the presence of amide, ester, ketone, and nitrile functional groups, which are intrinsically more prone to enolization than the carboxyl group (**5ag**–**5aj**).

Next, the scope of aldehydes **3** was examined using carboxylic acid **4b**. A series of aromatic aldehydes bearing an electron-donating, an electron-withdrawing, and a naphthyl group were competent substrates (**5bb**–**5fb**). Introduction of a substituent at the *ortho* or *meta* position of the aromatic ring did not affect the result (**5gb** and **5hb** *vs.* **5cb**). Reactions with aliphatic aldehydes also proceeded in high yield and selectivity by increasing DBU to 5 equiv and the concentration to 0.3 M (**5ib**–**5nb**). Aliphatic aldehydes are especially difficult substrates for catalytic asymmetric direct aldol reactions because they can enolize easily under basic conditions.[13]

Table 1. Optimization of Reaction Conditions[a]



entry	[B]	ligand	[Si]	yield (%)	dr *syn*/*anti*	ee (%)
1[b]	$BH_3{\cdot}SMe_2$	**L1**	none	0	N.D.	N.D.
2[b]	$(AcO)_4B_2O$	**L1**	none	6	N.D.	N.D.
3[b,c]	$BH_3{\cdot}SMe_2$	**L1**	Me_3SiCl	0	N.D.	N.D.
4[b,c]	$(AcO)_4B_2O$	**L1**	Me_3SiCl	42	2.4/1	12
5[b]	$(AcO)_4B_2O$	**L1**	Me_3SiCl	48	2.4/1	11
6[b]	$(AcO)_4B_2O$	**L1**	$(EtO)_3SiCl$	92	13/1	3
7	$(AcO)_4B_2O$	**L1**	$(EtO)_3SiCl$	71	15/1	6
8	none	none	$(EtO)_3SiCl$	0	N.D.	N.D.
9	$(AcO)_4B_2O$	**L2**	$(EtO)_3SiCl$	79	11/1	62
10	$(AcO)_4B_2O$	**L3**	$(EtO)_3SiCl$	82	4.7/1	78
11	$(AcO)_4B_2O$	**L4**	$(EtO)_3SiCl$	72	1.6/1	85
12	$(AcO)_4B_2O$	**L5**	$(EtO)_3SiCl$	82	1.8/1	86
13	$(AcO)_4B_2O$	**L6**	$(EtO)_3SiCl$	71	5.5/1	86
14[d]	$(AcO)_4B_2O$	**L6**	$(EtO)_3SiCl$	69	16/1	86



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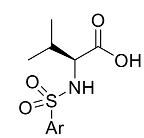
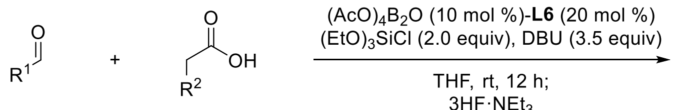


L1 Ar = 4-Me-C_6H_4
L2 Ar = 2,6-F_2-C_6H_3
L3 Ar = 2,4,6-F_3-C_6H_2
L4 Ar = C_6F_5
L5 Ar = 4-MeO-C_6F_4
L6 Ar = 4-Me_2N-C_6F_4

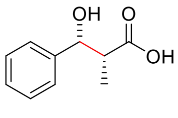
[a]Standard conditions (for entries 7–14): A mixture of **4a** (2 equiv), silylating reagent (2 equiv), and DBU (4 equiv) in THF (0.5 mL) was stirred at room temperature (rt) for 30 min (solution A). A boron source (B: 20 mol %) and a ligand (20 mol %) in THF (0.5 mL) were stirred at rt for 30 min in another vessel (solution B). Solution B and **3a** (1 equiv) were added successively to solution A, and the mixture was stirred at rt for 12 h. [b]In toluene. [c]The silylating reagent was added as the final component. [d]DBU (3.5 equiv) and 0.1 M.

Table 2. Substrate Scope[a]

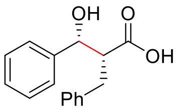


3 + **4** (2 equiv) → **5**

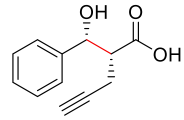
carboxylic acids



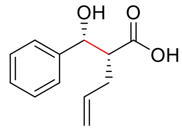
5aa
69%, 16/1 dr
86% ee



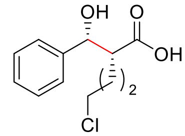
5ab
89%, >20/1 dr, 90% ee
76%, 19/1 dr, 89% ee[b]
64%, >20/1 dr, 90% ee[c]



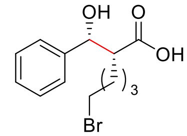
5ac
91%, 11/1 dr
86% ee



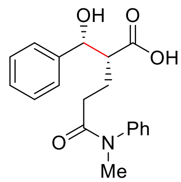
5ad
84%, >20/1 dr
92% ee



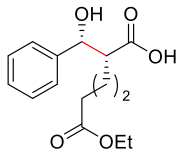
5ae
70%, >20/1 dr
94% ee



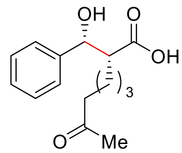
5af
53% (70%)[d], >20/1 dr
94% ee



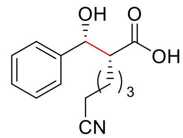
5ag
82%, 12/1 dr
94% ee



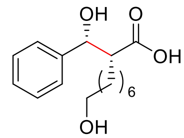
5ah
72%[e,f], >20/1 dr
93% ee



5ai
57%[e,f], >20/1 dr
94% ee

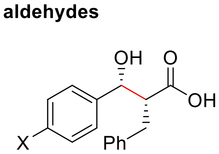


5aj
81%, 7.3/1 dr
97% ee

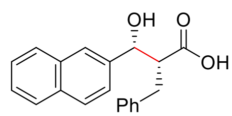


5ak
56% (88%)[d,e,h,i], >20/1 dr
90% ee

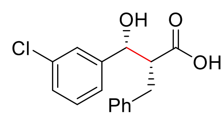
aldehydes



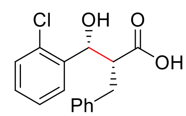
X	yield (%)	dr *syn*/*anti*	ee (%)
Me (**5bb**)	41	>20/1	87
Cl (**5cb**)	82	19/1	89
Br (**5db**)	88	18/1	85
CF_3 (**5eb**)	93	16/1	83



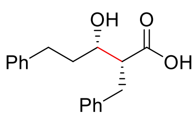
5fb
93%, >20/1 dr
86% ee



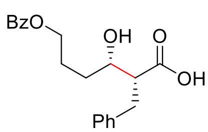
5gb
93%, 16/1 dr
90% ee



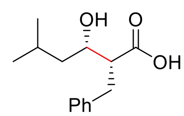
5hb
87%, >20/1 dr
90% ee



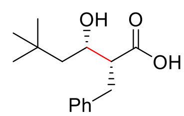
5ib
92%[g], 9.9/1 dr
92% ee



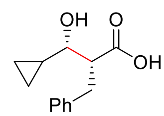
5jb
71%[g], 11/1 dr
87% ee



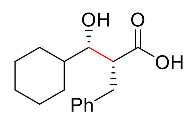
5kb
72%[g], >20/1 dr
91% ee



5lb
86%[g], 9.0/1 dr
90% ee

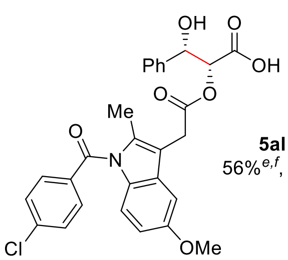


5mb
74%[g], 4.4 /1 dr
86% ee

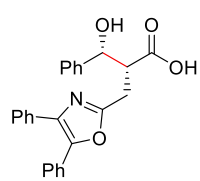


5nb
42%[g], >20/1 dr
87% ee

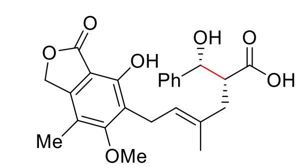
multifunctional substrates



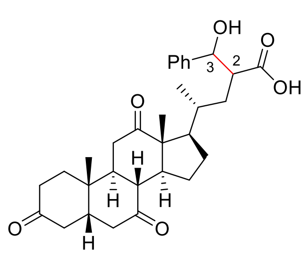
5al acemetacin
56%[e,f], 11/1 dr, 82% ee



5am oxaprozin
91%, 7.6/1 dr, 84% ee

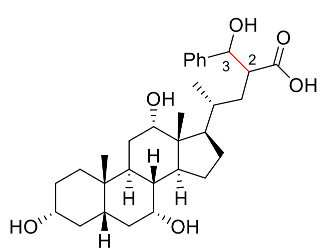


5an mycophenolic acid
69%[e,h,i], 17/1 dr, 87% ee



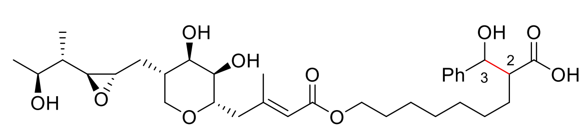
dehydrocholic acid

5ao (2*R*,3*R*)
63% yield[e,f], >20/ 1/ <1/ <1 dr
***iso*-5ao** (2*S*,3*S*)
42% yield[e,f,j], 39/ 4.6/ 1/ <1 dr



cholic acid

5ap (2*R*,3*R*)
68% yield[e,h,i,k], >20/ 1/ <1/ <1 dr
***iso*-5ap** (2*S*,3*S*)
50% yield[e,h,i,j,k], >20/ 1/ <1/ <1 dr



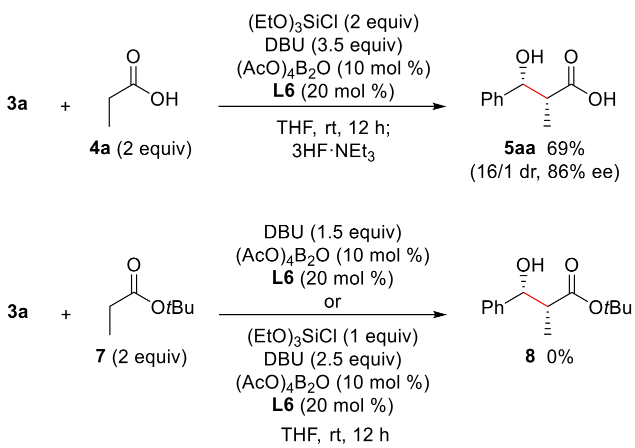
mupirocin

5aq (2*R*,3*R*)
38% yield[e,h,i,k,l], >20/ 1/ <1/ <1 dr
***iso*-5aq** (2*S*,3*S*)
56% yield[e,h,i,j,k,l], >20/ 1/ <1/ <1 dr

[a]General reaction conditions: **4** (0.60 mmol), **3** (0.30 mmol), $(EtO)_3SiCl$ (0.60 mmol), DBU (1.05 mmol), $(AcO)_4B_2O$ (0.03 mmol), **L6** (0.06 mmol), THF (3.0 mL), room temperature, 12 h. Isolated yield, enantiomeric excess (ee), and diastereomeric ratio (dr) shown in the Table were determined after conversion to the corresponding methyl esters, except for **5ak**.[16] [b]4 mol % $(AcO)_4B_2O$ and 8 mol % **L6** were used. [c]6 mmol scale reaction. [d]NMR yield is shown in parentheses. [e]Concentration was 0.2 M. [f]4 equiv of DBU was used. [g]Concentraion was 0.3 M, and 5 equiv of DBU was used. [h]4 equiv of $(EtO)_3SiCl$ was used. [i]6 equiv of DBU was used. [j]***ent*-L6** was used. [k]10 equiv of aldehyde **3** was used. [l]30 mol % $(AcO)_4B_2O$ and 60 mol % **L6** were used.

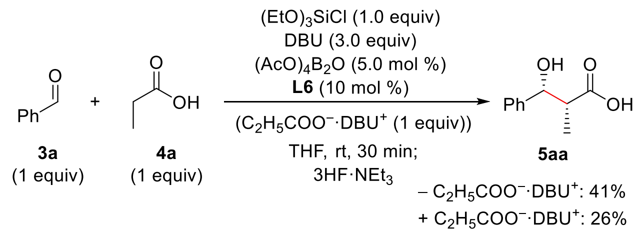
Finally, we applied our method to more complex carboxylic acids containing multiple functional groups. By using commercially available NSAIDs, acemetacin (**4l**) and oxaprozin (**4m**), the corresponding aldol products **5al** and **5am** were obtained in high yield and selectivity. An immunosuppressant drug, mycophenolic acid (**4n**), containing a phenolic hydroxy group afforded **5an** in 69% yield with 17/1 dr and 87% ee. The reaction between **3a** with dehydrocholic acid (**4o**) bearing three keto groups proceeded chemoselectively at the α-position of the carboxyl group. The reaction was stereodivergent, producing isomeric products depending on the chirality of the boron catalyst: using ligand **L6** or ***ent*-L6**, product **5ao** or ***iso*-5ao** was obtained in high stereoselectivity, respectively. Cholic acid bearing three hydroxy groups afforded products **5ap** and ***iso*-5ap** in excellent selectivity, which was again controlled by the catalyst. The stereodivergent reaction also proceeded from mupirocin, an antibiotic drug containing hydroxy, epoxy, α,β-unsaturated ester, and carboxyl groups, in high chemo- and stereoselectivity (**5aq** and *iso*-**5aq**).

Scheme 2. Comparison between Siloxy Ester and *t*Bu Ester

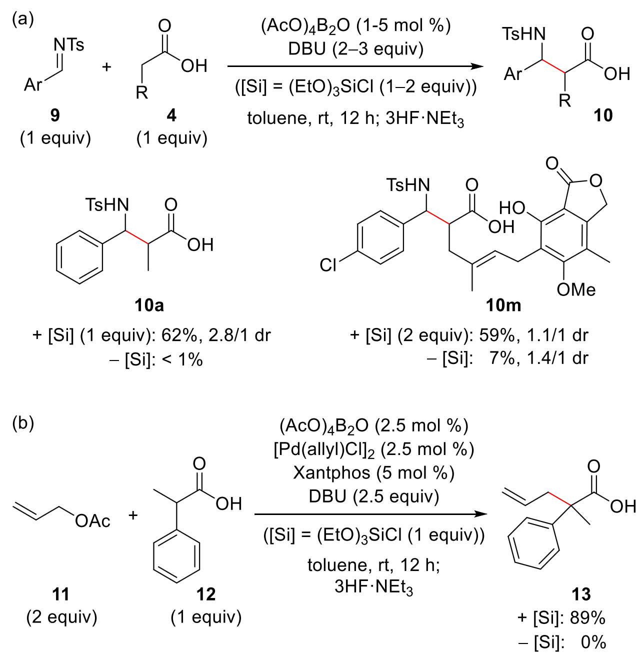


To gain mechanistic insights, we conducted a series of experiments. First, we compared the reactivity between siloxy esters and alkyl esters. Whereas the reaction between aldehyde **3a** and carboxylic acid **4a** proceeded to afford product **5aa** in 69% yield through the corresponding siloxy ester, the reaction between **3a** and *t*Bu ester **7** did not proceed at all, irrespective of the presence or absence of $(EtO)_3SiCl$ (Scheme 2). The acidity of carbonyl α-proton may dictate the contrasting reactivity: calculated pK_a values for $CH_3COOSi(OEt)_3$ and $CH_3COOtBu$ were 20 and 26, respectively.[16,18] The significantly higher acidity of siloxy esters compared to alkyl esters might be partly due to divalent coordination of carboxylate to a hypervalent silicone atom, which was previously proposed by Yamamoto and colleagues on the basis of ^{29}Si NMR in mechanistic studies of the silyl ester-mediated peptide coupling reaction.[19]

Scheme 3. Inhibitory Effects of Carboxylate



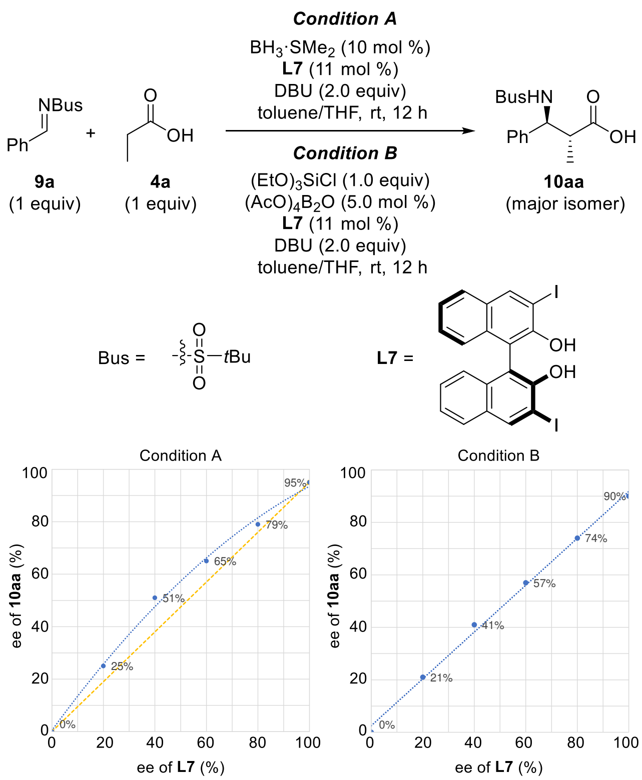
Scheme 4. Acceleration of Mannich and Allylation Reactions by Siloxy Ester Formation



Acidification of the α-proton of carboxylic acids may not be the sole cause for rate acceleration by the silylating reagent, however. During the initial optimization, we noticed that increasing the amount of carboxylate decreased the reactivity. Inhibitory effects of an excess carboxylate were likely due to coordination to the boron catalyst, which attenuated its Lewis acidity by forming a borate. The following experiments support our hypothesis (Scheme 3); whereas **5aa** was obtained in 41% yield for 30 min under the standard conditions, yield decreased to 26% in the presence of 1 equiv propionate. Therefore, silyl ester formation would decrease the detrimental coordination of free carboxylate to the boron catalyst.

If the acceleration effects of silylating reagents are caused by acidification of the α-proton and/or attenuation of the carboxylate coordination to the boron catalyst through silyl ester formation, the effects would be general for other boron-catalyzed α-functionalizations of carboxylic acids. Therefore, we applied the present conditions to previously developed reactions,[7] and found that this is indeed the case (Scheme 4). Mannich reaction[7a] between **9** and **4a** or **4m** proceeded in the presence of 2 mol % boron catalyst and $(EtO)_3SiCl$, producing **10a** or **10m** in 62% or 59% yield, respectively (Scheme 4a). Allylation reaction[7b] between **11** and **12** afforded **13** in 89% yield using 5 mol % boron catalyst and 5 mol % palladium catalyst in the presence of $(EtO)_3SiCl$ (Scheme 4b). The products were obtained in up to only 7% yield under the previous conditions without the silylating reagent.

Scheme 5. Effects of $(EtO)_3SiCl$ on Relationships between Enantiomeric Excesses of Catalyst and Products in Mannich Reaction



We propose the active nucleophile for this catalytic asymmetric aldol reaction to be chiral Si/B enediolate **2** based on the following non-linear effects experiments.[20] We first observed a linear relationship between enantiomeric excesses of the catalyst (20, 40, 60, 80, and >99% ee) and product **5ab** (19, 36, 54, 71, and 90% ee, respectively) for the aldol reaction between **3a** and **4b** in the presence of $(EtO)_3SiCl$.[16] Because the catalytic aldol reaction did not proceed in the absence of $(EtO)_3SiCl$ (Table 1, entry 2), however, it was not possible to compare this result to control conditions in the absence of $(EtO)_3SiCl$. Therefore, we investigated boron-catalyzed asymmetric Mannich reaction using BINOL-derived ligand **L7**,[7a] an optimized chiral ligand for the Mannich reaction, which proceeded either in the absence or the presence of $(EtO)_3SiCl$ (Scheme 5). Positive non-linear effects were observed in the absence of $(EtO)_3SiCl$ (Condition A), supporting our idea that the reaction proceeds through diboron enediolate **1**. In the presence of $(EtO)_3SiCl$ (Condition B), however, the relationship was linear. Thus, the reaction may not involve intermediates or active species containing more than one boron atom. The most probable active species is Si/B enediolate **2**. The fact that enantio- and diastereoselectivity depended on the silyl group (Table 1, entries 5 and 6) is also consistent with the hypothesis that the silyl group is involved in the stereo-determining step.

We then performed density functional theory (DFT) calculations to rationalize the overall reaction pathway.[16] Computed free energy profile is shown in Figure 1. First, we searched possible intermediates for deprotonation of triethoxysilyl ester derived from **4a** (Figure S1).[16] Among them, deprotonation of $\mathbf{I_1}$, where the siloxy ester coordinated to the Lewis acidic chiral boron catalyst, showed the lowest free energy barrier ($\mathbf{TS_1}$, 4.1 kcal/mol, Figure 2A). Other intermediates furnished relatively large free energy barriers. Therefore, we chose $\mathbf{I_1}$ as the starting point of the reaction pathway. After deprotonation, intermediate $\mathbf{I_2}$, which was 8.2 kcal/mol more stable than $\mathbf{I_1}$, was formed. Then, reconstitution of $\mathbf{I_2}$ generated Si/B hetero enediolate intermediate $\mathbf{I_3}$ or $\mathbf{I_4}$ with only 3.3 or 5.9 kcal/mol higher energy than $\mathbf{I_2}$, respectively. Because the energy difference between $\mathbf{I_3}$ and $\mathbf{I_4}$ was only 2.6 kcal/mol, we searched transition states for the asymmetric aldol reaction starting from $\mathbf{I_3}$ or $\mathbf{I_4}$.

The asymmetric aldol reaction from $\mathbf{I_3}$ proceeded in an inner-sphere fashion through a six-membered chair transition state $\mathbf{TS_2}$, which was only 4.4 kcal/mol higher energy than $\mathbf{I_3}$ (Figure 2B). We also calculated an outer-sphere transition state from $\mathbf{I_4}$ and aldehyde **3a** coordinating to another chiral boron complex. The transition state was, however, 11.7 kcal/mol higher than $\mathbf{TS_2}$, indicating that the outer-sphere mechanism did not contribute to the reaction. Thus, we concluded that the asymmetric aldol reaction proceeded through $\mathbf{I_3}$ and $\mathbf{TS_2}$, leading to the (2*R*,3*R*)-product. Among calculated transition states, $\mathbf{TS_2}$ existed in 80% probability.[16] Other transition states affording (2*S*,3*S*)-, (2*R*,3*S*)-, and (2*S*,3*R*)-products existed in 12.5%, 7.5%, and 0% probabilities, respectively. Thus, the calculated *syn*/*anti* ratio was 93/7. This value is consistent with the experimental result of 16/1 dr for **5aa** (Table 2). Furthermore, the computed ee value was 73%, which is qualitatively in good agreement with the experimental data (86% ee).

After asymmetric aldol reaction, boron aldolate $\mathbf{I_5}$ with 29.1 kcal/mol below the entry point ($\mathbf{I_1}$) was generated. Due to the existence of an oxophilic silyl group in the molecule, ligand exchange proceeded between boron and silicon atoms in $\mathbf{I_5}$ to generate a catalytically active boron carboxylate $\mathbf{I_7}$, which was only 1.7 kcal/mol higher energy than $\mathbf{I_5}$.

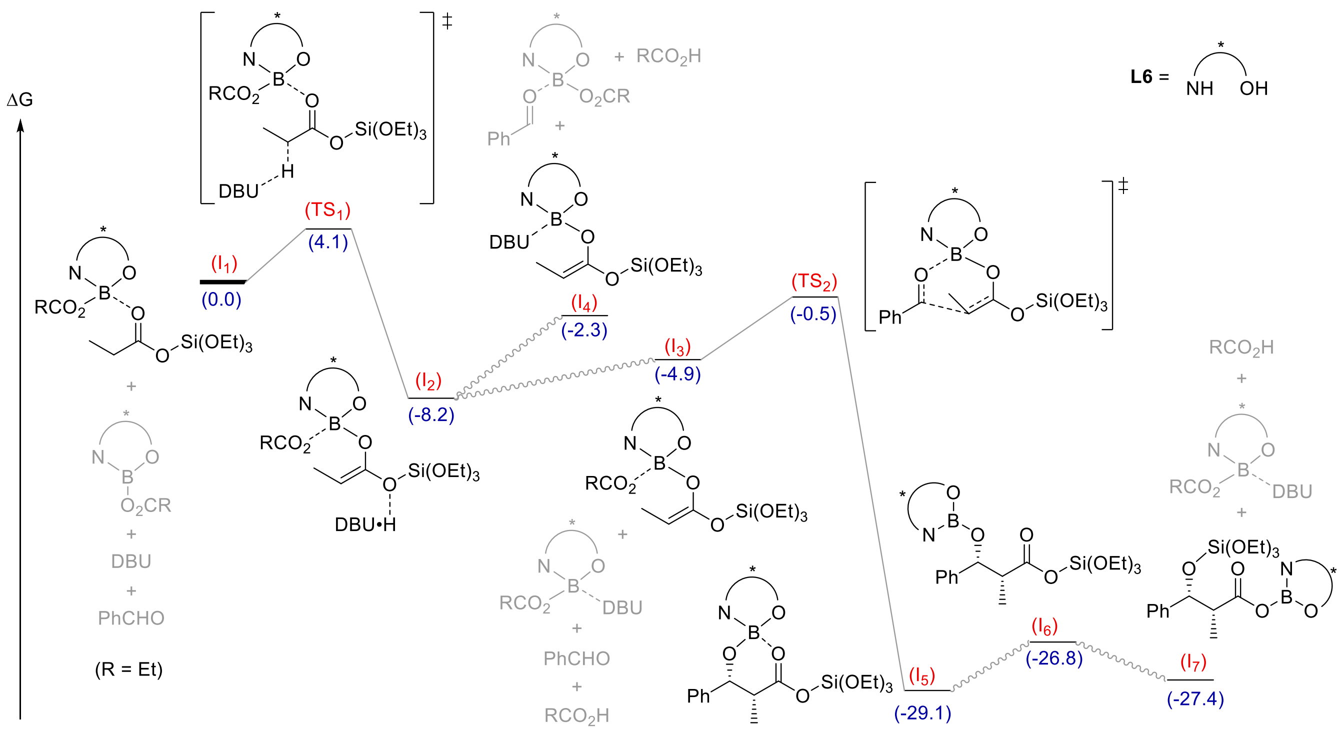


Figure 1. Computed free energy profile for the boron-catalyzed asymmetric aldol reaction. Relative free energies are in kcal/mol.

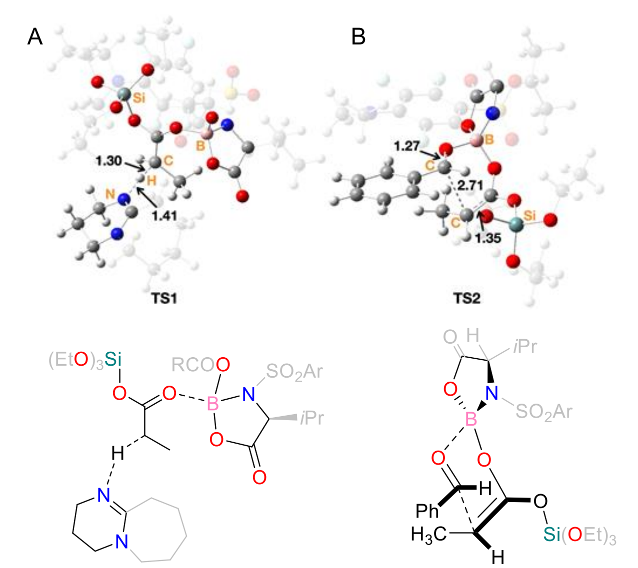


Figure 2. Transition state structures for deprotonation (A: **TS1**) and asymmetric aldol reaction (B: **TS2**) steps.

Conclusions

We developed a chiral boron-catalyzed, carboxylic acid-selective, and asymmetric aldol reaction, which was for the first time applicable to multifunctional substrates at late stages. The reaction proceeded chemoselectively at the α-position of a carboxyl group, even when substrates contained functional groups of intrinsically more acidic protons, such as ketones, esters, nitriles, and amides. Catalyst-controlled stereodivergent reactions were also possible. The transformation of carboxylic acids to siloxy esters in the reaction mixture, which can be easily cleaved in the workup operation, was critical for this catalysis. Mechanistic studies suggested three main roles of the siloxy ester formation: 1) acidification of the α-proton for acceleration of the enolization step, 2) attenuation of detrimental coordination of carboxylate to the boron catalyst, and 3) facilitation of the catalyst turnover through silylation of the boron aldolate intermediate. DFT calculations confirmed that deprotonation of the siloxy ester has a low energy barrier, and the subsequent asymmetric aldol reaction between the Si/B hetero enediolate intermediate and aldehydes proceeded in an inner sphere fashion. The computed reaction selectivity was consistent with the experimental results. We are currently applying this method to late-stage diversification of complex natural products to identify new compounds with better pharmaceutical properties.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/

All data including experimental procedures and compound characterization, NMR, and HPLC are available (PDF).

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Notes

The authors declare no competing financial interest.

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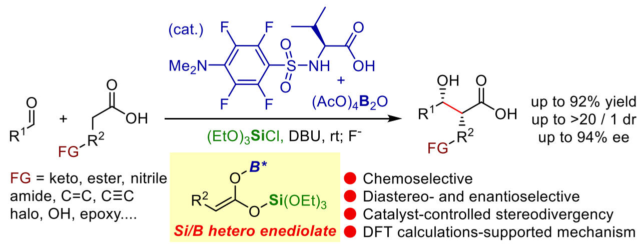

(cat.)
Me2N
(AcO)4B2O
(EtO)3SiCl, DBU, rt; F-
up to 92% yield
up to >20 / 1 dr
up to 94% ee
FG = keto, ester, nitrile
amide, C=C, C≡C
halo, OH, epoxy....
Si/B hetero enediolate
Chemoselective
Diastereo- and enantioselective
Catalyst-controlled stereodivergency
DFT calculations-supported mechanism