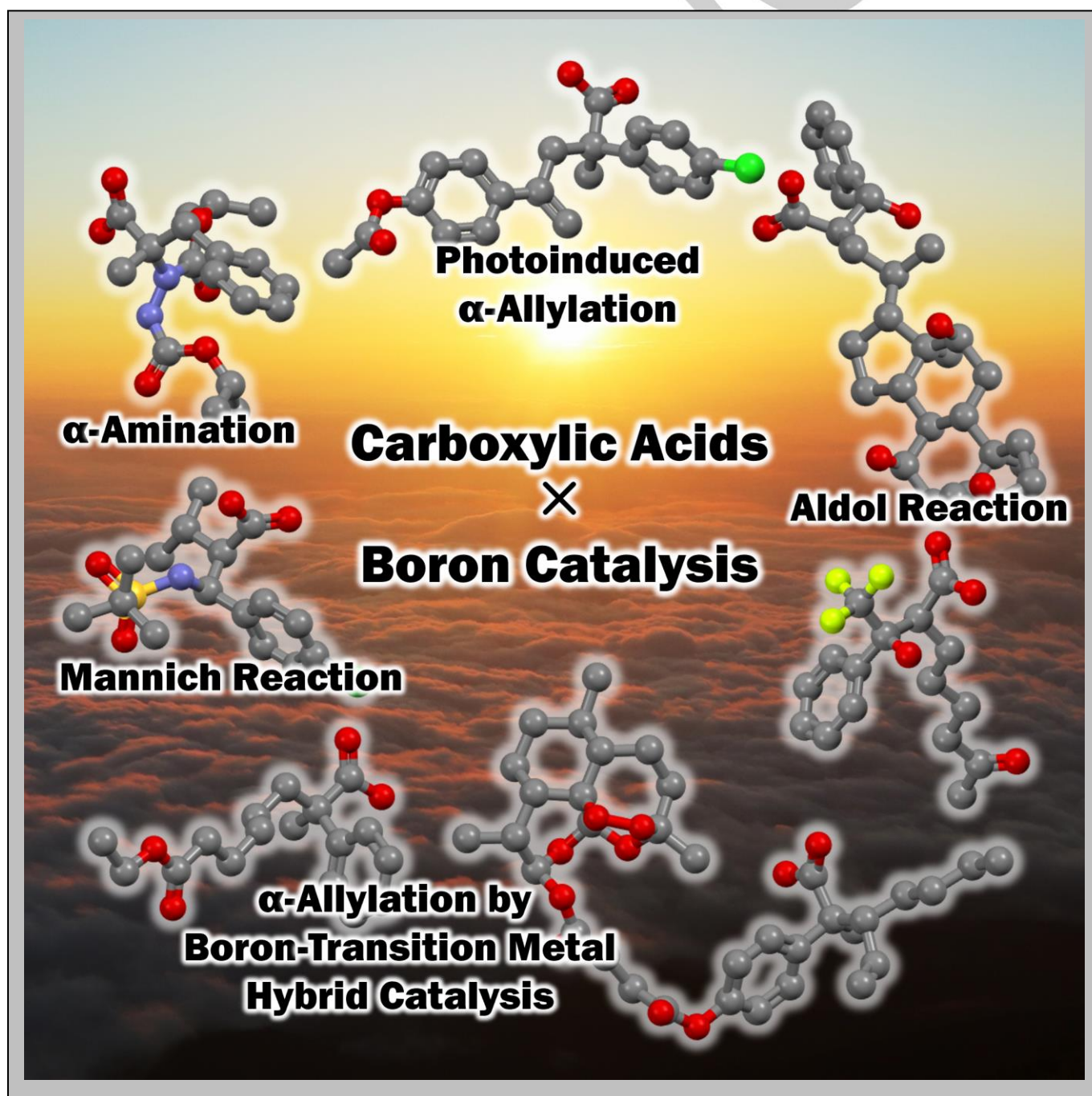| Title	Boron-Catalyzed alpha-Functionalizations of Carboxylic Acids
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Boron-Catalyzed α-Functionalizations of Carboxylic Acids

Yohei Shimizu,*[b][c] and Motomu Kanai*[a]

Abstract: Catalytic, chemoselective, and asymmetric α-functionalizations of carboxylic acids promise up-grading simple feedstock materials to value-added functional molecules, as well as late-stage structural diversifications of multifunctional molecules, such as drugs and their leads. In this personal account, we describe boron-catalyzed α-functionalizations of carboxylic acids developed in our group (six reaction types). The reversible boron carboxylate formation is key to the acidification of the α-protons and enolization using mild organic bases, allowing for chemoselective and asymmetric bond formations of carboxylic acids. The ligand effects on reactivity and stereoselectivity, substrate scopes, and mechanistic insights are summarized.
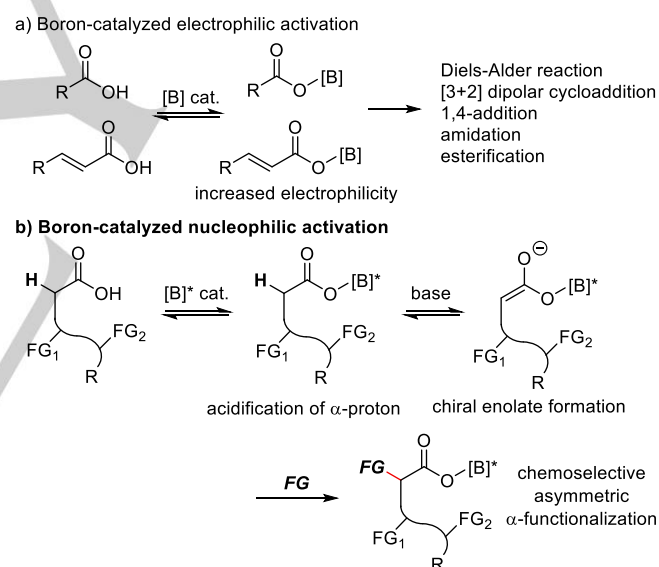
1. Introduction

Carboxylic acids are ubiquitous in natural products, pharmaceuticals, agrochemicals, and other biologically active compounds. Some carboxylic acids are abundant biomass available from vegetables, wooden materials, food-wastes, etc.[1] Hence, the catalysis to transform carboxylic acids into value-added compounds is of great importance. An approach to transform carboxylic acids is α-functionalization *via* enolate formation. The catalytic enolization of carboxylic acids, however, is challenging, because carboxylate formation is facile and attenuates the acidity of the α-protons. Thus, more than two equivalents of strong bases, such as butyllithium, are necessary to generate dianionic enediolate species, hampering the utility of carboxylic acid-enolates in organic synthesis, especially for the substrates bearing multiple functional groups.[2] Consequently, catalytic, chemoselective, and asymmetric α-functionalizations of carboxylic acids are highly desirable but remain as a formidable challenge.

Yamamoto demonstrated the utility of boron catalysts in the pioneering study on the asymmetric Diels-Alder reaction of α,β-unsaturated carboxylic acids (Scheme 1a).[3] The electrophilicity of carboxylic acids is enhanced by the reversible formation of boron carboxylates, thereby the Diels-Alder reaction is facilitated. Since then, boron-catalyzed electrophilic activation of carboxylic acids has found various applications,[4] including [3+2] dipolar cycloadditions,[3c] 1,4-addition reactions,[5] and dehydrative amidations/esterifications.[6] In contrast, the boron-

catalyzed enolate formation of carboxylic acids had been almost neglected. Nevertheless, a notable exception is a borinic acid-catalyzed aldol reaction of pyruvic acid derivatives reported by Taylor.[7] This work has proved the potential of boron compounds for the catalytic enolization of carboxylic acids. However, non-activated carboxylic acids remained unexplored.

Because the electrophilicity of carbonyl groups correlates with the acidity of α-protons, we envisaged that enolization of boron carboxylates would be possible using mild organic bases (Scheme 1b). The introduction of chiral ligands on the boron catalyst would lead to the generation of chiral enolates, enabling asymmetric catalysis. Furthermore, selective and reversible covalent bond formation between substrates and a boron catalyst would allow for furnishing carboxylic acid selectivity in the presence of multiple functional groups. Based on this hypothesis, we began our exploration of boron catalysis for chemoselective and asymmetric α-functionalizations of carboxylic acids. In this personal account, we summarize the progress of the boron-catalyzed α-functionalizations of carboxylic acids according to reaction types: Mannich reaction, aldol reaction, α-amination, α-allylation by boron/transition metal hybrid catalysis, and photoinduced α-allylation.

a) Boron-catalyzed electrophilic activation

b) **Boron-catalyzed nucleophilic activation**

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Scheme 1. Activation of Carboxylic Acids by Boron Catalysts.

Yohei Shimizu was born in Nagano, Japan. He graduated from the University of Tokyo (2006) and received his Ph.D. (2011) from the same university. He became an assistant professor at the University of Tokyo in 2011. He moved to Hokkaido University as a lecturer (2018) and currently is an associate professor there since 2020. His current research interests include the development of novel boron catalysis and photo-induced radical reactions for chemoselective transformations.
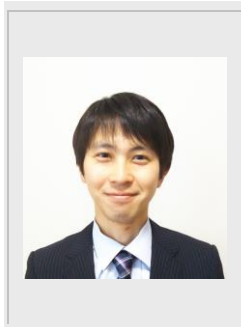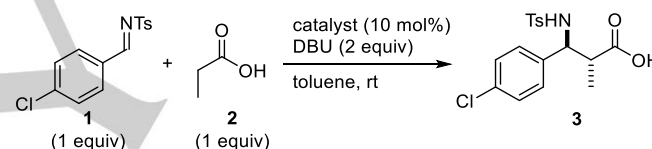
Motomu Kanai received his master's degree from The University of Tokyo (UTokyo) in 1991. In 1992, he obtained an assistant professor position at Osaka University. He received his Ph.D. from Osaka University in 1995. Then, he moved to University of Wisconsin, USA, for postdoctoral studies. In 1997, he returned to UTokyo as an assistant professor. After doing a lecturer (2000~2003) and associate professor (2003~2010), he was promoted to full professor (since 2010). He acted as a principal investigator of ERATO Kanai Life Science Project (2011~2017) and a head investigator of MEXT Grant-in-Aid for Scientific Research on Innovative Areas, "Hybrid Catalysis" (2017~2022). His research interest is catalysis linking physical and life sciences.

2. Mannich reaction

The catalytic asymmetric Mannich reaction of activated carbonyl compounds, such as 1,3-dicarbonyls and aldehydes, has been studied as a method for providing a versatile β-amino carbonyl motif.[8] Simple carboxylic acids, however, remained challenging substrates due to the low acidity of the α-protons.[9] Particularly, there was no report on the direct use of carboxylic acids for catalytic Mannich reaction before our report.[10]

2.1. Boron-Catalyzed Mannich Reaction

We began with exploring various boron compounds for the Mannich reaction of propionic acid **2** with N-tosyl aldimine **1** using 2 equivalents of DBU as a base. $BH_3 \cdot SMe_2$ is identified as a suitable catalyst (Table 1, entry 1: 95% yield, *syn/anti* 1:10). Although $BH_3 \cdot THF$ also shows comparable reactivity, $BH_3 \cdot SMe_2$ is superior in terms of reproducibility. Other boron compounds (entries 2-5), such as $BF_3 \cdot Et_2O$, Bu_2BOTf, $B(OH)_3$, and $PhB(OH)_2$, do not promote the reaction at all, while catechol borane gives the product in low yield (entry 6, 25% yield, *syn/anti* 1:6.5). The acid/base reaction between **2** and catalytic

BH_3 produces boron carboxylate,[11] in which the α-proton is markedly acidified. The theoretical calculation indicates that the pK_a value of the α-proton of triacetoxy boron is 22.4, whereas those of lithium acetate and acetone are 33.3 and 23.4, respectively. Thus, deprotonation of the α-proton proceeds by DBU to generate propionic acid-enolate. The following nucleophilic addition of the enolate to N-Ts-imine **1** produces N-Ts-β-amino acid **3**.

The method is applicable to various imines, including aromatic imines (**4**), aliphatic imines (**5**), and an α,β-unsaturated imine (**6**) (Scheme 2). The boron catalysis is carboxylic acid-selective in the presence of intrinsically more enolizable carbonyl groups, amide (**7**), ester (**8**), and ketone (**9**). Taking advantage of this chemoselectivity, the reaction is applied to drugs (**10** from anti-inflammatory loxoprofen), natural products (e.g. **11** from jasmonic acid), and tetrapeptide **12**, showcasing the utility in late-stage diversification of drug lead compounds. Specifically, the alkene moiety of jasmonic acid is intact, indicating faster acyloxyborane formation than hydroboration of the C-C double bond.

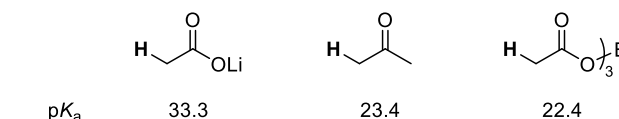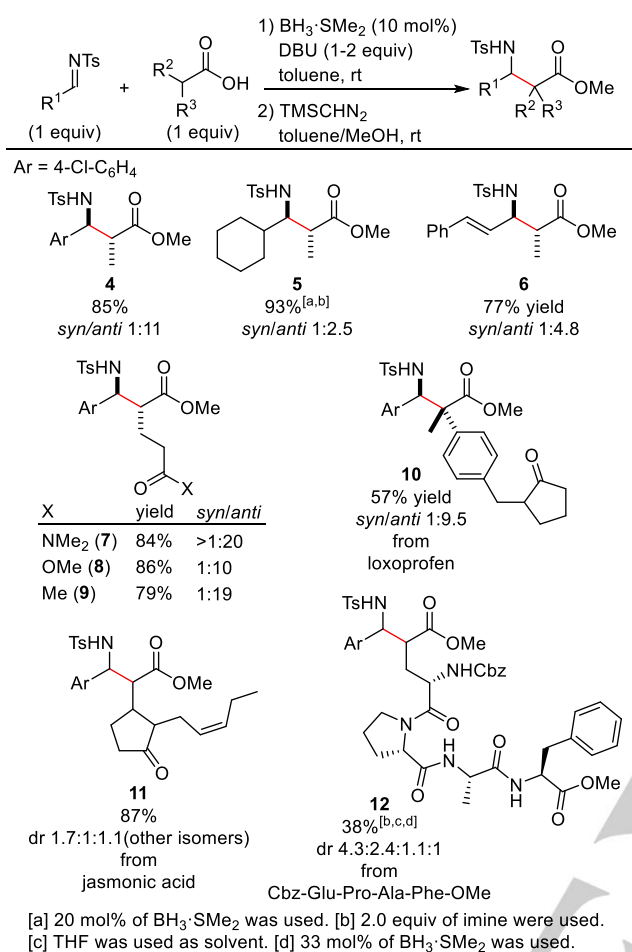**Table 1.** Screening of Boron Catalysts for Mannich Reaction of Carboxylic Acids

entry	catalyst	yield (%)[a]	*syn/anti*[a]
1	$BH_3 SMe_2$	95	1:10
2	$BF_3 Et_2O$	0	-
3	Bu_2BOTf	0	-
4	$B(OH)_3$	0	-
5	$PhB(OH)_2$	0	-
6	CatBH	25	1:6.5

pK_a	33.3	23.4	22.4

[a] Determined by ^{1}H NMR analysis.

Scheme 2 (left panel)

1) BH$_3$·SMe$_2$ (10 mol%)
DBU (1-2 equiv)
toluene, rt
2) TMSCHN$_2$
toluene/MeOH, rt

Ar = 4-Cl-C$_6$H$_4$

4
85%
syn/anti 1:11

5
93%[a,b]
syn/anti 1:2.5

6
77% yield
syn/anti 1:4.8

X	yield	syn/anti
NMe$_2$ (**7**)	84%	>1:20
OMe (**8**)	86%	1:10
Me (**9**)	79%	1:19

10
57% yield
syn/anti 1:9.5
from
loxoprofen

11
87%
dr 1.7:1:1.1(other isomers)
from
jasmonic acid

12
38%[b,c,d]
dr 4.3:2.4:1.1:1
from
Cbz-Glu-Pro-Ala-Phe-OMe

[a] 20 mol% of BH$_3$·SMe$_2$ was used. [b] 2.0 equiv of imine were used.
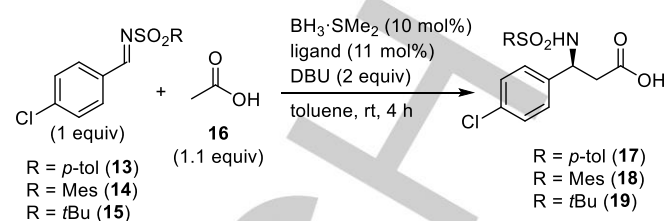[c] THF was used as solvent. [d] 33 mol% of BH$_3$·SMe$_2$ was used.

Scheme 2. Selected Examples of Boron-Catalyzed Mannich Reaction.

2.2. Catalytic Asymmetric Mannich Reaction

Next, we extended the reaction to asymmetric catalysis by introducing a chiral ligand to the boron catalyst. Since the boron atom is trivalent, two covalent bonds are available for a chiral ligand, leaving one covalent bond for boron carboxylate formation with a carboxylic acid substrate. Thus, bidentate ligands are investigated (Table 2). Although amino acid-derived ligand **L1** induces only 28% ee (entry 1),[12] simple (R)-BINOL **L2** exhibits promising enantioselectivity (43% ee, entry 2). Introducing substituents at the 3,3'-positions of the BINOL scaffold (entries 3-6, **L3-L6**), (R)-3,3'-I$_2$-BINOL **L6** is found to be an effective ligand for inducing high enantioselectivity. Changing the p-toluene sulfonyl group of imine **13** to sterically more demanding substituents (**14** and **15**), both yield and ee increase (entries 7 and 8). Finally, imine **15** with a tert-butyl sulfonyl (Bus) group furnishes product **19** in high yield and ee in a toluene/THF mixed solvent (entry 9, 83% isolated yield, 94% ee).

Table 2 (right panel)

Table 2. Optimization for the boron-catalyzed asymmetric Mannich reaction of carboxylic acids

BH$_3$·SMe$_2$ (10 mol%)
ligand (11 mol%)
DBU (2 equiv)
toluene, rt, 4 h

R = p-tol (**13**)
R = Mes (**14**)
R = tBu (**15**)

16
(1.1 equiv)

R = p-tol (**17**)
R = Mes (**18**)
R = tBu (**19**)

entry	imine	ligand	yield (%)[a]	ee (%)[b]
1	**13**	**L1**	95	-28
2	**13**	**L2**	19	-43
3	**13**	**L3**	2	-
4	**13**	**L4**	58	72
5	**13**	**L5**	73	41
6	**13**	**L6**	72	81
7	**14**	**L6**	77	90
8	**15**	**L6**	95	90
9[c]	**15**	**L6**	quant (83)	94

L1

L2: X = H
L3: X = Ph
L4: X = CF$_3$
L5: X = Br
L6: X = I
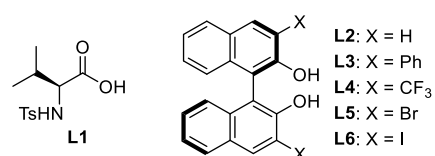
[a] Determined by ^{1}H NMR analysis. The number in parentheses is isolated yield after conversion of the Mannich product into methyl ester. [b] Determined by chiral HPLC analysis after conversion of the Mannich products into methyl esters. [c] A toluene/THF (19/1) mixed solvent was used.
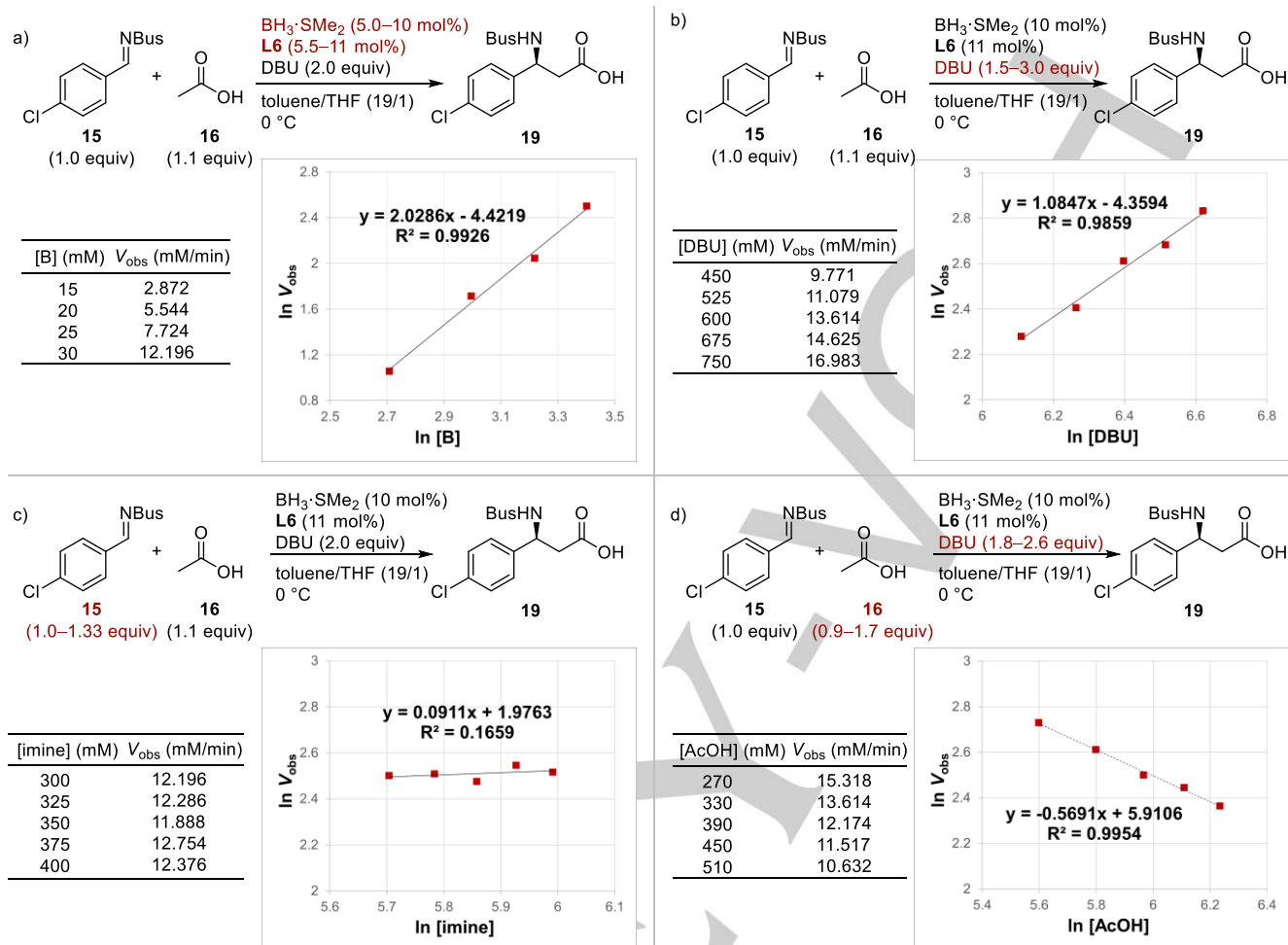
Under the optimized conditions, aromatic aldimines generally produce excellent enantioselectivity (**20** and **21**) (Scheme 3). Aliphatic aldimines are still difficult substrates; **22** is obtained in 50% yield and 53% ee using (R)-3,3'-Br$_2$-BINOL **L5** instead of **L6**. α-Substituted carboxylic acids are also competent to produce **23**-**25** in moderate to good yield (49-97%) with high enantioselectivity for major diastereomers (91-98% ee).
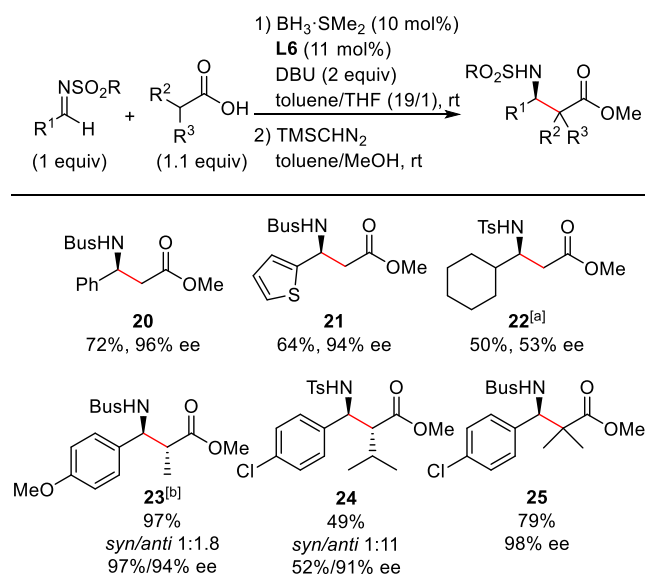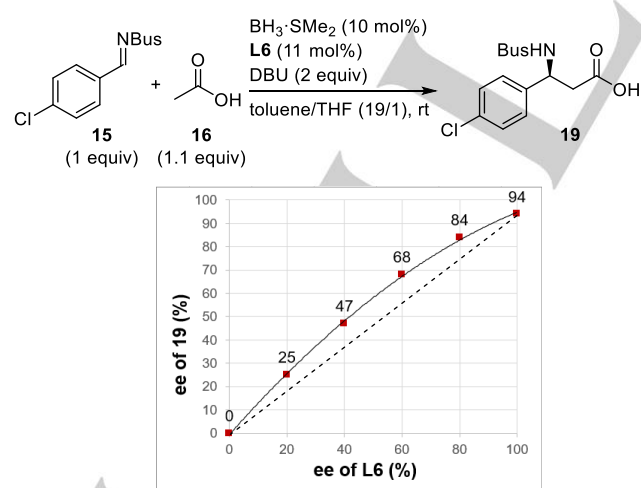
Scheme 3. Selected Examples of Boron-Catalyzed Asymmetric Mannich Reaction.

To gain mechanistic insights, we performed kinetic studies for the asymmetric Mannich reaction between acetic acid (**16**) and 4-Cl-benzaldimine **15** using (*R*)-3,3'-I$_2$-BINOL **L6** as a ligand at 0 °C. The initial reaction rate dependency on the concentration of each component is 2nd order to BH$_3$-**L6** catalyst (Scheme 4a), 1st order to DBU (Scheme 4b), 0th order to imine (Scheme 4c), and -0.6th order to acetic acid, respectively (Scheme 4d). The results highlight three important features of the reaction mechanism. First, the rate dependencies on imine (0th order) and DBU (1st order) suggest that the rate-determining step (rds) is deprotonation of carboxylic acids to form enolate species. Second, the rate dependency on the boron catalyst (2nd order) indicates that two boron catalysts are involved in rds, forming diboron enediolate species. The formation of diboron enediolate species is further supported by the observation of positive non-linear effects (Scheme 5).[13] Third, the negative order (-0.6th) to acetic acid indicates the existence of an off-cycle caused by acetate anion.

a)

BH$_3$·SMe$_2$ (5.0–10 mol%)
L6 (5.5–11 mol%)
DBU (2.0 equiv)
toluene/THF (19/1)
0 °C

15 (1.0 equiv) + **16** (1.1 equiv) → **19**

[B] (mM)	V_{obs} (mM/min)
15	2.872
20	5.544
25	7.724
30	12.196

$y = 2.0286x - 4.4219$
$R^2 = 0.9926$

b)

BH$_3$·SMe$_2$ (10 mol%)
L6 (11 mol%)
DBU (1.5–3.0 equiv)
toluene/THF (19/1)
0 °C

15 (1.0 equiv) + **16** (1.1 equiv) → **19**

[DBU] (mM)	V_{obs} (mM/min)
450	9.771
525	11.079
600	13.614
675	14.625
750	16.983

$y = 1.0847x - 4.3594$
$R^2 = 0.9859$

c)

BH$_3$·SMe$_2$ (10 mol%)
L6 (11 mol%)
DBU (2.0 equiv)
toluene/THF (19/1)
0 °C

15 (1.0–1.33 equiv) + **16** (1.1 equiv) → **19**

[imine] (mM)	V_{obs} (mM/min)
300	12.196
325	12.286
350	11.888
375	12.754
400	12.376

$y = 0.0911x + 1.9763$
$R^2 = 0.1659$

d)

BH$_3$·SMe$_2$ (10 mol%)
L6 (11 mol%)
DBU (1.8–2.6 equiv)
toluene/THF (19/1)
0 °C

15 (1.0 equiv) + **16** (0.9–1.7 equiv) → **19**

[AcOH] (mM)	V_{obs} (mM/min)
270	15.318
330	13.614
390	12.174
450	11.517
510	10.632

$y = -0.5691x + 5.9106$
$R^2 = 0.9954$

Scheme 4. Kinetic Studies on Boron-Catalyzed Asymmetric Mannich Reaction of Acetic Acid.

BH$_3$·SMe$_2$ (10 mol%)
L6 (11 mol%)
DBU (2 equiv)
toluene/THF (19/1), rt

15 (1 equiv) + **16** (1.1 equiv) → **19**

Scheme 5. Non-Linear Relationship between Enantiomeric Excesses of Boron Catalyst and Mannich Product.

Based on our mechanistic investigations, we propose a catalytic cycle for the boron-catalyzed asymmetric Mannich reaction of carboxylic acids as shown in Scheme 6. First, BH$_3$ reacts with carboxylic acid and ligand **L6**, generating the boron carboxylate intermediate accompanied by hydrogen gas evolution. The rate-determining enolization of boron carboxylate by DBU is facilitated by the second boron carboxylate species acting as a Lewis acid catalyst to generate a diboron enediolate species. The thus-generated chiral enediolate reacts with imine to form a borylated product. Finally, ligand exchange between the borylated product and DBU carboxylate produces DBU salt of the Mannich product with the regeneration of boron carboxylate for the next catalytic cycle. The negative reaction rate dependency regarding carboxylic acid is likely due to the formation of inactive borate species, in which Lewis acidity of the boron atom is attenuated.
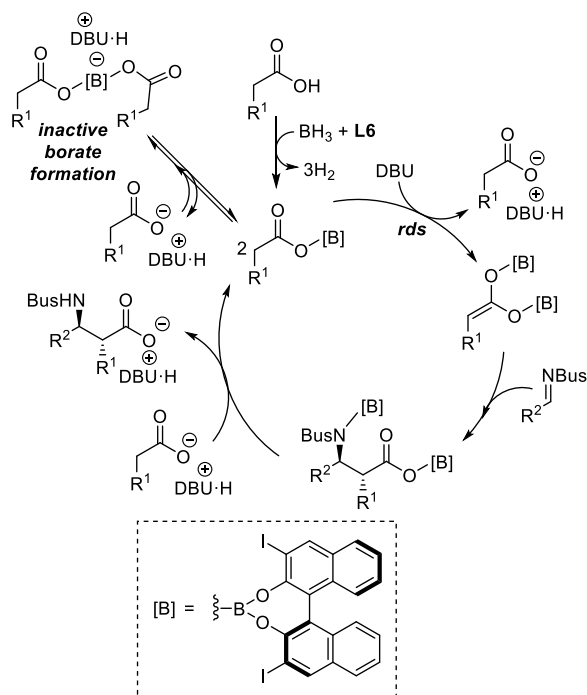
Scheme 6. Proposed Catalytic Cycle of Boron-Catalyzed Asymmetric Mannich Reaction.
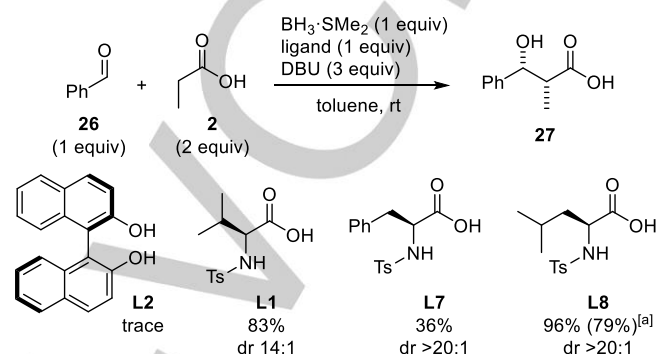
3. Aldol reaction

Aldol reaction is a fundamental C-C bond-forming reaction.[14] Carboxylic acids are scarcely used for aldol reaction due to the difficulty in enolate formation. In this context, the R_2BOTf-mediated carboxylic acid-aldol reaction using iPr_2NEt as a base reported by Evans is a pioneering example.[15] Later, Ramachandran showcased that the combination of R_2BX and NEt_3 is also effective.[16,17] While these precedents showed the utility of boron compounds for carboxylic acid-aldol reaction, the catalytic asymmetric aldol reaction of carboxylic acids remained unprecedented.[18]

3.1. Boron-Mediated Aldol Reaction

Despite the successful boron-catalyzed Mannich reaction of carboxylic acids, various boron compounds do not promote catalytic aldol reaction between benzaldehyde (**26**) and propionic acid (**2**). Nonetheless, in the presence of 1 equivalent $BH_3 \cdot SMe_2$ and 3 equivalents DBU, the reaction of **26** and **2** provides a meaningful amount of **27** (30% yield, *syn/anti* 8.5:1).[19] Other boron compounds, e.g. $BF_3 \cdot Et_2O$, BBr_3, and phenylboronic acid, do not promote the aldol reaction at all. Importantly, reactivity and diastereoselectivity are improved by installing a ligand on the boron atom (Scheme 7). In particular, the use of *N*-sulfonyl amino acids (**L1**, **L7**, and **L8**), rather than (*R*)-BINOL **L2**, is effective, among which Ts-L-Leu **L8** exhibited the highest performance to afford **27** in high yield and high *syn*-selectivity (79% isolated yield, dr >20:1). Aliphatic aldehyde **28**,

however, does not afford product **29** using **L8** (Scheme 8) likely due to competitive deprotonation of **28**. This problem is overcome by introducing L-valine-derived ligands containing a highly electron-withdrawing sulfonyl substituent on the nitrogen atom (**L9** and **L10**). The ligands facilitate selective enolization of carboxylic acids in the presence of aliphatic aldehydes. **L9** shows the highest reactivity despite low diastereoselectivity, while **L10** exhibited good reactivity and diastereoselectivity.

[a] Isolated yield after conversion of the aldol product into methyl ester was shown in parentheses.

Scheme 7. Ligand Effect on Boron-Mediated Aldol Reaction of Propionic Acid and Benzaldehyde.
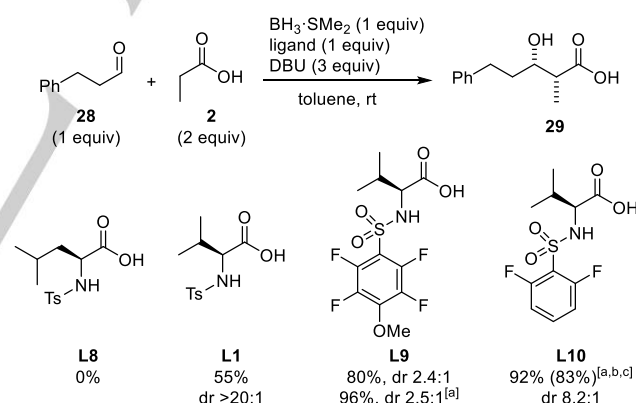

[a] $C_6H_5CF_3$ was used as solvent. [b] 2.5 equiv DBU were used. [c] Isolated yield after conversion of the aldol product into methyl ester was shown in parentheses.

Scheme 8. Ligand Effect on Boron-Mediated Aldol Reaction of Propionic Acid and Hydrocinnamaldehyde.

Employing either **L8**, **L9**, or **L10**, **2** reacts with aromatic, aliphatic, and α,β-unsaturated aldehydes (Scheme 9, **30**, **31**, and **32**). When a ketone-containing carboxylic acid is used, the reaction proceeds only at the α-position of the carboxy group (**33**, 48% yield, *syn/anti* 15:1). This result is in sharp contrast to the reaction under Evans' conditions (2.1 equivalents Bu_2BOTf and 2.2 equivalents iPr_2NEt),[15] promoting the aldol reaction at the α-position of the ketone carbonyl moiety (**34**, 39% yield). Thus, our method shows complementary chemoselectivity. The carboxylic

acid-selectivity is further confirmed by the substrates containing amide (**35**) and ester (**36**) groups. Alkene (**37**) and alkyne (**38**) moieties are intact. Anti-inflammatory drugs, loxoprofen (**39**) and indomethacin (**40**), also afford the products in high yield.


[a] 2.5 equiv DBU were used. [b] **L9** was used as a ligand.
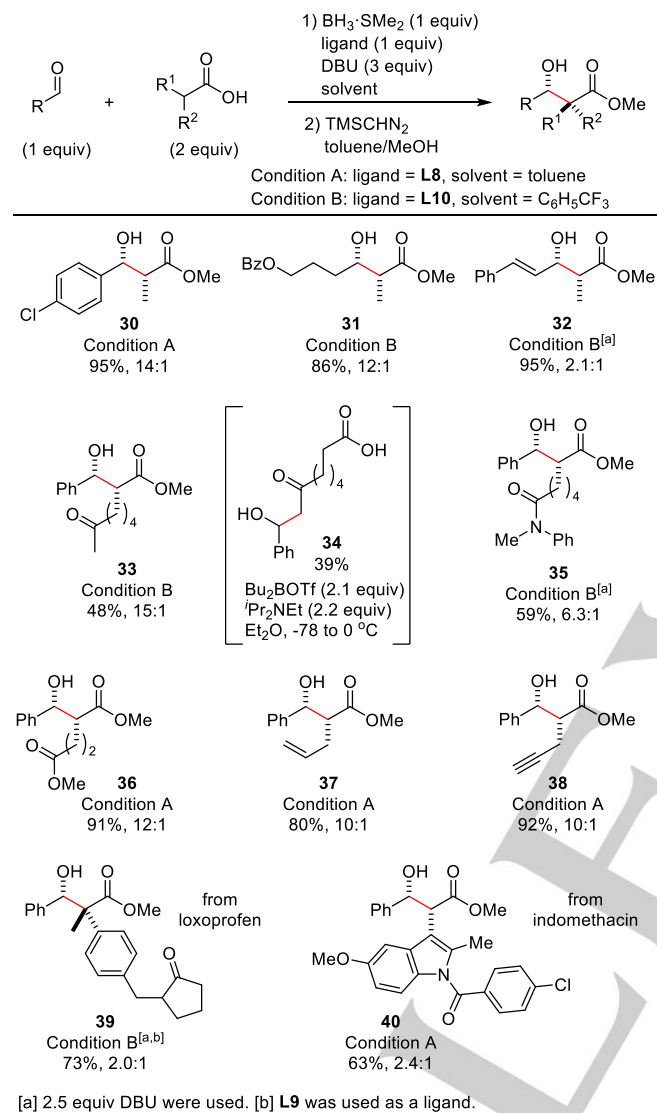
Scheme 9. Selected Examples of Boron-Mediated Aldol Reaction.

3.2. Boron-Catalyzed Aldol Reaction with Trifluoromethyl Ketones

The requirement of a stoichiometric amount of $BH_3 \cdot SMe_2$ for the aldol reaction is likely due to the formation of catalytically inactive, stable boron aldolate **41** (Scheme 10). Destabilization of the boron aldolate is necessary for catalyst turnover. Thus, the boron-catalyzed aldol reaction of carboxylic acids with trifluoromethyl ketones is examined, resulting in sterically congested unstable boron aldolate **42**, thereby facilitating the

regeneration of catalytically active boron carboxylate species (**43** and **44**).[20] The carboxylic acid aldol reaction with trifluoromethyl ketones proceeds using a catalytic amount of $BH_3 \cdot SMe_2$ (Scheme 11). This method is again carboxylic acid-selective (**48**, **49**, and **50**) and applicable to modifications of an *N*-protected amino acid (**51**) and a natural product (**52**). Tertiary alcohols containing a trifluoromethyl group are a unique motif in biologically active compounds due to the electronegativity and lipophilicity of fluorine atoms.[21] Therefore, this catalytic method will contribute to drug discovery and development by introducing the motif at a late stage of the synthesis.
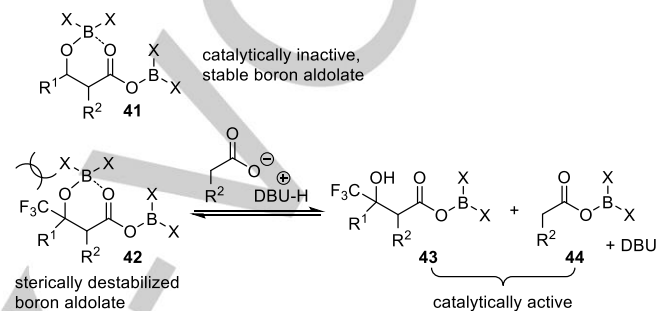

Scheme 10. Postulated Boron Aldolate Complexes and Hypothesis to Realize Catalyst Turnover.
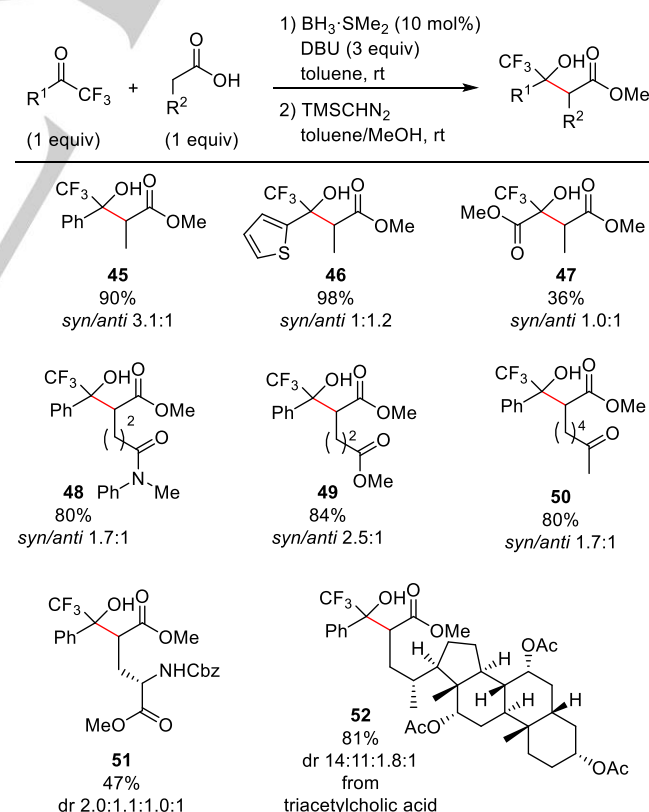
Scheme 11. Selected Examples of Boron-Catalyzed Aldol Reaction with Trifluoromethyl Ketones.
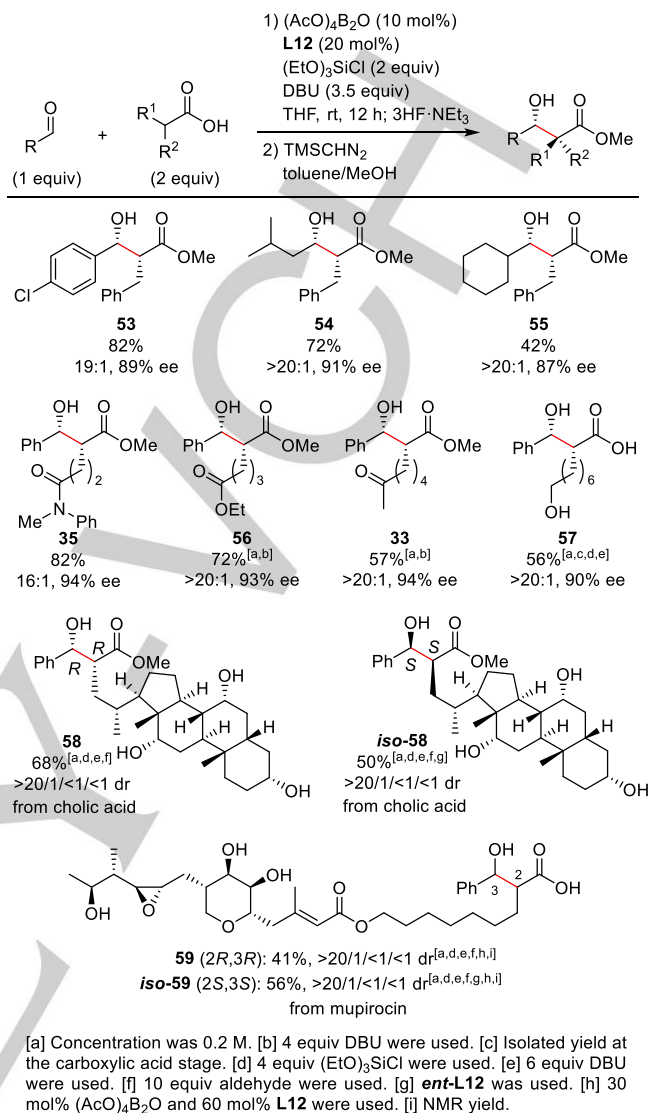
3.3. Boron-Catalyzed Asymmetric Aldol Reaction of Aldehydes under Traceless Siloxy Ester Formation

The same approach is not applicable to realize the boron-catalyzed aldol reaction between carboxylic acids and aldehydes. Hence, we conceive *in-situ* pre-conversion of carboxylic acids to siloxy esters to facilitate the catalyst turnover.[22] The addition of a silyl chloride facilitates the catalyst turnover, and 2 equivalents $(EtO)_3SiCl$ exhibit the highest performance for the reaction between propionic acid (**2**) and benzaldehyde (**26**) using $(AcO)_4B_2O$ as a boron catalyst (Scheme 12). *N*-Aryl sulfonyl amino acid ligands bearing fluorine substituents (**L11** and **L12**) are crucial to induce enantioselectivity. Although a ligand with pentafluorobenzene group (**L11**) shows high enantioselectivity (85% ee), diastereoselectivity is only 1.6:1. Substitution of the 4-fluorine atom with an electron-donating Me_2N group (**L12**) significantly improves diastereoselectivity without eroding the reactivity and enantioselectivity. Further improvement of diastereoselectivity is achieved by decreasing the amount of DBU from 4 equivalents to 3.5 equivalents and concentration from 0.2 M to 0.1 M (69% yield, 18:1 dr, 86% ee).


[a] 3.5 equiv DBU were used in 0.1 M THF. Yield of the isolated product.
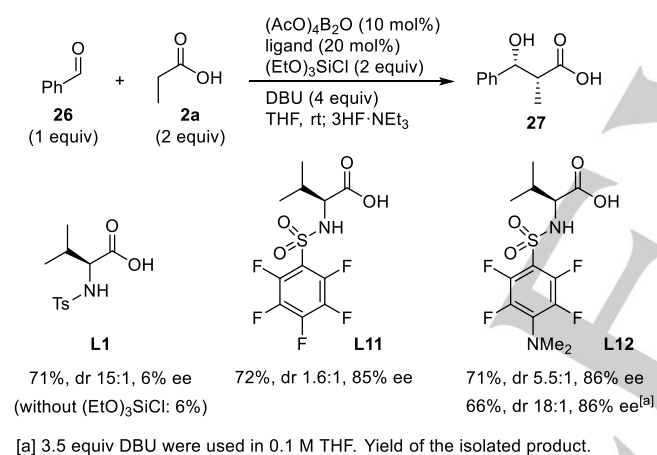
Scheme 12. Ligand Effects on Boron-Catalyzed Aldol Reaction.

Substrate scope is broad (Scheme 13). Both aromatic (**53**) and aliphatic (**54**, **55**) aldehydes are applicable, affording the aldol products in high enantio- and diasteoselectivity. The carboxylic acid-selectivity over other carbonyl groups (**35**, **56**, and **33**) retains in the presence of $(EtO)_3SiCl$. A carboxylic acid bearing a free hydroxy group (**57**) is competent by increasing the amounts of $(EtO)_3SiCl$ and DBU to 4 and 6 equivalents, respectively. A polyhydroxy natural product, cholic acid (**58** and ***iso*-58**), is also applicable by adjusting the amount of $(EtO)_3SiCl$ and DBU. Notably, newly generated stereocenters are highly controlled by the chiral ligand: **L12** provides (2*R*,3*R*)-isomer **58** and ***ent*-L12** provides (2*S*,3*S*)-isomer ***iso*-58** exclusively. The catalyst-dependent stereodivergency is also observed for an epoxide-containing natural product, mupirocin (**59** and ***iso*-59**).

[a] Concentration was 0.2 M. [b] 4 equiv DBU were used. [c] Isolated yield at the carboxylic acid stage. [d] 4 equiv $(EtO)_3SiCl$ were used. [e] 6 equiv DBU were used. [f] 10 equiv aldehyde were used. [g] ***ent*-L12** was used. [h] 30 mol% $(AcO)_4B_2O$ and 60 mol% **L12** were used. [i] NMR yield.

Scheme 13. Selected Examples of Boron-Catalyzed Asymmetric Aldol Reaction.

The siloxy ester and *tert*-butyl ester of propionate show contrasting reactivity (Scheme 14); the aldol product is obtained in high yield from siloxy ester, while no product is formed from *tert*-butyl ester regardless of the presence or absence of $(EtO)_3SiCl$. Calculated pK_a values for $CH_3COOSi(OEt)_3$ (pK_a 19.6) and $CH_3COOtBu$ (pK_a 26.0) are supportive of the results. In addition, siloxy ester formation suppresses the catalyst-deactivating coordination of carboxylate to the Lewis acidic boron catalyst (see Scheme 6).
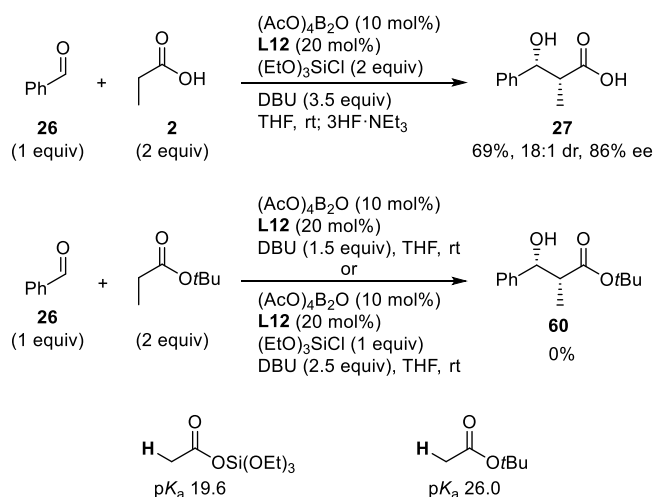
Calculated by Gaussian 16 (B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)).

Scheme 14. Comparison of the Reactivity of Siloxy Ester and *tert*-Butyl Ester.

The relationship between enantiomeric excesses of chiral ligand **L12** and aldol product **27** is linear (Scheme 15a) in contrast to the nonlinear relationship observed in the asymmetric Mannich reaction of carboxylic acids (Scheme 5). Indeed, the nonlinearity of the asymmetric Mannich reaction disappears under the present reaction conditions (Scheme 15b). These results are consistent with our hypothesis that only one chiral boron catalyst is involved in the catalytic cycle, and a chiral Si/B enediolate is the most plausible active enolate.
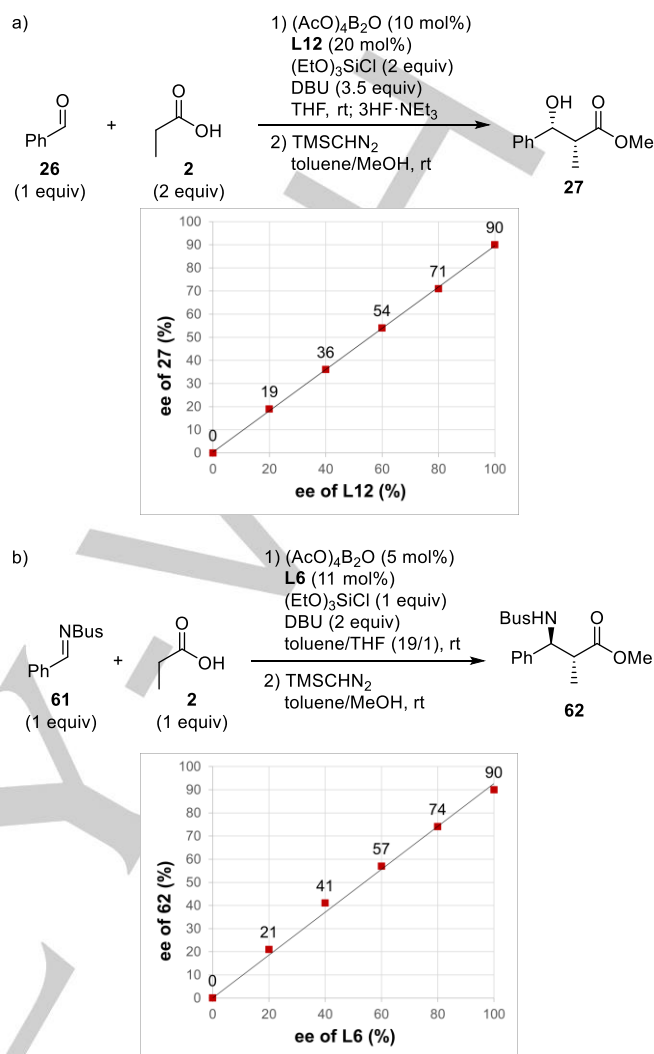
Scheme 15. Effects of (EtO)$_3$SiCl on Relationships between Enantiomeric Excesses of Catalyst and Products in Aldol Reaction (a) and Mannich Reaction (b).

Density functional theory (DFT) calculations provide important insights into the reaction mechanism (Figure 1). Deprotonation of the siloxy ester proceeds through coordination to the chiral boron catalyst (**I$_1$**) to afford (*Z*)-enolate **I$_2$**. After reconstitution to **I$_3$**, the asymmetric aldol reaction proceeds through a six-membered boat transition state **TS$_2$**, giving (2*R*,3*R*)-boron aldolate **I$_5$**, whose configurations are matched with product **27**. Finally, the ligand exchange between the boron and the silicon atoms proceeds to generate catalytically active boron carboxylate **I$_7$**, which is only 1.7 kcal/mol higher in energy than **I$_5$**. This low-barrier Si/B exchange is in accord with the fact that the boron catalyst turns over by the addition of the silyl chloride.
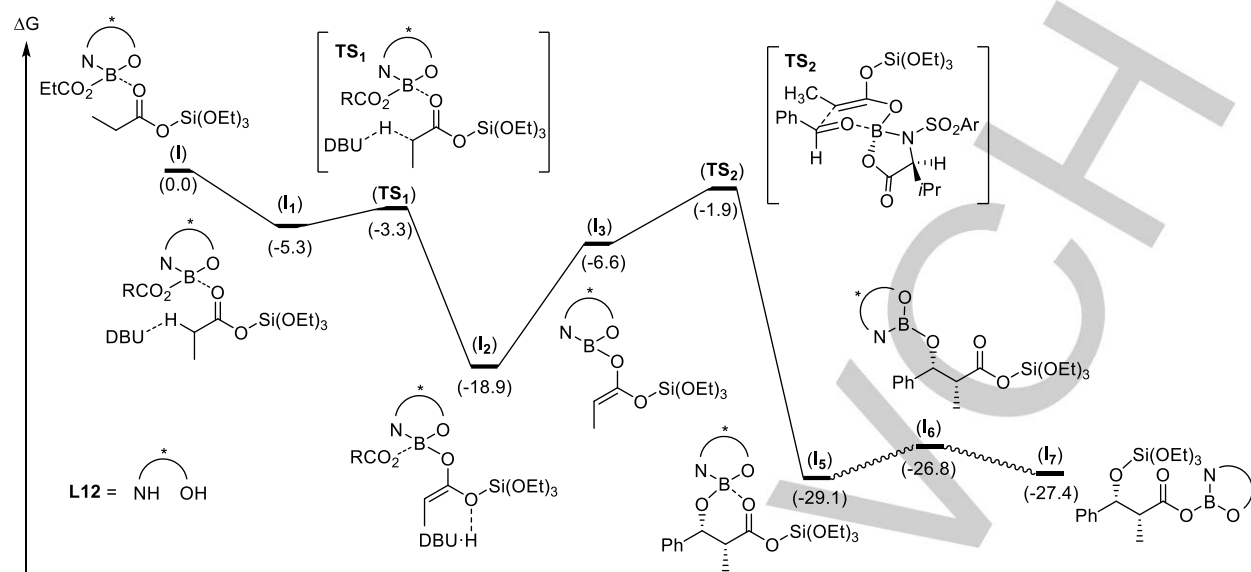
Figure 1. Computed Free Energy Profile for the Boron-Catalyzed Asymmetric Aldol Reaction. Relative free energies are in kcal/mol.

4. α-Amination

The boron-catalyzed enolate formation is effective not only for C-C bond formations but also for the C-N bond formation.[23,24] When dialkyl azodicarboxylate is used as an electrophilic nitrogen source, α-amination of carboxylic acids proceeds smoothly by the boron catalysis to afford α-amino acid derivatives (Scheme 16).[25] $(AcO)_4B_2O$ is the suitable boron catalyst compared to $BH_3 \cdot SMe_2$ and other boron sources. Sterically demanding α,α-disubstituted glycine derivatives (**66**, **67**, and **68**) are readily obtained from the corresponding carboxylic acids. The use of chiral ligand **L9** results in moderate enantioinduction (Scheme 17, **70**: 79% yield, 45% ee), proving the potential of the reaction to procure chiral amino acid derivatives from simple carboxylic acids.
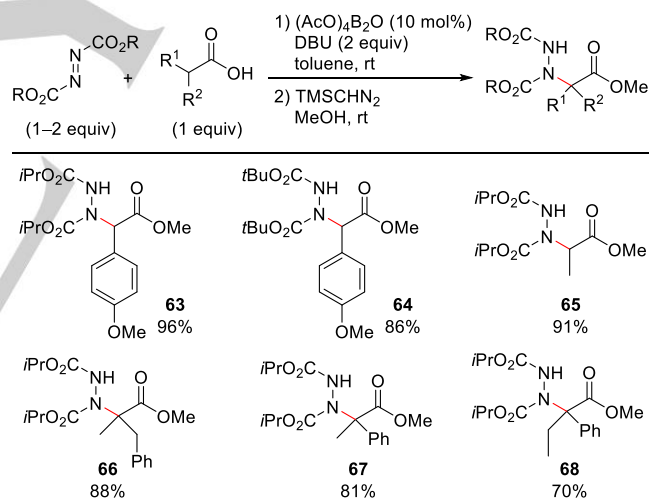
Scheme 16. Selected Examples of Boron-Catalyzed α-Amination of Carboxylic Acids.
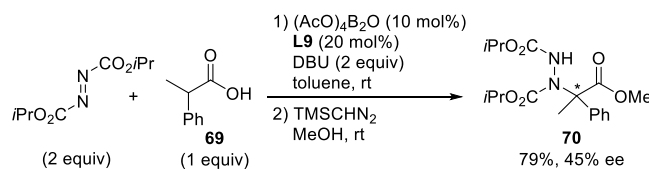
Scheme 17. Boron-Catalyzed Asymmetric α-Amination of Carboxylic Acids.

Since the α-amination product contains a COOH group, sequential condensation with glycine methyl ester is possible to afford dipeptide derivative **73** (78% yield for 2 steps) (Scheme 18a). TFA-mediated Boc group cleavage from **64** followed by N−N bond scission by hydrogenolysis under Raney-Ni/H$_2$ conditions provides α-amino acid methyl ester **74** (Scheme 18b).
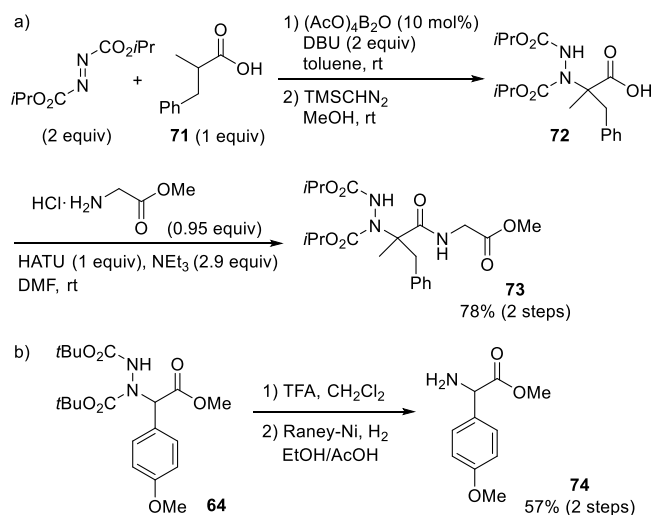

Scheme 18. Transformations of α-Amination Products.

5. Boron/Transition Metal Hybrid Catalysis

To broaden the utility, we combined the boron-catalyzed chemoselective enolate formation of carboxylic acids with transition metal-catalyzed electrophile generation.

5.1. Boron/Palladium Hybrid Catalysis for Linear-Selective Migratory Allylation of Carboxylic Acids

To assess the feasibility of the hybrid catalysis, we conceived allyl group migration from *O*-allyl esters to α-*C*-allyl carboxylic acids by employing π-allylpalladium chemistry.[26,27] The generation of π-allylpalladium species from *O*-allyl ester concomitantly produces carboxylate, which is intercepted and activated by the boron catalyst to form boron enediolate (Scheme 19). The generated π-allylpalladium species and the boron enediolate couple to afford the α-*C*-allyl carboxylic acid.
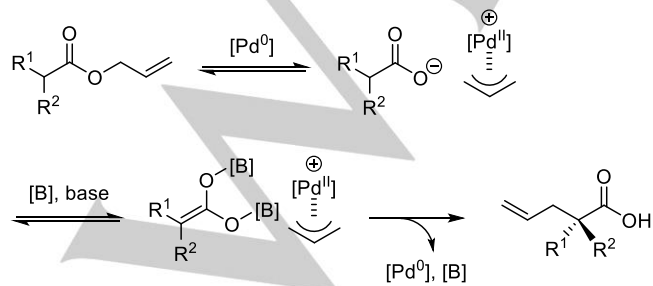

Scheme 19. Working Hypothesis for Migratory Allylation of Carboxylic Acids by Boron/Palladium Hybrid Catalysis.

The reaction proceeds in high yield and enantioselectivity using (AcO)$_4$B$_2$O-**L9** as the boron catalyst and [Pd(allyl)Cl]$_2$-**L$_{Pd}$** as the palladium catalyst,[28] constructing a chiral quaternary carbon (Table 3, entry 1, 91% yield, 90% ee). A proper combination of chiral ligands on the boron and palladium catalysts (entries 2-6), including chirality match/mismatch (entries 1 vs 5), is crucial to afford high enantioselectivity. The base also affects the enantioselectivity; enantioselectivity is excellent when using *N*-methyl-pyrrolidine (entries 7 and 8).

Table 3. Optimization of boron/palladium hybrid catalysis for asymmetric migratory allylation of *O*-allyl esters to α-*C*-allyl carboxylic acids.
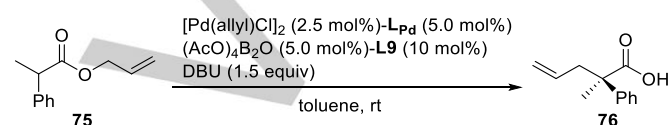

entry	Deviation from optimized conditions	yield (%)[a]	ee (%)
1	none	(91)	90
2	xantphos instead of **L$_{Pd}$**	92	30
3	(*R,R*)-Ph-BPE instead of **L$_{Pd}$**	99	55
4	without **L9**	99	32
5	***ent*-L9** instead of **L9**	97	4
6	**L6** instead of **L9**	22	69
7	*N*-Me-pyrrolidine instead of DBU	55	97
8[b]	*N*-Me-pyrrolidine instead of DBU	83 (75)	96
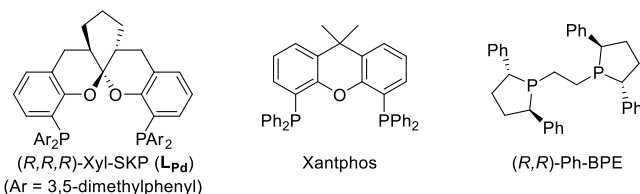
[a] Yield of isolated product in parentheses. [b] (AcO)$_4$B$_2$O (10 mol%) and **L9** (20 mol%) were used.

The optimized conditions are applicable to various α-aryl *O*-allyl esters (Scheme 20, **77**, **78**, and **79**). Less enolizable substrates (**80**) bearing α,α-dialkyl substituents are also competent. In this case, (*S$_p$,S$_p$,R,R*)-DMM-Mandyphos is the

better ligand for the palladium catalyst than **L_Pd**. Substituents at the allyl group are also tolerated (**81** and **82**). Allyl groups are introduced in a linear fashion regardless of the substrate structures, linear- or branch-allyl ester (**82**). The chemoselectivity of the boron catalyst secures the C-C bond formation at the α-position to the carboxy group in the presence of other carbonyl groups (**84** and **85**).
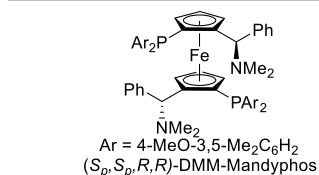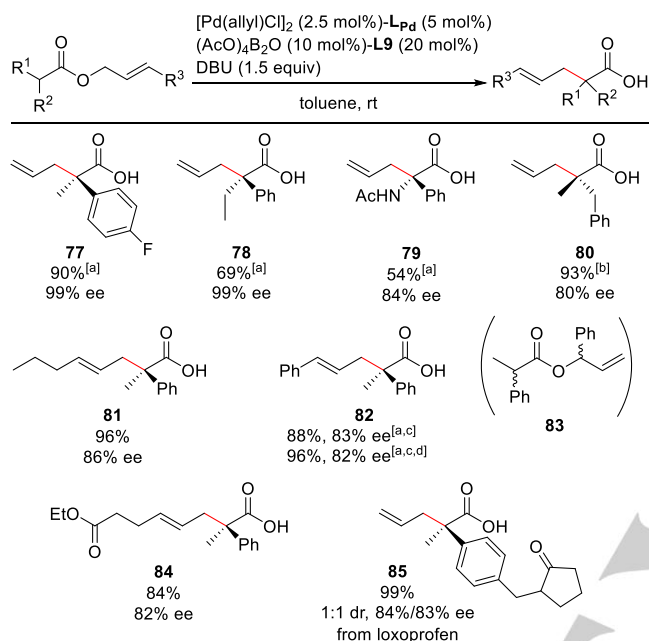
Scheme 20. Selected Examples of Asymmetric Migratory Allylation of Carboxylic Acids by Boron/Palladium Hybrid Catalysis.

When an equimolar mixture of two allyl carboxylates (**86** and **87**) is subjected to the reaction conditions, all four possible products (**88**, **89**, **90**, and **91**) are obtained (Scheme 21a). The result indicates that the reaction proceeds through ionization of the allyl ester to generate boron enolate and π-allylpalladium species, and the coupling between the two active species proceeds in an intermolecular fashion. Consistent with this notion, the intermolecular reaction (Scheme 21b) between carboxylic acids and allyl acetate proceeds with comparable enantioselectivity to the migratory allylation (compare **76** in Scheme 21b and Table 3).
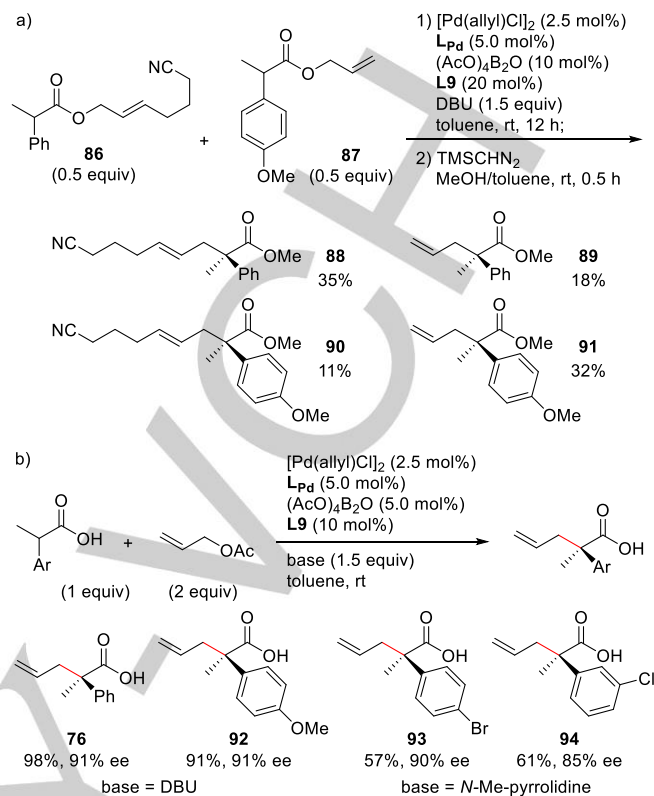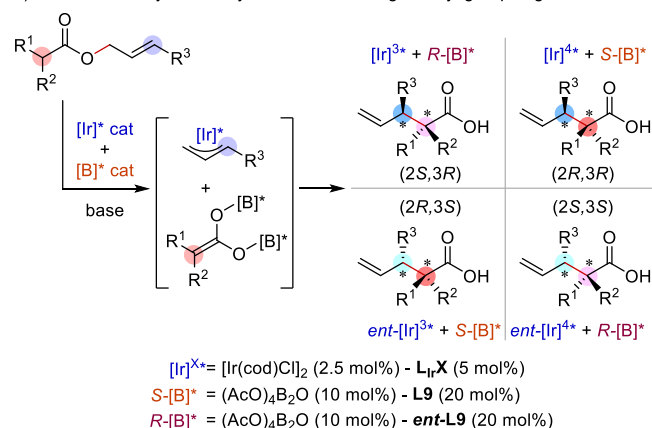

Scheme 21. Intermolecular α-Allylation of Carboxylic Acids.
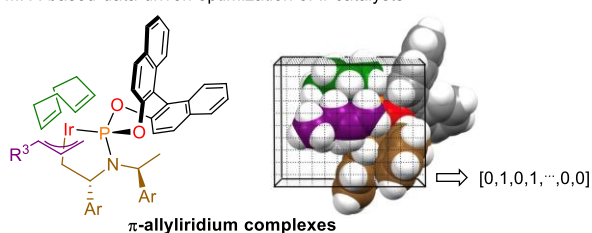
5.2. Boron/Iridium Hybrid Catalysis for Branch-Selective Migratory Allylation of Allyl Esters

A branch-selective migratory allylation producing contiguous tertiary-quaternary stereocenters is possible by employing chiral boron/iridium hybrid catalysis.[29,30] In addition to the branch/linear constitutional selectivity (b/l), enantioselectivity and diastereoselectivity must be controlled in this reaction. Moreover, stereodivergent accessibility to all the stereoisomers is desirable to maximize the utility of the reaction (Scheme 22a).[31] Although traditional try-and-error optimization approaches to controlling multiple selectivities are complicated and unsuccessful, a data-driven approach has proved effective.[32] Since the π-allyliridium complex is the key intermediate for determining b/l and stereoselectivities, this complex is used for molecular field analysis (MFA), regression analysis between the reaction outcomes and molecular fields of calculated 3D molecular structures (Scheme 22b).[32c] With one set of molecular fields obtained from the calculation of the π-allyliridium complex, four sets of target variables are obtained: b/l and diastereoselectivity (dr) in reactions using ligands **L9** and **ent-L9**. We employ steric indicator fields composed of indicator variables (0 and 1 values) as the molecular fields, and LASSO[33] and Elastic Net[34] as regression methods.[35] This approach efficiently visualizes the important factor on a 3D model of the π-allyliridium complex to lead to further design of the ligand on the iridium catalyst.

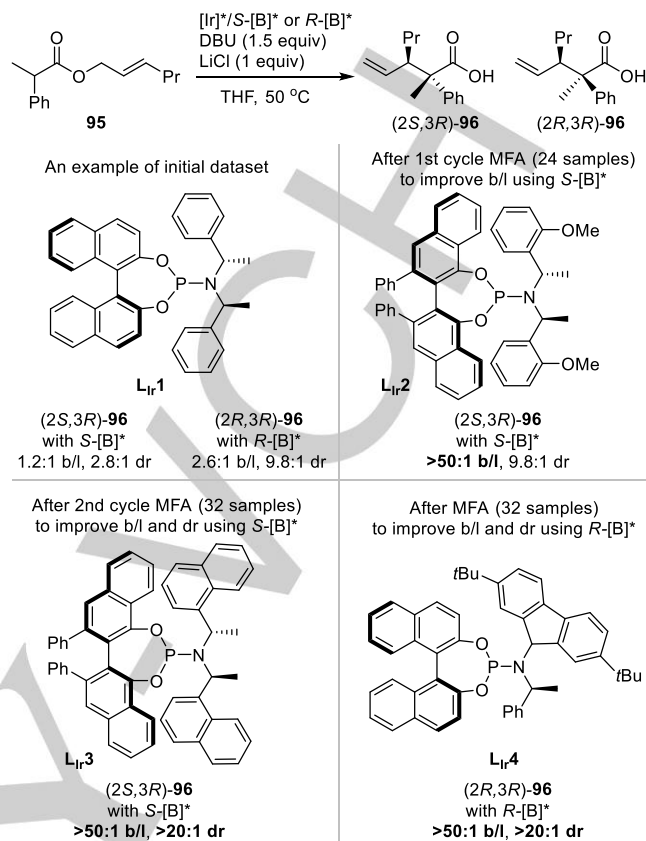a) Boron/iridium hybrid catalysis for stereodivergent allyl group migration

[Ir]^X*= [Ir(cod)Cl]₂ (2.5 mol%) - **L_Ir**X (5 mol%)
S-[B]* = (AcO)₄B₂O (10 mol%) - **L9** (20 mol%)
R-[B]* = (AcO)₄B₂O (10 mol%) - **ent-L9** (20 mol%)

b) MFA-based data-driven optimization of Ir catalysts

π-allyliridium complexes

**Scheme 22.** Data-Driven Optimization of Boron/Iridium Hybrid Catalysis for Stereodivergent Asymmetric Migratory α-*C*-Allylation.

Scheme 23. MFA-Based Ligand Development.

Initial training datasets are constructed using readily available 12 phophoramidite ligands and two substrates to afford four sets of 24 target variables (b/l and dr using either *S*-[B]* or *R*-[B]*). Examples of the initial data using **L_Ir1** is shown in Scheme 23. Apparently, b/l and dr are far from satisfactory for both reactions with *S*-[B]* and *R*-[B]*, composed of (AcO)₄B₂O (10 mol%)-**L9** and -**ent-L9** (20 mol%), respectively. According to the visualized indication of ligand modification suggested by the MFA using initial datasets, 4 new ligands are designed to improve b/l selectivity when using *S*-[B]*. Indeed, one of the new ligands **L_Ir2** exhibits markedly improved b/l selectivity (>50:1) with 9.8:1 dr. To further improve dr, a second MFA is performed using the data of all 32 reactions, including those using 4 new ligands. This time, visualized indications of ligand modification for both b/l and dr improvements are considered, leading to the design of **L_Ir3**, which affords (2*S*,3*R*)-**96** with 99% ee, >50:1 b/l, and >20:1 dr. Similarly, a ligand of iridium catalyst for (2*R*,3*R*)-**96** is designed by performing MFA with the data of 32 reactions. Designed ligand **L_Ir4** exhibits excellent performance, giving (2*R*,3*R*)-**96** with 99% ee, >50:1 b/l, and 20:1 dr when *R*-[B]* is used.

The optimized combinations of the chiral boron and iridium catalysts are as follows: *S*-[B]*/[Ir]³* for (2*S*,3*R*)-products and *R*-[B]*/[Ir]⁴* for (2*R*,3*R*)-products. The developed hybrid catalysis exhibits broad applicability, good functional group tolerance (**99-104**), and generally excellent selectivity (Scheme 24). Stereodivergent catalysis applicable to the synthesis of β-aliphatic-substituted carbonyl compounds bearing quaternary-tertiary contiguous stereocenters had yet to be developed before our achievement.
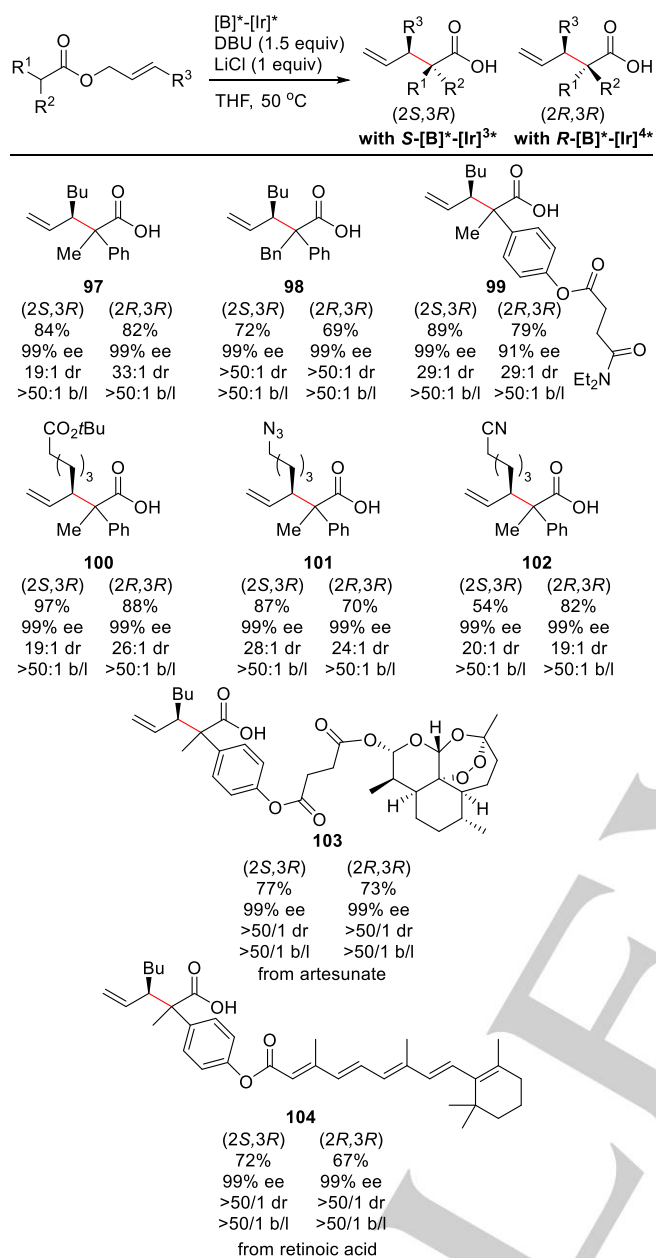
Scheme 24. Selected Examples of Asymmetric Migratory Allylation of Carboxylic Acids by Boron/Iridium Hybrid Catalysis.

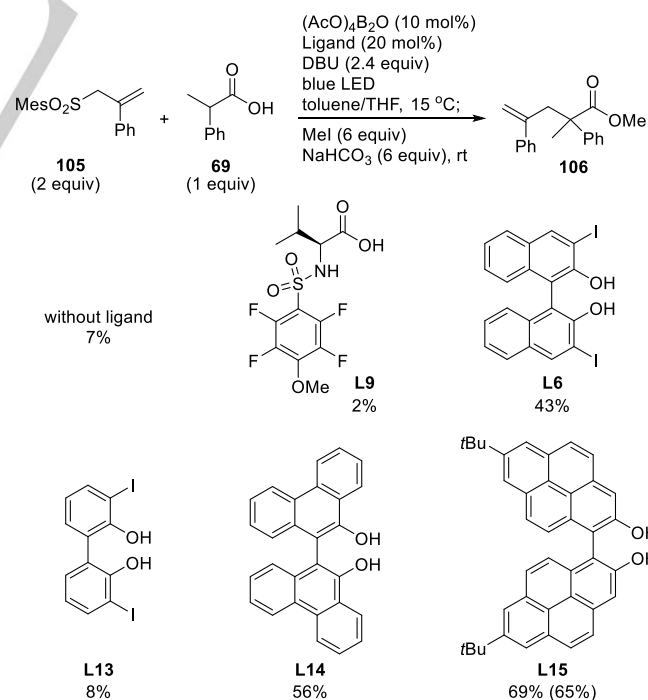# 6. Visible Light-Driven α-Allylation of Carboxylic Acids

Radical reactions of carboxylic acids exhibit unique reactivities.[36] Catalytic generation of α-radical of carboxylic acids,[37] however, is not trivial, since decarboxylation occurs easily.[38] We anticipate that boron carboxylate formation would suppress the undesired decarboxylation. Photoexcitation of the electron-rich boron enediolate would induce single-electron transfer to a proper

electron-accepting reagent and generate radical species for subsequent reaction sequence (Scheme 25).
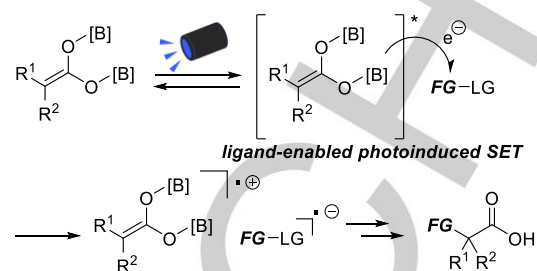
Scheme 25. Working Hypothesis for Visible Light-Driven α-Functionalization of Carboxylic Acids.

The photoinduced radical reaction of carboxylic acid **69** and allyl sulfone **105** proceeds using a boron catalyst and DBU under blue LED irradiation, affording α-allyl carboxylic acid **106** (Scheme 26).[39] Control experiments indicate that the boron catalyst, DBU, and blue LED irradiation are all necessary to promote the reaction. Importantly, ligands on the boron atom are highly influential to the reactivity. The reaction proceeds in only 7% yield without ligand, and there is no improvement when using **L9**. In contrast, yield markedly improves using 3,3'-I_2-BINOL ligand **L6**. While yield drops significantly when a ligand with biphenyl scaffold **L13** is used, an extension of the π-system of the scaffold (**L14**) endows a positive effect, and bipyrenol **L15** is identified as the optimal ligand.[40]


Scheme 26. Ligand Effect on Visible Light-Induced Boron-Catalyzed α-Allylation of Carboxylic Acids.

Miscellaneous α-aryl carboxylic acids, including the anti-inflammatory drug loxoprofen (**109**) afford α-allylated products (**107-112**) (Scheme 27). For the reaction producing α-aryl acetic acid **112**, higher yield is obtained with 3,3'-I$_2$-BINOL ligand **L6** rather than bipyrenol ligand **L15**.


[a] Ligand **L6** was used.
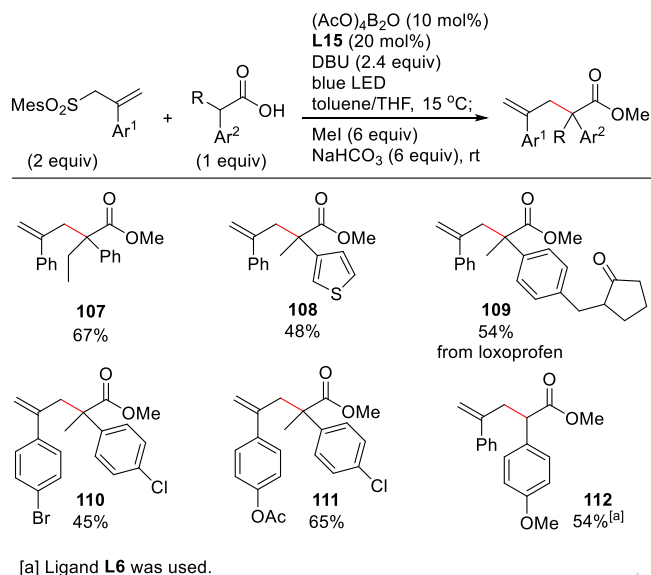
Scheme 27. Selected Examples of Visible Light-Driven α-Allylation of Carboxylic Acids

To gain mechanistic insights of the reaction, a radical clock experiment is conducted (Scheme 28). When an alkene-tethered α-aryl acetic acid **113** is subjected to the reaction conditions, consecutive cyclization and allylation proceed to provide **114** in 25% yield, along with α-allylation product **115** in 7% yield. The result dictates radical formation at α-position of the carboxy group to induce 5-exo cyclization.
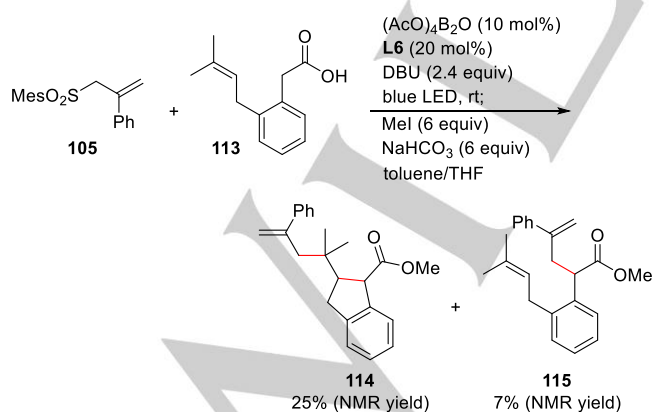

Scheme 28. Radical Clock Experiment.

Allyl radical generation is also assessed by performing the reaction with an equimolar mixture of carboxylic acid **116** and ketene silyl acetal **117** (Scheme 29a). This reaction gives α-allylation products derived from **116** (**118**, 39% yield) and **117** (**119**, 24% yield), suggesting the generation of an allyl radical from **105**. In contrast, α-allylation of **117** does not proceed in the absence of **116** and (AcO)$_4$B$_2$O (Scheme 29b). This result indicates that the allyl radical is not generated without carboxylic acid and the boron catalyst and that the phenoxy anion of **L15** does not act as a single-electron reductant to generate allyl radical from allyl sulfone **105** upon photoirradiation. Hence, the actual single-electron reductant in the reaction is likely a photoexcited boron enediolate species.
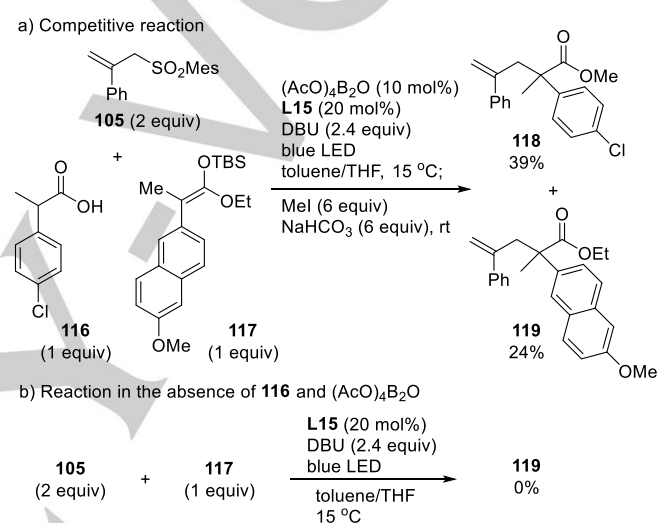
Scheme 29. Control Experiments using Ketene Silyl Acetal.

A plausible catalytic cycle based on the above observations is proposed in Scheme 30. α-Deprotonation of the boron carboxylate **A** by DBU forms an electron-rich boron enediolate **B**, and this species is photoexcited (**B***) by blue LED irradiation. Single-electron transfer from **B*** to allyl sulfone **C** followed by elimination of the sulfinate anion from the resulting anion radical **C·⁻** generates a radical pair consisting of cation radical **B·⁺** of the boron enediolate and allyl radical **C·**. Allyl radical **C·** may react with either cation radical **B·⁺** or closed shell species **B**. In the former case, immediate radical−radical coupling of radical pair **B·⁺/C·** affords α-allylation product **D**. Finally, the exchange of the carboxylate groups between **D** and the DBU salt of the starting material produces the α-allylated carboxylic acid as a DBU salt with the regeneration of boron carboxylate **A**. Alternatively, allyl radical **C·** may react with closed shell **B** to propagate a radical chain process. If this is the case, highly electron-rich α,α-dioxy carbon radical **E·** would be formed and undergo a single-electron reduction of allyl sulfone to produce boron carboxylate **D** and allyl radical **C·**.
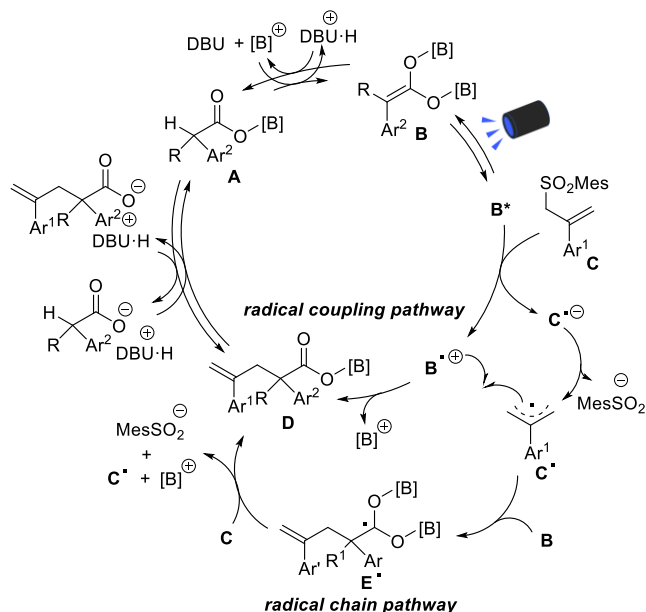
Scheme 30. Proposed Catalytic Cycle for Boron and Visible-Light-Driven α-Allylation of Carboxylic Acids.

7. Conclusion

This personal account has described the development of boron-catalyzed α-functionalizations of carboxylic acids. Activation of carboxylic acids through reversible covalent bond formation between the carboxy group and the boron catalyst potently acidifies the α-proton and facilitates enolate formation through deprotonation with mild organic bases. The thus-generated boron enediolates are reactive in Mannich reaction, aldol reaction, α-amination, and α-allylation by boron/transition metal hybrid catalysis or photoinduced radical reactions. The notable feature of the boron catalysis is chemoselectivity; those reactions proceed selectively at the α-position of carboxylic acid in the presence of other enolizable functional groups, such as amide, ester, and ketone. Moreover, the introduction of ligands on the boron atom enhances the reactivity and controls the enantio- and diastereoselectivity. Further expansion of the reaction types and applications to the synthesis of value-added functional molecules can be expected in the future.

Acknowledgements

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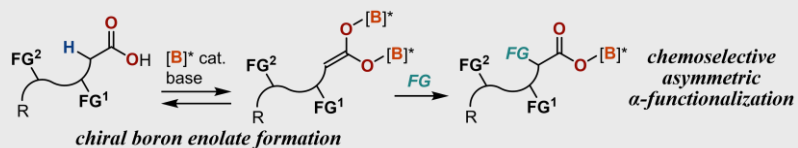**Entry for the Table of Contents** (Please choose one layout)

Layout 2:

PERSONAL ACCOUNT

chiral boron enolate formation ... *chemoselective asymmetric α-functionalization*

The development of boron-catalyzed α-functionalization of carboxylic acids is summarized (six reaction types). The reversible covalent bond formation between carboxylate and the boron catalyst enables chemoselective enolization using mild organic bases. Enhancement of the catalytic activities and controlling the stereoselectivities are possible by introducing ligands to the boron catalyst.

Yohei Shimizu,* Motomu Kanai*

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