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Ligand-Promoted, Boron-Mediated Chemoselective Carboxylic Acid Aldol Reaction

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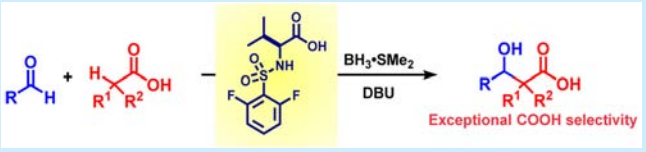
Supporting Information

ABSTRACT: The first carboxylic acid selective aldol reaction mediated by boron compounds and a mild organic base (DBU) was developed. Inclusion of electron-withdrawing groups in the amino acid derivative ligands reacted with $BH_3 \cdot SMe_2$ forms a boron promoter with increased Lewis acidity at the boron atom and facilitated the carboxylic acid selective enolate formation, even in the presence of other carbonyl groups such as amides, esters, ketones, or aliphatic aldehydes. The remarkable ligand effect led to the broad substrate scope including biologically relevant compounds.



Boron-mediated aldol reactions are a well-established C−C bond forming reaction at the α-position of a carbonyl group and have numerous applications in synthetic organic chemistry.[1] Nonetheless, the aldol reaction of boron enolates derived from carboxylic acids has been largely neglected because of the difficulty in forming enolates from carboxylic acids.[2,3] In pioneering studies, Evans et al. used 2.1 equiv of R_2BOTf (R = butyl or cyclohexyl) and 2.2 equiv of $^iPr_2NEt$.[4,5] Recently, Ramachandran et al. reported a systematic study of an enolization and aldol reaction of propionic acid using R_2BX (i.e., dicyclohexylbromoborane) in combination with NEt_3.[6,7] Although those boron-mediated carboxylic acid aldol reactions proceeded under mild conditions, the scope of carboxylic acids has, to date, been limited to propionic acid and 3,3,3-trifluoropropionic acid.[8] Herein, we report a ligand-promoted and boron-mediated carboxylic acid aldol reaction applicable to a broad range of carboxylic acids, including biologically relevant compounds. The unprecedented carboxyl group selectivity was realized by a proper design of the ligand on the boron atom (Figure 1).

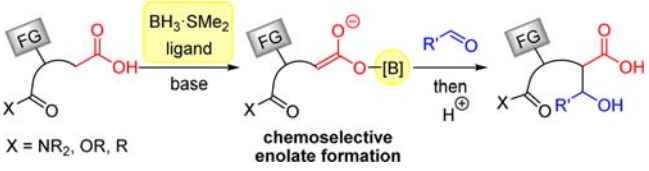


Figure 1. Carboxylic acid selective enolate formation for aldol reaction.

We previously reported a boron-catalyzed carboxylic acid Mannich-type reaction using DBU as a mild organic base.[9,10] The same catalytic conditions, however, were not directly applicable to the aldol reaction (Table 1, entry 1). Therefore, we began our investigation of the carboxylic acid aldol reaction by applying a stoichiometric version of those previous conditions. Plausible active species are enolates or enols generated from triacyloxyboranes; thus, we used 3 equiv of propionic acid (**2a**) with $BH_3 \cdot SMe_2$ and benzaldehyde (**1a**) for the initial investigation.[11] The aldol reaction, however, proceeded in only 30% yield (entry 2). We expected that introducing ligands with higher electron-withdrawing ability to the boron atom would facilitate enolization of the propionic acids, leading to an increase in the reactivity. Consequently, we investigated various monodentate acids, but none were effective (entries 3−6). Sterically less hindered triacyloxyboranes are prone to undergo disproportionation,[12] and we therefore assumed that introducing sterically demanding bidentate ligands on the boron atom would generate more rigid and stable active species. Although BINOL and phthalic acid were not effective (entries 7 and 8), *N*-toluenesulfonyl-protected valine (Ts-L-Val) was a promising ligand,[13] improving the yield to 40% (entry 9). *N*-Acetyl- and *N*-Boc-protected valines were not suitable (entries 10 and 11), probably due to their relatively weak electron-withdrawing ability compared to the Ts group.[14]

Further investigation using Ts-L-Val revealed that 2 equiv of **2a** dramatically improved both the yield and diastereoselectivity (entry 12). A preliminary ^{11}B NMR study indicated that the second equivalent of **2a** would facilitate the generation of ligand-chelated acyloxyborane species and enhance the acidity of the α-protons.[15] Studies of other amino acid derivatives as ligands indicated that the steric bulkiness of the α-substituent was important for obtaining a high yield (entries 13−17).[16] Ts-L-Leu was identified as the best ligand, affording the product in 79% isolated yield and >20/1 *syn*-selectivity (entry 17). Although the reaction proceeded with 2 equiv of DBU, the use of 3 equiv of DBU led to the faster reaction rate. In any case so far, the enantiomeric excess of the product was at most 30%.

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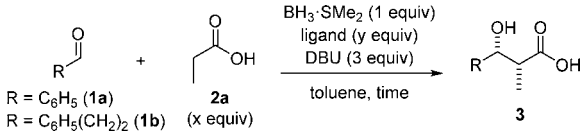
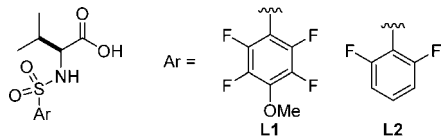
Table 1. Optimization of Boron-Mediated Carboxylic Acid Aldol Reaction[a]



entry	1	x	ligand	y	time (h)	yield (%)	*syn*/*anti*
1[b]	1a	1	-	-	5	0	-
2	1a	3	-	-	5	30	8.5/1
3	1a	1	TFA	2	5	9	1.3/1
4	1a	1	BzOH	2	5	16	3.3/1
5	1a	1	$PhSO_3H$	2	5	12	1.1/1
6	1a	1	$(PhO)_2PO_2H$	2	5	12	1/1.4
7	1a	1	(*R*)-BINOL	1	5	trace	-
8	1a	1	phthalic acid	1	5	2	3.0/1
9	1a	1	Ts-L-Val	1	5	40	2.4/1
10	1a	1	Ac-L-Val	1	5	3	-
11	1a	1	Boc-L-Val	1	5	2	-
12	1a	2	Ts-L-Val	1	5	83	14/1
13	1a	2	Ts-L-Ala	1	5	4	-
14	1a	2	Ts-L-Met	1	5	40	>20/1
15	1a	2	Ts-L-Phe	1	5	36	>20/1
16	1a	2	Ts-L-Ile	1	5	84	14/1
17	1a	2	Ts-L-Leu	1	5	96 (79)[c]	>20/1
18	1b	3	-	-	12	0	-
19	1b	2	Ts-L-Leu	1	12	0	-
20	1b	2	Ts-L-Val	1	12	55	>20/1
21	1b	2	**L1**	1	12	80	2.4/1
22[d]	1b	2	**L1**	1	12	96	2.5/1
23[d,e]	1b	2	**L2**	1	12	92 (83)[c]	8.2/1

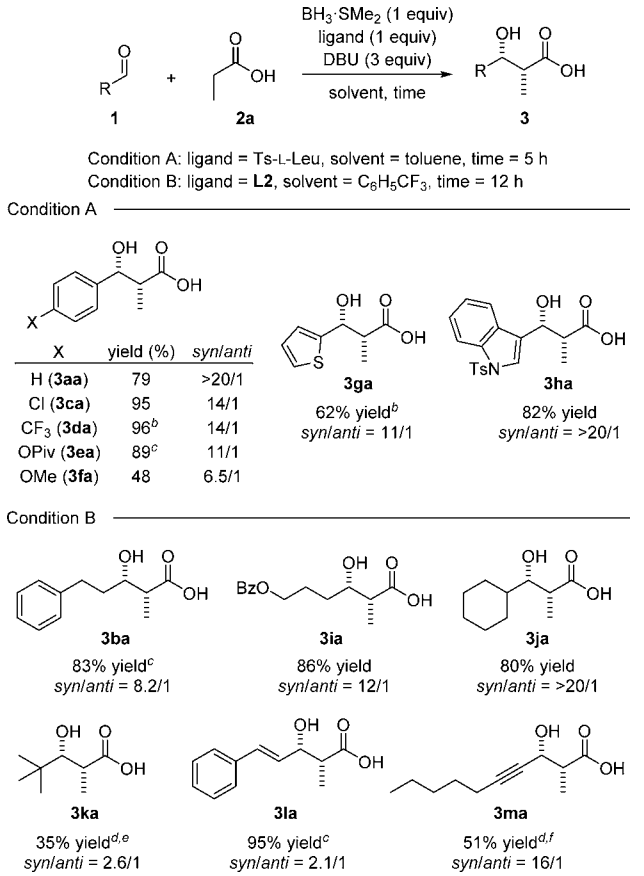
[a]**1** (0.30 mmol), $BH_3·SMe_2$ (0.30 mmol), and toluene (1.0 mL) were used. Yield and diastereomeric ratio were determined by ^1H NMR analysis using *t*-BuOMe as an internal standard. [b]10 mol % of $BH_3·SMe_2$ was used. [c]Isolated yield after conversion of the aldol products into methyl esters by $TMSCHN_2$ was shown in parentheses. [d]$C_6H_5CF_3$ (1.0 mL) was used as solvent. [e]2.5 equiv of DBU (0.75 mmol) were used.



The optimized reaction conditions for **1a** were not applicable to aliphatic aldehydes (e.g., hydrocinnamaldehyde (**1b**); entry 19). Careful reinvestigation of *N*-Ts-protected amino acids as a ligand revealed that using Ts-L-Val promoted the aldol reaction with **1b**, albeit in moderate yield (entry 20). The unsatisfactory result was likely due to competitive and undesired enolization of aliphatic aldehyde **1b** over the desired donor carboxylic acid enolate formation. To enhance the Lewis acidity of the boron atom and thus increase the feasibility of selective carboxylic acid enolate formation, electron-withdrawing groups were introduced to the sulfonyl moiety of the amino acid ligand (**L1**). As expected, the reactivity was significantly increased to give the product in 80% yield (entry 21). Although higher reactivity was obtained with **L1** in α,α,α-trifluorotoluene, the diastereoselectivity was still low (entry 22). Further modification of the sulfonyl group and reaction conditions revealed that the use of **L2** with 2.5 equiv of DBU was optimal for aliphatic aldehyde **1b** and improved the diastereoselectivity (*syn*/*anti* = 8.2/1) while maintaining high reactivity (83% yield) (entry 23).[17] These results indicate that the carboxylic acid selective enolate formation and the following aldol reaction can proceed in high yield and diastereoselectivity by introducing a properly designed ligand on the boron atom.

After establishing two complementary sets of optimal conditions for the aldol reactions of propionic acid (**2a**), we examined the substrate scope of aldehydes using either condition A or B: condition A used Ts-L-Leu as a ligand in toluene solvent, and condition B used **L2** as a ligand in α,α,α-trifluorotoluene (Scheme 1). Aromatic aldehydes containing

Scheme 1. Substrate Scope of Aldehydes[a]



[a]General reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), $BH_3·SMe_2$ (0.30 mmol), ligand (0.30 mmol), DBU (0.90 mmol), solvent (1.0 mL), room temperature. Diastereomeric ratio was determined by ^1H NMR analysis of crude mixture of **3**. Isolated yield was determined after conversion of the aldol products into methyl esters by $TMSCHN_2$. [b]2.0 mL of solvent were used. [c]2.5 equiv of DBU (0.75 mmol) were used. [d]**L1** (0.30 mmol) was used as a ligand. [e]Reaction time was 40 h. [f]2 equiv of DBU (0.60 mmol) were used.

electron-withdrawing groups afforded the aldol products (**3ca**–**3ea**) in high yield and high *syn*-selectivity (89–96% yield, *syn*/*anti* = >11/1), while the reaction with an electron-donating *p*-OMe substituted benzaldehyde produced a moderate yield and diastereoselectivity (**3fa**: 48% yield, *syn*/*anti* = 6.5/1). Heteroaromatic aldehydes were also applicable (**3ga** and **3ha**). Condition B was essential for reactions with aliphatic aldehydes (**1b**, **1i**, **1j**, and **1k**). Condition B using either **L2** or **L1** was also effective for α,β-unsaturated aldehydes (**1l**, **1m**).

Subsequently, the scope of carboxylic acid substrates was examined using both benzaldehyde (**1a**) and aliphatic aldehyde **1i** as electrophiles (Scheme 2). The alkenyl (**2b**) and the alkynyl (**2c**) groups remained intact, illustrating the rapid and selective formation of acyloxyboranes compared to hydroboration of the C–C double and triple bonds. We then examined the chemoselectivity toward the carboxyl group in the

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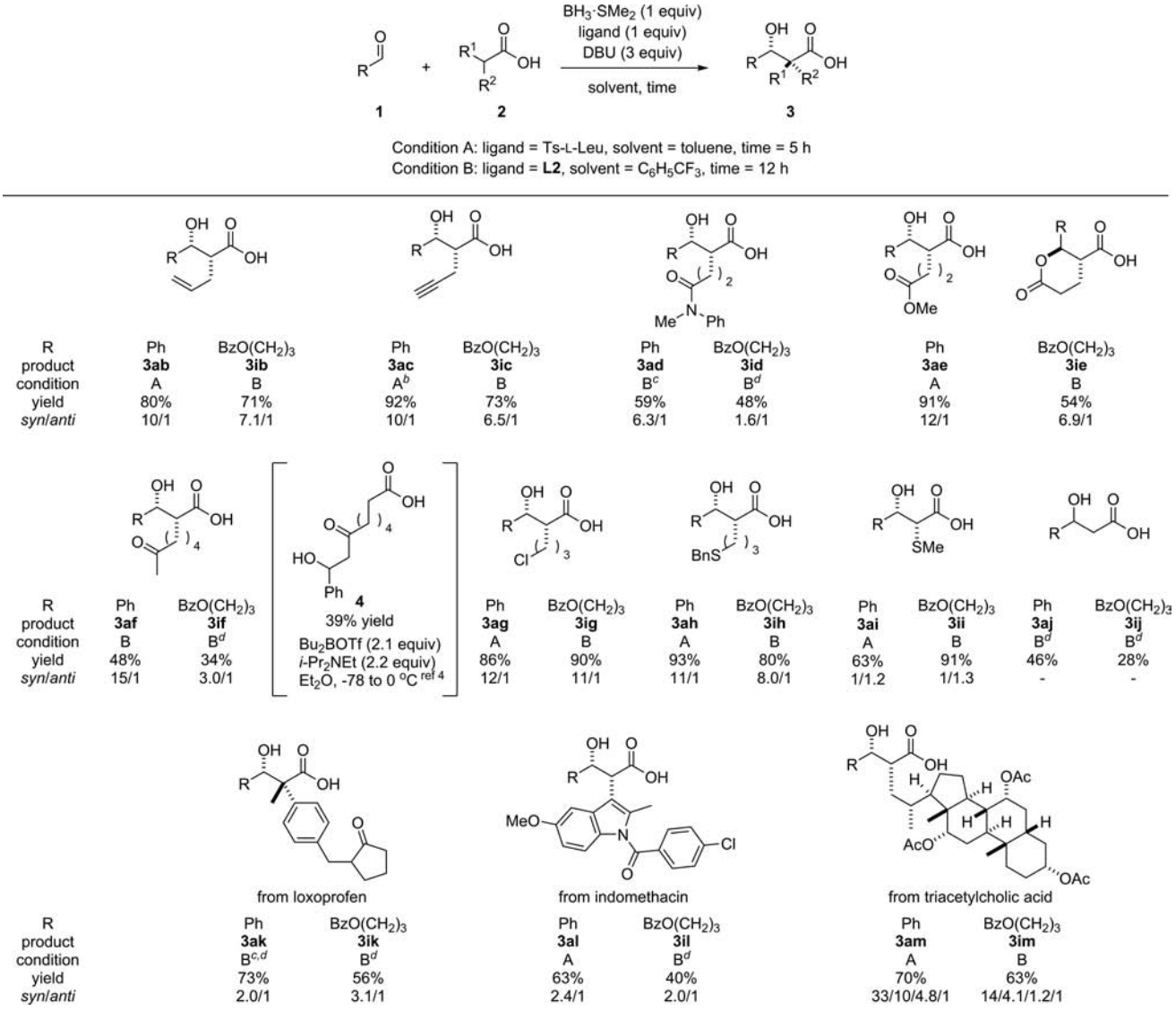
Scheme 2. Substrate Scope of Carboxylic Acids[a]



[a]General reaction conditions: **1** (0.30 mmol), **2** (0.60 mmol), $BH_3{\cdot}SMe_2$ (0.30 mmol), ligand (0.30 mmol), DBU (0.90 mmol), solvent (1.0 mL), room temperature. Diastereomeric ratio was determined by ^1H NMR analysis of crude mixture of **3**. Isolated yield was determined after conversion of the aldol products into methyl esters by $TMSCHN_2$. [b]2.0 mL of toluene were used. [c]2.5 equiv of DBU (0.75 mmol) were used. [d]**L1** (0.30 mmol) was used as a ligand.

presence of other carbonyl groups, which is extremely difficult to achieve under other reaction conditions. The boron-mediated aldol reaction proceeded exclusively at the α-position of the carboxyl group in the presence of amide (**2d**), ester (**2e**), and ketone (**2f**) groups, whose pK_a values of the α-protons are inherently lower than that of the carboxyl group. The aldol reaction between **1i** and ester-containing **2e** gave a mixture of the linear product and lactone **3ie**, which was converted to **3ie** by further treatment with DBU. The carboxyl group selectivity is a unique feature of our reactions, because the aldol reaction of **2f** under Evans' conditions[4] (Bu_2BOTf + i-Pr_2NEt) proceeded exclusively at the α-position of the ketone group to give **4** in 39% yield. A potentially reactive chloroalkyl moiety was tolerated (**2g**). The products were obtained in high yield for substrates containing coordinative thioether functional groups (**2h** and **2i**). Acetic acid (**2j**) produced less satisfactory results than α-substituted carboxylic acids, probably due to the easy disproportionation of acetoxyborane, even in the presence of sterically bulky amino acid ligand **L1**.[12]

Encouraged by the broad substrate scope enabled by the proper choice of ligands, we next applied this method to biologically relevant molecules to assess its utility for late-stage diversification[18] of drugs and drug-like molecules. The anti-inflammatory drugs loxoprofen (**2k**) and indomethacin (**2l**) were successfully transformed into the corresponding aldol products (**3ak**, **3ik**, **3al**, and **3il**) in moderate to good yield. It is noteworthy that the reaction of loxoprofen (**2k**) proceeded exclusively at the sterically congested α-position of the carboxyl group in the presence of the inherently more reactive and accessible ketone group. In this case, **L1** was the best ligand for furnishing **3ak** and **3ik** in high yield. The carboxylic acid selective aldol reaction of steroidal triacetylcholic acid (**2m**), which possesses three enolizable ester moieties, was also possible, affording two major diastereomers among four possible isomers in 70% yield (**3am**) and 63% yield (**3im**).

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In summary, we developed the first carboxylic acid selective aldol reaction mediated by boron compounds. The introduction of electron-withdrawing *N*-sulfonyl amino acid ligands on the boron atom enhanced the Lewis acidity of the boron atom, thereby facilitating carboxylic acid selective enolate formation, even in the presence of other carbonyl groups such as ketones, esters, amides, or aliphatic aldehydes. Moreover, the high functional group tolerance of the reaction was applicable to late-stage diversification of drugs and drug-like molecules. Further exploration of catalytic asymmetric aldol reactions of carboxylic acids and elucidation of the reaction mechanism are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00914.

Experimental procedure, mechanistic study, characterization data, and copies of ^{1}H, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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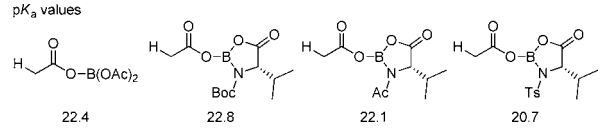
(14) The observed positive ligand effects of Ts-L-Val can be partly explained by enhanced acidity of the α-protons of the carboxylic acid after covalent bond formation with the ligand-chelated boron promoter. The pK_a values of the α-proton of the following acyloxyboranes were calculated by the Jaguar v8.5 pK_a module (Schrödinger, LLC, New York, NY, 2013), suggesting that the substituent of the ligand's nitrogen atom markedly affects acidity of the α-proton.



(15) See Supporting Information for details.

(16) Steric hindrance of the amino acid-derived ligands prevented the ligands from being reduced by BH_3·SMe_2. When Ts-L-Ala and Ts-L-Phe were mixed with propionic acid and BH_3·SMe_2 in a 1:2:1 ratio, the corresponding alcohols derived from the ligands were detected in 51% and 14% yield, respectively. In contrast, no reduction was observed when Ts-L-Val was mixed with propionic acid and BH_3·SMe_2.

(17) For the reaction between aromatic aldehyde **1a** and **2a**, the optimized conditions for the aliphatic aldehydes were inferior to the conditions of Table 1, entry 17: using **L2**, **3aa** was obtained in 73% yield with a *syn*/*anti* ratio of 1.4/1.

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