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

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(5) 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 . SMe₂ 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.

B oron-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 ${}^{i}Pr_2NEt$. Recently, Ramachandran et al. reported a systematic study of an enolization and aldol reaction of propionic acid using R₂BX (i.e., dicyclohexylbromoborane) in combination with NEt₃.⁶ 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 3,3,3trifluoropropionic 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 BH₃·SMe₂ 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.¹

Further investigation using Ts-L-Val revealed that 2 equiv of 2a dramatically improved both the yield and diastereoselectivity (entry 12). A preliminary ¹¹B 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

| R´ R = C ₆ H R = C ₆ H | 0 ₅ (1a ₅(CH | +) ₂) ₂ (1 | O OH 2a b) (x equiv) | BH ₃ lig D te | SMe ₂ (1 e and (y equ BU (3 equ oluene, tin | equiv) uiv) iiv) I ne | он о с он он з |
|--|----------------------------|--|--------------------------------------|-----------------------------------|---|--------------------------------|----------------------|
| entry | 1 | x | ligand | у | time (h) | yield (%) | syn/anti |
| 1 ^{<i>b</i>} | 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 ₃ H | 2 | 5 | 12 | 1.1/1 |
| 6 | 1a | 1 | (PhO) ₂ PO ₂ H | 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-∟-Met | 1 | 5 | 40 | >20/1 |
| 15 | 1a | 2 | Ts-L-Phe | 1 | 5 | 36 | >20/1 |
| 16 | 1a | 2 | Ts-L-lle | 1 | 5 | 84 | 14/1 |
| | 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-∟-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 |

^a1 (0.30 mmol), BH₃·SMe₂ (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. ^b10 mol % of BH₃· SMe₂ was used. ^cIsolated yield after conversion of the aldol products into methyl esters by TMSCHN₂ was shown in parentheses. ^dC₆H₅CF₃ (1.0 mL) was used as solvent. ^e2.5 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 $\alpha_{,}\alpha_{,}\alpha_{-}$ 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.

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 $\alpha_{,\alpha_{,}\alpha_{-}}$ trifluorotoluene (Scheme 1). Aromatic aldehydes containing Scheme 1. Substrate Scope of Aldehydes⁴ BH3.SMe2 (1 equiv) ligand (1 equiv) DBU (3 equiv) ОH solvent time 3 Condition A: ligand = Ts-L-Leu solvent = toluene time = 5 h Condition B: $\bar{\text{ligand}} = L2$, solvent = C₆H₅CF₃, time = 12 h Condition A OН ΩF vield (%) syn/anti х H (3aa) 79 >20/1 3ha 3ga CI (3ca) 95 14/1 62% yield^b 82% vield CF₃ (**3da**) 96^t 14/1syn/anti = 11/1 syn/anti = >20/1 OPiv (3ea) 894 11/1 OMe (3fa) 48 6.5/1 Condition B OH BZO 3ia 3ba 3ia 83% yield^c 86% yield 80% yield *synlanti* = 8.2/1 syn/anti = >20/1 svn/anti = 12/1 OH 3ka 3la 3ma 35% vield^{d,e} 95% yield 51% yield^{d,f} syn/anti = 2.6/1 syn/anti = 2.1/1 syn/anti = 16/1

After establishing two complementary sets of optimal

^{*a*}General reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), BH₃· SMe₂ (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 TMSCHN₂. ^{*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 Scheme 2. Substrate Scope of Carboxylic Acids⁴



^{*a*}General reaction conditions: **1** (0.30 mmol), **2** (0.60 mmol), BH₃·SMe₂ (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 TMSCHN₂. ^{*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 boronmediated 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' conditions⁴ ($Bu_2BOTf + i-Pr_2NEt$) 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 diversification¹⁸ of drugs and drug-like molecules. The antiinflammatory 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.or-glett.6b00914.

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

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Mukaiyama, T.; Matsuo, J. in *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 127–160.
(b) Mahrwald, R. In *Aldol Reactions*; Mahrwald, R., Ed.; Springer: Dordrecht Heidelberg, 2009; pp 23–38.

(2) Strong Brønsted bases are necessary to generate carboxylic acid enolates. For a recent advancement, see: (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936. (b) Ma, Y.; Stivala, C. E.; Wright, A. M.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 16853. (c) Lu, P.; Jackson, J. J.; Eickhoff, J. A.; Zakarian, A. *J. Am. Chem. Soc.* **2015**, *137*, 656.

(3) For selected examples of boron mediated asymmetric aldol reactions of ester or amide derivatives, see: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. J. Am. Chem. Soc. **1981**, 103, 2127. (b) Corey, E. J.; Kim, S. S. J. Am. Chem. Soc. **1990**, 112, 4976. (c) Abiko, A.; Liu, J.-F.; Masamune, S. J. Am. Chem. Soc. **1997**, 119, 2586. (d) Nuhant, P.; Allais, C.; Roush, W. R. Angew. Chem., Int. Ed. **2013**, 52, 8703.

(4) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. J. Am. Chem. Soc. 1981, 103, 3099.

(5) Aldol reactions of propionic acid and phenylacetic acid using dicyclohexylchloroborane/NEt₃ were reported: Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.

(6) (a) Ramachandran, P. V.; Chanda, P. B.; Otoo, B. *Tetrahedron Lett.* **2014**, *55*, 1289. (b) Ramachandran, P. V.; Otoo, B.; Chanda, P. B. *Tetrahedron Lett.* **2015**, *56*, 3019.

(7) TMSOTf-mediated aldol reactions of acetic acid, propionic acid, and butyric acid were also reported: Downey, C. W.; Johnson, M. W.; Lawrence, D. H.; Fleisher, A. S.; Tracy, K. J. *J. Org. Chem.* **2010**, *75*, 5351.

(8) Borinic acid catalyzed direct aldol reactions of pyruvic acids containing highly acidic α -protons were reported: Lee, D.; Newman, S. G.; Taylor, M. S. Org. Lett. **2009**, 11, 5486.

(9) Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. J. Am. Chem. Soc. 2015, 137, 7075.

(10) For selected examples of catalytic electrophilic activation of carboxylic acids with boron compounds, see: (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. J. Am. Chem. Soc. 1988, 110, 6254.
(b) Maki, T.; Ishihara, K.; Yamamoto, H. Tetrahedron 2007, 63, 8645.
(c) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. Angew. Chem., Int. Ed. 2008, 47, 2876. (d) Zheng, H.; McDonald, R.; Hall, D. G. Chem. - Eur. J. 2010, 16, 5454. (e) Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y. Org. Lett. 2014, 16, 4256. (f) Ishihara, K.; Lu, Y. Chem. Sci. 2016, 7, 1276.

(11) For the investigation of other boron compounds and bases, see Supporting Information.

(12) Brown, H. C.; Stocky, T. P. J. Am. Chem. Soc. 1977, 99, 8218.
(13) For selected examples of the combined use of amino acid derived ligands and BH₃, see: (a) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. J. Org. Chem. 1991, 56, 2276. (b) Yeung, Y.-Y.; Corey, E. J. Org. Lett. 2008, 10, 3877.

(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 $BH_3 \cdot SMe_2$. When Ts-L-Ala and Ts-L-Phe were mixed with propionic acid and $BH_3 \cdot SMe_2$ 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 $BH_3 \cdot SMe_2$.

(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.

(18) (a) Robles, O.; Romo, D. Nat. Prod. Rep. 2014, 31, 318.
(b) Wencel-Delord, J.; Glorius, F. Nat. Chem. 2013, 5, 369.