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Chemoselective Boron-Catalyzed Nucleophilic Activation of Carboxylic Acids for Mannich-Type Reactions

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Supporting Information

ABSTRACT: The carboxyl group (COOH) is an omnipresent functional group in organic molecules, and its direct catalytic activation represents an attractive synthetic method. Herein, we describe the first example of a direct catalytic nucleophilic activation of carboxylic acids with BH_3·SMe_2, after which the acids are able to act as carbon nucleophiles, i.e. enolates, in Mannich-type reactions. This reaction proceeds with a mild organic base (DBU) and exhibits high levels of functional group tolerance. The boron catalyst is highly chemoselective toward the COOH group, even in the presence of other carbonyl moieties, such as amides, esters, or ketones. Furthermore, this catalytic method can be extended to highly enantioselective Mannich-type reactions by using a (*R*)-3,3′-I_2-BINOL-substituted boron catalyst.

Carboxyl groups (COOH) are ubiquitous in a wide variety of organic compounds, including biologically active natural products and pharmaceuticals such as nonsteroidal anti-inflammatory drugs (NSAIDs)[1] or antibiotics.[2] Given the prevalence and importance of the COOH group, its direct catalytic functionalization represents a highly desirable addition to the methodological toolkit for the organic synthesis of complex molecules.[3] Moreover, it offers an attractive opportunity to introduce structural diversifications in late stages of drug lead optimization processes.[4] A fundamental issue that remains to be addressed in this context is the chemoselective activation of the COOH moiety in the presence of other functional groups within the same molecule. Apart from a desirable functional group tolerance, such a strategy would also be beneficial for the synthetic atom and step efficiency[5] by avoiding unnecessary protection/deprotection steps.

A seminal study on the catalytic electrophilic activation of carboxylic acids by Yamamoto successfully demonstrated the utility of boron mediators. Since then, boron catalysts have been used for Diels–Alder reactions and [3 + 2] dipolar cycloadditions of α,β-unsaturated carboxylic acids,[6] as well as for the amidation and esterification of carboxylic acids.[6b,7] A particularly noteworthy example was reported by Hall, who accomplished a Diels–Alder reaction that was selective toward α,β-unsaturated carboxylic acids.[6b] In this reaction, a boronic acid chemoselectively activates a COOH group in the presence of an α,β-unsaturated ester group, which is innately more reactive in comparison. Even though several impressive studies concerning the catalytic electrophilic activation of carboxylic acids can be found in the scientific literature, examples for the catalytic nucleophilic activation of carboxylic acids resulting in carbon nucleophiles, i.e. enolates, for the subsequent reaction with polar electrophiles, remain extremely limited.[8] This scarcity of reports is most likely due to the nontrivial catalytic formation of dianionic enolates from carboxylic acids. Nevertheless, notable advances for the use of carboxylic acid derived enolates have been made recently. Zakarian, for example, has reported the asymmetric alkylation and conjugate addition of carboxylic acids with stoichiometric amounts of chiral lithium amides.[9] Both of these reactions accomplish excellent levels of enantioselectivity, and the latter also achieves outstanding diastereoselectivity. However, the versatility of these reactions is, especially for multifunctional substrates, somewhat restricted by the use of excess BuLi and the limitation to acetic acids with an α-aryl substitution pattern. Herein, we report the first example of a direct catalytic nucleophilic activation (enolate formation) of carboxylic acids to act as carbon nucleophiles (Figure 1). The

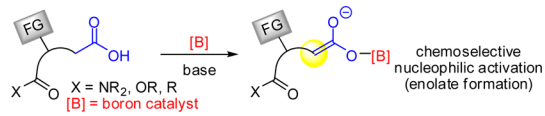

Figure 1. Chemoselective catalytic nucleophilic activation of carboxylic acids.

chemoselective formation of enolates was induced in a wide range of carboxylic acids by using a mild organic base (1,8-diazabicyclo[5.4.0]undec-7-ene; DBU) in combination with a catalytic amount of a boron mediator. The chemoselectivity of this reaction is reflected in high levels of functional group tolerance, and the catalytically formed boron enolates can subsequently react with imines in Mannich-type reactions. The described method can also be extended to asymmetric Mannich-type reactions, and the resulting *N*-protected β-amino acid derivatives represent an important structural motif in many biologically active compounds.[10]

We began our study inspired by the pioneering work of Evans,[11] who used unsaturated diborondiolates, generated from propionic acid, 2 equiv of R_2BOTf (R = *n*-butyl or cyclohexyl), and $^iPr_2NEt$ at 0 °C, in aldol reactions with benzaldehyde at −78 °C. The corresponding aldol adducts were obtained in high yield and moderate diastereoselectivity (87% yield, *syn*/*anti* = 35/65–

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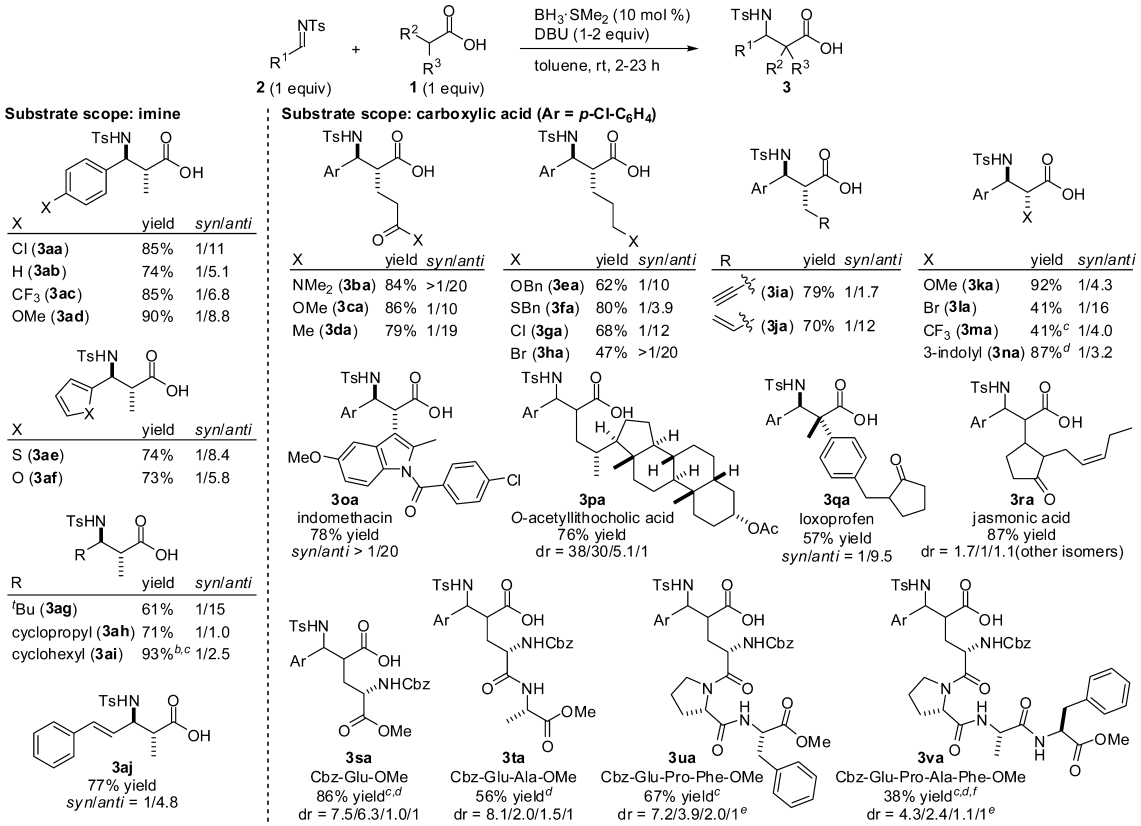
Table 1. Substrate Scope for the Chemoselective Boron-Catalyzed Mannich-Type Reactions of Carboxylic Acids[a]



[a]Isolated yield and diastereomer ratio were determined after conversion of the Mannich products into methyl esters (see Supporting Information). The diastereomer ratio was determined by ^{1}H NMR analysis. [b]20 mol % of $BH_3{\cdot}SMe_2$ was used. [c]2.0 equiv of imine were used. [d]THF was used as solvent. [e]Determined by HPLC analysis. [f]33 mol % of $BH_3{\cdot}SMe_2$ was used.

20/80). These results clearly indicate that the generation of a carboxylic acid derived enolate, arguably the most difficult step in the nucleophilic activation of carboxylic acids, is possible under mildly basic conditions when using a stoichiometric combination of a boron reagent and an amine. The necessity for stoichiometric amounts of R_2BOTf was tentatively assigned to the formation of relatively stable chelated boron aldolate intermediates, which should prohibit the catalyst turnover step. Therefore, we targeted Mannich-type reactions, another fundamental family of C−C bond forming reactions, which proceed through a presumably less stable boron-containing intermediate, thus putatively facilitating the catalyst turnover step. The Mannich-type reaction between propionic acid (**1a**) and Ts-protected aromatic aldimine **2a** (Ts = *p*-toluenesulfonyl) was studied as a model reaction in order to optimize reaction conditions (Table S1). Mild organic bases such as DBU, Et_3N, and $^iPr_2NEt$ were unable to generate the targeted Mannich adduct **3aa** in the absence of a boron catalyst, and therefore, we subsequently examined the impact of several boron compounds (10 mol %) on this reaction. $BF_3{\cdot}Et_2O$, $B(OMe)_3$, Bu_2BOTf, $B(OH)_3$, or $PhB(OH)_2$ did not afford **3aa**, while catechol borane (CatBH) afforded the Mannich adduct **3aa** in 25% yield. Ultimately, $BH_3{\cdot}SMe_2$ displayed the best catalytic performance, furnishing the desired Mannich adduct in excellent yield and high *anti*-selectivity (95% yield, *syn*/*anti* = 1/10).[12]

Having established a suitable catalyst, we proceeded to investigate the substrate scope of this reaction (Table 1). Aromatic imines containing an electron-withdrawing trifluoromethyl group, an electron-donating methoxy group, or heteroaromatic imines furnished the corresponding products in good yield and diastereoselectivity (**3ac**−**3af**). Aliphatic imines also afforded targeted products, albeit in marginally lower yields (**3ag**−**3ai**). It is noteworthy that this method also allowed the use of readily isomerizable aliphatic imines with an acidic α-proton such as an imine derived from cyclohexanecarboxaldehyde (**2i**). In this case, however, the use of 20 mol % of $BH_3{\cdot}SMe_2$ and 2 equiv of imine were required in order to obtain **3ai** in high yield. An α,β-unsaturated imine furnished exclusively the corresponding 1,2-adduct **3aj** without loss of reactivity.

Subsequently, we examined the versatility of this reaction with respect to carboxylic acid substrates using Ts-protected aromatic aldimine **2a**. $BH_3{\cdot}SMe_2$ preferentially binds and activates the COOH group through the formation of reversible covalent bonds, and a selective activation of the COOH moiety was observed even in the presence of other carbonyl groups such as amides, esters, or ketones (**3ba**−**3da**). Considering the acidity of α-protons in carboxyl, amide, ester, and keto groups (pK_a = 33.3, 31.9, 27.2, and 23.4, respectively),[13] the observed chemoselectivity is surprising and highly noteworthy. The reaction was moreover able to proceed chemoselectively in the presence of a wide variety of other functional groups, such as ethers, thioethers, chloroalkyls, bromoalkyls, C≡C alkynyls, and C=C alkenyls (**3ea**−**3ja**). Furthermore, carboxylic acids with α-functional groups such as methoxy, bromo, trifluoromethyl, or unprotected indolyl moieties could also be used in this reaction (**3ka**−**3na**). These results clearly demonstrate the high levels of chemical compatibility attainable with this method.

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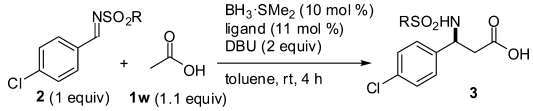
To demonstrate the potential utility of this method in late-stage functionalizations of complex molecules, we examined its applicability to biologically relevant molecules, containing multiple functional groups. The anti-inflammatory drug indomethacin (**1o**), for example, afforded **3oa** in good yield and high diastereoselectivity, while the use of steroidal *O*-acetyllithocholic acid (**1p**) resulted in the predominant formation of two out of four possible diastereomers (**3pa**). Remarkably, the reaction of loxoprofen (**1q**) and jasmonic acid (**1r**) occurred selectively at the sterically congested α-position of the COOH group, despite the presence of the inherently more reactive α-position of the keto group (**3qa** and **3ra**). A chemoselective reaction toward the α-carbon atom of the COOH group in Cbz-Glu-OMe (**1s**) successfully furnished product **3sa**, which encouraged us to examine other, more elaborate peptide substrates. To our delight, we observed that the Mannich-type reaction was also selective toward the α-carbon atom of the COOH group in dipeptide **1t**, even though the diastereoselectivity was relatively low (**3ta**). As the reaction also proceeded with tripeptide **1u** and tetrapeptide **1v**, it is feasible to conclude that these boron-catalyzed Mannich-type reactions provide sufficient chemoselectivity toward carboxylic acids in order to find applications in the derivatization of complex molecules in late stages of their syntheses.

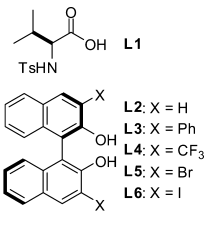
This method may also be extended to asymmetric Mannich-type reactions by using an asymmetric boron catalyst. Although enantioselective catalytic Mannich-type reactions of readily enolizable aldehydes or ketones are well-established,[14] direct asymmetric catalytic Mannich-type reactions under proton transfer conditions, using pronucleophiles in the carboxylic oxidation states, still remain extremely rare.[15] Our optimization studies initially examined the reaction between acetic acid (**1w**) and Ts-protected aromatic aldimine **2a** (Table 2), wherein a slight excess of **1w** (1.1 equiv) with respect to **2a** was used in order to suppress undesired 2-fold Mannich-type reactions. Compared with *N*-Ts-L-Val (**L1**: entry 1) and other amino acid based ligands (data not shown), BINOL (**L2**) furnished products in higher enantioselectivity but relatively low yield (19% yield, 43% ee; entry 2). Even though 3,3′-Ph_2-BINOL (**L3**) afforded merely trace amounts of product **3wa** (2% yield, entry 3), other 3,3′-disubstituted BINOL derivatives showed promising results (58−73% yield, 41−72% ee; entries 4 and 5), and especially the use of 3,3′-I_2-BINOL (**L6**) improved both yield and enantioselectivity (72% yield, 81% ee; entry 6). Subsequently, we investigated the effect of the *N*-protecting group of the imines. Imine **2k**, bearing an *N*-2-mesitylenesulfonyl group, exhibited higher enantioselectivity (77% yield, 90% ee; entry 7) relative to **2a**, and imine **2l**, containing an *N*-*tert*-butylsulfonyl (Bus) group, produced **3wl** in even higher yield and higher enantioselectivity (95% yield, 90% ee; entry 8). A complementary solvent screening revealed that the use of a binary toluene/THF solvent afforded the products in quantitative yield and excellent enantioselectivity (94% ee; entry 9).[16]

With the optimized reaction conditions in hand, we examined the substrate scope of these boron-catalyzed asymmetric Mannich-type reactions by employing a series of Bus-protected aromatic imines (Table 3). Aromatic imines with electron-withdrawing groups **2n**, **2o**, and **2p** generally furnished products in high yield and excellent enantioselectivity (entries 3−5). Although the reactivity of imine **2q**, containing an electron-donating methoxy substituent at the *para*-position, was lower, the corresponding product was still obtained in excellent enantioselectivity (entry 6). Imines **2r** and **2s**, bearing electron-withdrawing or -donating substituents at the *meta*-position, afforded the target compounds in good yield and excellent enantioselectivity (entries 7 and 8). Imines **2t** and **2u**, with electron-rich heteroaromatic rings, as well as imines **2v** and **2w**, with sterically demanding naphthyl groups, exhibited moderate reactivity, while the enantioselectivity remained high (entries 9−12). Aliphatic imine **2i** was also competent by using 3,3′-Br_2-BINOL (**L5**), instead of 3,3′-I_2-BINOL (**L6**), though the enantioselectivity was moderate (entry 13). The carboxylic acid substrates are not limited to acetic acid (**1w**), as e.g. propionic acid (**1a**) also furnished the corresponding Mannich

Table 2. Optimization for the Boron-Catalyzed Asymmetric Mannich-Type Reactions of Carboxylic Acids

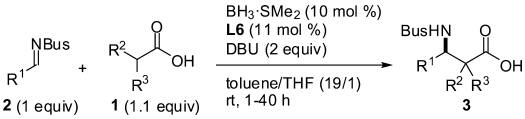


entry	R	product	ligand	yield (%)[a]	ee (%)[b]
1	*p*-tol (**2a**)	**3wa**	**L1**	95	-28
2	*p*-tol (**2a**)	**3wa**	**L2**	19	-43
3	*p*-tol (**2a**)	**3wa**	**L3**	2	n.d.
4	*p*-tol (**2a**)	**3wa**	**L4**	58	72
5	*p*-tol (**2a**)	**3wa**	**L5**	73	41
6	*p*-tol (**2a**)	**3wa**	**L6**	72	81
7	Mes (**2k**)	**3wk**	**L6**	77	90
8	^{t}Bu (**2l**)	**3wl**	**L6**	95	90
9[c]	^{t}Bu (**2l**)	**3wl**	**L6**	quant.	94



[a]Determined by ^{1}H NMR analysis using ^{t}BuOMe as an internal standard. [b]Determined by chiral HPLC analysis after conversion of the Mannich products into methyl esters. [c]A binary toluene/THF (19/1) solvent was used.

Table 3. Substrate Scope for the Boron-Catalyzed Asymmetric Mannich-Type Reactions of Carboxylic Acids[a]



entry	**2** (R^1)	**1** (R^2, R^3)	product	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (%)[d]
1	*p*-Cl-C_6H_4 (**2l**)	H, H (**1w**)	**3wl**	83	–	94
2	C_6H_5 (**2m**)	**1w**	**3wm**	72	–	96
3	*p*-F-C_6H_4 (**2n**)	**1w**	**3wn**	90	–	97
4	*p*-CF_3-C_6H_4 (**2o**)	**1w**	**3wo**	80	–	91
5	*p*-CO_2Me-C_6H_4 (**2p**)	**1w**	**3wp**	87	–	90
6	*p*-MeO-C_6H_4 (**2q**)	**1w**	**3wq**	49	–	96
7	*m*-Cl-C_6H_4 (**2r**)	**1w**	**3wr**	82	–	94
8	*m*-MeO-C_6H_4 (**2s**)	**1w**	**3ws**	64	–	94
9	2-thienyl (**2t**)	**1w**	**3wt**	64	–	94
10	2-furyl (**2u**)	**1w**	**3wu**	52	–	92
11	1-naphthyl (**2v**)	**1w**	**3wv**	43	–	89
12	2-naphthyl (**2w**)	**1w**	**3ww**	51	–	90
13[e,f]	cyclohexyl (**2i**)	**1w**	**3wi**	50	–	53
14[g]	*p*-Cl-C_6H_4 (**2l**)	Me, H (**1a**)	**3al**	99	1/1.9	93/95
15[g]	C_6H_5 (**2m**)	**1a**	**3am**	90	1/2.2	92/93
16[g]	*p*-MeO-C_6H_4 (**2q**)	**1a**	**3aq**	97	1/1.8	97/94
17[f]	*p*-Cl-C_6H_4 (**2a**)	^{i}Pr, H (**1x**)	**3xa**	49	1/11	52/91
18	*p*-Cl-C_6H_4 (**2l**)	Me, Me (**1y**)	**3yl**	79	–	98

[a]Isolated yield, diastereomer ratio, and enantiomeric excess were determined after conversion of the Mannich products into methyl esters (see Supporting Information). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]20 mol % of BH_3·SMe_2 and 22 mol % of **L5** were used. [f]A Ts-protected imine was used instead of a Bus-protected imine. [g]1.0 equiv of propionic acid (**1a**) was used.

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adducts with both electron-rich and -deficient aromatic imines in excellent yield and enantioselectivity, even though the diastereoselectivity remains to be improved (entries 14–16). Isovaleric acid (**1x**) afforded product **3xa** in high diastereo- and enantioselectivity (entry 17), and sterically demanding isobutyric acid (**1y**) afforded **3yl**, which contains a quaternary carbon atom at the α-position, in excellent enantioselectivity (entry 18).

After esterification of the Mannich adducts, the Bus-group could be successfully removed with aluminum chloride and anisole as described by Enders,[17] whereby the stereochemistry of the products was retained (see Supporting Information (SI)).

Our working hypothesis for the catalytic cycle is postulated in Figure 2. First, BH_3 reacts with carboxylic acid **1** and/or ligand

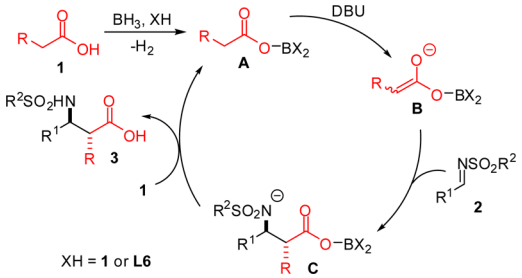

Figure 2. Proposed catalytic cycle for the boron-catalyzed Mannich-type reaction of carboxylic acids.

L6, generating acyloxyborane intermediate **A** accompanied by hydrogen gas evolution. Deprotonation of the α-proton of acyloxyborane intermediate **A** (the pK_a value of α-proton of **A** was calculated to be ca. 23)[13] by DBU generates boron enolate **B**, which reacts with imine **2** to afford intermediate **C**. Finally, the ligand exchange between **C** and **1** produces **3** with regenerating acyloxyborane **A** for the next catalytic cycle.[18]

In summary, we have developed the first catalytic protocol for the chemoselective formation of enolates from a wide variety of carboxylic acids by using $BH_3{\cdot}SMe_2$. The catalytically generated enolates were subsequently used in Mannich-type reactions with a wide range of imine electrophiles. These highly chemoselective reactions require DBU as an organic base, proceed under mild conditions, and display outstanding functional group tolerance. Furthermore, this method was successfully applied in asymmetric Mannich-type reactions by using chiral BINOL-substituted boron catalysts. The versatility of the presented concept, i.e. the selective nucleophilic activation of carboxylic acids, suggests that it should also find applications in other chemoselective C–C bond-forming reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04175.

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Notes

The authors declare no competing financial interest.

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(14) For recent reviews of enantioselective catalytic Mannich-type reactions of aldehydes or ketones, see: (a) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (c) Karimi, B.; Enders, D.; Jafari, E. *Synthesis* **2013**, *45*, 2769.
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(16) The absolute configurations of the products were determined after conversion to known compounds (see SI).
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(18) Isolated boron tripropionate reacted with imine **2a**, producing **3aa** in high to moderate yield under the standard reaction conditions. This result supports our hypothesis that acyloxyborane is an active intermediate for the reaction (see SI).

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