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Organocatalysis

Synthesis of Aldehydes by Organocatalytic Formylation Reactions of Boronic Acids with Glyoxylic Acid

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Abstract: Reported herein is a conceptually novel organocatalytic strategy for the formylation of boronic acids. New reactivity is engineered into the α -amino-acid-forming Petasis reaction occurring between aryl boronic acids, amines, and glyoxylic acids to prepare aldehydes. The operational simplicity of the process and its ability to generate structurally diverse and valued aryl, heteroaryl, and α , β -unsaturated aldehydes containing a wide array of functional groups, demonstrates the practical utility of the new synthetic strategy.

With more than four thousand commercially available aryl boronic acids, they have become one of the most versatile building blocks in organic synthesis.^[1] Notably, recent significant advances in borylation methods has made aryl boronic acids, particularly those that are heavily functionalized, more readily accessible.^[2] The unique reactivity of substances in this family has led to a myriad of carbon-carbon and carbonheteroatom bond-forming processes, which are either difficult to carry out or show poor functional-group tolerance, and/or low efficiency when their halide counterparts are employed as substrates. These reactions, which include the introduction of oxygen,^[3] nitrogen,^[4] and halogen,^[5] as well as alkyl, alkynyl, alkenyl, and alkyl moieties,^[6] are generally accomplished using transition-metal complexes (Scheme 1a). However, to the best of our knowledge, no examples of catalytic formylation reactions of arylboronic acids exist.

Aldehydes occupy a unique position in organic chemistry owing to the versatility of the aldehyde group, which is capable of undergoing various transformations.^[7] Classical methods^[8] for aldehyde synthesis generally require large amounts of reagents and multistep sequences, and they often result in the production of at least stoichiometric amounts of byproducts. Furthermore, the harsh reaction conditions

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Scheme 1. Functionalization of versatile boronic acids and formylation reactions.

needed for these processes are often not compatible with substances possessing acid- and base-sensitive functional groups. Finally, control of the regiochemical courses of these reactions makes it difficult to introduce aldehyde functionality at desired positions. Because of these limitations, the development of protocols for introduction of the aldehyde functional group in a selective and predictable manner, and with a high functional-group tolerance remains a key challenge in preparative organic chemistry.

The state-of-the-art methods for the synthesis of synthetically important aldehydes, such as palladium-catalyzed formylation reactions of aryl halides with CO/H₂, pioneered by Heck,^[9] mainly rely on precious transition metals. While significant advances have been made in developing improved protocols,^[10] these approaches generally require high temperatures and the use of expensive palladium complexes as promoters. Moreover, in some cases, toxic CO gas^[10a-c] and tin compounds^[10b] are used. In addition, these methods are incompatible with arenes bearing bromide, iodide, and OTf groups, as well as others. These drawbacks demand that a more cost-effective, environmentally friendly, and mild method for aldehyde synthesis be devised.

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In considering ways to address the challenges associated with devising a new, truly environmentally friendly strategy for the synthesis of aldehydes, our attention was drawn to the mild, three-component amino-acid-forming Petasis reaction (Scheme 1 b).^[11] This process is carried out using aryl boronic acids (1), glyoxylic acid (2), and amines (3), and does not require the use of transition metals for activation. We believed that this process would serve as the foundation of an organocatalytic aldehyde-forming protocol if the in situ formed α -amino acid **6** were properly designed to undergo O2-promoted oxidative decarboxylation to form the iminium ion 7. In situ hydrolysis of the iminium ion formed in this way would produce the aldehyde product 4 and liberate the amine as part of a catalytic cycle. The critical challenge in developing a new formylation procedure based on this strategy is devising a system and conditions under which oxidative decarboxylation of 6 would occur. Knowledge gained from our earlier studies of oxidative enamine catalysis,^[12] aniline-catalyzed direct functionalization of aldehydes,^[13] and single-electrontransfer (SET) promoted formylation^[14] and decarboxylation^[15] reactions inspired us to propose that SET-induced decarboxylation of amino acids, derived from the Petasis reaction of N-alkylaniline derivatives such as tetrahydroquinoline and indoline, might undergo O₂-promoted oxidative decarboxylation. This reasoning is based on a consideration of the respective oxidation potentials of +0.66 and +0.63 V (vs. AgCl/Ag in CH₃CN, see SI) for 1-methyl-1,2,3,4-tetrahydroquinoline and N-methylindoline, and the reduction potential for $O_2(g)$, that is, +0.682 V (AgCl/Ag in water).^[16] These data suggest that SET to O2 from the tetrahydroquinoline and indoline moieties of the corresponding amino acids would be exergonic and, thus rapid. In contrast, E^{red}_{1/2} (vs. AgCl/Ag) in CH₃CN of aliphatic amines such as N-methylpyrrolidine and its Petasis adduct 2-phenyl-2-(pyrrolidin-1-yl)acetic acid are 0.82 V and 1.16 V, respectively, and suggests that the latter substance would not be rapidly oxidized by O2. When coupled to the fact that aminium radicals formed by SET oxidation of α -amino acids undergo rapid decarboxylation, and that the resulting α -amino radicals are rapidly oxidatively converted into iminium ions,^[15] the data suggest that O_2 will promote oxidative decarboxylation of the secondary-aniline-derived Petasis adducts 6 to generate 7, which upon hydrolysis will form the target aldehydes 4 and regenerate the amine organocatalyst 3.

Proof-of-concept of the newly proposed formylation strategy began with a study of the reaction of 4-methoxyphenylboronic acid (1a) with glyoxylic acid monohydrate (2) in the presence of tetrahydroquinoline (3a) in CH₃CN under ambient conditions and an air atmosphere (Table 1). In full accord with our proposal, the process proceeds efficiently to form the desired aldehyde 4a in 75 % yield. (entry 1). In the absence of air, 4a is not generated (entry 2) but instead the Petasis product is formed. In addition to O₂, 3a is essential for the process (entry 3). Furthermore, only the Petasis-reactionderived amino acid is formed when pyrrolidine is used as the promoter and reaction conditions which are identical to those used for 3a-catalyzed conversion of 1a into 4a are employed (entry 4). Lower catalyst loading delivered poorer yield (entry 5). However, we showed that the protocol can be Table 1: Exploration and optimization.

MeO 1a	B(OH) ₂ + CHOCO ₂ H • H ₂ O 2 RT, air, 24–36 h, CH ₃ CN	MeO 4a CHO
Entry	Deviation from standard conditions ^[a]	Yield [%] ^[b]
1	_	75 (75) ^[c]
2	under N ₂ (without O ₂)	0
3	without 3 a	0
4	Pyrrolidine ^[d]	0
5	10 mol % 3 a used	23
6	20 mol% 3a and 3.04 g of 1a used	77 ^[c]

[a] Standard reaction conditions: unless otherwise specified, a mixture of **1a** (0.2 mmol, 1.0 equiv), **2** (0.21 mmol, 1.05 equiv), and **3a** (30 mol%) in CH₃CN (5.0 mL) was stirred at RT under ambient conditions for 24–36 hours. See the Supporting Information for detail. [b] Yields were determined by using ¹H NMR spectroscopy with dimethyl maleate as an internal standard. [c] Yields of isolated products. [d] Petasis product observed.

adapted to a large-scale synthesis of aldehydes with 20 mol% **3a** when 3.04 grams of **1a** were used to produce 2.10 grams (77% yield) of **4a** (entry 6).

The new methodology described above is applicable to the synthesis of a variety of aromatic aldehydes (Scheme 2). Notably, the efficiency of the reaction is not significantly



Scheme 2. Scope of the formylation reaction with aryl boronic acids. [a] Standard reaction conditions: unless otherwise specified, see reaction conditions in Table 1. Yields refer to those of isolated products. [b] NMR yield with dimethyl maleate as an internal standard. [c] Reaction carried out at 70 °C for 24 hours. [d] Reaction carried out at 40 °C for 36 h. affected by variations in the aryl boronic acids, as is demonstrated by the observation that the electronic nature and position of substituents on the aromatic ring of the substrates do not impact the yields of these reactions. Notably, the mild nature of the formylation reaction enables survival of a variety of functional groups. Particularly noteworthy is the fact that the process is orthogonal to palladium-catalyzed formylation reactions, which use aryl bromides and iodides as substrates. In the new process, formylation of aromatic boronic acids bearing chloride, bromide, iodide, and OTf groups occurs without affecting aryl-halide and aryl-OTf functionalities (eg., formation of 4j, and 4ad-ag). Furthermore, the formylation protocol is applicable to the production of *p*-nitrobenzaldehyde (40) and pentafluorobenzaldehyde (4y), which are difficult reactions to achieve when transitionmetal catalytic methods are employed.^[10] In addition, a variety of structurally diverse aromatic-ring-containing boronic acids effectively participate in the process as demonstrated by the formation of the aldehydes 4v-x in high yields. Moreover, pharmaceutically relevant heteroaromatic aldehyde building blocks (eg., 4z-4ac) are efficiently prepared starting with the corresponding boronic acids. Finally, the new formylation procedure was found to be applicable to a late-stage synthetic elaboration of a steroidal boronic acid to generate the biologically relevant aldehyde 4ah.

A major effort has been given to the development of formylation reactions of indoles, all of which take advantage of the high nucleophilic reactivity of the C3-position.^[17] Devising methods for formylation at other positions of this heterocycle ring system are plagued by difficulties associated with regiocontrol and poor functional-group compatibility. Given the fact that other regioisomeric formyl indoles are highly valuable building blocks for the synthesis of a broad range of indole-ring-containing substances, we explored formylation reactions of several N-Boc-protected indole boronic acids. As can be seen by viewing the results outlined in Scheme 2, N-Boc-protected 6-, 5-, and 4-boronic acid derivatives of indole are efficiently converted into the corresponding formylindoles **4ai–ak** utilizing the newly developed protocol.

Notably, the reaction of 4-cyanophenylboronic acid under the optimized reaction conditions produced the target aldehyde **4n** along with a significant amount (33%) of 4cyanophenol (Scheme 2). This observation indicates that a reactive oxygen species (e.g., hydrogen peroxide, superoxide ion), formed under the oxygen-rich conditions, oxidizes 4-cyanophenylboronic acid to form the corresponding phenol.^[3b] We observed that side-product phenols of this type, in reactions which form **4j**, **4m**,**n** and **4v**, can be reduced by carrying out the processes at 70 °C.

To determine if the scope of the new procedure could be expanded to include the preparation of the enals **9** (Scheme 3), which are versatile substances used in iminium catalysis,^[18] we explored formylation reactions of several alkenylboronic acids (**8**). By using the optimized reaction conditions developed for formylation of aryl boronic acids (see above), which utilize **3a** as the organocatalyst, β -styryl boronic acid is transformed into cinnamaldehyde (**9a**) but in only 10% yield (see Scheme S2 in the Supporting Informa-



Scheme 3. Formylation reactions of alkenyl boronic acids. [a] Standard reaction conditions: unless otherwise specified, see Scheme 2 and the Supporting Information for details. [b] Yields of isolated products. [c] *cis*-Styrylboronic acid used. Boc = *tert*-butoxycarbonyl.

tion). A brief screen of amines demonstrated that indoline (**3b**) is a superior catalyst for preparation of **9a** from the corresponding boronic acid, and takes place in 70% yield. Moreover, we observed that formylation reactions employing **3b** as the organocatalyst occur efficiently to produce the corresponding enals **9** (Scheme 3) with moderate to high efficiency. However, we found that the *cis* styrylboronic acid **8a** also generated the *trans* enal **9a** under the formylation reaction conditions. It is known that **8a** produced a Petasis product which contains a *cis* styryl moiety.^[19] This observation suggests that the initially formed *cis* radical intermediate in the SET-promoted decarboxylation process equilibrates to form the thermodynamically more stable *trans* counterpart prior to oxidation to form the iminium ion (see Scheme 4 and Scheme S3).^[20]

The results presented suggest that the initially formed amino acid 6, produced by the Petasis reaction between boronic acids, glyoxylic acid (2), and aromatic amines like 3a, undergo the oxidative decarboxylation to produce the iminium ion precursor of aldehyde 7 (Schemes 1 b and 4). Several experiments were carried out to gain information about subtle features of the process and the validity of our mechanistic proposals. First, the in situ formed Petasis product 6k and iminium ion 7k intermediate in the 3apromoted reaction of phenylboronic acid with 2 were



Scheme 4. Experiments to elucidate subtle features and proposed catalytic cycle involving oxidative SET decarboxylation for the formylation reaction.

detected by using in situ mass spectrometric analysis (see the Supporting Information). Moreover, we found that the 3apromoted reaction of glyoxylic acid with phenylboronic acid, carried out under O₂-free conditions, does not generate the corresponding aldehyde 4k (Table 1, entry 2). Furthermore, the amino acid 6k, the proposed Petasis intermediate in this formylation process, was independently synthesized (see the Supporting Information) and found to be quantitatively transformed under an air atmosphere (CDCl₃, RT, overnight, ¹H NMR analysis) into benzaldehyde (4k) and amine 3a [Scheme 4, Eq. (1)]. Aliphatic-amine-like pyrrolidine participate in the formation of the Petasis product, but the derived amino acids do not undergo subsequent oxidative decarboxylation in air (Table 1, entry 4). Thus, the selection of a proper amine catalyst is critical requirement for the success of the new formylation protocol. As discussed above, the Nalkylaniline derivatives have lower redox potentials than that of O₂ and, therefore, they undergo rapid SET oxidation in air (O_2) . In contrast, aliphatic amines can be oxidized by O_2 but only with the assistance of light in the presence of photosensitizer.^[15, 17, 21] In a similar manner to the photochemical processes,^[15,22] the O₂-mediated SET process initially generates the aminium radical 10k and superoxide ion (Scheme 4). The aminium radical 10k then undergoes decarboxylation to form the α -amino radical **11**k, which is oxidized to produce the iminium ion 7k with concurrent production of H_2O_2 ^[15] We observed phenol side products in the formylation reaction, particularly 4j, 4m,n, and 4v. It is believed that their formation comes from the oxidation of boronic acids by H_2O_2 (see above).^[3b]

In conclusion, in the study described above we uncovered an unprecedented organocatalytic method for facile installation of the highly valued aldehyde functional group from aryl and alkenyl boronic acids. The reaction is truly environmentally friendly and atom economical. The simple aniline derivatives, tetrahydroquinoline and indoline, serve as catalysts for the process and the feedstock chemical glyoxylic acid is used as the formylation reagent. The reaction is performed under metal-free, mild, and operationally simple conditions, and produces nontoxic CO₂ and boric acid as by-products. The new formylation reaction displays a broad substrate range which includes aryl, heteroaryl, and alkenyl boronic acids, and it tolerates a wide array of functional groups. Notably, the process is capable of selectively installing the aldehyde group in halogen-containing aryl boronic acids, and stands in contrast to the difficulty of executing these transformations using transition metal promoted formylation processes. Furthermore, selective formylation of N-Boc indole derived boronic acids can be utilized to generate indole aldehydes that have the formyl group at positions other than C3. It is expected that the simplicity and efficiency of the new formylation reaction will make it useful in approaches for the practical production of highly valued aromatic and α , β unsaturated aldehydes.

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Conflict of interest

The authors declare no conflict of interest.

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