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Catalytic Activation of *Cis*-Vicinal Diols by Boronic Acids: Site-Selective Acylation of Carbohydrates

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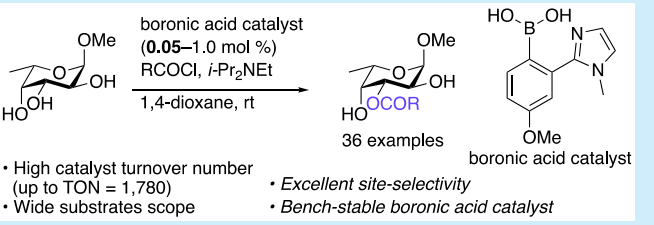
Supporting Information

ABSTRACT: Site-selective acylation of unprotected carbohydrates by using stable, storable, and easily handled imidazole-containing organoboronic acid catalysts is described. This catalytic process with low catalyst loading enables the introduction of a wide variety of acyl functional groups into the equatorial position of *cis*-vicinal diols in unprotected hexapyranosides with excellent site selectivity. This is the first example that uses a Lewis base-containing boronic acid to enhance the nucleophilicity of hydroxy groups.



Carbohydrates play important roles in many biological processes, rendering the development of efficient synthetic methods toward carbohydrates crucial for glycobiology research. However, general methods for carbohydrate transformations require tedious manipulation and multistep protection/deprotection procedures that result in low yields; therefore, the development of direct site-selective functionalization of unprotected carbohydrates is highly desirable. In particular, the catalytic site-selective transformation of free hydroxy groups at specific positions on unprotected carbohydrates would represent a very effective and straightforward functionalization approach.[1] Over the past few decades, beginning with catalytic use of tin reagents,[2] a wide variety of transition-metal catalysts,[3−5] organocatalysts,[6−11] and peptide catalysts[12] have been developed. More recently, organoboron catalysis has emerged as a new approach for the site-selective activation of hydroxy groups.[13−15] Organoboron compounds have been widely used as regioselective protective or transient masking agents for carbohydrates and polyols by taking advantage of their high molecular recognition ability for *cis*-vicinal or 4,6-diols moieties of unprotected hexapyranosides,[16] affording five- or six-membered cyclic boronic esters (Figure 1a).[17] Tricoordinated cyclic organoboronic esters attenuate the nucleophilicity of boron-bound oxygen atoms by the flow of lone-pair electrons of oxygens to the empty p-orbital of boron atom. In contrast, Aoyama and co-workers demonstrated that the nucleophilicity of the hydroxy group in carbohydrates could be enhanced by the formation of tetracoordinate borate complexes through intermolecular coordination of nitrogen of Lewis base[18a] or intramolecular coordination of oxygen[18b] to the boron atom (Figure 1b,c). Although these approaches require stoichiometric amounts of organoboron reagents, innovative catalytic methods have been recently developed for the site-selective activation of unprotected sugars via tetracoordinated organoboron adducts using diarylborinic acids (Ar_2BOH) or 9-hetero-10-boraanthracene-derived borinic acids by Taylor and co-workers (Figure 1d).[13,14,19,20] Despite the effectiveness of borinic acid catalysis in transformations such as site-selective acylation,[13a] alkylation,[13b,g,14a] sulfonylation,[13d] sulfation,[14c] and glycosylation[13c,e,f,14a,b] of unprotected sugars, there is still

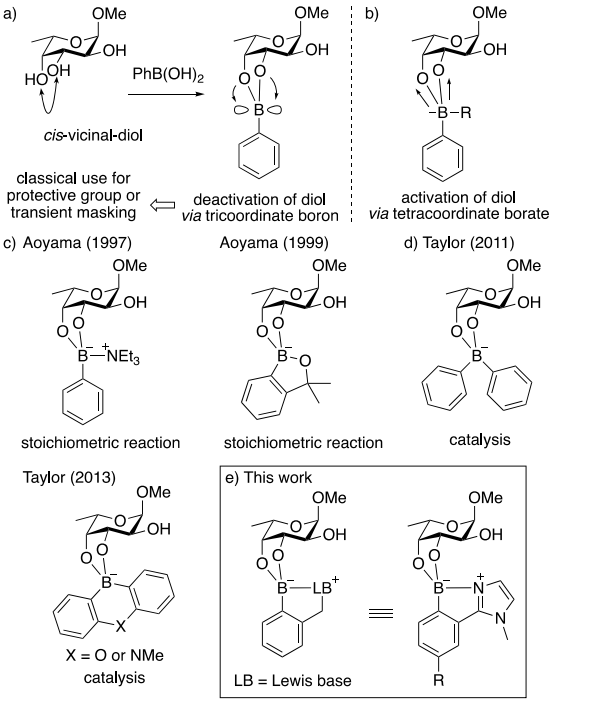


Figure 1. Enhancement of nucleophilicity by organoboron compounds. Previous work (a−d) and our working hypothesis (e).

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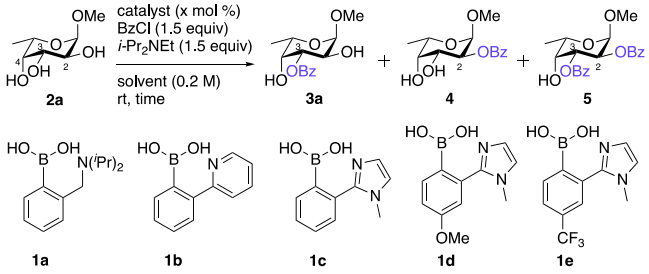
room for improvement of their catalytic efficiency, often requiring the use of relatively large amounts of catalyst (5−10 mol %).[14a] Therefore, the development of easily handled organoboron catalysts that enable facile structural modification for the site-selective transformation of unprotected carbohydrates still remains a challenge.

Herein, we report 2-(*N*-methyl-2-imidazolyl)phenylboronic acids as catalysts for the highly site-selective acylation of unprotected carbohydrates with low catalyst loading. Toward this goal, we designed functionalized arylboronic acids that incorporate a Lewis basic site. The key feature of our mechanistic hypothesis is the catalytic activation of a hydroxy group in the carbohydrate via formation of a tetracoordinate borate complex through the intramolecular coordination of the Lewis basic site to boron (Figure 1e).

We selected the site-selective acylation of unprotected carbohydrates as a model reaction and several air- and moisture-stable boronic acids incorporating a Lewis basic site as catalysts (Table 1). The reaction of methyl α-L-fucopyranoside (**2a**) possessing three free hydroxy groups with benzoyl chloride (1.5 equiv) in the presence of 5.0 mol % of 2-(*N*,*N*-diisopropylaminomethyl)phenyl boronic acid (**1a**)[21] in dichloromethane proceeded at room temperature to give 3-benzoylated product **3a** in 14% yield along with 2-benzoylated site-isomer byproduct **4** in 3% yield after 4 h (entry 1). Although the reaction using 2-(2′-pyridyl)phenylboronic acid (**1b**)[22] led to poor conversion (entry 2), a dramatic improvement in terms of yield and site selectivity was attained using 2-(*N*-methyl-2-imidazolyl)phenylboronic acid (**1c**)[23] as catalyst, providing **3a** in excellent yield with perfect site selectivity (entry 3). These results suggest that the incorporation of the *N*-methyl-2-imidazolyl group to the phenylboronic acid promotes tetracoordinated borate formation in the *cis*-vicinal diol of the carbohydrate, thereby enhancing the nucleophilicity of the oxygen atoms. Attempts to reduce the catalyst loading resulted in longer reaction times and a decrease in site selectivity (entries 4−6). We then screened a variety of solvents[24] and identified 1,4-dioxane as an optimal solvent under the low catalyst loading, giving the product **3a** in quantitative yield even in the presence of 0.5 mol % of **1c** (entry 7). To improve the catalytic activities further, we then examined the electronic tuning of the catalyst (entries 8 and 9). Thus, the presence of a methoxy group at the *para* position to boron in the benzene ring (**1d**) afforded **3a** in quantitative yield with perfect site selectivity within 4 h (entry 8). In contrast, a slight decrease in the catalytic activity was observed with trifluoromethyl-containing catalyst **1e**, although a high site-selectivity was maintained (entry 9). These results indicate that introducing an electron-donating group in the catalyst is essential for increasing the catalytic activity. By using **1d**, the catalyst loading could be reduced further to 0.2 mol %, and **3a** was obtained in 99% isolated yield (entry 10). This result means that **1d** shows higher catalytic activity compared to previous borinic acid catalysts in this reaction (see SI-Table 4 for details). Comparatively, *N*,*N*-dimethylaminopyridine (DMAP), commonly used as a nucleophilic acylation catalyst, was less effective for the site-selective monobenzoylation (entry 11). Moreover, the reaction hardly proceeded in the absence of a catalyst, affording only a trace amount of **3a** (entry 12).

The present catalytic system using **1d** could be applied easily to gram-scale monobenzoylation, giving **3a** in 95% yield without any loss of site selectivity (Scheme 1).

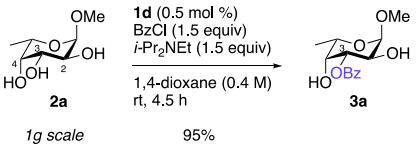
Table 1. Optimization of Reaction Conditions.[a]



entry	catalyst (*x* mol %)	solvent	time (h)	yield[b] (%) **3a**/**4**/**5**	total yield[b] (%)
1	**1a** (5.0)	CH_2Cl_2	4	14/3/−	17
2	**1b** (5.0)	CH_2Cl_2	4	5/1/−	6
3	**1c** (5.0)	CH_2Cl_2	4	>99/−/−	>99
4	**1c** (1.0)	CH_2Cl_2	4	92/4/2	98
5	**1c** (1.0)	CH_2Cl_2[c]	4	92/5/1	98
6	**1c** (0.5)	CH_2Cl_2[c]	8.5	84/3/7	94
7	**1c** (0.5)	1,4-dioxane[c]	17.5	99/−/<1	99
8	**1d** (0.5)	1,4-dioxane[c]	4	>99/<1/−	>99
9	**1e** (0.5)	1,4-dioxane[c]	24	93/<1/<1	93
10[d]	**1d** (0.2)	1,4-dioxane[c]	7	>99/−/<1	>99 [99][e]
11	DMAP (5.0)	CH_2Cl_2	4	44/5/38	87
12[d]	−	1,4-dioxane[c]	7	1/1/−	2

[a]Reaction conditions: methyl α-L-fucopyranoside (**2a**) (0.20 mmol), benzoyl chloride (0.30 mmol), and *i*-Pr_2NEt (0.30 mmol) in the presence of boronic acid catalyst in solvent at room temperature (25 °C). [b]The yields were determined by ^{1}H NMR analysis of the crude product mixture using 1,1,2,2-tetrachloroehtane as an internal standard. [c]Performed in 0.4 M. [d]2.0 equiv of benzoyl chloride and *i*-Pr_2NEt were used. [e]Isolated yield of **3a**.

Scheme 1. Gram-Scale Site-Selective Monobenzoylation



With the effective catalyst in hand, we next studied the substrate generality of the reaction (Scheme 2). The reaction of 6-*O*-TBS-protected methyl galactopyranoside **2b** with 0.5 mol % of **1d** proceeded smoothly within 4 h, giving 3-benzoylated product **3b** in 99% isolated yield. The reaction of allyl α-D-galactopyranoside **2c** and allyl β-D-galactopyranoside **2d** led to the respective derivatives **3c** and **3d** in high yield, evidencing that the stereochemistry of the anomeric position does not influence the site selectivity of the catalytic monobenzoylation. High yields and selectivities were maintained in the case of propargyl galactopyranoside **2e** or phenyl thiogalactopyranoside **2f**, the latter proving that the Lewis basic thioether was well tolerated. The protocol could be applied also to several carbohydrates **2g**−**j**, affording the corresponding 3-benzoylated products **3g**−**j** in high yields (93−97%). These results reveal that the present catalytic system enables the monobenzoylation of the equatorial hydroxy group of the *cis*-vicinal diol moiety with high site selectivity. It is comparable to the regioselectivity observed in borinic acid catalysis.[13a]

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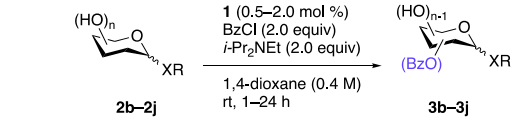
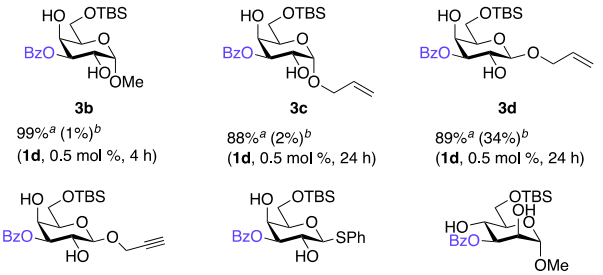
Scheme 2. Boronic Acid Catalyzed Site-Selective Monobenzoylation of Carbohydrates



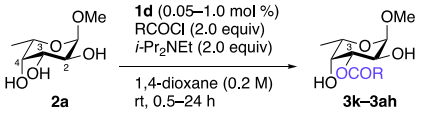


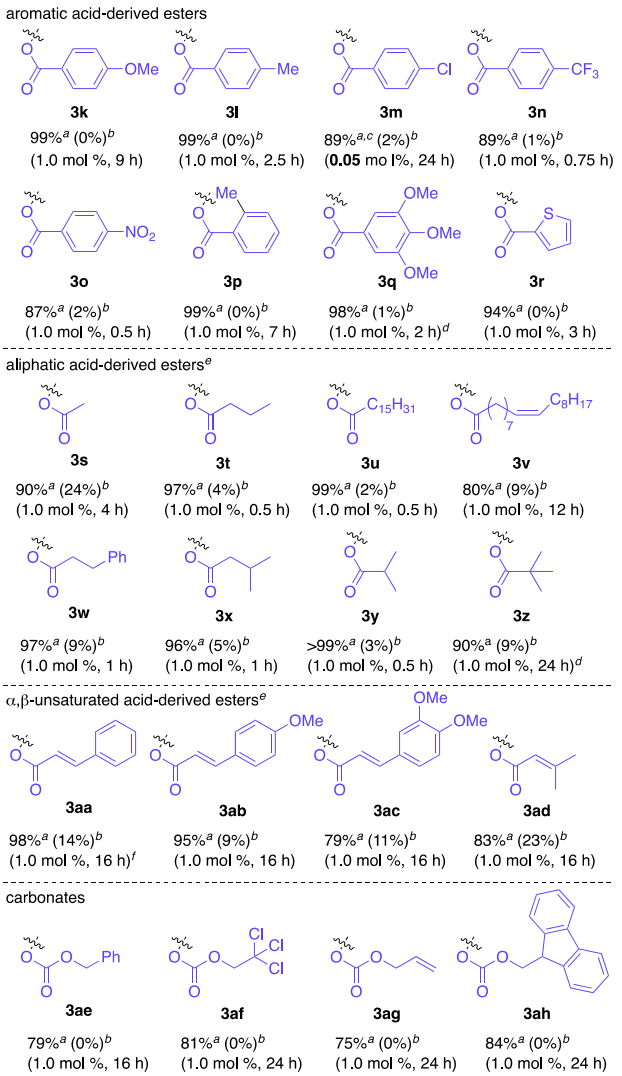
[a]Isolated yield. [b]Yields in the absence of catalyst are in parentheses. The yields were determined by ^{1}H NMR analysis of the crude product mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c]Performed in 1,4-dioxane (0.2 M).

To investigate the scope of the reaction, we applied the optimum reaction conditions to several acylating reagents (Scheme 3). A wide range of benzoyl chloride derivatives bearing an electron-donating or electron-withdrawing group on the aromatic ring successfully afforded the corresponding 3-acylated products **3k−q** in high to excellent yields (87%−99%). For **3m**, the catalyst loading could be reduced to 0.05 mol % without any loss of site selectivity and with a high catalyst turnover number (TON = 1780). The introduction of substituents at *ortho*- or *meta*-position did not affect the product yield or selectivity (**3p,q**). A sulfur-containing heteroaromatic acyl chloride could be applied also, giving readily **3r** in 94% yield. In all cases, negligible yields were obtained in the absence of catalyst **1d**. A variety of acid chlorides derived from aliphatic carboxylic acids was applicable by changing the base to collidine. Even in the case of the highly reactive acetyl chloride, only 3-acylated product **3s** was obtained in 90% yield. With a long reaction time, the reaction with sterically hindered pivaloyl chloride afforded ester **3z** in high yield. Notably, *α,β*-unsaturated acid chlorides could be applied as well, and the corresponding products **3aa−ad** were obtained in high to excellent yields (79%−98%). To the best of our knowledge, this is the first use of *α,β*-unsaturated acid chlorides for the site-selective acylation of unprotected carbohydrates. Moreover, the protocol could be applied to the site-selective introduction of carbonate groups, and the reaction with chloroformates afforded the corresponding Cbz-, Troc-, Alloc-, and Fmoc-protected products **3ae−ah** in high yields.

Next, we examined the site-selective dibenzoylation of unprotected carbohydrates (Scheme 4). Treatment of fully unprotected mannopyranoside **2k** with 4.0 equiv of benzoyl

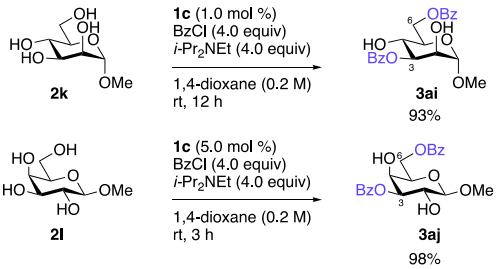
Scheme 3. Boronic Acid Catalyzed Site-Selective Monoacylations





[a]Isolated yield. [b]Yields in the absence of catalyst are in parentheses. The yields were determined by ^{1}H NMR analysis of the crude product mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c]Turnover number (TON) = 1780. [d]3.0 equiv of acyl chloride and base were used. [e]Collidine was used instead of *i*-Pr_2NEt. [f]4.0 equiv of acyl chloride and collidine were used.

Scheme 4. Boronic Acid Catalyzed Site-Selective Dibenzoylations



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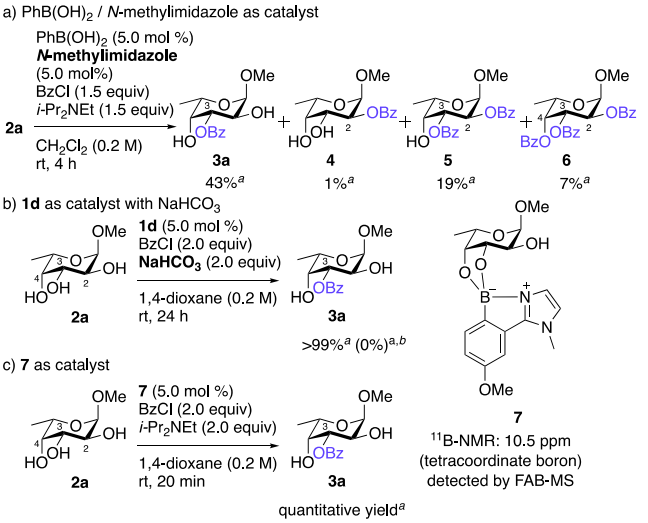
chloride and *i*-Pr_2NEt using 1.0 mol % of **1c** selectively afforded 3,6-dibenzoylated product **3ai** in 93% yield. This result suggests that **3ai** was produced via activation of both diol groups (1,3-diol and *cis*-vicinal diol). Although the reaction of galactopyranoside **2l** with 1.0 equiv of benzoyl chloride showed a modest product ratio for 3-monobenzoylated product and 6-monobenzoylated product,[25] 3,6-dibenzoylated product **3aj** was obtained in excellent yield (98%) by using an excess amount of the reagents.

Control experiments were performed to clarify the mechanism of the reaction. The relevance of the intramolecular imidazolyl substituent on the arylboronic acid to obtain monoacylated products with high site selectivity was evidenced by using a combination of phenylboronic acid and *N*-methylimidazole as catalyst, which provided 3-benzoylated product **3a** in only 43% yield along with 2-benzoylated product **4** (1%), dibenzoylated product **5** (19%), and tribenzoylated product **6** (7%) (Scheme 5a).

Scheme 5. Control Experiments for Mechanistic Studies



[a]The yields were determined by ^{1}H NMR analysis of the crude product mixture using 1,1,2,2-tetrachloroethane as an internal standard. [b]Yields in the absence of catalyst are in parentheses.

The possibility of an activation mechanism by the coordination of *i*-Pr_2NEt to boron with formation of a tetracoordinated borate was ruled out by performing the reaction with sodium hydrogen carbonate instead of organic amine (Scheme 5b), which afforded the desired 3-benzoylated product quantitatively with perfect site selectivity. Moreover, boronic ester **7**, prepared from boronic acid **1d** and substrate **2a**, showed high catalytic performance to give product **3a** in excellent yield within short time (Scheme 5c). In order to gain evidence for the tetracoordinate borate intermediate in this catalytic cycle, a ^{11}B NMR experiment of boronic ester **7** was conducted, and the observed signal at 10.5 ppm indicates a tetracoordinated boron. In addition, the mass spectrum of boronic ester **7** showed an *m*/*z* 375.1727 (calcd *m*/*z* for 7 $[M + H]^+$ 375.1727) corresponding to the complex from boronic acid **1d** and substrate **2a**. These results support that the reaction proceeded via a tetracoordinated borate species formed by intramolecular coordination of imidazole nitrogen to boron.

From these results, we propose the catalytic cycle shown in Figure 2. Tetracoordinated borate **7** is formed initially by the

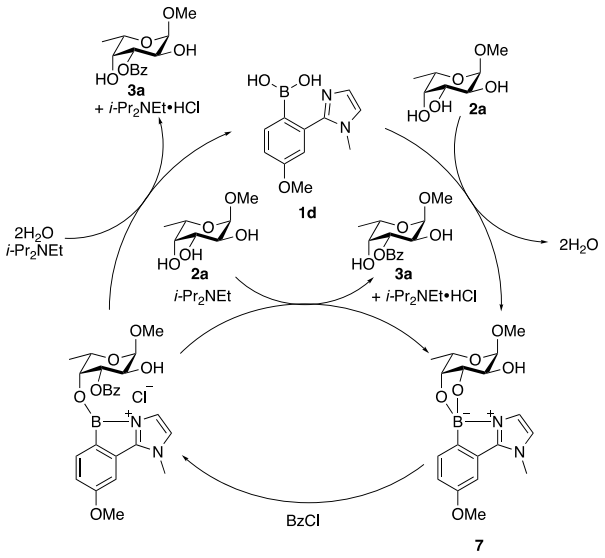


Figure 2. Proposed catalytic cycle.

dehydrative reaction of boronic acid **1d** and *cis*-vicinal 3,4-diol of **2a**, according to the molecular recognition of organoboronic acid. Subsequently, acylation proceeds at the equatorial nucleophilic oxygen. Finally, exchange with water or unreacted substrate gives the corresponding product and regenerates boronic acid catalyst **1d** or active intermediate **7** for the next catalytic cycle.

In conclusion, we have developed an imidazole-containing boronic acid catalyzed site-selective acylation of unprotected carbohydrates, relying on the enhanced nucleophilic reactivity of hydroxy groups via formation of a tetracoordinated borate intermediate through the intramolecular interaction of boron with imidazole nitrogen. This catalytic process enables the introduction of a wide variety of acyl groups into the equatorial position of *cis*-vicinal diol in unprotected hexapyranosides with excellent site selectivity. The imidazole-containing boronic acid catalyst is readily synthesized,[26] easily handled, and storable at least over a year at ambient temperature. Catalyst loading can be reduced to 0.05 mol % while affording high catalyst TON up to 1780 (s/c = 2000). We are currently investigating further applications of boronic acid catalysts for the site-selective functionalization of unprotected carbohydrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01231.

Preparation of catalysts, experimental procedures, and characterization data including ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(26) Catalysts **1d** and **1e** can be readily prepared from the corresponding aryl aldehydes over four steps. Imidazole-containing boronic acid catalysts were bench stable over at least one year without decomposition. See the Supporting Information for details.

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