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Direct Amidation of Carboxylic Acids Catalyzed by *ortho*-Iodo Arylboronic Acids: Catalyst Optimization, Scope, and Preliminary Mechanistic Study Supporting a Peculiar Halogen Acceleration Effect

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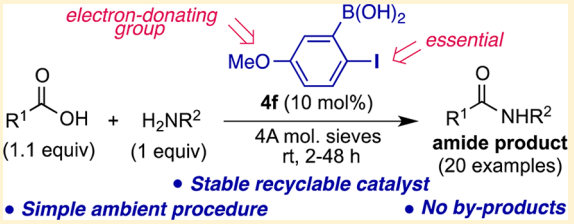
Supporting Information

ABSTRACT: The importance of amides as a component of biomolecules and synthetic products motivates the development of catalytic, direct amidation methods employing free carboxylic acids and amines that circumvent the need for stoichiometric activation or coupling reagents. *ortho*-Iodophenylboronic acid **4a** has recently been shown to catalyze direct amidation reactions at room temperature in the presence of 4A molecular sieves as dehydrating agent. Herein, the arene core of *ortho*-iodoarylboronic acid catalysts has been optimized with regards to the electronic effects of ring substitution. Contrary to the expectation, it was found that electron-donating substituents are preferable, in particular, an alkoxy substituent positioned para to the iodide. The optimal new catalyst, 5-methoxy-2-iodophenylboronic acid (MIBA, **4f**), was demonstrated to be kinetically more active than the parent des-methoxy catalyst **4a**, providing higher yields of amide products in shorter reaction times under mild conditions at ambient temperature. Catalyst **4f** is recyclable and promotes the formation of amides from aliphatic carboxylic acids and amines, and from heteroaromatic carboxylic acids and other functionalized substrates containing moieties like a free phenol, indole and pyridine. Mechanistic studies demonstrated the essential role of molecular sieves in this complex amidation process. The effect of substrate stoichiometry, concentration, and measurement of the catalyst order led to a possible catalytic cycle based on the presumed formation of an acylborate intermediate. The need for an electronically enriched *ortho*-iodo substituent in catalyst **4f** supports a recent theoretical study (Marcelli, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 6840−6843) with a purported role for the iodide as a hydrogen-bond acceptor in the orthoaminal transition state.



INTRODUCTION

The amide bond is ubiquitous in nature and synthetic chemicals. It assembles amino acids to form peptides and proteins, and it is an important component of many other natural products. Amides are also found in the structures of several synthetic commodity chemicals such as polymeric materials, insecticides, nutraceuticals, and pharmaceutical drugs (Figure 1). In this respect, it has been estimated that as much as 25% of all synthetic pharmaceutical drugs contain an amide unit.[1,2]

A host of sophisticated and efficient methods employing dehydrating-activating reagents have been developed for direct

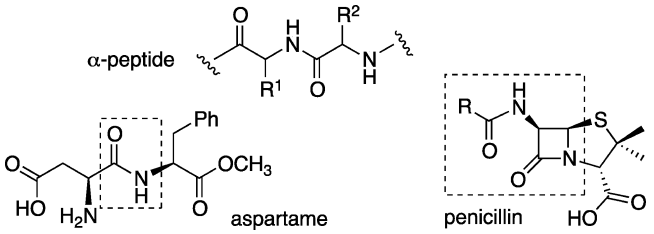


Figure 1. Examples of important amide-containing compounds.

("in situ") coupling of carboxylic acids and amines.[3−5] Common coupling reagents such as carbodiimides, phosphonium or uronium salts are expensive, often-toxic, and provide poor atom-economy.[3−5] These reagents and their associated co-reagents, including bases, supernucleophiles, and other additives, are required in a stoichiometric excess and generate large amounts of wasteful byproduct that complicate the isolation of the desired amide product. It is therefore not surprising that the amidation reaction has been deemed the top-priority research area by the *ACS Green Chemistry Institute Roundtable*.[6] In this regard, the ideal direct amidation reaction between carboxylic acids and amines would be a waste-free, catalytic and operationally simple process occurring at ambient temperature. Such a process would optimize atom economy while minimizing energy consumption. Despite the favorable thermodynamic stability of the resulting amide unit, the simple thermal dehydration between an amine and a carboxylic acid is plagued by a large activation energy.[7−13] The initial formation of a stable ammonium carboxylate salt impedes the dehydration step, and the intermediate salt collapses to provide the amide product only at high temperatures (from 85 °C for some

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substrate combinations,[11] and up to well over 150 °C for others[7]) (Figure 2). Such conditions are incompatible with

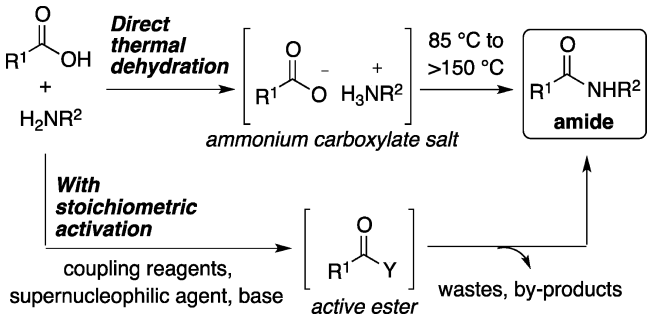

Figure 2. Direct in situ amide formation from carboxylic acids and amines.

highly functionalized molecules, and this issue makes it very challenging to develop a general method to access amides directly between free carboxylic acids and amines in a simple and atom-economical fashion at ambient temperature.[14−21] A number of alternate direct methods for the preparation of amides from other functional groups have been developed in the past decade;[22−33] however, the ready availability of carboxylic acids and amines makes them ideal precursors for the development of a direct amidation method.

Boron based compounds, used in a stoichiometric fashion, have long been known to promote direct amidation reactions.[34−38] In 1996, Yamamoto and co-workers described the first catalytic use of arylboronic acids for direct amidations.[39] Electron-poor arylboronic acids were found to be superior. However, even the most efficient one, 3,4,5-trifluoro-phenylboronic acid (**1**), required refluxing solvent at temperatures over 110 °C for several hours.[39,40] Other efficient arylboronic acids have been reported,[41] such as Whiting's 2-(diisopropyl-aminomethyl)phenylboronic acid, **2**,[42,43] and boric acid,[44−47] but all these catalysts function at elevated temperatures (Figure 3).[7]

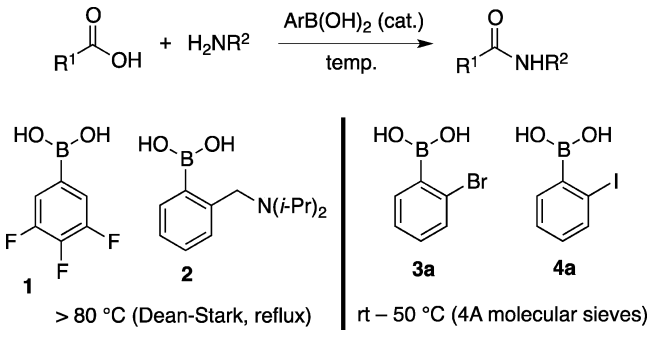

Figure 3. Known boronic acid catalysts for direct amidation.

Our interest in the applications of functionalized arylboronic acids as reaction catalysts[48−51] led to our objective of identifying a catalyst for direct amidation that would function under practical and mild conditions at room temperature. Using a model amidation reaction between phenylacetic acid and benzylamine, we systematically evaluated numerous arylboronic acids in different organic solvents combined with the use of activated molecular sieves to scavenge water, the sole byproduct of the reaction. A handful of arylboronic acids were found to be active at room temperature, and *ortho*-bromophenylboronic acid (**3a**) and *ortho*-iodophenylboronic acid (**4a**) were identified as the most efficient catalysts (Figure 3).[52] Compared to the bromide **3a**, the novel iodo derivative **4a** was found to give higher yields within shorter reaction times for a wide range of aliphatic carboxylic acids and primary amines when using methylene chloride or toluene as the solvents. Both of these catalysts were found to be superior to 3,4,5-trifluorophenylboronic acid[39,40] and boric acid.[44−47] However, even with catalyst **4a**, a few substrate types provided no reaction or low yields at room temperature, which prompted us to develop improved catalysts. In this article, we report the rational optimization of a second-generation catalyst along with a detailed evaluation of its substrate scope and a mechanistic investigation.

RESULTS

1. Catalyst Optimization. To improve upon optimal catalyst **4a**, we planned to delineate the underlying steric and electronic factors by exploring the effect of substituents on the four leftover positions of the *ortho*-haloaryl framework. All of the targeted arylboronic acids are not available commercially and had to be made according to our recent halogenation procedure,[53] or via other methods (see the Supporting Information). All the catalysts were subjected to two model reactions by stopping the reactions prior to completion. This procedure ensured that the most active catalysts could be compared more accurately and rapidly. A limitation of this approach, however, is that small differences in yields (ca. 5%) should not be considered significant. Because excess amine slows down the amidation,[52] it was deemed preferable to use a slight excess of the carboxylic acid in these prototypic reactions. Moreover, the order of addition is critical. It is essential to premix the carboxylic acid and the catalyst in the presence of molecular sieves for several minutes prior to addition of the amine. Control reactions with a simultaneous addition of both substrates with the catalyst provided less than 5% yield of amide product after several days. The mechanistic implications of this drastic effect are discussed in Section 4.

At the onset, we suspected that the perturbation of the boron center by the electronic density of the large iodide substituent could be responsible for the surprising catalytic activity of **4a**. Even though the optimal electronic effects were unclear at this stage, we suspected that a combination between electron-poor substituents (cf. Yamamoto's catalyst **1**) and *ortho*-halogens (cf. our catalysts **3a**/**4a**) may be desirable. Therefore, hybrid catalysts such as **3b** were designed. However, because the electronic density of the iodo substituent may be important, electron-rich catalysts such as **4b** with electron-donating groups at carbons 3−4−5 were designed as well (Figure 4).

Examination of Substituent Electronic Effects on the Catalytic Activity of 2-Iodoarylboronic Acids. Electron-Poor ortho-Iodoarylboronic Acids. We began this study by

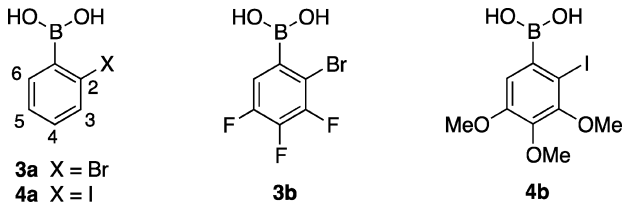

Figure 4. Exploiting ring substitution at carbons 3−4−5 for catalyst optimization.

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exploring electronic modifications of the aryl ring. The most important aspect of this manipulation is to avoid altering the free *ortho* position next to the boronyl group, which, according to our preliminary work,[52] needs to remain unsubstituted in order to preserve the reactivity of the catalyst. At this stage, the catalyst candidates were directly related to the idea of combining the features of Yamamoto's catalyst **1**,[39] which has three fluoride substituents at positions 3, 4 and 5, and our catalyst with an iodo or bromo substituent at the ortho position. In the event, two different electron-poor arylboronic acids, **3b** and **4c** (Figure 5) were prepared successfully by

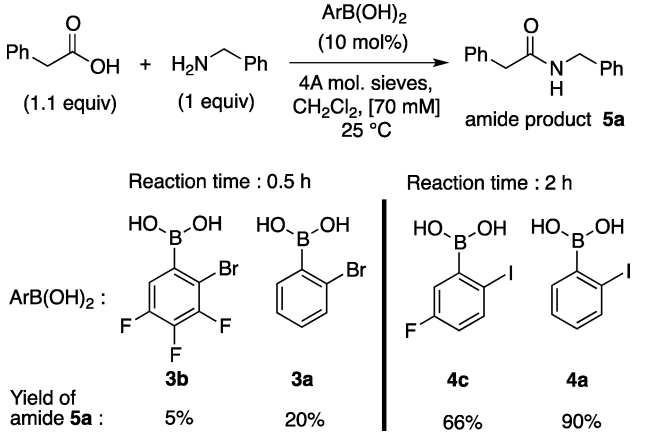


Figure 5. Comparison in product yield between electron-poor *ortho*-haloarylboronic acids **3b** and **4c** and neutral *ortho*-haloarylboronic acid **3a**/**4a** in a direct amidation reaction between phenylacetic acid and benzylamine under optimized conditions.

selective monomagnesiation of the diiodide or bromo-iodo precursors,[54,55] followed by electrophilic trapping with trialkylborates (see the Supporting Information). We subjected these catalysts to the model amidation reaction between phenylacetic acid and benzylamine. Side-by-side reactions were carefully set up under different reaction times to compare the reactivity of these catalysts with the corresponding first-generation catalysts: *ortho*-bromo or *ortho*-iodophenylboronic acids **3a** and **4a**. As seen with the results of Figure 5, the use of electronically impoverished *ortho*-haloarylboronic acids leads to a decrease in activity. Although the monofluorinated catalyst **4c** was only moderately less efficient than **4a**, the trifluorinated derivative **3b** showed a significant suppression of activity. Thus, the hybrid of **1** and **3a**, 3,4,5-trifluoro-2-bromophenylboronic acid **3b**, led to a disappointing yield of 5% of the desired amide **5a** compared to 20% for 2-bromophenylboronic acid **3a** after a premature, 30-min reaction time between the same substrates. This result was particularly surprising since both Yamamoto's and Whiting's catalysts showed optimal catalytic efficiency when decorated with electron-poor substituents.[39,40,42]

These results strongly support the idea that the electronic density of the iodine substituent next to the boronyl group is important and can be modulated with the other substituents on the arene core. In the current case, the electronic density of the *ortho*-halo group is lower in the less active catalysts **3b** and **4c** due to the presence of electron-withdrawing groups.

Electron-Rich ortho-Iodoarylboronic Acids. Having recognized the antagonistic effect of electron-withdrawing groups and especially fluorine substituents on the reactivity of *ortho*-haloarylboronic acid catalysts, we turned our attention to the effect of electron-donating substituents. It was envisioned that these compounds would be made in a similar approach to that of electron-poor arylboronic acids **3b** and **4c**, through selective monomagnesiation of the diiodide or bromoiodide intermediates followed by trapping with a borate reagent.[54,55] The resulting *ortho*-iodophenylboronic acids **4d** and **4e** were synthesized in good yields (see the Supporting Information) and were subjected to the model amidation reaction between phenylacetic acid and benzylamine. Side-by-side reactions with these catalysts were analyzed in comparison with the neutral *ortho*-iodophenylboronic acid **4a** (Figure 6), and it was found that electron-rich *ortho*-iodoarylboronic acids **4d** and **4e** are similar or marginally better than first-generation catalyst **4a**.

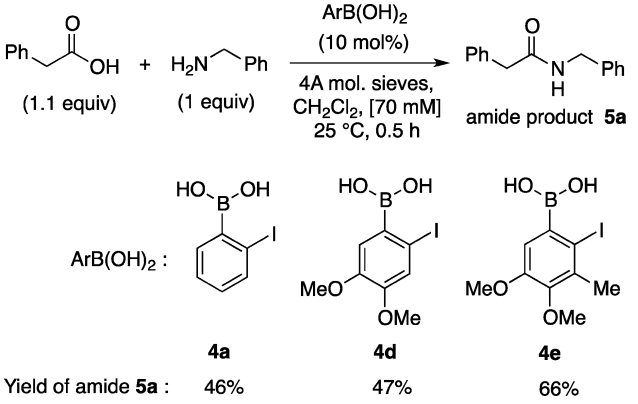
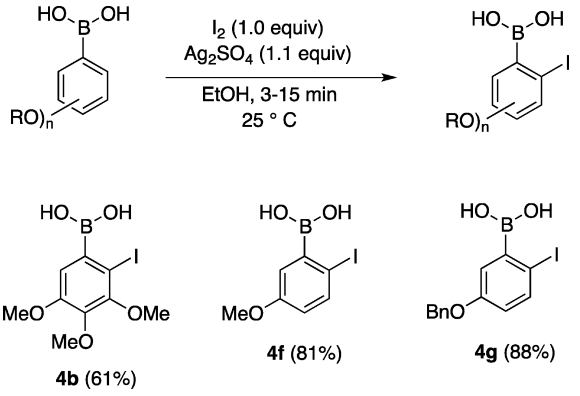


Figure 6. Comparison in product yield between electron-rich *ortho*-iodophenyl boronic acids **4d** and **4e** and first-generation catalyst **4a** in a direct amidation reaction between phenylacetic acid and benzylamine under optimized conditions.

On the basis of the disappointing results obtained with catalysts **4d** and **4e**, we wondered whether the presence of an additional electron-donating methoxy group *para* to the boron atom may partially cancel out the benefit of a more electron-rich iodide by making the boronic acid less acidic. In this context, we prepared boronic acids **4f** and **4g** (Scheme 1) with

Scheme 1. Direct and Regioselective *ortho*-Iodination of Arylboronic Acids Employed to Synthesize 4b, 4f and 4g[14]



a single electron-donating substituent only *para* to the iodo group. We concluded that the direct iodination of electron-rich arylboronic acids would be the easiest and the most direct way to make these compounds since the diiodide precursors required for the metalation/borylation approach are not commercially available and are challenging to synthesize. To this end, a new methodology was developed using mild Ag(I)

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mediated regioselective iodination and bromination of arylboronic acids.[53] Using this method, we prepared electron-rich arylboronic acids **4b**, **4f**, and **4g** as shown in Scheme 1.

We then subjected these electron-rich arylboronic acids to the model direct amidation reaction between phenylacetic acid and pyrrolidine for a set time of 6 h before the reaction reaches completion (Figure 7). All new electron-rich arylboronic acids

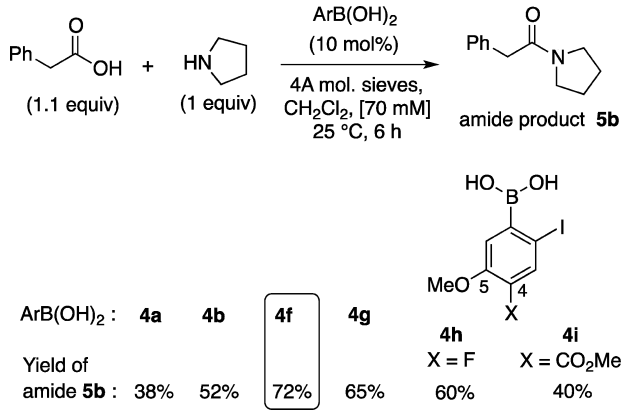

Figure 7. Comparison in amide product yield between electron rich *ortho*-iodoarylboronic acids **4a**, **4b**, **4f**, and **4g**, and the electronically balanced **4h** and **4i** in a direct amidation reaction between phenylacetic acid and pyrrolidine under optimized conditions. See Scheme 1 for the structures of **4b**, **4f**–**4g**.

4b, **4f**, and **4g** reproducibly showed a superior reactivity compared to *ortho*-iodoarylboronic acid **4a**. For example, electronically enriched catalyst **4f** led to 72% of the amide product, while catalyst **4a** provided only 38% under identical conditions. When compared with the outcome of catalyst **4b** (52% yield of amide product), this data tends to confirm the detrimental effect of a methoxy substituent positioned para to the boron atom.

The results with **4f** and **4g** confirmed that having an electron-donating group *para* to the boronic acid, such as in **4b**, is not desirable for catalytic activity. In this context, we elected to prepare and test a few more arylboronic acids with both an electron-donating group (i.e., methoxy) at carbon 5 and an electron-withdrawing group (i.e., F or CO_2R) at carbon 4 (*para* to the boronyl group). Thus, catalysts **4h** with a fluoro, and **4i** with a methyl ester were made using the same iodination methodology. Unfortunately, these catalysts did not afford a further increase of product yield compared to catalyst **4f** in the model amidation reaction (Figure 7).

These results point to a specific electronic requirement for optimal activity in *ortho*-iodoaryl boronic acid catalysts. More precisely, a greater electron density on the iodide atom seems favorable. It can also be envisaged that a closer distance between the iodide and the boron atom is desirable. To explore this possibility, we hypothesized that a catalyst such as **4j** (Figure 8), which displays a much smaller distance of 3.04 Å between the iodide and boron atoms,[56] might dramatically enhance the catalytic reactivity. Unfortunately, this boronic acid led to less than 5% yield of the desired amide product under the conditions of Figure 7. Although a more exhaustive comparison of data between a large panel of boronic acids would be necessary in order to draw conclusions, this result suggests that a precise distance between the iodide atom and the $B(OH)_2$ group is needed. Overall, by providing the highest product yield in the model amidations, the most active *ortho*-iodoarylboronic

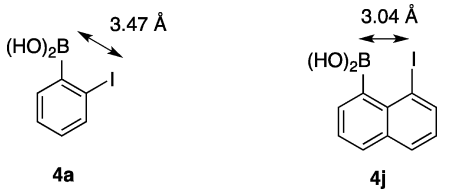

Figure 8. Interatomic B–I distances for boronic acids **4a** and **4j**.[56]

acid catalyst turned out to be 5-methoxy-2-iodophenylboronic acid (MIBA) **4f**.

Recognizing that assessing catalytic activity based on yields of isolated products is a rapid but limited methodology, we compared actual rate constants in the early stage of a model amidation between phenylacetic acid and pyrrolidine catalyzed by **4a** and **4f** (Figure 9). These kinetic experiments were

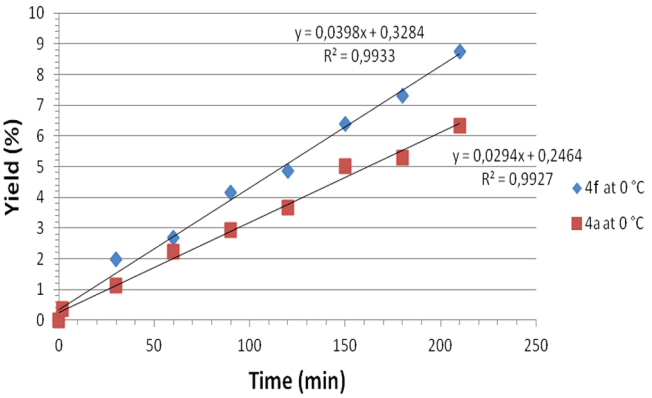

Figure 9. Comparison of rate constants between **4a** and **4f**.

performed at 4 and 25 °C, and the analysis assumed the reaction is first order in acid, amine, and catalyst (see Section 4). The values obtained indicate that catalyst **4f** provides a reaction rate approximately 1.4 times higher than the original catalyst **4a**.

$$V = k[\text{acid}]^a[\text{amine}]^b[\text{cat}]^c \quad a = b = c = 1 \qquad (1)$$

$$k_{\mathbf{4a},4\,^\circ\text{C}} = 1.02\ \text{L}^2\ \text{mol}^{-2}\ \text{s}^{-1} \quad k_{\mathbf{4f},0\,^\circ\text{C}} = 1.40\ \text{L}^2\ \text{mol}^{-2}\ \text{s}^{-1}$$

$$k_{\mathbf{4a},25\,^\circ\text{C}} = 582\ \text{L}^2\ \text{mol}^{-2}\ \text{s}^{-1} \quad k_{\mathbf{4f},25\,^\circ\text{C}} = 780\ \text{L}^2\ \text{mol}^{-2}\ \text{s}^{-1}$$

Although the kinetic advantage of catalyst **4f** over **4a** is moderate, **4f** provides a considerable and consistent increase of the reaction yields and a decrease of reaction times for all substrate types (see Section 3).

2. Optimization of Reaction Parameters with MIBA Catalyst 4f. Having identified the optimal catalyst, 5-methoxy-2-iodophenylboronic acid (MIBA) **4f**, we turned our attention to the optimization of reaction parameters, including reaction solvent, dehydrating agent, and substrate stoichiometry and concentration.

Optimization of Reaction Solvent, Concentration, and Catalyst Loading. According to our original findings,[52] amidations catalyzed by **4a** were found to proceed more efficiently in solvents such as CH_2Cl_2 and toluene. We decided to reexamine these solvents as well as other solvents including greener ones like Me-THF or CPME (cyclopentylmethylether) in a model amidation using the second-generation catalyst **4f** (Table 1). It is noteworthy that in previous and subsequent

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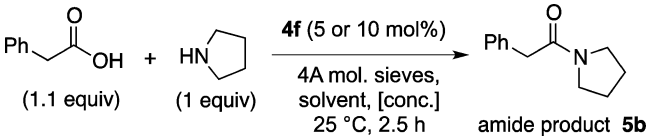
Table 1. Optimization of Solvent and Reactant Concentration with Catalyst 4f[a]



entry	solvent[b]	conc (M)	mol % of 4f	yield (%)[c]
1	Et_2O	0.07	10	0
2	acetone	0.07	10	0
3	acetonitrile	0.07	10	0
4	DMF	0.07	10	0
5	EtOH	0.07	10	0
6	THF	0.07	10	2
7	nitromethane	0.07	10	11
8	**toluene**	**0.07**	**10**	**52**
9	**CH_2Cl_2**	**0.07**	**10**	**50**
10	Me-THF	0.07	10	32
11	CPME	0.07	10	38
12	MTBE[d]	0.07	10	26
13	**chlorobenzene**	**0.07**	**10**	**53**
14	1,2-DCE	0.07	10	31
15	CH_2Cl_2[e]	0.07	10	72
16	**CH_2Cl_2[e]**	**0.1**	**10**	**94**
17	CH_2Cl_2[e]	0.125	10	81
18	CH_2Cl_2[e]	0.25	10	73
19	CH_2Cl_2[e]	0.07	5	64
20	CH_2Cl_2[e]	0.1	5	58
21	CH_2Cl_2[e]	0.125	5	74
22	CH_2Cl_2[e]	0.25	5	56

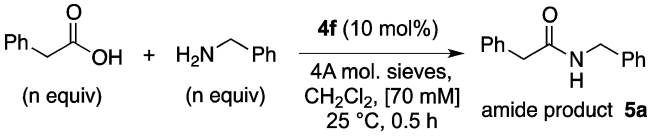
[a]Reaction conditions: Carboxylic acid (0.55 mmol, 1.1 equiv), boronic acid (5 or 10 mol %) and the amine (0.5 mmol, 1 equiv) were stirred at room temperature (25 °C) for 2.5 h in solvent containing powdered activated 4A mol. sieves (1 g). [b]Solvents were dried and distilled prior to use. [c]Isolated yields. [d]Methyl-*tert*-butylether. [e]Entries 15−22: Reaction time 6 h.

experiments (not shown), we observed that the optimal reaction solvent may vary depending on the particular combination of substrates employed. It is therefore advisible to optimize any new combination of substrates with at least a few different solvents (typically, CH_2Cl_2 and toluene).

In our previous study with catalyst **4a**, a concentration of 0.07 M for the carboxylic acid was found to be optimal when using CH_2Cl_2 as solvent.[52] With the new catalyst **4f** and the chosen model substrates, CH_2Cl_2 is still a preferred solvent (entry 9), equal to toluene (entry 8) and chlorobenzene (entry 13) (Table 1). Although THF (entry 6) has not been reconfirmed as an efficient solvent, 2-Me-THF provided promising results (entry 10). A slight increase in the reaction concentration led to a higher yield of amide product **5b** after a set reaction time. Specifically, a 0.10 M concentration was found to be optimal when using 10 mol % of catalyst **4f**, providing 94% conversion to the desired amide product (entry 16). Further increasing the concentration up to 0.25 M is not advantageous (entries 17−18). This surprising effect regarding the reaction concentration is discussed in Section 4. Taking advantage of increased reaction rates at higher concentrations, we checked whether the loading of the catalyst **4f** could be lowered to 5 mol % without a negative impact on the product yield. Unfortunately, a lower catalyst loading provided the amide product in a significantly lower yield (entries 19−22).

Optimization of Relative Stoichiometry of Substrates. We then proceeded to optimize the relative stoichiometry of the amine and carboxylic acid with CH_2Cl_2 as the solvent. Although this study had been done with the first-generation catalyst **4a**,[52] it was deemed valuable to repeat with the new second-generation catalyst **4f**. The reaction between phenylacetic acid and benzylamine was employed as a model amidation reaction. A 20 mol % excess of the carboxylic acid provided a 50% yield of the amide product after 1.5 h at room temperature (Table 2, entry 1), whereas using 10 mol % excess did not lead to a significant decrease in yield (entry 2) compared to the equimolar reaction (entry 3). On the other hand, the use of a 10-mol % and a 20-mol % excess of the amine led to a significant decrease in amide product. These results confirm that excess amine or carboxylic acid retard the reaction. Mechanistic implications of these observations will be discussed further in Section 4.

Table 2. Optimization of Relative Stoichiometry of Substrates with Catalyst 4f[a]



entry	acid (equiv)	amine (equiv)	yield (%)[b]
1	1.2	1.0	50
2	1.1	1.0	60
3	1.0	1.0	64
4	1.0	1.1	42
5	1.0	1.2	32
6	2.0	1.0	22
7	1.0	2.0	7

[a]Reaction conditions: Carboxylic acid, boronic acid (0.05 mmol, 0.1 equiv) and the amine were stirred at room temperature (25 °C) for 1.5 h in dry CH_2Cl_2 containing powdered activated 4A mol. sieves (1 g). [b]Isolated yields.

Optimization of Dehydrating Agent. Another important aspect of the boronic acid catalyzed amidation reaction is the use of activated molecular sieves as a dehydrating agent. Amide product cannot form without it (Table 3, entry 1), which confirms the inhibitory effect of water on the formation of active reaction intermediates. As summarized in Table 3, different kinds of molecular sieves and dehydrating agents were tested in a model amidation reaction.

This screen revealed that 4A molecular sieves (activated powder, ≈325 mesh particle size) is the most efficient dehydrating agent for this process. A reactivation of the molecular sieves by oven heating at 250 °C for a few days or by Kugelrohr for 2 h at 250 °C under high vacuum is necessary for the reproducibility of this direct amidation method. After identifying 4A molecular sieves as the best dehydrating agent, we undertook a second screen to determine the optimal quantity necessary to get the highest yield (Table 4). Different amounts of molecular sieves were used, and it appears that 1 g is the minimum required in a 0.5 mmol scale reaction to obtain a near-quantitative yield of product within a short reaction time (entry 4). The result of entry 5 confirms that molecular sieves alone cannot catalyze the reaction in the absence of catalyst **4f**. Molecular sieves had been shown to catalyze direct amidations

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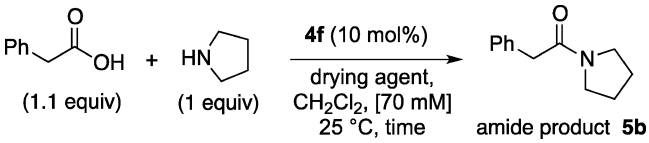
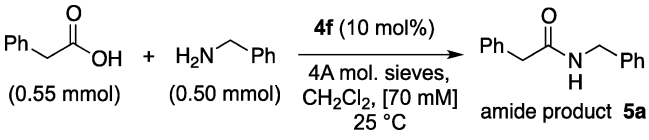
Table 3. Comparison in Product Yield for Different Dehydrating Agents Using Catalyst 4f in a Direct Amidation Reaction Between Phenylacetic acid and Pyrrolidine[a]



entry	drying agent	reaction time (h)	yield (%)[b]
1	none	24	0
2	3A mol. sieves	1.5	54
3	4A mol. sieves	1.5	79
4	5A mol. sieves	1.5	22
5	$CaCl_2$	24	<5
6	$MgSO_4$	24	<5
7	Na_2SO_4	24	<5
8	$CaSO_4$	24	<5
9	LiCl	24	<5
10	CaH_2	24	<5
11	silica	24	<5

[a]Reaction conditions: Carboxylic acid (0.55 mmol, 1.1 equiv), boronic acid (0.05 mmol) and the amine (0.5 mmol, 1 equiv) were stirred at room temperature (25 °C) for 1.5 h in dry CH_2Cl_2 containing the drying agent (1 g). [b]Isolated yields.

Table 4. Optimization of Molecular Sieves Amount with Catalyst 4f[a]



entry	4A mol. sieves (g)	time (h)	yield (%)[b]
1	0.7	1.5	85
2	0.8	1.5	91
3	0.9	1.5	93
4	1	1.5	>97
5	1 (no cat)	48	<5

[a]Reaction conditions: Carboxylic acid (0.55 mmol, 1.1 equiv), boronic acid (0.05 mmol) and the amine (0.5 mmol, 1 equiv) were stirred at room temperature (25 °C) in dry DCM containing powdered activated 4A mol. sieves. [b]Isolated yields.

at very high temperatures,[57] but no such effect was observed under our reaction conditions at room temperature.

On the basis of the maximum amount of water released during the process (1 equiv, 0.5 mmol, 9 mg), it appears that a high excess of molecular sieves is required (~20–25 equiv).[58] This can be rationalized by the need for maintaining exhaustively dry conditions that preserve moisture sensitive reactive intermediates. The role of molecular sieves is discussed in detail in Section 4.

3. Study of Scope Comparing Optimal Catalysts. In order to compare the activity of the new MIBA catalyst **4f** against the first-generation catalyst **4a**, we examined a number of amidation reactions between different amine and carboxylic acid substrates (Table 5). Analogously to our previous report,[52] the preferred substrates for the second-generation catalyst system turned out to be aliphatic carboxylic acids and amines. The reaction gave excellent yields within two hours at room temperature for the majority of aliphatic substrates (Table 3, entries 1–8). The successful use of palmitic acid highlights the suitability of detergent-like acids (entry 6). A comparison with catalysts **1** and **2** was included in entries 1 and 2 and confirmed the greater efficiency of catalyst **4f**. Moreover, all the examples of Table 5 afford significantly improved yields with the optimal catalyst **4f** compared to first-generation **4a**. Although an acyclic secondary amine failed (entry 9), cyclic amines worked well and provided high yields of the desired amides (entries 7, 8).

Aromatic amines are unreactive (not shown), and aromatic carboxylic acids were found to require a higher temperature and afforded lower yields after 48 h (entry 10). Catalysts **1** and **2** provided even lower yields under the same conditions. On the other hand, heteroaromatic carboxylic acids provided amide products in moderate to good yields in reactions performed at 50 °C (entries 11–13). Highly functionalized substrates containing phenol, pyridine, and indole units were successfully employed to make biologically relevant amide products using this simple and highly atom-economical process (entries 14–17). For example, amides of the drug indomethacin are known to display potent biological properties such as the inhibition of COX-2 enzymes.[59,60] Considering their reported method of preparation employs excess coupling reagents and a chromatographic purification, it is remarkable that indomethacin amides can be made with such ease using the new catalyst **4f** (entries 18, 19). Ibuprofen amides have been reported to display improved anti-inflammatory activity with less toxicity.[61] Here, the amidation of optically active (*S*)-ibuprofen with benzylamine led to the corresponding amide with less than 5% racemization using either catalysts **4a**[52] or **4f** (entry 20). Given the propensity of ibuprofen and its amides to racemize,[62] this result provides a clear testimony of the mildness of these low-temperature conditions. Overall, the direct amidation reaction using 10 mol % of 5-methoxy-2-iodophenylboronic acid catalyst **4f** provides faster reactions and higher product yields when compared to our first-generation catalyst **4a** under identical reaction times.[52] These direct catalytic amidations are operationally very simple. They employ near equimolar amounts of acid and amine substrates, require no (or little) heating or cooling and generate no byproduct, and they afford pure amide products after a simple filtration and acid–base extractions to remove any unreacted substrates. It is noteworthy that entry 1 was repeated on a larger scale (5 mmol) where the boronic acid catalyst was successfully recovered in high yield (90%) from simple acidification and extractions of the basic aqueous phase. Thus, catalyst **4f** is stable under the reaction conditions and is resistant to aqueous protodeboronation. Moreover, when resubjected to the same amidation reaction, the recovered catalyst afforded the same yield of product.

4. Mechanistic Studies. A previously proposed mechanism for boronic acid catalyzed amidations was supported by the apparent observation of a monoacyl boronate intermediate **I** (Figure 10), but the involvement of a diacylboronate **I**[2] could not be ruled out.[39,40] Intermediate **I** would provide electrophilic activation of the carboxylate group via boron conjugation and internal H-bonding. Our own efforts aimed at observing an acylborate intermediate by NMR were in vain due to technical complications caused by the need for molecular sieves. Nonetheless, a number of reasonable mechanistic possibilities can be eliminated. For example, the intermediacy of carboxylic acid anhydrides can be ruled out based on the observation that no formation of acetic anhydride was observed when acetic acid and **4a** are mixed alone under the same amidation conditions as in Table 5. Moreover, in the same conditions, butyric anhydride reacted efficiently with *N*-methylbenzylamine, a substrate that

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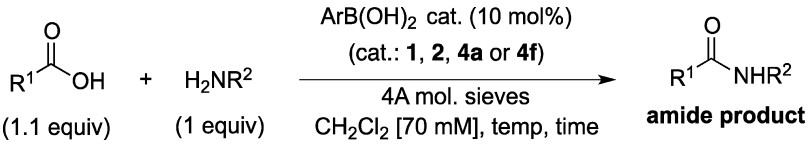
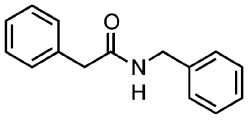
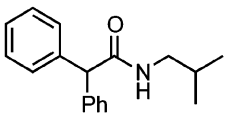
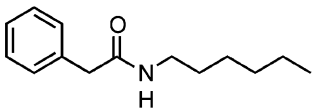
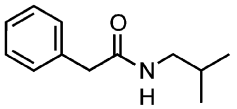
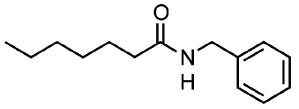
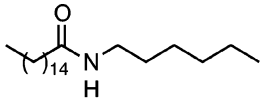
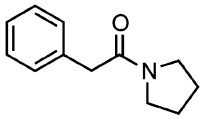
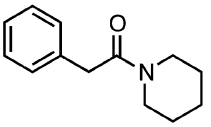
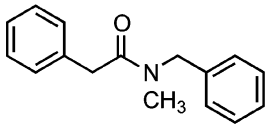
Table 5. Substrate Scope in the Second-generation Catalytic Direct Amide Bond Formation of Carboxylic Acids[a]



entry	product	temp (°C)	time (h)	yield (%)[b] with catalyst: 1	2	4a	4f
1		rt	2	41	3	71	**98**
2		rt	6	17	3	44	**58**
3		rt	6	-	-	60	**85**
4		rt	2	-	-	68	**90**
5		rt	6	-	-	80	**92**
6		rt	6	-	-	70	**95**
7		rt	6	-	-	66	**91**
8		rt	48	-	-	55	**70**
9		rt	48	-	-	0	**0**

dx.doi.org/10.1021/jo3013258 | J. Org. Chem. XXXX, XXX, XXX–XXX

Table 5. continued

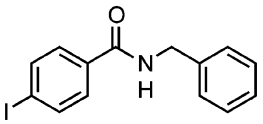
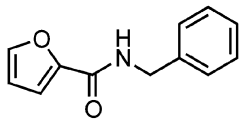
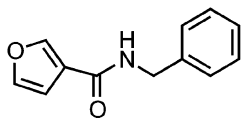
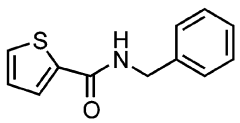
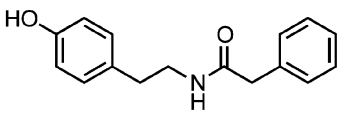
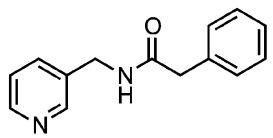
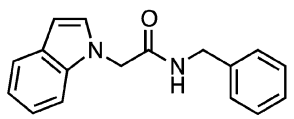
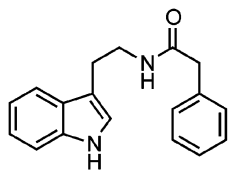
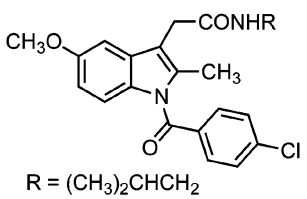
entry	product	temp (°C)	time (h)	yield (%) [b] with catalyst: 1	2	4a	4f
10		50	48[c,d]	12	5	22	**30**
11		50	48[c]	-	-	38	**53**
12		50	48[c]	-	-	32	**44**
13		50	48[c]	-	-	51	**73**
14		rt	24	-	-	45	**70** [e]
15		40	48[c]	-	-	80	**99** [e]
16		rt	4	-	-	73	**99**
17		rt	2.5	-	-	48	**68** [e]
18	 R = $(CH_3)_2CHCH_2$	rt	6	-	-	50	**65**

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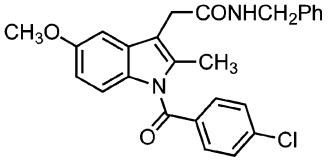
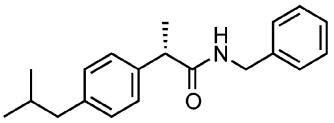
Table 5. continued

entry	product	temp (°C)	time (h)	yield (%)[b] with catalyst: 1	2	4a	4f
19		rt	2	-	-	62	**85**
20		rt	48[c]	-	-	55[f]	**80**[f]

[a]Reaction conditions: Carboxylic acid (0.55 mmol, 1.1 equiv), boronic acid (0.05 mmol, 10 mol %) and the amine (0.5 mmol, 1 equiv) were stirred at room temperature (25 °C) in dry CH_2Cl_2 containing powdered activated 4A mol. sieves (1 g). [b]Isolated yields. [c]With 20 mol % catalyst. [d]With toluene as solvent. [e]Purified by silica gel chromatography. [f]Less than 5% racemization observed by HPLC.

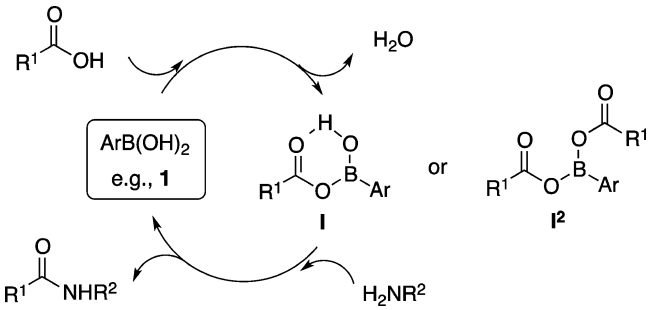


Figure 10. Simplified catalytic cycle with acylborate intermediates.

failed by direct amidation catalyzed by **4a** and **4f**.[52] Regarding the role of the *ortho*-iodide substituent, we established that the acidity of **4a** is not abnormal (i.e., pK_a of 8.9 vs 8.8 for $PhB(OH)_2$)[52] and thus cannot explain the exceptional catalytic activity of **4a** and **4f**. Because of the reverse trend of efficacy observed in the *ortho*-halide series (I > Br > Cl > F),[52] inductive effects alone cannot account for the superiority of catalysts **4a** and **4f**. Because of the size and electron density of the iodo substituent and X-ray crystallographic observations such as the unusual angular distortion of the B−C−C bonds (117°, 126°) of boronic acid **4a**,[56] subtle electronic or structural effects may be at play. Indeed, the fact that the para isomer[52] and the naphthyl derivative **4j** are significantly less effective indicates the importance of the geometric position of the ortho iodide substituent. Other reaction variables that appear to play an intriguing role in this amidation reaction are the nature of the reaction solvent, the role of water and molecular sieves, and the relative stoichiometry and concentration of acid and amine substrates. This section attempts to clarify these issues and propose a role for the iodide substituent in the reaction mechanism.

Studies on the Role of Molecular Sieves. Under anhydrous conditions it is known that boronic acids can dehydrate and form oligomeric anhydrides.[63] Those anhydrides quickly breakdown in the presence of water. Since catalyst **4f** was initially expected to dehydrate in the presence of activated molecular sieves, it brought the possibility that the active form of the catalyst may be a boronic anhydride such as the cyclic six-membered boroxine (Figure 11).

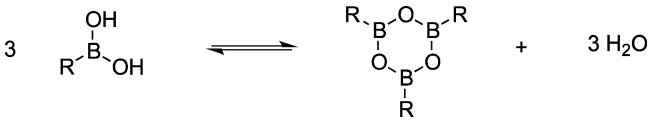
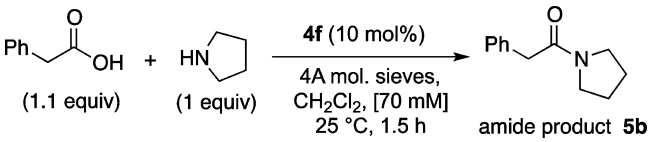


Figure 11. Equilibrium formation of the cyclic boroxine.

In order to address this issue, we prepared different forms of the catalyst, i.e., the free boronic acid, the pure boroxine, and mixtures of both in different ratio. All these species have been engaged in the amidation process, furnishing the expected product in the same yield (Table 6, entries 1−4). In order to address the ability of boroxine to catalyze the amidation reactions, we attempted a reaction with 100 mol % boroxine in the absence of molecular sieves (entry 5). Considering that the boroxine itself could possibly act as a water-trapping agent, it is surprising that no amide product was observed, which suggests that boroxine is not an active catalyst.

Table 6. Comparison in Product Yield Between Different Forms of Boronic Acid Catalyst 4f[a]



entry	form of catalyst **4f**	yield (%)[b]
1	free boronic acid	81
2	boroxine	78
3	free boronic acid/boroxine (1:1)	77
4	free boronic acid/boroxine (1:4)	82
5	boroxine (100 mol %, 24 h, no sieves)	0

[a]Reaction conditions: Carboxylic acid (0.55 mmol, 1.1 equiv), the catalyst and the amine (0.5 mmol, 1 equiv) were stirred at room temperature (25 °C) for 1.5 h in dry DCM containing powdered activated 4A mol. sieves (1 g). [b]Isolated yields.

Intrigued by these results we undertook a deeper investigation by ^{1}H NMR spectroscopy. Samples of the above forms of the catalyst were stirred for 10 min in dry $CDCl_3$ in the presence of 4A molecular sieves at room temperature. In all cases, the free boronic acid was observed as the only form

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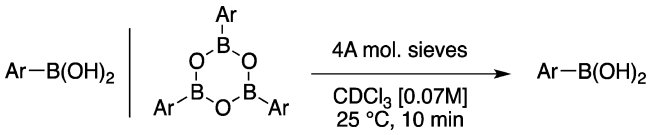
present in the reaction mixture (Table 7), which is very surprising considering the presence of a water-trapping agent

Table 7. NMR Study of the Boronic Acid: Boroxine Equilibrium in the Presence of 4A Molecular Sieves[a]



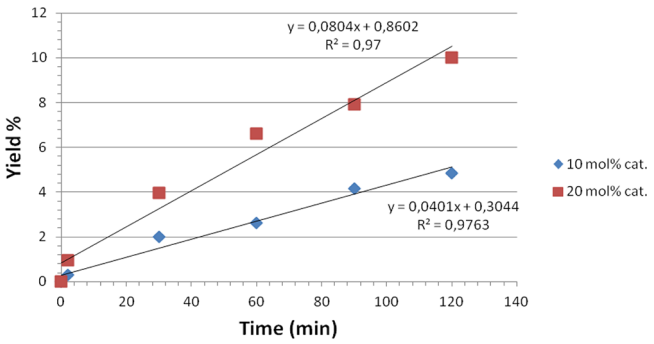
entry	substrate	proportion of boronic acid (%)[b]
1	free boronic acid	100
2	boroxine	100
3	free boronic acid/boroxine (1:1)	100
4	free boronic acid/boroxine (1:4)	100

[a]Reaction conditions: The catalyst was stirred at room temperature (25 °C) for 10 min in dry $CDCl_3$ containing powdered activated 4A mol. sieves (1 g). [b]Conversion to free boronic acid based on ^1H NMR. The reaction mixture was filtered through a short pad of Celite and directly analyzed by ^1H NMR.

expected to displace the equilibrium toward the formation of boroxine. However, it is noteworthy that when a smaller amount of sieves was employed, some boroxine remained. These results indicate that even dried molecular sieves, when used in excess, contain a sufficient quantity of embedded water to hydrolyze any boronic anhydrides into the free boronic acid, the active catalyst.

To explain this outcome, we speculate that the molecular sieves, as a reversible desiccant, play a dual role in this direct amidation reaction. They act as a trap for the water produced in this reaction, which is essential in order to avoid hydrolysis of the acylboronate intermediate leading to the transition state of amidation (see the Discussion section). At the same time, molecular sieves act as a reservoir of water, making enough water available to suppress the formation of boronic anhydrides and favor the active free boronic acid catalyst. Less reversible drying agents such as the hygroscopic salts examined in Table 3 may favor formation of boronic anhydrides and not allow their breakdown, thus giving no possibility for catalysis of amide production. Alternatively, basic dessicants might inhibit the reaction by reacting with the carboxylic acid.

Kinetic Studies. In order to obtain more mechanistic insights, we undertook kinetic experiments to determine the rate order in substrates and catalyst. However, the formation of an ammonium carboxylate salt complicates this study. Furthermore, since the carboxylic acid/amine ratio is crucial to the efficacy of the reaction (vide supra), it cannot easily be varied systematically to give a simple relationship, which makes it difficult to determine their respective rate order. Nevertheless, it was possible to measure the catalyst order. Two sets of reactions were examined using 10 and 20 mol % of boronic acid **4f**, and formation of the amide product in the early stage of the amidation reaction was followed by HPLC (Figure 12). Because the velocity needs to be measured at an early stage (linear part on the kinetic profile), the reaction needed to be slowed by using a more difficult combination of model substrates: phenylacetic acid and pyrrolidine. Moreover, the reaction was set up at 4 °C with an ice bath in order to further decrease the rate as much as possible for accurate measurements. Graphic determination confirmed that the reaction is first order in catalyst, which is in agreement with the density



$$V_{10\ mol\%} = k[Acid]^{\alpha}[Amine]^{\beta}[Cat]^{\gamma}$$

$$V_{20\ mol\%} = k[Acid]^{\alpha}[Amine]^{\beta}[Cat]^{2\gamma}$$

$$V_{20\ mol\%}/\ V_{10\ mol\%} = 2.0 \quad \rightarrow \gamma = 1$$

Figure 12. Determination of catalyst (**4f**) rate order in a direct amidation reaction between phenylacetic acid and pyrrolidine.

functional theory (DFT) calculations of Marcelli discussed below.[64]

DISCUSSION: PROPOSED CATALYTIC CYCLE

Altogether, the results of this study point toward a complicated catalytic reaction process with multiple variables. A number of observations, such as control experiments probing the effect of molecular sieves on the anhydride–boronic acid equilibrium, catalyst order determination, and DFT calculations,[64] strongly suggest that the free boronic acid is the active catalyst. Marcelli's DFT calculations imply the formation of an acylborate intermediate en route to the orthoaminal transition state (**TS**) shown in Figure 13A.[64] Strangely, according to the theoretical transition state, a water molecule is involved in the orthoaminal breakdown. At first sight, this seems incompatible with the need for maintaining exhaustively dry conditions in this reaction. Presumably, this amidation process requires a large excess of molecular sieves in order to trap the water byproduct, rapidly and efficiently, and avoid hydrolysis of important acylborate intermediates (e.g., **I**). The sieves would also exert a second role as a reservoir of water for hydrolyzing boronic anhydrides and maintain a high concentration of free boronic acid. The effect of the concentration of substrates is complicated by the equilibrium formation of the corresponding ammonium-carboxylate salt. In the course of rigorous mechanistic investigations on the direct amidation reaction, Whiting and co-workers found that the thermal uncatalyzed reaction is unlikely to proceed through the salt form.[13] Moreover, it was demonstrated that the extent of salt formation is heavily dependent on the nature of the carboxylic acid and the amine, and is more favored with the more basic aliphatic amines. With the model substrates used in our study, the reaction rate peaks at about 0.1 M concentration; above that threshold the proportion of salt increases and the amount of free acid and free amine may diminish to a detrimental level. The relative stoichiometry of substrates is equally important. Presumably, a slight excess of either substrate further favors salt formation and thus decreases the available concentration of the neutral form of the limiting substrate. A larger excess of one

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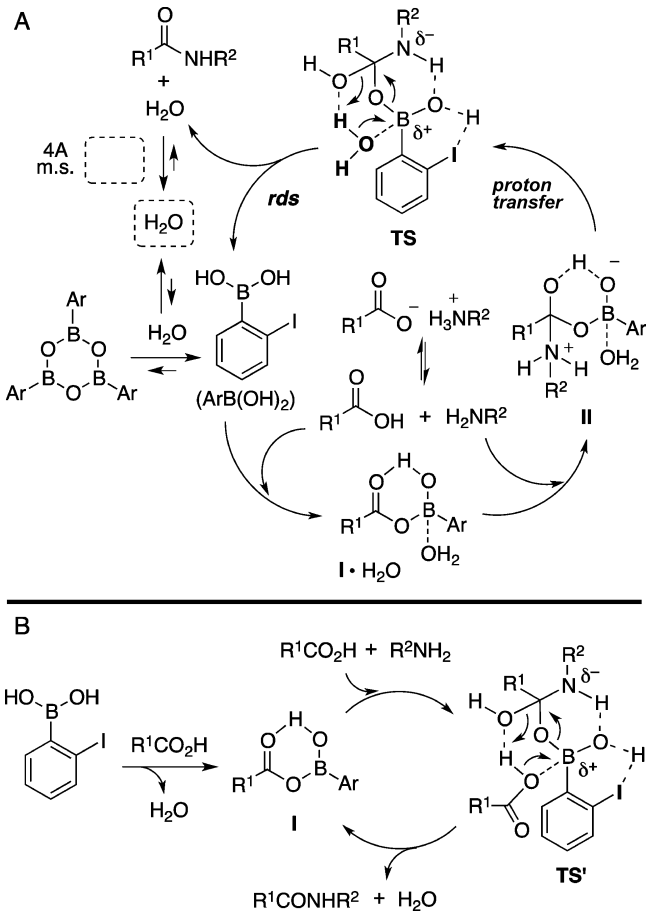

Figure 13. Proposed catalytic cycle for direct ambient amidation catalyzed by boronic acids **4a** or **4f**. (A) Cycle with DFT transition structure TS.[64] (B) Alternate cycle with recycling of acylborate I and nonhydrated acid-assisted transition structure TS′.

substrate may also break the neutral pH and lead to a disruption of the subtle H-bonding network leading to the transition structure (**TS**) shown in Figure 13A.

The catalyst accelerates the orthoaminal formation step (**I** to **II**) by activating the acyl group for nucleophilic attack by the amine. Elimination of water from the orthoaminal intermediate as depicted in the DFT-calculated transition state (**TS**) becomes the rate-determining step.[64] This step was proposed to be facilitated by a halogen−hydrogen bond that decreases overall degrees of freedom while rendering the boron more electrophilic to ease the required shuffling of B−O bonds (i.e., formation/cleavage of bonds involving a water molecule shown in bold in **TS**).[64] In this scenario, compared to **4a**, the optimal catalyst **4f** with a slightly more basic iodide involves a stronger I−H bond and a consequently lower activation energy. The fact that amidations of some secondary amines are also accelerated (despite the absence of N−H···O bond in **TS**) suggests that the I−H bond does not necessarily affect the entire H-bonding network involved in the transition state. In the same line, the use of more basic ortho substituents was found to be unfavorable, likely because it would become protonated, or break the charge neutrality of this H-bonding network. Thus, the iodide appears to be ideal, with the right size, geometry, and basicity.[64]

The required order of addition (premixing of the acid, catalyst, and sieves prior to addition of the amine) presents another odd observation to rationalize. A logical explanation for this initiation phase reasserts the formation of an acylborate of type **I** as the actual catalytic species. Thus, as shown in Figure 13B, nonhydrated monoacylborate **I** would form upon the initiation phase. Its formation may be inhibited in the presence of the amine. However, once formed in the absence of amine, **I** can react with added amine via transition structure **TS**′. In **TS**′, a molecule of carboxylic acid (in lieu of H_2O in **TS**) could assist the orthoaminal breakdown to eliminate water and regenerate **I** without involvement of the free boronic acid precatalyst. This alternative catalytic cycle fits with the experimental data and does not invoke the contradictory need for an attendant molecule of water in the presence of molecular sieves.

CONCLUSION

The development of a mild and general direct amidation reaction is of great interest in organic synthesis and process chemistry. Driven by this goal, this study described the rational design and optimization of *ortho*-iodoarylboronic acids as stable and recyclable catalysts for direct amidation between free carboxylic acids and amines. Compared to the parent 2-iodophenylboronic acid (**4a**), the optimal new catalyst, 5-methoxy-2-iodophenylboronic acid (**4f**), led to a notable increase of product yields for the reactions of a wide variety of carboxylic acids and amines performed under identical reaction times. It is remarkable that amidation reactions involving aliphatic carboxylic acids and amines can be performed catalytically within a few hours at ambient temperature, making it clearly advantageous over the most popular methods employing stoichiometric reagents. These direct catalytic amidations are operationally simple. They employ near equimolar amounts of acid and amine substrates, generate no byproduct, and afford pure amide products usually after a simple filtration and acid−base extractions. Some substrate classes, such as aromatic and heteroaromatic carboxylic acids, required the use of slightly elevated reaction temperatures to afford acceptable yields of products. A mechanistic study confirmed the essential role of molecular sieves and ruled out boronic anhydrides as the active catalyst. The optimal ring substitution pattern of catalyst 4f, with an electron-donating 5-methoxy group, supports a role for the ortho-iodo substituent as hydrogen-bond acceptor in the orthoaminal transition structure. Although a plausible catalytic cycle was proposed on the basis of preliminary experiments, more work is required in order to characterize the putative acylborate intermediate and provide a clearer mechanistic picture.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were performed under argon atmosphere using flame-dried glassware. Toluene, THF and dichloromethane were dried from a double cartridge solvent purification system. Et_2O, acetonitrile were distilled from CaH_2. Acetone was distilled from 4A molecular sieves. Anhydrous DMF, Me-THF, and absolute EtOH were commercially available. Analytical thin layer chromatographies were performed on silica gel 60 F254 plates. NMR spectra were recorded on 300, 400, or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbon (^{13}C) were used as internal standards. NMR experiments were performed in deuterated solvent with an added drop of deuterated water to minimize formation of the corresponding boronic anhydrides. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used

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in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; sept, septet. Because of their low intensity (resulting from quadrupolar coupling), ^{13}C signals arising from the quaternary carbon bearing the boronic acid group were not always observed and therefore were not always listed. High-resolution mass spectra (TOF analyzer) were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained with frequencies expressed in cm^{-1}. X-ray crystallography was performed using a CCD diffractometer. Powdered 4A molecular sieves (<5 μm) were dried overnight under high vacuum (<2 mbar) at 250 °C using a Kugelrohr instrument. All the different catalysts were stored in a fridge, under inert atmosphere.

Preparation of Catalysts 4b, 4f, 4g, 4h, and 4i. All these catalysts were prepared according to the procedure reported in our previous work.[53]

Preparation of 2-Bromo-3,4,5-trifluorophenylboronic acid 3b. To a solution of 1-iodo-2-bromo-3,4,5-trifluorobenzene (0.5 g, 1.48 mmol) in 40 mL of a mixture of THF and Et_2O (1:1) was added dropwise at −78 °C isopropylmagnesium chloride (2 M in THF, 0.74 mL, 1.48 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (1.0 mL, 4.44 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added, and the resulting precipitate was isolated to give the desired product as a light yellow solid in 84% yield (0.32 g): mp 189−192 °C; IR (Microscope, cm^{-1}) 3224, 3067, 1642, 1595, 1514, 1412, 1359, 1209, 1058; ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 2H), 7.35 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, ^1H and ^{19}F decoupled) δ 149.2, 147.1, 139.1, 116.3, 107.1; ^{13}C NMR (125 MHz, DMSO-d_6, ^1H decoupled) δ 149.2 (dd, J = 9.2 Hz, J = 201.4 Hz), 147.1 (dd, J = 9.2 Hz, J = 235.2 Hz), 139.1 (ddd, J = 16.4 Hz, J = 32.0 Hz, J = 251.3 Hz), 116.3 (d, J = 15.9 Hz), 107.1 (d, J = 16.2 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ 126.0 (dd, J = 4.9, 21.8 Hz, 1F), 136.5 (dq, J = 21.1, 6.4 Hz, 1F), 157.8 (dt, J = 29.7, 7.9 Hz, 1F); HRMS (EI) for $C_6H_3{}^{11}B^{79}BrF_3O_2$ calcd. 253.93616, found 253.93690.

Preparation of 2-Iodophenylboronic acid 4a.[52] To a solution of 1,2-diiodobenzene (10.2 g, 30.8 mmol) in 300 mL of THF at −78 °C was added dropwise isopropyl magnesium chloride (2 M in THF, 15.4 mL, 30.8 mmol). The mixture was stirred at that temperature for 2 h, and then triisopropyl borate (17.4 g, 92.4 mmol) was added. The solution was slowly warmed to room temperature and stirred overnight. HCl (10% aq, 80 mL) was added. The final product was obtained in 50% yield (3.82 g) as a white solid by precipitation in hexane: mp 162−164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 0.7, 7.9 Hz, 2H), 7.52 (dd, J = 1.8, 7.5 Hz, 1H), 7.26 (dt, J = 1.0, 7.4 Hz, 1H), 6.97 (dt, J = 1.9, 7.4 Hz, 1H), 6.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.0, 130.6, 126.7, 99.4; ^{11}B NMR (100 MHz, $CDCl_3$) δ 29.0.

Preparation of 2-Iodo-5-fluorophenylboronic acid 4c. To a solution of 4-fluoro-1,2-diiodobenzene (1.0 g, 3.08 mmol) in 60 mL of a mixture of THF and Et_2O (1:1) was added dropwise at −78 °C isopropylmagnesium chloride (2 M in THF, 15.4 mL, 3.08 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (2.0 mL, 9.20 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added, and the resulting precipitate was isolated to give the desired product as a white solid in 52% yield (0.43 g) as a 6:1 mixture of regioisomers favoring the titled product: IR (Microscope, cm^{-1}) 3356, 1583, 1566, 1476, 1454, 1387, 1328, 1264; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, 1H, J = 5.1 Hz, J = 8.7 Hz), 7.5 (dd, 1H, J = 3.3 Hz, J = 8.9 Hz), 6.87 (ddd, 1H, J = 3.2 Hz, J = 7.9 Hz, J = 8.6 Hz), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (d, J = 7.1 Hz), 123.8 (d, J = 20.9 Hz), 119.7 (d, J = 22.0 Hz); HRMS (EI) for $C_6H_5{}^{11}BFIO_2$ calcd. 265.94113, found 265.94121.

Preparation of 2-Iodo-4,5-dimethoxyphenylboronic acid 4d. To a solution of 1,2-diiodo-4,5-dimethoxybenzene (2.0 g, 5.13 mmol) in 120 mL of a mixture of THF and Et_2O (1:1) was added dropwise at −78 °C isopropylmagnesium chloride (2 M in THF, 2.67 mL, 5.39 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (10.89 mL, 15.39 mmol) was added. The solution was warmed to room temperature overnight; then a saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added, and the resulting precipitate was isolated to give 1.05 g of the pure product as a white solid in 67% yield: mp >163 °C (decomposition); IR (Microscope, cm^{-1}) 2959, 1585, 1506, 1373, 1310, 1263, 1199; ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 2H), 7.17 (s, 1H), 6.80 (s, 1H), 3.69 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.3, 147.8, 121.0, 116.6, 87.5, 55.4, 55.2; HRMS (ESI) for $C_{10}H_{14}{}^{11}BIO_4INa$ (dimethylester) calcd. 358.99221, found 358.99259.

Preparation of 2-Iodo-3-methyl-4,5-dimethoxyphenylboronic acid 4e. To a solution of 1,2-diiodo-4,5-dimethoxy-3-methylbenzene[65] (2.0 g, 4.95 mmol) in 120 mL of a mixture of THF and Et_2O (1:1) was added dropwise at −78 °C isopropylmagnesium chloride (2 M in THF, 2.72 mL, 5.44 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (10.50 mL, 14.84 mmol) was added. The solution was warmed to room temperature overnight; then saturated solution of NH_4Cl was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (50 mL, 3 times) and dried over Na_2SO_4, filtered and concentrated. To the concentrated sample, hexane was added, and the resulting precipitate was isolated to give 0.90 g of the pure product as a white solid in 56% yield: mp 157−161 °C; IR (Microscope, cm^{-1}) 3283, 944, 1577, 1539, 1344, 1077, 993; ^1H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 2H), 6.73 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.1, 146.8, 133.9, 114.9, 95.2, 60.2, 55.9, 21.8; HRMS (EI) for $C_9H_{12}{}^{11}BIO_4$ calcd. 321.98733, found 321.98740.

Preparation of 2-Iodo-5-methoxyphenylboronic acid 4f.[53] A solution of iodine in EtOH (4.72 mmol, 1.00 equiv, 0.30 M) was added dropwise to a mixture of 4-methoxyphenylboronic acid (4.72 mmol, 1.00 equiv) and silver(I) sulfate (2.60 mmol, 0.55 equiv) in EtOH (15 mL) at room temperature. After complete addition of iodine the reaction was stirred at room temperature for 15 min. The reaction mixture was filtered through a pad of Celite 545, and most of EtOH was removed under vacuum. Water (50 mL) was then added to the filtrate, and the mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with aqueous sodium sulfite, brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel (hexane/ethylacetate 3:1) to yield the pure desired product in 70% yield (0.92 g) as a white solid: mp >150° (decomposition); ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 3.2 Hz, 1H), 6.54 (dd, J = 3.2, 8.6 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 139.6, 120.6, 117.6, 88.1, 55.2.

Preparation of 8-Iodonaphthalen-1-ylboronic acid 4j. To a solution of 1,8-diiodonaphthalene (0.70 g, 1.84 mmol) in 40 mL of a mixture of THF and Et_2O (1:1) was added dropwise at −78 °C isopropylmagnesium chloride (2 M in THF, 1.0 mL, 2.02 mmol). After the mixture was stirred for 2 h at that temperature, B(O*i*-Pr)$_3$ (3.9 mL, 5.52 mmol) was added. The solution was warmed to room temperature overnight. The aqueous layer was extracted with Et_2O (40 mL, 3 times). The combined ether extracts were dried over Na_2SO_4, filtered, concentrated, and the crude product was purified by column chromatography (hexanes/ethyl acetate 3/1) to provide the diisopropyl-8-iodonaphthalen-1-ylboronate in 95% yield (0.66 g): IR (Microscope, cm^{-1}) 2971, 2927, 1375, 1314, 1295, 1138, 1117, 805. ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, 1H, J = 7.3 Hz), 7.85 (dd, 1H, J = 1.3 Hz, J = 8.2 Hz), 7.78 (ddd, 1H, J = 0.36 Hz, J = 1.4 Hz, J = 8.0 Hz), 7.57 (dd, 1H, J = 1.4 Hz, J = 6.8 Hz), 7.48 (dd, 1H, J = 6.8

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Hz, J = 8.1 Hz), 7.15 (dd, 1H, J = 7.3 Hz, J = 8.1 Hz), 4.27 (sept, 2H, J = 6.1 Hz), 1.30 (d, 6H, J = 6.1 Hz), 1.14 (d, 6H, J = 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 136.8, 134.8, 132.4, 129.8, 129.6, 126.5, 125.6, 99.5, 66.7, 24.1; HRMS (ESI) for $C_{16}H_{21}{}^{11}BIO_2$ (M + H) calcd. 383.06767, found 383.06693.

Diisopropyl-8-iodonaphthalen-1-yl-1-boronate was dissolved in methanol, and the solvent was evaporated under reduced pressure three times. After concentrating the mixture under reduced pressure, a drop of water was added to the residue, and the desired product was isolated as colorless crystals in 73% yield (0.55 g): mp 128−131 °C; IR (Microscope, cm^{-1}) 3314, 3049, 1601, 1368, 1216, 813, 765; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (dd, 1H, J = 1.3 Hz, J = 7.3 Hz), 8.10 (s, 2H), 7.94 (dd, 1H, J = 1.2 Hz, J = 8.3 Hz), 7.84 (dd, 1H, J = 1.9 Hz, J = 7.7 Hz), 7.49 (m, 2H), 7.20 (dd, 1H, J = 7.3 Hz, J = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.4, 135.7, 134.2, 131.8, 129.3, 128.7, 126.5, 125.5, 100.1; HRMS (ESI) for $C_{10}H_8{}^{11}BClIO_2$ (M + Cl) calcd. 332.93579, found 332.93511.

Typical General Procedure for Boronic Acid Catalyzed Amidations. *N-Benzyl-2-phenylacetamide, with Catalyst Recovery (Table 5, Entry 1).* Into a 25 mL round-bottom flask equipped with a magnetic stir bar was added phenylacetic acid (75 mg, 0.55 mmol, 1.1 equiv), 2-iodo-5-methoxyphenylboronic acid **4f** (13.9 mg, 0.05 mmol, 10 mol %) and 1 g of activated molecular sieves 4 Å. Dichloromethane (7 mL) was added, and the mixture was stirred vigorously for 10 min. Then, benzylamine (55 μL, 0.5 mmol, 1 equiv) was added (in order to get reproducible results, it is necessary to use a gastight 100 μL syringe). The resulting mixture was stirred for 2 h under vigorous stirring at room temperature (24−25 °C). The reaction mixture was filtered through a pad of Celite 545; the filtrate was washed with aqueous acidic solution (pH = 3), aqueous basic solution (pH = 11) and brine. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title compound (71% using **4a**, 98% (110 mg) using **4f**, 41% using **1**, 3% using **2**) as a pure product (the catalyst can be recovered in up to 90% yield by acidification of the aqueous basic solution to pH 6−7 and extraction with EtOAc (5×)). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[66,67]

Preparation and Characterization of Amides (Table 5). *N-(2-Methylpropyl)-2,2-diphenylacetamide (Table 5, Entry 2).* The title compound was prepared using the general procedure for the boronic acid catalyzed amidations, and isolated as a light yellow solid (44% yield using **4a**, 58% (78 mg) using **4f**, 17% using **1** and 3% using **2** after 6 h): mp 107−109 °C; IR (Microscope cm^{-1}) 3265, 3085, 2959, 2929, 2869, 1949, 1881, 1640, 1560; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 10H), 5.96 (br s, 1H), 4.97 (s, 1H), 3.09 (dd, J = 6.1 Hz, J = 6.7 Hz, 2H), 1.73 (sept, J = 6.6 Hz, 1H), 0.83 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 139.7, 128.9, 128.7, 127.2, 59.2, 47.1, 28.4, 20.0; HRMS (ESI) for $C_{18}H_{22}NO$ (M + H) calcd. 268.1696, found 268.1692; for $C_{18}H_{21}NNaO$ (M + Na) calcd. 290.1515, found 290.151.

N-Hexyl-2-phenylacetamide (Table 5, Entry 3). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (60% yield using **4a** and 85% yield (93 mg) using **4f** after 6 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[66]

N-(2-Methoxypropyl)-2-phenylacetamide (Table 5, Entry 4). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations, and isolated as a brown solid (68% yield using **4a** and 90% yield (93 mg) using **4f** after 2 h): mp 67−69 °C; IR (Microscope cm^{-1}) 3278, 3085, 2958, 2926, 2871, 1956, 1643, 1561; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 5.98 (br s, 1H), 3.52 (s, 2H), 2.99 (dd, J = 6.1 Hz, J = 6.8 Hz, 2H), 1.66 (sept, J = 6.7 Hz, 1H), 0.78 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 135.3, 129.3, 128.8, 127.1, 46.9, 43.7, 28.4, 20.0; HRMS (ESI) for $C_{12}H_{18}NO$ (M + H) calcd. 192.1383, found 192.138; for $C_{12}H_{17}NNaO$ (M + Na) calcd. 214.1202, found 214.1197.

N-Benzylhexanamide (Table 5, Entry 5). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (80% yield using **4a** and 92% yield (94 mg) using **4f** after 6 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[68]

N-Hexylhexadecanamide (Table 5, Entry 6). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations, and isolated as a white solid (70% yield using **4a** and 95% yield (161 mg) using **4f** after 6 h): mp 62−64 °C; IR (Microscope, cm^{-1}) 3292, 2918, 2872, 2849, 1638; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (br s, 1H), 3.20 (q, J = 7.0 Hz, 2H), 2.13 (t, J = 7.3 Hz, 2H), 1.64−1.54 (m, 2H), 1.50−1.40 (m, 2H), 1.32−1.18 (m, 32H), 0.90−0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 39.5, 36.9, 31.9, 31.5, 29.7, 29.7, 29.7, 29.6 (3C), 29.6, 29.5, 29.4, 29.3, 29.3, 26.6, 25.8, 22.7, 22.5, 24.1, 14.0; HRMS (ESI) for $C_{22}H_{46}NO$ (M + H) calcd. 340.3574, found 340.3574; for $C_{22}H_{45}NNaO$ (M + Na) calcd. 362.3393, found 362.3394.

2-Phenyl-1-(pyrrolidin-1-yl)ethanone (Table 5, Entry 7). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (66% yield using **4a** and 91% yield (86 mg) using **4f** after 6 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[69]

2-Phenyl-1-(piperidin-1-yl)ethanone (Table 5, Entry 8). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (55% yield using **4a** and 70% yield (71 mg) using **4f** after 48 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[70]

N-Benzyl-4-iodobenzamide (Table 5, Entry 10). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (22% yield using 20 mol % of **4a** and 30% yield (51 mg) using 20 mol % of **4f** at 50 °C in toluene after 48 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[71]

N-Benzylfuran-2-carboxamide (Table 5, Entry 11). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations and isolated as a light yellow solid (38% yield using 20 mol % of **4a** and 53% yield (53 mg) using 20 mol % of **4f** at 50 °C in DCM after 48 h): mp 111−113 °C; IR (Microscope, cm^{-1}) 3302, 3063, 3031, 2926, 1649, 1594, 1526, 1475; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 0.7, 1.7 Hz, 1H), 7.38−7.26 (m, 5H), 7.15 (dd, J = 0.7, 3.5 Hz, 1H), 6.65 (br s, 1H), 6.51 (dd, J = 1.8, 3.5 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 147.9, 143.9, 138.0, 128.8, 127.9, 127.7, 114.4, 112.2, 43.2; HRMS (ESI) for $C_{12}H_{12}NO_2$ (M + H) calcd. 202.0863, found 202.0863; for $C_{12}H_{11}NNaO_2$ (M + Na) calcd. 224.0682, found 224.0677. (Note that the product was described in the literature,[72] but the above NMR data is of higher definition.)

N-Benzylfuran-3-carboxamide (Table 5, Entry 12). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (32% yield using 20 mol % of **4a** and 44% yield (44 mg) using 20 mol % of **4f** at 50 °C in DCM after 48 h): mp 120−122 °C. The product's ^{1}H and ^{13}C NMR and MS characterization data matched data found in the literature.[73,74]

N-Benzylthiophene-2-carboxamide (Table 5, Entry 13). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (51% yield using 20 mol % of **4a** and 73% yield (79 mg) using 20 mol % of **4f** at 50 °C in DCM after 48 h). The product's ^{1}H and ^{13}C NMR characterization data matched data found in the literature.[75]

N-[2-(4-Hydroxyphenyl)ethyl]-2-phenylacetamide (Table 5, Entry 14). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (45% yield using **4a** and 70% yield (89 mg) using **4f** after 24 h): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (br s, 1H), 7.30−7.24 (m, 2H), 7.23−7.18 (m, 3H), 6.99 (t, J = 5.6 Hz, 1H), 6.91−6.87 (m, 2H), 6.74−6.70 (m, 2H), 3.45 (s, 2H), 3.34 (q, J = 6.7 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 155.8, 135.7, 129.7, 129.6, 129.3, 128.7, 126.9, 115.6, 43.4, 41.3, 4.7. (Note that the product was described in the literature,[76] but no ^{13}C NMR data was reported.)

2-Phenyl-N-(pyridine-2-ylmethyl)acetamide (Table 5, Entry 15). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations, and isolated as a white solid (80% yield using 20 mol % of **4a** and 99% yield (112 mg) using 20 mol % of

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4f at 40 °C after 48 h): mp 100−102 °C; IR (Microscope, cm^{-1}) 3279, 3084, 2922, 1641, 1588, 1554; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46−8.43 (m, 1H), 7.60 (dt, J = 1.7, 7.7 Hz, 1H), 7.36−7.24 (m, 5H), 7.18 (d, J = 7.8 Hz, 1H), 7.16−7.12 (m, 1H), 6.75 (br s, 1H), 4.51 (d, J = 5.1 Hz, 2H), 3.63 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.4, 149.0, 136.7, 134.9, 129.4, 128.9, 127.2, 122.3, 121.9, 44.6, 43.7.

1-(1H-Indol-1-yl)-3-phenylpropan-2-one (Table 5, Entry 16). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations, and isolated as a brown solid (73% yield using **4a** and 99% yield (123 mg) using **4f** after 4 h): mp 143−146 °C; IR (Microscope, cm^{-1}) 3279, 3058, 3029, 2922, 1911, 1657, 1550; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.32−7.16 (m, 6H), 7.08−7.04 (m, 3H), 6.61 (d, J = 2.9 Hz, 1H), 5.78 (br s, 1H), 4.81 (s, 2H), 4.36 (d, J = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 137.5, 136.2, 128.8, 128.6, 128.2, 127.5, 127.2, 122.8, 121.4, 120.6, 109.3, 103.7, 50.1, 43.1; HRMS (ESI) for $C_{17}H_{17}N_2O$ (M + H) calcd. 265.1335, found 265.1336; for $C_{17}H_{16}N_2NaO$ (M + Na) calcd. 287.1155, found 287.1154.

N-[2-(1H-Indol-3-yl)ethyl]-2-phenylacetamide (Table 5, Entry 17). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (46% yield using **4a** and 68% yield (95 mg) using **4f** after 2.5 h): ^1H NMR (500 MHz, $CDCl_3$) δ 10.56 (br s, 1H), 7.87 (t, J = 5.3 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.27−7.21 (m, 4H), 7.20−7.15 (m, 1H), 7.04 (dt, J = 1.1, 7.1 Hz, 1H), 6.99−6.93 (m, 2H), 3.41 (s, 2H), 3.39 (q, J = 5.9 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 136.7, 136.7, 129.3, 128.4, 126.6, 122.8, 121.3, 118.6, 118.6, 112.2, 111.7, 43.1, 40.2, 25.5. (Note that the product was described in the literature,[77] but the above NMR data is of higher resolution.)

2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-N-(2-methylpropyl) acetamide (Table 5, Entry 18). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (50% yield using **4a** and 65% yield (134 mg) using **4f** after 6 h). The product's ^1H and ^{13}C NMR characterization data matched data found in the literature.[52]

N-Benzyl-2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetamide (Table 5, Entry 19). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations (62% yield using **4a** and 85% yield (190 mg) using **4f** after 2 h). The product's ^1H and ^{13}C NMR characterization data matched data found in the literature.[52]

(2S)-N-Benzyl-2-[4-(2-methylpropyl)phenyl]propanamide (Table 5, Entry 20). The title compound was prepared using the general procedure for the boronic acid catalyzed amidations and isolated as a yellow oil (70% yield using **4a** and 95% yield (140 mg) using **4f** after 48 h). The product's IR, ^1H and ^{13}C NMR, and MS characterization data matched data found in the literature.[78] $[\alpha]_D^{20}$ 7.1 (c = 0.88, CH_2Cl_2) for >95% ee. Chiral HPLC analysis revealed less than 5% racemization (see the chromatograms in Supporting Information). HPLC (Chiralcel OD) 1:99 i-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T = 0.5 °C, t_{major} = 154.4 min, t_{minor} = 167.3 min, ee = >95%.

Kinetic Experiments (Figures 9 and 12). The rate constants were determined using the amidation model reaction between phenylacetic acid and pyrrolidine at 4 °C (ice−water bath) in DCM using 10 mol % catalyst (**4a**/**4f**) in the presence of 4A molecular sieves. The formation of the amide was monitored by HPLC. A sample was taken every 30 min and quickly filtered to remove molecular sieves. The solvent was quickly evaporated under reduced pressure, and the resulting mixture was dissolved in water/acetonitrile (1:1 v/v mixture) and submitted for HPLC analysis. The peak area was converted into yield (%) using a calibration curve. The same procedure was repeated to determine the rate constant at 25 °C as well as the rate order in catalyst. HPLC conditions: column, Agilent SB-C18 2.1 × 30 mm; flow rate, 0.5 mL/min; temperature, 40 °C; detection, UV, λ = 220 nm. See the Supporting Information for an example of data set and chromatogram.

NMR Study of the Boronic Acid (Table 7). A mixture of catalyst (0.015 mmol, 4 mg) and 4A molecular sieves (286 mg) in 2 mL of $CDCl_3$ was stirred under inert atmosphere for 10 min at room temperature. Then the mixture was filtered through a pad of Celite 545 and directly submitted for NMR analysis.

Tris(2-iodo-5-methoxyphenyl)boroxin. The boroxine was prepared by solubilizing the catalyst in toluene followed by evaporation under high vacuum. This sequence was repeated 3 times: ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 3.3 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 6.54 (dd, J = 3.3, 8.6 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.8, 122.4, 118.3, 90.1, 55.7

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Reproductions of NMR spectra, example of data for kinetic experiments, chiral HPLC chromatograms for entry 20 (Table 5), and crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): All three co-authors are also co-inventors of provisional patents describing these catalysts.

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