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Boric Acid Catalyzed Direct Amidation between Amino-Azaarenes and Carboxylic Acids

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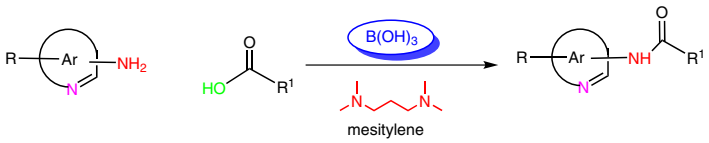

34 examples with isolated yields ranging from 47–82%

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Abstract A novel and facile boric acid catalyzed direct amidation between amino-azaarene compounds and carboxylic acids has been developed. The amidation proceeded cleanly and provided good to excellent yields of the desired amides. Boric acid is a green and inexpensive catalyst. We have also found that *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine acted as an additive accelerating this boric acid catalyzed amidation. A mixed acid anhydride is postulated to be the active intermediate responsible for this successful amidation. This direct amidation is an atom- and step-economical reaction.

Key words amidation, boric acid, azaarenes, aminopyridine, *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine

Amide compounds are present in a vast array of industrial synthetic chemicals and in a wide variety of naturally occurring bioactive products. They are very important compounds in many fields including fine chemicals, dyes and pigments, agricultural chemicals, photographic products, polymers, soft matter, new materials, and in particular active pharmaceutical ingredients (API) and medicinal products. Amide function containing compounds are of significant importance. In fact, presently about 25% of the pharmaceutical/medicinal products in the market have one or several amide functionalities.[1–10] The preparation of amides is a very important synthetic transformation in organic chemistry. ACS Green Chemistry Institute Pharmaceutical Roundtable have expressed that amide bond formation is one of the most important chemical reactions used in industry.[11] Many well-established procedures for the preparation of amide-containing compounds are known in the literature.[12] The most widely practiced methods are indirect amidations, for example, via carboxylic acid chloride or mixed acid anhydrides as the electrophiles, which react with amines in the presence of an acid scavenger. Despite the vitality of amide compounds in organic chemical industry and its wide scope of applications in pharmaceutical industry, many common known procedures for the preparation of amides are still inefficient. The aforementioned protocol via acid chloride intermediate suffers from serious drawbacks. Most notable drawbacks are the limited stability of many intermediate acid chlorides and the use of hazardous reagent for their preparation (thionyl chloride, oxalyl chloride, etc.), which release volatile corrosive by-products. The environmental aspect is of primary concern in chemical industry. Moreover, incompatible functional groups present either in the acid molecules or in the amine molecules with chlorinating reagents or with the resulting acid chlorides need to be protected to ensure the chemoselective amide formation. In some procedures, the use of coupling reagents such as DCC/HOBt, EDC, BOP-Cl, and others is beneficial.[13–15] However, stoichiometric quantities of coupling reagents in the amidation formation are required. In addition, tedious separation of the resulting by-products in stoichiometric quantities formed by the coupling reagents after the completion of the amidation is generally needed.

Direct amidation of carboxylic acids with amines is a well-known topic. Several mediators including organometallic compounds such as $Ti(OPr)_4$,[16] Cp_2ZrCl_3,[17] $ZrCl_4$,[18] and boron compounds such as arylboronic acids and borates in catalytic amount or in stoichiometric quantity or in excess employed in direct amidations have been reported. Direct amidation promoted by boron compounds is of high interest and has been attracted considerable attention.[19,20] Cur-

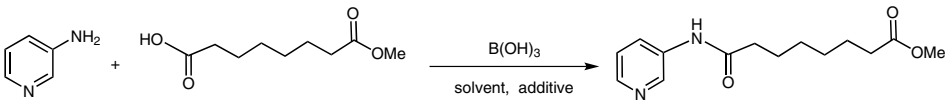
rently, there is a focus on the development of new, atom- and step-economical, and eco-friendly methods for the direct amidation of carboxylic acids with amines.

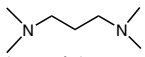
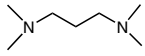
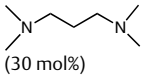
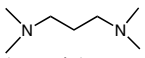
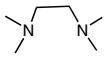
Boric acid direct amidation is highly effective for a number of amide compounds formed directly between aliphatic or aromatic carboxylic acids and primary or secondary amino-arene derivatives.[21,22] A wealth of boric acid catalyzed amidations have been devoted to the applications of the synthesis of active pharmaceutical ingredients (API).[23–26] The aforementioned boric acid catalyzed amidation has received many applications in green chemistry as well.[19] Boric acid catalyzed direct amidation offers the advantage of atom- and step-economy and obviates protection/deprotection steps. This methodology has the aforementioned advantages in a potentially green and sustainable setting in chemical and pharmaceutical industries. In sharp contrast, to the best of our knowledge, there is no report on the direct amidation of amino-azaarenes catalyzed by boric acid in the literature.

Carboxamides containing an azaarene moiety play an important role in medicine for the treatment of various bacterial and fungal diseases caused by pathogenic bacterial and fungal strains.[26] Recently, Sheppard et al. reported the direct amidation using excess of $B(OCH_2CF_3)_3$.[20] While the reported method using $B(OCH_2CF_3)_3$ was very successful for direct amidation of aniline compounds, the method met with difficulty when it was applied to aminopyridine compounds,. As a matter of fact, only two examples of direct amidation of amino-azaarenes were reported: pyridin-3-amine to 2-phenyl-*N*-(pyridin-3-yl)acetamide and pyridin-2-amine to 2-phenyl-*N*-(pyridin-3-yl)acetamide using an excess of $B(OCH_2CF_3)_3$ in a sealed tube at 100 °C for 24 hours. The amidations were performed under harsh conditions, and the yields of the amide products were low (53% and 12%, respectively). Our continuing interests in direct boric acid catalyzed amidation have led us to investigate the feasibility of the amidation between a carboxylic acid and an amino-azaarene compound.

The strength of π-electron system in azaarene ring renders the exo-amine group less nucleophilic making the direct amidation still challenging. During the course of our discovery program directed towards the preparation of histone deacetylase enzyme inhibitors [HDACi] comprising an azaarene ring, potential chemotherapeutic agents against

Table 1 Amidation Conditions for Boric Acid Catalyzed Direct Amidation Between Pyrinin-3-amine and 8-Methoxy-8-oxooctanoic Acid[a]



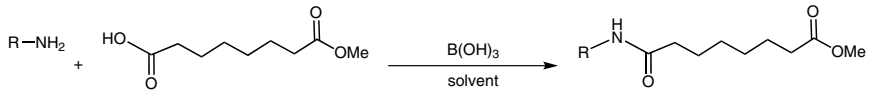
Entry	$B(OH)_3$ (mol%)	Additive (mol%)	Solvent(s)	Time (h)	Yield (%)
1	0	0	aromatic solvents[b]	48	0
2	10	0	toluene	48	<5
3	20	0	xylene	48	30
4	30	0	xylene	48	49
5	30	0	xylene	24	33
6	30	 (30 mol%)	xylene	24	80
7	30	 (30 mol%)	xylene	7	10
8	30	 (30 mol%)	mesitylene	7	82
9	30	0	mesitylene	7	35
10	10	 (30 mol%)	mesitylene	7	38
11	30	 (30 mol%)	mesitylene	7	80

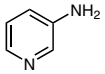
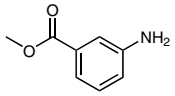
[a] Reaction conditions: amine (5 mmol), acid (5.5 mmol), and solvent (70 mL), temp: solvent at reflux.
[b] Toluene, xylene, or mesitylene.

the proliferation of human cancer cells,[27–29] we had reasons to examine the feasibility of boric acid catalyzed direct amidation. The rationale behind this project is the expectation that without the use of coupling agent and any hazardous acid chloride intermediates, the boric acid could mediate the direct amidation of the amino group of azaarenes. In order to ascertain the feasibility, we decided to concentrate on the experimental conditions to achieve the boric acid catalyzed direct amidation between a carboxylic acid and an amino-azaarene compound. Of importance is that the amidation with amino-azaarenes, if successful, will be complementary to that seen in the boric acid catalyzed direct amidation with amino-arene compounds. Thus, we decided to prepare a series of precursors of HDACi comprising pyridinylamido and quinolinylamido functionalities using boric acid as catalyst for the direct catalyzed amidation.

Our work began with the investigation of general reaction conditions for the boric acid catalyzed amidation of the amino group of azaarenes with carboxylic acids. First, different reaction conditions were investigated including amount of catalyst, solvents, temperature, and additive in order to assess the feasibility of the amidation and eventually identify the quasi-optimal reaction conditions to achieve the amidation of amino-azaarenes. We commenced by screening the reaction conditions to determine the best conditions for carrying out the boric acid catalyzed amidation between pyridin-3-amine and 8-methoxy-8-oxooctanoic acid. To ensure the critical role of boric acid in the amidation, we have first verified that the direct amidation did not produce any desired amide in the absence of boric acid after 48 hours of heating at reflux in aromatic solvents (toluene, xylene, or mesitylene) (Table 1, entry 1). Then, a low amount of boric acid (10 mol%) was used to carry out the amidation of pyridin-3-amine in toluene at reflux. While the amidation reaction with aniline derivatives in toluene at reflux for few hours offered quantitative yield of the corresponding amide, we found that the same reaction with pyridin-3-amine produced less than 5% yield of the desired amide after 48 hours of reaction (entry 2). Increasing the amount of boric acid to 20 mol% and elevating the reaction temperature by shifting from toluene at reflux to xylene at reflux brought modest improvement in amide formation (yield: 30%, entry 3). Further increase in the loading of $B(OH)_3$ to 30% level did provide even higher yield (49%, entry 4). The results indicated that the employment of boric acid at higher loading could effectively catalyze the direct amidation for azaarene compound at reflux temperature of xylene for 48 hours. However, long reaction times are not practical in preparative chemistry. By shortening the reaction time from 48 to 24 hours, a lower yield of the desired amide (33%) was obtained (entry 5 vs entry 4). Later, we discovered that by employing an additive such as *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine at 30 mol% level, we could achieve effectively the catalyzed amidation (yield: 80%) after 24 hours with the same amount of boric acid (30 mol%) (entry 6). The aforementioned additive did bring a beneficial effect to this direct boric acid catalyzed amidation. Taking full advantage of the beneficial effect of the additive, it was decided to reduce the reaction time from 24 to 7 hours at the same time maintaining a high yield in amide. The experiment was carried out but unfortunately was not successful; only 10% of the desired amide was obtained (entry 7). We realized that merely reduction of reaction time without raising the temperature of the reaction would not do any benefit to the amidation. The same reaction was repeated as described in entry 6 with mesitylene as solvent instead of xylene for the purpose of a higher reaction temperature. By operating at higher temperature for a shorter reaction time (7 h) the same high yield of 82% was obtained in the reaction using xylene as solvent for 24 hours (entry 8 vs entry 6). This finding suggested that if other reaction conditions were kept unchanged, one could be able to

Table 2 Control Experiments[a]



Entry	RNH_2	Solvent	$B(OH)_3$ (mol%)	Time (h)	Yield (%)[b]
1		toluene	10	48	<5[c]
2		toluene	10	48	70

[a] $B(OH)_3$-catalyzed amidation between a saturated carboxylic acid and an amino-azaarene and that between a saturated carboxylic acid and methyl 3-aminobenzoate (less nucleophilic aniline). Reaction conditions: amine (5 mmol), acid (5.5 mmol), and toluene (70 mL), reflux.
[b] Isolated yields.
[c] Entry 2 in Table 1.

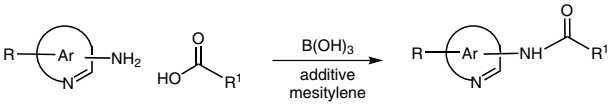
achieve the amidation in high yields for a shorter reaction time by operating the reaction at higher temperature. Thus far, the reaction conditions used in entry 8 appeared to be the best conditions in our study. We still wanted to understand the importance of the additive (the factor of the additive) in the amidation when operated at high temperature (mesitylene at reflux). Thus, the same reaction was repeated as described in entry 8 without using the additive in the amidation. Under this condition, the yield of the amidation was reduced approximately to half (entry 9). Likewise, with the reduction of the $B(OH)_3$ loading to 10%, the yield of the amidation was also reduced approximately to half (entry 10). We conclude that both 30% loading of boric acid and additive are needed for the amidation. Finally, it is noteworthy that *N*,*N*,*N*′,*N*′-tetramethylethylenediamine can provide equally the same beneficial effect (entry 11).

The experimental results in Table 1 indicate that in an amidation of an azaarene compound, a co-catalytic system comprising 30 mol% of boric acid relative to the amount of stating material 3-aminopyridine in the presence of *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine at 30 mol% level in mesitylene at reflux temperature could be the quasi-optimum condition for the direct amidation (Table 1, entry 7).

In addition, the results in Table 2 clearly indicate that there is a significant difference in the reactivity of amidation between amino-azaarene and methyl 3-aminobenzoate (less nucleophilic aniline), as evidenced by the yields of the isolated amides in the absence of any additive.

Encouraged by these findings, the aforementioned experimental conditions were used to expand the scope of the boric acid catalyzed direct amidation of amino-azaarene compounds including pyridinylamines and quinolinylamines with either saturated (Table 3) or α,β-unsaturated (Table 4) carboxylic acids.

Table 3 Boric Acid Catalyzed Direct Amidation of Amino-Azaarenes with Saturated Carboxylic Acids[a]



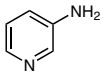
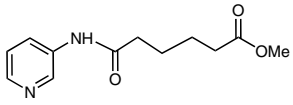
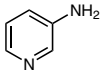
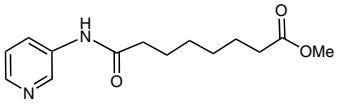
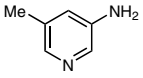
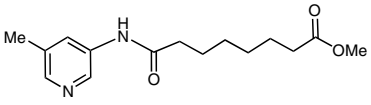
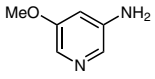
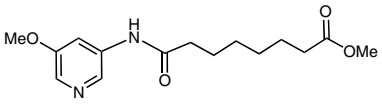
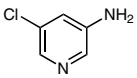
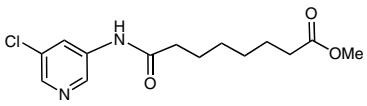
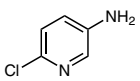
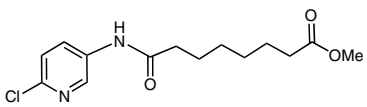
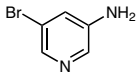
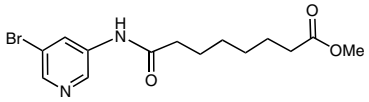
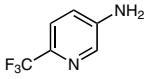
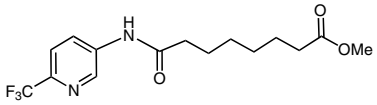
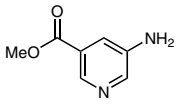
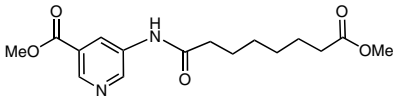
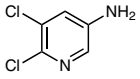
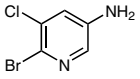
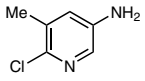
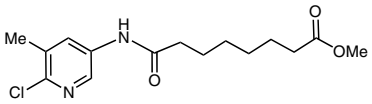
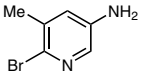
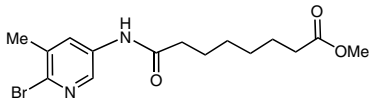
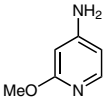
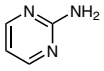
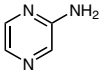
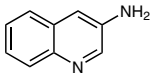
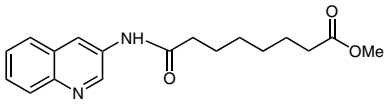
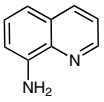
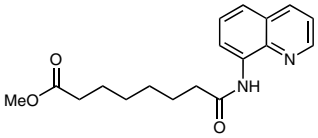
Amide	Amino-azaarenes	Amide product	Yield (%)[b]
1			61
2			82
3			70
4			75
5			62
6			63

Table 3 (continued)

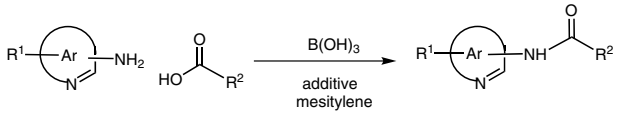
Amide	Amino-azaarenes	Amide product	Yield (%)[b]
7			53
8			78
9			47
10		no amidation observed	–
11		no amidation observed	–
12			86
13			84
14		no amidation observed	–
15		no amidation observed	–
16		no amidation observed	–
17			74
18			80

[a] Reaction conditions: amine (5 mmol), acid (5.5 mmol), $B(OH)_3$ (1.5 mmol), additive (1.5 mmol) and mesitylene (70 mL), reflux, 7 h.
[b] Isolated yields.

A number of important generalizations emerge from the data from Tables 3 and 4. First, our discovery that the combination of $B(OH)_3$ and *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine is an efficient catalyst system to promote the direct amidation of pyridine-3-amine. The amidation is regiospecific in that acylation occurred only at the amino

group. As shown in the examples in Tables 3 and 4, the boric acid catalyzed amidation works well. In fact, the amidations were completed within 7 hours. First, they were clean and provided good to excellent yields without using any environmentally toxic chemicals and/or coupling agents. Second, activating groups such as methyl or methoxy groups in the pyridine ring render the amidation much readily. De facto, the amidation reactions were completed within 5 hours in the cases of products **3** and **4** (Table 3). Third, with one deactivating group: such as Cl, Br, CF_3, and ester, the amidation proceeded normally providing acceptable yields (51–78%) (products **5**–**9**). Fourth, with two deactivating groups on the pyridine ring: two Cl or one Cl and one Br (products **10** and **11**), no amidation was observed under the studied experimental conditions. Fifth, an interesting interplay was found between the activating and deactivating groups on the pyridine ring. When one of deactivation group (for example Cl) on the pyridine ring was replaced by an activating group (Me), the nucleophilic strength of the amino group was restored. The amidation worked again and good yields of the desired amides were obtained (products **12** and **13**). Sixth, the direct amidation of pyridin-4-amine met with failure even if there is an activating group (for example: methoxy) on the pyridine ring (product **14**). The failure was probably due to the tautomerization of pyridin-4-amine, and the formation of pyridine-4(1*H*)imine. Seventh, when there are two nitrogen atoms in the same ring, such as aminopyrazine and aminopyrimidine, no amidation was achieved (products **15** and **16**). This failure might be due to the weak nucleophilic strength of the amino group. Eighth, the direct amidation of the amine group of fused arene rings such as quinoline systems sailed smoothly without any difficulty providing excellent yields of the desired quinolinylamides (products **17** and **18**). Our boric acid catalyzed amidation worked well with α,β-unsaturated carboxylic acids as well. As shown in Table 4, the direct amidation offered good yields of α,β-unsaturated carboxamides. Sheppard et al.[20] reported the use of an excess of $B(OCH_2CF_3)_3$ to promote the amidation. Our study of boric acid catalyzed amidation of aminopyridines offered advantage over the reported amidation mediated by $B(OCH_2CF_3)_3$ in that we used 30 mol% of inexpensive $B(OH)_3$ instead of an excess of much more expensive $B(OCH_2CF_3)_3$, which is not commercially available. The preparation of $B(OCH_2CF_3)_3$ involved the employment of an excess of CF_3CH_2OH and the separation required distillation. $B(OCH_2CF_3)_3$ is moisture-sensitive and special handling is needed for its use. We have compared our method with the one reported by Sheppard et al.[20] using an excess of expensive $B(OCH_2CF_3)_3$. The results are given in Table 5.

Table 4 Boric Acid Catalyzed Direct Amidation of Amino Azaarenes with α,β-Unsaturated Carboxylic Acids[a]



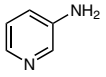
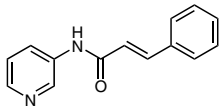
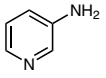
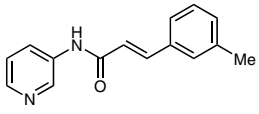
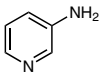
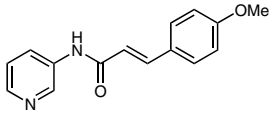
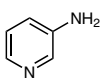
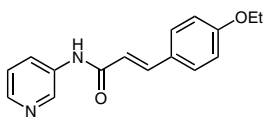
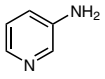
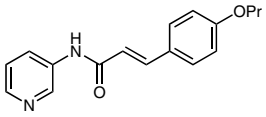
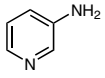
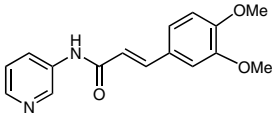
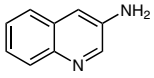
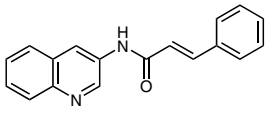
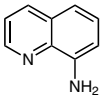
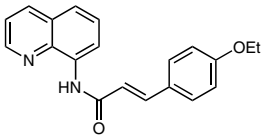
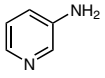
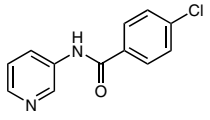
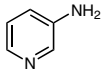
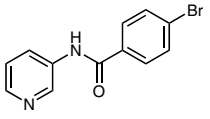
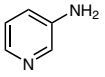
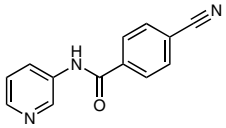
Amide	Amino-azaarenes	Amide product	Yield (%)[b]
19			81
20			60
21			70
22			77

Table 4 (continued)

Amide	Amino-azaarenes	Amide product	Yield (%)[b]
23			64
24			63
25			71
26			61
27			56[c]
28			51[c]
29			72[c]

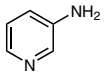
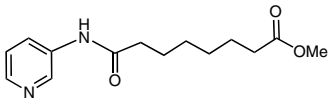
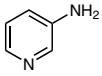
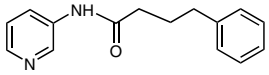
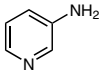
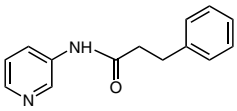
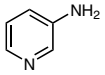
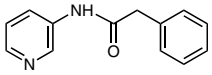
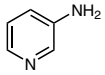
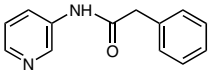
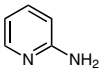
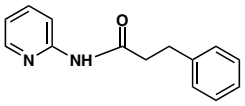
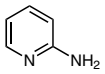
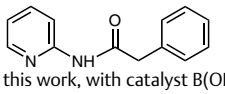
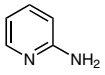
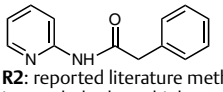
[a] Reaction conditions: amine (5 mmol), acid (5 mmol), $B(OH)_3$ (1.5 mmol), additive (1.5 mmol), and mesitylene (70 mL), reflux, 8 h.
[b] Isolated yields.
[c] Refluxing time: 10–12 h.

The data in Table 5 indicate that the boric acid catalyzed amidation of 3-aminopyridine and 2-aminopyridine is superior to the amidation mediated by an excess of $B(OCH_2CF_3)_3$,[20] because boric acid catalyzed amidation not only obviated the need of the harsh conditions (sealed tube at high temperature), but did offer better yields of the amidation products than that obtained from the amidation mediated by an excess of $B(OCH_2CF_3)_3$[20] (products **2**, **30**, **31**, and **32** versus compound **R1**] and (products **33** and **34** versus compound **R2**].

The mechanism of the boric acid catalyzed amidation could be complicated. The reaction could involve many intermediates before giving rise to the final amidation product (Scheme 1 and Scheme 2).[1,30–36] Among many plausible intermediates, one of them could be a mixed acid anhydride [Int. **1**] formed between carboxylic acid and boric acid (Scheme 2).[30–36]

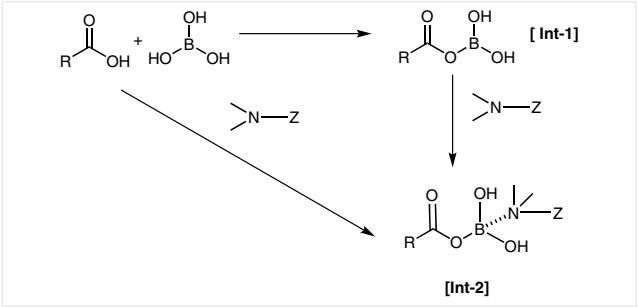
In conclusion, we have developed and reported hereby a novel and facile boric acid catalyzed direct amidation for aminopyridines and aminoquinolines without employing any environmentally hazard chemicals or coupling agents. To the best of our knowledge, such catalyzed amidation has not been previously reported in the literature. The reported amidation methodology offers advantage of atom- and step-economy. By virtue of the operational simplicity of this methodology, this boric acid catalyzed amidation might, therefore, qualify for large-scale preparation, as well as for the excellent chemoselectivity profile, which can make protection/deprotection sequence obsolete. There-

Table 5 Comparison of Boric Acid Catalyzed Amidation with the Amidation Mediated by an Excess of $B(OCH_2CF_3)_3$[20]

Amide	Aminopyridine	Amide product[a]	Yield (%)[b]
2			82
30			73
31			75
32		 this work, with catalyst $B(OH)_3$	59
R1		 **R1**: reported literature method using $B(OCH_2CF_3)_3$20 in a sealed tube at high temperature for 24 h	53
33			75
34		 this work, with catalyst $B(OH)_3$	57
R2		 **R2**: reported literature method using $B(OCH_2CF_3)_3$20 in a sealed tube at high temperature for 24 h	12

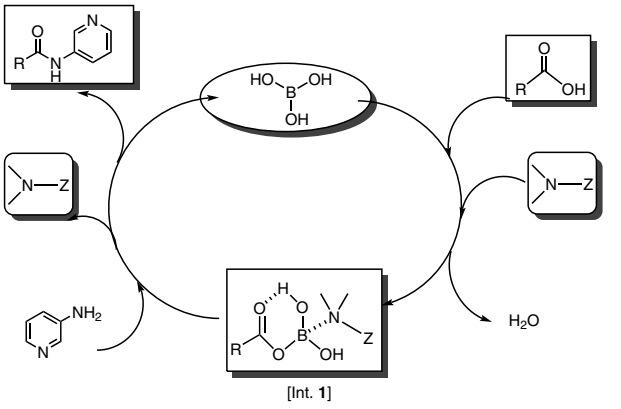
[a] Reaction conditions: amine (5 mmol), acid (5.5 mmol acid), $B(OH)_3$ (1.5 mmol), additive (1.5 mmol), and mesitylene (70 mL), reflux, 7 h.
[b] Isolated yields.

fore, this direct amidation could allow organic molecule architects for quick building of molecular complexity. We believe that the successful development and application of this boric acid mediated direct amidation of aminopyridine and aminoquinoline have opened up a new possibility of practical direct amidation because many naturally existing products and new medicinally useful compounds comprising either pyridinylamido or quinolinylamido moiety could be made by this boric acid catalyzed amidation method. Our research projects on further the possibility of the direct amidation of other azaarenes catalyzed by boric acid are ongoing towards this goal.



Scheme 1 Plausible intermediates in the catalytic cycle

^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AV III 400 spectrometer (400 MHz). The chemical shifts were reported in ppm relative to Me_4Si as an internal standard. Mass spectra were obtained using a Waters Xevo G2 QTof mass spectrometer. TLC on precoated plates with silica gel F254, purchased from Qingdao Haiyang Chemical Co. Ltd., was employed to monitor the progress of the reaction. CH_2Cl_2 was purchased from Beijing Chemical Works and dried over molecular sieves 4Å before use. EtOH was purchased from



Scheme 2 The catalytic cycle of boric acid catalyzed amidation

Beijing Chemical Works and dried over molecular sieves 4Å before use. All reagents of analytical grade were purchased from Sigma-Aldrich, Beijing Inno-Chem Co. Ltd., Alfa Aesar, Beijing Chemical Works, and other commercial sources. They were used without further purification. All reactions were carried out in oven-dried glassware. Dry N_2 was used to purge the reactor and all the glass apparatus before the reaction and to protect the reaction during the entire operation.

Boric Acid Catalyzed Amidation; Methyl 8-Oxo-8-(pyridin-3-ylamino)octanoate (2); Typical Procedure for Products Listed in Tables 1–3

To an oven-dried 100 mL three-necked round-bottomed flask equipped with two glass stoppers, a vacuum-jacketed Dean–Stark trap topped with a reflux condenser fitted with a N_2 inlet, and a Teflon-coated magnet stirring bar were placed pyridin-3-amine (0.5 g, 5.3 mmol), boric acid (0.1 g, 1.6 mmol), and mesitylene (70 mL). To the stirred reaction mixture were added *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.6 mmol) and 8-methoxy-8-oxooctanoic acid (1.5 g, 8 mmol) in one portion. The stirred reaction mixture was heated at gentle reflux at ca. 164 °C for 7 h. TLC analysis (eluent: EtOAc) indicated the complete disappearance of the amine starting material. After cooling to r.t., the mixture was poured into petroleum ether (350 mL) leading to the immediate precipitation of an off-white solid. Stirring was continued for an additional 30 min and the precipitate was then filtered through a sintered glass funnel. The collected solid was thoroughly washed with petroleum ether and H_2O, and dried in vacuo at r.t. for 24 h, then purified by flash chromatography to afford methyl 8-oxo-8-(pyridin-3-ylamino)octanoate as an off-white solid; yield: 1.14 g (82%); mp 52.6–53.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.07 (1 H, s), 8.73 (2 H, d, *J* = 2.47 Hz), 8.24 (1 H, m), 8.04 (1 H, m), 7.33 (1 H, m), 3.59 (1 H, s), 2.32 (4 H, m), 1.60 (2 H, t, *J* = 7.03 Hz), 1.54 (2 H, t, *J* = 7.41 Hz), 1.31 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 171.76, 143.90, 140.66, 135.88, 125.87, 123.54, 51.13, 36.12, 33.19, 28.24, 28.17, 24.74, 24.27.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{20}N_2O_3$: 265.1553; found: 265.1557.

Boric Acid Catalyzed Amidation; *N*-(Pyridin-3-yl)cinnamamide (19); Typical Procedure for Products Listed in Tables 4 and 5

To an oven-dried 100 mL three-necked round-bottomed flask equipped with two glass stoppers, a vacuum-jacketed Dean–Stark trap topped with a reflux condenser fitted with a N_2 inlet, and a Teflon-coated magnet stirring bar were placed pyridin-3-amine (0.47 g, 5mmol), boric acid (0.1 g, 1.5 mmol), and mesitylene (70 mL). To the stirred reaction mixture were added *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.20 g, 1.5 mmol) and cinnamic acid (1.11 g, 7.5 mmol) in one portion. The stirred reaction mixture was heated at gentle reflux at ca. 164 °C for 8 h. TLC analysis (eluent: EtOAc) indicated the complete disappearance of the amine starting material. Upon cooling to r.t., precipitation of an off-white solid occurred immediately, which was filtered through a sintered glass funnel. The collected solid was thoroughly washed with petroleum ether and H_2O, and then dried in vacuo at r.t. for 24 h, then purified by flash chromatography to afford of *N*-(pyridin-3-yl)cinnamamide as an off-white solid; yield: 0.80 g (81%); mp 175.3–176.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.44 (1 H, s), 8.85 (1 H, s), 8.29 (1 H, m), 8.16 (1 H, d, *J* = 8.52 Hz), 7.65 (3 H, t, *J* = 6.70 Hz), 7.45 (4 H, m), 6.85 (1 H, d, *J* = 15.9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.01, 144.26, 140.82, 135.89, 134.51, 129.94, 129.02, 127.79, 126.11, 123.68, 121.55.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{12}N_2O$: 225.1029; found: 225.1030.

Preparation of Compounds Listed in Table 3

Methyl 6-Oxo-6-(pyridin-3-ylamino)hexanoate (1); Typical Procedure

To an oven-dried 100 mL three-necked round-bottomed flask equipped with two glass stoppers, a vacuum-jacketed Dean–Stark trap topped with a reflux condenser fitted with a N_2 inlet, and a Teflon-coated magnet stirring bar were placed 3-aminopyridine (0.5 g, 5.3 mmol), boric acid (0.1 g,1.6 mmol), and mesitylene (70 mL). To the stirred reaction mixture were added *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.6 mmol) and 6-methoxy-6-oxohexanoic acid (1.27 g, 8 mmol) in one portion. The stirred reaction mixture was heated at gentle reflux at 164 °C for 7 h. TLC analysis (eluent: EtOAc) indicated the complete disappearance of the amine starting material. After cooling to r.t., the mixture was poured into petroleum ether (350 mL) leading to the immediate precipitation of an off-white solid. Stirring was continued for an additional 30 min and the precipitate was then filtered through a sintered glass funnel. The collected solid was thoroughly washed with petroleum ether and H_2O, and dried in vacuo at r.t. for 24 h to afford methyl 6-oxo-6-(pyridin-3-ylamino)hexanoate as a light-brown solid; yield: 0.76 g (61%); mp 41.3–42.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.14 (1 H, s), 8.73 (1 H, s), 8.23 (1 H, d, *J* = 4.89 Hz), 8.02 (1 H, d, *J* = 8.27 Hz), 7.31 (1 H, m), 3.59 (3 H, s), 2.34 (4 H, m), 1.59 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.67, 172.03, 144.41, 141.16, 136.35, 126.37, 124.03, 51.68, 36.30, 33.49, 24.87, 24.50.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_{16}N_2O_3$: 237.1240; found: 237.1272.

The syntheses of other compounds (compounds **3** to **18**) were carried out according to the aforementioned typical procedures as described for compounds **1** and **2**.

Methyl 8-[(5-Methylpyridin-3-yl)amino)-8-oxooctanoate (3)

Prepared from 5-methylpyridin-3-amine (1.08 g, 10 mmol), boric acid (0.19 g, 3 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 3 mmol), and 8-methoxy-8-oxooctanoic acid (1.92 g, 10.2 mmol); yield: 1.94 g (70%); light-brown solid; mp 65.53–67.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (1 H, s), 8.51 (1 H, s), 8.08 (1 H, s), 7.89 (1 H, s), 3.58 (3 H, m), 2.29 (7 H, m), 1.56 (4 H, m), 1.29 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.79, 172.21, 144.73, 138.44, 135.99, 133.25, 126.72, 51.62, 33.69, 28.73, 28.68, 24.77.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{15}H_{22}N_2O_3$: 279.1709; found: 279.1703.

Methyl 8-[(5-Methoxypyridin-3-yl)amino)-8-oxooctanoate (4)

Prepared from 5-methoxylpyridin-3-amine (0.5 g, 4 mmol), boric acid (0.08 g, 1.2 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.16 g, 1.2 mmol), and 8-methoxy-8-oxooctanoic acid (0.90 g, 4.8 mmol); yield: 0.88 g (75%); light-brown solid; mp 72.2–73.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.10 (1 H, s), 8.31 (1 H, d, J = 1.62 Hz), 7.98 (1 H, d, J = 2.50 Hz), 7.76 (1 H, m), 3.81 (3 H, s), 3.59 (3 H, s), 2.32 (4 H, m), 1.56 (4 H, m), 1.30 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 171.91, 155.25, 136.56, 132.78, 131.39, 110.62, 55.39, 51.13, 36.19, 33.19, 28.23, 28.17, 24.70, 24.26.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{15}H_{22}N_2O_4$: 295.1659; found: 295.1662.

Methyl 8-[(5-Chloropyridin-3-yl)amino]-8-oxooctanoate (5)

Prepared from 5-chloropyridin-3-amine (0.5 g, 4 mmol), boric acid (0.08 g, 1.2 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.16 g, 1.2 mmol), and 8-methoxy-8-oxooctanoic acid (0.94 g, 5 mmol); yield: 0.72 g (62%); off-white solid; mp 76.5–78 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.32 (1 H, s), 8.61 (1 H, d, J = 2.44 Hz), 8.30 (1 H, d, J = 2.26 Hz), 8.26 (1 H, t, J = 2.44 Hz), 3.59 (3 H, s), 2.33 (4 H, m), 1.57 (4 H, m), 1.31 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 172.25, 141.98, 138.71, 136.74, 130.53, 124.99, 51.13, 36.16, 33.18, 28.18, 24.56, 24.25.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{14}H_{19}ClN_2O_3$: 299.1163; found: 299.1164.

Methyl 8-[(6-Chloropyridin-3-yl)amino]-8-oxooctanoate (6)

Prepared from 6-chloropyridin-3-amine (0.5 g, 4 mmol), boric acid (0.08 g, 1.2 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.16 g, 1.2 mmol), and 8-methoxy-8-oxooctanoic acid (0.94 g, 5 mmol); yield: 0.75 g (63%); off-white solid; mp 99.9–100.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.23 (1 H, s), 8.60 (1 H, d, J = 2.67 Hz), 8.08 (1 H, d, J = 8.90 Hz), 7.46 (1 H, t, J = 8.90 Hz), 3.59 (3 H, s), 2.33 (4 H, m), 1.56 (4 H, m), 1.29 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 171.86, 143.22, 140.17, 135.49, 129.55, 124.11, 51.13, 36.10, 33.18, 28.17, 24.65, 24.25.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{14}H_{19}ClN_2O_3$: 299.1163; found: 299.1164.

Methyl 8-[(5-Bromopyridin-3-yl)amino]-8-oxooctanoate (7)

Prepared from 5-bromopyridin-3-amine (1.42 g, 8.2 mmol), boric acid (0.15 g, 2.46 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.32 g, 2.46 mmol), and 8-methoxy-8-oxooctanoic acid (1.57 g, 8.37 mmol); yield: 1.49 g (53%); light brown solid; mp 79.7–80.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.31 (1 H, s), 8.65 (1 H, s), 8.39 (2 H, d, J = 9.55 Hz), 3.59 (3 H, s), 2.33 (4 H, m), 1.57 (4 H, m), 1.28 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 172.21, 144.10, 138.93, 136.95, 127.75, 119.58, 51.13, 36.15, 33.18, 28.16, 24.60, 24.25.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{14}H_{19}BrN_2O_3$: 343.0658 and 345.0638; found: 343.1500 and 345.1000.

Methyl 8-Oxo-8-{[6-(trifluoromethyl)pyridin-3-yl]amino}octanoate (8)

Prepared from 6-(trifluoromethyl)pyridin-3-amine (0.5 g, 3 mmol), boric acid (0.06 g, 0.9 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.12 g, 0.9 mmol), and 8-methoxy-8-oxooctanoic acid (0.87 g, 4.63 mmol); yield: 0.8 g (78%); off-white solid; mp 92.6–93.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (1 H, s), 8.87 (1 H, d, J = 2.06 Hz), 8.33 (2 H, d, J = 8.79 Hz), 7.8 5 (1 H, d, J = 8.61 Hz), 3.59 (3 H, s), 2.39 (2 H, t, J = 7.72 Hz), 2.31 (2 H, t, J = 7.54 Hz), 1.57 (4 H, m), 1.31 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.30, 172.38, 140.48, 138.76, 126.25, 121.19, 51.13, 36.19, 33.17, 28.16, 24.57, 24.25.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{15}H_{19}F_3N_2O_3$: 333.1427; found: 333.1430.

Methyl 5-(8-Methoxy-8-oxooctanamido)nicotinate (9)

Prepared from methyl 5-aminonicotinate (0.5 g, 3 mmol), boric acid (0.06 g, 0.9 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.12 g, 0.9 mmol), and 8-methoxy-8-oxooctanoic acid (0.94 g, 5 mmol); yield: 0.45 g (47%); off-brown solid; mp 98.8–100.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (1 H, s), 8.91 (1 H, d, J = 2.39 Hz), 8.75 (2 H, d, J = 1.96 Hz), 8.64 (1 H, t, J = 2.39 Hz), 3.89 (3 H, s), 3.58 (3 H, s), 2.30 (4 H, m), 1.60 (4 H, m), 1.30 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 172.17, 165.13, 144.09, 135.95, 125.81, 125.39, 52.45, 51.13, 36.15, 33.19, 28.16, 24.64, 24.25.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{16}H_{22}N_2O_5$: 323.1608; found: 323.1604.

Methyl 8-[(6-Chloro-5-methylpyridin-3-yl)amino]-8-oxooctanoate (12)

Prepared from 6-chloro-5-methylpyridin-3-amine (0.5 g, 3 mmol), boric acid (0.07 g, 1.05 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.14 g, 1.05 mmol), and 8-methoxy-8-oxooctanoic acid (1 g, 5.3 mmol); yield: 0.94 g (86%); off-white solid; mp 73.2–75 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (1 H, s), 8.42 (1 H, d, J = 2.54 Hz), 8.04 (2 H, d, J = 2.26 Hz), 3.59 (3 H, s), 2.31 (7 H, m), 1.56 (4 H, m), 1.30 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.30, 171.81, 143.54, 137.63, 135.50, 131.80, 129.77, 51.13, 36.07, 33.18, 28.21, 24.69, 24.25, 19.18.

HRMS (ESI): m/z (M + H)$^+$ calcd for $C_{15}H_{21}ClN_2O_3$: 313.1320; found: 313.1321.

Methyl 8-[(6-Bromo-5-methylpyridin-3-yl)amino]-8-oxooctanoate (13)

Prepared from 6-bromo-5-methylpyridin-3-amine (0.5 g, 3 mmol), boric acid (0.06 g, 0.9 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.12 g, 0.9 mmol), and 8-methoxy-8-oxooctanoic acid (0.8 g, 4 mmol); yield: 0.8 g (84%); off-white solid; mp 71.0–71.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.22 (1 H, s), 8.43 (1 H, d, J = 2.55 Hz), 8.02 (2 H, d, J = 2.26 Hz), 3.62 (3 H, s), 2.31 (7 H, m), 1.58 (4 H, m), 1.31 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.31, 171.85, 138.14, 136.23, 135.81, 134.37, 129.22, 51.13, 36.10, 33.18, 28.21, 24.67, 24.25, 21.46.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{21}BrN_2O_3$: 357.0815 and 359.0794; found: 357.0818 and 359.0800.

Methyl 8-Oxo-8-(quinolin-3-ylamino)octanoate (17)

Prepared from quinoline-3-amine (0.5 g, 3.5 mmol), boric acid (0.07 g, 1.05 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.14 g, 1.05 mmol), and 8-methoxy-8-oxooctanoic acid (1 g, 5.3 mmol); yield: 0.81 g (74%); light yellow solid; mp 92.1–93.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.35 (1 H, s), 8.90 (1 H, d, *J* = 2.24 Hz), 8.72 (1 H, s), 7.93 (2 H, d, *J* = 8.37 Hz), 7.58 (2 H, d, *J* = 8.07 Hz), 3.58 (3 H, s), 2.40 (2 H, t, *J* = 7.63 Hz), 2.30 (2 H, t, *J* = 7.63 Hz), 1.64 (2 H, m), 1.54 (2 H, m), 1.32 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.80, 172.58, 144.93, 144.54, 133.44, 128.98, 128.34, 128.10, 127.74, 122.20, 51.63, 33.69, 28.77, 28.70, 24.78.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{22}N_2O_3$: 315.1709, found: 315.1712.

Methyl 8-Oxo-8-(quinolin-8-ylamino)octanoate (18)

Prepared from quinoline-8-amine (0.5 g, 3.5 mmol), boric acid (0.07 g, 1.05 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.14 g, 1.05 mmol), and 8-methoxy-8-oxooctanoic acid (1 g, 5.3 mmol); yield: 0.88 g (80%); light yellow solid; mp 92.3–95 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.99 (1 H, s), 8.92 (1 H, d, *J* = 4.14 Hz), 8.47 (1 H, d, *J* = 9.12 Hz), 7.76 (4H, m), 3.59 (3 H, s), 2.32 (4 H, m), 1.66 (4 H, m), 1.35 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.40, 173.30, 171.99, 150.35, 148.09, 133.99, 131.39, 129.00, 125.89, 121.45, 120.80, 51.13, 33.53, 33.21, 28.34, 28.21, 25.03, 24.32.

HRMS (ESI) (M + H)$^+$ calcd for $C_{18}H_{22}N_2O_3$: 315.1709; found: 315.1712.

Preparation of Compounds Listed in Table 4

The syntheses of compounds **20–29** were carried out according to the aforementioned typical procedure as described for compound **19**.

(*E*)-*N*-(Pyridin-3-yl)-3-(*m*-tolyl)acrylamide (20)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and (*E*)-3-(*m*-tolyl)acrylic acid (0.82 g, 5 mmol); yield: 0.70 g (60%); off-white solid; mp 91.7–92.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.41 (1 H, s), 8.83 (1 H, d, *J* = 2.44 Hz), 8.29 (1 H, m), 8.16 (1 H, m), 8.14 (1 H, m), 7.61 (1 H, d, *J* = 16.26 Hz), 7.44 (2 H, d, *J* = 8.94 Hz), 7.36 (2 H, m), 7.24 (1 H, d, *J* = 7.56 Hz), 6.85 (1 H, *J* = 15.93 Hz), 2.36 (3 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.02, 144.23, 140.86, 140.78, 138.19, 135.89, 134.45, 130.64, 128.92, 128.29, 126.06, 125.00, 123.68, 121.41.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{14}N_2O$: 239.1185. found: 239.1186.

(*E*)-3-(4-Methoxyphenyl)-*N*-(pyridin-3-yl)acrylamide (21)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and (*E*)-3-(4-methoxyphenyl)acrylic acid (0.89 g, 5 mmol); yield: 0.88 g (70%); off-white solid; mp 149.3–150.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (1 H, s), 8.83 (1 H, d, *J* = 2.33 Hz), 8.28 (1 H, m), 8.14 (1 H, m), 7.59 (3 H, t, *J* = 7.97 Hz), 7.38 (1 H, m), 7.01 (2 H, d, *J* = 8.69 Hz), 6.67 (1 H, d, *J* = 15.80 Hz), 3.81 (3 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.82, 161.21, 144.58, 141.25, 141.09, 136.52, 129.96, 127.57, 126.49, 124.14, 119.44, 114.98, 55.79.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{14}N_2O_2$: 255.1134, found: 255.1136.

(*E*)-3-(4-Ethoxyphenyl)-*N*-(pyridin-3-yl)acrylamide (22)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and (*E*)-3-(4-ethoxyphenyl)acrylic acid (0.96 g, 5 mmol); yield: 1.03 g (77%); off-white solid; mp 208.5–210.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (1 H, s), 8.83 (1 H, s), 8.28 (1 H, m), 8.14 (1 H, m), 7.59 (3 H, m), 7.37 (1 H, m), 6.99 (1 H, d, *J* = 8.38 Hz), 6.66 (1 H, d, *J* = 15.52 Hz), 4.09 (2 H, m), 1.34 (3 H, t, *J* = 7.15 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.83, 160.50, 144.57, 141.25, 141.13, 136.53, 129.97, 127.42, 126.49, 124.14, 119.32, 115.37, 63.74, 15.04.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{16}H_{16}N_2O_2$: 269.1291; found: 269.1292.

(*E*)-3-(4-Propoxyphenyl)-*N*-(pyridin-3-yl)acrylamide (23)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and (*E*)-3-(4-propoxyphenyl)acrylic acid (1.03 g, 5 mmol); yield: 0.90 g (64%); off-white solid; mp 189.5–190.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (1 H, s), 8.83 (1 H, s), 8.27 (1 H, m), 8.16 (1 H, d, *J* = 8.62 Hz), 7.57 (3 H, m), 7.37 (1 H, m), 7.02 (2 H, d, *J* = 8.50 Hz), 6.68 (1 H, d, *J* = 6.68 Hz), 3.99 (2 H, t, *J* = 6.90 Hz), 1.75 (2 H, m), 0.99 (3 H, t, *J* = 7.15 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.34, 160.17, 144.07, 140.75, 140.62, 136.03, 129.47, 126.92, 125.99, 123.64, 118.83, 114.92, 69.09, 21.93, 10.33.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{18}N_2O_2$: 283.1447; found: 283.1450.

(*E*)-3-(3,4-Dimethoxyphenyl)-*N*-(pyridin-3-yl)acrylamide (24)

Pepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (1.04 g, 5 mmol); yield: 0.90 g (63%); off-white solid; mp 207.4–207.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.35 (1 H, s), 8.84 (1 H, s), 8.28 (1 H, m), 8.16 (1 H, m), 7.58 (1 H, d, *J* = 16.02 Hz), 7.37 (1 H, m), 7.22 (2 H, m), 7.03 (1 H, d, *J* = 7.64 Hz), 6.71 (1 H, d, *J* = 16.77 Hz), 3.82 (6 H, d, *J* = 7.64 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.01, 144.26, 140.82, 135.89, 134.51, 129.94, 129.02, 127.79, 126.11, 123.68, 121.55.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{16}H_{16}N_2O_3$: 285.1240; found: 285.1243.

***N*-(Quinolin-3-yl)cinnamamide (25)**

Prepared from quinoline-3-amine (0.37 g, 2.5 mmol), boric acid (0.05 g, 0.8 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.10 g, 0.8 mmol), and cinnamic acid (0.37 g, 2.5 mmol) in mesitylene (70 mL); yield: 0.48 g (71%); off-white solid; mp 219.1–219.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.72 (1 H, s), 9.01 (1 H, s), 8.84 (1 H, s), 7.97 (2 H, t, *J* = 8.34 Hz), 7.67 (5 H, m), 7.46 (3 H, m), 6.94 (1 H, d, *J* = 15.89 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.28, 144.46, 144.22, 140.89, 134.51, 132.97, 129.98, 129.04, 128.55, 127.83, 127.08, 122.08, 121.57.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{18}H_{14}N_2O$: 275.1185; found: 275.1181.

(*E*)-3-(4-Ethoxyphenyl)-*N*-(quinolin-8-yl)acrylamide (26)

Prepared from quinoline-8-amine (0.72 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.20 g, 1.5 mmol), and (*E*)-3-(4-ethoxyphenyl)acrylic acid (0.96 g, 5 mmol) in mesitylene (70 mL); yield: 0.97 g (61%); off-white solid; mp 204.1–205.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.18 (1 H, s), 8.94 (1 H, s), 8.58 (1 H, s), 7.98 (d, *J* = 7.15 Hz), 7.88 (1 H, d, *J* = 7.55 Hz), 7.79 (1 H, t, *J* = 7.55 Hz), 7.60 (4 H, m), 7.03 (3 H, m), 4.10 (2 H, m), 1.35 (3 H, t, *J* = 7.15 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.16, 160.42, 150.92, 148.60, 140.89, 134.54, 131.76, 129.91, 129.62, 127.65, 126.27, 122.82, 121.35, 121.21, 119.74, 115.38, 63.74, 15.07.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{20}H_{18}N_2O_2$: 319.1447; found: 319.1443.

4-Chloro-*N*-(pyridin-3-yl)benzamide (27)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and 4-chlorobenzoic acid (0.78 g, 5 mmol), then purified by flash chromatography; yield: 0.65 g (56%); light-brown solid; mp 146.3–147.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.51 (1 H, s), 8.92 (1 H, s), 8.33 (1 H, s), 8.19 (1 H, s), 8.02 (2 H, s), 7.65 (2 H, s), 7.41 (1 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.29, 145.19, 142.48, 137.20, 136.10, 133.50, 130.16, 129.03, 127.86, 124.02.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_9ClN_2O$: 233.0482; found: 233.0476.

4-Bromo-*N*-(pyridin-3-yl)benzamide (28)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and 4-bromobenzoic acid (1.005 g, 5 mmol), then purified by flash chromatography; yield: 0.70 g (51%); light-brown solid; mp 162.2–163.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.52 (1 H, s), 8.92 (1 H, s), 8.33 (1 H, s), 8.19 (1 H, s), 7.93 (2 H, s), 7.79 (2 H, s), 7.41 (1 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.41, 145.20, 142.49, 136.09, 133.86, 131.97, 130.33, 127.86, 126.16, 124.02.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{12}H_9BrN_2O$: 276.9977 and 278.9957, found: 276.9971 and 278.9952.

4-Cyano-*N*-(pyridin-3-yl)benzamide (29)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and 4-cyanobenzoic acid (0.73 g, 5 mmol), then purified by flash chromatography; yield: 0.81 g (72%); light-brown solid; mp 105.2–106.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.69 (1 H, s), 8.93 (1 H, s), 8.35 (6 H, m), 7.42 (1 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.03, 145.46, 142.50, 138.82, 135.90, 133.01, 129.06, 127.93, 124.07, 118.72, 114.60.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{13}H_9N_3O$: 224.0825; found: 224.0816.

Preparation of Compounds Listed in Table 5

4-Phenyl-*N*-(pyridin-4-yl)butanamide (30)

Prepared from pyridin-3-amine (0.5 g, 5.3 mmol), boric acid (0.10 g, 1.6 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.6 mmol), and 4-phenylbutanoic acid (1.31 g, 8 mmol); yield: 0.92 g (73%); off-white solid; mp 92.3–93.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (1 H, s), 8.72 (2 H, d, *J* = 2.37 Hz), 8.24 (1 H, m) 8.02 (1 H, m), 7.31 (3 H, m), 7.23 (3 H, m), 2.63 (2 H, t, *J* = 7.42 Hz), 2.36 (2 H, t, *J* = 7.42 Hz), 1.91 (2 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.98, 144.40, 142.05, 114.18, 136.35, 128.81, 128.75, 126.41, 126.28, 124.03, 36.05, 35.04, 27.04.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{15}H_{16}N_2O$: 241.1342; found: 241.1339.

3-Phenyl-*N*-(pyridin-3-yl)propanamide (31)

Prepared from pyridin-3-amine (0.94 g, 10 mmol), boric acid (0.19 g, 3 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.39 g, 3 mmol), and 3-phenylpropanoic acid (1.50 g, 10 mmol); yield: 1.7 g (75%); white solid; mp 120–121.9 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.14 (1 H, s), 8.73 (1 H, m), 8.25 (1 H, m), 8.04 (1 H, d, *J* = 8.27 Hz), 7.29 (6 H, m), 2.94 (2 H, t, *J* = 7.06 Hz), 2.67 (2 H, t, *J* = 8.48 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.95, 143.98, 140.99, 140.67, 135.78, 128.30, 128.20, 125.92, 125.95, 123.57, 37.76, 30.65.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{14}N_2O$: 227.1185; found: 227.5947.

2-Phenyl-*N*-(pyridin-3-yl)acetamide (32)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and 2-phenylacetic acid (0.68 g, 5 mmol), then purified by flash chromatography; yield: 0.62 g (59%); light-brown solid; mp 107.9–108.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.38 (1 H, s), 8.74 (1 H, s), 8.24 (1 H, d, *J* = 4.07 Hz), 8.02 (1 H, d, *J* = 7.58 Hz), 7.33 (5 H, m), 3.68 (2 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.15, 144.66, 141.20, 136.28, 136.08, 129.62, 128.80, 127.08, 126.49, 124.09, 43.55.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{12}N_2O$: 213.1029; found: 213.1021.

3-Phenyl-*N*-(pyridin-2-yl)propanamide (33)

Prepared from pyridin-2-amine (0.94 g, 10 mmol), boric acid (0.19 g, 3 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.39 g, 3 mmol), and 3-phenylpropanoic acid (1.53 g, 10.2 mmol); yield: 1.0 g (75%); off-white solid; mp 81.7–82.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.48 (1 H, s), 8.30 (1 H, d, *J* = 4.44 Hz), 8.10 (1 H, d, *J* = 8.88 Hz), 7.76 (1 H, m), 7.28 (4 H, m), 7.18 (1 H, m), 7.08 (1 H, m) 2.91 (2 H, t, *J* = 7.52 Hz), 2.67 (2 H, t, *J* = 8.77 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.31, 152.04, 147.85, 141.07, 138.05, 128.26, 128.24, 125.90, 119.16, 113.37, 37.63, 30.63.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{14}H_{14}N_2O$: 227.1185; found: 227.5945.

2-Phenyl-*N*-(pyridin-2-yl)acetamide (34)

Prepared from pyridin-3-amine (0.47 g, 5 mmol), boric acid (0.10 g, 1.5 mmol), *N*,*N*,*N*′,*N*′-tetramethylpropane-l,3-diamine (0.21 g, 1.5 mmol), and 2-phenylacetic acid (0.68 g, 5 mmol), then purified by flash chromatography, yield: 0.60 g (57%); light-brown solid; mp 105.5–106.9 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (1 H, s), 8.32 (1 H, s), 8.04 (1 H, s), 7.75 (1 H, s), 7.34 (4 H, m), 7.09 (1 H, s), 3.72 (2 H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.49, 152.50, 148.41, 138.61, 136.27, 129.64, 128.77, 127.03, 119.87, 113.81, 43.44.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{13}H_{12}N_2O$: 213.1029; found: 213.1021.

Methyl 3-(8-Methoxy-8-oxooctanamido)benzoate (Table 2, entry 2)

Prepared from methyl 3-aminobenzoate (0.76 g, 5 mmol), boric acid (0.03 g, 0.5 mmol), and 8-methoxy-8-oxooctanoic acid (1.04 g, 5.5 mmol), then purified by flash chromatography; yield: 1.12 g (70%); light-brown solid; mp 105.5–106.9 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.10 (1 H, s), 8.28 (1 H, s), 7.82 (1 H, s), 7.61 (1 H, s), 7.44 (1 H, s), 3.85 (3 H, s), 3.58 (3 H, s), 2.31 (4 H, d, *J* = 6.10 Hz), 1.57 (4 H, m), 1.30 (4 H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.80, 172.01, 166.59, 140.14, 130.50, 129.62, 124.01, 123.90, 119.93, 52.64, 51.63, 33.69, 28.74, 28.68, 24.77.

HRMS (ESI): *m*/*z* (M + H)$^+$ calcd for $C_{17}H_{23}NO_5$: 322.1655; found: 322.1650.

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Supporting Information

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