Recent progress in the synthesis of pyridinylboronic acids and esters

Yuxin Liu, Lawrence J. Milo, Jr., and Jack H. Lai*

Department of Biochemistry, Tufts University School of Medicine, Boston, MA 02111, USA
E-mail: Jack.lai@tufts.edu

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Abstract

Recent progress in the synthesis of (un)substituted pyridinylboronic acids and esters is reviewed. Five approaches to the synthesis of (un)substituted pyridinylboronic acids and esters are summarized: (1) halogen-metal exchange (HMe) and borylation, (2) metal-hydrogen exchange via directed *ortho*-metallation (D*o*M) followed by borylation, (3) palladium-catalyzed cross-coupling of halopyridines with tetraalkoxydiborane or dialkoxyhydroborane (4) iridium or rhodium catalyzed C-H or C-F borylation, and (5) [4+2] cycloadditions.

Keywords: Pyridine, organometal, borylation, boronylation, boronic acids, synthesis

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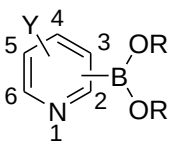
1. Introduction

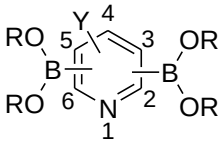
Substituted pyridines are important components of many drugs and drug candidates. In recent years, the wide application of Suzuki-type cross-coupling reactions[1] has led to a rapid growth in the synthesis of heterocyclic boronic acids and esters and a concomitant rise in their use, utility, and flexibility in organic synthesis. An important sub-class of these heterocylic boronic acids and esters include pyridinylboronic acids and esters that are suitable for use in combinatorial approaches to drug design and discovery.[2]

Most pyridinylboronic acids and esters contain only one boronic acid substituent on the pyridine ring (general structure represented as **1**). 6-Pyridinylboronic acids are herein treated as 2-pyridinylboronic acids, and pyridinyl-5-boronic acids are treated as pyridinyl-3-boronic acids for the corresponding nitrogen-boron positions. Compounds bearing multiple boronic acids and esters on a pyridine ring have been observed in very limited cases, and only as 2,4-, 2,5- 2,6-, and 3,5-disubstituted pyridinylboronic acids and esters (general structure represented as **2**).[3,4]



1

R = H,alkyl
Y = H,Functional Group(s)



2

R = H,alkyl
Y = H,Functional Group(s)

Except for cases of very limited scope, such as 5- or 6-halo- (Br or Cl) and some 3-alkoxy substituted pyridinyl-2-boronic acids (**1**, R = H, boron at 2-position),[5,6] most (un)substituted 2-pyridinylboronic acids are not stable due to protodeboronation.[3-7] 2-Pyridinylboronic esters exhibit much greater stability than the corresponding acids. In addition, several air- and water-stable 2-pyridinylboronic esters have been developed and will be discussed later.

Generally, 3-pyridinylboronic acids and esters (**1**, boron at 3-position) and 4-pyridinylboronic acids and esters (**1**, boron at 4-position) show good stability. 5-Pyridineboronic acids are simply treated as 3-pyridinylboronic acids herein.

In 2003, Tyrrell and Brookes published a review on the synthesis of heterocyclic boronic acids, which included that of pyridinylboronic acids and esters.[8] However, up until that time there had been only limited progress on the synthesis of pyridinylboronic acids and esters, and especially of 2-pyridinylboronic acids and esters. Since then, many articles have been published that report improved reactivity and selectivity of (un)substituted pyridinylboronic acids and esters, or improved stability of 2-pyridinylboronic acids and esters. Also, new approaches have been developed for the synthesis of (un)substituted pyridinylboronic acids and esters, which include transition metal-catalyzed C-H/C-F bond activation[9,10] and [4+2] cycloaddition chemistry.[11]

Because of the importance of pyridines in organic synthesis, our aim here is to summarize these advances and to provide an up-to-date review on the synthesis of pyridinylboronic acids and esters based on the recent literature.

2. The synthesis of pyridinylboronic acids and esters

Thus far, there are five methods used in the synthesis of pyridinylboronic acids and esters: (1) the metal-halogen exchange of the corresponding pyridinyl halides followed by borylation using trialkylborates, (2) the metal-hydrogen exchange of the corresponding substituted pyridine under directed *ortho*-metallation (D*o*M) followed by borylation using trialkylborates, (3) palladium-catalyzed cross coupling of halopyridines with tetraalkoxydiboron or dialkoxyhydroborane, (4) iridium- or rhodium-catalyzed C-H or C-F bond activation followed by borylation, and (5) [4+2] cycloaddition.

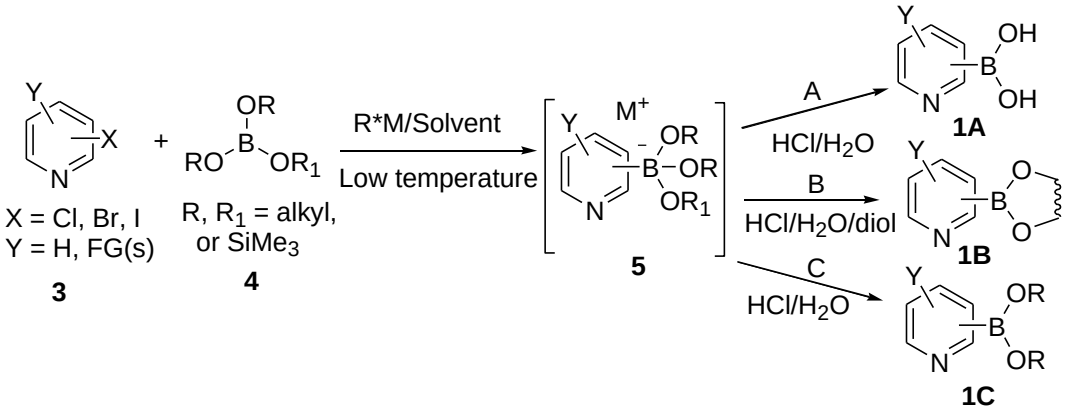
2.1. The synthesis of pyridinylboronic acids and esters by halogen-metal (Li, Mg or Sn) exchange / borylation

The halogen–metal exchange, followed by borylation, is the most fundamental method for the preparation of pyridinylboronic acids and esters, and still remains the least expensive and most reliable large-scale preparation method.

2.1.1. The general procedure of halogen-metal (Li or Mg) exchange/borylation. The general procedure for halogen-metal (Li or Mg) exchange/borylation of the corresponding pyridinyl halides (**3**) is shown in (Scheme 1).

Trimethyl borate $B(OMe)_3$ (**4a**, R = R_1 = Me),[8] triisopropyl borate $B(Oi\text{-}Pr)_3$ (**4b**, R = R_1 = ^{i}Pr),[8] tributyl borate $B(OBu)_3$ (**4c**, R = R_1 = n-Bu)[8,12] and tris(trimethylsilyl) borate $B(OSiMe_3)_3$ (**4d**, R = R_1 = $SiMe_3$)[13] are the most commonly used starting non-cyclic trialkylborates, while the most commonly used cyclic borates are MeO-Bpin (**4e**),[14] ^{i}PrO-Bpin (**4f**),[15] and MPB-O^{i}Pr (**4g**).[16] Under some circumstances, **5** was obtained as a stable intermediate and used directly for Suzuki coupling,[17] but it was generally transformed into a stable pyridinylboronic acid or ester via path **A**, **B**, or **C** prior to use in the coupling reaction. For example, most 3-pyridinylboronic

acids and 4-pyridinylboronic acids are stable and can be obtained by quenching the reaction mixture with aqueous acid or base (path **A** in Scheme 1, via **4a-d,** R = R_1).[8] Stable cyclic pyridinylboronic esters (**1B**) can also be obtained from intermediate **5** by a "one-pot" procedure with the addition of an alkanediol (such as pinacol), or an alkanediol derivatives (path **B** *via* **4a-d,** R = R_1);[8] When a cyclic borate (**4e-g**) is used, the cyclic pyridinylboronic ester (**1C**) is obtained as described by path **C** after quenching the reaction mixture with aqueous acid or base.[14-16]



Scheme 1. The general procedure for halogen-metal exchange (HMe) and borylation for the synthesis of pyridinylboronic acids and esters, FG(s) = Functional Group(s).

There are two general protocols employed that use the metal-halogen exchange, both of which typically use either an organolithium (RLi) or an organomagnesium halide (RMgX). The usual procedure often refers to the procedure where the addition of the organometal to the halopyridine occurs first and is followed by the addition of the trialkyl borate. The revised protocol often employs the *in situ* quench procedure, wherein the organometal is added to a cooled mixture of the halopyridine and trialkyl borate. The latter generally gives much better results when the halopyridine bears functional groups, such as esters and nitriles, that are incompatible with organometallic reagents.[18] The organometal, solvent, and temperature also have a large effect on the borylation: different results were obtained using 3-bromopyridine under varying conditions.[19]

2.1.2. The selectivity of halogen-metal (Li or Mg) exchange / borylation. Generally, mono-substituted halogenopyridines, iodopyridine and bromopyridine easily underwent metal-halogen exchange and gave better yields of pyridinylboronic acids and esters even when no other functional group(s) were present (**3**, Y = H; X = Br or I).[12,18-23] With simple chloropyridines and fluoropyridines (**3**, Y = H; X = F or Cl) it was generally difficult to affect the metal-halogen exchange transformation.

In cases where the pyridine ring bears two or more halogen atoms, generally only one halogen is selectively exchanged and boronylated, even in the case of 3,5-dibromopyridine with **4b**[24] and 3,5-diiodopyridine with **4e**.[14] The selectivity depends upon the halogens and their

positions in the pyridine ring. Systematic studies by Rault *et al*.[5,23-28] and Bryce *et al*.[29-32] resulted in the preparation of shelf-stable halopyridinylboronic acids and esters. 3- and 4-Halopyridines bearing other functional groups such as 6´-methoxy,[22,31] 6´-ethoxy[29] and 6´-trifluoromethyl[32] also undergo such transformations with yields typically between 60 and 90%. The early results relating to 3- and 4-pyridinylboronic acids and esters were partly reviewed by Tyrrell *et al*.[8] and also briefly summarized by Snieckus *et al*.[33]

2.1.3. The synthesis of 2-pyridinylboronic acids and esters by halogen-metal (Li or Mg) exchange / borylation. 2-Pyridinylboronic acids and esters using halogen-metal exchange (HMe) are generally synthesized from 2-bromopyridines (**3**, X = 2-Br).[5,6,13,17,34-42] In the particular case of compound **3** (X = 2-I), 2-iodopyridine was used.[16] To improve the stability (particularly in air and water), pyridine-2-boronates such as **6**,[34] **7**,[35,36] and **8**[37,38] were developed.

Table 1. The synthesis of 2-pyridinylboronic acids via halogen-metal exchange (H-Me) followed by borylation according to Scheme 1

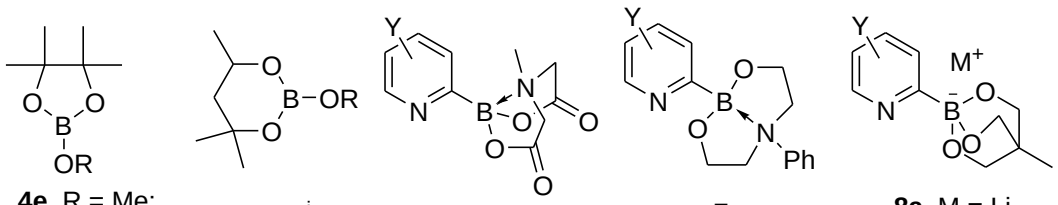
Entry	X	Y	Borate	R*M	Solvent / temperature (ºC)	Path	Product	Yield (%)	Ref.
1	2-Br	H	**4a**	*n*-BuLi	Et_2O/-78	-[a]	**5**, R=R_1=Me	100	39,40
2	2-Br	H	**4b**	*n*-BuLi	toluene:THF[b] /-78	-[a]	**5**, R=R_1=^{i}Pr	99	17
3	2-Br	H	**4b**	*n*-BuLi	THF/-78	B	**6**	59	34,41
4	2-Br	H	**4b**	*n*-BuLi	THF/-78	B	**7**	75-81	35,36
5	2-Br	H	**4b**	*n*-BuLi	THF/-78	B	**8a**	82-86	37,38, 42
6	2-Br	H	**4d**	*i*-PrMgCl	THF/rt→0	A	**1A**	70	13
7	2-Br	6-Br	**4b**	*n*-BuLi	THF/-78	A/B	**1A**/**1B**(Pin)[d]	56/55[e]	5
8	2-Br	6-Cl	**4b**	*n*-BuLi	THF/-78	A/B	**1A**/**1B**(Pin)[d]	38/45[e]	5
9	2-Br	5-Cl	**4b**	*n*-BuLi	THF/-78	A/B	**1A**/**1B**(Pin)[d]	47/36[e]	5
10	2-Br	3-OR′[c]	**4b**	*n*-BuLi	THF/-78	A	**1B**	70-75	6
11	2-Br	5-Me	**4b**	*n*-BuLi	THF/-78	B	**7**	52	36
12	2-Br	6-OMe	**4b**	*n*-BuLi	THF/-78	B	**7**	44	36
13	2-Br	6-OMe	**4b**	*n*-BuLi	toluene:THF[b] /-78	-[a]	**5**, R=R_1=^{i}Pr	90	17
14	2-Br	5-F	**4b**	*n*-BuLi	toluene:THF[b] /-78	-[a]	**5**, R=R_1=^{i}Pr	96	17
15	2-Br	5-CN	**4b**	*n*-BuLi	toluene:THF[b] /-78	-[a]	**5**, R=R_1=^{i}Pr	99	17

Table 1. Continued

Entry	X	Y	Borate	*R*M*	Solvent / temperature (°C)	Path	Product	Yield (%)	Ref.
16	2-Br	6-Me	**4b**	*n*-BuLi	THF/-78	B	**6**	58	34
17	2-Br	5-Me	**4b**	*n*-BuLi	THF/-78	B	**6**	51	34
18	2-Br	4-Me	**4b**	*n*-BuLi	THF/-78	B	**6**	42	34
19	2-Br	6-OMe	**4b**	*n*-BuLi	THF/-78	B	**6**	81	34
20	2-Br	6-CF_3	**4b**	*n*-BuLi	THF/-78	B	**6**	89	34
21	2-Br	5-CF_3	**4b**	*n*-BuLi	THF/-78	B	**6**	56	34
22	2-Br	4-CF_3	**4b**	*n*-BuLi	THF/-78	B	**6**	53	34
23	2-Br	6-Br	**4b**	*n*-BuLi	THF/-78	B	**6**	69	34
24	2-Br	5-Br	**4b**	*n*-BuLi	THF/-78	B	**6**	69	34
25	2-I	6-Br	**4g**	*i*-PrMgCl[f]	THF/0	C	**1C**[g]	92	16

[a] The intermediate was obtained and used directly. [b] Toluene:THF ratio 4:1 v/v.
[c] R′ = $(CH_2)_{n-1}CH_3$; n = 6,8,10,12,18.
[d] Pyridinylboronic acids (**1A**) were obtained via path A, the pinacol boronate esters (**1B**(Pin)) obtained via path B.
[e] The yields refer to the corresponding product **1A** and **1B**(Pin). [f] +LiCl.
[g] 2-bromo-6-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)pyridine was obtained.

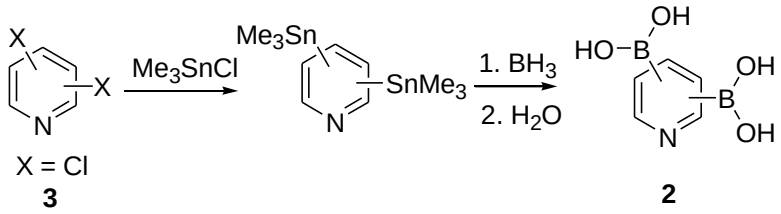
A summary of the results regarding the synthesis of these 2-pyridinylboronic acids and esters is given in (Table 1).



4e, R = Me; **4f**, R = ^{i}Pr — **4g**, R = ^{i}Pr — **6** — **7** — **8a**, M = Li; **8b**, M = K

2.1.4. The synthesis of pyridinediboronic acids via halogen-organotin (Sn) exchange of the corresponding pyridinyl halides and borylation. Though not widely applied, the organotin and halogen exchange followed by BH_3 borylation and hydrolysis is an alternative approach for the synthesis of pyridinylboronic acids and esters. Unlike the halogen-metal (Li or Mg) exchange which was followed by borate, the organotin-halogen exchange was followed by reaction with

borane and subsequent hydrolysis. The organotin method provides a successful approach to the synthesis of pyridinediboronic acids and esters (Scheme 2).[3]

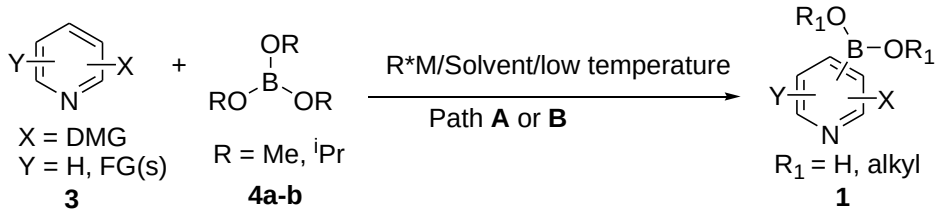


Scheme 2. The synthesis of pyridinediboronic acids via organotin pyridine.

2.2. The synthesis of pyridinylboronic acids and esters by directed *ortho*-metalation(D*o*M) and boronylation

Directed *ortho*-metalation (D*o*M)[43-45] followed by borylation with trialkylborate provides another approach for the synthesis of pyridinylboronic acids and esters bearing Directed Metalation Groups (DMGs).

2.2.1. The general procedure of directed *ortho*-metalation (D*o*M) and borylation. The general procedure of Directed *ortho*-Metalation (D*o*M) and borylation method is shown in (Scheme 3).



Scheme 3. The Directed *ortho*-Metalation (D*o*M) and borylation of substituted pyridine, FG(s) = functional group(s), DMG = directed metalation groups.

Table 2. A summary of the reported results for the synthesis of pyridinylboronic acids and esters via directed *ortho*-metalation (D*o*M)/borylation from substituted pyridine (Scheme 3)

Entry [a]	X	Y	Borate	R*M	Path	Yield (%)	Ref.
1[b]	2-F	H	**4b**	LDA	A	63	24
2	2-Cl	H	**4b**	LDA	A	65	24
3	2-Br	H	**4b**	LDA	A	45	24
4	4-Cl	H	**4b**	LDA	A	43	24
5	2-CN	H	**4b**	LiTMP	A	65~70	46-48
6	2-OMe	H	**4b**	LDA	A	58	31
7	2-OEt	H	**4b**	LDA	A	70	49
8	2-Cl	5-CF_3	**4b**	LDA	A	25	32

Table 2. Continued

Entry [a]	X	Y	Borate	R*M	Path	Yield (%)	Ref.
9	2-F	6-F	**4b**	LDA	A	70	50
10	2-Cl	6-Cl	**4b**	LDA	A	73	50
11	2-OMe	6-OMe	**4b**	LDA	A	70	50
12	2-$CONEt_2$	H	**4b**	LDA	A	20	33
13	4-$CONEt_2$	H	**4b**	LDA	A	20	33
14 [c]	3-F	H	**4b**	LDA	A/B [d]	46/55 [e]	25,33
15	3-Cl	H	**4b**	LDA	A/B [d]	38/51 [e]	25
16	3-Br	H	**4b**	LDA	A/B [d]	32/48 [e]	25
17	3-CN	H	**4b**	LiTMP	A	42	46-48
18	3-Cl	2-Cl	**4b**	LDA	A	56	50
19	3-OMe	2-OMe	**4b**	n-BuLi	A	60	50
20	3-CN	2-Cl	**4b**	LiTMP	A	53	46
21	3-CF_3	6-Cl	**4b**	LDA	A	25	32
22	3-Cl	6-OMe	**4b**	LDA	A	48	30
23	3-Br	6-OEt	**4b**	LDA	A	23	29
24	3-$CONEt_2$	H	**4b**	LDA	A	60	33
25	3-$CH_2SO_2NEt_2$	H	**4b**	LDA	A	40	33
26	3-CH_2NHBoc	H	**4a**	n-BuLi	A	66	51
27	3-$OCONEt_2$	H	**4b**	LDA or t-BuLi	A	61,65	33,52,53

[a.] All metalations were carried out in THF, and at -78 ºC, except for Entry 7 (-50 ºC). [b] The products for Entries 1-13 are 3- pyridinylboronic acids (R_1 = H) using path A. [c] The products for Entries 14-27 are 4- pyridinylboronic acids or esters. [d] Both Paths A and B were used. 4- pyridinylboronic acids (R_1= H) were obtained using path A, pinacol esters were obtained using Path B.

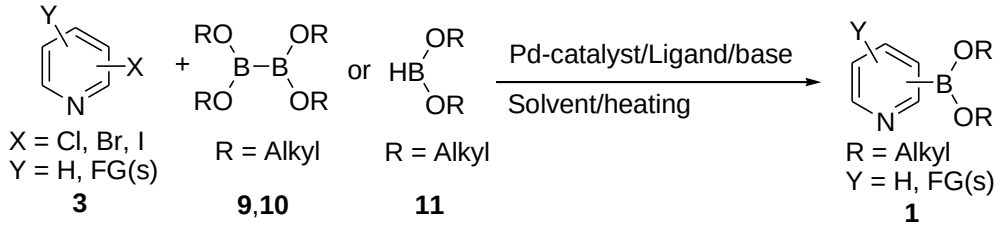
Pyridinylboronic acids were obtained by quenching the reaction mixture with aqueous acid or base (path **A**), [24] while pyridinylboronic esters (generally the pinacol ester) were obtained by a "one-pot" procedure by the addition of an alkyldiol (e.g. pinacol) to the reaction mixture (path **B**).[25]

2.2.2. The selectivity of directed *ortho*-metalation (D*o*M) and borylation. Halo-, alkoxy-, amide- and cyano- groups are commonly observed as Directed *ortho*-Metalation Groups

(DMGs).[24-33] *2*-DMG or *4*-DMG substituted pyridines lead to the formation of 3- (or 5-) pyridinylboronic acids and esters, *6*-DMG was simply treated as *2*-DMG herein. *3*-DMG or *5*-DMG substituted pyridines lead only to the formation of 4-pyridinylboronic acids and esters. 2-Pyridinylboronic acids and esters were not obtained using this methodology. A summary of the results using this method is given in Table 2.

2.3. Synthesis of pyridinylboronic acids and esters by palladium-catalyzed cross-coupling of halopyridines with tetraalkoxydiboron or dialkoxyhydroborane

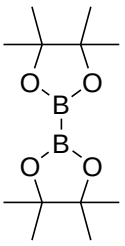
The Suzuki-type cross-coupling method is widely used for the preparation of the majority of pyridinylboronic esters. It has a broad substrate scope and good tolerance for most functional groups. The general procedure is shown in (Scheme 4).



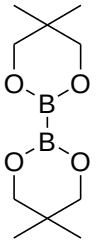
Scheme 4. The general procedure of Pd-catalyzed Suzuki-coupling of halopyridines with tetraalkoxydiboron or dialkoxyhydroborane, FG(s) = Functional Group(s).

Bromopyridines (**3**, X = Br), iodopyridines (**3**, X = I) and chloropyridines (**3**, X = Cl) can all be used as suitable substrates. The most commonly used tetraalkoxydiboron was bis(pinacolato)diboron (B_2Pin_2, **9**).[54-62] Other tetraalkoxydiboron compounds such as (neopentyl-glycolato)diboron (**10**) were also reported.[63] Dialkoxyhydroborane compounds like (pinacolato)-hydroborane (HBPin, **11**) are occasionally reported as well.[64] The Pd-catalyst and ligands play critical roles in the cross-coupling reaction, especially for chloropyridines.[56] Compound **12** was found to be an effective ligand for the transformation of chloropyridines, where it can be used either directly as the ligand in the cross-coupling reaction,[56] or in preparation of the catalyst (e.g. **13,** where L = **12**).[57]

KOAc is generally used as the base, as stronger bases (e.g. K_3PO_4 and K_2CO_3) may lead to side reactions such as homo-coupling.[56,57] Dioxane, DMSO, and DMF are usually employed as solvents, and the duration and temperature of the reactions are variable.[57] A summary of the literature results is presented in Table 3.



9, B_2Pin_2



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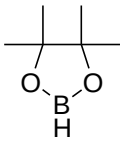
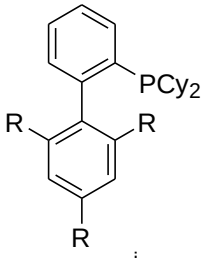


11, HBpin



12, R = ^{i}Pr

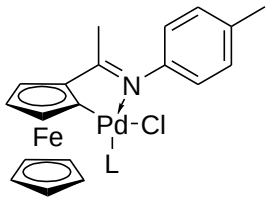


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Table 3. A summary of (un)substituted pyridinylboronic acids and esters prepared from pyridinyl halides via a Pd-catalysed cross-coupling reaction (Scheme 4)

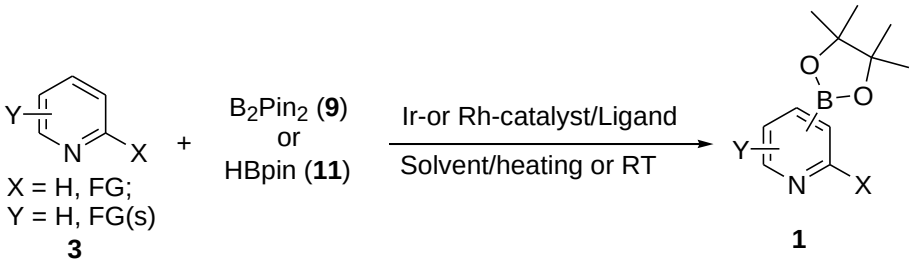
Entry	X	Y	Boron species	Pd catalyst / ligand	Base / solvent / temperature (ºC) / time	Yield (%)	Ref.
1	3-Br	H	**9**	$PdCl_2$(dppf)	KOAc/DMF/130/2 h	99	54
2	3-Cl	H	**9**	$Pd(dba)_2Pcy_3$	KOAc/dioxane/80/48 h	82	55
3	3-Cl	H	**9**	$Pd_2(dba)_3$ /**12**	KOAc/dioxane/110/5 h	82	56
4	4-Cl	2-OMe	**9**	**13**, L = **12**	KOAc/dioxane/80/6 h	77	57
5	4-Cl	2-CN	**9**	**13**, L = **12**	KOAc/dioxane/80/6 h	75	57
6	4-Br	2-NMe_2	**9**	**13**, L = PCy_3	KOAc/dioxane/80/3 h	74	57
7	4-Br	2-OMe	**9**	**13**, L = PCy_3	KOAc/dioxane/80/3 h	91	57
8	3-Br	6-CN	**9**	$PdCl_2$(dppf)	KOAc/DMSO/80/25 h	64	58
9	3-Br	6-(2′-Py)	**9**	$PdCl_2$(dppf)	KOAc/DMSO/105/12 h	74	59
10	3-Br	5-CO_2Et	**9**	$PdCl_2(dba)_3/PCy_3$	KOAc/DMF/80/18 h	30	60
11	4-I	2,6-di(CO_2Me)	**9**	$PdCl_2$(dppf)	KOAc/DMSO/105/16 h	45	61
12	4-I	2-OMe,3-NHCbz	**9**	$PdCl_2(PPh_3)_2$	KOAc/dioxane/105/24 h	77	62
13	3-Br	6-CN	**10**	$PdCl_2$(dppf)	KOAc/DMSO/80/48 h	36	63
14	3-Br	6-OCH_2Ar	**11**	$PdCl_2(PPh_3)_2$	Et_3N/dioxane/100/16 h	78	64

2.4. The synthesis of pyridinylboronic acids and esters by Iridium- or rhodium- catalyzed C-H bond and C-F bond borylation

Iridium- or rhodium-catalyzed borylation of arenes via C-H activation was introduced by Smith[65] and Miyaura[66], and has been summarized by Miyaura and Hartwig et al.[9]

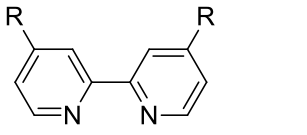
2.4.1. The general procedure of iridium- or rhodium-catalyzed C-H bond borylation. Iridium- or rhodium-catalyzed borylation of pyridine or substituted pyridines via C-H activation is one of the most promising methods for the preparation of pyridinylboronic acids because of its high atom efficiency and because it can be conducted under mild reaction conditions compared

with traditional halogen-metal exchange reactions. This method is generally applied to the synthesis of pyridinylboronic acid pinacol esters. The general procedure is shown in Scheme 5 where X represents H or a functional group at the *2'*- position.

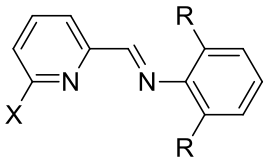


Scheme 5. The general procedure of iridium- or rhodium-catalyzed borylation of pyridines FG(s) = Fuctional Group(s).

Ligands play important roles in the yield and regioselectivity of iridium- and rhodium-catalyzed C-H bond borylation reactions. Two main types of ligand are reported in the literature for the synthesis of pyridinylboronic acids esters: bipyridine compounds (**14a-d**) and pyridinylimine compounds (**15a, b**).[67-75]



14a, R = H; **14b**, R = tBu;
14c, R = COOH; 1**4d**, R = OMe



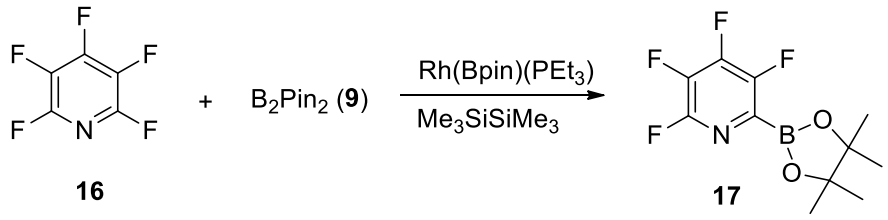
15a, X = H, R = ^{i}Pr ;
15b, X = Me, R = ^{i}Pr

2.4.2. The regioselectivity of the iridium- or rhodium- catalyzed C-H bond borylation. The regioselectivity of the borylation of **3** was also studied. In general, the 2,6-disubstituted pyridine gave only 4-pyridinylboronic esters, while pyridine or monosubstituted pyridines gave a mixture of 3- and 4-pyridinylboronic esters.[73-75] The borylation selectivity with ligands **14b** and **14d** were observed to be different: borylation occurred in the position adjacent to the nitrogen atom in **14b** (R = *t*Bu), but occurred at the 5-position (i.e. *ortho* to the methoxy groups) in **14d** (R = OMe).[73]

A summary of the results of Ir-catalyzed C-H borylation described in the literature is provided in Table 4.

2.4. The rhodium- catalyzed C-F bond activation of perfluoropyridine and borylation

Perfluoropyridine (**16**) was found to be capable of undergoing Rh-catalyzed C-F bond borylation to give 3,4,5,6-tetrafluoropyridine-2-boronic acid pinacol ester (**17**) in 45% yield.[10] (Scheme 6).



Scheme 6. Rhodium catalyzed C-F activation of perfluoropyridine and borylation.

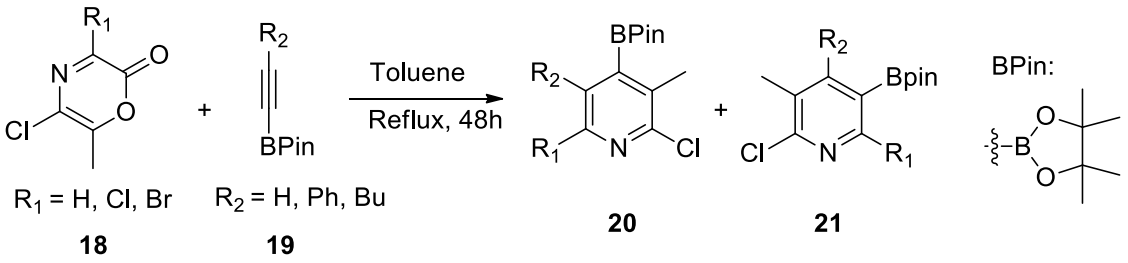
Table 4. Iridium- or rhodium-catalysed C-H borylation of (un)substituted pyridines (Scheme 5)

Entry	X	Y	Boron species	Catalyst / ligand	Solvent / temperature (ºC) / time	Yield (%)	Ref.
1	Cl	6-Cl	**11**	(Ind)Ir(COD)/dppe	cyclohexane/100/4 h	69	67
2	Cl	6-Cl	**9**	½[IrCl(COD)]$_2$/**15a**	octane/80/12 h	73	68
3	Cl	6-Cl	**9**	½[IrCl(COD)]$_2$/**15b**	octane/80/12 h	71	68
4	Cl	6-Cl	**11**	½[IrCl(COD)]$_2$/**15a**	octane/80/12 h	93	68
5	Cl	6-Cl	**11**	½[IrCl(COD)]$_2$/**15b**	octane/80/12 h	90	68
6	Cl	6-Cl	**9**	[(COD)Ir(μ-OMe)$_2$/**14b**	MBTE/80/3min(μw)	98	69
7	Cl	6-Cl	**9**	[(COD)Ir(μ-OMe)$_2$/**14b**	MBTE/80/20min	96	69
8	Cl	6-Cl	**9**	BPDCA-cat [a]	methylcyclohexane/80/ 12 h	77	70
9	Me	6-Me	**11**	η^5(C$_5$Me$_5$)Rh(η^4-C$_6$Me$_6$)	-[b]/150/6 h	41	71
10	Cl	6-Me	**9**	½[Ir(OMe)(COD)]$_2$ /**14b**	hexane/25/4 h	84	72
11	Cl	6-Me	**11**	½[Ir(OMe)(COD)]$_2$ /**14b**	hexane/25/2 h	75	72
12	Ph	H	**9**	[(COD)Ir(μ-OMe)$_2$/**14b**	hexane/25/16 h	-[c]	73
13	CN	5-Br	**11**	[(COD)Ir(μ-OMe)$_2$/**14b**	THF/25/18 h	81[d]	74
14	H	H	**9**	½[IrCl(COD)]$_2$/**14b**	octane/100/16 h	42[e,f]	75

[a] Prepared from ½[IrCl(COD)$_2$]/**14c**/B$_2$Pin$_2$(**9**)/benzene/80 ºC/4 h, [b] No solvent.
[c] Crude product, a 1 : 1 mixture of 2-Ph-4-(Bpin)- and 2-Ph-5-(Bpin)-pyridine.
[d] A 2:1 mixture of 5-Br-3-(Bpin)- and 5-Br-4-(Bpin)-pyridine-2-carbonitrile.
[e] A 2:1 mixture of 3-(Bpin)- and 4-(Bpin)-pyridine, [f] Diborylated products were also formed (12-17%).

2.5. The synthesis of pyridinylboronic acids and esters by [4+2] cycloaddition

An alternative strategy to the synthesis of functionalized pyridinylboronic esters employs a [4+2] Diels-Alder-like cycloaddition with an alkynylboronate (**19**). Typical overall yields using this method were found to be between 62 and 88%. The regioselectivity varied from 20:1 to 1:2 for **20** / **21**, depending on the substituents, R_1 and R_2, on the diene and dienophile. This strategy allows for a diverse range of intermediates to be generated in good yield.[11]



Scheme 7. The [4+2] cycloaddition for the synthesis of substituted pyridinylboronic pinacol esters.

3. Conclusions

The methods described herein demonstrate that the preparation of pyridinylboronic acids can be achieved through diverse chemistry. This diversity provides flexibility in the functional groups present on the starting pyridines, as the limitations of one procedure may be overcome by the use of an alternative method.

We wanted to provide an up-to-date review on the synthesis of pyridinylboronic acids and esters, given the rapid rise in the use of and types of boronic acids and esters in organic synthesis and the importance of these compounds in drug design and discovery.. With the rapid development of new chemistry in recent years, new and effective approaches to the synthesis of functionalized pyridinylboronic acids and esters can be expected.

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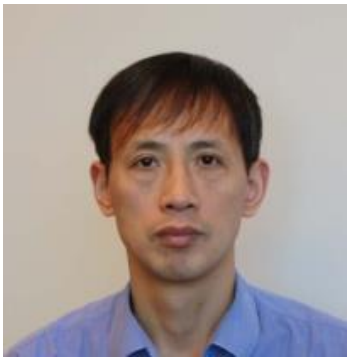
Authors' Biographies



Yuxin Liu was born in 1971 in Henan, China. He is a senior research associate in the Tufts University School of Medicine Biochemistry Department. He recived his B.Sc in 1992 from the Department of Chemistry, Zhengzhou University and subsequently got M.Sc. in 1995. He has awarded his Ph.D. degree in medicinal chemistry in 1999 from the Institute of Materia Medica, Chinese Academy of Medicinal Sciences & Peking Union Medical College. He did his postdoctoral work at Shanghai Institute of Organic Chemistry, Chines Academy of Sciences. His research interests are the synthesis and structure investigation of *N*-heterocycles and boronic acids compounds, and the design and synthesis of small molecular drugs.

Lawrence J. Milo, Jr. is a post-doctoral researcher in the Biochemistry Department at Tufts University School of Medicine and an analytical chemist at NITTO DENKO Avecia, Inc. Dr. Milo obtained his B.S. degree in molecular genetics from the University of Rochester in 2002 and completed a senior research thesis under the advisership of Howard Federoff and William Bowers. In 2010, Dr. Milo received his Ph.D. in biochemistry from Tufts University School of Medicine under William Bachovchin. In his doctoral work, he designed, synthesized, and tested peptidylboronic acid-based pro- and pro-soft inhibitors for serine and serine-like proteases. Through this work he evaluated their efficacy *in vitro* and in cell-based assays, and studied biologically relevant chemical properties of these compounds by NMR, through enzymatic assay, and through chemical kinetic and theromodynamic analysis. As a post-doctoral researcher, Dr. Milo continues to pursue his research interests in drug design, medicinal chemistry, and understanding mechanisms of drug action.

Jack H. Lai is a faculty member at Tufts University School of Medicine, serving as a research Assistant Professor of the Biochemistry Department. Dr. Lai obtained his BS degree in Biology from Tunghai University in Taiwan. Dr. Lai obtained his Master's Degree in Oncology (Niagara University and Rosswell Park Cancer Institute in 1994) and Ph.D. in Medicinal Chemistry from the State University of New York at Buffalo in 1996. He finished his postdoctoral training in the Department of Cell Biology at Harvard Medical School in 1997. His research interests include computer-aided rational drug design of small molecule-based peptide mimetics technology. By leveraging his proprietary web-based laboratory information tracking system (Calentrack™), Dr. Lai has successfully implemented an aggressive expansion of compound collection for drug development.

