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Lithium trihydroxy/triisopropoxy-2-pyridylborate salts (LTBS): synthesis, isolation, and use in modified Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

We describe herein shelf-stable, isolable, and characterizable pyridyl lithium trihydroxy and triisopropoxy 2-borate salts (LTBS) for use in modified Suzuki–Miyaura cross-coupling reactions that can be produced in quantities greater than one hundred grams. Pyridyl LTBS provide a viable cross-coupling alternative to unstable 2-pyridylboronic acids, boronates, and trifluoroborate salt derivatives. We also demonstrate the synthesis and cross-coupling of shelf-stable LTBS reagents of other sp^2-hybridized nitrogen-containing heterocycles including thiazole, pyrazine, quinoline, and isoquinoline heterocycles.

Introduction

Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions have become invaluable methods for constructing carbon-carbon bonds due to their efficiency, environmentally benign byproducts, and the wide range of functional groups compatible with the reaction conditions.[1,2] Highlighting the significance of the approach is the awarding of the 2010 Nobel Prize in Chemistry to Heck, Negishi, and Suzuki 'for palladium-catalyzed cross couplings in organic synthesis'. Many boronic acids, boronates, and potassium trifluoroborate salts have been developed to accommodate the fast growing demand for the construction of C–C, C–N, and C–O bonds. Pyridines and other sp^2-hybridized nitrogen-containing heterocycles are unique in that the substitution of boronic acids on carbons at positions adjacent to the nitrogen is inherently unstable. Therefore, the incorporation of a boronic acid functionality at this position is not trivial. Two recent reviews have addressed this issue and surveyed a broad range of alternatives.[3,4] There are numerous reports of boronic acid substituents at positions 3, 4, and 5 of the pyridine ring. However, few reports of the isolation, purification, and characterization of boronic acids at the pyridyl 2-position exist. Exceptions include halo-2-pyridinylboronic acids and their esters,[5] azaheteroarylboronic acids,[6] and *N*-methyliminodiacetic acid (MIDA)-protected boronate esters.[7,8] A limited number of reports can be found in which lithium triisopropoxyborate salts were generated in situ and immediately used for coupling[10,18] or for conversions into pinacol[5] and MIDA[8] boronates. A single report by Billingsley and Buchwald details the coupling of a limited number of triisopropoxyborates in high yields using sealed Schlenk tubes equipped with Teflon screw valves.[9] There is a single report for the synthesis of unsubstituted 2-pyridylborate,[11] while in 1957, Mikhailov and Kozminskaya reported the synthesis of lithium triisobutoxy-2-pyridylborate and its subsequent conversion into lithium trihydroxy-2-pyridylborate.[12] The synthesis of aryl trihydroxyborates has been previously published, but no heteroaryl analogs were included.[13] Herein, we expand upon the earlier work of Billingsley and Buchwald by elaborating on the scaffolds. We report the large-scale synthesis (grams to >100 g) of pyridyl LTBS and additional LTBS heterocycles that were demonstrated as coupling partners for aryl bromides under ambient pressure. The work presented represents an approach that is more broadly applicable, albeit at a modest decrease in yield. Further optimization of these preliminary coupling conditions is expected to provide higher yielding procedures.

Results and discussion

To address the unmet need for the availability of stable 2-pyridylborates, we report the scalable synthesis of LTBS versions of pyridine and other sp^2-hybridized nitrogen heterocycles and describe broadly the applicable coupling conditions for performing

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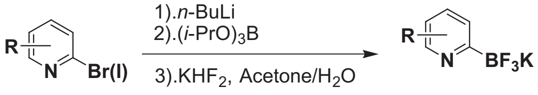
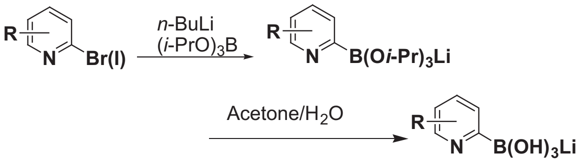


Scheme 1. Synthesis of potassium 2-pyridyltrifluoroborates.



Scheme 2. General scheme for LTBS synthesis.

Suzuki–Miyaura cross-coupling reactions under N_2 at ambient pressure.

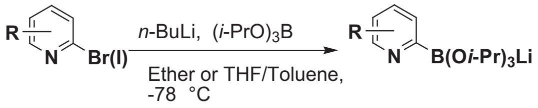
Initial efforts on multi-gram scales (17–285 g) to produce 2-pyridyltrifluoroborate salts using the method outlined in Scheme 1 were unsuccessful. The desired products were obtained in ~15% yields and were not reproducible in several experiments.

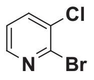
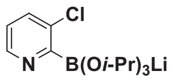
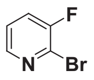
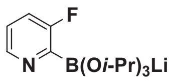
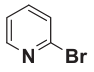
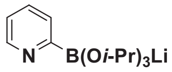
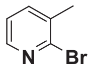
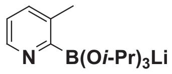
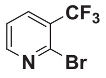
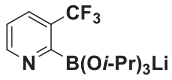
Using the general conditions outlined in Scheme 2, 24 LTBS were produced in moderate to high yields with high purity (>95 % by ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR (where applicable); see Experimental Section).

Synthesis of lithium 2-pyridyl triisopropoxyborate salts

The triisopropoxyborates that were synthesized are shown in Table 1 along with yields from the corresponding halides.

Table 1
Synthesis of triisopropoxy LTBS from the corresponding halides

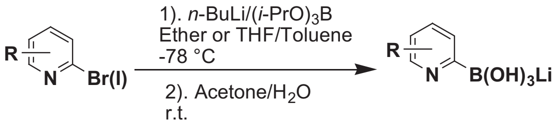


Entry	Starting halide	LTBS	Yield (%)
1		 **1**	53
2		 **2**	55
3		 **3**	74
4		 **4**	81
5		 **5**	33

Synthesis of lithium 2-pyridyl trihydroxyborate salts

Trihydroxyborates were generated from the corresponding triisopropoxyborate by treating with water (Table 2). For some 2-pyridyl borates, protodeboronation occurs during the hydrolysis, requiring they remain in the triisopropoxy form. In particular, this

Table 2
Synthesis of trihydroxy LTBS from the corresponding halides



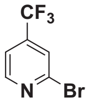
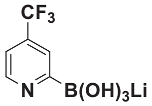
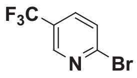
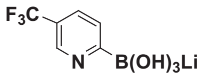
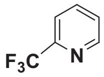
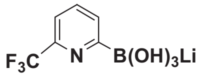
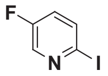
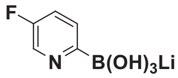
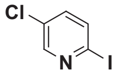
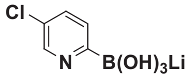
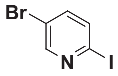
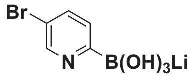
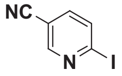
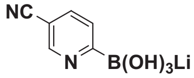
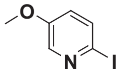
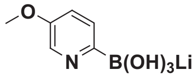
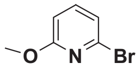
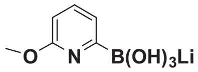
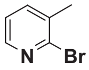
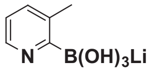
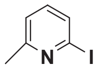
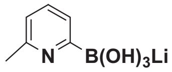
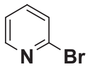
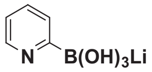
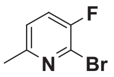
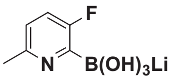
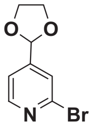
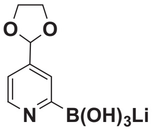
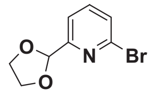
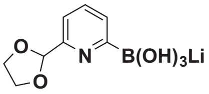
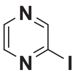
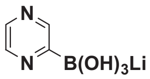
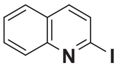
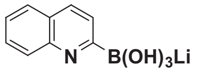
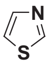
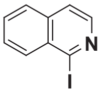
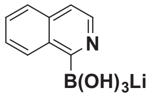
Entry	Starting halide	LTBS	Yield (%)
6		 **6**	47
7		 **7**	46
8		 **8**	35[a]
9		 **9**	64
10		 **10**	37
11		 **11**	53
12		 **12**	42
13		 **13**	75
14		 **14**	89
15		 **15**	45
16		 **16**	95
17		 **17**	76

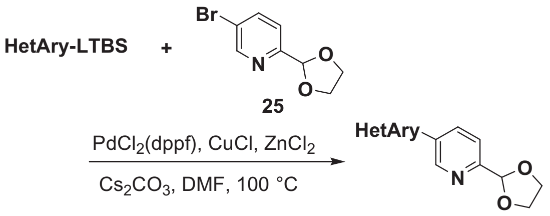
Table 2 (*continued*)

Entry	Starting halide	LTBS	Yield (%)
18		 **18**	100
19		 **19**	54
20		 **20**	85

[a] Lithiation was accomplished by de-protonation with LTMP.

Table 3
Other heterocyclic LTBS synthesized

Entry	Starting halide	LTBS	Yield (%)
21		 **21**	54
22		 **22**	48
23		 **23**	71
24		 **24**	52



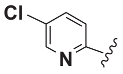
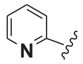
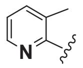
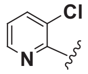
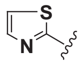
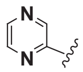
Scheme 3. Reaction conditions for enhanced coupling reactions.

was commonly observed for pyridyl LTBS that have a functional group at the 3-position, with exceptions being lithium (3-methylpyridin-2-yl)triisopropoxyborate, **4**, as well as the unsubstituted lithium (pyridin-2-yl)triisopropoxyborate, **3** (Table 1).

Synthesis of non-pyridine sp^2-hybridized nitrogen containing heterocyclic LTBS

In addition to 2-pyridylborates, LTBS of other heterocycles with borates on carbons alpha to sp^2-nitrogens were prepared: pyrazine, quinoline, thiazole, and isoquinoline (Table 3). This should be also applicable to other remaining heterocycles containing sp^2-hybridized nitrogen atoms, such as oxazoles, imidazoles, pyrazoles, isoxazoles, triazoles, pyridazines, pyrimidines, triazines etc.

Table 4
Cross-coupling reactions for LTBS with 5-bromo-2-(1,3-dioxolan-2-yl)pyridine (**25**)[a]

Entry	LTBS	HerAry	Yield (%)
1	10	 **26**	32 (12)[b]
2	17	 **27**	27
3	4	 **28**	37
4	1	 **29**	52
5	23	 **30**	56
6	21	 **31**	17

[a] Standard conditions: LTBS (2.0 equiv), **25** (1.0 equiv), $PdCl_2(dppf)$ (0.05 equiv), CuCl (0.1 equiv), $ZnCl_2$ (1.0 equiv), Cs_2CO_3 (2 equiv), in DMF (100 mL), the mixture was heated to specified temperature and time.

[b] Yield shown in parenthesis represents the conditions without applying $ZnCl_2$.

Suzuki–Miyaura cross-coupling reactions of LTBS

The LTBS in Tables 1–3 are stable at room temperature or at refrigerator temperature under inert atmosphere for extended period of time,[19] and are suitable coupling partners with aryl halides. These 2-pyridylborates may also be useful intermediates for preparing other boronic acid surrogates, including, boronic acids,[5] glycol esters,[5] organotrifluoroborates, phenyldiethanolamine boronates,[5,15,16] cyclic-*N*-triolboronates,[14] and MIDA-boronate esters.[8]

Ultimately, in order for these reagents to serve as key building blocks for Suzuki–Miyaura cross-coupling reactions, successful use needs to be demonstrated. Typical conditions for Suzuki–Miyaura cross-coupling reactions include a palladium catalyst such as, $PdCl_2(dppf)$, $Pd(PPh_3)_4$, $Pd(OAc)_2$ etc and bases such as, Cs_2CO_3, K_2CO_3, KOAc etc to facilitate coupling to an aryl halide. Previous work reports utilizing four different 2-pyridyl triisopropoxyborates, with additional substitutions at only the 5- or 6- positions, for Suzuki–Miyaura cross-coupling reactions.[9] However**,** couplings required elevated pressure, which may limit the application to scale-up and commercialization. To address this concern, we have developed a novel coupling process that is compatible with the isolated LTBS reagents described in this paper using an ambient pressure reaction vessel. The process involves incorporation of $ZnCl_2$ as well as a catalytic amount of CuCl as shown in Scheme 3.

The coupling reactions of selected LTBS reagents and the corresponding heteroarylbromide are shown in Table 4. Most notably, adding zinc chloride and replacing the role of copper as main transmetallating reagent increased the yield by more than threefold when compared to standard Suzuki–Miyaura coupling conditions. Yield enhancement can be seen in the example of lithium 5-chloro-2-pyridylborate **10** (entry **1**) coupling with the heteroarylbromide. Here it was clearly demonstrated that using the co-catalyst CuCl with $ZnCl_2$ enhanced cross-coupling when compared to reaction conditions lacking $ZnCl_2$. The specific role of $ZnCl_2$ is currently under investigation.

In summary, the LTBS compounds reported in this work represent unique reagents that overcome the limitations of typical pyridylboronic acids, namely the instability of substituted pyridine 2-boronic acids. Furthermore, we report the isolation of stable substituted and unsubstituted borates at the α-position of sp^2-hybridized nitrogen heterocycles besides pyridine. In addition to developing new reagents for Suzuki–Miyaura cross-coupling reactions, we have identified conditions for enhancing their reactivity in Pd-catalyzed cross-coupling. Through incorporation of CuCl (catalytic quantity) and $ZnCl_2$ (stoichiometric quantity) we were able to significantly enhance the cross-coupling of LTBS in an ambient pressure reaction vessel. This finding is expected to have broad utility in a variety of additional reaction mechanisms as mentioned in a recent publication.[17] Although further optimization of the coupling conditions is still necessary,[20] this report presents the first example of successful coupling reactions using substituted 2-pyridylborates and *N*-heterocycles as starting materials in conjunction with the use of zinc chloride and copper chloride to enhance the reactivity under the irradiation of microwave.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.145.

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19. Stability seems to be general under inert atmosphere except LTBS **5** that decomposed in less than 48 h at room temperature. For example: LTBS **3** is stable up to a month.[9] LTBS **17** underwent 10% of protodeboronation after 21 months in a refrigerator (4 °C), while LTBS **4**, **10**, **13**, and **21** remain pure in the refrigerator after 22 months.
20. Since cesium carbonate (Cs_2CO_3) and zinc chloride ($ZnCl_2$) are extremely hygroscopic, the use of these flame-dried reagents may enhance the yield greatly as kindly suggested by a reviewer.