A General Method for Suzuki–Miyaura Coupling Reactions Using Lithium Triisopropyl Borates

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Abstract

Conditions for the Suzuki-Miyaura coupling of lithium triisopropyl borates are reported, as well as a procedure for a one-pot lithiation, borylation, and subsequent Suzuki-Miyaura coupling of various heterocycles with aryl halides. These borate species are much more stable towards protodeboronation than the corresponding boronic acids, and can conveniently be stored on benchtop at room temperature.

The Suzuki-Miyaura cross-coupling (SMC) reaction has become an indispensable tool for the preparation of a wide variety of organic molecules and materials.1,2 Key to the success of this reaction is the inherent compatibility of organoboron compounds with many functional groups,3 their low toxicity, and the fact that many organoboronic acids are commercially available. However, under the most commonly used SMC conditions, many organoboronic acids, especially five-membered heterocyclic boronic acids, are prone to decomposition via protodeboronation and other processes.4 To address these issues, both improved catalyst systems5 and protected or masked boronate substrates6 have been developed, allowing for the cross-coupling of inherently unstable boronic acids such as five-membered heterocycles7 and polyfluorophenyl boronic acids.5a

Lithium triisopropyl borates (LTB) are often accessed as intermediates in the syntheses of commonly used masked boronates such as the organotrifluoroborates8 and N-methyliminodiacetic acid (MIDA) boronates.9 Specifically lithium triisopropyl 2-pyridinylborates, have been employed directly as nucleophiles for SCM reactions.6a However, the coupling of other LTB nucleophiles, particularly those derived from heterocycles that form unstable boronic acids, has been largely unexplored. Herein, we report the use of lithium triisopropyl borates as nucleophiles in SCM reactions for a wide range of heterocycles.

Lithium triisopropyl borates (LTB) 3 are readily prepared via a one-pot procedure.6d For the borates depicted in Scheme 2, lithiation at −78 °C was followed by the addition of triisopropyl borate, after which the solution was gradually warmed to room temperature. The solvent was then removed and the resulting LTB was dried under vacuum at 80 °C. The

Supporting Information Available. Experimental procedures along with experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet://pubs.acs.org.
crude borate salt, still containing lithium borate, was directly used in SMC reactions without any further purification based on a 100 % yield.10

Using this procedure, lithium triisopropyl borates 5-12 were synthesized and subsequently used as nucleophiles in SMC reactions with various aryl and heteroaryl electrophiles. We began by evaluating the use of LTBs under conditions previously reported for the SMC using a diphenyl phosphine oxide ligand.6a While these couplings were successful, we found that by using XPhos precatalyst 13 we could obtain higher yields of coupled products under milder reaction conditions and in a shorter reaction times (Scheme 3). The use of precatalyst 13 was crucial in that it rapidly generates of the catalytically active Pd(0)Lc catalyst at the low reaction temperature (40 °C) required for the efficient coupling of these sensitive borates. The reactions were run with 3 mol % catalyst loading in a 1:2 THF/aqueous 0.5 M K3PO4 solution. Decreasing the loading of 13 from 3 to 1 mol % resulted in a slightly lower yield (14b–96% vs. 14c–84%).

Aryl bromides, chlorides, and triflates were all competent electrophiles and could be coupled with good to excellent yields. Significantly, the mild reaction conditions allowed for the coupling of (L)-4-bromophenylalanine without any erosion in enantioselectivity.24

We were next interested in evaluating the stability of these unpurified heteroaryl triisopropyl borates if not used immediately for a SMC, and found that borates 5 – 12 were remarkably robust. When used in a SMC reaction, these borates reacted to provide products in comparable yields even after being stored at room temperature for a month in a closed vial under air. In fact, the use of aryl borates 5, 7, and 10 gave comparable yields in SCM reactions after storage under air for up to 4 months. In comparison, 2-furanyl boronic acid loses 90 % activity following storage under air for just 15 days9a.

We hypothesize that the bulky isopropyl groups in the LTB protect the borate against protodeboronation. Since no reaction was observed with LTB under anhydrous SMC reaction conditions, we also presume that hydrolysis of the LTBs to their corresponding boronic acids is required for fast and efficient transmetallation. However, an advantage of using the boronate complex as nucleophile is that the reaction occurs in a THF/water mixture as solvent with no additional base added, as upon hydrolysis, basic isopropylate is released. The pH-value of a typical reaction mixture in THF with water as cosolvent is between 12 and 13. Thus, the use of LTB nucleophiles allows for SMC reaction with base-sensitive substrates such as nitro aromatics, methyl esters, or oxazoles (Scheme 4).11

We next sought to combine the lithiation, borylation, and SMC reaction into a one-pot procedure. Previously, we showed that an analogous one-pot sequence could be successfully applied to flow conditions.12 To this end, the aqueous base was directly added to the crude solution of LTB at −78 °C, followed by the aryl halide, precatalyst 13, and stirring the SMC at 40 °C for 2 hours. We found that product formation occurred in yields similar to those of SMC reactions conducted with isolated LTB (Scheme 5). We investigated conducting the SMC at lower catalyst loading (1 mol %) and found that, particularly for aryl bromide electrophiles, the products were obtained in slightly lower yields (14e to 14g). In the case of aryl chloride electrophiles, however, 1 mol % of precatalyst 13 was sufficient (14h). Under the optimized conditions, a broad scope of heterocyclic aryl halides were successful SMC substrates. For the electrophilic coupling partner, pyridines (32, 34, and 36), pyrimidines (33 and 37), 1H-indoles (35), aromatic aldehydes (42), 3-chloro-1,2-benzisothiazole (39), and pyrazines (40) were all good substrates. Notably, aryl bromides could also be selectively coupled in the presence of chlorides (41). Nucleophiles bearing acidic protons were incompatible and required the use of protecting groups. In particular, a TIPS-protected...
pyrrole and a SEM-protected pyrazole worked well in the lithiation/borylation sequence to provide products 37 (Scheme 5) and 45 (Scheme 6) in good yields.

The use of Boc or benzyl protection groups, however, resulted in decomposition and/or protecting-group cleavage. While methyl-imidazole only gave a trace amount of coupling product, a trityl-protected imidazole electrophile resulted in good yields 50, the use of an N-methyl-1H-imidazole as the LTB resulted in low yields of coupled product 42.

Subsequently, we evaluated the lithiation/borylation/SMC reaction sequence using non-halogenated heterocycles as LTB precursors via initial ortho-lithiation. In this sequence, thiophene (46 and 47), benzothiophene (43 and 44), SEM-pyrazole (45), benzofuran (48 and 50), and 1,5-difluorobenzene (49) performed well (Scheme 6). However, furan, in contrast to bromofuran, did not yield the desired product. Three equivalents of the heteroarene were required in order to achieve full conversion.

In conclusion, we have demonstrated that lithium triisopropyl borate salts are convenient and efficient coupling partners for Suzuki-Miyaura reactions, particularly when a sensitive heterocycle is required as the boronate component. In addition to providing a general procedure for the synthesis of LTBs and mild conditions for their coupling, we have developed conditions for a one-pot lithiation/borylation/SMC coupling sequence which provides a variety of heterocyclic bioaryl products in good yields. We expect that these triisopropyl boronate salts, which are stable at room temperature under an atmosphere of air, will find widespread use.

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

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References

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(10). It should be noted that, while 6-bromo-2-methylquinoline was effectively transformed into 8, during attempts to transform 4-bromoquinoline and N-methylbenzimidazole into their corresponding LTBs, the addition of a n-butyl group to the 2-position was observed.

(11). The Suzuki-Miyaura reactions described in this paper worked, in general, in THF with water as cosolvent. For some heterocyclic substrate combinations, however, the use of THF combined with aqueous potassium phosphate solution afforded higher yields.

Scheme 1.
Preparation and use of Lithium triisopropyl borates 3 as nucleophiles for Suzuki-Miyaura reactions.
Scheme 2.
Synthesis of lithium triisopropyl borates. These were isolated and used in coupling reactions without purification.
Reaction conditions: ArBr (3.16 mmol), THF (3 mL), toluene (12 mL), n-BuLi (1.4 mL, 2.5 M in hexanes, 3.48 mmol, 1.1 equiv), B(OiPr)₃ (0.75 mL, 3.48 mmol, 1.1 equiv), −78 °C to rt, 8 h.
Scheme 3.
Heteroaryl triisopropyl borates as nucleophile in SMC reactions.
a) 1% precat 13 was used; b) 87% yield after storing lithium triisopropyl 2-furanyl borate for 4 months in a closed vial on bench top; c) 6% Z-isomer was obtained, that corresponds to the same E/Z-ratio as in the starting material.; d) 4-bromopyridine was used as HCl salt. (e) without racemization. (f) Reaction conditions: ArX (0.25 mmol, 1.0 equiv), 3 (0.375 to 0.75 mmol, 1.5 to 3.0 equiv), 13 (3 mol %), THF (0.5 mL), and K₃PO₄ aq (0.5 M, 1.0 mL), 2 h, 40 °C. Isolated yields are the average of two runs. (g) 3 equivalents of 3 were used.
Scheme 4.
SMC reaction in THF/water enables the coupling of base sensitive substrates.
Reaction conditions: 3 (0.375 mmol, 1.5 equiv), Ar’X’ (0.25 mmol, 1.0 equiv), 13 (3 mol %), THF (0.5 mL), water (1.0 mL). Isolated yields based on two runs.
Scheme 5.
One pot lithium-halogen exchange, borylation, and SCM reaction.
(a) 2% precatalyst 13 was used. (b) 1% precatalyst 13 was used. (c) Reaction conditions:
ArX (0.375 mmol, 1.5 equiv), THF (0.5 mL), n-BuLi (2.5 M in hexanes, 0.41 mmol, 1.7 equiv), B(OiPr)₃ (0.41 mmol, 1.7 equiv), −78 °C, 1 h, K₃PO₄ aq (0.5 M, 1.0 mL), ArX (0.25 mmol, 1.0 equiv), 13 (3 mol %), 2 h, 40 °C. Isolated yields are the average of two runs. (d) 3 equivalents of ArX was used.
Scheme 6.
One pot lithium-halogen exchange, borylation, and SCM reaction of heteroarenes.
Reaction conditions: ArX (0.75 mmol, 3.0 equiv), THF (1.0 mL), n-BuLi (2.5 M in hexanes, 0.83 mmol, 3.3 equiv), B(OiPr)₃ (0.83 mmol, 3.3 equiv), −78 °C, 1 h, K₃PO₄ aq (0.5 M, 2.0 mL), ArX (0.25 mmol, 1.0 equiv), 1₃ (3 mol %), 2 h, 40 °C. Isolated yields are the average of two runs. (a) The reaction was run for 5 h instead of 2 h.