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A Non-cryogenic Method for the Preparation of 2-(Indolyl) Borates, Silanes, and Silanols

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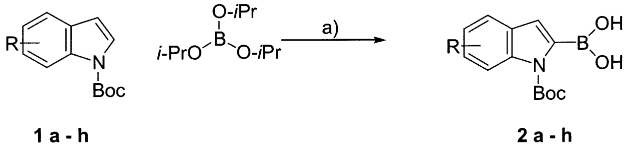
Abstract: 2-Indolyl borates are prepared via addition of LDA to a mixture of *N*-Boc-indole and triisopropyl borate at 0−5 °C. Following acidic hydrolysis, the boronic acids are isolated by crystallization in good to excellent yield (73−99%). The method is quite general, tolerating a wide range of functional groups, and also provides access to 2-silyl derivatives (80−91%).

The 2-aryl-substituted indoles, e.g., 2-aryltryptanes, are important *privileged structures*[1] and are present in a wide range of pharmacophores, e.g., GnRH antagonists.[2] Palladium-catalyzed cross coupling has emerged as a general route to these compounds.[3] This cross-coupling methodology relies on the accessibility of the appropriately functionalized partners that enter the reaction.[4] Very often, the 2-indolylboronic acid is a partner in the Suzuki−Miyaura reaction, and these boronic acids are prepared by lithiation at <−70 °C.[5,6] In this paper, we describe a simple non-cryogenic approach for the metalation of *N*-Boc indoles with an in situ electrophilic quench leading to the isolation of the corresponding boron or silicon derivatives.

Recently, we required an elaborated 2-substituted indole. We initially chose to investigate the use of a Suzuki−Miyaura cross-coupling of an *N*-Boc-protected indole. The indole was metalated in the 2-position and quenched with triisopropyl borate at −78 °C. Although the boronic acid was obtained in high yield following hydrolysis (>90%), the cryogenic conditions were not ideal for operation on a larger scale. To overcome this liability, we investigated the metalation of *N*-Boc with an in situ electrophilic quench.[7] We have discovered that addition of LDA (2.0 M in *n*-heptane/ethylbenzene/THF, 1.2 equiv) to a solution of *N*-Boc indole (1 M in THF) and triisopropyl borate (1.5 equiv) at 0−5 °C also produces the boronic acid in near-quantitative yield (Scheme 1).

SCHEME 1[a]



[a] Key: (a) (i) *N*-Boc indole, 1.0 M in THF, 0−5 °C, 1.2 equiv of LDA (2.0 M), (ii) 2N HCl.

TABLE 1. Preparation of *N*-Boc-2-indoyl Borates

entry	R =	yield (%)	entry	R =	yield (%)
1	**2a,** 4-Cl	99	5	**2e**, 5-OMe	89
2	**2b**, 5-Cl	94	6	**2f**, 5-Me	85
3	**2c**, H	96[a]	7	**2g**, 5-CN	81[a]
4	**2d**, 5-Br	92[a]	8	**2h**, 5-F	73[a]

[a] Assay yield by HPLC using an analytically pure standard.

With this observation in hand, we set out to demonstrate the broad generality of this metalation strategy. A number of commercially available indoles were *N*-Boc protected under standard conditions (Table 1). The resulting *N*-Boc indoles were taken forward without further purification to yield the desired boronic acids after isopropyl borate ester hydrolysis. A number of features are noteworthy. All reactions were unoptimized but the yields were uniformly good to excellent. In the cases where lower yields were observed, the deprotected indole was typically observed and accounted for the mass balance. The reaction tolerates a wide variety of functional groups and substitution patterns in the indole. The metalation of *N*-Boc-5-cyanoindole (entry 7) is significant since reaction at −78 °C followed by addition of the electrophile led to 65% assay yield. However, metalation with in situ trapping at higher temperature increased the yield to 81%.

Encouraged by the successful synthesis of the boronic acids, we moved to the more ambitious goal of expanding the methodology to silicon electrophiles. The palladium-catalyzed, cross-coupling reactions of organosilicon compounds to organic halides has emerged as a viable alternative to the well-established and versatile Stille−Migita−Kosugi coupling of organostannanes and Suzuki−Miyaura coupling of organoboranes. Pioneering studies by Kumada and Hiyama have shown that activation of organofunctional silicon compounds is possible by addition of a fluoride source to promote the palladium-catalyzed, cross-coupling reactions to various organic halides.[8] Chloro- and fluoro-organosilanes and orthosiliconates[9] have been successfully employed in cross-coupling reactions. Most noteworthy is the demonstrated synthetic potential of silacyclobutanes,[10] silanols,[11] silyl

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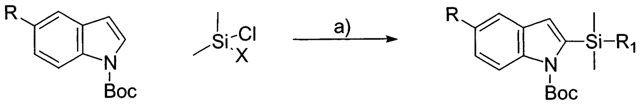
TABLE 2. Preparation of *N*-Boc-2-indoyl Silanes and Silanols



1 b, f **3 a - c**

entry	R	electrophile	R^1	yield (%)
1	**3a,** Cl	X = Me	Me	84
2	**3b**, Me	X = H	H	86
3	**3c**, Me	X = Cl	OH	91

[a] Key: (a) (i) *N*-Boc indole, 1.0 M in THF, 0−5 °C, 1.2 equiv of LDA (2.0 M); (ii) water or saturated $NaHCO_3$.

hydrides,[12] and cyclic silyl ethers[13] for extremely mild cross-coupling reactions. The silicon groups have excellent spectroscopic traceability facilitating reaction optimization in their preparation, in the cross-coupling event, and in downstream impurity tracking. We have investigated the metalation reaction in the presence of a range of silicon electrophiles (Table 2). The reactions are unoptimized but they demonstrate that we can access the silyl and silane derivatives in good yields. The silicon electrophiles appear to be less reactive than triisopropyl borate under these conditions, and the mass balance is accounted for by the starting indole resulting from the loss of the *tert*-butyloxy carbonyl group. Silanols offer significant advantages because of their high reactivity in part due to "the mechanistically fascinating duality of the silanol moiety as a prosthetic group for controlled carbon−carbon bond formation and as an activator for the coupling." [14] The reactivity at mild reaction temperatures (typically room temperature) and their compatibility with other silyl protecting groups further enhance the synthetic utility of the silanols. Attempts to use hexamethylcyclohexasiloxane as electrophile met with failure and resulted in recovery of the unprotected indole. However, reaction with the dichlorodimethylsilane followed by bicarbonate workup[11] gave the desired 2-silanol (^{29}Si NMR, δ −5.9 ppm) in 91% yield.

In conclusion, we have developed a synthetically useful, operationally simple, and general synthesis of *N*-Boc-2-indolyl borates, silanes, and silanols. The reaction proceeds with good to excellent yields and has broad functional group compatibility. Our observations emphasize that significant folklore exists regarding the use of de facto cryogenic metalation, and this approach will clearly find application in other systems.

Experimental Section

Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. LDA was obtained from commercial sources as a 2.0 M solution in *n*-heptane/ethylbenzene/THF. Triisopropyl borate was reagent grade. THF contained <200 μg/mL of water as determined by Karl Fischer titration. All reactions were monitored by HPLC analysis using a Zorbax SB-C18, 4.6 × 250 mm column. Eluent: CH_3CN and a 0.1% H_3PO_4/20 mM $NaClO_4$ buffer. Initial conditions 70% CH_3CN, with a gradient to 90% CH_3CN over 7 min. Flow rate: 1.5 mL/min, UV detection at 220 nm.

General Procedure for the Preparation of 2-Indolyl Borates. To a solution of *N*-Boc-4-chloroindole **1a** (2.00 g; 7.95 mmol) in THF (10 mL) was added triisopropyl borate (2.8 mL; 12.1 mmol). The solution was cooled to 0−5 °C in an ice bath, and LDA (2.0 M, 10 mmol) was added over 1 h. After 30 min, the reaction was quenched by the addition of 2 N HCl. The organic layer was separated, dried over $MgSO_4$, and concentrated to a solid that was recrystallized from acetonitrile/water to give **2a** (2.34 g, 99% yield): mp 97.8−99.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.40 (2H, br s), 8.06−8.01 (1H, m), 7.29−7.24 (2H, m), 6.63 (1H, s), 1.59 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.0, 140.6 (br) 137.4, 129.3, 125.5, 125.0, 122.6, 114.0, 109.7, 85.2, 28.0. Anal. Calcd for $C_{13}H_{15}BClNO_4$: C, 52.83; H, 5.12; N, 4.74; Cl,12.00. Found: C, 52.85; H, 4.99; N, 4.66; Cl, 11.86.

General Procedure for Silanes or Siloxanes. To a solution of *N*-Boc-5-chloroindole **1b** (2.00 g, 7.95 mmol) in THF (10 mL) was added chlorotrimethylsilane (1.5 mL, 11.8 mmol). The solution was cooled to 0 °C in an ice bath. LDA (2.0 M in THF, 10 mmol) was added over 1 h. After the addition was complete, the reaction was aged for 30 min and quenched with water. The organic layer was separated and dried over $MgSO_4$. The organics were filtered and concentrated. Flash chromatography on silica gel (5% EtOAc /hexane) gave **3a** as a colorless solid (2.15 g, 84% yield): mp 95.2−96.3 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.86 (1H, d, J = 9 Hz), 7.62 (1H, d, J = 2 Hz), 7.28 (1H, dd, J = 9, 2 Hz), 6.84 (1H, s), 1.62 (9H, s), 0.26 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.9, 143.5, 136.1, 132.4, 127.5, 124.9, 120.6, 119.1, 117.0, 85.3, 28.1, 0.4. Anal. Calcd for $C_{16}H_{22}ClNO_2Si$: C, 59.33; H, 6.85; N, 4.32; Cl,10.95; Si, 8.67. Found: C, 59.79; H, 6.82; N, 4.12; Si, 8.69.

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Supporting Information Available: General procedure for the preparation of the starting *N*-Boc indoles and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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