Direct Introduction of a Boryl Substituent into the 2-Position of Azulene: Application of the Miyaura and Smith Methods to Azulene

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Dedicated to Prof. Klaus Hafner on the occasion of his 75th birthday

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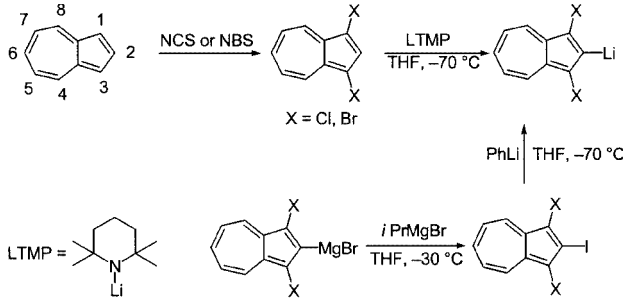
The 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl group was directly introduced into the 2-positions of azulenes with high selectivity by the C–H activation method with use of iridium catalysis.

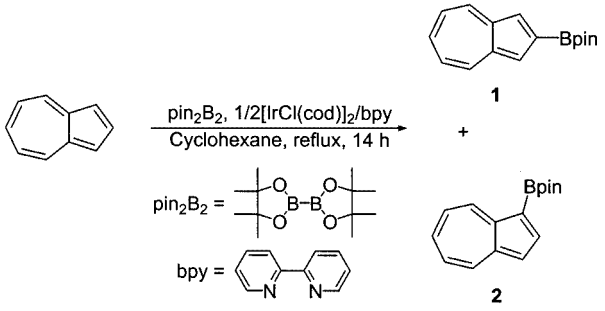
Introduction

Because of π-electron polarization, azulene undergoes nucleophilic addition at its 4-, 6-, and 8-positions and electrophilic substitution at its 1- and 3-positions.[1] Azulene derivatives bearing substituents at the 2-, 5-, or 7-positions have therefore previously been produced simply by the construction of the azulene skeleton, which introduces the substituent at an early stage of each synthetic method.[2]

We have very recently reported a simple method for the introduction of substituents into the 2-position of azulene by making use of the *ortho*-coordination of halogen atoms situated at the 1- and 3-positions; this was also the first paper on the generation of azulenyllithium and azulenylmagnesium halides (Scheme 1).[3] From the viewpoint of synthesis, however, no versatile dehalogenation method for the 1- and 3-positions has yet been established. Here we report the direct introduction of a boryl function into the 2-position of the azulene skeleton (Scheme 2).



Scheme 1



Scheme 2

Results and Discussion

Miyaura[4] and Smith III[5] have independently demonstrated the C−H activation method with iridium catalysis to give the 4,4,5,5-tetramethyl-1,3,2-dioxaborolane derivatives of benzenoid hydrocarbons. According to these papers, the substitution should take place at the carbon processing the more acidic hydrogen, a more crowded C−H function being less reactive.

Table 1 shows our results for the application of this method to some azulene derivatives. An outstanding result is the production of 2-(2-azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**) in a good yield of 70%. Taking both the total yields of borylated products **1** and **2** and the number of equivalents of the Bpin unit in pin_2B_2 into account, both boryl groups in pin_2B_2 are used in the reaction.[4,5] The other significant finding is that, in contrast to the case

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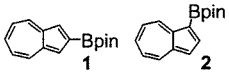
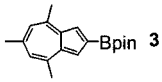
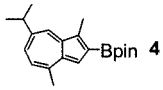
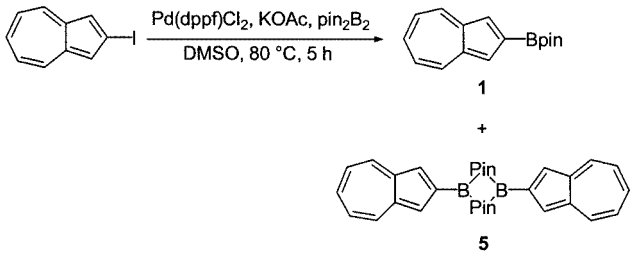
Table 1. Direct borylation at the 2-positions of azulenes

Azulenes[a]	Product(s)	Time (h)	Yield (%)[b]
	 **1** **2**	14	70 (**1**), 10 (**2**)
	 **3**	24	32[c]
	 **4**	24	5[d]

[a] Azulene derivative (2.2 equiv.), pin_2B_2 (1.0 equiv.) and 1/2-$[IrCl(COD)]_2$/bpy (10 mol %) in cyclohexane. [b] Yields based on the number of equivalents of the Bpin unit in pin_2B_2. [c] Recovery of the starting azulene derivative (61%). [d] Recovery of the starting azulene derivative (89%).

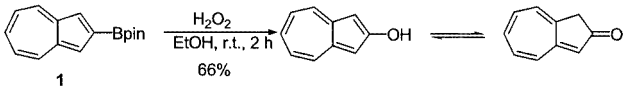
of benzenoid hydrocarbons cited in the literature, the highly acidic hydrogens on the seven-membered ring are never replaced. This site selectivity seems to be governed by the formation of a π complex between the five-membered ring and an iridium center in preference to the seven-membered ring,[6] with the more electron-poor 2-position in the five-membered ring being borylated. Attempted reactions with 6-formylazulene and 6-(hydroxymethyl)azulene resulted in the recovery of the starting azulenes (74 and 93%, respectively). The electron-withdrawing formyl group may be lowering the reactivity of the five-membered ring toward the π complex formation. The hydroxy group seems to play an active role in the destruction of the reactive intermediate involving the boron atom. Steric effects should be another important factor, since substrates bearing methyl groups at the 1- or 4-positions are converted into the 2-substituted products **3** and **4** only in low yields. 1,3-Di-*tert*-butylazulene and 1-(trifluoroacetyl)azulene did not give the borylated products at all and the starting materials were recovered almost intact (91% in both cases).

For comparison with the method described above, we have also carried out the substitution of the iodine atom in 2-iodoazulene by a boryl group by use of a palladium catalyst (Scheme 3).[7] Interestingly, two derivatives were formed, one of which was identified as the desired product **1**[7] while the structure of the other was tentatively assigned as the dimeric product **5**. Under the iridium-catalyzed conditions, the carbon−iodine bond in 2-iodoazulene did not undergo borylation and only the starting azulene was recovered (82%), although the 2-position of azulene is the most reactive site under these conditions. Similar results have been observed in the iridium-catalyzed borylation of haloarenes.[4,5]



Scheme 3

The boryl function was effectively transformed into a hydroxy function by treatment with hydrogen peroxide to give the 2-hydroxyazulene,[8] an important compound for the consideration of keto−enol tautomerism involving an aromatic nucleus with the low aromatic energy (Scheme 4).



Scheme 4

In conclusion, this methodology has allowed us easy access to 2-substituted azulenes, the syntheses of which required many reaction steps when the conventional method was used.

Experimental Section

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C with a Bruker Avance 400S (400 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (EI) were determined with a Waters LC−MS Integrity System at an ionization potential of 70 eV. UV/Vis spectra were measured in MeCN or cyclohexane with a Shimadzu UV-1600PC spectrophotometer.

General Procedure for Direct Borylation: Bis(pinacolato)diboron (pin_2B_2; 0.5 mmol), 2,2′-bipyridine (0.05 mmol), and chloro(1,5-cyclooctadiene)iridium(I) dimer (0.025 mmol) were added to a solution of azulene (1.1 mmol) in dry cyclohexane (3 mL). After argon gas had been bubbled into the mixture for 10 min, the mixture was heated at reflux for 14 h under argon. The resulting solution was concentrated to leave an oily residue, which was chromatographed (silica gel; hexane/EtOAc, 5:1) to give the borylated product.

2-(2-Azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1): Blue solid, yield 70%; m.p. 99−101 °C (ref.[7] 99−101 °C). ^1H NMR: δ = 1.40 (s, 12 H), 7.12 (t, *J* = 9.8 Hz, 2 H), 7.58 (t, *J* = 9.9 Hz, 1 H), 7.76 (s, 2 H), 8.35 (d, *J* = 10.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 24.93, 83.72, 122.72, 125.07, 138.17, 138.74, 140.68 ppm. One azulene skeleton C signal was not observed. MS: *m*/*z* (%) = 128 (29) [$C_{10}H_8$], 154 (99) [$C_{10}H_7BO$], 169 (19), 181 (84), 254 (100) [M^+]. UV/Vis (cyclohexane): λ_{max} (ε) = 282 (115000), 332 (9100), 347 (11400), 360 (4400), 435 (1520), 612 (1520), 665 (1490), 747 nm (1000). $C_{16}H_{19}BO_2$ (254.1): calcd. C 75.62, H 7.54; found C 75.22, H 7.55.

2-(1-Azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2): Purple solid, yield 10%; m.p. 56−57 °C. ^1H NMR: δ = 1.43 (s, 12 H), 7.30 (t, *J* = 9.7 Hz, 1 H), 7.40 (t, *J* = 9.9 Hz, 1 H), 7.43 (d, *J* = 3.7 Hz, 1 H), 7.68 (t, *J* = 9.9 Hz, 1 H), 8.36 (d, *J* = 3.7 Hz, 1 H), 8.42 (d, *J* = 9.5 Hz, 1 H), 9.20 (d, *J* = 9.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.96, 82.89, 119.03, 124.64, 125.13, 136.42, 137.39, 138.24, 144.62, 145.59, 147.07 ppm. One azulene skeleton C signal was not observed. MS: *m*/*z* (%) = 128 (28) [$C_{10}H_8$], 154 (49) [$C_{10}H_7BO$], 239 (9) [M^+ − Me], 254 (100) [M^+]. UV/Vis (MeCN): λ_{max} (ε) = 203 (18890), 229 (17530), 282 (51830), 286 (47280), 292 (50450), 336 (4460, sh), 344 (5740), 360 (5340), 551 (355), 584 (310, sh), 648 (130, sh), 724 nm (35, sh). $C_{16}H_{19}BO_2$ (254.1): calcd. C 75.62, H 7.54; found C 75.34, H 7.45.

4,4,5,5-Tetramethyl-2-(4,6,8-trimethyl-2-azulenyl)-1,3,2-dioxaborolane (3): Blue solid, yield 32%; m.p. 162−163 °C. ^{1}H NMR: δ = 1.40 (s, 12 H), 2.61 (s, 3 H), 2.88 (s, 6 H), 7.01 (s, 2 H), 7.74 (s, 2 H) ppm. ^{13}C NMR: δ = 24.90, 25.15, 28.91, 83.51, 123.22, 127.06, 136.63, 147.67, 148.17 ppm. One azulene skeleton C signal was not observed. MS: *m*/*z* (%) = 196 (28) [$M^+ - C_6H_{12}O$], 223 (43) [$M^+ - C_4H_9O$], 296 (100) [M^+]. UV/Vis (MeCN): λ_{max} (ε) = 214 (15110), 249 (30710), 291 (59700), 332 (9010), 301 (60400), 351 (5950), 366 (5200), 568 nm (610). $C_{19}H_{25}BO_2$ (296.2): calcd. C 77.04, H 8.5; found C 76.87, H 8.62.

2-(1,4-Dimethyl-7-isopropyl-2-azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4): Blue oil, yield 5%. ^{1}H NMR: δ = 1.36 (d, *J* = 6.9 Hz, 6 H), 1.40 (s, 12 H), 2.83 (s, 3 H), 2.84 (s, 3 H), 3.06 (m, 1 H), 6.94 (d, *J* = 10.5 Hz, 1 H), 7.39 (dd, *J* = 1.9, 10.5 Hz, 1 H), 7.61 (s, 1 H), 8.24 (d, *J* = 1.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 12.60, 24.21, 24.69, 24.95, 38.18, 83.21, 120.29, 124.81, 133.33, 134.98, 136.25, 136.90, 137.57, 139.75, 146.14 ppm. One azulene skeleton C signal was not observed. MS: *m*/*z* (%) = 209 (58) [$C_{15}H_{17}B$ + H], 224 (24) [$C_{15}H_{17}BO$], 309 (87) [M^+ − Me], 324 (100) [M^+]. UV/Vis (MeCN): λ_{max} (ε) = 205 (13160), 217 (13080), 248 (21550), 296 (37130), 341 (4020), 356 (5070), 635 (485), 674 (470), 750 nm (210, sh). $C_{21}H_{29}BO_2$ (324.3): calcd. C 77.78, H 9.01; found C 77.52, H 9.35.

Cross Coupling Reaction between 2-Iodoazulene and Bis(pinacolato)-diboron: DMSO (6 mL) was added to a flask charged with [Pd(dppf)Cl_2] (0.03 mmol), KOAc (3.0 mmol), and bis(pinacolato)-diboron (1.1 mmol), followed by 2-iodoazulene (1.0 mmol). The mixture was stirred at 80 °C for 5 h, the reaction was quenched with H_2O (20 mL), and the resulting mixture was extracted with benzene (3 × 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated to leave a residue, which was chromatographed (silica gel; hexane/EtOAc, 5:1) to give the products **1** and **5** in 42 and 22% yields (based on 2-iodoazulene), respectively.

Dimeric Compound 5: Green solid, yield 22%; m.p. 103−105 °C. ^{1}H NMR: δ = 1.40 (s, 24 H), 7.12 (t, *J* = 9.8 Hz, 4 H), 7.58 (t, *J* = 9.9 Hz, 2 H), 7.76 (s, 4 H), 8.35 (d, *J* = 10.0 Hz, 4 H) ppm. ^{13}C NMR: δ = 24.93, 83.73, 122.73, 125.07, 138.18, 138.76, 140.68 ppm. Signals due to two carbon atoms in the azulene skeleton were not observed. MS: *m*/*z* (%) = 128 (17) [$C_{10}H_8$], 154 (55) [$C_{10}H_7BO$], 169 (12), 181 (83), 254 (100), 380 (16). UV/Vis (cyclohexane): λ_{max} (ε) = 286 (130000), 336 (11400), 351 (12700), 364 (4100), 415 (1730), 438 (1990), 615 (900), 670 (910), 755 nm (450).

Oxidation by Hydrogen Peroxide: Hydrogen peroxide (30% aqueous solution, 10 equiv.) was added at 0 °C to a solution of **1** (0.20 mmol) in ethanol (2 mL), and the resulting solution was stirred for 2 h at this temperature. After addition of water (5 mL), the reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined extracts were dried over Na_2SO_4. Concentration of the extracts afforded an oily residue, which was chromatographed (silica gel; hexane/EtOAc, 5:1) to give 2-hydroxyazulene.

Red needles, yield 66% (based on **1**); m.p. 114.5−116 °C (ref.[8] 115.5−116.5 °C).

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