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EFFECTIVE METHODS FOR INTRODUCING SOME ARYL AND HETEROARYL SUBSTITUENT ONTO 1-AZAAZULENE NUCLEI[†]

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Abstract - Introduction of aryl and heteroaryl groups onto 1-azaazulene ring was achieved by addition-elimination reaction and Suzuki coupling. Reaction of 2-chloro-1-azaazulenes with 2-aryllithium and 2-heteroaryllithium followed by dehydrogenation with *o*-chloranil gave 8-aryl- and 8-heteroaryl-2-chloro-1-azaazulene in good yields. Suzuki coupling of 3-iodo-1-azaazulenes with phenylboronic acid in the presence of Pd catalyst afforded 3-phenyl-1-azaazulenes in excellent yield. Suzuki coupling of 2-bromo-1-azaazulenes with phenylboronic acid gave 2-phenyl-1-azaazulenes. Suzuki coupling of 2,3-dibromo-1-azaazulene with phenylboronic acid preferentially occurred at C-2. Reaction of 3-iodo-1-azaazulene with bis(pinacolato)diboron produced 3,3'-bis(1-azaazulene) derivative.

INTRODUCTION

The chemistry of azaazulenes is of interest for their physical and chemical properties as well as physiological properties.¹ Aryl and heteroaryl substituted 1-azaazulene derivatives would expect to have potential physiological activities. Therefore researches of versatile methods for introducing side chain to 1-azaazulene nuclei are important. Previously we reported that Grignard reaction is excellent method for the synthesis of aryl substituted 1-azaazulenes,^{2,3} and also reported sporadically about the reaction of 1-azaazulenes with aryllithium.^{4,5} We now report the full detail of the reaction of 1-azaazulenes with aryl- and heteroaryllithium, where excellent methods for introducing heteroaryl groups to 8-position were provided. For introduction of aryl groups onto 2- and 3-position of 1-azaazulene ring, we also utilized Suzuki coupling reaction⁶ of 2-bromo-1-azaazulenes and 3-bromo- or 3-iodo-1-azaazulenes with phenyl-

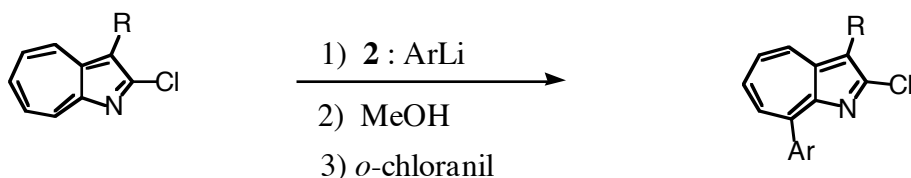
[†]Dedicated to the memory of the late Professor Kenji Koga.

boronic acid. We also tried to synthesis of (1-azaazulen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, which would be a good precursor for 3-heteroaryl-1-azaazulenes, but 3,3-bi(1-azaazulene) was as a major product and (1-azaazulen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained only in low yield.

RESULTS AND DISCUSSION

We previously reported that phenylmagnesium bromide added to 1-azaazulenes to give a mixture of 4-, 6-, and 8-phenyl-1-azaazulenes; where the reactivity towards the Grignard reagent increases in the order $C(8) \gg C(4) > C(6)$.^{2,3} It is known that aryllithium preferentially undergoes 1,2-addition reaction than conjugate addition reaction. Moreover, lithium can effectively coordinate at nitrogen of 1-azaazulene. Accordingly, it is considered that the reaction of 1-azaazulene with aryllithium would occur at C(8) exclusively. Therefore we examined the reaction of 1-azaazulenes with aryllithium for introducing aryl group on 8-position of 1-azaazulenes.

Treatment of 2-chloro-1-azaazulene (**1a**) with phenyllithium followed by methanol gave an addition product, and a successive dehydrogenation with tetrachloro-*o*-benzoquinone (*o*-chloranil) treatment afforded 2-chloro-8-phenyl-1-azaazulene^{2,3} (**3aa**) in 82% yield along with recovered **1a** (13%). Similar treatments of **1a** and **1b** with aryllithium (**2**: Ar = Ph, 2-nitrophenyl, 2-pyridyl, 2-pyrazinyl, 2-thiazolyl, 4-imidazolyl derivative, and 3-pyrazolyl derivative) gave 8-aryl-1-azaazulenes (**3aa-3bg**) in good yields (Table 1). The structures of obtained compounds were analyzed by spectroscopic data as well as elemental analyses as shown in EXPERIMENTAL.



1a: R = H

1b: R = CO₂Et,

3aa: R = H, Ar = phenyl

3ba: R = CO₂Et, Ar = phenyl

3ab: R = H, Ar = 2-nitrophenyl

3bb: R = CO₂Et, Ar = 2-nitrophenyl

3ac: R = H, Ar = 2-pyridyl

3bc: R = CO₂Et, Ar = 2-pyridyl

3ad: R = H, Ar = 2-pyrazinyl

3bd: R = CO₂Et, Ar = 2-pyrazinyl

3ae: R = H, Ar = 2-thiazolyl

3be: R = CO₂Et, Ar = 2-thiazolyl

3af: R = H, Ar = 1-EtOCHMe-1*H*-imidazol-4-yl

3bf: R = CO₂Et, Ar = 1-EtOCHMe-1*H*-imidazol-4-yl

3ag: R = H, Ar = 1*H*-imidazol-4-yl

3bg: R = CO₂Et, Ar = 1*H*-imidazol-4-yl

3ah: R = H, Ar = 1-EtOCHMe-3-1*H*-pyrazolyl

3bh: R = CO₂Et, Ar = 1-EtOCHMe-3-1*H*-pyrazolyl

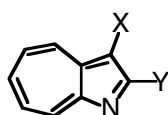
In all case, 8-substituted products were obtained exclusively, except for unconsumed 1-azaazulene. In the reaction of 1-(1-ethoxyethyl)-1*H*-pyrazol-4-yl lithium, **3bf** was not obtained, instead, 8-(1*H*-imidazol-

4-yl)-1-azaazulene (**3bg**), which was a deprotected product of ethoxyethyl group from **3bf** by silica gel, was isolated as a secondary product. (Entry 12). Thus it is confirmed that addition-elimination reactions of 1-azaazulenes with aryllithium are excellent methods to introduce aryl group at 8-position on 1-azaazulenes.

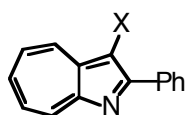
Table 1. Reaction of 1-azaazulenes with aryllithium

Entry	1-Azaazulene	Reagents	Yields (%)	
1	1a	Phenyllithium	3aa (82)	1a (13)
2	1b	Phenyllithium	3ba (76)	1b (19)
3	1a	1-iodo-2-nitrobenzene / phenyllithium	3ab (54)	1a (3)
4	1b	1-iodo-2-nitrobenzene / phenyllithium	3bb (66)	
5	1a	2-bromopyridine / butyllithium	3ac (73)	1a (20)
6	1b	2-bromopyridine / butyllithium	3bc (60)	1b (15)
7	1a	iodopyrazine / butyllithium	3ad (53)	
8	1b	iodopyrazine / butyllithium	3bd (61)	
9	1a	2-bromothiazole / butyllithium	3ae (98)	
10	1b	2-bromothiazole / butyllithium	3be (58)	
11	1a	1-(1-ethoxyethyl)-4-iodo-1 <i>H</i> -imidazole / butyllithium	3af (55)	
12	1b	1-(1-ethoxyethyl)-4-iodo-1 <i>H</i> -imidazole / butyllithium	3bg (70)	
13	1a	1-(1-ethoxyethyl)-3-bromo-1 <i>H</i> -pyrazole / butyllithium	3ah (51)	1a (37)
14	1b	1-(1-ethoxyethyl)-3-bromo-1 <i>H</i> -pyrazole / butyllithium	3bh (46)	1b (40)

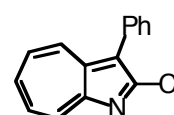
For introduction of aryl groups on 1-azaazulene nuclei, coupling reactions would be also considered as excellent methods. We previously reported that 3-ethynyl-1-azaazulenes were synthesized from 3-iodo-1-azaazulenes by Sonogashira reaction which is Pd-catalyzed coupling reaction of alkyne with aryl halide.⁷ So, it is expected that introducing of aryl groups on 1-azaazulene nuclei would be attained by Suzuki coupling which is also Pd-catalyzed reaction. In addition, halogen substituted 1-azaazulenes were easily obtained. Therefore, we next investigated Suzuki coupling of halo-1-azaazulenes.



4a : X = H, Y = Br
4b : X = CO₂Et, Y = Br
4c : X = Y = Br
4d : X = Br, Y = Cl
4e : X = I, Y = Cl



5a : X = H
5b : X = CO₂Et
5c : X = Br
5d : X = Ph



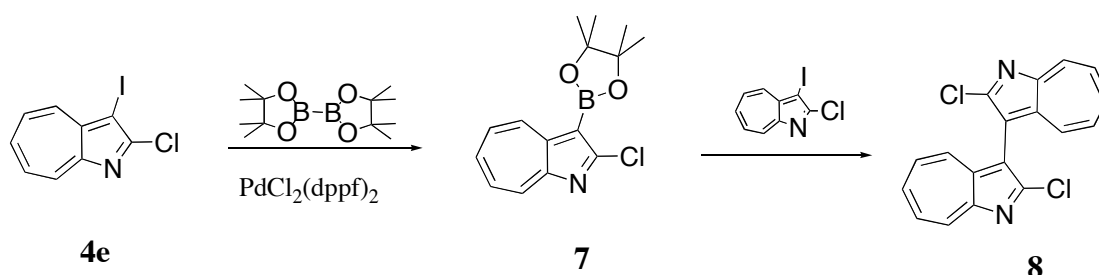
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Treatment of 2-bromo-1-azaazulene (**4a**) with phenylboronic acid in the presence of PdCl₂(PPh₃)₂ and potassium carbonate in toluene under reflux for 6.5 h gave 2-phenyl-1-azaazulene⁸ (**5a**) in 72% yield

along with recovered **4a** (7%). Similar treatment of **4b** with phenylboronic acid gave **5b** in 66% yield. When 2,3-dibromo-1-azaazulene (**4c**) was treated with phenylboronic acid, 3-bromo-2-phenyl-1-azaazulene (**5c**) was obtained in 87% yield. The bromination of **5a** with NBS gave **5c**. Thus the structure of **5c** was unequivocally decided. The results show that the bromo group at C-2 on 1-azaazulene is more reactive than that of C-3.

Phenylation of C-3 by the Suzuki coupling was examined using 3-bromo-2-chloro-1-azaazulene (**4d**) and 2-chloro-3-iodo-1-azaazulene (**4e**). When **4d** was treated with 1.5 equivalent molar of phenylboronic acid in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and potassium carbonate in toluene under reflux for 4 h, 2-chloro-3-phenyl-1-azaazulene⁹ (**6**) was obtained in 31% yield along with 2,3-diphenyl-1-azaazulene¹⁰ (**5d**) (21%) and **4d** (31%). Interestingly, the chloro group at C-2 was also substituted under the reaction. It is thought that the phenylation at C-3 is rather slow and the phenyl group at C-3 would activate the C-2 position. It is known that iododerivatives are more reactive than bromoderivatives on Suzuki coupling.⁶ Thus, similar treatment of **4e** with phenylboronic acid in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ and potassium carbonate gave **6** in 83% yield. In this case, **6** yielded exclusively and **5d** was not obtained.

Introducing the boron moiety onto the 1-azaazulene nuclei, such as (1-azaazulen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, would have a potential usefulness for synthesis of aryl substituted 1-azaazulenes. Therefore, we next examined the synthesis of (2-chloro-1-azaazulen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**). A mixture of 2-chloro-3-iodo-1-azaazulene with 1.5 equivalent of bis(pinacolato)diboron in the presence of $\text{PdCl}_2(\text{dppf})_2$ and potassium carbonate in DMSO was heated at 80 °C for 5 h. From the mixture, 3,3'-bi(2-chloro-1-azaazulene) (**8**) and **7** were isolated in 57% and 14% yields, respectively. Although we could not obtain **7** in pure state as yet, the formation of **7** was sure and its structure was deduced by spectroscopic data. Compound (**8**) would be produced by the reaction of **7** with **4e** and was obtained as major product, in spite of the using excess bis(pinacolato)diboron. Therefore, it is thought that the Suzuki coupling of **7** with **4e** would be faster than the formation of **7** from **4e**. X-Ray structure analysis, as well as spectroscopic data and elemental analysis elucidated the structure of **8**. ORTEP drawing¹¹ of **8** is shown in Figure 1.



EXPERIMENTAL

Mps are measured using a Yanagimoto micro-melting apparatus and uncorrected. ^1H NMR spectra (including HH-COSY and CH-COSY NMR) were recorded on a Bruker AVANCE 400S (400 MHz) and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400S (100.6 MHz) using deuteriochloroform as a solvent with tetramethylsilane as an internal standard unless otherwise stated; J values are recorded in Hz.

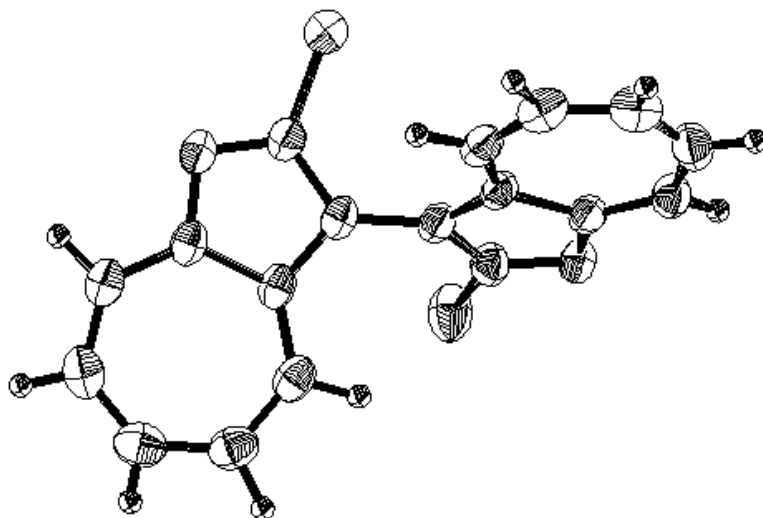


Fig. 1. ORTEP drawing of **8** with thermal ellipsoids (50% probability).

IR spectra were recorded for KBr pellets on a Nicolet FT-IR Impact 410. MS spectra were taken with on an LC-MS Waters Integrity System. Elemental analyses were taken with a Perkin Elmer 2400II. Kieselgel 60 was used for column chromatography and Kieselgel 60G was used for thin-layer chromatography.

Reaction of phenyl lithium with 2-chloro-1-azaazulene (**1a**)

Under argon atmosphere, a solution of 0.86 M phenyllithium (1.5 mL, 1.50 mmol) was added to the solution of 2-chloro-1-azaazulene (**1a**) (0.164 g, 1.00 mmol) in dry THF (10.0 mL), at $-80\text{ }^{\circ}\text{C}$ and stirring was continued for 2 h. To the mixture methanol (5.0 mL) was added, and then the reaction temperature was raised to rt. To the mixture *o*-chloranil (0.369 g, 1.5 mmol) was added and the mixture was stirred for 24 h. The mixture was poured into water and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with benzene to give 2-chloro-8-phenyl-1-azaazulene (**3aa**)^{2,3} (0.176 g, 82%) and recovered (**1a**) (0.021 g, 13%).

3aa: Reddish orange needles (from hexane), mp $120\text{--}121\text{ }^{\circ}\text{C}$ (lit.,^{2,3} mp $120\text{--}121\text{ }^{\circ}\text{C}$); δ_{H} 7.29 (1H, s), 7.44–7.54 (3H, m, H-*m,p*-Ph), 7.56–7.65 (1H, m, H-5), 7.78 (2H, dm, *J* 6.8, H-*o*-Ph), 7.86–7.88 (2H, m, H-6 and 7), and 8.46 (1H, d, *J* 9.8, H-4); δ_{C} 112.86, 128.14, 128.38, 128.80, 130.92, 133.65, 134.68, 136.58, 140.81, 147.73, 148.55, 152.68, and 157.19. Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{NCl}$: C, 75.16; H, 4.21; N, 5.84. Found: C, 75.37; H, 4.10; N, 5.81.

In a similar manner, **3ba** yielded from **1b** and phenyllithium in 76% yield along with **1b** (19%).

3ba: Reddish orange needles (from hexane), mp 154-155.5 °C (lit.,^{2,3} mp 154-155.5 °C); δ_{H} 1.49 (3H, t, J 7.1, Me), 4.50 (2H, q, J 7.1, CH₂), 7.49-7.56 (3H, m, H-*m,p*-Ph), 7.74-7.76 (2H, m, H-*o*-Ph), 7.89 (1H, dm, J 10.4, H-7), 8.00-8.07 (2H, m, H-5 and 6), and 9.65 (1H, d, J 9.8, H-4); δ_{C} 14.42, 60.63, 112.10, 128.21, 129.11, 130.96, 131.64, 136.17, 137.11, 138.41, 140.48, 147.75, 150.80, 153.78, 158.38, and 163.75; ν_{max} / cm⁻¹ 1684 (C=O). *Anal.* Calcd for C₁₈H₁₄NO₂Cl: C, 69.98; H, 4.53; N, 4.49. Found: C, 69.72; H, 4.54; N, 4.55.

Synthesis of 2-chloro-8-(2-nitrophenyl)-1-azaazulene (**3ab**)

Under argon atmosphere, to the solution of 1-iodo-2-nitrobenzene (0.749 g, 3.01 mmol) in dry THF (5.0 mL) at -100 °C (liquid N₂ / Et₂O) was introduced slowly a solution of 0.86 M phenyllithium (3.5 mL, 3.00 mmol), and was stirred for 50 min at -100 °C. Then the solution of 2-chloro-1-azaazulene (**1a**) (0.366 g, 2.23 mmol) in dry THF (7.0 mL) was added to the mixture, and stirring was continued for 0.5 h at -100 °C. To the mixture methanol (5.0 mL) was added, and then the reaction temperature was raised to rt. To the mixture *o*-chloranil (0.990 g, 4.03 mmol) was added and the mixture was stirred for 2 h. The mixture was poured to water and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with benzene to give 2-chloro-8-(2-nitrophenyl)-1-azaazulene (**3ab**) (0.344 g, 54%) and recovered **1a** (0.009 g, 3%).

3ab: Red prisms (from hexane-dichloromethane), mp 143.5-145 °C; δ_{H} 7.27 (1H, s, H-3), 7.56 (1H, d, J 7.6, H-6'), 7.64 (1H, dd, J 8.2 and 7.6, H-4'), 7.70 (1H, dd, J 9.8 and 9.6, H-5), 7.75 (1H, t, J 7.6, H-5'), 7.77 (1H, d, J 10.6, H-7), 7.91 (1H, dd, J 10.6 and 9.6, H-6), 8.19 (1H, d, J 8.2, H-3'), and 8.49 (1H, d, J 9.8, H-4); δ_{C} 113.41, 124.97, 129.71, 129.79, 132.06, 132.42, 133.51, 135.38, 136.42, 137.46, 145.41, 147.57, 149.54, 153.20, and 157.84; ν_{max} / cm⁻¹ 1518 and 1369 (NO₂). *Anal.* Calcd for C₁₅H₉N₂O₂Cl: C, 63.28; H, 3.19; N, 12.45. Found: C, 63.34; H, 3.26; N, 12.41.

In a similar manner, the reaction of **3b** with 2-nitrophenyllithium in **2b** gave **3bb** in a 66% yield.

3bb: Orange prisms (from hexane-dichloromethane), mp 163.5-164.5 °C; δ_{H} 1.47, (3H, t, J 7.1, Me), 4.48 (2H, q, J 7.1, CH₂), 7.53 (1H, d, J 7.6, H-6'), 7.67 (1H, dd, J 8.1 and 7.5, H-4'), 7.77 (1H, dd, J 7.6 and 7.5, H-5'), 7.96 (1H, d, J 10.2, H-7), 8.00 (1H, dd, J 10.2 and 10.0, H-5), 8.09 (1H, dd, J 10.2 and 10.0, H-6), 8.21 (1H, d, J 8.1, H-3'), and 9.66 (1H, d, J 10.2, H-4); δ_{C} 14.81, 61.08, 112.74, 125.03, 130.08, 132.25, 132.92, 133.67, 134.53, 136.07, 137.94, 139.33, 147.44, 149.39, 154.22, 159.10, and 163.83; ν_{max} / cm⁻¹ 1704 (C=O), 1518 and 1369 (NO₂); m/z (rel intensity) 358 (M⁺, 3), 356 (M⁺, 9), 312 (33), 311 (26), 310 (97), 284 (33), 282 (100), 238 (36), and 237 (31). *Anal.* Calcd for C₁₈H₁₃N₂O₄Cl: C, 60.60; H, 3.67; N, 7.85. Found: C, 60.59; H, 3.67; N, 7.91.

Synthesis of 2-chloro-8-(2-pyridyl)-1-azaazulene (**3ac**)

Under argon atmosphere, 1.5 M butyllithium (2.6 mL, 3.90 mmol) was added to the solution of 2-bromopyridine (0.30 mL, 3.00 mmol) in dry ether (20 mL) at -90 °C. To the mixture 2-chloro-1-azaazulene (**1a**) (0.492 g, 3.00 mmol) in dry ether (20 mL) was added, and the mixture was stirred for 1.5 h

at $-30\text{ }^{\circ}\text{C}$, then methanol (5 mL) was added. After the mixture was warm to rt, *o*-chloranil (0.738 g, 3.0 mmol) was added to the mixture and the mixture was stirred for 17 h. To the mixture was added water, and the mixture was extracted with chloroform, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel column with ethyl acetate—hexane (1 : 5) to give 2-chloro-8-pyridyl-1-azaazulene (**3ac**) (0.526 g, 73%) and recovered **1a** (0.097 g, 20%).

3ac: Orange needles (from hexane-dichloromethane), mp $137\text{--}139\text{ }^{\circ}\text{C}$; δ_{H} 7.32 (1H, s, H-3), 7.40 (1H, ddd, J 7.6, 4.8, and 1.2, H-5'), 7.69 (1H, dd, J 9.8 and 9.4, H-5), 7.88 (1H, ddd, J 7.8, 7.6, and 1.8, H-4'), 7.98 (1H, ddd, J 11.6, 9.8 and 1.1, H-6), 8.31 (1H, dddd, J 7.8, 1.2, 1.1, and 0.9, H-3'), 8.34 (1H, d, J 11.6, H-7), 8.49 (1H, dm, J 9.4, H-4), and 8.81 (1H, ddd, J 4.8, 1.7, and 0.9, H-6'); δ_{C} 112.84, 123.48, 128.62, 129.29, 133.50, 134.56, 135.82, 136.97, 145.42, 148.61, 149.65, 152.57, 157.11, and 157.64; m/z (rel intensity) 242 (M^+ , 36), 241 (65), 240 (M^+ , 92), 239 (100), 205 (50), 177 (12), 120 (11), 102 (9), and 89 (15). *Anal.* Calcd for $\text{C}_{14}\text{H}_9\text{N}_2\text{Cl}$: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.99; H, 3.58; N, 11.45.

In a similar manner, **3bc**, **3ad**, **3bd**, **3ae**, **3be**, **3af**, **3bf**, **3ag**, and **3bg** were synthesized (Table 1).

3bc: Yellow needles (from hexane-dichloromethane), mp $149\text{--}151\text{ }^{\circ}\text{C}$; δ_{H} 1.50 (3H, t, J 7.1, Me), 4.51 (2H, q, J 7.1, CH_2), 7.42 (1H, dd, J 7.4 and 4.1, H-5'), 7.89 (1H, dd, J 7.9 and 7.4, H-4'), 7.96 (1H, dd, J 10.0 and 9.8, H-5), 8.14 (1H, dd, J 10.7 and 9.8, H-6), 8.26 (1H, d, J 7.9, H-3'), 8.52 (1H, d, J 10.7, H-7), 8.47 (1H, d, J 4.1, H-6'), and 9.67 (1H, d, J 10.0, H-4); δ_{C} 14.81, 61.09, 124.14, 129.17, 133.00, 136.29, 136.69, 137.44, 139.22, 147.81, 148.96, 150.12, 153.95, 156.99, and 164.00. *Anal.* Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: C, 65.29; H, 4.19; N, 8.96. Found: C, 65.46; H, 4.26; N, 9.12.

3ad: Orange needles (from hexane-dichloromethane), mp $122\text{--}124\text{ }^{\circ}\text{C}$; δ_{H} 7.36 (1H, s, H-3), 7.73 (1H, dd, J 9.8 and 9.6, H-5), 8.00 (1H, d, J 10.9 and 9.6, H-6), 8.28 (1H, d, J 10.9, H-7), 8.53 (1H, d, J 9.8, H-4), 8.67 (1H, d, J 2.5, H-6'), 8.77 (1H, dd, J 2.4 and 1.2, H-5'), and 9.58 (1H, d, J 1.2, H-3'); δ_{C} 113.22, 129.73, 132.91, 134.79, 137.12, 142.01, 143.88, 144.15, 148.53, 149.29, 152.63, 153.07, and 158.58; ν_{max} / cm^{-1} 1560 (C=N); m/z (rel intensity) 243 (M^+ , 30), 242 (34), 241 (M^+ , 100), 240 (62), 189 (32), 187 (53), 128 (11), 127 (12), and 125 (11). *Anal.* Calcd for $\text{C}_{13}\text{H}_8\text{N}_3\text{Cl}$: C, 64.61; H, 3.34; N, 17.39. Found: C, 63.99; H, 3.14; N, 16.91.

3bd: Yellow prisms (from hexane-dichloromethane), mp $149\text{--}151\text{ }^{\circ}\text{C}$; δ_{H} 1.59 (3H, t, J 7.1, Me), 4.52 (2H, q, J 7.1, CH_2), 8.01 (1H, ddd, J 10.3, 9.7, and 0.9, H-6), 8.47 (1H, dd, J 10.2 and 9.7, H-5), 8.47 (1H, d, J 10.3, H-7), 8.69 (1H, br d, J 2.3, H-6'), 8.78 (1H, dd, J 2.3 and 1.6, H-5'), 9.53 (1H, br s, H-3'), and 9.70 (1H, dd, J 10.2 and 0.9, H-4); δ_{C} 14.41, 60.82, 112.54, 133.02, 135.72, 137.35, 138.92, 144.09, 144.27, 148.54, 149.34, 152.61, 153.54, 159.60, and 163.46; ν_{max} / cm^{-1} 1712 and 1697 (C=O); m/z (rel intensity) 315 (M^+ , 1), 313 (M^+ , 3), 263 (16), 262 (59), 248 (33), 247 (100), 220 (13), 193 (32), and 165 (25). *Anal.* Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_3\text{O}_2\text{Cl}$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.99; H, 3.14; N, 13.89.

3ae: Orange needles (from hexane-dichloromethane); mp $133\text{--}134\text{ }^{\circ}\text{C}$; δ_{H} 7.28 (1H, s, H-3), 7.71 (1H, dd, J 9.8 and 9.6, H-5), 7.78 (1H, d, J 3.1, H-3'), 8.00 (1H, dd, J 11.3 and 9.6, H-6), 8.16 (1H, d, J 3.1, H-5'),

8.44 (1H, d, J 9.8, H-4), and 9.33 (1H, d, J 11.3, H-7); δ_{C} 113.17, 127.04, 130.06, 130.63, 134.30, 136.49, 136.70, 142.61, 148.13, 150.54, 156.51, and 163.55; $\nu_{\text{max}} / \text{cm}^{-1}$ 1556 (C=N). *Anal.* Calcd for $\text{C}_{12}\text{H}_7\text{N}_2\text{ClS}$: C, 58.42; H, 2.86; N, 11.35. Found: C, 58.36; H, 2.81; N, 11.42.

3be: Yellow prisms (from hexane-dichloromethane), mp 179-180 °C; δ_{H} 1.50 (3H, t, J 7.1, Me), 4.51 (2H, q, J 7.1, CH_2), 7.82 (1H, d, J 3.2, H-3'), 7.96 (1H, dd, J 10.2 and 9.6, H-5), 8.14 (1H, d, J 3.2, H-5'), 8.15 (1H, dd, J 11.0 and 9.6, H-6), 9.54 (1H, d, J 11.0, H-7), and 9.60 (1H, d, J 10.2, H-4); δ_{C} 14.42, 60.71, 112.45, 127.90, 133.19, 133.23, 136.68, 133.25, 138.58, 142.90, 147.83, 151.16, 157.50, 162.83, and 163.43; $\nu_{\text{max}} / \text{cm}^{-1}$ 1689 (C=O) and 1562 (C=N). *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_2\text{ClS}$: C, 56.52; H, 3.48; N, 8.79. Found: C, 56.43; H, 3.34; N, 8.89.

3af: Orange needles (from hexane-dichloromethane), mp 222-224 °C; δ_{H} 0.94 (3H, t, J 7.0, Me), 1.65 (3H, d, J 5.7, Me), 3.01 (1H, br q, J 7.0, MeCH_2O), 3.17 (1H, br q, J 7.0, MeCH_2O), 5.06 (1H, q, J 5.7, MeCHO), 7.23 (1H, s, H-3), 7.28 (1H, s, H-5'), 7.29 (1H, s, H-3'), 7.65 (1H, dd, J 9.8 and 9.7, H-5), 7.85 (1H, dd, J 10.7 and 9.7, H-6), 8.05 (1H, d, J 10.7, H-7), and 8.43 (1H, d, J 9.8, H-4); δ_{C} 15.14, 22.75, 64.28, 84.99, 113.65, 117.33, 128.72, 130.59, 134.26, 135.30, 135.60, 137.33, 146.53, 148.19, 153.06, and 158.71; $\nu_{\text{max}} / \text{cm}^{-1}$ 1562 (C=N). *Anal.* Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_3\text{OCl} \cdot 0.6 \text{CHCl}_3$: C, 52.05; H, 4.36; N, 10.90. Found: C, 52.67; H, 3.99; N, 10.85.

3bg: Yellow prisms (from hexane-chloroform), mp 230-232 °C; δ_{H} 1.42 (3H, t, J 7.1, Me), 4.43 (2H, q, J 7.1, CH_2), 7.83 (1H, dd, J 10.2 and 9.6, H-5), 8.03 (1H, ddd, J 11.0, 9.6, and 1.1, H-6), 9.33 (1H, d, J 11.0, H-7), 9.48 (1H, dd, J 10.2 and 1.1, H-4), and 13.95 (1H, br s, NH); δ_{C} 14.40, 60.82, 111.95, 120.51, 130.60, 132.20, 133.28, 136.21, 137.03, 139.08, 147.80, 148.54, 150.33, 156.09, and 163.32; $\nu_{\text{max}} / \text{cm}^{-1}$ 3210 (NH), 1689 (C=O). *Anal.* Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_2\text{Cl} \cdot 0.75 \text{CHCl}_3$: C, 48.34; H, 3.28; N, 10.73. Found: C, 48.59; H, 2.98; N, 9.92.

3ah: Red oil; δ_{H} 1.21 (3H, t, J 7.0, Me), 1.49 (3H, d, J 6.0, Me), 3.49 (1H, dt, J 9.4 and 7.0, MeCH_2O), 3.55 (1H, dt, J 9.4 and 7.0, MeCH_2O), 5.62 (1H, q, J 6.0, MeCHO), 7.20 (1H, s, H-3), 7.51 (1H, dd, J 9.6 and 9.5, H-5), 7.81 (1H, ddd, J 11.1, 9.5, and 0.9, H-6), 8.15 (d, J 11.1, H-7), 8.33 (1H, br s, H-4'), 8.34 (1H, br d, J 9.6, H-4), and 9.10 (1H, br s, H-5'); δ_{C} 14.89, 22.04, 64.38, 87.96, 112.86, 121.68, 127.94, 130.16, 131.80, 134.44, 136.47, 139.28, 140.32, 146.88, 150.56, and 155.01; $\nu_{\text{max}} / \text{cm}^{-1}$ 1596 and 1582 (C=N).

3bh: Yellow prisms (from hexane-chloroform), mp 123-124 °C; δ_{H} 1.22 (3H, t, J 7.0, Me), 1.49 (3H, d, J 7.1, Me), 1.81 (3H, d, J 6.0, Me), 3.49 (1H, dt, J 9.4 and 7.0, MeCH_2O), 3.57 (1H, dt, J 9.4 and 7.0, MeCH_2O), 4.49 (2H, q, J 7.1, CH_2), 5.63 (1H, q, J 6.0, MeCHO), 7.77 (1H, ddd, J 10.2 and 9.6, H-5), 7.96 (1H, ddd, J 10.7, 9.6, and 1.2, H-6), 8.32 (1H, br d, J 10.7, H-7), 8.33 (1H, br s, H-4'), 9.11 (1H, br s, H-5'), and 9.52 (d, J 10.2 and 0.9, H-4); δ_{C} 14.43, 14.89, 22.07, 60.56, 64.48, 88.10, 112.10, 121.48, 131.02, 132.25, 132.47, 136.62, 138.24, 140.48, 141.70, 146.71, 151.51, 156.51, and 163.80; $\nu_{\text{max}} / \text{cm}^{-1}$ 1690 (C=O); m/z (rel intensity) 375 (M^+ , 9), 373 (M^+ , 38), 303 (16), 302 (13), 301 (76), 300 (48), 258 (24), 256 (100), 231 (21), 230 (21), 229 (56), and 228 (49). *Anal.* Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_3\text{Cl} \cdot 0.2 \text{CHCl}_3$: C, 57.98; H, 5.12; N, 10.56. Found: C, 58.07; H, 4.71; N, 10.29.

Reaction of 2-bromo-1-azaazulene with phenylboronic acid

A mixture of 2-bromo-1-azaazulene (**4a**) (0.1165 g, 0.5 mmol), phenylboronic acid (0.091 g, 0.075 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.007 g, 0.01 mmol) in toluene (10 mL) was heated for 6.5 h at 110 °C. The mixture was poured into water, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with benzene to give 2-phenyl-1-azaazulene⁸ (**5a**) (0.083 g, 72%) and **4a** (0.016g, 7%).

5a: Red needles (from hexane-dichloromethane), mp 155-156 °C (lit.,⁸ mp148-149.5 °C); δ_{H} 7.45 (1H, dm, J 7.3, H-*p*-Ph), 7.52 (2H, dm, J 7.6, H-*m*-Ph), 7.60 (1H, dd, J 11.2 and 9.8, H-5), 7.73 (1H, like t, J 9.2, H-7), 7.76 (1H, s, H-3), 7.76 (1H, dd, J 11.2 and 10.0, H-6), 8.32 (2H, dm, J 7.5, H-*o*-Ph), 8.51 (1H, d, J 9.8, H-4), and 8.67 (1H, dm, J 9.0, H-8); δ_{C} 110.70, 128.15, 128.85, 128.91, 129.70, 129.93, 134.64, 135.24, 135.31, 136.61, 148.06, 158.75, and 167.25. *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{N}$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.86; H, 5.30; N, 6.77.

Reaction of ethyl 2-bromo-1-azaazulene-3-carboxylate with phenylboronic acid

A mixture of ethyl 2-bromo-1-azaazulene-3-carboxylate (**4b**) (0.140 g, 0.5 mmol), phenylboronic acid (0.091 g, 0.075 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.007 g, 0.01 mmol) in toluene (10 mL) was heated for 5 h at 110 °C. The mixture was poured into water, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with chloroform to give ethyl 2-phenyl-1-azaazulene-3-carboxylate (**5b**) (0.091 g, 66%).

5b: Yellow prisms (from hexane-dichloromethane), mp 57-59 °C; δ_{H} 1.25 (3H, t, J 7.1, Me), 4.36 (2H, q, J 7.1, CH_2), 7.40-7.50 (3H, m, H-*m,p*-Ph), 7.80-8.00 (5H, m, H-5,6,7 and H-*o*-Ph), 8.79 (1H, dd, J 9.8 and 1.3, H-8), and 9.48 (1H, dd, J 10.3 and 0.7, H-4); δ_{C} 14.06, 60.34, 113.49, 127.81, 128.01, 129.23, 130.08, 130.35, 131.95, 132.02, 136.33, 137.08, 137.78, 138.85, 148.08, 158.75, 165.26, and 169.80; $\nu_{\text{max}} / \text{cm}^{-1}$ 1683 (C=O) *Anal.* Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.90; H, 5.33; N, 5.11.

Reaction of 2,3-dibromo-1-azaazulene with phenylboronic acid

A mixture of 2,3-dibromo-1-azaazulene (**4c**) (0.144 g, 0.5 mmol), phenylboronic acid (0.183 g, 1.50 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.007 g, 0.01 mmol) in toluene (10 mL) was heated for 3 h at 110 °C. The mixture was poured into water, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with chloroform to give 3-bromo-2-phenyl-1-azaazulene (**5c**) (0.123 g, 87%) as reddish oil. Trituration of the oil with pentane gave reddish purple solid.

5c: Reddish purple needles (from pentane), mp 36-38 °C; δ_{H} 7.49 (1H, dm, J 7.3, H-*p*-Ph), 7.55 (2H, dm, J 7.5, H-*m*-Ph), 7.73 (1H, dd, J 10.5 and 9.8, H-5), 7.79 (1H, dd, J 10.1, and 9.8, H-6), 7.87 (1H, dd, J 10.5 and 9.6, H-7), 8.34 (2H, dm, J 7.5, H-*p*-Ph), 8.55 (1H, d, J 10.1, H-4), and 8.65 (1H, dm, J 9.6, H-8); δ_{C} 99.72, 128.50, 129.31, 129.80, 129.86, 130.09, 134.60, 134.91, 136.59, 138.06, 144.71, 156.75, and 162.90; $\nu_{\text{max}} / \text{cm}^{-1}$ 1578 (C=N). *Anal.* Calcd for $\text{C}_{15}\text{H}_{10}\text{NBr}$: C, 63.40; H, 3.55; N, 4.93. Found: C, 63.17; H, 3.44; N, 5.10.

Bromination of 2-phenyl-1-azaazulene

A mixture of 2-phenyl-1-azaazulene (**5a**) (0.0512 g, 0.25 mmol), NBS (0.067 mg, 0.375 mmol), and dibenzoyl peroxide (0.010g, 0.04 mmol) in carbon tetrachloride (10 mL) was stirred at rt for 4 h. The mixture was poured into water and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel with benzene to give **5c** (0.055 g, 77%).

Reaction of 2-chloro-3-bromo-1-azaazulene with phenylboronic acid

A mixture of 2-chloro-3-bromo-1-azaazulene (**4d**) (0.122 g, 0.5 mmol), phenylboronic acid (0.091 g, 0.75 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.007 g, 0.01 mmol) in toluene (10 mL) was heated for 4 h at 110 °C. The mixture was poured into water, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with benzene to give recovered **4d** (0.038 g, 31%), 2-chloro-3-phenyl-1-azaazulene⁹ (**6**) (0.037 g, 31%), and 2,3-diphenyl-1-azaazulene¹⁰ (**5d**) (0.029 g, 21%), successively.

5d: Purple needles (from pentane), mp 119-121 °C (lit.,¹⁰ mp 121-122 °C); δ_{H} 7.29-7.36 (3H, m, H-*m,p*-Ph), 7.37-7.51 (5H, m, H-*o,m,p*-Ph), 7.53 (1H, ddd, *J* 10.2, 9.3 and 1.2, H-6), 7.73 (1H, dd, *J* 10.2, and 9.5, H-7), 7.79 (1H, dd, *J* 10.0 and 9.3, H-5), 7.82-7.87 (2H, m, H-*o*-Ph), 8.32 (1H, d, *J* 10.0, H-4), and 8.73 (1H, dd, *J* 9.5 and 1.2, H-8); δ_{C} 125.79, 127.28, 128.32, 128.74, 128.80, 129.04, 129.53, 130.04, 130.88, 134.40, 135.04, 135.55, 136.01, 137.42, 145.73, 157.59, and 164.50; $\nu_{\text{max}} / \text{cm}^{-1}$ 1596 (C=N).

6: Red oil; δ_{H} 7.40-7.60 (5H, m), 7.61 (1H, dd, *J* 10.1 and 9.5, H-5), 7.76 (1H, dd, *J* 10.0, and 9.6, H-7), 7.86 (1H, dd, *J* 10.0 and 9.5, H-6), 8.42 (1H, d, *J* 10.1, H-4) and 8.61 (1H, d, *J* 9.6, H-8); δ_{C} 124.20, 127.74, 129.68, 129.85, 130.23, 130.34, 132.00, 134.24, 136.02, 138.44, 143.48, 155.44, and 156.21; $\nu_{\text{max}} / \text{cm}^{-1}$ 1592 (C=N); *m/z* (rel intensity) 375 (M^+ , 9), 373 (M^+ , 38), 303 (16), 302 (13), 301 (76), 300 (48), 258 (24), 256 (100), 231 (21), 230 (21), 229 (56), and 228 (49); Picrate of **6**: orange needles, mp 199 °C (decomp) (lit.,⁹ mp 199 °C (decomp)). *Anal.* Calcd for $\text{C}_{21}\text{H}_{13}\text{N}_4\text{O}_7\text{Cl}$: C, 53.79; H, 2.77; N, 11.95. Found: C, 53.96; H, 2.61; N, 11.97.

Reaction of 2-chloro-3-iodo-1-azaazulene with phenylboronic acid

A mixture of 2-chloro-3-iodo-1-azaazulene (**4e**) (0.145 g, 0.5 mmol), phenylboronic acid (0.091 g, 0.75 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.007 g, 0.01 mmol) in toluene (10 mL) was heated for 8 h at 110 °C. The mixture was poured into water, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with benzene to give **6** (0.100 g, 83%).

Reaction of 2-chloro-3-iodo-1-azaazulene with bis(pinacolato)diboron

A mixture of 2-chloro-3-iodo-1-azaazulene (0.145 g, 0.5 mmol), bis(pinacolato)diboron (0.192 g, 0.75 mmol), potassium carbonate (0.138 g, 1.0 mmol), and $\text{PdCl}_2(\text{dppf})_2$ (0.025 g, 0.03 mmol) in DMSO (10

mL) was heated for 5 h at 80 °C. The mixture was poured into water, and extracted with benzene. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel column with chloroform to give ethyl 3,3'-bi(2-chloro-1-azaazulene) (**8**) (0.047 g, 57%) and (2-chloro-1-azaazulen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**) (0.018 g, 14%), successively.

7: Yellow powder; δ_{H} 1.43 (12H, s, Me), 7.82 (1H, like t, J 10.2, H-5), 7.87 (1H, dd, J 10.2 and 9.6, H-7), 7.93 (1H, like t, J 9.6, H-6), 8.62 (1H, dd, J 9.6 and 1.0, H-8), and 9.19 (1H, d, J 9.9, H-4); δ_{C} 25.36, 83.87, 112.38, 131.73, 131.98, 135.79, 137.46, 138.50, 154.05, 159.09, and 164.99.

8: Red prisms (from hexane-dichloromethane), mp >300 °C; δ_{H} 7.68 (2H, dd, J 10.1 and 9.4, H-5), 7.90 (2H, like t, J 9.9, H-7), 7.96 (2H, like t, J 9.6, H-6), 8.11 (2H, d, J 10.1, H-4), and 8.73 (2H, dd, J 9.5 and 1.1, H-8); δ_{C} 113.66, 129.20, 129.88, 133.76, 135.41, 137.62, 144.07, 155.46, and 157.02; ν_{max} / cm^{-1} 1590 and 1580 (C=N); m/z (rel intensity) 327 ($\text{M}^+ + 1$, 26), 325 ($\text{M}^+ + 1$, 44), 255 (6), 253 (8), 228 (14), 111 (30), and 100 (100). *Anal.* Calcd for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{Cl}_2$: C, 66.48; H, 3.10; N, 8.61. Found: C, 66.79; H, 3.27; N, 8.45.

X-Ray structure determination

Crystal data of 8: dark red prism, $\text{C}_{18}\text{H}_{10}\text{N}_2\text{Cl}_2$, $M = 325.20$, monoclinic, space group C2/c , $a = 12.477(2)$ Å, $b = 7.385(2)$ Å, $c = 15.134(2)$ Å, $\beta = 93.89(1)^\circ$, $V = 1476.1(4)$ Å³, $Z = 4$, $D_{\text{calc}} = 1.463$ g/cm³, crystal dimension 0.22 x 0.48 x 0.62 mm. Data were measured on a Rigaku AFC 5S radiation diffractometer with graphite-monochromated Mo-K α radiation. Total 1912 reflections (1827 unique) were collected using ω -2 θ scan technique with in a 2 θ range of 55.0°. The structure was solved by direct methods (SIR92),¹² and refined a full-matrix least squares methods using TEXAN structure analysis software¹³ with 100 variables and 1174 observed reflections [$I > 2\sigma(I)$]. The final refinement converged to $R = 0.055$ and $R_w = 0.062$.

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