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Palladium-Catalyzed Coupling Reactions for the Functionalization of BODIPY Dyes with Fluorescence Spanning the Visible Spectrum

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The BODIPY fluorophore can easily be functionalized at the 3- (and 5-)position(s) with one or two aryl, ethenylaryl and ethynylaryl moieties by palladium-catalyzed coupling reactions of the 3,5-dichloroBODIPY derivative using the Stille, Suzuki, Heck and Sonogashira reactions. The fluorescence excitation and emission spectral maxima of the novel BODIPY derivatives range from green to near-infrared. The new class of ethynylaryl-substituted BODIPY dyes are extremely bright fluorescent compounds.

Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) derivatives[1] have become the preferred fluorophores in new fluorescent probes that have found widespread applications in numerous fields of modern medicine and science.[2] This is a result of their valuable characteristics, such as their elevated photostability relative to other dyes (such as fluorescein), their relatively high absorption coefficients and fluorescence quantum yields as well as a relatively short synthesis for the simpler derivatives. Furthermore, BODIPY dyes can be photoexcited with visible light (excitation/emission wavelengths above 500 nm) and show narrow absorption and emission bands with high peak intensities. Moreover, they are amenable to structural modification so that their spectroscopic properties can be fine-tuned by introducing suitable substituents at the right positions. Some recent articles on BODIPY-based chemosensors have described probes for H^+,[3] Na^+,[4] K^+,[5] Ca^{2+},[6] Zn^{2+},[7] Ag^+[8] and Cu^+.[9]

While there are several possible positions on the borondipyrromethene chromophore at which functionalization can be carried out, appropriate substituents at the 3(,5)-position(s) can cause a shift in the excitation and emission bands as a function of solvent polarity/polarizability. Recently, we reported the functionalization of BODIPY dyes by nucleophilic substitution of the 3,5-dichloro substituents of 3,5-dichloro-4,4-difluoro-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**1**).[10] Hence, BODIPY derivatives with uncommon substituents, such as oxygen, nitrogen, sulfur and carbon nucleophiles, at the 3,5-positions could be synthesised. 3,5-DichloroBODIPY analogs such as **1** appear to have a reactivity similar to that of a heterocyclic imidoyl chloride[11] and thus it occurred to us that transition-metal-catalyzed reactions could be a viable way of preparing conjugated BODIPY derivatives **2** (i.e., asymmetrically substituted) and **3** (i.e., symmetrically substituted) by the Stille, Suzuki, Heck and Sonogashira coupling reactions (Scheme 1).

Lately, BODIPY derivatives with absorption and emission spectra shifted towards longer wavelengths have been synthesized by extending the conjugation of the BODIPY core at the 3,5-positions. This normally would involve the synthesis of the corresponding 2-substituted pyrrole building block **4** followed by a condensation reaction with an aromatic aldehyde or acyl chloride **5** (Scheme 2).

Starting from 2-arylpyrroles (**4** with $R^1 = R^2 = H$, $R^3 =$ aryl), this pathway was indeed followed for the synthesis of BODIPY dyes with 3,5-diaryl substituents.[6,12] Similarly, a pair of 3,5-distyryldifluoroboradiaza-*s*-indacenes were obtained by the same reaction pathway (Scheme 2) starting from 2-styrylpyrrole.[13] Borondipyrromethene analogs with an ethenylaryl (vinylaryl) substituent at the 3-position have been synthesized by an alternative condensation reaction[8,14] between an appropriate aldehyde and the corresponding 3,5-dimethylBODIPY derivatives. A series of patented BODIPY dyes[15] with 3(,5)-(di)vinylaryl and vinylheteroaryl substituents as bathochromic moieties have been prepared via dipyrromethene intermediates formed by acid-catalyzed condensation of appropriately substituted 2-(or 5-)acylpyrrole with a suitably substituted pyrrole followed by cyclization with $BF_3 \cdot Et_2O$ in the presence of a base. Difluoroboradiaza-*s*-indacene dyes with ethynylaryl substitu-

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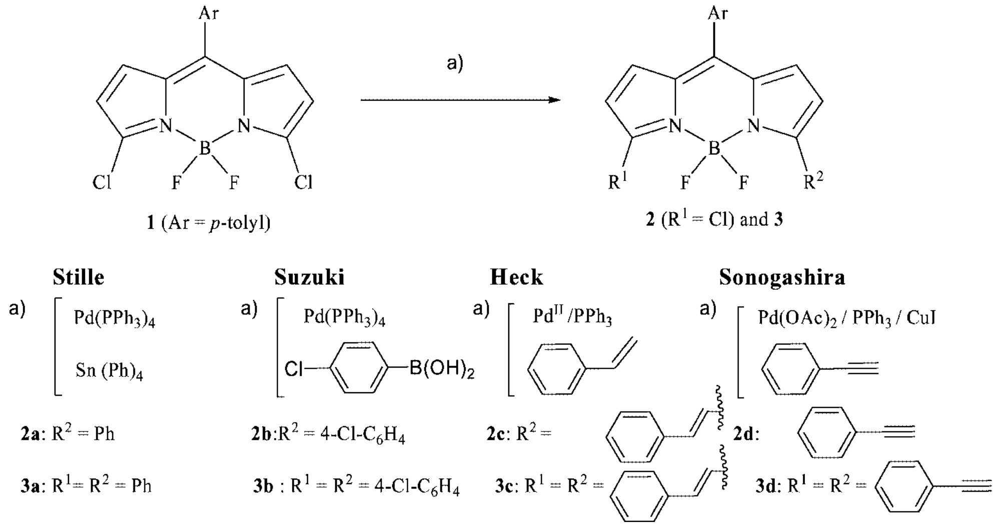
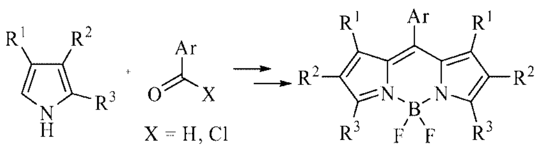


Scheme 1. Palladium-catalyzed coupling reactions of **1**.



4 **5** **6**

Scheme 2. General synthesis of BODIPY.

ents at the 3(,5)-position(s) are, to the best of our knowledge (from a computerized structure search), hitherto unknown.

Here we wish to report that the replacement of the chlorine atoms of the 3,5-dichloroBODIPY derivative **1** by aryl, ethenylaryl and ethynylaryl can be readily achieved by palladium-catalyzed reactions (Stille, Suzuki, Heck and Sonogashira) under mild conditions. Asymmetrical monosubstituted (**2**) and symmetrical disubstituted (**3**) products can be successfully prepared as shown in Scheme 1. The derivatives **2** can be modified further because the imidoyl chloride can be replaced by another (O, S, N or C) nucleophile[5,10] or an aryl, vinylaryl or ethynylaryl group by transition-metal-catalyzed coupling reactions. The UV/Vis absorption and fluorescence data of these novel fluorophores indicate that the extended conjugation shifts their excitation and emission maxima to longer wavelengths than comparable alkyl-substituted materials and frequently leads to extremely bright, fluorescent dyes.

Results and Discussion

Synthesis

First, the 3,5-dichloroBODIPY derivative **1** was allowed to react under the conditions of the Stille coupling reaction[16] for a relatively short time (30 min) with an equimolar amount of tetraphenyltin. In this case, the monophenyl-substituted BODIPY **2a** was obtained as the main product. If the reaction was run for a longer time (24 h) with twice the amount of tetraphenyltin, the disubstituted compound **3a** was obtained. An alternative arylation method is the Suzuki coupling reaction.[17] Thus, **1** was treated with one equivalent of 4-chlorophenylboronic acid under microwave irradiation[18] for a short time to afford the monoarylated derivative **2b**. Attempts to carry out the reaction without microwave irradiation were not successful. Two equivalents of the boronic acid and a longer reaction time afforded the diarylated **3b**.

Next, the Heck coupling reaction[19] was tried starting from 3,5-dichloroBODIPY **1** and styrene. With a slight excess of styrene and Pd^{II}/triphenylphosphane as catalyst,[20] the monosubstituted BODIPY **2c** was obtained. Longer reaction times and a greater excess of styrene yielded the disubstituted derivative **3c**. Only the *trans* isomers of **2c** and **3c** were observed.

Finally, the Sonogashira reaction[21] with **1** and phenylacetylene was tried under standard conditions.[22] Again, the monosubstituted derivative **2d** could be obtained selectively (as monitored by thin-layer chromatography, TLC) by controlling the reaction time and using only one equivalent of acetylene. The disubstituted compound **3d** was obtained analogously by increasing the amount of equivalents used and the reaction time. Compounds **2d** and **3d** are the first reported 3-ethynyl- and 3,5-diethynyl-substituted difluoroboradiaza-*s*-indacene derivatives. We should mention that Burgess and co-workers[23] reported the synthesis of 2-(9-anthrylethynyl)-substituted BODIPY derivatives by the Sonogashira reaction of the corresponding 2-iodoBODIPYs, but the absorption spectra of these compounds did not show a significant bathochromic shift and the resulting dyes had in general a rather low fluorescence quantum yield.

The reaction conditions and yields of the palladium-catalyzed coupling reactions of **1** are compiled in Table 1.

Table 1. Palladium-catalyzed coupling reactions of **1**.

Reagent (equiv.)	Solvent	Temp. [°C]	Reaction time	Product	Yield [%]
Tetraphenyltin (1)	toluene	reflux	30 min	**2a**	63
Tetraphenyltin (2)	toluene	reflux	24 h	**3a**	50
4-$ClC_6H_4B(OH)_2$[a] (1)	DME[b]	150	5 min	**2b**	60
4-$ClC_6H_4B(OH)_2$[a] (2)	DME[b]	150	20 min	**3b**	68
Styrene (1.5)	DMF	100	1 h	**2c**	61
Styrene (2.5)	DMF	100	8 h	**3c**	52
Phenylacetylene (1)	DMF/Et_3N[c]	80	1 h	**2d**	59
Phenylacetylene (2.2)	DMF/Et_3N[c]	80	3 h	**3d**	57

[a] MW irradiation, 200 W. [b] 1,2-Dimethoxyethane. [c] A 1:1 (v/v) mixture.

Spectroscopic Properties

To study the spectroscopic properties of the new BODIPY dyes **2** and **3**, their UV/Vis absorption and fluorescence spectra in methanol and cyclohexane were recorded. As an example, Figure 1 shows the absorption and steady-state fluorescence emission spectra of **2a** and **3d** dissolved in methanol and **2c** and **3c** in cyclohexane. The absorption spectra of all the new dyes are of comparable shape to those of previously described borondipyrromethene dyes,[24] that is, a narrow absorption band with a maximum above 520 nm, assigned to the S_0–S_1 transition. An additional, weaker, broad absorption band, attributed to the S_0–S_2 transition, is observed at a shorter wavelength. The absorption spectra of the monosubstituted compounds **2** are always blue-shifted (by 20 to 50 nm) relative to the corresponding disubstituted derivatives **3**. All compounds show emission features typical of BODIPY, that is, a narrow, slightly Stokes-shifted fluorescence emission band of mirror image shape. The emission maxima of compounds **3** are shifted to longer wavelengths (by 30 to 60 nm) relative to the corresponding 3-chloro-substituted dyes **2**.

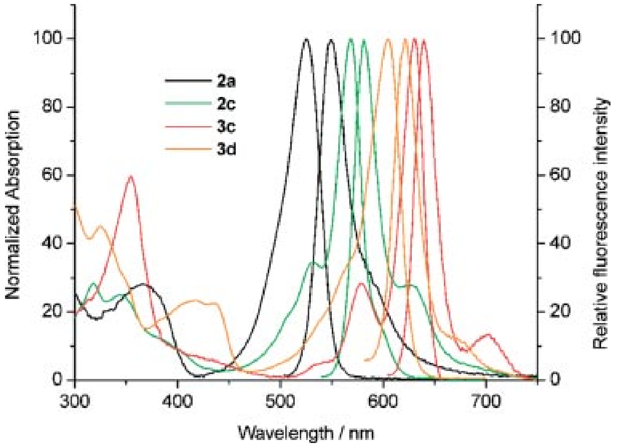


Figure 1. Normalized absorption and fluorescence emission spectra of **2a** (black) in methanol, **2c** (green) in cyclohexane, **3c** (red) in cyclohexane and **3d** (orange) in methanol.

Introduction of styryl substituents (at the 3-position in **2c** and at the 3- and 5-positions in **3c**) causes the largest bathochromic shift in both the absorption (excitation) and emission spectra. The fluorescence quantum yields of **2c** and **3c** (>0.5) are significantly higher than those of the corresponding aryl-substituted dyes **2a**, **2b** and **3a**, **3b**. BODIPY derivatives **2d** and **3d** (with ethynylaryl groups) also shift the spectral maxima to longer wavelengths compared with aryl-substituted dyes, but to a lesser degree than the vinylaryl compounds **2c** and **3c**. Additionally, the fluorescence quantum yields of **2d** and **3d** are extremely high (ca. 1.0). The replacement of the chlorine atoms by aryl, ethenylaryl and ethynylaryl residues yields dyes with absorption (excitation) maxima ranging from green to red and emission maxima stretching to the near-infrared spectral region with very high (nearly 1.0) fluorescence quantum yields.

Table 2 summarizes the photophysical data [the wavelengths of the spectral maxima (λ_{abs}, λ_{em}), the Stokes shifts ($\Delta\tilde{\nu} = \tilde{\nu}_{abs} - \tilde{\nu}_{em}$ with $\tilde{\nu}_{abs} = 1/\lambda_{abs}$ and $\tilde{\nu}_{em} = 1/\lambda_{em}$) and the fluorescence quantum yields (φ_f)] of all the new BODIPY compounds (**2a**–**d**, **3a**–**d**) in methanol and cyclohexane. The excitation maxima coincide exactly with the absorption maxima. The absorption (excitation) and emission spectra are shifted considerably by the substitution pattern at the 3- and 5-positions relative to the alkyl-substituted analogues.

Table 2. Absorption and fluorescence emission spectroscopic data of compounds **2a**–**d** and **3a**–**d** in methanol and cyclohexane.

BODIPY	Solvent	$\lambda_{abs,max}$ [nm]	$\lambda_{em,max}$ [nm]	$\Delta\tilde{\nu}$ [cm^{-1}]	φ_f[a]
2a	MeOH	525	549	833	0.04
	cyclohexane	530	553	785	0.08
2b	MeOH	525	549	833	0.03
	cyclohexane	529	551	755	0.11
2c	MeOH	564	579	459	0.55
	cyclohexane	569	581	363	0.72
2d	MeOH	556	569	411	0.98
	cyclohexane	564	575	339	1.00
3a	MeOH	547	582	1100	0.21
	cyclohexane	553	585	989	0.31
3b	MeOH	554	590	1101	0.39
	cyclohexane	559	591	969	0.56
3c	MeOH	626	639	325	0.92
	cyclohexane	630	642	297	0.96
3d	MeOH	605	622	452	1.00
	cyclohexane	615	626	286	1.00

[a] Fluorescence quantum yield measured with rhodamine 6G in water (φ_f = 0.78) or cresyl violet acetate in methanol (φ_f = 0.55) as reference. The φ_f values are corrected for possible differences in refractive index between the solvents used for sample and reference measurements.

A complete, detailed photophysical study of the new aryl, styryl and ethynylaryl-substituted difluoroboradiaza-*s*-indacene derivatives will be published separately.

Conclusions

To conclude, the readily obtained 3,5-dichloroBODIPY can be selectively coupled to one or two aryl, vinylaryl and ethynylaryl groups in good yields using well-known palladium-catalyzed (Stille, Suzuki, Heck and Sonogashira) coupling reactions. In this way, we now have a successful, straightforward approach towards symmetrical and asymmetrical BODIPY compounds with substitution patterns that are otherwise difficult to realize. For such compounds a multi-step procedure would normally be needed, starting from 2-substituted pyrroles that are difficult to obtain.[12] This is especially true for the hitherto unknown acetylene derivatives **2d** and **3d**. The asymmetrical derivatives **2** can be transformed further because the imidoyl chloride can be exchanged for another (O, S, N, C) nucleophile[5,10] or aryl, vinylaryl and ethynylaryl group by transition-metal-catalyzed coupling reactions. Structural modification of the difluoroboradiaza-*s*-indacene core with conjugation-extending residues at the 3- (and 5-)position(s) significantly affects the photophysics of the BODIPY fluorophore, causing bathochromic shifts in both the absorption and emission spectra compared with the alkyl-substituted counterparts and often leads to extremely high fluorescence quantum yields.

Experimental Section

General Methods: ^{1}H, ^{13}C and DEPT NMR spectra were recorded with a Bruker-300 Avance instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. All spectra were recorded in CDCl$_3$. ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane (δ = 0.00 ppm), using the residual solvent signal as the internal reference. ^{13}C chemical shifts are reported in ppm with CDCl$_3$ (δ = 77.67 ppm) as the internal standard. Chemical shift multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Low-resolution mass spectra were obtained with a Hewlett–Packard 5989A MS instrument (EI mode). High-resolution mass data were obtained with a KRATOS MS50TC instrument. Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. The absorption measurements were performed with a Perkin–Elmer Lambda 40 UV/Vis spectrophotometer. Corrected steady-state excitation and emission spectra were recorded on a SPEX Fluorolog instrument. To determine the relative fluorescence quantum yields (φ_f), only dilute solutions with an absorbance below 0.1 at the excitation wavelength were used. The fluorescence quantum yields (φ_f) of the indicators were determined using rhodamine 6G in water (φ_f = 0.78) or cresyl violet acetate in methanol (φ_f = 0.55).[25] The φ_f values reported in this work are the average values of multiple (generally three) independent measurements. All measurements were performed at 20 °C.

Synthesis of 5-Chloro-4,4-difluoro-3-(phenylethynyl)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (2d): Copper(I) iodide (0.0143 mmol, 2.8 mg), Pd(OAc)$_2$ (0.0143 mmol, 3.2 mg) and triphenylphosphane (0.02857 mmol, 7.5 mg) were added to 3,5-dichloro-4,4-difluoro-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**1**) (0.2857 mmol, 100 mg) under argon. Phenylacetylene (0.2857 mmol, 31 µL) was added to this mixture through a syringe, followed by triethylamine (1 mL) and *N*,*N*-dimethylformamide (DMF, 1 mL). The reaction mixture was heated at 80 °C (oil bath) for 1 h. After the appearance of a new product, as indicated by a color change and detected by TLC, the reaction was quenched by addition of 1 M HCl (50 mL). The product was extracted with diethyl ether (3×40 mL) and the organic layers washed with H$_2$O (3×40 mL). The solvent was dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether/dichloromethane (60:40, v/v) as eluent. Compound **2d** (70.2 mg, 59% yield) was obtained as blue crystals. M.p. 193–194 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.70–7.67 (m, 3 H, *ortho* and *para*), 7.43 (m, 4 H), 7.33 (d, J = 7.3 Hz, 2 H), 6.91 (d, J = 5.5 Hz, 1 H), 6.88 (d, J = 4.6 Hz, 1 H), 6.7 (d, J = 4.6 Hz, 1 H), 6.43 (d, J = 3.7 Hz, 1 H), 2.47 (s, CH$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 160.4 (s), 135.7 (d), 134.2 (s), 133.1 (s), 130.8 (d), 129.7 (s), 129.1 (s), 128.3 (d), 127.1 (d), 125.3 (d), 122.1 (s), 119.5 (s), 117.2 (d), 110.4 (d), 89.6 (s), 80.2 (s), 21.3 (q) ppm. LRMS (EI, 70 eV): *m*/*z* (%) = 416 (100) [M]$^+$, 418 (32), 322 (25), 301 (11), 291 (10), 230 (12), 221 (13), 217 (22), 207 (13), 203 (10). HRMS: calcd. for C$_{24}$H$_{16}$BClF$_2$N$_2$ [M]$^+$ 416.1063: found 416.1062.

Synthesis of 4,4-Difluoro-3,5-bis(phenylethynyl)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (3d): Copper(I) iodide (0.0143 mmol, 2.7 mg), Pd(OAc)$_2$ (0.0143 mmol, 3.2 mg) and triphenylphosphane (0.003 mmol, 7.5 mg) were added to a suspension of **1** (0.2857 mmol, 100 mg) under argon. Phenylacetylene (0.63 mmol, 69 µL) was added to this mixture through a syringe followed by triethylamine (1 mL) and DMF (1 mL). The reaction mixture was heated at 80 °C (oil bath) for 3 h. After disappearance of the starting material (monitored by TLC), work-up was carried out by the addition of 1 M HCl (50 mL). The water layer was extracted with diethyl ether (3×40 mL) and the combined extracts washed with water (3×40 mL). The solvent was dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of petroleum ether and dichloromethane (80:20, v/v) to give **3d** as blue crystals (78.6 mg, 57% yield). M.p. >300 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.73–7.71 (m, 4 H), 7.47 (d, J = 8.2 Hz, 2 H), 7.42–7.40 (m, 6 H), 7.36 (d, J = 8.2 Hz, 2 H), 6.91 (d, J = 3.7 Hz, 2 H), 6.74 (d, J = 4.6 Hz, 2 H), 2.49 (s, CH$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 143.2 (s), 138.7 (s), 134.1 (d), 133.9 (s), 133.1 (s), 131.4 (d), 130.5 (d), 129.8 (d), 128.1 (s), 127.3 (d), 125.6 (s), 125.0 (d), 117.2 (d), 92.6 (s), 81.3 (s), 21.7 (q) ppm. LRMS (EI, 70 eV): *m*/*z* (%) = 482 (100) [M]$^+$, 453 (16), 452 (12), 396 (25), 385 (17), 383 (42), 382 (17), 353 (49), 341 (15), 340 (12), 305 (13), 303 (132), 291 (12), 290 (23), 282 (26), 262 (100). HRMS: calcd. for C$_{32}$H$_{21}$BF$_2$N$_2$ [M]$^+$ 482.1766; found 482.1773.

Synthesis of 5-Chloro-4,4-difluoro-3-(styryl)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (2c): A mixture of **1** (0.286 mmol, 100 mg), Pd(OAc)$_2$ (0.025 mmol, 5.6 mg, 3 mol-%) and triphenylphosphane (0.0026 mol, 3 mg, 7 mol-%) was stirred at room temperature under argon for 10 min. Styrene (0.429 mmol, 0.5 mL) was added followed by dry triethylamine (0.857 mmol, 0.1 mL) and DMF (1 mL). The reaction mixture was heated at 100 °C for 1 h in a one-necked flask. After completion of the reaction (monitored by TLC), the mixture was poured into water (40 mL). The organic layer was extracted with CH$_2$Cl$_2$ (3×40 mL) and dried (MgSO$_4$). The solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel with petroleum ether/dichloromethane (60:40, v/v) as eluent. Compound **2c** (72.9 mg, 61% yield) was obtained as violet crystals. M.p. 195–196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.80 (s, 1 H), 7.74 (s, 1 H), 7.65 (d, J = 6.4 Hz, 2 H), 7.42–7.32 (m, 4 H), 7.33 (d, J = 8.2 Hz, 2 H), 6.99 (d, J = 4.6 Hz, 1 H), 6.94 (d, J = 4.6 Hz, 1 H), 6.74 (d, J = 3.6 Hz, 1 H), 6.37 (d, J = 3.6 Hz, 1 H), 2.5 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.8 (s), 141.1 (d), 140.6 (s), 138.9 (s), 136.4 (s), 134.6 (s), 131.7 (d), 130.9 (d), 130.0 (d), 129.5 (d), 129.3 (d), 128.5 (d), 128.1 (d), 119.4 (s), 117.5 (d), 115.6 (d) ppm. LRMS (EI, 70 eV): *m/z* (%) = 418 (100) $[M]^+$, 420 (30), 399, 384 (7), 363 (6), 348 (6), 322 (17), 316 (9), 287 (8), 279 (7), 247 (10), 207 (12), 193 (13), 179 (15), 165 (19), 163 (16), 153 (14). HRMS: calcd. for $C_{24}H_{18}BClF_2N_2$ $[M]^+$ 418.1220; found 418.1209.

Synthesis of 4,4-Difluoro-3,5-bis(styryl)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (3c): In a one-neck flask, a mixture of **1** (100 mg, 0.286 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg, 3 mol-%) and triphenylphosphane (0.003 mol, 3 mg, 7 mol-%) was stirred at room temperature under argon for 10 min. Styrene (0.629 mmol, 0.7 mL), dry triethylamine (1.143 mmol, 0.2 mL) and DMF (1 mL) were added to the mixture and heated at 100 °C for 8 h. After disappearance of the starting material (monitored by TLC), the reaction was quenched by the addition of H_2O (40 mL). The organic layer was extracted with CH_2Cl_2 (3 × 40 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel with petroleum ether/dichloromethane (80:20, v/v) as eluent giving **3c** as a blue solid (72.3 mg, 52% yield). M.p. 172–173 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (s, 1 H), 7.76 (s, 1 H), 7.66 (d, J = 8.4 Hz, 4 H), 7.44–7.39 (m, 6 H), 7.35 (s, 2 H), 7.33–7.1 (m, 4 H), 6.93 (d, J = 4.6 Hz, 2 H), 6.84 (d, J = 4.6 Hz, 2 H), 2.46 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.9 (s), 139.5 (s), 139.3 (s), 135.9 (d), 135.8 (s), 135.6 (s), 130.9 (d), 129.8 (d), 129.0 (s), 128.4 (d), 128.3 (d), 128.1 (d), 126.9 (d), 118.8 (d), 115.5 (d), 20.7 (q) ppm. LRMS (EI, 70 eV): *m/z* (%) = 486 (100) $[M]^+$, 467 (46), 409 (12), 397 (12), 307 (19), 257 (14). HRMS: calcd. for $C_{32}H_{25}BF_2N_2$ $[M]^+$ 486.2079; found 486.2084.

Synthesis of 5-Chloro-3-(*p*-chlorophenyl)-4,4-difluoro-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (2b): *p*-Chlorophenylboronic acid (0.25 mmol, 39.1 mg), Na_2CO_3 (0.75 mmol, 79.5 mg) and a catalytic amount of $Pd(PPh_3)_4$ (0.008 mmol, 8.6 mg) were added To a solution of **1** (0.25 mmol, 87.5 mg) in 1,2-dimethoxyethane (DME, 3 mL). The reaction was stirred under microwave irradiation for 5 min at 150 °C and 200 W. The reaction was quenched by the addition of H_2O (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by chromatography on silica gel, eluting with a mixture of petroleum ether and dichloromethane (80:20, v/v) to give **2b** as a red solid (64.2 mg, 60% yield). M.p. 167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.9 (d, J = 8.6 Hz, 2 H), 7.5 (d, J = 7.8 Hz, 2 H), 7.4 (d, J = 8.6 Hz, 2 H), 7.3 (d, J = 7.8 Hz, 2 H), 7.0 (d, J = 4.6 Hz, 1 H), 6.9 (d, J = 3.6 Hz, 1 H), 6.6 (d, J = 4.6 Hz, 1 H), 6.5 (d, J = 3.6 Hz, 1 H), 2.40 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.8 (s), 139.6 (s), 138.8 (s), 138.1 (s), 137.4 (d), 136.1 (s), 135.4 (s), 131.9 (s), 131.2 (d), 130.1 (s), 130.9 (d), 130.5 (d), 129.4 (s), 128.9 (d), 119.7 (d), 115.3 (d), 22.6 (q, CH_3) ppm. LRMS (EI, 70 eV): *m/z* (%) = 426 (100) $[M]^+$, 428 (67), 430 (12), 413 (16), 411 (25), 393 (24). HRMS: calcd. for $C_{22}H_{15}BCl_2F_2N_2$ $[M]^+$ 426.0673; found 426.0677.

Synthesis of 3,5-Bis(*p*-chlorophenyl)-4,4-difluoro-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (3b): Compound **1** (0.25 mmol, 87.5 mg) was dissolved in DME (3 mL). *p*-Chlorophenylboronic acid (0.5 mmol, 78.1 mg) and $NaHCO_3$ (0.75 mmol, 79.5 mg) were added in the presence of a catalytic amount of tetrakis(triphenylphosphane)palladium (0.008 mmol, 8.6 mg). The reaction mixture was stirred under microwave irradiation for 20 min at 150 °C with a power of 200 W. After addition of H_2O (30 mL), the organic layer was extracted with CH_2Cl_2 (3 × 40 mL). The residue was purified by chromatography with petroleum ether/dichloromethane (70:30, v/v) as eluent to give **3b** as dark red crystals (85.4 mg, 68% yield). M.p. 172–173 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.81 (d, J = 8.2 Hz, 4 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.41 (d, J = 8.2 Hz, 4 H), 7.36 (d, J = 8.2 Hz, 2 H), 6.93 (d, J = 3.7 Hz, 1 H), 6.61 (d, J = 3.7 Hz, 2 H), 2.49 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.7 (s), 145 (s), 141.2 (s, C–Cl), 136.9 (s), 136.2 (s), 131.7 (d), 131.5 (d), 131.4 (d), 131.0 (d), 129.5 (s), 128.9 (d), 121.1 (d), 21.8 (q, CH_3) ppm. LRMS (EI, 70 eV): *m/z* (%) = 502 (100) $[M]^+$, 504 (36), 506 (7), 487 (5), 467 (3), 391 (3), 368 (4). HRMS: calcd. for $C_{28}H_{19}BCl_2F_2N_2$ $[M]^+$ 502.0986; found 502.0987.

Synthesis of 5-Chloro-4,4-difluoro-3-phenyl-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (2a): Under argon, **1** (0.286 mmol, 100 mg) was dissolved in toluene (5 mL) and a 1 M solution of Na_2CO_3 (5 mL) was added. Tetrakis(triphenylphosphane)palladium catalyst (0.003 mmol, 3 mg) was added followed by an injection of tetraphenyltin (0.286 mmol, 0.1 mL). The reaction mixture was refluxed under argon for 30 min. The layers were separated and the water layer extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by chromatography on silica gel with petroleum ether/dichloromethane (60:40, v/v) as eluent to give **2a** as red crystals (70.6 mg, 63% yield). M.p. 197 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.9–7.8 (m, 3 H), 7.40–7.44 (m, 4 H), 7.35 (d, J = 8.2 Hz, 2 H), 6.99 (d, J = 3.7 Hz, 1 H), 6.91 (d, J = 3.7 Hz, 1 H), 6.65 (d, J = 3.7 Hz, 1 H), 6.53 (d, J = 3.7 Hz, 1 H), 2.48 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.5 (s, C–Cl), 146.6 (d), 143.0 (s), 141.4 (s), 137.4 (s), 136.43 (s), 134.7 (s), 132.8 (d), 131.5 (d), 131.0 (d), 130.9 (d), 130.5 (d), 129.4 (s), 128.9 (d), 120.7 (d), 118.6 (d), 21.8 (q, CH_3) ppm. LRMS (EI, 70 eV): *m/z* (%) = 392 (100) $[M]^+$, 394 (39), 378 (11), 377 (30), 357 (9). HRMS: calcd. for $C_{22}H_{16}BClF_2N_2$ $[M]^+$ 392.1063; found 392.1061.

Synthesis of 4,4-Difluoro-3,5-diphenyl-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (3a): A 1 M solution of Na_2CO_3 (5 mL) was added to **1** (0.286 mmol, 100 mg) in toluene (5 mL) and the solution was purged with argon. $Pd(PPh_3)_4$ (0.0026 mmol, 3 mg) catalyst was added. Tetraphenyltin (0.571 mmol, 0.2 mL) was added through a syringe and the reaction mixture was refluxed under argon for 24 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), the solvent evaporated and the brown residue purified by chromatography on silica gel using a mixture of petroleum ether and dichloromethane (90:10, v/v) as eluent. Compound **3a** (62.1 mg, 50% yield) was obtained as violet crystals. M.p. 231 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.88 (dd, J = 2.9, J = 1.5 Hz, 4 H), 7.51 (d, J = 8 Hz, 2 H), 7.42 (dd, J = 2.9, J = 1.5 Hz, 4 H), 7.35 (d, J = 8 Hz, 2 H), 7.25 (t, J = 1.4 Hz, 2 H), 6.92 (d, J = 3.7 Hz, 2 H), 6.62 (d, J = 3.7 Hz, 2 H), 2.49 (s, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.09 (s), 140.08 (s), 136.78 (s), 133.1 (s), 131.97 (d), 131.18 (d), 131.01 (d), 129.81 (d), 129.77 (s), 129.36 (d), 128.54 (d), 121.11 (d), 21.43 (q) ppm. LRMS (EI, 70 eV): *m/z* (%) = 434 (96) $[M]^+$, 433 (29) $[M]^+$, 419 (10), 368 (13), 313 (7), 236 (15). HRMS: calcd. for $C_{28}H_{21}BF_2N_2$ $[M]^+$ 434.1766; found 434.1760.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **2a**–**d** and **3a**–**d**.

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