RESEARCH ARTICLE doi.org/10.1002/adsc.202300408

Advanced Synthesis & Catalysis

β-Functionalization of 4a-aza-8a-boranaphthalene via Iridium-catalyzed C–H Borylation

Isabel Valencia,[a] David Sucunza,[a] Francisco Mendicuti,[b] Patricia García-García,[a,*] and Juan J. Vaquero[a,*]

[a] Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Química "Andrés M. del Río" (IQAR). Universidad de Alcalá (IRYCIS), 28805 Alcalá de Henares, Spain
E-mail: patricia.garciagarci@uah.es; juanjose.vaquero@uah.es

[b] Departamento de Química Analítica, Química Física e Ingeniería Química, Instituto de Investigación Química "Andrés M. del Río" (IQAR). Universidad de Alcalá, 28805 Alcalá de Henares, Spain

Manuscript received: April 24, 2023; Revised manuscript received: June 12, 2023;
Version of record online: July 17, 2023

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202300408

Abstract: A general method for the functionalization of 4a-aza-8a-boranaphthalene in the position β to the nitrogen atom has been developed. This method is based on a regioselective iridium-catalyzed C–H activation process for the introduction of a boronate group, which can subsequently be transformed into a variety of aryl or alkynyl groups via cross-coupling reactions. Selective mono- or difunctionalization can be achieved by controlling the reaction conditions during the borylation step. The photophysical properties of the obtained 3- or 3,6-substituted BN-naphthalenes have been evaluated, and some of them have been found to be significantly fluorescent, with fluorescence quantum yields up to 0.85.

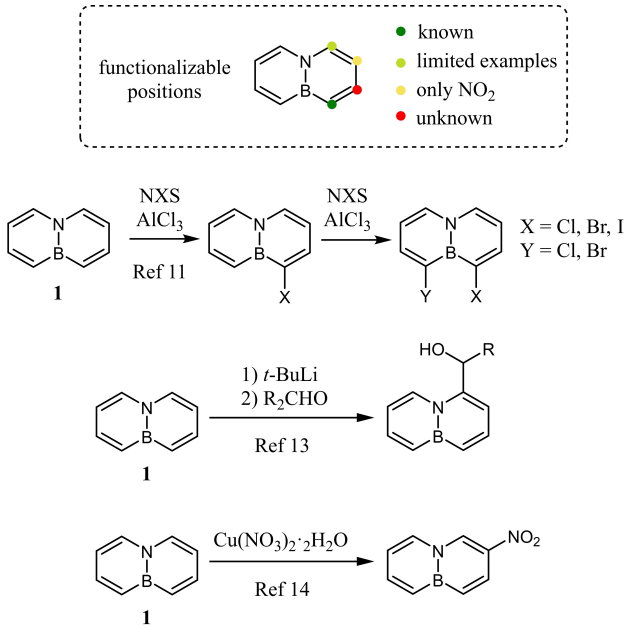
Keywords: BN-naphthalene; C–H activation; iridium; cross-coupling; catalysis

Introduction

BN-arenes show unique properties due to the presence of a polar B–N bond, while retaining aromaticity and being structurally similar to their all-carbon counterparts.[1] They have been recognized in the last few years as useful entities for the exploration of a new chemical space, and have found applications in medicinal chemistry,[2] in the design of novel ligands for coordination compounds[3] and, mainly, in the development of novel optoelectronic materials.[4] The successful implementation of novel applications of BN-arenes in any of the fields mentioned necessarily requires the availability of efficient methods for their synthesis.[5] In this regard, postfunctionalization of simple systems provides the most straightforward strategy for the preparation of substituted derivatives.[6]

Substituted naphthalene rings are present in many bioactive compounds,[7] and preliminary results on the use of BN-naphthalenes as their isosteres in medicinal chemistry have been reported.[8] For example, analogs of phosphodiesterase (PDE10 A) inhibitors containing a borazaronaphthyl group exhibited remarkable potency and metabolic stability, making them viable candidates for further studies.[8a] Moreover, two BN-isosters of propranolol have been shown to display potency and ADME – tox profiles comparable to propranolol, while having excellent bioavailability and brain penetration.[8b] Further exploration of the promising use of BN-analogs as naphthalene isosters requires the availability of methods for regioselective functionalization of the different sites of the BN-naphthalene core.[9] Moreover, functionalization of BN-naphthalene would provide a handle for the bottom-up construction of BN-polycyclic aromatic hydrocarbons (BN-PAHs).[10]

With regard to 4a-aza-8a-boranaphthalene (**1**) (Scheme 1), the isomer of BN-naphthalene in which both the nitrogen and the boron atoms are located in bridgehead positions, functionalization in α to the



Scheme 1. Functionalization of BN-naphthalene **1**.

boron atom is well established by halogenation,[11] which can be followed by further derivatization via cross-coupling reactions. Friedel-Crafts acylation also occurs at the same position.[12] In addition, some examples of functionalization in the position α to the nitrogen, via lithiation based protocols, have been reported.[13] However, the introduction of groups at β carbons is limited to a single example of nitration,[14] and methodologies for the versatile functionalization of these positions have not yet been reported.

We envisioned that iridium-catalyzed borylation,[15] which is largely dominated by steric effects,[16] could be a potential strategy to achieve β-functionalization of 4a-aza-8a-boranaphthalene **1** via C–H activation. Electronic effects, which also play a role in the regioselectivity of these reactions,[16] would favor the selective functionalization of only one of the two non-equivalent β positions.

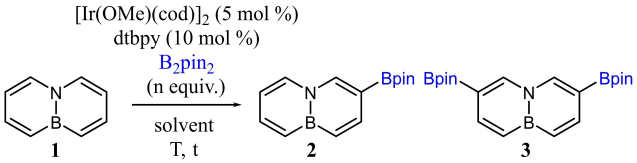
In the context of BN-arenes, C–H borylation of BN-benzenes[17] and 1-aza-2-boranaphthalenes[18] has been reported, and in both cases the presence of a N–H bond has been found to be essential for a high regioselectivity. Examples of iridium-catalyzed borylation of BN-arenes with the nitrogen atom in the bridgehead position have not been reported so far. Interestingly, the introduction of a boronate group would provide a versatile platform for further derivatizations.

Results and Discussion

In light of the above, we initially explored the borylation of BN-naphthalene **1** under conditions based on those reported for the borylation of BN-benzenes, using $[Ir(OMe)(cod)]_2$/dtbpy as catalytic system and 1.1 equivalents of B_2pin_2 in MTBE at room temperature, but only starting material was recovered (Table 1, entry 1).

Changing the solvent to hexane resulted in a 32% conversion to 3-borylated BN-naphthalene **2**, together with traces of diborylated compound **3** (entry 2). This

Table 1. Optimization of reaction conditions.[a]



entry	solvent	t (h)	T (°C)	eq	**2** (%)[b]	**3** (%)[b]
1	MTBE	24	rt	1.1	–	–
2	Hexane	24	rt	1.1	32	2
3	Hexane	72	rt	1.1	38	15
4	Hexane	24	35	1.1	53	19
5	Hexane	24	50	1.1	42	32
6	Hexane	24	80	1.1	30	52
7	Cyclohexane	24	35	1.1	**56**	35
8	Hexane	3	85	2.2	8	75
9	Cyclohexane	5	85	2.2	3	65
10	Decane	5	85	2.2	–	77
11	Decane	6	85	3	–	**87**

[a] Reactions conducted using 0.2 mmol of **1** in 1 mL of solvent.
[b] Conversion estimated by ^{1}H NMR spectroscopy (300 MHz)

result demonstrates that functionalization at the position β to the N atom is, in fact, possible by means of iridium-catalyzed borylation. Longer reaction times did not significantly increase the conversion to **2**, whereas the amount of diborylated product **3** started to rise (entry 3). With regard to temperature, the overall conversion improved upon heating, although higher temperatures favor diborylated compound **3** (entries 4–6). The best compromise between conversion and selectivity was achieved at 35 °C. At this temperature, the use of cyclohexane as solvent slightly improved the conversion to **2**, which reached a significant 56% (entry 7).

The observed regioselectivity can be suitably explained based on the previous results for the borylation of other BN-arenes[17,18] (Figure 1) and computational studies carried out by Molander.[9] Thus, borylations of BN-benzene and 1-aza-2-boranaphthalene occur at the electronically most favored position, which is the C–H bond located closer to the N–H bond. This position is, according to computational studies, the one with a greater anionic stability, which favors the borylation reaction that is known to have a significant proton-transfer character in the transition state.[19] However, if the nitrogen is substituted, no borylation at this position is observed in any of the cases, which is attributed both to the impossibility of an outer-sphere hydrogen-bond coordination with directing effect, and to the steric impediment imposed by the substituent at the nitrogen atom. In fact, these results corroborate the high influence of steric effects already described for iridium-catalyzed borylation reactions.[16]

Therefore, it is not surprising that for 4a-aza-8a-boranaphthalene, in which the N atom is located in bridgehead position (no N–H bond is present), the position α to the N atom, which is significantly hindered by peri-interaction, is not borylated despite being the one with a higher anionic stability according to the calculations done by Molander.[9]

With borylation at α position excluded by steric reasons, the selectivity between positions β and γ, which do not have significant steric interference, can be explained by electronic effects. Computational calculations performed by Molander attribute a higher anionic stability to the β position, which agrees with the observed selectivity. It is worth noting that for the borylation of *N*-substituted 1-aza-2-boranaphthalene, in which a 7:3 ratio of products is observed, a difference of anionic charge stabilization of 3.07 kcal/mol is calculated for the two borylated positions, whereas for the borylation of 4a-aza-8a-boranaphthalene reported in this work the difference for the anionic stability in β and γ is 6.73 kcal/mol, which is in agreement with the higher selectivity experimentally observed.

We also tried to optimize conditions for the synthesis of diborylated BN-naphthalene **3**. By increasing the number of equivalents of B_2pin_2 to 2.2 and using high temperatures good conversion to **3** was observed, together with minor amounts of **2** (entry 8). Among several solvents tried (entries 8–10), the best selectivity and highest conversion to **3** was obtained using decane as solvent (entry 10). A further increase in the number of equivalents of B_2pin_2 to 3 led to a higher conversion of 87%, with complete selectivity towards diborylated BN-naphthalene **3** (entry 11).

Thus, the optimal conditions for the monoborylation of **1** turned out to be the use of 5 mol% $[Ir(OMe)(cod)]_2$ and 10 mol% dtbpy, with 1.1 equiv. of B_2pin_2 in cyclohexane at 35 °C for 24 h. Under these conditions, 3-borylated BN-naphthalene **2** was isolated in a moderate 39% yield (Scheme 2). It should be noted that the small amounts of **3** formed in this reaction can be easily separated by column chromatography, thus allowing the isolation of pure **2**. Moreover, reaction of **1** with the same catalytic system, but using 3 equivalents of B_2pin_2 in decane at 85 °C for 6 h, led to **3** in good isolated yield (Scheme 2).

The introduction of a Bpin group provides a useful handle for further functionalization. Thus, palladium-catalyzed Suzuki cross-coupling of borylated compounds **2** and **3** with different (hetero)aryl bromides[20] resulted in a family of β-aryl BN-naphthalenes **4** and **5** in good yields (Scheme 3).

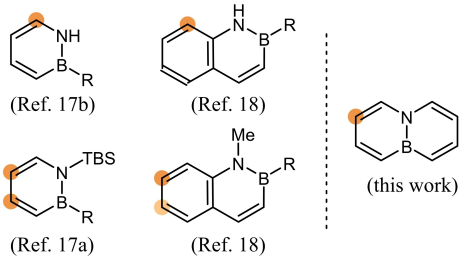
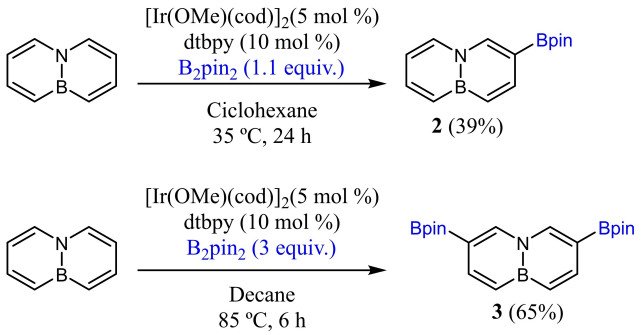
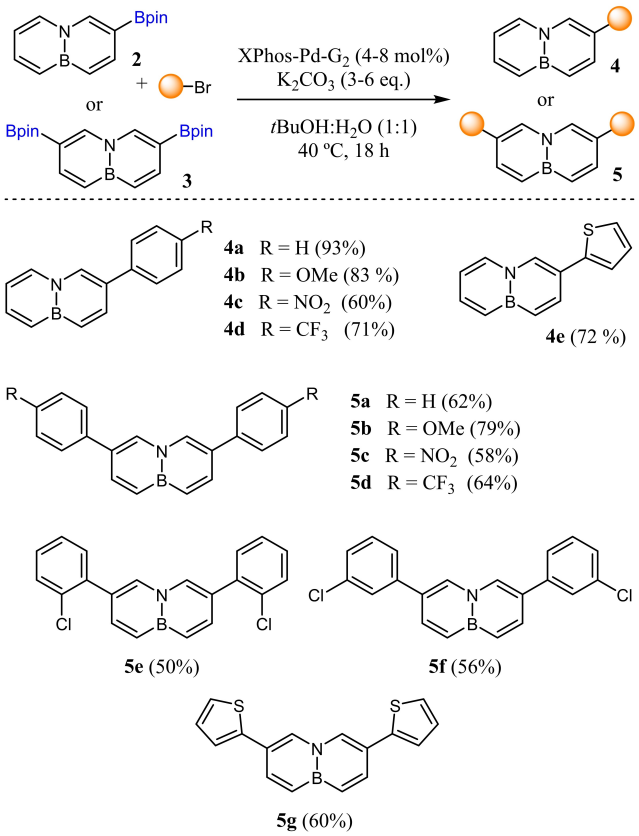


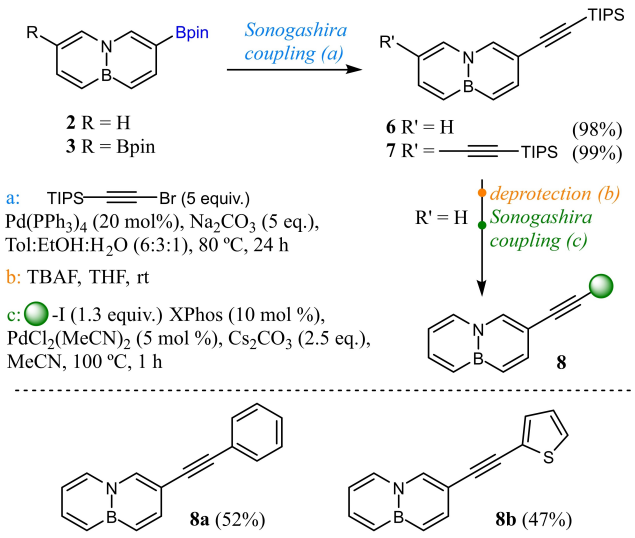
Figure 1. Experimentally observed sites of borylation for BN-arenes.



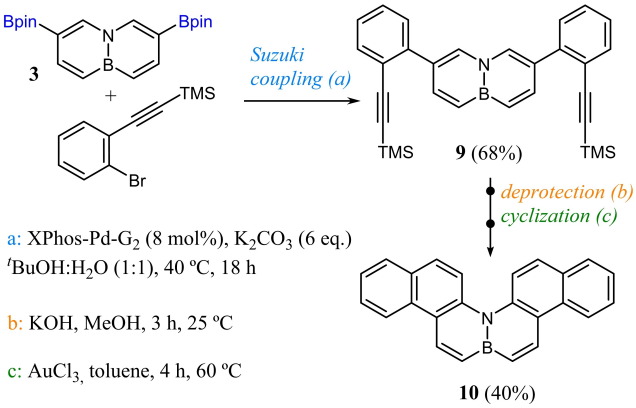
Scheme 2. Synthesis of 3-borylated BN-naphthalene **2** and 3,6-diborylated BN-naphthalene **3**.



Scheme 3. Synthesis of 3-aryl-BN-naphthalenes **4** and 3,6-diaryl-BN-naphthalenes **5**.



Scheme 4. Synthesis of 3-alkynyl-BN-naphthalenes **6** and **8** and 3,6-dialkynyl-BN-naphthalene **7**.



Scheme 5. Synthesis of BN-naphtho[1,2-*c*]chrysene **10**.

Aromatic groups with either electron-donating (**4b**, **5b**) or electron withdrawing (**4c**,**d**, **5c**,**d**) groups can be efficiently introduced in the position β to the nitrogen atom in the 4a-aza-8a-boranaphthalene core using this methodology. *Ortho*- and *meta*-substitution is also tolerated (**5e**,**f**), and the possibility of incorporating heteroaromatic groups, such as thiophene, has been demonstrated as well (**5g**).

Moreover, β-alkynyl BN-naphthalenes are also accessible via functionalization of borylated intermediates **2** and **3** (Scheme 4). Thus, the Sonogashira reaction of **2** and **3** with triisopropylsilylacetylene leads to compounds **6** and **7**, respectively, in excellent yields. In addition, conversion of **6** to the terminal alkyne by treatment with TBAF (tetrabutylammonium fluoride), followed by a Sonogashira coupling with the corresponding (hetero)aryl iodide, provides 3-alkynyl-BN-naphthalenes **8** in moderate global yields after the two steps.

Finally, the introduction of Bpin groups in the 4a-aza-8a-boranaphthalene core enables the construction of novel BN-PAHs via bottom-up approaches (Scheme 5). For example, the Suzuki cross-coupling reaction of **3** with TMS-protected *o*-bromophenylacetylene, under the usual conditions previously depicted in Scheme 3, gives rise to diarylated BN-naphthalene **9** in good yield. After deprotection of the terminal alkyne under basic conditions, a double metal-catalyzed 6-*endo* cyclization would afford previously unknown BN-naphtho[1,2-*c*]chrysene **10**.

Initial attempts of cycloisomerization using $PtCl_2$ as catalyst showed the viability of this strategy, although a low combined 27% yield for both steps was obtained. The use of $AuNTf_2PPh_3$ as catalyst lead to a less selective cyclization, with significant amounts of products coming from an *exo*-cyclization also formed. Lastly, $AuCl_3$-catalyzed cycloisomerization provided **10** with a moderate 40% yield for the deprotection-cyclization sequence.

Once we had developed an efficient methodology for the synthesis of β-substituted BN-naphthalenes, we focused on an evaluation of their main photophysical properties, the summary of which is shown in Table 2 (for additional parameters, including rate constants for

Table 2. UV/Vis and photophysical parameters for representative BN-naphthalene derivatives measured in cyclohexane at 25 °C.

cmpnd	ε ($10^{-3}\times M^{-1}$ cm^{-1}) λ (nm)[a]	λ_{abs} (λ_{exc}) (nm)[b]	λ_{em} (nm)[c]	ϕ[d]	τ <τ> (ns)[e]
napht	4.9 ± 0.2 (**285**)	266, 275, 285 (**285**)	325, 334	0.23	15.8 (m)
1	3.4 ± 0.1 (**270**)	268(s), 279, 289, 301 (**270**)	320, 327(s)	0.03	1.3 (b)
8a	16.9 ± 0.2 (**312**)	331, 325(s), 318, 312, 300(s) (**312**)	336, 352	0.59	1.2 (m)
8b	13.2 ± 1.3 (**307**)	342, 327, 319, 307(s) (**307**)	349, 362(s)	0.03	1.9 (m)
6	6.1 ± 0.1 (**296**)	320, 313, 307, 300, 296, 289 (**296**)	340(s), 352	0.12	1.0 (m)
7	20.0 ± 1.7 (**296**)	340, 333, 325, 319, 312, 306, 301 (**296**)	338(s), 359, 374, 395(s)	0.23	2.2 (m)
4a	13.5 ± 0.5 (**297**)	286(s), 297, 313(s) (**296**)	350, 359, 382(s)	0.40	2.6 (m)
4b	11.6 ± 1.3 (**305**)	281(s), 291 (s), 305(s) (**305**)	352, 364, 386(s)	0.14	3.2 (m)
4d	3.7 ± 0.8 (**300**)	283(s), 302(s) (**283**)	332, 345, 364(s)	0.16	2.1 (m)
4e	5.5 ± 0.3 (**312**)	336(s), 315 (s), 296(s) (**312**)	352(s), 366, 386(s)	0.17	0.9 (m)
5a	10.9 ± 0.1 (**297**)	305, 316(s) (**305**)	364, 374, 397(s)	0.72	2.6 (m)
5b	5.8 ± 0.1 (**319**)	319 (**319**)	356(p), 368, 395(s)	0.74	2.3 (m)
5d	13.5 ± 0.1 (**313**)	313 (**313**)	352, 365, 389(s)	0.85	2.2 (m)
5g	6.8 ± 0.2 (**336**)	315 (**312**)	352, 369, 394(s)	0.26	0.7 (m)
10	5.4 ± 0.3 (**347**)	347, 318, 308, 298 (**347**)	338(s), 357(s), 373, 398, 428	0.20	3.1 (b)

[a] Molar absorptivities measured at λ.
[b] Peaks and shoulders (s) of the π–π* absorption band appearing toward the red in the absorption spectra; excitation wavelengths for obtaining emission spectra (λ_{exc}, in bold).
[c] Peaks and shoulders (s) in the emission spectra; selected emission wavelength (in bold) for monitoring the fluorescence intensity profiles.
[d] Standard for fluorescence quantum yields (ϕ) was 9,10-diphenylanthracene in cyclohexane (ϕ = 0.93).[22]
[e] Fluorescence lifetimes obtained upon excitation of 296 nm (or 279 nm for **1**) using a NanoLed (Horiba). Intensity profiles were adjusted to monoexponential (m) or biexponential (b) decay functions.

radiative (k_r) and nonradiative (k_{nr}) deactivation processes and radiative lifetime (τ_r) see the SI).

The absorption spectra for all compounds exhibited two bands in the range 250–400 nm (Figure 2), the least energetic of which can be assigned to a π–π* transition. As expected, this band was significantly displaced to the blue for all derivatives relative to their higher conjugated BN-phenanthrene and BN-tetraphene counterparts.[21] In addition, irrespective of the substituent character, the spectra for the mono- or disubstituted BN-naphthalene derivatives studied appeared displaced to the red relative to unsubstituted derivative **1**. The extending of π-delocalization due to the presence of an additional phenyl ring when going from monosubstituted (**4a**, **4b**, **4d**, **4e**) compounds to their disubstituted (**5a**, **5b**, **5d**, **5g**) partners, also provoked a bathochromic displacement of the spectra. The greater electron-donor (−C_6H_4-OMe) or withdrawing (− C_6H_4-CF_3) substituent character also influenced the placement of the π–π* transition band. Thus **4b** (**5b**) extended this band a few nanometres toward the red compared to **4d** (**5d**), with spectra for **4a** (**5a**) somewhat in between. The presence of the heteroaromatic thiophene group (**8b**, **4e** and **5g**) caused the spectra to shift significantly to longer wavelengths when compared to those obtained for their phenyl substituent-containing partners (**8a**, **4a** and **5a**). The effect of a larger conjugation due to the presence of PhC≡C substituent in **8a** (or ThC≡C in **8b**) also displaced the π–π* band to the red relative to the one observed for compound **4a** (**4e**), which contained the Ph-group (or Th−) linked directly to the BN-naphthalene core. However, the molar absorptivity values did not seem to show any correlation with the greater or lesser conjugation, the number of substituents in the BN-naphthalene or its electron donor or acceptor character.

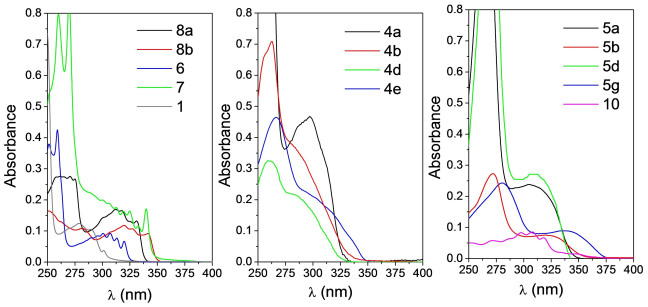


Figure 2. UV-Vis absorption spectra for selected compounds in dilute solutions of cyclohexane at 25 °C.

The emission spectra (Figure 3) showed similar characteristics to the absorption spectra. Thus, the emission of all BN-naphthalene derivatives, were significantly displaced to the blue relative to the higher

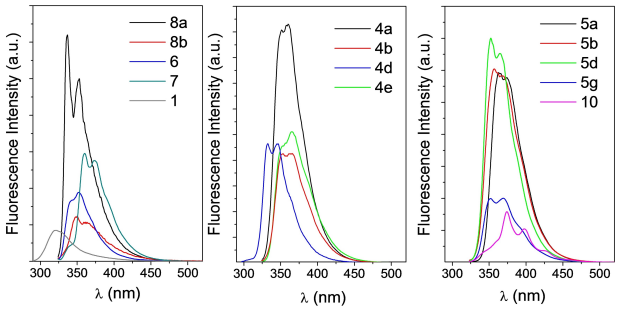


Figure 3. Emission spectra for selected compounds in dilute solutions of cyclohexane at 25 °C.

conjugated BN-phenanthrene and BN-tetraphene ones.[21] Spectra for mono- or disubstituted BN-naphthalene derivatives appeared rather displaced to the red relative to **1**. Something similar occurred when going from monosubstituted (**4a**, **4b**, **4d**, **4e**) compounds to their disubstituted (**5a**, **5b**, **5d**, **5g**) partners due to the increasing in the π-delocalization. Bathochromic displacements of the spectra were always observed. The electron donor or withdrawing character effects made the peaks for **4b** (**5b**) shift slightly to the red compared to **4d** (**5d**). The presence of the thiophene in **8b** and **4e** caused the spectra to slightly shift to the red when compared to those obtained for **8a** and **4a**, their phenyl substituent-containing partners. This effect, however, was not observed when comparing **5g** and **5a**. The larger conjugation due to the presence of a C≡C linker in **8a** (or **8b**) did, however, not translate into displacement to the red of the emission upon comparison with the spectra for compound **4a** (**4e**). In addition, the high conjugation for **10**, compared with the rest of the disubstituted BN-naphthalenes, displaced the maxima of emission to the red.

Fluorescence quantum yields (ϕ) are also collected in Table 2. Some of the compounds exhibited significantly larger values than those obtained for **1**, which was rather low, and naphthalene. In general, disubstituted derivatives, regardless of the character of the substituted group, showed larger values than their monosubstituted counterparts. The quantum yields for **5a**, **5b** and **5d** (0.72, 0.74 and 0.85 respectively) but also for **8a** (0.59), which is a monosubstituted derivative, were particularly large. The fluorescence decay profiles were obtained upon excitation with nanoleds emitting at 296 nm (or 279 nm and 335 nm for **1** and **10** respectively) by fixing the fluorescence emission at λ_{em} (in bold, Table 2). The fluorescence intensity profiles for all mono- and disubstituted BN-naphthalene derivatives could be reasonably fitted to monoexponential decay functions. The decay profile for **10**, however, was biexponential with components (contributions) around 1.4 (81%) and 9.3 ns (19%) and a weighted average lifetime ($<\tau>$) of 3.1 ns. The fluorescence lifetimes for all derivatives (in the range of 0.7 to 3.2 ns) were significantly lower than those obtained for the BN-phenanthrene and BN-tetraphene compounds.[21]

Conclusion

Functionalization of 4a-aza-8a-boranaphthalene in the position β to the N atom has been achieved via iridium-catalyzed C–H borylation. Optimization of the reaction conditions has allowed selective mono- or diborylation. Subsequent palladium-catalyzed cross-coupling reactions lead to a variety of previously unattainable BN-naphthalenes substituted with aryl or alkynyl groups at position 3 or disubstituted at positions 3 and 6. Moreover, hitherto unknown BN-PAH **10** has been synthesized in three steps from diborylated BN-naphthalene **3**, thus showing the potential of borylated BN-naphthalenes as useful building blocks for the bottom-up construction of BN-PAHs. Some of the BN-arene derivatives synthesized using the reported methodology exhibited rather high fluorescence quantum yields (up to $\phi_F = 0.85$).

Experimental Section

Synthesis of 3-borylated BN-naphthalene 2: to an oven-dried Biotage microwave vial equipped with a stir bar were added $[Ir(OMe)(cod)]_2$ (52 mg, 0.078 mmol, 5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (dtbpy) (42 mg, 0.154 mmol, 10 mol%), and bis(pinacolato)diboron (B_2pin_2) (432 mg, 1.704 mmol, 1.1 equiv.), and 7.8 mL of cyclohexane (0.2 M). The catalyst mixture was aged for 10 minutes during which it turned color from light yellow to dark brown. The neat azaborine substrate **1** (200 mg, 1.550 mmol, 1.0 equiv.) was added to the catalyst mixture. The reaction was stirred for 24 hours at room temperature. Following solvent removal the crude material was purified by silica gel chromatography using 2% EtOAc/hexane as eluent to yield 3-borylated BN-naphthalene **2** as a white solid (154 mg, 39%).

Synthesis of 3,6-diborylated BN-naphthalene 3: to an oven-dried Biotage microwave vial equipped with a stir bar were added $[Ir(OMe)(cod)]_2$ (26 mg, 0.039 mmol, 5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (dtbpy) (21 mg, 0.077 mmol, 10 mol%), and bis(pinacolato)diboron (B_2pin_2) (590 mg, 2.325 mmol, 3 equiv.), and 3.9 mL of decane (0.2 M). The catalyst mixture was aged for 10 minutes during which it turned color from light yellow to dark brown. The neat azaborine substrate **1** (100 mg, 0.775 mmol, 1.0 equiv.) was added to the catalyst mixture. The reaction was stirred for 6 hours at 80 °C. Following solvent removal the crude material was purified by silica gel chromatography using 2% EtOAc/hexane as eluent to yield 3,6-diborylated BN-naphthalene **3** as a white solid (195 mg, 65%).

General procedure for the palladium-catalyzed cross coupling of 2: to a microwave vial with a stir bar were added borylated compound **2** (20 mg, 0.078 mmol, 1.0 equiv), K_2CO_3

(32 mg, 0.234 mmol, 3.0 equiv), and XPhos-Pd–G2 catalyst (2.5 mg, 0.003 mmol, 4 mol%). The reaction vial was then capped and purged with argon. A solvent mixture of degassed *t*-BuOH/H_2O (1:1, 0.15 mL/0.15 mL, 0.25 M) was added, followed by the liquid aryl bromide (1.1 equiv). The reaction vessel was then heated at 40 °C for 18 h. Upon cooling, H_2O was added to the solution, which was extracted with CH_2Cl_2 three times, dried (Na_2SO_4), and concentrated in vacuo. The product was further purified by column chromatography with silica gel to yield 3-substituted BN-naphthalenes **4**.

General procedure for the palladium-catalyzed cross coupling of 3: to a microwave vial with a stir bar were added borylated compound **3** (1.0 equiv.), K_2CO_3 (6.0 equiv.), and XPhos-Pd–G2 catalyst (8 mol%). The reaction vial was then capped and purged with argon. A solvent mixture of degassed *t*-BuOH/H_2O (1:1, 0.25 M) was added, followed by the liquid aryl bromide (2.2 equiv.). The reaction vessel was then heated at 40 °C for 18 h. Upon cooling, the solution was added H_2O, extracted with CH_2Cl_2 three times, dried (Na_2SO_4), and concentrated in vacuo. The product was further purified by column chromatography with silica gel to yield 3,6-disubstituted BN-naphthalenes **5**.

Synthesis of 3-((triisopropylsilyl)ethynyl)-*4a*-aza-*8a*-boranaphthalene (6): to a microwave vial with a stir bar were added **2** (45 mg, 0.18 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (8.3 mg, 0.007 mmol, 4 mol%), a solution of bromo(triisopropylsilyl)acetylene (94 mg, 0.36 mmol, 2.0 equiv.) in toluene (0.1 mL), toluene (3.0 mL), EtOH (1.50 mL), and 2 M aq. Na_2CO_3 (0.5 mL, 2.5 equiv.). The resulting mixture was stirred at 80 °C for 24 h under Ar and shielded from light. After cooling to room temperature and evaporation of solvents, the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. After evaporation of solvent, the residue was purified by column chromatography on silica gel eluted with hexane to give **6** (55 mg, 0.18 mmol, 98%) as a white oil.

Synthesis of 3,6-bis((triisopropylsilyl)ethynyl)-*4a*-aza-*8a*-boranaphthalene (7): To a microwave vial with a stir bar were added **3** (20 mg, 0.0516 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (11.9 mg, 0.010 mmol, 20 mol%), a solution of bromo(triisopropylsilyl)acetylene (67 mg, 0.258 mmol, 5.0 equiv.) in toluene (0.1 mL), toluene (0.73 mL), EtOH (0.43 mL), and 2 M aq. Na_2CO_3 (0.13 mL, 5.0 equiv.). The resulting mixture was stirred at 80 °C for 24 h under Ar and shielded from light. After cooling to room temperature and evaporation of solvents, the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. After evaporation of solvent, the residue was purified by column chromatography on silica gel eluted with hexane to give **7** (25 mg, 0.051 mmol, 99%) as a white solid.

Synthesis of 3-((phenyl)ethynyl)-*4a*-aza-*8a*-bora naphthalene (8a): compound **6** (60 mg, 0.194 mmol, 1.0 equiv.) was dissolved in 1.0 mL of THF. A TBAF solution (1.0 M; 0.97 mL, 0.97 mmol, 5.0 equiv.) was added, and the mixture was stirred for 1 hour at room temperature. At the conclusion of the reaction, the solvent was removed under reduced pressure. The resulting crude material was filtered through a pad of silica gel (eluent Et_2O) to afford 3-ethynyl-4a,8a-borazaronaphthalene as a white oil, which could be used as is in the next step without further purification. To an oven-dried Biotage microwave vial equipped with a stir bar was added $PdCl_2(MeCN)_2$ (2.6 mg, 0.01 mmol, 5 mol%), XPhos (14.0 mg, 0.03 mmol, 15 mol%) and Cs_2CO_3 (163 mg, 0.5 mmol, 2.5 equiv.). The vial was sealed with a cap lined with a disposable Teflon septum, evacuated under vacuum, and purged with argon three times. Acetonitrile (2.0 mL, 0.1 M) and iodobenzene (29 µL, 0.26 mmol, 1.3 equiv.) were added, and the resulting suspension was stirred at room temperature for 30 min. Then, 3-ethynyl-4a,8a-borazaronaphthalene (30 mg, 0.2 mmol, 1.0 equiv.) was added with the minimum amount of acetonitrile, and the mixture was heated to 100 °C for 1 hour. Afterwards, the reaction was cooled to room temperature and diluted with CH_2Cl_2 and water. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (Hexane) to give **8a** as a white solid (24 mg, 0.10 mmol, 52%).

Synthesis of 3-((thiophen-2-yl)ethynyl)-*4a*-aza-*8a*-boranaphthalene (8b): Compound **6** (40 mg, 0.13 mmol, 1.0 equiv.) was dissolved in 0.7 mL of THF. A TBAF solution (1.0 M; 0.65 mL, 0.65 mmol, 5.0 equiv.) was added, and the mixture was stirred for 1 hour at room temperature. At the conclusion of the reaction, the solvent was removed under reduced pressure. The resulting crude material was filtered through a pad of silica gel (eluent Et_2O) to afford 3-ethynyl-4a,8a-borazaronaphthalene as a white oil, which could be used as is in the next step without further purification. To an oven-dried Biotage microwave vial equipped with a stir bar was added $PdCl_2(MeCN)_2$ (1.8 mg, 0.007 mmol, 5 mol%), XPhos (10.0 mg, 0.02 mmol, 15 mol%) and Cs_2CO_3 (107 mg, 0.3 mmol, 2.5 equiv.). The vial was sealed with a cap lined with a disposable Teflon septum, evacuated under vacuum, and purged with argon three times. Acetonitrile (1.3 mL, 0.1 M) and 2-iodothiophene (19 µL, 0.17 mmol, 1.3 equiv.) were added, and the resulting suspension was stirred at room temperature for 30 min. Then, 3-ethynyl-4a,8a-borazaronaphthalene (20 mg, 0.13 mmol, 1.0 equiv.) was added with the minimum amount of acetonitrile, and the mixture was heated to 100 °C for 1 hour. Afterwards, the reaction was cooled to room temperature and diluted with CH_2Cl_2 and water. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (Hexane) to give **8b** as a brown solid (15 mg, 0.06 mmol, 48%).

Synthesis of 3,6-bis(2-((trimethylsilyl)ethynyl)phenyl)-*4a*-aza-*8a*-boranaphthalene (9): A 10 mL microwave vial was charged with 1-bromo-2-(2-(trimethylsilyl)-ethynyl)benzene (86 mg, 0.34 mmol, 2.2 equiv.), **3** (60 mg, 0.16 mmol, 1.0 equiv.), [Pd(dppf)Cl_2] (9 mg, 0.012 mmol, 6 mol%), potassium phosphate (200 mg, 0.94 mmol, 6.0 equiv.) and MTBE (2.6 mL). Then, degassed water (1.2 mL) was added. The reaction was heated at 80 °C for 6 h in a microwave reactor. The mixture was extracted with diethyl ether (3 × 4 mL). The combined organic phases were concentrated in vacuo and the crude residue was purified by column chromatography on silica

gel (1% EtOAc/Hexane) to yield a brown oil **9** (48 mg, 0.10 mmol, 64%).

Synthesis of BN-naphtho[1,2-*c*]chrysene (10): 3,6-(2-((trimethylsilyl)ethynyl)phenyl BN-naphthalene **(9)** (61 mg, 0.13 mmol) was dissolved in methanol (4.25 mL). Potassium hydroxide (15.0 mg, 0.26 mmol) was added and the mixture was stirred for 3 h at 25 °C, until the complete deprotection of the alkyne was confirmed by TLC analysis. The reaction mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent was removed in vacuo. The crude deprotected alkyne was placed in a pressure tube and gold(III) trichloride (11.0 mg, 0.08 mmol, 60 mol%) and toluene (4.25 mL) were added. The mixture was heated at 100 °C for 4 h. After cooling, it was filtered over a plug of celite eluting with CH_2Cl_2. The solvents were removed in vacuo and the crude residue was purified by column chromatography on silica gel (Hexane) to yield a yellow solid **10** (17 mg, 0.05 mmol, 40%).

Acknowledgements

We are grateful to the Ministerio de Ciencia e Innovación, AEI and FEDER (project PID2020-115128RB-I00, PID2021-1242470B-C21, PID2020-118384GB-I00 and FPU predoctoral grant for I. V.) and Instituto de Salud Carlos III (FEDER funds, ISCIII RICORS2040/RD21/0005/0005) for financial support.

References

[1] a) A. Abengózar, P. García-García, M. A. Fernández-Rodríguez, D. Sucunza, J. J. Vaquero, *Adv. Heterocycl. Chem.* **2021**, *135*, 197–259; b) Z. X. Giustra, S.-Y. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 1184–1194; c) M. J. D. Bosdet, W. E. Piers, *Can. J. Chem.* **2009**, *87*, 8–29; d) Z. Liu, T. B. Marder, *Angew. Chem.* **2008**, *120*, 248–250; *Angew. Chem. Int. Ed.* **2008**, *47*, 242–244.

[2] a) K. Boknevitz, J. S. Italia, B. Li, A. Chatterjee, S.-Y. Liu, *Chem. Sci.* **2019**, *10*, 4994–4998; b) P. Zhao, D. O. Nettleton, R. G. Karki, F. J. Zecri, S.-Y. Liu, *ChemMedChem* **2017**, *5*, 358–361; c) H. Lee, M. Fischer, B. K. Shoichet, S.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 12021–12024; d) D. H. Knack, J. L. Marshall, G. P. Harlow, A. Dudzik, M. Szaleniec, S.-Y. Liu, J. Heider, *Angew. Chem.* **2013**, *125*, 2660–2662; *Angew. Chem. Int. Ed.* **2013**, *52*, 2599–2601.

[3] a) C. R. McConnell, P. G. Campbell, C. R. Fristoe, P. Memmel, L. N. Zakharov, B. Li, C. Darrigan, A. Chrostowska, S.-Y. Liu, *Eur. J. Inorg. Chem.* **2017**, *2017*, 2207–2210; b) F. Sun, M. Huang, Z. Zhou, X. Fang, *RSC Adv.* **2015**, *5*, 75607–75611; c) J. A. Bailey, M. F. Haddow, P. G. Pringle, *Chem. Commun.* **2014**, *50*, 1432–1434.

[4] For reviews, see: a) S. K. Mellerup, S. Wang, *Trends Chem.* **2019**, *1*, 77–89; b) J. Huang, Y. Li, *Front. Chem.* **2018**, *6*, 341; c) J.-Y. Wang, J. Pei, *Chin. Chem. Lett.* **2016**, *27*, 1139–1146.

[5] For reviews, see: a) G. Bélanger-Chabot, H. Braunschweig, D. K. Roy, *Eur. J. Inorg. Chem.* **2017**, *2017*, 4353–4368; b) M. M. Morgan, W. E. Piers, *Dalton Trans.* **2016**, *45*, 5920–5924; c) X.-Y. Wang, J.-Y. Wang, J. Pei, *Chem. Eur. J.* **2015**, *21*, 3528–3539.

[6] For a review, see: C. R. McConnell, S.-Y. Liu, *Chem. Soc. Rev.* **2019**, *48*, 3436–3453.

[7] For a review, see: S. Makar, T. Saha, S. K. Singh, *Eur. J. Med. Chem.* **2019**, *161*, 252–276.

[8] a) A. Vlasceanu, M. Jessing, J. P. Kilburn, *Bioorg. Med. Chem.* **2015**, *23*, 4453–4461; b) F. J. R. Rombouts, F. Tovar, N. Austin, G. Tresadern, A. A. Trabanco, *J. Med. Chem.* **2015**, *58*, 9287–9295.

[9] A. Bhattacharjee, G. H. M. Davies, B. Saeednia, S. R. Wisniewski, G. A. Molander, *Adv. Synth. Catal.* **2021**, *363*, 2256–2273.

[10] See, for example: K. Zhao, Z.-F. Yao, Z.-Y. Wang, J.-C. Zeng, L. Ding, M. Xiong, J.-Y. Wang, J. Pei, *J. Am. Chem. Soc.* **2022**, *144*, 3091–3098.

[11] F. Sun, L. Lv, M. Huang, Z. Zhou, X. Fang, *Org. Lett.* **2014**, *16*, 5024–5027.

[12] Y. Zhang, F. Sun, W. Dan, X. Fang, *J. Org. Chem.* **2017**, *82*, 12877–12887.

[13] a) P.-F. Zhang, J.-C. Zeng, F.-D. Zhuang, K.-X. Zhao, Z.-H. Sun, Z.-F. Yao, Y. Lu, X.-Y. Wang, J.-Y. Wang, J. Pei, *Angew. Chem.* **2021**, *133*, 23501–23507; *Angew. Chem. Int. Ed.* **2021**, *60*, 23313–23319; b) A. Abengózar, M. A. Fernández-González, D. Sucunza, L. M. Frutos, A. Salgado, P. García-García, J. J. Vaquero, *Org. Lett.* **2018**, *20*, 4902–4906.

[14] Y. Zhang, W. Dan, X. Fang, *Organometallics* **2017**, *36*, 1677–1680.

[15] a) R. Bisht, C. Haldar, M. M. M. Hassan, M. E. Hoque, J. Chaturvedi, B. Chattopadhyay, *Chem. Soc. Rev.* **2022**,*51*, 5042–5100; b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.

[16] J. S. Wright, P. J. H. Scott, P. G. Steel, *Angew. Chem.* **2021**, *133*, 2830–2856; *Angew. Chem. Int. Ed.* **2021**, *60*, 2796–2821.

[17] a) C. R. McConnell, F. Haeffner, A. W. Baggett, S.-Y. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 9072–9078; b) A. W. Baggett, M. Vasiliu, B. Li, D. A. Dixon, S.-Y. Liu, *J. Am. Chem. Soc.* **2015**, *137*, 5536–5541.

[18] G. H. M. Davies, M. Jouffroy, F. Sherafat B Saeednia, C. Howshall, G. A. Molander, *J. Org. Chem.* **2017**, *82*, 8072–8084.

[19] B. A. Vanchura, S. M. Preshlock, P. C. Roosen, V. A. Kallepalli, R. J. Staples, R. E. Maleczka, Jr., D. A. Singleton, M. R. Smith, III, *Chem. Commun.* **2010**, *46*, 7724–7726.

[20] Conditions adapted from: J. S. Compton, B. Saeednia, C. B. Kelly, G. A. Molander, *J. Org. Chem.* **2018**, *83*, 9484–9491.

[21] I. Valencia, P. García-García, D. Sucunza, F. Mendicuti, J. J. Vaquero, *J. Org. Chem.* **2021**, *86*, 16259–16267.

[22] A. M. Brouwer, *Pure Appl. Chem.* **2011**, *83*, 2213–2228.