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Synthesis of Functionalized Helical BN-benzo[*c*]phenanthrenes

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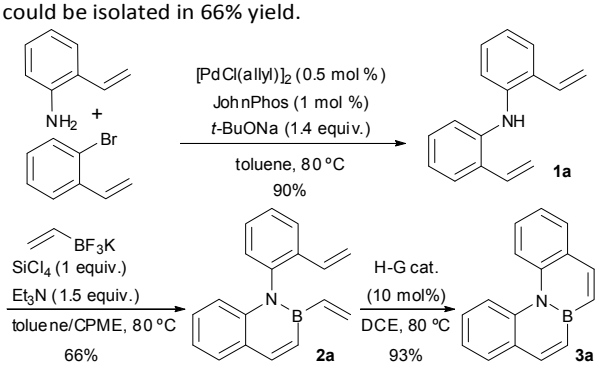
A novel parent BN-benzo[*c*]phenanthrene, with helical chirality and remarkable structural features, has been easily obtained in three steps with a global yield of 55%. Moreover, Cl-substituted derivatives have been prepared and these have served as useful starting materials for the development of palladium-catalyzed cross-coupling reactions.

The replacement of C=C units in aromatic compounds by isoelectronic B–N bonds has emerged in recent years as an efficient tool for the preparation of novel materials.[1] This strategy offers an interesting approach to increasing chemical space and has found application in different areas such as medicinal chemistry[2] and materials science.[3] BN/CC-isosterism is of particular relevance in the field of polycyclic aromatic hydrocarbons (PAHs),[4] in which the new optical and electronic properties induced by the presence of a dipole have been exploited in the development of diverse optoelectronic devices.[5] The advances in the field of BN-polycyclic aromatic hydrocarbons (BN-PAHs) have been significant in the last decade, but they are still hampered by the lack of general and mild methodologies for the preparation of these compounds in sufficient quantities.[6] Post-functionalization of BN-PAH cores is an appealing alternative for the synthesis of families of compounds with modulated properties, but is mainly limited to bromination followed by cross-coupling reactions.[5c,7-8] The use of chloro-substituted BN-aromatic compounds as precursors for palladium-catalyzed cross-coupling reactions has not been demonstrated to date. It is well known that aryl chlorides, although more widely available, are less reactive than aryl bromides and require harsher conditions,[9] the compatibility of which with the BN-aromatic cores needs to be proved. Herein we report the preparation of a novel family of BN-PAHs, including the parent BN-benzo[*c*]phenanthrene **3a** and Cl-substituted derivatives, which have proven to be useful starting materials for post-functionalization by cross-coupling reactions.

The synthesis of **3a** (Scheme 1) starts with a high-yielding Buchwald–Hartwig reaction between commercially available *o*-bromostyrene and *o*-vinylaniline to yield **1a**. Initial attempts to direct borylative cyclization of **1a** to **3a** in the presence of BCl_3 failed, but we were able to obtain **3a** in a two-step sequence. Based on the conditions reported by Molander et al. for related secondary amines,[10] cyclization of **1a** with vinyl trifluoroborate was initially attempted at 40 °C in the absence of NEt_3, but decomposition of **1a** occurred under these conditions. The use of 1.5 equivalents of NEt_3 inhibited the decomposition processes, but only starting material was recovered after 48 h. Finally, an increase in the reaction temperature to 80 °C allowed full conversion in 24 h and **2a** could be isolated in 66% yield.



Scheme 1 Synthesis of BN-benzo[*c*]phenanthrene **3a.** JohnPhos = (2-Biphenyl)di-tert-butylphosphine; H-G cat = (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium.

The last step of the synthesis of **3a** was the ring closing metathesis of **2a**. An excellent yield was obtained on using 10 mol% of Hoveyda–Grubbs (H-G) catalyst. Second generation Grubbs' catalyst was also effective for this transformation, but a lower yield was obtained (73% in CH_2Cl_2 at 40 °C). Overall, the novel BN-benzo[*c*]phenanthrene **3a** was prepared in only three steps with a 55% overall yield.

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† Electronic Supplementary Information (ESI) available: Experimental details, X-ray crystallographic data for **3a** and NMR spectra for all new compounds (PDF).
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The structure of **3a** was confirmed by X-ray diffraction analysis (Figure S1).[11] The B–N bond length (1.450(2) Å) is similar to those reported for other BN-aromatic compounds.[12] The heterocycle adopts a twisted conformation with an angle between the non-BN rings of 38.9° (Figure S2), thus leading to left- and right-handed helical enantiomers. The molecules of both enantiomers are associated in pairs by π···π interactions with a perpendicular separation of 3.41 Å, and they are aligned in an antiparallel orientation with respect to the B–N bond (Figure S2).[13] The pairs of enantiomers are connected by hydrophobic interactions that maintain an angle between the BN rings of 44.1°. The non-parallel arrangement of the BN rings for neighbouring molecules produces an alternating pattern (Figure 1).

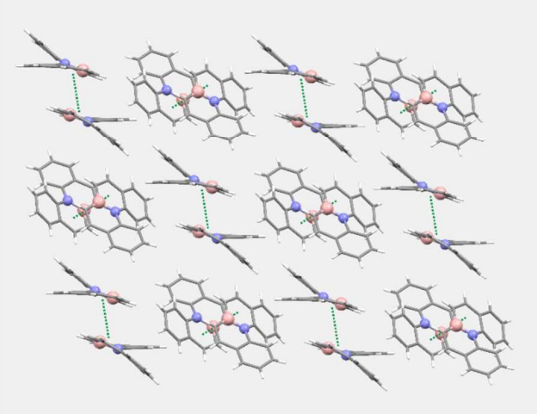


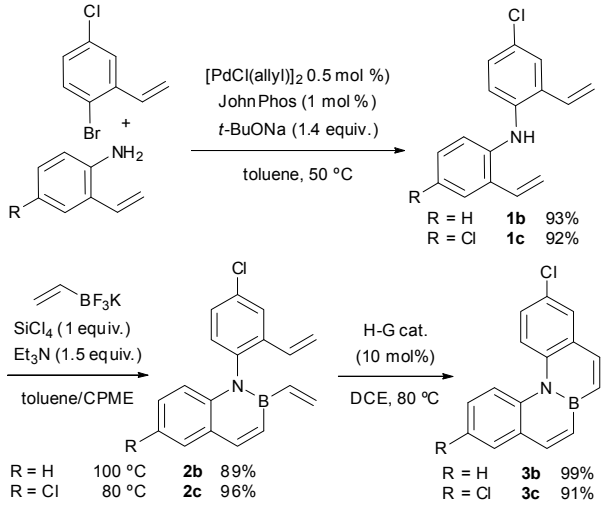
Figure 1. Pattern of the pairs of enantiomers in the crystal packing for **3a**.

Interestingly, the BN-heterocycle shows a significantly higher deviation from planarity than the all-carbon analogue benzo[*c*]phenanthrene (angle between the non-BN rings of 26.7°).[14] The packing of a crystal for the all-carbon derivative reveals a herringbone motif formed by molecules of a single enantiomer (Figure S3), so the presence of the BN unit has a significant impact on the structure of the molecule.

BN-benzo[*c*]phenanthrene **3a** is a white solid (m.p. = 68-70 °C) stable towards air and moisture. The UV-vis spectrum of **3a** in cyclohexane exhibits an absorption maximum at 330 nm, and a weak emission is observed at 375 nm (Figure 2, Φ_f = 0.03). The reactivity of **3a** was briefly surveyed. Bromination under the conditions used for structurally related 4a-aza-10a-boraphenanthrene (NBS/$AlCl_3$, CH_2Cl_2, −35 °C)[15] was unsuccessful, and starting material was recovered. This result is consistent with the fact that 4a-aza-10a-boraphenanthrene is brominated only in the BN-aromatic ring that is not benzo-fused, despite the use of excess NBS, and is attributed to the low stability of the intermediate formed after the attack of the Br^+ species to the benzofused BN-aromatic ring.[15] Moreover, the use of Br_2 as the brominating reagent led to decomposition, even at −78 °C, whereas conversion was not observed at all upon treatment with IPy_2BF_4 in DCM at room temperature.

Next, we faced the synthesis of substituted derivatives of this novel heterocyclic compound. In particular, we focused on the synthesis of chlorinated substrates for potential use as precursors in palladium-catalyzed cross-coupling reactions.

Cl-substituted BN-benzo[*c*]phenanthrenes **3b** and **3c** (Scheme 2) were efficiently prepared by a synthetic route analogous to that depicted in Scheme 1 for the synthesis of the parent compound. Initially, the Buchwald–Hartwig amination step was carried out at 80 °C for 24 h and this gave full conversion but low yields (47% **1b**, 18% **1c**). Gratifyingly, excellent yields were obtained on lowering the temperature to 50 °C (48 h). The borylative cyclization with vinyl trifluoroborate was then carried out. For the synthesis of **2b** this reaction was performed at 100 °C as incomplete conversion was observed at 80 °C. Finally, ring closing metathesis under the conditions optimized for the synthesis of **3a** gave rise to **3b** and **3c** with excellent overall yields.



Scheme 2 Synthesis of Cl-substituted BN-benzo[*c*]phenanthrenes **3b**,**c**. JohnPhos = (2-Biphenyl)di-tert-butylphosphine; H-G cat = (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium.

Compound **3c** was selected as a model substrate to test the viability of a Pd-catalyzed Suzuki coupling with phenylboronic acid. Initial assays with $Pd_2(dba)_3$/P(*t*-Bu)$_3$ (dba = dibenzylideneacetone) as the catalyst were disappointing and gave very low yields of **3d**. We next tried $Pd(OAc)_2$/JohnPhos and the results are summarized in Table 1. Evidence for conversion was not observed on using KF as a base in THF (entry 1) or K_3PO_4 in toluene (entry 2) with 5 mol% catalyst. In contrast, the reaction gave full conversion with *t*-BuONa as base and on increasing the catalyst loading to 10 mol%, but the isolated yield of **3d** was low (entry 3). A further increase in the catalyst loading did not have any impact on the results (entry 4), but a significant improvement in the yield was achieved by increasing the number of equivalents of phenylboronic acid to 4 (2 equiv. per Csp^2–Cl bond) (entry 5). Gratifyingly, heating the reaction up to 110 °C allowed the isolation of **3d** in high yield (entry 6). Under these optimized conditions, **3b** was also efficiently coupled with phenylboronic acid to give the corresponding phenyl-substituted derivative **3e** in good yield (Table 2, entry 2).

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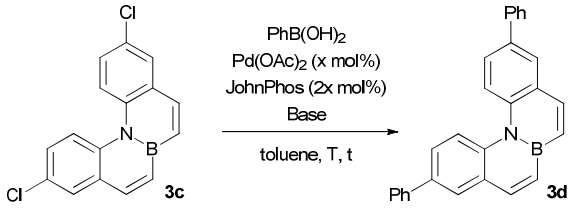
Table 1. Optimization of the Suzuki reaction of **3c** with phenylboronic acid.

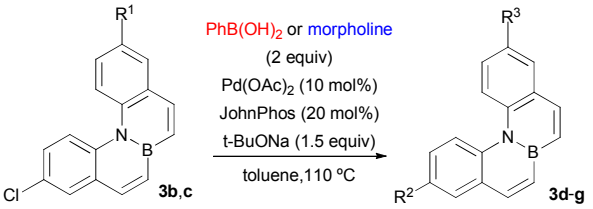


entry	Base (equiv)	$Pd(OAc)_2$	$PhB(OH)_2$	T	t (h)	yield **3d** [%]
1[a]	KF (6)	5 mol%	3 equiv	67	24	-[b]
2	K_3PO_4 (4)	5 mol%	3 equiv	110	24	-[b]
3	*t*-BuONa (3)	10 mol%	2.4 equiv	90	48	18
4	*t*-BuONa (3)	20 mol%	2.4 equiv	90	48	16
5	*t*-BuONa (3)	10 mol%	4 equiv	90	48	40
6	*t*-BuONa (3)	10 mol%	4 equiv	110	48	80

[a] Reaction performed in THF. [b] Starting material was recovered.

Moreover, related conditions were also found to be useful for the Buchwald–Hartwig amination of Cl-substituted BN-aromatic polycyclic compounds. By simply replacing phenylboronic acid with morpholine in the reactions outlined above, amino-substituted BN-benzo[*c*]phenanthrenes **3f**,**g** were obtained in yields of up to 84% (Table 2, entries 3,4).

Table 2. Pd-catalyzed cross-couplings of Cl-substituted BN-benzo[*c*]phenanthrenes.

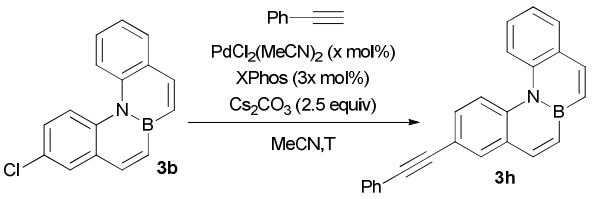


entry	R^1	R^2	R^3	**3**	yield [%]
1[a]	Cl	Ph	Ph	**3d**	80
2[a]	H	Ph	H	**3e**	67
3	Cl	*N*-morpholino	*N*-morpholino	**3f**	84
4	H	*N*-morpholino	H	**3g**	63

[a] Using 4 equiv. $PhB(OH)_2$ or morpholine and 3 equiv. *t*-BuONa.

We also evaluated the Sonogashira couplings of **3b**,**c**. An initial optimization was performed on **3b** as a model substrate, phenylacetylene as the alkyne counterpart and $PdCl_2(MeCN)_2$/Xphos as the catalytic system, with acetonitrile as solvent and Cs_2CO_3 as base (Table 3). The first reactions using 5 mol% of the palladium catalyst and 2 equivalents of alkyne at 80 °C led to low yields. Significant decomposition was observed after prolonged reaction times (entry 1), whereas poor conversion was achieved with shorter times (entry 3). The best compromise between reactivity and decomposition was obtained after 12 h, but only a modest yield of **3h** could be isolated under these conditions. Only starting material was recovered on lowering the temperature to 60 °C, even after 24 h (entry 4), whereas an increase in temperature to 100 °C did not lead to an improved yield (entry 5). Moreover, decomposition was observed when the number of equivalents of alkyne was increased to 4 (entry 6). A higher catalyst loading led to a small improvement in the isolated yield of **3h** (entry 7). Finally, by reducing the amount of alkyne and heating to 100 °C, a good isolated yield was obtained in a short reaction time, without the need to increase the catalyst loading (entry 8).

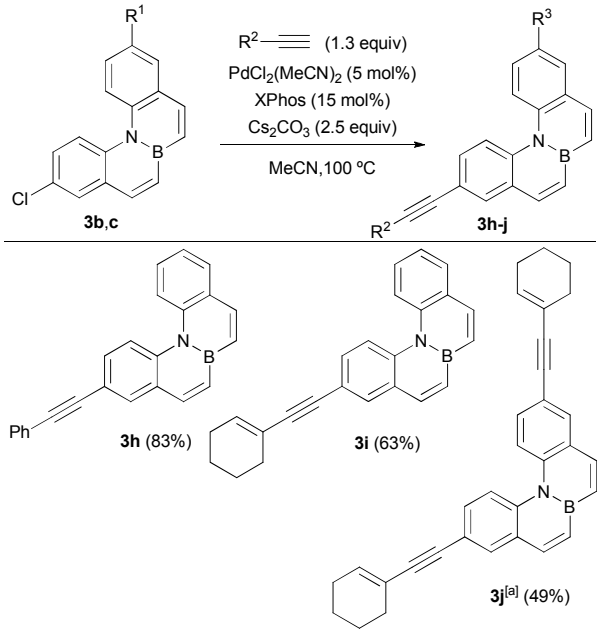
Table 3. Optimization of the reaction of **3b** with phenylacetylene.



entry	$PdCl_2(MeCN)_2$	Alkyne	T	t (h)	yield **3h**[%]
1	5 mol%	2 equiv	80	24	25
2	5 mol%	2 equiv	80	12	39
3	5 mol%	2 equiv	80	6	25
4	5 mol%	2 equiv	60	24	-[a]
5	5 mol%	2 equiv	100	8	22
6	5 mol%	4 equiv	80	12	-[b]
7	7 mol%	2 equiv	80	12	47
8	5 mol%	1.3 equiv	100	4	83

XPhos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [a] Starting material was recovered. [b] Decomposition was observed.

Alkynyl-substituted BN-benzo[*c*]phenanthrenes **3h**,**i** were synthesized under these conditions in good to excellent yields, starting from Cl-functionalized precursor **3b**. Both an aromatic and an alkenyl substituent at the alkyne were well tolerated. Moreover, a symmetric dialkynyl-BN-benzo[*c*]phenanthrene **3j** was prepared in moderate yield (Scheme 3).



[a] Using 2.6 equiv. of alkyne and 5 equiv. of Cs_2CO_3

Scheme 3 Pd-catalyzed Sonogashira reactions of Cl-substituted BN-benzo[*c*]phenanthrenes.

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The absorption and emission spectra of selected benzo[*c*]phenanthrenes are shown in Figure 2. The optical propierties of this novel heterocycle are not significantly modified by the effect of substituents. Chloro-substitued derivative **3c** shows a very similar behaviour to the parent compound **3a**, whereas in the presence of an alkynyl substituent (**3h**) the emission maxima is slightly red-shifted and a small increase of the fluorescence quantum yield is observed (**3a**, Φ_f = 0.03; **3c**, Φ_f = 0.01; **3h**, Φ_f = 0.10) .

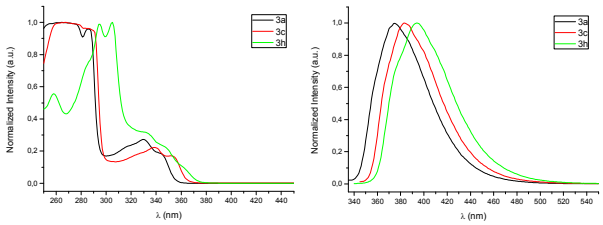

Figure **2**. UV/vis absortion (left) and emission (right) spectra of selected BN-benzo[*c*]phenanthrenes in cyclohexane.

In conclusion, the synthesis of a new family of BN-PAHs has been reported. We have achieved the first synthesis of parent BN-benzo[*c*]phenanthrene **3a**, which shows helical chirality and structural properties clearly different from that of the all-carbon analogue. The synthesis was carried out under mild conditions and in only three steps from commercially available materials to give a remarkable 55% overall yield. Moreover, this synthetic route has been applied to the highly efficient preparation of Cl-substituted BN-PAHs, which served as starting materials for the synthesis of diversely substituted BN-benzo[*c*]phenanthrenes through post-functionalization by cross-coupling reactions. Couplings of Cl-substituted BN-PAHs had not been previously reported and were not straightforward, but a careful optimization allowed the development of reaction conditions that were compatible with the azaborine system and good yields could be obtained in Suzuki, Buchwald–Hartwig and Sonogashira coupling reactions. It is worth noting that the compatibility of BN-aromatic compounds with the conditions required for the coupling of Csp^2-Cl bonds opens the door to synthetic strategies based on sequential functionalization of C–Br and C–Cl bonds, such as the one reported in this work and many others that can be envisioned for the preparation of BN-PAHs and their post-functionalization.

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Conflicts of interest

There are no conflicts to declare.

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