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Annulative π-Extension of Indoles and Pyrroles with Diiodobiaryls by Pd Catalysis: Rapid Synthesis of Nitrogen-Containing Polycyclic Aromatic Compounds

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A palladium-catalyzed one-step annulative π-extension (APEX) reaction of indoles and pyrroles that allows rapid access to nitrogen-containing polycyclic aromatic compounds is described. In the presence of palladium pivalate and silver carbonate, diverse indoles or pyrroles coupled with diiodobiaryls in a double direct C–H arylation manner to be transformed into the corresponding π-extended compounds in a single step. The newly developed catalytic system enables the use of various pyrroles and indoles as templates with a series of diiodobiaryls to provide structurally complicated and largely π-extended nitrogen-containing polycyclic aromatic compounds that are otherwise difficult to synthesize.

Introduction

With desirable electronic properties and diverse biological activities, nitrogen-containing fused aromatics have long been recognized as privileged structures in the fields of organic materials and pharmaceutical science.[1] As these properties can be readily tuned via skeletal modification of the core *N*-heteroarene structure, significant efforts have been devoted to develop new synthetic approaches for the π-extended nitrogen-containing polycyclic aromatic compounds (N-PACs). Representative classical approaches include (i) intramolecular carbon–nitrogen bond formation of biaryl amines,[2] (ii) intramolecular carbon–carbon bond formation of diaryl amines,[3] and (iii) stepwise functionalization and π-extension of indoles and pyrroles.[4] However, these methods require the use of prefunctionalized heteroaromatics such as halogenated pyrroles, anilines and indoles, and stepwise transformations from unfuctionalized (hetero)aromatics. To achieve maximum efficiency in N-PAC construction, a more direct and 'intuitive' method for π-extension of unfunctionalized pyrroles and indoles is called for.

Recently, we have introduced several new one-step methods for the annulative π-extension (APEX) of unfuctionalized (hetero)aromatics (Figure 1a).[5-7] Because such APEX reactions directly transform easily available unfunctionalized (hetero)arenes to polycyclic aromatic hydrocarbons, nanographenes and π-extended heteroaromatics in a double direct C–H arylation manner, these protocols offer large benefits in the context of cost, simplicity, and step/atom economy.[8]

Recently, we[7] and others[9-14] have reported transition-metal-catalyzed APEX reactions of indoles and pyrroles using various π-extension units such as alkyne,[9] alkene,[7a,10] 1-vinylpropargyl alcohols,[11] α-diazocarbonyl compounds,[12] α-bromochalcone,[13] α-bromocinnamate,[13] cyclic diaryliodonium salts,[14] dibenzogermoles[7b] and diiodobiphenyls[7c] (Figure 1b). However, these APEX reactions are limited in terms of lack of variety in π-extending agents, narrow substrate scope, and low functional group tolerance. Herein, we report a new catalytic APEX reaction that allows efficient pyrrole-to-indole, pyrrole-to-carbazole and indole-to-carbazole π-extensions. Our newly established catalytic system featuring palladium pivalate and silver carbonate in a mixed DMF/DMSO solvent system enabled the rapid synthesis of structurally complicated N-PACs from readily available unfunctionalized pyrroles/indoles and diiodobiaryls.

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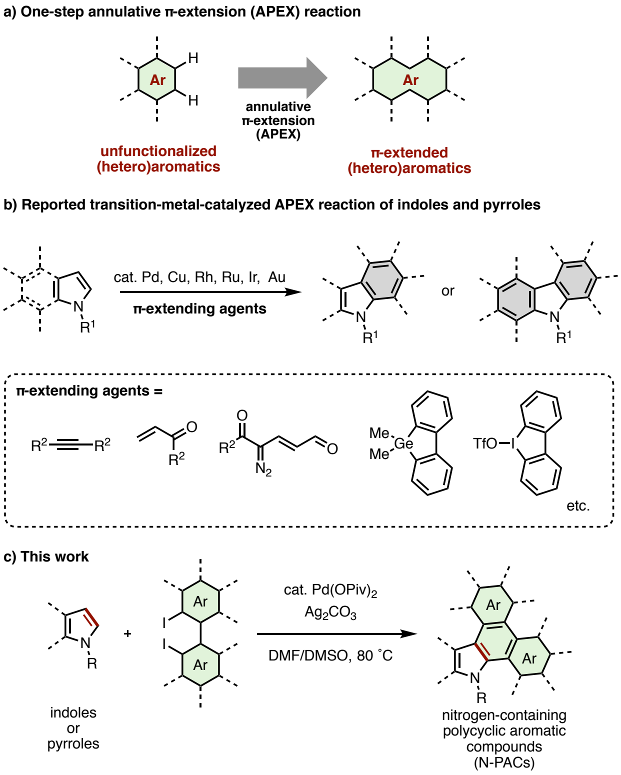

Figure 1 a) General scheme of annulative π-extension (APEX) reaction of unfunctionalized (hetero)aromatics. b) Previous transition-metal-catalyzed APEX reactions of indoles and pyrroles. c) Palladium-catalyzed APEX reaction of indoles and pyrroles with diiodobiaryls (this work).

Results and discussion

We began our study by optimizing the reaction conditions for indole-to-carbazole extension of *N*-methylindole (**1a**) using 2,2′-diido-1,1′-biphenyl (**2a**) as a π-extending agent (Table 1). After extensive screening, we discovered that **1a** (1.0 equiv) coupled with **2a** (1.5 equiv) in the presence of $Pd(OAc)_2$ (5 mol%) and Ag_2CO_3 (3.0 equiv) at 80 °C in 7:3 mixture of dimethylformamide (DMF) and dimethylsulfoxide (DMSO) to provide *N*-methyldibenzo[*a*,*c*]carbazole (**3aa**) in 54% yield (entry 1). Use of palladium pivalate [$Pd(OPiv)_2$] instead of $Pd(OAc)_2$ improved the yield to 61% (entry 2), but other palladium sources such as $PdCl_2$, PdI_2, $Pd(PPh_3)_4$, $Pd(OCOCF_3)_2$ and $Pd(CH_3CN)_4(BF_4)_2$ failed to give more than trace amounts of product (entries 3–7). Decreasing the amount of Ag_2CO_3 to 1.5 equiv (relative to **1a**) further increased the yield of **3aa** to 78% (entry 8). The use of silver carboxylate salts (AgOAc, AgOPiv, or $AgOCOCF_3$) instead of Ag_2CO_3 resulted in much lower yield (entries 9–11). The silver cation itself was essential for this reaction; the use of Na_2CO_3, K_2CO_3 or Cs_2CO_3 instead of Ag_2CO_3 failed to give any product (see Electronic Supporting Information (ESI) for details). The use of the DMF/DMSO mixed solvent system was important for obtaining maximum conversion; highly polar single solvents such as *N*,*N*-dimethylacetamide (DMAc), DMF, DMSO, CH_3CN provided **3aa** in diminished yield (29–10%, see ESI for details), while less polar solvents such as 1,2-dichloroethane, 2,2,2-trifluoroethanol, 1,4-dioxane and toluene completely suppressed the reaction. Although higher reaction temperature accelerated the consumption of the starting material, the yield of **3aa** was decreased (entries 12 and 13). Finally, we confirmed that the APEX reaction did not proceed in the absence of Pd catalyst or Ag_2CO_3 (entries 14 and 15). Although the use of additional ligands for Pd and the use of dibromobiphenyl in place of diiodobiphenyl as the π-extension reagent were also investigated, these modifications proved ineffective (see ESI for details). Ultimately the conditions in entry 8 were deemed optimal for the present indole-to-carbazole APEX reaction.

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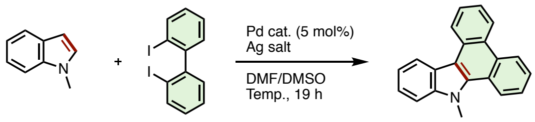
Table 1 Screening of reaction conditions for the Pd-catalyzed indole-to-carbazole APEX reaction of *N*-methylindole (**1a**) and diiodobiphenyl (**2a**).



1a
0.20 mmol
2a
1.5 eq.
3aa

entry	Pd cat.	Ag salt	Temp. (°C)	Yield[a] (%)
1	$Pd(OAc)_2$	Ag_2CO_3 (3.0 eq.)	80	54
2	$Pd(OPiv)_2$	Ag_2CO_3 (3.0 eq.)	80	61
3	$PdCl_2$	Ag_2CO_3 (3.0 eq.)	80	3
4	PdI_2	Ag_2CO_3 (3.0 eq.)	80	2
5	$Pd(PPh_3)_4$	Ag_2CO_3 (3.0 eq.)	80	4
6	$Pd(OCOCF_3)_2$	Ag_2CO_3 (3.0 eq.)	80	0
7	$Pd(CH_3CN)_4(BF_4)_2$	Ag_2CO_3 (3.0 eq.)	80	0
8	$Pd(OPiv)_2$	Ag_2CO_3 (1.5 eq.)	80	78 (66)[c]
9	$Pd(OPiv)_2$	AgOAc (3.0 eq.)	80	33
10	$Pd(OPiv)_2$	AgOPiv (3.0 eq.)	80	0
11	$Pd(OPiv)_2$	$AgOCOCF_3$ (3.0 eq.)	80	0
12	$Pd(OPiv)_2$	Ag_2CO_3 (1.5 eq.)	100	57
13[b]	$Pd(OPiv)_2$	Ag_2CO_3 (1.5 eq.)	100	58
14	none	Ag_2CO_3 (1.5 eq.)	80	0
15	$Pd(OPiv)_2$	none	80	0

[a] Yield was determined by ^1H NMR analysis using dodecane as an internal standard. [b] Reaction time was 1 h. [c] Isolated yield in the parenthesis. Piv = pivaloyl.

A possible reaction mechanism of current indole-to-carbozole APEX reaction is shown in Scheme 1. Oxidative addition of **2a** to palladium species (Pd(0) or Pd(II)) occurs to form biphenylylpalladium intermediate **A**.[15] Then, the removal of iodide by silver salt may activate Pd complex **A**[16] to form electron-deficient aryl-Pd species[17], which then react with indole at the C2 position to afford intermediate **B**. Through the control experiments on the C–H arylations of 1,2-dimethylindole and 1,3-dimethylindole with iodobenzene, the present APEX reaction seems to occur through the C2-arylation of indole rather than C3-arylation in the first step (see ESI for details). Final step would be well-established Pd-catalyzed intramolecular C–H/C–I coupling to afford the cyclized compound **3aa** (Figure 2).[18]

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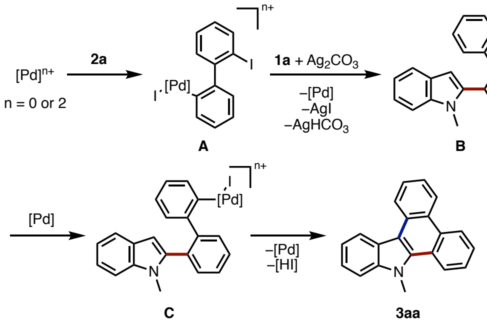
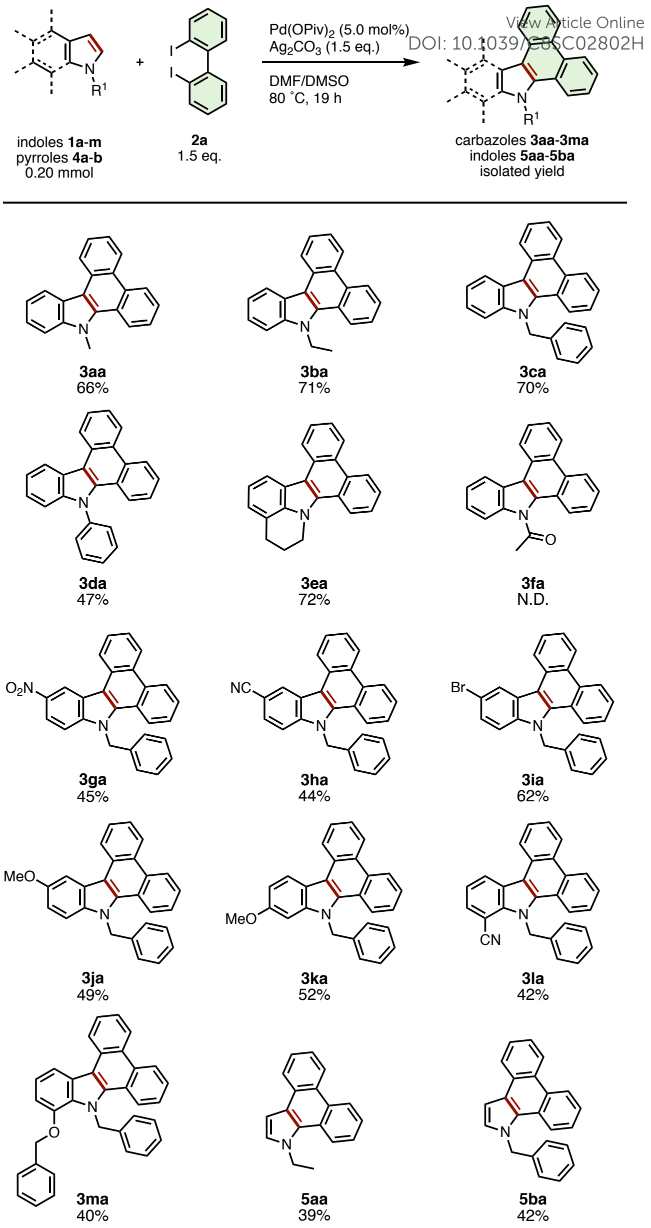


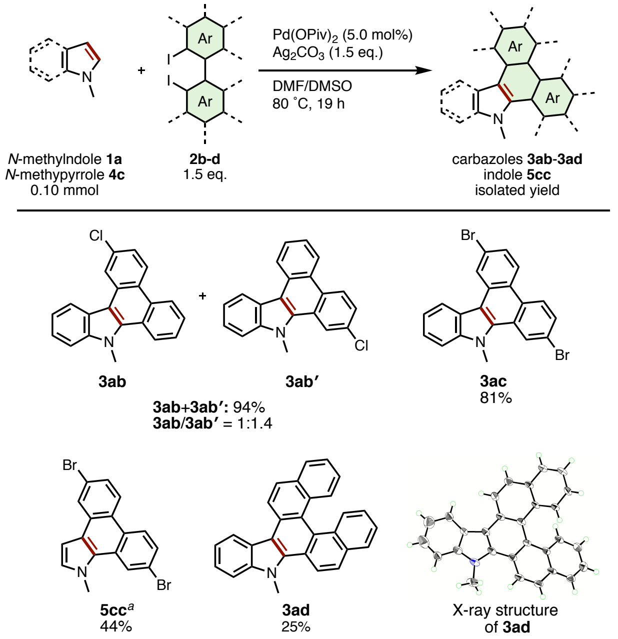
Scheme 1 Proposed reaction mechanism for the Pd-catalyzed APEX reaction of *N*-methylindole (**1a**) with 2,2′-diiodo-1,1′-biphenyl (**2a**).

Under the optimized conditions, various types of π-extended carbazoles/indoles **3**, **5** were prepared from the corresponding indole/pyrrole derivatives **1**, **4** and diiodobiaryls **2**. Scheme 2 illustrates the scope of applicable indole and pyrrole derivatives (**1a**–**1m**). *N*-Alkyl (**2a**, **2b**), *N*-benzyl (**2c**), *N*-phenyl (**2d**) indoles and cross-linked lilolidine (**2e**) were converted smoothly to dibenzocarbazoles **3ba**–**3da** in good to moderate yield, however the reaction of *N*-acetyl indole **2f** did not provide the expected π-extension product **3fa**. The presence of substituents at the 5-, 6-, or 7-positions of the indole ring was well-tolerated, giving various nitro- (**3ga**), cyano- (**3ha**, **3la**), bromo- (**3ia**), methoxy- (**3ja**, **3ka**), and benzyloxy-substituted (**3ma**) dibenzocarbazoles in moderate yields (40-62%). These results suggest that substituents on the benzene ring of indole do not critically affect the reaction progress. Interestingly, we found that the current APEX reaction between *N*-substituted pyrroles and **2a** was mono-selective for the formation of dibenzoindoles **5aa** and **5ba** in 39% and 43% yields; only trace amounts of the di-APEX tetrabenzocarbazole products, the main products of our previous report,[7c,19] were observed. As synthetic methods to prepare the dibenzo[*e*,*g*]indole skeleton remain limited and inefficient,[20] the current APEX protocol provides a valuable, streamlined entry to this compound class.



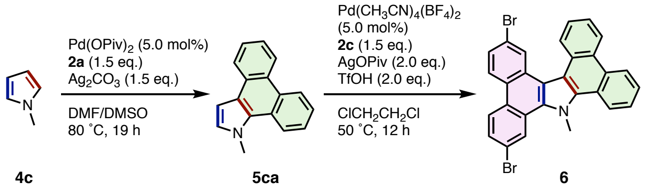
Scheme 2 Substrate scope of indoles and pyrroles in the APEX reaction with 2,2′-diiodo-1,1′-biphenyl (**2a**).

The scope of diiodobiaryls in the current APEX reaction is shown in Scheme 3. The reaction of *N*-methylindole (**2a**) with unsymmetrical 4-chloro-2,2′-diiodo-1,1′-biphenyl (**2b**) gave a 1:1.4 regioisomeric mixture of **3ab** and **3ab′** in 94% combined yield. APEX reactions of **1a** and **4a** with 4,4′-dibromo-2,2′-diiodo-1,1′-biphenyl (**2c**) smoothly occurred to give dibromodibenzocarbazole **3ac** and dibromodibenozoindole **5cc** in 81% and 44% yield, respectively. To our delight, the reaction of **1a** with 2,2′-diiodo-1,1′-binaphthalene (**2d**) gave dinaphthocarbazole **3ad** containing a [5]helicene moiety in 25% yield, whose helical structure was confirmed by X-ray crystallographic analysis. As this example clearly demonstrates, the late-stage attachment of complex, extended polyaromatic units is one of the most remarkable characteristics in the present APEX reaction.



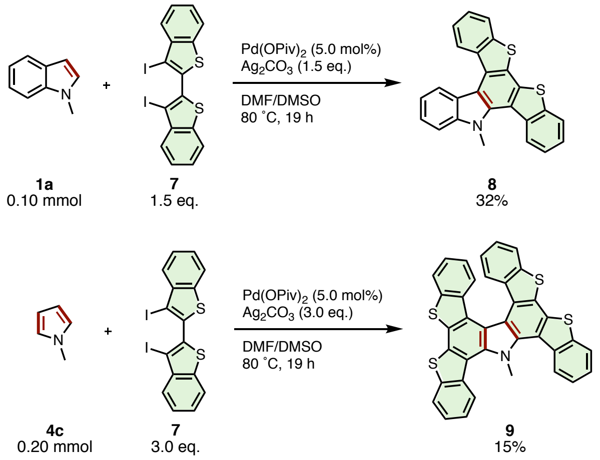
Scheme 3 Substrate scope of diiodobiaryls. ^{a}0.20 mmol scale.

To demonstrate the power of the current APEX reaction to build complex, unsymmetrical N-PACs from simple starting materials, we employed a two-step sequence to synthesize tetrabenzocarbazole **6**, a compound difficult to prepare via known methods (Scheme 4). First, APEX reaction of *N*-methylpyrrole (**4c**) with **2a** was carried out to give the corresponding *N*-methyldibenzoindole (**5ca**) in 37% yield. Notably, this reaction did not give double-APEX product which is the major product in the previously developed APEX reaction of *N*-phenylpyrrole.[8b] Then, **5ca** was further reacted with 4,4′-dibromo-2,2′-diiodo-1,1′-biphenyl (**2c**) by using Pd(CH$_3$CN)$_4$(BF$_4$)$_2$/AgOPiv/TfOH catalytic system[8b] to give the desired product **6** in 33% yield.[21] Rapid access to a new class of unsymmetrically substituted tetrabenzocarbazole is notable, and should contribute to the exploration of new compounds for organic electronics application.



Scheme 4 Sequential APEX reactions of *N*-methylpyrrole (**4c**) for the synthesis of usymmetrically substituted tetrabenzocarbazole **6**.

The current APEX reaction also provided a facile route to polycyclic aromatic compounds containing both nitrogen and sulfur (N-S-PACs) (Scheme 5). *N*-methylindole (**1a**) coupled with 3,3′-diiodo-2,2′-bibenzothiophene (**7**) to give di(benzothieno)carbazole **8** in 32%. To our delight, the reaction of *N*-methylpyrrole (**4c**) with diiodo-2,2′-bibenzothiophene **7** afforded a double APEX product, tetra(benzothieno)carbazole **9**, in 15% yield. While the yields were low, the generation of these novel N-S-PAC structures, which are highly interesting from the viewpoint of optoelectronic properties yet otherwise difficult to synthesize by conventional organic reactions, is notable.



Scheme 5 APEX reactions of *N*-methylindole (**1a**) and *N*-methylpyrrole (**4c**) with 3,3′-diiodo-2,2′-bibenzothiophene (**7**) for the synthesis of N-S-PACs.

The structural and electronic properties of **8** and **9** were elucidated via X-ray crystallography, UV-Vis/photoluminescence spectroscopy, and DFT/TD-DFT calculations at the B3LYP/6-31G(d) level of theory (Figure 2). Single crystal X-ray structures (Figures 2a, 2b, S2 and S3) reveal that compound **8** adopts a relatively flattened structure in the solid state (Figure 2a), while compound **9** possesses a twisted structure owing to the embedded heterohelicene moiety. DFT calculations for **8** (Figure 2c) reveal delocalization of the HOMO (–5.23 eV) over the entire molecule, while the LUMO (–1.49 eV) localizes on a benzothienocarbazole wing. On the other hand, the HOMO and LUMO of **9** are delocalized over entire molecule, and thus the energy level of LUMO (–1.72 eV) is slightly lower than that of **8**. The UV–vis absorption spectra of **8** and **9** in CH$_2$Cl$_2$ show that both compounds have broad absorption bands between 300 and 450 nm (Figure 3e). Absorption maxima were found at 294, 317, 339, 357, 381 and 399 nm in **8**, and the corresponding peaks were also found in **9** at 305, 332, 348, 393 and 412 nm. The TD-DFT calculations revealed that the longest-wavenumber absorptions in **8** and **9** (399 and 412 nm) are attributed to the allowed HOMO–LUMO transitions (see ESI for details). The fluorescence spectra of **8** and **9** in CH$_2$Cl$_2$ display broad emissions with emission maxima of 427 and 437 nm, respectively (Figure 2e).

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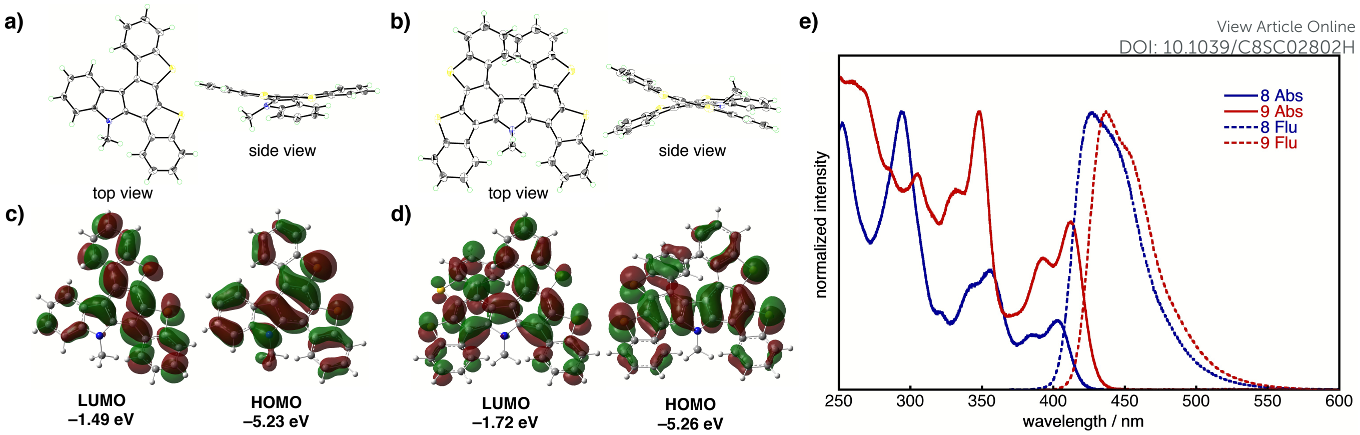

Figure 2 Top and side views of the X-ray crystal structures of a) **8** and b) **9**. Thermal ellipsoids are drawn at 50% probability. Pictorial frontier molecular orbitals and energy levels of c) **8** and d) **9** calculated using the B3LYP/6-31G(d) level of theory. e) Normalized UV–vis absorption and fluorescence spectra of **8** and **9** in CH_2Cl_2 at rt._

Conclusions

In summary, we have developed a novel palladium-catalyzed APEX reaction to enable the annulative π-extension of indoles/pyrroles with diiodobiaryls. Use of the $Pd(OPiv)_2/Ag_2CO_3$ catalytic system in a mixed DMF/DMSO solvent allows the preparation of a diverse range of N-PACs in a single step, including several previously unsynthesized structures. Rapid access to exotic scaffolds such as complex, unsymmetrically substituted tetrabenzocarbazoles and extended N-heteroarenes featuring multiple helicene moieties is a particular highlight of the present APEX protocol. Developed APEX methodology also has great potential for the efficient and rapid synthesis of planar and non-planar π-extended N-PACs such as π-extended azacorannulenes, aza-buckybowls and pyrrolopryrroles which are regarded as one of promising materials for optelectronics.[22] Further investigations into the reaction mechanism and applications of this APEX method towards the synthesis of larger π-extended heteroaromatics are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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