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Facile synthesis of annulated heterocyclic benzo[*kl*]acridine derivatives via one-pot N–H/C–H coupling†

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An efficient N–H/C–H one-pot coupling method for the preparation of benzo[*kl*]acridines has been developed based on palladium-catalyzed domino synthesis. Using commercially available starting materials such as dihalonaphthalenes and diphenylamines, and combining amination with catalysts for C–H activation, up to 95% overall yield can be achieved.

With the development of organic electronics and photonics, nitrogen-containing heteroarene building blocks such as carbazoles, indoles, and imidazoles have been intensively studied for application in organic light-emitting diodes (OLED), organic photovoltaics (OPV), and organic field-effect transistors (OFET).¹ In addition, these compounds are used not only as active components, but also as auxiliary layer ingredients, for instance hole/electron transporting/blocking materials.

Particularly, many carbazole-based polymers and oligomers exhibit outstanding performance in electronic devices.²

Using 2-azido-1,1'-biphenyl derivatives as starting materials, Smith and Brown established carbazole synthesis by thermal cyclization in 1951.³ Cadogan reported a more practical carbazole forming protocol in 1965 from 2-nitro-1,1'-biphenyl derivatives refluxed in triethylphosphite.⁴ Later, 2,2'-bisfunctionalized (halogen/pseudohalogen) biphenyls made it possible to obtain *N*-alkylated/arylated carbazoles under Buchwald–Hartwig reaction conditions.⁵ However, all three methods are limited due to the additional preparation of biphenyl building blocks. Recent synthetic methods offer a more powerful and elegant domino process that takes advantage of transition metal catalyzed amination between aryl halides and primary/secondary amines as well as intramolecular C–C coupling of aryl halides and C–H bonds.⁶ Additionally, transition metal-, typically palladium-mediated domino annulations are implemented under mild reaction conditions and provide access to *N*-alkylated/arylated carbazoles from secondary amines.⁷

Up to now, six-membered N–H containing neutral aromatic compounds *e.g.* 7*H*-benzo[*kl*]acridines have received little attention. One reason is that the Cadogan reaction is not favorable for the formation of *N*-doped six-membered rings.⁸ Moreover, bisfunctional biaryl precursors for the Buchwald–Hartwig *N*-annulations are not easily obtained.

Several recent patents claim *N*-substituted benzo[*kl*]acridine derivatives as electroluminescent materials.⁹ However, the syntheses of those benzo[*kl*]acridines were rather complicated, including multi-step reactions.¹⁰ For example (Scheme 1), the “three-step” synthesis of 7*H*-benzo[*kl*]acridine with an overall yield of only 40% actually requires the synthesis of the commercially unavailable starting material, *i.e.* *N*-(8-bromonaphthalen-1-yl)acetamide (**B**).^{9e}

Herein, we describe a novel palladium-catalyzed domino reaction for the preparation of benzo[*kl*]acridine derivatives.

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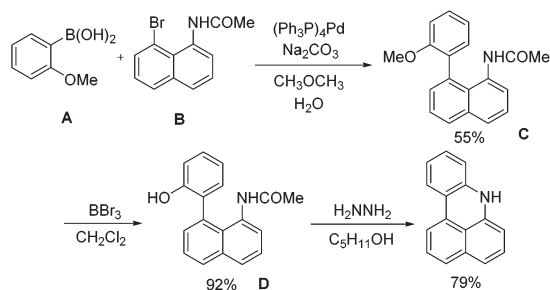
†Electronic supplementary information (ESI) available: Full experimental details and characterization data (PDF); crystal structures of **3c** and **3d** (CIF). CCDC 1494768 and 1494769. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6qo00371k

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Scheme 1 Synthesis of 7H-benzo[k]acridine.

To the best of our knowledge, there is no report on one-pot reactions for their synthesis. Our strategy is to couple commercial dihalonaphthalenes *e.g.* 1,8-dibromonaphthalene (**1a**) or 1,8-diiodonaphthalene (**1b**), with readily available secondary aromatic amines, such as diphenylamines (Table 1).

During the course of studies targeting 1,8-bis(diphenylamino)naphthalenes by the reaction between **1a** and diphenylamine (**2a**) using a conventional Buchwald–Hartwig catalyst system, *i.e.* Pd₂(dba)₃, (*t*Bu)₃P and base NaOtBu, we noted the formation of an unprecedented six-membered ring fusion product **3a** (in yield of 25%) where a new C–C bond was formed between the naphthalene and the α-phenyl position of the diphenylamino group. Mass spectral characterization indicated 1-(diphenylamino)naphthalene as a byproduct. Additionally, after 24 hours, the reaction of **1a** and **2a** catalyzed by a common arylation catalyst, *i.e.* Pd(OAc)₂ with Cy₃P, only generated **3a** in 50% yield. Therefore, it can be concluded that the amination takes place first followed by C–C coupling. Scheme 2 suggests a possible reaction mechanism similar to that for the one-pot synthesis of carbazoles proposed by Bedford and Cazin.¹¹ The reaction includes two sequential and independent catalytic cycles: (1) aromatic amination in cycle 1, and (2) C–H activation and cyclization.

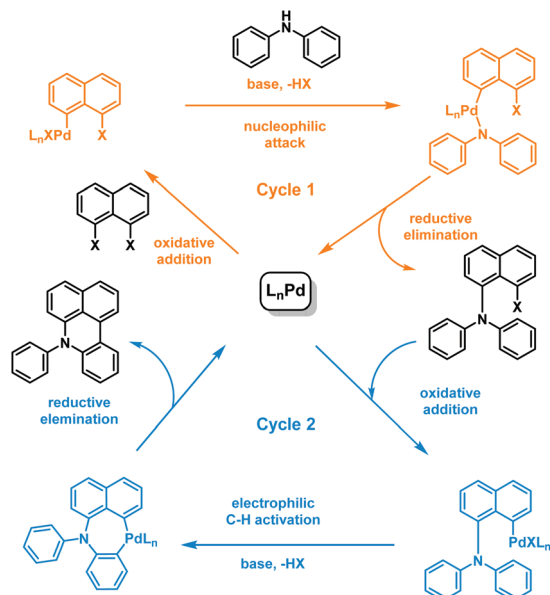
Considering the likely two-step reaction mechanism, we evaluated a mixed catalyst system for both the Buchwald–Hartwig amination and activated C–H coupling conditions, *i.e.* Pd₂(dba)₃ and ligand (*t*Bu)₃P for amination and Pd(OAc)₂ with Cy₃P for arylation. In this way, we successfully minimized the dehalogenated byproduct. The reactions were carried out in toluene as a solvent. Six different diphenylamines were evaluated in the reaction, namely diphenylamine (**2a**), di(*p*-*tert*-octylphenyl)amine (**2b**), 5*H*-dibenzo[*bf*]azepine (**2c**), 10*H*-phenothiazine (**2d**), 10*H*-phenoxazine (**2e**) and 9*H*-carbazole (**2f**). Among these amines, the reactions of diphenylamines **2a** and **2b** exhibited the best results, especially with 1,8-diiodonaphthalene (**1b**) giving yields as high as 95% (entries 2 and 4). The reaction of the four *ortho*-linked diphenylamines **2c–2f**, however, showed lower yields. Particularly, **3e** was not stable and easily decomposed in solution. Moreover there was no **3f** formed in the reaction between **2a** and **2f**, instead the main product was perylene (over 90%), which is the homo-coupling product of **2a**. It has been reported that perylene can be synthesized *via* 1,8-dihalogenated (I or Br) naphthalene in Ni(0)-

Table 1 Synthesis of annulated heterocyclic benzo[*k*]acridine derivatives^a

Entry	Halide	Aromatic amine	Product	Yield ^b [%]
1	1a			91
2	1b			95
3	1a			84 ^c
4	1b			95 ^c
5	1a			79
6	1b			83
7	1a			85
8	1b			89
9	1a			77
10	1b			81
11	1a			0
12	1b			0

^a Reaction conditions: **1** (3.5 mmol), **2** (3 mmol), NaOtBu (7 mmol), Pd(OAc)₂ (3 mol%), Pd₂(dba)₃ (3 mol%), Cy₃P (7 mol%), (*t*Bu)₃P (7 mol%), dry toluene, 90 °C, 10 h. ^b Yields of isolated product. ^c R1 is *tert*-octyl.

mediated reactions (yields are up to 88%),¹² but we can find no report of the Pd-catalyzed analogue. On the other hand, carbazole substituted naphthalenes have been obtained *via* amination under either Buchwald–Hartwig¹³ or Ullmann¹⁴ conditions. Therefore, in the cases of entries 11 and 12 there remain some puzzling questions: (1) why were only the starting material carbazole and the homo-coupling product perylene present? (2) Why was no Buchwald–Hartwig amination product observed, *i.e.* 1-carbazolenaphthalene? And (3) why was the yield of homo-coupling so high? As we continue to investigate the scope of this powerful ring-forming cascade reaction, we will also attempt to answer these questions.



Scheme 2 Possible reaction mechanism of domino reaction.

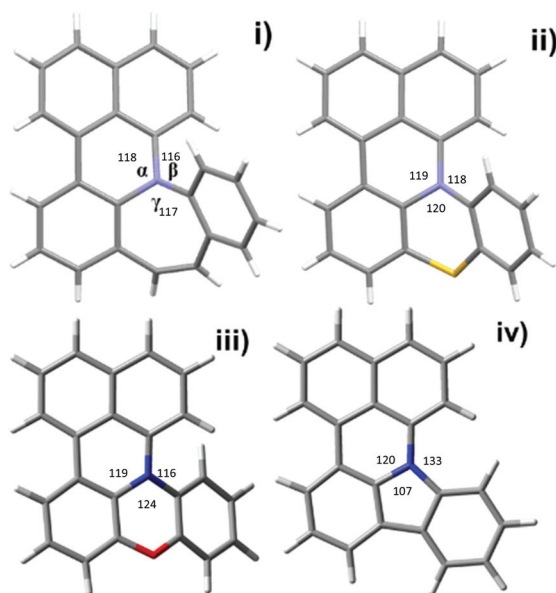


Fig. 1 Single crystal structures of **3c** (i) and **3d** (ii) obtained by X-ray analysis as well as the molecular structures of **3e** (iii) and **3f** (iv) calculated under DFT optimization on B3LYP 6-311++G(d,p) set. The (α , β , γ) angles of **3c**–**3f** are (118°, 116°, 117°) & (calc. 118°, 117°, 118°), (119°, 118°, 120°) & (calc. 119°, 121°, 118°), (calc. 119°, 116°, 124°), and (calc. 120°, 133°, 107°), respectively.

In order to understand the different behaviors of these amines (**2c**–**2f**), it is necessary to analyze the molecular structures of **3c**–**3f**. We obtained single crystals of **3c** and **3d** by slow diffusion of petroleum ether into CH_2Cl_2 solutions. Furthermore, the molecular geometry of **3c**–**3f** was calculated *via* density functional theory by Gaussian 09 W software. As

shown in Fig. 1, the angles (α , β and γ) between adjacent C–N bonds are nearly the same for the cases of **3c** (118°, 116°, 117°) and **3d** (119°, 118°, 120°). However, for **3e**, the γ angle (124°) is much larger than both α (119°) and β (116°). Nevertheless, the α , β , and γ (120°, 133°, 107°) of **3f** are largely different. It seems that the uniformity of α , β , and γ (the best will be that α , β , and γ are all close to 120°) is strongly related to both the stability of the compounds and the reaction yields. Among **3c**–**3f**, the yields of **3c** and **3d** are better than that of **3e**, while **3f** has never been reported and cannot be synthesized also by this one-pot reaction method.

Conclusions

Herein, we have reported a novel N–H/C–H domino synthesis of benzo[*kl*]acridine derivatives consisting of an amination and a direct C–H bond arylation starting from readily available anilines and 1,2-dihalonaphthalenes. Remarkably, up to 95% overall yield can be achieved *via* a one-pot reaction, enabling easy access to useful benzo[*kl*]acridine derivatives. Additionally, since the stable products **3a**, **3c** and **3d** are potentially suitable for optoelectronic application, we have also checked the optical and electrochemical properties of these compounds (see Fig. S1 and Table S1 in the ESI†). We believe that these compounds and their derivatives will be good candidates for organic optical and electronic devices.

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