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Orchestrated catalytic double rollover annulation: Rapid access to N-enriched cationic and neutral PAHs†

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Disclosed herein is a rhodium(III)-catalyzed novel one-step back-to-back double rollover annulation on pyridine and pyrazine backbones leading to structurally and optoelectronically diverse class of nicely decorated multi-ring-fused, extensively π-conjugated, N-enriched PAH molecules by virtue of orchestrated quadruple C–H activation events. Selected N-PAHs have been utilized as potential mitochondria and lysosome markers.

Polycyclic aromatic hydrocarbons (PAHs) represent a privileged class of molecules, immensely important in organic electronics.[1] Interestingly, PAHs decorated with heteroatoms such as boron (B), nitrogen (N), and sulfur (S) exhibit modulated optoelectronic properties due to modified molecular energy levels and intermolecular interactions.[1,2] Especially, the N-containing PAHs (N-PAHs) have drawn a considerable recent attention by covering a wide range of applications in diverse fields including materials science (semiconductors, light emitting diodes, NLOs), and biology (imaging agents).[2] Therefore, appreciable efforts are being devoted toward construction of tailored N-PAH architectures with variable number, position and valence state of the substituting N atoms thus allowing a systematic structure-property understanding for judicious development of application-apt molecules. Moreover, in parallel to neutral N-PAH molecules, cationic N-PAHs can display further tuneability of optoelectronic and supramolecular properties due to the partially delocalized charge within the π-conjugated ring framework.[2] To fulfil the increasing demand of rapid synthesis of a variety of such neutral and cationic PAHs including N-PAHs, annulative π-extension (APEX) of (hetero)aromatic molecules via transition metal-catalyzed C–H activation reactions has emerged as a powerful protocol (Fig. 1A).[3] The features such as step-economy, high efficiency and selectivity, operational convenience etc. bring large benefits to the APEX

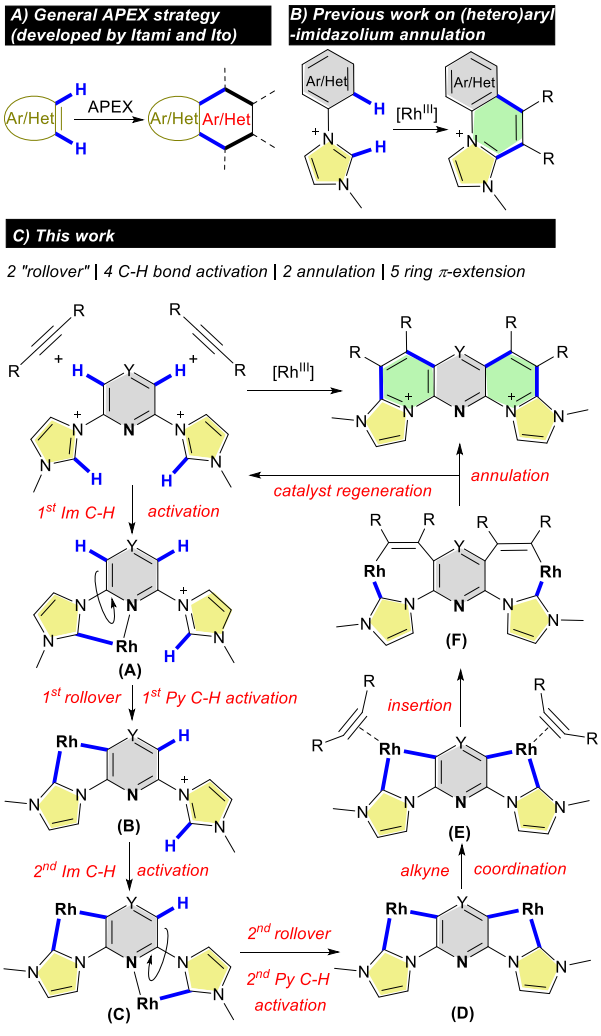

Fig. 1 A) General scheme for annulative π-extension (APEX) reactions; B) previous work on annulative π-extension of aryl/heteroaryl-imidazolium motifs; C) working hypothesis of the present double rollover annulation protocol.

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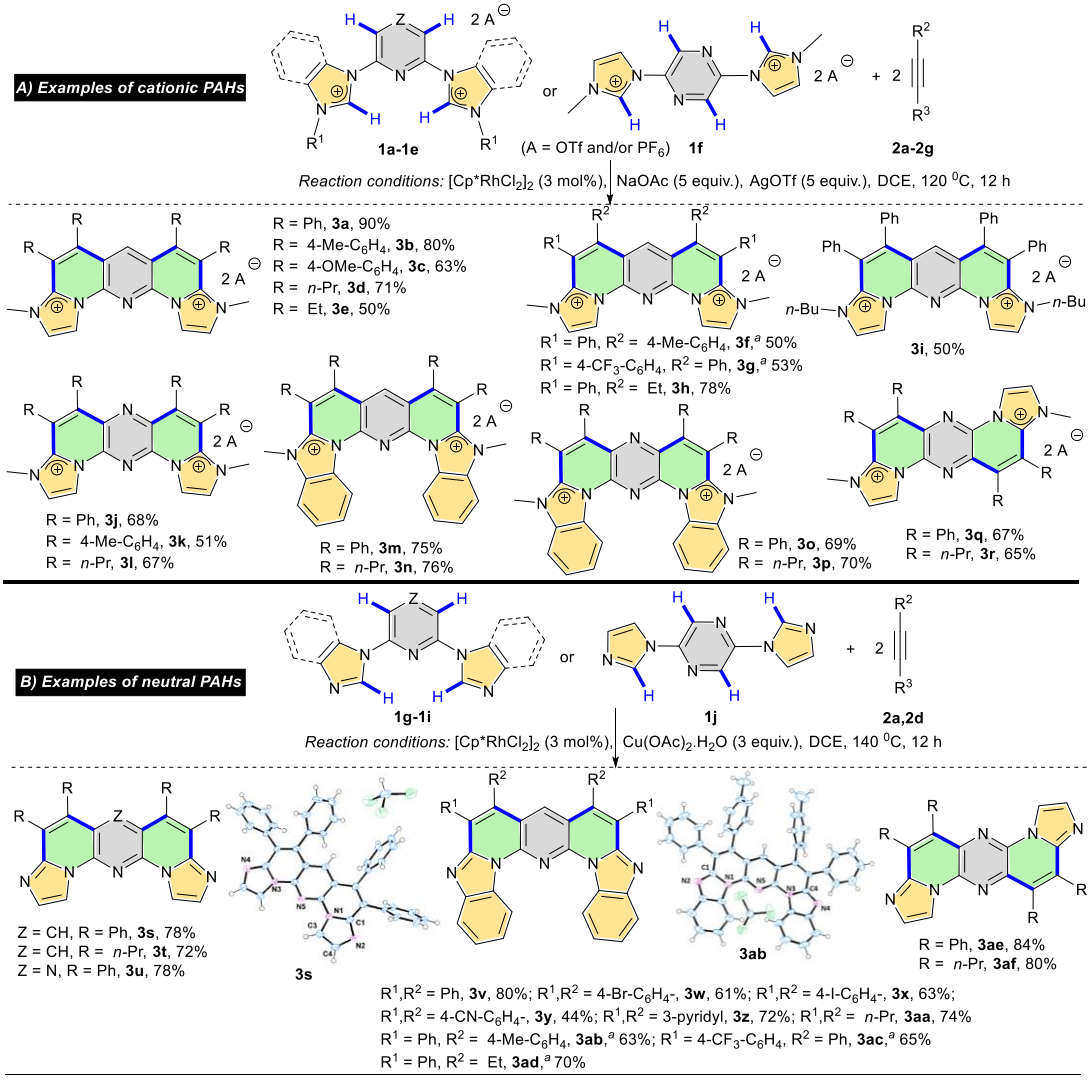
protocol compared to traditional multistep methods. In this context, beyond double C–H activation, there has been a special focus toward inventing one-pot multiple C–H activation-annulation approach to fuse multiple π-conjugated rings surrounding the parent (hetero)arene backbone via sequential and extremely selective π-extension steps, thereby adding more value to this novel chemistry. However, realization of such challenging methodologies has been extremely limited to only a few reports.[4].

To target N-PAHs, our group has been successfully exploring Cp*Rh^{III}-catalyzed APEX on imidazolium-containing arenes/heteroarenes via double C–H activation followed by annulation with alkyne partner (Fig. 1B).[4b,5] In the course of crafting multiple ring-fused, extensively π-conjugated, N-enriched PAH architectures, herein we report an orchestrated 'double rollover' quadruple C–H activation annulation strategy on pyridine and pyrazine backbones with doubly-substituted imidazolium motifs (Fig. 1C). This double rollover strategy overcomes the challenge of direct multiple C–H functionalization, in the presence of potentially poisoning environment of strong chelating coordination by free N and N-heterocyclic carbene (NHC) donors.[6]

Initially, an optimization study was conducted for the present Cp*Rh^{III}-catalyzed double rollover annulation reaction by using 2,6-bis(1-methylimidazolium) pyridine hexafluorophosphate (**1a**) as the parent pyridine compound and diphenylacetylene (**2a**) as the annulating partner to yield the pentacyclo-fused cationic N-PAH **3a** (Table 1A, and ESI, Table S1). The resulting optimal conditions of employing $[Cp^*RhCl_2]_2$ (3 mol%) as catalyst, NaOAc (5 equiv.) as base, and AgOTf (5 equiv.) as oxidant in 1,2-dichloroethane solvent at 120 °C for a reaction time of 12 h afforded **3a** in 93% yield. Other bases (KOAc, $NaHCO_3$, K_2CO_3), other oxidants (AgOAc, $Cu(OAc)_2$, $Cu(BF_4)_2$), or other catalysts ($[Cp^*Co(CO)I_2]$) were found to be inferior or ineffective. Similarly, shorter reaction time or lower catalyst/oxidant loading resulted in lower yield of **3a**. Absence of catalyst, base or oxidant led to the failure of annulation. (for details, see ESI, Table S1).

Applying the standardized conditions, a series of multiple ring-

Table 1 Examples of A) cationic and B) neutral N-PAHs synthesized via double rollover annulation strategy



[a] For these compounds, all possible regioisomers were formed, but only the major regioisomer has been shown. For regioisomeric ratio, see ESI.

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reacting various 2,6-imidazolum-substituted pyridines and pyrazines with several internal alkynes (Table 1A). Diarylalkynes and dialkylalkynes could be used for this annulation. Notably, phenyl–aryl and phenyl–alkyl unsymmetrical alkynes provided the major regioisomers **3f**, **3g** and **3h** in higher yields, and other isomers in lower or negligible yields which could not be separated and isolated. Notably, the major isomers resulted from the insertion of the alkyne into the C_{py}-Rh bond via placing the more electron-rich aryl rings at the β-position to the metal. Benzimidazolium-substituted pyridines and pyrazines were also applied successfully to furnish the desired seven ring-fused N-enriched polycyclic cations (**3m**-**3p**) in good yields. Furthermore, to access different annulation and structural pattern within the products, 2,5-imidazolum-substituted pyrazines were employed which afforded the zigzag pentacyclo-fused PAHs **3q** and **3r** in good yields. Interestingly, this protocol could also be modified further to produce neutral analogues of the above multiple ring-fused N-PAHs. In this case, $[Cp^*RhCl_2]_2$ (3 mol%) was used as catalyst in combination with $Cu(OAc)_2$ (3 equiv.) as base as well as oxidant in toluene to annulate the 2,6- and 2,5-(benz)imidazole-substituted pyridines and pyrazines providing the desired neutral N-PAHs with a variety of functional groups on the backbone (**3s**-**3af**) in 44-84% yields (Table 1B).

To examine the hypothesis of the Cp^*Rh^{III}-catalyzed 'double rollover' annulation, although all the highly reactive intermediates could not be isolated, two key bimetallic rhodacyclic intermediates **4** and **5** akin to the species **C** and **D** as shown in Fig. 1 were possible to be isolated from a reaction of compound **1a** and $[Cp^*RhCl_2]_2$ (**1a**:Rh = 1:2) in presence of NaOAc, (Fig. 2A). Intermediate **4** consisted two different types of Rh metal centers – one center featuring imidazolium C–H activated C_{NHC}–Rh along with pyridine N-coordinated N_{py}–Rh bonding while the other center featuring imidazolium C–H activated C_{NHC}–Rh along with pyridine rollover C–H activated C_{py}–Rh bonding (Fig. 2B). Monometallic intermediate with only either (C_{NHC}–Rh–N_{py}) or (C_{NHC}–Rh–C_{py}) type of bonding environment (species **A** or **B**, Fig. 1) could not be isolated even after using a stoichiometry of **1a**:Rh = 1:1. The double rollover intermediate **5** having (C_{NHC}–Rh–C_{py}) bonding mode at both the metal centers was formed upon further reaction of **4** with NaOAc and AgOTf (Fig. 2A,B). The plausible involvement of the intermediates **4** and **5** during the catalytic annulation reaction was confirmed separately by performing both catalytic as well as stoichiometric reactions as shown in Fig. 2C. These key findings suggested the hypothesized catalytic cycle (Fig. 1C).

Evaluation of the electronic property of these multi-ring-fused π-extended molecules at the frontier molecular orbital (FMO) level by DFT (density functional theo-retical) calculations showed that the HOMO (highest occupied molecular orbital) is located on the di-aryl/dialkyl alkene side of the motifs whereas the LUMO (lowest unoccupied molecular orbital) is located over the central polycyclic backbone (Figure 3A). This well-defined FMO property allowed us to decrease the HOMO-LUMO energy gap via either selectively destabilizing the HOMO upon introducing electron-donating group at the diaryl

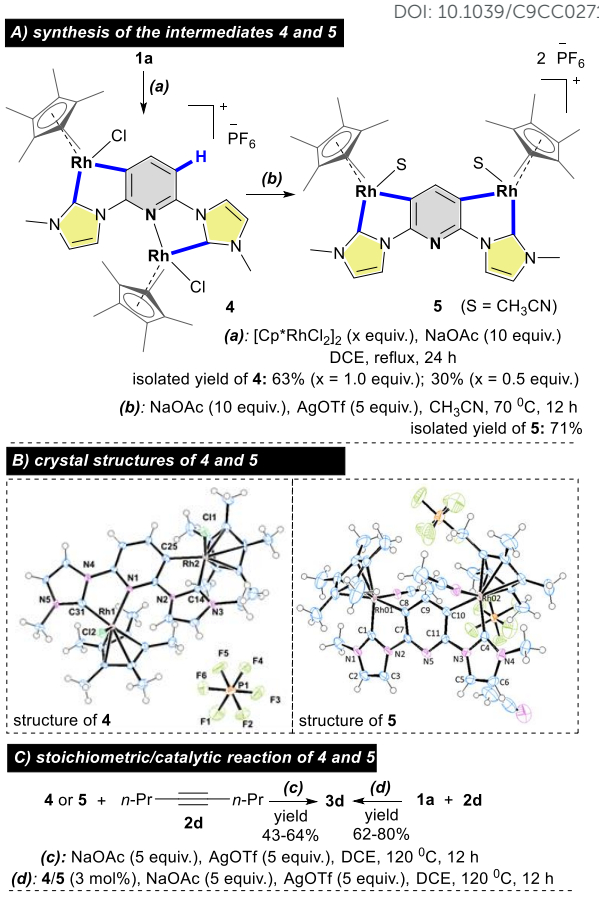

Fig. 2 A) Synthesis of intermediates **4** and **5**; B) crystal structures of **4** and **5**; C) stoichiometric and catalytic control experiments with **4** and **5**.

alkene moiety or selectively stabilizing the LUMO upon making the polycyclic backbone more electron-deficient, as going from **3a** to **3b** and **3j** respectively (Figure 3A). In effect, the molecules exhibited variable and tuneable fluorescence colours from blue to cyan to green to dark orange at a wavelength region of 440 nm–575 nm (Figure 3B,C).

Finally, a cationic N-PAH **3j** and a neutral N-PAH **3s** were applied in cellular imaging studies as specific mitochondria and lysosome-targeted biomarkers.[7] Thus **3j** was found to localize selectively in the mitochondria of BHK-21 cells (baby hamster kidney cell line) as verified by colocalization experiments with commercial MitoTracker Red showing excellent overlap with Pearson's correlation coefficient of 0.92±0.04 (Figure 3D, a,b,c). Similar co-staining studies in CHO cells (Chinese hamster ovary cells) with **3s** and commercial LysoTracker Red indicated selective labelling of lysosomes in the living cells with the corresponding Pearson's correlation coefficient of 0.94±0.02 (Figure 3E, a,b,c). Moreover, **3j** and **3s** exhibited low toxicity to the cultured cells in the working concentration range of 1 to 100 μM, as evaluated by MTT assay (Figure 3D, d and 3E, d).

In conclusion, we have successfully demonstrated a challenging double rollover annulation protocol for step-economic construction of structurally and optoelectronically diverse class of multiple ring-fused, extensively π-conjugated,

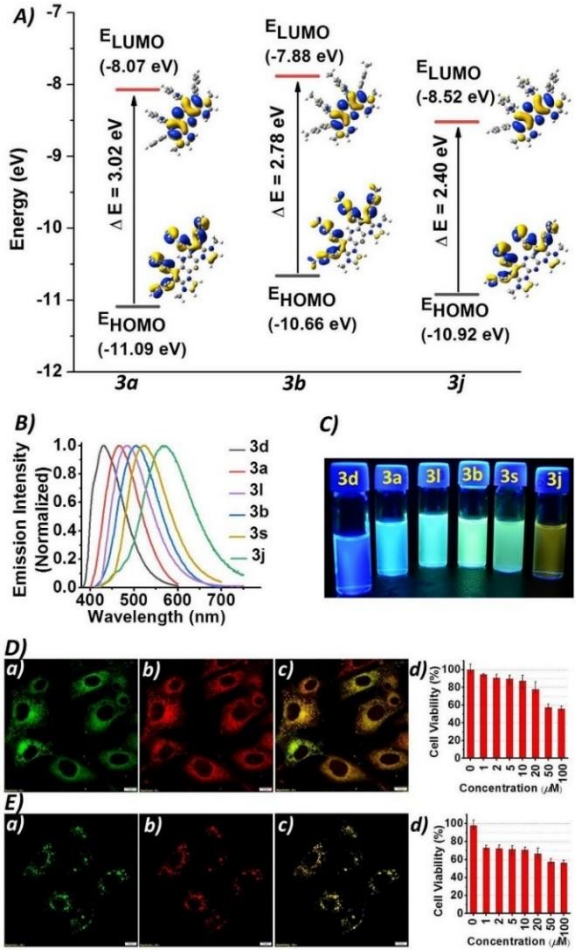

Fig. 3 A) Frontier molecular orbital (FMO) diagram of **3a**, **3b** and **3j**; B) fluorescence spectra (2 μM in H_2O) and C) images of selected N-PAHs (10 μM in H_2O); live-cell confocal microscopy images showing the subcellular localization of D) **3j** in BHK-21 cells stained with a) 5 μM **3j**, b) 300 nM of MitoTracker Red, c) merge image of a) and b); d) MTT assay of **3j** showing cell viability (concentration range 0–100 μM), and E) of **3s** in CHO cells stained with a) 5 μM **3s**, b) 300 nM of LysoTracker Red, c) merge image of a) and b); d) MTT assay of **3s** showing cell viability (concentration range 0–100 μM).

N-enriched, cationic and neutral PAH molecules, via orchestrated quadruple C–H activation events on strongly-chelating pyridine and pyrazine frameworks enabled by commonly used Cp*Rh(III) catalyst. Selected designer molecules displayed potential as fluorescent bioimaging probes with specificity toward mitochondria and lysosome.

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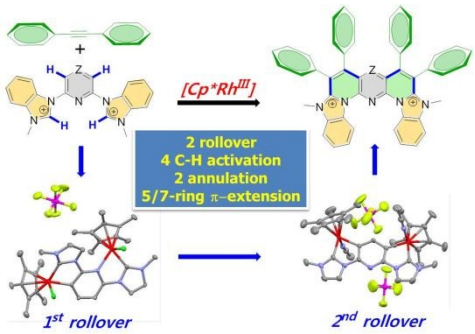

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