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Exploring a unique reactivity of N-heterocyclic carbenes (NHC) in rhodium(III)-catalyzed intermolecular C–H activation/annulation†

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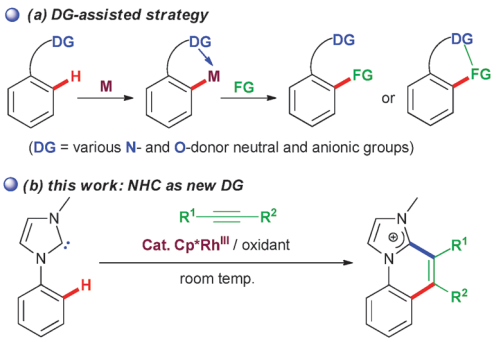
Disclosed herein is the unique conjugative role of N-heterocyclic carbene (NHC) ligands as a directing group in aromatic C–H activation, coupled with a facile NHC–alkenyl annulative reductive elimination which guided the Rh^{III}-catalyzed intermolecular annulations of imidazolium salts and alkynes under ambient conditions leading to structurally important imidazo[1,2-*a*]quinolinium motifs.

The tremendous success of N-heterocyclic carbene (NHC) ligands in homogeneous catalysis portrays a true reflection of their unique stereoelectronic properties and strong metal–C_{NHC} bonding, and the excellent stability of their metal complexes toward heat, air and moisture.[1] The robust and inert metal–C_{NHC} backbone is considered a key factor for providing the opportunity to explore catalytic strong bond activation and oxidative functionalization without any self-transformative side reactions. While these ideal spectator ligand-like features of NHCs impart remarkable catalytic properties to their transition metal complexes, the same features have made them hitherto unknown to function as directing groups (DGs) in very powerful and promising C–H functionalization strategies for C–C and C–heteroatom bond-forming catalysis (Scheme 1a),[2] in spite of the fact that a few directed cyclometalation (C–H activation) reactions were studied previously using the NHC-platform.[3] Addressing this challenge, herein, we report such an unprecedented reactivity of NHCs, where they participate as directing groups in a Rh^{III}-catalyzed C–H activation–alkyne insertion–annulation sequence to readily access imidazo[1,2-*a*]-quinolinium salts from imidazolium salts and internal alkynes at ambient temperature (Scheme 1b). In addition, although two examples of catalytic *intramolecular* annulation reactions, involving a Ni^0/Ni^{II}-based NHC–alkyl reductive elimination and a Rh^{I}-based NHC–alkene insertion pathway, have been reported,[4] a directed



Scheme 1 (a) Directing group (DG)-assisted C–H functionalization strategy (FG = functionalizing group); and (b) NHC as a new directing group in a catalytic C–H activation–alkyne insertion–annulation sequence.

catalytic *intermolecular* C–H functionalization–annulation reaction using NHC motifs and leading to important organic molecules has not been realized so far. Exploitation of non-NHC-based (hetero)-arene substrates toward oxidative annulation *via* double C–H activation has recently received growing attention.[5] It is worth mentioning here that the imidazo/benzimidazo-fused quinolinium scaffolds are, similarly to other aza-fused heterocycles, important structural motifs present in various biologically active compounds and pharmaceuticals, and are hence in great synthetic demand.[6] These types of molecules have high affinities for DNA because of their planar geometries and charged backbones, and they show effective antitumor or anticancer activities.[6] Additionally, these molecules display fluorescence properties which might be useful in organic light-emitting diode (OLED) applications.[7] Our new finding exemplifies a novel approach for the easy synthesis of such an important class of heterocyclic skeletons under ambient conditions, in contrast to high-temperature (60–160 °C) or multistep methodologies.[8]

As imidazolium salts are well-known precursors for the synthesis of transition-metal–NHC complexes *via* silver-transmetalation routes, we first conducted a one-pot stoichiometric annulation reaction to test the feasibility of our hypothesis on a directed C–H activation–insertion–reductive elimination sequence using

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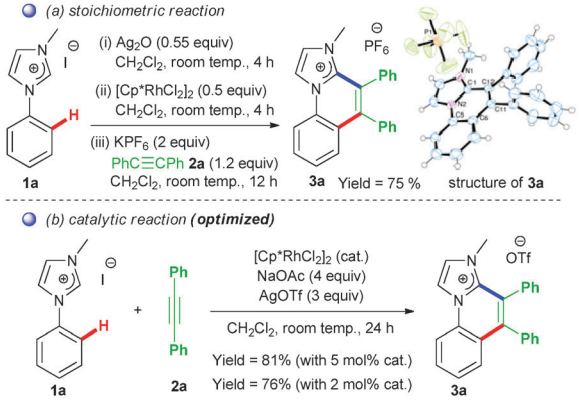
† Electronic supplementary information (ESI) available: full experimental details; NMR and mass spectra; CIFs of **4**, **3a-PF$_6$**, **3a-OTf**, **3f**, **3m** and **3p**. CCDC 1020425–1020430. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc07170k

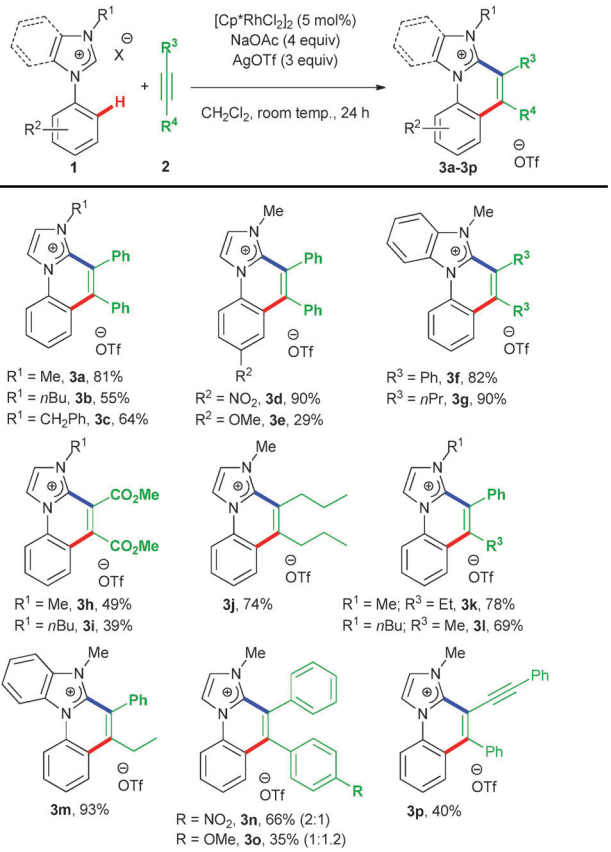


Scheme 2 (a) A one-pot stoichiometric annulation reaction *via* a silver-transmetalation route; and (b) optimized catalytic conditions (see ESI†).

the NHC–Rh^{III} backbone. Accordingly, a successful annulation reaction between 1-methyl-3-phenylimidazolium iodide (**1a**) and diphenylacetylene (**2a**) in the presence of Ag_2O and $[Cp^*Rh^{III}Cl_2]_2$ with the use of KPF_6 as an additive, affording the desired annulated product **3a** in a 75% yield (for full spectroscopic and crystallographic characterization see ESI†), indicated that the NHC–alkenyl annulative reductive elimination indeed proceeds smoothly at room temperature (Scheme 2a).

Motivated by the above results, we initiated the catalytic annulation studies, starting from **1a** and **2a** in the presence of Ag_2O and using $[Cp^*Rh^{III}Cl_2]_2$ as the catalyst precursor in dichloromethane at room temperature. Thus, the reaction of **1a** (0.1 mmol) with **2a** (0.12 mmol) was readily promoted by $[Cp^*Rh^{III}Cl_2]_2$ (5 mol%), Ag_2O (0.055 mmol) and the oxidizing agent AgOTf (0.2 mmol), affording the annulated product **3a** in moderate yield (66%) after 24 h (entry 3; Table S1, ESI†). The silver-transmetalation and subsequent functionalization methodology did not enhance the yield of the desired product substantially, even when increasing the amounts of Ag_2O and AgOTf (Table S1, ESI†). We then endeavoured to couple another popular method of metal–NHC bond formation from imidazolium salts, by using NaOAc as a base, with the ensuing insertion–annulation cascade. Delightedly, the use of NaOAc (0.4 mmol) proved to be beneficial and resulted in the formation of **3a** in an 81% yield after 24 h with 5 mol% catalyst and 0.3 mmol of AgOTf (Scheme 2b, and ESI†). A thorough optimization study was performed to evaluate the importance of the appropriate catalyst precursor, coligand, halide abstractor and metal oxidation state (see ESI†). It is significant to note that with 2 mol% catalyst, the yield of the product was found to be 76% under the same conditions (Scheme 2b). This result provided a turn over number (TON) of 19 per Rh atom and a turn over frequency (TOF) value of 0.79 h^{-1}, which are good results at room temperature conditions. Significantly high TON (86 per Rh atom) and TOF (43 h^{-1}) values were obtained with a loading of 0.5 mol% catalyst under reflux conditions. These TON and TOF values for the present catalytic system are superior to the majority of those for similar annulations catalysts (see ESI† for details). However, this methodology suffers from the use of a large amount of additives (3 equiv. of AgOTf and 4 equiv. of NaOAc).

Table 1 Substrate scope[a]



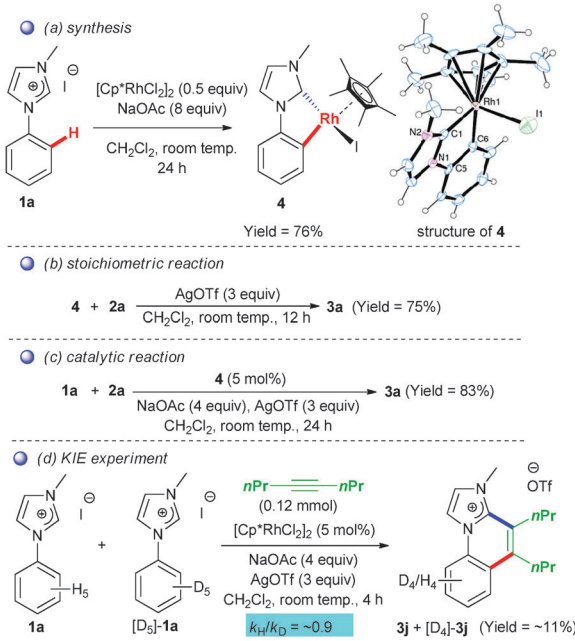
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), catalyst (0.005 mmol), additives (as mentioned), CH_2Cl_2 (3.0 mL), N_2 atm.

Efforts towards the improvement of this by using alternative oxidants like Cu(II) or HOTf/O_2 are in progress.

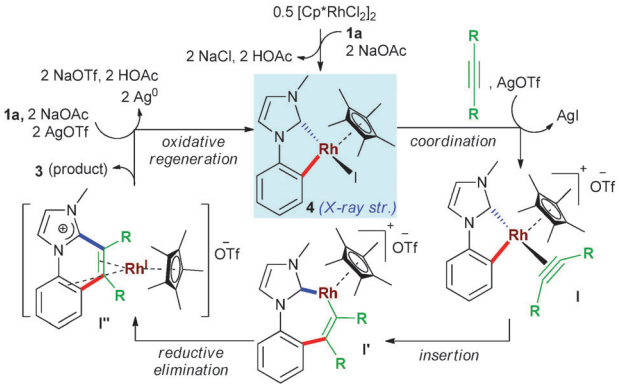
This unique annulative reactivity of NHC ligands was further explored by performing reactions with various types of imidazolium salts having different wingtip substituents (*N*-substituents in azoliums) with several internal alkynes to provide annulated products in moderate to good yields under optimized reaction conditions (Table 1). Like for the *N*-methyl substituent in **1a**, the reaction was also successful with *N*-butyl and *N*-benzyl wingtip groups in the imidazolium substrates, providing good yields of the corresponding products (**3b** and **3c**). Modification of the *N*-phenyl wingtip of the imidazolium moiety at the *para* position showed a direct effect on the reaction; a NO_2 group afforded **3d** in excellent yield (up to 90%) whereas a OMe group afforded only 29% of the corresponding product **3e**. A benzimidazolium substrate provided an excellent yield of the annulated product **3f**. Treatment of electron deficient alkynes, like dimethyl acetylene dicarboxylate (DMAD), produces lower yields (39–49%) of the annulated products (**3h–3i**) compared with treatment of diphenyl acetylene with different imidazolium partners. On the other hand, the reaction was found to be high-yielding with dialkyl acetylene, providing 90% and 74% yields for **3g** and **3j** respectively. Interestingly, phenyl–alkyl unsymmetrical alkynes provided single regioisomers of **3k**, **3l**, and **3m** in high yields. On the other hand, alkynes bearing two different aromatic

rings produced regioisomeric pairs, in a 2 : 1 ratio for **3n** (with a NO_2 group) and a 1 : 1.2 ratio for **3o** (with a OMe group) in 66% and 35% combined yields, respectively. Notably, the reaction of two equivalents of imidazolium salt **1a** with a dialkyne moiety afforded only mono annulated product **3p** in 40% yield. Steric factors might have played the main role in inhibiting double annulation.

To obtain insight into the reaction mechanism, a series of control experiments were performed. First and foremost, isolation of the NHC-cyclometalated rhodium(III) intermediate **4** was accomplished in excellent yield by using NaOAc as a base in the reaction of **1a** and $[Cp^*Rh^{III}Cl_2]_2$ in CH_2Cl_2 at room temperature (Scheme 3a), followed by its full spectroscopic and crystallographic characterization (see ESI† for details). Interestingly, the stoichiometric reaction of **4** with **2a** at room temperature in the presence of AgOTf easily afforded the annulated product **3a** in good yield (Scheme 3b). Furthermore, **4** was successfully utilized as a catalyst in the reaction of **1a** and **2a** to form **3a** in high yield under the standardized conditions (Scheme 3c). The satisfactory performance of the cyclometalated complex **4** in the above stoichiometric as well as catalytic annulation reactions implied that it is a tenable intermediate in the catalytic cycle. Moreover, the deuterium kinetic isotope effect (DKIE) value of ~0.9 indicated that the phenyl *ortho*-C–H cleavage was not involved in the rate-limiting step (Scheme 3d). In the H/D exchange experiment, only 6.2% D incorporation into the *ortho*-C–H of the phenyl ring of the resulting product was achieved, and 3.5% deuteration at the phenyl *ortho*-C–H of the unreacted substrate suggests that the phenyl C–H metalation is very weakly reversible. On the other hand, a relatively moderate D incorporation (~23%) at the imidazolium C–H of the unreacted substrate indicates a partially reversible imidazolium C–H metalation during the catalysis (see ESI†).



Scheme 3 (a) Synthesis, (b/c) stoichiometric/catalytic use of the cyclometalated intermediate **4**, and (d) kinetic isotope effect experiment.



Scheme 4 Postulated catalytic cycle.

On the basis of the above results and the reported directing-group assisted C–H activation–annulation chemistry,[2,5,8a–f] a plausible catalytic cycle is shown in Scheme 4. In the presence of NaOAc, $[Cp^*Rh^{III}Cl_2]_2$ forms the five-membered cyclometalated complex **4** from the substrate **1a**, *via ortho*-C–H activation directed by the coordinated NHC ligand. After halide abstraction from **4** by AgOTf, the alkyne coordinates to generate intermediate **I**. Insertion of the coordinated alkyne into the Rh–C_{aryl} bond of **I** provides the seven-membered rhodacycle intermediate **I′**. The possibility of a competitive NHC–alkyne insertion can not be ruled out, considering a few previous stoichiometric studies which show such a reactivity, albeit under a non-competitive environment.[4b,9] Subsequent reductive elimination from **I′** affords the annulated product **3** and a Cp^*Rh^{I} species **I″**,[8b] which is oxidized by AgOTf to Cp^*Rh^{III} for further NHC-directed C–H activation of **1a** to continue the catalytic cycle. Preliminary investigations by combined time-dependent ^{1}H NMR spectroscopy and ESI-MS analysis indicated the generation of the postulated Cp^*Rh^{I} intermediate **I″** (Fig. S10, ESI†).[8b] Detailed experimental and DFT studies are underway in order to fully investigate the proposed intermediates and also the NHC–alkyne insertion pathway for subsequent annulation.[4b]

In conclusion, we demonstrated a unique conjugative reactivity of cyclometalated NHC ligands in rhodium(III)-catalyzed intermolecular annulation, leading to important imidazo[1,2-*a*]-quinolinium structural motifs at room temperature. A series of control studies suggested the proposed mechanistic sequence involving NHC-directed C–H activation/insertion/annulative reductive elimination/oxidative catalyst regeneration in the catalytic cycle. Full investigations and further applications in other reactions are currently ongoing in our laboratory.

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