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Toward Polynuclear Ru–Cu Catalytic Dehydrogenative C–N Bond Formation, on the Reactivity of Carbazoles

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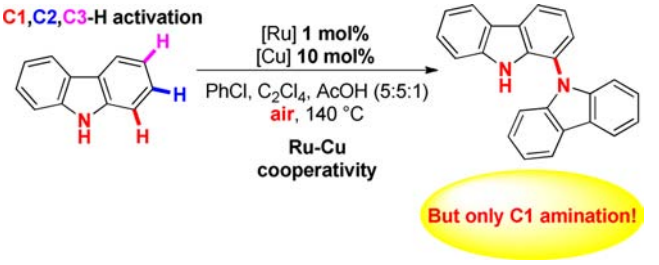
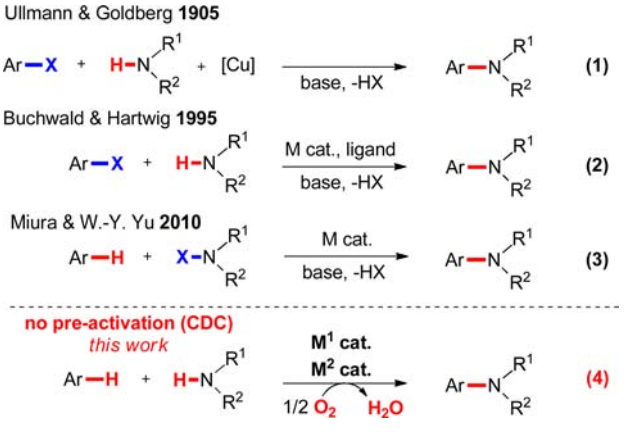
ABSTRACT



The cooperative action of Ru and Cu catalysts enables direct polynuclear C–H and N–H activation for the dehydrogenative N-carbazolation of carbazoles, selectively at the C1 position. Initial mechanistic experiments are presented and discussed.

Since 1905, and the founding works of Ullmann and Goldberg (eq 1),[1] the condensation of N-nucleophiles onto aromatic positions has remained an intense field of research, as many natural molecular structures and synthetic targets contain nitrogen atoms.[2] The celebrated Pd-catalyzed version developed by Buchwald and Hartwig (1995, eq 2)[3] has allowed milder reaction conditions and a broader amine scope, although preactivated substrates (aryl halides) and elaborate ligand systems are often required. Recently, Miura, Wing-Yiu Yu, and others have introduced an alternative strategy, which relies on C–H activation[4] in combination with preactivated (and/or preoxidized) electrophilic aminating reagents (eq 3).[5]



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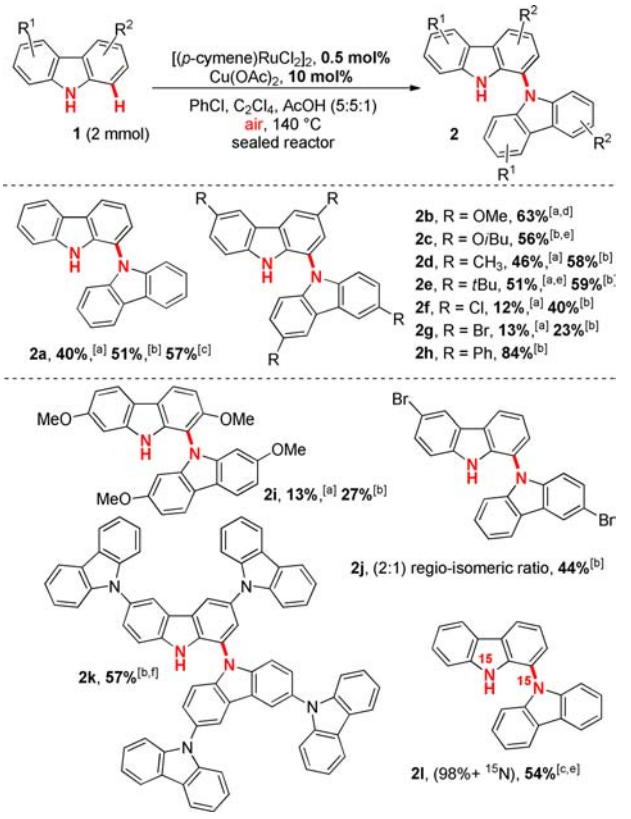
The latter still suffer however from an arguably tedious preparation, and the low atom efficiency in the overall coupling reaction. Thus, the development of direct cross-dehydrogenative-coupling (CDC)[6] amination methods by double C−H/N−H activation still constitutes an immense challenge (eq 4). In this emerging field, promising contributions have been made recently by Buchwald,[7] J.-Q. Yu,[8] and others,[9] relying on Pd catalyzed C−H activation techniques, in combination with often intramolecular and/or protected substrates. Ru C−H activation catalysts, however,[10] have been underexploited in dehydrogenative C−N bond forming reactions. We present here the outline and potential of such technology.

Scheme 1. Ru−Cu Dehydrogenative C−N Carbazolation of Carbazoles, Isolated Yields[a]



[a] Reaction time: 23 h. [b] 7 days. [c] 14 days. [d] Entry **2b**: no yield improvement beyond 23 h. [e] 1 mmol scale. [f] 0.65 mmol scale.

We focused our initial efforts on carbazoles, because they are ubiquitous heterocyclic cores in natural products and, yet, have been underinvestigated as far as late-stage C−H activation reactions are concerned.[11] Furthermore, carbazoles are an interesting study case because they possess up to eight different and competing C−H positions, a substantial challenge in terms of C−H activation regioselectivity.

We report here on the cooperative action of Ru and Cu catalysts enabling direct C−H and N−H activation for the dehydrogenative *N*-carbazolation of carbazoles, selectively at the C1 position.[12] After probing a series of typical C−H activation methods,[13] we identified the best conditions as presented in Scheme 1 (**2a**−**l**). Long reaction

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(13) See Supporting Information for experimental details.

(14) Product **2l** possesses two quaternary carbons displayed as reciprocal dd ($^1J_{13C\text{-}15N}$ = 16 Hz, $^2J_{13C15N}$ = 1 Hz) in the $^{13}C\{^1H\}$ NMR, thus confirming the *ortho* configuration of the two ^{15}N centers. $^1H-^{15}N$ HMBC (^1H: 400 MHz, ^{15}N: 41 MHz, $CDCl_3$) δ (ref. CH_3NO_2, ppm): −276.5 (s, tertiary N), −291.7 (s, NH). For a representative survey of azole derivatives, see: *Nitrogen NMR*; Witanowski, M., Webb, G. A., Eds.; Plenum Publishing: 1973; ISBN 0-306-30734-0.

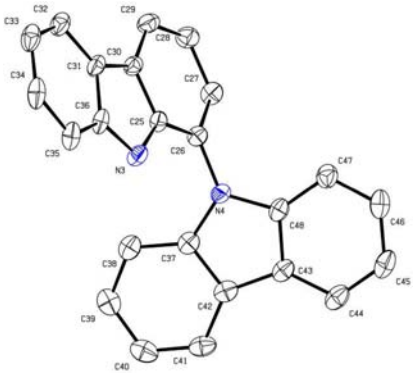
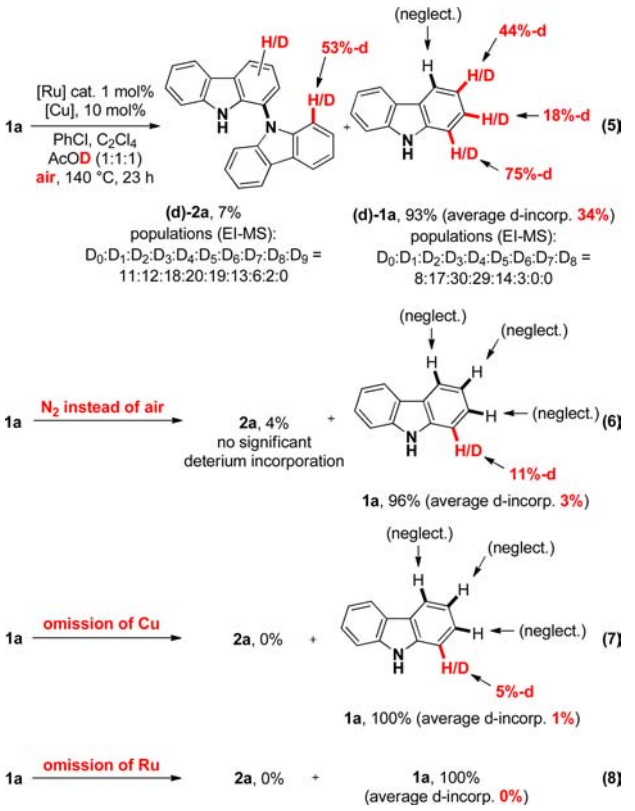


Figure 1. X-ray structure: **2a** (ORTEP view, 30% probability level). Selected torsion angle (deg): C37−N4−C26−C25 = 67.3(4).

times are helpful because of the chelate poisoning effect of the products. Omission of either the Cu or Ru salt shuts down the reactivity. For convenience in referencing, we named this class of compounds Lauternazole (Figure 1).[14,15]

Our initial mechanistic studies were very insightful for understanding this intriguing reaction. We first engaged carbazole **1a** in the presence of deuterium-labeled acetic acid-d1 (eq 5). Interestingly, the unreacted carbazole **1a** was isolated with an impressive deuterium grade, not only at C1 (75% d-incorp.) but also at C2 (18% d-incorp.) and especially C3 positions (44% d-incorp.), which is surprising as no coupling products were ever observed at C2 or C3. This may indicate that (1) the catalyst approaches the substrate from the top, through coordination to its electron-rich π-aromatic system (hence C−H activation at C2 and C3), and (2) the initial C−H activation is not rate-limiting (because reversible). The final C−N reductive elimination, an event known to be difficult, may be in fact the rate-limiting step. Most surprising, however, was the observation that running the deuterium scrambling experiment under a strict N_2 atmosphere completely suppresses the C−H activation reactivity (11% d-incorp., at C1 only, eq 6). Consequently, O_2 not only is required as an oxidant but also is probably a critical catalyst modifier, responsible for the formation of the true active species.[16] In addition, no deuteration was observed when the Cu or Ru salt was respectively omitted (eqs 7 and 8). This indicates that both Ru and Cu are required early on in the C−H activation step.



In its initial stage, the reaction is clearly first-ordered in Ru, although with a slightly broken kinetic order of 0.7, possibly due to the competing initial Ru-dimer dissociation process. There is however a clear zero kinetic order in Cu, which is somewhat surprising at first, because Cu is strictly required to effect reactivity. Nevertheless, we also

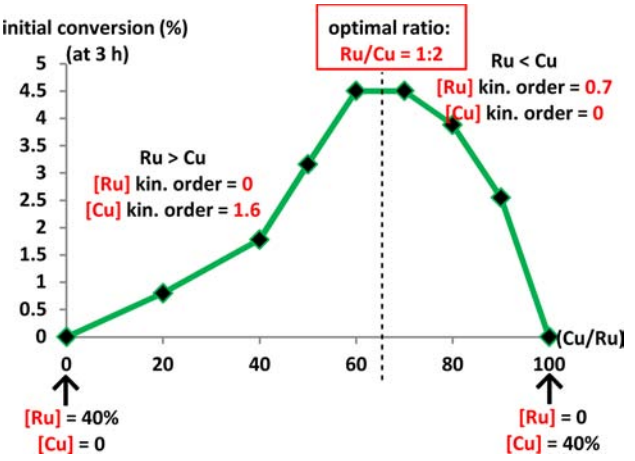
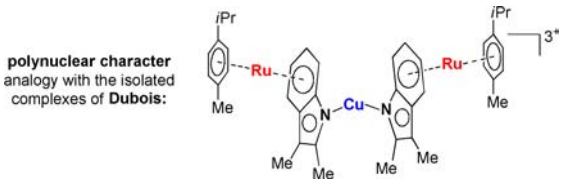


Figure 2. Initial reactivity Job plot. [Ru] + [Cu] = 40% catalytic loading; reaction time, 3 h, in otherwise standard conditions (2 mmol scale).

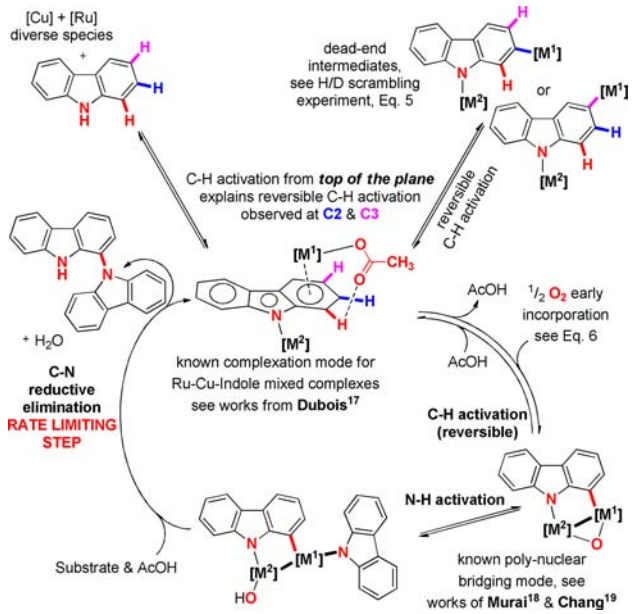
(15) It was found possible to gram-scale the reaction. 20 mmol of **1a** in a large sized reactor at 150 °C lead to 1.5 g of **2a**; see exptl part.

(16) The importance of oxo-complexes in C−H activation reactivity: Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060.

(17) For mixed Ru(II)−Cu(I) *hetero*-dinuclear complexes with indoles as, respectively, a π- and N-ligand, see for example: Chen, S.; Carperos, V.; Noll, B.; Jeffrey Swope, R.; Rakowski DuBois, M. *Organometallics* **1995**, *14*, 1221.



Scheme 2. Proposed and Initial Mechanistic Elements



performed a series of kinetic experiments at high Ru loading, in which [Ru] > [Cu]. Under those conditions, we measured the second-order kinetics for Cu (1.6) and, reciprocally, zero order in Ru. Therefore, it can be assumed that both Ru and Cu are involved in the rate-limiting step(s) of the reaction. Surprised by the unexpectedly high Cu order, we performed a reactivity-based Job plot experiment where the two variables are [Ru] and [Cu]. The highest initial rate was not obtained at the expected 1:1 ratio, but clearly at the optimal ratio of 1:2 (Ru/Cu, Figure 2). Therefore, as much as one Ru center and two Cu centers could be jointly involved in the rate-limiting step. Based on these experiments and on polynuclear organometallic literature precedents by Dubois,[17] Murai,[18] and Chang,[19] we propose the initial mechanistic elements of Scheme 2. These remain *hypothetical* at this stage but seem in accordance with our kinetic data and the mentioned literature.

In summary, we expect that the surprising elements of reactivity presented here will seed novel types of oxidative amination reactions, particularly through synergic association of different metal catalysts.[20]

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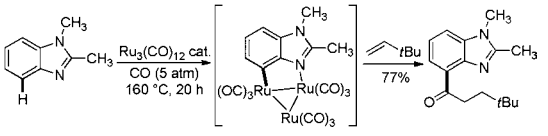
Supporting Information Available. Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For a polynuclear Ru catalyzed C−H activation reaction of some azole derivatives, see: Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522.



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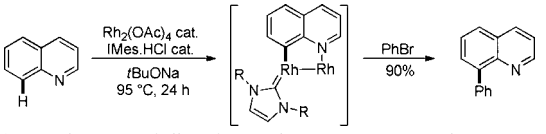

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