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COMMUNICATION

A catalytic intramolecular nitrene insertion into a copper(I)–*N*-heterocyclic carbene bond yielding fused nitrogen heterocycles

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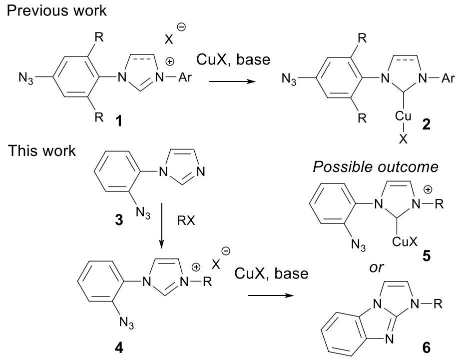
N-(2-azidophenyl)azolium salts were easily prepared and reacted with copper(I) in conditions allowing the formation of NHC complexes. In these conditions, the formation of benzimidazo-fused heterocycles occurred in catalytic, efficient and very mild conditions. The reaction is proposed to proceed *via* dinitrogen elimination and imido/nitrene–NHC cyclization.

N-Heterocyclic Carbenes (NHCs) have become one of the most powerful tools in synthetic chemistry.[1] Chiefly, they play the role of ancillary ligands allowing the preparation of transition metal complexes (e.g. Pd,[2] Au,[3] Cu[4]…) which have found plethoric applications in catalysis.[5] These complexes are often stable due to electronic and steric effects. Thus, cases for which the NHC departs from its archetypical ancillary ligand role are rarely encountered.[6] One of these occurrences was encountered with a tripodal tris-NHC complex that underwent an imido insertion into the metal–$C_{carbene}$ bond furnishing a new carbon-nitrogen double bond.[7] This bimolecular process is believed to proceed via an azide decomposition to imido with dinitrogen release through cobalt(III)/cobalt(I) intermediates. Other rare cases imply the formation of $C_{carbene}$–nitrogen bonds from NHC complexes[8] or with other types of metal carbenes, all being stoichiometric.[9] In contrast to these examples, NHC complexes have been used as nitrene insertion catalysts without any reaction at the NHC center.[10]

Previously, we have reported that azolium salts distally tagged with azides **1** yielded stable Cu-NHC complexes **2**.[11] We decided to introduce the azide function in close proximity to the precarbenic center through the preparation of *N*-(-2-azidophenyl)imidazolium salts **4**, from azide precursors **3** (Scheme 1). Azolium salts **4** allow in principle to form either stable bidentate NHC–azide chelates[12] or benzimidazo[1,2-*a*]imidazoles through NHC-nitrene cyclization. The latter possibility requires that nitrene decomposition occurs in a step following the formation of the metal-NHC complex. We demonstrate in this Communication that the latter reactivity may be harnessed as a highly efficient and *catalytic* synthetic access to nitrogen-rich fused heterocycles.



Scheme 1. Attempted preparation of chelated Cu-(NHC-N_3) complexes and C=N cyclization.

The 1-(2-azidoaryl)imidazolium salt starting materials could be obtained using several facile well-established synthetic pathways. *E.g*, the precursor **3** was obtained in gram-scale with 81% yield using a 3-step synthesis from imidazole and 1-fluoro-2-nitrobenzene (see ESI for details).[13] The formation of the imidazolium salts **4a,b** using benzyl or 2-picolyl chloride occurs smoothly in excellent yield at 80°C (see ESI). Then, in order to prepare the metal-NHC complexes, we examined the reactivity of **4a** and **4b** with $CoCl(PPh_3)_3$ and CuCl in presence of a 6-fold excess of aqueous ammonia. These conditions were previously reported for the synthesis of copper(I)-NHC complexes.[14] No reaction were observed with the cobalt complex but using CuCl, a vigorous gas evolution was observed with the formation of a precipitate. This proved to be the pure *1H*-benzimidazo[1,2-*a*]imidazole derivative **6a** or **6b** instead of complexes **5**. Compounds **6a,b** were isolated in ~95% yield and were fully characterized by ^{1}H- and ^{13}C-NMR, IR (lack of the azide band) spectroscopies, HRMS and CHN elemental analyses (Scheme 2). The definitive structural proof was obtained by the X-ray diffraction[‡] for **6b**, Scheme 2.

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Electronic Supplementary Information (ESI) available: experimental conditions, ^{1}H and ^{13}C NMR spectra, crystallographic details, DFT data. See DOI: 10.1039/x0xx00000x

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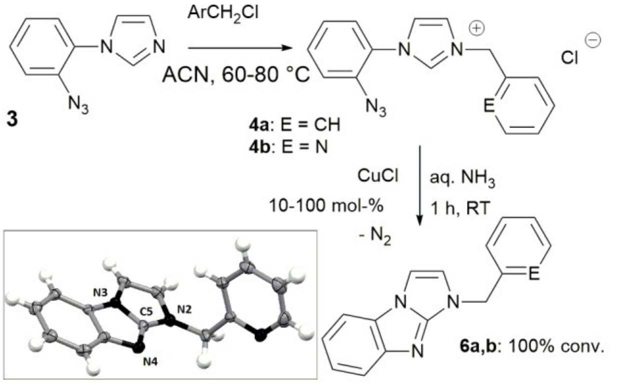


Scheme 2. Preparation of azido substrates and their cyclization; insert: structure of **6b** by X-ray diffraction; selected distances N2-C5 1.361 Å, N3-C5, 1.373 Å, N4-C5, 1.319 Å

This synthetic route deserves some literature comparisons. On the one hand, benzimidazo[1,2-*a*]imidazoles are recognized as interesting scaffolds for drug design or optoelectronic applications. They are accessible *via* lengthy conventional multistep organic syntheses.[15] Recently, elegant metal-catalyzed procedures have been developed, but they still need prolonged reaction times at high temperatures:[16] *e.g.* copper-catalyzed aerobic oxidative intramolecular C-H amination has been reported for *9H*-benzimidazo[1,2-*a*]imidazole synthesis from 2-(1H-imidazol-1-yl)-aniline, but requires 24-55 h in refluxing *m*-xylene.[16a] On the other hand, the azide group is a well-known precursor for nitrenes whose insertion in C-H bonds allows the preparation of heterocycles.[17] Metal-catalyzed C_{sp3}-H aminations from azides have been achieved with exquisite selectivity.[18] In the last decade, C_{sp2}-H aminations have emerged and azides are again among the preferred precursors.[19] Usually, the catalyst is sophisticated and/or requires a precious metal. In this context, our study compares well with the rhodium-catalyzed synthesis of carbolines from aryl azides reported by Driver *et al.*. His very efficient and mild protocol requires nevertheless 5 mol-% of (expensive) $[Rh_2(esp)_2]$.[20] The efficiency of our *room temperature*[21] conditions and the use of a nonprecious metal prompted us to perform a detailed study.

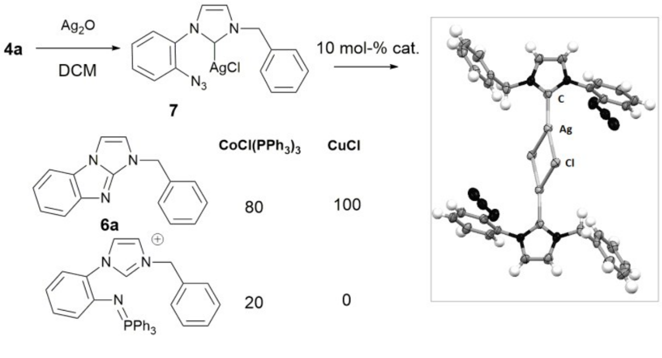
First, the effect of ammonia, metal, and solvent were examined for the formation of **6a** (Table 1). The initial conditions (entry 1) were taken from our previous report on copper-NHC synthesis and were shown to allow full conversion of precursors related to **4b** to copper complexes within 1 h at RT.[14] Lowering the amount of ammonia doesn't affect the conversion (entries 1-2). Importantly, the reaction could be conducted efficiently within 1 h with substoichiometric CuCl (10 mol-%, entry 3), keeping the amount of ammonia to 1.0 eq. (entry 4).[22] To the best of our knowledge, this is the first case of a catalyzed imido insertion into a carbene-metal bond. Negative controls (entries 5 and 6) show that copper and ammonia are necessary for the reaction. Various solvent such as ethanol, acetonitrile, DMF, DMSO and THF (entries 7, 9-12) could be used instead of water. A lower metal loading caused reduced yield despite long reaction times (entry 8).

Table 1. Optimization of the preparation of 6a.

Entry	Eq. CuCl	Eq. NH_3	Solvent	Conversion[a]
1	1.0	6.0	Water	>95%
2	1.0	1.0	Water	>95%
3	0.1	1.0	Water	93%
4	0.1	0.6	Water	60%
5	0	1.0	Water	0%
6	0.1	0	Water	0%
7	0.1	1.0	Ethanol	>95%
8	0.01	1.0	Ethanol	62%[b]
9	0.1	1.0	MeCN	>95%
10	0.1	1.0	DMF	>95%
11	0.1	1.0	DMSO	>95%
12	0.1	1.0	THF	>95%

[a] reaction duration: 1h [b]after 48h

The conditions reported in entry 7 were further modified to check the influence of metal source and base. The presence of copper(I) was necessary as other metal salts (10 mol-%, $MnCl_2$, $FeCl_2$, $CoCl_2$, $CoCl(PPh_3)_3$, $ZnCl_2$, $NiCl_2$, $NiCl_2(dme)$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $CuCl_2$) were inefficient to perform the reaction.[23] However, other stable copper(I) sources were usable such as Cu_2O, $[Cu(MeCN)_4](PF_6)$ and the preformed NHC complex [CuCl(IPr)][14a] which give 87%, 92% and 86% conversion, respectively. Ammonia proved to be an optimal base for this catalytic reaction as changing the base to Na_2CO_3, NaOH or NaOEt gave inferior results (yield reduced to 65% in the first case due to limited conversion, complete conversion but extensive degradation in the two latter cases).



Scheme 3. Cyclization through silver transmetalation. Insert: structure of the dimer of **7** by X-ray diffraction; selected structural parameters Ag-C: 2.089 Å, Ag-Cl: 2.403 Å, Ag...Cl: 2.793 Å, C-Ag-Cl: 163.5 °, Ag-Cl...Ag: 90.15°.

As an alternative to the ammonia protocol, we also considered the silver to metal transmetallation.[24] Indeed, the reaction of **4a** with silver(I) oxide afforded **7** (Scheme 3) without any gas evolution.[25] Subsequently, 10 mol-% of copper(I) were added: to our delight, a gas evolution was observed and compound **6a** could be isolated in quantitative yield. Using 10 mol-% of $CoCl(PPh_3)_3$, **6a** was identified in the crude mixture

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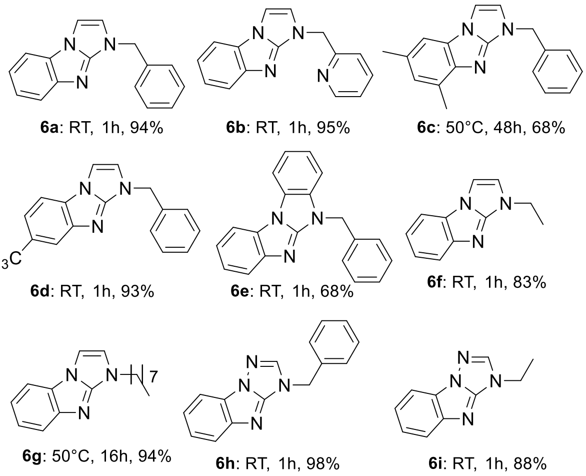
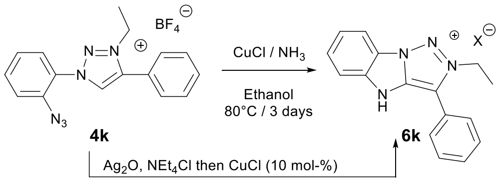
accompanied by an iminophosphorane imidazolium resulting from a Staudinger reaction (~80/20 by HPLC-HRMS). While the cyclization by the Ag_2O route could be performed in one-pot conditions, the intermediate silver-NHC complex **7** could be isolated and fully characterized. In the solid state, the structure shows a well-known $Ag_2(\mu\text{-}Cl)_2$ diamond core arising from Ag…Cl-Ag interaction with usual bond lengths and angles and no interaction between Ag and N_3. Interestingly, **7** could also undergo cyclization in rather inefficient conditions (ESI). All these observations, as well as mechanistic precedents, strongly support the involvement of a metal imido-NHC intermediate.

The cyclization reaction using copper(I)/ammonia protocol was applied to other representative azolium salts with good yields (Scheme 4) and most of the products were obtained as analytically pure materials after simple extraction. Besides **6a**,**b** the method tolerates the presence of alkyl substitutions on the benzimidazole ring (**6c**) as well as an electron-withdrawing group (trifluoromethyl, **6d**). The reaction also applied to a benzimidazolium salt to yield **6e**[16c] and to *N*-alkyl substituted products (**6f,g**) as well. The cyclization was not restricted to the imidazolium salts but also applied in the same conditions to 1,2,4-triazolium salts leading to benzo[4,5]imidazo[1,2-b]-1,2,4-triazole **6h,i** in good yields.[26] However, the cyclization of a *N*-(2-azidobenzyl)-imidazolium (**4j**, ESI) failed (after several days at 90°C the starting material was recovered unchanged).



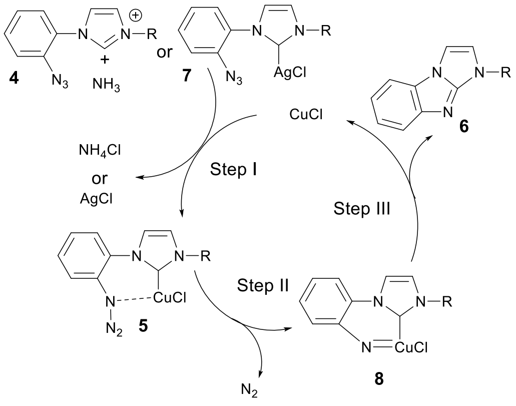
Scheme 4.. Isolated yields for the cyclization products.

Similarly, the 1,2,3-triazolium **4k** stayed unchanged at room temperature for several hours. However, increasing the temperature to 80°C and extending time to 3 days allowed a clean conversion to a benzo[4,5]imidazo[1,2-c]-1,2,3-triazol-2-ium specie (Scheme 5).[26b] To avoid anion scrambling issues, **6k** was also obtained using copper(I) oxide as the metal source (in somewhat less efficient conditions: 4 days, 90°C, 20 mol-% Cu_2O). We also tested the silver oxide/catalytic CuCl procedure (scheme 3) and found that the reaction took place in few minutes, once the formation of the silver complex was complete. The lower reactivity of **4k** could be explained by the lower acidity of the 1,2,3-triazolium proton in comparison to the imidazolium's[27] which slows down the formation of the Cu-NHC complex intermediate.



Scheme 5. Cyclization of a 1,2,3-triazolium salt.

A proposed mechanism is sketched in Scheme 6. The Cu^I-NHC complex **5** is formed either by direct metalation in the presence of ammonia or by transmetalation from a silver precursor (step I). Copper chelation to azide and extrusion of dinitrogen (step II) forms the complex **8**, which includes formally a copper(III) center chelated by both imido and carbene donors. This intermediate is expected to undergo a carbene-nitrene reductive cyclization to compound **6** (step III) with copper(I) chloride regeneration. This can be explained by the electrophilic nature of the imido donor which inserts into the copper-NHC bond. Compared to previous reports of stoichiometric transformations,[7,8] the catalytic nature of the process is facilitated by the ease of formation of the copper-NHC complex using either protocol and the intramolecular nature of the reaction.



Scheme 6. Postulated catalytic reaction mechanism

To support the proposed mechanism, we examined the energetic profile of steps II and III by DFT calculations for model compounds 1-(2-azidophenyl)-4-methyl imidazolium and 1-(2-azidophenyl)-4-methylbenzimidazolium (Table S5).

The calculations show that dinitrogen generation forming the carbene-imido complex and reductive elimination of copper (step II-III, Scheme 6) are both exergonic and that the higher transition state energy (step II) is only ~10 kcal mol^{-1}. In the intermediates of type **8**, the complex is favorably organized for reductive elimination with $N_{nitrene}$-Cu-$C_{carbene}$ angles < 90°, which is in line with a low TS energy (1-5 kcal mol^{-1}). The reactivity could be explained by the weak N-N_2 and the strong N≡N bonds, and by the extended conjugation in the final product.

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In conclusion, we have reported a novel synthetic method based on a cyclization reaction leading to the formation of polycyclic nitrogen-rich compounds. This process is believed to occur through reductive elimination from copper(III) in a chelated carbene-copper-nitrene intermediate. This constitutes the first catalytic and synthetically efficient occurrence of this type of cyclization with *N*-heterocyclic carbenes not acting as spectator ligands but as reactive partners. This against-the-rules reactivity of NHC ligands may open new horizons in synthesis by redirecting the extensive literature reports for the preparation of azolium salts to the preparation of diversified heterocyclic scaffolds.[28]

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‡ CCDC 1491878 and 1529895 contains the supplementary crystallographic data for this Communication.

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