



## A tetraiodo cuprate NHC-MIC biscarbene proligand: coordination chemistry and preliminary catalysis

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catalysis

### RESUMEN

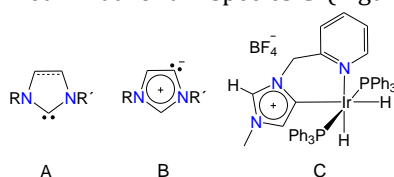
La preparación de una sal híbrida conteniendo cationes imidazolio/triazolio [NHC-MIC]<sup>2+</sup> fue llevada a cabo en tres pasos sintéticos utilizando la cicloadición de azida-alquino catalizada por cobre (CuAAC) y la subsecuente *N*-metilación del 1,2,3 triazol. Deprotonación selectiva de la sal mixta con NaH en presencia de un precursor metálico (M = Pd, Rh) permite la síntesis de NHC-metálicos conteniendo fragmentos catiónicos de tipo triazolio [NHC·(M)-MIC]<sup>+</sup>. La subsecuente deprotonación del triazolio con KO<sup>t</sup>Bu en presencia de **M** permite entonces la síntesis de complejos inusuales tipo quelato conteniendo carbenos clásicos tipo NHC y carbenos mesoiónicos MIC con estructura general [NHC·(M)·MIC]<sup>+</sup>MX<sub>2</sub>. Todos los compuestos han sido caracterizados mediante RMN de <sup>1</sup>H y <sup>13</sup>C, FT-IR y cristalografía de rayos-X de monocristal. Estudios catalíticos preliminares de los nuevos complejos en procesos de formación de α-cetoamidas serán discutidos.

### ABSTRACT

A novel linked imidazolium/triazolium salt [NHC-MIC]<sup>2+</sup> was prepared in three synthetic steps using copper catalyzed alkyne azide cycloaddition (CuAAC) and *N*-methylation protocols. Metallation of the imidazolium moiety using KHMDS in presence of a metallic precursor (M = Pd, Rh) yields NHC-anchored/pendent triazolium species [NHC·(M)-MIC]<sup>+</sup> in good yields. The subsequent deprotonation of the triazolium fragment with KO<sup>t</sup>Bu in presence of one equivalent of M delivers the rare chelating mixed classical NHC/mesionic biscarbene complexes with the general formula [NHC·(M)·MIC]<sup>+</sup>MX<sub>2</sub>. All the complexes were fully characterized by <sup>1</sup>H and <sup>13</sup>C NMR, FT-IR and single crystal X-ray diffraction. Preliminary catalytic performances of the new complexes in the oxidative preparation of α-ketoamides will be discussed.

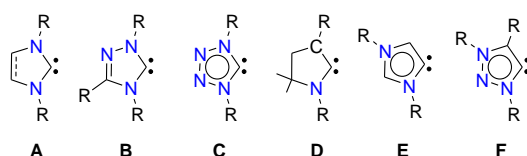
## Introduction

Since the discovery of free, isolable N-Heterocyclic carbenes (NHCs) by Arduengo in 1991 (Arduengo et al. 1991), the use of these ligands has risen tremendously, especially in homogeneous catalysis and organometallic chemistry (Diez-González et al. 2009). The intense interest in NHCs and related species has led to several variations of these ligands, a consequence of their readily tunable properties. Interestingly, until 2001 all imidazol-ylidene based NHCs invariably contained their lone pair located in the C-2 position (**A**). NHC having the free carbene functionality at the C-4 (**B**) position was first reported by Crabtree (Crabtree et al. 2001) by means of the internal metallation of a pyridine functionalized imidazolium species **C**. (Figure 1).



**Figure 1.** Classical NHCs (**A**), mesoionic carbenes (**B**), and mesoionic carbene iridium complex (**C**)

Since this discovery, a number of groups have targeted these species owing to their impressive electron donating properties that overpass even the donating properties of classical NHCs. These “wrong way” carbenes were first termed “abnormal” carbenes due to the unusual localization of the lone pair, however in 2010, Bertrand and coworkers suggested the mesionic carbene (MICs) nomenclature due to the fact that no neutral resonance forms of these ligands can be drawn (Bertrand, et al, 2010). At present, a series of ligands based on imidazole(2-ylidenes) (**A**), triazole- (**B**, **F**), tetrazole- (**C**), cycloalkylamino- (CAAC, **D**), and imidazole(4-ylidenes) (**E**) scaffolds have been developed and successfully employed in numerous organic and organometallic applications (Schuster et al, 2009) (Scheme 1).



**Scheme 1.** Most commonly used NHCs.

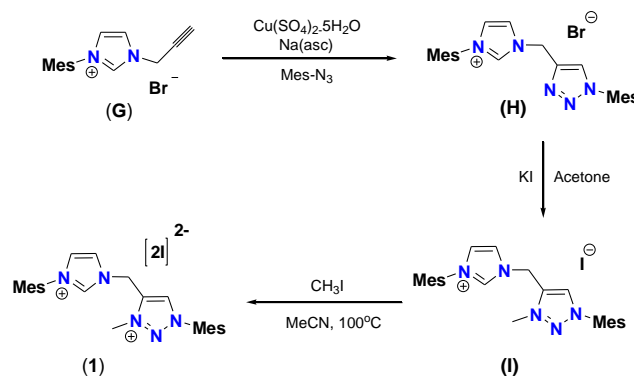
Our interest in biscarbene ligands for the preparation of multicentered transition metal complexes (Mendoza-Espinosa et al. 2015) led us to target the preparation of unsymmetrical ligands which are still rare in the literature but could provide a versatile platform for the

preparation of metal complexes with various coordination and electronic environments (Albrecht et al. 2009). Consequently, we sought the synthesis of a hybrid NHC/MIC ligand and its use as bridge in the preparation of metal complexes with several coordination modes and electronic properties. We consider that a ligand capable to combine two metals with different properties into one catalyst can potentially function as tandem catalyst in which a pair of metals mediate two mechanistically different catalytic processes in one pot with high atom economy (Zamora et al. 2012). In dicarbene-bridged tandem catalysis, it seems unlikely that symmetric dicarbenes, having the same carbene unit bound to each metal, will be optimal in promoting the required differing reactivity at the different metals. With this background, is the objective of the present work to develop unsymmetrical biscarbenes to provide a greater flexibility in tuning the electronic and steric properties around the metal centers.

## Metodology

### Synthesis of imidazolium/triazolium salt (**1**)

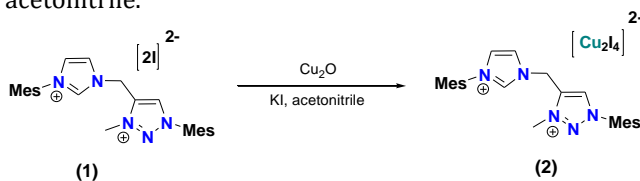
The preparation of the hybrid salt **1** was performed according to Scheme 2. The first step involves the copper catalyzed cycloaddition of precursor **G** with mesityl azide in acetonitrile at 100°C. After 72 h of reflux, the isolation of the product by means of precipitation and filtration produces the cationic precursor **H**. Further treatment of the latter with excess of KI and then methyl iodide delivers the expected imidazolium/triazolium hybrid (**1**). Pure product was obtained after recrystallization of the crude material with acetonitrile/diethyl ether in 65% yield.



**Scheme 2.** Synthesis of hybrid salt **1**.

### Synthesis of Tetraiodo cuprate imidazolium/triazolium salt (2)

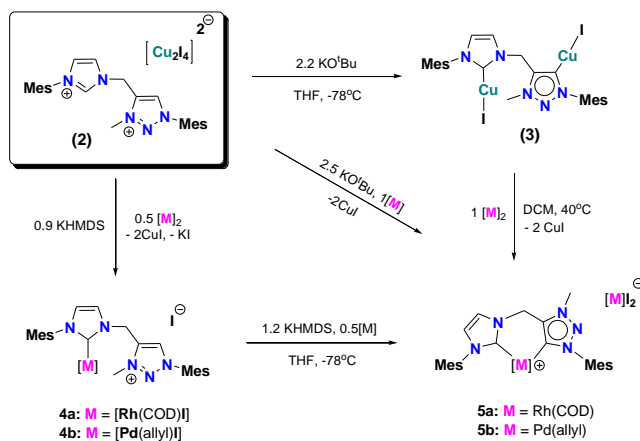
A mixture of the solid salt **1** (1 mmol), Cu<sub>2</sub>O (1.2 mmol), and KI (2 mmol) were added to a pressure tube under air. Acetonitrile (10 mL) was added to the reaction mixture and the resulting suspension was refluxed at 80°C for 16 hr (Scheme 3). After cooling down to room temperature, filtration of the insoluble material via cannula yields a yellowish supernatant that is further precipitated by the addition of copious amounts of diethyl ether. The resulting brown solid is washed three times with 20 mL portions of diethyl ether and the pure product is obtained after recrystallization from acetonitrile.



Scheme 3. Synthesis of tetraiodo cuprate hybrid salt **2**.

### Synthesis of NHC-MIC bimetallic copper complex (3)

The cuprate salt **2** (0.5 mmol) and potassium tert-butoxide (1.1 mmol) were charged in a Schlenk flask purged with nitrogen. Dry THF (7 mL) were added at 0°C and the reaction mixture was stirred for 6 h while it reached room temperature (Scheme 4). The reaction mixture was filtered via cannula and the solution was evaporated under vacuum. The residue was extracted with 10 mL of dichloromethane (DCM) and vacuum dried to yield the crude product. Pure complex **3** was obtained in 91% after recrystallization from a mixture of DCM/Hexanes.



Scheme 4. Synthesis of carbene transition metal complexes **3**, **4** and **5**.

### Synthesis of NHC-anchored/pendent triazolium species [NHC:(M)-MIC]<sup>+</sup> (4a-b)

The cuprate salt **2** (0.5 mmol) potassium hexamethyldisilazane (KHMDS, 0.45 mmol), and the proper metal dimer (0.25 mmol) were charged in a Schlenk flask purged with nitrogen. Dry THF (7 mL) were added at -78°C and the reaction mixture was stirred for 16 h while it reached room temperature (Scheme 4). The reaction mixture was filtered via cannula and the solution was evaporated under vacuum. The residue was extracted with 10 mL of dichloromethane (DCM) and vacuum dried to yield the crude product. Pure complexes **4a** or **4b** were obtained in 53 and 49%, respectively, after chromatographic column separation using mixture of DCM/acetone (2:1).

### Synthesis of NHC-MIC bimetallic complexes (5)

#### Method A

The respected monometallic NHC complex of the type **4** (0.25 mmol), KHMDS (0.51 mmol), and the metal precursor [M]<sub>2</sub> (0.125 mmol) were charged in a Schlenk flask. THF (5 mL) were added at -78°C and the reaction was stirred for 16 h while it reached room temperature. The reaction mixture was filtered via cannula and the solution was evaporated under vacuum. The residue was extracted with 5 mL of dichloromethane (DCM) and vacuum dried to yield the crude product. Pure complexes **5a** or **5b** were obtained in 75 and 81%, respectively after recrystallization using a mixture of DCM/hexanes.

#### Method B

The bimetallic copper complex **3** (0.25 mmol) and the dimeric metal precursor [M]<sub>2</sub> (0.25 mmol) were charged in a Schlenk flask. DCM (5 mL) were added and the reaction mixture was stirred at 40°C for 3 hr. The suspension was filtered via cannula and the solution dried under vacuum. Pure **5a** or **5b** were obtained after recrystallization from THF-MeCN/hexanes in 67 and 59% yield, respectively.

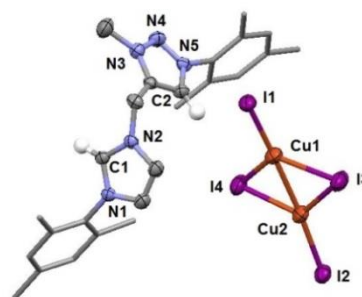
**Method C:** The cuprate salt **2** (0.5 mmol), KO<sup>t</sup>Bu (1.25 mmol), and the dimeric metal precursor [M]<sub>2</sub> (0.5 mmol) were charged in a Schlenk flask. THF (10 mL) were added and the reaction mixture was stirred at -78°C for 12 hr. The final suspension was filtered via cannula and the solution dried under vacuum. Pure **5a** or **5b** were obtained after recrystallization from THF-MeCN/hexanes in 73 and 65% yield, respectively.

## Results and discussion

### Synthesis and characterization

Albrecht and Bertrand have reported the synthesis of a MIC by coupling an aryl azide with phenylacetylene (PhCCH) using “click” chemistry to form a 1,2,3-triazole, followed by alkylation at *N*-3 to generate a cationic triazolium ring, which can later be deprotonated to form the MIC. In a subsequent report by Elsevier et al. (Elsevier et al, 2014), the preparation of various triazolyl-functionalized NHCs, in which the triazolyl group functioned as a pendent hemilabile *N* donor, was outlined in which an azide was coupled with the pendent propargyl arm ( $-\text{CH}_2\text{CCH}$ ) of an imidazolium salt. Inspired by both of these studies, we began investigating the synthesis of the targeted hybrid NHC/MIC precursors by combining these two methodologies. According to Scheme 1, reaction of the propargyl imidazolium salt with mesitylazide ( $\text{MesN}_3$ ) in the presence of copper sulfate and sodium ascorbate yields the 1,2,3-triazolyl compound (**E**), for which all  $^1\text{H}$  and  $^{13}\text{C}$  NMR resonances are typical for systems involving both imidazolium and triazolyl groups. To avoid any mixture of anions in the final product, complex **E** was treated with excess of KI to exchange the bromine ion and the triazolyl compound **F** was then reacted with MeI to generate the expected mixed salt **1** in good yields. Formation of the desired product was easily monitored by the emergence of a new signal in the  $^1\text{H}$  NMR spectrum at ca.  $\delta$  4.5, indicating methylation of the triazolyl moiety (at *N*-3). Most of the other resonances in the  $^1\text{H}$  NMR spectrum shift only slightly, with the exception of the now-acidic triazolium proton, which moves to higher frequency (ca.  $\delta$  8.9 ppm).

The initial exploration on the coordination capabilities of salt **1** was carried out by its “one pot” reaction with KHMDS and CuI. After work up the  $^1\text{H}$  NMR spectroscopy showed a complex mixture with no copper carbene complexes observed. As the *in-situ* deprotonation process with a strong metallic base proved unsuccessful, we then performed the reaction of **1** with  $\text{Cu}_2\text{O}$  and KI in acetonitrile. The NMR spectroscopy showed no deprotonation but instead a noticeable shift in the imidazolium and triazolium  $\text{CH}^+$  peaks. After recrystallization from MeCN/diethyl ether, the crystal structure of the new product was obtained and the ORTEP diagram is depicted in figure 2. The structure of the new compound **2** comprises a mixed imidazolium/triazolium salt with a tetraiodo cuprate anion which neutralizes the overall salt charge.

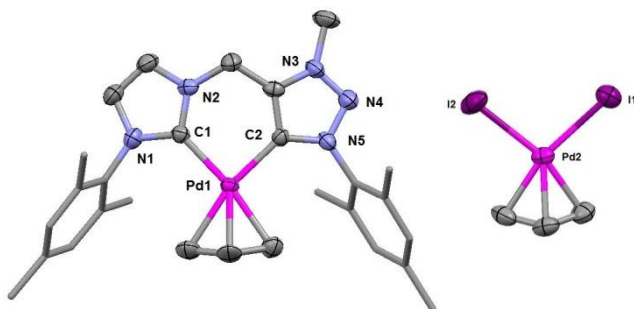


**Figure 2.** Molecular structure of salt **2** with ellipsoids shown at 50% of probability. Selected hydrogen atoms have been omitted for clarity.

Having still a dicationic precursor with potential as a proligand for asymmetric biscarbenes, we tested the possibility of deprotonating salt **2** with a strong base in hope that the copper source could lead *in situ* to the bimetallic copper complex. Thus, salt **2** was treated with excess of  $\text{KO}^t\text{Bu}$  in THF at  $-78^\circ\text{C}$ . After work up and purification, the expected bimetallic complex **3** was isolated in 91% yield as a white solid. The preparation of complex **3** was confirmed by elemental analyses and by NMR spectroscopy by disappearance of the  $\text{CH}^+$  signals above 9 ppm in  $^1\text{H}$  and the presence of two new carbenic-copper signals at 155 and 175 ppm in  $^{13}\text{C}$  NMR. With the recent reports by Cazin and Furst on the use of copper carbenes as NHC-transfer reagents for heavier NHC transition metal complexes, we decided to investigate if this methodology could be applied to our mixed NHC-MIC biscarbene. Indeed, the reaction of complex **3** with equimolar amounts of  $[\text{Rh}(\text{COD})\text{Cl}]_2$  or  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  allows for the high yield transmetalation process delivering complexes **5a** and **5b** in a single step (Scheme 3). Confirmation of the synthesis of **5a** and **5b** was achieved by  $^{13}\text{C}$  NMR. At first glance, we expected the structure of complexes of the type **5** to contain an equivalent metal center coordinated to each of the NHC/MIC carbenes in a monodentate fashion; however X-Ray analysis of the single crystals of complex **5b** unveiled a unusual coordination mode for a biscarbene ligand.

According to figure 3, the mixed NHC/MIC biscarbene ligand coordinates only one of the palladium centers (Pd1) in a bidentate fashion generating a cationic fragment. The second palladium center with negative nature (Pd2) compensates the overall molecule charge being bounded to an allyl fragment and two iodine atoms. In the cationic fragment, the Pd1-C1 and Pd1-C2 bond distances are 2.062(8) and 2.047(9) Å

respectively, which denotes the stronger donation of the MIC moiety to the metal center.



**Figure 3.** Molecular structure of complex **5b** with ellipsoids shown at 50% of probability. Hydrogen atoms have been omitted for clarity.

The six-membered ring formed by the biscarbene and the metal center resides in a quasi-planar conformation with only slight deviations at the CH<sub>2</sub> linker (torsion angles 5.21 and 12.3 °). The mesityl fragments are orientated orthogonal to the six-membered ring plane providing steric protection to the palladium center. The anionic fragment shows a palladium center in a distorted trigonal planar geometry with Pd-C and Pd-I bond distances in the range of reported analogue complexes.

Rationalizing that the copper intermediate **3** is generated by deprotonation with KO<sup>t</sup>Bu and that further transmetalation generates complexes of the type **5**, we explored the possibility of performing this conversion in a single step. Thus, the “one-pot” reaction of salt **2** with excess of KO<sup>t</sup>Bu in presence of equimolar amounts of the proper [M]<sub>2</sub> (M = Pd(allyl)Cl, Rh(COD)Cl) yields complexes **5a** or **5b** in 73 and 65%, respectively. Analytically pure products are obtained after recrystallization from THF-MeCN/hexanes.

1,2,3-triazol-5-ylidenes (MICs) have been shown to be significantly better electron donors than imidazole-2-ylidene NHCs; therefore, it was assumed that the MIC(H<sup>+</sup>) fragment will be less acidic and therefore harder to deprotonate than the NHC(H<sup>+</sup>) counterpart. Thus, with the aim of synthesizing NHC-anchored/pendent triazolium species, we attempted the partial metallation of salt **2** using NaH in presence of ½ of [Rh(COD)Cl]<sub>2</sub>. <sup>1</sup>H NMR analysis of the crude mixture showed the generation of complex **3** as a major product in mixture with unreacted material and traces of a new complex which showed the metallation with the Rh(COD) moiety. After several trials, we discovered that the reaction of **2** with 0.9 equivalents of KHMDS and ½ of [Rh(COD)Cl]<sub>2</sub> at -78°C results in the generation of the partially metallated complex **4a** in 53% yield together

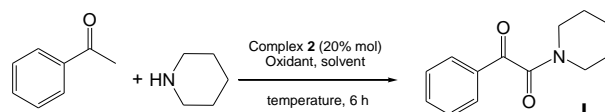
with a small amount of complex **3** (12%). Pure **4a** is isolated after chromatographic column separation and was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, FT-IR and elemental analyses. The same strategy can be applied to the insertion of the Pd(allyl) fragment rendering complex **4b** in 49% yield. The partial metallation results demonstrate the faster deprotonation of the NHC(H<sup>+</sup>) moiety and preference of the NHC ligand for coordination to heavier transition metals rather than copper which is present in the starting dicationic salt.

To complete the metallation trials, the MIC(H<sup>+</sup>) fragment from complexes of the type **4** was deprotonated with a slight excess of KHMDS in presence of 0.5 equivalents of [M]<sub>2</sub> in THF. The reaction proceeds cleanly delivering the respective complexes of the type **5** in high yields (75-81%).

### Catalytic trials

The activation and utilization of molecular oxygen as an oxygen source and oxidant agent in synthetic organic chemistry, has attracted great interest in academia and industrial scenarios owing to its low cost, and environmentally benign features. The recently developed aerobic oxidative reactions employing molecular oxygen, offer particularly appealing approaches to α-ketoamides. Although a Cu(I) catalyzed synthesis of α-ketoamides in neat conditions was reported previously, it cannot be applied to solid substrates such as tetrahydro-β-carbolines. Moreover, despite the predominant utility of Cu(I) halides in organic reactions, their poor solubility in water and most organic solvents can cause issues with catalyst activity, reliability and reproducibility. In this regard, a stable and isolable Cu(I) complex [(tetrabutylammonium) di-μ-iodo-diiododicuprate(I)] with enhanced solubility in water and proficient in the production of several α-ketoamides was identified recently. Motivated by these results, we decided to test the potential of salt **2** in the catalytic preparation of α-ketoamides using molecular oxygen as the oxidant source.

As a model reaction, we chose the use of acetophenone and piperidine as starting materials, complex **2** as catalyst, water/ethanol as solvents (1:1 ratio) and several oxidant agents. The results of various reaction conditions are depicted in table 1.

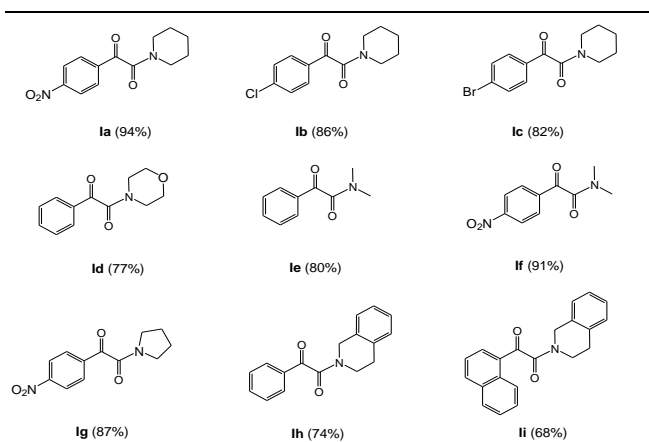


**Table 1.** The results of various reaction conditions.

Entry	oxidant	solvent	temp (°C)	yield (%)
1	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	H <sub>2</sub> O/EtOH	40	>5
2	H <sub>2</sub> O <sub>2</sub>	H <sub>2</sub> O/EtOH	40	14
3	NBS	H <sub>2</sub> O/EtOH	40	>7
4	TBHP	H <sub>2</sub> O/EtOH	40	23
5	O <sub>2</sub>	H <sub>2</sub> O/EtOH	40	58
6	O <sub>2</sub>	H <sub>2</sub> O/MeCN	40	33
7	O <sub>2</sub>	H <sub>2</sub> O/EtOH	60	83
8	O <sub>2</sub>	H <sub>2</sub> O/MeCN	60	41
9	O <sub>2</sub>	EtOH	60	33

Reaction conditions: Acetophenone (1 mmol), piperidine (2 mmol), catalyst (20% mol), oxidant (5 mmol), solvent (3 mL). The yields are the average of two runs.

As observed in table 1, the best conversion to product is reached using molecular oxygen as oxidant, a mixture of water/ethanol as solvent, and 60°C for 6h. The scope of the reaction can be extended to several secondary amines and substituted acetophenones according to Scheme 5.


**Scheme 5.** Scope of the direct oxidative synthesis of  $\alpha$ -ketoamides from aryl ketones and secondary amines.

## Conclusion

In conclusion, a novel linked imidazolium/triazolium salt [NHC-MIC]<sup>2+</sup> has been prepared in three synthetic steps using copper catalyzed alkyne azide cycloaddition (CuAAC) and *N*-methylation protocols. Reaction of precursor **1** with Cu<sub>2</sub>O yields a novel tetraiodo cuprate mixed salt which **2** is successfully deprotonated to generate the dicopper complex **3** in good yields. Metallation of the imidazolium moiety using KHMDS in presence of a metallic precursor (M = Pd, Rh) yields NHC-anchored/pendent triazolium species [NHC·(M)-MIC]<sup>+</sup> in good yields. Further deprotonation of the triazolium fragment with KHMDS in presence of one equivalent of [M]<sub>2</sub> delivers the rare chelating mixed

classical NHC/mesionic biscarbene complexes with the general formula [NHC·(M)-MIC]<sup>+</sup>MX<sub>2</sub>. Crystal structure of complex **5b** unveils a rare coordination fashion for a biscarbene ligand where the second metal center is outside the primary coordination sphere. Preliminary catalytic trials of the salt **2** on the oxidative synthesis of  $\alpha$ -ketoamides from aryl ketones and secondary amines was carried out demonstrating the good performance on this process using oxygen as oxidant agent and environmentally friendly solvents such as water and ethanol.

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