

# Simple and versatile synthesis of copper and silver *N*-heterocyclic carbene complexes in water or organic solvents†

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A novel synthetic route leading to *N*-heterocyclic carbene copper complexes has been developed by using air-stable and commercially available copper(I) oxide and imidazolium salts starting materials.

Most often the development of catalytic processes strongly depends on the accessibility and cost of the pre-catalyst. The synthesis of catalysts based on inexpensive metals such as iron<sup>1</sup> and copper<sup>2</sup> has been the topic of recent reports. For the latter case, several studies have demonstrated the effective role of *N*-heterocyclic carbene (NHC) copper species of the type  $[\text{CuX}(\text{NHC})]$  ( $\text{X}$  = halide) in catalytic transformations. These include reduction of carbonyl compounds,<sup>3</sup> reductive aldol condensation,<sup>4</sup> carbene transfer reactions,<sup>5</sup> amination reactions,<sup>6</sup> trifluoromethylation reaction in a cross-coupling type process,<sup>7</sup> hydrosilylation<sup>8,9</sup> and Huisgen [3+2] cycloaddition.<sup>10</sup> These complexes have also exhibited interesting biological activity as anti-tumour agents.<sup>11</sup> The most common synthetic pathways leading to  $[\text{CuX}(\text{NHC})]$  complexes involve the reaction of  $\text{CuX}$  with the pre-formed or *in situ*-formed NHC.<sup>12</sup> Drawbacks of such methodologies are the use of a strong base under strictly inert conditions and the generation of inorganic waste by-products.<sup>9,13</sup> Danopoulos<sup>14</sup> and more recently Douthwaite<sup>15</sup> have synthesised neutral chelating NHC copper complexes by reaction of copper oxide and imidazolium salts (Fig. 1). In such reactions, the only side-product is  $\text{H}_2\text{O}$ .

To the best of our knowledge, this methodology is limited to the complexes shown in Fig. 1, and no investigation on the possible versatility of such a straightforward route has been disclosed. Herein, we report the development of such an elegant synthetic strategy for the high yield generation of linear neutral  $[\text{CuCl}(\text{NHC})]$  complexes.† Six ligands were selected for this study (Fig. 2) bearing saturated or unsaturated  $\text{C}^4\text{-C}^5$  backbone, and aryl or alkyl substituents on the nitrogen atoms. This selection was made in order to test the scope and limitations of the approach.

Initial efforts were focused on the reaction of the imidazolium and imidazolinium chlorides with  $\text{Cu}_2\text{O}$  in dichloromethane, a solvent commonly used for the synthesis of silver analogues (Scheme 1).<sup>16</sup> This strategy proved successful at room temperature with IMes and SIPr as clearly indicated by the  $^1\text{H}$  NMR spectra

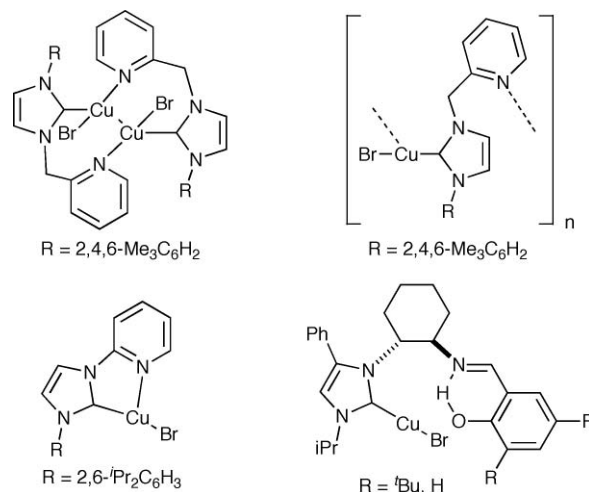


Fig. 1 Complexes obtained from  $\text{Cu}_2\text{O}$ .

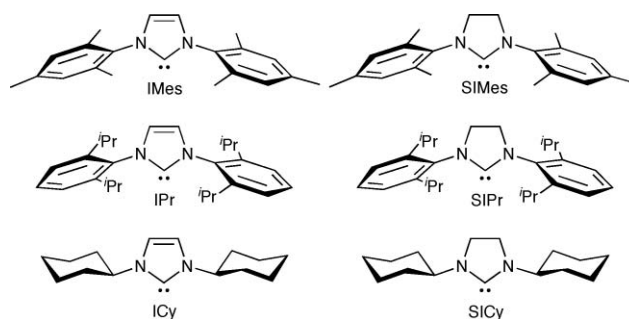


Fig. 2 *N*-Heterocyclic Carbenes (NHC) used in this study.

	NHC	Temp.	Conv.*
	IMes	rt	100
	SIMes	40	14
	IPr	40	<5
	SIPr	rt	93
	ICy	40	47
	SICy	40	-

\*Conversion determined by  $^1\text{H}$  NMR

Scheme 1 Synthesis of  $[\text{CuCl}(\text{NHC})]$  complexes in  $\text{CH}_2\text{Cl}_2$ .

that show the loss of the imidazolium proton  $\text{NCHN}$ . In contrast, all other NHCs studied led to poor conversions despite harsher reaction conditions (reflux  $\text{CH}_2\text{Cl}_2$ ).

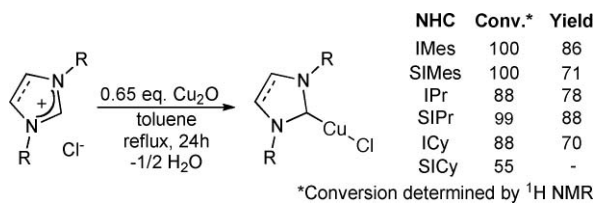
This disparity in reactivity cannot be rationalised by steric or electronic reasons. For instance, despite the fact that SIPr is bulkier than IPr,<sup>17</sup>  $[\text{CuCl}(\text{SIPr})]$  is formed relatively easily at room temperature whilst  $[\text{CuCl}(\text{IPr})]$  is formed in less than 5% in refluxing dichloromethane. No general trend could be found and

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† Electronic supplementary information (ESI) available: Synthesis and purification of all complexes and their  $^1\text{H}$  NMR spectra.  $^1\text{H}$  and  $^{13}\text{C}$ - $\{^1\text{H}\}$  NMR spectra of A. CCDC reference number 761660. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0dt00128g

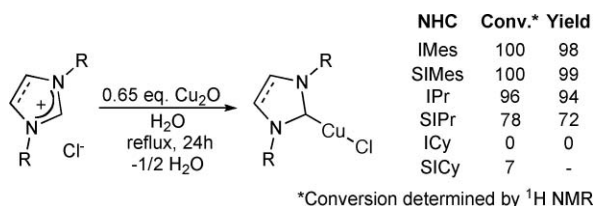
systematic studies were hence conducted in order to optimise the reaction conditions to produce [CuCl(NHC)] complexes.

To avoid the use of chlorinated solvents, that are toxic and not desirable for industrial applications, toluene was employed to allow higher reaction temperatures. This proved an efficient methodology as all NHCs described here led to the corresponding complex in good to quantitative conversions and moderate to excellent isolated yields (Scheme 2).



**Scheme 2** Synthesis of [CuCl(NHC)] complexes in toluene.

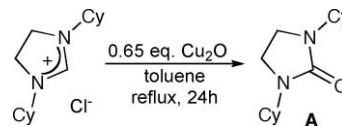
The viability of such a reaction has been demonstrated on 25 g scale for one of these complexes, [CuCl(IPr)]. We then reasoned that if higher operating temperatures were the only factor of importance in this reaction, then the possibility of employing water as a reaction medium should be considered. Imidazolium salts are soluble in water, whilst copper(I) oxide is insoluble in virtually all solvents. Therefore, using water as solvent might lead to increased reaction yields as the imidazolium salts would be completely solubilised. In addition, the [CuCl(NHC)] complexes should precipitate from water, which could be a driving force for the reaction and facilitate product isolation. On the other hand, the use of water as solvent in a reaction releasing a molecule of water seems counter-intuitive as removal of the water formed during the reaction is also a way to drive it to completion. As can be seen in Scheme 3, the use of water as a solvent for this reaction proved viable for NHCs bearing aryl groups. For alkyl  $N,N'$ -substituted salts, the formation of the Cu-complex seemed somehow impeded (Scheme 3).



**Scheme 3** Synthesis of [CuCl(NHC)] complexes in water.

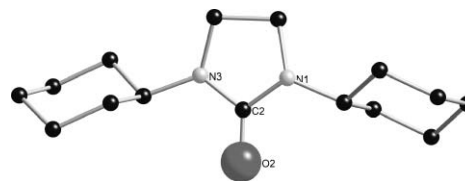
Surprisingly, in the case of SICy, when the reaction is carried out in toluene, the disappearance of a substantial amount of the starting material SICy·HCl was observed with the concomitant clean formation of a new compound, **A**. Whilst the  $^1\text{H}$  NMR data obtained for **A** could easily be mistaken for the data expected for Cu-complex bearing SICy, the  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum leaves no doubt that [CuCl(SICy)] has not been formed. This assertion is based on the absence of the characteristic signal for the carbene carbon atom that is expected to be shifted to low field (typically *ca.* 200 ppm).<sup>18</sup> On the other hand, a quaternary carbon atom with a chemical shift of 160 ppm was observed. This chemical shift is consistent with the presence of a C=O group, which was further confirmed by IR spectroscopy (signal observed at

1670  $\text{cm}^{-1}$ ). Therefore, the reaction of SICy·HCl with  $\text{Cu}_2\text{O}$  would form the corresponding ketone, 1,3-dicyclohexylimidazolidin-2-one, **A**, instead of the expected Cu-NHC complex (Scheme 4).



**Scheme 4** Synthesis of 1,3-dicyclohexylimidazolidin-2-one, **A**.

In order to confirm this hypothesis, single crystals suitable for X-ray diffraction were grown by slow evaporation of a saturated  $\text{CH}_2\text{Cl}_2$  solution of **A**. The X-ray analysis permitted to unambiguously confirm the identity of **A** (Fig. 3).



**Fig. 3** X-ray crystal structure of the imidazolidin-2-one (**A**).

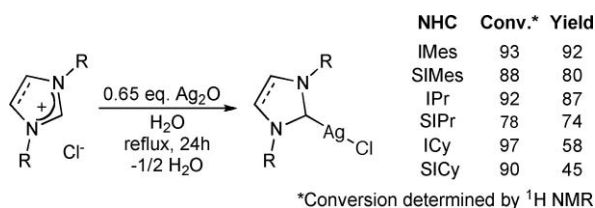
The structure clearly shows the product to be 1,3-dicyclohexylimidazolidin-2-one with a C=O bond distance of 1.244(4) Å in agreement with a classical carbonyl bond. This heterocycle, initially described in 1950<sup>19</sup> has never been examined by X-ray diffraction. Imidazolidinones were originally synthesised by heating a slight excess of urea with a 1,2-diamine.<sup>20</sup> These molecules have attracted attention in the development of polymers used as synthetic fibres as shown by DuPont. These cyclic ureas are also of interest as respiratory stimulants.<sup>21</sup>

At this point, the mechanism of formation of the imidazolidinone remains obscure. It might involve the transfer of oxygen from copper oxide after deprotonation of SICy·HCl. Studies are currently underway in our laboratory to establish the mechanistic pathway by which this reaction occurs.

Cu-NHC systems are not the only NHC complexes of interest in Group 10, indeed, the silver analogues have also attracted increasing interest for different applications. For instance, Ag-NHC complexes are nowadays commonly used as NHC transfer agents in transition metal chemistry<sup>22</sup> and have displayed interesting antimicrobial<sup>23</sup> activity. Facile synthetic routes leading to high yields of these complexes continues to be highly desirable. Reaction conditions reporting the synthesis of Ag-NHC complexes from  $\text{Ag}_2\text{O}$  oftentimes make use of chlorinated solvents under anhydrous conditions.<sup>24</sup> To the best of our knowledge, there are only a few examples of such reactions performed in water.<sup>25</sup> With the copper results in hand, we reasoned that silver complexes would be worthy of investigation under these simple aqueous synthetic conditions. These studies proved the methodology quite successful when the reactions are carried out at reflux (Scheme 5).

It must be mentioned that the complexation of SICy on silver is, as for copper, problematic since a mixture of products was obtained under both reaction conditions (RT and reflux).

In summary, we have developed a versatile, efficient, and inexpensive synthetic route to [CuCl(NHC)] complexes. Noteworthy, the synthesis can be performed in non-chlorinated solvents



**Scheme 5** Synthesis of [AgCl(NHC)] complexes in H<sub>2</sub>O.

as well as *in water*! The aqueous synthetic methodology has been extended to the silver congeners. As the most frequently encountered members of the NHC ligand family can now be easily appended to copper, ongoing studies in our laboratory are aimed at investigating these compounds as catalysts and bioactive entities. Finally, work is being carried out on the potential exploitation of copper for the synthesis of imidazolidin-2-ones. Results of these studies will be reported in due course.

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## Notes and references

† General protocol for the synthesis of the complexes: A glass vial equipped with a magnetic stirring bar was charged with Cu<sub>2</sub>O (1.52 mmol, 95% purity) and the NHC-HCl (2.34 mmol). The vial was purged with Argon prior to addition of degassed solvent and the reaction mixture was stirred at the required temperature for 24 h. The conversion was determined by NMR and the complexes were purified and isolated as colourless solids. Synthesis of 1,3-dicyclohexylimidazolidin-2-one, **A**: In a glass vial, copper oxide (0.217 g, 1.52 mmol) and 1,3-dicyclohexylimidazolium chloride (0.634 g, 2.34 mmol) were dissolved in Argon purged toluene (4.8 mL). The reaction mixture was heated at reflux for 24 h. The crude solid obtained after removal of the solvent, was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, filtered and dried under vacuum. 1,3-Dicyclohexylimidazolidin-2-one was obtained as a colourless solid in 45% yield (0.263 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ (ppm) 3.64 (m, 2H, CH), 3.18 (s, 4H, NCH<sub>2</sub>), 1.73–0.84 (m, 20H, CH<sub>2</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz) δ (ppm) 160.13 (C=O), 51.35 (CH), 38.48 (NCH<sub>2</sub>), 30.15 (CH<sub>2</sub>), 25.89 (CH<sub>2</sub>). IR (NaCl) ν<sub>C=O</sub> 1670 cm<sup>-1</sup>. HRMS (ESI) [M+H]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>O: 251.2118, found: 251.2120.

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