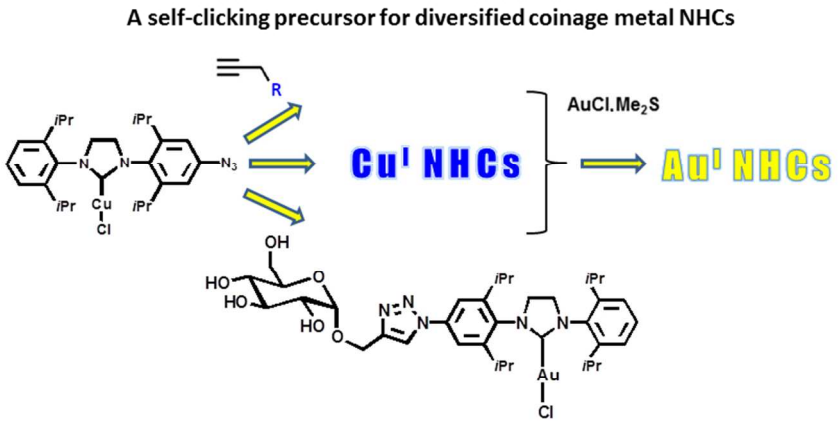
Dalton Transactions

'Auto–Click' Functionalization for Diversified Copper(I) and Gold(I) NHCs.

Journal:	*Dalton Transactions*
Manuscript ID:	DT-COM-02-2014-000429
Article Type:	Communication
Date Submitted by the Author:	10-Feb-2014
Complete List of Authors:	GAUTIER, Arnaud; CNRS, Blaise Pascal University, Chemistry Cisnetti, Federico; Université Blaise Pascal, Chemistry Gibard, Clémentine; Université Blaise Pascal, Chemistry IBRAHIM, Houssein; université Blaise Pascal, chemistry Laurent, Morel; Universite Blaise Pascal, biology HESLING, Cédric; Clermont University, GReD Guillot, Regis; ICMMO UMR8182 CNRS,



254x190mm (96 x 96 DPI)

Journal Name

RSCPublishing

ARTICLE

'Auto–Click' Functionalization for Diversified Copper(I) and Gold(I) NHCs.

Cite this: DOI: 10.1039/x0xx00000x

Houssein Ibrahim,[a] Clémentine Gibard,[a] Cédric Hesling,[b] Régis Guillot,[c] Laurent Morel,[b,d,e] Arnaud Gautier*,[a,f] and Federico Cisnetti*[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Azide–tagged Cu^{I}–NHC react in an 'auto–click' process to furnish complexes functionalized by 1,2,3-triazoles bearing diverse subsitutents. The resulting Cu^{I} complexes are amenable to further transmetallation to Au^{I}. The whole strategy proceeds with mild conditions compatible and constitutes an efficient entry to functionalised metal-NHCs with biorelevant moieties.

.

Introduction.

Metal–NHCs (M–NHCs) have attracted considerable interest over the last decades as a leading family of contemporary organometallic chemistry for catalytic purposes and more recently as metal–based drugs.[1,2] Therefore, it is highly desirable to develop concise synthetic routes permitting both straightforward variations of the metal and ligand (for reactivity, stability or solubility purposes). For the modulation of the organic core, two strategies are routinely used to access to new metal NHC complexes: *i*) pre–functionalization[3] consisting in *i-1*) the elaboration of the functionalized azolium precursor, then *i-2*) the introduction of the metal and *ii*) post–functionalization,[4] consisting in *ii-1*) the introduction of the metal, then *ii-2)* the chemical modification of the carbene ligand. We have recently reported that NHCs can react as catalyst for their own functionalization in a CuAAC model reaction giving a so–called 'auto–click' behaviour.[4e] This auto-functionalization has been rarely reported with preformed metal complexes and most of the examples consist in 'metal-chelating' azides (metal=Pd^{II}, Cu^{I}).[5] Thus, this remains restricted to organometallics of limited stability. Combining this auto-functionalization with a subsequent transmetallation[6] would be highly valuable to rapidly give rise on demand to new stable metal–NHCs of high structural diversity (Fig. 1).

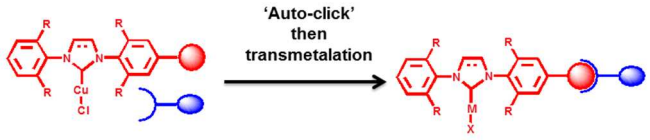


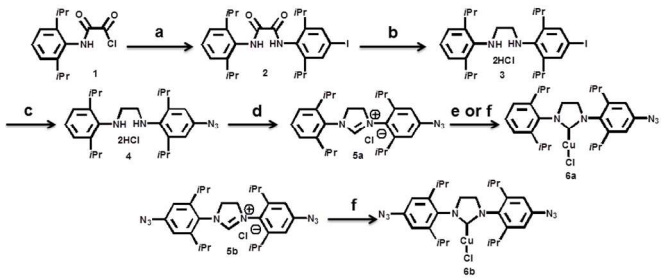
Fig. 1. Synthetic strategy.

There are scarce examples of biomolecule-tagged metal–NHCs[4a,b] whereas such complexes currently enjoy a great interest as anti–cancer drug candidates. For example, by targeting the mitochondrial proteins TxR, an important enzyme regulating the redox system, Au^{I} and Au^{III}–NHCs offer important opportunities to circumvolve the cisplatin resistances.[7] Herein we report a straightforward synthetic route for architecturally sophisticated Cu^{I} and Au^{I}–NHCs bearing bio–relevant pendants. The reaction products could bear a coumarin or a glucose moiety (without the need of any protection–deprotection sequence). A special attention was paid to the SIPr ligand as it has been shown that its complexes display good biological activities.[8]

Results and discussion.

In this article, we decided to investigate the 'auto-click products' of the symmetric bis-azido Cu complex **6b**[4e] along with its mono-azido analogue **6a** (Scheme 1). The symmetric

imidazolinium salt **5b** was obtained by a known protocol[4e] while the new dissymmetric mono-N_3 imidazolinium salt **5a** was obtained in a 4-step sequence (Scheme 1) without any chromatographic purification.



Scheme 1. Synthesis of copper precursor **6a** and **6b**. Reagents and conditions: a) 4-iodo-2,6-diisopropylaniline, K_2CO_3, DCM, 92%. b) $BF_3.Et_2O$, $NaBH_4$, THF; then EtOH, HCl, 69%. c) NaN_3, CuI (10 mol–%), $MeNH(CH_2)_2NHMe$ (15 mol–%), sodium ascorbate (20 mol–%), DMSO : H_2O (v/v) 9 :1, 70°C, 83% ; then EtOH, HCl, 69%. d) $HC(OEt)_3$, EtOH, reflux, 88%. e) Ag_2O, DCM; then CuCl, 64%. f) CuCl, NH_3 (aq.), **6a**: 77%, **6b**: 89%.

The known oxalamide derivative **2**[9a] was obtained in good yield from the condensation[9b] of compound **1** and 4-iodo-2,6-diisopropylaniline.[9c] **2** was converted into the 1,2–diamine bis hydrochloride **(3)** after reduction by *in situ* generated diborane and treatment with HCl.[10] Copper catalysed iodine substitution[11] efficiently furnished the azido diamine hydrochloride **4** which, after a classical orthoformate cyclization, afforded the imidazolinium chloride **5a**. The imidazolinium salts **5a** and **5b** were converted into the targeted Cu^I–NHCs in average to good yields either by the standard silver route (**6a**: 64%) or by a newly reported direct metallation protocol using aqueous ammonia (**6a**: 77%, **6b**: 89%).[12]

With **6a** in hands, the conditions required for the 'auto-click' reaction were evaluated by ^1H NMR (Table 1). Previous studies using symmetric bis-azido Cu^I–NHC **6b** were made difficult by the overlap of ^1H NMR signals precluding a clear view of the process.[4e]

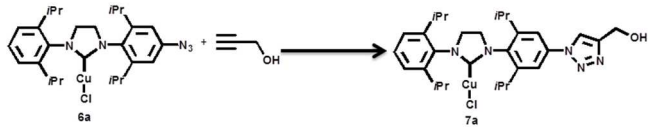


Table 1. Conversion determined by ^1H NMR. [(a)]

Solvent	Temp.	Time (h)	Conversion (%)
$CHCl_3$	50	19	0
MeOH	50	19	0
DMSO (1% H_2O)	50	19	74
DMSO (1% H_2O)	70	19	decomposition
Acetonitrile	35	19	100
Acetonitrile	70	2	100

(a): [**6**]: 0.03M; Propargyl alcohol: 2.0 eq.

A total lack of reactivity in chloroform and methanol was observed whereas conversions occurred in DMSO and acetonitrile. Interestingly, acetonitrile proved to be the solvent of choice as the reaction could take place from fairly low (35°C) to higher (70°C) temperatures without noticeable decomposition or formation of the 1,5 isomer (careful examination of the ^1H and ^{13}C spectra). Indeed, we have previously shown that thermal Huisgen reaction (leading to the 1,5 isomer) between non-activated alkynes and azolium bearing azides did not occur even at higher temperature. In the case of gold(I)-NHC and dimethyl acetylene dicarboxylate (as an activated alkyne), the thermal [2+3] cycloaddition yields only 65% at 60°C after 10 days.[3f] In comparison to acetonitrile, wet DMSO was less efficient at low temperature and induces decomposition at higher. The kinetic profile of this 'auto–click' reaction was examined by ^1H NMR at 70°C by monitoring the disappearance of the azide **6** (aromatic protons at 7.0 ppm) and the appearance of the 1,2,3–triazole of **7a** (H-triazole at 8.4 ppm and aromatic protons at 7.8 ppm**)**, Fig. 2 and ESI. The kinetic profile clearly shows that the reaction occurs after an induction period, indicating that **6a** is not the active catalytic species. The fact that the reaction occurs in coordinating conditions, *i.e.* wet DMSO and acetonitrile (at lower temperature for the latter) suggests that solvolysis of the copper–chloride bond could lead to the formation of a cationic Cu^I–NHC that acts as the real catalytic species.

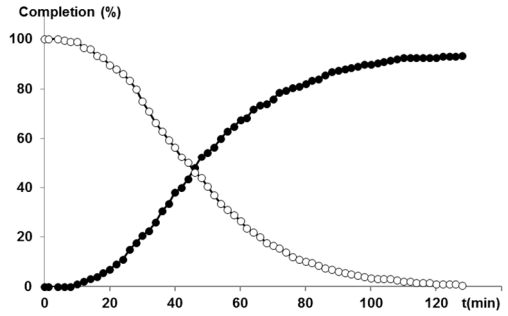
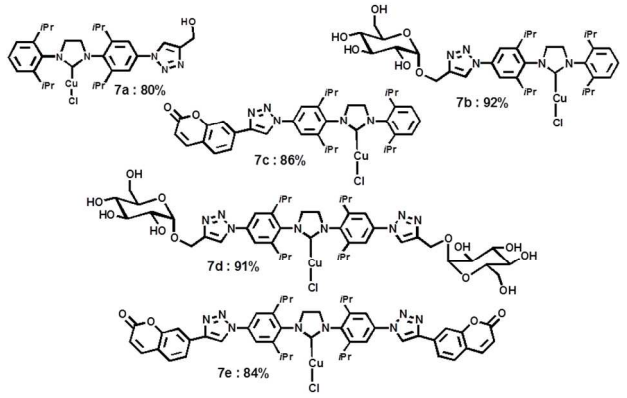


Fig. 2. Kinetic profile at 70 °C in CD_3CN for auto–click reaction of the **6a** to **7a**.

Other Cu^I–NHCs could be synthesized efficiently from **6a,b** using the same protocol (Scheme 2). Indeed, the method is not limited to the functionalization by simple alcohol pendants but also applies to biologically relevant substituents as shown by complexes **7b-e** possessing glucose or a fluorescent coumarin appendages. It is important to note that **7b** and **7d** are synthetized from an unprotected sugar precursor.[13]



Scheme 2. Isolated yields of 'auto–clicked' copper-NHCs.

Structural proof of the coumarin derivative **7c** was provided by X–Ray diffraction.†† Distances and angles fall into the classical ranges of what was reported for the CuCl(SIPr) complex (Fig.3).[14] The dihedral angles between the triazole and both 2,6–diisopropyl aniline and coumarin are low (11° and 8°, respectively) which allows an extended conjugation.

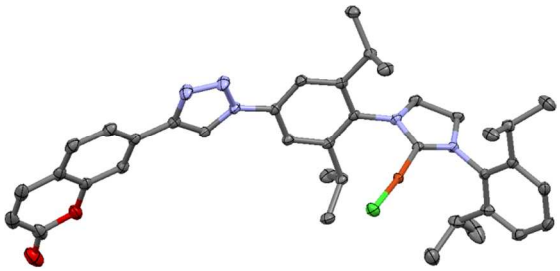


Fig. 3. Ellipsoid plot (50% probability) of Cu^{I} complex **7c**. d(C–Cu)= 1.887 Å. d(Cu–Cl)=2.103 Å. (C–Cu–Cl)= 174.5° (hydrogens and solvents not shown for clarity).††

Then, we tested the Cu^{I} complex **7a** as carbene transfer agent for synthetizing the corresponding gold(I) complex **8a** using gold(I) chloride-dimethyl sulfide complex as reported by Furst and Cazin (Fig. 4).[6] The conversion was estimated by integrating the signals corresponding to the cyclic methylene protons (N–CH_2–CH_2–N) for **7a** *vs* **8a** and **9a**. The screened conditions are gathered in Table 2.

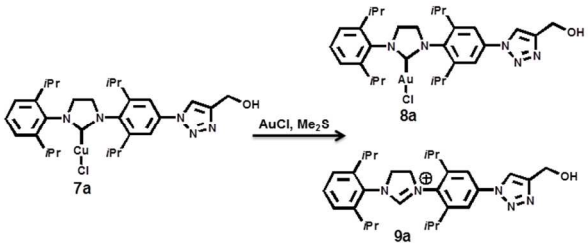


Fig. 4. Transfer process leading to gold(I) complex and imidazolinium as a side-product.

In our hands, the carbene transfer in dichloromethane proved to be difficult as a large amount of imidazolinium **9a** was formed. Switching to acetonitrile as a coordinating solvent gave higher amounts of the expected Au^{I}–NHC **8a** at room temperature; however completion was not reached even after an extended period of 3 days. Increasing the temperature to 50°C was deleterious as shown by the increased proportion of imidazolinium **9a**. When the reaction was performed in DMSO, a larger amount of **9a** was formed. However, we finally found that a mixture of DMSO and MeCN (1/1) allowed a clean and complete conversion to **8a** (without any detectable formation of **9a)**.

Table 2. NMR conversion.

Solvent	Temp. (°C)	Time (h)	Product ratio (%) **7a/8a/ 9a** [(a)]
CH_2Cl_2	50	16	0/ 43/ 57
MeCN	25	72	29/ 62/ 9
MeCN	50	16	20/ 53/ 27
DMSO	30	16	52/ 48/ 0
DMSO/ MeCN (1/1)	30	16	0/ 100(63)[(b)]/ 0

(a): NMR conversion. (b) Yield of isolated pure **8a**.

As earlier work reported that the transfer reaction occured well with all classical NHCs ligands (SIMes, IMes, IPr) but SIPr, these optimized conditions are likely to extend the scope of copper-to-gold transmetalations.[6] Thus, the success for the transfer reaction seems to be ligand- and solvent- dependent. Following this protocol, we were also able to obtain Au^{I} complexes **8b**†, **8c** and **8d** in average to good yield (Fig. 5). It is noteworthy that **8b** and **8d** are obtained in a one pot–two step procedure from their Cu^{I} carbene precursors **7b,d** bearing unprotected glucose moiety. However we were unable to obtain a total and clean transmetallation from the Cu^{I}–NHC **7e**, probably because of its high insolubility.

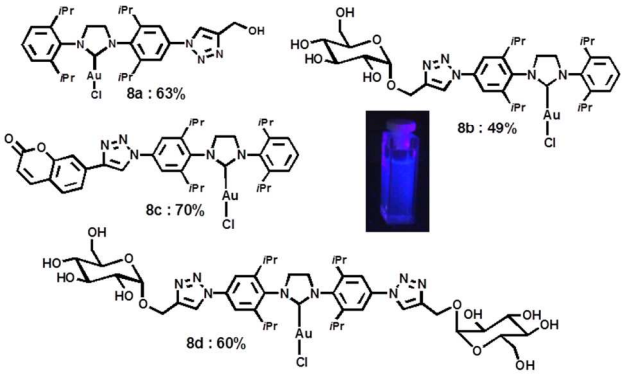


Fig. 5: isolated yields of gold–NHCs and fluorescence of **8c** under UV excitation.

Compound **8c** (and **7c**) are fluorescent due to their coumarin substituent as shown in Fig. 6 (10^{-5} M in HEPES buffer/ 1% DMSO) under UV irradiation. Therefore, the fluorescence data of copper and gold complexes **7d** and **8c** were determined (Fig. 6 and Table 3).

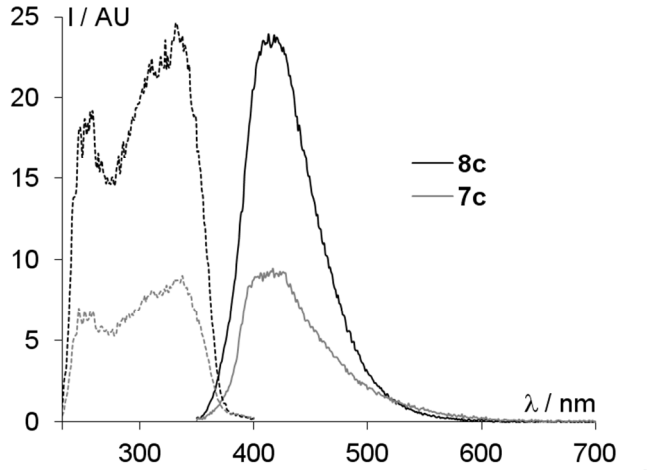


Fig. 6. Excitation and emission spectra of compounds **7c** and **8c**, 10^{-5} mol L^{-1} HEPES buffer/1% DMSO.

Table 3. Fluorescence data.

	excitation λ_{max} (nm)	emission λ_{max} (nm)	$\Phi(\%)^{(a)}$
7c	333	418	8
8c	336	418	18

(a) Fluorescence quantum yield (quinine sulfate as standard).[15]

In view of the fluorescent properties of the gold(I)–NHC **8c** that fall into classical DAPI filters wavelengths, we investigated its uptake and intracellular distribution in human prostate cancer (PC3) cell line. After incubating PC3 cells with **8c** for 18h (10µM), a significant blue fluorescence was detected in the cytoplasm but not in the nucleus. It could be specifically localized in mitochondria as could be shown by the merge of almost all luminescent spots due to **8c** fluorescence with those caused by red-MitoTracker dye (Fig. 7).[16]

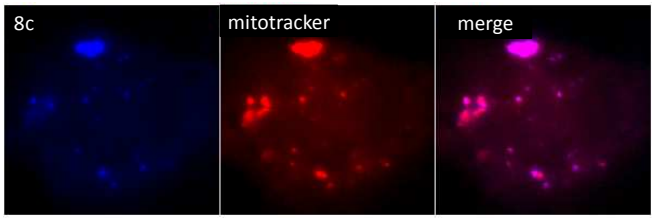


Fig. 7: Co-localization of **8c** and MitoTracker. Left: PC3 cell visualized with DAPI filters ($\lambda_{ex.}$ 365nm; λ_{em}:397nm). Centre: PC3 cell visualized with DsRED filter (λ_{ex}:565nm; λ_{em}:620nm). Right: merged images.

Conclusion.

We have reported that the combination of the 'auto–click' reaction with a transmetallation process constitutes an efficient tool for the construction of functionalized gold–NHCs of high diversity, for example bearing a fluorescent biomarker or an unprotected sugar. Thus, this synthetic route avoids the need of tedious protection–deprotection sequence. Other applications are currently under investigation in our laboratory.

Experimental.

General remarks.

NMR spectra were recorded in Fourier transform mode with a Bruker AVANCE 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz) at 298 K. Data are reported as chemical shifts (δ) in ppm. Residual solvent signals were used as internal references (^{1}H, ^{13}C). Electrospray (positive mode) high resolution mass spectra were recorded on a Q-TOF micro spectrometer (Waters), using internal (H_3PO_4) and external lock masses (leucine-enkephalin [M + H]+: m/z = 556.2766). Metal complexes were dissolved in acetonitrile prior to the measurement. IR spectra were recorded on a Shimadzu Fourier Transform Infrared Spectrophotometer FTIR-8400S. Elemental analyses were performed at the Service de Microanalyse, Université Henry Poincaré, Vandoeuvre-les-Nancy, France.

Synthesis.

(2,6-diisopropylphenylcarbamoyl)formyl chloride (**1**): 2,6-Diisopropylphenylamine (20mL, 0.107 mol) was added to 500 mL of dry toluene. A solution of oxalyl chloride (25 mL, 0.29 mol) in 150 mL of dry toluene was added dropwise while stirring vigorously at 0°C (ice-water bath) during 15 min. The mixture was further stirred for 1 hour and was filtered to remove the white solid that forms. The filtrate evaporated under reduced pressure, giving a yellow solid which was triturated with a minimum amount of *n*-pentane to give a white solid; 10.44 g were obtained after drying under vacuum (36% Yield). ^{1}H NMR (DMSO–d_6, 400 MHz) δ = 10.22 (s, 1H, NH), 7.29 (t, 1H, J = 7.0 Hz, H_{Ar}), 7.17 (d, 1H, J =7.0Hz, H_{Ar}), 2.98 (sept, 2H, J = 6.4Hz, C*H*$(CH_3)_2$), 1.11(d, 12H, J=6.4Hz, CH(C*H*$_3)_2$). This product was used without any further purification in the next step.

N-(2,6-diisopropylphenyl)-*N'*-(4-iodo-2,6-diisopropylphenyl) oxalamide (**2**): according to a modified literature procedure.[9b] At first, 4-iodo-2,6-diisopropylaniline was azeotroped 3 times with cyclohexane to remove water that may crystallize with this material (when stored for a long period, and that will dramatically reduce the yield). Then, 4-iodo-2,6-diisopropylaniline[9c] (20.00 g, 66.0 mmol, 1.0 eq.) was dissolved in 500 mL anhydrous dichloromethane under argon. Na_2CO_3 (17.5 g, 165 mmol, 2.5 eq.) was added followed by 1 (19.38 g, 72.4 mmol, 1.1 eq.) in one portion (slight heating and gas evolution were apparent). After 2 hours at room temperature the reaction mixture was filtered over a fritted glass. The solid residue was washed with boiling dichoromethane until no more solid dissolved. The combined organic fractions were evaporated under reduced pressure to yield 32.50 g of a white solid (60.80 mmol, 92% yield). Spectroscopic characterizations identical to literature.[17]

N-(2,6-diisopropylphenyl)-*N'*-(4-iodo-2,6-diisopropylphenyl) ethane-1,2-diamine dihydrochloride (**3**): compound **2** (16.00 g, 29.93 mmol, 1.0 eq.) and $NaBH_4$ (6.80 g, 180 mmol, 6.0 eq) were added to 160 mL anhydrous THF. The solution was cooled at 0°C and $BF_3.Et_2O$ (30 mL, 33.60 g, 237 mmol, 7.9

eq.) was added dropwise over 20 minutes. The reaction mixture was stirred at room temperature for 2 hours and then refluxed overnight. The mixture was cooled to 0°C and treated with a 50 mL of a 1:4 *v*/*v* mixture of 36% aq. HCl and methanol under vigorous stirring and then evaporated to dryness, 1 M NaOH (200 mL) was added and extraction with 3×200 mL Et_2O was performed. Drying over Na_2SO_4 and evaporation *in vacuo* afforded a brownish oil. This material was treated under vigorous stirring with an ethanolic HCl solution – freshly prepared by adding with caution at 0°C 6.4 mL (89.8 mmol) of acetyl chloride to 65 mL anhydrous ethanol. After a few minutes a solid separated from the supernatant. Filtration afforded 12.01 g of an off-white powder (20.75 mmol, 69% yield).
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.45 (s, 2H, H_{Ar}), 7.39 (t, 1H, J = 7.0 Hz, H_{Ar}), 7.32 (d, 1H, J = 7.0 Hz, H_{Ar}), 3.47-3.38 (m, 6H, CH_2 + 2C*H*(CH_3)$_2$), 3.32-3.26 (m, 2H, C*H*(CH_3)$_2$), 1.18 (d, 12H, J = 6.4 Hz, CH(C*H*$_3$)$_2$), 1.12 (d, 12H, J = 6.4 Hz, CH(C*H*$_3$)$_2$).
^{13}C NMR (DMSO-d_6, 100 MHz) δ = 145.7 (C_{qAr}), 142.8 (C_{qAr}), 137.7 (C_{qAr}), 133.2 (C_{Ar}-H), 130.7 (C_{qAr}), 129.3 (C_{Ar}-H), 125.6 (C_{Ar}-H), 92.3 (C_{qAr}), 50.8 (CH_2), 47.3 (CH_2), 27.3 (CH), 27.2 (CH), 24.5 (CH_3), 24.1 (CH_3).
HRMS (ESI+): calculated for $C_{26}H_{40}IN_2$ $[M\text{-}H\text{-}2Cl]^+$: 507.2236, found:507.2240.

N-(4-azido-2,6-diisopropylphenyl)-N'-(2,6-diisopropylphenyl) ethane-1,2-diamine dihydrochloride (**4**): compound **3** (11.00 g, 19.00 mmol, 1.0 eq.) was treated with 140 mL sat. aq. $NaHCO_3$, extracted with 3×140 mL Et_2O and the joint organic phases evaporated (Na_2SO_4). To the resulting oil were added H_2O (10 mL) and DMSO (90 mL). Ascorbic acid (670.1 mg, 3.80 mmol, 20 mol-%), sodium hydroxide (152.2 mg, 3.80 mmol, 20 mol-%), sodium azide (2.470 g, 38.00 mmol, 2.0 eq.) and *N*,*N'*-dimethylethane-1,2-diamine (307 µL, 251.5 mg, 2.85 mmol, 15 mol-%) were subsequently added and the resulting solution was degassed by argon bubbling for 20 minutes. CuI (362.3 mg, 1.90 mmol, 10 mol-%) was added and the reaction mixture was stirred at 70°C for 3 hours. After cooling to room temperature, brine (220 mL) was added and extraction was performed with 3×110 mL of diethyl ether. The combined organic phases were washed with saturated aq. NH_4Cl (2×110 mL) and water (2×110 mL). Drying (Na_2SO_4) and solvent evaporation furnished a brownish oil which was treated with ethanolic HCl solution – freshly prepared by adding with caution at 0°C 5.7 mL (76 mmol) of acetyl chloride to 55 mL anhydrous ethanol. After 20 minutes of vigorous stirring a precipitate was formed. Filtration and washing with ice-cold methanol afforded 7.70 g (15.57 mmol, 83% yield) of 4as a white powder.
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.38-7.27 (m, 3H, H_{Ar}), 6.88 (s, 2H, H_{Ar}), 3.47-3.34 (m, 8H, CH_2 + C*H*(CH_3)$_2$), 1.19 (d, 12H, J = 6.4 Hz, CH(C*H*$_3$)$_2$), 1.15 (d, 12H, J = 6.4 Hz, CH(C*H*$_3$)$_2$).
^{13}C NMR (DMSO-d_6, 100 MHz) δ = 145.3 (C_{qAr}), 142.8 (C_{qAr}), 137.7 (C_{qAr}), 131.7 (C_{qAr}), 128.9 (C_{Ar}-H), 125.4 (C_{Ar}-H), 125.3 (C_{qAr}), 115.3 (C_{Ar}-H), 50.3 (CH_2), 48.0 (CH_2), 27.5 (CH), 27.3 (CH), 24.5 (CH_3), 24.1 (CH_3).
IR (ν, cm^{-1}): 2965, 2115 (N_3), 1569, 1463, 772.
HRMS (ESI+): calculated for $C_{26}H_{40}N_5$: $[M\text{-}H\text{-}2Cl]^+$ 422.3284, found 422.3261.

N-(4-azido-2,6-diisopropylphenyl)-*N'*-(2,6-diisopropylphenyl) imidazolinium chloride (**5a**): compound **4** (2.00 g, 4.04 mmol) was suspended in a mixture of 20 mL $HC(OEt)_3$ and 10 mL absolute ethanol. 1 drop of formic acid was added and the reaction mixture was refluxed. After 2 hours a clear solution was obtained. Concentration under reduced pressure affords a white solid which was filtered and washed with methyl *tert*-butyl ether to give 1.67 g (3.57 mmol, 88% yield) of a white powder.
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.60 (s, 1H, $CH_{Imidazolinium}$), 7.56 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.43 (d, 2H, J = 7.7 Hz, H_{Ar}), 7.11 (s, 2H, H_{Ar}), 4.54 (s, 4H, CH_2), 3.12-3.05 (m, 4H, C*H*(CH_3)$_2$), 1.35 (d, 12H, J = 6.6 Hz, CH(C*H*$_3$)$_2$), 1.20 (d, 12H, J = 6.6 Hz, CH(C*H*$_3$)$_2$).
^{13}C NMR (DMSO-d_6, 100 MHz) δ = 160.4 (NCHN), 148.5 (C_{qAr}), 146.1 (C_{qAr}), 142.1 (C_{qAr}), 131.1 (C_{Ar}-H),129.8 (C_{qAr}), 126.7 (C_{qAr}), 124.8 (C_{Ar}-H), 115.5 (C_{Ar}-H), 53.7 (CH_2), 53.6 (CH_2), 28.5 (CH), 28.2 (CH), 25.0 (CH_3), 24.6 (CH_3), 23.3 (CH_3), 23.0 (CH_3).
IR (ν, cm^{-1}): 2965, 2100 (N_3), 1610, 1264, 804,758.
HRMS (ESI+): calculated for $C_{27}H_{38}N_5$ $[M\text{-}Cl]^+$: 432.3127, found: 432.3191

(*N*-(4-azido-2,6-diisopropylphenyl)-*N'*-(2,6-diisopropylphenyl) imidazolin-2-ylidene)-chlorocopper(I) (**6a**):
Using silver oxide method.
1-Synthesis of silver carbene: compound **5a** (1.50 g, 3.20 mmol, 1.0 eq.) was dissolved in 130 mL dichloromethane, silver oxide (482.7 mg, 2.08 mmol, 0.65 eq.) was added and the solution was stirred overnight at room temperature in the dark. The resulting suspension was filtered over celite and evaporated. 1.60 g (2.79 mmol, 88% yield) of a white solid was obtained. This material was used without any further purification in the next step
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.25 (d, 2H, J = 7.7 Hz, H_{Ar}), 6.86 (s, 2H, H_{Ar}), 4.08-4.04 (m, 4H, CH_2), 3.08-2.99 (m, 4H, C*H*(CH_3)$_2$), 1.35-1.33 (m, 24H, CH(C*H*$_3$)$_2$).
^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ = 208.5 (2d, J = 215 Hz, 248 Hz, $C_{carbene}$), 150.7 (C_{qAr}), 148.3 (C_{qAr}), 142.6 (C_{qAr}), 136.4 (C_{qAr}), 133.5 (C_{qAr}), 131.1 (C_{Ar}-H), 125.9 (C_{Ar}-H), 116.6 (C_{Ar}-H), 55.5 (d, J = 8.4 Hz, CH_2), 55.3 (d, J = 8.4 Hz, CH_2), 30.1 (CH), 29.8 (CH), 26.3 (CH_3), 25.9 (CH_3), 24.7 (CH_3), 24.4 (CH_3).
2- Synthesis of copper carbene (**6a**): 1.10 g (1.92 mmol, 1.0 eq.) of the preceding solid and CuCl (569.9 mg, 5.76 mmol, 3.0 eq.) were dissolved in 110 mL dichloromethane. The resulting mixture solution was stirred 3h at room temperature in the dark. The resulting suspension was filtered over celite and evaporated obtain a solid. This material was taken up in CH_2Cl_2 and *n*–

pentane added dropwise while stirring until a white solid formed. This material was recovered by filtration and washed with *n*-pentane: 738.9 mg (1.39 mmol, 73% yield).

Using direct metallation with ammonia: **5a** (468 mg, 1.0 mmol, 1.0 eq.) was suspended in 10 mL of water. Freshly prepared copper(I) chloride (149 mg, 1.50 mmol, 1.5 eq.) was added and the solution was degassed by bubbling argon for 5–10 minutes. Then, under vigorous stirring, aqueous ammonia (14.0 mol L^{-1}, 430 µL, 6.0 mmol, 6, 6.0 eq.) was added with a syringe through the stopper and the solution was stirred for 2 hours. The solution was extracted with 3X10 mL of dichloromethane, dried over K_2CO_3 and evaporated under reduced pressure. The crude product was dissolved in 5mL of dichloromethane and 30mL of pentane was added dropwise under stirring. The resulting white precipitate was filtered, washed with *n*–pentane and dried to give 409 mg, (77 %).

^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ = 7.44 (t, 1H, J = 7.0 Hz, H_{Ar}), 7.34 (d, 2H, J = 7.0 Hz, H_{Ar}), 7.02 (s, 2H, H_{Ar}), 4.23 (broad s, 4H, CH_2), 3.31-3.22 (m, 4H, C*H*$(CH_3)_2$), 1.38-1.33 (m, 24H, CH(C*H*$_3)_2$).

^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ = 204.6 ($C_{carbene}$), 150.7 (C_{qAr}), 148.3 (C_{qAr}), 142.4 (C_{qAr}), 136.3 (C_{qAr}), 133.4 (C_{qAr}), 131.0 (C_{Ar}-H), 125.7 (C_{Ar}-H), 116.5 (C_{Ar}-H), 55.3 (CH_2), 55.1 (CH_2), 30.2 (CH), 29.9 (CH), 26.3 (CH_3), 26.0 (CH_3), 24.5 (CH_3), 24.3 (CH_3).

IR (ν, cm^{-1}) = 2970, 2108 (N_3), 1485, 1458, 1270, 644.

E. A. Calcd for $C_{27}H_{39}N_5Cl$ C: 61.12%, H: 7.03%, N: 13.20%; found C: 61.36%, H: 7.06%, N: 12.89%

(*N,N*'-bis-[4-azido-2,6-diisopropylphenyl]imidazolin-2-ylidene)-chlorocopper(I) (**6b**):

Using direct metallation with ammonia. **5b** (1.50g, 2.95 mmol, 1eq) was dissolved in 30 mL of water and degassed for 20 min. Then, copper(I) chloride (436 mg, 4.43 mmol, 1.5 eq.) was added and the flask was stoppered and degassed by bubbling argon for 5 min. Then, concentrated aqueous ammonia (15.7 mol L^{-1}, 1.13 mL, 17.7 mmol, 6.0 eq.) was added with a syringe through the stopper, and the reaction vessel was degassed for 1 more minute. The mixture was stirred vigorously for 4h at RT. The reaction mixture was transferred to a separating funnel containing 30 mL of dichloromethane. Extraction was performed three times. The combined organic phases were dried over K_2CO_3, and evaporated. The crude was recrystallized in DCM (80 mL) by the dropwise addition of *n*–pentane (200mL) to afford 1.49 g of a pale yellow product (89%).

^{1}H, ^{13}C NMR and IR according to literature precedent.[4e]

(*N*-(2,6-diisopropylphenyl)-*N*'-[4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-2,6-diisopropylphenyl]imidazolin-2-ylidene)-chlorocopper (I) (**7a**): compound **6a** (250 mg, 0.471 mmol, 1 eq.) was dissolved in 5 mL of acetonitrile, and propargyl alcohol (55.6 µL, 0.942 mmol, 2 eq.) was added. The mixture was heated to 50°C for 16 hours during which a solid precipitated. After cooling the reaction mixture to 0°C for 2 hours, the resulting powder was recovered by filtration. The mother liquor was cooled again overnight at 0°C and filtered again to furnish a second crop: 220 mg (0.374 mmol, 80% yield).

^{1}H NMR (CD_3CN, 400 MHz) δ = 8.34 (s, 1H, $CH_{triazole}$), 7.73 (s, 2H, H_{Ar}), δ = 7.46 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.34 (d, 2H, J = 7.7 Hz, H_{Ar}), 4.72 (d, 2H, J = 5.3 Hz, CH_2OH), 4.09 (s, 4H, CH_2), δ = 3.38 (t, 1H, J = 5.3 Hz, OH), 3.29-3.14 (m, 4H, C*H*$(CH_3)_2$), 1.40-1.31 (m, 24H, CH(C*H*$_3)_2$).

^{13}C NMR (CD_3CN, 100 MHz) δ = 203.1 ($C_{carbene}$), 151.0 (C_{qAr}), 150.3 (C_{qAr}), 148.5 (C_{qAr}), 139.4 (C_{qAr}), 136.3 (C_{qAr}), 136.0 (C_{qAr}), 131.1 (C_{Ar}-H), 125.8 (C_{Ar}-H), 122.3 ($CH_{triazole}$), 118.1 (C_{Ar}-H), 56.9 (CH_2), 55.1 (CH_2), 54.9 (CH_2), 30.2 (CH), 29.7 (CH), 26.1 (CH_3), 25.8 (CH_3), 24.4 (CH_3), 24.1 (CH_3).

IR (ν, cm^{-1}): 3477, 2966, 1601, 1486, 1462, 1329, 1277, 1034.

HRMS (ESI+): calculated for $C_{32}H_{44}N_6OCu$ $[M\text{-}Cl+CH_3CN]^+$: 591.2873, found: 591.2875

(*N*-[2,6-diisopropyl-4-(4-(α-D-glucopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl]-*N*'-(2,6-diisopropylphenyl) imidazolin-2-ylidene)-chlorocopper (I) (**7b**): compound **6a** (200 mg, 0.377 mmol, 1.05 eq.) was dissolved in 10 mL acetonitrile, and propargyl α-d-glucopyranoside[13] (2.45 mL from a solution prepared in methanol (0.146 M), 0.359 mmol, 1.0 eq.) was added. The mixture was heated to 50°C for 16h. The solution was filtered over celite and evaporated. The solid was taken up with 5 mL of dichloromethane and 20 mL of *n*-pentane was added dropwise while stirring to give 248 mg of a white powder (0.331 mmol, 92% yield).

^{1}H NMR (CD_3CN, 400 MHz) δ = 8.56 (s, 1H, $CH_{triazole}$), 7.74 (s, 2H, H_{Ar}), δ = 7.44 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.32 (d, 2H, J = 7.7 Hz, H_{Ar}), 4.96 (d, 1H, J = 3.1 Hz, $CH_{anomeric}$), [4.85 (d, 1H, J = 12.1 Hz), 4.70 (d, 1H, J = 12.1 Hz), CH_2OC], 4.07 (s, 4H, CH_2-CH_2), 3.83-3.59 (m, 6H, CH_2OH + 2C*H*OH + 2OH), 3.46-3.30 (m, 3H, 2 C*H*OH + 1OH), 3.26-3.12 (m, 5H, C*H*$(CH_3)_2$ + CH_2OH), 1.38-1.28 (m, 24H, CH(C$H_3)_2$).

^{13}C NMR (CD_3CN, 100 MHz) δ = 203.1 ($C_{carbene}$), 151.0 (C_{qAr}), 148.5 (C_{qAr}), 139.2 (C_{qAr}), 136.4 (C_{qAr}), 136.0 (C_{qAr}), 131.1 (C_{Ar}-H), 125.8 (C_{Ar}-H), 123.9 ($CH_{triazole}$), 118.1 (C_{Ar}-H), 99.6 ($CH_{anomeric}$), 75.2 (CHOH), 73.8 (CHOH), 73.4 (CHOH), 71.8 (CHOH), 62.9 (CH_2OH), 61.8 (CH_2OC), 55.1 (CH_2), 54.9 (CH_2), 30.2 (CH), 29.7 (CH), 26.1 (CH_3), 25.8 (CH_3), 24.4 (CH_3), 24.2 (CH_3); one quaternary carbon not detected.

IR (ν, cm^{-1}): 3396 (br), 2966, 2868, 1631, 1599, 1485, 1456, 1277, 1147, 1037.

HRMS (ESI+): calculated for $C_{36}H_{51}N_5O_6Cu$ $[M\text{-}Cl]^+$: 712.3135, found: 712.3162.

(*N*-[2,6-diisopropyl-4-(4-(2-oxo-2*H*-chromen-6-yl)-1*H*-1,2,3-triazol-1-yl)phenyl]-*N*'-(2,6-diisopropylphenyl)imidazolin-2-ylidene)-chlorocopper (I) (**7c**): compound **6a** (250 mg, 0.471 mmol, 1.0 eq.) was dissolved in 6 mL acetonitrile, and 6-ethynyl-2*H*-chromen-2-one[18] (88.2 mg, 0.518 mmol, 1.1 eq.) was added. The mixture was heated to 50°C for 16 hours during which white solid precipitated. After cooling to room temperature, the solid was filtered and washed with ice–cooled acetonitrile: 285 mg (0.407 mmol, 86% yield).

^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.64 (s, 1H, $CH_{triazole}$), 8.12 (d, 1H, J = 9.6 Hz, H_{Ar}), 7.98 (d, 1H, J = 7.8 Hz, H_{Ar}), 7.95 (s, 1H, H_{Ar}), 7.92 (s, 2H, H_{Ar}), 7.89 (d, 1H, J = 7.8 Hz, H_{Ar}), δ = 7.47 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.36 (d, 2H, J = 7.8 Hz, H_{Ar}), 6.54 (d, 1H, J = 9.6 Hz, H_{Ar}), 4.16 (s, 4H, CH_2), 3.26-3.21 (m, 2H, C*H*(CH_3)$_2$), 3.16-3.09 (m, 2H, C*H*(CH_3)$_2$), 1.44-1.28 (m, 24H, CH(C*H*$_3$)$_2$).
^{13}C NMR (HSQC, DMSO-d_6, 100 MHz) δ = 143.3 (C_{Ar}-H), 129.2 (C_{Ar}-H), 129.0 (C_{Ar}-H), 124.1 (C_{Ar}-H), 121.3 ($CH_{triazole}$), 121.0 (C_{Ar}-H), 115.9 (C_{Ar}-H), 116.0 (C_{Ar}-H), 112.2 (C_{Ar}-H), 53.3 (CH_2), 28.3 (CH), 28.0 (CH), 24.8 (CH_3), 24.3 (CH_3), 23.4 (CH_3), 22.9 (CH_3).
Insufficient solubility of **7c** in common NMR solvents prevented the recording of a standard ^{13}C NMR spectrum.
IR (ν, cm^{-1}): 1722 (C=O), 1620, 1483, 1244, 1113, 1045, 937, 848.
HRMS (ESI+): calculated for $C_{40}H_{46}N_6O_2Cu$ [M-Cl+CH_3CN]$^+$: 705.2978, found: 705.2954.

(*N,N'*-bis[2,6-diisopropyl-4-(4-(α-D-glucopyranosyloxy)methyl)-1H-1,2,3-triazol-1-yl)phenyl]-imidazolin-2-ylidene) chlorocopper(I) **(7d)**: compound **6b** (200 mg, 0.349 mmol, 1.05 eq.) was dissolved in 6 mL acetonitrile, and propargyl α-D-glucopyranoside (183mg, 0.838 mmol, 2.4eq) in 6mL of was added. The mixture was heated to 50°C for 3.5h. The solution was filtered over celite and evaporated. The solid was taken up with 6 mL of dichloromethane and 25 mL of *n*-pentane was added dropwise while stirring to give 320 mg of a white powder (0.317 mmol, 91% yield).
^{1}H NMR (MeOD, 400 MHz) δ = 8.74 (s, 2H, $CH_{triazole}$), 7.82 (s, 2H, H_{Ar}), 4.99 (d, 2H, J = 3.7 Hz, $CH_{anomeric}$), 4.94 (d, 2H, J = 12.6 Hz), 4.78 (d, 2H, J = 12.6 Hz), CH_2OC], 4.23 (s, 4H, CH_2-CH_2), 3.72-3.64 (m, 8H, CH_2OH + 2CHOH), 3.46-3.43 (dd, 2H, 2 CHOH, J=3.7Hz), 3.29 (q, 4H, $CH(CH_3)_2$, J=6.8Hz), 1.45 (d, 24H, $CH(CH3)_2$, J=6.8Hz).
^{13}C NMR (MeOD, 100 MHz) δ = 203.1 ($C_{carbene}$), 151.2 (C_{qAr}), 139.6 (Cq_{Ar}), 136.5 (C_{qAr}), 124.0 ($CH_{triazole}$), 118.1 (C_{Ar}-H), 100.0 ($CH_{anomeric}$), 75.2 (CHOH), 74.2 (CHOH), 73.7 (CHOH), 72.0 (CHOH), 62.9 (CH_2OH), 61.7 (CH_2OC), 55.2 (CH_2), 30.6 (CH), 25.8 (CH_3), 24.1 (CH_3).
IR (ν, cm^{-1}) = 3400(br), 2962, 1633, 1603, 1483, 1329, 1258, 1029.

(*N,N'*-bis[2,6-diisopropyl-4-(4-(2-oxo-2*H*-chromen-6-yl)-1*H*-1,2,3-triazol-1-yl)phenyl)imidazolin-2-ylidene)-chlorocopper (I) **(7e):**
Compound **6b** (200 mg, 0.35 mmol, 1.0 eq.) was dissolved in 2.5 mL acetonitrile and 2.5mL of methanol, and 6-ethynyl-2*H*-chromen-2-one (131 mg, 0.77 mmol, 2.2 eq.) was added. The mixture was heated to 50°C for 24 hours. After cooling to room temperature, the orange solid was filtered and washed with acetonitrile, methanol and small part of DMSO: 205.2 mg (0.23mmol, 64% yield).
^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.64 (s, 2H, $CH_{triazole}$), 8.12 (d, 2H, J = 9.5 Hz, H_{Ar}), 7.98 (d, 2H, J = 7.8 Hz, H_{Ar}), 7.94 (s, 4H, H_{Ar}), 7.89 (d, 2H, J = 7.8 Hz, H_{Ar}), 6.53 (d, 2H, J = 9.5 Hz, H_{Ar}), 4.22 (s, 4H, CH_2), 3.26 (hept, 4H, C*H*(CH_3)$_2$ J = 6.8 Hz), 1.44 (d, 12H, CH(C*H*$_3$)$_2$ J = 6.8 Hz), 1.39 (d, 12H, CH(C*H*$_3$)$_2$ J = 6.8 Hz).
^{13}C NMR (HSQC, DMSO-d_6, 100 MHz) δ = 144.9(C_{Ar}-H), 130.5(C_{Ar}-H), 122.7($CH_{triazole}$), 122.2(C_{Ar}-H), 117.3(C_{Ar}-H), 117.2(C_{Ar}-H), 113.6(C_{Ar}-H), 54.7(CH_2), 29.7(CH), 24.7(CH_3), 25.9(CH_3).
Insufficient solubility of **7e** in common NMR solvents prevented the recording of a standard ^{13}C NMR spectrum.
IR (ν, cm^{-1}) = 2963, 1723, 1603, 1483, 1258, 1105, 1044, 939, 847.
HRMS (ESI+): calculated for $C_{51}H_{51}N_9O_4Cu$ [M-Cl+CH_3CN]$^+$: 916.3360, found: 916.3400.

(*N*-(2,6-diisopropylphenyl)-*N*'-[4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-2,6-diisopropylphenyl]imidazolin-2-ylidene)-chlorogold(I) (**8a**): compound **7a** (60.0 mg, 0.102 mmol, 1.0 eq.) and AuCl.Me_2S (45.0 mg, 0.153 mmol, 1.5 eq.) were dissolved in 6 mL of 50/50 acetonitrile/DMSO. The resulting mixture solution was stirred overnight at 30°C. The resulting suspension was stirred for 30 minutes with a small amount of silica and potassium carbonate in dichloromethane and then was filtered over celite. The solvent was removed under high vacuum. The resulting solid was taken up in CH_2Cl_2 and *n*–pentane was added dropwise while stirring. A white powder was formed, recovered by filtration and washed with *n*–pentane: 46.0 mg (0.064 mmol, 63% yield).
^{1}H NMR ((CD_3)$_2$CO, 400 MHz) δ = 8.60 (s, 1H, $CH_{triazole}$), 7.88 (s, 2H, H_{Ar}), 7.46 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.34 (d, 2H, J = 7.7 Hz, H_{Ar}), 4.77 (d, 2H, J = 5.7 Hz, C*H*$_2$OH), 4.43 (t, 1H, J = 5.77 Hz, OH), 4.35-4.31 (m, 4H, CH_2), 3.41-3.33 (m, 2H, C*H*(CH_3)$_2$), 3.31-3.24 (m, 2H, C*H*(CH_3)$_2$), 1.50 (d, 6H, J = 6.8 Hz , CH(C*H*$_3$)$_2$), 1.43 (d, 12H, J = 6.8 Hz , CH(C*H*$_3$)$_2$), 1.34 (d, 6H, J = 6.8 Hz , CH(C*H*$_3$)$_2$).
^{13}C NMR ((CD_3)$_2$CO, 100 MHz) δ = 197.1 ($C_{carbene}$), 150.8 (C_{qAr}), 148.2 (C_{qAr}), 139.7 (C_{qAr}), 136.0 (C_{qAr}), 135.9 (C_{qAr}), 131.2 (C_{Ar}-H), 125.9 (C_{Ar}-H), 121.9 ($CH_{triazole}$), 117.7 (C_{Ar}-H), 57.3 (CH_2), 55.2 (CH_2), 54.9 (CH_2), 30.5 (CH), 30.0 (CH), 25.9 (CH_3), 25.6 (CH_3), 24.8 (CH_3), 24.6 (CH_3).
IR (ν, cm^{-1}): 3323, 2962, 1604, 1502, 1464, 1280, 1055, 1018, 887.
HRMS (ESI+): calculated for $C_{32}H_{44}N_6OAu$ [M-Cl+CH_3CN]$^+$: 725.3242, found: 725.3275.
E. A. Calcd for $C_{30}H_{41}AuClN_5O$, $1H_2O$ C: 48.82%, H: 5.87%, N: 9.49%; found C: 49.10%, H: 5.70%, N: 9.47%.

(*N*-[2,6-diisopropyl-4-(4-(α-D-glucopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl]-*N*'-(2,6-diisopropylphenyl) imidazolin-2-ylidene)-chlorogold(I) (**8b**): compound **7b** (100 mg, 0.134 mmol, 1.0 eq.) and AuCl.Me_2S (58.8 mg, 0.200 mmol, 1.5 eq.) were dissolved in 6 mL of 50/50 Acetonitrile/DMSO. The resulting mixture solution was stirred overnight at 30°C. The resulting suspension was stirred for 30 minutes with a small amount of silica and potassium carbonate and then was filtered over celite and evaporated. The resulting

solid was dissolved in 1 mL of acetone and *n*-pentane (7 mL) was added dropwise while stirring to give of a white solid recovered by filtration and washed with ice–cooled methanol: 58.0 mg, 0.066 mmol, 49% yield).

^{1}H NMR (CD_3CN, 400 MHz) δ = 8.52 (s, 1H, $CH_{triazole}$), 7.74 (s, 2H, H_{Ar}), δ = 7.48 (t, 1H, *J* = 7.7 Hz, H_{Ar}), 7.33 (d, 2H, *J* = 7.7 Hz, H_{Ar}), 4.98 (d, 1H, *J* = 3.1 Hz, $CH_{anomeric}$), [4.88 (d, 1H, *J* = 12.6 Hz) 4.73 (d, 1H, *J* = 12.6 Hz), CH_2OC], 4.12 (s, 4H, CH_2-CH_2), 3.76 (s, 1H, OH), 3.66-3.53 (m, 3H, C*H*$_2$OH + 1C*H*OH), 3.46-3.35 (m, 3H, 2C*H*OH + 1OH), 3.30-3.21 (m, 3H, 1C*H*OH + 2C*H*$(CH_3)_2$), 3.19-3.10 (m, 3H, 2C*H*$(CH_3)_2$ + 1OH), 2.91 (s, 1H, OH), 1.43-1.32 (m, 24H, CH(C*H*$_3)_2$).

^{13}C NMR (CD_3CN, 100 MHz) δ = 196.0 ($C_{carbene}$), 151.1 (C_{qAr}), 148.4 (C_{qAr}), 139.5 (C_{qAr}), 136.1 (C_{qAr}), 135.7 (C_{qAr}), 131.3 (C_{Ar}-H), 125.9 (C_{Ar}-H), 123.9 ($CH_{triazole}$), 118.1 (C_{Ar}-H), 99.6 ($CH_{anomeric}$), 75.2 (CHOH), 73.8 (CHOH), 73.4 (CHOH), 71.8 (CHOH), 62.9 (CH_2OH), 61.8 (CH_2OC), 55.1 (CH_2), 54.9 (CH_2), 30.2 (CH), 29.7 (CH), 26.1 (CH_3), 25.8 (CH_3), 24.4 (CH_3), 24.2 (CH_3); one quaternary carbon not detected.

IR (ν, cm^{-1}): 3385(br), 2966, 1627, 1485, 1458, 1277, 1037.

HRMS (ESI+): calculated for $C_{40}H_{46}N_6O_2Au$ $[M\text{-}Cl]^+$: 836.3505, found: 836.3478.

(*N*-[2,6-diisopropyl-4-(4-(2-oxo-2*H*-chromen-6-yl)-1*H*-1,2,3-triazol-1-yl)phenyl]-*N*'-(2,6-diisopropylphenyl)imidazolin-2-ylidene)-chlorogold(I) (**8c**): compound **7c** (90.0 mg, 0.128 mmol, 1.0 eq.) and AuCl.Me_2S (56.6 mg, 0.192 mmol, 1.5 eq.) were dissolved in 7 mL of 50/50 Acetonitrile/DMSO. The resulting mixture solution was stirred for 72h at 30°C. The resulting suspension was stirred for 30 minutes with a small amount of silica and potassium carbonate in dichloromethane and then was filtered over celite. The solvent was removed under high vacuum. The resulting solid was taken up in CH_2Cl_2 and MeOH was added dropwise while stirring. A white powder formed and was recovered by filtration and washed with methanol: 74.1 mg (0.089 mmol, 70% yield).

^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.64 (s, 1H, $CH_{triazole}$), 8.12 (d, 1H, *J* = 9.4 Hz, H_{Ar}),7.98 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.95 (s, 1H, H_{Ar}), 7.92 (s, 2H, H_{Ar}), 7.89 (d, 1H, *J* = 8.0 Hz, H_{Ar}), δ = 7.48 (t, 1H, *J* = 7.9 Hz, H_{Ar}), 7.36 (d, 2H, *J* = 7.9 Hz, H_{Ar}), 6.54 (d, 1H, *J* = 9.4 Hz, H_{Ar}), 4.20 (s, 4H, CH_2), 3.25-3.20 (m, 2H, C*H*$(CH_3)_2$), 3.15-3.10 (m, 2H, C*H*$(CH_3)_2$), 1.44-1.42 (m, 12H, CH(C*H*$_3)_2$), 1.35-1.33 (m, 12H, CH(C*H*$_3)_2$).

^{13}C (HSQC) NMR (DMSO-d_6, 100 MHz) δ = 143.6 (C_{Ar}-H), 129.5 (C_{Ar}-H), 129.0 (C_{Ar}-H), 124.1 (C_{Ar}-H), 121.2 ($CH_{triazole}$), 120.7 (C_{Ar}-H), 115.9 (C_{Ar}-H), 115.6 (C_{Ar}-H), 112.0 (C_{Ar}-H), 53.2 (CH_2), 28.2 (CH), 27.8 (CH), 24.5 (CH_3), 23.6 (CH_3), 23.5 (CH_3), 22.9 (CH_3).

Insufficient solubility of **8c** in common NMR solvents prevented the recording of a standard ^{13}C NMR spectrum.

IR (ν, cm^{-1}): 1743 (C=O), 1620, 1492, 1396, 1219, 1099, 1026.

HRMS (ESI+): calculated for $C_{40}H_{46}N_6O_2Au$ $[M\text{-}Cl\text{+}CH_3CN]^+$: 839.3348, found: 839.3369

E. A. Calcd for $C_{38}H_{43}AuClN_5O_2$, 3/2dmso C: 51.76%, H: 5.51%, N: 7.36%; found C: 51.57%, H: 5.30%, N: 7.51%.

(*N,N'*-bis[2,6-diisopropyl-4-(4-(α-D-glucopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)phenyl]-imidazolin-2-ylidene)-chlorogold(I) (**8d**): Compound **7d** (50 mg, 0.05 mmol, 1.0 eq.) was dissolved in 2.5 mL of 50/50 Acetonitrile/DMSO and the resulting mixture solution was stirred 24h at 50°C. The resulting suspension was stirred for 30 minutes with a small amount of silica and potassium carbonate, then filtered over celite and evaporated. The resulting solid was taken-up with 5mL of methanol, filtered over a millipore filter and evaporated. The resulting solid was dissolved in 1 mL of methanol then 5mL of acetone was added dropwise and the product was precipitated by a slow addition of *n*-pentane (5 mL) while stirring. The resulting off-white solid was recovered by filtration and washed with acetone: 34.0 mg, 0.066 mmol, 60% yield

^{1}H NMR (MeOD, 400 MHz) δ = 8.75 (s, 2H, $CH_{triazole}$), 7.82 (s, 2H, H_{Ar}), 5.0 (d, 2H, J = 3.7 Hz, $CH_{anomeric}$), 4.96 (d, 2H, J = 12.6 Hz), 4.79 (d, 2H, J = 12.6 Hz), CH_2OC], 4.26 (s, 4H, CH_2-CH_2), 3.72-3.64 (m, 8H, CH_2OH + 2CHOH), 3.45 (dd, 2H, 2 CHOH, J=3.7Hz), 3.29-3.26 (q, 4H, $CH(CH_3)_2$, J=6.8Hz), 1.46 (dd, 24H, $CH(CH_3)_2$, J=6.8Hz).

^{13}C NMR (MeOH-d_4, 100 MHz) δ = 196.6($C_{carbene}$), 151.1 (C_{qAr}), 140.4 (C_{qAr}), 136.0(C_{qAr}), 118.2(C_{Ar}-H), 100.0($C_{anomeric}$), 75.0 (CHOH), 74.3(CHOH), 73.6(CHOH), 71.9(CHOH), 62.5(CH_2OH), 61.7(*C*H_2OC), 55.4(CH_2), 54.9(CH_2), 30.5(CH), 25.3 (CH_3), 24.3(CH_3), *C triazole missing*.

IR (ν, cm^{-1}) = 3400 (br), 2967, 1603, 1483, 1348, 1279, 1038.

Localization of 8c in PC3 cell line.

Cells were plated on a glass slide and cultured in red phenol free RPMI 1640 until reaching 60% of confluence. Then, they were incubated with 10 µM of 8c for 18h at 37°C, 5% CO_2. Cells were washed three times by PBS 1X at 37°C and treated by 200 nM MitoTracker (M7513, Life Technologies) for 30 min. Cells were washed again three times by PBS 1X at 37°C then fixed using 4% PFA for 15 min at room temperature. After three additional washes by PBS 1X, cells were stocked in PBS1X/Glycerol (50/50) and fluorescence was captured by a Zeiss axioplan2 microscope using Zeiss filter sets #01 and #31 for visualizing **8c** and red-MitoTracker respectively (100x magnification).

Fluorescence spectroscopy

Stock solutions of compounds **7c** and **8c** were prepared in DMSO at 10^{-2} mol L^{-1}. 30 µL of each stock solution was added to 2970 µL of pH = 7.2, 0.5 mol L^{-1} HEPES-NaOH buffer (final concentration 10^{-5} mol L^{-1}).

Quantum yields were determined using a solution of quinine sulphate 0.5 mol L^{-1} aqueous H_2SO_4 and used as standard for quantum yield determination.[19]

Fluorescence spectra were recorded with a Cary Eclipse fluorimeter. The spectra were recorded in 1 cm luminescence cells. The slits were set to 2.5/2.5 nm (excitation/emission) for all measurements. Absorption spectra for quantum yields determination were recorded with a Cary spectrophotometer.

Acknowledgements. Region Auvergne (PNC) is acknowledged for financial support.

Notes and references

[a] Clermont Université, Université Blaise Pascal, Institut de Chimie de Clermont-Ferrand, BP 10448, F-63000 Clermont-Ferrand, FRANCE. Email : federico.cisnetti@univ-bpclermont.fr.
[b] Clermont Université, Université Blaise Pascal, GReD, BP 10448, F-63000 Clermont-Ferrand, FRANCE
c Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bât. 420, Université Paris-Sud, UMR CNRS 8182, F-91405 ORSAY Cedex, France.
[d] CNRS, UMR 6293, GReD, F-63001 Clermont-Ferrand, FRANCE.
[e] Inserm, UMR 1103, GReD, F-63001 Clermont-Ferrand, FRANCE.
[f] CNRS, UMR 6296, ICCF, F-63171 AUBIERE, France. Email: arnaud.gautier@univ-bpclermont.fr.

† The complex **8b** shows only moderate cytotoxicity: 35% of inhibition of cell growth on MCF–7 cells at 10μM.
†† CCDC 977560 for **7c**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure. The unit cell contains two very similar but non-equivalent molecules. Thus, values of Fig. 3 correspond to the average.
Electronic Supplementary Information (ESI) available: NMR and crystallographic details. See DOI: 10.1039/c000000x/

1 (a) S. Díez–González, N. Marion and S. P Nolan, *Chem. Rev.* 2009, **109**, 3612–3676; (b) O. Schuster, L. Yang, H. G. Raubenheimer and M. Albrecht, *Chem. Rev.* 2009, **109**, 3445–3478. (c) N–Heterocyclic Carbenes in Synthesis, ed. S. P. Nolan Wiley–VCH, 2006, Weinheim. (d) N–Heterocyclic Carbenes From Laboratory Curiosities to Efficient Synthetic Tools, ed. S. Díez–González, RSC publishing, 2010.

2 (a) K. M. Hindi, M. J. Panzner, C. A. Tessier, C. L. Cannon and W. J. Youngs, *Chem. Rev.* 2009, **109**, 3859–3884; (b) L. Oehninger, R. Rubbiani and I. Ott, *Dalton Trans.* 2013, **42**, 3269–3284. (c) W. Lui and R. Gust, *Chem. Soc. Rev.*, 2013, **42**, 755–773 (d) A. Gautier and F. Cisnetti, *Angew. Chem. Int. Ed.* 2013, **52**, 11976–11978.

3 For azide-alkyne pre–functionalization of metal NHCs, see: (a) S. Warsink, R. M. Drost, M. Lutz, A. L. Spek and C. J. Elsevier, *Organometallics*, 2010, **29**, 3109–3116. (b) H. Chayanant, H.–L. Su, H. S. Bazzi and D. E. Bergbreiter, *Org. Lett.*, 2009, **11**, 665–667. (c) S. Gu, H. Xu, N. Zhang and W. Chen, *Chem. Asian J.*, 2010, **5**, 1677–1689. (d) Y. He and C. Cai, *Chem. Commun*, 2011, **47**, 12319–12321. (e) C. Gaulier, A. Hospital, B. Legeret, A. F. Delmas, V. Aucagne, F. Cisnetti and A. Gautier, *Chem. Commun.*, 2012, **48**, 4005–4007 (f) A. Hospital, C. Gibard, C. Gaulier, L. Nauton, V. Thery, M. El–Ghozzi, D. Avignant, F. Cisnetti and A. Gautier, *Dalton Trans*. 2012, **41**, 6803–6812.

4 For post–functionalization of metal NHCs see representative examples: (a) RuAAC: E. Chardon, G. L. Puleo, G. Dahm, G. Guichard and S. Bellemin–Laponnaz, *Chem. Commun* 2011, **47**, 5864–5866. (b) RuAAC: E. Chardon, G. L. Puleo, G. Dahm, S. Fournel, G. Guichard, S. Bellemin-Laponnaz, *ChemPlusChem*, 2012, **77**, 1028–1038 (c) Photochemical: V. W. W. Yam, J. K. W. Lee, C. C. Ko, N. Zhu, *J. Am. Chem. Soc.* 2009, **131**, 912-913. (d) CuAAC (also for prefunctionalisation) S. Warsink, R. M. Drost, M. Lutz, A. L. Spek and C. J. Elsevier, *Organometallics* 2010, **29**, 3109–3116 (e) CuAAC (catalyst and substrate): C. Gibard, D. Avignant, F. Cisnetti and A. Gautier, *Organometallics*, 2012, **31**, 7902–7908. (f) CuAAC: S. Gauthier, N. Weisbach, N. Bhuvanesh and J. A. Gladysz, *Organometallics* 2009, **28**, 5597–5599 (g) enolate reactivity: L. Benhamou, N. Vujkovic, V. César, H. Gornitzka, N. Lugan, and G. Lavigne, *Organometallics*, 2010, *29*, 2616–2630. (h) enolate reactivity: L. Benhamou, V. César, H. Gornitzka, N. Lugan, and G. Lavigne, Chem. Commun. 2009, 4720-4722. (i) Huisgen and SPAAC: ref. 3f (j) nucleophilic substitution: H. V. Huynh and Q. Teng, *Chem. Commun.*, 2013, **49**, 4244–4246.

5 (a) M. Barz, E. Herdtweck and W. R. Thiel, *Angew. Chem. Int. Ed*. 1998, **37**, 2262–2264. (b) D. Urankar and J. Kosmrlj, *J. Comb. Chem*. 2008, **10**, 981–985. (C) W. S. Brotherton, H. A. Michaels, J. T. Simmons, R. J. Clark , N. S. Dalal and L. Zhu, *Org. Lett.*, 2009, **11**, 4954–4957. (d) S. A. Ingale and F. Seela *J. Org. Chem*. 2013, **78**, 3394-3399 (e) C. Uttamapinant, A. Tangpeerachaikul, S. Grecian, S. Clarke, U. Singh, P. Slade, K. R. Gee and A. Y. Ting, *Angew. Chem. Int. Ed*. 2012, **51**, 5852–5856.

6 M. R. L. Furst and C. S. J. Cazin, *Chem. Commun*, 2010, **46**, 6924–6925.

7 (a) T. Zou, C. T. Lum, S. S–Y Chui and C.–M. Che, *Angew. Chem. Int. Ed.* 2013, **52**, 2930–2933. (b) J. Lemke, A. Pinto, P. Niehoff, V. Vasylyevaa and N. Metzler–Nolte, *Dalton Trans*, 2009, 7063–7070. (c) R. Rubbiani, E. Schuh, A. Meyer, J. Lemke, J. Wimberg, N. Metzler-Nolte, F. Meyer, F. Mohr and I. Ott, *Med. Chem. Commun*. **2013**, *4*, 942-948. (d) R. Rubbiani, S. Can, I. Kitanovic, H. Alborzinia, M. Stefanopoulou, M. Kokoschka, S. Mönchgesang, W. S. Sheldrick, S. Wölfl and I. Ott, *J. Med. Chem*. 2011, **54**, 8646-8657. (e) J. L. Hickey, R. A. Ruhayel, P. J. Barnard, M. V. Baker, S. J. Berners–Price and A. Filipovska, *J. Am. Chem. Soc*. 2008, **130**, 12570–12571.

8 For silver, see: (a) L. Eloy, A.–S. Jarrousse, M.–L. Teyssot, A. Gautier, L. Morel, C. Jolivat, T. Cresteil and S. Roland, *ChemMedChem*, 2012, **7**, 805–814. For copper, see: (b) M.–L. Teyssot, A.–S. Jarrousse, A. Chevry, A. De Haze, C. Beaudoin, M. Manin, S. P. Nolan, S. Diez–Gonzalez, L. Morel and A. Gautier, *Chem. Eur. J*. 2009, **15**, 314–318.

9 (a) T. Makino, H. Masu, K. Katagiri, R. Yamasaki, I. Azumaya and S. Saito, *Eur. J. Inorg. Chem.*, 2008, 4861–4865. (b) E. Tzur, A. Ben-Asuly, C.E. Diesendruck, I. Goldberg, N.G. *Angew. Chem. Int. Ed.*, 2008, **47**, 6422–6425. (c) H. Ibrahim, C. Gibard, A. Hospital, C. Gaulier, N. Hewitt, A. Gautier and F. Cisnetti, *Protocol Exchange* (2012) doi:10.1038/protex.2012.058.

10 H. C. Brown, Organic synthesis via borane., Aldrich Chemical Co., Inc., 1997, Milwaukee.

11 J. Andersen, U. Madsen, F. Björkling and X. Liang *Synlett* 2005, 2209–2213.
12 C. Gibard, H. Ibrahim, A. Gautier and F. Cisnetti, *Organometallics*, 2013, **32**, 4279–4283.
13 A. S. Rowan, N. I. Nicely, N. Cochrane, W. A. Wlassoff, A. Claiborne and C. J. Hamilton, *Org. Biomol. Chem*., 2009, **7**, 4029–4036.
14 S. Díez–González, E. D. Stevens and S. P Nolan, *Chem. Commun*, 2008, 4747–4749.
15 (a) D. F. Eaton, *Pure Appl. Chem*. 1988, **60**, 1107–1114. (b) A. M. Brouwer, *Pure Appl. Chem.*, 2011, **83**, 2213–2228 (c) Fluorescence quantum yields found here are compatible with what is reported for other 'clicked' coumarin: J. A. Key, S. Koh, Q. K. Timerghazin, A. Brown and C. W. Cairo, *Dye Pigm*., 2009, **82**, 196–203.
16 Many gold–NHcs are known to localize at the mitochondria vicinity, for selected examples, see: ref 7a, 7e.
17 T. Makino, H. Masu, K. Katagiri, R. Yamasaki, I. Azumaya and S. Saito, *Eur. J. Inorg. Chem*., 2008, 4861 –4865.
18 M. Chtchigrovsky, A. Primo, P. Gonzalez, K. Molvinger, M. Robitzer, F. Quignard and F. Taran, *Angew. Chem. Int. Ed*. 2009, **48**, 5916-5920.
19 (a) D. F. Eaton, Pure Appl. Chem. 1988, 60, 1107–1114. (b)A. M. Brouwer, *Pure Appl. Chem*., 2011, **83**, 2213–2228.

