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CuAAC Functionalization of Azide-Tagged Copper(I)-NHCs Acting as Catalyst and Substrate

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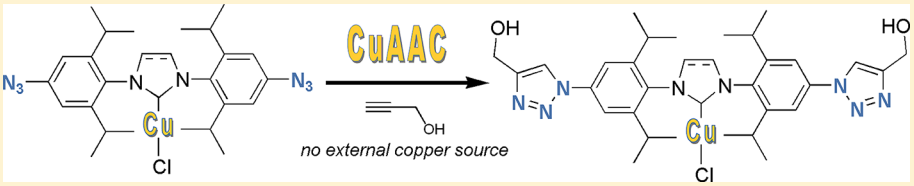
Supporting Information



ABSTRACT: Azide-tagged copper(I) complexes of N-heterocyclic carbenes (NHCs) analogous to the well-known bis[2,6-diisopropylphenyl]imidazol-2-ylidene (IPr) and bis[2,6-diisopropylphenyl]imidazolin-2-ylidene (SIPr) were synthesized and characterized. These complexes were able to act as catalyst and substrate in a model copper-catalyzed azide−alkyne (CuAAC) reaction with propargyl alcohol, yielding functionalized copper(I)-NHC complexes.

The strong metal−carbon bond of metal N-heterocyclic carbene (NHC) complexes associated with the remarkable electron-donating properties of the carbene ligand and their steric protection of the metal center has allowed them to become a leading family of contemporary organometallic chemistry.[1] Thus, they have attracted considerable interest over the last few decades, first as laboratory curiosities and later on for their high catalytic efficiency. It is noteworthy that their use as metal-based drugs is also being actively explored.[2]

Therefore, straightforward strategies for the functionalization of NHC ligands are of importance, as they allow modulation of solubility, lipophilicity, and reactivity. Indeed, several methods are now available to synthesize functionalized metal-NHCs. Resulting structures include chiral metal-NHCs, neutral tethered oligonuclear NHC complexes, and catalysts decorated with charged and/or polar groups for solubility modulation.[3] Most of these methods rely on a prefunctionalization strategy—i.e., the imidazol(in)ium precursors are functionalized before the metalation step. However, postfunctionalization approaches allow more modular synthetic pathways (Chart 1).

Although azide−alkyne chemistry has allowed numerous successes in postfunctionalization of coordination or organometallic complexes,[4] it has seldom been used on metal-NHCs. Elsevier and co-workers reported a single example of copper-catalyzed azide−alkyne cycloaddition (CuAAC) on a palladium complex precursor to yield **1** (Chart 2).[5] Guichard, Bellemin-Laponnaz, and co-workers were the first to explore in detail the practicability of a catalytic azide−alkyne postfunctionalization route for metal-NHCs in order to generate functionalized complexes such as **2** and **3**.[6] The ability of the ruthenium complex $Cp^*RuCl(PPh_3)_2$ to catalyze the formation of the triazole as a 1,5-regioisomer[7] starting from alkynyl complex precursors was highlighted—however, CuAAC reactions were not successful with their precursors. Importantly, this Ru-catalyzed strategy allowed the synthesis of biomolecule conjugates. Recently, we have reported a synthetic strategy implying azide−alkyne precursors allowing both pre-[8,9] and postfunctionalization.[9] In the latter case, the introduction of the desired functional group is performed by [2 + 3] Huisgen cycloaddition onto the metal−NHC. The azide-tagged gold(I)−NHC complex **4** was subjected to a thermal cycloaddition (50 °C, 10 days) with dimethyl acetylenedicarboxylate to yield the cycloadduct **5**. Alternatively, an instantaneous exothermic reaction was observed with the strained alkyne bicyclo[6.1.0]-non-4-yn-9-ylmethanol at room temperature, to afford the bis-triazole gold(I)-NHCs **6**.

In our effort to delineate efficient methods to synthesize functionalized metal-NHCs, we hypothesized that copper(I)-NHC complexes bearing azide functions could act as both a catalyst and a substrate in a CuAAC functionalization strategy. To verify such an assumption, we chose the unsaturated [*N*,*N*′-bis(4-azido-2,6-diisopropylphenyl)imidazol-2-ylidene]-chlorocopper(I) (**7a**) and its saturated analogue [*N*,*N*′bis(4-azido-2,6-diisopropylphenyl)imidazolin-2-ylidene]-chlorocopper(I) (**7b**), which we reacted with propargyl alcohol (Chart 3), to exemplify a functionalization allowing both solubility modulation and the possibility of further modification.

RESULTS AND DISCUSSION

The Cu(I)-NHC **7a** was straighforwardly obtained by the silver transmetalation route from the known complex **9a**,[9] synthesized from the corresponding imidazolium chloride **8a** (Scheme 1).

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Chart 1. Functionalization Strategies

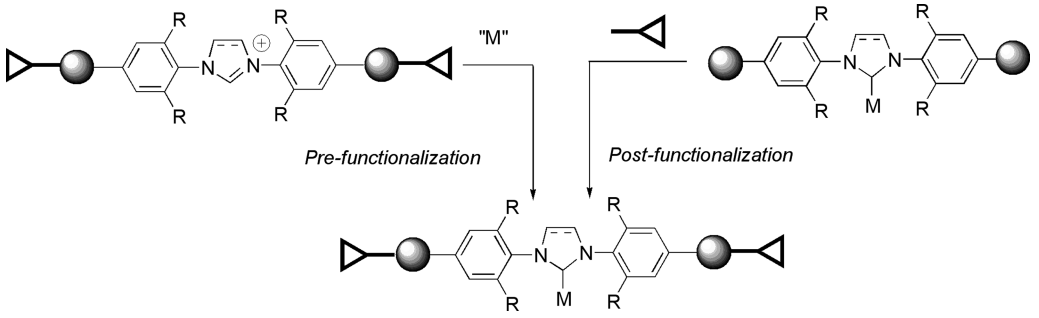


Chart 2. Postfunctionalization of Metal-NHCs Performed by Azide−Alkyne Chemistry

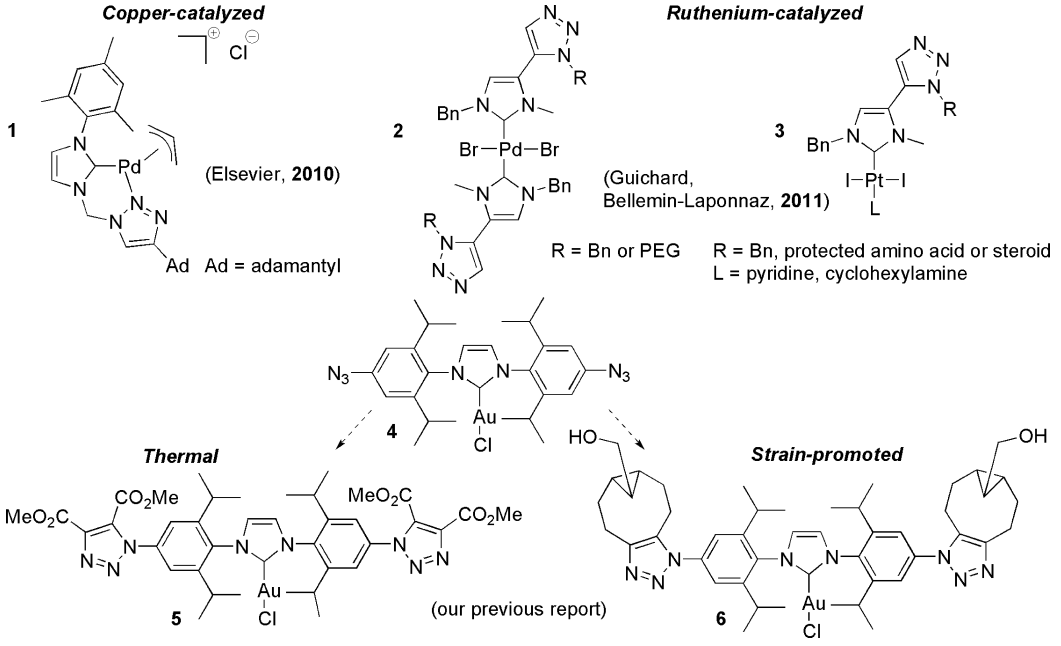
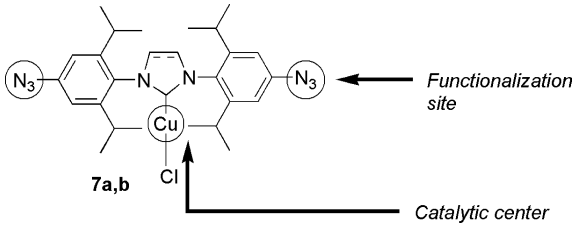
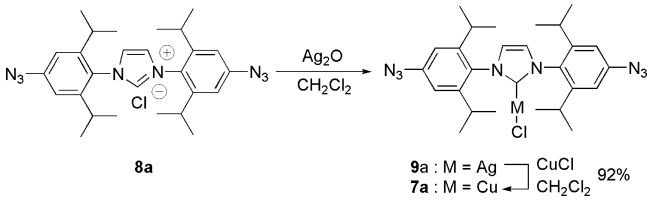


Chart 3. Postfunctionalization of Cu-NHCs 7



Scheme 1. Synthetic Route to the Copper-NHC 7a



Gratifying, the Cu(I)-NHC complex **7a** is bench-stable for several months. Slow diffusion of *n*-pentane in a dichloromethane solution at 4 °C affords crystals suitable for X-ray diffraction. NMR and microanalysis show the presence of nonvolatile—i.e., remaining in the sample after prolonged drying under vacuum—dichloromethane in samples of **7a** (this also applies to **7b**). Indeed, electron density corresponding to such a disordered solvent was detected (see the Experimental Section). Not unexpectedly, the coordination geometry proved to be very similar to those of the known [(IPr)CuCl] (**10**) (Figure 1 and Table 1).[10] The azide groups are found 7.0 Å away from the copper center. Owing to this distance and to the rigid nature of the phenylene spacer, these groups are obviously unable to interact with the copper atom, as expected. Interestingly, azide−azide dipolar interactions are apparent in the structure packing (dipole−dipole distances 3.31 and 3.64 Å) and may be partially responsible for the crystal integrity, as was found for its gold(I) and silver(I) counterparts.[9]

The synthetic route to **7b**, depicted in Scheme 2, starts with the known diiodoazadiene **11**,[11] which was reduced according to a classical procedure to the diamine **12**. Introduction of azides was performed using the copper(I) catalytic system reported by Andersen et al.[12] Cyclization of **13**·2HCl using the classical procedure affords the imidazolinium salt **8b**.[13] This reaction sequence was performed on a gram scale with a global yield of 63%. **7b** is finally obtained similarly to **7a** using silver oxide metalation followed by copper chloride transmetalation.

In preliminary experiments to synthesize the expected triazole-decorated Cu-NHCs, the reactions between **7a,b** and propargyl alcohol were examined (Scheme 3). After 2 days in dry DMSO-d_6

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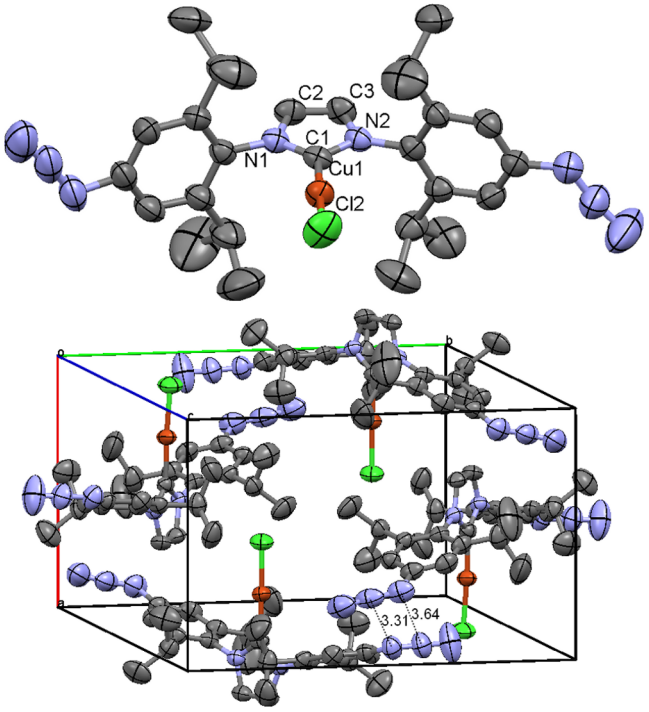


Figure 1. Ellipsoid plot of [(IPrN$_3$)CuCl] (**7a**) (top) and the corresponding packing diagram (bottom). Ellipsoids are shown at the 50% probability level, and H atoms are omitted for clarity.

Table 1. Selected Bond Lengths (Å) and Angles (deg) in Copper Complexes 7a and [(IPr)CuCl] (10)

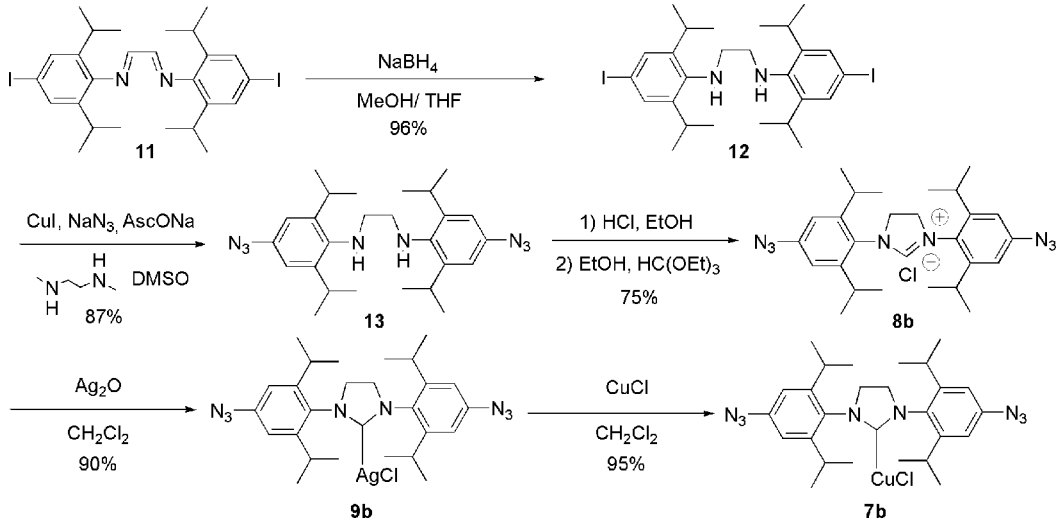
	7a	10[12]
Cu1−C1	1.886(3)	1.953(8)
N1−C1	1.350(4)	1.320(7)
N2−C1	1.347(4)	1.320(7)
C2−C3	1.310(5)	1.368(15)
Cu1−Cl2	2.0933(11)	2.089(4)
N1−C1−N2	104.4(3)	108.9(6)
C1−Cu1−Cl2	176.46(11)	180.0

at 50 °C, ^{1}H NMR revealed a total lack of reactivity, as was also observed in $CDCl_3$. However, we found out that the reaction rates were dramatically increased by the addition of 1% (v/v) of water into the reaction medium. Indeed, complete disappearance of both **7a** and **7b** occurs after an overnight reaction and the single products **14a,b** are observed by ^{1}H NMR in the crude mixture. The unique reaction product—only the triazole 1,4-regioisomer is expected to be formed in CuAAC[14]—along with the result of control experiments[15] performed with azolium salts **8a,b** instead of the corresponding copper carbenes **7a,b** unambiguously prove the catalytic nature of the reaction. As the reaction is sterically impossible *intra*molecularly (see above for structural discussion), copper complexes catalyze in an *inter*molecular fashion their functionalization with alkynes.[16] The necessary presence of water for the reactivity is reminiscent of the behavior of the water-activated latent catalyst [(SIPr)CuCl] (**10b**) reported by Díez-González and Nolan.[17] However, attempts performed with higher water content did not proceed to completion: 10% (v/v) of water resulted in a significant amount of imidazol(in)ium byproduct, and "on water" conditions did not allow any detectable conversion.

Comparisons of ^{1}H NMR spectra between starting materials **7a,b** and the products showed a striking difference in the aromatic part with the emergence of the characteristic singlet of the triazole moiety and a modification of the aromatic signature for both complexes. Moreover, the total extinction of the IR stretching band at 2100 cm^{-1} confirmed a reaction through the azide functions. Compounds **14a,b** were isolated after evaporation of the DMSO under high vacuum and precipitation with ether from an ethanol solution in 75% and 69% yields, respectively. Importantly, neither NMR spectroscopy nor elemental analysis allows the determination of the homoleptic or heteroleptic nature of the complexes and, unfortunately, all attempts to form crystals suitable for X-ray diffraction were unsuccessful.

To confirm the neutral nature of the metal-NHCs, conductivity measurements[18] for complexes **14a,b** were performed in DMSO. For the sake of comparison, we measured under the same conditions the conductivity due to (IPr)CuCl (**10**), (SIPr)CuCl, and [(IPr)$_2$Cu]PF$_6$, as well as silver complex **16** and gold complex **17** (Chart 4, Table 2).

Scheme 2. Synthetic Route to the Copper-NHC 7b



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Scheme 3. CuAAC Reactions of Complexes 7

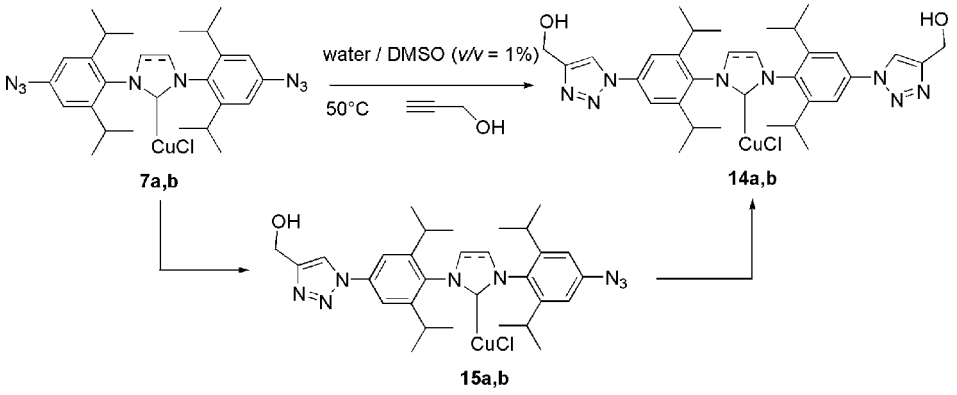

Chart 4. Gold(I) and Silver(I) Complexes Related to 7a

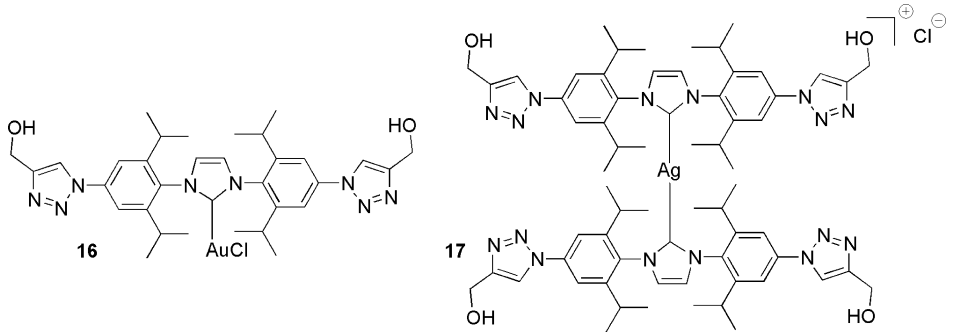

Table 2. Molar Conductivities Λ_M (S cm^{-2} mol^{-1}) of Solutions of Copper(I)-NHCs in DMSO[a]

	14a	14b	(IPr)CuCl	(SIPr)CuCl	$[(IPr)_2Cu]PF_6$	16	17
nature	neutral	neutral	neutral	neutral	cationic	cationic	neutral
Λ_M	2.7	1.2	0.9	0.6	26.4[19]	20.2[19]	1.8

[a]Conditions: T = 20 °C, c = 2.5 × 10^{-3} M.

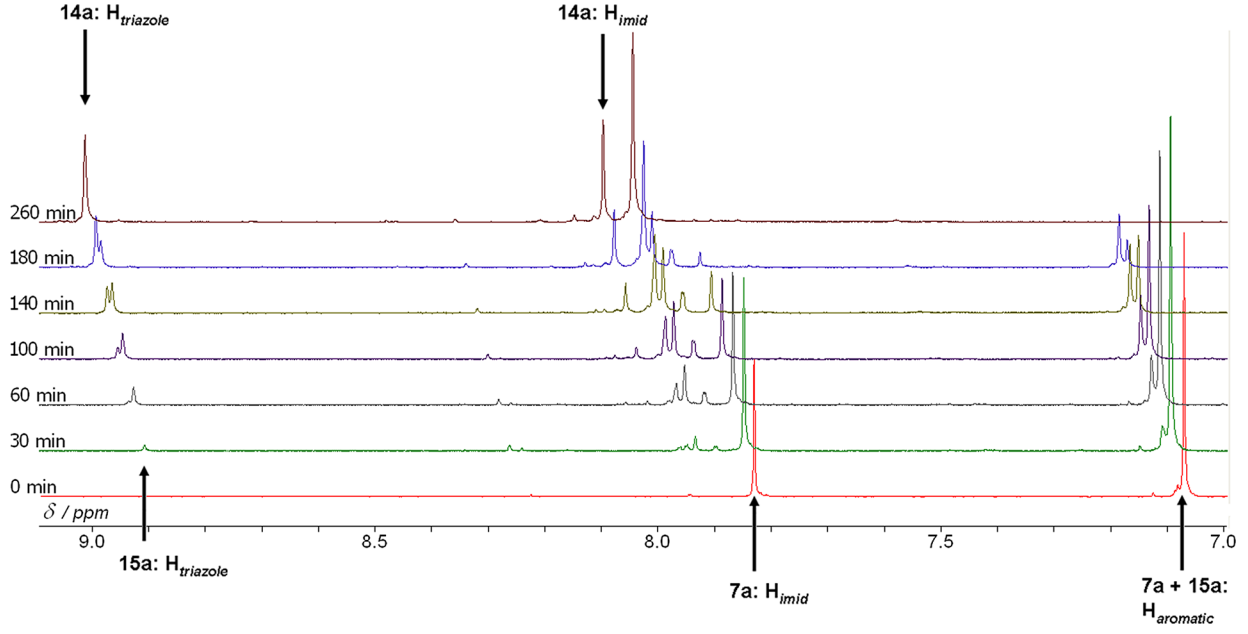

Figure 2. Formation of **14a** from **7a** and propargyl alcohol in DMSO-d_6 with 1% H_2O at 50 °C as a function of time.

With the carbene ligand kept constant, this set of data is in agreement with the ionicity of **16** and **17**, both of which were demonstrated independently.[9] Therefore, the neutral nature of **14a,b** is confirmed.

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In order to get more information about the reactivity, the kinetic profiles of functionalization of **7a,b** with propargyl alcohol were studied by ^{1}H NMR at 50 °C in water/DMSO-d_6 (1% v/v). A time-dependent complication of the aromatic region was observed, associated with the formation of a dissymmetric compound assignable to the monotriazoles **15a,b**. Logically, at the last stage of the reactions, simplification of the spectra occurred, due to the formation of the final symmetrical compounds **14a,b** (Figure 2, Scheme 3, and the Supporting Information).

SUMMARY

Two copper(I) N-heterocyclic carbenes bearing azide functions were synthesized and characterized. For this purpose, an efficient and gram-scale synthesis route to a azide-tagged saturated imidazoliniun salt was developed, starting from easily accessible compounds. The azido complexes undergo a CuAAC reaction without the need for any additional copper(I) source, thus leading to a process usable in the postfunctionalization context. In addition to the few other metal-NHC postfunctionalization reactions reported to date, this process could pave the way for the synthesis of a library of copper(I) complexes using a modular approach. Further studies in this direction are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Considerations. NMR spectra for compound characterization 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. The kinetic survey of CuAAC reactions was performed with a Bruker AVANCE 500 spectrometer (^{1}H at 500 MHz). 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). IR spectra were recorded on a Shimadzu FTIR-8400S Fourier transform infrared spectrophotometer. Elemental analyses were performed at the Service de Microanalyse, Université de Lorraine, Vandoevre-les-Nancy, France. X-ray diffraction intensity data were collected at T = 293 K with a Bruker APEX-II CCD diffractometer (Mo Kα radiation (λ = 0.7107 Å)). The structure was solved by direct methods with SHELXS-97[20] and refined with SHELXL-97[21] implemented in the CRYSTALS program package.[22] The contribution of the highly disordered solvent molecule present in the lattice was handled by the use of the PLATON/SQUEEZE procedure.[23] Conductivity measurements were performed at 20 °C in duplicate with solutions prepared independently using a Radiometer Analytical CDM210 conductivity meter equipped with a standard 1 cm measurement cell. *Warning! Organic and inorganic azides may pose safety concerns due to their potential explosivity.* However, none of the organic azides described herein are considered to be dangerous according to a commonly accepted rule ($N_C/N_N \geq 3$).[24] Compounds **8a**,[9] **9a**,[9] [(IPr)CuCl] (**10**),[25] [(SIPr)CuCl],[17] [(IPr)$_2$Cu](PF$_6$),[26] **11**,[11] **16**,[9] and **17**[9] were synthesized using literature procedures.

Synthesis of {*N*,*N*′-Bis[4-azido-2,6-diisopropylphenyl]-imidazol-2-ylidene}chlorocopper(I) (7a). **9a** (100 mg, 0.163 mmol) was dissolved in 2 mL of degassed dichloromethane, copper(I) chloride (47.9 mg, 0.49 mmol) was added, and the mixture was stirred for 1 h. The resulting suspension was filtered over Celite and the filtrate evaporated to afford a yellow powder. Yield: 92 mg (92%). Crystallization conditions for X-ray structural studies: a solution of **7a** (10 mg in 0.5 mL of dichloromethane) was layered with 8 mL of *n*-pentane in a test tube which was placed in a closed vessel at 4 °C. Monocrystalline prisms were recovered after 3 days. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.90 (s, 2H, C*H* imidazole), 7.10 (s, 4H, C*H* aromatic), 2.45 (hept, J = 6.8 Hz, 4H, C*H*(CH$_3$)$_2$), 1.20 (d, J = 6.8 Hz, 24H, CH(C*H*$_3$)$_2$). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, ppm): δ 178.7 (*C* carbene), 147.5 (*C* aromatic), 141.3 (*C* aromatic), 131.2 (*C* aromatic), 124.7 (CH imidazole), 114.7 (CH aromatic), 28.5 (CH-(CH$_3$)$_2$), 24.0 (CH(CH$_3$)$_2$), 23.0 (CH(CH$_3$)$_2$). IR: $\tilde{\nu}$ (cm^{-1}) 2964, 2112 (N$_3$), 1597, 1472, 1337, 1310, 1280, 1240. HRMS (ESI$^+$): calculated for $C_{29}H_{37}CuN_9$ $[M - (Cl + CH_3CN)]^+$ 574.2468, found 574.2455. Anal. Found: C, 53.83; H, 5.75; N, 17.70. Calcd for $C_{27}H_{34}ClCuN_8 \cdot 0.5CH_2Cl_2$: C, 53.96; H, 5.76; N, 18.28.

Synthesis of Diiododiamine 12. Azadiene **11** (10.6 g, 16.9 mmol) was dissolved in 75 mL of a 6/4 THF/MeOH mixture. $NaBH_4$ (639 mg, 16.9 mmol) was added cautiously in portions to this solution. After 2 h, TLC analysis (1/1 ethyl acetate/cyclohexane) indicated the total disappearance of **11** and the formation of a single product. The excess $NaBH_4$ was quenched by addition of saturated aqueous NH_4Cl while keeping the temperature at room temperature with a cool water bath. Organic solvents were evaporated, and the resulting aqueous slurry was extracted with 3 × 50 mL of Et_2O. The joint organic phases were dried over $MgSO_4$ and evaporated, yielding 10.07 g (96%) of **12** as an off-white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 (s, 4H, CH aromatic), 3.28 (hept, J = 6.8 Hz, 4H, C*H*(CH$_3$)$_2$), 3.14 (s; 4H, CH$_2$), 1.31 (d, J = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$), 1.26 (d, J = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 145.3 (C aromatic), 143.1 (C aromatic), 133.7 (CH aromatic), 88.9 (CI), 52.1 (CH$_2$), 27.9 (CH(CH$_3$)$_2$), 24.2 (CH(CH$_3$)$_2$). IR: $\tilde{\nu}$ (cm^{-1}) 3367 (NH), 2960, 2861, 1572, 1454, 1331, 1191. HRMS (ESI$^+$): calcd for $C_{26}H_{39}N_2I_2$ $[M + H]^+$ 633.1203, found 633.1198. Anal. Found: C, 49.58; H, 6.12; N 4.42. Calcd for $C_{26}H_{38}I_2N_2$: C, 49.38; H, 6.06; N, 4.43.

Synthesis of Diazidodiamine 13. **12** (8.53 g, 13.5 mmol), NaN_3 (3.51 g, 54 mmol), *N*,*N*′-dimethylethane-1,2-diamine (218 μL, 2.03 mmol, 15 mol %), and sodium ascorbate (267 mg, 1.35 mmol, 10 mol %) were added to 200 mL of a 9/1 DMSO/H_2O mixture. The resulting solution was deoxygenated under a flux of Ar. Copper(I) iodide (1.35 mmol, 10 mol %) was then added, and the mixture was stirred for 7 h at 70 °C in the dark. The reaction mixture was poured on 300 mL of ice−water, and **13** was recovered as a brown powder after filtration, washing with water, and desiccation. Yield: 5.42 g (87%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 (s, 4H, CH aromatic), 3.28 (hept, J = 6.8 Hz, 4H, C*H*(CH$_3$)$_2$), 3.14 (s; 4H, CH$_2$), 1.31 (d, J = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$), 1.26 (d, J = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 144.8 (C aromatic), 140.5 (C aromatic), 135.3 (C aromatic), 114.4 (CH aromatic), 52.3 (CH$_2$), 28.1 (CH(CH$_3$)$_2$), 24.1 (CH(CH$_3$)$_2$). IR: $\tilde{\nu}$ (cm^{-1}) 3354 (NH), 2969, 2931, 2101 (N3), 1598, 1463, 1336, 1242. HRMS (ESI$^+$): calculated for $C_{26}H_{39}N_8$ $[M + H]^+$ 463.3298, found 463.3291.

Synthesis of *N*,*N*′-Bis[4-azido-2,6-diisopropylphenyl]-imidazolinium Chloride (8b). **13** (2.10 g, 4.54 mmol) was treated with an excess (about 3 equiv) of ethanolic HCl (freshly prepared by the cautious addition of 1.3 mL of acetyl chloride to 15 mL of absolute ethanol). After 30 min with vigorous stirring the double chlorhydrate **13**·2HCl which separated was recovered by filtration and washed with cold ethanol. This powder was taken up in 60 mL of a 1/1 HC(OEt$_3$)/EtOH mixture, which was refluxed for 2 h. After the mixture was cooled to room temperature and evaporated, the residue was triturated in 30 mL of Et_2O. The resulting powder was recovered by filtration, washed with cold ether, taken up in 5 mL of CH_2Cl_2, and reprecipitated by the dropwise addition of 40 mL of *n*-pentane. Yield: 1.74 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42 (s, 4H, CH aromatic), 3.28 (hept, J = 6.8 Hz, 4H, CH(CH$_3$)$_2$), 3.14 (s; 4H, CH$_2$), 1.31 (d, J = 6.8 Hz, 12H, CH(CH$_3$)$_2$), 1.26 (d, J = 6.8 Hz, 12H, CH(CH$_3$)$_2$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 160.7 (NCHN), 148.4 (C aromatic), 142.1 (C aromatic), 126.6 (C aromatic), 115.4 (CH aromatic), 53.7 (CH$_2$), 28.5 (CH(CH$_3$)$_2$), 24.6 (CH(CH$_3$)$_2$), 23.0 (CH(CH$_3$)$_2$). IR: $\tilde{\nu}$ (cm^{-1}) 2966, 2103 (N$_3$), 1620, 1461, 1337, 1275. HRMS (ESI$^+$): calculated for $C_{27}H_{37}N_8$ $[M]^+$ 473.3141, found 473.3140. Anal. Found: C, 63.73; H, 7.32; N, 21.59. Calcd for $C_{27}H_{37}ClN_8$: C, 63.70; H, 7.33; N, 22.01.

Synthesis of {*N*,*N*′-Bis[4-azido-2,6-diisopropylphenyl]-imidazolin-2-ylidene}chlorosilver(I) (9b). **8b** (500 mg, 0.98 mmol) was dissolved in 40 mL of dichloromethane, silver oxide (147 mg, 0.64 mmol) was added, and the mixture was stirred for 2 h at room temperature in the dark. The resulting suspension was filtered over Celite, and the filtrate was evaporated under reduced pressure to afford

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an off-white powder. Yield: 544 mg (90%). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.03 (s, 4H, CH aromatic), 4.12 (s; 4H, CH_2) 3.07 (hept, J = 6.8 Hz, 4H, $CH(CH_3)_2$), 1.31 (d, J = 6.8 Hz, 12H, $CH(CH_3)_2$), 1.24 (d, J = 6.8 Hz, 12H, $CH(CH_3)_2$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 148.9 (C aromatic), 141.8 (C aromatic), 131.3 (C aromatic), 115.6 (CH aromatic), 54.0 (d, J = 8 Hz, CH_2), 29.3 ($CH(CH_3)_2$), 25.4 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$) (carbene carbon not detected). IR: $\tilde{\nu}$ (cm^{-1}) 2961, 2107 (N_3), 1597, 1488, 1460, 1332, 1269. Anal. Found: C, 52.68; H, 6.02; N, 18.07. Calcd for $C_{27}H_{36}AgClN_8$: C, 52.65; H, 5.89; N, 18.19.

Synthesis of {*N*,*N*′-Bis[4-azido-2,6-diisopropylphenyl]-imidazolin-2-ylidene}chlorocopper(I) (7b). 9b (100 mg, 0.163 mmol) was dissolved in 10 mL of degassed dichloromethane, copper(I) chloride (47.9 mg, 0.49 mmol) was added, and the solution was stirred for 1 h. The suspension that formed was filtered over Celite and evaporated to afford a yellow powder. Yield: 89.5 mg (95%). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.02 (s, 4H, CH aromatic), 4.06 (s; 4H, CH_2), 3.07 (hept, J = 7.0 Hz, 4H, $CH(CH_3)_2$), 1.31 (d, 12H, J = 7.0 Hz, $CH(CH_3)_2$), 1.26 (d, 12H, J = 7.0 Hz, $CH(CH_3)_2$). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 201.3 (C carbene), 148.8 (C aromatic), 140.5 (C aromatic), 131.5 (C aromatic), 115.1 (CH aromatic), 53.6 (CH_2), 28.4 ($CH(CH_3)_2$), 24.8 ($CH(CH_3)_2$), 23.1 ($CH(CH_3)_2$). IR: $\tilde{\nu}$ (cm^{-1}) 2964, 2105 (N_3), 1597, 1487, 1461, 1334, 1270. HRMS (ESI$^+$): calculated for $C_{29}H_{39}CuN_9$ [M − (Cl + CH_3CN)]$^+$ 576.2625, found 576.2625. Anal. Found: C, 55.74; H, 6.28; N, 18.36. Calcd for $C_{27}H_{36}ClCuN_8 \cdot 0.25CH_2Cl_2$: C, 55.21; H, 6.21; N, 18.90.

Synthesis of {*N*,*N*′-Bis[2,6-diisopropyl-4-(4-hydroxymethyl-1,2,3,1*H*-triazol-1-yl)phenyl]imidazol-2-ylidene}chlorocopper-(I) (14a). 7a (200 mg, 0.338 mmol) was dissolved in 10 mL of 99/1 DMSO/water, and propargyl alcohol (100 μL, 1.75 mmol) was added. The mixture was stirred at 50 °C for 16 h. The solvent was removed under high vacuum, and the resulting solid was dissolved in 15 mL of methanol and precipitated by dropwise addition of 40 mL of diethyl ether to afford **14a** as a pale yellow powder after filtration. This procedure was repeated two times after concentration of the mother liquor. Yield: 178.7 mg (75%). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.98 (s, 2H, *CH* triazole), 8.06 (s, 2H, *CH* imidazole), 7.96 (s, 4H, *CH* aromatic), 5.40 (t, J = 5.5 Hz, 2H, *OH*), 4.66 (d, J = 5.5 Hz, 4H, CH_2OH), 2.54 (hept, J = 7.0 Hz, 4H, $CH(CH_3)_2$), 1.30 (m, 24H, $CH(CH_3)_2$). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, ppm): δ 178.5 (*C* carbene), 149.4 (*C* aromatic), 147.7 (*C* aromatic), 138.2 (*C* aromatic), 133.9 (*C* aromatic), 124.7 (*CH* imidazole), 121.4 (CH triazole), 115.6 (*CH* aromatic), 55.1 (CH_2OH), 28.8 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$), 23.0 ($CH(CH_3)_2$). IR: $\tilde{\nu}$ (cm^{-1}) 3400 (broad, OH), 2964, 1601, 1478, 1329, 1223, 1021. Anal. Found: C, 57.30; H, 6.19; N, 15.41. Calcd for $C_{67}H_{88}Cl_2Cu_2N_{16}O_4 \cdot {}^1/_3$dmso: C, 57.13; H, 6.27; N, 15.83.

Synthesis of {*N*,*N*′-Bis[2,6-diisopropyl-4-(4-hydroxymethyl-1,2,3,1*H*-triazol-1-yl)phenyl]imidazolin-2-ylidene}-chlorocopper(I) (14b). 7b (114 mg, 0.192 mmol) was dissolved in 6 mL of 99/1 DMSO/water, and propargyl alcohol (112 μL, 1.90 mmol) was added. The mixture was heated to 50 °C for 15 h. The solvent was removed under high vacuum, and the resulting solid was dissolved in 10 mL of methanol and crystallized by dropwise addition of 25 mL of diethyl ether to afford a pale yellow powder after filtration. This procedure was repeated two times after concentration of the mother liquor. Yield: 96.3 mg (69%). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.93 (s, 2H, CH triazole), 7.88 (s, 4H, CH aromatic), 5.36 (t, J = 5.5 Hz, 2H, OH), 4.64 (d, J = 5.5 Hz, 4H, CH_2OH), 4.17 (s, 4H, CH_2), 3.18 (hept, 4H, J = 6.8 Hz, $CH(CH_3)_2$), 1.40 (d, J = 6.8 Hz, 12 H, $CH(CH_3)_2$), 1.34 (d, J = 6.8 Hz, 12 H, $CH(CH_3)_2$). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 201.1 (C carbene), 149.0 (C aromatic), 137.5 (C aromatic), 134.3 (C aromatic), 121.3 (CH triazole), 115.8 (CH aromatic), 55.0 (CH_2OH), 53.6 (NCH_2CH_2N), 28.5 ($CH(CH_3)_2$), 24.8 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)_2$) . IR: $\tilde{\nu}$ (cm^{-1}) 3400 (broad, OH), 2963, 1601, 1479, 1333, 1250, 1021. Anal. Found: C, 56.54; H, 6.52; N, 15.73. Calcd for $C_{33}H_{44}ClCuN_8O_2 \cdot 0.5$dmso: C, 56.50; H, 6.55; N, 15.50.

Crystal data for 9a: monoclinic, space group $P2_1/n$, a = 9.7500(4) Å, b = 15.3223(7) Å, c = 22.0934(9) Å, β = 90.538(2)°, V = 3300.4(2) Å^3, Z = 4, D_{calcd} = 1.146 g cm^{-3}, final R ($I > 3\sigma(I)$) R1 = 0.0497 and wR2 = 0.0529, GOF = 1.068. CCDC-885582 contains supplementary crystallographic data for this compound.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving selected ^{1}H and ^{13}C NMR spectra and a CIF file giving crystallographic data for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Díez−González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (b) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445. (c) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (d) *N-Heterocyclic Carbenes From Laboratory Curiosities to Efficient Synthetic Tools*; Díez-González, S., Ed.; RSC Publishing: London, 2010.

(2) (a) Hindi, K. M.; Panzner, M. J.; Tessier, C. A.; Cannon, C. L.; Youngs, W. J. *Chem. Rev.* **2009**, *109*, 3859. (b) Teyssot, M.-L.; Jarrousse, A.-S.; Manin, M.; Chevry, A.; Roche, S.; Norre, F.; Beaudoin, C.; Morel, L.; Boyer, D.; Mahiou, R.; Gautier, A. *Dalton Trans.* **2009**, 6894. (c) Gautier, A.; Cisnetti, F. *Metallomics* **2012**, *4*, 23.

(3) For reviews, see: (a) Kühl, O. *Functionalized N-Heterocyclic Carbene Complexes*; Wiley: Chichester, U.K., 2010. (b) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643.

(4) For examples of the use of CuAAC in the general context of metal complex postfunctionalization see: (a) Gauthier, S.; Weisbach, N.; Bhuvanesh, N.; Gladysz, J. A. *Organometallics* **2009**, *28*, 5597. (b) McDonald, A. R.; Dijkstra, H. P.; Suijkerbuijk, B. M. J. M.; van Klink, G. P. M.; van Koten, G. *Organometallics* **2009**, *28*, 4689. (c) Urankar, D.; Košmrlj, J. *Inorg. Chim. Acta* **2010**, *363*, 3817. (d) Warsink, S.; Drost, R. M.; Lutz, M.; Spek, A. L.; Elsevier, C. J. *Organometallics* **2010**, *29*, 3109. (e) Yang, H.; Li, L.; Wan, L.; Zhou, Z.; Yang, S. *Inorg. Chem. Commun.* **2010**, *13*, 1387. (f) Das, M. R.; Wang, M.; Szunerits, S.; Gengembre, L.; Boukherroub, R. *Chem. Commun.* **2009**, 2753. (g) Sun, Y.; Chen, Z.; Puodziukynaite, E.; Jenkins, D. M.; Reynolds, J. R.; Schanze, K. S. *Macromolecules* **2012**, *45*, 2632. (h) Benson, M. C.; Ruther, R. E.; Gerken, J. B.; Rigsby, M. L.; Bishop, L. M.; Tan, Y.; Stahl, S. S.; Hamers, R. J. *ACS Appl. Mater. Interfaces* **2011**, *3*, 3110. (i) Stengel, I.; Strassert, C. A.; Plummer, E. A.; Chien, C.-H.; De Cola, L.; Bäuerle, P. *Eur. J. Inorg. Chem.* **2012**, 1795.

(5) Warsink, S.; Drost, R. M.; Lutz, M.; Spek, A. L.; Elsevier, C. J. *Organometallics* **2010**, *29*, 3109.

(6) Chardon, E.; Puleo, G. L.; Dahm, G.; Guichard, G.; Bellemin-Laponnaz, S. *Chem. Commun.* **2011**, *47*, 5864.

(7) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337.

(8) Gaulier, C.; Hospital, A.; Legeret, B.; Delmas, A. F.; Aucagne, V.; Cisnetti, F.; Gautier, A. *Chem. Commun.* **2012**, *48*, 4005.

(9) Hospital, A.; Gibard, C.; Gaulier, C.; Nauton, L.; Thery, V.; El−Ghozzi, M.; Avignant, D.; Cisnetti, F.; Gautier, A. *Dalton Trans.* **2012**, *41*, 6803.

(10) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157.

(11) Pignataro, L.; Papalia, T.; Slawin, A. M. Z.; Goldup, S. M. *Org. Lett.* **2009**, *11*, 1643.

(12) Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005**, 2209.

(13) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.

(14) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
(15) For control experiments, we prepared solutions analogous to those used for functionalization reactions with propargyl alcohol containing imidazolium salts **8a,b** instead of the corresponding copper(I) complexes. After 24 h at 50 °C <10% of 1,4-triazole products were observed by ^{1}H NMR with traces of another compound, possibly the 1,5-regioisomer, and unreacted starting material as the main species.
(16) For mechanistic considerations in CuAAC see: (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2005**, 51. (b) Buckley, B. R.; Dann, S. E.; Heaney, H. *Chem. Eur. J.* **2010**, *16*, 6278. (c) For the mechanism of Cu(I)-NHCs, see: Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558.
(17) Díez-González, S.; Stevens, E. D.; Nolan, S. P. *Chem. Commun.* **2008**, 4747.
(18) Examples of the use of this technique to determine the ionicity of metal-NHCs include: (a) Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972. (b) Liu, S.-T.; Lee, C.-I.; Fu, C.-F.; Chen, C.-H.; Liu, Y.-H.; Elsevier, C. J.; Peng, S.-M.; Chen, J.-T. *Organometallics* **2009**, *28*, 6957. (c) Jiménez, M. V.; Fernández-Tornos, J.; Pérez-Torrente, J. J.; Modrego, F. J.; Winterle, S.; Cunchillos, C.; Lahoz, F. J.; Oro, L. A. *Organometallics* **2011**, *30*, 5493.
(19) Values in the range of what could be expected for a 1/1 electrolyte in DMSO: Geary, W. J. *Coord. Chem. Rev.* **1971**, *7*, 81.
(20) Sheldrick, G. *SHELXS-97 Program for Crystal Structure Solution*; University of Gottingen, Gottingen, Germany, 1997.
(21) Sheldrick, G. *SHELXL-97 Program for Crystal Structure Refinement*; University of Gottingen, Gottingen, Germany, 1997.
(22) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
(23) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7.
(24) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.
(25) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.
(26) Díez-González, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355−2358.