In situ generation of novel acyclic diaminocarbene-copper complex[†]

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A novel acyclic diaminocarbene–copper complex appears to be generated from a chloroamidinium salt and Cu(1)-thiophenecarboxylate in the presence of Grignard reagent based on $^{13}\mathrm{C}$ NMR studies and is a highly efficient catalyst for $\mathrm{S_N2'}$ -allylic alkylation.

N-Heterocyclic carbene ligands (NHC) have drawn much attention recently due to their highly σ -donating capacity, and most carbene ligands are largely based on imidazoline-derived cyclic frameworks.^{1,2} Nevertheless, stable acyclic diamino-carbenes (ADC) as well as their metal complexes are known.^{3,4}



Crystal structures of acyclic carbenes show substantially larger N–C–N angles (121.0°) than those of their cyclic analogs (104.7°), suggesting greater steric demands are exerted by acyclic carbenes.^{3d} Furthermore, acyclic diaminocarbenes are more electron-donating than NHCs,⁴ⁱ but despite these interesting properties, there are not many reported examples of acyclic carbene ligands mainly because preparation of acyclic carbenes and metal-ADC complexes are quite challenging.^{3,4} Intermolecular formamidinium ion formation often gives low yield along with by-products,^{3b} and the formamidinium proton is less acidic,⁵ requiring a much stronger base such as lithium diisopropylamide for deprotonation to generate the carbene species.^{3d} As an alternative to the deprotonation route, Fürstner and co-workers reported a novel way to generate ADC-metal complexes via oxidative addition of Pd into the C-Cl bond of chloroamidinium salts.^{4g} Recently we reported a concise synthesis of biisoquinoline-based chiral tricyclic diaminocarbene ligands (BIQ) and their Pd and Cu complexes.⁶ While we were screening Cu metal precursors for the allylic alkylation reaction, we serendipitously discovered a new route to ADC-Cu complexes. Herein we wish to report our preliminary results on in situ generation of ADC-Cu complexes from readily available N, N, N', N'-tetrasubstituted ureas.

In the attempted synthesis of Cu(II)-BIQ complex 2 from imidazolium precursor 1 and $CuCl_2$, unexpectedly chloroimidazolium salt 3 was isolated and characterized by X-ray crystallography (eqn (1)).† Interestingly, when this complex was used in the $S_N 2'$ allylic alkylation reaction,⁷ it gave a very similar result compared to BIQ–CuCl (7) (eqn (2)).



The possibility that Cu–carbene species might be generated from chloroimidazolium–CuCl₂ salt (**3**) and EtMgBr under the allylic alkylation conditions led us to try commercially available chloroamidinium $\mathbf{8}\cdot\mathbf{BF_4}^-$ as a potential acyclic carbene precursor. We were pleased to find that the highly S_N2' selective allylic alkylation reaction was efficiently catalyzed by the mixture of $\mathbf{8}\cdot\mathbf{BF_4}^-$ and CuCl₂ (entry 1, Table 1). Cu(1) salts such as CuCl (entry 2) or CuTC (entry 3) also gave identical results to those with CuCl₂. Note that acyclic carbene **9** prepared by the reported deprotonation protocol^{4d} also gave a similar result, which is consistent with the idea of in situ carbene

Table 1 S_N2' Allylic alkylation catalyzed by Cu–carbene complexes



Entry	Ligand precursor	Cu salt	Yield $(\%)^a$	$\gamma: \alpha^b$
1	$8 \cdot BF_4^-$	CuCl ₂	82	93:7
2	$8 \cdot BF_4$	CuCl	81	93:7
3	8 BF4	CuTC	83	94:6
4^c	9	CuTC	71	90:10
5	IMes ^d	CuTC	57	92:8
6	$8 \cdot BF_4^-$	None	25	94:6
7	None	CuTC	9	13:87

^{*a*} Isolated yield. ^{*b*} Determined by ¹H NMR. ^{*c*} 10 mol% of ADC **9** and CuTC were used. ^{*d*} Isolated free carbene. TC = thiophene carboxylate, IMes = 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene.

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^{*a*} Reaction conditions: 5 mol% $8 \cdot BF_4^-$, 5 mol% CuTC, 1.5 equiv. EtMgBr, Et₂O, 0 °C, 1 h. ^{*b*} 15 mol% CuTC and $8 \cdot BF_4^-$ were used. PMP = *p*-methoxyphenyl.

generation (entry 4). Isolated NHC (IMes) showed similarly high γ selectivity ($\gamma:\alpha = 92:8$) despite the slightly reduced yield (entry 5). Both the copper salt and the chloroamidinium seem to be necessary for good yields (entries 6 and 7). However, $8 \cdot BF_4^-$ without CuTC (entry 6) still manages to give high γ selectivity ($\gamma : \alpha = 94 : 6$) whereas CuTC without 8.BF₄⁻ (entry 7) showed very different selectivity ($\gamma : \alpha = 13 : 87$).⁸

This ADC–Cu catalyst (8·BF₄⁻ with CuTC) shows excellent γ selectivity for various allylic substrates (Table 2). Symmetrical dibenzoate substrate 10 can be used owing to high γ selectivity (entry 1), and quaternary centers can be generated from tri-substituted alkene substrates in high yield (entries 3–5). The reaction with nitrogen atom containing substrate 16 was sluggish and 15 mol% of catalyst loading was required (entry 5). However, this ADC–Cu catalyst appears to be more reactive than the NHC–Cu catalyst (IMesCuCl)⁹ which gave 24% yield of 17 under identical conditions.

A series of ¹³C NMR studies were performed to monitor the reaction of chloroamidinium, CuTC and Grignard reagent. ¹³C-labeled chloroamidinium precursor ($8' \cdot Cl^-$) was prepared to quickly detect the weak but characteristic ¹³C resonance of the sp²-hybridized carbene carbon (Scheme 1). Then ¹³C-labeled chloroamidinium ($8' \cdot Cl^-$), CuCl and Grignard reagent were mixed in THF- d_8 and monitored by ¹³C NMR at low temperature (Fig. 1).¹⁰



Scheme 1 Preparation of ¹³C-labeled chloroamidinium precursor $8' \cdot Cl^-$.

When a mixture of chloroamidinium $\mathbf{8'} \cdot \mathbf{CI}^-$ and CuCl was treated with PhMgBr, the starting material $\mathbf{8'} \cdot \mathbf{CI}^-$ was fully



Fig. 1 Direct ¹³C NMR monitoring (at -60 °C) of carbene–metal complex generation using ¹³C-labeled chloroamidinium precursor (8'·Cl⁻).

converted to two species showing typical metal-carbene sp^2 carbon resonances at 206 and 217 ppm (Fig. 1a).⁴ The 161 and 168 ppm resonances are assigned to aryl and alkyl amidinium compounds, 19' and 20', respectively.^{11,12} We speculated that the signals at 206 ppm and 217 ppm might be assigned to Cu–carbene complex $(9'-Cu)^{13}$ and Mg–carbene complex (9'-Mg),¹⁴ respectively. These tentative assignments are supported by the following observations: when chloroamidinium $8' \text{ Cl}^-$ was treated with PhMgBr in the absence of CuCl (Fig. 1b), the 216 ppm resonance appeared as the only carbene species (9'-Mg). When this mixture was further treated with CuCl (Fig. 1c), the 216 ppm resonance is completely converted to the resonance at 206 ppm (9'-Cu). When a mixture of $8' \cdot Cl^{-1}$ and CuCl was treated with EtMgBr (Fig. 1d), the Cu-carbene resonance at 207 ppm (9'-Cu) was again observed while the 216 ppm resonance was not detected in this case. Importantly, these assignments are also in accord with the ¹³C NMR studies with known acyclic carbene species^{4d,15} prepared from deprotonation of ${}^{13}C$ -labeled formamidinium ion $22' \cdot PF_6^-$ (Scheme 2).⁺



Synthesis of ¹³C-labeled formamidinium

Scheme 2 Preparation of 13 C-labeled formamidinium precursor $22' \cdot PF_6^-$ and observed 13 C resonance values.

One of the plausible mechanistic scenarios might involve metal–halide exchange between chloroamidinium and $R_2CuMgBr$ (eqn (3))¹⁶ or a two-step sequence of magnesium–chloride exchange^{17a} followed by transmetallation.^{17b} However, more detailed mechanistic study is necessary.



In conclusion, highly $S_N 2'$ -selective allylic alkylation can be catalyzed by a mixture of chloroamidinium salt and Cu(I)-thiophenecarboxylate in the presence of Grignard reagent. ¹³C NMR study results are in accord with generation of an acyclic diaminocarbene–copper species. Development of chiral chloroamidinium precursors for enantioselective reaction is currently in progress.

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