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Cyclic (Alkyl)- and (Aryl)-(amino)carbene Coinage Metal Complexes and their Applications

Rodolphe Jazzar*, Michele Soleilhavoup*, and Guy Bertrand*

UCSD-CNRS Joint Research Laboratory (UMI 3555), Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093-0358, United States

*E-mail: rjazzar@ucsd.edu

*E-mail: msoleilhavoup@ucsd.edu

*E-mail: gbertrand@ucsd.edu

ABSTRACT: Cyclic (alkyl)- and (aryl)-(amino)carbenes (CAACs and CAArCs) are stronger σ -donors and π -acceptors than imidazol-2-ylidenes and imidazolidin-2-ylidenes, the well-known N-heterocyclic carbenes (NHCs). Consequently, they form strong bonds with coinage metals, and stabilize both low and high oxidation states. This Focus Review shows that CAACs and CAArCs have allowed for the isolation of copper and gold complexes which were believed to be only transient intermediates. This has not only allowed for a better understanding of the mechanism of known processes but has also led to the development of novel coinage metal-catalyzed reactions. In addition to their role in homogeneous catalysis, CAAC and CAArC coinage metal complexes have recently found applications in medicinal chemistry, as well as in materials science. When possible, the performance of CAAC and CAArC ligands are compared with those of classical NHCs.

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1. INTRODUCTION

Since their discovery in 2005,^{1,2} five-membered cyclic (alkyl)(amino)carbenes (CAAC) **1** have been the subject of several reviews.^{3,4,5,6,7,8} However none of them have comprehensively covered their coordination chemistry towards coinage metals. Even more importantly many significant discoveries in this field have been made in recent years and thus have not been discussed in the previous review articles. This Focus Review will not be limited to CAACs **1**, but will also include six-membered cyclic (alkyl)(amino)carbenes (CAAC-6) **2**,⁹ bicyclic (alkyl)(amino)carbenes (BiCAAC) **3**,¹⁰ the so-called saturated abnormal NHCs (*sa*NHC) **4**,¹¹ as well as cyclic (aryl)(amino)carbenes (CAArC) **5**¹² and **6**,¹³ (Figure 1). Because of the importance of classical NHCs in coinage metal chemistry,^{14,15,16,17,18,19} we will compare the results obtained with **1-6** with those of imidazol-2-ylidenes **7**²⁰ and imidazolidin-2-ylidenes **8**.²¹

To understand the advantages and disadvantages of carbenes **1-6** compared to classical NHCs **7** and **8**, a comparison of their electronic properties is necessary. This will be only briefly summarized since detailed analyses have already been reported in the previous reviews mentioned above. Although the calculated energy of the HOMO and LUMO of carbenes vary slightly depending on the level of theory, the same trend has been observed. Figure 1 summarizes the results obtained at the B3LYP/def2-TZVPP level of theory with ultrafine grid. With the exception of the so-called *sa*NHC **4**, all the cyclic (alkyl)(amino)carbenes **1-3** are both more σ -donating and π -accepting than NHCs **7** and **8**,²² because of the presence of the electropositive carbon and of only one π -donor amino group. Cyclic (aryl)(amino)carbenes **5-6** are still strong electron donors, but they are by far more π -accepting than all the other carbenes considered in this review, although less than the diamidocarbenes reported by Hudnall and Bielawski (LUMO: - 2 eV).²³ It is important to note that although carbenes **1-3** as well as NHCs **7** and **8** can be isolated and are stable in solution and in the solid state, carbenes **4-6** have not yet been isolated.

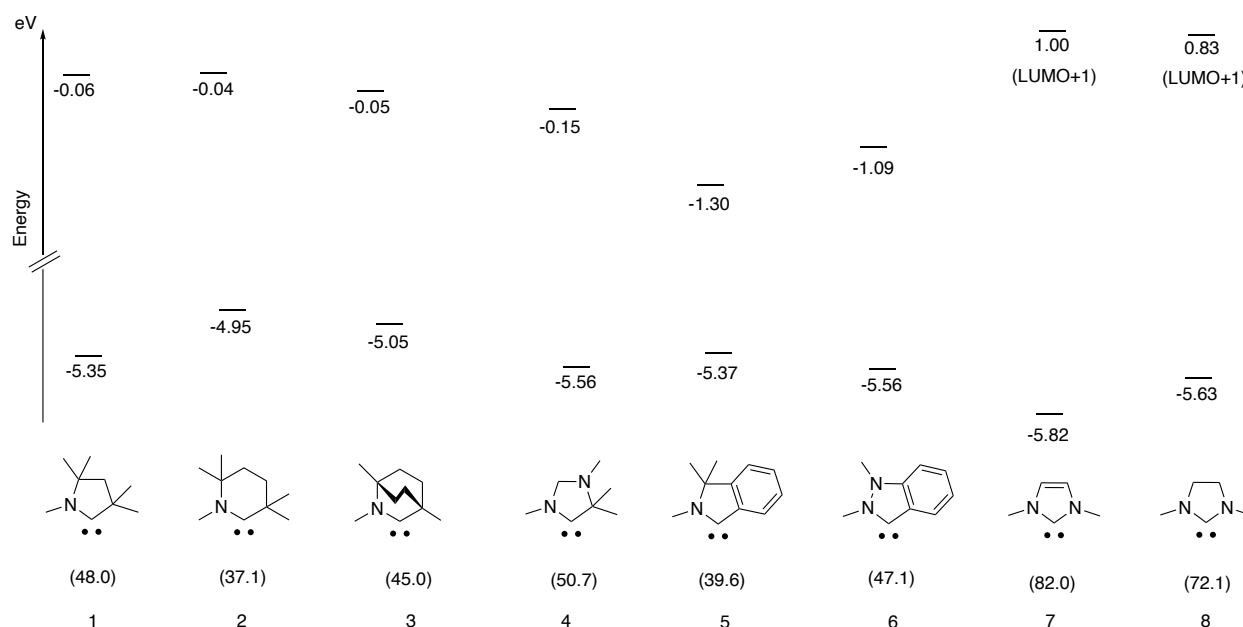


Figure 1. Calculated energy of the HOMO and LUMO of carbenes **1-6**, considered in this Focus Review, and of NHCs **7** and **8** for comparison (B3LYP/def2-TZVPP level of theory with ultrafine grid).

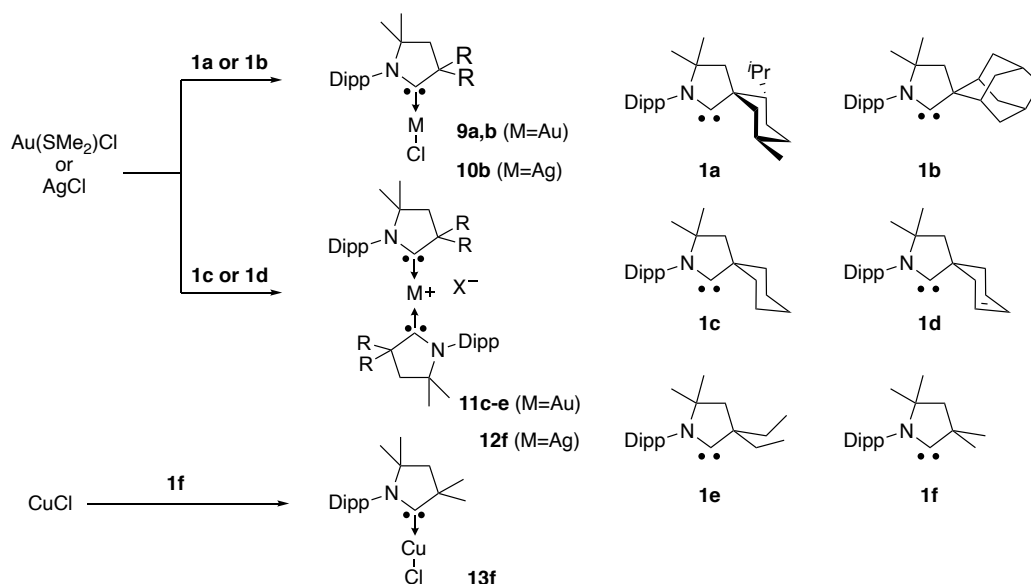
2. COORDINATION CHEMISTRY OF CYCLIC (ALKYL)- AND (ARYL)-(AMINO)CARBENES WITH COINAGE METALS

2.1. Synthesis of (CAAC)MCl (M = Cu, Ag, Au) Complexes

The steric bulk and flexibility of the substituents on the α -carbon of CAACs have a dramatic effect on their complexation to gold²⁴ and silver²⁵ (Scheme 1). When bulky and rigid substituents, such as menthyl or adamantyl, are present, the corresponding LAuCl complexes **9a** and **9b**, as well as LAgCl **10b** can readily be isolated. When the smaller and flexible cyclohexyl, cyclohexylene, ethyl or methyl groups are used, the mono-carbene gold and silver complexes can be observed and utilized as such, but are difficult to isolate; instead, the cationic bis(carbene) complexes such as **11c-e** and **12f** are obtained. Since cationic bis(carbene) complexes **11** and **12** are certainly more inert than the mono-carbenes counterparts **9** and **10**, these findings provide a good indication of the range of substituents, which might allow CAAC gold and silver complexes to find catalytic applications. In contrast, mono-carbene copper complexes are readily isolable even with small CAACs such as **1f** as shown by **13f**.^{26,27} Note that all these gold, silver and copper complexes can

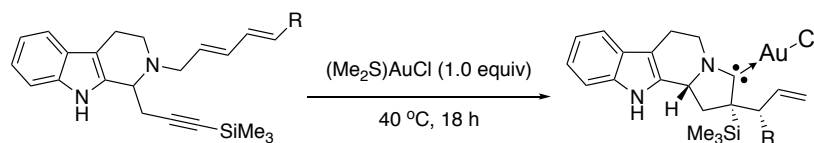
be prepared by simple addition at room temperature of the free carbene **1** to $\text{Au}(\text{SMe}_2)\text{Cl}$, AgCl and CuCl , respectively. Alternatively, following the seminal discovery by Lin *et al.*²⁸ on the ability of Ag(I) -NHC complexes to transfer Ag-bound NHC ligands to another metal, both the silver **10**²⁵ and even the copper complexes **13**²⁹ can undergo a transmetalation to give the desired CAAC-coinage metal complexes.

Scheme 1. Synthesis of (CAAC)MCl complexes (M = Au, Ag, Cu)



Cyclic (alkyl)(amino)carbene gold complexes have also been prepared via an elegant cyclization-rearrangement cascade (Scheme 2).³⁰ This protocol allows for the preparation of a variety of chiral CAAC–gold complexes in a highly stereoselective manner.

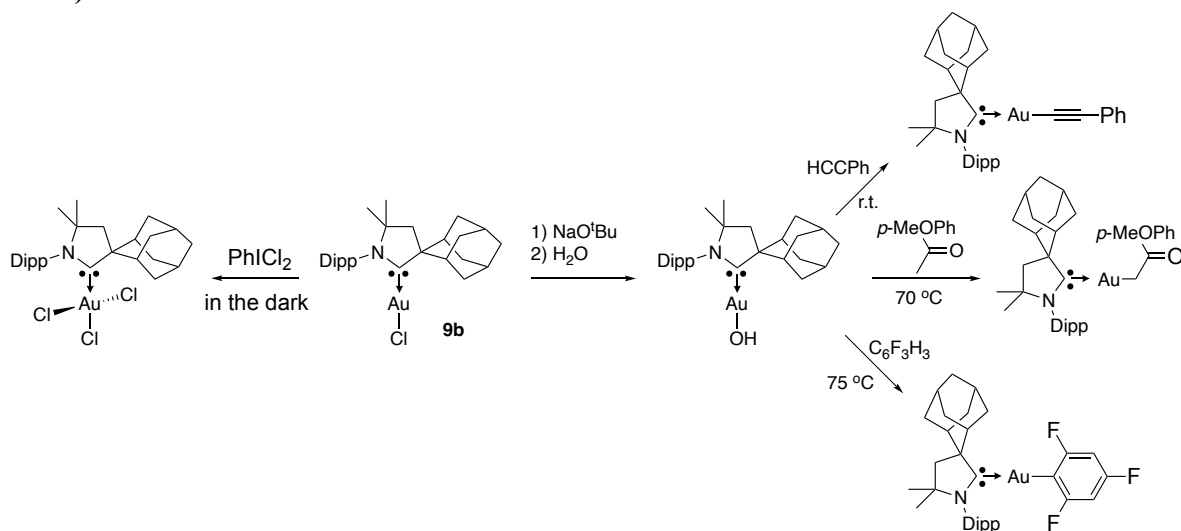
Scheme 2. Synthesis of CAACAuCl complexes via a cyclization-rearrangement cascade.



2.2. Synthesis of Various Gold(I) and Gold(III) Complexes from (CAAC)AuCl and (CAAC)AuOH

Romanov and Bochmann prepared a variety of gold(I) and gold(III) complexes,³¹ using (CAAC)AuCl and (CAAC)AuOH complexes, the latter being more basic than (NHC)AuOH³² (Scheme 3). Indeed, by studying the reactivity of (CAAC)gold-hydroxide complexes towards a variety of fluoroarenes, they concluded that they can activate C–H bonds with pKa values lower than about 31.5. Surprisingly, despite the more electron-donating properties of CAACs, compared to NHCs, their gold complexes proved to be more resistant to oxidation and more prone to halogen cleavage of the Au–C bonds than (NHC)gold(I) complexes.

Scheme 3. Synthesis of various gold(I) and gold(III) complexes from (CAAC)AuCl and (CAAC)AuOH

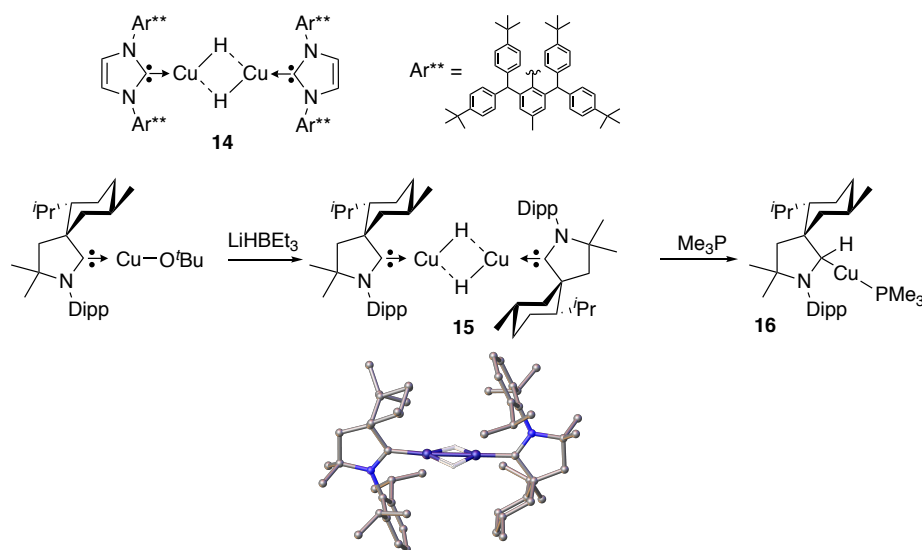


2.3. Synthesis of (CAAC)CuH Complexes

In contrast to monomeric gold hydrides, which can readily be isolated,^{33,34} copper hydrides have the propensity to aggregate³⁵ as evidenced by the widely used Stryker reagent [(Ph₃P)CuH]₆.³⁶ With the exception of the recently reported complex **14**,³⁷ featuring the extremely bulky 1,3-bis[2,6-bis[di(4-tert-butylphenyl)-methyl]-4-methylphenyl]imidazol-2-ylidene (IPr**),³⁸ dimeric (NHC)copper hydride complexes are unstable with a few exceptions^{39,40,41} (Scheme 4). In contrast, the dimeric (CAAC)copper hydride **15** was isolated and can be stored in solution for weeks at

room temperature.⁴² Interestingly, addition of an L ligand to **15** led to **16** in which the hydride has shifted to the carbene carbon. This unprecedented rearrangement suggests that the presence of a second L ligand, in addition to the extremely strong σ -donating CAAC, makes the copper very electron-rich, and confirmed the low-lying LUMO of CAACs.

Scheme 4. The crystalline copper hydride dimer supported by bulky NHCs (14) and CAACs (15), and the unprecedented rearrangement of the latter by addition of a L ligand

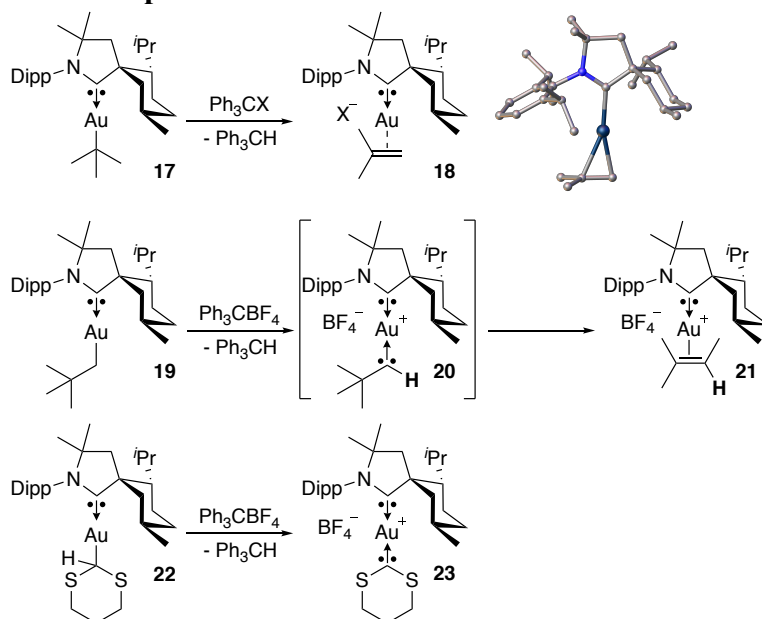


2.4. Synthesis of CAAC-Coinage Metal Alkene, Alkynes, and Aryl π -Complexes

α - and β -Hydride abstractions from alkyl complexes, affording metal-carbene and metal-alkene complexes, respectively, are well known reactions. However, it was only in 2013 that such processes were reported for gold.⁴³ When the *tert*-butyl gold complex **17** was treated with triphenylcarbenium tetrafluoroborate, an instantaneous reaction occurred, affording the gold(I)-alkene complex **18**, demonstrating the possibility of β -hydride abstraction (Scheme 5). To probe the α -hydride abstraction, the gold(I)-neopentyl complex **19** was reacted with $\text{Ph}_3\text{C}^+\text{BF}_4^-$, and the two diastereomeric gold(I)-(2-methylbut-2-ene) complexes **21** were isolated, although the reaction was drastically slower than in the case of **17**. All attempts to characterize the putative carbene intermediate **20** failed, which is not surprising since, with rare exceptions,^{44,45,46,47,48,49,50} non-

heteroatom substituted carbene gold complexes are very unstable. However, when triphenylcarbenium tetrafluoroborate was reacted with the gold(I) dithianyl complex **22**, the expected cationic bis(carbene) gold(I) complex **23** was obtained, demonstrating the α -hydride abstraction process.

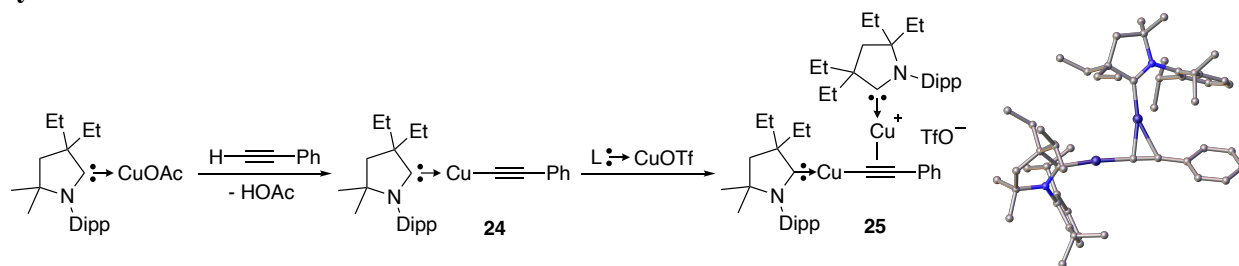
Scheme 5. α - and β -hydride abstractions from alkyl gold complexes **17 and **19**, respectively, lead to alkene π -complexes, whereas α -hydride abstraction from **22** affords the corresponding carbene complex **23****



In addition to alkenes, as in **18** and **21**, alkynes and even arenes can give π -complexes with (CAAC)coinage metals. The most striking example is arguably the cationic π,σ -bis(copper) acetylide **25** (Scheme 6).⁵¹ Indeed, in 2013, Fokin *et al.* reported that “monomeric copper-acetylide complexes (similar to **24**) are not reactive towards organic azides unless an exogenous copper catalyst is added”.⁵² They postulated that the catalytically active complex in the Cu-catalyzed azide-alkyne “click reaction”^{53,54,55} was in fact a cationic π,σ -bis(copper) acetylide. They further stated that these dinuclear species were “non-isolable and highly reactive intermediates”. However, in 2015, our group first prepared the mononuclear copper complex **24** by adding lithium phenyl acetylide with (CAAC)CuOAc. Note that with the exceptions of (NHC)copper acetylides,⁵⁶ these complexes are usually polymeric. Then, addition of (CAAC)CuOTf to **24** gave the desired

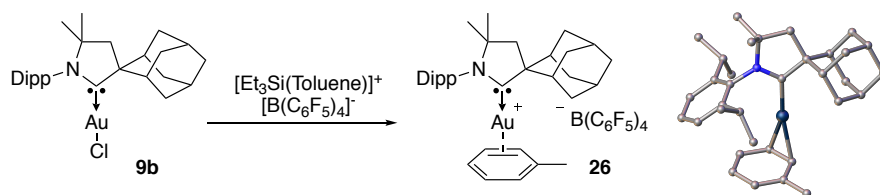
cationic dinuclear complex **25**, which proved to be air-stable and thermally robust. In solution, a very fast exchange between the two (CAAC)Cu units occurred, but in the solid state an X-ray diffraction study shows two different types of coordination, π and σ . The isolation of complex **25** has allowed for a detailed mechanistic study of the Cu-catalyzed azide-alkyne “click reaction” (See Section 3.3.).

Scheme 6. Synthesis of the monocopper acetylide **24 and supposedly unstable dinuclear complex **25**, which is the catalytically active complex in the Cu-catalyzed azide-alkyne cycloaddition “click reaction”**



The most common catalytic systems in gold catalysis involve LAuCl complexes, which through *in situ* salt metathesis generate the active species, supposedly a cationic monoligated LAu⁺ complex. Because of their strong σ -donating properties, CAACs are certainly good candidates to stabilize such compounds. However, treatment of a toluene suspension of **9b** with $[(\text{Toluene})\text{SiEt}_3]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ cleanly led to complex **26** (Scheme 7).⁵⁷ Though not a truly “naked” cation, the η^2 -binding mode hardly perturbs the aromatic ring, allowing this complex to behave as the proposed active cation for mechanistic studies. Note that a few similar complexes bearing bulky phosphine ligands have also been isolated.⁵⁸

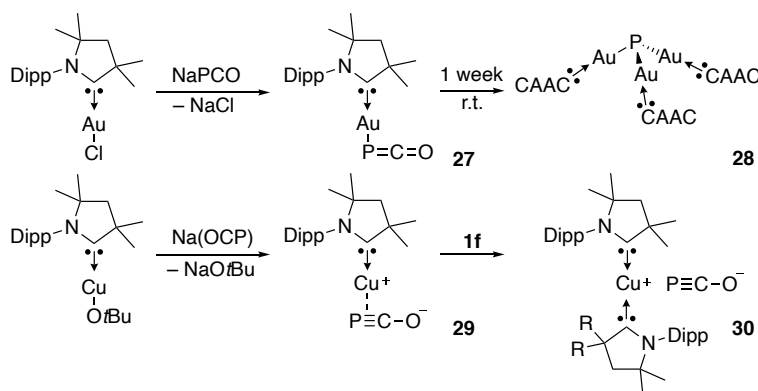
Scheme 7. Synthesis of the crystalline $[(\text{CAAC})\text{Au}(\eta^2\text{-toluene})]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ complex **26**



2.5. Synthesis of CAAC-Coinage Metal PCO Complexes

The ability of CAACs to efficiently stabilize metals in low oxidation states has been used to study the complexation of phosphaehtynolate salts $M^+(PCO)^-$, which are strong reducing agents.⁵⁹ It has been found that NaPCO reacts with (CAAC)AuCl and (CAAC)CuO^tBu cleanly affording **27** and **29**, respectively (Scheme 8).⁶⁰ Despite the similarities of the solid state structures, a computational study shows that the coordination modes of PCO with gold and copper are η^1 and η^2 , respectively, which leads to a difference in reactivity. The gold complex **27** is stable in the solid state but rearranges over the course of a week in solution at room temperature into the trinuclear complex **28**. The copper complex **29** decomposes in a few hours and is very reactive. A simple addition of free CAAC **1f** to **29** gives rise the cationic bis(CAAC)Cu complex **30**, in which the PCO fragment is the anionic counterpart.

Scheme 8. The coordination modes of PCO with gold and copper are η^1 and η^2 , respectively, which induces different reactivity

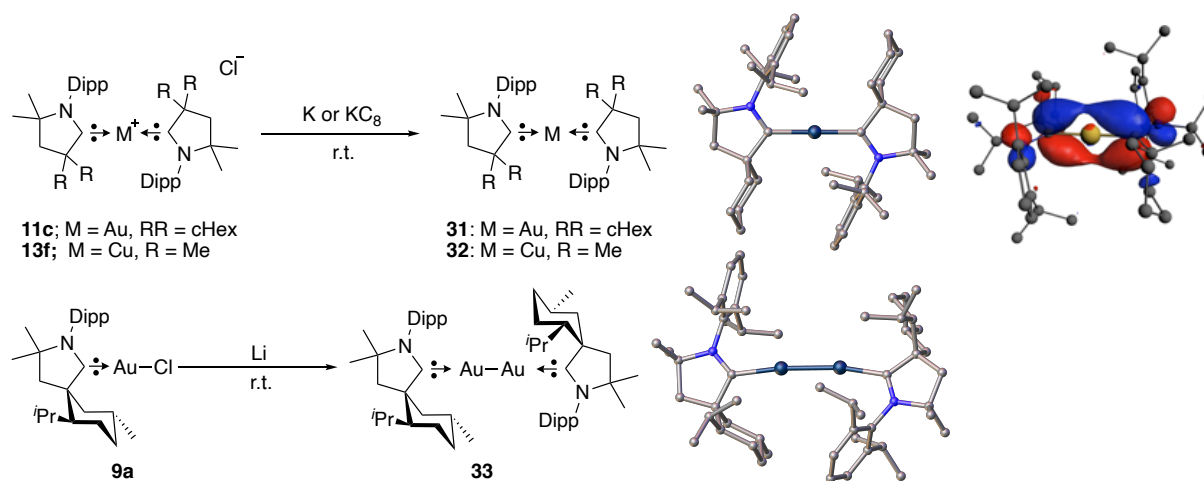


2.6. Synthesis of CAAC-Coinage Metal(0) Complexes

The applications above highlighted the advantages of the strong electron-donating properties of CAACs. However, their strong π -accepting properties^{61,62} can also be exploited to stabilize electron-rich centers and paramagnetic species.^{63,64} Indeed, it has been shown that the cationic bis(CAAC) gold **11c** and copper **13f** complexes can be reduced by a potassium mirror and KC_8 , respectively, to offer the bis(CAAC)Au⁶⁵ and Cu⁶⁶ complexes **31** and **32** with the metal in the

formal oxidation state zero (Scheme 9).⁶⁷ In both cases, X-ray diffraction studies revealed a linear geometry with both five-membered ring CAACs being co-planar. The bonding situation for both complexes is very similar. Calculations, using the NBO method, showed that the spin density is localized on the carbene carbons (**31**: 60 %; **32**: 68%) and the nitrogen atoms (**31**: 20 %; **32**: 18%) while only 17 % and 10% resides at gold and copper. The shape of the SOMO indicates that the unpaired electron is delocalized over the $p(\pi)$ AOs of the carbene and the $p(\pi)$ AO of Au; consequently, the electronic configuration of gold is $d^{10}s^0p^1$. Similarly, in complex **32** the copper center has a d^{10} electronic configuration, the unpaired electron being delocalized over two carbene carbon atoms.⁶⁸

Scheme 9. Synthesis of mononuclear gold(0) and copper(0) complexes 31 and 32; solid state structure and SOMO of 31; synthesis and solid state structure of the dinuclear gold(0) complex 33

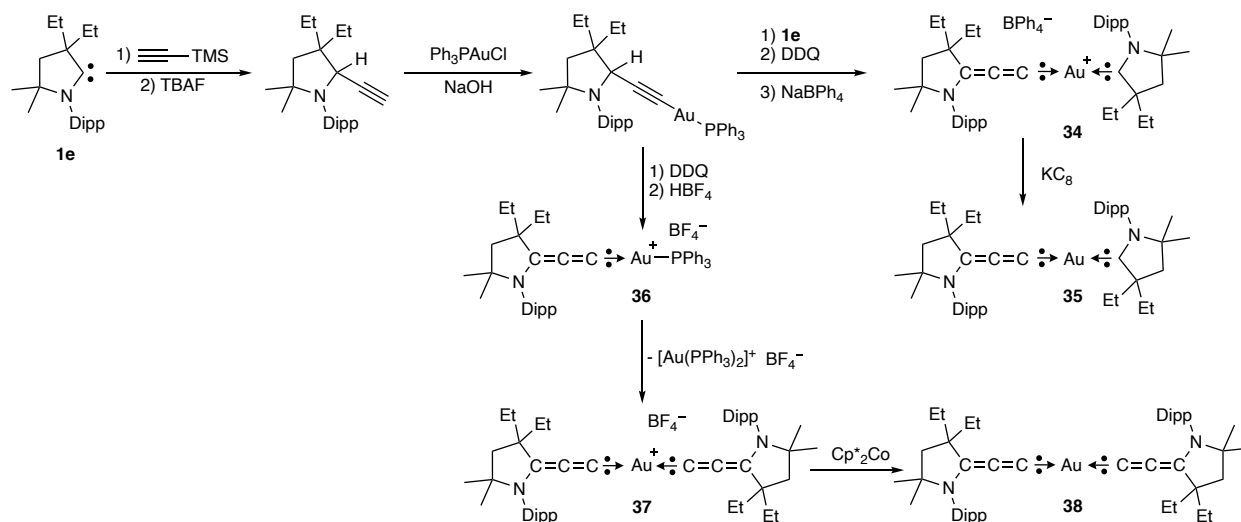


On the other hand, the reduction of the gold complex **9a**, in which the small cyclohexyl-CAAC of **11c** has been replaced by the bulky menthyl-CAAC, gave rise to the dinuclear complex **33** (Scheme 9). As predicted by Schwerdtfeger and Boyd⁶⁹ for the model compound $(H_3P)Au-Au(PH_3)$, the C1-Au1-Au2-C2 skeleton is almost linear and the Au-Au bond short [2.552 Å]. Note that naked Au_2 has a calculated Au-Au bond length of 2.546 Å, which is very close to that observed in **33**. Interestingly, calculations found that in contrast to the mononuclear complex **31**, the Au_2 fragment in **33** binds the ligands through its electronic 2S ($d^{10}s^1p^0, J = 1/2$) ground state. It is important to

note that before this work, apart from elemental gold, the zero oxidation state had only been found in mixed gold(0)/gold(I) complexes,⁷⁰ as exemplified by $[(\text{Ph}_3\text{PAu})_6]^{2+}2(\text{BF}_4^-)$ ⁷¹ and $[(t\text{Bu}_3\text{PAu})_4]^{2+}2(\text{BF}_4^-)$.⁷² A nice demonstration of the efficiency of CAACs to stabilize gold(0) complexes comes from the work of Sadighi *et al.*⁷³ who have shown that, in contrast to **33**, (NHC)Au-Au(NHC) complexes were unstable and led to colloidal gold.

CAACs also allowed for the isolation of neutral, paramagnetic, formally gold(0) (allenylidene)(carbene) and bis(allenylidene) complexes (Scheme 10).⁷⁴ Note that although a large number of allenylidene transition metal complexes are known,⁷⁵ this is rare with gold, and all involve gold(I)⁷⁶ and gold(III).⁷⁷ The (allenylidene)(carbene)Au(I) complex **34** was obtained in a few steps, and subsequent reduction with one equivalent of KC_8 in THF at room temperature, afforded the neutral gold complex **35** as yellow crystals. The Mulliken spin density analysis showed that 93.9% of the spin density resides on the CCC fragment, with only 3.8 and 1.8% located on the CAAC ligand and the Au atom, respectively. Consequently, **35** has very weak gold(0) character, and can be viewed as a gold(I) complex with a paramagnetic anionic ligand.

Scheme 10. Preparation of (allenylidene)(carbene) and bis(allenylidene) gold complexes 35 and 38, respectively



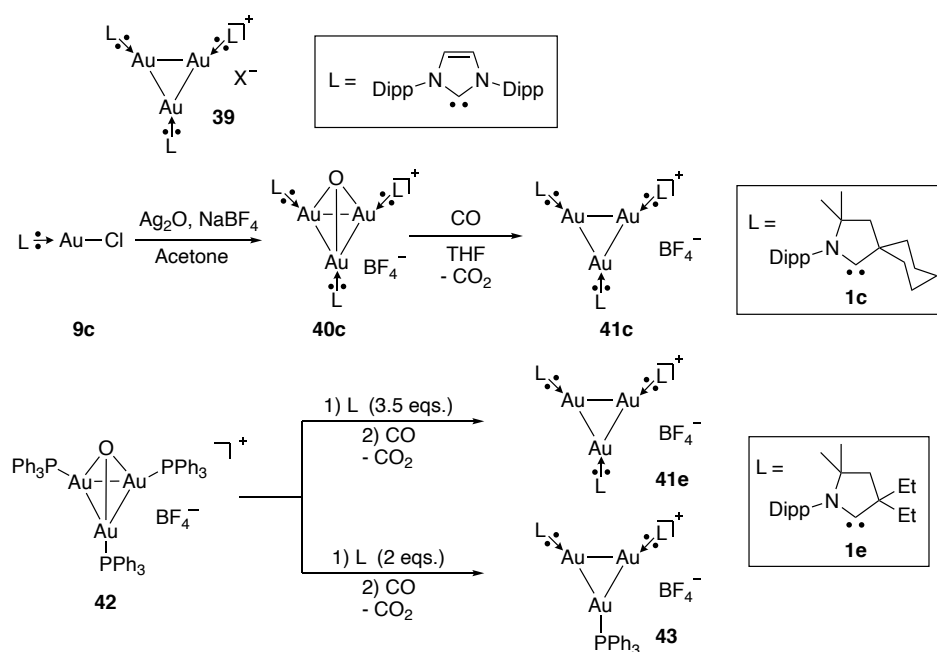
The cationic bis(allenylidene) gold(I) complex **37** can be prepared step by step using the same strategy as for **34**, but also by dismutation of complex **36** (Scheme 10). The cyclic voltammogram

of **37** showed two well-defined one-electron reversible reductions at -1.69 and -2.04 V versus Fc^+/Fc . The first reduction potential is shifted to an even more positive value than that of the (allenylidene)(CAAC)gold(I) complex **34** (-1.73 V) demonstrating that the allenylidene behaves as a stronger π -acceptor than CAACs. However, chemical reduction of **37** resulted in a dark green solution, which was EPR active, but all attempts to grow single crystals of **38** led to decomposition. Notably, only bis(allenylidene) complexes of Ag,⁷⁸ Pd,^{78,79} Pt,⁷⁹ and Ru⁸⁰ have been isolated so far.

2.7. Synthesis of CAAC-Coinage Metal Clusters

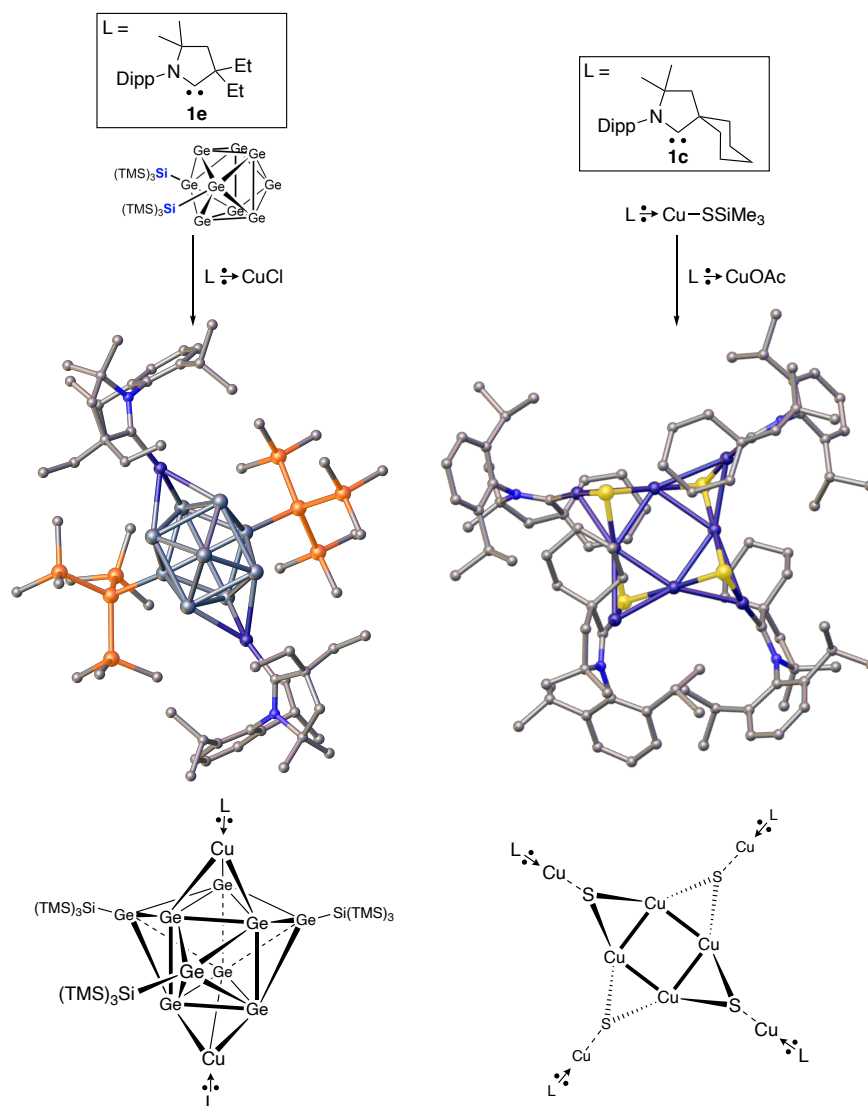
A variety of gold clusters,^{81,82} including nanoparticles are available, and have found numerous applications.^{83,84,85} All of these species are positively charged, and the isolation of **31**, **33** and **35** indicate that CAACs might also be able stabilize neutral clusters of different sizes, mimicking gold surfaces. Therefore, the preparation of the smallest possible clusters, namely tris(gold) clusters, was attempted.⁸⁶ Note that before this work, there was only one example of such a small cluster, namely the NHC supported cluster **39** reported by Sadighi *et al.*⁸⁷ (Scheme 11). Small phosphine-supported gold clusters are usually prepared by reduction of μ_3 -oxo complexes $[(\text{R}_3\text{PAu})_3\text{O}]^+\text{X}^-$ **42**.^{88, 89} Although, it has been reported that the analogous NHC-supported μ_3 -oxo species cannot be prepared,⁸⁷ the reaction of (CAAC)AuCl complex **9c** with Ag_2O , in presence of NaBF_4 , cleanly gave rise to the desired cluster **40c**. Subsequent reduction with carbon monoxide⁹⁰ afforded the cationic tris(gold) cluster **41c**. Interestingly, similar CAAC-supported clusters such as **41e** and mixed (CAAC)(phosphine)-supported cluster **43** can be obtained by ligand exchange, using the readily available phosphine-supported μ_3 -oxo complex **42** as a precursor. Unfortunately, all attempts to obtain the corresponding neutral trinuclear Au(0) clusters failed.

Scheme 11. The only known trinuclear Au cluster 39; preparation of CAAC-Au clusters 41e and 43



To be comprehensive, there are also two reports describing CAAC supported copper clusters (Scheme 12). Fassler *et al.*⁹¹ has explored the coordination of Ge₉ Zintl clusters to (CAAC)Cu(I) fragments. All the resulting clusters feature (η¹-CAAC)Cu(η³-Ge₉) units, and their structures have been compared with analogous clusters supported by NHCs.⁹² Corrigan *et al.*⁹³ prepared a series of phosphorescent homo- and hetero-metallic copper(I)-chalcogenide clusters by the reaction of a copper(I) trimethylsilylchalcogenolate (CAAC)CuESiMe₃ (E = S, Se) with (CAAC)CuOAc).

Scheme 12. Preparation of CAAC copper(I) clusters with main group elements.

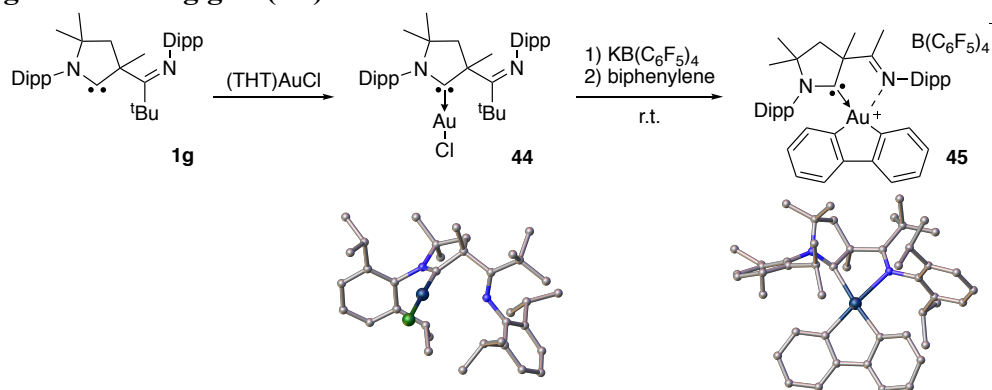


2.8. Synthesis of Hemilabile CAAC-Gold(I) and (III) Complexes. Oxidative addition at Gold(I)

The hemilabile CAAC **1g** has been used as a ligand to access gold(I) complexes, but more interestingly gold(III) complexes (Scheme 13).⁹⁴ Indeed, it is recognized that oxidative addition at gold(I) is kinetically and thermodynamically difficult,^{95,96} but Bourissou *et al.*^{97,98} and Toste *et al.*⁹⁹ have shown that peculiar cationic gold(I) complexes react with biphenylene to give the corresponding gold(III).¹⁰⁰ The imine nitrogen of **1g** does not coordinate the gold(I) center of **44**

(Au–N > 3.39 Å). However, upon addition of biphenylene at room temperature, in the presence of $\text{KB}(\text{C}_6\text{F}_5)_4$, the gold(III) complex **45** was obtained, in which the imine ligand coordinates the gold center (Au–N = 2.25 Å). Since a stoichiometric mixture of monodentate (CAAC)AuCl complex and $\text{KB}(\text{C}_6\text{F}_5)_4$, does not react with biphenylene even upon heating to 80 °C, it can be concluded that the pendant imine moiety stabilizes the gold(III) center. This result suggests that hemilabile bidentate CAACs should be suitable ligands for catalysis involving high oxidation states and might outcompete the corresponding NHCs.¹⁰¹

Scheme 13. The imine nitrogen of **1g** favors the oxidative addition of biphenylene by stabilizing the resulting gold(III) center



2.9. Coordination Chemistry of CAAC-6 and BiCAACs

Six-membered ring CAAC gold(I) complexes have been used to compare the steric properties of CAAC-6 with those of five-membered ring CAACs.⁹ From the X-ray data of **9b** and **46b**, it was found that the corresponding CAAC-6 **2b** has a percent buried volume (%Vbur)^{102,103,104} of 51.2% compared to 47.8% for CAAC **1b** (Figure 2). This is mainly due to the wider carbene bond angle (**2b**: 117.9 °; **1b**: 106.4 °).

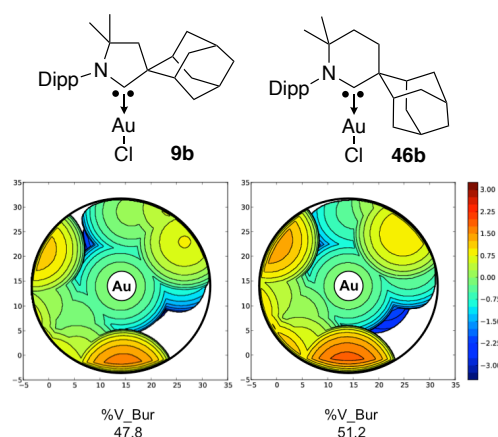
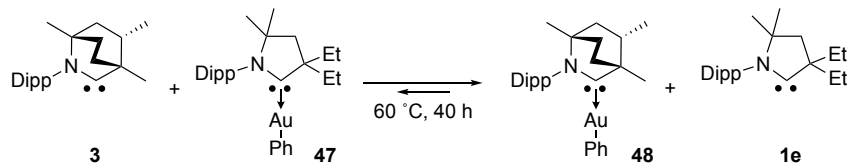


Figure 2. Probing sterics of CAAC-5 versus CAAC-6. Modified with permission from ref 9. Copyright 2018 American Chemical Society.

BiCAAC **3**, due to its higher HOMO and lower LUMO, forms even stronger gold–carbon bonds than CAAC **1e**.¹⁰ Indeed, when one equivalent of BiCAAC **3** was added to the (CAAC)AuPh complex **47**, an equilibrium featuring a 65/35 ratio of (BiCAAC)AuPh **48** and (CAAC)AuPh **47**, along with free CAAC **1e** and BiCAAC **3**, was observed after 40 h at 60 °C (Scheme 14).

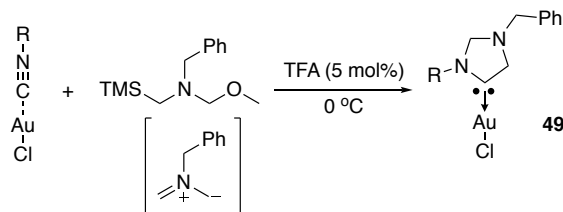
Scheme 14. Ligand exchange reactions at gold showing that BiCAAC **3** forms even stronger gold–carbon bonds than CAAC **1e**



2.10. Synthesis of Saturated Abnormal Carbene and Cyclic (Aryl)(amino)carbene Coinage Metal Complexes

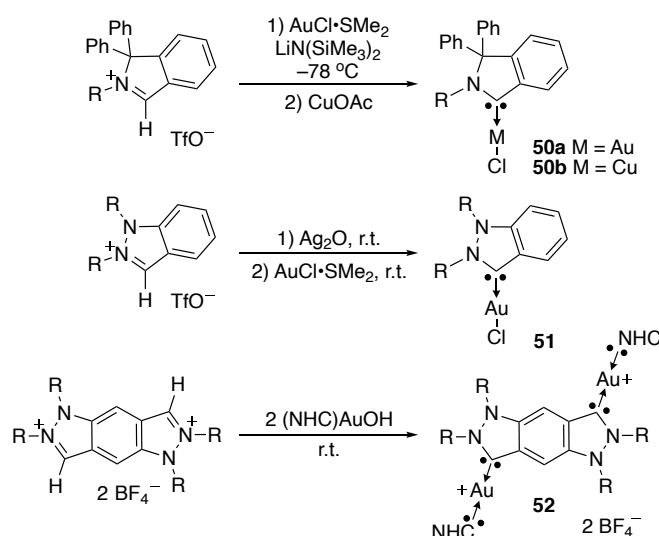
The so-called saturated abnormal carbenes **4** reported by Hashmi *et al.*^{11,105} have not yet been isolated, nor is its cationic precursor readily prepared. Therefore, *sa*NHC-gold complexes **49** have to be synthesized in the coordination sphere of gold, through a [3+2] dipolar cycloaddition of isonitrile gold complexes to an azomethine ylide, generated from the commercially available N-benzyl-N-methoxymethyl-N-(trimethylsilyl)methylamine (Scheme 15).

Scheme 15. Synthesis of the saturated abnormal carbene-gold complex **49**



Cyclic (amino)(aryl)carbenes **5-6** have never been isolated either, but their cationic precursors are readily available. Gold complexes can be prepared by deprotonation of the corresponding aldiminium salts with $\text{LiN}(\text{SiMe}_3)_2$ at -78°C in the presence of $(\text{Me}_2\text{S})\text{AuCl}$ as shown for **50a**,¹² whereas the copper analogue is obtained by treatment of the salt precursor with CuOAc .¹⁰⁶ Alternatively, a transmetallation route can be used as exemplified by the preparation of **51**,^{13,107,108,109} or even by reaction with the Nolan NHC gold(I) hydroxide $[\text{IPrAuOH}]$ ^{32,110} as described by Breher *et al*¹¹¹ for the dinuclear complex **52** (Scheme 16). Note that complexes based on ditopic NHCs, analogous to **52** have been discussed as building blocks for electronically coupled systems.^{112,113}

Scheme 16. Synthesis of cyclic (amino)(aryl)carbene gold and copper complexes



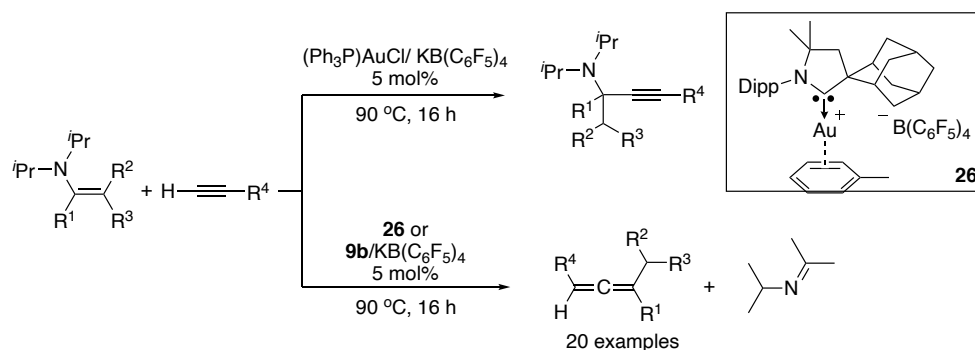
3. CYCLIC (ALKYL)(AMINO)CARBENE COINAGE METAL COMPLEXES IN CATALYSIS

In the past two decades, efficient and selective gold and copper catalysts have been developed to promote a variety of chemical transformations, as evidenced by the number of reviews summarizing various aspects of this growing field.^{114,115,116,117,118,119} Due to the peculiar electronic and steric properties of cyclic (alkyl)(amino)carbenes, their coinage metal complexes were found to be active in new catalytic reactions, which are discussed below.

3.1. Catalytic Cross-Coupling of Two Unsaturated Carbon Centers Leading to Allenes

The first breakthrough in catalysis with (CAAC)gold complexes was the serendipitous discovery that the gold cation **26**, either isolated or prepared *in situ* by mixing (CAAC)AuCl **9b** with one equivalent of $\text{KB}(\text{C}_6\text{F}_5)_4$ in toluene, promotes the cross-coupling of enamines and terminal alkynes to yield allenes (Scheme 17).⁵⁷ This observation was very surprising since this reaction usually affords propargyl amines as observed with other catalysts,¹²⁰ including (CAAC)AuCl **9b** or $(\text{Ph}_3\text{P})\text{AuCl}/\text{KB}(\text{C}_6\text{F}_5)_4$. Mono-, di-, and tri-substituted enamines and aryl-, alkyl-, and trimethylsilyl-substituted alkynes can be used, including sterically hindered substrates.

Scheme 17. In contrast with other catalysts, the (CAAC)gold cation **26 promotes the cross-coupling of enamines and terminal alkynes to yield allenes**

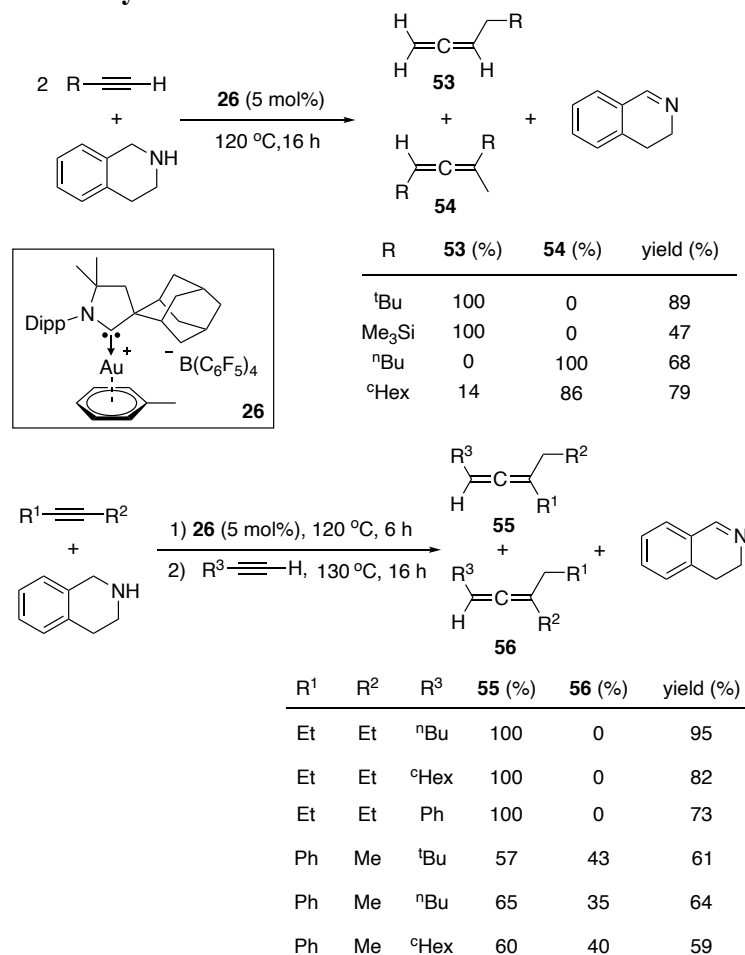


Gold complex **26** is also a very efficient catalyst for hydroamination of alkynes (see Section 3.2.).

Of particular interest, it promotes the addition of secondary amines, which allowed for the

synthesis of tertiary enamines with alkyl substituents at nitrogen.¹²¹ Therefore, taking into account the results discussed above, a one-pot preparation of allenes was developed by coupling two alkynes, using a sacrificial secondary amine. This synthetic strategy was applied to the homo- and hetero-coupling of alkynes. For example, in the presence 1,2,3,4-tetrahydroisoquinoline as dihydrogen donor, the homocoupling of *tert*-butylacetylene gave rise to allene **53** in 89% yield (Scheme 18). This allene results from the *anti*-Markovnikov addition of the amine to the alkyne and the same regioselectivity was observed with trimethylsilylacetylene, probably because of the steric hindrance of both reactants. However, with *n*-butyl acetylene, the allene **54**, resulting from the Markovnikov addition of the amine was formed, whereas with cyclohexylacetylene a 14/86 mixture of the two isomeric allenes **53** and **54** was obtained. For the cross-coupling reaction, a set of four different terminal alkynes was tested with 3-hexyne as an internal alkyne, and again 1,2,3,4-tetrahydroisoquinoline as a sacrificial amine. After heating at 130 °C for 16 h, the expected allenes were obtained in good to excellent yields.

Scheme 18. One-pot preparation of allenes by homo- and heterocoupling of two alkynes, using a sacrificial secondary amine



The coupling of two alkynes to form allenes is one of the very rare chemical transformations that combines two different reactions, yet relies on a single catalyst. Since gold complexes are known for their excellent functional group tolerance, this one-pot process should find applications in the synthesis of complex molecules.

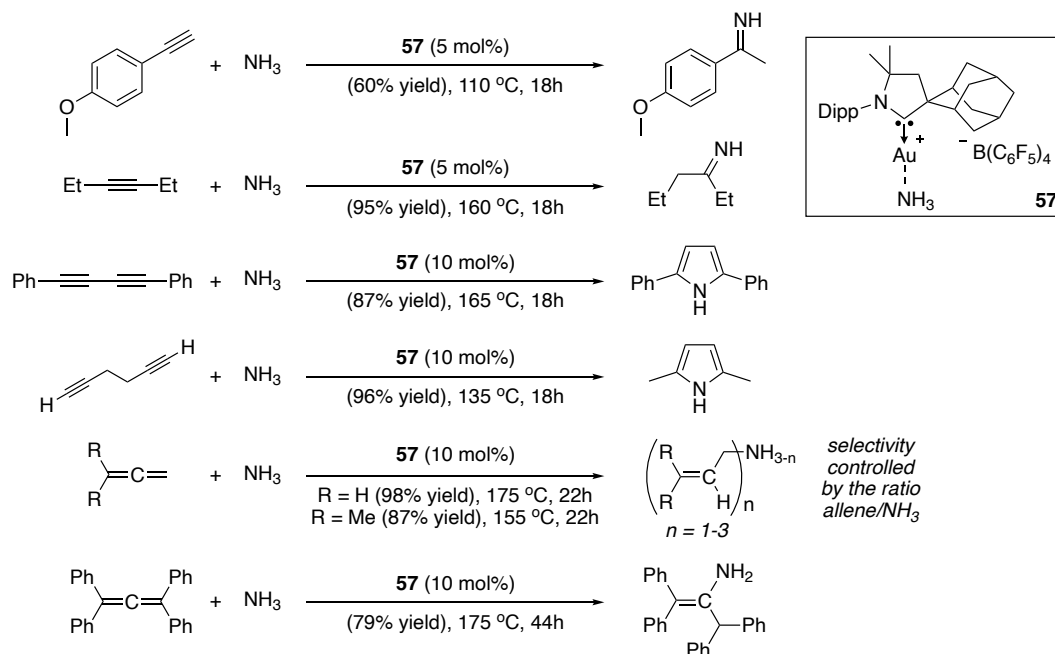
3.2. Gold Catalyzed Hydroamination of Alkynes and Allenes, and Hydroammoniumation and Methylation of Alkynes

Although various homogeneous catalysts,^{122,123} including gold¹²⁴ and copper¹²⁵, have been used to effect the so-called hydroamination reaction, the cationic gold complexes **26** and **57** were the first homogeneous catalysts able to promote the catalytic hydroamination of alkynes and allenes with ammonia (Scheme 19).¹²⁶ Before this discovery, there were only two publications dealing

with the homogeneous catalytic functionalization of NH_3 . Indeed in 2006, Shen and Hartwig,¹²⁷ and Surry and Buchwald¹²⁸ reported the palladium-catalyzed coupling of aryl halides with ammonia in the presence of a stoichiometric amount of base. The difficulties in using NH_3 as a reagent for transition metals^{129, 130, 131} stems from the formation of inert Lewis acid–base complexes, the so-called Werner complexes.

Despite these challenges, in the presence of 5 mol% of $(\text{CAAC})\text{AuNH}_3$ **57**, NH_3 adds to terminal alkynes at 110 °C leading to the Markovnikov imine, whereas for internal alkynes heating at 160 °C is necessary to obtain the expected tautomer of the corresponding enamines (Scheme 19). A very detailed computational study by Ujaque *et al.*¹³² concluded that the electronic properties of CAACs render the formation of the alkyne complex energetically achievable, despite the stability of the Werner complex, thus enabling for the hydroamination reaction to take place. Nitrogen heterocycles, such as pyrroles, could also be prepared in excellent yields in one step from diynes. These products result from the Markovnikov addition of NH_3 , followed by ring-closing hydroamination. The scope of the reaction is not limited to alkynes, complex **57** also promotes the NH_3 hydroamination of allenes. For the parent allene and the 1,1-dialkyl substituted derivative, the NH_2 group adds exclusively at the less-hindered terminus; however mono-, di-, and trisubstituted amines are formed. Tetrasubstituted allenes also undergo hydroamination with ammonia, but a different regioselectivity was observed. The NH_2 fragment adds to the central carbon, probably because of steric factors, and only the monohydroamination product was obtained.

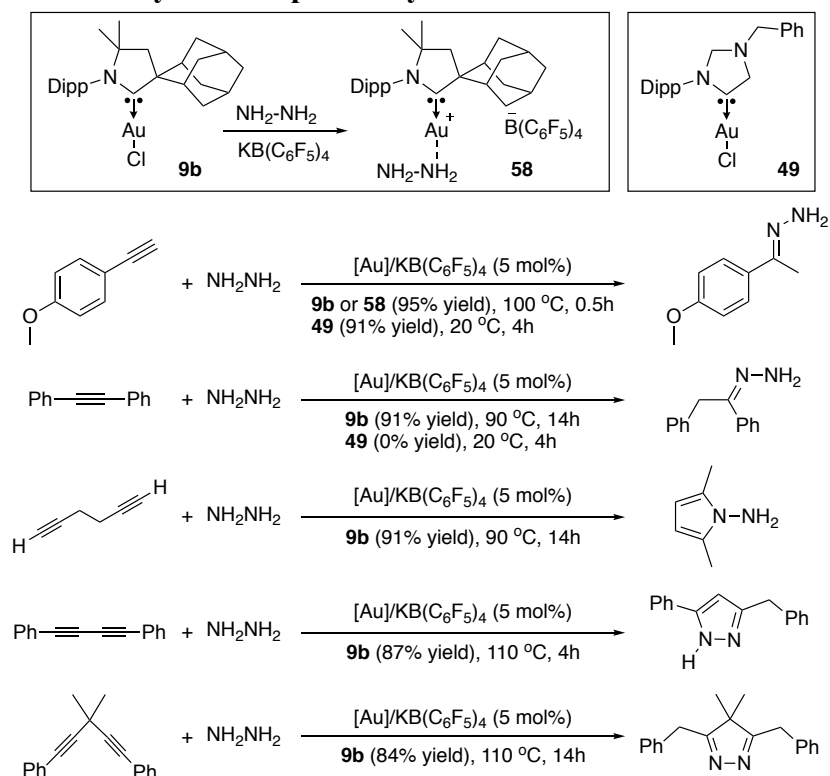
Scheme 19. (CAAC)AuNH₃ complex **57** was the first complex able to promote the hydroamination of alkynes and allenes with ammonia



Like NH₃, parent hydrazine is a difficult substrate for transition metal catalyzed reactions. Before our work,¹³³ there was no report on hydroamination reaction with hydrazine, and only one example of transition-metal catalyzed functionalization of H₂NNH₂, namely the palladium catalyzed cross-coupling with aryl chlorides and tosylates.¹³⁴ There are several difficulties associated with hydrazine. Akin to ammonia, H₂NNH₂ forms inert Werner complexes. In addition, hydrazine is known to be a strong reducing reagent that leads to inactive metal(0) particles. As an illustration, the formation of gold particles has been reported in the reaction of gold chloride with hydrazine,¹³⁵ and cationic trinuclear phosphine–gold complexes of the type (R₃PAu)₃(O)⁺X[–] have been shown to promote the dehydrogenation of H₂NNH₂ to give N₂ complexes.¹³⁶ In contrast, a stoichiometric amount of (CAAC)AuCl **9a**¹³³ and KB(C₆F₅)₄ reacts cleanly with hydrazine to give the corresponding Werner complex **58**, which is active for the hydrohydrazination of a variety of alkynes and bis(alkynes) at rather high temperatures (90–100 °C) (Scheme 20). Interestingly, in the presence of KB(C₆F₅)₄, (*sa*NHC)AuCl complexes **49**¹³⁷ [or even (*anti*-Bredt-NHC)AuCl],^{138,139} in

other words complexes featuring rather π -accepting carbenes, promote the same reaction at room temperature, although the scope of applications is much narrower. Indeed, with complex **49** the hydrohydrazination of alkyl substituted alkynes as well as internal alkynes does not occur. Lledos *et al.*¹⁴⁰ performed a very sophisticated computational study and concluded that the mechanism of the hydrazination reaction involved the substitution of the hydrazine ligand by the alkyne, leading to a gold π -complex. After the nucleophilic attack of hydrazine on the activated carbon-carbon triple bond, nitrogen to carbon atom proton transfer occurs assisted by the nucleophile. Then carbon to nitrogen atom gold migration yields the enamine intermediate. Lastly, a second nucleophile-assisted nitrogen to carbon atom proton transfer leads to the more stable imine tautomer.

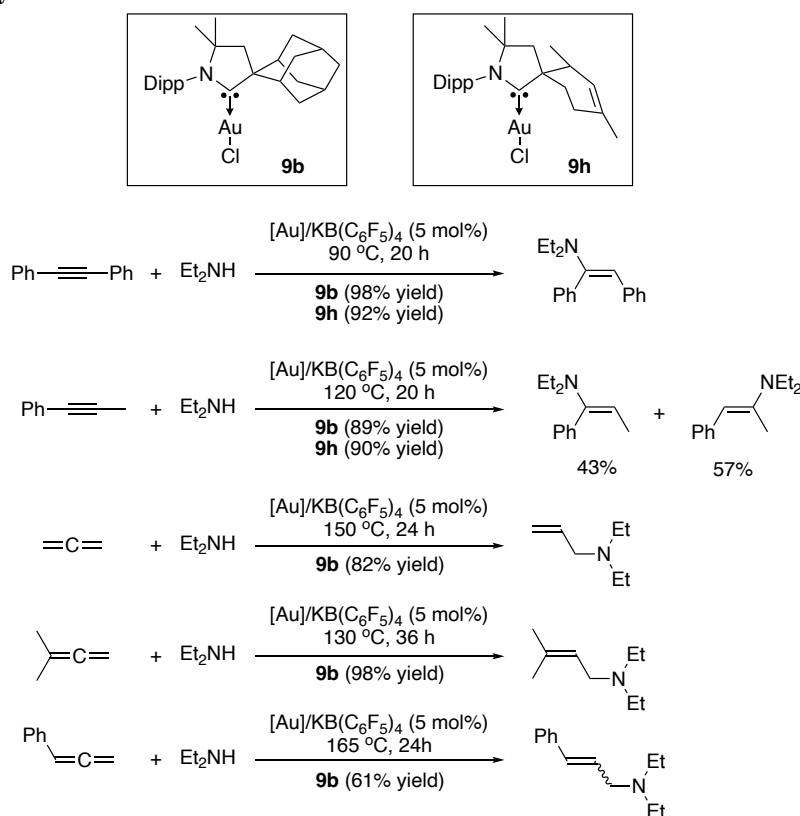
Scheme 20. (CAAC) and (saNHC) gold complexes **58 and **49** promote the hydrohydrazination of alkynes with parent hydrazine**



Secondary dialkylamines are also challenging substrates as they are very basic, and in addition early transition metals cannot be employed to promote hydroamination reactions, because of the

involvement of an imido complex ($LxM=NR$) in the catalytic cycle.¹⁴¹ Consequently, there are very few examples of intermolecular hydroamination reaction with secondary amines. It was found that a stoichiometric amount of $KB(C_6F_5)_4$ and gold(I) complex **9b**¹²¹ or **9g**¹⁴² catalyzes the addition of many types of secondary amines to terminal as well as internal alkynes, including the first examples of intermolecular hydroamination of internal alkynes with secondary alkyl amines (Scheme 21). In the presence of $KB(C_6F_5)_4$, complex **9b** also promotes the hydroamination of allenes with secondary amines, including dialkylamines.¹⁴³ Interestingly, for all the amines considered, the amino fragment always adds to the less substituted terminus of the CCC skeleton, giving access to allyl amines, which are important building blocks.

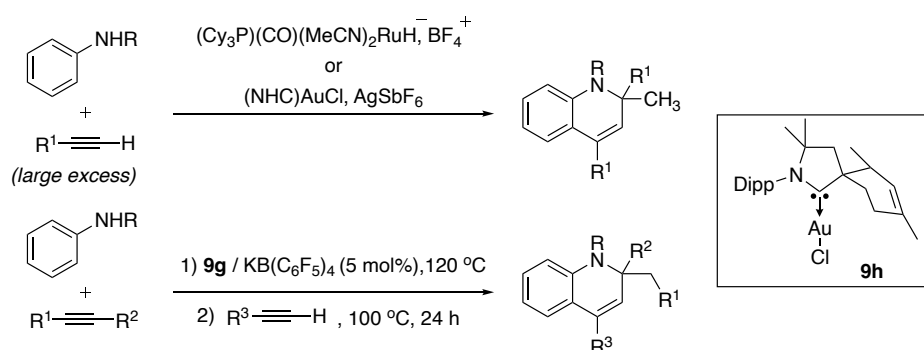
Scheme 21. CAAC-catalyzed intermolecular hydroamination of alkynes and allenes with secondary dialkylamines



In Scheme 18, it was shown that the ability of $(\text{CAAC})\text{Au}^+$ complex **26** to promote the hydroamination of internal alkynes with secondary amines allowed for the one-pot preparation of allenes by coupling two alkynes, using a sacrificial secondary amine. Similarly, following the

works by Yi *et al.*¹⁴⁴ and Che *et al.*,¹⁴⁵ our group developed a one-pot three-component synthesis of 1,2-dihydroquinolines, involving a tandem hydroamination-hydroarylation protocol.¹⁴² Interestingly, for both the ruthenium-based and the (NHC)AuCl/AgSbF₆ catalysts of Yi and Che, respectively, only terminal alkynes could be used and since the second molecule of alkyne reacts quickly, the C2 and C4 substituents are the same (Scheme 22). With a stoichiometric mixture of **9g** and KB(C₆F₅)₄ (5 mol%) the only serious limitation for the three-component cyclization is the use of a terminal alkyne for the second step. Consequently, the dihydroquinoline skeleton can be readily decorated with three different R¹, R² and R³ substituents.

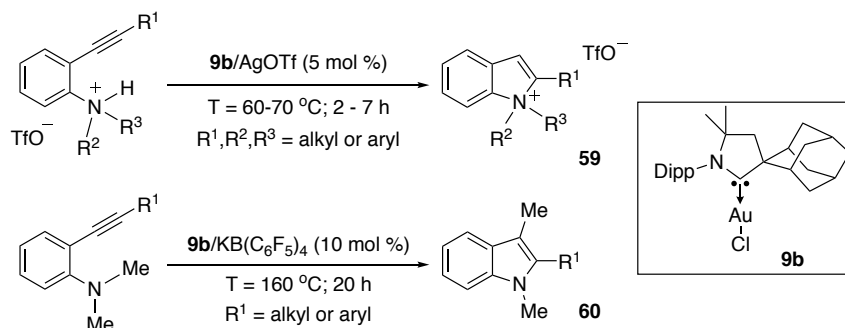
Scheme 22. Comparison of the scope of the previously reported one-pot three-component synthesis of 1,2-dihydroquinolines with that observed with CAAC-gold **9g /KB(C₆F₅)₄**



In the course of mechanistic studies of the gold-catalyzed hydroamination of alkynes, two novel reactions were discovered, namely the intramolecular hydroammoniumation and aminomethylation of carbon–carbon triple bonds (Scheme 23).¹⁴⁶ Indeed, it was found that in the presence of 5 mol% of a 1:1 mixture of complex **9b** and AgOTf, the conjugate acid of 2-alkynylbenzenamines undergo cyclization affording **59** in excellent yield after a few hours at 60 - 70 °C. Aryl and alkyl substituents are tolerated on the alkyne and on the amine, and not surprisingly the cyclization is facilitated when weakly basic amines are used. Examples of direct addition of a carbon–nitrogen bond to a carbon–carbon triple bond are very rare, and involve relatively weak C-N bonds, such as in allylamines or amides.^{147,148} However, 10 mol% of a 1:1 mixture of complex **9b** and KB(C₆F₅)₄ promotes the intramolecular aminomethylation of 2-alkynyl-N,N'-dimethyl-

benzenamines giving rise to the corresponding indoles **60** in very good yields after 20 h at 160 °C. This cyclization tolerates aryl or alkyl substituents on the alkyne, but is limited to N,N'-dimethylbenzenamines.

Scheme 23. Intramolecular hydroammoniumation and aminomethylation of carbon–carbon triple bonds giving **59 and **60**, respectively**



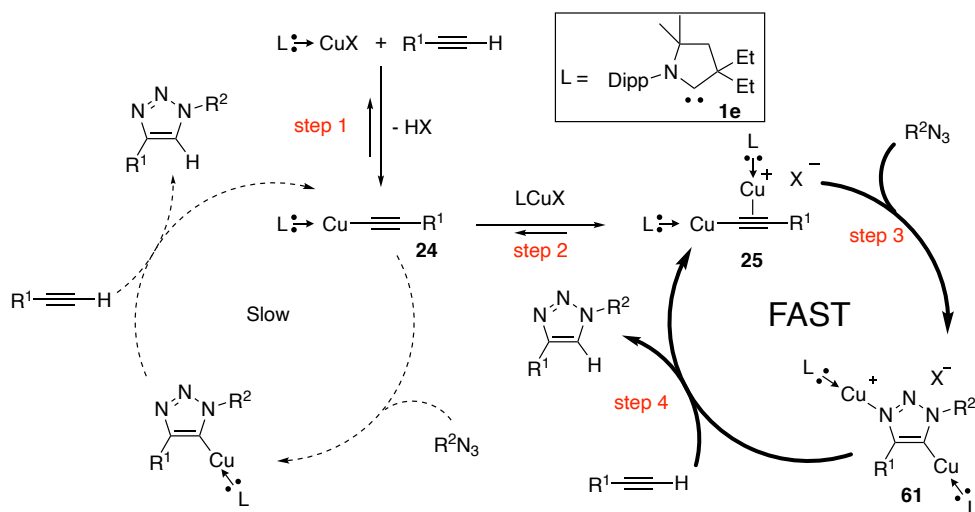
Importantly, many of the reactions described in this section required very drastic conditions, as exemplified by the NH_3 hydroamination of tetrasubstituted allenes, which requires 44 hours at 175 °C (Scheme 19). This is a clear demonstration of the very unusual thermal stability of cationic (CAAC)gold(I) complexes, which is due to the peculiar electronic properties of CAACs.

3.3. (CAAC)-Mono- and -Bis-(copper)acetylide Complexes in Catalysis.

The isolation of the mono- and bis-(copper)acetylide complexes **24** and **25**⁵¹ has not only allowed for a better understanding of the mechanism of the Cu-catalyzed azide-alkyne “click reaction”, but has also led to the development of novel copper-catalyzed reactions.

For the CuAAC, it has been possible to demonstrate several important features of the mechanism. Although both **24** and **25** are active in the catalytic cycle, the dinuclear complex **25** is involved in the kinetically favored pathway (Scheme 24). The resting state of the catalytic cycle is the bis(copper) triazole complex **61**. Lastly, the alkyne serves as the proton source for the demetallation of **61**, which regenerates **25**, leaving out the mononuclear complex **24** from the catalytic cycle.

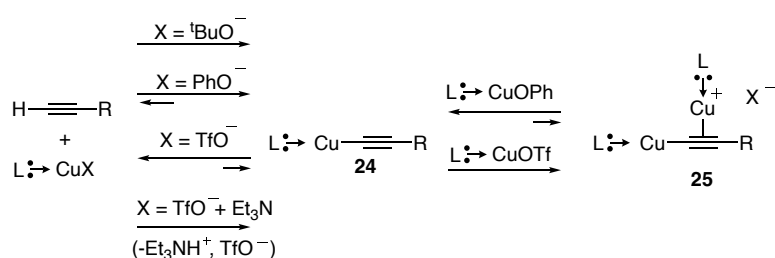
Scheme 24. Both the mono-copper **24** and the bis-copper acetylide **25** are active in the CuAAC reaction, but the latter is more efficient. The alkyne is the proton source for the demetallation step, which regenerates **25**, thereby excluding **24** from the preferred catalytic cycle. Reproduced with permission from ref 51. Copyright 2015 AAAS.



The CuAAC reactions promoted by CAAC-supported copper complexes are slow enough to be monitored, and to study the successive steps of the catalytic cycle. Of particular interest, the influence of the X ligand has been investigated by carrying out stoichiometric reactions.¹⁴⁹ For the metalation step giving **24** (step 1), which involves a deprotonation of the alkyne, basic ligands are the most efficient (Scheme 25). Indeed, with $X = tBuO$, the metalation is fast and irreversible, whereas with PhO , a dynamic equilibrium can only be observed by NMR. Lastly, with TfO , no spectroscopic evidence for the formation of **24** can be found, but the latter can be obtained by adding an external base like triethylamine. In contrast, the formation of the bis(copper)acetylide **25** (step 2) is favored by non-nucleophilic ligands with TfO being the best. For step 3, the bis(copper)triazole **61** was only observed when $X = TfO$; but when $X = Cl$, AcO , or PhO , a C-monometallated triazole was obtained. For the last step of the catalytic cycle, namely the proto-demetalation of triazole by the alkyne (step 4), all X ligands performed similarly (k_{obs} between $0.5 \cdot 10^{-4} \text{ s}^{-1}$ and $2.2 \cdot 10^{-4} \text{ s}^{-1}$), except for the acetate ($k_{obs} > 370 \cdot 10^{-4} \text{ s}^{-1}$). This acceleration is characteristic of a base assisted proton transfer mechanism as observed in biological systems.¹⁵⁰

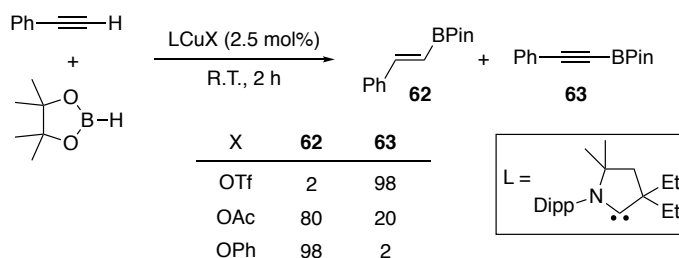
From these results, it appears that the acetate is a good compromise, basic enough for the metalation step, not too nucleophilic to prevent the formation of the bis(copper)acetylide **25**, and very efficient in promoting the proto-demetalation step. This rationalized why the acetate is often used in CuAAC reactions.

Scheme 25. Influence of the X ligand on the first two steps of the CuAAC reaction

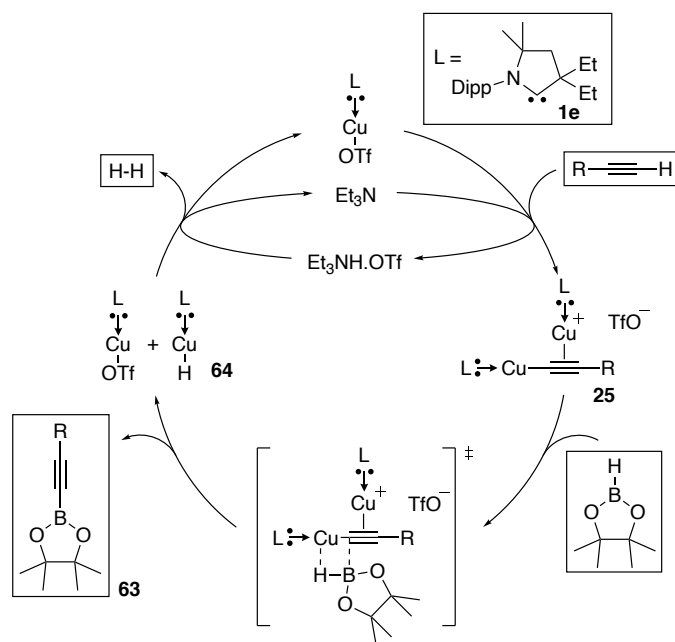


The knowledge of the influence of the X ligand¹⁵¹ on the formation of **24** versus **25** has allowed for the rational design of copper catalysts that selectively promote either the hydroboration¹⁵² or the dehydrogenative borylation¹⁵³ of terminal alkynes with pinacolborane (Scheme 26). Indeed, in complexes **24**, which can be prepared with LCuOPh, the triple bond is available for hydroboration leading to alkenyl boronic esters **62**. In contrast, in dinuclear complexes **25**, which are readily obtained by reacting LCuOTf with terminal alkynes in the presence of triethylamine with ammonium triflate as the byproduct, the triple bond is protected. The polarized copper–carbon bond of **25** can undergo a σ -bond metathesis with pinacolborane giving rise to the alkynyl boronic ester **63**, along with the copper hydride **64** (Scheme 27). The latter reacts with ammonium triflate to regenerate LCuOTf and triethylamine with the elimination of dihydrogen.

Scheme 26. Influence of the X ligand on the fate of the reaction of pinacolborane with phenyl acetylene



Scheme 27. Postulated catalytic cycle for the dehydrogenative borylation of terminal alkynes with pinacolborane. Modified with permission from ref 153. Copyright 2017 Royal Chemical Society.



Both the dehydrogenative borylation and the hydroboration processes are readily applicable to a broad range of terminal alkynes bearing functionalities such as OMe, CN, F, Cl, TMS and CO₂Me. Importantly, the alkenyl (**62**) and alkynyl boronic esters (**63**) were isolated in good to excellent yields via simple filtration through a short plug of dry neutral alumina. This straightforward protocol allows for gram-scale synthesis of these boronic esters.

Note that the catalytic dehydrogenative borylation of C(sp³)-H and C(sp²)-H bonds discovered by Hartwig *et al.*¹⁵⁴ and Smith *et al.*¹⁵⁵ are well studied.¹⁵⁶ In contrast, there are only a few reports by Ozerov *et al.*^{157,158,159} for C(sp)-H bonds, using iridium and palladium complexes supported by pincer ligands, and one by Tsuchimoto *et al.*¹⁶⁰ with zinc triflate, which has a rather narrow scope.

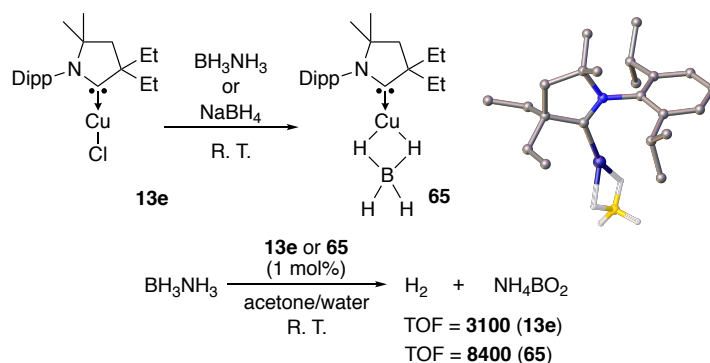
3.4. (CAAC)-Coinage Metals for the Activation of Small Molecules

3.4.1. (CAAC)-CuBH₄ Complexes for the Catalytic Hydrolytic Dehydrogenation of BH₃NH₃ and for the Reduction of CO₂ into Formate with H₂.

Ammonia borane (BH₃NH₃) and metal borohydrides M(BH₄)_n are excellent hydrogen storage materials.¹⁶¹ Developing catalysts based on cheap transition metals capable of releasing H₂ at room

temperature with a high rate of hydrogen generation is vital for the large-scale application of these inorganic compounds.¹⁶² It was first observed that the CAAC copper complex **13e** reacts with BH_3NH_3 or NaBH_4 to give **65** in which two hydrogen atoms of BH_4 interact with the metal (Scheme 28). Interestingly, in contrast to other LCuBH_4 complexes, as exemplified by $(\text{Ph}_3\text{P})\text{CuBH}_4$ which decomposes at $-20\text{ }^\circ\text{C}$,¹⁶³ **65** is perfectly stable at room temperature. Then, it was found that $(\text{CAAC})\text{CuBH}_4$ **65** and $(\text{CAAC})\text{CuCl}$ **13e** complexes are highly efficient catalyst for the hydrolytic dehydrogenation of BH_3NH_3 .²⁶ Indeed, when a 1 mol% acetone/water solution of **13e** was added to BH_3NH_3 , 2.6 moles of H_2 were released per mole of BH_3NH_3 over 5 minutes, which corresponds to a turnover frequency (TOF) of 3100 mol of H_2 per mol of **13e** per hour. More impressive, by using 1 mol% of **65**, the hydrolytic dehydrogenation reaction was finished within 2 minutes at room temperature, with 2.8 moles of H_2 released per mole of BH_3NH_3 , thus giving a TOF of 8400. This TOF is more than 1000 times higher than that reported with CuCl_2 ,¹⁶⁴ and compares well with those obtained in the hydrolytic dehydrogenation of ammonia borane promoted by noble metal catalysts.¹⁶¹ Importantly, **13e** and **65** are very robust. The catalytic solution can be handled in air and recycled more than 15 times without significant loss of activity.

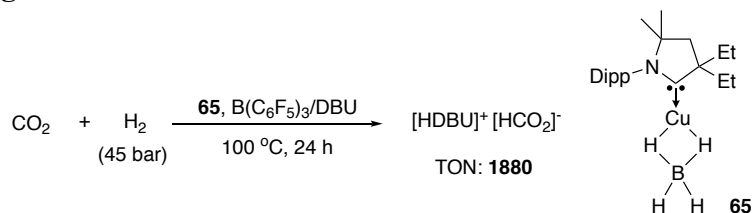
Scheme 28. Preparation of $(\text{CAAC})\text{CuBH}_4$ **65 and hydrolytic dehydrogenation of BH_3NH_3**



Following the pioneering work of Inoue *et al.*,¹⁶⁵ the reduction of CO_2 into formic acid with H_2 has successfully been performed with a variety of noble metal catalysts¹⁶⁶ and TONs up

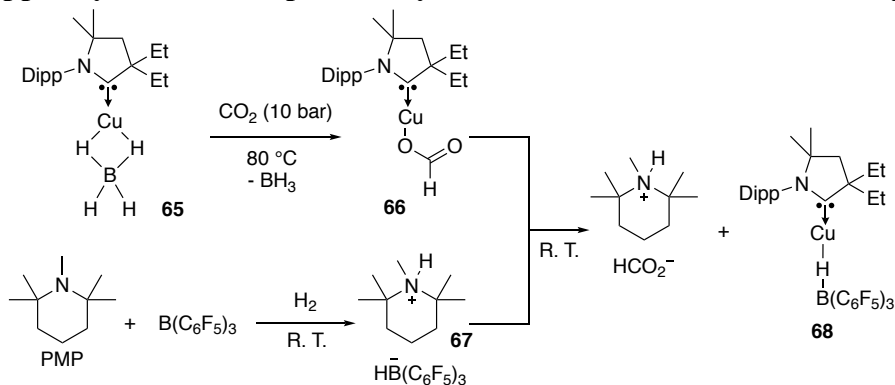
to 3,500,000.¹⁶⁷ However, this is not the case with abundant and inexpensive first-row metals such as copper. Indeed, although copper hydrides efficiently insert CO₂ as shown by the numerous copper-catalyzed carboxylation reactions,^{168, 169} they have difficulty activating molecular hydrogen; consequently, TONs below 500 are usually obtained.¹⁷⁰ On the other hand, frustrated Lewis pairs (FLPs)^{171,172} are well-known to activate H₂^{173,174} but cannot reduce CO₂ catalytically because of the formation of a strong B–O bond.¹⁷⁵ It then became reasonable to believe that a copper hydride activating CO₂, working in tandem with a Lewis pair as H₂ activator, would provide an efficient synergy for the catalytic reduction of CO₂ with H₂. Indeed, it was found that using the copper borohydride complex **65** as a copper hydride surrogate and B(C₆F₅)₃/DBU as the frustrated Lewis pair, CO₂ was cleanly reduced into the formate after 24 hours at 100 °C with TONs reaching 1880 (Scheme 29).^{176,177}

Scheme 29. Tandem copper hydride–Lewis pair catalyzed reduction of carbon dioxide into formate with dihydrogen.



Interestingly, the elementary steps of the catalytic cycle were reproduced stoichiometrically (Scheme 30). The copper borohydride complex **65** reacted with CO₂ (10 bar) at 80 °C giving the insertion product **66** upon elimination of BH₃. Then it was confirmed that a known FLP, namely B(C₆F₅)₃ and 1,2,2,6,6-pentamethylpiperidine (PMP), cleaved molecular hydrogen to give **67**.¹⁷⁸ Lastly, it was shown that at room temperature a stoichiometric amount of **66** reacted within minutes with **67** to give the formate and the borane-stabilized monomeric (CAAC)CuH–BCF adduct **68**.

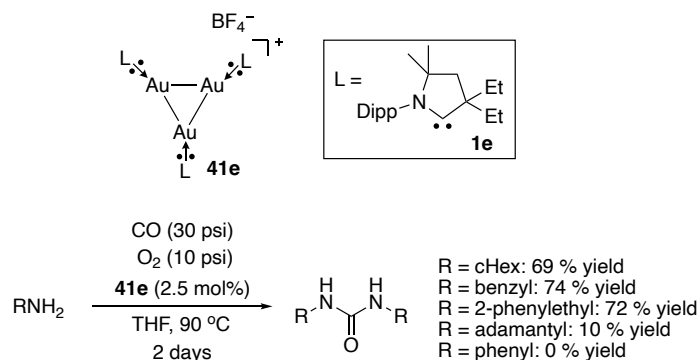
Scheme 30. Stoichiometric reactions mimicking the elementary steps of the catalytic cycle of the tandem copper hydride–Lewis pair catalyzed reduction of carbon dioxide by H₂



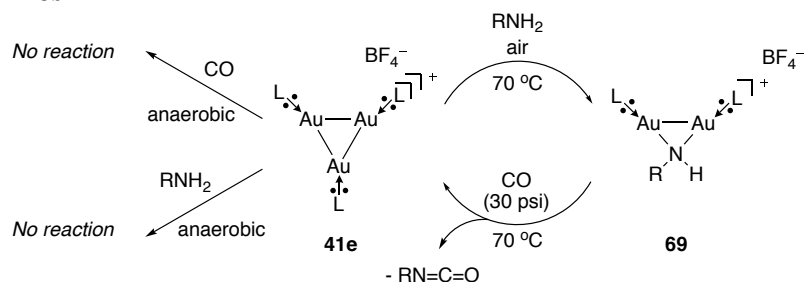
These results suggest that the synergy between a transition metal center and a Lewis pair could be extended to other reactions.

3.4.2. Trinuclear (CAAC) Gold Clusters as Catalysts for the Carbonylation of Amines

In 2012 Corma *et al.*^{179, 180, 181} reported that very small metallic gold clusters could display catalytic activities that are much higher than those obtained with gold nanoparticles and mononuclear homogeneous gold catalysts. This striking discovery led to the question of whether very small, well-defined clusters, capped with ligands, such as **40-43** (Scheme 11), could also behave as efficient catalysts.⁸⁶ To tackle this question, the carbonylation of amines, which is the simplest and most environmentally friendly route for the preparation of urea derivatives,¹⁸² was chosen. It was found that 2.5 mol% of trinuclear gold complex **41e** catalyzed the carbonylation of cyclohexylamine under 30 psi of CO and 10 psi of O₂. After 2 days at 90 °C, the N,N'-dicyclohexylurea was formed in 69% yield (Scheme 31). Similarly, benzyl amine and 2-phenylethylamine were converted into the corresponding urea in 74% and 72% yields, respectively. In the case of the more sterically hindered substrates, such as 2-adamantylamine, the conversion was significantly decreased, while no reaction was observed with the less basic aniline. Importantly, no decomposition of **41e** could be observed during these reactions, demonstrating its robustness.

Scheme 31. Carbonylation of amines catalyzed by the trinuclear gold cluster **41e**


The well-defined nature of **41e** allowed for a mechanistic study of the carbonylation reaction. It has been found that CO does not react with **41e** or the amine in the absence of air. However, **41e** reacts with cyclohexylamine in the presence of oxygen, leading after two days at 70 °C to the dinuclear complex **69**, which was isolated (Scheme 32). Then, when CO was added to **69**, the trinuclear cluster **41e** was recovered along with cyclohexyl isocyanate and traces of urea. Note that upon addition of amine, which transforms **41e** into **69**, two gold centers are oxidized, while in the addition of CO to **69** giving back **41**, two gold centers are reduced. This is a very rare example of a gold catalyzed process involving a definite change of oxidation state of the metal.^{183,184,185}

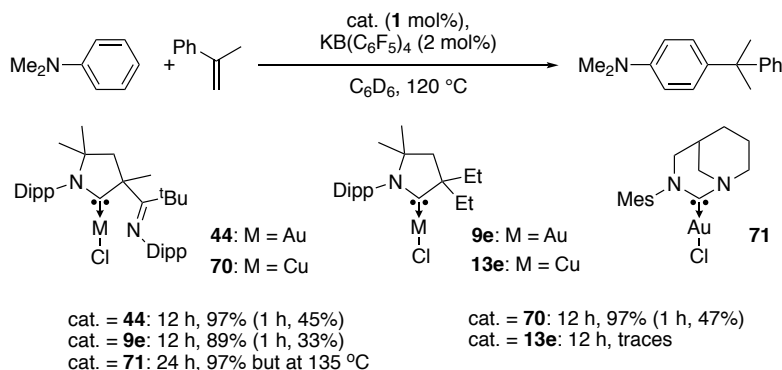
Scheme 32. Stoichiometric reactions for a better understanding of the catalytic cycle of the carbonylation of amines


3.5. Miscellaneous

3.5.1. (CAAC)-Gold and -Copper Catalysts for the Hydroarylation of Styrene with Anilines

Friedel–Crafts reactions, such as the intermolecular hydroarylation of alkenes,^{186,187} usually require Lewis acid catalysts, and are therefore rarely efficient for basic substrates, such as amines. However, in the presence of $\text{KB}(\text{C}_6\text{F}_5)_4$, the (CAAC)AuCl complex **44**, featuring the hemilabile CAAC **1g**, promoted the hydroarylation of α -methylstyrene with N,N-dimethyl aniline (Scheme 33).⁹⁴ A 97% conversion was observed after only 12 h at 120 °C, which is slightly better than that with the CAAC supported gold complex **9e**, and even the *anti*-Bredt gold complex **71**, which requires 24 h at 135 °C.¹⁸⁸ Even more striking, the analogous copper complex **70** also promotes the same hydroarylation reaction at 120 °C with a 97% conversion after 12 h. Importantly, under the same experimental conditions, the monodentate CAAC copper complex **13e** gave only traces of the hydroarylation product. The superiority of complex **70** over **13e** might be due to the presence of a basic moiety on the side chain of the CAAC ligand, which could assist a formal proton transfer. Although examples of intramolecular copper-catalyzed hydroarylation of alkenes have been reported,¹⁸⁹ **70** was the first copper complex able to promote the intermolecular version.

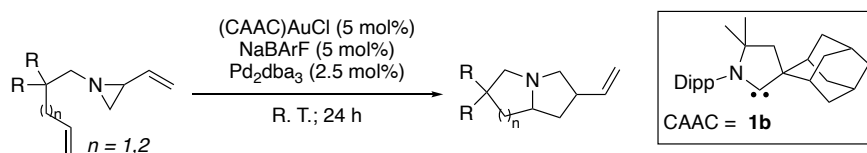
Scheme 33. Comparison of (carbene)-gold and -copper catalysts for the hydroarylation of α -methylstyrene with anilines



3.5.2. (CAAC)Gold(I) Complexes in Gold/Palladium Dual Catalysis

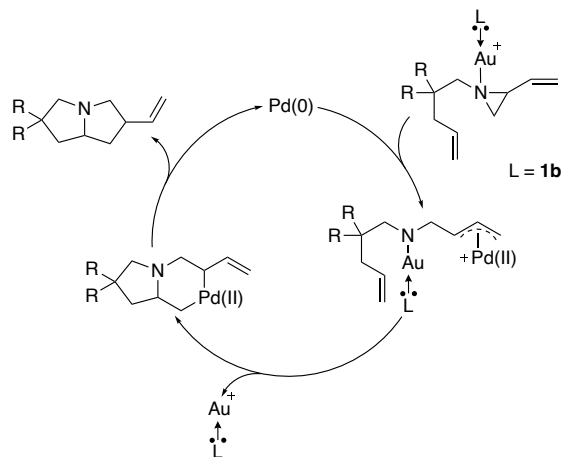
Blum *et al.* developed elegant dual-catalytic systems combining the Lewis acidic activity of Au(I) with a Lewis basic transition metal catalyst.^{190,191} They reported that a stoichiometric mixture of (CAAC)AuCl **13b** and NaBAr^F (5 mol%), with Pd₂dba₃ (2.5 mol%) promotes at room temperature the rearrangement of vinyl aziridines into pyrrolizidine and indolizidine frameworks (Scheme 34).¹⁹² The scope of the reaction is reasonably broad as long as bulky R substituents are used to increase the Thorpe-Ingold effect. Methyl substitution at the internal position of the tethered alkene was tolerated, as well as increasing the olefin tether length.

Scheme 34. Gold/palladium promoted rearrangement of vinyl aziridines into pyrrolizidines



Following a very detailed mechanistic study, the authors concluded that the reaction did not proceed through carbophilic Au(I) catalysis. Instead, the Au(I) complex would act as an azaphilic Lewis acid helping the aziridine oxidative addition to Pd(0) (Scheme 35). The resulting Pd(II) intermediate would then undergo a *syn*-aminometalation, followed by a reductive elimination from the palladacyclic intermediate. This mechanistic hypothesis seems to contradict most of the reports emphasizing the carbophilicity of Au(I) towards carbon-carbon multiple bonds. However, most of these reports deal with alkynes, and therefore, the competitive binding of gold to heteroatoms should be seriously considered, when alkenes are involved.

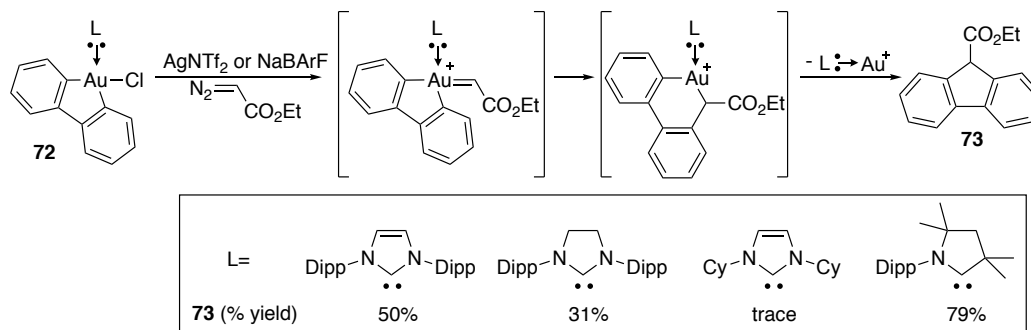
Scheme 35. Postulated catalytic cycle for the gold/palladium promoted rearrangement of vinyl aziridines into pyrrolizidines. Modified with permission from ref 191. Copyright 2012 American Chemical Society.



3.5.3. (CAAC)-Gold(III) Complexes in Migratory Insertion of Carbenes into Au(III)-C Bonds.

In 2018, Toste *et al.*¹⁹³ reported the first examples of migratory insertion of carbenes generated from silyl- or carbonyl- diazoalkanes into Au–carbon bonds. Indeed, abstraction of chloride from **72** with AgNTf₂ or NaBAR^F followed by addition of ethyl diazoacetate at room temperature, led to the formation of the fluorene derivative **73** as the major product (Scheme 36). This reaction appeared very sensitive to the experimental conditions used, especially the solvent and the amount of water, and its scope is rather limited. Interestingly for this Focus Review, a detailed study of the influence of the ligand has been done, and CAACs led to the highest yields, presumably through promotion of reductive elimination after migratory insertion in favor of other processes. It is noteworthy that although the migratory insertion of unsaturated carbon-based species into metal–carbon bonds is well-established for most transition metals,¹⁹⁴ this is not the case for gold,^{195,196,197} with rare exceptions.¹⁹⁸ Therefore, as concluded by the authors, “This study paves the way for homogeneous gold-catalyzed processes incorporating carbene migratory insertion steps.”

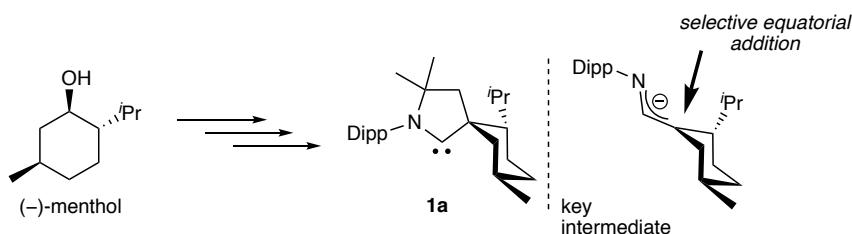
Scheme 36. The superiority of CAAC ligands for the migratory insertion of carbenes generated from diazoalkanes into Au–carbon bonds.



3.6. Chiral CAAC Ligands in Enantioselective Catalysis

Chiral NHCs were first used as ligands for transition metal-based catalysts in 1996.^{199,200} However, up until now, only imidazol-2-ylidenes **7**, imidazolidin-2-ylidenes **8** and 1,2,4-triazol-5-ylidenes (Enders carbene)²⁰¹ have been used as ligands for enantioselective transformations.²⁰² Since CAACs feature a quaternary carbon adjacent to the carbene carbon, and thus in closer proximity to the active site than NHCs, it is surprising that the first report of their use as ligands in enantioselective catalysis only appeared in 2019.²⁰³ This is even more astonishing since already in 2005, it has been shown that enantiopure CAACs, such as **1a**, could be prepared without enantio- or diastereo-selective separations from inexpensive starting materials such as (-)-menthol.¹ The key step of the synthesis of enantiopure CAACs is based on the well-known propensity of bulky reactants to approach the cyclohexane moiety selectively from the equatorial direction, as shown for the menthylCAAC **1a** (Scheme 37).

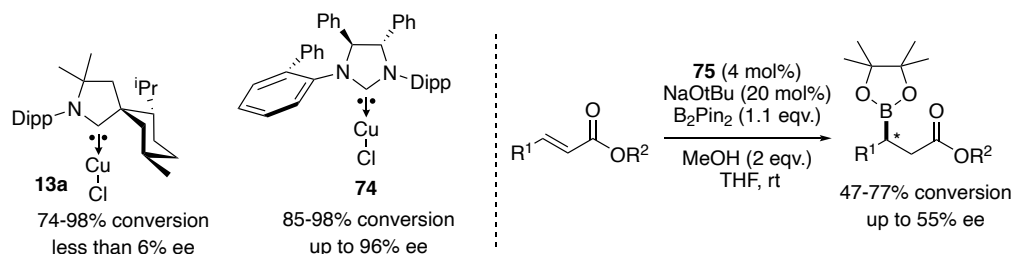
Scheme 37. Synthesis of the enantiopure menthyl-CAAC **1a** with the key step



The menthyl-CAAC **1a** was benchmarked in the copper-catalyzed asymmetric conjugate borylation reaction, a chemical transformation which allows for the preparation of very useful

chiral organoboron building blocks.^{204,205} Although the menthyl CAAC copper complex **13a** was very active in the addition of bis(pinacolato)diboron to various α,β -unsaturated esters, an almost complete lack of asymmetric induction was observed (Scheme 38). In comparison, Hoveyda reported that the chiral NHC copper complex **74** gave β -boryl carbonyl compounds in up to 96% ee.²⁰⁶

Scheme 38. Comparing menthylCAAC-CuCl **13a, NHC-CuCl **74** and cholesterolCAAC-CuCl **75** in the asymmetric conjugate borylation reaction**



The absence of enantioselectivity observed with **13a** is believed to be due to a conformational inversion of the menthyl ring,²⁰⁷ since the two conformers have antagonistic stereo-inducing effects (Figure 3).

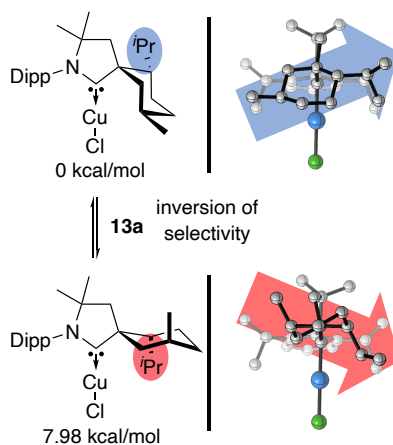


Figure 3. Proposed justification for the lack of asymmetric induction with catalyst **13a**. Adapted with permission from ref 207. Copyright 2019 American Chemical Society.

To circumvent this issue, a more rigid chiral CAAC was prepared, using once again a precursor derived from the chiral pool, namely the 5 α -cholestan-3-one. The X-ray data of the

corresponding copper complex **75** show a distinctive orientation of the cholestanyl backbone, which gives rise to the topographic steric map showed in Figure 4. As can be seen, the corresponding quadrant diagram suggests facial stereoselectivity in catalyst-substrate adducts. As the menthylCAAC-CuCl **13a**, the cholesterolCAAC-CuCl **75** readily promotes the asymmetric conjugate borylation in moderate to good isolated yields (47 to 77%), but with enantiomeric excesses reaching 55% (Scheme 38).

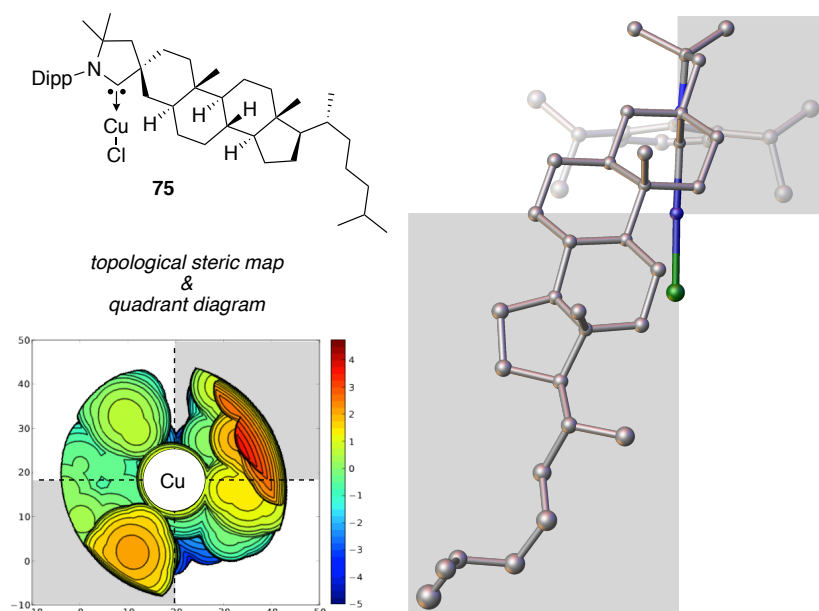


Figure 4. X-ray crystal structure of **75** and an overlaid topological steric map with a quadrant diagram. Adapted with permission from ref 207. Copyright 2019 American Chemical Society.

These results suggest that the use of chiral CAACs should not be overlooked in metal-catalyzed asymmetric transformations. These carbenes are readily available from precursors belonging to the chiral pool, not restricted to chiral amines (as for NHCs), but extends to chiral aldehydes, a much larger feedstock.

4. BIOLOGICAL APPLICATIONS OF CYCLIC (ALKYL)(AMINO)CARBENE COINAGE METAL COMPLEXES

The biological properties of coinage metal NHC complexes (NHC = imidazol-2-ylidenes **7** and imidazolidin-2-ylidenes **8**) have been widely investigated, and are the subject of numerous reviews.^{18,208,209,210,211} NHC-gold complexes show antimicrobial activity in several bacterial

strains, they are antioxidant and antiparasitic agents that could be relevant in diseases such as leishmaniasis where there is no optimal drug treatment, and they have antitumor activity. NHC-Ag complexes have been shown to be effective against a wide range of both Gram-positive and Gram-negative bacterial strains, and they feature comparable or better antitumor activity than standard chemotherapeutics such as cisplatin and 5-fluorouracil.

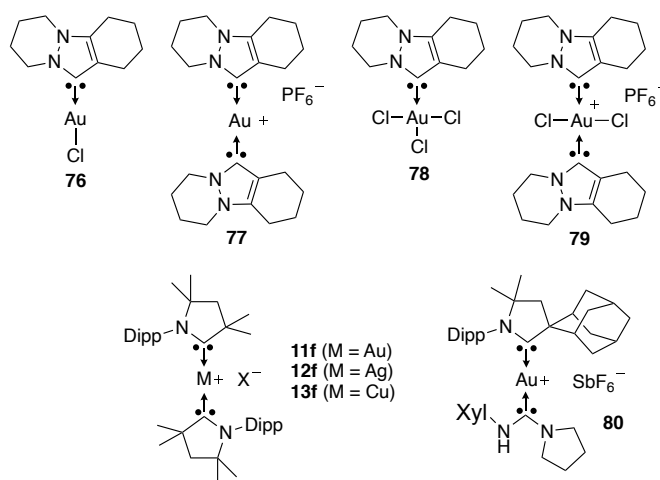
The success of NHC-coinage metal complexes in medicinal applications has been rationalized by their great stability in biological media, which is due to their robustness towards ligand dissociation. Since cyclic (alkyl)- and (aryl)-(amino)carbene-coinage metal bonds are even stronger than those of NHCs, it seems reasonable to believe that these complexes could find medicinal applications. However, this field is still in its infancy.

In 2012, Huynh *et al.*^{212, 213} studied the cytotoxic activities of gold(I) and gold(III) complexes **76-79**, bearing cyclic (amino)carbenes derived from pyrazoles, towards the NCI-H1666 non-small cell lung cancer cell line (Scheme 39). The neutral monocarbene complexes **76** and **78** displayed 2 orders of magnitude lower activity as compared to the cationic bis(carbenes) **77** and **79**. This is in line with what has been previously referred to as delocalized lipophilic cations, which readily pass through the lipid membrane of mitochondria and eventually lead to mitochondria-induced apoptosis. Importantly, the cationic bis(carbene) complexes **77** and **79** showed better activities than cisplatin.

Similarly, in 2017, Bochmann *et al.*²¹⁴ prepared a series mono- and bis-CAAC complexes of copper, silver and gold (Scheme 39). They were tested against a panel of human cancer cell lines including leukemia (HL 60), breast adenocarcinoma cells (MCF-7) and human lung adenocarcinoma epithelial cell lines (A549), which are known to have varying degrees of cisplatin resistance. These complexes appeared to be highly cytotoxic, with IC₅₀ values in the sub-micromolar to ~100 nanomolar range, even against cisplatin-insensitive MCF-7 and A549 cells. As in the case of complexes **76-79**, cationic bis-carbene complexes of Au, Ag and Cu **11f-13f**

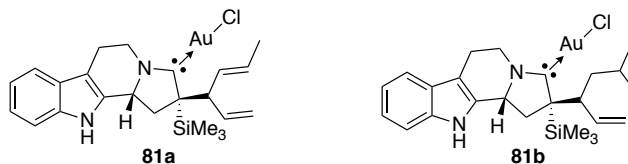
proved particularly effective with the mixed-carbene gold complex **80** being the most potent of the series (Scheme 39). Interestingly, the authors concluded that although the mechanism of cell growth control by these complexes remains to be established, the inhibition of thioredoxin reductase, which is a common pathway for gold NHC compounds could be ruled out as a primary pathway.

Scheme 39. Cationic bis(carbene) gold **77 and **79** displayed 2 orders of magnitude higher cytotoxicity than the neutral monocarbene complexes **76** and **78**, and are more potent than cisplatin towards the NCI-H1666 non-small cell lung cancer cell line. Cationic bis(carbenes) **11f**-**13f** proved particularly effective against cisplatin-insensitive MCF-7 and A549 cells, the mixed-carbene gold complex **80** being the most potent of the series**



The CAAC–gold complexes, prepared via a cyclization-rearrangement cascade³⁰ (Scheme 2), feature CAACs based on indole alkaloid scaffolds, which are by themselves often biologically active, including against cancer cells. It was found that complexes **81** displayed cytotoxicity towards the human ovarian cancer cell line A2780 and colorectal adenocarcinoma cell line HT29 at low micromolar or submicromolar concentration. Some of these complexes such as **81a** appeared to have strong but nonselective anticancer activity against all cancer cell lines, while others displayed interesting selectivity (Scheme 40). For example, **81b** is cytotoxic to HeLa cells and was the only complex active against the breast cancer cell line MCF7 in micromolar concentration.

Scheme 40. Gold complexes based on indole alkaloid scaffolds. 81a displays strong but nonselective anticancer activity, while 81b is cytotoxic to HeLa cells and the breast cancer cell line MCF7



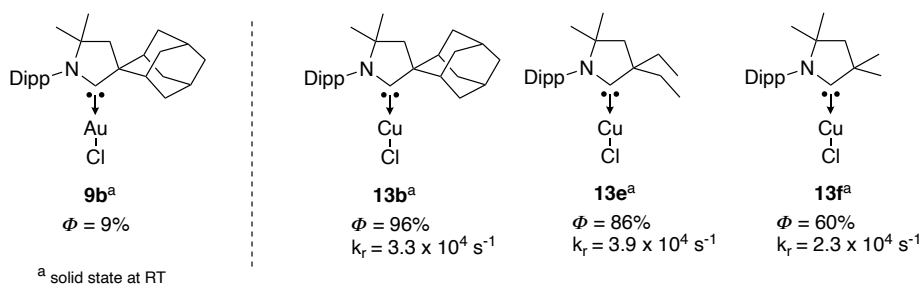
Overall, these preliminary investigations show that CAAC coinage metal complexes hold promise for medicinal applications.

5. OPTOELECTRONIC APPLICATIONS OF CYCLIC (ALKYL)(AMINO)CARBENE COINAGE METAL COMPLEXES

Since the pioneering discovery of electroluminescence by French chemist and physicist André Bernanose,^{215,216} and the preparation of an electroluminescent device using organic materials as the emitting element by Ching Tang and Steven Van Slyke at Eastman Kodak,²¹⁷ Organic Light-Emitting Diodes (OLEDs) have become vital components of many current technologies. In part due to their efficiency and greater contrast-ratio (black OLED emits no light), OLEDs are traditionally found in television and smartphone displays. However, with the advent of foldable and rollable OLED displays, or even 3D printing of transparent OLED displays,²¹⁸ it is forecast that the global demand in light emitting OLED materials will double by 2023. Traditionally, these devices rely on expensive heavy transition metals such iridium, platinum, and ruthenium, as well as rare metal-based phosphors which intrinsically pose serious economical and sustainable challenges in a global economy.²¹⁹ In recent years, focus has been put toward the development of d¹⁰-coinage metal alternatives which, aside from their low cost and low toxicity, are inherently more advantageous thanks to their fully filled *d*-orbitals which prevent internal quenching of excited states by low-lying d*–d transitions.²²⁰ In particular, three- and four-coordinate Cu(I) complexes bearing phosphine and *N*-heterocyclic ligands with good π -acceptor properties

exhibiting low-lying metal-to-ligand charge-transfer (MLCT) and thermally activated delayed fluorescence (TADF) have been intensely investigated as emitting dopants in OLEDs.^{221,222} Recently, two-coordinate copper complexes with linear geometry [(L)CuX], where L is a carbene and X an anionic ligand, have emerged as a new class of strongly photoemissive materials.²²³ In 2016, Bochmann *et al.* observed that the adamantylCAAC-CuCl complex **13b** displayed unexpected photoactivity ($\Phi_{\text{PL}} = 96\%$ in the solid state) in marked contrast with the gold analogue **9b** which was found to be comparatively inefficient (Scheme 41).²²⁴ As highlighted across several reports, the quantum yield in (CAAC)CuCl complexes is directly linked to the steric environment provided by the ligand in the order **13b**²²⁵ > **13e**^{225,226} > **13f**,^{226,227} and is a consequence of the increased rigidity of the system. Moreover, these reports underline for the first time the unique properties of CAACs (*i.e.* stronger σ -donation destabilizing the M(d) orbitals and π -acceptance stabilizing the LUMO) with respect to NHC ligands which are much less efficient.²²²

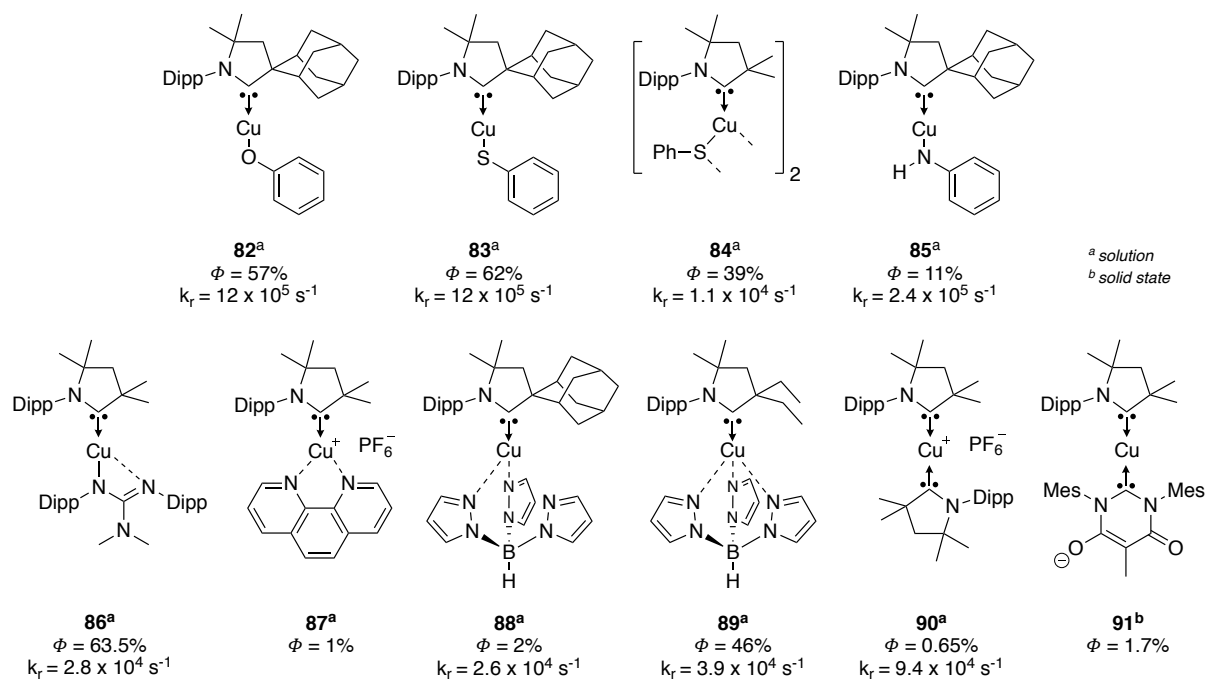
Scheme 41. The quantum yield in (CAAC)CuCl complexes is linked to the sterics (Φ : Quantum yield; k_r : radiative rate constant)



Examining the influence of the anionic ligand, Romanov *et al.* prepared the phenolato- **82**, the thiopheno- **83** and the amido- **85** which displayed moderate photoactivity (Scheme 42);²²⁶ note that the later was reported by Steffen *et al.* to afford dimer **84** with the smaller CAAC **1f**.²²⁷ However, a diverse array of anionic ligands have since been investigated with coordination geometries varying from hemilabile to linear-monodentate, including the formamidinato **86**,²²⁸ phenanthroline **87**,²²⁷ the trispyrazolylborate **88-89**²²⁵ derivatives, bis-CAAC **90**²²⁷ and

zwitterionic mix-carbene **91**,²²⁹ all resulting in distinct changes in photophysical behavior. It is worth mentioning that the introduction of flexible electron-rich N-donors such as the formamidinato **86** extends the photophysical properties toward the development of power-efficient white organic light-emitting diode (WOLEDs).²²⁸ With lighting accounting for 15% of global electricity consumption and 5% of worldwide greenhouse gas emissions, the production of WOLEDs based on abundant copper sources could have a substantial environmental and economical impact.

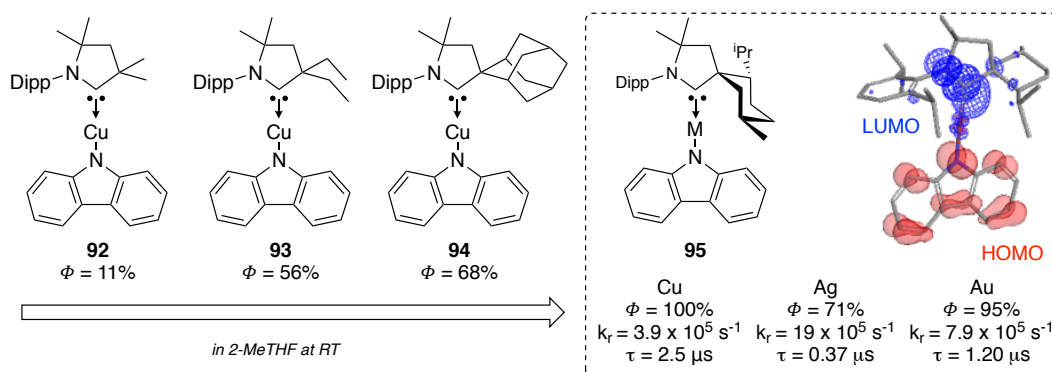
Scheme 42. Influence of the anionic ligand on the quantum yields



Notwithstanding these promising reports, it is most likely the introduction of a second redox-active ligand, a carbazole moiety, that has so far yielded the most significant advancement in the field of coinage metal-based phosphors (Scheme 43). In 2017 and 2019, Di *et al.* and Thompson *et al.* respectively reported that both adamantyl- **1b**²³⁰ and menthyl- **1a**²³¹ CAAC afford very emissive materials when bound to copper with an anionic carbazole moiety. Emission is also tailored to the rigidity of the ligand as in complexes **92-95**. Initially believed to originate from rotationally

assisted spin-state inversion,²³⁰ the luminescence properties of linear carbene–metal–amide (CMA) complexes were later shown to stem from thermally activated delayed fluorescence (TADF). This occurs through singlet ligand to ligand charge transfer (LLCT) between the electron rich carbazole (HOMO) and the electron-accepting carbene (LUMO). This is favored by a coplanar ligand conformation and coupling through the metal *d* orbitals.^{231,232,233,234,235}

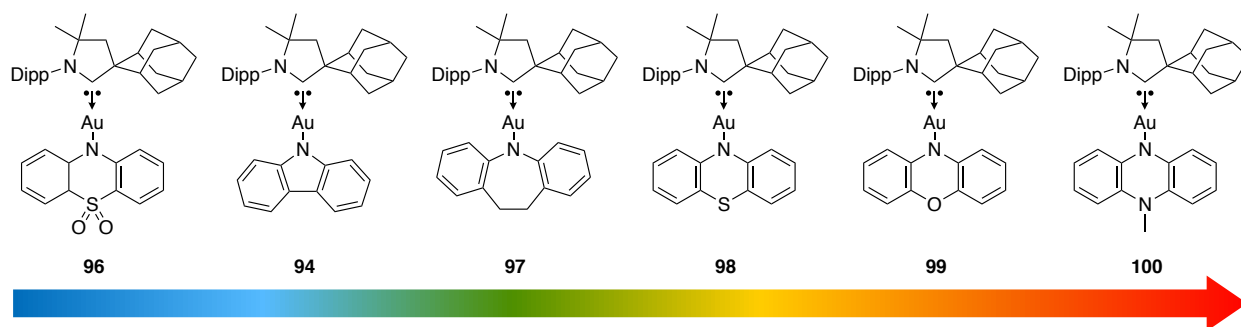
Scheme 43. Carbene metal amides emitters



Thanks to these CMA emitters, OLEDs devices with external quantum efficiencies (EQEs) up to 25% have been reported with Cu,^{230,231} and Au^{236,237,238} but also with Ag.^{25,239} As noted by Thompson *et al.* in a systematic study,²⁴⁰ despite blatant structural similarities, group 11 metals CMA emitters display marked photophysical differences. However, the metal ions in CMA are best described as redox “innocent” and only serve as a monatomic electronic conduit that modulates communication between the two redox active ligands. Capitalizing on these properties, emissions across the visible spectrum are readily achieved by simple modification of the carbazole moiety.²³¹ In fact, by combining (1b)gold with sulfone **96**, dibenzazepine **97**, phenothiazine **98**, phenoxazine **99** or phenazine **100**, as conformationally flexible 7-membered carbazole surrogates, Romanov *et al.* could tune the luminescence from blue to deep red (Scheme 43).²⁴¹ Note that with these non-rigid anionic ligands, copper analogues were found to be less emissive as illustrated by **96** [$\Phi_{\text{PL}} = 89.6\%$ (Au) vs. 49.5% (Cu) - in toluene]. This observation was proposed to parallel the

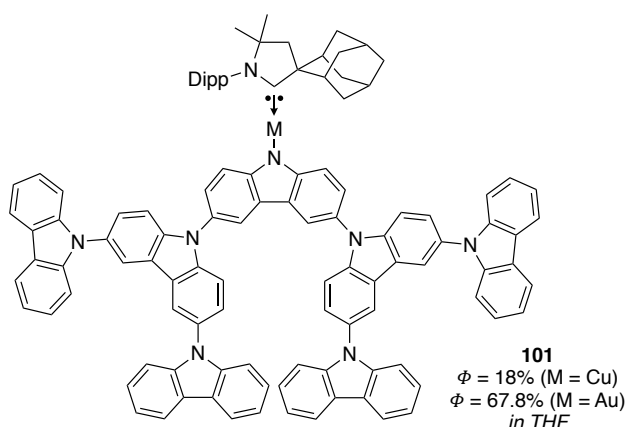
lower oscillator strength coefficients for the $S_1 \rightarrow S_0$ transition as well as smaller contribution of the copper orbitals into the LUMO with respect to the gold analogues.

Scheme 44. Tuning the luminescence from blue to deep red



A similar effect was also observed in carbazole dendrimers **101**,²⁴² which thanks to their excellent thermal stability and solubility allowed for the fabrication of solution-processed OLEDs (EQEs = 10%; practical brightness of 1000 cd/m²; maximum luminance of 29000 cd/m²). As suggested by the authors, the physical properties displayed by these dendritic complexes could be suitable for the engineering of flexible OLEDs through inkjet or roll-to-roll printing.²⁴³

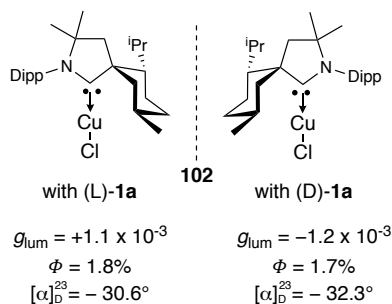
Scheme 45. Dendritic phosphor emitters



Recently, Ung *et al.* opened new avenues in the field of polarized OLEDs in demonstrating that the chiral framework of the menthylCAAC **1a** allows for yellow circularly polarized luminescence

(CPL) in copper complexes **102** (Scheme 46).²⁴⁴ Note that until this report, transition metal complexes exhibiting CPL were mainly limited to helical or axially chiral species.^{245,246}

Scheme 46. Chiral CAAC-Cu complexes for circularly polarized luminescence



We can expect that the broad range of CAACs,⁶ and especially the emergence of original chiral CAACs motifs,²⁰³ should allow for further discoveries in the field of CMA emitters and efficient chiral CMA CPL emitters.

6. CONCLUSIONS AND OUTLOOK

Classical NHC (imidazol-2-ylidenes and imidazolidin-2 ylidenes) gold complexes have been described as early as 1973,²⁴⁷ and their silver and copper complexes in 1993.²⁴⁸ In marked contrast, the first members of CAAC and CAAC coinage metal complexes have only been reported in 2008²⁴ and 2015,¹² respectively. Nevertheless, despite their much more recent discovery, they have already found numerous applications, which are mainly the result of their peculiar steric and electronic properties. These carbenes, initially used in the isolation of low valent metals, have shined in the stabilization of transient catalytic intermediates, such as bis(copper)acetylides, the active catalytic species of the CuAAC Click reaction. The isolation of these species has led to a better understanding of reaction mechanisms, but more importantly to the discovery of new catalytic reactions, such as the copper catalyzed dehydroborylation of alkynes. The stability of CAAC-coinage metal complexes allowed for carrying out reactions under very drastic conditions, and thus to perform very difficult chemical transformations such as the hydroamination of alkynes

and allenes with ammonia and parent hydrazine. In addition to their uses in catalysis, recent results show that their applications in medicinal and materials science holds an even greater potential. Notably, the extent of the recent breakthroughs made in the preparation of efficient coinage metal OLEDs could have a tangible technological impact on our society.

Altogether, we believe that the results summarized in this review article will lead to even more innovations with the newer members of the CAAC ligand family, namely, the bicyclic CAACs (BiCAACs), the 6-membered CAACs (CAAC-6), the aryl versions (CAArCs), the chiral ChiCAACs, and the bidentate CAACs (BICAACs).

AUTHOR INFORMATION

ORCID

Rodolphe Jazzar: 0000-0002-4156-7826

Michele Soleilhavoup: 0000-0001-5339-921X

Guy Bertrand: 0000-0003-2623-2363

Notes

The authors declare no competing interest.

Biographies

Rodolphe Jazzar was an undergraduate at the University of Poitiers and Liverpool, before obtaining his PhD in 2003 under the supervision of Prof. M. Whittlesey from the University of Bath. Following postdoctoral positions with Prof. E. P. Kündig (University of Geneva) and Prof. G. Bertrand (UC Riverside), he joined the CNRS in 2008 as a research fellow working in the field of C(sp³)-H activation in collaboration with Prof. O. Baudoin (UCB Lyon). In 2014, he moved to the UCSD/CNRS Laboratory at the University of California, San Diego. Capitalizing on a

mechanistic approach, his research interests are aimed toward the development of new catalytic methodologies, especially the enantioselective versions, using CAACs and other carbene ligands.

Michèle Soleilhavoup studied chemistry at the University Paul Sabatier in Toulouse and received her PhD in 1993 under the supervision of Guy Bertrand. From 1993 to 1995, she worked for BASF AG at Ludwigshafen. In 1995, she moved to the University Paris VI as a “Chargée de Recherche CNRS”, and from 2000 to 2001, she worked in the Remi Chauvin's group at the Laboratoire de Chimie de Coordination in Toulouse. In 2002, she joined the UCR/ CNRS Joint Research Laboratory at the University of California, Riverside and in 2012 the UCSD/CNRS Laboratory at the University of California, San Diego. Her current research interests are focused on the chemistry of carbenes and their application as tunable ligands for transition metal catalysts.

Guy Bertrand was an undergraduate in Montpellier, and obtained his PhD from the University of Toulouse. From 1988 to 1998 he was a “Director of Research” at the Laboratoire de Chimie de Coordination du CNRS, and from 1998 to 2005 the Director of the Laboratoire d’Hétérochimie Fondamentale et Appliquée at the University Paul Sabatier (Toulouse). From 2001 to 2012 he has been at the University of California at Riverside, and since 2012 he is Distinguished Professor and Director of the UCSD/CNRS Joint Research Laboratory at the University of California, San Diego. His research spans a wide range of topics at the border between organic and inorganic chemistry. He is a member of the French Academy of Sciences.

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