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Cyclic (Alkyl)(Amino)Carbenes (CAACs): Stable Carbenes on the Rise

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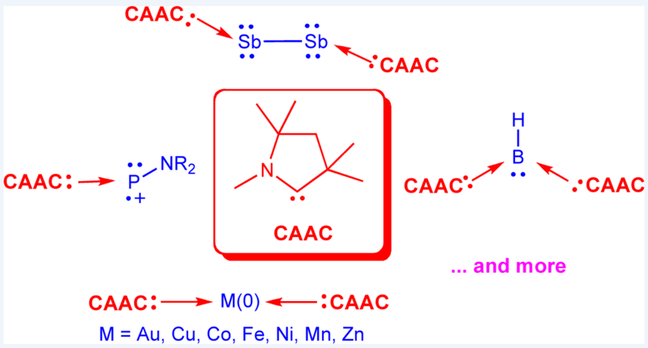

CONSPECTUS: Carbenes are compounds that feature a divalent carbon atom with only six electrons in its valence shell. In the singlet state, they possess a lone pair of electrons and a vacant orbital and therefore exhibit Lewis acidic and Lewis basic properties, which explains their very high reactivity. Following the preparation by our group in 1988 of the first representative, a variety of stable carbenes are now available, the most popular being the cyclic diaminocarbenes. In this Account, we discuss another class of stable cyclic carbenes, namely, cyclic (alkyl)(amino)carbenes (CAACs), in which one of the electronegative and π-donor amino substituents of diaminocarbenes is replaced by a σ-donating but not π-donating alkyl group. As a consequence, CAACs are more nucleophilic (σ-donating) but also more electrophilic (π-accepting) than diaminocarbenes. Additionally, the presence of a quaternary carbon in the position α to the carbene center provides steric environments that differentiate CAACs dramatically from all other ligands. We show that the peculiar electronic and steric properties of CAACs allow for the stabilization of unusual diamagnetic and paramagnetic main group element species. As examples, we describe the preparation of room temperature stable phosphorus derivatives in which the heteroatom is in the zero oxidation state, nucleophilic boron compounds, and phosphorus-, antimony-, boron-, silicon-, and even carbon-centered neutral and cationic radicals. CAACs are also excellent ligands for transition metal complexes. The most recent application is their use for the stabilization of paramagnetic complexes, in which the metal is often in a formal zero oxidation state. Indeed, bis(CAAC)M complexes in which the metal is gold, copper, cobalt, iron, nickel, manganese, and zinc have been isolated. Depending on the metal, the majority of spin density can reside either on the metal or on the carbene carbons and the nitrogen atoms of the CAAC ligand. In contrast to diaminocarbenes, the higher basicity of CAACs makes them poor leaving groups, and thus they cannot be used for classical organocatalysis. However, because of their superior electrophilicity and smaller singlet−triplet gap, CAACs can activate small molecules at room temperature, such as CO, H_2, and P_4, as well as enthalpically strong bonds, such as B−H, Si−H, N−H, and P−H. Lastly, excellent results have been obtained in palladium, ruthenium, and gold catalysis. CAAC−metal complexes are extremely thermally robust, which allows for their utilization in harsh conditions. This property has been used to perform a variety of gold-catalyzed reactions in the presence of basic amines, including ammonia and hydrazine, which usually deactivate catalysts.

1. INTRODUCTION

For a long time carbenes were only been considered as transient species. However, in 1988 our group isolated [bis(diisopropylamino)phosphino](trimethylsilyl)carbene, **A**,[1] demonstrating that with the right set of substituents carbenes could be much more stable than originally believed (Figure 1). Three years later, Arduengo[2] reported the preparation of the imidazol-2-ylidene **B**, the first representative of a family of stable carbenes known today as N-heterocyclic carbenes (NHCs).[3,4] Following the pioneering work by Herrmann,[5] NHCs have been recognized as excellent ligands for transition metal-based catalysts;[6] they are also organic catalysts in their own right,[7] and their silver complexes even feature medicinal properties.[8] In contrast, the first types of stable carbenes discovered in our group (**A** and **C**−**F**)[9,10] have not yet found remarkable applications, but our most recent families (**G**−**K**)[11] are beginning to attract some attention.[12] Among them, the cyclic (alkyl)(amino)carbenes (CAACs), **K**,[13] are clearly the most popular, as can be seen by the results summarized in this Account.

2. PREPARATION, CHARACTERIZATION, AND ELECTRONIC PROPERTIES OF CAACs

Among the different synthetic approaches, the so-called "hydroiminiumation" route is the most practical and economical way to prepare CAAC precursors (Figure 2).[14] Deprotonation of aldimines **1** leads to the corresponding 1-aza-allyl anions, which readily react with 3-halogeno-2-methylpropene to afford alkenyl aldimines **2**. Addition of excess HCl, followed by heating at 50 °C for 16 h, gives rise to the desired cyclic aldiminium salts **3** (a few salts of type **3** are commercially available).[15] The overall transformation (**1** to **3**) can be performed in over 80% yield,

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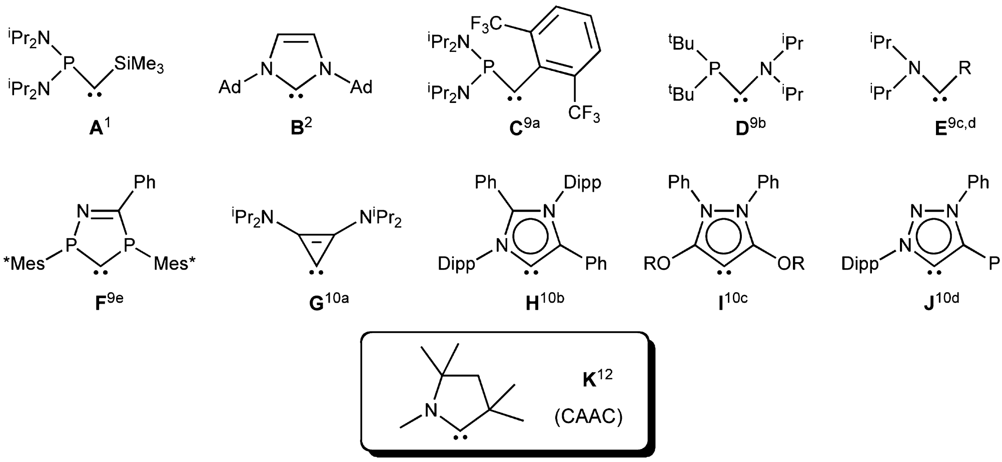


Figure 1. Imidazol-2-ylidene **B**, the first representative of the NHC family, and stable carbenes discovered in our group (**A** and **C**−**K**), with the cyclic (alkyl)(amino)carbenes (CAACs), **K**, being the subject of this Account.

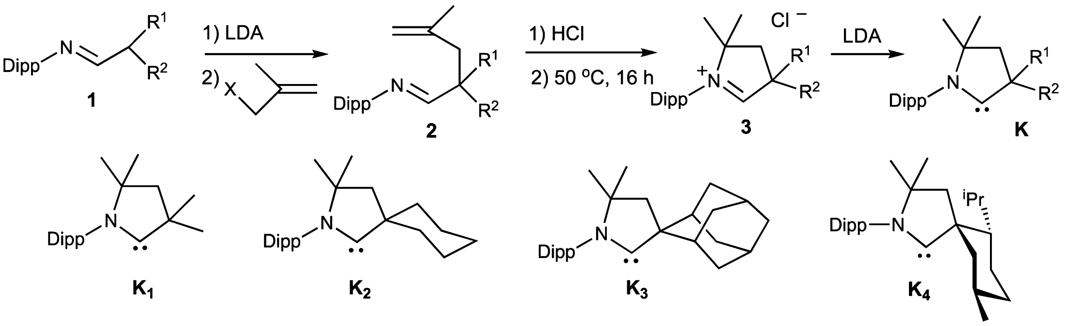


Figure 2. Most convenient synthesis and some examples of CAACs.

whereas the deprotonation of **3**, which affords the desired CAACs, is almost quantitative.

This synthetic route has a very broad scope up to the aldiminium salts **3**, but the deprotonation step has limitations, mainly because of the weak acidity of the aldiminium proton. The 2,6-diisopropylphenyl substituent (Dipp) is by far the best option for the nitrogen atom, since when a mesityl group is used deprotonation of the methyl substituents also competes with the formation of the carbene. However, with a 2,6-diethylphenyl group, the corresponding CAAC(H^+)s can be deprotonated in situ in the presence of a metal fragment, allowing the preparation of the corresponding CAAC metal complexes.[16] The sp^3-carbon adjacent to the nitrogen group must be a quaternary carbon; otherwise its deprotonation competes with that of C1, but the choice of the R^1 and R^2 substituents is virtually unlimited. For example, $\mathbf{K_1}$ with methyl groups as R^1 and R^2 is perfectly stable at room temperature in the solid state and in solution for at least 2 weeks, and more bulky groups can be appended as seen with $\mathbf{K_{2-4}}$. The presence of a quaternary carbon in the position α to the carbene center provides steric environments that differentiate CAACs dramatically from all other ligands such as phosphines (cone) and NHCs (wings); moreover optically pure CAACs can readily be prepared, as exemplified by $\mathbf{K_4}$ derived from menthol.

The replacement of one of the electronegative and π-donating amino substituents of NHCs **B** by a σ-donating but not π-donating alkyl group makes CAACs more nucleophilic (σ-donating) but also more electrophilic (π-accepting) than NHCs. Indeed, the HOMO of $\mathbf{K_1}$ (−4.9 eV) is slightly higher in energy and the singlet−triplet gap (45 kcal/mol) is significantly smaller than those of saturated NHCs (−5.2 eV and 68 kcal/mol, respectively). These features are reflected by the very low field ^{13}C NMR signal of the carbene carbon (>300 ppm) and ^{31}P chemical shift of CAAC−phosphinidene adducts (CAAC-PPh).[17]

3. CAACs FOR THE STABILIZATION OF UNUSUAL DIAMAGNETIC AND PARAMAGNETIC MAIN GROUP ELEMENT SPECIES

In 2008, Robinson and co-workers[18] prepared the silicon(0) compound **4** featuring a Si═Si double bond, demonstrating that NHCs could stabilize main group elements in their zero oxidation state (Figure 3).[19] Using CAACs instead of NHCs, we were also able to prepare a diatomic phosphorus(0) adduct **7**[20] and a mixed-element derivative, namely, the phosphorus mononitride **5**.[21] Although CAACs and NHCs are both efficient for stabilizing these species, their very different electronic properties, especially the better π-accepting properties of CAACs, make a considerable difference. This is well illustrated by the redox behavior of bis(carbene)−P_2 adducts **6** and **7**.[22] The cyclic voltammogram of the (NHC)$_2P_2$ adduct **6** shows two reversible one-electron oxidations, whereas the corresponding (CAAC)$_2P_2$ compound **7** shows only one.

These observations prompted us to use CAACs to stabilize electron-rich main group element species; boron derivatives were chosen as showcases. Indeed, up to the discovery in 2006 of the boryl anion **8**,[23] nucleophilic boron compounds were not known, and even nowadays they are very rare (Figure 4).[24] We first targeted the neutral trivalent nucleophilic boron derivative **9a**, which is isoelectronic with amines.[25] We reasoned that the presence of two CAAC ligands would diminish the Lewis basicity

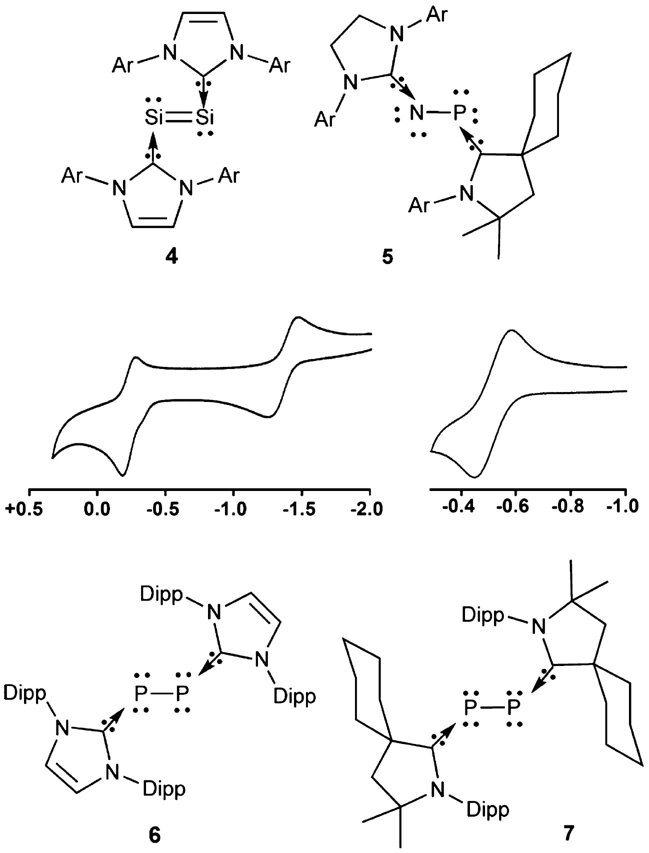


Figure 3. NHCs and CAACs for the stabilization of main group elements in the zero oxidation state and cyclovoltammograms of **6** and **7**, illustrating the different electronic properties of these carbenes.

by accepting electron density. Compound **9a**, which can be regarded as the parent borylene supported by two Lewis bases, was isolated and is stable at room temperature for months. In the solid state, the boron center is in a planar environment, and the boron−carbon bond distances are halfway between typical B−C single and double bonds. These observations suggest that, as hypothesized, there is delocalization of the lone pair of electrons at boron to the empty p-orbitals of the carbene centers. This is confirmed by calculations since the HOMO of **9a** is an electron lone pair in the p(π)-orbital of boron, which mixes in a bonding fashion with the p(π) atomic orbital of both carbene carbons. We also reported the preparation of derivatives **9b**,**c**, which feature two different carbene ligands.[26] In both cases, the superior π-accepting properties of CAACs was evidenced by the much shorter boron−CAAC bond length (~1.42 Å) compared with the other boron−carbene bond (~1.56 Å). Despite the delocalization of the lone pair, the boron center of **9a**−**c** remains electron rich, as shown by the reaction with trifluoromethanesulfonic acid, which leads to the conjugate acids (L)(L′)BH_2^+, TfO^-. Kinjo and co-workers[27] have even recently shown that these organoboranes can act as L ligands for transition metals.

Before our recent work,[28] the preparation of nucleophilic boron compounds had always been achieved by reduction of suitable precursors. All attempts to deprotonate a borohydride had been unsuccessful,[23] in line with the higher electronegativity of H versus B, which makes hydrogens hydridic in nature. To increase the acidity of these hydrogens, we used the π-accepting properties of CAACs, in addition to cyano substituents. We found that potassium bis(trimethylsilyl)amide (KHMDS) was able to deprotonate **10**, and after addition of dibenzo-18-crown-6, we isolated the monomeric boryl anion **11** (Scheme 1). The crucial role played by CAACs in the stabilization of **11** is shown by the shortening of the boron−(CAAC)carbon bond distance (1.47 Å) compared with that in **10** (1.62 Å) and the trigonal planar geometry of boron. Despite its substitution pattern, **11** acts as a nucleophile as shown by its reactivity with isopropyl iodide and (trimethylphosphine)gold chloride. Because of the low electronegativity of boron, these compounds are potential strong electron-donor ligands, which could lead to highly catalytically active complexes.

The ability of CAACs to delocalize electron density from a neighboring center prompted us, and others, to use these carbenes for isolating main group element radicals.[29] The superior efficiency of CAACs over NHCs for doing this task was first demonstrated by comparing the EPR data and the calculated spin density for the $(NHC)_2P_2$ and $(CAAC)_2P_2$ radical cations $\mathbf{6}^{+\bullet}$ and $\mathbf{7}^{+\bullet}$ (Figure 5). Although these two paramagnetic species are both stable at room temperature, 46% of the spin density is delocalized on the CAAC fragments, while only 23% is on the NHCs.[22] Other phosphorus-centered radical cations, such as the phosphinyl $\mathbf{12}^{+\bullet}$[30] and the phosphorus mononitride $\mathbf{5}^{+\bullet}$,[21] boron-centered radical cations, such as $\mathbf{9a}^{+\bullet}$,[26] and the air-stable organic mixed valence system $\mathbf{13}^{+\bullet}$[31] could be isolated.

The stabilizing effect of CAACs is not limited to radical cations (Figure 6). The most striking example of their ability to stabilize

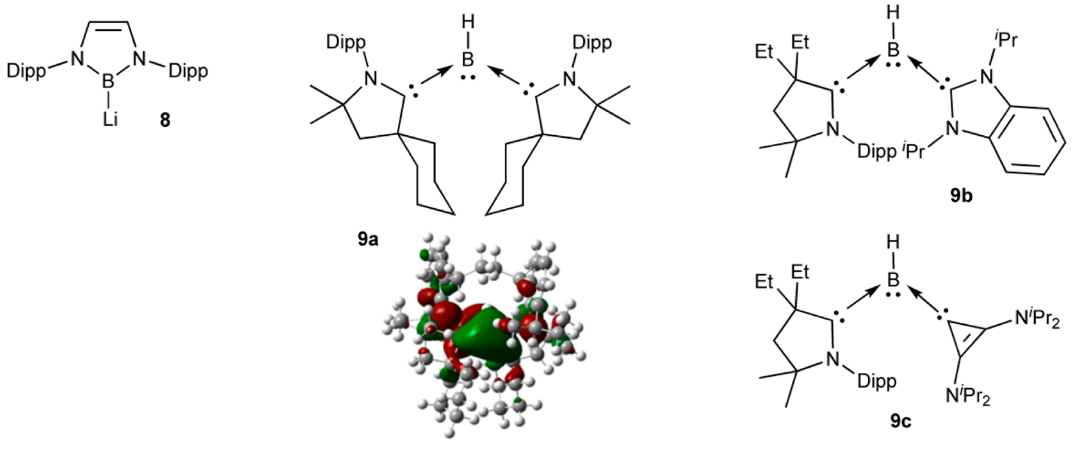
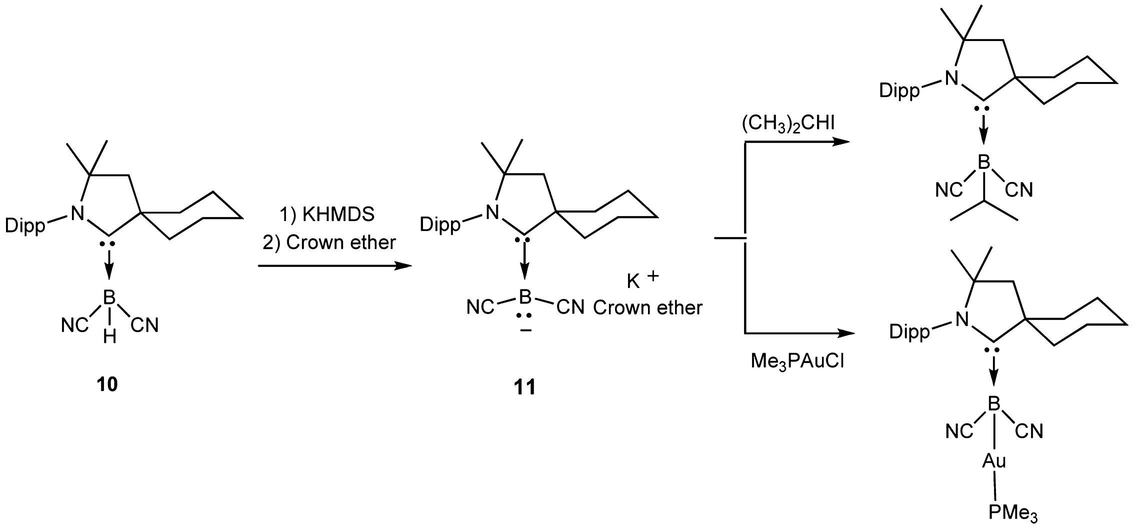


Figure 4. First boryl anion **8**, neutral trivalent nucleophilic boron derivatives **9a**−**c**, and HOMO of **9a**.

Scheme 1. Synthesis and Reactivity of Boryl Anion 11



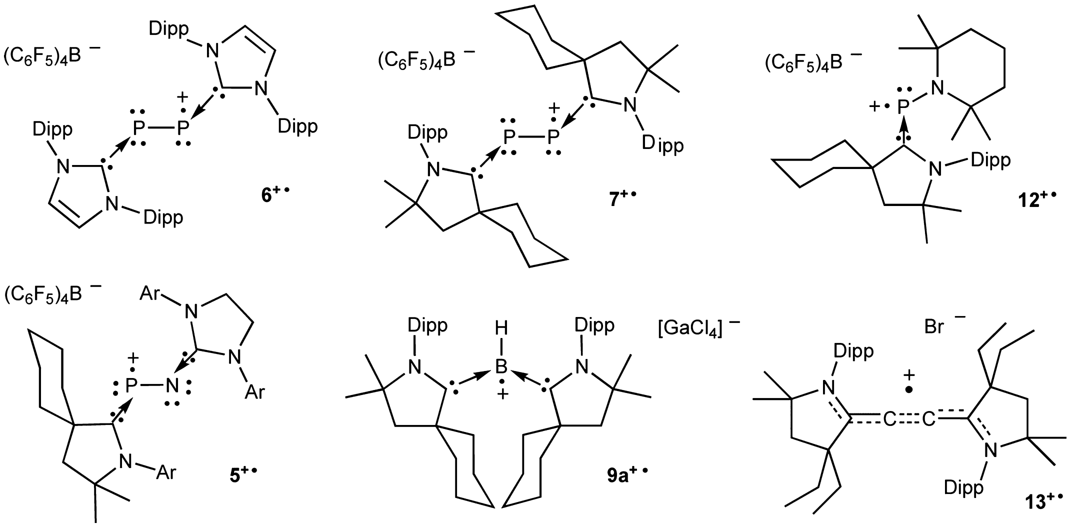


Figure 5. CAAC-stabilized radical cations.

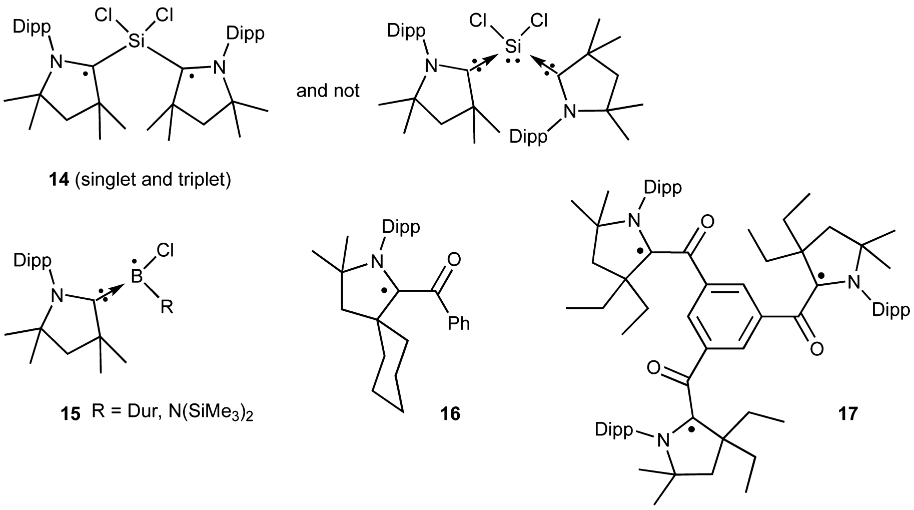
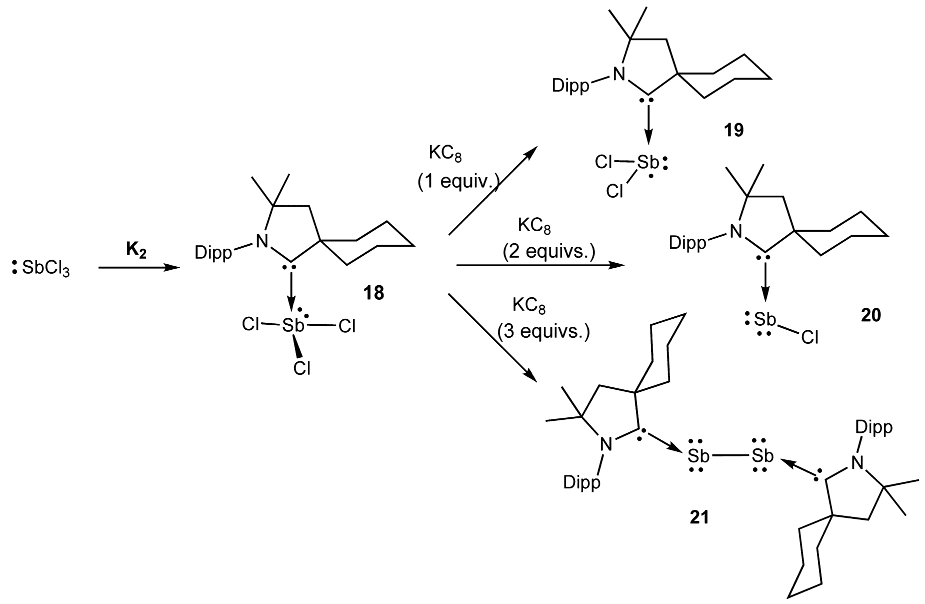


Figure 6. Room temperature stable singlet and triplet diradical **14**, boryl radicals **15**, and (amino)(carboxy) radicals **16** and **17**.

neutral paramagnetic species has been reported by Roesky.[32] He found that for the deep blue bis(CAAC)−SiCl$_2$ adduct **14**, the two nonbonding electrons were not localized at silicon, as expected for a silylene but an unpaired electron resided on each

Scheme 2. One-, Two-, and Three-Electron Reduction of a CAAC−$SbCl_3$ Adduct, 18



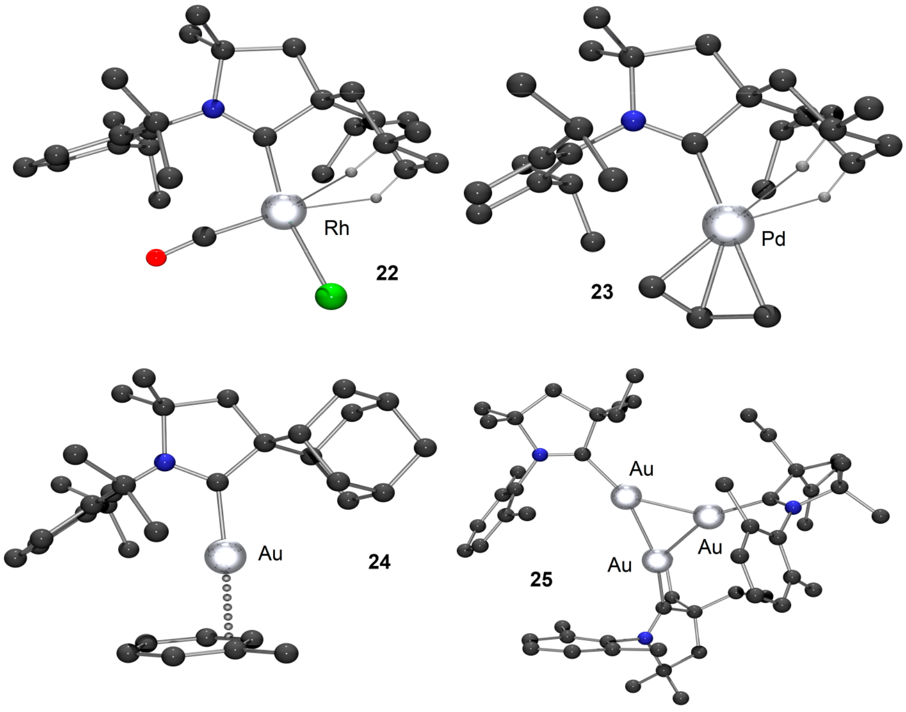


Figure 7. Solid state structure of complexes **22**−**25**.

carbene center. Moreover, he was able to isolate both the singlet and the triplet biradical as two polymorphs of **14**, the singlet being air stable for up to a week. Another demonstration of the usefulness of CAACs is the isolation of boryl radicals **15**[33] and of purely organic radicals, namely, (amino)(carboxy) radicals **16** and **17**.[34] It is well-known that captodative substitution around a carbon radical center has a strong stabilizing effect but not to the extent of allowing for isolation of well-defined monomers. Radical **16** can be stored at room temperature for weeks under inert atmosphere without any apparent decomposition. These radicals are readily synthesized by addition of a CAAC to an acyl chloride, followed by reduction with tetrakis(dimethylamino)-ethylene. This synthetic strategy affords an easy entry to a plethora of (amino)(carboxy) radicals, as shown by the preparation of the tris(radical) **17**.

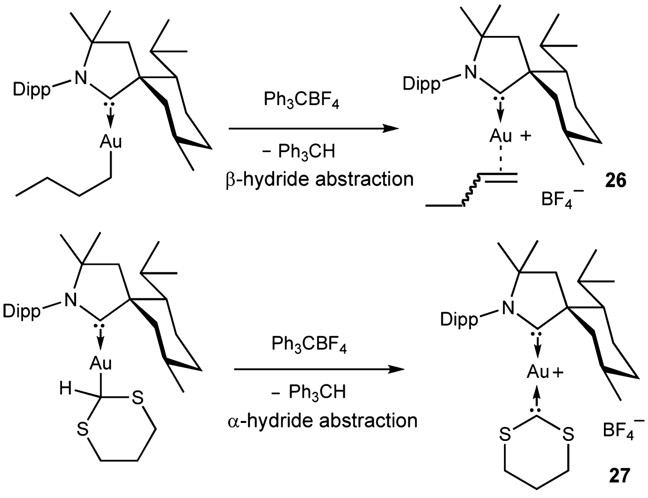
Calculations and EPR data show that, in all of the CAAC-stabilized radicals mentioned above, more than half of spin density is localized on the former carbene carbon, with an additional 20−25% on the CAAC-nitrogen; in other words, the CAAC is a very efficient redox-active ligand.

As can be seen in this section, CAACs can stabilize main group elements in various oxidation states. A further and definitive demonstration is given by the preparation of a family of stable antimony compounds, **18**−**21**,[35] in which the formal oxidation state of the metalloid varies from 3 to 0 (Scheme 2). This is a very rare example of a single ligand stabilizing a metal or a metalloid center in four different oxidation states.

4. CAACs FOR THE STABILIZATION OF UNUSUAL DIAMAGNETIC AND PARAMAGNETIC TRANSITION METAL COMPLEXES

CAACs also allow for the preparation of unusually stable low coordinate metal complexes. This was first demonstrated by the isolation of the 14-electron RhCl(CO)(K_4) complex **22** (Figure 7).[36] Its surprising stability is partly due to the steric hindrance provided by the menthyl ring but more importantly by the presence of agostic interactions with H atoms of the cyclohexyl ring. This is also the case for the cationic 14-electron palladium complex Pd(Allyl)(K_4)$^+BF_4^-$, **23**. Interestingly, all attempts to prepare similar complexes using bulky NHCs and phosphines failed.[37] Bulky CAACs have also been used to prepare several monuclear cationic gold complexes.[38,39] Among them, (K_3)Au(η^2-toluene)$^+B(C_6F_5)_4^-$, **24**, is a very rare example of a pseudo-naked (L)Au$^+$ complex. We also found that CAACs allow for the preparation of mixed-valence gold(I)/gold(0) trinuclear clusters such as **25**,[40] the smallest members of the $(L_nAu_m)^{x+}$ family.[41,42] The synthetic route involves a simple ligand exchange from the readily available μ^3-oxo-$[(Ph_3PAu)_3O]^+$ complex, followed by reduction with carbon monoxide. This synthetic methodology paves the way for the preparation of a variety of mixed-valence gold(I)/gold(0) polynuclear clusters.

Scheme 3. β- and α-Hydride Abstraction in Gold(I)−Alkyl Complexes



Recently, Hashmi and co-workers[43] demonstrated that the thermally induced β-H elimination reactions of gold−alkyl complexes are not possible because of the high energy of the three coordinate gold(I)−alkene−hydride complex intermediate. Thanks to the strong electron-donor properties of CAACs, we have been able to abstract both β- and α-hydrogen atoms of gold(I) alkyl complexes (Scheme 3). The β-hydride abstraction leads to stable alkene−gold complexes **26**, whereas α-hydride abstraction is a novel route to prepare gold−carbene complexes **27**.[44,45]

The most recent application of CAACs in transition metal chemistry is their use for the stabilization of paramagnetic complexes, in which the metal is often in a formal zero oxidation state (Figure 8). We prepared the bis(CAAC) complexes **28** of gold,[46] copper,[47] cobalt, and iron,[48] and Roesky and co-workers synthesized the analogous nickel,[49] manganese,[50] and zinc[51] complexes. Calculations and EPR data show that for the iron and cobalt complexes, the majority of spin density resides on the metal (Fe, 72%; Co, 60%) with moderate delocalization onto the carbon and nitrogen atoms. In contrast, for the other metals, spin density is mainly localized on the carbene carbons and the nitrogen atoms, with less than 17% on the metal.

These results demonstrate that CAACs are polarizable ligands, a highly needed property for the stabilization of zero-valent mononuclear metal complexes.

5. CAACs FOR THE ACTIVATION OF SMALL MOLECULES AND IN TRANSITION METAL CATALYSIS

In line with the seminal work by Breslow on the thiazolium catalyzed benzoin condensation,[52] NHCs have been demonstrated to be excellent organocatalysts.[7] Because of their higher basicity, CAACs are a poor leaving group and thus cannot be used for this task. However, because of their superior electrophilicity and smaller singlet−triplet gap, CAACs can activate at room temperature small molecules, such as CO,[53] H_2,[54] and P_4,[20,55] as well as enthalpically strong bonds, such as B−H, Si−H, N−H, and P−H (Scheme 4).[56]

From a fundamental point of view, these results are interesting since they demonstrate that CAACs can undergo oxidative addition, just like transition metals do.[57] These reactions are considered as key steps in transition-metal catalyzed hydrosilylation, hydroboration, hydrophosphination, hydroamination, etc., but unfortunately we have not been able to develop any catalytic system, mainly because of the excessive strength of carbon−hydrogen bonds. However, reading the literature, we realized that (i) NH_3, which reacts instantaneously with CAAC K_4 at −78 °C, is a difficult substrate for transition metals due to the formation of inert Werner-type complexes[58] and (ii) that

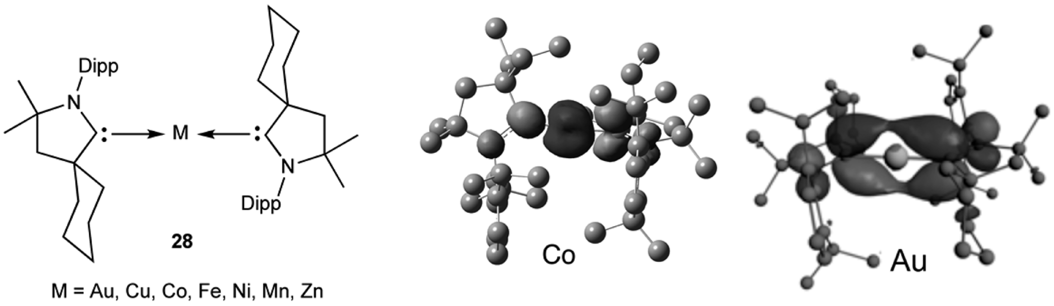
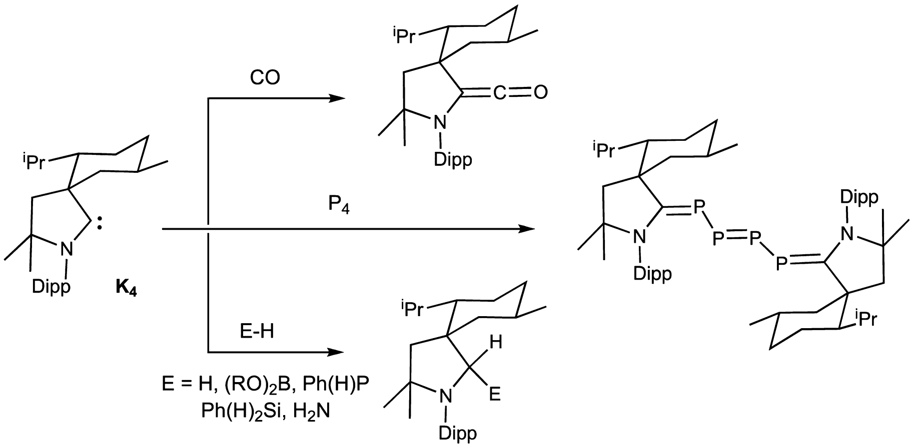
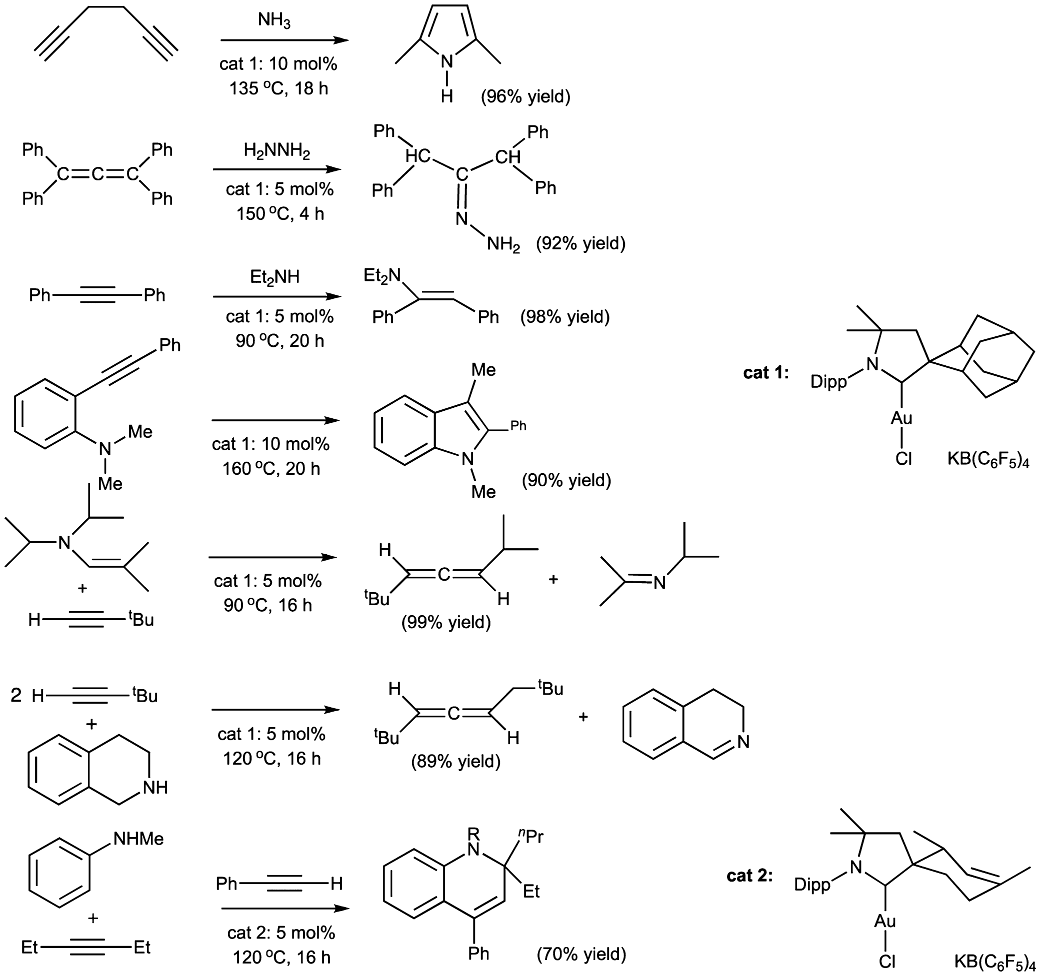


Figure 8. Isolated bis(CAAC)M(0) complexes **28**, and graphical representation of the SOMO of the cobalt and gold complexes.

Scheme 4. CAACs Activate a Variety of Small Molecules

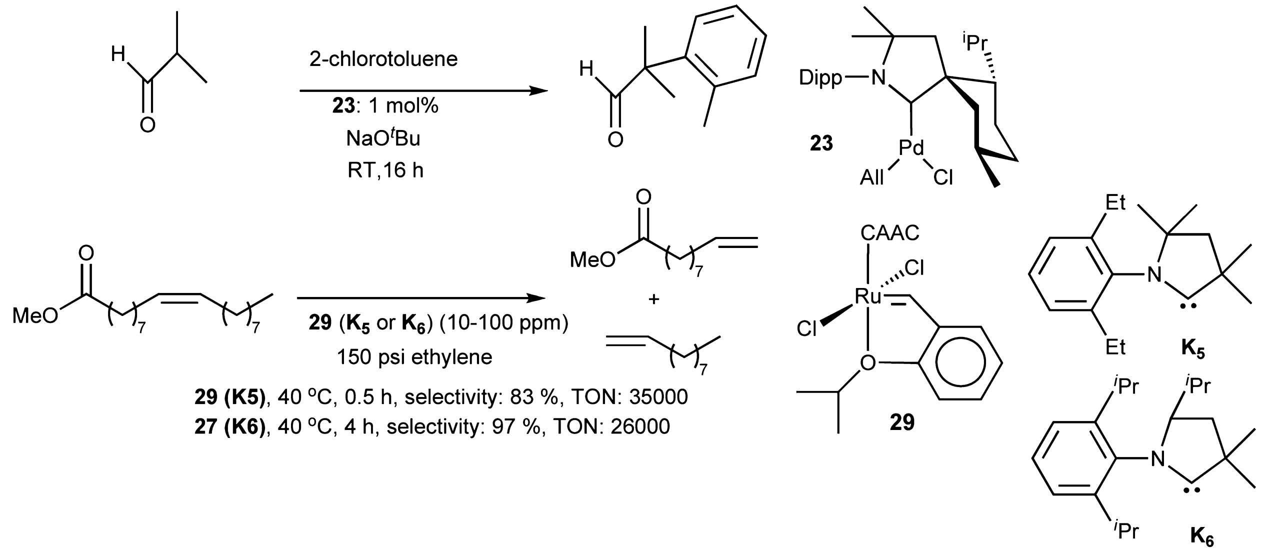


Scheme 5. Some Examples of (CAAC)gold Catalyzed Reactions



gold complexes are among the best catalysts for hydroamination reactions. Thus, we decided to combine CAACs with gold and were fortunate to rapidly find that cationic (CAAC)gold complexes were not only very efficient catalysts to promote the addition of ammonia[59] and hydrazine[60] to alkynes and allenes but also powerful catalysts for the intermolecular hydroamination with secondary alkyl amines[61] (Scheme 5). Importantly, CAAC–gold complexes are thermally very robust, as illustrated by the first examples of methylamination of alkynes, which only occur at 160 °C.[62] We also discovered that cationic (CAAC)gold complexes promote the reaction of enamines with terminal alkynes to afford allenes, with elimination of imines.[38a] This is the first general catalytic reaction allowing the coupling of two unsaturated carbon centers to build the three-carbon allenic skeleton. These results are in marked contrast with those obtained with a variety of transition metal complexes; indeed, usually terminal alkynes add to enamines, affording propargyl amines. The excellent catalytic activity of gold complexes

Scheme 6. CAAC as Ligands for Palladium and Ruthenium Based Catalysts



supported by a CAAC ligand encouraged us to investigate cascade reactions. Noteworthy are the one-pot synthesis of allenes by coupling two alkynes using a sacrificial secondary amine[61a] and the one-pot three-component preparation of 1,2-dihydroquinoline derivatives involving a tandem hydroamination–hydroarylation reaction.[63]

CAACs are strong σ-donors, which make them good candidates as ligands for palladium-catalyzed α-arylation of carbonyl compounds and for ruthenium-catalyzed olefin metathesis reactions (Scheme 6). We found that the air stable palladium complex **23** was the first catalyst able to promote the α-arylation of propiophenone with aryl chloride at room temperature with turnover number up to 7000.[13] Even more striking, 1 mol % of **23** also allows for the efficient coupling of 2-chlorotoluene with isobutanal at room temperature with no trace of aldol condensation. These results compare extremely favorably with the best catalysts reported so far.[64] In collaboration with Grubbs, we reported that replacing the NHC ligand of the second generation of Grubbs and Hoveyda–Grubbs ruthenium complexes by a small CAAC (**K$_5$**) gave rise to the most active catalysts known so far for the ethenolysis of methyl oleate.[16b] TONs of 35 000 were achieved for this reaction, which is of industrial importance since it allows for the transformation of internal olefins derived from seed oils to terminal olefin feedstocks. Shi and co-workers[65] reported that similar complexes bearing backbone-monosubstituted CAACs (**K$_6$**) were more selective.

6. CONCLUSIONS

Inevitably, CAACs have to be compared with the widely used NHCs (imidazol-2-ylidenes and imidazolidin-2-ylidenes).[66] The presence of a quaternary carbon in the position α to the carbene center makes their steric environments very different from those of NHCs and allows for the synthesis of optically pure CAACs. More importantly, the overall electron-donating properties of CAACs are superior to those of NHCs, although they are concomitantly more electrophilic (π-accepting), which implies that CAACs are much stronger σ-donors than NHCs. As a consequence of the higher basicity, CAACs are poorer leaving groups and cannot be used in organocatalysis in which NHCs excel. In contrast, the higher electrophilicity allows for the activation of small molecules and enthalpically strong bonds and for the stabilization of electron rich and paramagnetic species.

The peculiar electronic properties of CAACs make metal–carbon bonds very strong, and therefore CAAC–transition metal complexes are very robust. A good demonstration is given by the gold-catalyzed hydroamination of unactivated alkynes and allenes with ammonia, hydrazine, and secondary amines, which require extremely drastic experimental conditions.

We predict a very bright future for CAACs, especially in the field of catalysis. So far, CAACs have only been used as ligands for palladium-, gold-, and ruthenium-based catalysts, and only for a few types of reactions. The robustness of CAAC complexes should be used for many other catalytic systems. Optically active versions are readily available, and so far there is no report on their use in asymmetric catalysis. The stability of CAAC complexes in which the metal is in the zero oxidation state not only is a demonstration that CAACs are very efficient redox active ligands but might allow for new types of catalytic cycles, a hypothesis under active investigation in our group.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Michèle Soleilhavoup received her Ph.D. in 1993 from the University of Toulouse under the supervision of Guy Bertrand. After two years at BASF AG at Ludwigshafen, she became Chargée de Recherche CNRS at University Paris VI. From 2000 to 2001, she worked in the Laboratoire de Chimie de Coordination in Toulouse, before joining the UCR/CNRS Joint Research Laboratory and in 2012 the UCSD/CNRS Laboratory at the University of California, San Diego. Her current research interests are focused on carbene chemistry and application of carbenes as tunable ligands for transition metal catalysts.

Guy Bertrand obtained his Ph.D. from the University of Toulouse in 1979. 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. From 2001 to 2012, he has been Distinguished Professor and Director of the UCR/CNRS Joint Research Chemistry Laboratory at the University of California at Riverside and now at the University of California, San Diego. He is a member of the French Academy of Sciences.

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