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Anti-Bredt *N*-heterocyclic carbene: an efficient ligand for the gold(I)-catalyzed hydroamination of terminal alkynes with parent hydrazine†

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An anti-Bredt *N*-heterocyclic carbene gold(I) chloride complex was synthesized by taking advantage of the reversible insertion of the free carbene into the NH bond of hexamethyldisilazane. This precatalyst promotes the parent hydrazine hydroamination of terminal alkynes at room temperature.

Over 2×10^5 tonnes of hydrazine (H_2NNH_2) are produced annually and processed worldwide for pharmaceutical, agrochemical, polymer and aeronautic industries.[1] Despite its industrial importance, and the central role of carbon–nitrogen bond formation in organic synthesis, this cheap N-containing building block has rarely been used as a substrate in homogeneous organometallic catalysis. Several issues hamper its use with transition metal catalysts. Its strong reducing properties can lead to inactive metal(0) particles[2] or undesired side-reactions on organic co-substrates.[3] Like ammonia,[4] hydrazine also gives rise to Werner-type complexes, which are usually inert.[5,6] There are only two reports of successful metal catalyzed functionalizations of hydrazine. In 2010, Lundgren and Stradiotto[7] demonstrated that the use of an electron rich bulky P-ligand (Mor-DalPhos) allowed for the Pd-catalyzed cross-coupling of hydrazine with aryl chlorides and tosylates. A year later our group reported that cationic gold(I) complexes,[8] bearing a cyclic (alkyl)(amino)carbene (CAAC)[9] **A** ligand (Chart 1) promoted the hydroamination[10] of alkynes and allenes with parent hydrazine;[11] however, elevated temperatures, typically 90–110 °C, were required. Here we report the preparation of a new gold(I) complex, which allows for the room temperature hydroamination of terminal alkynes with hydrazine.

The peculiar electronic properties of CAACs **A** clearly account both for the robustness of cationic gold complexes and the reactivity of the corresponding Werner complexes.

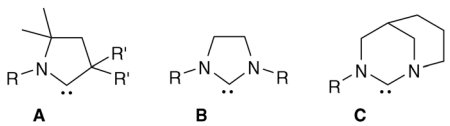
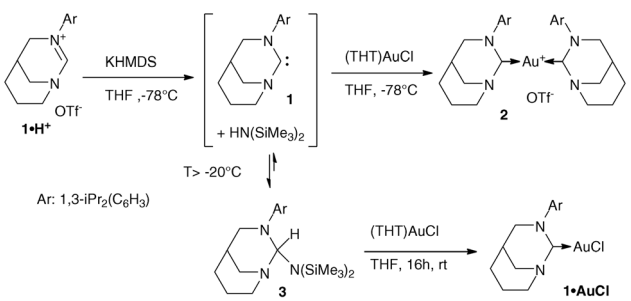


Chart 1

Of particular importance, because of the presence of only one nitrogen π-donor substituent, CAACs **A** are considerably more π-accepting[12] than classical *N*-heterocyclic carbenes (NHCs) **B**.[13–15] Recently, we reported the preparation of NHCs of type **C** in which one of the two nitrogen atoms of classical NHCs is placed in a strained bridgehead position, thus being restricted from donating its lone pair.[16] Compared to classical NHCs **A**, this topological feature considerably increases the π-accepting character of the carbene, without diminishing its σ-donor properties. As a result, these so-called "anti-Bredt NHCs" **C** resemble CAACs **A** more than NHCs **B**, and thus are potential ligands for efficient gold-catalyzed intermolecular hydroaminations.

In an attempt to synthesize the (carbene)gold chloride **1·AuCl**, imidazolium salt **1·H**$^+$ was reacted with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C, and subsequent addition of one equivalent of chloro(tetrahydrothiophene) gold(I)[17] yielded a black-red slurry (Scheme 1). After workup, mass spectroscopy showed a molecular peak at m/z = 765.41 indicating the formation of the bis(carbene)Au(I) complex **2**,



Scheme 1 Synthesis of gold complexes **2** and **1·AuCl**.

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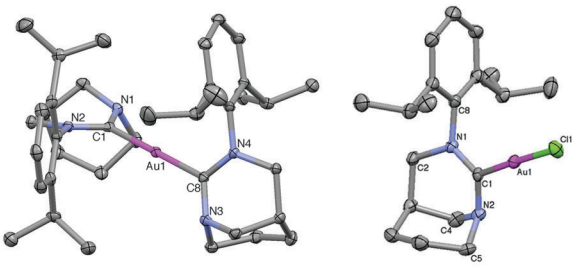


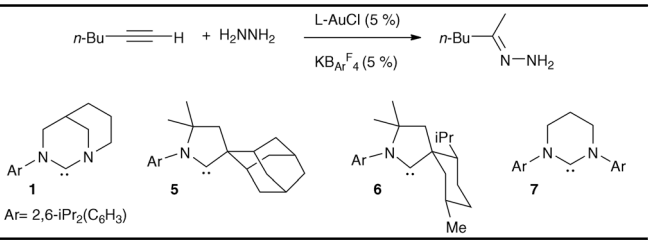
Fig. 1 X-ray structure of **2** (left) and **1·AuCl** (right) with thermal ellipsoids drawn at 50% probability level. Triflate anion of **2**, hydrogen atoms and solvent molecules are omitted for clarity.

instead of the desired complex **1·AuCl**. Under the same experimental conditions, but using two equivalents of carbene **1**, complex **2** was isolated in good yield (85%) and fully characterized. In the ^{13}C NMR spectrum, both carbene ligands gave a single set of signals, including a singlet at 223 ppm, in the range expected[18] for a carbene carbon coordinated to gold, indicating the diastereoselective formation of the bis(carbene)gold complex **2**. An X-ray diffraction study showed that it was the *meso* isomer (Fig. 1).

Bis(carbene) gold(I) complexes[19] are known to be catalytically inactive, and therefore we looked for an alternative synthetic route to access complex **1·AuCl**. We reported that metal free carbene **1** could only be isolated if separated from hexamethyldisilazane (HMDS) at −78 °C, otherwise the carbene inserts into the NH bond of HMDS upon warming to −20 °C, giving adduct **3**.[16] However, careful examination of the ^{13}C NMR spectrum of the crude reaction mixture of **1·H$^+$** with KHMDS revealed that, in addition to **3**, small amounts (approx. 5%) of unreacted carbene **1** and free HMDS, were present even at room temperature. Importantly, the corresponding NMR signals persisted despite two succesive crystalizations of **3** (Fig. 2). These results demonstrate that the insertion of carbene **1** into the N–H bond of HMDS is reversible and that this unprecedented equilibrium is not completely shifted towards adduct **3**.[20]

We wondered whether the slow release of carbene **1** in the presence of a gold(I) precursor could prevent the formation of bis(carbene) gold complex **2** and favor the selective formation of the mono(carbene) gold(I) chloride complex **1·AuCl**. Indeed, addition of freshly prepared **3** to a slight excess of (tetrahydro thiophene)gold(I) chloride yielded, after stirring overnight at room temperature, the desired **1·AuCl**, which was isolated in 57% yield, and comprehensively characterized including a single crystal X-ray diffraction study (Fig. 1). Importantly, **1·AuCl** is stable for weeks in solution and in the solid state. No evidence of disproportionation into **2** was observed.

Table 1 Catalytic hydroamination of 1-hexyne with hydrazine



Entry	L	Solvent	Temp.	Time (h)	Conversion[a] (%)
1	**1**	$CDCl_3$	rt	3	42
2	**1**	CD_2Cl_2	rt	3	56
3	**1**	THF-d_8	rt	3	68
4	**1**	C_6D_6	rt	3	91
5	**5**	C_6D_6	rt	4	22
6	**6**	C_6D_6	rt	16	10
7	7	C_6D_6	rt	16	<5

[a] Determined by ^1H NMR with 1,4-di-*tert*butylbenzene as an internal standard.

In marked contrast with CAAC–gold complexes, which typically require a temperature higher than the standard boiling point of the solvent, a mixture of **1·AuCl** (5 mol%) and $KB_{Ar}{}^{F}{}_{4}$ (5 mol%) promoted the hydrazine hydroamination of 1-hexyne at room temperature. A brief screening of solvents (Table 1, entries 1–4) showed that benzene gave the best results; a 91% conversion was reached after 3 hours (entry 4). Under the same experimental conditions, only a 20% conversion was observed after 4 hours with the C-adamantyl substituted CAAC **5** as ligand, and 10% conversion after 16 h in the case of CAAC **6**, which features a more bulky menthyl group (entries 5 and 6); the six-membered classical NHC **7** proved to be even less efficient (entry 7).

As shown in Table 2, for alkyl substituted terminal alkynes, the efficiency of the catalyst decreases when the steric hindrance of the substrates increases (entries 1–5). Note that for the extreme case of *tert*-butyl acetylene, only a 29% conversion was observed after 1.5 day at room temperature, completion of the reaction required heating at 90 °C for 6 h. The activation of electron-poor alkynes is of course more challenging. Phenyl-, anisyl- and 1-cyclohexenyl-acetylenes, weakly react at room temperature. However, the corresponding hydrazones were obtained in good to excellent yields after heating at 75–90 °C for few hours (entries 6–9). The hydrohydrazination of diphenylacetylene occurs with complete conversion in chloroform within 6 hours but only at 110 °C (entry 10).

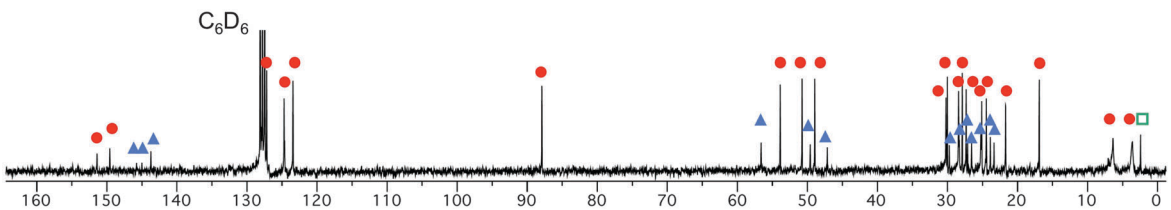
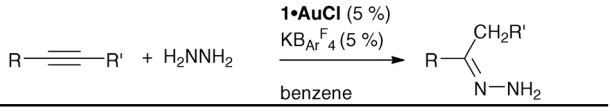


Fig. 2 ^{13}C NMR spectra of purified **3** (●) after a night at room temperature in C_6D_6, featuring signals of free carbene **1** (▲) and $HN(SiMe_3)_2$ (□).

Table 2 Catalytic hydroamination of alkynes with hydrazine



Entry	R, R′	Temp.	Time (h)	Conversion[b] (%)	Yield (%)
1	*n*Butyl, H	rt	3	91	83
2	Cyclohexyl, H	rt	18	78	71
3	Benzyl, H	rt	4	87	83
4	*tert*Butyl, H	rt	36	29	—
5	*tert*Butyl, H	90 °C	6	88	79
6	Phenyl, H	rt	12	<5	—
7	Phenyl, H	90 °C	3	100	87
8	4-Methoxyphenyl, H	90 °C	4	100	95
9	1-Cyclohexenyl, H	75 °C	6	100	77
10[a]	Ph, Ph	110 °C	6	100	82

[a] $CDCl_3$ was used as the solvent. [b] Determined by ^{1}H NMR with 1,4-di-*tert* butylbenzene as an internal standard.

The last result indicates that the high efficiency of **1·AuCl** may be limited to terminal alkynes.

To summarize, the anti-Bredt NHC gold(I) complex **1·AuCl** promotes the addition of hydrazine to terminal alkynes under unprecedented mild conditions. Since the electronic properties (strong σ-donor and π-acceptor) of anti-Bredt NHCs are similar to those of CAACs, the superior catalytic activity of **1·AuCl** can be attributed to steric factors. In contrast to the CAAC series, the non-hindered mono(anti-Bredt)NHCs gold complex **1·AuCl** does not undergo a dismutation into a catalytically inactive bis(carbene) gold(I) complex.

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