Gold Complexes

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A Cyclization–Rearrangement Cascade for the Synthesis of Structurally Complex Chiral Gold(I)–Aminocarbene Complexes**

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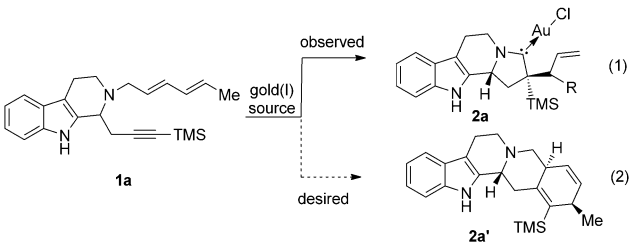
Dedicated to Professor George M. Whitesides on the occasion of his 75th birthday

Abstract: *A facile synthesis of chiral cyclic alkyl amino-carbene–gold(I) complexes from gold-free 1,7-enyne substrates was developed. The novel cyclization–rearrangement reaction sequence is triggered by the addition of (Me_2S)AuCl to different 1,7-enynes and leads to structurally unique carbene–gold(I) complexes in high yields. These novel complexes are catalytically active and inhibit the proliferation of different human cancer cell lines.*

Gold carbene chemistry has undergone rapid growth in the last decade[1] and carbene–gold complexes have found widespread applications in catalysis,[2] supramolecular chemistry,[3] liquid crystal research,[4] and medicinal chemistry.[5] The replacement of traditionally employed N-heterocyclic carbenes (NHC) in gold complexes by cyclic alkyl amino carbenes (CAAC)[6] leads to a unique class of stable gold-carbenes.[7] CAACs contain a σ-donor sp^3 carbon adjacent to the carbene and they may coordinate transition metals better than NHCs, thiazolidine, and P-heterocyclic carbenes (PHCs). The steric bulk on the quaternary carbon α to the carbene in CAAC–gold complexes further differentiates them from gold complexes with other ligands, including NHCs. Although, CAAC–Au complexes have shown promising properties and interesting reactivity profiles,[6–8] the field is still in its infancy. Clearly, further synthetic developments providing access to structurally diverse complexes and their exploration are in high demand. A frequently used synthesis strategy employs the cyclization of metal-free precursors to the corresponding carbene complexes of gold(I) and gold(III) as the key step.[8] Although appealing, this strategy has not yet yielded CAAC–gold(I) complexes. Previous syntheses of CAAC–Au^I complexes follow multistep protocols that require the isolation of the free carbene, which has to be bound to the metal center in a separate step, thus severely limiting the scope to a few gold complexes.[6,9] The presence of a stereogenic center at the C5 position next to the carbene makes this class of carbenes unique and is highly important for the stability and the catalytic properties of the carbene or its metal complexes. Currently available synthesis methods do not allow the introduction of sufficient structural diversity at the quaternary carbon atom next to the carbene which limits the possibilities to optimize the carbene or its metal complexes for different applications. Here we report a novel and efficient one-step procedure for the synthesis of chiral CAAC–Au^I complexes from simple gold-free precursors through a mechanistically unique cyclization–rearrangement sequence. This cascade transformation was serendipitously discovered during efforts aimed at the synthesis of hexacyclic compounds inspired by the alkaloid yohimbine by means of gold-catalyzed annulation [Scheme 1, Eq. (1) versus Eq. (2)].

As depicted in Equation (3) (Table 1), the protocol for the formation of CAAC–Au^I complexes involves the treatment of a 1,2-dichloroethane solution of ene-yne **1** with a solution of (Me_2S)AuCl under argon in the dark at 40 °C for the indicated period of time. The cyclization substrate derived from the tetrahydro-β-carboline moiety by formal derivatization of the NH with a 2,4-hexadien-1-yl moiety (compound **1a**) within 18 h cleanly delivered the CAAC–Au^I complex **2a** in 90 % yield (Table 1 and Figure 1). The apparent cyclization–rearrangement cascade gives direct access to novel and



Scheme 1. Discovery of a novel cyclization–rearrangement that gives access to chiral CAAC–Au^I complexes.

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Table 1: Formation of cyclic alkyl amino carbene gold complexes by direct cyclization of metal free precursors.

Entry	Substrate	Time [h]	Yield [%]	Product[a]
1	R = –Me, **1a**	18	90	R = –Me, **2a**
2	R = –*i*Pr, **1b**	18	95	R = –*i*Pr, **2b**
3	R = –Me, **1c**	18	75	R = –Me, **2c**
4	R = –Ph, **1d**	18	79	R = –Ph, **2d**
5	R = –Ph–OMe, **1e**	18	86	R = –Ph–OMe, **2e**
6	R = –Ph–MeO, **1f**	22	75	R = –Ph–MeO, **2f**
7	R = –Ph–NO_2, **1g**	34	73	R = –Ph–NO_2, **2g**
8	R = –Ph–NMe_2, **1h**	18	46	R = –Ph–NMe_2, **2h**
9	**1i**	18	61	**2i**
10	**1j**	18	98	**2j**

[a] Typical reaction conditions: A solution of $(Me_2S)AuCl$ in 1,2-DCE (0.02 M) was added dropwise to the stirred solution of the cyclization substrate in 1,2-DCE (0.02 M) at 25 °C under argon, protected from light. The flask was flushed with argon and then inserted into an oil bath at 40 °C and heated for the indicated amount of time. For details, see the Supporting Information.

structurally complex as well as chiral CAAC–gold complexes in a highly stereoselective manner. The scope of the reaction with different substrates is depicted in Table 1 (entries 1–10).

An X-ray diffraction analysis of a single-crystal of compound **2a**, obtained by slow evaporation of a dichloromethane (DCM) solution at room temperature, corroborated the product as the CAAC–Au^I complex (Figure 1).[10] The expected linear coordination of the two ligands on the gold atom (C14-Au-Cl angle of 179.1°) in **2a** is in good agreement

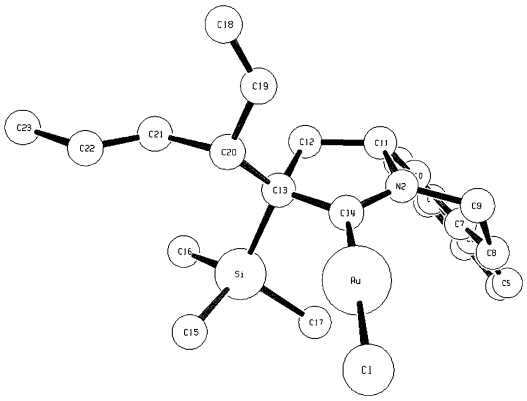


Figure 1. ORTEP plot of CAAC–Au^I complex **2a**; ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity.

with literature data[11] for related Au^I complexes.[12] The C14–Au bond (1.960 Å) is slightly shorter than typically reported for CAAC–Au^I complexes (1.983–1.987 Å),[11] suggesting an increased carbene nucleophilicity due to the β-silicon effect.[13] The β-silicon effect also seems to cause a slight distortion of the structural parameters pertinent to the carbene ring. In particular, the C14–C13 bond length (1.491 Å) appears shorter than values reported for CAAC–Au^I complexes with only carbon substituents (1.531–1.572 Å).[11] This finding suggests hyperconjugative stabilization of the carbene by the adjacent C13–Si σ-bond. In line with this argument, the C13–Si bond appears to be slightly elongated (1.933 Å) when compared to the typical values found in complexes with a TMS group (1.875 Å)[14] suggesting partial electron donation to the carbene center. Consistent with this model is the observation that the C14–N2 bond is slightly longer (1.330 Å) than typically reported for CAAC–Au^I complexes (1.259–1.304 Å).[11] Interestingly, ^{13}C NMR analysis of the carbene–gold complexes **2a–h** revealed an upfield shift of the carbene C1 signal ($\delta = 222.5$–225.9 ppm) as compared to the literature range reported for the carbene C1 of CAAC–Au^I complexes with only carbon substituents (235.0–239.9 ppm).[11] This observation is again consistent with a β-silicon effect observed in the crystal structure of **2a**.

Slight structural perturbations notwithstanding, the X-ray diffraction analysis provided a data set consistent with the proposed structure of **2a** as a CAAC–Au^I complex. This unique gold carbene complex displays interesting structural features that include: 1) the presence of a skipped diene side chain, indicative of allylic transposition of a 2,4-hexadien-1-yl moiety and 2) the perturbation of the position of the TMS group with respect to the alkyne terminus suggests that a 1,2-silicon shift had occurred.[15] These features clearly indicate that a multistep cascade process must have occurred involving gold-free enynes and leading to CAAC–Au^I complexes (**2**). To the best of our knowledge, chemical transformations involving an intramolecular allylic alkylation of this type with gold salts as substrates have not been reported before.

To explore the substrate scope of this mechanistically unique cascade process the substituents on the allyl moiety were varied. Ene-yne substrate **1b** with an isopropyl substituted *trans*-olefin yielded the corresponding carbene **2b** in

excellent yield under the same reaction conditions (entry 2, Table 1). As depicted in entry 2, substrate **1c**, incorporating a *trans*-crotyl moiety reacted efficiently to deliver CAAC–Au^{I} complex **2c** in 75% yield after chromatographic purification on silica gel. In order to introduce an aryl group on the quaternary carbon, the cinnamyl-substituted compound **1d** was employed, which reacted cleanly to deliver CAAC–Au^{I} complex **2d** as a white solid. The CAAC–Au^{I} complex **2d** was purified by successive rinsing with cyclohexane and cold DCM and single-crystals of **2d** were grown by slow evaporation from a DCM solution at room temperature. X-ray diffraction analysis of the resulting single-crystals unambiguously confirmed the structure of the CAAC–Au^{I} complex (Figure 2).[10]

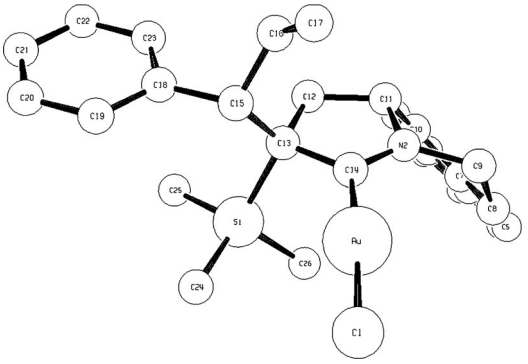
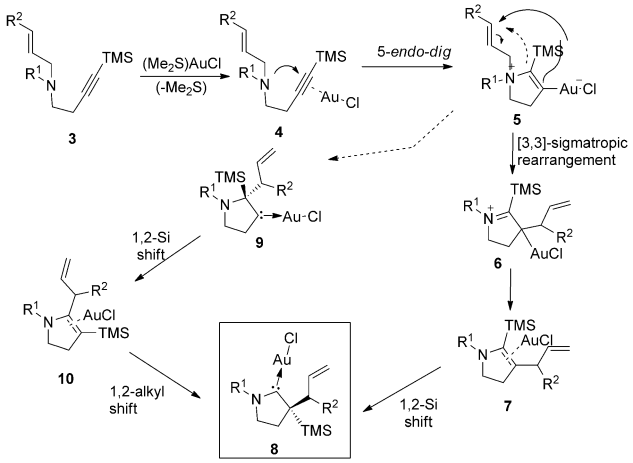


Figure 2. ORTEP of CAAC–Au^{I} complex **2d**; ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity. C14-Au-Cl 176.4°, C14–Au 1.985 Å, C14–C13 1.488 Å, C14–N2 1.291 Å, N2-C14-C13 111.2°, C13–Si 1.939 Å.

Complexes **2e**–**h** containing electron-rich and -poor aryl groups at the quaternary center of the carbene gold complex (Table 1) were prepared with similar efficiency. The reaction times strongly depend on the electronic and steric properties of the aryl substituents on the allyl system. In particular, the reaction of the sterically hindered *ortho*-methoxyphenyl compound **1f** required 22 h for complete conversion giving rise to complex **2f**. We were pleased to find that substrate **1g**, containing an electron-poor *p*-nitrophenyl group also reacted and yielded **2g** after 34 h at 40 °C. During the cyclization of substrate **1h**, in which the dimethylaniline functionality is incorporated, some amount of colloidal gold was formed and the carbene–gold complex **2h** was obtained in moderate yield (entry 8, Table 1).

In order to get access to CAAC–Au^{I} complexes with structurally different frameworks, substrate **1i**, derived from the tetrahydroisoquinoline scaffold, was employed in the carbene-forming reaction. Gratifyingly, the reaction efficiently led to the formation of complex **2i** in 61% yield. A structurally more simple carbene–gold complex **2j** embodying a monocyclic CAAC–Au^{I} complex was obtained from the acyclic substrate **1j** in excellent yield (entry 10, Table 1).

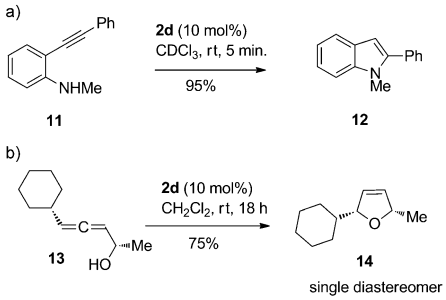
The observed migration of the trimethylsilyl group and the allylic system in the CAAC–Au^{I} complexes (**2**) supports the notion that a cyclization–rearrangement reaction sequence must have occurred. A mechanistic proposal for



Scheme 2. Carbene formation through 5-*endo-dig* cyclization followed by allylic alkylation and 1,2-Si shift.

the formation of CAAC–Au^{I} complexes is presented in Scheme 2. We assume that a gold-promoted 5-*endo*-dig cyclization of alkynylamine **3** leads to the formation of the zwitterionic vinyl–gold complex **5**.[7g] An aza-Cope type sigmatropic rearrangement yields iminium precursor **6** which eventually provides the gold(I)–olefin complex **7**. This intermediate then undergoes a 1,2-silicon migration[15] resulting in the carbene **8** as the final product.[16] In an alternative scenario, intermediate **5** can advance through alkylation on the β-carbon of the vinyl system, resulting in a high-energy carbene **9**, which can isomerize through carbon and silicon migrations to the thermodynamically more stable carbene **8**.[17]

The catalytic potential of the CAAC–Au^{I} complexes was ascertained in two intramolecular cyclization reactions (Scheme 3). The intramolecular hydroamination reaction of



Scheme 3. Cyclization reactions catalyzed by **2d**.

N-methyl-2-(2-phenylethynyl)aniline (**11**) formed the indole **12** [Scheme 3a].[7f] Thus, 10 mol% of gold complex **2d** in $CDCl_3$ at room temperature yielded the desired indole in 95% yield.[7f] The cycloisomerization of allenol **13**[18] was efficiently catalyzed by gold complex **2d** in dichloromethane yielding the substituted dihydrofuran **14** as a single diastereomer in high yield [Scheme 3b].[19]

Recently, it has been discovered that metallo-NHC complexes may inhibit the growth of cancer cell lines.[5a]

The CAAC–gold complexes (**2a–i**) described here contain additional structural features of indole alkaloid scaffolds, which are also often biologically active, including activity against cancer cells. Therefore, we investigated the novel carbenes in assays monitoring the viability of different cancer cell lines. The results of the screening (see Figure S1 in the Supporting Information) are very encouraging and suggest further medicinal chemistry research on CAAC–Au^I complexes. The human ovarian cancer cell line A2780 was highly sensitive to the carbenes **2a–i**, which displayed cytotoxicity at low micromolar or submicromolar concentration (IC_{50} range: 0.55 μM to 2.52 μM). A similar sensitivity was determined for the human colorectal adenocarcinoma cell line HT29 (except for **2a**, which was only mildly active). Gold complex **2i** appears to possess strong but nonselective anticancer activity against all cancer cell lines tested (IC_{50} range: 1.0 μM to 5.7 μM). However, other carbene complexes displayed interesting selectivity. Complex **2b** was cytotoxic to HeLa cells ($IC_{50} = 4.70 \pm 0.28$ μM) and was interestingly the only complex active against the breast cancer cell line MCF7 in micromolar concentration ($IC_{50} = 9.54 \pm 0.19$ μM). In addition, complexes **2b**, **2d**, and **2f** displayed activity against highly metastatic pancreatic cancer cells (IC_{50} range 7.42 to 10.0 μM) as well as a human colorectal cancer cell line (IC_{50} range 4.97 μM to 11.53 μM, for details see Figure S1).

In conclusion, we have discovered a novel cyclization–rearrangement cascade leading to structurally diverse chiral CAAC–Au^I complexes. This reaction sequence features a gold-promoted addition of a tertiary amine to an alkyne, an intramolecular allylic alkylation, and a 1,2-Si shift leading to CAAC–Au^I complexes. The structural features as well as the catalytic and biological potential of these novel carbene complexes should inspire research in different lines of applications.

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[10] CCDC 980994 (**2a**) and 980995 (**2d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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