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Saturated Abnormal NHC–Gold(I) Complexes: Synthesis and Catalytic Activity

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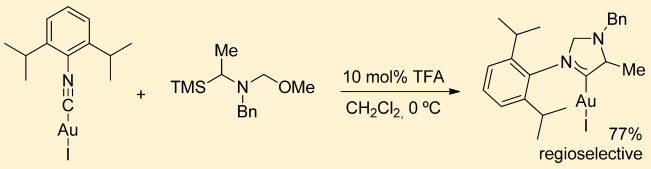
Supporting Information

ABSTRACT: New saturated abnormal N-heterocyclic carbene complexes of gold(I) have been prepared by a 1,3-dipolar cycloaddition of an in situ generated azomethine ylide with an isocyanogold(I) choride. A series of different substituents on the nitrogen atom of the 1,3-dipole are tolerated without problem. Substitutents on a carbon atom of the 1,3-dipole are problematic in the case of the isocyanogold(I) chlorides; only low yields are obtained. However, the corresponding isocyanogold(I) iodide shows good reactivity, and these abnormal N-heterocyclic carbenes bear the substituent in a position α to the carbene carbon, as proven by a crystal structure analysis of one of the products. Some of the new saturated abnormal N-heterocyclic carbene complexes were then tested in the gold-catalyzed phenol synthesis; moderate turnover numbers of 252–380 could be reached.



INTRODUCTION

Interest in the synthesis of N-heterocyclic carbene complexes (NHCs)[1] with reduced heteroatom stabilization[2] has increased in the last few years. In contrast to normal NHCs (**I**; Figure 1),

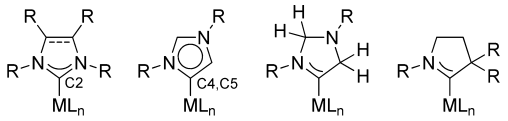


Figure 1. Normal NHC (**I**), unsaturated abnormal NHC (**II**), saturated abnormal NHC (**III**), and CAAC (**IV**).

the unsaturated abnormal NHCs (aNHCs, **II**; Figure 1) bear the metal at a carbon atom in the two-carbon tether and not at the carbon atom between the two nitrogen atoms. The saturated analogues, saturated aNHCs (**III**; Figure 1), with regard to the electronic situation very much resemble the very successful cyclic alkyl amino carbenes (CAACs, **IV**; Figure 1).[3] Both species possess only one nitrogen atom close to the carbene atom; in addition, the saturated aNHCs have one nitrogen atom in the backbone of the heterocyclic ring.

The first examples of unsaturated aNHC metal complexes were reported by the groups of Crabtree,[4] Lassaletta,[5] and Nolan.[6] Since the report of a free isolable unsaturated aNHC by Bertrand in 2009,[7] several unsaturated aNHCs have been bound to various elements, including palladium,[8] iridium,[9] and other transition metals,[10] as well as main-group elements.[11] New synthetic and catalytic applications are continuously appearing for these metal complexes, such as Suzuki–Miyaura cross-coupling,[6,8a,e] hydrogen transfer reactions,[9a,b,10c] and other transformations, probably due to the fact that the unsaturated aNHCs are stronger donors than their normal analogues.[2] Despite the interest in these compounds, the procedures for the synthesis of unsaturated aNHC metal complexes usually suffer from regioselectivity issues (normal versus abnormal binding mode), which are usually circumvented by blocking the C2 position of the heterocycle or by means of bulky substituents neighboring this position. Otherwise, mixtures of unsaturated aNHC and normal NHC complexes and low yields were typically obtained.[8d,9c,e] On the other hand, after one saturated intermediate was assumed during the preparation of an unsaturated analogue,[4] in a previous publication[12] we communicated the synthesis of saturated abnormal NHC–gold(I) complexes by [3 + 2] cycloaddition[13] between azomethine ylides and isocyanogold(I) complexes. In that study only the commercially available *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine was reacted with a variety of isocyanogold(I) complexes, giving access to saturated abnormal NHC–gold(I) complexes with different substituents on the nitrogen atom at the carbene carbon atom. This strategy completely avoids the regioselectivity issues, as the carbon atom which becomes the carbene carbon is already precoordinated to the metal in the isonitrile precursor, and thus it for the first time allows the synthesis of aNHCs even without bulky substituents flanking the carbene atom.

In the context of providing easy access to a library of NHC–gold(I) complexes starting from isocyanides,[14] we present here the synthesis of saturated abnormal NHC–Au(I) complexes bearing a variety of substituents both at the nitrogen next to the carbene carbon and at the nitrogen atom in the backbone as well as their evaluation as catalysts.

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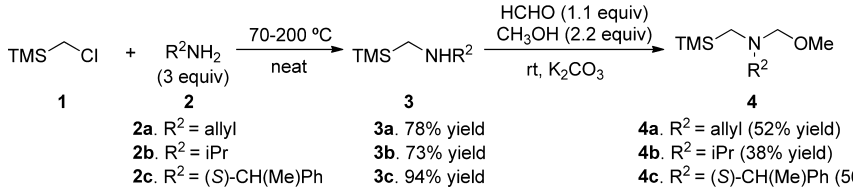
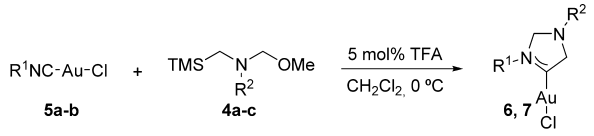
Scheme 1. Synthesis of the Precursors for Symmetrical Azomethine Ylides



RESULTS AND DISCUSSION

Synthesis of the aNHC–Gold(I) Complexes. For the preparation of saturated aNHC–gold(I) complexes with different substituents on the remote nitrogen of the heterocycle, we first needed to establish a reliable and practical route to the required azomethine ylide precursors. As shown in Scheme 1, a route proceeding through alkylation of amines **2** by the silylated building block **1** and subsequent installation of a methoxymethyl group on the synthetic intermediate **3** allowed us to place an allyl group and a chiral substituent at the central position of the building block **4**. Even though the second step of this short sequence is not highly efficient, the starting materials are readily accessible and thus overall even larger amounts of **4** can easily be prepared.

Table 1. Synthesis of Saturated aNHCs from Symmetrical 1,3-Dipole Precursors[a]



Entry	R^1 in **5**	R^2 in **4**	**6**, **7** (yield)
1	**(5a)**	**(4a)**	**6a** (68%)
2	**(5a)**	**(4b)**	**6b** (52%)
3	**(5a)**	**(4c)**	**6c** (73%)
4	**(5b)**	**(4a)**	**7a** (82%)
5	**(5b)**	**(4b)**	**7b** (61%)
6	**(5b)**	**(4c)**	**7c** (65%)

[a]Reaction conditions: 0.2 mmol of isocyanogold(I) complex **5**, 0.4 mmol of **4** (2 equiv), 0.01 mmol of trifluoroacetic acid, 2 mL of CH_2Cl_2, 1–3 h, 0 °C.

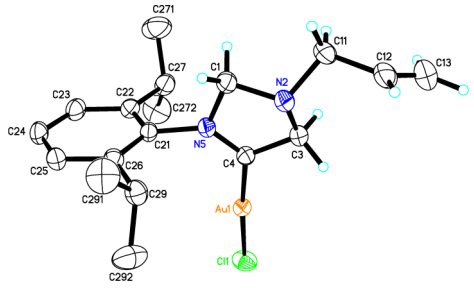


Figure 2. Solid-state molecular structure of **7a**.

In order to demonstrate a broad applicability of the methodology, the symmetrical 1,3-dipole precursors **4a–c** were reacted with isocyanogold(I) complexes **5a,b** in the presence of a catalytic amount of trifluoroacetic acid at 0 °C. These new results are summarized in Table 1. Although the yields differed, all six combinations were successful; the lowest yield (52%) was obtained in the case of **6b** (entry 2), and the best value (82%) was achieved with the allyl substituent (entry 4).

X-ray diffraction analysis of single crystals of **7a**, obtained by recrystallization from dichloromethane/hexane, unambiguously showed the abnormal binding mode (Figure 2).[15]

Precursors **10a–d** for asymmetrical 1,3-dipoles were synthesized following a strategy similar to that outlined in Scheme 1. The monoalkylation of benzylamine by means of commercially available (1-chloroethyl)trimethylsilane (**8a**) or readily accessible aromatic analogues **8b–d** (obtained by trimethylsilylation of the corresponding benzyl halides) afforded the secondary amines **9a–d**, which underwent methoxymethylation to yield the *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)amines **10a–d** (Scheme 2).

Initial attempts at cycloaddition of (*tert*-butylisocyano)-chlorogold(I) **5a** with **10a** provided only traces of the desired aNHC–gold(I) complex, independent of the amount of trifluoroacetic acid employed (5 or 30 mol %). Nevertheless, the cycloaddition of **5b** with the same 1,3-dipole precursor (**10a**) afforded the corresponding aNHC–gold(I) complex in a modest but considerable 23% yield with excellent regioselectivty (assignment of the obtained regioisomer by the crystal structure analysis of another substrate; see Figure 3). Encouraged by this result, we postulated that a modification of the isocyanogold(I) complex might lead to an improvement of the chemical yield—obviously in the two currently used fragments, the frontier orbitals did not match properly for an efficient cycloaddition.[16] According to Sustmann's classification,[17] azomethine ylides undergo type I cycloadditions. The dominant FMO interaction is that of the $HOMO_{dipole}$ with the

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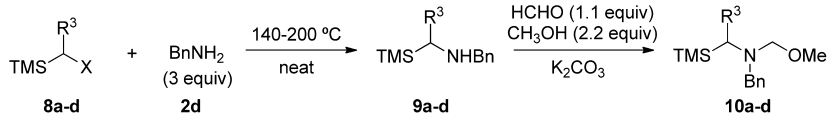
Scheme 2. Synthesis of the Precursors for Asymmetrical Azomethine Ylides

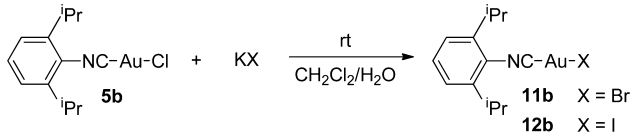


8a. X = Cl, $R^3 = CH_3$
8b. X = Br, $R^3 = C_6H_5$
8c. X = Cl, R^3 = 4-MeO-C_6H_4
8d. X = Br, R^3 = 4-Br-C_6H_4

9a. 78% yield
9b. 91% yield
9c. 82% yield
9d. 83% yield

10a. $R^3 = CH_3$ (69% yield)
10b. $R^3 = C_6H_5$ (72% yield)
10c. R^3 = 4-MeO-C_6H_4 (50% yield)
10d. R^3=4-Br-C_6H_4 (59% yield)

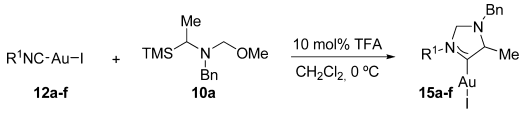
Scheme 3. Preparation of the Isocyanogold(I) Bromide and Iodide from the Corresponding Chloride by Metathesis

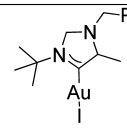
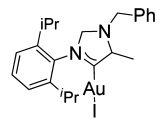
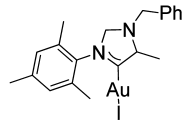
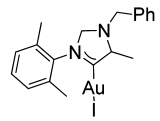
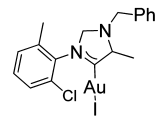
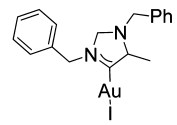


$LUMO_{alkene}$.[18] The alkyl donor on the azomethine ylide increases the $HOMO_{dipole}$ energy, and thus we assumed that increasing the LUMO energy of the isocyanogold(I) complex should reinstall reactivity. The two substituents, the aryl group on the isonitrile and the halide on the gold, were the only two options to achieve this. Since for a specific abnormal saturated NHC complex a modification of the aryl group was not desirable, we switched to bromide and iodide as less electronegative halides on the gold(I) center. Thus the analogous isocyanogold(I) bromide and iodide complexes **11b** and **12b**, prepared by simple ligand exchange from the chloro counterparts as shown in Scheme 3, were subjected to cycloaddition with 1,3-dipole precursor **10a** in the presence of catalytic amounts of trifluoroacetic acid. While the bromo derivative did not have any beneficial effect on the transformation, the analogous gold(I) iodide complex was by far superior and afforded the aNHC–Au(I) complex in a greatly improved yield (77%, Scheme 4). Since this halide ligand on the precatalyst is eliminated with the help of silver salts for the formation of the active catalyst anyway, there is no disadvantage in preparing the aNHC–Au(I) iodides instead of the common chlorides.

In order to show the versatility of the method, several aNHC–gold(I) complexes bearing different R^1 substituents were prepared (Table 2). It became evident that in the case of aliphatic substituents there were still problems; with the bulky ^{t}Bu substituent on the isonitrile (entry 1) only a 19% yield was achieved and with Bn also only 21% was isolated (entry 6). With aromatic substituents the yields were better; 46% of product was accessible in the case of **12d** (entry 4), and the other three combinations gave good yields between 62% and 77% (entries 2, 3, and 5).

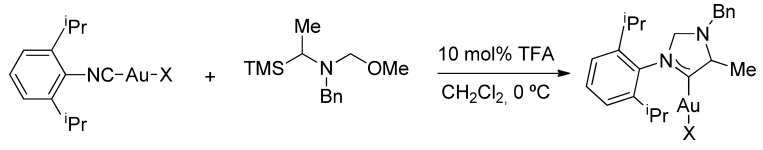
Table 2. Synthesis of Saturated aNHCs from Asymmetrical 1,3-Dipole Precursors[a]



Entry	R^1 in **12**	**15** (yield)
1	 (**12a**)	 **15a** (19%)
2	 (**12b**)	 **15b** (77%)
3	 (**12c**)	 **15c** (62%)
4	 (**12d**)	 **15d** (46%)
5	 (**12e**)	 **15e** (68%)
6	 (**12f**)	 **15f** (21%)

[a]Reaction conditions: 0.2 mmol of isocyanogold(I) complex **12**, 0.4 mmol of **10a** (2 equiv), 0.02 mmol of trifluoroacetic acid, 2 mL of CH_2Cl_2, 1–3 h, 0 °C.

Scheme 4. Superiority of the Iodide in 1,3-Dipolar Cycloaddition with 1-Methyl-2-benzylazomethine Ylide



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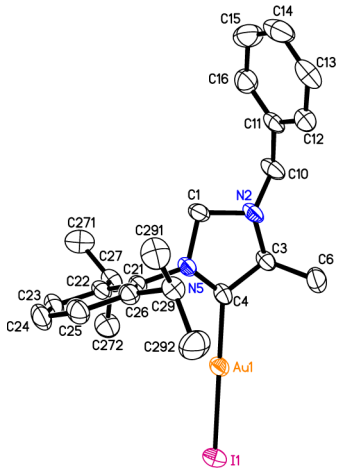


Figure 3. Solid-state molecular structure of **15b**.

The regioselectivity in this case could be unambiguously confirmed by an X-ray crystal structure analysis of **15b** (Figure 3);[15] the methyl group is at the position next to the carbene carbon. It must be noted that the regioisomeric compound with the methyl substituent in the position between the two nitrogen atoms has not been detected.

Aryl-substituted compounds **10b–d** were also reacted with the isocyanogold(I) iodide complex **12b** in the presence of 10 mol % of TFA. In all cases only a small amount of the corresponding saturated aNHC–Au(I) complex was observed. However, the use of a large excess of 1,3-dipole precursor **10b** (10 equiv) and a substoichiometric amount of trifluoroacetic acid (50 mol %) allowed the isolation of the saturated aNHC–Au(I) complex **16b** in a modest 31% yield (Scheme 5).

Test of the Catalytic Activity in the Furan-yne Reaction. As model reactions to evaluate the catalytic activity of the saturated aNHC–Au(I) complexes that were synthesized, gold-catalyzed phenol synthesis was chosen.[19] Since for this reaction for the substrates **17** and **19** already quite reasonable turnover numbers (TONs) had been achieved,[14d,20] we chose a catalyst loading of 0.25 mol % (with higher catalyst loadings a complete conversion to the product was achieved, and we wanted to explore the limit for the TON), more difficult test substrates (Scheme 6), and activation by $AgNTf_2$ according to Gagosz.[21] The results are summarized in Table 3.

Clearly all the catalysts are good catalysts; the TONs range from 252 to 336, which are good but not outstanding numbers for this type of test reaction, which follows a special mechanism.[22] These best TONs reached so far are 730 for **17**[23] and 1900 for **19**.[24]

Scheme 6. Two More Challenging Substrates Chosen for the Test Reactions

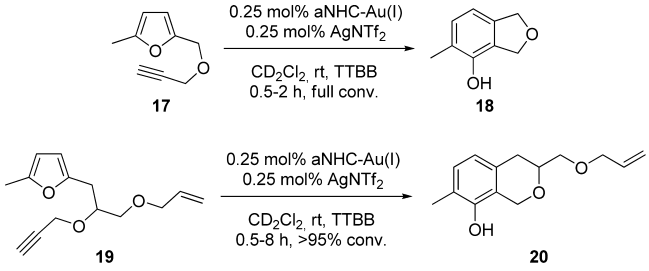
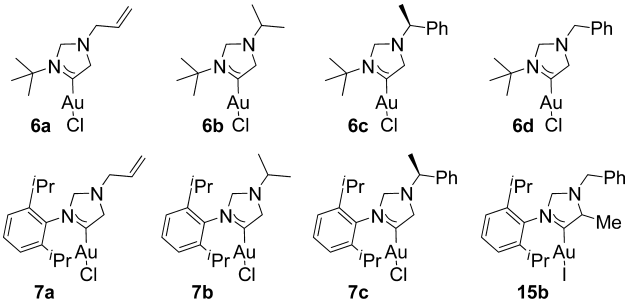


Table 3. Catalytic Studies with Abnormal NHCs[a]



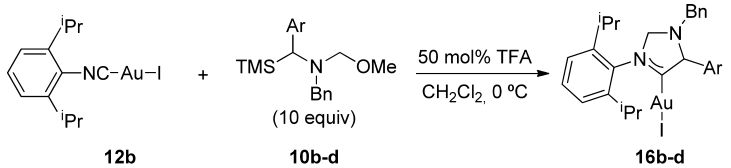
aNHC–Au(I)	yield of **18** (%)	TON for **18**	yield of **20** (%)	TON for **20**
6a	78	312	92	368
6b	63	252	91	364
6c	73	292	89	356
6d	64	256	88	352
7a	69	276	95	380
7b	66	264	92	368
7c	71	284	95	380
15b	78	312	95	380

[a]Reaction conditions: 200 μmol of substrate **17** or **19**, 0.50 μmol of aNHC–Au(I) (0.25 mol %), 0.50 μmol of $AgNTf_2$ (0.25 mol %), 8 μmol of tri-*tert*-butylbenzene as internal standard (TTBB), 600 μL of CD_2Cl_2, room temperature, 0.5–8 h. The yield was determined by ^{1}H NMR.

CONCLUSION

Now a broad variation of aNHC–gold(I) complexes are accessible, and the use of the gold(I) iodide precursor could be very useful for future access to other new carbene ligands by 1,3-dipolar cycloadditions. With functionalized side chains, such as the allyl group in this investigation, further modification of the aNHC complexes and even an attachment to solid supports[25] should be possible and should open new perspectives.

Scheme 5. Use of Isocyanogold(I) Iodides Does Not Allow an Efficient Synthesis with 1-Aryl-2-benzyl-Substituted Azomethine Ylide



16b. Ar = C_6H_5 (31% yield)
16c. Ar = 4-MeO-C_6H_4 (<10% yield)
16d. Ar = 4-Br-C_6H_4 (<10% yield)

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■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental details and characterization data and CIF files giving crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

[§]Crystallographic investigation.

Notes

The authors declare no competing financial interest.

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