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Au(III) complexes with tetradentate cyclam based ligands

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Abstract

Chiral cyclam (1,4,8,11-tetraazacyclotetradecane) derivatives were synthesized stepwise from chiral mono-Boc-1,2-diamines and (dialkyl)malonyl dichloride via the open diamide-di-(*N*-Boc-amino) intermediates (65-91%). Deprotection and ring closure with a second malonyl unit afforded the cyclam tetraamide precursors (80-95%). The new protocol allowed preparation of the target cyclam derivatives (53-59%) by a final optimized hydride reduction. Both the open tetraamine intermediates and the cyclam derivatives successfully coordinated with AuCl₃ to give moderate to excellent yields (50-96%) of the corresponding novel tetracoordinated *N,N,N,N*-Au(III) complexes with alternating five- and six-membered chelate rings. Testing of catalytic ability of the cyclam based *N,N,N,N*-Au(III) complexes demonstrated high catalytic activity of some complexes in selected test reactions (full conversion in 1-24h, 62-97% product yields).

Keywords

Au(III); Coordination studies; Cyclopropanation; carboalkoxylation ; cyclam derivatives

Introduction

The importance of gold for humankind dates long back, and gold is linked to the evolution of many parts of the society. Contrary to the general fascination and importance of gold, the potential as homogenous catalyst has been neglected, compared to a range of other transition metals. The utilization of gold in synthetic organic chemistry has become a topic of interest during the last decades, as evidenced by the increasing number of review articles published in this period.^[1] Whereas both gold(I) and gold(III) are proven to be catalytic active forms of gold, gold(I) has so far, received main attention, likely due to the higher stability, as demonstrated by development of a high number of gold(I) catalyzed transformation and ligated gold(I) complexes, along with improved mechanistic understanding.^[2] In contrast, gold(III) catalysis were for a long time mostly based on inorganic salts, such as AuCl₃, AuBr₃, or pyridine-AuCl₃ and Pic-AuCl₂. However, Au(III) complexes with various coordinated ligands are about to become more explored. Different from the linear coordination mode of gold(I), gold(III) forms square planar complexes. This allows for greater steric control around the reaction center by using polydentate ligands. An interesting group of ligands which may coordinate to all the four coordination sites of gold(III), are represented by polyamine ligands, such as cyclam (1,4,8,11-tetraazacyclotetradecane), cyclen (1,4,7,10-tetraazacyclododecane), ethylenediamine and triethylenetetraamine derivatives. Such polyamine coordinated Au(III) complexes have mainly been prepared for studies on selective uptake of Au(III) from water,^[3] for X-ray crystal structures,^[4] or for investigation of biological properties.^[5]

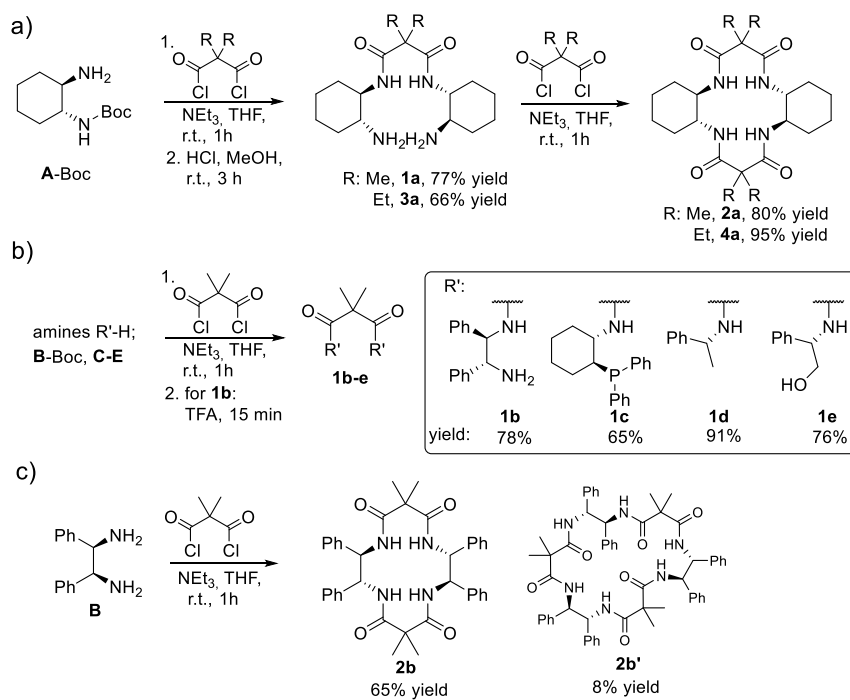
Cyclam is known as a tetraamino-macrocyclic ligand, which binds strongly to give complexes with many transition metal cations. While catalytic applications of square planar cyclam complexes are reported for metals, such as Ni,^[6] Cu,^[7] Fe^[8], catalytic properties of cyclam coordinated gold(III) complexes are not known. Triggered by this knowledge gap, we wanted to develop new chiral cyclam coordinated gold(III) complexes. Additionally, these

complexes were interesting for evaluation of the catalytic effect of the Au(III) complex upon substitution of all coordinating halides by nitrogen donors. We hereby present the synthesis of chiral cyclam ligands and related polyamino compounds, along with Au(III) coordination studies and evaluation of the catalytic ability of the successfully obtained Au(III) complexes in two model reactions.

Results and Discussion

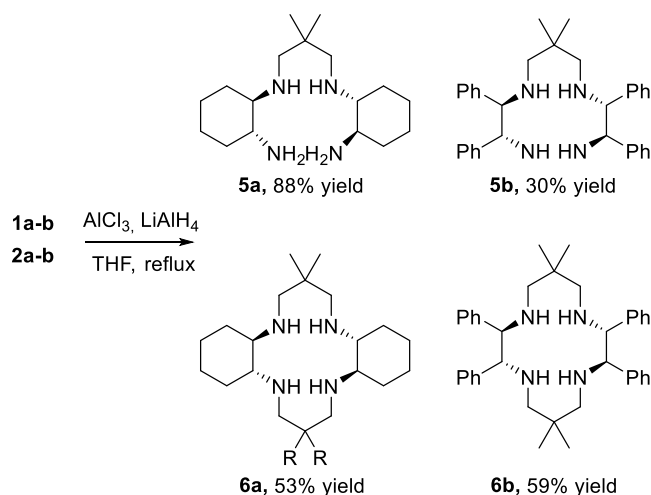
Synthesis of potential ligands:

Chiral cyclam derivatives have previously been directly synthesized from (1*R*, 2*R*)-cyclohexane-1,2-diamine (**A**) and malonyl dichloride,^[9] giving 36% yield of the wanted cyclam tetraamide product **2a**. Additionally, a macrocyclic by-product (14%) was formed by condensation of three units of diamine **A** and malonyl dichloride. To inhibit the formation of the trimer, we decided to prepare the cyclams in an indirect way. In fact, increased yields of cyclam derivative **2a** (68% yield over three steps) were obtained by malonyl reaction of the mono-Boc-protected diamine (**A**-Boc) followed by Boc-deprotection with HCl, and final ring closure of diamide-diamine intermediate **1a** with a second malonyl unit to give tetraamide product **2a** (Scheme 1a). The equivalent ethyl-substituted cyclam **4a** was prepared in comparable yield (63% over the three steps) by the same method with diethylmalonyl chloride. This method also allowed for isolation of the open diamide-diamine **1a** (77%). In addition, the similar potential ligands **1b-e** (65-91%, Scheme 1b) were likewise prepared from amines **B-E**. The phenyl-substituted cyclam tetraamide derivative **2b** was prepared by the original direct method^[9] (65%, Scheme 1c), as the mono-Boc amine **B**-Boc was less accessible.



Scheme 1. Synthetic protocols for preparation of potential ligands **1-4**.

As amide coordination to Au(III) in general is challenging, and not successful in our hands, as discussed below, we wanted to prepare the reduced amine products (**5a-b**, **6a-b**) from amides **1a-b** and **2a-b**. Initially, by refluxing diamide-diamines **1a-b** and cyclam amide precursors **2a-b** in THF with LiAlH_4 for 3 days,^[9] complex product mixtures of partly and fully reduces species were obtained for all amides except **2a**. In order to activate the amides for reduction, improved reaction conditions were obtained by adding AlCl_3 to the reactions. Complete reduction of polyamides **1a-b** and **2a-b** yielded the open tetraamine products **5a-b** and the target cyclams **6a-b** with four secondary amine functions in moderate to high yields (30-88%, Scheme 2) within 1 - 2 days.



Scheme 2. Reduction of diamides **1a-b** and tetraamides **2a-b**.

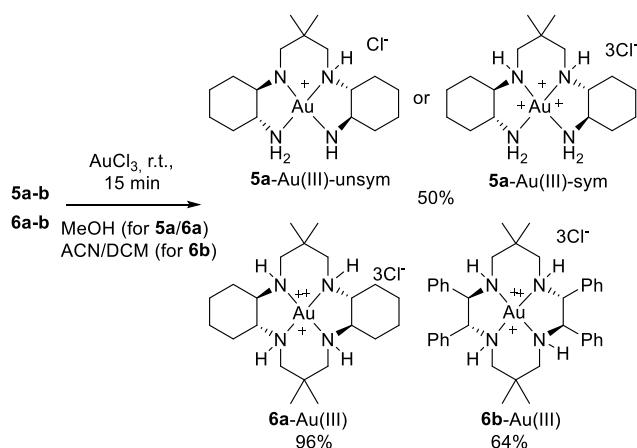
Au(III) coordination studies:

Amide coordinated Au(III) complexes has so far scarcely been reported.^[10] This is likely a result of the electron deficient character of the amide nitrogens. Coordination was initially tested with the cyclam tetraamide derivatives **2a-b** and **4a**. Judged from ¹H NMR, these ligands showed no interaction with Au(III), as expected. Similar resistance to coordinate was observed for the open diamides **1c-e**. The phosphorus containing ligand **1c** did undergo phosphorus oxidation instead of Au(III) coordination. No effect was obtained by refluxing or by adding additives, such as silver salts, NaOH or NH₄PF₆.

Given the previously reported coordinating studies of unsubstituted cyclam,^[3a, 4b, 5h] the prepared new tetraamine ligands **5a-b** and **6a-b** (Scheme 2) were promising candidates for Au(III) coordination. Both ligands **5a** and **6a** readily coordinated with AuCl₃ in methanol and gave moderate to excellent yields of tetracoordinated **5a**-Au(III) and **6a**-Au(III) *N,N,N,N*-complexes with alternating five- and six-membered chelate rings (50% and 96%, respectively, Scheme 3).

Monitoring the formation of complex **5a**-Au(III), using ¹H NMR, and ¹H,¹⁵N HMBC, clearly indicated a tetra-nitrogen-coordinated complex. This was evidences by changes in NMR shift values, $\Delta\delta^{15}\text{N}_{\text{coord}} = \delta^{15}\text{N}_{\text{complex}} - \delta^{15}\text{N}_{\text{ligand}}$, by coordination. The observed $\Delta\delta^{15}\text{N}_{\text{coord}}$ values

were in the range of 16.3 - 32.0 ppm for both the primary and secondary amine nitrogens, indicating a characteristic deshielding effects upon Au(III) coordination.^[11] Likewise, $\Delta\delta^1\text{H}_{\text{coord}}$ 0.3-0.5 ppm for all the neighboring N-CH and N-CH₂ protons indicated ligand tetra-coordination to Au(III), as well. The observation of four different ¹⁵N values for the nitrogens of ligands **5a** coordinate, in addition to ¹H and ¹³C indicating a unsymmetrical structure. Hence, the structure **5a**-Au(III)-unsym (Scheme 3), arise as the most likely structure, although not confirmed by X-ray analysis due to lack of suitable crystals. Comparable effects for ligand **6a**, $\Delta\delta^1\text{H}_{\text{coord}}$ 0.3-0.6 ppm, were also observed for the corresponding N-CH and N-CH₂ neighboring protons by formation of complex **6a**-Au(III) (Figure 1).



Scheme 3. Au(III) coordination conditions for ligands **5a-b** and **6a-b**. Coordination of **5b** was unsuccessful.

Further on, cyclam **6b** readily coordinated to AuCl_3 in a mixture of acetonitrile and dichloromethane, to obtain sufficient solubility of cyclam **6b**, allowing formation of **6b**-Au(III) in 64% yield (Scheme 3). The corresponding $\Delta\delta^1\text{H}_{\text{coord}}$ values of **6b**-Au(III) were similar to those discussed for **6a**-Au(III). Surprisingly, tetraamine **5b** did not behave in a similar way as the other ligands, instead giving a complex mixture, as judged by ¹H NMR, when attempted coordinated to Au(III). Changing the source of Au(III) or the solvents methanol, acetonitrile and dichloromethane did not improve the outcome. Both purification and characterization of

the Au(III) complexes were challenging as a result of low stability, and HRMS or elemental analysis could not be obtained, due to sample decomposition. Attempts to obtain crystals for X-ray analysis by slow diffusion of *n*-pentane into a DCM solution of the complexes, were unsuccessful.

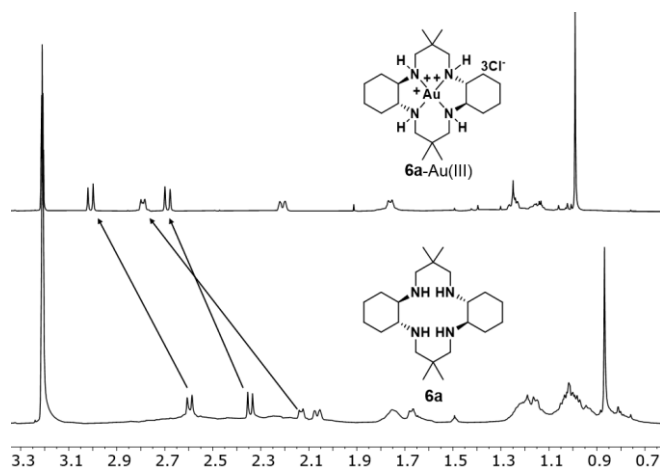


Figure 1. ¹H NMR study of the formation of complex **6a**-Au(III) by AuCl₃ coordination to ligand **6a**.

Catalytic activity:

For evaluation of the catalytic ability of the new Au(III) complexes, alkyne carboalkoxylation^[12] and cyclopropanation of styrene with propargylester^[13] (Table 1) were selected as test reactions. These reactions have previously been studied with different gold(I) and gold(III) catalysts and a variety of substrates, thus providing a solid background for comparison. A large difference in catalytic activity was observed for cyclam gold complex **6a**-Au(III) *versus* the open cyclam analogues **5a**-Au(III). Complex **5a**-Au(III) afforded full conversion in alkyne carboalkoxylation in 5.5 hours, compared to in 24 hours for complex **6a**-Au(III) (Table 1, entries 1-2). The same trend was observed for Au(III) catalysis of the cyclopropanation reaction, where complex **5a**-Au(III) and **6a**-Au(III) gave full conversion in 1 hour and 12 hours, respectively (Table 1, entries 4 and 5). The cyclopropyl product **11** was obtained in > 90% yield and high *cis* diastereoselectivity (up to 74% de), similar to our previous

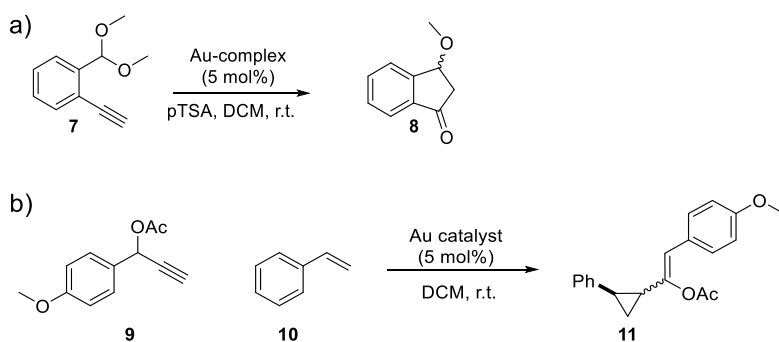
studies,^{13c} which showed that JohnPhos-Au(I) and pyr-menthol-Au(III) complexes provided high amounts of the initially formed *cis* diastereomer in this model reaction. In contrast, some BOX-Au(III) complexes have the additional ability to rapidly transform the initially formed *cis* product into the isomerized *trans* product. Thus, the proper choice of gold catalyst allows highly stereoselective formation of either *cis* or *trans* cyclopropanation products and facilitates isolation of pure isomers.

Despite the chiral nature of these ligands, no enantioselectivity was observed in the test reactions. Evaluation of complex **6b**-Au(III) in both reactions, revealed a large difference in catalytic activity and complex stability between the structurally similar **6a**-Au(III) and **6b**-Au(III) cyclam complexes, with a cyclohexyl and a diphenyl-C2 bridge between the nitrogens, respectively. In both test reactions, an immediate color change into dark red/brown took place after addition of complex **6b**-Au(III), indicating low stabilization of the coordinated diphenyl-ligand and fast release of Au. The de-coordination resulted in full conversion within 15 min in both reactions (Table 1, entries 3 and 6), compared to 24 and 12 hours for complex **6a**-Au(III) (Table 1, entries 2 and 5), where the ligand seems to stabilize and deactivate the Au(III) during the reaction. Attempts to improve the **6b**-Au(III) complex stability by anion exchange with less coordinating anions failed, as addition of different standard silver salts resulted in decomposition of the Au(III) complex. Consequently, the counter-anion exchange method was not possible.

Since the ligand **6b** seems to de-coordinate, resulting in the cyclam Au(III) complex not being the active catalyst, and the presence of chloride anions, the activity of the **6b**-Au(III) precatalyst was compared to AuCl₃. AuCl₃ showed slightly faster conversion into the product, 5 min vs. 15 min, however comparable *cis:trans* ratio was obtained. The reduced reaction time indicate that **6b**-Au(III) indeed is an precatalyst that needs some activation time before catalyzing the reaction.

Although the decomposition of complex **6b**-Au(III) resulted in rapid conversion into products, it is undesirable, as the impact of the ligand on the reaction selectivity is lost. This different stability, caused by small differences in the design of the two cyclam ligands, is in accordance with the unsuccessful Au(III) coordination of the diphenyl-C2 bridged **5b** ligand, in contrast to the readily coordinating cyclohexyl bridged **5a** tetraamine, as discussed above (Scheme 3).

Table 1. The catalytic activity of Au(III) complexes evaluated in a) alkyne carboalkoxylation and b) cyclopropanation of styrene with propargyl ester.



Entry	Complex	Reaction time	Yield product
a) Carboalkoxylation of alkyne			8:
1	5a -Au(III)	5.5 h	62%
2	6a -Au(III)	24 h	80%
3	6b -Au(III)	15 min	13%
b) Cyclopropanation			11 (<i>cis:trans</i>):
4	5a -Au(III)	1 t	90% (77:23)
5	6a -Au(III)	12 h	97% (87:13)
6	6b -Au(III)	15 min	58% (12:88)
7	AuCl ₃	5 min	80% (13:87)

Conclusion

A new stepwise procedure was developed for improved preparation of chiral cyclam derivatives (**5a-b**, **6a-b**) from chiral mono-Boc-1,2-diamines and (dialkyl)malonyl dichloride. The four-step approach included ring closure of the initial open diamide-diamines intermediates **1** with a second malonyl unit, affording the cyclam tetraamides **2**. The target cyclam derivatives (**5**, **6**) were obtained by optimized LiAlH_4 reduction by AlCl_3 activation of the polyamides (**1**, **2**).

Successful Au(III) coordination of the open tetraamine ligand **5a** and the new cyclam derivatives **6a-b** gave the corresponding tetracoordinated *N,N,N,N*-Au(III) cyclam **5a** and **6a-b** complexes (50-96%) with alternating five- and six-membered chelate rings. Verification of cyclam tetraamino-coordination was obtained by ^1H , ^{15}N HMBC NMR. The polyamides (**1**, **2**) failed to undergo Au(III) coordination, which confirmed the previously observed resistance of amides to coordinate to Au(III).

The catalytic ability of the new Au(III) complexes were screened in selected test reactions. High catalytic ability was shown for novel *N,N,N,N*-Au(III) complexes **5a** and **6a** in alkyne carboalkoxylation and propargyl ester cyclopropanation (full conversion in 1-24h, 62-97% product yields). No enantioselectivity was observed in the test reactions.

The activity and stability of the Au(III) complexes were strongly depending on the structure of the tetraamine ligands, demonstrating the importance of ligand design. Hence, the present study on cyclam based Au(III) complexes contributes to better knowledge of tetraamine ligand preparation and Au(III) coordination, as well as an increased understanding of Au(III) ligand design for optimal reaction outcomes.

Supporting Information

Supporting Information File 1

Experimental procedures and NMR data for new ligands and gold(III) complexes, as well as method for testing of catalytic activity.

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