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[19] Correct C,H analyses for **5** and **6** were obtained.

Cationic Gold(I) Complexes: Highly Efficient Catalysts for the Addition of Alcohols to Alkynes**

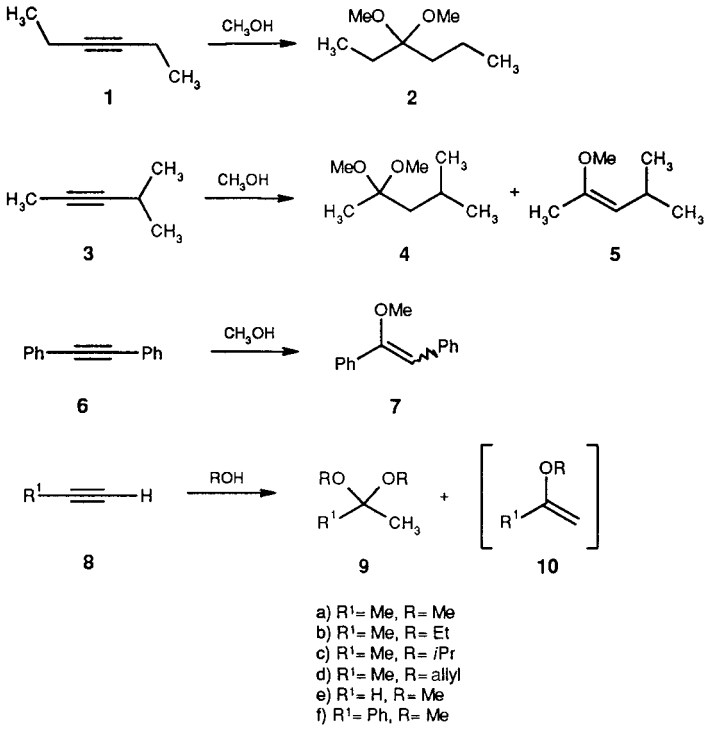
J. Henrique Teles,* Stefan Brode, and Mathieu Chabanas

In memory of Dr. Marco Häser

The mercury(II)-catalyzed addition of alcohols to alkynes has been known for almost three-quarters of a century.[1] The original catalyst has been further developed,[2] but its preparation by the heating of red mercury(II) oxide with boron trifluoride etherate and trichloroacetic acid in methanol still retains a touch of alchemy, and very little is known about the reaction mechanism.[2g] This material catalyzes the addition of primary, secondary, and even some tertiary alcohols to acetylene[2a] as well as to mono-[2b] and disubstituted acetylenes.[2c] However, it has the serious drawback that under the reaction conditions the mercury(II) is quickly reduced to metallic mercury, which is catalytically inactive, so 100 moles of product at most can be produced per mole of mercury(II) salt introduced.

An alternative mercury-free catalyst for this reaction has long been sought, but with little success.[3] Two recent papers describe the use of gold(III) catalysts ($NaAuCl_4$) for the addition of water and methanol to nonactivated alkynes,[4] but this catalyst shows the same disadvantage: It is quickly reduced to inactive metallic gold, so no more than 50 moles of product can be synthesized per mole of gold. The fact that the literature on homogeneous catalysis with gold complexes is extremely sparse,[4, 5] and that until recently gold was thought to be "catalytically dead,"[6] made the quest for an efficient gold(I) catalyst all the more interesting.

Here we report a new, very efficient class of gold(I) catalysts for the addition of alcohols to alkynes under mild conditions ($T = 20 – 50\,^{\circ}C$, H^+ as cocatalyst).[7] In numerous studies carried out in our laboratory we have found that cationic gold(I) complexes of the general type [L – Au^+] (where L is a phosphane, a phosphite, or an arsine)[8] are excellent catalysts for the addition of alcohols to alkynes. These catalysts achieve total turnover numbers of up to 10^5 moles of product per mole of catalyst, with turnover frequencies of up to 5400 h^{-1}. They are neither water nor air sensitive, and the reaction can usually be conducted without a solvent. Scheme 1 shows examples of the addition of alcohols to unsubstituted alkynes with methyl(triphenylphosphane)gold(I) and methanesulfonic acid as precursors for in situ generation of the catalyst.



Scheme 1. Addition of alcohols to unsubstituted alkynes in the presence of the catalyst prepared from methyl(triphenylphosphane)gold(I) and methanesulfonic acid.

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[**] We are obliged to Dr. M. Schulz and Dr. E. Zeller for helpful discussions and to Dr. N. Walker for the X-ray structure determination of **12**.

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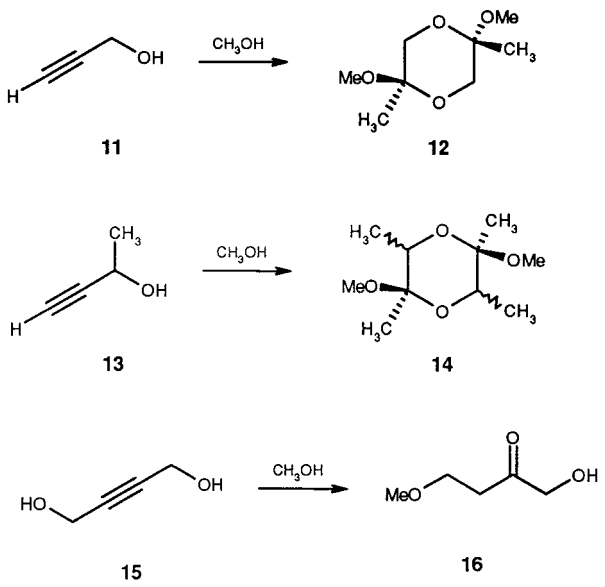
In the case of internal, symmetrical alkynes such as 3-hexyne (**1**), the only product formed in the presence of excess alcohol is 3,3-dimethoxyhexane (**2**).[9] With unsymmetrical alkynes such as methylisopropylacetylene (**3**) only acetal **4** is formed as a result of addition to the less sterically hindered position, together with a small amount of enol ether **5**. The regioselectivity of the gold catalysts is thus higher than that of mercury catalysts.[10] With diphenylacetylene (**6**) the main product is enol ether **7**, even in the presence of a large excess of methanol. At low conversions the *Z* isomer predominates ($Z:E \approx 8:1$), but in the course of the reaction it partially isomerizes (probably through the corresponding acetal), and at the end of the reaction the *Z*:*E* ratio is about 2:1, which is close to the equilibrium ratio.[11]

Terminal alkynes such as **8a–e** are also suitable substrates. In this case addition occurs almost exclusively at the more highly substituted carbon atom to produce the expected acetals **9a–e**. Phenylacetylene yields a mixture of the enol ether **10f** and the acetal **9f** in a ratio of 2:1.

Propargyl alcohols also react smoothly. 2-Propynol (**11**), 1-butyne-3-ol (**13**), and 2-butyne-1,4-diol (**15**) react with excess methanol to give the expected products **12**,[12] **14** (as a mixture of isomers), and **16**.[2f, 13] However, 1,4-dichloro-2-butyne and propynoic acid methyl ester do not react at all (Scheme 2).



Scheme 2. Gold(I)-catalyzed addition of methanol to propargyl alcohols.

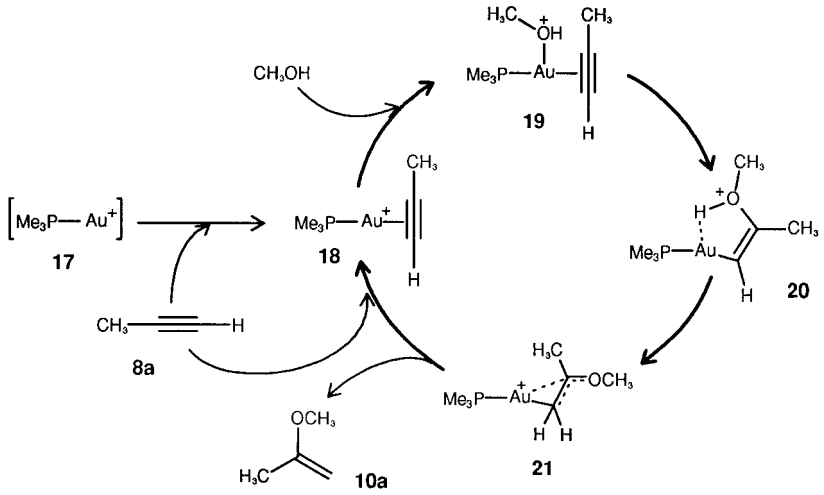
The reactivity of the alkynes increases with increasing electron density of the triple bond and decreases with increasing steric hindrance. The reactivity of the alcohols decreases by a factor of about ten when going form primary to secondary alcohols. Tertiary alcohols and phenols are unreactive.[14]

The influence of catalyst structure on activity was also studied, with the addition of methanol to propyne as a model reaction (**8a** + 2 MeOH → **9a**). The nature of the ligand L in the cationic gold complex has a considerable influence upon catalytic activity. Initial turnover frequencies for the addition of methanol to propyne were measured with different [L–Au$^+$] catalysts.[15] The activity order for the ligands tested was as follows (initial turnover frequencies [h^{-1}] in parentheses): Ph_3As (430) < Et_3P (550) < Ph_3P (610) < $(4\text{-F-}C_6H_4)_3P$ (640) < $(MeO)_3P$ (1200) < $(PhO)_3P$ (1500).[16] As expected, electron-poor ligands lead to an increase in activity, but the stability of the complexes decreases. The catalyst with L = $(PhO)_3P$ is more than twice as active as that with L = Ph_3P; however, the former is completely deactivated after only 2500 turnovers, whereas the latter is still active after 5000 turnovers.

As mentioned above, H$^+$ is necessary as a cocatalyst,[2h] but a Lewis acid such as boron trifluoride can also be utilized because it is rapidly hydrolyzed to trimethyl borate and HF under the reaction conditions.[17] The turnover frequency increases in a roughly linear fashion with the concentration of H$^+$.

Anions present in the solution are also a very important factor with respect to catalytic activity. With the combination [Ph_3PAuX] and $BF_3 \cdot OEt_2$ the reactivity increases as one progresses from soft to hard anions (initial turnover frequencies [h^{-1}] in parentheses): I^- (2) < Cl^- (7) < NO_3^- ≈ CF_3COO^- ≈ $CH_3SO_3^-$ (700).[18] For very hard anions the turnover frequency levels off, probably because of the presence of excess fluoride from the hydrolysis of BF_3. This interpretation is supported by the fact that the catalyst generated from [$Ph_3PAu(CH_3SO_3)$] and $BF_3 \cdot OEt_2$ (TOF = 700 h^{-1}) is less active than that generated under halide-free conditions from [Ph_3PAuCH_3] and CH_3SO_3H (TOF = 1500 h^{-1}).

Based on these experimental results and ab initio calculations[19] we propose the following mechanism for catalytic addition of alcohols to alkynes (illustrated in Scheme 3 for the addition of methanol to propyne). The cationic gold(I) complex **17**, generated for example by protonolysis of a methylgold complex, will not exist in free form but will instead coordinate with whatever donors are present in solution, as shown by ^{31}P NMR spectroscopy. If [Ph_3PAuCH_3] is treated with one equivalent of CH_3SO_3H in [D_2]dichloro-



Scheme 3. Proposed mechanism for the addition of methanol to propyne catalyzed by the trimethylphosphanegold(I) cation.

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methane at $-40\,^{\circ}C$ and then cooled to $-80\,^{\circ}C$, one observes in the ^{31}P NMR spectrum two broadened peaks at $\delta = 36$ and 28, which we attribute to dichloromethane and methanesulfonate complexes of the triphenylphosphanegold(I) cation.[20] Addition of five equivalents of methanol at $-80\,^{\circ}C$ gives rise to a single broad peak at $\delta = 38$, tentatively assigned to the methanol complex. If five equivalents of 3-hexyne are instead added at $-80\,^{\circ}C$ a single broadened peak is observed at $\delta = 28$ (tentatively assigned to the alkyne complex), which remains almost unchanged up to $0\,^{\circ}C$. Ab initio calculations provide the following relative stabilities for complexes between the trimethylphosphanegold(I) cation (**17**) and several neutral ligands (energies [kJ mol^{-1}] relative to the 2-butyne complex are given in parentheses): dichloromethane $(+63)$ < water $(+44)$ < acetylene $(+38)$ < methanol ≈ 1,4-dioxane $(+24)$ < propyne $(+18)$ < tetrahydrofuran $(+2)$ < 2-butyne (0) < dimethylsulfide (-18) < triphenylphosphane (-114). As expected, the soft bases triphenylphosphane and dimethylsulfide give the most stable complexes. Somewhat surprisingly, mono- and disubstituted alkynes are better ligands than methanol or dioxane, which favor the formation of **18**.

The gold(I) propyne complex (**18**) is then attacked by a molecule of methanol. Ab initio calculations predict this attack to occur by an associative mechanism that involves coordination of methanol to gold to give the intermediate complex **19**.[21] This precoordination is computed to be exothermic by -24 kJ mol^{-1}. The calculated activation energy for rearrangement of **19** to **20** is only 43 kJ mol^{-1}, and the overall reaction is exothermic by -37 kJ mol^{-1}. Both **19** and the transition state between **19** and **20** are sterically quite crowded, and this may be the reason why secondary alcohols react almost ten times more slowly than primary alcohols. Interestingly, the isomer of **20** shown (the *Z* isomer) is stabilized by almost 10 kJ mol^{-1} with respect to the *E* isomer as a result of a close contact between gold and hydrogen (2.26 Å) within a planar five-membered chelating ring.

The rearrangement of **20** to **21** could in principle proceed along either of two pathways: deprotonation at oxygen with reprotonation at carbon, or a 1,3-hydrogen migration. The relative importance of these two pathways cannot easily be predicted with ab initio calculations. Nevertheless, we were able to locate the transition state for 1,3-hydrogen migration. This pathway, in which gold functions as a proton shuttle, has a computed activation energy of only 67 kJ mol^{-1}, and the migrating hydrogen atom is transferred to the position *cis* to the methoxyl group. However, rotation about the C–C double bond in **21** has a low activation energy (less than 70 kJ mol^{-1}). The catalytic cycle is then closed by a ligand exchange that again produces **18** (this ligand exchange is calculated to be endothermic by 41 kJ mol^{-1}). Another possibility is that intermediate **21**, whose structure resembles that of protonated 2-methoxypropene, adds a second mole of methanol and then undergoes protodeauration to give 2,2-dimethoxypropane directly. These pathways are indistinguishable, because under the reaction conditions there is very rapid equilibrium between methanol, 2-methoxypropene, and 2,2-dimethoxypropane.

Experimental Section

Typical procedure for the addition of methanol to propyne: A mixture of methanol (2.5 mol) and a Lewis or Brønsted acid (1.25 mmol) was heated to $40\,^{\circ}C$ and saturated with propyne before the gold catalyst (0.125 mmol Au) was added.[8] During the reaction a continuous stream of propyne was introduced at a constant rate. Aliquots were taken at regular intervals, and the reaction was quenched by addition of an excess of solid sodium methanolate. The concentrations of methanol, 2,2-dimethoxypropane, and 2-methoxypropene were determined by GC and used to calculate turnover numbers and frequencies.

trans-2,5-Dimethyl-2,5-dimethoxy-1,4-dioxane (**12**): Propargyl alcohol (15.1 mol, 848 g, freshly distilled), methanol (59.6 mol, 1908 g), and concentrated sulfuric acid (15 mmol, 1.47 g) were mixed and heated to $55\,^{\circ}C$. A solution of methyl(triphenylphosphane)gold(I)[22] (148 μmol, 70.4 mg) in 125 mL of dioxane was then added within 10 h. The mixture was stirred for an additional 10 h, and then most of the remaining methanol was removed by distillation at reduced pressure. The residual solution was neutralized with 30% sodium methanolate in methanol and cooled in an ice bath. Precipitated product was collected by filtration and dried. A second batch of product can be obtained by further concentration of the mother liquor. Total yield of isolated product: 1238 g (93%). Colorless crystals, m.p. 127–129 °C (literature value: 126–128 °C).[12, 23]

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[10] Mercury-catalyzed addition of water to **3** leads to a 2:1 mixture of the two isomeric ketones 4-methyl-2-pentanone and 2-methyl-3-pentanone; J. W. Hartman, W. C. Hiscox, P. W. Jennings, *J. Org. Chem.* **1993**, *58*, 7613.

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[12] Compound **12** is formed as a mixture of two isomers that rapidly equilibrate under the reaction conditions. The *trans* isomer with methoxy groups in axial positions crystallizes preferentially from the reaction mixture and can be obtained pure in greater than 90% yield with only 10^{-4} mol% catalyst.
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[17] Amazingly, even HBF_4 is quickly hydrolyzed to trimethylborate under the reaction conditions.
[18] The same turnover rate ($700\ h^{-1}$) is observed when the catalyst is generated from the oxonium salt [$(Ph_3PAu)_3O^+BF_4^-$] and $BF_3 \cdot OEt_2$.
[19] All ab initio calculations were performed with the TURBOMOLE program package. For an overview of TURBOMOLE, see R. Ahlrichs, M. von Arnim in *Methods and Techniques in Computational Chemistry: METECC-95* (Eds.: E. Clementi, G. Corongiu) STEF, Cagliari, **1995**, P. 509–554. Geometries were calculated at the RI-DFT level (K. Eichkorn, O. Treutler, H. Ihm, M. Häser, R. Ahlrichs; *Chem. Phys. Lett.* **1995**, *242*, 652) with the Becke–Perdew functional and the TURBOMOLE SV(P) basis sets (K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theor. Chem. Acc.* **1997**, *97*, 119). For gold, the 60-mwb relativistic pseudopotential was utilized (D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123). Energies were calculated at the MP2 level with TZVP basis sets through the recently developed RI-MP2 implementation (F. Weigend, M. Häser, *Theor. Chem. Acc.* **1997**, *97*, 331).
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[21] Coordination of methanol with **18** to form the T-shaped complex **19** disturbs the structure only slightly. The angle between phosphorus, gold, and the center of the triple bond changes from 179° in **18** to 175° in **19**. The Au–O bond in **19** is very long (3.7 Å compared to 2.1 Å for a Au–O single bond), and the P-Au-O angle is 83°.
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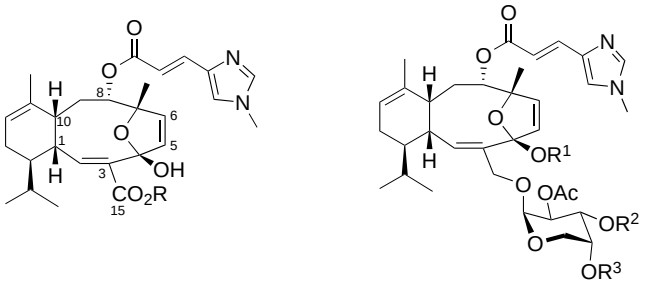
Synthesis and Biological Activity of Sarcodictyins**

K. C. Nicolaou,* Sanghee Kim, Jeffrey Pfefferkorn, Jinyou Xu, Takashi Ohshima, Seijiro Hosokawa, Dionisios Vourloumis, and Tianhu Li

Isolated from certain species of soft corals, the sarcodictyins (**1**, **2**),[1, 2] eleutherobin (**3**),[3, 4] and the eleuthosides (**4**, **5**)[5] have become important synthetic targets because of their novel molecular architectures, biological activities, and medicinal potential (Figure 1). Of special interest is their taxol-like mechanism[6] of action, which involves tubulin polymeri-



1: R = Me
2: R = Et

3: R^1 = Me, R^2 = H, R^3 = H
4: R^1 = H, R^2 = Ac, R^3 = H
5: R^1 = H, R^2 = H, R^3 = Ac

Figure 1. Structures of sarcodictyins A (**1**) and B (**2**), eleutherobin (**3**), and eleuthosides A (**4**) and B (**5**).

zation and microtubule stabilization and results in tumor-cell death. The combination of the scarcity and the appealing biological activity of these materials prompted us to initiate a program directed at their chemical synthesis. We recently disclosed the first total syntheses of sarcodictyin A (**1**)[7] and eleutherobin (**3**).[8] Here we report the first synthesis of sarcodictyin B (**2**), the construction of a sarcodictyin library, and the tubulin-polymerization and cytotoxic properties of members of that library, including their action against a number of taxol-resistant tumor-cell lines.

To conveniently access a sarcodictyin library, an improved method for their construction was devised (Scheme 1), which

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