

Stereo- and Regioselective Alkyne Hydrometallation with Gold(III) Hydrides

Anna Pintus, Luca Rocchigiani, Julio Fernandez-Cestau, Peter H. M. Budzelaar,* and Manfred Bochmann*

Dedicated to Professor Gerhard Erker on the occasion of his 70th birthday

Abstract: The hydroauration of internal and terminal alkynes by gold(III) hydride complexes $[(C^{\wedge}N^{\wedge}C)AuH]$ was found to be mediated by radicals and proceeds by an unexpected binuclear outer-sphere mechanism to cleanly form *trans*-insertion products. Radical precursors such as azobisisobutyronitrile lead to a drastic rate enhancement. DFT calculations support the proposed radical mechanism, with very low activation barriers, and rule out mononuclear mechanistic alternatives. These alkyne hydroaurations are highly regio- and stereospecific for the formation of *Z*-vinyl isomers, with *Z/E* ratios of >99:1 in most cases.

Gold vinyl complexes have frequently been implicated as intermediates in gold-catalyzed transformations of alkynes and allenes,^[1–3] most commonly by nucleophilic attack.^[2] Although vinyl complexes can be obtained by transalkylation,^[4] in a number of cases they could also be isolated as reaction intermediates,^[5,6] including some rare examples of structurally characterized gold(III) vinyl compounds.^[7]

The formation of gold vinyl complexes by hydroauration, that is, addition of gold hydrides to C–C multiple bonds, has been reported in only two cases. Tsui et al. showed that the gold(I) hydride $[(IPr)AuH]$ reacts with internal alkynes, $RC\equiv CR$, under *trans* insertion if $R = COOMe$, but there was no reaction with $R = Et$ or Ph [$IPr = 1,3$ -bis(2,6-diisopropylphenyl)imidazol-2-ylidene].^[8] More recently, we isolated the gold(III) hydride $[(C^{\wedge}N^{py^{\wedge}}C)AuH]$ (**1a**, Figure 1), which was found to insert allenes to give vinyl complexes, whereas acetylenes failed to react.^[9] Given the coordinative saturation of square-planar gold(III) compounds and the reluctance of these complexes to bind a fifth ligand, the mechanistic aspects

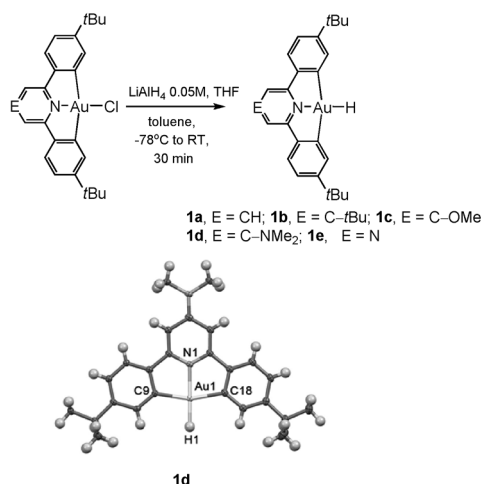


Figure 1. Synthesis of gold(III) hydrides and crystal structure of **1d**. The Au–H hydrogen atom was identified in the electron density map. Selected bond distances [Å] and angles [°] for **1d**: Au1–H1 1.64(5), Au1–N1 2.019(3), Au1–C9 2.060(3), Au1–C18 2.058(4); N1–Au1–C9 81.06(13), N1–Au1–C18 80.79(13), C9–Au1–H1 98.2(19), C18–Au1–H1 100.0(19), N1–Au1–H1 179.2(19), C9–Au1–C18 161.85(14). THF = tetrahydrofuran.

of these formal insertion reactions remained obscure. Such fundamental reactions have a direct bearing on the role of gold catalysts in organic transformations.^[10–12]

Gold(III) forms square-planar structures typical of d^8 transition metals, a complex type where ligand exchange kinetics are largely controlled by the *trans* effect.^[13] We therefore considered the possibility of enhancing the reactivity of the Au^{III} –H bond by introducing σ - and π -donor substituents at the 4-position of the pyridine ring, for example, *t*Bu (**1b**), OMe (**1c**), and NMe₂ (**1d**; Figure 1).^[14] In the course of these studies we discovered that trace amounts of radicals play an important role and greatly enhance gold hydride reactivity.

Treatment of $[(L^R)AuCl]$ with a THF solution of $LiAlH_4$ gave the hydrides **1a–d** in high yields.^[15] The pyrazine-based complex $[(C^{\wedge}N^{pz^{\wedge}}C)AuCl]$ ^[16] reacted similarly to give **1e**.

The Au–H NMR chemical shifts show only a slight dependence on the pyridine substituent: $\delta = -6.51$ (**1a**),^[9a] -6.41 (**1b**), -6.48 (**1c**), -6.26 (**1d**), and -6.50 (**1e**) (in CD_2Cl_2). The nature of the compounds was confirmed by the crystal structure of **1d**, which shows the NMe₂ substituent coplanar with the pyridine ring. An analysis of the molecular charge distributions by density functional theory (DFT)

[*] Dr. A. Pintus, Dr. L. Rocchigiani, Dr. J. Fernandez-Cestau, Prof. Dr. M. Bochmann
School of Chemistry, University of East Anglia
Norwich Research Park, Norwich, NR4 7TJ (UK)
E-mail: m.bochmann@uea.ac.uk

Prof. Dr. P. H. M. Budzelaar
Department of Chemistry, University of Manitoba
Winnipeg, Manitoba R3T 2N2 (Canada)
E-mail: Peter.Budzelaar@umanitoba.ca

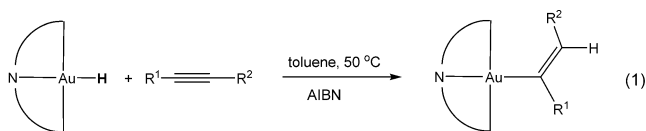
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under <http://dx.doi.org/10.1002/anie.201607522>. CCDC 1495244, 1495245, and 1495246 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

calculations showed only a marginal effect of the pyridine *p*-substituents on the Au–H bond polarity (see the Supporting Information), and indeed there was little difference in reactivity between the complexes.

For reasons of solubility we chose the methoxy derivative **1c** to explore hydroauration reactivity. Solutions of freshly prepared compounds were found to react with internal and terminal alkynes over several days to weeks ($[D_8]$ toluene, room temperature). Remarkably, the hydroaurations proceeded with essentially quantitative regio- and stereoselectivity, to give exclusively the *trans*-insertion products.

Given that square-planar gold(III) compounds of type **1** stabilized by rigid pincer ligands have no coordination sites available for substrate binding, the mechanism of this alkyne hydroauration was not obvious. Earlier computational attempts to search for the coordination of a phosphine to the metal perpendicular to the molecular plane had failed to find any evidence for an energy minimum.^[17] Computations with an alkyne as a possible ligand gave analogous results: there was no evidence for a coordinative alkyne–gold interaction. A [2+2] pathway by suitable alignment of the C≡C and Au–H bonds was therefore ruled out. This finding then led to the possibility of an outer-sphere mechanism, conceivably bimolecular. Such an outer-sphere pathway might be provided by the assistance of either a cation or possibly a radical. Given that our alkyne reactions were conducted in nonpolar solvents under mild reaction conditions, and also given the known light sensitivity of many gold compounds, the participation of trace amounts of radical species seemed most plausible.

Indeed, a partially complete alkyne insertion reaction was found to stop as soon as TEMPO was added as a radical scavenger (TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide). Conversely, the addition of a radical source such as azobisisobutyronitrile (AIBN) greatly accelerated the alkyne insertions and reduced the reaction time from days to minutes, without affecting the regio- and stereoselectivity of the process. To accelerate the decomposition of AIBN, the reactions were carried out at 50 °C [Eq. (1)].



A survey of alkynes with different substitution patterns and functional groups resulted in the formation of the vinyl complexes **2–13** (Table 1). In most cases only the *Z*-vinyl products could be detected, the exceptions being **10** and **13** where minor amounts of the *E* isomer were also formed. The structures were unequivocally assigned by NMR/NOE studies (see the Supporting Information). In particular, vinyl ¹³C resonances for α - and β -carbon atoms appear in the range of $\delta = 159.6$ – 134.2 and $\delta = 130.8$ – 123.9 ppm, respectively, and are in agreement with the data for the previously reported vinyl complex $[(C^{\wedge}N^{\wedge}Py^{\wedge}C)AuC(Me)=CMe_2]$.^[9a] In the case of terminal vinyl moieties, the ³*J*(H,H) values fall within the

Table 1: Alkyne hydroauration with **1c** in the presence of AIBN.^[a]

Substrate	Major product	Yield [%] ^[b]	<i>Z/E</i> ^[b]	<i>t</i> [min]	
Ph≡		2	90	>99:1	85
Ph≡Me		3	>95	>99:1	5
Ph≡Ph		4	>95	>99:1	35
Me3Si≡		5	>95	>99:1	5
<i>t</i> BuMe2Si≡		6	90	>99:1	110
Bu ⁿ ≡		7	>95	>99:1	35
Et≡Et		8	85	>99:1	60
		9	>95	>99:1	60
		10	>95	82:18	40
		11	75	>99:1	25
Ph≡CH(OH)		12	>95	>99:1	40
		13	>95	80:20	1020

[a] Reaction conditions: $[D_8]$ toluene, 50 °C; conversion of **1c** was > 95% in all cases; [b] Determined by NMR spectroscopy.

range typical of *Z* couplings [9.0–10.8 Hz, the only exceptions being of **5** and **6**, for which a ³*J*(H,H) of 13.5 Hz is observed owing to the β effect of silicon]. For the 1,2-disubstituted vinyl derivatives $[Au]-C(R^1)=CHR^2$, ¹H NMR NOE experiments revealed the presence of dipolar interactions between the vinyl–H and both R¹ and R², and the absence of such interactions between R¹ and R².

The hydroaurations proceed with high regio- and stereospecificity. For example, of the four possible isomers of the MeC≡CPh insertion, only a single product was formed, **3**, in which the gold center is bound in α -position to the methyl group rather than the phenyl substituent. With silyl acetylenes, the gold is distal to the SiR₃ group. This regioselectivity is in contrast to that obtained in a number of alkyne hydrometallation products, for example hydrostannations,^[18,19] hydrosilylations,^[20] hydroaluminations,^[21] and hydroalladations,^[22] where the metal is predominantly attached α to the phenyl substituent.

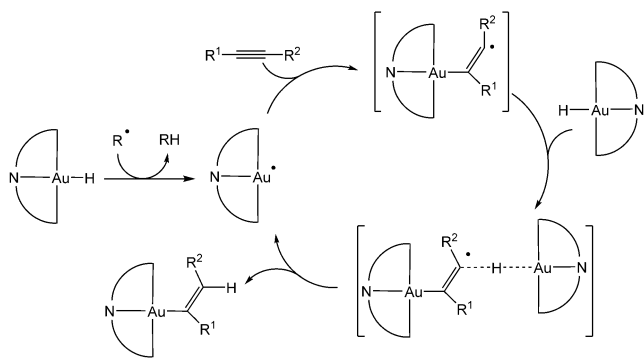
Gold(III) hydrides are stable to polar solvents, water, and even acetic acid, and indeed a range of functional groups is tolerated, including OH, NH, CHO, and COOH. Interest-

ingly, *N*-propargyl carboxamides, which are well-known for their facile cycloisomerization to oxazoles in the presence of gold catalysts,^[2,23] form exclusively the gold vinyl **13** without cyclization. Less reactive internal alkynes such as 3-hexyne also gave clean hydroauration products.

The stereochemical stability of the gold(III) vinyl products in our system contrasts with a recent report of extensive *cis*–*trans* isomerization by AIBN in radical-initiated hydrostannations of propargylic ethers.^[24] However, exposure of our gold vinyls to light induced slow isomerization; for example, irradiating a solution of **2** for 1 hour with UV light changed the *Z/E* ratio from greater than 99:1 to about 1:1.

Scheme 1 depicts the proposed reaction sequence. Thermal cleavage of AIBN provides radicals capable of H-abstraction from the gold(III) hydride. Since the reactions are conducted in the presence of excess alkyne, the gold(II) radical thus formed is rapidly trapped. Reaction of the resulting gold-vinyl radicals with a second molecule of **1** generates the gold-vinyl product. This scenario also effortlessly explains the observed *trans* hydroauration stereochemistry. The gold(II) radical is evidently sufficiently long-lived to provide regiochemical control. For example, in the case of MeC≡CPh, a phenyl-stabilized vinyl radical will be preferred over its methyl-substituted isomer, thus resulting in the formation of **3**, which is precisely what is observed. Further support for the proposed intermediacy of (C[∧]N[∧]C)Au[•] is the formation of trace amounts of the known^[9,25] gold(II) dimer [(C[∧]N[∧]C)Au]₂, which was detected as a by-product in some reactions.^[26] We have previously shown that (C[∧]N[∧]C)Au[•] is capable of attacking [(C[∧]N[∧]C)AuH] to give a μ-H intermediate as part of the electrochemical reduction of **1a**.^[27]

The validity of this mechanistic proposal was probed by DFT calculations for the addition of LAuH to the acetylenes H≡CH, HC≡CPh, and MeC≡CPh [L = (C[∧]N[∧]C)]. All mononuclear pathways tried had prohibitive free-energy barriers (> 35 kcal mol⁻¹), thus excluding their contribution under the present reaction conditions. Acetylene coordination to LAu[•] was found to have a small barrier (1–4 kcal mol⁻¹) and is modestly exergonic (2 to 12 kcal mol⁻¹). The most stable adducts have Au next to the H or Me substituent of the acetylene. From there on, an incoming LAuH molecule moves without much distortion towards the second acetylenic C on an essentially flat potential-energy surface. Transition states having one imaginary frequency with the correct motion were located in all cases, but the surface is so flat



Scheme 1. Proposed alkyne *trans*-hydroauration pathway.

that not too much importance should be attached to the C[•]–H distances in these optimized transition states. After including thermal and dispersion corrections, the free-energy barrier for hydride transfer from the incoming LAuH to the second acetylene carbon atom is 2–6 kcal mol⁻¹, thus leading to the experimentally observed *trans* adduct. Structures for stationary points on the radical path towards the preferred adduct of MeC≡CPh are shown in the Supporting Information (see Figure S50, see also Tables S3 and S4 for total and relative energies for all species studied). The energy profiles for this path and its non-observed regioisomeric alternative are summarized in Figure 2.^[28] The computational results therefore support the proposed radical chain mechanism and rule out alternative mononuclear mechanistic variations. An alternative pathway assisted by the LAu⁺ cation instead of a radical was also explored for comparison but appears less favorable (see the Supporting Information).

The release of the gold vinyl was exemplified in the case of **3**. Treating an NMR sample of **3** in [D₆]benzene with a crystal of iodine at room temperature generated the iodoalkene *Z*-C(I)(Me)=CHPh in quantitative yield, with retention of stereochemistry. As in the case of alkyne hydroauration, the mechanism of gold–carbon bond cleavage is likely not to be straightforward. This aspect is currently under investigation.

In summary, the results provide the first demonstration of the addition of unsaturated substrates to gold–hydrogen bonds by a radical-initiated outer-sphere mechanism. This intermolecular pathway overcomes the inability of gold(III) pincer complexes to bind unsaturated substrates and to follow intramolecular coordinative mechanisms of the type that are commonplace for other transition metals. There is a growing body of evidence that single-electron transfer steps may be involved in certain gold reactions, such as the photochemically induced oxidative additions to gold(I).^[29] The present results support the notion that odd-electron gold(II) species and outer-sphere processes may play an important role in gold reaction pathways.

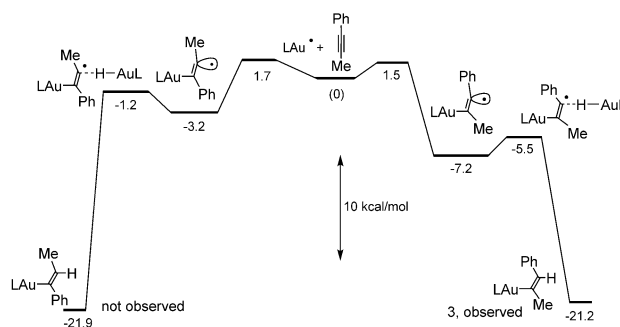


Figure 2. Free-energy profile (kcal mol⁻¹) for LAu[•]-mediated *trans* addition of LAuH to MeC≡CPh (L = C[∧]N[∧]C).

Acknowledgments





This work was supported by the European Research Council. M.B. is an ERC Advanced Investigator Award holder (grant no. 338944-GOCAT). We are grateful to the EPSRC National

Communications

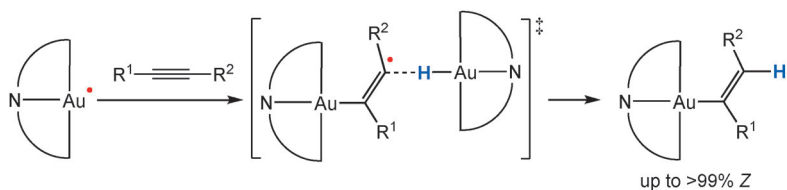
VIP

Reaction Mechanisms



A. Pintus, L. Rocchigiani,
J. Fernandez-Cestau, P. H. M. Budzelaar,*
M. Bochmann*    

Stereo- and Regioselective Alkyne
Hydrometallation with Gold(III) Hydrides



Gold(II) provides a helping hand: Gold-(III) pincer complexes overcome their lack of substrate binding sites by participating in a radical-mediated bimolecular pathway. Gold(III) hydrides react with

alkynes in the presence of a radical source in a kinetically controlled reaction to give *trans*-hydroauration products with high regio- and stereoselectivity.