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

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

Abstract: The hydrometallation of internal and terminal alkynes by gold(III) hydride complexes [(C^N^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 hydrometallations 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 hydroamination, that is, addition of gold hydrides to C–C multiple bonds, has been reported in only two cases. Tsu et al. showed that the gold(I) hydride [[IPr]AuH] reacts with internal alkynes, RC≡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 [(CNpz)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 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^2 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, iBu (1b), OMe (1c), and NMe_2 (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^2)AuCl] with a THF solution of LiAlH_4 gave the hydrides 1a–d in high yields.[15] The pyrazine-based complex [(C^N^C)AuCl][16] reacted similarly to give 1e.

The Au–H NMR chemical shifts show only a slight dependence on the pyridine substituent: δ = −6.51 (1a), −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 NMe_2 substituent coplanar with the pyridine ring. An analysis of the molecular charge distributions by density functional theory (DFT)
calculations showed only a marginal effect of the pyridine \( p \)-
substituents on the \( \text{Au--H} \) 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
\( 1\text{c} \) to explore hydoroauration 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 hydoroaurations pro-
ceeded with essentially quantitative regio- and stereoselec-
tivity, to give exclusively the \( \text{trans} \)-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
hydoroauration 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 \( 2\text{-}[2] \) pathway by suitable alignment of the
\( \text{C} \equiv \text{C} \) and \( \text{Au--H} \) 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 condi-
tions, 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)].

\[
\begin{align*}
\text{Au} + \text{R}-\equiv\equiv\text{R} & \quad \text{toluene, 50 °C} \\
\text{H} & \quad \text{AIBN} \\
\text{Au} & \quad \text{R}_1-\equiv\equiv\text{R}_2
\end{align*}
\]

A survey of alkynes with different substitution patterns
and functional groups resulted in the formation of the vinyl
complexes 2–13 (Table I). In most cases only the \( Z \)-vinyl
products could be detected, the exceptions being 10 and 13.
The structures were unequivocally assigned by NMR/NOE studies
(see the Supporting Information). In particular, vinyl
\(^{13}\text{C} \) resonances for \( \alpha- \) and \( \beta \)-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 \( [(\text{C}^\text{NPy})\_\text{C}]\text{AuC(Me)}=\text{CMe}_2 \).\(^{[20]} \) In the case of
terminal vinyl moieties, the \( J(\text{H, H}) \) values fall within the
range typical of \( Z \) couplings \( 9.0-10.8 \) Hz, the only exceptions
being of 5 and 6, for which a \( J(\text{H, H}) \) of 13.5 Hz is observed
owing to the \( \beta \) effect of silicon. For the 1,2-disubstituted vinyl
derivatives \( \text{[Au}-(\text{R})\_\text{C}=\text{CHR}) \), \(^{1} \text{H} \) NMR NOE experiments
revealed the presence of dipolar interactions between the
vinyl–H and both \( \text{R}_1 \) and \( \text{R}_2 \), and the absence of such
interactions between \( \text{R}_1 \) and \( \text{R}_2 \).

The hydoroaurations proceed with high regio- and stereoselectivity. For example, of the four possible isomers of the
MeC\(_2\)CPh insertion, only a single product was formed, 3, in
which the gold center is bound in \( \alpha \)-position to the methyl
group rather than the phenyl substituent. With silyl acety-
lenes, the gold is distal to the SiR\(_2 \) group. This regioselectivity
is in contrast to that obtained in a number of alkyne hydrometallation products, for example hydrostanna-
lations\(^{[18,19]} \), hydroisilylations\(^{[20]} \), hydroalumination,\(^{[21]} \) and hydropalladation,\(^{[22]} \) where the metal is predominantly
attached \( \alpha \) 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-

<table>
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<th>Substrate</th>
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<th>[Yield]</th>
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<td>85</td>
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<tr>
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<td>&gt; 95</td>
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<tr>
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<td>&gt; 99:1</td>
<td>35</td>
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<tr>
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<td>&gt; 99:1</td>
<td>5</td>
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<tr>
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[a] Reaction conditions: [D\(_8\)]_toluene, 50°C; conversion of \( 1\text{c} \) was > 95% in all cases; [b] Determined by NMR spectroscopy.

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 product 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 alkene, 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 π-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)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 exergic (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 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 LAuH 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=C(Me)=CHPh in quantitative yield, with retention of stereochemistry. As in the case of alkene 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 intramolecular 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).

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