INVESTIGATION OF GOLD-VINYL INTERMEDIATES OPENS NEW AVENUES IN GOLD CATALYSIS

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DIETER WEBER: Investigation of Gold-Vinyl Intermediates Opens New Avenues in Gold Catalysis
(Under the direction of Professor Michel R. Gagné)

The mechanism of gold(I)-catalyzed intramolecular hydroarylation of allenes was studied in detail. While monitoring the reaction by NMR, an unexpected dinuclear gold-vinyl intermediate was observed, that was proposed to contain a geminally diaurated carbon center stabilized by an aurophilic interaction. Isolation of this intermediate was achieved by inhibiting catalytic turnover with a base. Addition of suitable ligands abstracted one gold unit and yielded a monogold-vinyl complex, which was structurally confirmed by X-ray diffraction analysis. The reactivity of both intermediates was studied.

To better understand the formation of digold-vinyl intermediates, a variety of arylgold(I) model complexes were synthesized. A mixture of mono- and digold-aryl complexes revealed averaged proton signals by NMR. The chemical shift of these resonances could be used to determine the percentage of monogold bound as digold, which allowed for quantification of anion and ligand effects on digold formation. In addition, it was observed that Brønsted acids affected the coordinating ability of anions through homoconjugate acid/base pairs.

Trends observed in model systems were confirmed by mechanistic studies on the intramolecular hydroalkoxylation of allenes. Depending on the reaction conditions a digold or a monogold resting state was observed. Kinetic isotope effect studies and isotope labeling experiments were conducted to identify the catalytic role of digold. Data suggested that the
digold intermediate operated off cycle and acted as an inactive catalyst reservoir, which seemed inhibitory for efficient catalysis. Further mechanistic studies revealed that digold formation altered kinetic data as well, which complicated the interpretation of Hammett studies and the development of rate laws.

It was also found that silver and palladium intercepted gold-vinyl intermediates as well. Silver affected the mechanism of the intramolecular hydroarylation of allenes, which could explain previously observed silver effects in gold catalysis. Organogold complexes could engage in cross-coupling chemistry by transmetallating their organic group to Pd. Further studies led to a palladium-catalyzed homo-coupling of gold-aryl model complexes was observed, which was driven by a bimetallic Au(I)/Pd(0) RedOx process. Other new avenues in gold catalysis include the Lewis acid mediated activation of silver-free catalyst precursors and a new mechanistic proposal for the origin of chirality in gold-catalyzed reactions.
TO MY FAMILY AND FRIENDS
ACKNOWLEDGEMENT

“The things you do for yourself are gone when you are gone,
but the things you do for others remain as your legacy” – Kalu Kalu

With this quote I would like to express thanks to everyone that has supported me. I would not be at this point of my life without your constant love, service, and sacrifices. I will not mention specific names or institutions, but I will hold these blessings in my remembrance, and do my best to carry forward a legacy of genuine love and service for others.
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<tr>
<td>( ^\circ \text{C} )</td>
<td>degrees Celsius</td>
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<tr>
<td>( \mu )</td>
<td>micro ((10^{-6}))</td>
</tr>
<tr>
<td>( 3c-2e ) bond</td>
<td>three-center-two-electron bond</td>
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<tr>
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<td>9-bromo-9-borabicyclo[3.3.1]nonane</td>
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<tr>
<td>( \text{BEMP} )</td>
<td>2-\textit{tert}-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine</td>
</tr>
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<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
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</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
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<td>benzoyl</td>
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<td>doublet of doublets of doublets</td>
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</tr>
<tr>
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</tr>
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<td>DTBP</td>
<td>2,6-di-tert-butyl pyridine</td>
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<td>doublet of triplets</td>
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<td>E⁰</td>
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<td>enantioenrichement</td>
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<td>Abbreviation</td>
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<td>Lewis acid</td>
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<td>m</td>
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<tr>
<td>MeO</td>
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<td>MeO-BIPHEP</td>
<td>2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1’-biphenyl</td>
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<tr>
<td>Mes</td>
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<tr>
<td>MS</td>
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<tr>
<td>^{n}Bu</td>
<td>n-butyl</td>
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<tr>
<td>NHC</td>
<td>nitrogen heterocyclic carbene</td>
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<tr>
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<tr>
<td>NTf₂</td>
<td>bis(trifluoromethane)sulfonimide</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<td>acetate</td>
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<td>binolphosphate</td>
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<td>trifluoromethanesulfonate</td>
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<td>para-toluenesulfonate</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PnP</td>
<td>1,1-bis(diphenyl)phosphinoalkane with n methylene spacers</td>
</tr>
</tbody>
</table>
ppb  parts per billion
ppm  parts per million
R    organic group
RedOx reduction / oxidation
RT   room temperature
s    singlet
t    triplet
T    temperature
TADDOL  $\alpha,\alpha,\alpha,\alpha$-tetraaryl-1,3-dioxolane-4,5-dimethanol
'tBu  tert-butyl
td    triplet of doublets
TFA   trifluoroacetate
THF   tetrahydrofuran
tht   tetrahydrothiophene
TLC   thin layer chromatography
Tol   tolyl
Ts    para-toluenesulfonyl
V     volume (variable)
V     volt (unit)
X     halogen atom unless otherwise defined
Xyl   xylol
Xyl-BIPHEP  2,2$'$-bis(dixylylphosphino)-1,1$'$-biphenyl
Xyl-BINAP  2,2$'$-bis(dixylylphosphino)-1,1$'$-binaphthyl
Xyl-PHANEPHOS  4,12-bis(dixylylphosphino)[2.2]paracyclophane

Y  anion

Z  atomic nuclear charge
1.1 General Properties of the Element Gold

Gold is a precious metal that can be found in nature in its elemental form as gold nuggets, in gold veins, or as gold grains because of its chemical inertness towards oxidation in air or water. In its pure form, gold has a bright yellow color and is a dense, soft, malleable, and ductile metal. It is also a very good conductor of heat and electricity. In contrast to most other heavy metals, gold is non-toxic in its elemental form. Because of these properties, metallic gold is often used in jewelry, currency, electrical wiring, and as fillings in dentistry.

However, gold is not entirely chemically inert. It readily dissolves upon exposure to aqua regia, which converts gold(0) into chloroauric acid (HAuCl₄), or in basic aqueous cyanide solutions under aerobic conditions, which transforms gold(0) to [Au(CN)₂]⁻. The latter reaction is often used for gold extractions in gold mines. Interestingly, the properties of gold change drastically at higher oxidation states. Gold(I) and gold(III) complexes are typically
much more reactive and toxic. Depending on the ligand environment, such complexes have found use in organic synthesis as homogenous catalysts and also in medicine. For example, Auranofin, a neutral gold(I) glucosylthiolate complex, was found to be active for the treatment of rheumatoid arthritis (Figure 1-1).¹ Other gold complexes are currently being investigated as potential chemotherapeutic drugs.²

![Figure 1-1. Structure of the pharmaceutical Auranofin.](image)

In contrast to the chemical properties of many other metals, only one isotope of gold exists: ¹⁹⁷Au. As a result, mass spectrometric analysis of gold compounds lack a characteristic isotope pattern. ¹⁹⁷Au has a nuclear spin I = 3/2 and therefore is NMR active. Due to its low NMR sensitivity and quadrupolar moment, only few gold NMR spectra are known.³ The NMR activity of gold does not affect ¹H, ¹³C, or ³¹P NMR spectra, and because of the diamagnetic character of most oxidation states, gold-catalyzed reactions and gold-containing compounds can be analyzed by NMR.

Gold is very stable in its elemental state and gold(0) can be viewed as a thermodynamic sink. Because gold is a noble metal, it has high RedOx energy barriers, which means that

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strong oxidants are required to oxidize gold(0) to gold(I) \( (E^0 = 1.67 \text{ V}) \) and gold(0) to gold(III) \( (E^0 = 1.498 \text{ V}) \).\(^4\) In organic or aqueous solution, gold(I) ions slowly disproportionate to gold(0) and gold(III), with the formation of gold(0) driving the reaction. This process can typically be observed by the formation of a gold mirror on the glass wall. However, gold(I) species can be stabilized by suitable ligands, such as phosphines, N-heterocyclic carbenes (NHC’s), or chloride. These ligands are commonly found in catalysis.

The electron configuration of gold(0) is \([\text{Xe}]6s^25d^10\). Six stable oxidation states of gold are known: gold(–I), gold(0), gold(I), gold(II), gold(III), and gold(V); an oxidation pattern that greatly differs from the other coinage metals (silver and copper). The coordination number of these compounds ranges from two to six (Figure 1-2).

\[ \begin{align*}
\text{gold(–I)} & \quad \text{gold(0)} & \quad \text{gold(I)} & \quad \text{gold(II)} & \quad \text{gold(III)} & \quad \text{gold(V)} \\
[\text{Cs}]^+\text{[Au]}^- & \quad \text{Cl–Au–PPh}_3 & \quad \text{Cl–Au–Au–Cl} & \quad \text{Ph}_3\text{P–Au–Br} & \quad \text{Br} & \quad \text{[Xe}_2\text{F}_{11}]^+\text{[F}_2\text{AuF}_2]^- \\
\end{align*} \]

**Figure 1-2.** Different oxidation states of gold in selected examples.

The electron affinity of gold (2.039 eV) is much higher than that of silver (1.202 eV).\(^5\) This allows access to the negative oxidation state gold(–I) with an electron configuration of \([\text{Xe}]6s^25d^{10}\) as seen in semiconductor CsAu.\(^6\) The existence of gold(–I) was further supported by the solid state structure of a related compound \([(\text{NMe})_4]^+\text{[Au]}^-\).\(^7\)

Gold(I) complexes have the electronic configuration of [Xe]6s^05d^{10}. They are generally two-coordinate with a linear geometry, but higher coordination numbers are also known. In gold catalysis, gold(I) is the most prevalent oxidation state.

Examples of gold(II) compounds ([Xe]6s^05d^9) consist mostly of binuclear species with a Au–Au bond, a coordination number of four, and a square planar geometry. Alternatively to gold(II), these compounds can also be viewed as complexes with a mixed oxidation state of a Au(III)–Au(I) pair. There are a few examples of “real” mononuclear gold(II) complexes, which are paramagnetic and EPR active compounds and validate that the oxidation state gold(II) is truly accessible.

Gold(III) complexes have the electronic configuration of ([Xe]6s^05d^8) and display the expected d^8 square planar geometry with a coordination number of four. This oxidation state is also common in gold catalysis.

Gold(V) compounds ([Xe]6s^05d^6) are extremely rare and appear in octahedral geometry with a coordination number of six. The high oxidation state gold(V) can be obtained by reaction of [AuF_4]– with sunlight-dissociated F_2 to produce [AuF_6]–. Interestingly, this reaction proceeds more easily with gold(III) than with the corresponding silver(III) complex. Even using the most potent oxidant KrF_2, [AgF_4]– could not be converted to silver(V)

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[AgF$_6$].$^{13}$ This non-periodic oxidation behavior can largely be attributed to the impact of a large relativistic effect and lanthanide contraction.

The relativistic effect originates in the periodically increasing atomic nuclear charge ($Z$), which raises the average velocity of the nucleus penetrating electrons (s electrons and to a lesser extent p electrons).$^{14}$ According to Einstein’s relativity theory, the increase in velocity (higher kinetic energy) results in a higher mass of these electrons, which causes them to occupy a smaller space (orbitals) than without the relativistic effect. Therefore, the s electrons are closer and stronger bound and shield the nuclear charge, so that d and f electrons are weaker bound (to fulfill the law of energy conservation), which increases the size of the d and f orbitals (Figure 1-3).

![Figure 1-3](image)

**Figure 1-3.** Effects of relativity and lanthanide contraction on outer-shell orbitals of gold.

The relativistic effect reaches a maximum in gold because it is the first element with a fully occupied 5d and 4f shell (lanthanide contraction). Both the relativistic effect and the lanthanide contraction synergistically decrease the size of the gold atom to that of the silver


atom, which strongly affects its physical and chemical properties. In fact, Schmidbaur was able to demonstrate that the gold(I) ion was smaller than the silver(I) ion.\textsuperscript{15} The strong relativistic effect and the lanthanide contraction explain the accessibility of the extreme oxidation states gold(–I) and gold(V), the high Pauling electronegativity of $\chi = 2.540$ [similar to carbon ($\chi = 2.550$), sulfur ($\chi = 2.580$), and iodine ($\chi = 2.660$)], the initial resistance of gold towards oxidation, and relatively lower energy barrier of further oxidation once oxidized. The latter periodic anomaly is revealed by the first and second ionization potentials of gold in comparison to silver (Table 1-1).

<table>
<thead>
<tr>
<th>Table 1-1. Comparison of ionization potentials (in eV) of gold and silver.\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st}: $M(0)$ $\rightarrow$ $M(I)^+ + e^-$</td>
</tr>
<tr>
<td>9.225</td>
</tr>
<tr>
<td>2\textsuperscript{nd}: $M(I)^+$ $\rightarrow$ $M(II)^{2+} + e^-$</td>
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</table>

The consequences of a large relativistic effect particularly influence the reactivity of gold(I) complexes,\textsuperscript{17} which form unique weak metal-metal interactions in their solid state and in solution. There are three different bonding interactions between metals:\textsuperscript{18}

(1) metallic bonding between atoms described by electron gas models, band structures, or Fermi surface concepts;


(2) covalent bonding between oxidized metal atoms with open subshells as exemplified by the quadruple bond in [Re$_2$Cl$_8$]$^{2-}$;

(3) non-covalent bonding between metal atoms with closed subshells, such as d$^{10}$ or s$^2$ subshells.

Most examples of this third category were originally observed while studying the reactivity of organogold(I) complexes. Because of the many examples with Au–Au contacts, Schmidbaur proposed the special terms aurophilicity and aurophilic bonding. Aurophilic interactions between two gold atoms are placed into the category of weak forces, comparable to hydrogen bonding (5–10 kcal mol$^{-1}$). Aurophilic bonding is indicated by a Au–Au distance of 2.8–3.5 Å in X-ray crystal structures, a wide range, because the mutual approach of two gold centers reveals a relatively flat energy profile. Because other closed shell metals have revealed similar behavior, the general terms metallophilicity and metallophilic bonding were also introduced.

### 1.2 Gold in Organometallic Chemistry

Long before gold complexes were identified as promising sources for homogenous catalysts (early 1990’s), a variety of Au(I) and Au(III) organogold compounds were synthesized and studied. Since this dissertation focuses on gold in its +1 oxidation state, only those are discussed.

The Nesmeyanov Institute of Organoelement Compounds and Institute of Common and Inorganic Chemistry at Moscow State University began its studies on “univalent” organogold(I) complexes in 1970 and published more than 100 articles in Russian chemistry.

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The synthesis of alkyl-, alkenyl-, alkynyl-, benzyl-, allyl-, aryl-, cyclopentadienyl-, cymantrenyl-, and ferrocenylgold(I)-complexes was described and their reactivity studied. These seminal studies were carried out by Nesmeyanov, Grandberg, and Baukova. Other main contributors to this research field were the research groups of contemporaries such as Puddephatt, Schmidbaur, and Kochi, and shortly thereafter by Gimeno, Laguna, and many others. The key findings of these studies that are relevant for this dissertation are summarized in this section.

An important basis for the synthesis of organogold(I)-complexes is the preparation of (sulfide)Au(I)Cl precursors. These complexes are prepared by the addition of a sulfide, typically dimethyl sulfide (DMS) or tetrahydrothiophene (tth), to an aqueous solution of chloroauric acid (HAuCl₄) (Scheme 1-1). (DMS)AuCl is commercially available.


The coordinating sulfide in these gold(I) precursors is readily replaced by any stronger coordinating ligand, such as phosphines, phosphites, or NHC’s. Examples of representative formations are shown in Scheme 1-2.

Scheme 1-2. Representative examples for the synthesis of LAuCl species with L = PPh₃ and 1,3-bis-(2,6-di-iso-propylphenyl)imidazol-2-ylidine (IPr).

There are several methods to synthesize organogold(I)-complexes of the structure LAuR (R is any organic group) from LAuCl complexes. Most common synthetic methods transmetallate an R-group from organolithium (RLi)³¹ or Grignard reagents (RMgBr),³² but

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organoboron (RB(OH)₂)³³ and organomercury compounds (R₂Hg)³⁴ have also been used. The direct auration of C–H bonds with [O(AuPPh₃)₃]⁺[BF₄]⁻,³⁵ IPrAuOH,³⁶ or 'Bu₃PAuCl³⁷ (in combination with Ag₂O) offers an alternative pathway for the synthesis of organogold(I)-complexes. A third synthetic route, the isolation of organogold(I)-intermediates from catalytic reactions, is discussed later in this dissertation (see section 1.5 and chapter 3).

Organogold(I)-complexes differ in their chemical properties from other late transition metal complexes. For example, most organogold(I)-compounds are insensitive to air and water, tolerate a neutral or basic aqueous workup, are soluble in diethyl ether (sometimes also in boiling hexanes), and, in certain cases, can even be purified by flash column chromatography on silica. This organic molecule-like behavior of organogold(I)-complexes can probably be attributed to the high RedOx potential, low oxophilicity, and non-polar character of the carbon–gold σ-bond (Δξ of 0.01),³⁸ which is less polar than a carbon–hydrogen σ-bond (Δξ = 0.35).³⁹ In the course of this work, it was found that the ligand on gold strongly influences the stability of organogold(I)-complexes. For example, bulky NHC’s or Buchwald phosphines (e.g. JohnPhos) seem to have a stabilizing effect in comparison to PPh₃.


³⁹ A bond is generally considered polar covalent if Δξ is between 0.4 and 1.7 Pauling units.
Due to the large relativistic effect gold has a carbophilic character that is visible in organogold(I)-complexes. When isostructural carbon–metal bonds C–M (M = Cu(I), Ag(I), and Au(I)) were compared in crystallographic studies, the length of the C–Au $\sigma$-bond (2.268(5) Å) was between the C–Cu $\sigma$-bond (2.147(8) Å) and the C–Ag $\sigma$-bond (2.396(5) Å).\(^{40}\)

Organogold(I)-complexes also have a tendency to form multinuclear aggregates in their solid state and in solution, caused by aurophilic bonding. After first observations were highlighted by Puddephatt\(^{41}\) and Schmidbaur,\(^{42}\) dinuclear compounds with aurophilic interactions were investigated in detail by Nesmeyanov and Grandberg. While studying the reactivity of the ferrocenylgold(I)-complex (FcAuPPh\(_3\)) with the Brønsted acid HBF\(_4\), the formation of geminally diaurated complex [Fc(AuPPh\(_3\))\(_2\)]\(^+\)[BF\(_4\)]\(^-\) was observed. This compound could be obtained as a white precipitate in a 95% yield (Scheme 1-3).\(^{43}\)

$$\begin{align*}
2 \text{Fe} & \quad \text{1 equiv HBF}_4 \quad \text{Et}_2\text{O} \\
\text{Fe} & \quad \text{Et}_2\text{O}, -78^\circ\text{C or RT} \\
\text{AuPPh}_3 & \quad \text{[BF}_4\text{]}^- \\
\text{[BF}_4\text{]}^- & \quad \text{Fe}
\end{align*}$$

**Scheme 1-3.** Observation of geminally diaurated gold complex [Fc(AuPPh\(_3\))\(_2\)]\(^+\)[BF\(_4\)]\(^-\).


Later studies by the same group showed that \([\text{Ph}_3\text{PAu}]^+\text{[BF}_4^-\text{]}\) was the reactive cationic gold species to form dinuclear gold complexes. Therefore, digold \([\text{Fc(AuPPh}_3\text{)_2}]^+\text{[BF}_4^-\text{]}\) could alternatively be synthesized from ferrocene or FcAuPPh\(_3\) (Scheme 1-4).

![Scheme 1-4. Synthetic pathways for \([\text{Fc(AuPPh}_3\text{)_2}]^+\text{[BF}_4^-\text{]}\) via alternative generations of \([\text{Ph}_3\text{PAu}]^+\text{[BF}_4^-\text{]}\).](image)

Ferrocene could be converted to the digold species by direct auration with a mixture of \([\text{O(AuPPh}_3\text{)_3}]^+\text{[BF}_4^-\text{]}\) and HBF\(_4\).\(^{44}\) Other pathways included the reaction of FcAuPPh\(_3\) with in situ generated \([\text{Ph}_3\text{PAu}]^+\text{[BF}_4^-\text{]}\) (by the metathesis of Ph\(_3\)PAuCl and AgBF\(_4\)) and the addition of a different digold \([R(\text{AuPPh}_3\text{)_2}]^+\text{[BF}_4^-\text{]}\) that bound \([\text{Ph}_3\text{PAu}]^+\) less strongly than FcAuPPh\(_3\) (e.g. \([4-\text{Me-C}_6\text{H}_4-(\text{AuPPh}_3\text{)_2}]^+\text{[BF}_4^-\text{]}\)).

The structure of $[\text{Fc} \text{(AuPPh}_3)_2]^+ \text{[BF}_4^-]$ was confirmed by X-ray diffraction analysis (Figure 1-4), and revealed a hyperconjugated C(sp$^2$) atom with a Au$_2$C-three-center-two-electron (3c-2e) bond. The connectivity was stabilized by an aurophilic interaction between the two gold(I) atoms and a second metallophilic bond between one gold(I) atom and the low spin iron(II) center of ferrocene. $^1$H NMR signals were shifted downfield (relative to the monogold complex) and the diastereotopic phosphine ligands revealed two resonances at $\delta = 36.4$ and $\delta = 38.2$ ppm by $^{31}$P NMR. $^{13}$C NMR data were not reported.

An alternative method to identify diaurated gold complexes was their characteristic reactivity. Nesmeyanov and Grandberg illustrated in studies with the digoldaryl model system $[\text{4-Me-C}_6\text{H}_4-(\text{AuPPh}_3)_2]^+ \text{[BF}_4^-]$ that one $[\text{Ph}_3\text{PAu}]^+$ unit could be abstracted by a

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variety of ligands L to efficiently form the corresponding monogoldaryl species (Scheme 1-5).

\[
\begin{align*}
\left[ \text{Ar} \right]^{+} \text{AuPPh}_3 ^{\text{BF}_4}^{-} + L & \rightarrow \text{Ar}^{+} \text{AuPPh}_3 ^{\text{BF}_4}^{-} + [\text{Ph}_3 \text{PAuL}]^{+} [\text{BF}_4]^{-} \\
L = R & \text{AuPPh}_3 ^{-} \text{CN}^{-}, \text{CF}^{-}, \text{I}^{-}, \text{PPPh}_3, \text{morpholine}
\end{align*}
\]

**Scheme 1-5.** Characteristic reactivity of digold complexes with abstracting ligands L.

\[
\begin{align*}
[L-\text{AuPPh}_3]^{+} + L' & \rightarrow L + [L'-\text{AuPPh}_3]^{+}
\end{align*}
\]

**Scheme 1-6.** Donor strength of ligands measured by competitive [Ph₃PAu]⁺ exchange.

The competitive transfer of a [Ph₃PAu]⁺ unit from digold [L–AuPPh₃]⁺ to another ligand L’ was used to determine the donor strength of ligands (Scheme 1-6); these studies showed that more basic C–Au σ-bonds had a stronger affinity for cationic gold. Interestingly, C–Au σ-bonds competed with the ligating ability of morpholine, a secondary amine.

The concept of aurophilicity and the generation of hyperconjugated carbon atoms were investigated in detail by Schmidbaur. The synthesis of unusual complexes highlighted these novelties in organogold chemistry. For example, the sum stabilization of multiple aurophilic contacts (Au–Au distance 3.003 Å) was impressively demonstrated by the synthesis of
[(Ph₃PAu)₆C]²⁺[MeOBF₃]₂⁻, which revealed an octahedral coordination of the carbon center by six [Ph₃PAu]⁺ units (Figure 1-5).⁴⁶

Schmidbaur also studied the properties of dinuclear gold complexes. Mono- and digold complexes of the heteroaromatics furan and thiophene were synthesized and structurally characterized (Figure 1-6).⁴⁷ ¹H NMR data showed downfield shifted resonances and ³¹P NMR revealed one signal at δ ≈ 36 ppm for both enantiotopic phosphine ligands. While ¹³C NMR spectra showed a characteristic doublet for the ipso-carbon of monogold species, the same carbon could not be detected in digold complexes, probably due to the quadrupolar moment of gold. These data confirmed the findings of Grandberg and Nesmeyanov.

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Due to their accessibility and stability, the organometallic chemistry of gold mainly focused on the synthesis of organogold(I)-aryl complexes. In an interesting example, Thibonnet synthesized organogold(I)-aryl complexes as monomers for new organometallic polymers.48 While characterizing a variety of Ph₃PAu-aryl complexes, several interesting characteristics were noted. The proton decoupled $^{13}$C{$^1$H} NMR data revealed a characteristic doublet for the *ipso*-carbon bound to gold with a large coupling constant ($^2J_{PC}$.

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= 110 Hz), which typically had a chemical shift between $\delta = 160$ and 180 ppm. When the structure of each complex was verified by X-ray analysis, some gold-aryl compounds revealed aurophilic bonds between two molecules (Figure 1-7). These unsupported aurophilic interactions were only present in the solid state.

![Figure 1-7. ORTEP view of two molecules of 4-MeO-C₆H₄-AuPPh₃. Ellipsoids are drawn at the 50% probability level. H atoms are omitted for clarity.]

Similar to arylgold(I)-complexes, gold-vinyls also contain a C(sp²)-Au $\sigma$-bond, but only few examples of structurally characterized organogold(I)-vinyl complexes existed when the work contained in this thesis was initiated. The first synthesis of a gold-vinyl species was reported by Nesmeyanov and Grandberg in 1972, who synthesized the parent vinyl CH₂CH-AuPPh₃ from Ph₃PAuCl and vinylmagnesium bromide.⁴⁹ In a later study, when the reactivity of CH₂CH-AuPPh₃ with HBF₄•Et₂O was investigated, the formation of the digold-vinyl

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[CH₂CH-(AuPPh₃)₂][BF₄]⁻ was proposed based on its reactivity,⁵⁰ but no crystallographic evidence was provided for either the monogold nor the digold complex.

Much later, in 2006, Laguna was able to verify the proposed connectivity of the monogold-vinyl complex by X-ray analysis of single crystals of cis-1,2-dimethylvinyl-AuPPh₃ (Figure 1-8).⁵¹ This study was especially important as it represented at the time the closest structural example to proposed gold-vinyl intermediates in catalysis.

![Figure 1-8. ORTEP view of one of the independent molecules of cis-1,2-dimethylvinyl-AuPPh₃. Ellipsoids show 30% probability levels; phenyl H atoms are omitted for clarity.](image)

Seminal work by Kochi in 1973 pointed towards another novelty of organogold(I) chemistry. While the isolation of late transition metal-alkyl complexes is typically challenging due to rapid β-hydride-elimination to give an olefin and a metal-hydride species, Kochi reported the synthesis of several primary, secondary, and even tertiary gold-alkyl complexes. These compounds were stable at room temperature and showed no indication of


Surprisingly, even when solid samples of gold-alkyl complexes were decomposed at 118°C, none of the expected \( \beta \)-hydride-elimination products were detected. Instead, gas-chromatographic analysis revealed alkyl-homocoupling. The reduced gold appeared as a black solid mixed with PPh\(_3\). The intrinsic stability of gold centers towards \( \beta \)-hydride-elimination allowed the recent synthesis of chiral gold-alkyl complexes by Glueck and Toste.\(^{53}\) The Gagné group also studied the reactivity of gold-alkyl complexes, specifically their transformations with different electrophiles. These results are not summarized in this dissertation, but can be read elsewhere.\(^{54}\)

### 1.3 Gold in Homogenous Catalysis

Traditional palladium chemistry, which was awarded the Nobel Prize in 2010,\(^{55}\) typically consists of the cross-coupling of a carbon-nucleophilic and a carbon-electrophilic component to form a new C–C bond. General mechanistic schemes for these reactions are shown in Scheme 1-7.

Five reaction steps, which may themselves consist of multiple elemental reactions, are included in Pd(0)/Pd(II) catalytic cycles: oxidative addition, reductive elimination, migratory insertion, \( \beta \)-elimination, and transmetallation. With the exception of transmetallation, these reaction steps require flexibility in the oxidation state and coordination number of the metal center. Because first and second row late transition metals exhibit low energy barriers for


RedOx reactions and flexible coordination spheres, they are most often used in cross-coupling chemistry.

![Scheme 1-7. Typical mechanisms for traditional palladium cross-coupling chemistry.](image)

However, third row late transition metals, and especially gold, generally display high energy barriers for RedOx reactions, which inhibits oxidative additions or reductive eliminations on gold centers. Additionally, gold does not engage in $\beta$-elimination or migratory insertion processes, which further inhibits Au(I)/Au(III) cycles that would be analogous to Pd catalysis. It seems that, out of the five basic late-transition metal reactions, gold complexes only undergo transmetallation.

The catalytic activity of gold complexes is rooted in another phenomenon. Because cationic gold is isolobal to a proton and other organic or inorganic groups, it can engage in electrophilic catalysis. The relativistic effect and the lanthanide contraction significantly decrease the size of the 6s orbital and increase the sizes of the 5d orbitals (Figure 1-3). This

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leads to an alteration of electron density around the metal center and increases the π-acidity (6s orbital) and π-backbonding (5d orbitals) ability of the gold atom in the Dewar-Chatt-Duncanson model.\textsuperscript{57} Therefore, cationic and neutral gold(I) complexes act as carbophilic soft Lewis acids that activate C–C multiple bonds for nucleophilic attack and other rearrangements. Cationic or neutral gold(III)-complexes can also activate C–C multiple bonds, but display a more oxophilic and harder Lewis acid character than gold(I) species.\textsuperscript{58}

There are often several C–C multiple bonds in a substrate that gold could potentially activate. Typically, gold has the strongest propensity towards alkyne, then allene, and lastly alkene activation. Since alkynes and allenes offer a larger thermodynamic driving force than alkenes, this trend is also reflected in the number of reactions published with each C–C multiple bond. Interestingly, recent studies by Widenhoefer revealed that the stability of cationic π-η\textsuperscript{2}-gold-complexes follow an opposing trend: alkenes > alkynes > allenes.\textsuperscript{59} These data suggest that the gold-coordination and the gold mediated activation of a C–C multiple bond are two different processes. This was also recently proposed by Toste.\textsuperscript{60}

Active gold catalysts require one open coordination site at the metal center to engage in catalysis. Therefore, neutral gold salts, such as AuCl or AuCl\textsubscript{3} and gold cations [LAu]\textsuperscript{+} can be used. Cationic gold is typically generated in situ by the combination of Ph\textsubscript{3}PAuCl and a silver activator with a weakly coordinating counterion (Scheme 1-8).

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There are drawbacks for the in situ generation of cationic gold. Because of the prominent formation of a gold mirror (disproportionation) at the end of the reaction, the catalyst species \([\text{Ph}_3\text{PAu}]^+\) cannot be isolated or reused. Additionally, silver salts are generally very hygroscopic. This causes difficulties in properly weighing the activator and maintaining a non-acidic reaction medium. There are also substrates in gold catalysis that are catalyzed by silver as well. Therefore, silver free and isolable gold catalysts have been developed by Gagosz, Sadighi, Nolan, Toste, Echavarren, and Shi (Figure 1-9).

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64 D. S. Laitar, P. Muller, T. G. Gray, J. P. Sadighi, *Organometallics* 2005, 24, 4503.


With the main focus on the development of many new reactions, gold catalysis has been a very active research field since the late 1990’s. Gold-catalyzed transformations can be categorized as follows: nucleophilic functionalization reactions of C–C multiple bonds, cycloisomerization reactions of polyunsaturated substrates, cycloadditions, sigmatropic rearrangements, and coupling reactions.

The inter- and intramolecular nucleophilic functionalization of alkynes, allenes, and alkenes is by far the most common reactivity observed in gold catalysis (Scheme 1-9).

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70 The division of gold-catalyzed reactions into these categories was inspired by the following review articles: (a) H. C. Shen, *Tetrahedron* 2008, 64, 3885; (b) H. C. Shen, *Tetrahedron* 2008, 64, 7847.

Scheme 1-10. Representative examples of hydrofunctionalization reactions catalyzed by gold(I).
Depending on the nucleophile (Nu), these transformations can, for example, be subdivided in hydroalkoxylation (Nu = O), hydroamination (Nu = N), or Friedel-Crafts type hydroarylation reactions (Nu = Ar). Representative examples of these reactions with allenes, alkenes, and alkynes were published by Widenhoefer\textsuperscript{71} and Echavarren\textsuperscript{72} (Scheme 1-10).

Cycloisomerization reactions can also be subdivided. On the one hand, cycloisomerizations can be simple reactions, where a C=C double bond attacks as a nucleophile. This reaction class is mechanistically related to hydrofunctionalization reactions (hydroalkylation). On the other hand, cycloisomerization reactions may alternatively proceed via gold-carbene intermediates, and yield complex products because of additional multistep rearrangements or insertions into C=C double bonds. Typical examples for both reaction types are the cycloisomerization of 1,6-ene-allenes and the cycloisomerization of 1,6-enynes published by Gagné\textsuperscript{73} and Echavarren,\textsuperscript{74} respectively (Scheme 1-11). Intramolecular hydrofunctionalizations of C–C multiple bonds and cycloisomerizations follow the Baldwin cyclization rules.\textsuperscript{75}


The existence of gold-carbene intermediates in gold catalysis remains heavily debated in the gold community, but recent observations of intermolecular cyclopropanation of C=C double bonds by Echavarren supported the existence of “free” gold-carbene intermediates.

Cycloadditions in gold catalysis are not pericyclic reactions, such as the Diels-Alder reaction, that follow the Woodward-Hoffmann rules. Instead, these reactions proceed via mechanistically complex cycloisomerization reactions that formally yield \([a+b]\) cycloaddition products. Toste demonstrated the ligand- and substrate-controlled access of \([2+2]\), \([3+2]\), \([4+2]\), and \([4+3]\) cycloaddition products from ene-allenes. A representative example for a ligand-controlled reaction pathway is shown in Scheme 1-12.

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Scheme 1-12. Ligand-controlled selectivity for [4+2] vs. [4+3] cycloaddition of a diene-allene.\textsuperscript{80}

Sigmatropic rearrangements, another reaction type that typically belongs to pericyclic reactions, are also catalyzed by gold. These transformations are not nearly as prominent as hydrofunctionalization, cycloisomerization, or cycloaddition reactions. Toste published a pioneering example of a [3,3]-sigmatropic rearrangement in the Claisen rearrangement of propargyl-vinyl ethers (example shown in Scheme 1-13, top).\textsuperscript{81} Interestingly, propargyl esters preferred a different reaction pathway (Scheme 1-13, bottom).

Scheme 1-13. Claisen rearrangement (top) with propargyl-vinyl ether and different reaction mode with propargyl esters (bottom).


Despite the differences in reactivity between gold and palladium, coupling reactions were realized as well.\textsuperscript{82} These transformations can be subdivided in the following categories: C–H functionalization, oxidative coupling reactions, and dual Pd/Au catalysis.

Early examples of C–H functionalization\textsuperscript{83} centered mostly around Au(III) catalysis. There are only a few reports in the literature that indicate reductive elimination from a Au(III) center, typically under harsh conditions. An illustrative example is the coupling of arenes and alkyl triflates published by He in 2004 (Scheme 1-14).\textsuperscript{84} The reaction required electron rich arenes and high temperatures (120ºC) to produce any products. Branched coupling products were also obtained. Mechanistic studies indicated intermediary gold(III)-aryl complexes.

\begin{equation}
\text{Scheme 1-14. C–H functionalization of electron rich arenes.}
\end{equation}


In another interesting example, Zhang and coworkers demonstrated that the low reactivity of gold(I) in cross-coupling chemistry could be overcome by the addition of an external strong oxidant, such as Selectfluor (Scheme 1-15).85

Scheme 1-15. Oxidative coupling reactions with gold(I) and Selectfluor.

Based on recent studies on the reactivity of vinyl- and alkylgold(I) complexes with Selectfluor,86 a central role of these intermediates is suggested. After in situ oxidation of a gold(I)-intermediate, a short-lived cationic gold(III)-species is generated. Transmetallation of a phenyl-group from phenylboronic acid and subsequent reductive elimination yield the coupled product (Scheme 1-16).

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Another approach to further expand the accessibility of coupling chemistry in gold-catalyzed reactions was attempted by the combination of gold and palladium catalysis. Because gold and palladium reveal an orthogonal reactivity, such systems were envisioned. Typically, gold-catalyzed reactions are terminated by protodemetalation, the reaction of a gold intermediate with a proton. Seminal work by Blum in 2009 illustrated, that instead of protodemetalation organogold complexes could also efficiently transmetallate their R-group to a palladium catalyst (Scheme 1-17). Further reports by Blum and Hashmi initiated the research field of dual Au-Pd catalysis (see also chapter 8).

**Scheme 1-17.** Palladium-catalyzed cross-coupling of organogold complexes and organic iodides.

### 1.4 Enantioselective Gold Catalysis

In asymmetric catalysis, the Halpern mechanism and the Curtin-Hammett principle are used as a mechanistic rationale to explain enhanced enantioselectivities. In late transition
metal catalysis, bidentate C₂-symmetric ligands have proven to be a powerful method to achieve chiral induction. However, in gold(I) catalysis the use of bidentate C₂-symmetric ligands is challenging for two reasons. On the one hand, gold(I)-complexes prefer a linear coordination geometry, which significantly increases the distance between the chiral ligand and the substrate, directly influencing the degree of chirality transfer. On the other hand, gold(I)-complexes prefer a low coordination number of two, which inhibits chelation of the metal center by the bidentate ligands. As a result, gold catalysts with bidentate ligands are always binuclear in gold. It is not well understood how two gold centers influence the efficiency of chiral induction in gold catalysis.

Despite these difficulties and uncertainties, enantioselective gold-catalyzed reactions were realized. In some cases, elegant ligand design and alternative approaches for chiral induction were necessary. In 2005, the first gold-catalyzed example using a bidentate C₂-symmetric ligand was published by Echavarren. In the alkoxycyclization of 1,6-enynes a 94% ee was observed using (R)-Tol-BINAP(AuCl)₂ as a precatalyst. The reaction suffered from a slow conversion and ee’s were highly sensitive to the gold-silver ratio. After a reaction time of 168 h only 54% product could be isolated (Scheme 1-18).

\[
\begin{align*}
\text{PhO}_2\text{S} & \quad \text{Ph} \\
\text{PhO}_2\text{S} & \quad \text{PhO}_2\text{S} \\
\text{C≡C} & \quad 168 \text{ h, DCM, RT} \\
1.6 \text{ mol\% (R)-Tol-BINAP(AuCl)₂} & \quad \text{2.0 mol\% AgSbF₆} \\
& \quad 10 \text{ equiv MeOH} \\
\rightarrow \\
\text{PhO}_2\text{S} & \quad \text{PhO}_2\text{S} \\
\text{Ph} & \quad \text{OMe} \\
52\% \text{ yield, } 94\% \text{ ee}
\end{align*}
\]

Scheme 1-18. First enantioselective gold-catalyzed reaction using chiral bidentate ligands.

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Not all enantioselective reactions suffered from a slow reaction rate. Widenhoefer and coworkers published an enantioselective version of the hydroalkoxylation of allenes with (S)-DTBM-MeO-BIPHEP(AuCl)₂ as the precatalyst in 2007. After 18 h at –20°C in toluene, 67% product could be isolated with a 93% ee (Scheme 1-19).

![Scheme 1-19. Enantioselective hydroalkoxylation of allenes.](image)

Recent comparison studies by Mikami showed that precatalyst (R)-3,5-Xyl-BIPHEP(AuCl)₂ led to higher ee’s than (R)-3,5-Xyl-BINAP(AuCl)₂. Interestingly, (R)-3,5-Xyl-BIPHEP(AuCl)₂ revealed a Au–Au interaction in the solid state, which was absent in precatalyst (R)-3,5-Xyl-BINAP(AuCl)₂. These observations led Mikami to propose that aurophilic interactions between the two gold centers might be important to achieve a high enantioselectivity.⁹³

Gade and coworkers made a similar observation. While studying multinuclear precatalysts in the hydroamination of allenes, a novel C₃-symmetric trinuclear gold catalyst showed increased efficiency in achieving a high enantioselectivity.⁹⁴ However, the exact role of Au–Au contacts in enantioselective reactions remains unclear.

Monodentate ligands have also been used efficiently in enantioselective gold catalysis. In contrast to bidentate ligands, monodentate ligands move the chiral information closer to the metal center, increasing the likelihood of successful chiral communication between the


ligand and substrate. Fürstner demonstrated this using newly designed phosphoramidite ligands with a TADDOL backbone (Scheme 1-20). These ligands were not only readily available but also furnished high yields and enantioselectivities in [2+2] cycloaddition reactions.

![Scheme 1-20](image)

**Scheme 1-20.** High ee’s with a phosphoramidite ligand in the enantioselective [2+2] cycloaddition.

Another new ligand design was recently published by Slaughter. It was demonstrated that chiral nitrogen acyclic carbenes (NAC) with a 1,1’-binaphtyl backbone gave a high enantioselectivity in the cyclization of alkynylbenzaldehydes (Scheme 1-21). A weak gold-arene interaction in the solid state structure of the catalyst was proposed to explain high enantioselectivities.

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Scheme 1-21. A new NAC ligand design led to high ee’s in the alkynylbenzaldehyde cyclization.

In 2007, Toste and coworkers circumvented issues associated with the limited coordination chemistry of gold. Instead of chiral ligands, chiral anions were successfully used in the intramolecular hydroalkoxylation, hydroaminaton, and hydrocarboxylation of allenes (Scheme 1-22). A close ion pairing between a carbocationic gold-intermediate and the chiral anion was proposed to cause enantioselectivity during a stereochemistry determining cyclization step.

Scheme 1-22. Enantioselective hydroalkoxylation using bulky chiral phosphate anions.

1.5 Observation of Intermediates in Gold Catalysis

Gold catalysis has been a very competitive research field. So far, the main focus has been the development of new reactions, new concepts for asymmetric catalysis, and their application in total synthesis.\textsuperscript{98} Therefore, detailed mechanistic studies are rare, despite the diamagnetic character of gold, which allows convenient monitoring of catalytic reactions by NMR. Since the mechanism of gold(I)-catalyzed reactions and the observation of key intermediates by NMR are a main focus of this dissertation, preceding observations of reaction intermediates in gold-catalyzed reactions are summarized.

One of the first synthetically applied gold-catalyzed reactions was the Hashmi phenol synthesis, a reaction in which four bonds of the substrate are broken and four new bonds are formed (Scheme 1-23).\textsuperscript{99}

![Scheme 1-23. Mechanistic studies on the Hashmi phenol synthesis.](image)


In subsequent mechanistic studies, both valence isomers, the oxepin and arene-oxide intermediate, could be observed by \(^1\)H NMR at \(-20^\circ\text{C}\) using a novel Au(III)-alkoxypyridine catalyst.\(^{100}\) At low temperatures, the concentration of organic intermediates could be enriched to 80%. Such samples were stable under these conditions for weeks. Additionally, a X-ray structure of an arene-oxide model and deuterium labeling studies with the oxepin were reported.

Another organic intermediate could be observed in the gold(III)-catalyzed reaction of N-propargyl-carboximides to oxazoles. While monitoring the reaction by \(^1\)H NMR, an initial build up of an alkylidene oxazoline was noted, which then converted to the final product (Scheme 1-24).\(^{101}\) In later studies, it was found that only gold(III) catalysis yielded oxazoles. In the presence of gold(I) catalysts, the alkylidene oxazoline was formed as the sole product.\(^{102}\)

![Scheme 1-24. Observation of an intermediary alkylidene-oxazoline by \(^1\)H NMR.](image)

Upon exposure to a gold catalyst, propargylic esters rearrange in many different ways. While studying their reactivity in 2005, Zhang was able to directly observe an intermediary


[3,3]-rearranged allenic ester by $^1$H NMR (Scheme 1-25). In later studies, Gevorgyan confirmed the intermediacy of allenic esters by studying the gold-mediated rearrangement of propargyl-phosphates.104

Scheme 1-25. Observation of an allenic ester intermediate in the rearrangement of propargyl esters.

In a tandem intermolecular hydroamination/hydroarylation reaction of phenylacetylene with indoline published by Che in 2007, the hydroamination product, an enamine intermediate, was observed by $^1$H NMR within the first 10 minutes of conversion (Scheme 1-26).105 It reacted with a second molecule of phenylacetylene to give the final product after 17 h.

Scheme 1-26. Observation of an enamine intermediate in the intermolecular tandem hydroamination/hydroarylation of indole and phenylacetylene.

In the gold(III)-catalyzed tandem amination/hydroamination published by Liang in 2008 a yne-allylamine intermediate was observed by $^1$H NMR. This intermediate formed presumably via a gold-catalyzed $S_N2'$-type addition to the substrate.

Scheme 1-27. Observation of a yne-allyl amine intermediate in the tandem amination/hydroamination reaction.

Cyclobutenes were also observed as intermediates in gold catalysis. Typically, cyclobutenes are prone to quickly open via a thermally driven electrocyclic ring-opening to

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1,3-dienes. However, annelated with medium sized rings, they were isolated as intermediates in the gold-catalyzed cycloisomerization of enynes (Scheme 1-28).\textsuperscript{107}

![Scheme 1-28. Observation of cyclobutenes as intermediates in the gold-catalyzed enyne cycloisomerizations.]

While the work contained in this dissertation was in progress, Hammond and coworkers reported the first isolated gold-vinyl intermediate,\textsuperscript{108} which was obtained as a by-product of the gold(I)-catalyzed reaction of alleneoates. These gold complexes could be synthesized by the stoichiometric addition of cationic gold to alleneoates and were characterized by X-ray crystallography (Scheme 1-29).

![Scheme 1-29. Isolation of key intermediates in the gold-catalyzed cyclization of alleneoates.]


Due to the electron withdrawing group in the *anti* position to the gold-carbon bond this compound proved to be very stable and was isolable by column flash chromatography on silica. With this result, Hammond provided the first evidence for the viability of vinyl-gold(I) complexes in mechanisms of gold(I)-catalyzed reactions. Since then, many isolated gold-intermediates were reported.\(^\text{109}\)

Chapter 2. Previous Work in the Gagné Research Group

The development of new gold(I)-catalyzed reaction in the Gagné group is outlined. Proposed mechanisms are discussed. The motivation for further mechanistic studies is described.

2.1 The Development of New Gold-Catalyzed Reactions

The cyclization of polyolefins using electrophilic catalysis has been a focus in the Gagné research group since 2004. Due to their electrophilic nature Pt(II) and Pd(II) catalysts were originally used. However, upon extension to 1,6-ene-allenes Pt(II)-catalysts gave multiple products. A variety of Lewis acids were screened, which revealed gold(I) salts as efficient catalysts for the cyclization of 1,6-ene-allenes to vinyl-cyclohexenes. Catalyst optimization using C₂-symmetric chiral ligands led in 2007 to the first gold catalysis paper published by the Gagné research group. Therein, the use of [(R)-3,5-Xyl-BINAP(AuCl)₂] as a chiral precatalyst was reported to give good yields (83%, combination of both regioisomers) and


111 M. A. Tarselli, *Doctoral Dissertation* 2008, University of North Carolina at Chapel Hill.

enantioselectivities (77% ee) after 16 h (Scheme 2-1). This study became one of the leading examples in gold catalysis of efficiently using a C₂-symmetric chiral phosphine ligand.

Scheme 2-1. Enantionselective cycloisomerization of 1,6-ene-allenes to vinylcyclohexenes.

Interestingly, the optimized yield and selectivity were only obtained when the catalyst was generated in situ. Isolated and silver free [(R)-3,5-Xyl-BINAP(AuOTf)₂] (5 mol%) led to an extended reaction time and significantly lower enantioselectivity (21% ee, 24 h). A higher enantioselectivity (34% ee) could be regained by addition of AgCl, but the optimized conditions could not be restored. An explanation for this silver-effect was not given (see chapter 7).

The substrate scope was then extended to arene-allene 1 and its derivatives to yield vinylated products such as 2 (Scheme 2-2). In contrast to the ene-allene cycloisomerization, the intramolecular hydroaylation of arene-allenes proved to be more reactive with phosphite-gold(I) catalysts than with phosphine-gold(I) species. More electron rich catalysts, such as NHCAuCl were unreactive. These results showed that the reaction

favored electron deficient gold(I) catalysts. It was also observed that the application of 
\([R]-3,5\text{-Xyl-BINAP}(\text{AuCl})_2\) resulted in no enantioselectivity.

Scheme 2-2. Gold-catalyzed intramolecular hydroarylation of allenes.

When the reactivity of allenes with aromatic nucleophiles was further studied, the 
intermolecular hydroarylation of allenes could be achieved. Addition of 1,1-dimethyl allene 
to a suspension of \((p\text{-Cl-C}_6\text{H}_4\text{O})_3\text{PAuCl} / \text{AgBF}_4\) and 1,3,5-trimethoxy benzene led to the 
hydroarylated product with an optimized yield of 67\% (Scheme 2-3).\textsuperscript{114}

Scheme 2-3. Intermolecular hydroarylation of allenes.

The molecular complexity of products was significantly increased when 
multifunctionalized epoxy-allenes were shown to undergo cascade cycloisomerization to 
cyclic polyethers (Scheme 2-4).\textsuperscript{115} Cyclic ether skeletons with 5-, 6-, and 7-membered rings,


endo-cyclization to novel 9-membered rings, and multi-cascade synthesis of tricyclic ethers were accessible.

![Scheme 2-4](image)

**Scheme 2-4.** Cascade cyclization of epoxy-allenes to polycyclic ethers.

### 2.2 Proposed Mechanisms

While the Gagné group did not explicitly publish any mechanistic proposals, all newly developed reactions were assumed to follow simple mechanisms. A representative catalytic cycle of the intramolecular hydroarylation of 1,6-arene-allenes is shown in Scheme 2-5, but similar mechanistic proposals containing the same key steps could be theorized for the cycloisomerization of 1,6-ene-allenes, the intermolecular hydroarylation of allenes, and the cascade cyclization of epoxy-allenes.

In the first step $[\text{R}_3\text{PAu}]^+$ initiated the process through $\pi$-coordination to the allene functionality in 1, which then is activated for an intramolecular Friedel-Crafts-type nucleophilic attack by the aromatic ring. Subsequent rearomatization formed vinylgold(I) complex 3a, which protodeaurated with the generated acid to give 2 and $[\text{R}_3\text{PAu}]^+$. The regeneration of $[\text{R}_3\text{PAu}]^+$ turned the catalytic cycle over.
A crucial difference between proposed mechanisms for the ene-allene cycloisomerization and the arene-allene hydroarylation was the elimination of a proton from the carbocationic gold-vinyl intermediate to regioisomeric products. While ene-allenes eliminated to two regioisomers, arene-allenes gave only one product. This regioisomeric preference in the hydroarylation of allenes could be rationalized by the kinetically and thermodynamically favorable elimination of a tertiary proton that led to an aromatic product (Scheme 2-6). Such a driving force was absent in the cycloisomerization of 1,6-ene-allenes.

Scheme 2-5. Proposed mechanism of the gold(I)-catalyzed intramolecular hydroarylation of allenes.
Scheme 2-6. Rationale for regioisomeric mixtures from carbocationic vinylgold intermediates.

2.3 Research Objectives and Motivation

As outlined in chapter 1, only few intermediates in gold-catalyzed reactions were observed when the work for this dissertation was initiated. Importantly, no gold-containing intermediate had so far been isolated, which raised doubt in the synthetic community whether gold salts truly catalyzed these reactions. In most gold-catalyzed reactions, protons are generated either during catalysis or from the reaction of trace amounts of water with gold or silver salts. Since H⁺ is isolobal to gold, it can also operate as an alternative electrophilic catalyst and activate C–C multiple bonds for nucleophilic attack.¹¹⁶

In 2007, the lack of mechanistic understanding of gold-catalyzed processes was pointed out in a comprehensive review by Hashmi, which stated: “there exists no direct proof for most intermediates shown in the mechanistic proposals” and “in most cases, it is still unknown what the active [catalyst] species really looks like”.¹¹⁷ Most mechanistic schemes

¹¹⁶ Therefore, it is crucial to run control experiments to distinguish gold catalysis from potential Bronsted acid catalysis, see: A. S. K. Hashmi, Catal. Today. 2007, 122, 211.

in gold catalysis are primarily based on organometallic gold chemistry and computational modeling.

The Gagné research group developed several gold-catalyzed reactions of allenes. Interested in gaining mechanistic insight into the cycloisomerization of ene-allenes and the hydroarylation of arene-allenes, it was attempted to intercept gold-vinyl intermediates during catalysis and compare their NMR spectra with synthesized model complexes. While the synthesis of a cyclohexyl-substituted gold-vinyl was successful (Scheme 2-7), no gold intermediate was successfully intercepted during catalysis. These initial studies were carried out by graduate student Michael A. Tarselli, which became the basis for this dissertation.

Scheme 2-7. Synthesis of gold-vinyl model complex.

Because of a lack of mechanistic knowledge the seemingly simple intramolecular hydroarylation of allenes was investigated in detail. With the isolation of two gold-vinyl intermediates, a mono- and a diaurated species (see chapter 3), many mechanistic questions concerning the catalytically active species could be addressed. However, these answers raised more questions, specifically concerning aurophilic bonding and digold intermediates in gold catalysis. Illuminating these effects became the motivation for this work.
Chapter 3. Gold-Vinyl Intermediates in the Intramolecular Hydroarylation

NMR studies on the gold(I)-catalyzed intramolecular hydroarylation of allenes are reported. The isolation, characterization, and properties of a monogold- and digold-vinyl intermediate are discussed. The observation of digold intermediates with different phosphine ligands, counterions, and allene substrates is described. The crystal structure of an unexpected σ-π-diaurated digold is displayed. The importance of aurophilic interactions in gold catalysis is demonstrated.

3.1 Introduction

Previous work in the Gagné research group showed that the intramolecular hydroarylation of allene 1 to the vinylated tetralin derivative 2 was catalyzed by [Ph3PAu]+.118 The proposed catalytic cycle shown in Scheme 3-1, is initiated by the π-coordination of [Ph3PAu]+ to 1,119 which activated the allene for nucleophilic attack by the aromatic ring.120 Subsequent


rearomatization generated vinylgold(I) complex 3a, which protodeaurated with the generated acid to give 2 and [Ph₃PAu]⁺.¹²¹

**Scheme 3-1.** Proposed mechanism of the gold(I)-catalyzed intramolecular hydroarylation of allenes.

The seemingly well-behaved nature of this reaction was motivation to initiate studies to refute or validate this mechanism. This work has led to surprising results concerning the nature of the catalyst resting state and parts were published in Angewandte Chemie.¹²²

¹²¹ For this substrate regioselective elimination is observed, however ene-allenes eliminate to a regioisomer mixture; see: M. A. Tarselli, A. R. Chianese, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2007, 46, 6670.

3.2 Monitoring Catalysis by $^{31}$P NMR

Preliminary studies identified the Gagosz catalyst Ph$_3$PAuNTf$_2$ (4a•NTf$_2$) as a convenient source of [Ph$_3$PAu]$^+$ that did not require in situ activation of Ph$_3$PAuCl with silver salts.$^{123}$ Monitoring the reaction of 1 with 10 mol% 4a•NTf$_2$ by $^{31}$P-NMR showed two sharp peaks in a 1:1 ratio at $\delta \approx 36$ ppm (Figure 3-1). Upon completion of the reaction, these peaks had diminished, and the Gagosz catalyst reappeared at 30 ppm.

![Figure 3-1. Monitoring the reaction of 1 by $^{31}$P NMR.](image)

According to the mechanistic proposal in Scheme 3-1, the signals at $\delta \approx 36$ ppm were surprising. Neither the anticipated gold-vinyl 3a nor Gagosz catalyst 4a•NTf$_2$ were expected to exhibit resonances in that region. Published examples of gold-vinyl complexes showed chemical shifts between $\delta = 43$ to 45 ppm; Gagosz catalyst had a chemical shift of $\delta \approx 30$ ppm.$^{124}$

![Figure 3-2. Monitoring the reaction of 1 to 2 by $^1$H NMR.](image)

The reaction was also monitored by $^1$H NMR. Allene resonances of 1 at 5.0 ppm and 4.8 ppm were clearly distinguishable from the vinyl-signals of product 2 at 5.8 ppm, 4.9 ppm, and 4.7 ppm (Figure 3-2). Additional signals, presumably from a reaction intermediate, were

visible in the baseline. Based on these data, the reaction of substrate 1 with catalyst 4a•NTf₂ was ideal for further mechanistic studies.

### 3.3 Isolation and Characterization of Intermediates

To isolate intermediates, substoichiometric reactions of 4a•NTf₂ and 1 in the presence of a base were attempted. It was presumed that a suitable base would inhibit protodemetallation and yield a gold-containing intermediate. The effect of different Brønsted bases was screened in the reaction of 1 with 10 mol% 4a•NTf₂ (Table 3-1).

Bulky tertiary amines, such as piperidine-resin and NPh₃ did not affect catalysis (Table 3-1, entries 1 and 2). In contrast, inorganic carbonates, sodium hydride, tertiary and primary amines, potassium tert-butoxide, and 2,6-lutidine inhibited an efficient reaction of 1 and catalyst 4a•NTf₂, likely due to coordination of the base to the catalytically active cationic gold species (Table 3-1, entries 3-12). Derivatives of 2,6-di-tert-butyl pyridine efficiently suppressed catalytic turnover via protodemetallation (Table 3-1, entries 13-15), and were suitable to isolate reaction intermediates. It was found later that 2,6-di-iso-propyl pyridine or derivatives of the phosphazene base BEMP (2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) were viable alternatives (Table 3-1, entries 16-18).

Surprisingly, in the presence of 2,6-di-tert-butylpyridine (DTBP) incomplete conversion was observed for the stoichiometric reaction of 1 and 4a•NTf₂ by ¹H NMR. Addition of a second equivalent of 4a•NTf₂ was necessary to drive the reaction to completion. The ¹H and ³¹P NMR of the crude product are shown in Figure 3-3.
Table 3-1. Base screen in the catalytic reaction of 1 with 10 mol% 4a•NTf₂ to inhibit catalytic turnover via protodemetalation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NPh₃</td>
<td>CD₂Cl₂</td>
<td>Catalytic turnover</td>
</tr>
<tr>
<td>2</td>
<td>PL-PIP (piperidine) resin</td>
<td>CD₂Cl₂</td>
<td>Catalytic turnover</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ / 18-Crown-6</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>CD₃NO₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>NaHCO₃</td>
<td>CD₃NO₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>NaH</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>NEt₃</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>N-2,2,6,6-Pentamethylpiperidine</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>2,6-Lutidine</td>
<td>CD₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>2,6-di-tert-butylpyridine (DTBP)</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
<tr>
<td>14</td>
<td>4-methyl-2,6-di-tert-butylpyridine</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
<tr>
<td>15</td>
<td>2,6-di-tert-butylpyridine-resin</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
<tr>
<td>16</td>
<td>2,6-di-iso-propylpyridine</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
<tr>
<td>17</td>
<td>BEMP (Phosphazene base)</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
<tr>
<td>18</td>
<td>BEMP-resin</td>
<td>CD₂Cl₂</td>
<td>Intermediate interception</td>
</tr>
</tbody>
</table>

³¹P NMR data for the stoichiometric reaction revealed the same two resonances at δ ≈ 36 ppm (1:1 ratio) that were also observed under catalytic conditions. The ¹H NMR showed chemical shifts between 2.7 ppm and 3.4 ppm, which indicated the presence of a single carbocycle consistent with a vinylgold(I) connectivity.
Figure 3-3. Crude $^{31}$P NMR (left) and $^1$H NMR (right) of the stoichiometric reaction of 1 and 2 equiv of $4a$•$NTf_2$ in the presence of DTBP.
Other features of the spectroscopic data were inconsistent with 3a. For example, $^1$H-NMR showed a 2:1 ratio of the PPh$_3$ to carbocycle resonance. In addition, closer examination of the multiplicity of the vinyl peaks revealed heteronuclear coupling between the vinyl proton that was *anti* to Au and *two* phosphorous atoms, rather than the single phosphine expected for a simple vinylgold(I) complex like 3a. These data therefore suggested that the catalytic intermediate was the doubly metallated gold-vinyl species 5a•NTf$_2$ (Figure 3-4).

**Figure 3-4.** Proposed structure of digold intermediate 5a•NTf$_2$.

These spectroscopic and reactivity observations coupled with the work of Grandberg, Nesmeyanov, and Schmidbaur on aryl-gold(I) organometallic complexes suggested that 5a•NTf$_2$ was a diaurated structure that engaged the vinyl anion in a bridging 3-center-2-electron mode and was stabilized by a Au–Au interaction. X-ray crystal structures of bridging aryl compounds are known, and a computational study implicated the

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intermediacy of a bridging vinyl in the cycloisomerization of enynes.\textsuperscript{129} The phosphines in such a chiral structure would be diastereotopic and account for the inequivalent resonances in the $^{31}$P-NMR.

Grandberg reported that the geminally diaurated parent species $[(\text{Ph}_3\text{PAu})_2\text{CH}=$CH$_2]^+[\text{BF}_4]^{-}$ was unstable and characterizable only by its IR and reactivity. In contrast, the more crowded nature of $5a\bullet\text{NTf}_2$ presumably contributed to its thermal stability. The stabilizing Au–Au bond interactions are well established and measure to be worth 5-10 kcal mol\textsuperscript{-1}.\textsuperscript{130}

Attempts to separate $5a\bullet\text{NTf}_2$ from 2,6-di-tert-butylpyridine and its conjugate acid proved to be challenging. While the mixture of $5a\bullet\text{NTf}_2$ and impurities was soluble in dichloromethane, acetone, acetonitrile, methanol, tetrahydrofuran, nitromethane, and ethyl acetate, it was insoluble in pentanes and hexanes. Diethyl ether, toluene, carbon tetrachloride, and water were suitable for extracting some impurities, but these solvents also dissolved substantial quantities of $5a\bullet\text{NTf}_2$. None of the solvents above led to decomposition of $5a\bullet\text{NTf}_2$. Successful removal of the base was achieved by dissolving the reaction mixture in dichloromethane, rinsing with saturated aqueous Na$_2$CO$_3$, drying over Na$_2$SO$_4$, and removing the volatiles under reduced pressure resulting in a brown oil. Then, the crude oil was extracted with cooled diethyl ether (−78°C), which partially removed the base. Cooled diethyl ether was used to dissolve less $5a\bullet\text{NTf}_2$. Diethyl ether was decanted from the crude oil, and any remaining diethyl ether was removed under high vacuum. This procedure resulted in the formation of a beige foam. The purification-extraction process with cooled


diethyl ether was repeated ten times and 5a•NTf₂ could be isolated in a 35% yield. A ¹H NMR of purified 5a•NTf₂ is shown in Figure 3-5.

**Figure 3-5.** ¹H NMR of purified 5a•NTf₂. Residues of water (1.56 ppm) and diethyl ether (3.48 ppm and 1.21 ppm) were visible. Signals corresponding to DTBP were removed.

Figure 3-6. Single crystals obtained from samples of 5a•NTf₂.
Crystallization of 5a•NTf₂ proved to be difficult and has not been achieved. Although crystals suitable for X-ray analysis were obtained by layering a solution of 5a•NTf₂ in dichloromethane with diethyl ether or pentanes, preliminary structural information did not match the proposed structure of 5a•NTf₂ (Figure 3-6). Both structures had been reported previously by other research groups.\textsuperscript{131}

Attempted purification of 5a•NTf₂ on chromatographic media led to its decomposition. While florisil and silica protodeaured 5a•NTf₂ to 2, short plugs of neutral alumina resulted in the formation of Ph₃PAuCl and vinylgold(I) complex 3a,\textsuperscript{132} the originally proposed catalyst resting state (Scheme 3-2). It was later determined that the neutral alumina was a source of Cl⁻ counterions, due to contamination.

\textbf{Scheme 3-2.} Decomposition of 5a•NTf₂ on chromatographic media to 2 and 3a.


\textsuperscript{132} The monogold-vinyl structure was assumed based on similar NMR data to the previously synthesized cyclohexyl-substituted gold-vinyl model complex, see Scheme 2-7.
Upon addition of diethyl ether, white crystals of Ph$_3$PAuCl formed, which allowed the separation of Ph$_3$PAuCl from 3a. The solution of remaining 3a was concentrated and methanol was added. After three weeks, single crystals suitable for X-ray diffraction analysis were obtained (Figure 3-7), which unambiguously confirmed the structure of monogold-vinyl. Corresponding $^1$H and $^{31}$P NMR data of purified 3a are shown in Figure 3-8.

Figure 3-7. ORTEP diagram of intermediate 3a with 50% probability ellipsoids; most hydrogen atoms are omitted for clarity. Key bond lengths [Å] include: Au1-P1 [2.2913(5)], Au1-C2 [2.050(2)], and C1-C2 [1.324(4)].

133 CCDC 736429 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Figure 3-8. NMR data of purified intermediate 3a.
The experimental data of the isolated intermediates supported the proposed dinuclear structure of 5a•NTf₂ (Table 3-2).

**Table 3-2.** Comparison of chemical shifts in ¹H NMR. “Signal of these protons were not distinguishable.

![Chemical structures of 3a and 5a•NTf₂](image)

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical shift in 3a [ppm]</th>
<th>Chemical Shift in 5a•NTf₂ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>5.62 (dd)</td>
<td>5.91 (ddd)</td>
</tr>
<tr>
<td>1b</td>
<td>4.97 (dd)</td>
<td>6.43 (d)</td>
</tr>
<tr>
<td>3</td>
<td>4.06 (ddd)</td>
<td>4.50 (m)</td>
</tr>
<tr>
<td>4a</td>
<td>2.72 (ddd)</td>
<td>3.00 (ddd)</td>
</tr>
<tr>
<td>4b</td>
<td>2.38 (dd)</td>
<td>2.72 (dd)</td>
</tr>
<tr>
<td>6a</td>
<td>3.22 (d)</td>
<td>3.28 (d)</td>
</tr>
<tr>
<td>6b</td>
<td>3.09 (dd)</td>
<td>3.14 (dd)</td>
</tr>
<tr>
<td>8/10⁺</td>
<td>6.27 (s), 6.16 (s)</td>
<td>6.31 (d), 6.19 (d)</td>
</tr>
<tr>
<td>13/14/16/18⁺</td>
<td>3.73 (s), 3.72 (s), 3.70 (s), 3.59 (s)</td>
<td>3.73 (s), 3.65 (s), 3.53 (s), 3.40 (s)</td>
</tr>
<tr>
<td>PPh₃</td>
<td>7.34 – 7.45 (m, 15H)</td>
<td>7.20 – 7.50 (m, 30H)</td>
</tr>
</tbody>
</table>

Comparison of signals obtained by ¹H NMR for 3a and 5a•NTf₂ showed significant differences in chemical shifts. Upon digold formation protons 1 to 10 were shifted downfield and signals for protons 13 to 18 were moved upfield. This could be explained by the
delocalized positive charge in the 3-center-2-electron bond of 5a•NTf₂. The closer protons were located to the delocalized charge of that bond, the further downfield shifted their resonances. Therefore, the NMR signal for H₁ᵇ changed from 4.97 ppm to 6.43 ppm, whereas resonances for H₁ᵃ and H₃ only shifted from 5.62 ppm to 5.91 ppm and 4.06 ppm to 4.50 ppm, respectively. The protons corresponding to the carbocycle (H⁴, H⁶) and the aromatic ring (H⁸, H¹⁰) also showed different resonances depending on their distance to the delocalized charge.

The unusual environment of C² was also observed in ¹³C NMR spectra. Complex 5a•NTf₂ gave no signal for C², but the spectrum of 3a gave a doublet at 189.6 ppm for this carbon atom. Hammond noted a similar signal for the analogous carbon in his gold-vinyl complex.¹³⁴ The absence of a resonance for geminally diaurated carbon C² in 5a•NTf₂ was consistent with data reported by Schmidbaur,¹³⁵ where it was proposed that geminally diaurated C-atoms showed no ¹³C signal due to the quadrupole moment of gold.

### 3.4 Reactivity of Intermediates

The isolation of 3a and 5a•NTf₂ provided a rare opportunity to study the comparative reactivity of reaction intermediates. Compound 3a was found to readily react with stoichiometric quantities of HX (X = OAc, Cl, NTf₂) to yield 2 and the expected gold(I) species (Scheme 3-3).¹³⁶ When only 0.5 equivalent of HNTf₂ was added, clean conversion to 5a•NTf₂ and 2 occurred. Similarly clean and rapid was the conversion of 3a and 4a•NTf₂ to

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5a•NTf₂, a process that presumably competed favorably with protodeauration under catalytic conditions.

Scheme 3-3. Reactivity of 3a with Brønsted acids and Gagosz catalyst 4a•NTf₂.

The reactivity of 5a•NTf₂ with Brønsted acids differed greatly from 3a. Treatment with excess acetic acid (pKₐ = 4.76) left 5a•NTf₂ untouched, while 3a immediately protodeauridad to 2. Digold 5a•NTf₂ was also unreactive with α-bromo-acetic acid (pKₐ = 2.86) (for 12 h), and only traces of 2 were observed with excess HTFA (pKₐ = −0.25). Therefore, the second equivalent of [Ph₃PAu]⁺ in 5a•NTf₂ hindered protodeauration.
Paralleling the characteristic digold reactivity established by Nesmeyanov, Grandberg, and Schmidbaur, compound 5a•NTf₂ extruded Ph₃PAuL and 3a upon reaction with a suitable ligand L (Scheme 3-4).¹³⁷

Scheme 3-4. Characteristic digold reactivity of intermediate 5a•NTf₂.

To demonstrate that compounds 3a and 5a•NTf₂ were viable reaction intermediates, their reactivity was probed with allene 1. Although 5a•NTf₂ and 3a were expectedly unreactive with 1, they could each be activated with HNTf₂ to reveal 4a•NTf₂. The subsequent conversion of 1 to 2 indicated that both, 5a•NTf₂ and 3a were catalytic intermediates (Scheme 3-5).

Scheme 3-5. Starting the catalytic cycle with intermediates 3a or 5a•NTf₂ and HNTf₂.

These results clearly indicated that complexes 3a and 5a•NTf₂ were each viable intermediates in the intramolecular hydroarylation of allenes, which meant that the originally proposed mechanistic scheme (Scheme 3-1) was incomplete, because an additional digold structure needed to be added. The bridging structure in 5a•NTf₂ was found to be considerably more stable than 3a, and served to sequester the key Lewis acidic species [Ph₃PAu]⁺ more quickly than the latter promoted allene activation. Although 5a•NTf₂ was less reactive with Brønsted acids than 3a, both could be activated by HNTf₂ to generate catalytically active 4a•NTf₂. Therefore, it was not yet clear, whether 5a•NTf₂ operated on or off cycle under true catalytic conditions. These data also suggested that aurophilicity might play a much more important role in gold catalysis than previously envisioned.

3.5 Variation of Anions

To elucidate whether the formation of digold species in catalysis was dependent on the anion of the catalyst 4a•Y (Y = counterion), different silver salts were investigated in an in situ activation protocol of Ph₃PAuCl (Table 3-3). In each case, 5a•Y was observed by ³¹P-NMR suggesting a purely outer sphere role for the anions. With OTf, however, a broad signal at 36 ppm was observed suggesting that this counterion had an inner sphere role and was promoting a dynamic process that equilibrated the two diasterotopic phosphines of 5a•OTf. The examination of more coordinating anions, such as Y = tosylate (OTs), trifluoroacetate (TFA), binolphosphate (OPE), ortho-nitrobenzoate (OONB), para-nitrobenzoate (OPNB), benzoate (OBz), and acetate (OAc), could not be pursued, as these catalysts were entirely unreactive with 1. Interestingly, when Y = OTs, TFA, or OPE were used, the ³¹P signal of the catalyst broadened, suggesting competitive ligand exchange between the anion and substrate.
Therefore, an alternative method was necessary to investigate the effect of anions on digold formation. This method is discussed in chapter 5.\textsuperscript{138}

**Table 3-3.** Resting state analysis of the reaction of 1 with in situ activated Ph$_3$PAuCl/AgY catalyst by \textsuperscript{31}P NMR. *Instead of two sharp signals in a 1:1 ratio, one broad signal at $\delta \approx 36$ ppm was observed.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst / Activator</th>
<th>Resting State</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$PAuNTf$_2$</td>
<td>5a•NTf$_2$</td>
</tr>
<tr>
<td>2</td>
<td>Ph$_3$PAuCl / AgNTf$_2$</td>
<td>5a•NTf$_2$</td>
</tr>
<tr>
<td>3</td>
<td>Ph$_3$PAuCl / AgPF$_6$</td>
<td>5a•PF$_6$</td>
</tr>
<tr>
<td>4</td>
<td>Ph$_3$PAuCl / AgSbF$_6$</td>
<td>5a•SbF$_6$</td>
</tr>
<tr>
<td>5</td>
<td>Ph$_3$PAuCl / AgOTf$^a$</td>
<td>5a•OTf$^a$</td>
</tr>
<tr>
<td>6</td>
<td>Ph$_3$PAuCl / AgBF$_4$</td>
<td>5a•BF$_4$</td>
</tr>
</tbody>
</table>

### 3.6 Protodemetallation and Competition Experiments

Protodemetallation studies were conducted with 3a to gain an understanding how anions affected digold formation during catalysis. When AcOH ($pK_a$(H$_2$O) = 4.76; $pK_a$(DMSO) = 12.3) was reacted with 3a, complete protodemetallation to 2 and Ph$_3$PAuOAc was observed. In contrast, the addition of DTBP•HNTf$_2$ ($pK_a$(H$_2$O) = 4.95; $pK_a$(DMSO) = 0.90)\textsuperscript{139} caused an instant conversion to a 1:1 mixture of 5a•NTf$_2$ and 2 (Scheme 3-6). The contrasting


\textsuperscript{139} For an explanation of the great difference between $pK_a$(H$_2$O) and $pK_a$(DMSO) of DTBP, see: R. L. Benoit, M. Fréchette, D. Lefebvre, *Can. J. Chem.* 1988, 66, 1159.
behavior suggested a strong anion effect on the thermodynamics of digold formation. These protodemetallation studies further revealed, that monogold-vinyl \(3a\) can be protodemetallated by DTBP•HNTf\(_2\), but digold \(5a•NTf_2\) cannot. This difference in reactivity was crucial to intercept digold \(5a•NTf_2\) from catalysis.

**Scheme 3-6.** Protodemetallation studies of \(3a\) with AcOH and DTBP•HNTf\(_2\) indicate a strong anion effect.

Catalyst \(4a•NTf_2\) and AcOH readily converted monogold \(3a\) to \(5a•NTf_2\) and \(2\), respectively. Since neither product reacted further with \(4a•NTf_2\) or AcOH, a competition experiment between digold formation and protodemetallation was carried out by adding \(3a\) to an excess of a 1:5 mixture of \(4a•NTf_2\) and AcOH, respectively. Despite the seven molar excess of AcOH full conversion of \(3a\) to \(5a•NTf_2\) was observed (Scheme 3-7).
While not quantitative, these data showed a clear preference for digold formation over protodemetalation when using the less coordinating counterion NTf₂. Since the dogma in Lewis acid catalysis points to less coordinating anions being better, these results indicate that at least in some scenarios there may be a downside to this position.

### 3.7 Variation of Phosphine Ligands

In 2010, Fürstner and co-workers¹⁴⁰ structurally characterized two model complexes of geminally diaurated vinyl reaction intermediates, which additionally supported the viability of proposed digold intermediate 5a•NTf₂ (Figure 3-9).

![Scheme 3-7](image1.png)

**Scheme 3-7.** Competition experiment between protodemetalation and digold formation.

In their work, two types of geminally diaurated complexes were reported, one where the hyperconjugated carbon atom had greater sp² character (cyclopropyl stabilized) and one where heteroatom stabilization generates a geminally diaurated carbon atom that is

principally of sp\(^3\) character. The latter was especially robust towards protonolysis. The experimentally validated stability of geminally diaurated complexes towards acids combined with the observation of metallophilic interactions in the hydroarylation of allenes suggested that digold formation may very well be a defining feature in gold(I)-catalyzed reactions of allenes or alkynes, as both substrate classes likely proceed via gold-vinyl intermediates.

Because the importance of aurophilicity and the role of dinuclear complex \(5a\cdot Y\) in gold catalysis was unclear, specifically in the intramolecular hydroarylation of allenes, further mechanistic studies were initiated. To investigate the circumstances affecting the stability of digold intermediates in catalysis several monomeric and bridging gold(I)-catalysts were investigated, by varying their electronic, steric, and chelating properties.

The phosphine basicity was manipulated through \(para\)-substituted variants of the parent catalyst \((p\cdot X\cdot C_6H_4)_3PAuNTf_2\) with \(X = CF_3\) \((4b\cdot NTf_2)\), \(F\) \((4c\cdot NTf_2)\), and \(Me\) \((4d\cdot NTf_2)\).\(^{141}\) Monitoring these reactions by \(^{31}\)P NMR indicated that a majority of the catalyst pooled at the digold intermediate \(5b\cdot NTf_2\), \(5c\cdot NTf_2\), or \(5d\cdot NTf_2\), respectively (Figure 3-10). With \(4b\cdot NTf_2\) (\(\delta = 30.3\) ppm) digold signals were detected at \(\delta = 36.4\) and 35.2 ppm, with \(4c\cdot NTf_2\) (\(\delta = 27.5\) ppm) digold signals were detected at \(\delta = 34.2\) and 33.6 ppm, while \(4d\cdot NTf_2\) (\(\delta = 28.0\) ppm) provided digold signals at \(\delta = 34.2\) and 34.0 ppm. High field \(^1\)H NMR further confirmed the catalytic presence of a digold species. Therefore, within this span of electronic perturbation, the formation of digold intermediate was dominant.\(^{142}\)


\(^{142}\) \(^1\)H and \(^{31}\)P NMR data also revealed the presence of a digold intermediate for the reaction of 1 with catalysts \((p\cdot X\cdot C_6H_4)_3PAuNTf_2\) (\(X = Cl\) \((4e\cdot NTf_2)\), \(OMe\) \((4f\cdot NTf_2)\)).
Digold intermediates were also observed with diphosphine catalysts. The reaction of 1 with Tf₂AuPPh₂(CH₂)₆Ph₂PAuNTf₂ (4g•NTf₂, P₆P(AuNTf₂)₂) as a catalyst revealed ⁴¹P NMR signals at 35.6 and 34.3 ppm in a 1:1 ratio implying a digold intermediate (Figure 3-11, top spectrum). Only P₆P(AuNTf₂)₂ (4g, δ = 27.5 ppm) could be cleanly isolated as the pre-activated NTf₂-salt, but ⁴¹P and ¹H NMR data suggested, that in situ generated P₅P(AuNTf₂)₂ (4h•NTf₂) and P₄P(AuNTf₂)₂ (4i•NTf₂) catalysts also proceeded via digold.
species. When the methylene spacer was reduced by using in situ generated dinuclear catalysts PnP(AuNTf₂)₂ catalysts with n = 1 (4j•NTf₂), 2 (4k•NTf₂), or 3 (4l•NTf₂), inconclusive spectra were obtained. It thus seemed likely that flexible diphosphines can span the two metals in the digold structure.

Figure 3-11. Detected digold intermediates by ³¹P NMR for the catalysis of 1 with the bridging 4g•NTf₂ and monodentate 4m•NTf₂ as catalysts.

The electronically similar monodentate catalyst EtPh₂PAuNTf₂ (4m•NTf₂, δ = 31.9 ppm) was also probed for the presence of a digold intermediate while catalyzing the reaction of 1. Likewise, digold signals at δ = 36.4 and 36.0 ppm were observed (Figure 3-11, bottom spectrum). Baseline signals in the ¹H NMR data confirmed the digold intermediate with both catalysts.
Sterically demanding catalysts also revealed digold intermediates. Monitoring the cyclization of 1 with \((o-\text{CH}_3-\text{C}_6\text{H}_4)_3\text{PAuNTf}_2\) \((4n\cdot\text{NTf}_2\), cone angle \(\Theta = 194^\circ\))\(^{143}\) suggested a digold structure. \(^{31}\text{P}\) NMR signals appeared at \(\delta = 22.6\ \text{ppm}\) and \(\delta = 15.8\ \text{ppm}\) in a 1:1 ratio. However, in contrast to previous cases, these resonances were significantly broadened relative to chemical shifts of digold intermediates. The signal corresponding to catalyst \(4n\cdot\text{NTf}_2\) \((\delta = -0.9\ \text{ppm})\) was observed throughout the reaction as well (Figure 3-12).\(^{144}\)

Because the \(^{31}\text{P}\) NMR data of the reaction of 1 with bulky catalyst \(4n\cdot\text{NTf}_2\) revealed different characteristics (broad asymmetric signals, no complete binding of catalyst as digold intermediate), further studies were pursued to confirm the presence of a digold intermediate during catalysis.

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\(^{143}\) (a) C. A. Tolman, *Chem. Rev.* 1977, 77, 313; for examples of gold(I)-complexes with bulky phosphines, see: (b) E. C. Alyea, G. Ferguson, S. Kannan, *Polyhedron* 2000, 19, 2211 and references therein.

\(^{144}\) \(^{31}\text{P}\) NMR signals in a 1:1 ratio implied also a digold resting state with Mes\(_3\)PAuNTf\(_2\) \((\Theta = 214^\circ)\). However, further studies with Mes\(_3\)PAuNTf\(_2\) were discontinued due to its instability in solution and extremely slow reaction rate.
3.8 X-ray Crystal Structure of Digold Intermediate

As mentioned in section 3.7, when the reaction of 1 with catalyst \((o-CH_3-C_6H_4)_3PAuNTf_2\) \((4n\cdot NTf_2)\) was monitored by \(^{31}P\) NMR, broad and asymmetrically shaped signals were observed in comparison to \((p-CH_3-C_6H_4)_3PAuNTf_2\) \((4d\cdot NTf_2)\) and other phosphines with a similar cone angle \(\Theta\) (compare Figure 3-10 and Figure 3-12).

The stoichiometric reaction of 1 with aliquots of \(4n\cdot NTf_2\) could be accomplished in the presence of excess DTBP avoiding any turnover via protodemetalation at room temperature (Scheme 3-8). \(^{31}P\) and \(^1H\) NMR data exhibited resonances that corresponded to the catalytic intermediate \(5n\cdot NTf_2\) (Figure 3-13).

![Scheme 3-8. Synthesis of digold 5n•NTf₂.](image)

However, the rate of the stoichiometric reaction was highly dependent on the gold catalyst. With 2 equiv of \(4a\cdot NTf_2\) complete conversion of 1 was observed within 30 minutes, whereas 2 equiv of \(4n\cdot NTf_2\) took over night to reach completion (13 h). This rate difference could probably be attributed to the stereoelectronic difference between Ph₃P and \((o-CH_3-C_6H_4)_3P\), the latter being more basic and sterically crowded.
Figure 3-13. \(^{31}\)P and \(^{1}\)H NMR data after addition of aliquots of \(4n\text{•NTf}_2\) to 1 in the presence of excess DTBP.
NMR samples of 5n•NTf₂ were stable in solution at room temperature and single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of 5n•NTf₂ in DCM layered with pentanes. ¹⁴⁵ NMR data of single crystals matched the digold spectra of the catalytic and stoichiometric reactions of 1 and 4n•NTf₂.

The crystal structure of 5n•NTf₂ did not reveal the expected geminal diauration binding mode as originally proposed for 5a•NTf₂ and indicated by crystallographic evidence from Fürstner. Instead, σ-π-diauration of the vinyl moiety was found as an alternative connectivity, which was also stabilized by an aurophilic bond (Figure 3-14).

Figure 3-14. ORTEP diagram of 5n•NTf₂ with 50% probability ellipsoids; most hydrogen atoms omitted for clarity. Key bond lengths [Å] include: Au1-Au2 [3.13563(18)], Au2-C2 [2.059(3)], Au1-C1 [2.275(3)], Au1-C2 [2.287(3)], and C1-C2 [1.369(5)].¹⁴⁶

¹⁴⁵ It is important to note that the bulk of single crystals was a mixture of 5n•NTf₂ and the decomposition product [(o-CH₃-C₆H₄)₃P]₂Au][NTf₂]⁻.

¹⁴⁶ CDCC 873041 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
The structure of $5n\cdot$NTf$_2$ was best described as a gold-vinyl (similar to $3a$) with a second gold unit $\pi$-bound to the olefin. The length of the Au2–C2 $\sigma$-bond (2.059(3) Å) was only slightly elongated in comparison to $3a$ (2.050(2) Å). The sum of the bond angles $\angle$(Au2–C2–C1), $\angle$(Au2–C2–C3), and $\angle$(C1–C2–C3) was calculated to 359.4°, which was comparable to $3a$ (sum of corresponding angles = 359.9°) and indicated no perturbation of the $\sigma$-connectivity between Au2 and C2.

The second gold atom (Au1) was $\pi$-bound to the olefin bond between C1 and C2. It was closely resembled by cationic gold(I) $\pi$-alkene complexes published by Widenhoefer.\textsuperscript{147} The distances between Au1–C1 (2.275(3) Å) and Au1–C2 (2.287(3) Å) were in agreement with distances in other $\pi$-coordinated olefins, which ranged from 2.199 Å to 2.365 Å. The shorter distance of Au–C1 could probably be contributed to the steric repulsion between the two bulky ($o$-CH$_3$-C$_6$H$_4$)$_3$P ligands. Additionally, as a result of $\pi$-complexation, the C1=C2 double bond (1.369(5) Å) was clearly elongated in comparison to $3a$ (1.324(4) Å).

Aurophilic bonding between Au1 and Au2 further stabilized the structure. The range for aurophilic interactions is quite large (2.8 Å – 3.5 Å), because of a relatively flat energy profile for the mutual approach of two gold atoms.\textsuperscript{148} The Au1–Au2 distance in $5n\cdot$NTf$_2$ (3.13563(18) Å) indicated aurophilic stabilization, but was much larger than in Fürstner’s geminally diaurated model complexes (2.7591(8) Å and 2.8013(3) Å). Thus far, $\sigma$-$\pi$ diauration was only observed with alkynes, but a supporting aurophilic bonding was not proposed in those complexes due to a long Au–Au distance (3.4312(3) Å).\textsuperscript{149}


The reason for a σ-π-diaurated binding mode could originate in the steric crowding between the bulky ligands and the aromatic ring in the substrate. The resulting repulsion of the ortho-Tol groups could distort the digold structure from a geminally diaurated to a σ-π-binding mode. Based on the broad and asymmetric signals of 5n•NTf₂ by ³¹P NMR and the contrasting sharp resonances with less bulky catalysts, it was proposed that the σ-π-diaurated structure of 5n•NTf₂ did not resemble the binding mode of previously isolated 5a•NTf₂. Since X-ray crystallographic evidence has not been forthcoming for 5a•NTf₂, a potential difference in connectivity between 5a•NTf₂ and 5n•NTf₂ could be derived from their respective characteristic reactivity with Brønsted acids (in particular acetic acid) and abstracting ligands. These studies will be pursued in the future.

3.9 Probing Different Allenes for Digold Intermediates

To establish the notion that digold formation should be feasible in a broad variety of allene activation reactions, a scan of previously reported transformations was undertaken. Therefore, the cycloisomerization of ene-allene 6, the cascade cyclization of epoxy-allene 8, and the hydroalkoxylation of hydroxy-allene 10 were investigated by ³¹P NMR for potential digold intermediates.

The cycloisomerization of ene-allene 6 with 10 mol% 4a•NTf₂ led to a regioisomeric mixture of 7a and 7b, whose ratio depended on the counteranion and the reaction conditions. In situ ³¹P NMR spectroscopic analysis indicated the presence of a digold species with a pair of singlets at δ = 36.9 and 36.5 ppm in addition to 4a•NTf₂ (δ ≈ 30 ppm) (Figure 3-15).¹⁵⁰

However, further studies are necessary to confirm the formation of a digold vinyl intermediate.

![Diagram of chemical reaction]  

**Figure 3-15.** $^{31}$P NMR signals at $\delta = 36.9$ ppm and 36.5 ppm indicated a digold intermediate for the cycloisomerization of ene-allene 6.

In situ $^{31}$P NMR spectroscopy also indicated that a digold vinyl complex built up in the cycloisomerization of epoxy-allene 8 (Figure 3-16).$^{151}$ $^{31}$P NMR resonances at $\delta = 37.1$ ppm and $\delta = 35.7$ ppm were observed in a 1:1 ratio during catalysis. As in the previous example, unreacted 4a•NTf$_2$ accounted for the balance of the catalyst speciation.

Originally reported by the Widenhoefer group the reaction of hydroxy-allene 10 with 1 mol% 4a•NTf$_2$ provided a mixture of 11 and 12.$^{152}$ Like the previous examples, in situ monitoring indicated that one digold species dominated the resting state speciation. This

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potential digold was characterized by the 1:1 ratio of peaks at $\delta = 37.8$ and 35.7 ppm; a broad singlet at $\delta \approx 30$ ppm for $4a\cdot$NTf$_2$ was also detected (Figure 3-17).

**Figure 3-16.** $^{31}$P NMR signals at $\delta = 37.1$ ppm and 35.7 ppm indicated a digold intermediate for the cycloisomerization of epoxy-allene 8.

**Figure 3-17.** $^{31}$P NMR signals at $\delta = 37.8$ ppm and 35.7 ppm indicated a digold intermediate for the hydroxyalkoxylation of allene 10.
The two products \textbf{11} and \textbf{12} were obtained in a 1:4 NMR ratio, respectively. The formation of product \textbf{12} was dependent on the anion of the catalyst. Product \textbf{12} was observed with NTf$_2$ and OTf, but less coordinating counterions, such as OTs, OBz, or OAc, formed only \textbf{11}. The mechanism of the intramolecular hydroalkoxylation was studied in collaboration with the Widenhoefer laboratory at Duke University. These results are summarized in chapters 4 and 6.

\section*{3.10 Experimental Data}

Experimental data of sections 3.2 to 3.4 were published and are available on the WWW under http://dx.doi.org/10.1002/anie.200902049. Data for sections 3.5 to 3.9 are listed below.

Conversion of \textbf{3a} with excess DTBP•HNTf$_2$ to \textbf{5a•NTf$_2$} and \textbf{2} (Scheme 3-6, bottom): In a NMR tube 4.3 mg \textbf{3a} were dissolved in 0.4 mL CD$_2$Cl$_2$ and NMR data was acquired. Aliquots of an in situ generated solution of DTBP•HNTf$_2$ were added dropwise. NMR data showed conversion to a 1:1 ratio of \textbf{5a•NTf$_2$} and \textbf{2} (Wb2-006).

Competition experiment of \textbf{3a} with an excess 5:1 mixture of AcOH and \textbf{4a•NTf$_2$} (Scheme 3-7): In a NMR tube small quantities of AcOH and \textbf{4a•NTf$_2$} were dissolved in 0.6 mL CD$_2$Cl$_2$. A 5:1 AcOH : \textbf{4a•NTf$_2$} ratio was determined by $^1$H NMR. A solution of 5.4 mg \textbf{3a} in 0.2 mL CD$_2$Cl$_2$ was added to the mixture. NMR data indicated sole conversion to \textbf{5a•NTf$_2$} (Wb2-080).

Synthesis of digold \textbf{5n•NTf$_2$} (Scheme 3-8 and Figure 3-13): In a NMR tube 3.5 mg (10.5 µmol) of \textbf{1} were dissolved in 0.5 mL CD$_2$Cl$_2$ and 5.3 mg DTBP were added. First, 1.6 mg (2.0 µmol) of \textbf{4n•NTf$_2$} were added and monitored by NMR. Full conversion of \textbf{4n•NTf$_2$} to \textbf{5n•NTf$_2$} was observed after 13 h by NMR. Another 11.6 mg (14.8 µmol) of \textbf{4n•NTf$_2$} were
added. Again, full conversion of $4n\text{•NTf}_2$ to $5n\text{•NTf}_2$ was observed after 13 h by NMR (Wb2-290-A).

Synthesis of single crystals of $5n\text{•NTf}_2$ (Figure 3-14): In a vial 5.9 mg (17.6 µmol) of 1, 18.9 mg (24 µmol) of $4n\text{•NTf}_2$, and 48 mg (1.5 equiv) of DTBP-resin were added and dissolved in 3-5 mL DCM, which initiated the reaction. An enriched sample of $5n\text{•NTf}_2$ was obtained after stirring over night. The reaction solution was filtered through a plug of glass wool to remove the resin and the solvent was removed in vacuo. The residue was dissolved in a minimal amount of DCM and layered with an excess amount of pentanes. Slow evaporation led to a mixture of single crystals of $5n\text{•NTf}_2$ and $[(\text{o-CH}_3\text{-C}_6\text{H}_4)_3\text{P}\text{Au}][\text{NTf}_2]$ (Wb2-298-B).

Resting state analysis with epoxy-allene 8 (Figure 3-16): In a NMR tube were added 0.15 mL of a stock solution of 8 (0.25 M), 0.35 mL CD$_2$Cl$_2$, and 0.36 mL of a stock solution of $4n\text{•NTf}_2$ (0.1 M). NMR analysis showed spectra that were consistent with a digold resting state (Wb1-183).

Resting state analysis with ene-allene 6 (Figure 3-15): In a NMR tube were added 7.4 mg of 6, 0.5 mL CD$_2$Cl$_2$, and 2.3 mg of $4a\text{•NTf}_2$. NMR analysis showed spectra that were consistent with a digold resting state (Wb3-026-B).
Chapter 4. Gold-Vinyl Intermediates in the Hydroalkoxylation of Allenes

In a collaborative effort with the Widenhoefer group at Duke University, gold-vinyl intermediates of the intramolecular hydroalkoxylation of allenes were isolated. A monogold and digold intermediate were fully characterized. Both intermediates could be identified as a catalyst resting state by NMR, depending on the reaction conditions.

4.1 Introduction

In a collaborative effort with the Widenhoefer group, the mechanism of intramolecular hydroalkoxylation of hydroxy-allene 10 was studied in detail. The catalyst resting state was analyzed by \(^{31}\)P and \(^1\)H NMR with different catalysts and anions. The Widenhoefer group primarily focused on JohnPhos, which allowed the isolation of mono- and digold-vinyl intermediates. These results were the basis of the collaboration. The Gagné group primarily pursued studies with PPh\(_3\) that enabled electronic alteration of the catalyst suitable for Hammett studies and comparison to previous results for the hydroarylation of allenes.

4.2 Results with JohnPhos (Widenhoefer Group)

From the stoichiometric reaction of 10 with in situ formed (JohnPhos)AuOTs (4o•OTs) in the presence of NEt\(_3\), the monogold-vinyl 13o was obtained in a 87% yield (Scheme 4-1).
Scheme 4-1. Synthesis of gold-vinyl intermediate 13o.

With vigorous stirring, complex 13o was slowly dissolved in gently boiling hexanes. Storing the warm solution at 4°C for 3 days gave colorless crystals suitable for X-ray diffraction analysis. The structure of 13o showed the same characteristics as the isolated gold-vinyl 3a from the hydroarylation.

Interestingly, when the stoichiometric reaction of 10 with 1 equiv of 4o•OTs was followed at –80°C by NMR, no conversion to gold-vinyl 13o was observed.
Instead, 50% conversion of 10 to digold 140•OTs was detected (Figure 4-2, (a)). The formation of digold was confirmed by addition of 1 equiv of 40•OTs to 130, which led to full conversion to the same digold species (Figure 4-2, (b)). Digold 140•OTs was clearly

\[153\] Added NEt₃ coordinates to cationic gold and reduces its electrophilicity. As a result, NEt₃ acts as an inhibitor for digold formation, see: A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, Organometallics 2012, 31, 644.
distinguishable from monogold 13o by $^1$H and $^{31}$P NMR (Figure 4-2, (c)). In catalytic studies, digold 14o•OTs was identified as the catalyst resting state. Single crystals of 14o•OTs suitable for structural analysis by X-ray diffraction were not obtained.

4.3 Results with Ph$_3$P (Gagné Group)

Studies by the Widenhoefer lab supported the previous observation (see Figure 3-17) that the intramolecular hydroalkoxylation of allene 10 formed a digold intermediate during catalysis.

Scheme 4-2. Enriched sample of 14a•NTf$_2$ (top) revealed characteristic digold reactivity (bottom).
Attempts to isolate the digold $14a$-$\text{NTf}_2$ from the stoichiometric reaction of $10$ with 2 equiv $4a$-$\text{NTf}_2$ in the presence of 1.5 equiv of resin bound DTBP failed. Only an enriched sample of digold $14a$-$\text{NTf}_2$ was obtained, but organic and gold impurities could not be removed (Scheme 4-2, top). However, the proposed structure of $14a$-$\text{NTf}_2$ was supported by 2D-NMR data.

The $^{31}$P NMR spectrum of $14a$-$\text{NTf}_2$ exhibited two signals at $\delta = 37.8$ and 35.7 ppm (1:1 ratio), which matched NMR data obtained under catalytic conditions (Figure 4-3, (d)). The signal at $\delta = 44.9$ ppm was assigned to the decomposition product $[(\text{Ph}_3\text{P})_2\text{Au}]^+\text{NTf}_2^-$. The structure of the organic impurity could not be determined.

Although $14a$-$\text{NTf}_2$ could not be isolated in pure form, crude samples of $14a$-$\text{NTf}_2$ were suitable for preliminary reactivity studies. Digold $14a$-$\text{NTf}_2$ was stable to acetic acid and addition of an excess of PPh$_3$ abstracted one [Ph$_3$PAu]$^+$ unit and yielded gold-vinyl $13a$ and [(Ph$_3$P)$_2$Au]$^+$, though separation of two gold species was not accomplished. Surprisingly, exposure of $14a$-$\text{NTf}_2$ to HCl caused cycloreversion to $10$ and the formation of Ph$_3$PAuCl, while no protodemetalation to $11$ was observed. These reactivity data of $14a$-$\text{NTf}_2$ supported the proposed digold structure.

The hydroalkoxylation of allene $10$ offered the opportunity to determine anion effects on catalytic digold formation, since this reaction initiated catalysis with stronger coordinating anions, such as OTs, OPNB, or OAc (in contrast to the hydroarylation of allene $1$).

Following the reaction of $10$ with 1-2 mol% $4a$-$\text{NTf}_2$ by $^1$H and $^{31}$P NMR, signals corresponding to the enriched sample of digold $14a$-$\text{NTf}_2$ could be observed during catalysis (Figure 4-3, (b)). After 90 minutes, the conversion of $10$ to $11$ and $12$ was complete and resonances corresponding to digold $14a$-$\text{NTf}_2$ disappeared (Figure 4-3, (c)). These data
suggested that $4a\cdot\text{NTf}_2$ rested as digold $14a\cdot\text{NTf}_2$ during catalysis. When monitoring the reaction of $10$ with 2 mol% $4a\cdot\text{OTs}$ only exo-cyclization to $11$ was observed. The rate of the reaction was with 2 mol% $4a\cdot\text{OTs}$ significantly faster than with 2 mol% $4a\cdot\text{NTf}_2$. $^{31}\text{P}$ NMR suggested formation of the digold intermediate $14a\cdot\text{OTs}$ during catalysis, however, this could not be confirmed by $^1\text{H}$ NMR due to the low catalyst loading (Figure 4-4).

**Figure 4-3.** Following the reaction of $10$ with 1-2 mol% $4a\cdot\text{NTf}_2$ by $^1\text{H}$ (left) and $^{31}\text{P}$ (right) NMR in CD$_2$Cl$_2$. (a) Excerpt of $^1\text{H}$ NMR spectrum of $10$; (b) Spectra during catalysis (6 minutes after catalyst addition); (c) Spectra after catalysis (90 minutes after catalyst addition). Chemical shifts of $14a\cdot\text{NTf}_2$ mostly disappeared by $^1\text{H}$ and $^{31}\text{P}$ NMR. (d) Spectra of enriched sample of $14a\cdot\text{NTf}_2$. Resonances in $^1\text{H}$ NMR for $14a\cdot\text{NTf}_2$ are marked with X.
When the reaction of 10 with 13 mol% 4a•OTs in the presence of excess DTBP was monitored by NMR, a monogold resting state (13a) was identified. A characteristic signal for 13a was observed by $^{31}$P NMR (Figure 4-5). Although an attempt was made to inhibit protodemetallation with DTBP, catalytic turnover was still observed, albeit at a slower reaction rate.

Figure 4-5. Monitoring the reaction of 10 with 2 mol% 4a•OTs in the presence of excess DTBP by $^{31}$P NMR. Signal at $\delta \approx 43$ ppm corresponds to 13a.
The monogold intermediate 13a was also observed as the catalyst resting state when the reaction of 10 with 10 mol% 4a•OONB was analyzed by $^1$H and $^{31}$P NMR (Figure 4-6). $^1$H NMR data showed characteristic signals in the vinyl region that were consistent with the gold-vinyl 13a. This hypothesis was supported by a $^{31}$P signal at $\delta \approx 44.5$ ppm, the characteristic $^{31}$P NMR region of gold-vinyls.

![Figure 4-6. Following the reaction of 10 with 10 mol% 4a•OONB by $^1$H (left) and $^{31}$P (right) NMR in CD$_2$Cl$_2$. (a) $^1$H NMR spectrum during catalysis (6 minutes after catalyst addition); (b) $^1$H NMR spectrum during catalysis (50 minutes after catalyst addition); (c) $^{31}$P NMR spectrum during catalysis (collected between 6-50 minutes of catalysis); (d) $^1$H and $^{31}$P NMR spectra after catalysis (12 h after catalyst addition). Resonances in $^1$H NMR for 13a are marked with X.](image_url)
Other anions were also probed. A digold resting state $14a\cdot Y$ was also indicated in experiments with $4a\cdot$TFA and potentially with $4a\cdot$OPE, but further data are needed for confirmation. The more coordinating counterions $4a\cdot$OPNB, $4a\cdot$OBz, and $4a\cdot$OAc clearly revealed the monogold resting state $13a$. Interestingly, all the reactions that proceeded through a monogold resting state exhibited a significantly slower rate in comparison to the digold cases. This could be explained by the coordinating ability of the counteranion or by the pK$_a$ of the in situ formed conjugated acid.

Overall, these observations demonstrated a strong counterion and base effect on the catalyst resting state of the gold(I)-catalyzed intramolecular hydroalkoxylation of allene $10$. Further studies were pursued to obtain a better understanding of digold formation (chapter 5) and effects on catalysis (chapter 6).

4.3 Experimental Data

Synthesis of enriched sample of $14a\cdot$NTf$_2$ (Scheme 4-2): In a vial were added 109 mg DTBP-resin and 130.7 mg (176 µmol) of $4a\cdot$NTf$_2$. The solids were dissolved in 3-5 mL DCM and a solution of 22.0 mg (88 µmol) $10$ in 1 mL DCM was added. The reaction mixture was stirred for 2 h. The resin was removed by a glass wool plug and the volatiles removed in vacuo. An enriched sample of $14a\cdot$NTf$_2$ as a brown foam was obtained. The reactivity with HCl, AcOH, and Ph$_3$P was probed (Wb2-194-A).

Resting state analysis of the reaction of $10$ with $4a\cdot$NTf$_2$ (Figure 4-3): In a NMR tube 15.4 mg of $10$ were dissolved in 0.5 mL CD$_2$Cl$_2$ and 1.0 mg $4a\cdot$NTf$_2$ were added. The reaction was monitored by NMR (Wb2-194-B).
Resting state analysis of the reaction of \textbf{10} with \textbf{4a•OTs} (Figure 4-4): In a NMR tube 41.7 mg of \textbf{10} were dissolved in 0.5 mL CD$_2$Cl$_2$. At −78°C 2.7 mg \textbf{4a•OTs} were added. The reaction was monitored by NMR at 274 K (Wb3-021-C).

Resting state analysis of the reaction of \textbf{10} with \textbf{4a•OTs} in the presence of DTBP (Figure 4-5): In a NMR tube 18.6 mg of \textbf{10} were dissolved in 0.5 mL CD$_2$Cl$_2$ and >2 equiv of DTBP were added. At room temperature 4.1 mg \textbf{4a•OTs} were added. The reaction was monitored by NMR (Wb3-021-E).

Resting state analysis of the reaction of \textbf{10} with \textbf{4a•OONB} (Figure 4-6): In a NMR tube 14.2 mg of \textbf{10} were dissolved in 0.5 mL CD$_2$Cl$_2$ and 3.6 mg \textbf{4a•OONB} were added. The reaction was monitored by NMR (Wb2-288-D).

Resting state analysis of the reaction of \textbf{10} with \textbf{4a•TFA}: In a NMR tube 16.4 mg of \textbf{10} were dissolved in 0.5 mL CD$_2$Cl$_2$ and ~1 mg \textbf{4a•TFA} were added. The reaction was monitored by NMR at 274 K (Wb3-021-F).
Chapter 5. Model Complexes Lead to a Better Understanding of Digold Formation

The synthesis and structural characterization of gold-vinyl and gold-aryl complexes is reported. Decomposition of digold complexes via homo-coupling is noted. Averaging proton signals are used to quantitatively measure electronic and anion effects on digold formation. The influence of Brønsted acids is described.

5.1 Introduction

As reported in chapters 3 and 4, the intramolecular hydrofunctionalization of allenes $1$ and $10$ proceeded via two gold-vinyl intermediates, a mononuclear and a dinuclear. Both gold-vinyls acted as catalyst resting states depending on the reaction conditions. The digold structure was suggested to result from the reaction of [LAu]$^+$ with monogold-vinyl intermediates (Scheme 5-1). The proposal that the digold resting states contained a (Au$_2$C)-three-center-two-electron bond, which was additionally stabilized by an aurophilic closed shell interaction of significant strength (5-10 kcal/mol),$^{154}$ was based on the aromatic digold compounds reported by Schmidbaur, Grandberg, and Nesmeyanov and confirmed by recent digold vinyl complexes from Fürstner.$^{155}$


Scheme 5-1. Monogold and digold complexes as intermediates in the hydrofunctionalization of allenes.

However, with the exception of above mentioned studies little was known about digold intermediates in gold catalysis. Since digold formation consumed an otherwise catalytically active [LAu]+ unit and the digold intermediate was shown to be less reactive towards H+\(^+\),\(^\text{156}\) one might reasonably surmise that digold formation was inhibitory to catalysis. These considerations prompted the studies contained in this chapter to experimentally delineate and quantify those factors influencing digold formation. Studies with gold-aryl model complexes were published in Angewandte Chemie.\(^\text{157}\)

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156 [LAu]+ and H+ are isolobal to one another: (a) H. G. Raubenheimer, H. Schmidbaur, Organometallics 2012, DOI: 10.1021/om2010113; (b) R. Hoffmann, Angew. Chem. Int. Ed. 1982, 21, 711.

5.2 Studies with Gold-Vinyl Model Complexes

Gold-vinyl complexes were synthesized from Ph₃PAuCl and the corresponding Grignard reagent. Samples were purified by crystallization from benzene layered with pentanes at 4°C. Single crystals suitable for X-ray analysis were obtained of the parent gold-vinyl 15a and the isopropenylgold complex 16a (Figure 5-1).

![Synthesis and structure of gold-vinyl complexes 15a and 16a](image)

**Figure 5-1.** Synthesis and structure of gold-vinyl complexes 15a and 16a. Key bond lengths [Å] in 15a: Au1-C1 [2.048(4)], C1-C2 [1.298(7)]. Key bond lengths [Å] in 16a: Au1-C1 [2.041(4)], C1-C2 [1.353(7)], C1-C3 [1.486(7)].

The bond distances observed in the crystal structures of 15a and 16a were in good agreement with the corresponding bond lengths of the isolated gold-vinyl intermediate 3a.

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158 CDCC 755225 (15a) and CDCC 769522 (16a) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Synthesis of digold complexes 17a•NTf₂ and 18a•NTf₂ was first attempted by the direct addition of 1 equiv of 4a•NTf₂ to samples of 15a and 16a, respectively. However, instant decomposition at room temperature to a dark red-brown solution was observed. Cooling the sample to −78ºC significantly slowed the process, but did not lead to complete inhibition. Digold-vinyl complex 17a•NTf₂ was more stable in its solid state, which was accessible by precipitation from diethyl ether. Addition of diethyl ether to a 0.8:1 solid mixture of Ph₃PAuNTf₂ (4a•NTf₂), and 15a at −78 ºC led to precipitation of the desired digold complex 17a•NTf₂. Crystallization or complete characterization of this complex by NMR was challenging due to its rapid decomposition, but might be possible at low temperatures.

The instability of digold complexes 17a•NTf₂ and 18a•NTf₂ in solution was also reported by Grandberg, but the decomposition product was not identified. The ³¹H NMR data obtained from the decomposition of 17a•NTf₂ was consistent with 1,3-butadiene. ³¹P NMR suggested the formation of [(Ph₃P)₂Au⁺][NTf₂]⁻ (Scheme 5-2). However, the dark red-brown colour of the decomposition solution could not be explained with either product, since both compounds are colorless. Because the solution did not result in the formation of a gold-mirror a Au(I)/Au(0) mixed cluster was proposed as a second gold by-product.


The decomposition of digold complexes to homo-coupled products was surprising. To confirm homo-coupling, the decomposition of \(18a\cdot\text{NTf}_2\) was investigated by NMR. \(^1\text{H}\) NMR data showed only one homo-coupling product, 2,3-dimethyl-1,3-butadiene, which indicated selective coupling at the Au–C bond (Scheme 5-3).

The homo-coupling hypothesis was confirmed in a cross-over experiment (Scheme 5-4). Addition of 2 equiv of \(4a\cdot\text{NTf}_2\) to a 1:1 mixture of \(15a\) and \(16a\), led to the in situ formation of the corresponding digold complexes. The 1:1 mixture of digolds \(17a\cdot\text{NTf}_2\) and \(18a\cdot\text{NTf}_2\) decomposed to three products: 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, and isoprene. Fürstner also reported that digold-vinyl complexes decomposed via a homo-coupling pathway.
Scheme 5-4. Decomposition of a 1:1 mixture of 17a•NTf₂ and 18a•NTf₂ to 2,3-butadiene, isoprene, and 2,3-dimethyl-1,3-butadiene.

From an academic mechanistic point of view these observations were quite interesting; especially, since homo-coupling from presumed gold-vinyl intermediates were known side reactions in a few gold-catalyzed reactions. Because of the limited availability of stable digold vinyl complexes with a (Au₂C)-three-center-two-electron bond, gold-aryl complexes were investigated as gold-vinyl models.

5.3 Studies with Gold-Aryl Model Complexes

To bypass the instability of gold-vinyl complexes readily available and easily modifiable aryl complexes were used as models for catalytically relevant vinyl complexes. Arylgold(I) complexes were synthesized from Ph₃PAuCl and the corresponding Grignard reagents, and were found to crystallize either in a monomeric form or with an unsupported Au–Au interaction that pairs the compounds (Figure 5-2). Solutions of these compounds were stable to decomposition in CD₂Cl₂ over a minimum of 12 hours.

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**Figure 5-2.** Synthesis of gold-aryl complexes with two structurally characterized examples. ORTEP diagrams of two Ph₃PAuAr complexes (Ar = 2,5-(OMe)₂-C₆H₃ and 3-Me-C₆H₄) with 50% probability ellipsoids; hydrogen atoms and second molecule in unit cell for Ar = 2,5-(OMe)₂-C₆H₃ are omitted for clarity. Key bond lengths [Å] in Ar = 2,5-(OMe)₂-C₆H₃: Au-C(ipso) [2.044(3)] and [2.045(3)]. Key bond lengths [Å] in Ar = 3-Me-C₆H₄: Au-C(ipso) [2.049(4)] and [2.061(4)], Au–Au [3.0580(2)].

The digold(I)-aryl complexes were available through a slight variation of the Grandberg-Nesmeyanov synthesis of geminally diaurated ferrocenyl complexes (see chapter 1.2). Addition of diethyl ether to a 0.8:1 solid mixture of Ph₃PAuNTf₂ (4a•NTf₂) and Ph₃PAuAr at −78 °C led to precipitation of the desired [(Ph₃PAu)₂Ar]⁺[NTf₂]⁻ salt. This procedure could

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163 CDCC 851149 (2,5-(OCH₃)₂-C₆H₃)AuPPh₃ and CDCC 851150 (3-CH₃-C₆H₄)AuPPh₃ contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

be applied to the synthesis of a variety of digold-aryl complexes (see experimental data in section 5.4). In two cases single crystals of sufficient quality for X-ray analysis were obtained to confirm atom connectivity, though twinning and disorder did not allow an analysis of metrical parameters (Figure 5-3).

**Figure 5-3.** Synthesis of digold-aryl complexes with two structurally characterized examples. ORTEP diagrams of digold aryl cations (Ar = 2,5-(OMe)₂-C₆H₃ and 2-Me-C₆H₄) with 50% probability ellipsoids; hydrogen atoms and anion omitted for clarity. Both structures suffered from twinning and disorder; only atom connectivity was considered reliable.¹⁶⁵

In general digold compounds were stable in their precipitated state, but decomposed slowly in CD₂Cl₂ solution via the homo-coupling pathway previously described for gold-

¹⁶⁵ CDCC 851147 [(2,5-(OCH₃)₂-C₆H₃)(AuPPh₃)₂][NTf₂] and CDCC 851148 [(2-CH₃-C₆H₄)(AuPPh₃)₂][NTf₂] contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
vinyl complexes. Electron deficient digold-aryl complexes (e.g. $24\text{a}\cdot Y$) decomposed at a significantly faster rate than electron rich digold-aryl complexes (e.g. $20\text{a}\cdot Y$), but was significantly slower than the homo-coupling of their vinyl-counterparts. Therefore, homo-coupling decomposition affected the following quantitative studies only in a minor way.

Digold-aryl complexes could also be generated in situ by the addition of $4\text{a}\cdot NTf_2$ to a solution of a monogold-aryl complex. One equiv of $4\text{a}\cdot NTf_2$ was shown to fully convert $(4$-$\text{MeO-C}_6\text{H}_4)\text{AuPPh}_3$ ($19\text{a}$) to $[(4$-$\text{MeO-C}_6\text{H}_4)(\text{AuPPh}_3)_2]^+\text{[NTf}_2^-]$ ($20\text{a}\cdot NTf_2$) (Figure 5-4). This transformation caused the aromatic and OMe resonances of the 4-anisyl fragment to shift downfield in the $^1H$ NMR.

![Chemical Structures](image)

**Figure 5-4.** Mononuclear and dinuclear arylgold(I) model complexes used to mimic catalytic gold-vinyl intermediates.

Substoichiometric quantities of $\text{Ph}_3\text{PAuNTf}_2$ ($4\text{a}\cdot NTf_2$) provided $^1H$ NMR spectra where the 4-anisyl fragment was time averaged and located between the signals of pure $19\text{a}$ and $20\text{a}\cdot NTf_2$. Since Grandberg and Nesmeyanov previously observed $[\text{Ph}_3\text{PAu}]^+$ exchange with ferroceny1gold complexes, it was surmised that a similar exchange was occurring to average gold-aryl, gold-cation, and digold spectra.$^{166}$ Evidence for fast exchange was provided by $^1H$

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NMR characterization of solutions obtained from the titration of 4a•NTf₂ into 19a. Incremental additions caused a steady downfield shifting of the 4-anisyl resonances until one equivalent of 4a•NTf₂ had been added, at which point the chemical shift matched pure 20a•NTf₂ (Figure 5-5). More than one equivalent of 4a•NTf₂ had no further effect on the chemical shift, suggesting that the equilibrium in Figure 5-5 strongly favored digold and that no trigold species were formed.

Averaged signals and a linear dependence of chemical shift on added 4a•NTf₂ were also observed for PhAuPPh₃ (21a) and (p-CF₃-C₆H₄)AuPPh₃ (23a) (see experimental data in section 5.4). Since the averaged signals reflect the weighted average of the mono- and digold-aryl chemical shifts, it thus provided the means to determine the equilibrium position as a function of structure and reaction variables. This technique was used to measure how counterions and aryl electronic effects influenced the propensity for digold formation.

When 1 equiv of different Ph₃PAuY complexes (4a•Y) were added to a solution of (4-MeO-C₆H₄)AuPPh₃ (19a), averaged 4-anisyl signals were observed by ¹H-NMR. The average percentage of 19a bound as digold was calculated from the measured chemical shifts of the two inequivalent aromatic hydrogens and the methoxy group and the correlations in Figure 5-5 with the explicit assumption that the time averaged 4-anisyl shifts in the digold were not sensitive to Y⁻.

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167 Similar studies with isolated gold-vinyl 3a did not reveal averaged ¹H NMR signals.

Figure 5-5. Addition of aliquots of 4a•NTf₂ to a solution of 19a caused a linear downfield shifting of the time averaged ¹H signals of 19a and 20a•NTf₂.
Table 5-1. Digold equilibrium percentages determined by the averaged proton signal method as a function of counterion and aryl ligand. *Determined by averaged $^1$H NMR signals of 0.1 mL of monogold (0.01 M), 0.1 mL of 4a•Y (0.01 M), 0.3 mL of CD$_2$Cl$_2$.

$\text{X–H–AuPPh}_3 + \text{Ph}_3\text{PAuNTf}_2(4a\cdot\text{Y}) \xrightleftharpoons[CD_2Cl_2, 296 \text{ K}]{\text{X–H–AuPPh}_3}[\text{Y}]^+$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>X = OCH$_3$</th>
<th>X = H</th>
<th>X = CF$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>2</td>
<td>OBz</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>OPNB</td>
<td>12 ± 2</td>
<td>6 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>4</td>
<td>OONB</td>
<td>1 ± 1</td>
<td>0 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>41 ± 1</td>
<td>8 ± 2</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>6</td>
<td>OTs</td>
<td>88 ± 1</td>
<td>73 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>7</td>
<td>NTf$_2$</td>
<td>100 ± 1</td>
<td>100 ± 1</td>
<td>93 ± 3</td>
</tr>
</tbody>
</table>

In the case of Y = OAc and OBz, added quantities of 4a•Y to 19a caused no shifting in the anisyl peaks, suggesting that no digold was formed under these conditions (Table 5-1). With less binding counterions shifting was observed, allowing equilibrium concentrations of digold to be calculated. In these cases, OONB (ortho-nitrobenzoate) provided 1 ± 1 % digold, 12 ± 2 % with OPNB (para-nitrobenzoate), and 41 ± 1 % and 88 ± 1 % digold for TFA (trifluoroacetate) and OTs (tosylate), respectively. Complete conversion to the digold form was calculated for the least coordinating NTf$_2$ (bistriflimide). This trend was reasonably rationalized by the pK$_a$ of the conjugate acids (with the exception of OONB), and suggested that it was strong ion pairing in Ph$_3$PAuY that inhibited digold formation for the more binding anions. As shown in the final two columns of Table 5-1, the affinity of Ph$_3$PAuY to
21a and 23a was considerably lower for the less electron rich aryl ligands, with significant quantities of digold only being observed for the least coordinating anions. This trend supports the notion that the (Au₂C)-three-center-two-electron interaction is electron deficient, and competes with the counterion.

To determine how the ratio of mono and digold was affected by concentration, aliquots of CD₂Cl₂ were added to a 1:1 mixture of 19a and Ph₃PAuOTs (Figure 5-6). As the component concentration was decreased 4.6 fold the percentage of 19a bound as digold only decreased from 89.2 % to 87.5 %, which was more muted than expected for a 2 to 1 stoichiometry, and likely reflects the diminished ion pairing in the more charge dispersed digold aryl complex compensating for the stoichiometry. In the context of catalysis, this observation suggests that digold formation is not heavily penalized at low catalyst loadings.

![Graph](image)

**Figure 5-6.** Dilution of a 1:1 solution of 19a and 4a•OTs with aliquots of CD₂Cl₂. Conditions: 0.2 mL of 19a (0.01 M), 0.2 mL of 4a•OTs (0.01 M), 0.1 mL of CD₂Cl₂. 0.2 mL aliquots of CD₂Cl₂ were added and ¹H NMR data were collected.
With this increased understanding of digold formation, it was attempted to study its competing, but essential product yielding step, protodemettallation. To understand this process independent of digold formation the reaction of 19a with 4 equivalents of AcOH was monitored by $^1$H NMR. Based on data in Table 5-1 it was expected that these conditions would avoid the presence of digold, which should inhibit protodemettallation. Acetic acid was chosen because it enabled pseudo-first order reaction conditions to be established. As expected, a smooth conversion of 19a to 25 and Ph$_3$PAuOAc (4a•OAc) was observed. Unexpected, however, was a steady downfield movement of the 4-anisyl resonances of 19a as the protodemettallation progressed (Figure 5-7 (●)).

![Diagram of reaction](image)

**Figure 5-7.** Growth in calculated percentage of 19a bound as digold 20a•OAc over the course of the protodemettallation of 19a with 4 equiv of AcOH (●). The round data points (●) correspond to the experiment with an additional equivalent of Ph$_3$PAuOAc (4a•OAc).
An even larger shift to digold was detected in the reaction of 19a and 10 equiv of AcOH (see experimental data in section 5.4). Although this observation suggested that digold was being formed during the protodemetalation with AcOH, no digold was detected on mixing 19a and Ph₃PAuOAc in the absence of AcOH (entry 1, Table 5-1). To probe whether the Δδ was due to a build up of Ph₃PAuOAc, the reaction was repeated in the presence of 1 equiv of Ph₃PAuOAc. As shown in Figure 5-7 (●), a near doubling in equilibrium digold was observed.

This behavior indicated that under these reaction conditions, the acetate anion was effectively less coordinating. The data suggested that an acid/base interaction between AcOH and R₃PAuOAc created a homoconjugate acid/base pair which caused the acetate to become less coordinating (Scheme 5-5). ¹⁶⁹

\[ \text{Ph}_3\text{PAuO}^- + \text{H}_2\text{OAc}^- \rightleftharpoons \text{Ph}_3\text{PAu(OAc)}^- \]

**Scheme 5-5.** Proposed homoconjugate acid/base pair inducing lower coordination ability of acetate.

Since the amount of digold was highly sensitive to the donor properties of the counterion (Table 5-1), such an interaction could reduce the degree of contact ion pairing. ¹⁷⁰ Titration of AcOH into Ph₃PAuOAc, however, lead to only a tiny shift in the phosphine resonance in the \(^{31}\)P NMR spectrum, suggesting that the thermodynamic effect was small, though the kinetic effect could be larger. Similar experiments with alternative counterions confirmed the

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generality of the observation as all cases (Y = OBz, OPNB, OONB, TFA, and OTs) led to significant downfield shifts consistent with an increase in digold formation.\textsuperscript{171}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Entry} & \textbf{Y} & \textbf{$k_{rel}^{e}$} \\
\hline
1 & None\textsuperscript{a} & 1.0 \\
2 & OAc\textsuperscript{b} & 0.9 \\
3 & OBz\textsuperscript{b} & 1.6 \\
4 & OPNB\textsuperscript{b} & $\geq 2.5$ \\
5 & OONB\textsuperscript{b} & $\geq 3.4$ \\
6 & TFA\textsuperscript{b} & $\geq 3.0$ \\
7 & OTs\textsuperscript{b} & 0.4 \\
8 & NTf\textsubscript{2}\textsuperscript{b} & 0.0\textsuperscript{d} \\
\hline
\end{tabular}
\caption{Rate of protodemetallation of 19a with AcOH in the presence of different Ph\textsubscript{3}PAuY (4a•Y) complexes: \textsuperscript{a}0.1 mL of 19a (0.01 M), 0.1 mL of CD\textsubscript{2}Cl\textsubscript{2}, 0.1 mL of internal standard mesitylene (0.025 M), 0.2 mL of AcOH (0.02 M). \textsuperscript{b}0.1 mL of 19a (0.01 M), 0.1 mL of 4a•Y (0.01 M), 0.1 mL of internal standard mesitylene (0.025 M), 0.2 mL of AcOH (0.02 M). \textsuperscript{c}For determination of $k_{rel}$ see the experimental section. \textsuperscript{d}In this reaction, all of 19a was bound as digold and no conversion to 25 was observed for 1 h.}
\end{table}

When the kinetics of protodemetallation for these latter experiments was determined, it became clear that the gold salts also affected the rate of this key catalytic step. As shown in Table 5-2, the effect of added Ph\textsubscript{3}PAuY on the kinetics for protodemetallation of 19a by

\textsuperscript{171} The formation of these acid/base pairs was supported by the addition of BF\textsubscript{2}•Et\textsubscript{2}O to Ph\textsubscript{3}PAuOAc, which was sufficiently activated to become catalytically active, see chapter 9.
AcOH depended non-linearly with the coordinating character of the anion. At the extreme of non-coordination, \( Y = \text{NTf}_2 \), a very slow rate was expected, as the digold does not react with AcOH. The increase in rate at intermediate donating ability, however, was unexpected and will require further study.

These studies have thus established, using \( \text{Ph}_3\text{PAuAr} \) complexes as models for catalytic gold vinyl intermediates, a number of important reactivity principles of relevance to catalytic activity and speciation. 1) electron rich aryl (and thus vinyl) ligands have a heightened propensity to form less reactive digold structures, 2) digold formation is more favorable for the less coordinating counterions (which is also influenced by Brønsted acids), and 3) exogenous gold salts can affect the rate of fundamental processes like protodemettallation even though they don’t appear in the balanced equation. Each of these scenarios are commonly encountered in gold(I) catalysis. For example, 1) explains why the isolable electron deficient Hammond-vinyl rests (and is isolated) in a monomeric form\(^{172}\) while the gold vinyl generated by the hydroarylation of allenes rests (and is isolated) in the digold form. These results additionally illuminate on the challenges of developing highly efficient multi-step catalysts. To maximize substrate activation, one typically aims for the least coordinating anions, and while this almost certainly maximizes the initiation step of a catalytic cycle, 2) demonstrates that these more activated \([\text{LAu}]^+\) ions are also more apt to intercept gold vinyl intermediates and generate more stable, less reactive, digold intermediates (e.g. for protodemettallation). The results reported herein, help provide a rationale for the inevitable search for catalysts that balance the competing demands of efficiently circumnavigating a catalytic cycle.

\(^{172}\) Blum has demonstrated that the Hammond-vinyl was not kinetically basic in comparison to \( \text{Ph}_3\text{PAuPh} \), see: (a) K. E. Roth, S. A. Blum, *Organometallics* **2010**, 29, 1712; (b) L.-P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, 130, 17642.
5.4 Experimental Data

Experimental data of section 5.3 are published and are available on the WWW under http://dx.doi.org/10.1002/anie.201107659. Data for section 5.2 are listed below.

Synthesis of **15a** and **16a** (Figure 5-1): In a 100 mL Schlenck flask ~500 mg of Ph3PAuCl were dissolved in 20 mL THF, cooled to 0°C, and 1.1-1.3 equiv Grignard reagent were added. The reaction mixture was stirred for 30 minutes at 0°C. The cooling bath was removed and the reaction was stirred for another 1.5 h at room temperature. The reaction was quenched with H2O and extracted three times with diethyl ether. The combined organic phases were dried over MgSO4 or K2CO3 and the volatiles removed in vacuo. The residue was dissolved in the minimum amount of benzene and layered with an excess of pentanes. Single crystals were obtained (Wb2-007 and Wb2-059).

Homo-coupling of **15a** (Scheme 5-2): In a NMR tube a 1:1 mixture of **15a** and **4a•NTf2** were dissolved in 0.5 mL CD2Cl2. Decomposition to 1,3-butadiene was observed by 1H NMR and the decomposition to (Ph3P)2AuNTf2 indicated by 31P NMR (Wb2-039).

Homo-coupling of **16a** (Scheme 5-3): In a NMR tube 7.5 mg of **16a** were dissolved in 0.5 mL CD2Cl2 and 12.2 mg of **4a•NTf2** were added. Decomposition to 2,3-dimethyl-1,3-butadiene was observed by 1H NMR and the decomposition to (Ph3P)2AuNTf2 indicated by 31P NMR (Wb2-067-1).
Chapter 6. Mechanistic Role of Digold Intermediates in Gold Catalysis

Three mechanistic models that include a digold intermediate are proposed. NMR experiments that point to an off cycle role of digold are reported. Kinetic data and Hammett experiments are discussed. The alteration of kinetic results by digold formation is described.

6.1 Introduction

The observation of digold intermediates in the two intramolecular hydrofunctionalization reactions of allenes (hydroarylation and hydroalkoxylation) required to revisit previous mechanistic proposals, since digold intermediates had to be included. This section will discuss several mechanistic models that incorporate digold in the catalytic cycle. Since mechanistic work in this dissertation focused on gold-vinyl intermediates, mechanistic proposals were simplified by combining allene activation and nucleophilic attack in one reaction step (even though these processes most likely consist of several elemental reactions). In addition, reactivity studies suggested reversible allene activation / nucleophilic attack for the hydroalkoxylation of allenes and even though this behavior was not supported for the hydroarylation of allenes, it was included in the general discussion of mechanistic models.
6.2 Mechanistic Models

It was proposed that digold intermediates in gold-catalyzed hydrofunctionalization reactions of allenes could operate either on or off cycle. Plausible mechanisms for both cases were developed that were also consistent with the observed reactivity of isolated intermediates.

Scheme 6-1. Proposed off cycle mechanism for an intramolecular hydrofunctionalization of allenes.

Shown in Scheme 6-1 is the proposed off cycle mechanism. After the monogold-vinyl intermediate forms, it engages in three reaction pathways: reversible cycloreversion \( \frac{k_1}{k_{-1}} \), reversible digold formation \( \frac{k_2}{k_{-2}} \), or irreversible protodemetalation \( k_3 \) to turn the catalytic cycle over.
In an on cycle scenario, the monogold-vinyl intermediate engages only in two reaction pathways: reversible allene activation / nucleophilic attack ($k_1/k_{-1}$) or reversible digold formation ($k_2/k_{-2}$). The irreversible protodemetallation of digold ($k_4$) turns over catalysis (Scheme 6-2).

**Scheme 6-2.** Proposed on cycle mechanism for an intramolecular hydrofunctionalization of allenes.

Under certain circumstances an on / off cycle could also be envisioned involving the protodemetallation of both monogold- and digold-vinyl intermediates (Scheme 6-3). This scenario would become feasible when the rates of protodemetallation of monogold and digold become approximately the same under catalytic conditions.
6.3 Kinetic Isotope Effect Studies and Isotope Labeling Experiments

Through kinetic isotope effect (KIE) studies and isotope labeling experiments of gold intermediates in catalysis, the off cycle role of digold was determined for the intramolecular hydroalkoxylation of allenes.

Protodemetallation studies of isolated monogold-vinyl 13o with AcOH and its isotopomer AcOD were pursued at room temperature. As expected, a KIE of 3.2 was measured, demonstrating the direct involvement of H⁺ in the rate determining step (Scheme 6-4, top). In contrast, the protodemetallation of digold-vinyl 14o•OTs with TsOH or TsOD at 5°C, revealed a KIE of 0.9, which indicated that digold dissociation was the rate-limiting step in this reaction.
Scheme 6-4. Stoichiometric kinetic isotope study with 13\text{\text{o}}/AcOX and 14\text{o}\cdot\text{OTs/TsOX under pseudo-first order conditions; } L = \text{P('Bu)₂(o-biphenyl)}, X = \text{H or D}.^{173}

When the catalytic reactions of 10 and 10-D were monitored by $^1\text{H}$ NMR at $-20^\circ\text{C}$ with a catalyst loading of 5 mol\% 4\text{o}\cdot\text{OTs}, a large kinetic isotope effect (KIE = 5.3) suggested that the protodemetallation of in situ formed monogold had to be turnover limiting despite the observation of a digold resting state (Scheme 6-5).

Scheme 6-5. Kinetic isotope effect in catalysis.$^{173}$

These protodemetallation studies pointed towards an off cycle role of digold 14\text{o}\cdot\text{OTs during catalysis as shown in Scheme 6-1.}$^{173}$

$^{173}$ These studies were carried out by collaborators T. J. Brown and R. A. Widenhoefer at Duke University.
Scheme 6-6. Expected detectable species for the catalytic conversion of 10-CD2 at –45ºC after in situ generation of catalytically active mixture of 14o•OTs and HOTs at –78ºC by reaction of 10 and 2 equiv of 4o•OTs (top box).

To support the notion that the digold operated off cycle, an isotope labeling experiment was conducted. At –78ºC the stoichiometric reaction of hydroxy-allene 10 with 2 equiv of (JohnPhos)AuOTs (4o•OTs) yielded digold 14o•OTs and HOTs in CD2Cl2. No catalytic turnover (protodemetalation) was observed at low temperatures by 1H NMR.174 To the in

174 If the mixture of reagents was strictly kept at low temperatures, the substrate 10 and digold 14o•OTs could be observed simultaneously despite vigorous shaking of the NMR tube. Monogold intermediate 13o was not detected. Full conversion of 10 was achieved by further shaking the NMR tube at ambient temperature while periodically dipping it into a dry ice / 1PrOH bath to maintain a low temperature. In most experiments, partial
situ generated 14o•OTs / HOTs mixture (Scheme 6-4, top box), 20 equiv of deuterium labeled allene 10-CD2 were added. Upon warming the reaction mixture to –45°C catalytic turnover of 10 and 10-CD2 to 11 and 11-CD2, respectively, could be followed by NMR. (Scheme 6-6).

*Figure 6-1.* Measured concentration of components during catalysis from 2.3% conversion (t = 0 min) to 7.3% conversion (t = 195 min) at –45°C: [11 + 11-CD2] (●), [11] (▲), [14o•OTs + 14o-CD2•OTs] (●), [14o•OTs] (■).

Mesitylene was used as an internal standard, which allowed the determination of the concentrations of [11 + 11-CD2] (Figure 6-1, ●), [11] (Figure 6-1, ▲), [14o•OTs + 14o-CD2•OTs] (Figure 6-1, ●), and [14o•OTs] (Figure 6-1, ■) by 1H NMR as the catalytic protodemetallation of digold 14o•OTs to product 11 occurred if the temperature of the NMR tube rose too high, however, this was not always observed.
reaction progressed. Figure 6-1 shows the reaction progression from 2.3 % conversion (t = 0 min) to 7.3 % (t = 195 min).

Several observations were made through this experiment: 1) the concentration of both products combined [11 + 11-CD2] increased at a significantly faster rate than [11] only. This observation was consistent with D2-allene 10-CD2 forming D2-monogold that bypassed digold formation and instead directly protodemetalled to D2-product. 2) the combined concentration of digold intermediates [14o•OTs + 14o-CD2•OTs] decreased only slightly as the reaction progressed, which illustrated that a significant amount of catalyst was bound in a catalytically non-productive digold reservoir.175 3) the concentration of [14o•OTs] decreased at a faster rate than the concentration of [11] increased, which was consistent with cycloreversion of monogold-vinyl and Brønsted acid under catalytic conditions. 4) towards the end of the reaction (all substrate consumed), no D2- or H2-allene was detected by NMR and all H2-digold had been replaced by D2-digold. Then, a drop in rate was noted qualitatively. In, fact the reaction could be warmed to 0°C or the sample removed from the cooling environment for seconds without complete consumption of digold.

Quantitative data could also be extracted from this experiment; however, these numbers should not be over interpreted since baseline signals of catalytic intermediates and products were integrated and compared: 1) it could be noted that at 7.3% conversion, not all of H2-digold 14o•OTs was replaced by D2-digold 14o-CD2•OTs. This behavior was consistent with an off cycle model. However, the on cycle role of digold could not be eliminated, if digold equilibrated with monogold 13o at a much fast rate than protodemetallation occurred. But because of the previously explained kinetic isotope effect studies, which clearly showed

175 A decrease in digold was also indicated while monitoring the hydroarylation of allene 1 by 31P NMR. See Figure 6-4.
that digold had to operate off cycle, the second interpretation could be disregarded. 2) the relative amount of D2-allene that bypassed digold formation during catalysis could be determined by dividing the concentration of D2-product \( \text{11-CD2} \) (calculated from \([\text{11} + \text{11-CD2}] - [\text{11}]\)) by the concentration of D2-digold \( \text{14o-CD2•OTs} \) (calculated from \([\text{14o•OTs} + \text{14o-CD2•OTs}] - [\text{14o•OTs}]\)). The calculated value indicated that 72% of D2-allene formed monogold that bypassed digold formation and protodemetallated directly. This meant that during the time window of the NMR experiment the rate of protodemetallation of monogold \( \text{13o} \) \( (\theta_3) \) was favored over the rate of digold formation \( (\theta_2) \): \( \theta_3/\theta_2 = 2.6/1 \neq k_3/k_2 \). 3) the relative relationship between cycloreversion and protodemetallation could also be calculated by dividing the concentration of H2-allene \( \text{10} \) (calculated from \([\text{14o•OTs}] - [\text{11}]\)) by the concentration of H2-product \( \text{11} \) (directly measured). This calculated value indicated that 81% of H2-monogold \( \text{13o} \) cycloverted to H2-allene \( \text{10} \) instead of protodemetallating to \( \text{11} \) \( (\theta_{-1}/\theta_3 = k_{-1}/k_3 = 4.2/1) \) under the explicit assumption that each cycloverted H2-allene \( \text{10} \) exchanged with D2-allene \( \text{10-CD2} \).\(^{176}\) These data clearly supported an off cycle role of digold.

### 6.4 Theoretical Discussion

Using the off cycle model for the intramolecular hydroalkoxylation of allene \( \text{10} \) (Scheme 6-7), the following rates can be calculated: protodemetallation \( (\theta_3) \), digold formation \( (\theta_2) \), and cycloreversion \( (\theta_{-1}) \):

\(^{176}\) This assumption is reasonable since an excess of D2-allene \( \text{10-CD2} \) was present in the reaction mixture generating pseudo-order kinetic conditions.
Evaluating the meaning of equations (1) – (3), it becomes clear why the measured ratio of reaction rates $\vartheta_1 / \vartheta_3$ in the previously discussed isotope labeling experiment equals $k_{-1}/k_3$ and why the ratio of $\vartheta_3 / \vartheta_2$ is not the same as $k_3/k_2$. The term $k_1[10]$ in equation (3) is close to zero due to the excess amount of 10-CD2 (pseudo-order kinetics). But the term $k_{-2}[14o]$ in
equation (2) is not affected in this manner as the concentration of \([^{14}O\bullet OTs]\) is not outcompeted by a higher concentration of its isotopomer. This can alternatively be understood by the fact that \(\vartheta_1\) and \(\vartheta_3\) are both on-cycle processes that consume monogold \(13O\) and therefore allow insight into rate constants. In the case of reaction rates \(\vartheta_3\) and \(\vartheta_2\) an irreversible on cycle and reversible off cycle reaction is compared and therefore does not allow conclusion about rate constants. It is important to note, that these statements are only true when all the catalyst has engaged in catalysis and turnover to product is observed.

Therefore, a reaction that forms off cycle digold can be segmented into three different stages: 1) initial burst phase to form digold. In this phase monogold \(13O\) prefers digold formation over protodemettalation due to a high concentration of unbound \([LAu]^+\) (\(\vartheta_3 < \vartheta_2\)). 2) monogold bypassing phase: Once most of \([LAu]^+\) is bound as digold in a catalytically inactive form, protodemettalation becomes more feasible, efficient catalysis proceeds (\(\vartheta_3 > \vartheta_2\)), and substrate forms monogold that protodemettalates directly and bypasses digold formation. This segment describes the longest phase of the catalytic reaction. 3) digold dissociation phase: Towards the end of the reaction, when all allene substrate is consumed, a drop in rate is observed, because now all monogold that protodemettalates to product has to stem from digold dissociation. Therefore, the rate of digold dissociation \(\vartheta_2\) becomes in this phase turnover limiting as no substrate remained to form monogold as well.

This simplistic picture of the reaction assumes that the relationship between reaction rates of protodemettalation \(\vartheta_3\) and digold formation \(\vartheta_2\) changes in the burst phase (phase 1) as a function of a decreasing concentration of \([LAu]^+\) (due to digold formation) to transition into the monogold bypassing stage (phase 2). Assuming a steady state concentration of
monogold-vinyl 13o, the dependence of \( \vartheta_3 \) and \( \vartheta_2 \) on the concentration of \([\text{LAu}]^+\) can be calculated:

\[
\frac{d[13o]}{dt} = k_1[\text{LAu}^+][10] + k_{-2}[14o] - k_{-1}[H^+][13o] - k_2[\text{LAu}^+][13o] - k_3[H^+][13o]
\]

and because \( \frac{d[13o]}{dt} = 0 \) (steady state approximation)

\[
[13o] = \frac{k_1[\text{LAu}^+][10] + k_{-2}[14o]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} (4)
\]

(4) in (1): \( \vartheta_3 = k_3[H^+] \left\{ \frac{k_1[\text{LAu}^+][10] + k_{-2}[14o]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} \right\} = \frac{k_2k_3[H^+]^2[14o][\text{LAu}^+] + k_{-2}k_3[H^+]^2[14o]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} (5)

(4) in (2): \( \vartheta_2 = k_2[\text{LAu}^+] \left\{ \frac{k_1[\text{LAu}^+][10] + k_{-2}[14o]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} \right\} - k_{-2}[14o]
\]

\[
= \frac{k_1k_2[10][\text{LAu}^+]^2 + k_2k_{-2}[14o][\text{LAu}^+]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} - k_{-2}[14o]
\]

\[
= \frac{k_1k_2[10][\text{LAu}^+]^2 - k_{-1}k_{-2}[H^+][14o] - k_{-2}k_3[H^+][14o]}{k_{-1}[H^+] + k_2[\text{LAu}^+] + k_3[H^+]} (6)
\]

Formulas of the reaction rates \( \vartheta_3 \) and \( \vartheta_2 \) (including the steady state approximation for monogold) illustrate their dependencies on the concentration of \([\text{LAu}]^+\). While the denominator of both equations (5) and (6) are the same, there are significant differences in the numerator. The numerator of the formula for the rate of protodemettallation \( \vartheta_3 \) is a linear function, whereas the numerator of the formula describing digold formation \( \vartheta_2 \) is a square function. Because the square function dominates at large concentrations of \([\text{LAu}]^+\) and the linear function gives higher values at low concentrations of \([\text{LAu}]^+\) there must be an intersection point of the two functions where the rate of protodemettallation equals digold formation (\( \vartheta_3 = \vartheta_2 \)). This intersection point can be calculated as follows:
(6) = (5): \( \vartheta_2 - \vartheta_3 = 0 \)

\[
k_1k_2[10][\text{LAu}^+]^2 - k_1k_3[H^+][10][\text{LAu}^+] - k_{-1}k_{-2}[H^+][14o] - 2k_{-2}k_3[H^+][14o] = 0 \quad (7)
\]

**Figure 6-2.** Dependence of formulas for reaction rates of protodemetalation (\( \vartheta_3 \)) and digold formation (\( \vartheta_2 \)) on a decreasing number of active catalyst [LAu\(^+\)] molecules as a result of digold formation. The decreasing number of substrate molecules (1 per 2 [LAu\(^+\)]), the increasing number of digold molecules (1 per 2 [LAu\(^+\)]), and the increasing number of H\(^+\) ions were considered. In addition, it was arbitrarily assumed that only 96% of substrate formed digold, the remaining 4% represented the steady state concentration of monogold. This model does not account for substrate to convert to product.

The graphs in Figure 6-2 show the mathematical functions that describe the rate of protodemetalation \( \vartheta_3 \) (5) and digold formation \( \vartheta_2 \) (6) plotted against a decreasing number of [LAu\(^+\)] molecules (concentration). This model represents how the reaction rates \( \vartheta_3 \) and \( \vartheta_2 \) are altered immediately after addition of catalyst (= no catalyst bound as digold). In phase 1, the burst phase, the rate of digold formation outcompetes the rate of protodemetalation.
However, the more [LAu]$^+$ is consumed and formed digold, the faster equalize the rates of protodemetallation and digold formation until the intersection point is reached ($\vartheta_3 = \vartheta_2$). Then, catalytic turnover becomes feasible from a rate perspective as monogold begins to favorably bypass digold formation and to protodemetallate to product. This simple model clearly demonstrates that it is possible to observe faster protodemetallation than digold formation in catalysis, even though in stoichiometric reactions this could not be supported.

The intersection point of functions $\vartheta_3$ and $\vartheta_2$ only describes the [LAu]$^+$ concentration at which the rate of protodemetallation of monogold-vinyl becomes faster than digold formation. But since it does not describe the concentration of [LAu]$^+$ that remains on cycle (catalytically active) it is not relevant for catalysis. Nevertheless, under the explicit assumption that a higher concentration of [LAu]$^+$ at which the intersection point is reached, correlates to a larger concentration of on cycle catalyst (which results in faster catalysis), this model does give a qualitative estimate to compare reactions rates at different conditions (different anion, catalyst, variation of catalyst loading, or changes in substrate concentration).

Different conditions are modeled in equation (7) by variables that describe the concentration of components (substrate [10], digold [140], protons [H$^+$]) or rate constants $k_1$, $k_{-1}$, $k_2$, $k_{-2}$, $k_3$. This distinction is important, since the variations in catalyst loading or substrate concentration does not affect transition state energies (equals maintaining the same rate constants in a series of experiments), but does influence the overall rate of the reaction by changing the concentration of on and off cycle intermediates and reagents. In contrast, changes in the basicity of the ligand (e.g. Hammett studies) alter the whole system by changing all rate constants and the concentration of all reaction components. The uncertainty

177 The catalytically active amount of [LAu]$^+$ (on cycle operating concentration) could perhaps be calculated by the intersection point of the differentiated functions (5) and (6) in respect to [LAu]$^+$. At this point both reaction rates are affected to the same degree by small changes in [LAu]$^+$ concentration.
about the concentration of catalyst that operates on cycle combined with the alteration of transition state energies of all on and off cycle processes have to be kept in mind while interpreting kinetic data and Hammett studies.

It should also be noted that these equations were developed based on a mechanistic model for the hydroalkoxylation of allenes including reversible allene activation / nucleophilic attack. In the hydroarylation reversible cyclization is most likely not present due to the stability of a newly formed C–C bond. Therefore, different rate formulas for protodemetallation (3′$_3$) and digold formation (3′$_2$) were developed excluding reversible cyclization. These formulas are simpler, but still reveal the same dependency on changes in [LAu]$^+$ concentration. Therefore an analogous intersection model to Figure 6-2 can be used for interpretation of kinetic data, since the catalytically active concentration of [LAu]$^+$ is different from the originally added amount of catalyst:

\[
3'_3 = \frac{k_1 k_3 [H^+] [\mathbf{1}] [LAu^+] + k_{-2} k_3 [H^+] [\mathbf{5a}]}{k_2 [LAu^+] + k_3 [H^+]} \tag{8}
\]

\[
3'_2 = \frac{k_1 k_2 [\mathbf{1}]^2 [LAu^+] - k_{-2} k_3 [H^+] [\mathbf{5a}]}{k_2 [LAu^+] + k_3 [H^+]} \tag{9}
\]

6.5 Kinetic Data

To obtain kinetic profiles, the hydroarylation of allene 1 was followed by $^1$H NMR with 5 mol% catalyst loading (4a•NTf$_2$). The reaction proceeded via the digold intermediate. The zero order ([1] vs. time) and first order plot (ln([1]/[1$_0$]) vs. time) are shown in Figure 6-3.
Figure 6-3. Zero order (top) and first order (bottom) plot of the hydroarylation of allenes. Reaction conditions: 200 µL of a stock solution of 1 (0.5 M); 100 µL of a stock solution of hexamethyl benzene (0.5 M), 150 µL of CD₂Cl₂; 50 µL of a stock solution of 4a•NTf₂ (0.1 M); room temperature.

Because no linear graphs were obtained, these data showed that the intramolecular hydroarylation of allene 1 displayed neither a zero order nor a first order dependence on substrate. However, evaluating the curvature of the first order plot, a surprising increase in the reaction rate was observed as the reaction progressed, despite the consumption of substrate. In fact, at low substrate concentrations, the fastest reaction rate could be measured.
A similar dynamic behavior was detected when monitoring the reaction by $^{31}$P NMR (Figure 6-4).\(^{178}\)

![Figure 6-4. Monitoring the reaction of 1 with 5 mol\% 4a•NTf$_2$ by $^{31}$P NMR. The digold signals at 36 ppm decreased as the reaction progressed and a second signal marked with X grew in.]

As the reaction progressed, the digold signals at 36 ppm decreased as another signal marked with X increased, which could correspond to catalytically active [LAu]$^+$ bound to various ligands in the reaction mixture. The implication that the concentration of digold

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178 These studies could only be pursued with a highly sensitive QNP cryoprobe on a Bruker 600 MHz NMR spectrometer.
correlated with the concentration of substrate might be important in solving this mechanistic puzzle of why the reaction rate increased as more substrate was consumed.

Figure 6-5. Order in substrate (top) and catalyst (bottom) using a least square fit for the hydroarylation of allene $\mathbf{1}$ in CD$_2$Cl$_2$. Reaction conditions (top): 50 µL, 100 µL, 150 µL, 200 µL, 250 µL, and 300 µL of a stock solution of $\mathbf{1}$ (0.25M); 100 µL of a stock solution of hexamethyl benzene (0.25M); 50 µL of a stock solution of $\mathbf{4a} \cdot \text{NTf}_2$ (0.05M); 300 µL, 250 µL, 200 µL, 150 µL, 100 µL, 50 µL, and 0 µL of CD$_2$Cl$_2$. Reaction conditions (bottom): 200 µL of a stock solution of $\mathbf{1}$ (0.25M); 100 µL of a stock solution of hexamethyl benzene (0.25M); 25 µL, 50 µL, 75 µL, and 100 µL of a stock solution of $\mathbf{4a} \cdot \text{NTf}_2$ (0.05M); 175 µL, 150 µL, 125 µL, and 100 µL of CD$_2$Cl$_2$. All data were collected at room temperature.

The profile of the first order plot allowed initial rate analysis. After an initial burst of substrate consumption, likely the result of rapid digold build up, first order plots were typically linear (up to 30% conversion of $\mathbf{1}$) and the relevant $k_{\text{obs}}$ values were obtained from
the slope of this first section. Figure 6-5 shows two graphs in which observed rate constant \( k_{\text{obs}} \) were plotted against variable substrate (top) or catalyst (bottom) concentrations. When the substrate concentration was varied, an inverse order was obtained, which supported the earlier observation of a faster rate at lower substrate concentrations. Because initial rates were plotted, any potential effect of product on the rate could be excluded.

Interestingly, when the catalyst concentration was varied, a first order dependence was obtained. Because \( k_{\text{obs}} \) values were determined after the initial burst phase (digold formation) these data implied a direct proportional relationship between the initial catalyst concentration and the amount of catalytically active catalyst \([\text{LAu}]^+\) that was not trapped in the digold reservoir.

Similar graphs were obtained, when the intramolecular hydroalkoxylation of allene 10 was studied with 4a•OTs as the catalyst, a reaction that also formed a digold intermediate during catalysis. When monitoring the consumption of 10 with 1 mol% 4a•OTs at 263 K by \(^1\text{H}\) NMR, neither a zero nor a first order dependence was observed (Figure 6-6). As the consumption of substrate progressed, the reaction rate increased. When the order of substrate and catalyst were determined by using the initial rates method (Figure 6-7), the reaction rate of the hydroalkoxylation of allene 10 with the catalyst 4a•OTs followed also an inverse dependence on substrate and a first order dependence on catalyst loading.

Based on the similarity of the kinetic profiles between the hydroarylation of 1 with 4a•OTs and the hydroalkoxylation 10 with 4a•OTs, it was assumed that obtained kinetic profiles and rate dependencies were characteristic for hydrofunctionalization reactions that proceed via a digold intermediate.
Figure 6-6. Zero order (top) and first order (bottom) plot of the hydroalkoxylation of allenes. Reaction conditions: 150 µL of a stock solution of 10 (0.10 M); 235 µL of a stock solution of hexamethyl benzene (0.05 M); 220 µL of CD₂Cl₂; 15 µL of a stock solution of 4a•OTs (0.01 M). All data were collected at 263K.

The reason for the steadily increasing rate of overall catalysis and the steadily decreasing concentration of digold intermediate as substrate was consumed could not be explained.
Figure 6-7. Order in substrate (top) and catalyst (bottom) using a least square fit for the hydroalkoxylation of allene 10. Reaction conditions (top): 50 µL, 100 µL, 150 µL, 200 µL, 250 µL, and 300 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 30 µL of a stock solution of 4a•OTs (0.01M); 320 µL, 270 µL, 220 µL, 170 µL, 120 µL, 70 µL, and 20 µL of CD2Cl2. Some data points were measured twice. Reaction conditions (bottom): 150 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 15 µL, 20 µL, 25 µL, and 30 µL of a stock solution of 4a•OTs (0.01M); 220 µL, 225 µL, 230 µL, and 235 µL of CD2Cl2. All data were collected at 263K.

As described in chapter 4 the intermediary formation of digold was inhibited in the hydroalkoxylation of allene 10 by using catalyst 4a•OONB (which has a better coordinating counterion than 4a•OTs; see Figure 4-6), or by the addition of excess DTBP to the reaction of 10 with 4a•OTs (see Figure 4-5). When kinetic studies (initial rates method) were pursued with catalyst 4a•OONB, variation of substrate concentration pointed towards a zero-order
dependence (Figure 6-8, top). These data were consistent with turnover limiting protodemetalation of monogold-vinyl.

**Figure 6-8.** Order in substrate (top) and catalyst (bottom) using a least square fit for the hydroalkoxylation of allene 10. Reaction conditions (top): 50 µL, 100 µL, 150 µL, 200 µL, and 250 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 150 µL of a stock solution of 4a•OONB (0.01M); 200 µL, 150 µL, 100 µL, 50 µL, and 0 µL of CD$_2$Cl$_2$. Reaction conditions (bottom): 150 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 25 µL, 50 µL, 100 µL, 150 µL, 200 µL, and 250 µL of a stock solution of 4a•OONB (0.01M); 225 µL, 200 µL, 150 µL, 100 µL, 50 µL, and 0 µL of CD$_2$Cl$_2$. Some data points were measured twice. All data were collected at 298K.
Figure 6-9. Order in substrate (top) and catalyst (bottom) using a least square fit for the hydroalkoxylation of allene 10. Reaction conditions (top): 50 µL, 75 µL, 100 µL, 125 µL, 150 µL, and 200 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 100 µL of a stock solution of 4a•OTs (0.01M); 100 µL of a stock solution of DTBP (0.2 M); 150 µL, 125 µL, 100 µL, 75 µL, 50 µL, and 0 µL of CD₂Cl₂. All data for this graph were collected at 298 K. Reaction conditions (bottom): 150 µL of a stock solution of 10 (0.10M); 100 µL of a stock solution of hexamethyl benzene (0.05M); 25 µL, 50 µL, 75 µL, 100 µL, 125 µL, and 150 µL of a stock solution of 4a•OTs (0.01M); 100 µL of a stock solution of DTBP (0.2 M); 125 µL, 100 µL, 75 µL, 50 µL, 25 µL, and 0 µL of CD₂Cl₂. All data for this graph were collected at 296 K.

However, when the catalyst concentration was varied, a broken order of 1.4 in catalyst concentration was obtained (Figure 6-8, bottom). The non-proportional rate acceleration with
an increasing catalyst concentration was difficult to rationalize. Perhaps the irregular protodemetallation rates of gold-aryl model complexes in the presence of different 4a•Y salts could lead to a plausible explanation (see Table 5-2). Similar graphs were obtained for the reaction of 10 with 4a•OTs in the presence of excess DTBP (Figure 6-9).

To correlate the effect of ligand electronic, steric, and chelation character on digold intermediates in catalysis, reaction rates for the hydroarylation of allene 1 were determined.\(^{179}\) The relevant \(k_{\text{obs}}\) values were obtained by measuring the consumption of [1] by in situ \(^1\)H NMR spectroscopy, and plotting ln([1]/[1]₀) versus time. After an initial burst of substrate consumption, likely the result of rapid digold build up, these plots were typically linear (up to 30% conversion of 1) and \(k_{\text{obs}}\) were obtained from the slope of this first section.

Table 6-1. Rate comparison with catalysts 4g•NTf₂ and 4m•NTf₂, for the conversion of 1.\(^a\) Reaction conditions: 200 \(\mu\)L of 0.1 M solution of 1; 100 \(\mu\)L of 0.05 M solution of hexamethyl benzene; 200 \(\mu\)L of 0.005 M solution of 4g•NTf₂. \(^b\) Reaction conditions: 200 \(\mu\)L of 0.1 M solution of 1; 100 \(\mu\)L of 0.05 M solution of hexamethyl benzene; 200 \(\mu\)L of 0.01 M solution of 4•NTf₂. \(^c\) Average of two kinetic experiment.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>(k_{\text{obs}}) ((s^{-1})^c)</th>
<th>(k_{\text{rel}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>5 mol% 4g•NTf₂</td>
<td>((1.33 \pm 0.03) \cdot 10^{-5})</td>
<td>0.2</td>
</tr>
<tr>
<td>2(^b)</td>
<td>10 mol% 4g•NTf₂</td>
<td>((3.30 \pm 0.23) \cdot 10^{-5})</td>
<td>0.4</td>
</tr>
<tr>
<td>3(^b)</td>
<td>10 mol% 4m•NTf₂</td>
<td>((7.75 \pm 0.23) \cdot 10^{-5})</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The effect of chelation on catalysis was measured by comparing the reaction rate of the bridging catalyst P6P(AuNTf$_2$)$_2$ (4g•NTf$_2$) and the mononuclear electronically similar catalyst EtPh$_2$PAuNTf$_2$ (4m•NTf$_2$), both of which revealed a digold intermediate (see Figure 3-11). As shown in Table 6-1 the catalytic reaction was significantly retarded (on a total gold loading basis) when the bridging catalyst 4g•NTf$_2$ was used. Using mononuclear catalyst 4m•NTf$_2$ as a baseline ($k_{rel} = 1.0$), catalytic turnover with bridging catalyst 4g•NTf$_2$ was significantly slower at the same total gold concentration (5 mol%, $k_{rel} = 0.2$) or even at the same catalyst concentration (10 mol%, $k_{rel} = 0.4$). A plausible explanation for these significant rate differences was favored digold formation over protodemetalation due to the bridging ligand found in catalyst 4g•NTf$_2$. Tethering of two [LAu]$^+$ units in 4g•NTf$_2$ forcefully increased the local concentration of [LAu]$^+$ around the putative monogold, providing a kinetic boost for digold formation (Scheme 6-8). This effect significantly increased the amount of inactive catalyst trapped in the digold reservoir.

Scheme 6-8. Hypothesis for the effect of bridging phosphines on catalytic processes.
The sensitivity of reaction rates to the steric properties of the ligand was measured by comparing the catalytic reactions of 1 with \((p-\text{CH}_3-\text{C}_6\text{H}_4)_3\text{PAuNTf}_2\) (4d•NTf₂), and \((o-\text{CH}_3-\text{C}_6\text{H}_4)_3\text{PAuNTf}_2\) (4n•NTf₂), which had similar electronic but vastly different steric properties (cone angle \(\Theta = 145^\circ\) and \(194^\circ\), respectively). Despite their difference in size only a slight difference in kinetic competence was noted (\(k_{\text{rel}} = 1.0\) for 4d•NTf₂, \(k_{\text{rel}} = 0.9\) for 4n•NTf₂), a result which clearly reflected the influence of the open coordination environment of the linear Au(I) geometry (Table 6-2). However, it should be noted that catalysts 4d•NTf₂ and 4n•NTf₂ might proceed via different digold intermediates that display a different binding mode, which could complicate the interpretation of reactions rates.

**Table 6-2.** Rate comparison with catalysts 4d•NTf₂ and 4n•NTf₂ for the conversion of 1. *Reaction rates were measured by ¹H NMR. Hexamethyl benzene was used as an internal standard. Reaction conditions: 150 \(\mu\text{L}\) of 0.1 M solution of 1; 100 \(\mu\text{L}\) of 0.05 M solution of hexamethyl benzene; 50 \(\mu\text{L}\) CD₂Cl₂; 200 \(\mu\text{L}\) of 0.01 M solution of 4•NTf₂. \(k_{\text{obs}}\) values are an average of two kinetic experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>(\Theta (^\circ))</th>
<th>(k_{\text{obs}} (\text{s}^{-1})^a)</th>
<th>(k_{\text{rel}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((o-\text{CH}_3-\text{C}_6\text{H}_4)_3\text{PAuNTf}_2) (4n•NTf₂)</td>
<td>194</td>
<td>((6.05 \pm 0.23) \cdot 10^{-5})</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>((p-\text{CH}_3-\text{C}_6\text{H}_4)_3\text{PAuNTf}_2) (4d•NTf₂)</td>
<td>145</td>
<td>((7.09 \pm 0.26) \cdot 10^{-5})</td>
<td>1.0</td>
</tr>
</tbody>
</table>

As summarized in Table 6-3 reaction rates were also affected by the electronic nature of the catalyst, with electron poor catalyst 4b•NTf₂ being fastest (\(k_{\text{rel}} = 2.1\)). The rate significantly dropped when the almost electron neutral catalyst 4c•NTf₂ was used (\(k_{\text{rel}} = 1.4\)) and dropped even further with electron rich catalyst 4d•NTf₂ (\(k_{\text{rel}} = 1.0\)). The interpretation
of these electronic effects was not trivial, because several reaction steps were either favored or disfavored with more electrophilic catalysts.

Table 6-3. Rate comparison with catalysts 4b•NTf₂, 4c•NTf₂, and 4d•NTf₂ for the conversion of 1.

> Reaction rates were measured by ¹H NMR. Hexamethyl benzene was used as an internal standard. Reaction conditions: 150 μL of 0.05 M solution of 1; 100 μL of 0.025 M solution of hexamethyl benzene; 200 μL CD₂Cl₂; 50 μL of 0.01 M solution of 4•NTf₂. The average of two kinetic experiments is listed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(p-X-C₆H₄)₃PAuNTf₂</th>
<th>k(obs) (s⁻¹)ᵃ</th>
<th>k_rel</th>
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6.6 Hammett Studies

A series of Hammett experiments were conducted with the hydroarylation and the hydroalkoxylation of allenes; the latter with the option to proceed via both, the digold or the monogold intermediate.

First the hydroarylation of allene 1 was investigated. Catalysts with Ph₃P-derivatives that contained different para-substituents X (4a-f•NTf₂) were used. Figure 6-10 shows the Hammett plot of ln(kₓ/kᵢH) against σᵞ using initial rate constants. A positive ρ = +2.24 was observed for this reaction that proceeded via a digold resting state.
Figure 6-10. Hammett plot of initial rate constants with catalysts 4a-f•NTf₂. Reaction conditions: 200 μL of 0.25 M solution of 1; 100 μL of 0.25 M solution of hexamethyl benzene; 150 μL CD₂Cl₂; 50 μL of 0.05 M solution of 4•NTf₂.

Figure 6-11. Hammett plot of initial rate constants with catalysts 4a•OTs, 4b•OTs, 4d•OTs, 4e•OTs. Reaction conditions: 150 μL of 0.10 M solution of 10; 100 μL of 0.05 M solution of hexamethyl benzene; 220 μL CD₂Cl₂; 30 μL of 0.01 M solution of 4•OTs. All data were collected at 263K.
A similar graph was obtained when the intramolecular hydroalkoxylation of 10 with 4•OTs catalysts was investigated (Figure 6-11). This reaction also proceeded via a digold intermediate. The Hammett plot of \( \ln(k_X/k_H) \) against \( \sigma_p \) gave a slightly lower positive \( \rho = +2.05 \) than the hydroarylation.

A monogold catalyst resting state was observed for the hydroalkoxylation of 10 with 4•OONB catalysts. Interestingly, the Hammett plot of \( \ln(k_X/k_H) \) against \( \sigma_p \) gave now a negative \( \rho = -2.13 \) (Figure 6-12), meaning that faster reaction rates were obtained with more basic ligands or in other words less electrophilic catalysts.

![Figure 6-12. Hammett plot of initial rate constants with catalysts 4a•OONB, 4b•OONB, 4c•OONB, 4d•OONB, 4e•OONB. Reaction conditions: 150 \( \mu \)L of 0.10 M solution of 10; 100 \( \mu \)L of 0.05 M solution of hexamethyl benzene; 100 \( \mu \)L of CD\(_2\)Cl\(_2\); 150 \( \mu \)L of 0.01 M solution of 4•OONB. All data were collected at 298K.](image-url)
Similar Hammett data was obtained when the reactions of 10 with 4•OTs catalysts in the presence of excess DTBP was investigated, since these conditions also provided the monogold resting state. These conditions exhibited a negative $\rho = -2.80$ (Figure 6-13).

Figure 6-13. Hammett plot of initial rate constants with catalysts 4a-f•OTs in the presence of excess DTBP. Reaction conditions: 150 $\mu$L of 0.10 M solution of 10; 100 $\mu$L of 0.05 M solution of hexamethyl benzene; 100 $\mu$L of a 0.20 M solution of DTBP in CD$_2$Cl$_2$; 150 $\mu$L of 0.01 M solution of 4•OTs. All data were collected at 298K.

The positive $\rho$ with a digold and the negative $\rho$ with a monogold resting state were not trivial to explain. Initially, it was thought that these data indicated a change of the turnover limiting step in catalysis depending on the observed catalyst resting state. Typically, a linear Hammett plot indicates that the transition state of the reactions does not change upon variation of the electronic character of the catalyst. In addition, the algebraic sign of $\rho$ indicates, how transition state energies are affected by the electronic variation of a reagent.
(positive $\rho =$ higher transition state energy with small $\sigma$ values; negative $\rho =$ lower transition state energy with small $\sigma$ values).

However, the digold intermediate isotope labeling experiment combined with the stoichiometric and catalytic kinetic isotope effect studies clearly demonstrated that protodemettallation was turnover limiting for on cycle catalysis, even when a digold reservoir was observed. Resting state analysis of reactions that proceeded via a monogold intermediate pointed also towards turnover limiting protodemettallation. Therefore, the experiments reported in this dissertation demonstrated that for the hydroalkoxylation of allenes, protodemettallation of monogold was turnover limiting for product yielding catalysis, regardless of the observed intermediate (monogold or digold). Because of the similarity of kinetic profiles and rate dependencies on substrate, a purely off cycle role of digold and the resulting turnover limiting protodemettallation was also assumed for the hydroarylation, however further experimentation is necessary to exclude turnover limiting allene activation / nucleophilic attack. Because the product yielding transition state was the same for reactions that proceeded via digold or monogold resting states, an alternative explanation had to be found to interpret the changing $\rho$ values with a digold resting state.

Scheme 6-9 shows a mechanistic model for the monogold cases. If allene activation / nucleophilic attack revealed a lower transition state energy than the protodemettallation of the monogold intermediate, a negative $\rho$ would be expected for this reaction. If allene activation / nucleophilic attack were turnover limiting, then a positive $\rho$ should be obtained. This can be rationalized by the energy diagrams shown in Figure 6-14, which illustrate how transition state energies of these processes are affected by the electronic alterations of the catalyst.
Scheme 6-9. Mechanistic model for a hydrofunctionalization reaction that proceeded only via a monogold resting state.

Figure 6-14. Energy diagrams of allene activation / nucleophilic attack (left) and protodemetallation of monogold (right) with qualitatively estimated transition state energy spreads depending on the electronic nature of the catalyst.

Because without digold formation all of the originally added [LAu]⁺ remained active throughout catalysis, the traditional interpretation of Hammett studies was used for reactions that proceeded via a monogold resting state.
Obviously, when a digold resting state was observed, the explanation of ρ values was not trivial. Using the off cycle mechanistic model in Scheme 6-10, a different energy diagram (Figure 6-15) was developed to understand whether a positive or negative ρ value would be expected for digold formation.

Scheme 6-10. Mechanistic model for hydrofunctionalization reactions that proceeded via a digold intermediate.

The transition energy spread diagram in Figure 6-15 shows that digold formation is favored with basic and disfavored with acidic ligands bound to cationic gold, therefore a negative ρ would be expected for digold formation and a positive ρ for its back reaction (digold dissociation). However, while it is important to understand the electronic effects of the catalyst on digold formation, it could not sufficiently explain the positive ρ values of the
catalytic Hammett experiments, since digold formation and digold dissociation were off cycle processes.

Figure 6-15. Energy diagram of competing digold formation and protodemetalation of monogold with qualitatively estimated transition state energy spreads depending on the electronic nature of the catalyst.

The only plausible explanation for positive $\rho$ values with off cycle digold was that the rate constant of protodemetalation $k_3$ was less affected by electronic alterations of the catalyst than the rate constant $k_2$ of digold formation. For example, when the most electrophilic and least electrophilic catalysts $4c\cdot Y$ ($p$-$X = CF_3$) and $4f\cdot Y$ ($p$-$X = OCH_3$), respectively, were used, the rate of digold formation $\vartheta_2$ or $\vartheta_2'$ for both catalysts was still larger than the rate of protodemetalation $\vartheta_3$ or $\vartheta_3'$. However, in comparison to $4f\cdot Y$, the more electrophilic $4c\cdot Y$ disfavored digold formation to a greater extent than it disfavored protodemetalation. As a result, a larger amount of originally added $[LAu]^{+}$ was catalytically active (stayed on cycle) with $4c\cdot Y$ than with $4f\cdot Y$, and therefore an overall faster rate was observed with $4c\cdot Y$. 
In other words, altering the electronic character of the catalyst from $4f\cdot Y$ to $4c\cdot Y$ lowered $k_2$ disproportionally more than it lowered $k_3$. Therefore, with the more electrophilic catalyst $4c\cdot Y$, a higher steady state concentration of monogold-vinyl was present in the reaction mixture, which outweighed the negative effects on $k_3$. As a result, the overall rate of catalysis increased with more acidic ligands bound to gold and an overall positive $\rho$ was expressed. This meant that the positive $\rho$ was an artifact of digold formation, and that because of its off cycle role, it masked mechanistic insight into the transition state of the turnover limiting step of catalysis from Hammett studies.

Because the on cycle process with a negative $\rho$ competed with a positive $\rho$ stemming from the variable steady state concentration of monogold-vinyl or the variable amount of on cycle catalyst, it should be possible to obtain flat ($\rho = 0$) or non-linear Hammett plots (changing $\rho$) depending on the reaction conditions, e.g. variation of substrate, different counterions, or addition of various bases. Because Hammett studies demonstrated that the amount of catalytically active catalyst was variable, other kinetic data had to be interpreted extremely carefully as well.

### 6.7 Experimental Data

Isotope labeling experiment (Scheme 6-6 and Figure 6-1): In a NMR tube were combined 0.15 mL CD$_2$Cl$_2$, 0.2 mL of a stock solution of $4o\cdot$OTs (0.01 M in CD$_2$Cl$_2$), and 0.05 mL of a stock solution of mesitylene (0.02 M in CD$_2$Cl$_2$). The solution was cooled to $-78^\circ\text{C}$ in a dry ice / isopropanol bath and 0.1 mL of a stock solution of $10$ (0.01 M in CD$_2$Cl$_2$) were slowly added. Full conversion to $14o\cdot$OTs was ensured by 1H NMR at $-60^\circ\text{C}$. Then, 0.2 mL of a stock solution of $10\cdot$CD$_2$ (0.1 M in CD$_2$Cl$_2$) were added slowly at $-78^\circ\text{C}$. The sample was
transferred back into the NMR spectrometer, which was warmed together with the sample to –45°C. At this temperature $^1$H NMR data was collected. Individual signals of mesitylene, 11 and 14OTs and combined signals of $[11+11-\text{CD}_2]$ and $[14+14-\text{CD}_2]$ could be integrated and their respective concentration calculated. These concentrations were plotted against time in Figure 6-1 (Wb3-062).
Chapter 7. Silver Effect in the Intramolecular Hydroarylation of Allenes

In the presence of excess $\text{Ag}^+$ a gold-silver resting state was observed instead of a digold intermediate. The gold-silver compound was isolated and characterized. Reactivity studies showed similarities between the gold-silver and digold vinyl complex. Both resting states were simultaneously observed in catalysis. When the reaction proceeded via the gold-silver intermediate, a significant drop in rate was identified.

7.1 Introduction

Silver salts are commonly used to activate metal halides for catalytic transformations, and this strategy is especially useful in homogenous gold catalysis.180 After control experiments demonstrating that the $\text{AgY}$ ($\text{Y} = \text{BF}_4, \text{OTf}, \text{NTf}_2$, etc.) activator does not catalyze the reaction of interest, the silver salts are often used in excess to ensure quantitative activation of the precatalyst.181 Despite proving that the silver salts themselves are unreactive, there are


examples of gold(I)-catalyzed reactions where Ag\(^+\) affected either activity or selectivity,\(^\text{182}\) but models for accommodating such observations are not well appreciated in the gold catalysis community. This chapter focuses on observations that point to Ag\(^+\) ions intercepting Au(I) catalytic intermediates and subsequently effecting catalyst speciation and reaction kinetics; a structural model is also suggested. This work was published in *Organic Letters*\(^\text{183}\).

### 7.2 The Observation and Isolation of a Gold-Silver Resting State

In the investigation of the gold(I)-catalyzed hydroarylation of \(1\) to \(2\) with Ph\(_3\)PAuNTf\(_2\) (4a•NTf\(_2\)) as the catalyst,\(^\text{184}\) it was noted that the catalyst rested at the digold-vinyl intermediate 5a•NTf\(_2\),\(^\text{185}\) which could additionally be synthesized by the combination of Ph\(_3\)PAuNTf\(_2\) (4a•NTf\(_2\)) and the monoaurated vinylgold(I)-complex 3a (see chapter 3). Based on the doubly aurated aryl compounds of Schmidbaur, 5a•NTf\(_2\) was formulated as an out of plane Au-C-Au 3-center-2-electron bond with a stabilizing d\(^{10}\) closed shell aurophilic interaction.\(^\text{186}\) Motivated by the observation of Ag\(^+\)-effects in gold(I)-catalysis and the known

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examples of auro-argentophilic closed shell interactions in polymetallic complexes, the effect of Ag$^+$ on the catalyst speciation was examined.\textsuperscript{187}

As expected, the catalyst generated \textit{in situ} from Ph$_3$PAuCl / AgNTf$_2$ (5 mol\% / 25 mol\%) was found to be effective for the conversion of 1 to 2, while the AgNTf$_2$ activator was much less reactive at RT.\textsuperscript{188} Monitoring the reactions by NMR, however, revealed a significantly different behavior from Ph$_3$PAuNTf$_2$ (4a$\bullet$NTf$_2$) alone. Instead of 5a$\bullet$NTf$_2$ being observed using 4a$\bullet$NTf$_2$, the Ag$^+$-containing reaction rested at a new structure with a singlet in the $^{31}$P NMR at $\delta = 41$ ppm (Figure 7-1 (a)). This compound, 26a$\bullet$NTf$_2$, could be independently synthesized by reacting a mixture of 4a$\bullet$NTf$_2$ and AgNTf$_2$ with 1 in the presence of DTBP, which acted to arrest protodemetallation.\textsuperscript{189} The resonances of this new species (Figure 7-1 (b)) exactly matched those observed in the $^1$H and $^{31}$P NMR of the \textit{in situ} monitored catalytic reactions. Figure 7-1 (c) and Figure 7-1 (d) additionally displayed the corresponding spectra for the isolated intermediates 5a$\bullet$NTf$_2$ and 3a, respectively.


\textsuperscript{189} In the presence of AgNTf$_2$, full conversion of 1 to 26a$\bullet$NTf$_2$ required only 1 equivalent of 4a$\bullet$NTf$_2$. In contrast 2 equivalents of 4a$\bullet$NTf$_2$ were needed for full conversion of 1 to 5a$\bullet$NTf$_2$ when no silver salt was present, see reference (185). Resin-bound DTBP was used for synthetic applications.
Figure 7-1. Comparison of $^1$H (top) and $^{31}$P NMR (bottom) data; a) Catalysis of 1 with 5 mol\% 4a$\cdot$NTf$_2$ in the presence of 20 mol\% AgNTf$_2$ in CD$_2$Cl$_2$; b) Compound 26a$\cdot$NTf$_2$ trapped with DTBP in CD$_2$Cl$_2$; c) Isolated 5a$\cdot$NTf$_2$ in CD$_2$Cl$_2$; d) Isolated 3a in CDCl$_3$. 
Analysis of the $^1$H NMR of $26\text{a} \cdot \text{NTf}_2$ indicated a complex with a PPh$_3$ to carbocyclic framework ratio of one. Both vinyl protons additionally were found to couple to one phosphorous nuclei ($J_{\text{syn}}^\text{PH} = 5 \text{ Hz}; J_{\text{anti}}^\text{PH} = 14 \text{ Hz}$), and like $5\text{a} \cdot \text{NTf}_2$ and previously reported multimetallated compounds, the quaternary bimetallated sp$^2$ carbon showed no signal in the $^{13}$C NMR, perhaps a result of the quadrupole moment of gold. High resolution mass spectrometry showed a m/z of 899.1046 (calcd 899.0966) for the [M–NTf$_2$]$^+$ ion with the isotope pattern expected for a Au-Ag containing compound.

7.3 Structural Proposals

Inspection of X-ray data for numerous simple Au-Ag complexes, e.g. A, suggested that Ag$^+$ likely bound to the vinyl carbon and the Au center without significantly perturbing the gold-vinyl structure (Figure 7-2).

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In other words, the 3-center-2-electron interaction was not equal and the stronger C–Au bond dominated the structure. Since only a single diastereomer was observed, one of the diastereofaces had to be preferentially populated. However, $\sigma$-$\pi$-dimetallation could not be excluded as a possible binding mode.

### 7.4 Reactivity of Gold-Silver Complex

Since the putative role of $26a\cdot$NTf$_2$ was to react with acid to give 2 and to regenerate $4a\cdot$NTf$_2$ and AgNTf$_2$, the acid stability of $26a\cdot$NTf$_2$ was tested (Scheme 7-1). Compound $26a\cdot$NTf$_2$ was unchanged in the presence of 5 equivalents of AcOH, but did provide traces of 2 with 35 equivalents over 48 h. One equivalent of the stronger acid HNTf$_2$ (generated in situ during catalysis) resulted in a rapid protodeauration to form 2. When treated with Br$,^{-}$, precipitation of AgBr drove the conversion of $26a\cdot$NTf$_2$ to the monoaurated gold-vinyl $3a$. Addition of Ph$_3$P did not resulted in silver abstraction, instead it seemed that the ligand

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191 Alternatively the two diastereofaces could be rapidly interconverting through a doubly argented intermediate or transition state. Laguna has recently reported a cluster with just such a bonding model, see (a) E. J. Fernández, A. Laguna, J. M. López-de-Luzuriaga, M. Montiel, M. E. Olmos, J. Pérez, R. C. Puelles, *Organometallics* 2006, 25, 4307; (b) E. J. Fernández, A. Laguna, J. M. López-de-Luzuriaga, M. Monge, M. Montiel, M. E. Olmos, M. Rodríguez-Castillo, *Organometallics* 2006, 25, 3639.
coordinated to the silver cation. This reactivity was indicated by a control experiment, in which 1 equiv of Ph$_3$PAgOTf$^{192}$ were added to gold-vinyl 3a. In both cases similar NMR data were obtained. However, further studies will be necessary to characterize these compounds.

Scheme 7-1. Reactivity of gold-silver complex 26a•NTf$_2$.

The rapid and clean reaction of 3a, a putative reaction intermediate, with 2 equiv of AgNTf$_2$ to form 26a•NTf$_2$, suggested that this process might be viable under catalytic conditions, and thus acted to trap intermediate Au(I)-compounds. Similarly, the dinuclear gold intermediate 5a•NTf$_2$ reacted with 3 equiv AgNTf$_2$ to provide the mixed metal species 26a•NTf$_2$ showing that even preformed digold structures could be driven to the heterometallic structure.$^{193}$

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7.5 Relevance for Catalysis

Such a silver-for-gold substitution seemed only slightly downhill as it was found in catalytic experiments that the resting state monitonically shifted from $\text{26a} \cdot \text{NTf}_2$ to $\text{5a} \cdot \text{NTf}_2$ as the Au/Ag ratio was increased. The change in speciation was especially dramatic when the gold was added as Ph$_3$PAuCl, which simultaneously decreased the Ag$^+$ concentration by precipitation of AgCl (Figure 7-3 and Figure 7-4). Under suitably balanced conditions it is therefore possible to detect both digold and mixed gold/silver resting states.$^{194}$

![Figure 7-3](image)

**Figure 7-3.** Change in catalyst resting state from $\text{26a} \cdot \text{NTf}_2$ (●) to $\text{5a} \cdot \text{NTf}_2$ (●) upon additions of Ph$_3$PAuCl to a solution of 0.1 mmol of 1 and 25 mol% AgNTf$_2$ in CD$_2$Cl$_2$.

The effect of excess AgNTf$_2$ on the kinetics of the cyclization was also investigated. At a Au(I) loading of 5 mol%, the rate with a threefold excess of Ag$^+$ was significantly retarded relative to the gold only experiment (Figure 7-5).

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$^{194}$ After adding $>15$ mol% $\text{4a} \cdot \text{NTf}_2$ some of it was also observed in the NMR, as was (Ph$_3$P)$_2$AuNTf$_2$.
Figure 7-4. Change in catalyst resting state from $26a\text{•NTf}_2$ (•) to $5a\text{•NTf}_2$ (♦) upon additions of $4a\text{•NTf}_2$ to a solution of 0.1 mmol 1 and 15.5 mol% AgNTf$_2$ in CD$_2$Cl$_2$.

Figure 7-5. ln [1] versus time [s] for the conversion to 2 by $^1$H NMR; 0.1 mmol 1, 5 mol% Ph$_3$PAuNTf$_2$ ($4a\text{•NTf}_2$), and 0.05 mmol hexamethyl benzene (internal standard) in 0.5 mL CD$_2$Cl$_2$; 6.2 mg (16 mol%) AgNTf$_2$ was added as a solid.
It was demonstrated that even if the reactants are untouched by Ag\textsuperscript{+}, silver ions could still influence gold-catalyzed reactions by intercepting key organogold intermediates to form dinuclear intermediates with their own unique reactivity. A structural model based on existing Au/Ag cluster chemistry literature was proposed, which may rationalize known Ag\textsuperscript{+}-effects.

### 7.6 Experimental Data

Experimental data are published and are available on the WWW under http://dx.doi.org/10.1021/ol902116b.
Chapter 8. Dual Gold/Palladium Catalysis

The transmetallation of R-groups from gold-vinyl and gold-aryl to palladium complexes is described. The development of a dual gold/palladium catalyzed reaction is attempted. An unexpected Au(I)/Pd(0) RedOx driven homo-coupling of a gold-aryl complex is reported.

8.1 Introduction

Pd(0)/Pd(II) catalyzed coupling reactions rely on five basic elementary steps: oxidative addition, reductive elimination, migratory insertion, β-elimination, and transmetallation.195 With the exception of transmetallation, gold complexes rarely facilitate these basic transformations, a partial consequence of their high barriers for Au(I)/Au(0) and Au(III)/Au(I) RedOx transitions196 along with their preference for low coordination numbers. Despite these differences Au(I)/Au(III) catalyzed cross-coupling reactions have been reported197,198 under the action of strong oxidants like Selectfluor,199 Phl(OAc)2,200 or peroxy


197 For short reviews on oxidative coupling reactions with gold, see: (a) H. A. Wegner, Chimia 2009, 63, 44; (b) P. Garcia, M. Malacria, C. Aubert, V. Gandon, L. Fensterbank, Chem. Cat. Chem. 2010, 2, 493.

198 Palladium impurities could play the key role in gold-only catalyzed coupling reactions, especially if no oxidant is present: (a) T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet, A. M. Echavarren, Org. Lett. 2010, 12, 3006; (b) A. Corma, R. Juárez, M. Boronat, F. Sánchez, M. Iglesias, H. García, Chem. Commun. 2011, 47, 1446.
acids. Mechanistic studies by Toste on systems utilizing Selectfluor suggest fascinating bimolecular reductive elimination mechanistic possibilities.

Fueled by the seemingly orthogonal reactivity modes of Au and Pd catalysts, are suggestions of tantalizing new cross-coupling schemes that sequence the reactivities of Au and Pd. Reports of at least partial success in interfacing Au- and Pd catalysis in this manner have been published by Blum, Hashmi, Sarkar, and Sestelo. In particular, Blum has reported an impressive example of bimetallic catalysis wherein a gold-vinyl intermediate obtained from an allene activation reaction could be intercepted by an in situ formed palladium π-allyl species to perform a vinyl-allyl coupling that was catalytic in both gold and


203 Intramolecular reductive elimination has also been observed: V. J. Scott, J. A. Labinger, J. E. Bercaw, Organometallics 2010, 29, 4090.


Palladium. It was found that undesirable RedOx reactions between Pd(0) and Au(I) could interfere with the normal operation of several putative catalytic cycles that couple the reactivity of Au and Pd. The work reported in this chapter was published in Chemical Communications.209

8.2 Palladium-Catalyzed RedOx Driven Homocoupling

Motivated by the potential of utilizing aryl and vinyl electrophiles to model the reactivity of C(sp2)-Au intermediates in Au(I)-catalysis, the palladium-catalyzed cross-coupling of isolated vinyl and arylgold(I)-complexes with aryl-triflates was studied.210 Unfortunately, attempts to couple complexes 3a or Hammond-vinyl and TolOTf with various Pd-catalysts failed (Figure 8-1 and Figure 8-2).213 TLC and GC-MS analysis indicated that at best only traces of the desired cross-coupled products were obtained (24 h).

In contrast, the same reaction conditions converted arylgold(I)-complex 27a into a variety of biaryl products (Scheme 8-1). The reaction progress was accompanied by the formation of brown particles, which gradually led to a gold mirror on the glass surface. Once TLC indicated complete conversion, GC-MS showed that three biaryl products, 28, 29, and 30,

210 Sestelo has coupled p-acetylphenyl triflate with in situ formed organometallic gold compounds (from RLi and Ph3PAuCl). Attempts to couple isolated Au-complexes 27a or PhAuPPh3 with TolOTf or p-acetylphenyl-triflate under these published conditions were unsuccessful, see M. Pena-López, M. Ayán-Varela, L. A. Sandareses, J. P. Sestelo, Chem. Eur. J. 2010, 16, 9905.
213 For ligands commonly used to couple sulfonate electrophiles, see: K. Dooleweerdt, B. P. Fors, S. L. Buchwald, Org. Lett. 2010, 12, 2350 and references therein.
were generated in an 8:85:7 ratio, respectively. The structure of 30 was confirmed by $^1$H NMR.

**Figure 8-1.** Structures of gold complexes 3a and Hammond-vinyl.

**Figure 8-2.** Various ligands utilized in attempted cross-coupling.

**Scheme 8-1.** Palladium-catalyzed coupling reaction of 27a.

A simple mechanistic scheme for the formation of 28 is shown in cycle C, Scheme 8-2. Whereas cross-coupling to 28 is initiated by oxidative addition of TolOTf, catalytic homo-
coupling of 27a to 29 requires a separate oxidant (cycle D, Scheme 8-2) to regenerate Pd(II) after reductive elimination of 3. Since no external oxidant was added (with the exception of TolOTf which would facilitate cross-coupling) further studies were initiated to gain insight.


As shown in Table 1, variation of the Pd catalyst did not significantly increase the amount of 28 (Table 8-1, entries 1-8), though reaction times did vary from catalyst to catalyst: Pd(II) sources tended to be faster. Control experiments showed that when no Pd catalyst was added, no conversion of 27a to coupled products was observed by TLC (Table 8-1, entries 9-11). Note: thermolysis of 27a in the GC injector port lead to 29.\textsuperscript{214}

\textsuperscript{214} GC-MS and GC data could not be used to determine the yield of incomplete reactions, since arylgold(I)-complexes pass through silica or florisil and homo-couple in the hot injector port.
Table 8-1. Ligand screen and control experiments. Reaction conditions: 5-10 mol% [Pd]/L; 2.5 equiv TolOTf; 10 mg (17.7 μmol) of 27a. \(^{a}\)dppf = 1,1'-bis(diphenylphosphino)ferrocene. \(^{b}\)PEPPSI-IPr = [1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene][3-chloropyridyl]palladium(II) dichloride. \(^{c}\)Incomplete conversion to coupled product was indicated by TLC; after the indicated period of time, the reactions was analyzed by GC-MS which thermally converts unreacted 27a to 29. \(^{d}\)No conversion indicated by TLC. \(^{e}\)Product ratio determined by GC-MS. \(^{f}\)See ref. 214.

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<th>Entry</th>
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<td>L3</td>
<td>&lt; 19 h</td>
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<tr>
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<td>L4</td>
<td>24 h(^{c})</td>
<td>(1 : 86 : 13)^{f})</td>
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<td>L1</td>
<td>19 h(^{c})</td>
<td>(13 : 73 : 14)^{f})</td>
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<td>(5 : 83 : 12)^{f})</td>
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<tr>
<td>10</td>
<td>TolOTf</td>
<td>None</td>
<td>None</td>
<td>19 h(^{d})</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>19 h(^{d})</td>
<td>–</td>
</tr>
</tbody>
</table>

The source of 29 and 30 was investigated by examining the role of each reaction component. When TolOTf was omitted, only 29 and 30 were formed (Figure 8-2, entry 1),
which clearly showed that TolOTf did not act as the oxidant for the formation of 29. Monitoring the reaction with Pd(OAc)$_2$ by TLC indicated that 27a was consumed within 5 h (Figure 8-2, entry 2), and that an initial burst$^{215}$ of coupled products was followed by a slower but steady reaction.

Using Pd$_2$(dba)$_3$ (Figure 8-2, entry 3), the initial burst was not observed and the reaction proceeded slowly. A slightly faster rate could be regained using Pd$_2$(dba)$_3$ in combination with TolOTf, but the reaction time was still not as rapid as when a Pd(II) source was used. These data suggest that it is a Pd(II) species that first engages Au(I) to produce homo-coupled products. Since the aryl groups of PAr’$_3$ ligands are known to transfer in Ni, Pd, and Pt reductive elimination reactions,$^{216}$ the possibility that 30 was phosphine derived was tested by utilizing ($p$-tol)$_3$PAuAr (27d) (Ar = 3,5-Xyl) (Figure 8-2, entries 4 and 5). Not surprisingly, a significant amount of 28 was observed. When Ph-Xphos (L1) was utilized as the phosphine ligand for Pd a small amount of 30 was also observed, pointing to two ligand sources for the aryl group (Figure 8-2, entry 5).

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$^{215}$ The initial burst was qualitatively observed by TLC. It is best explained by a fast first turnover of a Pd(II) source.

**Table 8-2.** No addition of TolOTf and variation of substrate. Reaction conditions: 5-10 mol% [Pd]/L; 10 mg (17.7 μmol) of 27a. "3.1 equivalents of PPh3 vs. 27a were added. Incomplete conversion to coupled product was indicated by TLC; after the indicated period of time, the reactions was analyzed by GC-MS which thermally converts 27a to 29. Only an initial burst to coupled product was observed. No conversion indicated by TLC. Product ratio determined by GC-MS. See ref. 214. An 0:84:16 mixture (NMR ratio) of products was isolated by flash column chromatography on silica (45% yield of 29, and a 5% yield of 30). 

![Reaction diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>[Pd]</th>
<th>L’</th>
<th>Time</th>
<th>28 : 29 : 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27a</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>&lt; 19 h</td>
<td>0 : 76 : 24</td>
</tr>
<tr>
<td>2</td>
<td>27a</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>&lt; 5 h</td>
<td>0 : 75 : 25</td>
</tr>
<tr>
<td>3</td>
<td>27a</td>
<td>Pd₂(dba)₃</td>
<td>L₁</td>
<td>19 hᵇ</td>
<td>0 : 98 : 2ᶠ</td>
</tr>
<tr>
<td>4</td>
<td>27d</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>5 hᵇ</td>
<td>19 : 80 : 1ᶠ</td>
</tr>
<tr>
<td>5</td>
<td>27d</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>5 hᵇ</td>
<td>18 : 82 : 0ᶠ</td>
</tr>
<tr>
<td>6</td>
<td>27p</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>5 hᶠ</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>27q</td>
<td>Pd(OAc)₂</td>
<td>L₁</td>
<td>12 hʳ</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>27a</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>&lt; 2 h</td>
<td>0 : 83 : 1⁷⁸⁰</td>
</tr>
<tr>
<td>9</td>
<td>27a</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ᵃ</td>
<td>12 hᵈ</td>
<td>–</td>
</tr>
</tbody>
</table>

In the case of the non-phosphine NHC complexes IPrAuAr (27p) and IMesAuAr (27q) (Ar = 3,5-Xyl) only an initial burst of homo-coupling was observed, with neither reaction progressing beyond this point (Figure 8-2, entries 6 and 7). These experiments suggested that
either the PAr’3 ligand was necessary to facilitate the reaction or that NHC ligands sufficiently stabilized the Au(I) state to inhibit the RedOx process. In the absence of added phosphine ligand Pd(OAc)2 fully converted 27a within 2 h at 58°C (Figure 8-2, entry 8). Conversely, 3.1 equivalents of PPh3 completely inhibited the conversion to 29 (Figure 8-2, entry 9), supporting the notion that stabilizing Au(I) either through NHC’s or excess phosphine could inhibit the RedOx reaction.217

We also attempted to elucidate with a Hg drop test whether the reaction was homogenous or heterogeneous.218 Unfortunately, this led to an instant decomposition of 27a as previously observed by Grandberg while studying the RedOx potential of gold complexes on Hg electrodes (Scheme 8-3).219

\[
2 \text{RAuPPh}_3 + \text{Hg}(0) \rightarrow \text{R}_2\text{Hg} + 2 \text{Au}(0) + 2 \text{PPh}_3
\]

**Scheme 8-3.** Hg(0)/Au(I) RedOx reaction observed by Grandberg.

The catalytic coupling of two nucleophiles requires an oxidant. Based on the Grandberg RedOx precedent, the observed gold mirror, and the experimental results we propose that reduction of Au(I) to Au(0) accounts for the necessary RedOx equivalents. As outlined in step a of Scheme 8-4, two equivalents of Au(I) are consumed to regenerate Pd(II) with the

217 The exact nature of the inhibiting effect of PPh3 is unclear, but we note that when it is in excess not even a single turnover occurs.


Au(0) eventually forming the gold mirror.\textsuperscript{220} Since the Hg drop experiment failed, the role of Pd and/or Au nanoparticles cannot be eliminated from consideration.

Scheme 8-4. Proposed mechanism for the homo-coupling of 27a.

In conclusion, a Pd-catalyzed homo-coupling of arylgold(I)-complexes has been observed. While of limited applicability in synthesis, these results have illuminated a point of incompatibility between these two metals and suggested strategies for overcoming these shortcomings. Since Au-mirrors are relatively common occurrences in gold-catalyzed reactions, these results demonstrate how two elements with orthogonal reactivity profiles can be RedOx incompatible and thus impede the development of dual Au(I)/Pd(0) catalysts.

8.3 Experimental Data

Experimental data are published and are available on the WWW under http://dx.doi.org/10.1039/c1cc11055a.

\textsuperscript{220} While this paper was under review Blum disclosed a nickel-catalyzed cross-coupling of organogold reagents: J. J. Hirner, S. A. Blum, \textit{Organometallics} \textbf{2011}, \textit{30}, 1299. Notable observations include RedOx chemistry between Au(I) and Ni(0) to generate paramagnetic Ni(I) (i.e. single electron processes) and gold mirrors. We are unable to confirm the presence of Pd(I) intermediates in the present chemistry.
Mechanistic studies on gold-vinyl intermediates and gold-aryl model complexes lead to new hypotheses of the stereochemistry determining step in gold catalysis and an alternative activation protocol of gold-catalyst precursors with hard Lewis acids. The collaborative development of a novel gold-catalyzed enantioselective Cope-rearrangement is noted.

9.1 Introduction

While studying the properties of monogold- and digold-vinyl intermediates in catalysis, several key features were recognized that opened new avenues in gold catalysis. Utilizing a second metal to intercept gold-vinyl intermediates has been described in chapters 7 and 8. However, other mechanistic factors that affect the outcome of a gold-catalyzed reaction are discussed below. These approaches may expand the utility of gold in asymmetric catalysis, in natural product synthesis, or in combined catalysis of hard / soft Lewis acids.

9.2 Origin of Chiral Induction in Gold Catalysis

In 2007 Toste published a powerful chiral counterion strategy for asymmetric gold catalysis in Science.\textsuperscript{221} The application of chiral phosphate anions allowed the synthesis of enantioenriched products obtained from the hydroalkoxylation of achiral allenes. Close ion

pairing between cationic gold intermediates and the counterion was believed to induce chirality during the cyclization step.\textsuperscript{222} This hypothesis was based on other enantioselective ACDC (asymmetric counterion directed catalysis).\textsuperscript{223} However, lessons learned about the mechanism of the hydroalkoxylation of 10 (chapter 4 and 6) offered an alternative explanation. Since monogold 13 and digold 14 favored kinetic cycloreversion to 10 over protodemetallation to 11, a dynamic kinetic resolution of an in situ formed racemic mixture of gold-vinyl intermediates and in situ formed chiral acid could be envisioned. Because of transition state energy differences in the protodeauration step of the matched vs. the unmatched gold-vinyl / chiral acid pair, this alternative model could explain the enantioselective outcome of these reactions (Scheme 9-1).

\begin{center}
\textbf{Scheme 9-1.} Dynamic kinetic resolution of in situ formed gold-vinyl intermediates and chiral Brønsted acids (bottom) as an alternative proposal for the close ion pair model (top) in enantioselective gold catalysis.
\end{center}


Stereochemistry determining protodemetalization could even be suggested for reactions where chiral gold catalysts are used. The formation of a diastereomeric mixture of gold-vinyl intermediates could also form a matched miss-matched pair with a non-chiral acid.

### 9.3 Lewis Acid Mediated Catalyst Activation

During studies with gold-aryl model complexes, a Brønsted acid effect was observed, in which the acid activated the counterion of gold complexes and increased the electrophilic character of the metal center (see chapter 5). This observation suggested that Lewis acids could be used to activate gold complexes with coordinating anions, such as OAc, for catalysis (Scheme 9-2).\(^{224}\)

![Scheme 9-2. Lewis acid mediated activation of Ph₃PAuOAc.](image)

Proof of principle was demonstrated for the hydroarylation of allene 1 (Scheme 9-4). A mixture of 1 and 10 mol% 4a•OAc in CD₂Cl₂ was monitored by NMR for 24 h. No catalysis was observed. Upon addition of BF₃•Et₂O (excess) the catalytic conversion of 1 to 2 was noted. NMR studies revealed characteristic signals of an intermediate digold species.

A Lewis acid mediated activation protocol could be applied to circumvent the current limitations of chiral phosphates. For example, the hydroarylation of 1 did not proceed in the

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presence of 4a-OPE indicating a narrower substrate spectrum with this catalyst due to the stronger coordination of OPE in comparison to other counterions.

**Scheme 9-3.** Proof of principle for a Lewis acid mediated activation of 4a-OAc using the intramolecular hydroarylation of 1 as a model reaction.

**Scheme 9-4.** Lewis acid mediated activation of gold catalysts with coordinating anions.

Furthermore, chiral Lewis acids could be used to selectively enhance the electrophilicity of one enantiomer of a racemic mixture of 4a-OPE (Scheme 9-4). This scenario could provide indirect stereochemical induction from the chiral Lewis acid to the final product by specifically activating the gold catalyst with the matching chiral anion.

### 9.4 Enantioselective Cope-Rearrangement

In collaborative work with fellow graduate student Ryan J. Felix and the Tantillo group at the University of California at Davis an enantioselective Cope-rearrangement was developed. Since its discovery in the 1940’s, no asymmetric variant of the Cope rearrangement of achiral
1,5-dienes has emerged, despite the successes that have been achieved with a number of its heteroatom variants (Claisen, aza-Cope, etc). This work describes the first example of an enantioselective Cope reaction that starts from an achiral diene (Scheme 9-5). A new gold(I) catalyst derived from double Cl\(^{-}\)-abstraction of (S)-3,5-xylyl-PHANEPHOS(AuCl)\(_2\) has been developed for the sigmatropic rearrangement of alkenyl-methylene cyclopropanes.

Scheme 9-5. Asymmetric Cope-rearrangement catalyzed by gold.

The synthetically useful vinyl cyclopropane products are obtained in high yield and enantioselectivity. Density functional theory calculations predict that: 1) the reaction proceeds via a cyclic carbenium ion intermediate, 2) the relief of strain in the methylene cyclopropane moiety provides the driving force for the rearrangement, and 3) metal complexation of the transition state structure lowers the rearrangement barriers. Because this study described new concepts to gold catalysis, it was published in *Nature Chemistry*.\(^{225}\)


M. A. Tarselli, *Doctoral Dissertation* **2008**, University of North Carolina at Chapel Hill.


T. J. Brown, A. Sugie, M. G. Dickens, R. A. Widenhoefer, *Organometallics* 2010, 29, 4207.


