The Golden Age of Chemistry

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Gold – Basic Facts

Gold is known in following oxidation states: -1, 0, +1, ([Xe] 4f^{14} 5d^{10}), +2, +3 ([Xe] 4f^{14} 5d^{8}), +5

- Complexes of Au(I) are usually 2-coordinate, linear, 14-e species whereas Au(III) complexes are typically 4-coordinate, square-planar, 16e (compare other d^{10} and d^{8} – [Ag(CN)_{2}]^-, Ph_{3}PAuCl or [Ni(CN)_{4}]^{2-}, [Rh(CO)_{2}Cl_{2}]^{-})

- π-complexes of Au(I) and Au(III) are thermally unstable while Cp-complexes show typically η^{1}-binding mode (highly fluxional at rt) – weak back-bonding is observed

- Relative stabilities of [Me_{3}PAuL]^{+} complexes have been calculated

  \[
  \text{CH}_{2}\text{Cl}_{2} \ (+63) < \text{H}_{2}\text{O} \ (+44) < \text{HCCH} \ (+38) < \text{MeOH} \ (+24) < \text{CH}_{3}\text{CCH} \ (+18) < \text{CH}_{3}\text{CCCH}_{3} \ (0) < \text{Me}_{2}\text{S} \ (-18) < \text{PPh}_{3} \ (-114)
  \]

  Teles ACIEE 1998, 37, 1415

- Among neutral M(CH_{2}CH_{2}) complexes M = Cu, Ag, Au, gold is the strongest binder

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Relativistic Effects in Gold

- Among heavy metals, gold shows largest relativistic effects

- The influence of relativistic effects can be illustrated be comparing Ag and Au
  - Energies of $s$ and $p$ orbitals are lowered but energy of $d$ orbitals is raised
  - Gold forms shorter and more covalent bonds
  - Destabilization of 5$d$ orbital in Au may explain tri- and pentavalency of Au
  - Yellow color of gold can be also explained by relativistic effects

![Relativistic contraction of 6s shell](image)

Relativistic contraction of 6s shell

Pyykkö *ACIEE* 2004, 44, 4412
Stoichiometric Reactions of Gold

- Grignard and lithium reagents undergo ligand exchange with Au(I) and Au(III) halides

\[ \text{AuBr}_3 + 2 \text{EtMgBr} \rightarrow \text{Et}_2\text{AuBr} + 2 \text{MgBr}_2 \]

- \( \text{R}_3\text{Au} \) and \( \text{RAu} \) are unstable in the absence of stabilizing ligands

- Highly nucleophilic phosphorus ylides are able to displace almost any ligand on Au

\[ \text{L Au Cl} + \text{R}_3\text{PCH}_2 \rightarrow [\text{L Au CH}_2\text{PPh}_3] \text{Cl} \]

- Oxidative addition of \( \text{X}_2 \) or \( \text{RLi} \) to Au(I) is a common process to obtain Au(III)

- Compounds of type \( \text{R-Au-L} \) are air and moisture stable but can be decomposed under acidic conditions

- Such exotic species as tetragnoldmethane can be obtained in a stable form

- Many compounds of gold show tendency to form molecular clusters that eventually is converted into molecular metal
Nanoparticles in Catalysis – A New “Gold” Rush

**Application of AgNP**

- Catalytic Oxidation of CO to CO$_2$
- Removal of alkylamines (Fe$_2$O$_3$-supported AuNPs) or dioxins (La$_2$O$_3$-supported AuNPs)
- Low-concentration sensors of H$_2$ and CO (Co$_2$O$_3$-supported AuNP)

Astruc *ACIEE* **2005**, 44, 7852
Typical Gold Catalysts

- Ph$_3$PAuCl (commercially available) is a common Au(I) precatalyst that can be converted into cationic gold by reactions with silver salts

\[
\text{Ph}_3\text{P}-\text{AuCl} + \text{AgX} \rightarrow \text{Ph}_3\text{PAu}^+ \text{X}^- + \text{AgCl}
\]

X = SbF$_6$, BF$_4$, OTf, etc

- \(\mu\)-Oxo-complexes of gold have also found applications in catalysis

\[
\text{LAuCl} \xrightarrow{1. \text{AgBF}_4} \text{LAu}^+ \text{O}^- + \text{AuL} \xrightarrow{2. \text{NaOH}} \text{BF}_4^- \]

L = phosphine


- Anhydrous AuCl$_3$ and NaAuCl$_4$ 2H$_2$O are common sources of Au(III)

- Various Au(I) carbene complexes are also known to be catalytically active
Au-Catalyzed Small Ring Rearrangements

- Early examples of strain-driven rearrangements using catalytic amounts of Au (III) involved very strained molecules (for example, Gassman *JACS* 1972, 94, 7741)

\[
\text{Cat (2mol\%)} 
\begin{array}{c}
\text{Aul}_3 \quad 0.2 \text{ h, 56\%} \\
\text{AuCN} \quad 24 \text{ h, 40\%} \\
\text{AuI}_3 \quad 0.1 \text{ h, 60\%}
\end{array}
\]

- Recently, a highly efficient rearrangement of alkynylcyclopropanols and cyclobutanols was described (Toste *JACS* 2005, 127, 9708)

\[
\begin{align*}
\text{[(p-CF}_3\text{C}_6\text{H}_4)\text{Ph}]AuCl (0.5-5\% \text{ mol}) & \quad \text{AgSbF}_6 (0.5-5\% \text{ mol}), \text{CH}_2\text{Cl}_2, \text{rt} \\
\end{align*}
\]

\[\text{Yields: 66-98\%}\]

- Reaction proceeds via 1,2-alkyl shift mechanism where the A\(^{1,3}\) strain interactions control the migratory preference

\[
\begin{align*}
\text{R} & \quad \text{Ph}, \text{R}_1 = \text{i-Pr}, \text{R}_2 = \text{H}, 91\% \\
\text{R} & \quad \text{H}, \text{R}_1 = \text{H}, \text{R}_2 = \text{i-Pr}, 80\%
\end{align*}
\]
Gold-Catalyzed Rearrangements of Enynes – a Mechanistic Puzzle

reactions with Au(I), Pt(II) and Ru(II) proceed via carbene

observed for Pt(II) Ga(III) and

and/or

5-exo-dig

6-endo-dig

Echavarren Chem. Eur. J. 2006, 12, 5916
Au-Catalyzed Cycloisomerization of Alkynes

Putative carbocation X can be either trapped intramolecularly or can undergo 1,2-alkyl shift.
Gold-Catalyzed Rearrangements of Enynes – a Mechanistic Puzzle

[Chemical structures and reaction schemes are shown with reaction conditions and yields.]

Echavarren *ACIEE* **2004**, *43*, 2402
High stereospecificity was observed in cyclization of E/Z alkenes:

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Trapping of Au-Carbene Intermediate


Echavarren *ACIEE* **2006**, *45*, 6029

However, additional evidence for terminal carbene can be obtained by trapping experiments.
Au-Catalyzed Cycloisomerization

-Au(I) promotes 5-exo-dig cyclization followed by Nazarov-type cyclization

-Electron-donating groups increase yield of this transformation - an alternative pathway is formal 2+2 cycloaddition

Echavarren *JACS* 2005, 127, 6178

-Au-promoted cycloisomerization followed by trapping with electron-rich aromatic afforded Friedel-Crafts-type products

Genét *ACIEE* 2006, 45, 7427

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Au-Catalyzed Prins Reaction

Echavarren *ACIEE* 2006, 45, 5452

Incorporation of strained carbocycle into the substrates leads to ring-expanded product

Yields: 39-93%
dr 1:1 to 30:1
Ene-Ynamide Isomerization

Exposure of labile cyclobutanones to peracid leads to formation of γ-lactones.

Imidates with substituents at 2 and 3 position of homoallyl chain undergo diastereoselective rearrangements.

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Au-Catalyzed Rautenstrauch Reaction

Vinyl propargyl esters undergo metal catalyzed rearrangement to cyclopentenones (Rautenstrauch JOC 1984, 49, 950)

Same transformation can be carried out using gold(I) catalyst that selectively transfers chirality of non-racemic substrates to cyclopentenone skeleton Toste JACS 2005, 127, 5802

High selectivity of was atributed to helicity of pentadienyl cation resulting from Lera JACS 2006, 128, 2434

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Au(I)-Promoted Rearrangement of Propargyl Esters

Propargyl esters undergo Au(I) promoted rearrangements followed by trapping with styrenes

Mechanistic proposal is consistent with the pathway favoring formation of carbene

Toste JACS 2005, 127, 18002
Au(I)-Catalyzed [4+3] Annulation

Key Features:
- Pt(II) and Ru(II) gave desired product in moderate yield
- only trans methylstyrenes underwent stereospecific reaction whereas cis gave 1:0.8 diastereomeric mixture

Toste JACS 2006, 128, 14480

Reaction Scope:

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Highly-Selective Claisen Rearrangements

- Catalytic Claisen rearrangement can be promoted by hard (Al(III)) and soft (Hg(II), Pd(II)) Lewis acids

- No general approach to catalytic Claisen rearrangement of propargyl vinyl ethers has been developed

- Cationic Au(I) efficiently homoallenyl alcohols

\[
\begin{align*}
\text{Conditions:} & \\
\text{A. } & \left[\text{Ph}_3\text{PAu}\right]_3\text{OBF}_4 (1\text{mol\%}), \text{CH}_2\text{Cl}_2, \text{rt} & \quad \text{NaBH}_4, \text{MeOH, rt} \\
& \quad 76\%, >20:1 \\
\text{B. } & \text{PhMe, 170 } ^\circ \text{C, 3h; NaBH}_4, \text{MeOH, rt} & \quad 90\%, 1:1.5
\end{align*}
\]

-Au-catalyzed Claisen rearrangement provides homoallenic alcohols in high dr and ee’s

- Other catalysts (Ph₃PAuOTf, Ph₃PAuBF₄) afforded allylic alcohols in low ee’s (racemization of the product)

Reaction Scope

![Reaction Scope](image)

Toste JACS 2004, 126, 15978

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Enol – Alkyne Cyclization

- Typical conditions for Conia-ene reaction require activation by heat, strong acid or base.
- Gold-catalyzed version of ene reaction proceeds under relatively mild conditions.

\[
\text{Ph}_3\text{PAuCl (1mol\%)} \quad \text{AgOTf (1mol\%)} \\
\text{CH}_2\text{Cl}_2, \text{rt}
\]

Toste JACS 2004, 126, 4526

- Similarly, silyl enol ethers can participate in an yne carbocyclization.

\[
\text{Ph}_3\text{PAuCl (10mol\%)} \quad \text{AgBF}_4 (10\text{mol\%}) \\
\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}, 40 ^\circ\text{C}
\]

Si = TBS, TIPS

Water as well as methanol can be used as an external proton source.

Toste ACIEE 2006, 45, 5991
Catalytic Addition of 1,3-Dicarbonyl Compounds

- No isomerization of double bond observed
- Tentative mechanism involves activation of olefin by Au(III)

\[ \text{AuCl}_3/\text{AgOTf} \quad \text{CH}_2\text{Cl}_2 \]

\[ n = 1-3 \]

yields: 35-59%

Li OL 2005, 7, 673

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\[ \text{NaAuCl}_4 \cdot 2 \text{H}_2\text{O} \text{ or AuBr}_3/\text{AgOTf} \]

(5mol%)

60-74%

23-90%

Marinelli Adv. Synth. Cat. 2006, 331
CC bond formation followed by trapping of oxabicyclic scaffolds

![Chemical structure](image)

Yields: 45-90%

Intramolecular cyclization can be also carried out using Cu(OTf)$_2$.

Benzannulation reaction proceeds also with dimethylacetals (3equiv of H$_2$O added).

DFT calculations provide support for formation of oxonianaphtalene aurate. However, formal [4+2] cycloaddition proceeds via Huisgen [3+2] cycloaddition.

Yamamoto *JACS* **2002**, *124*, 12650
Yamamoto *JACS* **2004**, *126*, 7458
Yamamoto *JOC* **2005**, *70*, 3682
Au(I)-Catalyzed [3+2] Cycloaddition

Formal AuBr₃-catalyzed [3+2] cycloaddition was reported as a major pathway in reaction carried out at elevated temperatures.

Importantly, *gem*-substituents favor formation of 5-membered rings.

Oh *OL* 2005, 7, 5289
Extension of Au-Catalyzed Domino Processes

Formation of benzo[a]fluorene may proceed via o-quinoid ketone

Dyker JOC 2006, 71, 6728

Shibata Synlett 2006, 411
Au-Catalyzed Benzannulation

Catalyst such as AgNO₃, Hg(ClO₄)₂, Pd(PPh₃)₄, Pd₂(dba)₃ CHCl₃, failed to promote this transformation.

- Only terminal alkynes underwent aromatization reaction.

Hashmi *JACS* **2000**, *127*, 6962
Hashmi *Cat. Today* **2002**, *72*, 19

In the presence of intramolecular alkyne acceptor, benzofurane scaffold can be obtained.

Hashmi *OL* **2001**, *3*, 3769

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Mechanistic Proposal

Low-temperature $^1$H NMR as well as trapping experiments indicated intermediacy of arene oxide.

Hashmi *ACIEE* 2005, 44, 2798

According to DFT calculations, Diels-Alder pathway is **thermodynamically** favored whereas carbene mechanism is **kinetically** favored.

Hashmi *Int. J. Quant. Chem.* 2007, 107, 359
Synthesis of Nitrogen-Containing Heterocycles

\[
\text{Reaction 1:}
\begin{align*}
\text{[(dppm)Au}_2\text{Cl}_2 (2.5\text{mol\%})]} & \xrightarrow{\text{AgSbF}_6 (5\text{mol\%}), \text{CH}_2\text{Cl}_2, 35 \degree \text{C}} \text{n-Bu} & \xrightarrow{n=1, R = H, 80\%} \text{n-Bu} \\
\text{n-Hex} & \xrightarrow{n=2, R = \text{Ph}, 84\%} \text{n-Bu} \\
\text{Yields: 15-98\%}
\end{align*}
\]

\text{Toste} \textit{JACS} \textbf{2005}, \textit{127}, 11260

\[
\text{Reaction 2:}
\begin{align*}
\text{R} & \xrightarrow{\text{NaAuCl}_4 \ 2\text{H}_2\text{O (2.5\text{mol\%})}} \xrightarrow{\text{EtOH, } \Delta T} \text{R} \\
\text{Yields: 15-98\%}
\end{align*}
\]

\text{Arcadi} \textit{JOC} \textbf{2000}, \textit{68}, 6959
Synthesis of Furans

Larock *JACS* **2004**, *126*, 11164

Schmalz *ACIEE* **2006**, *45*, 6704

Au(I) has proven to be superior to catalysts such as Au(II), Ag(I) or lanthanide salts.
Synthesis of Oxazoles and Furans

Aromatic and aliphatic substituents are tolerated
Mostly esters and ketones are suitable substrates

Kirsch *OL* 2005, 7, 3925

“Dimerization” of terminal alkynes can be carried out on substrates with alkyl, ether and ester functionalities (yields 35-50%)

Gasparrini *JACS* 1993, 115, 4401

Only terminal alkynes are suitable substrates
Aromatic and aliphatic ketones furnished oxazoles in good yields (48-95%)

Hashmi *OL* 2004, 6, 4391
Au-Catalyzed Arene Synthesis – CH Activation

Au (III) is capable to promote electrophilic activation of allenyl ketones followed by CH insertion and addition to enones

\[
\begin{align*}
\text{R} & \quad \text{R}_2 \quad \text{AuCl}_3 (1\text{mol\%}) \quad \text{MeCN} \\
\text{R} = \quad \text{MeO} \quad \text{R}_1, \text{R}_2 = \text{H, Me, Et} \\
yields: 46-74\%
\end{align*}
\]

Gold is a superior catalyst in cycloisomerization reactions

Catalyst: \((p\text{-Cymene})\text{RuCl}_2\text{PPh}_3 (1\text{mol\%}), 60 \, ^\circ\text{C}, 1\text{h}\)

Dixneuf \(T 1995, 51, 13089\)

AgBF\(_4\) (20mol\%), rt, 2h

Marshall \(JOC 1995, 60, 5966\)

-Putative furyl-gold intermediate can be trapped in an intramolecular reactions with alkocohol

-β-Hydride elimination is rarely observed in Au-catalyzed reactions

Hashmi \(ACIEE 2000, 39, 2285\)
Direct Activation of Aromatic CH Bonds

Kharasch showed that anhydrous AuCl₃ can promote electrophilic exchange of H in various benzene derivatives

Kharasch JACS 1931, 53, 3053

Introduction of stabilizing ligands (2,6-lutidine) led to isolation of stable complexes


Reetz reported A-catalyzed hydroarylation of unactivated arene electron-deficient alkynes

Reetz EJOC 2003, 3485

Inter and intramolecular catalytic addition of electron-rich arenes to electron-deficient alkynes using AuCl₃/AgOTf has also been reported

JOC 2004, 69, 3669
Activation of Indole CH Bonds

- Use of more electrophilic AuCl₃ leads to formation of thermodynamically less stable products

- Alkenylation via Friedel-Crafts cyclopropyl carbene mechanism are energetically accessible pathways

Echavarren *ACIEE* 2006, 45, 1105

Au-Catalyzed CH Activation

\[
\text{[(IPr)AuCl]/AgBF}_4 \text{ (2mol\%)} \quad \text{CH}_2\text{Cl}_2, \text{rt, 5 min}
\]

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, \text{rt, 5 min} & \quad \rightarrow \\
\text{R} & \quad \text{n-Bu} \\
\text{R} & \quad \text{n-Bu}
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{F}, & \quad 81\% \\
\text{R} = \text{Me}, & \quad 78\% \\
\text{R} = \text{OMe}, & \quad 63\%
\end{align*}
\]

[IPrAu]⁺ catalyzes formation of A and B from allene

Nolan *ACIEE* **2006**, 45, 3647
Catalytic Enantioselective Reactions of Au

**Plausible TS**

Hayashi *JACS* **1986**, *108*, 6406
Summary

High binding of gold to alkyne promotes various skeletal rearrangement reactions.

Gold shows low tendency to undergo “classical” 2-electron redox reactions and both Au(I) and Au(III) show similar reactivity.

Unlike many transition metals, gold in its common oxidation states shows low propensity for hydride elimination. However, typically for the late transition metals (XI, XII), easy protodemetallation is often observed.

In the presence of hard nucleophiles, gold acts as soft Lewis acid.