Angewandte Reviews

Metal Catalysis

DOI: 10.1002/anie.201101726

Similarities and Differences between the “Relativistic” Triad Gold, Platinum, and Mercury in Catalysis

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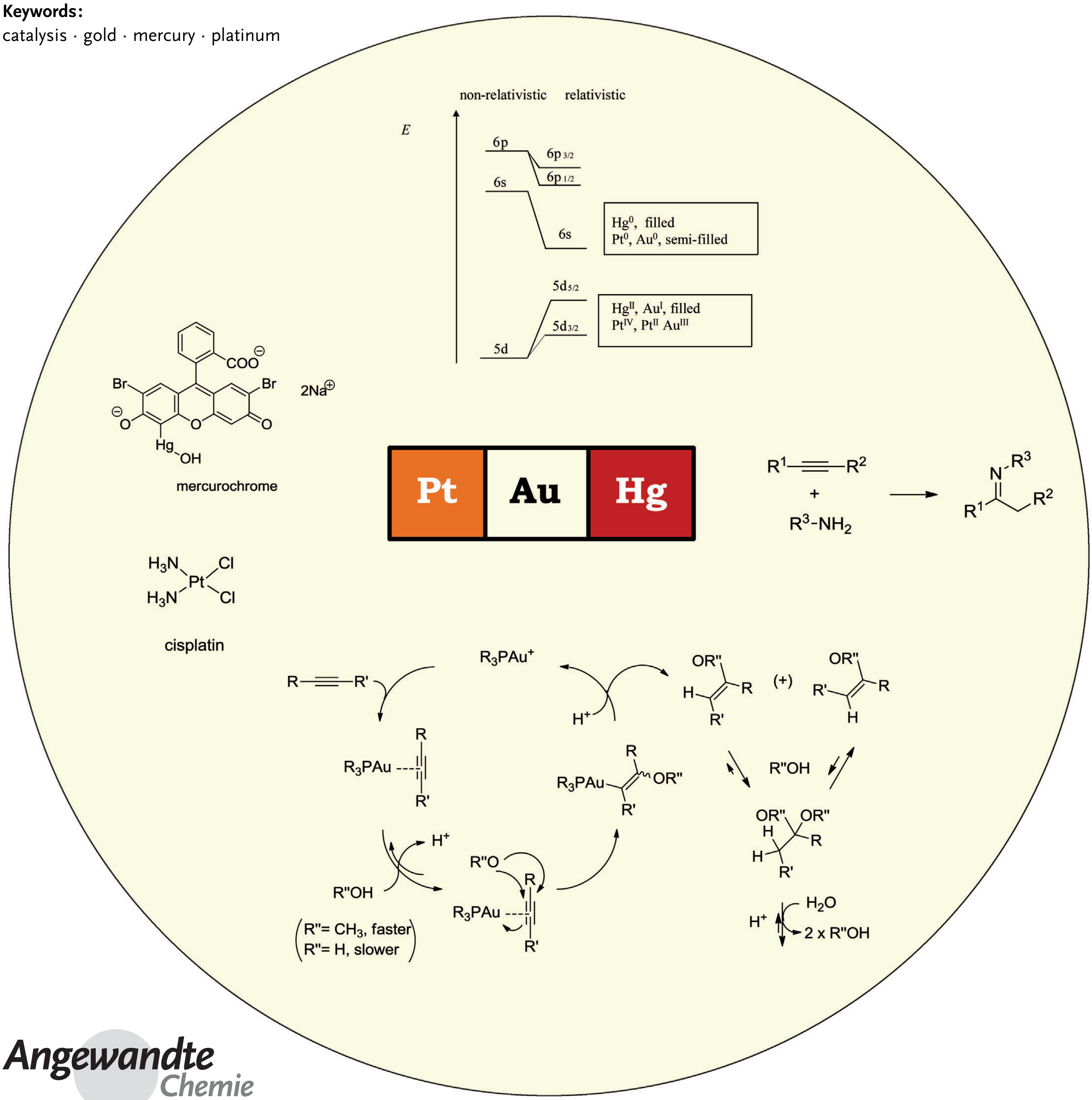
Keywords:
catalysis · gold · mercury · platinum



Angewandte Chemie

Relativistic effects in the valence shell of the elements reach a maximum in the triad Pt–Au–Hg and determine their catalytic activity in organic reactions. In this Review we examine the catalytic activity of Pt, Au, and Hg compounds for some representative reactions, and discuss the respective benefits and disadvantages along with other relevant properties, such as toxicity, price, and availability. For the reactions considered, gold catalysts are generally more active than mercury or platinum catalysts.

From the Contents

1. Introduction

Since the 19th century, chemists have used metals as catalysts for organic reactions. One of the earliest catalysts was mercury (Hg). In 1884, Kucherov unveiled that HgO catalyzed the hydration of alkynes, an unfeasible process under non-catalyzed conditions.[1] Hg salts proved to be excellent catalysts for different transformations, in particular those involving unsaturated C–C bonds. Based on this, Hg-based industrial processes were launched in the first half of the 20th century to manufacture important bulk chemicals, such as acetaldehyde. However, toxicity issues bloomed with time and Hg catalysis was systematically substituted in industry and research work on it has diminished.

Au, Pt, and Hg (in this order) are the catalytic atoms most affected by relativistic effects.[2–4] These perturbations in atom electronics introduce some similarities between them. Thus, after the discovery by Haruta[5] that gold nanoparticles were excellent catalysts for different reactions, researchers looked back into reactions catalyzed by Hg and replaced this by gold catalysts. Nevertheless, the expectations for gold surpassed those of Hg and has lead to new catalytic systems. In this Review we have attempted to present the possibilities of Au and Pt for reactions where Hg has been demonstrated to be an efficient catalyst.

2. Aims of the Review

The main aim of this Review is to give a general overview of the behavior of Pt, Au, and Hg compounds as catalysts in organic synthesis.[6] In the first part, those atomic properties of Pt, Au, and Hg directly involved in the catalytic process will be discussed. In the second part, analogies and differences in the catalytic behavior of Pt, Au, and Hg compounds for eleven representative reactions will be analyzed and correlated to the structural and electronic properties of the metal center. Two of those transformations, namely the oxidation of methane to methanol and the hydration of alkynes, will be more deeply discussed. Finally, other aspects, such as toxicity, price, and availability will also be taking in account and put in context.

3. Atomic Configuration of Pt, Au, and Hg: Relativistic Effects

The main atomic properties of Pt, Au, and Hg are explained by relativistic properties (Figure 1). Several Reviews have been published in this respect.[2–4]

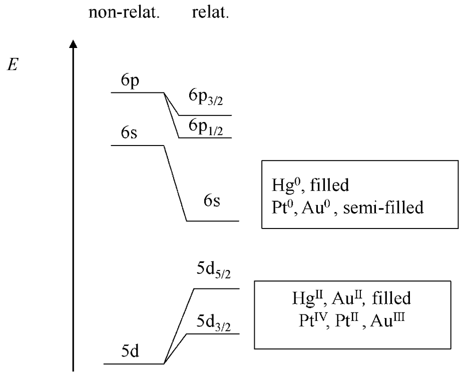


Figure 1. Schematic view of the molecular orbital energies for hypothetic Pt, Au, and Hg compounds before and after relativistic considerations.

Two main relativistic effects act on the atomic orbitals. The first one is the contraction of the 6s (and 6p) orbital in those elements with atomic number $Z > 70$. The mass of the 6s electrons (m: relativistic, m_0: non-relativistic) significantly increases in these elements since the relativistic radial velocity v (relative to the speed of light) becomes not negligible [Eq. (1)].

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$$m = m_0\sqrt{(1-(v/c)^2)}, \quad \langle v_r \rangle = Z; \\ \text{when } v \rightarrow c: \text{ relativistic effect} \qquad (1)$$

Since the Bohr radius of an s orbital is inversely proportional to m, contraction occurs. As an indirect effect, the contraction of the 6s orbital leads to the shielding of the 4f and 5d filled orbitals which, therefore, expand.

A second relativistic effect is the energetic spin-orbit splitting of the 6p (and 5d) orbitals since the sum of the orbital and spin angular momentum numbers ($j = l + s$) is also affected (Figure 1).

These two relativistic effects are only significant in some heavy metals, but particularly in Au, Pt, and Hg (in this order), and explain their "abnormal" electronic properties, including the high electronegativity and electron affinity, the large ionization potentials, and some other physical properties (Table 1).

Table 1: Electronic properties of Pt, Au, and Hg.

Metal	Electronic shell configuration	Oxidation states	Ionization potentials (1st/2nd) [eV]	Electronegativity [EN]	Electron Affinity [EA, kJ mol^{-1}]
Pt	[Xe]4 $f^{14}d^9 6s^1$	+2, +4	8.96/18.56	2.28	205.1
Au	[Xe]4 $f^{14}d^{10} 6s^1$	+1, +3	9.23/20.5	2.54	222.7
Hg	[Xe]4 $f^{14}d^{10} 6s^2$	+1, +2	10.44/18.76	2.00	<0

Since the highest occupied molecular orbital (HOMO) is stabilized for the corresponding metals (6s), the ionization potentials increase. This stabilization reaches its maximum in the "inert pair effect" observed for lead. Related to this, an extra electron will be stabilized in the low-lying lowest unoccupied molecular orbitals (LUMO) for Pt and Au (high electron affinity EA and electronegativity EN), something that will not occur with Hg since the 6s orbital is filled.

The macroscopic properties of these metals are also explained by the energy orbitals shown in Figure 1. Gold owes its yellow color to the decrease in the band gap between the 5d and the 6s orbitals that gives an electronic transition in the visible spectrum. Mercury is the only liquid metal at room temperature, a result of the stabilization of the 6s^2 pair that makes Hg–Hg interactions so weak that even monoatomic Hg is volatile.

The phenomenon called "aurophilicity"[7] is a particular characteristic of Au that also arises from the first relativistic effect. The electrostatic interaction of the destabilized 5d orbitals in Au^{I} complexes promotes Au–Au bonding through London forces at distances of around 3 Å, leading to intriguing effects. For instance, the EAs of mono-, di-, and tri-atomic gold follows the order $Au_3 > Au > Au_2$ (3.7, 2.3, and 1.9 eV, respectively). In contrast, the "metallophilicity" effect is not so pronounced, either for the isoelectronic Pt^0 (EAs 1.87, 1.90, and 2.1 eV for Pt_3, Pt_2, and Pt, respectively) because of the metal center tends to accommodate more ligands (4 or more), or for Hg^{II} because of the electropositive repulsion of the cations.

From a reactivity point of view, the orbital contraction leaves the LUMO in a low-lying level of energy in comparison with other transition metals of the same group, which translates into a higher Lewis acidity. In particular, as it can be seen in Figure 1, the LUMO for Au^{I} and Hg^{II} is the stabilized 6s orbital, thus their corresponding cationic metal salts can be considered as extremely "soft" Lewis species. Therefore, "soft" nucleophiles such as π C–C bonds would be preferentially activated in the presence of these "soft" metals, and this explains the high catalytic activity of Pt, Au, and Hg salts in reactions involving unsaturated C–C bonds.

4. Structural and Electronic Properties of Pt, Au, and Hg Compounds

Although Pt, Au, and Hg are all competent Lewis centers to activate soft C–H, C–C or C-Heteroatom bonds, the efficiency of the catalysis depends greatly on the type of compound (salt, complex or nanoparticle) involved. Thus, general electronic and structural properties for the different species must be considered before analyzing particular examples.

Avelino Corma was born in Moncófar, Spain, in 1951. He studied Chemistry at the Universidad de Valencia (1967–1973) and received his Ph.D. at the Universidad Complutense de Madrid in 1976. He was a Postdoc in the Department of Chemical Engineering at the Queen's University (Canada, 1977–1979). from 1990 to 2010 he was the director of the Instituto de Tecnología Química (UPV-CSIC) at the Universidad Politécnica de Valencia. His research is on catalysis, particularly synthesis, characterization, and reactivity in acid–base and redox catalysis. He is co-author of more than 800 articles and 100 patents on these subjects.

Antonio Leyva-Pérez was born in Sevilla, Spain, in 1974. He studied Chemistry at the Universidad de Valencia and received a Ph.D. degree from the Universidad Politécnica de Valencia in 2005, working on heterogeneous catalysis under the guidance of Prof. Hermenegildo García. He moved for postdoctoral studies to the group of Prof. Steven V. Ley at The University of Cambridge, U.K., working in the total synthesis of natural products. After two years, he joined the group of Prof. Avelino Corma at the Instituto de Tecnología Química (ITQ) in Valencia. His current research involves the development of metal-catalyzed organic reactions.

4.1. Pt, Au, and Hg Complexes[8]

The energy orbital diagram (Figure 1) also explains the more stable structures for the different oxidation states of Pt, Au, and Hg (Figure 2).

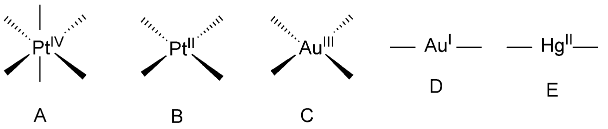


Figure 2. Main structures of Pt, Au, and Hg complexes.

$\mathrm{Pt^{IV}}$ is a d^6 species that needs six $2\,e^-$ donor ligands to achieve the stable $18\,e^-$ configuration (structure A). This saturated octahedral structure will hardly activate any incoming nucleophile, since the release of one ligand (giving a $16\,e^-$ species) is disfavored. In contrast, $\mathrm{Pt^{II}}$ complexes (B) are $16\,e^-$ square-planar structures that easily admit extra-coordination to a new molecule (to give an $18\,e^-$ species) or oxidative addition to form the corresponding $\mathrm{Pt^{IV}}$ complex (A).

$\mathrm{Au^{III}}$ complexes are isoelectronic with $\mathrm{Pt^{II}}$, d^8, and they also form $16\,e^-$ square-planar structures (C). $\mathrm{Au^{I}}$ is a d^{10} species that forms $14\,e^-$ linear structures (D). The occurrence of these linear $\mathrm{Au^{I}}$ complexes is explained by the high stabilization of the 6s orbital compared to the 6p (Figure 1): since the LUMO is exclusively composed by the 6s and the 6p orbitals, it has more s-character (ca. 50%). Thus, sp-hybridization occurs, giving the linear structure. In contrast to Pt, these $\mathrm{Au^{I}}$ low electron-count complexes do not tend towards oxidative addition, since the 5d orbital is filled. However, associative addition of an extra ligand is somewhat allowed (trigonal structures) when a significant π-back donation from the filled 5d orbitals to the ligands occurs, opening a way to incorporate reactants at the $\mathrm{Au^{I}}$ catalytic center.

As for $\mathrm{Au^{I}}$, the isoelectronic $\mathrm{Hg^{II}}$ species prefers to form $14\,e^-$ linear complexes (E). In this case, the access of the reactants must be preceded by the release of the ligands since a) no oxidative addition is possible, and b) associative addition hardly occurs since π-back donation from the $\mathrm{Hg^{II}}$ cation is less favored than in $\mathrm{Au^{I}}$. These general trends for the different oxidation states of Pt, Au, and Hg make important differences in the catalytic behavior of their compounds and should not be ignored.

4.2. Pt, Au, and Hg Nanoparticles

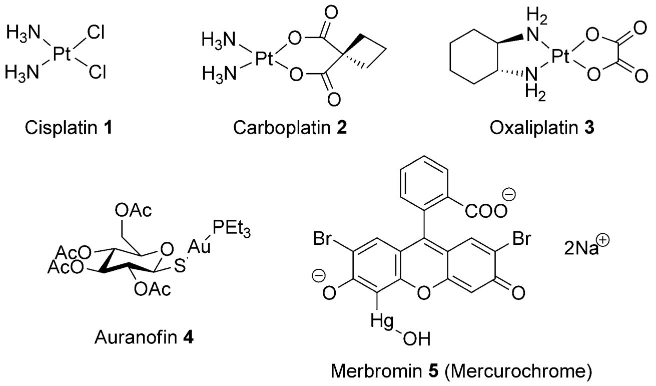
If metal nanoparticles are considered, physical structural parameters, such as size and shape, must be taken in account when analyzing the catalytic activity. Furthermore, potential interactions with the support and leaching effects can also play an important role on the activity and selectivity of the nanoparticle catalysts. However, this is only applicable to Pt and Au nanoparticles because Hg nanoparticles have not been described to date, probably because of the volatility of monoatomic Hg. Only recently the synthesis of HgO nanoparticles has been reported,[9] although no catalytic application was performed. Although catalysis by Pt[10] and Au[11] nanoparticles is a very active field, this will not be considered in this Review.

5. Toxicity, Price, and Availability

5.1. Toxicity

Toxicity of metals depends on bioavailability, accumulation, and excretion, interaction with cells, and their chemical nature, among other factors. The chemical nature of the compound plays a dramatic role since a particular element can be toxic or not depending on the compound considered. However, it is accepted that metals in cationic form, which coordinate the functional groups in biological systems or replace metals from the active sites, are dangerous species,[12] and it explains the different toxicity found for Pt, Au, and Hg.[13,14]

Platinum metal is not toxic while the salts and complexes indeed are. Cisplatin **1** and its analogues **2** and **3** have been used in the treatment of several cancer lines for more than three decades (Scheme 1).[15–17] The Pt atom binds thiol sulfurs and amino nitrogen atoms in proteins and nucleic acids with strong chemical bonds after ligand exchange. Thus, important undesired effects, such as nephrotoxicity, neurotoxicity, and more are regrettably found.

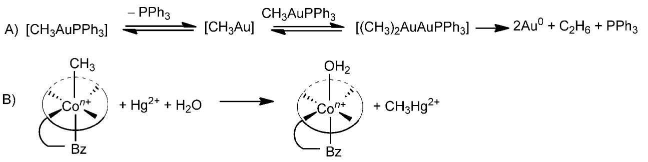


Scheme 1. Pt, Au, and Hg-containing drugs.

Gold metal is safe and is approved as a food additive by the EU. In contrast, gold salts and complexes are toxic, although some gold compounds, such as auranofin (**4**) have been used as antirheumatic agent for years.[18] Much controversy is still found for gold nanoparticles, which are currently used in many fields including catalysis,[11] optics,[19] and medicine. Toxicity issues seem to depend on the size, shape, and surface properties of the nanoparticles.[20] For instance,[21] particles small than 5 or bigger than 50 nm do not produce harmful effects, but those between 8 to 37 nm impart severe damage if injected intraperitoneally in mice. In another study,[22] 12.5 nm gold nanoparticles did not produce any specific tissue damage, including brain cells, and accumulation was proportional to the dosing level. However, other studies point to bioincorporation depending on both surface of the gold nanoparticle and cell type.[23] For gold clusters protected with monosulfonated triphenylphosphine, those ranging from 1.2 nm to 1.8 nm presented higher toxicity against various human cancer cell lines that those with smaller or larger sizes.[24]

Mercury metal is poorly absorbed by ingestion or skin contact and no severe damage can be observed in these cases. However, vapors are highly toxic since Hg is absorbed by the respiratory tract and then comes into the circulatory system. Mercury salts are highly toxic. But particularly damaging are the organomercurial compounds such as methyl- and dimethylmercury. The former was causing of the Minamata disease, one of the major disasters of the chemical industry, in where cationic methylmercury CH_3Hg^+, a by-product in the $HgSO_4$-catalyzed synthesis of acetaldehyde from acetylene (see Scheme 16), was systematically released into the Minamata Bay for 36 years and after bioaccumulating in fishes and seafood entered into the human diet. Two thousand people died and several thousands more were affected.

The environmental damage and toxicity caused by CH_3Hg^+ compared to CH_3Au or CH_3Pt^+ illustrates the subtle electronic differences that emerge from relativistic effects for the three metals. The strength of the σ M–CH_3 bond depends on its covalent character[8] that in turn depends on both the electronegativity and the softness of the metal. These two characteristics reach a maximum for Pt, Au, and Hg among the transition metals (see Table 1), thus strong M–CH_3 bonds should be expected, particularly for Au (electronegativity = 2.54). However, $AuCH_3$ and $PtCH_3{}^+$ are both unstable compounds that decompose spontaneously, unless stabilizing ligands are present.[25,26] In contrast, CH_3Hg^+ is a very stable cation that persists indefinitely in seawater or concentrated acidic solutions. The instability of $AuCH_3$ and $PtCH_3{}^+$ are explained by the ability of Au^I and Pt^{II} to accommodate additional ligands in their coordination spheres, which give access to intermolecular interactions that finally leads to decomposition pathways. For instance, in the case of gold, $AuCH_3$ decomposes to Au^0 and ethane after dimerization (Scheme 2 A)[25] but CH_3Hg^+ is a linear cation which high sp-character and tri-coordination is disfavored.



Scheme 2. A) Dimerization of methylgold(I) complexes and B) methylation of Hg^{II} by methylcobalamine. Bz = benzimidazole.

CH_3Hg^+ is so stable that serves to nature as shuttle in the Hg biocycle.[8,14,27] Methylcobalamine (the vitamin methyl-B_{12} co-enzyme) is a biological methylating agent that can alkylate Hg^{II} salts to CH_3Hg^+ in some seawater bacteria (Scheme 2 B). Reversibly, certain bacteria have a pair of enzymes, namely organomercury lyase and mercuric ion reductase, which cleave the Hg–C bond and reduce the corresponding cation to metallic Hg, respectively. The Hg^{2+} can combine with S^{2-} to deposit on soils or can form $Hg(CH_3)_2$ that, together with Hg^0, evaporates to the atmosphere. This mechanism allows Hg to become widespread in earth and it is the reason why Hg is considered a global pollutant. The retained Hg^0 bioaccumulates in shellfish and enters the trophic chain for humans. Pt and Au can also be methylated by methylcobalamine, but following a different mechanism.[27] It has been reported that organomercurial fungicides in amounts as low as 0.1 part per billion reduced phytoplankton photosynthesis in water.[28] However, other mercury compounds such as mercurochrome **5** have been used for years as pharmaceuticals.

A specific comparison between the three metals is rarely found in the literature.[29–31] However, as early as in the 19th century,[32] the higher disinfecting action of Hg, compared to Au and Pt compounds, was recognized. In plants, gold seems to be non-toxic[33,34] whereas Hg and Pt are potential poisons.[34]

From a practical point of view, toxicity of metal compounds has always to be considered and several metals including Hg have been released from the research activity due to "unacceptable" toxicity issues. However, from a scientific point of view, prejudices coming from accepted suppositions must be taken with care. A recent example was the case of thiomersal, a Hg-based preservative used in vaccines. After a supposed increase in autism cases upon vaccine administration in children, thiomersal was pointed out as the probable source of the problem, and was withdrawn from formulations. However, later studies clearly showed that no relationship existed between autism appearance and the Hg-based drug.

5.2. Price and Availability

Prices for the bulk metals and representative compounds are shown in Figure 3.

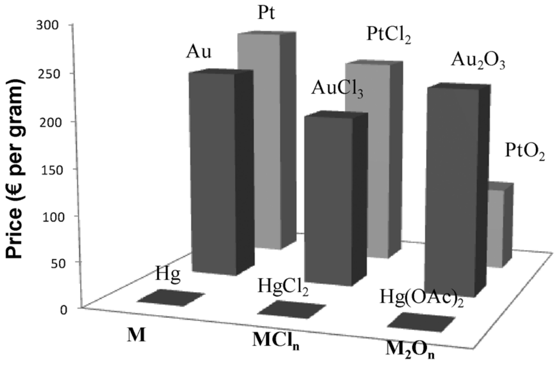


Figure 3. Prices for Hg, Au, and Pt compounds. Sources: London Metal Exchange (bulk), Sigma–Aldrich Co. (compounds).

Prices of Hg and derivatives do not exceed 1 Euro per gram, while Au and Pt derivatives are three orders of magnitude more expensive. This is related with the abundance and availability for each metal. Hg world reserves are estimated over 6×10^5 Tons, 1/3 of which is located in Spain. Mining has been nearly stopped in many countries. In contrast, Au reserves are estimated to be 1–2 orders of magnitude less, spread over many regions. For Pt, reserves are calculated as "platinum group metals" (Ru, Rh, Pd, Os, Ir, Pt) over 10^6 Tons, 80 % of which is located in South Africa.

6. Catalytic Activity

The catalytic activity of Pt, Au, and Hg for some representative reactions is presented in Table 2. Examples of inter- and intramolecular C–H, C–C, C–O, and C–N bond formation, including different reaction pathways, such as oxidation, hydroaddition, or cascade cyclization, are covered. Catalysts have been selected in order to have a fair comparison under similar reaction conditions and do not strictly represent the best catalytic activity for each transformation, although, when possible, the optimum catalyst has been included.

A general order of reactivity could be $Au^{I} > Hg^{II} > Pt^{II} > Au^{III} > Pt^{IV}$. Generally Au^{I} shows the higher catalytic activity in most of the processes presented in Table 2 (compare entries 4–16, 21–25) although Pt^{II} complexes are clearly superior in some cases (compare entries 1–3, 17–20). It is relevant that some "old" Hg-catalyzed reactions are still superior (entries 31–34) or hardly surpassed by Pt and Au-catalyzed processes (entries 35–39), especially if considering that the results corresponding to Hg-catalyzed reactions come from publications before 1990, except those by Nishizawa's group with $Hg(OTf)_2$.[76]

To explain the order of reactivity, several details must be taken into consideration. The possible incorporation of additional ligands into the coordination sphere of Pt^{II} and Au^{III} opens the door to decomposition pathways under reaction conditions, so ligand stabilization is a key issue to achieve any catalytic activity. Moreover, the use of weakly coordinating ligands is also precluded for Pt^{IV}, Pt^{II}, and Au^{III} for the same reason, thus limiting the range of Lewis acidity for those metals. As discussed above (see Section 4), linear complexes of Au^{I} and Hg^{II} do not suffer these drawbacks and that is the reason for their inherent superiority as catalysts. In any case, when a suitable ligand is used in Pt^{II} complexes, a good modulation of the active center can be achieved and high catalytic activities are eventually obtained.

A case-by-case comparison of the reactions outlined in Table 2 follows below. A comprehensive study for the two first reactions, namely the oxidation of methane to methanol and the hydration of alkynes, will be given because of their particular relevance and the amount of information available.

6.1. Oxidation of Methane to Methanol[77,78]

Activation of C–H bonds is a key issue in chemistry.[79] In particular, activation of CH_4 (the strongest of the alkylic C–H bonds, 440 kJ mol^{-1}) is a primary challenge that was first tackled with platinum compounds.[78] The direct transforma-

Table 2: Comparison of the catalytic activity of Pt, Au, and Hg compounds for representative transformations.

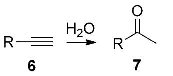
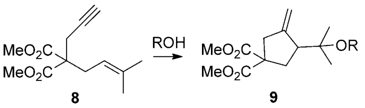
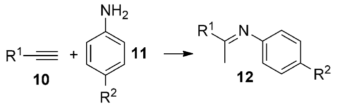
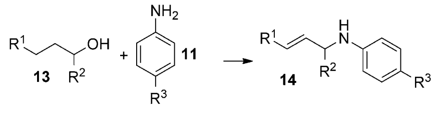
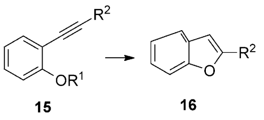
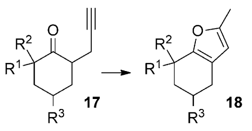
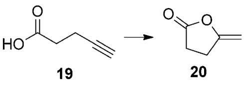
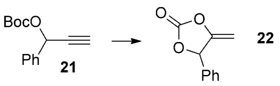
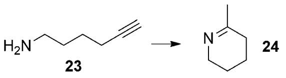
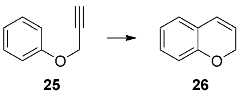
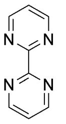
Entry	Transformation	Example	Catalyst (mol %)	Reaction Conditions	Yield [%]	Ref.
Intermolecular						
1	Oxidation of methane to methanol	$CH_4 \xrightarrow{H_2O} CH_3OH$	**27**-$PtCl_2$ (3.4)[c]	H_2SO_4 (conc.), 220 °C, 2.5 h	73	[35]
2			$Hg(OTf)_2$ (3.2)	H_2SO_4 (conc.), 180 °C, 3 h	43	[36]
3			Au_2O_3 (100)	H_2SO_4 (conc.), 180 °C, 1 h	<10	[37]
4	Hydration of alkynes	 **6** **7**	$PtCl_4$ (2)	CO atm., diglyme, 108 °C, 10 min	R = C_4H_9, 46	[38]
5			$[AuPPh_3CH_3]$ (0.01)/H_2SO_4 (2.5)	CO atm., MeOH, 70 °C, 1 h	R = C_6H_{13}, 99	[39]
6			$[AuPPh_3]NTf_2$ (1)	MeOH, RT, 24 h	R = C_6H_{13}, 93	[40]
7			$Hg(OTf)_2$·2 TMU (5)[a]	MeCN-DCM, RT, 12 h	R = C_9H_{19}, 96	[41]
8	Hydroxylative	 **8** **9**	$PtCl_2$ (5)	MeOH, 60 °C, 14–17 h	R = Me, 63	[42][c]
9	carbocyclization		$AuCl_3$ (5)		R = Me, 98	
10	of 1,6-enynes		$[Pt(MeCN)_2Cl_2]$/ 2 $AgSbF_6$ (5)		R = Me, 69	
11			$[AuPPh_3Cl]$/ $AgSbF_6$ (2)	MeOH, RT, 3 h	R = Me, 84	[45][d]
12			$PtCl_2$ (10)	Acetone, 40 °C, 17 h	R = H, 57	[44]
13			$Hg(OTf)_2$ (10)	$MeNO_2$-MeCN (9:1), RT, 20 h	R = H, 90	[47e]

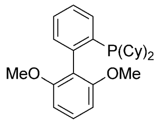
Table 2: (Continued)

Entry	Transformation	Example	Catalyst (mol %)	Reaction Conditions	Yield [%]	Ref.
14	Hydroamination of alkynes		$PtBr_2$ (0.3)	None, 60 °C, 10 h	$R^1 = C_4H_9$-, $R^2 = H$, 14	[48]
15			**28**-$AuNTf_2$ (2.5)[c]	DCM, RT, 24 h	$R^1 = C_6H_{13}$-, $R^2 = Me$, 68	[49][e]
16			$HgCl_2$ (5)	THF, RT, 6 h	$R^1 = C_6H_{13}$-, $R^2 = H$, 69	[51][f]
17	Amination of allyl alcohols		**29**-[Pt(cod)Cl_2] (1)[c]	DMF, 60 °C, 20 h	$R^1 = R^2 = Ph$, $R^3 = H$, 91	[53][g]
18			$AuCl_3$ (2)	CH_3CN, 50 °C, 3 h	$R^1 = R^2 = Ph$, $R^3 = I$, 84	[55]
19			**30** (2)-[Pt(cod)Cl_2](1)[c]	dioxane, 100 °C, 6 h	$R^1 = R^2 = R^3 = H$, 86	[56][h]
20			$HgBF_4$ (1)	THF, 65 °C	$R^1 = R^2 = R^3 = H$, 40	[58] [59]
21	Cyclohydroalkoxylation of alkynylphenols		$PtCl_2$ (5)	Toluene, RT, 3 h	$R^1 = H$, $R^2 = C_3H_7$, 83	[60]
22			[$AuPPh_3Cl$]/AgOTf (2)	Toluene, RT, 30 min	$R^1 = H$, $R^2 = Ph$, 95	[61]
23			$Hg(O_2CCF_3)_2$ (100)	THF, 25 °C, 15 min	$R^1 = Me$, $R^2 = C_3H_7$, 51[b]	[62]
24	Cycloisomerization of alkynones		[$AuPPh_3Cl$]/AgOTf (2)	Toluene, RT, 1 h	$R^1 = R^2 = H$, $R^3 = Me$, 80	[63]
25			$Hg(OTf)_2$ (5)	Benzene, RT, 30 min	$R^1 = R^2 = Me$, $R^3 = H$, 98	[64]
26	Oxycarbonylation of alkynes		[$AuPPh_3Cl$]/K_2CO_3 (10)	DCM, RT, 3 h	95	[65][i]
27			$AuCl_3$/K_2CO_3 (10)	DCM, 40 °C, 6 h	0	
28			$Hg(O_2CCF_3)_2$ (10)	DCM, RT, 2 h	81	[67]
29	Cyclization of propargyl *tert*-butyl carbonates		[$AuPPh_3$]NTf_2 (1)	DCM, RT, 10 h	74	[68][j]
30			$Hg(OTf)_2$ (5)	DCM, RT, 30 min	62	[70]
31	Cyclization of aminoalkynes		[PtH$(PEt_3)_2$]NO_3 (1)	DCM, 40 °C, 20 h	12	[71][k]
32			$AuCl_3$ (1)		24	
33			$AuCl_3$ (1)	MeCN, 82 °C, 20 h	40	
34			$Hg(NO_3)_2\cdot H_2O$ (1)		80	
35	Carbocyclization of arylalkynes		$PtCl_2$ (5)	Toluene, RT, 12 h	3	[73]
36			$PtCl_4$ (5)		19	
37			$AuCl_3$ (5)		6	
38			**31**-$AuSbF_6$ (1)[c]	DCM, RT, 1 h	62	[74]
39			$Hg(OTf)_2\cdot(TMU)_3$ (10)	MeCN, RT, 24 h	50	[75]

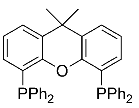
[a] TMU: tetramethylurea, DCM = CH_2Cl_2. [b] After removal of Hg with $NaBH_4$. [c] See also Refs. [43,44]. [d] See also Ref. [46]. [e] See also Ref. [50]. [f] See also Ref. [52]. [g] See also Ref. [54]. [h] See also Ref. [57]. [i] see also Ref. [66]. [j] See also Ref. [69]. [k] See also Ref. [72]. [l] Ligands **27**–**31**



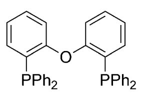
bpym, **27**



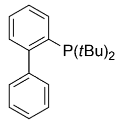
SPhos, **28**



XantPhos, **29**



DPEphos, **30**

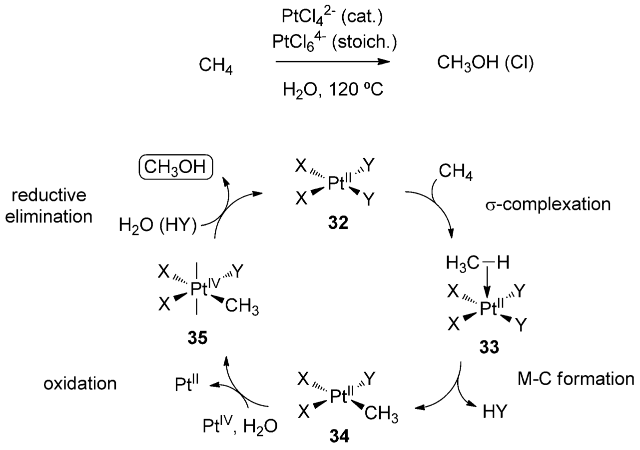


SPhos, **31**

tion of CH_4 to liquids, and more specifically to CH_3OH, is very challenging and of extreme relevance.

6.1.1. Platinum Catalysts

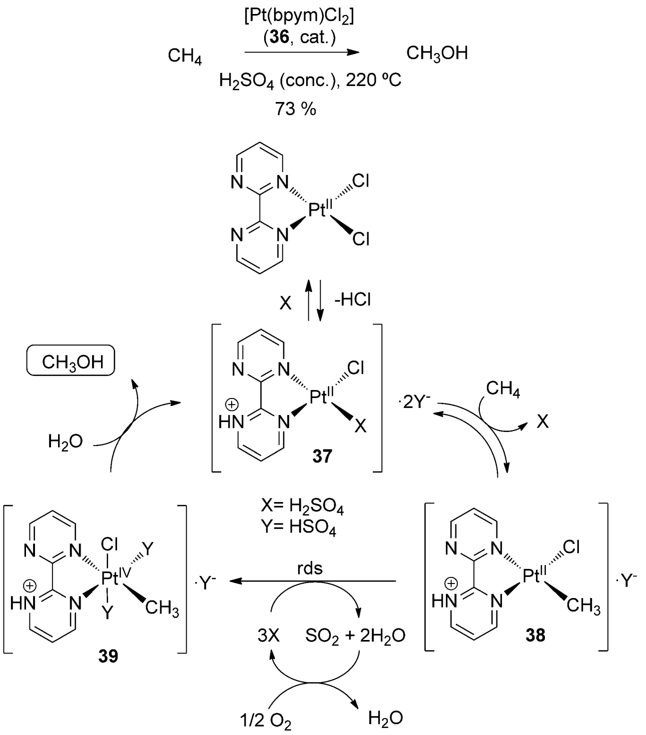
Platinum compounds showed early success as catalysts in CH_4 activation.[78] Based on the observation that H/D exchange occurred in alkanes with Pt salts in aqueous acid media, Shilov and co-workers used $[PtCl_4]^{2-}$ in water at 120 °C to transform methane in methanol (and chloromethane, Scheme 3).[80,81] To regenerate the catalyst, a stoichiometric oxidant ($[PtCl_6]^{2-}$) must be employed.



Scheme 3. Plausible mechanism for the Shilov's reaction.

The first reaction event in Scheme 3 consists of the σ-coordination of the C–H bond to form **33** through an associative (direct CH_4 coordination in the equatorial position as a fifth ligand) rather than a dissociative (loss of ligand Y, then coordination) mechanism. Then, according to deuterium exchange, a Pt–H bond should be formed, and this metal–H bond formation is thermodynamically favored in Pt (Pt–H, 335 $kJ\,mol^{-1}$) with respect to Au (Au–H, 292 $kJ\,mol^{-1}$) or Hg (Hg–H, 40 $kJ\,mol^{-1}$). After H removal as HY and formation of the intermediate **34**, oxidation of Pt^{II} to Pt^{IV} occurs to form the 18-electron intermediate **35** that finally collapses into the original catalyst **32** and the final reaction product. Unfortunately, Shilov's system showed little efficiency and poor stability, and Pt^0 was found after reaction. The presence of acids avoided Pt black formation, although an excess of acid inhibited H/D exchange.

Despite this, the Shilov type-chemistry is considered a landmark in C–H activation and inspired the study of many other related systems. In a first approach, other oxidants, such as O_2/Cu, were tried with moderate success and, after diverse attempts to catalyze the conversion of methane into methanol, the "Catalytica" system arose (Scheme 4).[35] In this process, bipyrimidine **27** (bpym) behaves as a privileged ligand for Pt since it is able to stabilize the +II oxidation state under the reaction conditions, avoiding catalyst decomposition. The ligand itself is stable under the harsh acidic conditions required (H_2SO_4 conc.) and the catalyst can be formed in situ from insoluble $PtCl_2$ and bpym. The system gives methylsulfated ester, with 81 % selectivity and 72 % yield, which can be finally hydrolyzed to methanol. H_2SO_4 (conc.) plays a triple role as solvent of the complex, acidic stabilizer, and oxidant. The SO_2 formed during the reaction can be reoxidized by molecular oxygen and the reaction cycle is then closed.



Scheme 4. Mechanism for the Pt "Catalytica" system.

Mechanistically, the process by "Catalytica" is similar to that of Shilov in that the three elementary steps, C–H activation, oxidation, and functionalization, are involved. However, in the Catalytica process, the σ-methane complex (C–H) coordination seems to proceed through a dissociative rather than by an associative mechanism on the 14-electron, T-shaped complex **37** (H_2SO_4 can be considered as a weak coordinating ligand). This difference can be explained by the more cationic character of Pt^{II} in **37** than in **32**, which favors a cationic mechanism. The C–H scission is also different and no Pt–H bond is formed before complex **38**. Nevertheless, the exact mechanism is not clear and two different pathways, electrophilic substitution and σ-bond metathesis, have been proposed. Oxidation to **39** is the rate determining-step (rds). H/D exchange is observed in D_2SO_4 below 150 °C without CH_3OSO_3H formation, while oxidation of the complex $[PtCl_2(bpym)]$ (**36**) occurs in H_2SO_4 only above 150 °C. This indicates that C–C activation is faster than the oxidation step. Moreover, if an external Pt^{IV} source ($H_2Pt(OH)_6$) is added to the system, CH_3OSO_3H is formed below 150 °C, indicating that the functionalization step is also faster than the oxidation $Pt^{II} \rightarrow Pt^{IV}$. However, if the H_2SO_4 concentration is diminished (< 90 %), the rate-limiting step becomes the C–H activation and the overall reaction is mainly inhibited. This effect comes from the coordination of water (or methanol) to intermediate **37** instead of the low-coordinating H_2SO_4 (X), the Pt center being now not sufficiently cationic to form the weak σ C–H bond with CH_4.

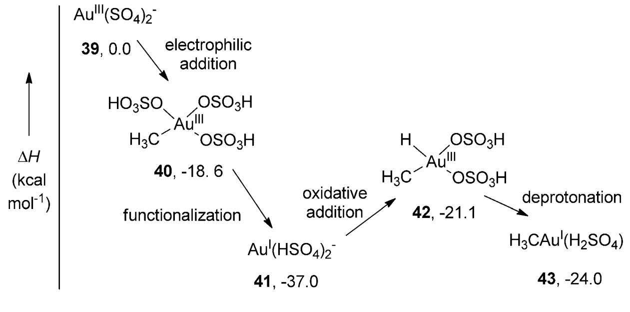
6.1.2. *Gold Catalysts*

Periana and co-workers also developed a catalytic system based on gold for the oxidation of methane to methanol [Equation (2) and (3)].[37]

$$Au_2O_3\text{ (1 equiv)} \xrightarrow[\substack{H_2SO_4\text{ (conc.), 180 °C}\\ 50\,\%}]{CH_4} CH_3OH + Au^0 \qquad (2)$$

$$CH_4 \xrightarrow[\substack{H_2SO_4\text{ (conc.), 180 °C}\\ <10\,\%}]{\substack{\text{Au (powder, cat.)}\\ H_2SeO_4\text{ (excess)}}} CH_3OH \qquad (3)$$

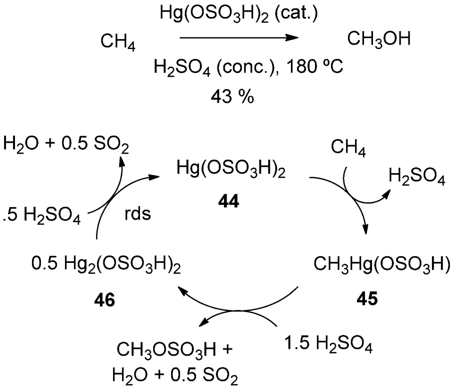
According to its electronic configuration (see Figure 1) and in contrast to Pt, Au does not follow a redox cycle and methanol is produced only if stoichiometric amounts of Au^{III} are used [Eq. (2)]. Under catalytic conditions, the catalytic cycle Au^I/Au^{III} [Eq. (3)] was only triggered when a more powerful oxidant than H_2SO_4 (H_2SeO_4) was used. Although a mechanistic proposal was not provided, some findings shed light about the possible reaction pathway (Scheme 5). Significant CH_3D formation suggests metal–CH_3 bond formation occurs, as it also happens for the Pt system. However, in contrast to the Pt catalyst, the oxidation of the complex is not the rate-determining step with Au since Au^0 is easily dissolved (oxidized) by the acidic mixture at a lower temperature (100 °C) than the one required for the catalytic reaction (180 °C). DFT calculations at the reaction temperature could not reveal if the active cationic species was Au^I or Au^{III}. According to the high cationic character of Au^{III} as sulfate, electrophilic substitution is thermodynamically favored (**40**), the energetic barrier is higher (+7.0 kcal mol^{-1}, not shown) than that of the pathway **41**→**43** (oxidative addition and deprotonation). However, taking into account that the initial species is Au^{III} and by calculating the relative population of gold species under the reaction conditions (Au^{III}:Au^I ≈2500:1), the energetic difference would be compensated and the Au^{III} pathway can be feasible. Besides, interconversion between species can occur, since the transformation **39**+**43**→**40**+**41** is exothermic (32 kcal mol^{-1}).



Scheme 5. DFT-calculated intermediates for the Au-catalyzed oxidation of methane to methanol.

6.1.3. *Mercury Catalysts*

As indicated in the introduction, Hg-catalyzed systems are often the seminal work to be mimicked by the other two metals. Indeed, the first efficient catalyst reported for this transformation was $Hg(OTf)_2$, developed as well by Periana et al.[36] at Catalytica. In this work, CH_4 was transformed to CH_3OSO_3H which was hydrolyzed to MeOH with an 85 % selectivity at 50 % conversion (43 % yield, Scheme 6).



Scheme 6. Hg-catalyzed oxidation of methane to methanol.

The first step in the reaction involves methane activation to form **45** after electrophilic substitution on $^{+}Hg(OSO_3H)$, according to its ionic character, although this assumption was not fully demonstrated. Computational studies were carried out later.[82] In any case, the methyl–metal intermediate **45** could be detected spectroscopically (NMR). In addition, an independently prepared sample of **45** reacted with D_2SO_4 to form CH_3D. More importantly, this sample gives all the corresponding products (methyl and mercurous bisulfate **46**, sulfur dioxide and methane) if heated at the reaction temperature in H_2SO_4. On the basis of the microscopic reversibility principle, this experiment definitively confirms the pathway **44**→**46**. Finally, the oxidation step **46**→**44** was also independently confirmed by heating **46** in H_2SO_4 to give **44** and SO_2 and resulted to be the rate-limiting step.

6.1.4. *Comparison of the Three Systems*

The "Catalytica" system clearly illustrates the different catalytic behavior of Pt, Au, and Hg as a function of their electronic properties. As it has been shown (see Figure 1), Pt is a switchable redox metal that uses the inner coordination sphere to accommodate the reactants and produce the reaction. Pt^{II} acts as activator of CH_4 while Pt^{IV} functionalizes the molecule. However, the metal becomes unstable[80,81] with time if not enough stabilization is provided by the ligands.[35] Gold(III), isoelectronic with Pt^{IV} but having a higher ionization potential, is able to functionalize the substrate under similar reaction conditions but only stoichiometrically, because the catalytic cycle does not operate. The Au^{I}/Au^{III} cycle starts under the action of a more powerful oxidant, but with moderate success. It is remarkable than the rate-determining step in these processes is not the CH_4 activation but the oxidation of the metal. Hg^{II} is very efficient as catalyst through an electrophilic mechanism and the key of this success is the stability of (methyl)mercury cations, since the high sp hybridization character of the linear bonds does not allow a third ligand to interfere with the metal center.

Hg is the most efficient catalytic metal for this transformation. Simple salts of Pt and Au are not sufficiently stable (Pt) or active (Au) to compete with the Hg-catalyzed system, and the requirement of additional ligands for Pt^{II} makes the system less appealing. From an economic point of view, the advantages of Hg are clear. However, the methylmercury intermediate involved (**45**) is extremely toxic and resembles to that responsible of the Minamata disease. Since the amounts of catalyst are high, the system presents major safety problems.

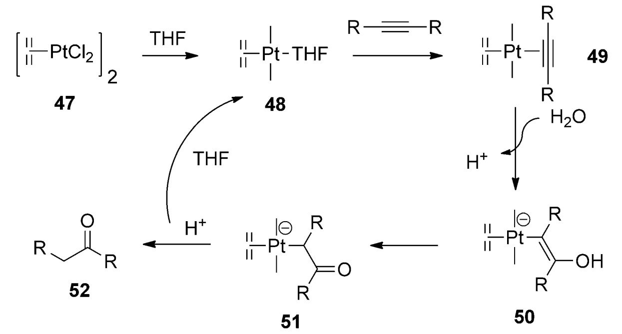
6.2. Hydration[83] and Hydroalkoxylation of Alkynes

Alkynes are suitable π-donors to be activated by π-Lewis acids, such as Pt, Au and Hg. The term "alkynephilicity" has been coined to illustrate the high affinity for these metals. It is worth mentioning that activation occurs similarly for other soft π-donors, such as alkenes,[4,84,85] but alkynes react preferentially in the presence of these metals by the inherent lower energy of the LUMO respect to alkenes. Among these reactions, the hydration of alkynes is a historically important, representative process since Hg-catalyzed production of acetaldehyde from acetylene was dominant in industry for several decades. Hydration can be considered a particular case of hydroalkoxylation reaction and, in fact, the most efficient processes are based on a hydroalkoxylation–hydrolysis sequence, thus they cannot be treated separately.

6.2.1. Platinum Catalysts

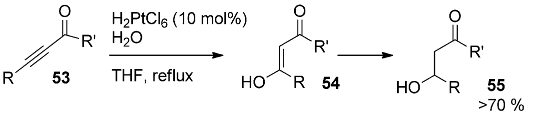
In the early 1990s, Pt was recognized as an active catalyst for the hydration of alkynes.[38,86–88] Firstly, Jennings and coworkers used Zeise's dimer **47** as a catalyst for the hydration of terminal and internal alkynes (Scheme 7).[86] The amount of catalyst needed was low (< 1 mol %) in boiling THF.

The mechanism they proposed suggests a cationic Pt species **48** that coordinates in a π-fashion the triple bond to give the cationic adduct **49**, which then is attacked by water to form the corresponding enol ether. A possible innersphere mechanism consisting in an intramolecular attack of water after coordination to Pt^{II} cannot be disregarded. In any case, the enol ether remains coordinated to Pt in **50** after a protonation regenerates the catalyst from **51** and releases the product **52**. Remarkably, hydroalkoxylation does not take place if MeOH is used as nucleophile instead of water. During the process, hydrogen bonds do not influence the reaction rate since no kinetic isotopic effect (KIE) is observed and acid addition does not accelerate the reaction. Indeed, the reaction is independent of [H_2O] and first order in alkyne concentration. Simple salts of Pt (PtX_2, X = Cl, Br, I) also performed well and the catalytic activity compared favorably with mercury catalysts (HgO, $HgSO_4$) in terms of selectivity.[87] However, the yields for internal alkynes were under 50 %.



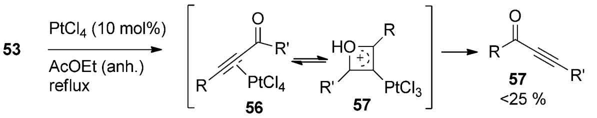
Scheme 7. Proposed mechanism for Zeise's dimer (**47**)-catalyzed hydration of alkynes.

Two years later, the group of Blum reported a H_2PtCl_6-catalyzed hydration of alkynones **53** [Eq. (4)].[88] In the same work, a curious $PtCl_4$-catalyzed 1,3-rearrengament of **53** under anhydrous conditions was described [Eq. (5)], although products **58** were obtained in low yields since one Cl^- ion from the catalyst can be incorporated instead to form the corresponding vinyl chlorinated compound.



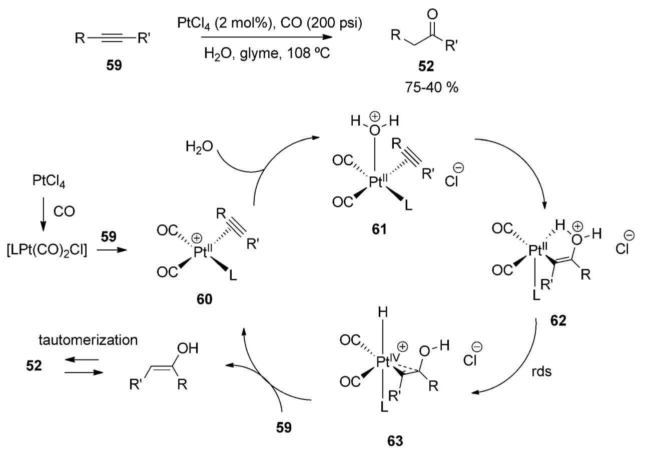
(4)

No mechanistic proposal was given for Equation 4, except that **54** is a by-product of the reaction that eventually disappeared if the initial amount of water was increased, **55** being finally the solely product of the reaction. Under strict anhydrous conditions a migration of the carbonyl occurred, leading to speculation that oxetane **57** was a possible intermediate. The same group reported later that $PtCl_4$/CO was a better catalyst for the hydration of alkynes (Scheme 8).[38,89]



(5)

Moderate yields for both terminal and internal alkynes **59** were found. The mechanism proposed[38] suggests a pre-reduction of Pt^{IV} to Pt^{II} under CO atmosphere to form the active species **60**. The catalytic activity observed for $PtCl_2$



Scheme 8. $[PtCl_4(CO)]$-catalyzed hydration of alkynes.

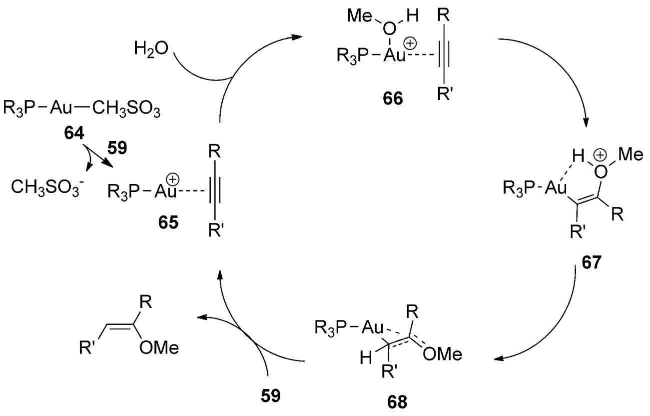
under similar conditions and X-ray photoelectron spectroscopy (XPS) measurements of the final mixture confirms this reduction. Differently from previous work,[86,87] a σ addition of water to Pt^{II} is firmly suggested, to form the $18e^-$ complex **61**. Intramolecular attack (**62**) followed by hydride transfer to Pt gives the Pt^{IV} complex **63**, which finally is reduced to **60** with the release of the product **52**. Observation of KIE suggests that **62**→**63** is the rate-limiting step of the reaction.

6.2.2. Gold Catalysts

Thomas and co-workers reported in 1976 that $HAuCl_4$ was able to catalyze the hydration of alkynes (Table 3, entry 1).[90] Unfortunately, only a couple of turnovers were achieved because metallic gold precipitates. However, a better performance of $HAuCl_4$ was found when compared to $HgCl_2$.

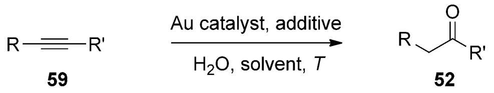
Utimoto and Fukuda[91] later found that $NaAuCl_4$ was more stable under similar reaction conditions and high yields of ketones were obtained (Table 3, entry 2). If water was not added to the reaction medium, MeOH acted as nucleophile and the corresponding acetals and one ketal were obtained in similar high yields. These results suggest that the hydration process comes from a previous hydroalkoxylation, although no mechanistic proposal was given. Curiously, diols do not give cyclic acetals.

Teles and co-workers, in a seminal paper, reported the use of cationic gold salts as catalysts for the hydroalkoxylation and hydration of alkynes (Table 3, entry 3).[92] The catalytic system was highly efficient with TOFs up to $5400\,h^{-1}$. The cationic Au was generated in-situ by different procedures, including Lewis acid-induced formation, protonation of the methyl derivative ($CH_4\uparrow$), and ligand exchange with the corresponding silver salt ($AgX\downarrow$). The so-formed active species **64** coordinates the alkyne **59** to start the catalytic cycle (**65**, Scheme 9).



Scheme 9. Early mechanism of the $[PR_3Au]^+$-catalyzed hydration of alkynes.

Table 3: Au-catalyzed hydration of alkynes.



Entry	Au catalyst (mol %)	Solvent	*T* [°C]	Additive	Alkynes	Yield [%]	Ref.
1	$HAuCl_4$ (33)	MeOH	reflux	–	terminal internal	<60 <40	[90]
2	$NaAuCl_4$ (2)	MeOH	reflux	–	terminal internal	>90 >90	[91]
3	$[AuPR_3X]$ X = Cl, CF_3CO_2, $MeSO_3$, NO_3, CH_3 (0.1–0.5)	MeOH	20–50	$BF_3{\cdot}OEt_2$ H_2SO_4, HBF_4, $MeSO_3H$	terminal internal	>95 >95	[92]
4	$[AuPPh_3CH_3]$(0.01–1)	MeOH	reflux	H_2SO_4, CF_3SO_3H	terminal internal	>95 40–90	[39]
5	$[Au^{III}Cl_xL_y]$ X = 1–3 (1.5–4.5)	MeOH	reflux	None, H_2SO_4, CF_3SO_3H	terminal internal	>95 >95	[93]
6	$[AuPPh_3L]$ L = CO_2R, SO_3R	THF or MeOH	25-reflux	$BF_3{\cdot}OEt_2$	internal	35–85	[94]
7	$[AuIPr]SbF_6$ (10–100 ppm)[a]	Dioxane or MeOH	120 °C	none	terminal internal	70–100 75–95	[95]
8	$[AuPR_3]NTf_2$ R = PPh_3, SPhos 28, $PtBu_3$ (0.5–5)	MeOH	25 °C	none	terminal internal	>95 >90	[40]

[a] IPr = 2,6-diisopropylphenylimidazol-2-ylidene.

As happened for water in the Pt-catalyzed hydration, it was proposed that methanol would coordinate the metal center to form the 16 e^- intermediate **66**. The formation of this intermediate was supported by ab-initio calculations and by the fact that the more hindered the alcohol, the lower the reaction rate. However, later studies have clearly shown that intermediate **66** is an artifact of the gas phase and that is quite unlikely in the liquid phase.[96] Moreover, later experimental work has demonstrated that the attack of oxygen[97a–98] and carbon[97b] nucleophiles on the gold–alkyne intermediate occurs preferentially through the opposite face of coordination (*anti*). In any case, the work by Teles and co-workers opened the door toward gold-catalyzed hydroadditons to alkynes and many of their assumptions are still accepted. For instance, although ab-initio calculations gave intermediates **67** and **68** are the more stabilized transition states, they also suggested that a double MeOH addition to form the ketal is energetically favorable.[92] Whatever the addition, single or double, the reaction pathway suggests a transition state where the C≡C has transferred a significant part of its π-electrons to the gold center to achieve a single C–C bond-type configuration, which allows free rotation (**68**).

The cation character of the Au center is of paramount importance for the reaction rate, as the rate with Au bound to weakly coordinating ligands ($CH_3SO_3^-$) clearly exceeds that when Au is coordinated to Cl (100 to 1). The influence of the ligand (PR_3) was also studied by Teles and co-workers,[92] and it was found that electron-poor ligands increased the reaction rate while decreased the stability of the complex. Thus, alkyl substituents performed more poorly than aryl groups, while $P(OPh)_3$ deactivates the catalyst faster than PPh_3. It could be thought that the higher activity of electron-poor phosphines fits the requirement of a more cationic Au^+ center, however back donation from the Au center to the alkyne does not contribute as much as π-donation of the alkyne to Au, thus the role of the ligand is mainly to stabilize the cationic center. In this sense, crowded tertiary phosphines seem to give the best results.[40]

Particular examples of hydration were also described by Teles and co-workers,[92] but Tanaka, Hayashi, and co-workers further developed the system towards hydration by preparing the catalyst from $[AuPPh_3CH_3]$ and acid (H_2SO_4 or CF_3SO_3H) in refluxing aqueous methanol (Table 3, entry 4).[39] Terminal alkynes were quantitatively hydrated to the corresponding ketones even at 0.01 mol% catalyst loadings, although internal alkynes only reacted moderately (0.2–1 mol% catalyst). The system was also highly efficient and TOFs up to 15 600 h^{-1} were obtained. It is remarkable that a CO atmosphere stabilizes the catalysts as much as the phosphine ligands. This observation correlates with the results obtained with $[PtCl_4(CO)]$.

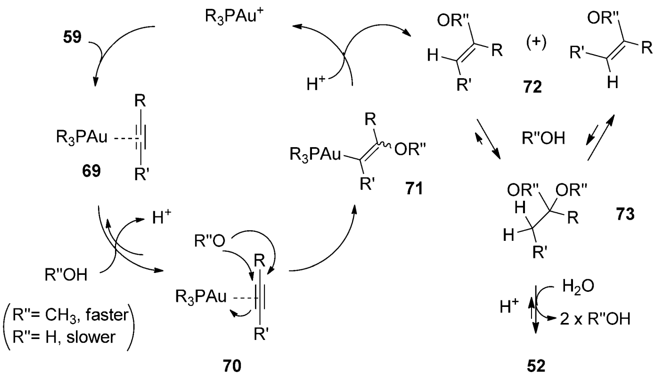
In spite of the resemblance between the Hayashi and Tanaka system and the Teles system, Hayashi and Tanaka proposed that the mechanism of hydration should be through direct attack of H_2O to the activated alkyne, without vinyl ether or ketal formation. The feasibility of the reaction in non-alcoholic solvents (particularly 1,4-dioxane) although in lower yields, and the similarity with Pt-catalyzed reactions supported this H_2O-attack mechanism.

Laguna and co-workers proposed a direct attack of H_2O when Au^{III} complexes are used as catalysts (Table 3, entry 5).[93] In contrast to the Au^I-catalyzed hydration of alkynes, cationic Au^{III} compounds do not catalyze the reaction in neutral medium, whereas anionic and neutral complexes do. Addition of acidic promoters increases the reaction yield and, at least, one of the ligands on the Au^{III} center must be Cl.

A further step was made by Schmidbaur and co-workers, who used isolated, instead of in-situ formed, cationic Au^I complexes as catalysts for the hydration of 3-hexyne (Table 3, entry 6).[94] As before, MeOH was the best solvent and the complex $[Au(PPh_3)(CO_2C_2F_5)]$ reached TOFs up to 3900 h^{-1} with $BF_3{\cdot}OEt_2$ as acidic promoter in refluxing methanol.

At this point, the use of acidic promoters seemed mandatory for those Au-catalyzed hydrations of alkynes where cationic Au complexes were used. However, two independent publications showed the possibility to avoid acids. In one, Nolan and co-workers used a N-heterocyclic carbene (NHC) ligand to stabilize the in-situ generated cationic Au complex ($[Au(IPr)Cl] + AgSbF_6 \rightarrow [AuIPr]SbF_6 + AgCl\downarrow$) and the resulting catalyst is the most efficient reported to date since loadings as low as 10 ppm were enough to complete the hydration (Table 3, entry 7).[95] Moreover, the versatility of the system is unprecedented at such low-loadings since internal alkynes are well transformed.

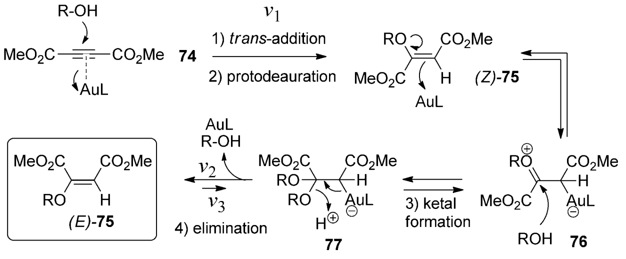
In the other publication, we reported that isolated $[AuPR_3]NTf_2$ complexes ($PR_3 = PPh_3$, SPhos, P*t*Bu_3) were active catalysts for alkyne hydration at room temperature, without the need of acidic promoters (Table 3, entry 8).[40] With these catalysts, both terminal and internal alkynes are transformed in high yields. A possible mechanism was proposed on the basis of kinetic studies (Scheme 10).



Scheme 10. $[AuPR_3]NTf_2$-catalyzed hydration of alkynes.

The first steps match those reported for the hydroalkoxylation of alkynes, giving intermediate **71** after alcohol coordination and inner- or outer-sphere attack. Kinetic evidence for a possible *syn* intramolecular (after coordination to Au) attack of the alcohol was found. However, later works have demonstrated that *anti*-addition occurs preferentially.[96–98] Proto-deauration restores the catalyst and releases the corresponding *E*-**72** vinyl ether. A fast isomerization to the more stable *Z*-**72** isomer (for diphenylacetylene, the molecule of study) was observed, which was explained by a second R″OH addition/elimination. Ketal **73** finally hydrolyzes to the corresponding ketone **52**. Control experiments in THF showed that MeOH is more efficient than H_2O in all these processes.

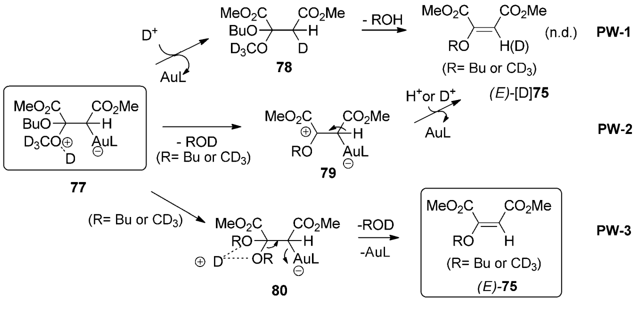
Ketal **73** is particularly informative as an intermediate when MeOH or H_2O are present in the reaction medium. In MeOH, the isomerization of vinyl ether **72** is faster. However, if H_2O is present, the equilibrium shifts towards ketone **52**. This clearly confirms the pathway **72**→**52**, although, at this point, a possible action of gold could be neither detected nor disregarded. Fortunately, the use of the more-stable vinyl ether **75**, coming from the hydroalkoxylation of dimethyl acetylenedicarboxylate (DMAD, **74**) under gold-catalyzed conditions, allowed the study of the addition/elimination step (Scheme 11).[98]



Scheme 11. Isomerization of vinyl ethers in the $[AuPR_3]NTf_2$-catalyzed alkoxylation of DMAD.

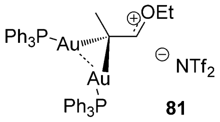
Kinetic and NMR spectroscopy experiments, including isotopically labeled molecules, assessed the initial formation of the *Z* isomer and showed that the gold catalyst indeed plays a role in the isomerization process: the initial rate of formation of the two isomers *Z*-**75** (v_1) and *E*-**75** (v_2) changed as a function of the nature of the gold catalyst (electron withdrawing (EWD), or electron donating (ED) phosphine). Moreover, the study of the elimination process also shows a possible participation of gold (Scheme 12).

When CD_3OD was used as a nucleophile on *Z*-**75** under gold catalysis, deuterated alkene *E*-[D]**75** should be expected as product. This could be formed either by proto-deauration and later alcohol elimination on **78** (pathway PW-1) or by the reverse process (alcohol elimination and then proto-deauration, PW-2). However, the final product detected was non-deuterated *Z*-**75** (PW-3), which implies that the double bond is formed by elimination of gold rather than by hydrogen elimination in intermediate **80**. In fact, gold could exert a directing effect, forcing the two ester groups to be eclipsed in the transition state and leading to the maleate *E*-**75** after deauration.



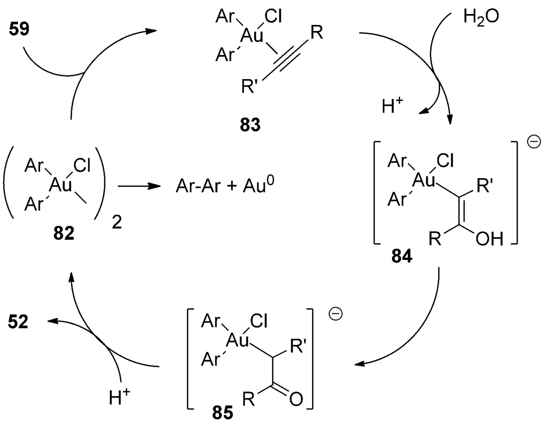
Scheme 12. Proposed elimination pathways from compound **77**.

These results are connected with recent studies by Fürstner and co-workers on the synthesis of diaurated species **81** (Scheme 13), and others.[99] These species would also explain the isomerization process observed for **75**.



Scheme 13. Fürstner's diaurated complex **81**.

The mechanistic studies above, together with the successfully adaptation of Teles' hydroalkoxylation method to the hydration reaction, and the fact that alcohols are usually the most active solvents, (Table 3, entries 1–5) suggest that direct H_2O addition to alkyne is hampered somehow under gold-catalyzed conditions. However, Laguna and co-workers proposed a mechanism based on the direct attack of H_2O when Au^{III} complexes are used as catalysts, and supported by different variable temperature NMR experiments (Scheme 14).[93]



Scheme 14. Au^{III}-catalyzed hydration of alkynes.

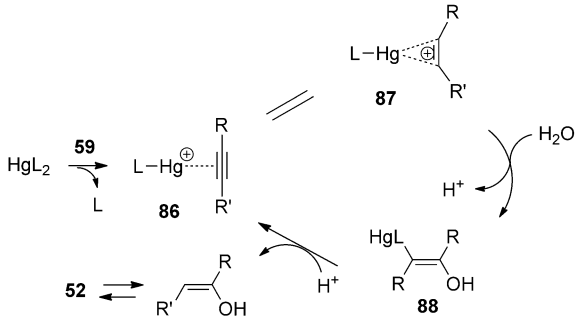
Alkyne **59** occupies the vacant coordination site in complex **82** to form **83** and then the hydroxy group attacks externally (**84**, detected by low-temperature NMR spectroscopy). Tautomerization and proto-deauration gives the starting catalyst **82** and ketone **52**. Reductive coupling of the aryl ligands leads to deactivation of the catalyst.

Lein and co-workers have studied theoretically the $AuCl_3$-catalyzed addition of H_2O to alkynes.[100] The results showed that two molecules of water are needed for the reaction to proceed, since a hydrogen-bonding network between the catalyst and the water molecules lowers the activation barrier and brings the reactive complex into place. Relativistic effects also play a role on the feasibility of the reaction.

With all these results it could be said that Au^I and Au^{III} compounds follow different reaction pathways when catalyzing the oxo-addition to alkynes. However, a possible reduction of Au^{III} to Au^I must not be disregarded.

6.2.3. *Mercury Catalysts*

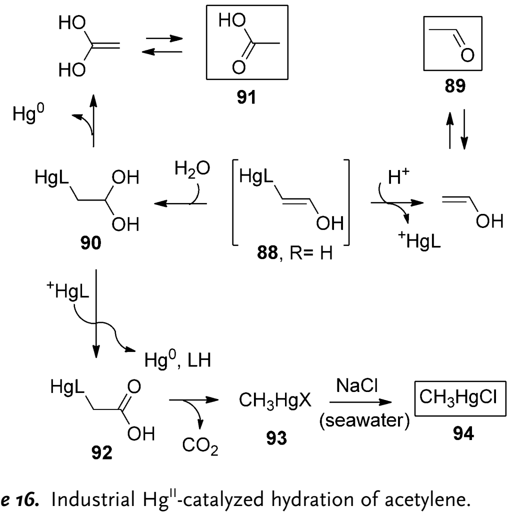
In 1884, Kucherov reported the use of Hg^{II} salts as catalysts for alkyne hydration.[1] Since then, many publications reported the use of mercury in different forms as a catalyst for the hydration of alkynes but, in general, none of them exceeded the activity shown by the Kucherov's catalyst, HgO/H_2SO_4. A possible mechanism for this early metal-catalyzed reaction is shown in Scheme 15.[83]



Scheme 15. Hg^{II}-catalyzed hydration of alkynes.

Alkyne coordination to Hg^{II} forms the cationic species **86** (**87** if taking into account that the most of the π-electronic density of the alkyne is transferred to the metal center) to which the hydroxy group is added. Then, the oxymercurial species **88** is proposed to be formed, in accordance with the well-known acetoxymercuration process. However, it is worth noting that **88** has never been isolated and it can only be speculated over its existence during the hydration process.

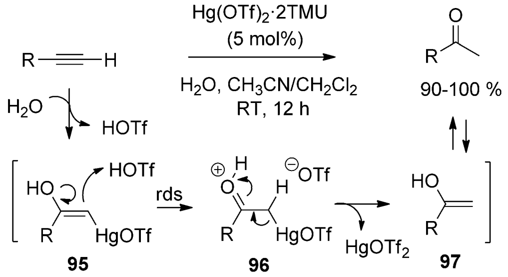
As was later shown for gold, the use of a low-coordinating counteranion lead to better results, as exemplified by the Hennion–Nieuwland catalyst, $HgO/BF_3{\cdot}OEt_2$.[101a] All these early advances in metal-catalyzed alkyne hydration lead to the development of industrial process based on the Hg-catalyzed hydration of acetylene, which gave access to many important oxygen-containing bulk chemicals and, in particular, acetaldehyde (Scheme 16).[76]



Scheme 16. Industrial Hg^{II}-catalyzed hydration of acetylene.

Following the reaction mechanism propose for the Kucherov's catalyst (Scheme 15), acetylene reacts with HgO and H_2SO_4 to give intermediate **88** which gives acetaldehyde **89** after proto-demercuration. However, a second H_2O addition to **88** can occur instead to give intermediate **90**. This intermediate has two possible reaction pathways: direct Hg reduction leading to acetic acid **91** or HgL-assisted oxidation to give intermediate **92** (with Hg reduction as well). **92** decarboxylates to give methylmercurial **93** which is finally transformed to chloromethylmercury **94** in seawater. This mechanism mainly explains the poisoning caused by mercury wastes from Chisso factory in Minamata Bay. The easy formation of toxic Hg species for different chemical pathways together with the biotransformations associated to Hg in microorganisms (see Section 5) has lead to the banning of Hg for industrial processes.

Recently, an alternative Hg^{II}-catalyzed hydration of alkynes that precludes formation of methylmercury species has been developed by Nishizawa and co-workers (Scheme 17).[41,76]



Scheme 17. $Hg(OTf)_2{\cdot}2TMU$-catalyzed hydration of terminal alkynes.

The use of the complex $Hg(OTf)_2{\cdot}2TMU$ (TMU: tetramethylurea) as the catalyst allows the smooth hydration of terminal alkynes at room temperature without methylmercury formation since the weak-coordinating ion OTf keeps Hg^{II} in the cationic form and thus precludes reductive pathways. The mechanism is similar to that for Kucherov's catalyst and the rate determining-step is **95**→**96**.[101b] Unfortunately, internal alkynes react only moderately under similar reactions conditions.

6.2.4. *Comparison of Platinum, Gold, and Mercury Catalysts*

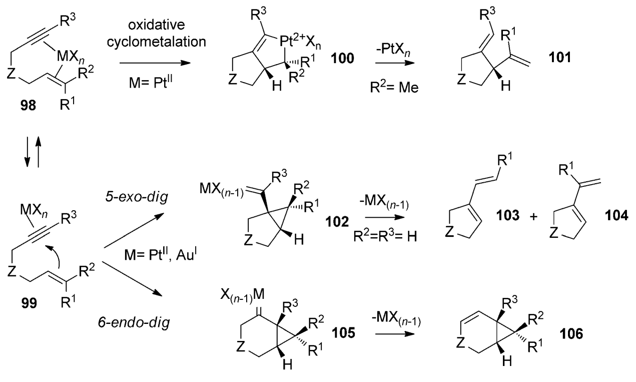
It is interesting to observe the analogies between Pt, Au, and Hg compounds as catalysts for the hydration of alkynes. The use of CO as a stabilizing agent for Pt^{II} and Au^{I} complexes or the higher activity of triflate-coordinated Au^{I} and Hg^{II} compared to the chloride complexes illustrate these analogies. In general, the d^{10} species Au^{I} and Hg^{II} are more active, particularly when bound to weakly coordinated ligands. In contrast, the d^{8} species Pt^{II} and Au^{III} are less active and weakly coordinated ligands apparently do not improve the catalytic activity. This behavior can be explained as a function of catalyst activity/stability. Au^{I} and Hg^{II} are diffuse linear cations that are hard to reduce to the elemental form under these reaction conditions ($E^0(Au^I) = 1.68 > E^0$-

(Au^{III}) = 1.50 V) . Although oxygen nucleophiles have little room to coordinate to the inner sphere of the complex, outer-sphere mechanisms for Hg^{II} and Au^{I} and, perhaps the addition of less-hindered nucleophiles (MeOH) for Au^{I}, circumvent this problem. Thus, an efficient cationic activation of the alkyne is achieved while maintaining a good stability of the cationic form of the metal throughout the process. In contrast, cations in high oxidation-states present transition states with more coordination sites, which give access to reductive elimination pathways.

A computational study at a fully relativistic level comparing the isoelectronic Au^{III} and Pt^{II} (as $AuCl_3$ and $[PtCl_2(H_2O)]$, respectively) as catalysts for nucleophilic additions to propyne has revealed that the nucleophilic attack is easier on the gold than in the platinum alkyne complex, confirming the superior activity of gold.[101c]

6.3. Hydroxylative Carbocyclization of 1,6-Enynes

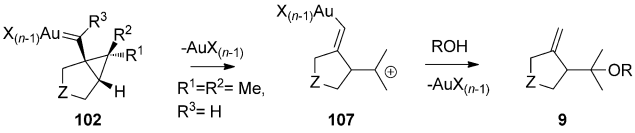
The cycloisomerization of enynes has been extensively reviewed from a mechanistic point of view (Scheme 18).[43,102]



Scheme 18. Pt^{II} or Au^{I}-cycloisomerization of enynes. Z = $C(CO_2Me)_2$, O, NR.

The square-planar Pt^{II} Lewis site is able to coordinate the alkyne and the alkene at the same time (**98**) while the linear Au^{I} is not (**99**). This way of coordination dramatically influences the reaction pathway. Pt^{II} can undergo oxidative cyclometalation (**100**),[47a,b] β-hydrogen elimination and reductive elimination to finally form the Alder-Ene-type product **101**. Au^{I}, in contrast, undergoes alkene attack to the alkyne, which can happen in two ways, 5-*exo-dig* and 6-*endo-dig*, finally giving products **103**/**104** and **106** after deauration. Pt^{II} and Au^{III} can also follow this reaction pathway, but less efficiently, owing to the competing di-coordination pathway.

The hydroxylative version comes from the 5-*exo-dig* pathway (Scheme 19). Intermediate **102** opens to give the carbocation **107** which is trapped by ROH to give **9**.

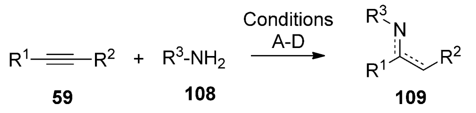


Scheme 19. Au^{I}-hydroxylative carbocyclization of 1,6-enynes. Z = $C(CO_2Me)_2$.

Au shows a higher catalytic activity for the hydroxylative carbocyclization of 1,6-enynes than Pt, independently of the species used (Table 2, compare entries 8, 9 and 10, 11), and it suggests that the greater the specificity to π-activate the alkyne in the presence of the alkene, the higher the reaction rate is. $AuCl_3$, however, led to erratic results[42] probably because of decomposition of the salt. The best results were achieved with ligand-stabilized cationic Au^{I} complexes (Table 2, entry 11). Phosphine-stabilized Au^{III}-catalyzed processes have been reported.[47c,d] Hg^{II}, like Au^{I}, also follows the 5-*exo-dig* pathway[47e] and thus activates selectively the alkyne to give product **9**, in better yields than Pt^{II} (Table 2, compare entries 12, 13) but less efficiently than Au (Table 2, compare entries 11–13).

6.4. Hydroamination of Alkynes

The intermolecular hydroamination of alkynes[59,103] was reported by Barluenga and co-workers with Hg catalysts in the 1980s.[51,52,104] $HgCl_2$, in catalytic amounts, allows the addition of aromatic amines to terminal and internal alkynes in good yields (Scheme 20, condition A).[51,104] When $Hg(OAc)_2$ was used, no catalysis was observed because Hg remains bound to the alkene (aminomercuration) and only after $NaBH_4$ reduction are the corresponding imines/enamines obtained. Alkyl amines only react in aminomercuriation processes.[52]

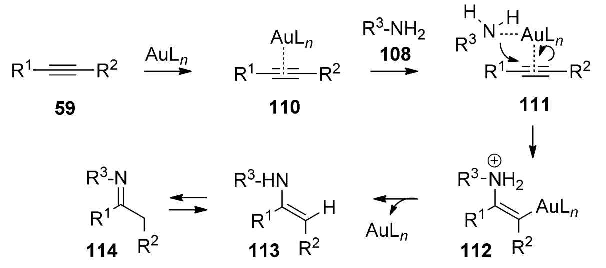


A) $HgCl_2$ (5 mol%), RT-60 °C, 1-6 h; R^1= alkyl, aryl, R^2= H, alkyl, R^3= aryl, 39-84 %
B) $PtBr_2$ (0.3 mol%), 60-100 °C, 10-20 h; R^1= *n*-butyl, Ph, R^2= H, R^3= Ph, 14-35 %
C) $AuPPh_3NTf_2$ (2-5 mol%), RT, 24 h; R^1= *n*-hexyl, Ph, R^2= H, R^3= alkyl, aryl, 57-95 %
D) $AuSPhosNTf_2$ (1-5 mol%), RT-80 °C, 24 h; R^1= alkyl, aryl, R^2= H, alkyl, aryl, R^3= aryl, 40-97 %

Scheme 20. Pt, Au, or Hg-catalyzed intermolecular hydroamination of alkynes.

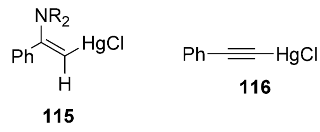
Pt^{II} has been also used as catalyst for the addition of aniline (**108**, R^3 = Ph) to alkynes, although yields were low (Scheme 20, condition B).[48] In contrast, Au^{I} complexes are highly active and, moreover, they can be recovered and recycled (Scheme 20, conditions C and D).[49] Curiously, the Au catalyst becomes selective for aromatic or alkylic substrates depending on the phosphine ligand and good selectivities are achieved for miscellaneous internal alkynes. Moreover, the nature of the phosphine ligand also influences the rate and reaction pathway and unexpected cascade reactions can be performed.[105]

Concerning the mechanism, it is widely accepted for Au that π-activation of the alkyne is the first step of the reaction (**110**, Scheme 21). Amine addition on the more electrophilic carbocation follows, although steric hindrance can modify the selectivity of the Markovnikov addition. It is still unknown whether the amine **108** attacks by an inner- or outer-sphere mechanism, although recent results with Au^I catalysts point to an inner-sphere mechanism (**111**). This proposal is based on reactivity issues and in-situ NMR spectroscopy experiments.[49] Regeneration of the catalyst after proto-deauration gives enamine **113** that may or may not tautomerize to imine **114**, depending on the nature of the substituents and the reaction conditions.



Scheme 21. Mechanism of the Au^I-catalyzed intermolecular hydroamination of alkynes.

No mechanistic proposal has been found for Pt. However, it is interesting to see the similarity between **112** and the intermediate **115**, proposed years before for the Hg-catalyzed hydroamination (Scheme 22).[52] No inner-sphere amine attack can occur in the case of Hg^{II} and thus a first σ-activated intermediate **116** is proposed and confirmed by reactivity experiments.



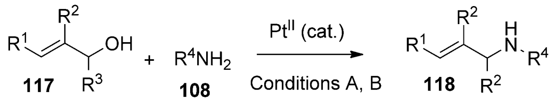
Scheme 22. Possible intermediates in the $HgCl_2$-catalyzed intermolecular hydroamination of alkynes.

Gold nanoparticles supported on chitosan catalyze the hydroamination of alkynes[106] which constitutes a rare example of a gold-supported catalyst for hydroaddition reactions.

6.5. Amination of Allyl Alcohols

The addition of amines to allyl alcohols is, in principle, a more convenient procedure to prepare allylamines that those based on Tsuji's chemistry (allyl cation generation from oxygen-derivatives, including carbonates, phosphonates) since water is the only by-product of the reaction. Recently, two groups[53,54,56] have reported the use of Pt^{II} phosphine complexes as efficient catalysts for this transformation (Scheme 23).

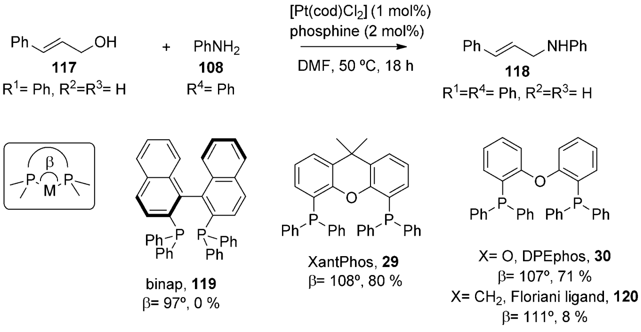
The nature of the phosphine ligand has a dramatic effect on the reactivity. The bite angle of the phosphine is particularly important in this respect (Scheme 24), although other factors, such as the oxygen in the structure of XantPhos **29** and DPEphos **30** are important.



A) $[Pt(cod)Cl_2]$ (1 mol%), XantPhos **29** (1 mol%), toluene or DMF, 60 °C, 1-6 h, microwave; R^1= H, alkyl, aryl, R^2= H, alkyl, R^3= H, alkyl, aryl, R^4= H, alkyl, aryl, 60-98 %

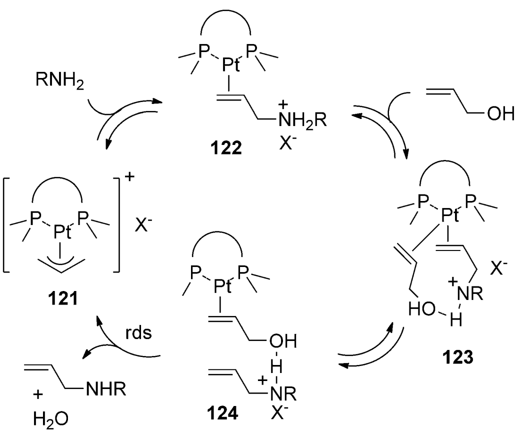
B) $[Pt(\eta^3\text{-allyl})(DPP\text{-}XantPhos)]PF_6$ (20 mol%), NH_4PF_6 (20 mol%), toluene/MeCN (1:1), 30-50 °C, 3-20 h, R^1= H, Ph; R^2= R^3= H, R^4= H, alkyl, aryl, 66-98 %

Scheme 23. Pt^{II}-catalyzed amination of vinyl alcohols.



Scheme 24. Influence of the bite angle of the phosphine ligand on the Pt^{II}-catalyzed amination of vinyl alcohols.

The mechanism has been well-studied, including DFT calculations,[53,54] and it starts with the reduction of Pt^{II} to Pt^0 by β-hydrogen elimination of a coordinated allyl alcohol (Scheme 25, **121**). The allyl cation so-generated is attacked by



Scheme 25. Proposed mechanism for the Pt^{II}-catalyzed amination of vinyl alcohols.

the amine while bound to the Pt^{II} center to give **122**. Then, an associative mechanism allows a second molecule of allyl alcohol to coordinate to the Pt center and form the $18e^-$ complex **123**. Release of product with concomitant dehydration of the allyl alcohol gives the original $16e^-$ complex **121**, which is ready to start a new catalytic cycle. This last step is irreversible and also the rate-determining step of the reaction, since all the other steps are in equilibrium.

The catalytic enhancement produced by these phosphines with Pt^0 cannot be translated to the isoelectronic Au^I and Hg^{II} species because these form linear complexes, precluding any chelating effect. Thus, results achieved with these metals are modest (Table 2, compare entries 17–20) although they can perform well in particular cases.

6.6. Cycloalkoxylation of Alkynylphenols

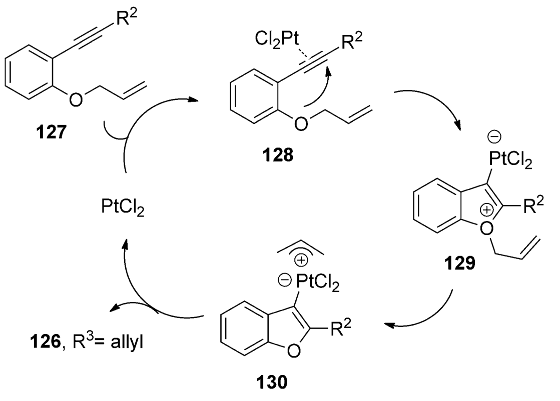
Larock and Harrison reported in 1984 the synthesis of benzofuranes by solvomercuration of aryl acetylenes (Table 2, entry 23).[62] Hg remains attached to the heterocycle, thus the process is non-catalytic and the corresponding benzofurane is obtained only after $NaBH_4$ reduction (Scheme 26, condition A).

A) $Hg(OX)_2$ (X= OAc, O_2CCF_3, 100 mol%), CH_3COOH or THF, 25 ºC, 30 min, then NaCl; R^1= Me, R^2= alkyl, aryl, R^3= HgCl, 30-70 %
B) $PtCl_2$ (0.5-5 mol%), toluene, 80 ºC, 1-5 h; R^1=R^3= H, R^2= alkyl, aryl, 88-98 %
$PtCl_2$ (5 mol%), toluene, 80 ºC, 1-12 h, R^1= R^3= allyl, benzyl, R^2= alkyl, aryl, 54-98 %
C) $AuPPh_3Cl$ / AgOTf (2 mol%), DCM, RT, 20-60 min, R^1=R^3= H, R^2= alkyl, aryl, 84-98 %

Scheme 26. Pt^{II}, Au^I, or Hg^{II}-promoted cycloalkoxylation of alkynylphenols.

The catalytic version has been achieved with other metals,[103] in particular palladium,[103b] and the Pt^{II}-catalyzed formation of benzofuranes was finally reported by Fürstner and Davies (Scheme 26, condition B).[60] The method also allows 2,3-functionalization of the final benzofurane **126** by using allylated or benzylated phenols **127** as the starting material (Scheme 27).

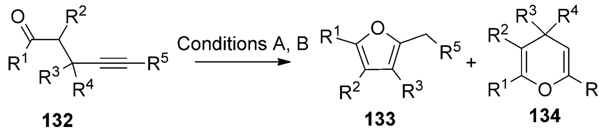
Pt^{II} activates the alkyne towards the nucleophilic addition of the oxygen atom in a Markovnikov fashion (**128**), as found for the intermolecular hydroalkoxylation of alkynes (see Section 6.2.), to give intermediate **129**. The allyl cation thus generated shifts to the more nucleophilic position (C–Pt, intermediate **130**) and the catalyst is regenerated after product release. The possible coordination of the alkene to the Pt^{II} center is not mentioned, but a competitive alkyne/alkene coordination to Pt^{II} cannot be discarded as it occurs with other enynes.[43,102] It would explain the higher amount of catalyst (5 mol %) needed to perform the reaction in comparison to free OH phenols (0.5–5 mol %). Au catalysis[103a] allows the use of milder conditions with similar high yields (Scheme 26, condition C, see also Table 2, entry 22).[61]



Scheme 27. Possible mechanism for the Pt^{II}-catalyzed cycloalkoxylation of alkynylphenols.

6.7. Cycloisomerization of Alkynones

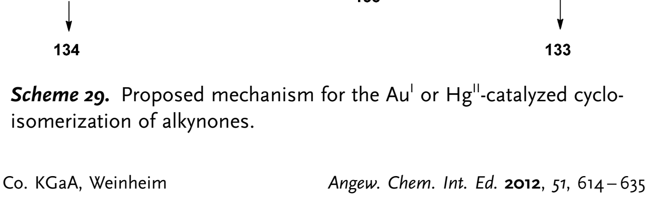
Furanes **133** are efficiently formed from alk-4-yn-1-ones **132** under Au^I, Au^{III}, or Hg^{II}-catalyzed conditions (Scheme 28).[63,64,103a] Au^I complexes are more efficient than Au^{III} salts but $Hg(OTf)_2$ shows a comparable catalytic activity to Au^I (Table 2, entries 24,25).



A) $AuPPh_3Cl$ / AgOTf (2 mol%), p-TsOH (only for **133**, 5 mol%), toluene, RT, 20-120 min; R^1= alkyl, aryl, R^2= H, alkyl, R^3= H, aryl R^4= H, R^5= H, aryl, **133**, 57-87 %
R^1= alkyl, aryl, R^2= H, R^3= alkyl, aryl, R^4= alkyl, R^5= alkyl, aryl, **134**, 53-67 %
B) $Hg(OTf)_2$ (1-5 mol%), benzene, RT, 0.5-6 h;
R^1= alkyl, aryl, R^2=R^3= H, R^4= ester, R^5= H, **133**, 70-98 %
R^1= Ph, R^2= R^3= R^4= H, R^5= Me, **134**, 67 %

Scheme 28. Au^I or Hg^{II}-catalyzed cycloisomerization of alkynones.

Different furanes **133** are formed under Au^I-catalyzed conditions (condition A) but the scope is narrower for Hg^{II} catalysis (condition B). The mechanism for both Au and Hg is similar and involves *5-exo-dig* attack of the ketone (or tautomeric enol) to the π-activated alkyne (intermediate **135**) with subsequent proto-demetalation and isomerization to give product **133** (Scheme 29). It is suggested that TsOH improves the reaction rate in Au^I catalysis owing to the



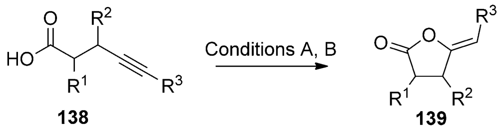
Scheme 29. Proposed mechanism for the Au^I or Hg^{II}-catalyzed cycloisomerization of alkynones.

tautomerization of the ketone and the easier proto-deauration.[63]

If the α-position to the triple bond is blocked, a 6-*endo-dig* mechanism operates and the 4*H*-pyrans **134** are formed. Curiously, the single substituent at the terminal position of the alkyne is enough to promote the formation of 4*H*-pyrans under Hg^{II} catalyzed conditions (Scheme 28, condition B).

6.8. Intramolecular Oxycarbonylation of Alkynes

The oxycarbonylation of alkynylcarboxilic acids **138** was reported with Hg^{II} catalysts in 1978.[107] Later optimized,[67] good yields of enol lactones **139** were obtained (Scheme 30, condition A, see also Table 2, entry 28).

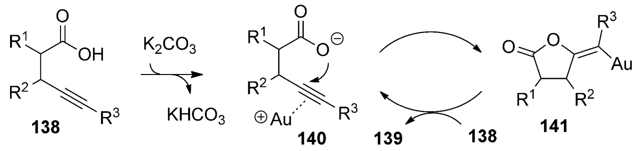


A) $Hg(OX)_2$ (X= OAc, $OCCF_3$, 10 mol%), DCM, RT, 0.5-48 h;
R^1= H, R^2= H, Ph, R^3= H, Me, $SiMe_3$, halogen, 49-86 %
B) AuCl / K_2CO_3 (10 mol%), MeCN, 20 °C, 2h;
R^1= H, NHFmoc, R^2= H, Me, R^3= H, *n*Bu, Ph, halogen, 60-98 %

Scheme 30. Au^I or Hg^{II}-catalyzed intramolecular oxycarbonylation of alkynes.

The Au-catalyzed version requires the use of base in catalytic amounts.[65,103a] Yields are similar and *Z*-enol lactones are typically formed. The scope with both catalysts is reasonable although silylacetylenes do not react under Au-catalysis while they do with Hg catalysts.

The mechanism of the Au^I-catalyzed reaction involves π-activation of the alkyne after deprotonation of the acid (intermediate **140**), 5-*exo-dig* attack of the nucleophilic oxygen, and final proto-deauration of intermediate **141** with another carboxylic group **138** that re-enters the cycle (Scheme 31).[65,66]

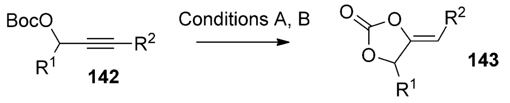


Scheme 31. Proposed mechanism for the Au^I-catalyzed intramolecular oxycarbonylation of alkynes.

Curiously, if Au^{III} is used instead of Au^I, dimerization of intermediate **141** occurs to give lactone dimers, although in low yields.[65b] No mechanistic proposal was formulated for the Hg^{II} system, but it should follow a similar pathway than Au^I.

6.9. Intramolecular Cyclization of Propargyl tert-*Butyl Carbonates*

A variant of the above-described cyclization of alkynylcarboxylic acids is that using Boc-protected carbonates **142** (Scheme 32). In this case, carbonates **143** are formed under

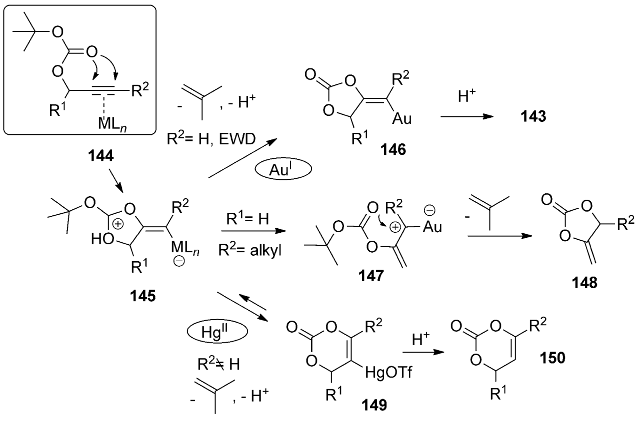


A) $[AuPPh_3NTf_2]$ (1 mol%), DCM, RT,1-24h;
R^1= H, alkyl, aryl, R^2= H, alkyl, halogen, ester, NR_2, 60-100 %
B) $Hg(OTf)_2$ (5 mol%), DCM, RT, 5-30 min;
R^1= H, alkyl, aryl, R^2= H, 62-99 %

Scheme 32. Au^I or Hg^{II}-catalyzed intramolecular cyclization of propargyl *tert*-butyl carbonates.

Au^I or Hg^{II}-catalysis.[68–70,103a] While the intramolecular cyclization of carbonates is not restricted to *tert*-butyl carbonates and other examples with either Au, Pt, or Hg catalysts can be found, we have not found other examples to specifically compare two, or all three, of these metals.[108a–c]

Although a higher amount of $Hg(OTf)_2$ is needed to obtain similar results than with $[AuPPh_3]NTf_2$ (Table 2, compare entries 29,30), both metals are effective and cyclic carbonates **143** are obtained in high yields. However, striking differences are observed depending on the nature of the alkyne substituent group (R^2) on the substrate. If $R^2 = H$, both catalysts behave similarly but if $R^2 \neq H$ two alternative pathways are followed: 5-*exo-dig* for Au^I and 6-*endo-dig* for Hg^{II} (Scheme 33).

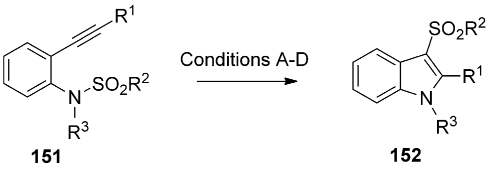


Scheme 33. Possible reaction pathways for the Au^I or Hg^{II}-catalyzed intramolecular cyclization of propargyl *tert*-butyl carbonates.

The common intermediate **145** can rearrange or not to give the final 5-membered cyclic carbonates **143** and **148**. However, a 6-membered cyclic carbonate is favored under Hg^{II}-catalyzed conditions since **145** opens up and closes again to the thermodynamically preferred intermediate **149**, after nucleophilic addition on the other carbon atom of the alkyne.

6.10. Cyclization of Aminoalkynes

The metal-catalyzed intramolecular hydroamination of alkynylamines (R-NH_2) has been extensively studied by Müller and co-workers.[71,72] Of several Group 7–12 transition metals none of the Pt, Hg, or Au compounds showed superior catalytic activity, although Hg^{II} achieved good yields (Table 2, compare entries 31–34). However, it was reported earlier that $NaAuCl_4{\cdot}2H_2O$ was able to catalyze this transformation in high yields.[103,108d] In any case, if the free amine is substituted by a sulfonyl-protected amino group (R-NH-SO_2R) in *o*-alkynylanilines, the catalytic activity improves dramatically (Scheme 34).



A) $Hg(OTf)_2$ (1 mol%), DCM, RT,15-60 min;
R^1= alkyl, aryl, R^2= tolyl, R^3= H, 84-100 %
B) $AuBr_3$ (10 mol%), toluene, 80 °C,1 h;
R^1= H, alkyl, aryl, R^2= alkyl, aryl, R^3= alkyl, 44-95 %
C) $PtCl_4$ (same conditions as above)
R^1= *n*Pr, R^2= tolyl, R^3= methyl, 52 %
D) $PtCl_2$ (same reactant and conditions as above), 42 %

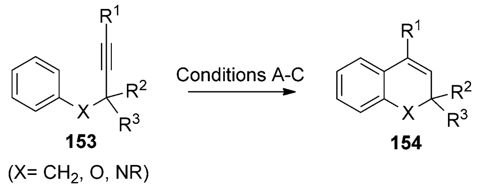
Scheme 34. Pt, Au, or Hg-catalyzed cyclization of *o*-alkynylsulfonylanilines.

$Hg(OTf)_2$ is a better catalyst in terms of catalytic activity and mildness (Scheme 34, condition A),[109a] although the scope is wider when using $AuCl_3$ (Scheme 34, condition B).[109b] $PtCl_4$ and $PtCl_2$ behaved similarly and showed poorer catalytic activity compared to $AuCl_3$ (Scheme 34, conditions C,D). The mechanism is similar to that of the intermolecular process (see Section 6.4).

6.11. Carbocyclization of Arylalkynes

The metal-catalyzed intramolecular hydroarylation of arylalkynes **153** is a convenient, atom-economical method to construct C–C bonds (Scheme 35).[110] The corresponding heterocycles **154** are formed in high yields when the appropriate Pt, Au, or Hg species is used (Table 2, compare entries 35–39).[73–75] The catalyst of choice seems to depend on the substrate, since Au and Hg catalysts only work for terminal alkynes while Pt catalysts present a wider scope.

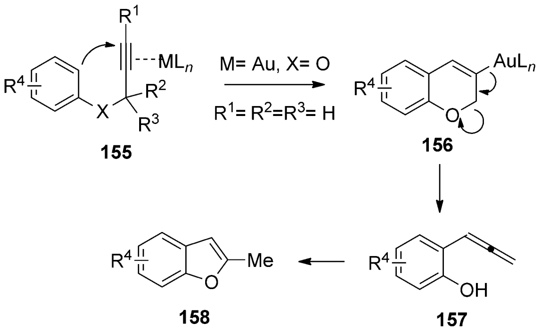
As for most of the other reactions in this Review, the carbocyclization of arylalkynes is not restricted to heterocycles **153** or to Au, Pt, or Hg catalysts, but this is the best example that we have found to specifically compare two or the three of these metals.[110] In the present reaction, the mechanism is similar to that described for the cyclization of enynes (see Section 6.3) and proceeds in a 6-*endo-dig* fashion (Scheme 36, intermediates **155** and **156**). However, an alternative reaction pathway was found when using Au catalysts in benzofurane derivatives.[74]



A) $PtCl_4$ (1-5 mol%), DCE or dioxane, RT-70 °C,1-24 h;
R^1= H, alkyl, aryl, ester, R^2=R^3= H, alkyl, O, 50-90 %
B) **31**-$PAuSbF_6$ (1 mol%), DCM, 18 °C,1 h;
R^1= H, R^2=R^3= O, 52-90 %
C) $Hg(OTf)_2{\cdot}(TMU)_3$ (0.2-10 mol%), MeCN, RT, 2-24 h;
R^1= H, alkyl, R^2=R^3= H, 50-95 %

Scheme 35. Pt, Au or Hg-catalyzed carbocyclization of arylalkynes.

Intermediate **156** leads to the final products **154** after proto-deauration but, if rearrangement occurs instead, allene intermediate **157** is formed and oxo-attack leads finally to **158**. This last step could also be metal catalyzed.



Scheme 36. Intermediates in the Au-catalyzed carbocyclization of arylalkynes and an alternative reaction pathway.

7. Summary and outlook

The "relativistic" triad of the transition metals, Pt, Au, and Hg, presents clear analogies from a general catalytic point of view, but has also important differences when analyzed on a reaction-by-reaction basis.

The three metals are excellent π-activators and, more generally, soft Lewis acids. These properties make them superior as catalysts to other transition and non-transition metals for the addition of carbon and heteroatom nucleophiles to unsaturated C–C bonds and even to C–H bonds.

Catalytic differences arise from the different atomic configuration for a particular oxidation state. Pt^{IV} is a d^6 octahedrally coordinated Lewis center that cannot accommodate an incoming reactant in its coordination sphere and, moreover, can easily be reduced. In many cases it acts as a pre-catalyst of the active reduced form. Pt^{II}, in contrast, forms very active d^8 square-planar complexes which can easily accommodate incoming substrates by oxidative addition or associative mechanisms. Moreover, the Lewis acidity of the cation can be modulated very precisely by the surrounding ligands. The isoelectronic and isostructural Au^{III} complexes cannot operate under oxidative addition conditions. Moreover, those complexes are easily reducible, which make them less desirable as catalysts compared to Pt^{II} compounds. As Pt^{IV}, Au^{III} can act as a precatalyst to form the active species under reaction conditions.

Au^{I} is a d^{10} cation whose low electron-count ($14e^-$) linear complexes allow a third reactant to coordinate to the Lewis center, thus acting as excellent catalysts by associative and/or dissociative mechanisms. Moreover, given the limited coordination sphere of a linear complex, Au^{I} discriminates between reactants more easily than Pt^{II} since it accommodates only the reacting groups without competing for other nucleophiles in the medium. The lack of oxidative addition/reductive elimination cycles for Au can be seen as an advantage since it precludes reduction to the parent metal during the catalytic cycle. Finally, the isoelectronic and isostructural Hg^{II} complexes can only operate by dissociative mechanisms, which hampers their catalytic versatility.

In summary, Au^{I} shows a superior catalytic activity among the different cations of the triad due to its efficiency, versatility and stability. It must be said that the "superior stability" of Au^{I} refers to other cations of the triad, such as Au^{III}, Pt^{IV}, and Pt^{II}, but not to Hg^{II}. If steric effects are considered, modulation of the Lewis acidity by the surrounding ligands is most effective in Pt^{II} complexes, which is useful in some reactions. Finally, Hg^{II} is, in principle, the most stable cation in the triad and does not need stabilizing ligands as Pt^{II} and Au^{I} do, which translates into simpler catalytic systems.

From the reactions shown in the text, it can be seen that there is still room for improvement. In fact, some results obtained with Hg-catalyzed methods are still not matched by Pt and Au. Modulation of the Lewis acidity of the cationic center is limited when working with simple salts, which are used in many cases as catalysts, while Lewis acidity can be modulated by ligand interactions in Au and Pt complexes. To our knowledge, there is not a single example of a ligand-modulated Hg^{II} catalyst. The use of metal nanoparticles is an alternative way to modulate the catalytic activity while stabilizing the catalyst. However, examples of C−C bond activation with Au and Pt nanoparticles are scarce and there are none with Hg.

Considering all the catalytic factors taken together with the price, toxicity, and availability of Pt, Au and Hg, the choice of one or another for large-scale reactions is not simple and depends on the recoverability of the catalyst, economic (Pt and Au),[49] and toxicity issues (Hg).

A.L.-P. thanks CSIC for a contract under JAE-doctors program. Financial support by Consolider-Ingenio 2010 (proyecto MULTICAT) and PLE2009 project from MCIINN is also acknowledged.

Received: March 10, 2011

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