Au^{III} Complexes Catalyze Deoximations/Transoximations at Neutral pH**

Carles Isart, David Bastida, Jordi Burés,* and Jaume Vilarrasa*

Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Reaction of gold trihalides with reducing agents such as thiols, NaBH₄ or hydroxylamine gives gold nanoparticles (Au NPs).^[1] In particular, NH₂OH is used to produce monodisperse colloidal Au NPs by “growing” of smaller particles or to form thin films of Au on glass substrates.^[2] Our interest in developing a mild catalytic method for the conversion of nitro/oxime/nitrone groups to carbonyl groups led us to examine first the interaction of gold(III)^[3] with simple oximes as a potential deoxygenation procedure.^[4] The hydrolysis of the coordination complexes of oximes and glyoximes with gold(III)^[5] has not been investigated. If a partial hydrolysis of oximes (to RR'C=O and NH₂OH) took place, NH₂OH would be oxidized in situ by Au^{III}, shifting the equilibrium to the right.

Our first challenge was to find a water-soluble and stable gold complex that could catalyze the hydrolysis of the robust oxime group^[6] at neutral pH and, as far as possible, at room temperature (RT). Under these conditions, prone-to-hydrolysis characteristic and protecting groups contained in a polyfunctional molecule would be compatible (or would have the highest chances of survival). To our delight, only AuBr₃ (99.9%) and AuCl₃ (99.99%) were capable, adjusting the pH with a standard solution of NaOH 1.000 M (99.99%),^[7] of promoting the hydrolysis of 4-phenyl-2-butanone oxime (Table 1), after screening Lewis acids that are quite soluble and stable in aqueous media [Sc(OTf)₃, LaCl₃·7H₂O, FeX₃, RuCl₃, RhCl₃, PtCl₄, CuX₂, AuX₃, InBr₃] and related compounds. Save AuX₃, none of these salts was a suitable initiator or catalyst at pH 4–8;^[8] in fact, when the solutions of most of them were neutralized, the corresponding hydroxides or oxide hydrates precipitated, as expected. Despite their lack of solubility in water, we also examined Pt^{II}, see entry 8, Cu^I, see entries 10–12,^[9] and Au^I salts, entry 17, because of their excellence as catalysts in other contexts, but no effect was observed. In short, among all these common transition metal cations, only Au^{III} species did work at neutral pH. However, 50 mol % of Au^{III} was required to complete the hydrolysis of 4-phenyl-2-butanone oxime (entry 21), as the active Au^{III} species disappeared by reduction to Au⁰ NPs by NH₂OH (as expected).

Thus, the next challenge was to develop a truly catalytic version of this hydrolysis (a cheaper process). We explored the possibility of trapping NH₂OH with carbonyl compounds capable of forming oximes more stable than the starting oxime (Table 1, entries 22–27). The best results for such a transoximation process were obtained with methyl

Table 1: Screening of MX_n and Additives

Entry	MX _n , mol %	Additive ^[a]	Conv. [%]
1	Sc(OTf) ₃ , 20	none	0
2	LaCl ₃ , 20	none	0
3	FeCl ₂ , 20	none	0
4	FeBr ₃ , 20	none	≤ 3
5	RuCl ₃ , 20	none	≤ 7
6	RhCl ₃ , 20	none	≤ 6
7	PdCl ₂ , 20	none	≤ 7
8	PtCl ₂ , 20	none	0
9	PtCl ₄ , 20	none	0
10	CuI, 20	none	≤ 4
11	Cu ₂ Cl ₂ , 10	none	0
12	Cu ₂ (OTf) ₂ , ^[b] 10	none	0
13	CuBr ₂ , 20	none	0
14	Cu(OTf) ₂ , 20	none	10
15	Ag ₂ SO ₄ , 20	none	≤ 4
16	InBr ₃ , 20	none	0
17	AuCl, 20	none	≤ 2
19	AuCl ₃ , 20	none	27
20	AuBr ₃ , 20	none	37 ^[c]
21	AuBr₃, 50	none	100^[c]
22	AuBr ₃ , 5	acetone excess ^[a]	60
23	AuBr ₃ , 5	CH ₃ COC(=O)CH ₂ COOEt	61
24	AuBr ₃ , 5	CH ₃ COC(=O)CH ₂ COCH ₃	70
25	AuBr ₃ , 5	formaldehyde hydrate	88
26	AuBr₃, 5	CH₃COC(=O)OCH₃	100
27	AuBr₃, 5	CH₃COC(=O)CH₃	100^[c]
28	—	CH ₃ COC(=O)CH ₃	0
29	AlBr ₃ , 5	CH ₃ COC(=O)CH ₃	0 ^[d]
30	FeBr ₃ , 5	CH ₃ COC(=O)CH ₃	5 ^[e]

[a] 100 mol % (except for the case with acetone as the co-solvent). [b] Copper(I) trifluoromethanesulfonate–toluene, 99.99%. [c] Same result in THF, CH₃CN, 1,4-dioxane, 2-propanol, and MeOH instead of EtOH (always with 20 % of H₂O, v/v). [d] Under these conditions, Ba²⁺, Ca²⁺, Cr³⁺, Mg²⁺, Mn²⁺, Mn³⁺, Ni²⁺, Sb³⁺, Sn²⁺, Sn⁴⁺, Ti⁴⁺, and Zn²⁺ also gave 0 %. [e] RuCl₃, RhCl₃, PdCl₂, CuI, Cu(OTf)₂, and Ag₂SO₄ gave < 2 %.

pyruvate (CH₃COC(=O)OCH₃ entry 26) and with diacetyl (biacetyl, 2,3-butanedione, entry 27).^[10] A parallel in silico screening, at the MP2 level,^[11] indicated that the diacetyl monoxime, CH₃COC(=NOH)CH₃, is especially stable, as compared to a long series of oximes. Nevertheless, Au^{III} species are crucial since, without AuBr₃, the exchange between 4-phenyl-2-butanone oxime and diacetyl did not occur (entry 28), nor at 100 °C (μW reactor).

To rule out the participation of the reported common impurities contained in 99.9% AuBr₃ at the ppm level (Aldrich trace analysis), the effect of 5 mol % or more of the following salts, at pH 7, was tested in the presence of diacetyl: AlBr₃, BaCl₂, CaCl₂, CrCl₃, MgBr₂, MnCl₂, MnF₃, NaBr (200 mol %), NiBr₂, SbCl₃, SnCl₂ + SnCl₄ (1:1), TiCl₄/Ti(OⁱPr)₄ (1:1), or ZnBr₂. All were inactive (see entry 29 and the corresponding footnote).

[*] C. Isart, D. Bastida, Dr. J. Burés, Prof. Dr. J. Vilarrasa
Chemistry Department, University of Barcelona
Av. Diagonal 647, 08028 Barcelona (Catalonia, Spain)
E-mail: jvilarrasa@ub.edu

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The Au^{III} species involved as initiator(s) or catalyst(s) were examined by electrospray ionization MS [ESI(–)-MS]. Aqueous solutions of AuBr₃, once adjusted to different pH values by addition of NaOH, afforded the spectra shown in Figure 1 (registered with a potential of 20 V, as no signals were observed below this value, while above it fragmentations of the main species occurred). At pH 5.4 (Figure 1a) the major anionic species was [AuBr₃(OH)][–], appearing as a quadruplet due to the almost 1:1 ⁷⁹Br/⁸¹Br isotopic distribution, but an equilibrium was noted with [AuBr₄][–] (quintuplet) and [AuBr₂(OH)₂][–] (triplet), due to a quick exchange of bromide and hydroxide ions (Scheme 1). At pH 7.0, [AuBr₂(OH)₂][–] predominated. Finally, at pH 7.9, the less colored species [AuBr₂(OH)₂][–] and [AuBr(OH)₃][–] (doublet) were the major ones (Figure 1c). All this agrees with spectrophotometric data just reported for these species.^[12]

Figure 1. Electrospray ionization MS (negative mode, 20 V) of 0.1 M AuBr₃ 99.9% + NaOH. a) ca. 100 mol % of NaOH added, pH 5.40. The major species is [AuBr₃(OH)][–], *m/z* 450.73/452.73/454.73/456.73, in equilibrium with AuBr₄[–] (quintuplet, centered at 516.64) and [AuBr₂(OH)₂][–] (triplet, centered at 390.81). b) ca. 170 mol % of NaOH added, pH 7.00. c) With ca. 240 mol % of NaOH, pH 7.89.

Scheme 1. Au^{III} species in equilibria.

In practice, Au^{III} solutions at pH 5.4 were slightly more active (50% conversion in 6 h, under the conditions of Table 1, entry 27, with 4-phenyl-2-butanone oxime) than those at pH 7.0 (50% in 8 h), whereas those at pH 7.9 were less active (50% in ca. 12 h) and those at pH ≥ 8.5, where [Au(OH)₄][–] predominated (Scheme 1, spectrum not given), were completely inactive. The addition of NaBr (from 10 to 100 equiv) was counter-indicated, as it stopped the progress of these reactions.^[13]

We were ready to examine the scope of the reaction at pH 7. Our protocol could be applied to many ketoximes (Table 2), without formation of amides via the Beckmann rearrangement. In general, 5 mol % of AuBr₃ was enough for the full conversion of each ketoxime plus diacetyl to ketone plus CH₃COC(=NOH)CH₃. In some cases only 2 mol % of AuBr₃ was required, at RT or at 60 °C. Under these smooth conditions, (i) an ester group (Table 2, entry 7) was not hydrolyzed, (ii) mono- and dioximes of diketones (entries 8 and 9) did not cyclize and the diketones generated did not undergo self-aldol reactions, (iii) conjugate additions to α,β-unsaturated ketoximes (entries 11 and 12) or to the resulting ketones were not observed, and (iv) the CHNO₂ stereocenter shown in entry 13 did not epimerize. Although not included in Table 2 to save space, hydroxyl protecting groups such as ^tBuMe₂Si (TBS) and 1,2-diol protecting groups such as isopropylidene were not affected,^[14] as expected bearing in mind that the medium was not acidic. No racemization took place with enantiopure compounds of entries 16 and 17^[15] and no epimerization was noted in the case of D-fructose oxime (entry 18). Free hydroxyl groups did not interfere with the hydrolysis (entries 17 and 18).

Table 2. Au^{III}-Catalyzed Transoximation of Ketoximes.

$ \begin{array}{c} \text{R} \text{---} \text{C} \text{---} \text{NOH} \\ \text{R}' \end{array} \xrightarrow[\text{RT, 15 h}]{\begin{array}{c} 5 \text{ mol \% AuBr}_3, \text{ pH } 7 \\ 100 \text{ mol \% of CH}_3\text{COC(=NOH)CH}_3 \\ \text{H}_2\text{O-EtOH (1:4, v/v)} \end{array}} \begin{array}{c} \text{O} \\ \text{R} \text{---} \text{C} \text{---} \text{R}' \end{array} $					
Entry	Oxime	Ketone yield [%]	Entry	Oxime	Ketone yield [%]
1		98	11		91 ^[b]
2		100	12		92 ^[d]
3		100 ^[a]	13		93 ^[a,b]
4		96	14		100 ^[b]
5		100	15		97 ^[a,b]
6		100	16		92 ^b
7		100 ^[b]	17		91
8		94	18		100 ^[a,e]
9		100 ^[c]			
10		100 ^[c]			

[a] With 2 mol % of AuBr₃ at pH 7. [b] Reaction carried out at 60 °C. [c] 200 mol % of diacetyl was added. [d] At 100 °C for 6 h. [e] In D₂O-THF. The expected mixture^[16] of β-D-fructopyranose (major), β-D-fructofuranose, and α-D-fructofuranose was obtained.

Application of our protocol to aliphatic and aromatic aldoximes (Table 3, entries 1–5) gave aldehydes without dehydration to nitriles. THF was preferable to EtOH or MeOH, to avoid contamination of the products with hemiacetals and acetals. Garner's aldehyde oxime (entry 6) and D-arabinose oxime (entry 7) were hydrolyzed with full retention of the configuration of their α stereocenter.

Finally, to gain insight into the role of the Au^{III} complexes, several experiments were followed by ESI(–)-MS.^[11] One representative example is shown in Figure 2. We chose in this experiment a solution of AuBr_3 at pH 6, as it showed an ESI spectrum between those of Figure 1a and 1b, with the three sets of high peaks corresponding to species $[\text{AuBr}_2(\text{OH})_2]^-$, $[\text{AuBr}_3(\text{OH})]^-$, and $[\text{AuBr}_4]^-$. By adding a saturated solution of 4-phenyl-2-butanone oxime in water to the stirred Au^{III} solution and injecting an aliquot, the spectrum of Figure 2a was obtained. The intensities of the triplet, quadruplet and pentuplet decreased and new peaks appeared (see arrows) due to new complexes: $[\text{AuBr}(\text{OH})_2(\text{oximate})]^-$ (d), $[\text{AuBr}_2(\text{OH})(\text{oximate})]^-$ (t), and $[\text{AuBr}_3(\text{oximate})]^-$ (q). In each case, the replacement of one bromide ion by the oxime (with loss of a proton) is the most likely and general explanation. In the light of the many spectra registered at different times it seems, however, that the Br^-/OH^- and $\text{HBr}/\text{H}_2\text{O}$ exchanges quickly occur under standard concentrations, to give equilibrium mixtures (also in oximate-containing complexes, as summarized in Scheme 2). Moreover, within 2 h (see Figure 2b) the signals of $[\text{AuBr}_x(\text{OH})_y]^-$ had been almost disappeared and the oximate-containing complexes were the main peaks. Their hydrated forms (see Scheme 2), the obvious transient intermediates in any oximation and/or hydrolytic deoximation procedure, were at the noise level. Nevertheless, enhancing the sensitivity 100 $\times$, even these relatively unstable intermediates could be observed (Figure 2b, left expansions). On the other hand, we could not detect the hydrated form $[\text{AuBr}_3(\text{O}-\text{NH}-\text{CRR}'\text{OH})]^-$ (signals too low).

With acetone oxime we observed *O*-oximate species^[11] such as $[\text{AuBr}_2(\text{OH})(\text{O}-\text{N}=\text{CMe}_2)]^-$ (at m/z 443.86/445.86/447.86). Its hydrated form (m/z 461.82/463.82/465.82), in spite of its relatively short half life, was also detected. Experiments with ^{15}N -labeled acetone oxime^[11] validated the structures of the intermediates. In the presence of diacetyl, complexes of diacetyl monoxime with Au^{III} were also detected (m/z 471.86/473.85/475.85).

Table 3: Au^{III} -Catalyzed Conversion of Aldoximes to Aldehydes.

$\text{R}-\text{CHO} \xrightarrow[\text{RT (A) or } 60^\circ\text{C (B), 15 h}]{\begin{array}{c} 5 \text{ mol \% AuBr}_3, \text{ pH } 7 \\ 100 \text{ mol \% of } \text{CH}_3\text{COCOCH}_3 \\ \text{H}_2\text{O}-\text{THF (1:4, v/v)} \end{array}} \text{R}-\text{CHO}$					
Entry	Oxime	Aldehyde yield [%]	Entry	Oxime	Aldehyde yield [%]
1		100 (A) 92 (A) ^[a]	5		60 (B) 91 (B) ^[b]
2		100 (B)	6		90 (A)
3		100 (B)	7		100 (A) ^[c]
4		100 (B)			

[a] With 2 mol % of AuBr_3 at pH 7. [b] 10 mol % of AuBr_3 at pH 7 and 120 mol % of diacetyl. [c] In 1:4 D_2O -THF. The anomeric mixture^[16] of β - and α -D-arabinopyranose (major) was isolated.

Figure 2. ESI(–)-MS spectra of the reaction of Au^{III} complexes with 4-phenyl-2-butanone oxime in H_2O . a) At pH ca. 6.0, after adding the oxime. b) Two h later, when the wine-red color of the solution had faded; regions where the main hydrated intermediates could appear are expanded. See the main text and Scheme 2 for explanations.

Scheme 2. Au^{III} species involved in Figure 2.^[17]

In Scheme 3, we suggest a plausible general mechanism (between pH 5.4 and 7.9 at least) for the reaction of transoximation between acetone oxime and diacetyl. In the absence of diacetyl the $k\text{O}$ complexes (Figure 3, bottom) may isomerize to the $k\text{N}$ complexes (via hydrolysis and/or by an *O*-to-*N* exchange). It is likely that these $k\text{N}$ species are involved in the known redox process that affords Au NPs and “ HNO ” ($2 \text{HNO} = \text{N}_2\text{O} + \text{H}_2\text{O}$).^[18]

In summary, AuBr_3 solutions, after neutralization, catalyze the deoximation by transoximation with diacetyl of 25 oximes, many of them really robust,^[6,19] in most cases at RT. No other metallic salts are capable of it (at neutral pH, neither between pH 4 and 8). The conditions are extremely mild: α -stereocenters do not epimerize, other functional groups and standard protecting groups are inert, ketoximes do not undergo Beckmann rearrangements, and aldoximes are not converted to nitriles. It is a paradox that the secret of success is to avoid the formation of Au NPs (so important in other contexts), as it means the disappearance of the Au^{III} species. Thus, a new episode in the “*aurocatalysis*” story is uncovered here. Studies of the performance of $[\text{AuBr}_x(\text{OH})_y]^-$ species in other reactions at neutral pH, where the central atom is still surprisingly active as a Lewis acid, are in progress.

Scheme 3. Plausible mechanism of the hydrolysis of acetone oxime in the presence of Au^{III} and diacetyl, at neutral pH.

Experimental Section

Representative deoxygenation procedure. Diacetyl (27 μ L, 26 mg, 0.3 mmol) and the Au^{III} “stock solution”^[7] (175 μ L, 0.015 mmol) were added to a solution of the ketoxime (0.3 mmol) in ethanol–water (4:1 v/v, 2 mL). The mixture was stirred at ca. 20 °C, overnight (usually for 15 h), in a closed vial. A N₂ atmosphere was unnecessary. Afterwards, the solution was diluted with dichloromethane (10 mL), water was added, and the layers were separated and re-extracted. The organic extracts were dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the crude was analyzed by ¹H NMR. Several reactions were performed later at 1.0 or 2.0-mmol scale. When purification was required it was carried out by flash column chromatography over silica gel, with hexane–EtOAc.

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- [7] To a solution of AuBr₃ in water (0.100 M) was added NaOH (1.000 M) until pH 7.0 (pHmeter). The resulting wine-red solution, 0.086 M in Au^{III}, was stable for months stored in a closed vial (“stock solution”). AuCl₃ was almost as active as AuBr₃ but solutions of AuCl₃ at pH 7.0 were “unstable” (a precipitate soon appeared).
- [8] Under the conditions of Table 1, entries 1–20, but without neutralization, EtOH–H₂O solutions of CuBr₂ (pH 2.17), Cu(OTf)₂ (pH 1.90), and RuCl₃ (pH 1.37) turned out to be more efficient than those of AuBr₃ (pH 1.45, 30% yield of ketone), and PtCl₄ solutions gave an outcome similar to AuBr₃, whereas all the remaining salts were very inefficient (< 15% of ketone). However, the addition of only 100 mol% of NaOH (pH values $\geq$ 4) deactivated completely Cu^{II}, Ru^{III}, and Pt^{IV} salts. In other words, only Au^{III} complexes are still active at neutral pH values.
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- [14] TBSO- and isopropylidene-containing fragments of total syntheses of macrolides in progress in our lab were used as models.
- [15] As checked by optical rotatory power (entry 16 of Table 2, entry 6 of Table 3) and chiral HPLC (for the TBS derivative of the ketone of entry 17 in Table 2).
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- [19] Provided that they are less robust than the very stable diacetyl monoxime. The mono and dioxime of 2,4-pentanedione can be hydrolyzed, with 5 mol % of AuBr₃ at pH 7, overnight, by adding 110 and 220 mol % of diacetyl, respectively, while the oxime of methyl pyruvate requires heating and a much larger excess of diacetyl