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Cycloisomerization versus Hydration Reactions in Aqueous Media: A Au(III)-NHC Catalyst That Makes the Difference

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ABSTRACT

A novel water-soluble Au(III)-NHC complex has been synthesized and successfully applied in the intramolecular cyclization of γ-alkynoic acids into enol-lactones under biphasic toluene/water conditions, thus representing a rare example of an active and selective catalyst for this transformation in aqueous media. Remarkably, competing alkyne hydration processes were not observed, even during the desymmetrization reaction of challenging 1,6-diyne substrates. In addition, after phase separation, the water-soluble Au(III) catalyst could be recycled 10 times without loss of activity or selectivity.

After a long induction period, gold complexes have emerged in recent years as versatile and powerful catalysts for synthetic organic chemistry.[1] The catalytic hydration of alkynes by Na[AuCl$_4$] reported by Fukuda and Utimoto in 1991 initiated rapid development of the field.[2] Since then, gold complexes have been widely employed in many organic transformations, with special focus on the electrophilic π-activation of unsaturated carbon–carbon bonds (alkynes, enynes, alkenes, allenes, etc.) toward nucleophiles.[1,3] Relativistic effects have been evoked to explain the superior effectiveness of gold as a π-activator compared to other transition metals.[4] In addition, it has also been largely demonstrated that the stability and Lewis acidity of Au(I) and Au(III) species can be easily modulated by the surrounding ligands, thus enabling the fine tuning of the activity and the chemo-, regio-, and/or stereoselectivity of

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the catalytic processes in which gold is involved.[5] In this context, gold complexes with *N*-heterocyclic carbene (NHC) ligands are gaining a great significance due to the stability provided by the strong σ-donation and weaker π-back-bonding ability of such ligands in comparison to the more commonly used tertiary phosphines.[6]

On the other hand, since the discoveries made by Breslow and Grieco in the early 1980s on the positive effect of water on the rate and *endo*/*exo* selectivity of Diels–Alder reactions,[7] the development of organic transformations in aqueous media has become one of the major cornerstones in modern chemistry.[8] In addition, the use of water as an alternative, available, safe, and cost-effective solvent fullfills the principles of "Green Chemistry",[9] creating an answer to the growing concerns associated with the environmental impact of chemical processes.[10] Following this general trend, several Au-catalyzed reactions conducted in aqueous media have been successfully developed in recent years.[1] However, concerning the use of gold-NHC systems, studies in water have been scarce and restricted to catalytic hydrations of alkynes[11] and nitriles[12] and Meyer–Schuster-type rearrangements.[13]

We wish therefore to describe herein that, despite the high tendency of gold to promote the hydration of $C\equiv C$ bonds,[1–3,11,14] cycloisomerization reaction of γ-alkynoic acids can be selectively performed in aqueous media in the presence of a new water-soluble Au(III)-NHC complex.[15] Such a catalytic reaction constitutes nowadays the major route for the construction of five-membered exocyclic enol-lactones with complete atom economy. It is also worthy of note that, although a plethora of transition-metal catalysts including gold have been developed for this synthetically useful transformation,[16–18] efficient systems able to operate in aqueous media are still rare.[19]

The route designed to synthesize the water-soluble Au(III)-NHC catalyst **3** is depicted in Scheme 1. First, the novel zwitterionic imidazolium salt **2** was prepared by reacting the known 2-(1*H*-imidazol-1-ylmethyl)pyridine **1**[20] with 1,3-propane sultone.[21] Then, sequential treatment of **2** with Ag_2O, $[AuCl(SMe_2)]$, and excess of $PhICl_2$ led to the clean formation of **3**, *via* the corresponding Ag(I)- and Au(I)-NHC intermediates.[22] Complex **3**, isolated as an air-stable yellow solid in 63% yield, was characterized by means of standard spectroscopic techniques as well as elemental analysis. In addition, X-ray-quality crystals were obtained by slow diffusion of toluene into a saturated DMSO solution, allowing us to confirm unambiguously the molecular structure of this new Au(III)-NHC derivative (see Supporting Information).

As expected, complex **3** readily dissolves in water at room temperature. However, in this medium an equilibrium is established between **3** and the zwitterionic derivative **4**, the latter resulting from the release of HCl and concomitant coordination of the pyridyl unit to the gold

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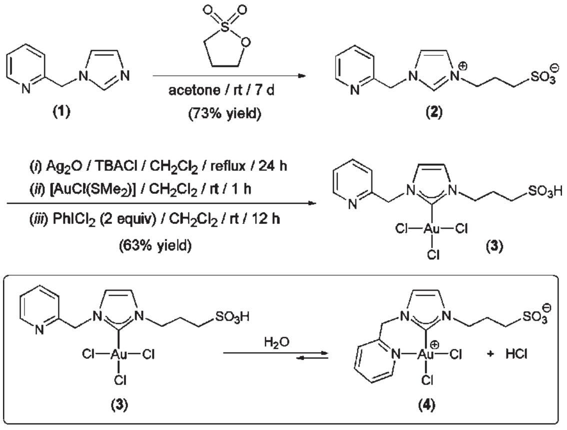
(22) Trace amounts of HCl in the dichloromethane employed is probably responsible for the protonation of the sulfonate group. In addition, HCl may also be present in the iodobenzene dichloride employed as oxidant, since it was synthesized by chlorination of iodobenzene with $NaClO_2$ in hydrochloric acid solution as described in Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, *4*, 551–557.

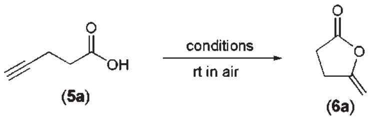
center (Scheme 1). Complex **4** is the major species present in solution at rt, and its structure was also determined by X-ray crystallography (see Supporting Information). Chelation of the NHC ligand in water is readily evidenced by ^1H NMR spectroscopy, where the singlet signal corresponding to the methylenic protons of the picolyl moiety in **3** (δ 5.63 ppm) undergoes an AB splitting (δ 5.65 and 5.81 ppm; J = 16.0 Hz) as a consequence of the conformational rigidity of the six-membered metallacycle in **4**.[23]

Scheme 1. Synthesis of Complex **3** and Its Behavior in Water



As shown in Table 1, complex **3** turned out to be an efficient and selective catalyst for the cycloisomerization of model 4-pentynoic acid **5a** in different mono- and biphasic water/organic solvent mixtures (entries 1–4). Reactions, performed at rt under aerobic conditions with a metal loading of 2.5 mol %, led to the quantitative transformation of **5a** into enol-lactone **6a**, with no byproduct resulting from the hydration of the C≡C bond of **5a** being detected by ^1H NMR spectroscopy in the crude reaction mixtures. Best results in terms of activity were obtained using a biphasic toluene/water solvent system,[24] where total consumption of **5a** was observed after only 1 h, thus allowing the isolation of **6a** in high yield (81%; entry 4). The process is also operative in pure water (entry 5). However, both the activity and selectivity of **3** in this medium were lower, the latter due to the partial hydrolysis of **6a** to form 3-acetylpropanoic acid.[25] Brønsted acid catalysis mediated by the HCl released after dissolving complex **3** in water can be ruled out, as demonstrated by the result shown in entry 6.[26] The use of a base (KOH, entry 7) associated with the catalyst allowed the formation of the desired lactone.[17a] Conversely, no catalytic activity was observed in the presence of the free ligand **2** alone (entry 8). These results fully support that the intramolecular nucleophilic attack of the carboxylic unit is taking place upon coordination of the alkyne to the metal center. The required vacant site is most probably generated by decoordination of the picolyl moiety in the *in situ* formed complex **4**, owing to the well-known hemilabile character of this group.[27] As shown in entries 9 and 10, simple Au(III) and Au(I) sources were comparatively much less effective and selective, thus highlighting the synthetic potential of complex **3**.

Table 1. Catalytic Cycloisomerization of **5a** in Aqueous Media[a]



entry	conditions	time (h)	yield (%)[e]
1^b	**3** (2.5 mol %), MeCN/H_2O	6	>99
2^b	**3** (2.5 mol %), Et_2O/H_2O	5	>99
3^b	**3** (2.5 mol %), CH_2Cl_2/H_2O	2	>99
4^b	**3** (2.5 mol %), toluene/H_2O	1	>99 (81)
5^c	**3** (2.5 mol %), H_2O	1	50^f
6^b	HCl (2.5 mol %), toluene/H_2O	1	1
$7^{b,d}$	**3** + KOH (2.5 mol %), toluene/H_2O	1	>99
8^b	**2** (2.5 mol %), toluene/H_2O	1	0
9^b	$AuCl_3$ (2.5 mol %), toluene/H_2O	4	90^g
10^b	AuCl (2.5 mol %), toluene/H_2O	6	70^f

[a] Reactions were performed at rt under aerobic conditions starting from 0.3 mmol of **5a**. [b] 1 mL of the corresponding organic solvent and 1 mL of distilled water were employed. [c] 2 mL of distilled water were employed. [d] 2.5 mol % of each reagent was employed. [e] Determined by ^1H NMR. Isolated yields are given in brackets. [f] A mixture of **6a** and 3-acetylpropanoic acid in ca. 3:1 ratio is formed. [g] A mixture of **6a** and 3-acetylpropanoic acid in ca. 5:1 ratio is formed.

The scope of the reaction was then studied for various γ-alkynoic acids in a biphasic toluene/water mixture (Table 2).[28] Complete conversions were observed for substrates **5b–h**, all bearing a terminal alkyne unit and alkyl or alkenyl side chains, after 2–4 h of stirring at rt in the presence of 2.5 mol % of **3** (entries 1–7). The reactions led to the selective formation of lactones **6b–h**, which could be isolated in good yields (66–97%), without detection of any byproduct by ^1H NMR in the crude reaction mixtures. As shown in entries 8 and 9, the process is also operative with the internal alkynes **5i–j**. Nevertheless, longer reaction times or higher temperatures were required. In addition, traces of the corresponding six-membered ring lactones, resulting from an *endo* instead of an *exo*

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(23) Related Au(III) complexes containing chelating picolyl-NHC ligands have been described. See, for example: (a) Pažický, M.; Loos, A.; Ferreira, M. J.; Serra, D.; Vinokurov, N.; Rominger, F.; Jäkel, C.; Hashmi, A. S. K.; Limbach, M. *Organometallics* **2010**, *29*, 4448–4458. (b) Topf, C.; Hirtenlehner, C.; Fleck, M.; List, M.; Monkowius, U. *Z. Anorg. Allg. Chem.* **2011**, *637*, 2129–2134. (c) See also ref 20.

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(25) Formation of 3-acetylpropanoic acid by direct hydration **5a** was discarded since, under the same reaction conditions, complex **3** is not able to hydrate terminal alkynes, such as 1-pentyne or 1-hexyne (only at 100 °C hydration could be observed). Note also that hydrolysis of lactones is a well-known process: Olson, A. R.; Hyde, J. L. *J. Am. Chem. Soc.* **1941**, *63*, 2459–2461.

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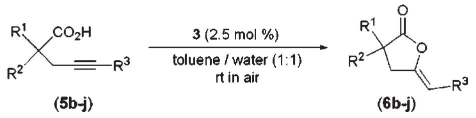
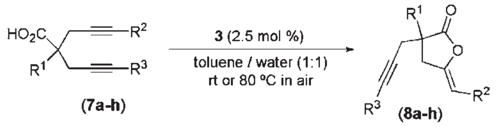
Table 2. Au(III)-Catalyzed Cycloisomerization of γ-Alkynoic Acids **5b**–**j** in a Biphasic Toluene/Water Medium[a]



entry	substrate	time (h)	yield (%)[b]
1	$R^1 = R^2 = Me; R^3 = H$ (**5b**)	2	84
2	$R^1 = CO_2Me; R^2 = R^3 = H$ (**5c**)	2	96
3	$R^1 = CO_2Me; R^2 = Me; R^3 = H$ (**5d**)	2	80
4	$R^1 = CO_2Me; R^2 = Et; R^3 = H$ (**5e**)	2	97
5	$R^1 = CO_2Et; R^2 = Bn; R^3 = H$ (**5f**)	2	92
6	$R^1 = CO_2Me; R^2 = CH_2CH{=}CH_2; R^3 = H$ (**5g**)	2	84
7	$R^1 = CO_2Me; R^2 = CH_2CH{=}CHPh; R^3 = H$ (**5h**)	4	66
8	$R^1 = CO_2Me; R^2 = Et; R^3 = Me$ (**5i**)	24	94[c]
9[d]	$R^1 = CO_2Me; R^2 = H; R^3 = Ph$ (**5j**)	2	28[c]

[a] Reactions were performed as described in ref 28. [b] Isolated yields. [c] Traces of the six-membered ring lactone were detected by ^{1}H NMR in the crude reaction mixture. [d] Reaction performed at 80 °C.

Table 3. Au(III)-Catalyzed Cycloisomerization of Bispropargylic Carboxylic Acids **7a**–**h** in a Biphasic Toluene/Water Medium[a]



entry	substrate	temp	time (h)	yield (%)[b]
1	$R^1 = R^2 = R^3 = H$ (**7a**)	rt	2	94
2	$R^1 = CO_2Me; R^2 = R^3 = H$ (**7b**)	rt	2	84
3	$R^1 = Ph; R^2 = R^3 = H$ (**7c**)	rt	2	88
4	$R^1 = H; R^2 = R^3 = Me$ (**7d**)	80 °C	2	84[c]
5	$R^1 = CO_2Me; R^2 = R^3 = Me$ (**7e**)	80 °C	1	90[d]
6	$R^1 = CO_2Me; R^2 = R^3 = Ph$ (**7f**)	80 °C	1	40
7	$R^1 = CO_2Me; R^2 = H; R^3 = Me$ (**7g**)	rt	2	80
8	$R^1 = CO_2Me; R^2 = H; R^3 = Ph$ (**7h**)	rt	6	86

[a] Reactions were performed as described in ref 28. [b] Isolated yields. [c] A mixture of **8d** and the corresponding six-membered ring lactone is formed in ca. 6:1 ratio. [d] A mixture of **8e** and the corresponding six-membered ring lactone is formed in ca. 3:1 ratio.

cyclization, were now detected in the ^{1}H NMR spectra of the crude mixtures.

Complex **3** proved also selective in the cyclization of more challenging bispropargylic carboxylic acids (Table 3).[29] Thus, starting from the symmetrical terminal 1,6-diynes **7a**–**c** (entries 1–3), enol-lactones **8a**–**c** containing a propargylic side arm intact could be generated in excellent yields (84–94%) under mild conditions. In contrast, desymmetrization of diynes **7d**–**f** containing internal C≡C bonds proved more difficult, and a higher temperature (80 °C) was required (entries 4–6). As in the case of **5i**–**j**, competitive formation of the corresponding six-membered ring lactones was again observed. The remarkable higher reactivity of terminal versus internal C≡C bonds was clearly evidenced in the reactions of the nonsymmetrical 1,6-diynes **7g**–**h** (entries 7 and 8), where only the former participated in the cyclization process leading to the exclusive formation of lactones **8g**–**h**.[30] In none of these desymmetrization processes were hydration byproducts detected.

One of the major advantages of biphasic catalysis is that it is associated with the recycling of the catalytic species.[31] In this context, we have found that, after separation of the toluene layer in which the lactone is soluble, the aqueous phase containing the catalytically active gold species can be reused. Thus, using the 1,6-diyne **7a** as model substrate, 10 consecutive reactions could be performed without any loss of activity or selectivity (quantitative yield over the 10 cycles).

In summary, we have demonstrated that non-hydrative transformations of functionalized alkynes can be efficiently and selectively performed in aqueous media by means of NHC-gold catalysis. This unprecedented fact, together with the possibility of an effective recycling, opens new research directions to expand the applications of NHC-gold complexes in synthetic organic chemistry.

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Supporting Information Available. Experimental details, characterization data, and crystallographic data for compounds **3** and **4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) **General procedure for the catalytic reactions.** To a biphasic system composed of 1 mL of toluene and 1 mL of distilled water were added 0.3 mmol of the corresponding alkynoic acid and 4.4 mg of complex **3** (0.0075 mmol; 2.5 mol %). The resulting mixture was stirred under air, at rt or 80 °C (see Tables 1–3), until complete consumption of the alkynoic acid was observed by TLC. The organic phase was then separated, the aqueous one was extracted with diethyl ether (2 × 2 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered over a short pad of silica gel using CH_2Cl_2 as eluent. The volatiles were removed under vacuum to yield the corresponding lactone in high yield and purity. When required, lactones were further purified by column chromatography over silica gel using hexane/EtOAc (9:1) as eluent.

(29) For related transformations catalyzed by NHC-gold complexes in organic media see ref 17d.

(30) From a mechanistic point of view, the cyclization processes reported herein proceed via an *anti*-addition of the carboxylic unit to the π-coordinated alkyne. This was inferred by performing the cyclization of **7a** into lactone **8a** in a biphasic toluene/D_2O mixture, reaction that led to the major incorporation of deuterium in *E* position of the exocyclic C=C bond of **8a** (details are given in the Supporting Information).

(31) *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

The authors declare no competing financial interest.