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Smaller, faster, better: modular synthesis of unsymmetrical ammonium salt-tagged NHC-gold(1) complexes and their application as recyclable catalysts in water†

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Received 24th June 2015, Accepted 8th July 2015 DOI: 10.1039/c5ob01286d Facile access towards a small library of unsymmetrical ammonium salt-tagged N-heterocyclic carbene gold(I) complexes is described, and their application as recyclable catalysts in cyclization reactions of acetylenic carboxylic acids and amides to lactones and lactams, respectively, in aqueous media is demonstrated. Catalyst **1ab** was applied in the synthesis of 2-*epi*-clausemarine A (**16**).

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Introduction

Sustainable chemistry is a frequently used term which indicates economic, ecological friendly and safe transformations. Accordingly, the development of new chemical reactions should combine waste prevention, use of nonhazardous solvents, and renewable raw materials.¹ In organometallic chemistry, main objectives are reusable catalysts, easy separation of products, and prevention of side reactions.² To achieve these goals, the use of water-soluble catalysts represents a desirable pathway. For this purpose, N-heterocyclic carbene (NHC) metal complexes were linked to water-soluble polymers^{3,4} or silicabased surfaces⁴ and carbohydrates.⁵ Moreover, they were functionalized with hydrophilic groups, such as carboxylates^{6,7} or sulfonates,^{7,8} resulting in improved water solubility and consequently an easier separation of the product and the catalyst, and also the opportunity for catalyst recycling.^{9,10}

Since the first synthesis of a sulfonated NHC-metal complex by Herrmann *et al.*, the number of reports about water-soluble NHC ligands has been increasing steadily. However, ammonium salt-tagged NHC ligands still play a minor role in transition metal catalysis,⁸ and only a limited number of publications deal with a direct synthesis of the ammonium function.^{11,12} More often, an amino group of the final NHC-metal complex is quaternized with a Brønsted acid.^{13–15} Recently, we reported the direct synthesis of ammonium salt-tagged IMesAuCl complexes and demonstrated their catalytic activity in cycloisomerization reactions of

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Fig. 1 Modular system for the synthesis of ammonium salt-tagged gold catalysts 1.

allenic and acetylenic alcohols in aqueous medium.¹¹ Moreover, we could successfully demonstrate their high stability and recyclability in water.

Here, we report an even more facile access towards ammonium salt-functionalized NHC–gold complexes. A shortened synthetic pathway is achieved by the application of a modular system which provides access to a small library of gold catalysts **1**. These ligands consist of an arylimidazole and a benzylic linker with an attached ammonium group (Fig. 1). The ammonium salt is introduced by aminoalkylation with trimethyl-, triethyl-, or tributylamine.

Results and discussion

The synthesis of the ammonium salt-tagged NHC-gold complexes **1** started with the formation of *N*-arylimidazoles **2a** and **2b** (Scheme 1). These were obtained from commercially available 2,4,6-trimethylaniline and 2,6-diisopropylaniline, respect-



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Scheme 1 Synthesis of building blocks **2** and **3** (DIBAL-H = diisobutylaluminum hydride; DCM = dichloromethane; DHP = 3,4-dihydro-2Hpyran; PPTS = pyridinium *p*-toluenesulfonate).

ively, according to a literature procedure with similar yields to those reported.¹⁶ The second building block **3** was formed by reduction of methyl 4-(chloromethyl)benzoate **5** with diisobutylaluminum hydride (DIBAL-H; 96% yield) and tetrahydropyranyl-(THP)-protection of alcohol **6** (63% yield).

The coupling of these building blocks was performed by heating **2a** or **2b** in acetonitrile in the presence of **3** to form the imidazolium salts **7a** and **7b** with 78% and 76% yield, respectively (Scheme 2). Here, the THP ether was cleaved during the acidic work-up. The alcohols 7 were chlorinated with thionyl chloride (90/96% yield) and an aminoalkylation with trimethyl-, triethyl-, or tributylamine gave the desired carbene precursors **9** (66–86% yield). These imidazolium salts were transformed into the corresponding gold(1) complexes in the presence of (Me₂S)AuCl and potassium *tert*-butoxide. The NHC gold complexes **1** were obtained with 71–86% yield.

The catalytic activity of the new unsymmetrical ammonium salt-tagged gold catalysts **1** was investigated in cycloisomerization reactions of acetylenic carboxylic acids and amides. The gold-catalyzed lactonization of acetylenic carboxylic acids in water was previously examined by Cadierno *et al.*¹⁷ who used zwitterionic water-soluble gold complexes with sulfonate and



Scheme 2 Synthesis of unsymmetrical ammonium salt-tagged gold(i) complexes 1.

Table 1 Cycloisomerization of carboxylic acid 10a to lactone 11a in the presence of gold catalyst 1ab

0 0 0 H 10a 1ab (2.5 mol%) H ₂ O, rt, 1 h 11a						
Medium	Water		Buffer solution ^{<i>a</i>}			
Cycle	Conv. ^b (%)	Yield ^c (%)	Conv. ^b (%)	Yield ^c (%)		
1	99	78	>99	89		
2	98	73	>99	87		
3	87	72	>99	88		
4	84	66	99	84		
5	79	63	97	81		

 a 1.0 M triethylammonium acetate solution (pH = 7). b Determined by $^1{\rm H}$ NMR. c Isolated yield.

pyridinium groups. Related studies were reported by Navarro Ranninger¹⁸ who applied platinum complexes and also investigated the hydrolysis of the lactone and its mechanism. Furthermore, copper and palladium complexes were also used in lactonization reactions of unsaturated carboxylic acids in aqueous medium.^{19,20} The corresponding cyclization of acetylenic amides to lactams was mainly performed in the presence of TBAF or bases in organic solvents.^{21,22} The only example of a metal-catalyzed cyclization was published by Nagasaka who used a lithium hexamethyldisilazide/AgOTf system.²³ As far as we know, this reaction has not yet been carried out in water.

As a benchmark reaction, we first investigated the cyclization of 4-pentynoic acid (10a) to lactone 11a in the presence of gold catalyst 1ab at room temperature in water (Table 1). A recycling of catalyst 1ab after product extraction with diethyl ether showed decreasing conversions (99-79%) and yields (78-63%) over five cycles. As the measured pH value of pentynoic acid $(pK_a = 4.21 \text{ (ref. 24)})$ in water is 2.44, the gold complex slowly decomposed with the formation of a black precipitate in the acidic medium. The use of a triethylammonium acetate buffer solution with pH = 7 led to high conversions over five cycles and enhanced yields of 89-81%. Notably, an activation of the gold catalyst with a silver salt is not necessary. At present, it is not clear whether complex 1 or a cationic gold species formed by dissociation of chloride is the catalytically active species, even though the rather high concentration of the strongly coordinating chloride anion (from the ammonium chloride side chain) in the reaction mixture certainly disfavors the latter.25

Next, we applied the full library of ammonium salt-tagged gold catalysts 1 to the cycloisomerization of different acetylenic carboxylic acids in aqueous buffer solution (Table 2). It turned out that the mesityl-substituted catalysts **1aa–ac** gave better results than their 2,6-diisopropylphenyl-substituted counterparts **1ba–1bc**. In particular, catalyst **1ab** gave high yields of lactones **11** (84–94%) in all cases. Even though the corresponding complex **1aa** showed a similar reactivity, it gave lower yields (69–86%) than **1ab**. These results were similar to **1bb**

Table 2 Cycloisomerization of carboxylic acids 10 to lactones 11 in the presence of gold catalysts 1 in aqueous buffer solution^a



^a Reaction times required for full conversion are given in the ESI. ^b Isolated vield. ^c 0.5 M solution of the carboxylic acid in THF was used. d At 50 °C.

Table 3 Cycloisomerization of carboxylic acid 10a to lactone 11a in the presence of different amounts of gold catalyst 1ab in aqueous buffer solution

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Entry	1ab (mol%)	Conversion ^{<i>a</i>} (%)	Yield ^a (%)		
1	2.5	>99	89		
2	1.0	97	83		
3	0.5	90	63		
4	0.1	57	37		

^a Determined by ¹H NMR (standard toluene).

(71–86%). The addition of THF as the cosolvent to carboxylic acids 10c-e was necessary in order to dissolve the (otherwise insoluble) substrates. Moreover, for carboxylic acid 10e the temperature had to be raised to 50 °C to decrease the reaction time to 0.5-4 h (otherwise, full conversion was obtained only after 24 h at room temperature).

In order to render the transformation even more sustainable, we decreased the catalyst loading. As shown in Table 3, similar results were obtained for the cycloisomerization of carboxylic acid 10a to lactone 11a with 1 mol% of 1ab instead of 2.5 mol% (entry 2 vs. 1). Even lower catalyst loadings of 0.5 or 0.1 mol% afforded incomplete conversion within 1 h (entries 3 and 4). However, increasing the reaction time to 3 h (with 0.5 mol% of 1ab; 79% yield) or 7 h (with 0.1 mol% 1ab; 74% yield) was sufficient to give a full conversion of 10a to 11a.

A possible side reaction to the cyclization is the gold-catalyzed hydration of the triple bond of the acetylenic acid in the aqueous reaction medium. This has been observed previously by other groups,^{17,18} but not (to this point) with the ammonium salt-tagged gold catalysts 1. Cadierno et al.¹⁷ have



Scheme 3 Gold-catalyzed cycloisomerization of 4-pentynoic acid (10a) and hydrolytic ring-opening of lactone 11a.

Table 4 Cycloisomerization of amides 13 to lactams 14 in the presence of gold catalysts **1** in aqueous buffer solution^a

P R P Ts	[Au] (2.5 mol%) 1 M Et ₃ N·HOAc H ₂ O, 50 °C, 1-4 h	
13		14

Catalyst		1aa	1ab	1ac	1ba	1bb	1bc
Substrate ^b	R	Yield ^c (%)					
13a	Н	95	92	89	86	90	92
13b	Me	84	78	80	87	79	72
13c	iPr	85	80	82	78	84	75
13d	Ph	77	90	89	81	92	91

^a Reaction	times	required	for full	conversio	n are	given	in	the	ESI.	^b 0.3
M solution of the amide in THF was used. ^c Isolated yield.										

detected the formation of ketoacid 12a from 10a with gold complexes within 1 h at rt, which led to moderate yields of lactone 11a (50%) in pure water (ratio of 11a/12a = 3:1). With our catalyst 1ab, however, there were no traces of 12a or any other side product within this time (Table 1). Only after a prolonged reaction time of 24 h in pure water, we could isolate 21% of ketoacid 12a together with 50% of lactone 11a (Scheme 3). In the triethylammonium acetate buffer solution, similar yields were obtained after 24 h (12a: 18%; 11a: 54%). After 3 days in buffer solution, 43% of 12a and 23% of 11a could be isolated, whereas in the absence of a gold catalyst, there was no formation of 12a. If we assume that the cyclization of 10a to 11a is irreversible, the ketoacid 12a is not formed by hydration of 10a but rather by a slow gold-catalyzed hydrolytic ring-opening of the lactone 11a. Accordingly, we could not observe any formation of acetophenone when phenylacetylene was heated to 60 °C for 24 h with gold complex 1ab in water. Under these conditions, only the more electron-rich 1-ethynyl-4-methoxybenzene gave 2% of the corresponding ketone.

In analogy to the acetylenic carboxylic acids 10, the corresponding tosylamides 13²⁶ can be smoothly cyclized to the lactams 14 with the unsymmetrical ammonium salt-tagged gold catalysts 1 in aqueous medium (Table 4). As the measured pH value of amide 13a in water is 3.72 (calcd $pK_a = 6.31$), we again used a buffer solution to avoid degradation of the catalyst. In general, all gold catalysts afforded high yields of lactams 13. Only complexes 1ac/1bc with tributylammonium groups needed extended reaction times of 2-4 h which has

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Clausemarine A (15)

Fig. 2 Furanocoumarin clausemarine A (15) isolated from Clausena lansium, and its 2-epimer 16.



Scheme 4 Synthesis of 2-epi-clausemarine A (16).

also been observed for the formation of lactones 11. In contrast to lactone 11a, treatment of lactam 13a with gold catalyst 1ab for 24 h at 50 °C did not afford any other product.

In order to apply the new gold catalysts 1 in target-oriented synthesis, we have chosen 2-epi-clausemarine A (16), an epimer of the furanocoumarin 15 which was isolated recently by Wu et al.27 from Clausena lansium, a grape-like fruit in Southeast Asia (Fig. 2). This contains an α -substituted lactone ring which can be formed by gold-catalyzed cyclization of a suitable acetylenic acid.

The substrate required for the gold-catalyzed step, the hydroxycarboxylic acid 17 (Scheme 4), was synthesized by Evans alkylation (see the ESI[†] for details). With 1 mol% of our gold catalyst 1ab in aqueous triethylammonium acetate solution containing THF as the cosolvent, the desired lactone 18 was obtained with 77% yield. Hydrogenation of the double bond and subsequent oxidation of the hydroxy group with 2-iodoxybenzoic acid (IBX) gave the cis-(S,S)-diastereomer 19. Other hydrogenation catalysts such as PtO₂ led to an opening of the lactone ring to the corresponding saturated hydroxycarboxylic acid. Treatment of 19 with vinylmagnesium bromide and PBr₃ afforded the labile allyl bromide 20 as a mixture of E/Z-isomers. Finally, conversion of 20 according to a known procedure²⁸ gave the target molecule 2-epi-clausemarine A (16).

Conclusions

We have developed new, rapid access to ammonium salttagged gold catalysts 1 with the possibility of further variation

of their unsymmetrical structure. The modular approach allowed the synthesis of a small library of catalysts 1 with overall yields of 32-47% starting from building blocks 2 and 3. Gold complexes 1 catalyze the cycloisomerization of acetylenic carboxylic acids and amides to the corresponding lactones and lactams in aqueous medium with good to excellent yields. An activation of the gold catalyst with a silver salt is not necessary. The acid-promoted degradation of the catalysts in pure water can be prevented by adjustment of the pH value to 7. The recyclability of gold catalyst 1ab was demonstrated for the benchmark reaction of carboxylic acid 10a to lactone 11a. In contrast to previous gold catalysts operating in water, formation of ketoacids as a side product can be avoided with gold complexes 1. Moreover, we could successfully apply catalyst 1ab in the synthesis of 2-epi-clausemarine A (16). Further examples of sustainable gold catalysts will be reported in due course.

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