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Synthesis and characterization of catalytically active thiazolium gold(I)-carbenes†

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Thiamin analogs were used to synthesize mono gold(I)-carbene derivatives in a single step under aqueous conditions. The resulting thiazolium gold(I)-carbenes catalyze 5-*endo*-dig carbocyclization of an acetylenic dicarbonyl compound in organic solvents and hydroalkoxylation of an allene in aqueous buffer.

The field of gold catalysis has burgeoned over the past several decades.[1,2] Gold catalysts enable construction of architecturally complex molecules from simple precursors under conditions that are unusually mild for metal catalysts.[3,4] Triphenylphosphines and N-heterocyclic carbenes (NHCs) are frequently used as ligands to control reactivity.[5] Thiamin pyrophosphate (TPP, **1**) is a biologically relevant thiazolium salt[6,7] that shares both chemical and structural similarities with commonly employed imidazolium-based NHCs (Fig. 1). Here we report a one-step route to mono gold(I)-carbenes of thiamin derivatives in aqueous buffer, together with their characterization and catalytic properties.

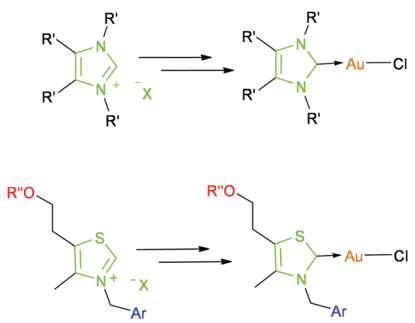

Fig. 1 Imidazolium gold(I)-carbenes (top) and analogous thiazolium-based derivatives (bottom). R′ = alkyl or aryl, R″ = H or diphosphate.

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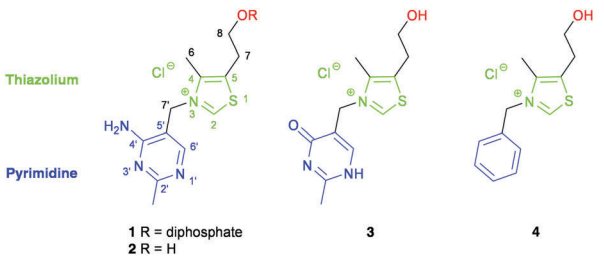


Fig. 2 Structures of thiamin diphosphate (**1**), vitamin B1 (**2**), oxythiamin (**3**) and benzylthiazolium (**4**).

Thiamin derivatives (Fig. 2) are hydrophilic salts with limited solubility in organic solvents. As a result, they are incompatible with standard routes to imidazolium-based gold(I)-carbenes, which include transmetallation of the corresponding copper or silver NHC complex,[8] reaction of the free carbene with a suitable gold precursor,[8] and treatment of imidazolium salts with weak bases in the presence of a gold complex[9–11] in organic solvents. Instead, we opted for a one-pot method in aqueous solution. Thiazolium carbenes were formed by abstraction of the C2 proton from the thiazolium ring in a range of basic buffers containing a small excess of (SMe_2)AuCl. In the case of TPP (**1**), vitamin B1 (**2**) and oxythiamin (**3**), no product was obtained. Instead, decomposition of the gold reagent to give purple colloidal gold was typically observed after stirring the reaction mixture for an hour at room temperature.[12] Decomposition of (SMe_2)AuCl might have been promoted by reactive groups in the ligand. Possibilities include the carbonyl moiety, the exocyclic amino and heterocyclic nitrogens of the pyrimidine ring or, alternatively, the pyrophosphate moiety.

Simple *N*-alkyl- and *N*-benzylthiazolium derivatives that lack these functional groups have been shown to be functional TPP mimics. For example, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (benzylthiazolium, **4**), which possesses a benzyl group in place of the pyrimidine ring, catalyzes a range of biomimetic TPP-dependent reactions.[13,14] Screening of reaction conditions with this analogue quickly afforded the desired gold(I)-carbene **5** as a white precipitate.

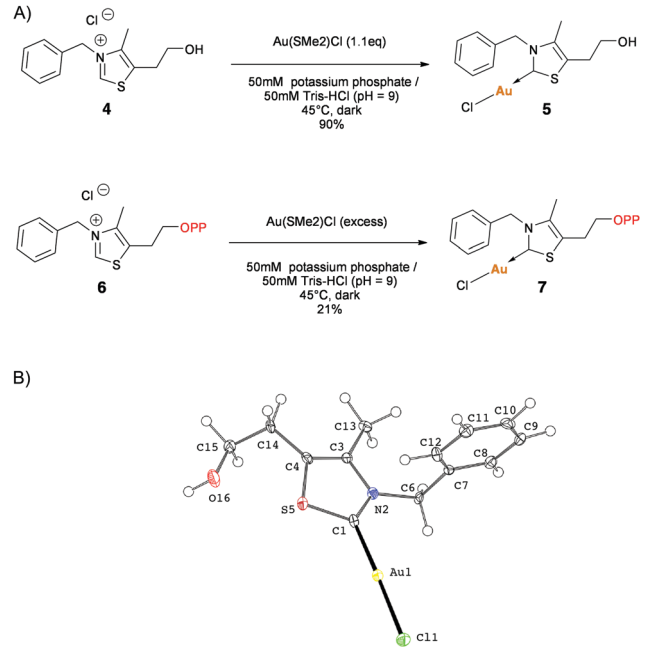
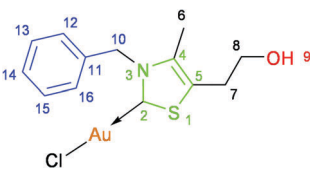


Fig. 3 (A) Formation of gold(I)-carbenes from benzylthiazolium **4** and benzylthiazolium pyrophosphate **6**. (B) X-ray crystal structure of **5**.

The gold(I) carbene was obtained in 90% yield by mixing *N*-benzylthiazolium (**4**) with 1.1 equivalents of $(SMe_2)AuCl$ in a 1 : 1 mixture of 50 mM Tris–HCl and potassium phosphate buffer (pH 9.0) at 45 °C for 2 h in the dark (Fig. 3A). As expected for formation of a C2 adduct, the ^1H signal for the C2 proton disappeared and the ^{13}C signal for the C2 carbon shifted from 154.91 ppm to 192.17 ppm (see Table 1). For comparison, the ^{13}C resonance of the C2 carbon of analogous NHC derivatives typically appears around 135 ppm and shifts to *ca.* 170 ppm for the corresponding gold(I) carbene.[15]

Elemental analysis of compound **5** confirmed the mass fractions of carbon, hydrogen, nitrogen, sulfur and chloride expected for

Table 1 ^{13}C NMR shifts for compounds **4**, **5**, **6** and **7**



	Compound #			
Carbon #	**4**	**5**	**6**	**7**
2	154.91	192.17	155.27	205.05
4	142.79	140.6	143.07	143.76
5	135.64	133.91	134.9	135.01
6	11.11	12.53	11.17	12.17
7	29.15	30.16	27.55	28.15
8	60.33	60.86	64.71	65.15
11	56.74	59.84	56.72	59.05
12	131.75	133.49	131.73	134.22
13–17	129.47	128.88	129.45	129.31
14–16	128.23	126.35	128.3	126.69
15	129.42	128.35	129.39	128.63

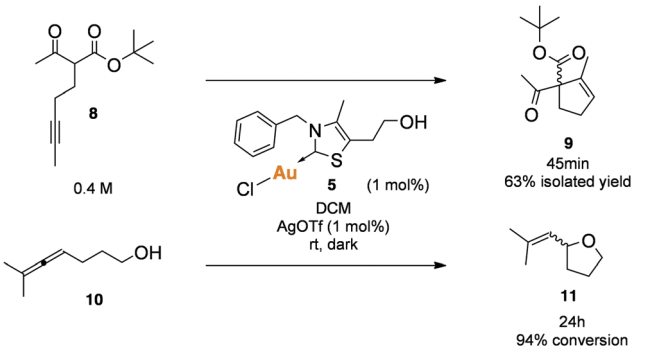


Fig. 4 Carbocyclization of acetylenic dicarbonyl **8** (top) and hydroalkoxylation of allene **10** (bottom) catalyzed by benzylthiazolium gold(I)-carbene **5**.

the benzylthiazolium gold(I)-carbene. X-ray crystallography provided definitive evidence for its structure. Diffraction quality crystals were obtained by slow diffusion of pentane into an ethyl acetate solution of **5**. As seen in Fig. 3B, the gold carbene is linear (C2–Au–Cl 178.06°) and sits in the plane of the thiazolium ring (see ESI†). The lengths of the C2–Au (1.980 Å) and the Au–Cl (2.287 Å) bonds are comparable to those observed for other NHC gold(I)-carbenes.[15] Although Maldi-TOF analysis gave the mass of a bis-carbene (663.2 *m*/*z*) rather than a mono-gold(I)-carbene (465.0 *m*/*z*), the compound presumably rearranged under the conditions of the measurement.

The benzylthiazolium gold(I)-carbene **5** was tested as a catalyst for two reactions that are efficiently catalyzed by imidazolium gold(I)-carbenes (Fig. 4). The first was the 5-*endo*-dig carbocyclization of an acetylenic dicarbonyl compound.[16] In the presence of silver triflate, compound **5** (1 mol%) promotes transformation of alkyne **8** into the cyclopentene derivative **9** in dichloromethane. The yield of isolated product was 63%, providing the first evidence that thiazolium gold(I)-carbenes are active catalysts. As a second reaction, we examined the gold(I)-catalyzed hydroalkoxylation of allenes.[4,17] Compound **5** (1 mol%) catalyzed the transformation of 6-methylhepta-4,5-dien-1-ol (**10**) to 2-(2-methylprop-1-en-1-yl)tetrahydrofuran (**11**), again in dichloromethane. The conversion, determined by NMR spectroscopy, was 94% after 24 h reaction at room temperature.

Notably, both model reactions were performed under "open-flask" conditions in wet solvents, highlighting the robustness of the catalyst. In their work on entrapped ionic gold catalysts, Toste *et al.* showed that the hydroalkoxylation of compound **10**, which had been generated enzymatically by hydrolysis of an acetyl ester, can also be carried out in phosphate buffer at pH 7 in yields ranging from 53 to 100%.[18] When we tested the catalytic activity of carbene **5** with allene **10** in 50 mM potassium phosphate buffer (pH = 7) containing 1 mM $MgCl_2$ and 15 to 30% DMSO, however, no product was observed by TLC after 24 h at room temperature or after 5 h at 40 °C, presumably due to the low solubility of the catalyst under these conditions.

Although thiazolium salts themselves readily dissolve in water, formation of the corresponding gold(I)-carbene decreases solubility substantially. The natural TPP cofactor contains a diphosphate moiety that greatly enhances hydrophilicity and, at the same time,

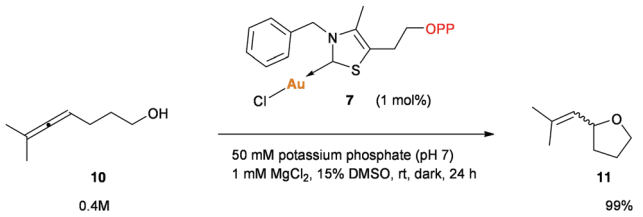


Fig. 5 Hydroalkoxylation of allene **10** catalyzed by benzylthiazolium pyrophosphate gold(I)-carbene **7**.

serves as a recognition handle for binding to enzyme active sites. We anticipated that pyrophosphorylation would similarly increase the solubility of the thiazolium gold(I)-carbene **5**, enabling homogeneous catalysis in aqueous media. Because direct attempts to phosphorylate **5** failed, we first transformed *N*-benzylthiazolium enzymatically into the corresponding pyrophosphate derivative (**6**) using ATP as the phosphate donor, and then formed the gold(I)-carbene *via* a modification of the procedure described above for **5** (Fig. 3A).

N-Benzylthiazolium (**4**) is readily accepted as a substrate by thiamin pyrophosphokinase (TPPK, EC 2.7.6.2), the biosynthetic enzyme that converts vitamin B1 (**2**) into TPP (**1**).[19] When the biocatalytic reaction was performed with 1 μM purified enzyme in aqueous buffer at 37 °C, product was obtained in 41% yield after purification by preparative HPLC. Precipitation of the enzyme during the 6 h incubation may have limited the yield of the biocatalytic conversion, so we immobilized the biocatalyst in a silica sol–gel matrix.[20,21] Although the overall yields did not improve, the immobilized pyrophosphokinase could be reused multiple times, increasing overall efficiency. The identity of the pyrophosphorylated product **6** was confirmed by LCMS, ^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopy, and X-ray crystallography (see ESI,† Table S2).

As observed for TPP, purple colloidal gold nanoparticles were formed when we simply mixed compound **6** with (SMe_2)AuCl under the conditions used to prepare **5**. We therefore compensated for the loss of (SMe_2)AuCl by supplementing the reaction with an additional equivalent. When the transformation was complete as judged by reversed-phase TLC and LCMS, the sample was purified by preparative HPLC. Under the HPLC conditions, three species were obtained, one of which was the desired thiazolium gold(I)-carbene chloride **7** (21% yield), the second, the more activated and less stable gold(I)-carbene acetonitrile derivative (8%), and the third, the bis-carbene (16%). The ^{1}H- and ^{13}C-NMR spectra of **7** resembled those of **5**, including the absence of a signal for the C_2 proton on the thiazolium ring and a 50 ppm downfield shift of the ^{13}C signal from 155.27 ppm to 205.05 ppm for the carbene carbon (Table 1). Like **5**, compound **7** catalyzes the intramolecular hydroalkoxylation of allenes (Fig. 5). In the case of **7**, however, the reactions were performed in 50 mM phosphate buffer at neutral pH containing 1 mM magnesium chloride and 15% DMSO to improve substrate solubility. The conversion of **10** to **11** determined by NMR was >99% after 24 h.

In summary, thiamin analogs were used to prepare novel mono thiazolium gold(I)-carbenes. The free NHC carbenes, generated from the thiazolium salts in aqueous buffer, were found to react directly and cleanly with (SMe_2)AuCl in a single step. The resulting compounds—both with and without a pyrophosphate moiety—were active catalysts for carbocyclization and hydroalkoxylation reactions. Because the pyrophosphate group of TPP is essential for supramolecular anchoring of the cofactor to thiamin-dependent enzymes, complexes between gold(I)-carbene **7** and suitable host proteins could give rise to novel gold-enabled biocatalysts.

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