Gold Carbenoids

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# Gold-Catalyzed Intramolecular Redox Reaction of Sulfinyl Alkynes: Efficient Generation of α-Oxo Gold Carbenoids and Application in Insertion into R–CO Bonds**

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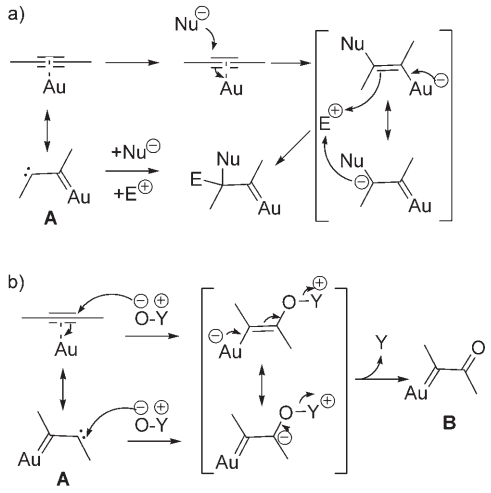
Gold catalysts are powerful soft Lewis acids for activating alkynes toward nucleophilic attack.[1] A remarkable feature of such systems is that the alkenylgold intermediate can react as an α-deprotonated gold carbenoid, reminiscent of an enolate, and be nucleophilic. Consequently, the Au alkyne complex can be considered equivalent to an α-carbene gold carbenoid (**A** in Scheme 1a). This rather unique reactivity has been




***Scheme 1.*** a) Nucleophilic/electrophilic reactivity of a Au alkyne complex. b) Generation of an α-oxo gold carbenoid by the reaction of a Au alkyne complex with an oxygen-delivering oxidant.

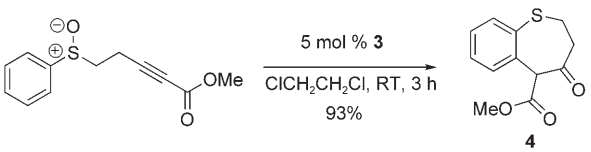
elegantly demonstrated in a range of reactions, including cyclopropanation of internal C–C double bonds,[2] 1,2-acyloxy migration of terminal propargyl esters,[3] the intramolecular acetylenic Schmidt reaction,[4] formation of Au-bounded 1,3-dipolar species,[5] and alkylthio migration.[6]

To further explore this chemistry, we envisioned that an oxygen-delivering oxidant could react with the Au alkyne complex or its equivalent α-carbene gold carbenoid via an addition–elimination process, donating an oxygen atom and leading to oxidative formation of a synthetically versatile α-oxo gold carbenoid **B** (Scheme 1b).[7] Herein, we report this Au-catalyzed redox process using a tethered sulfoxide as the oxidant.

We chose sulfoxide as the oxidant because of its ease of synthesis and handling; it was tethered to the C–C triple bond in order to facilitate the initial nucleophilic attack. Hence, sulfinyl alkyne **1**, readily prepared in two steps from thiophenol, was treated with various gold catalysts. While attempts to trap the expected α-oxo gold carbenoid intermediate using various substrates including styrene, benzyl alcohol, and ethyl vinyl ether failed, much to our surprise, tetrahydrobenzothiepinone **2** was formed in excellent yield when 5 mol% of dichloro(pyridine-2-carboxylato)gold(III) (**3**)[8] was used as catalyst in the absence of any additional substrate (Scheme 2).[9] The formation of **2** can be readily explained following the hypothesis outlined in Scheme 1b: Au activation of the C–C triple bond promotes a facile 5-*exo-dig* cyclization by the sulfoxide moiety; the resulting alkenylgold species is then capable of pushing out the sulfide moiety, forming Au carbenoid **C**; finally, cyclization by intramolecular reaction of the Au carbenoid moiety in **C** with the benzene ring leads to product **2**, presumably via electrophilic aromatic substitution. It is conceivable that a Au-containing cyclic sulfur ylide **D** may be formed reversibly upon sulfur attack of the carbenoid carbon atom. This ylide may not only provide temporary stabilization for the Au carbenoid but also serve to bring the phenyl group into close proximity to overcome unfavorable entropy for seven-membered ring formation.

This novel reactivity of the sulfinyl alkyne was also observed when a methoxycarbonyl group was attached to the C–C triple bond, and β-ketoester **4** was isolated in 93% yield [Eq. (1)]. Interestingly, dihydrobenzothiocinones **5** can also be formed from sulfoxides containing either a terminal alkyne or an alkynoate, albeit in lower yields [Eq. (2)].

With the hypothesis in Scheme 1b verified, we explored the synthetic potential of this chemistry. We envisioned that a pinacol-type rearrangement[10] can be coupled with the formation of α-oxo gold carbenoids. As shown in Scheme 3, migration of $R^1$ to the Au carbenoid in **E** would lead to the formation of β-hydroxyenone **7** or its β-dicarbonyl tautomer

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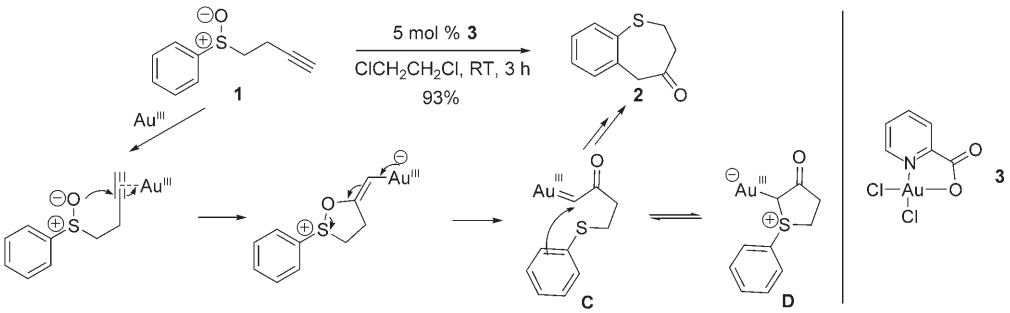
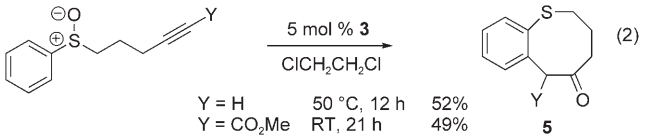
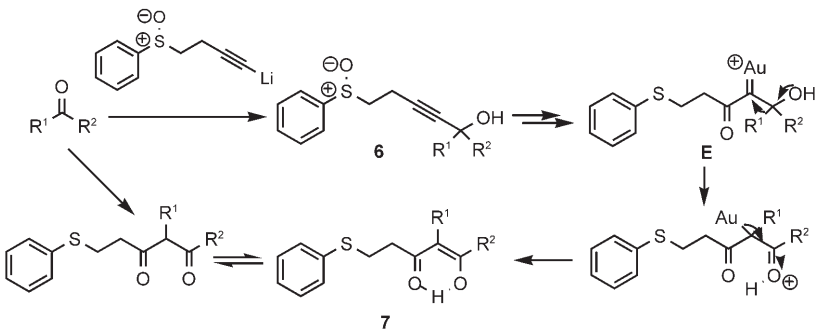


***Scheme 2.*** Proposed mechanism for the formation of tetrahydrobenzothiepinone **2**.



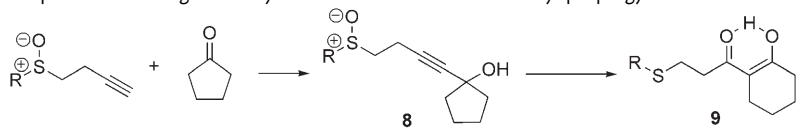
upon deauration. It is noteworthy that the benzenethio group in **7** can be readily eliminated upon oxidation,[11] yielding a versatile vinylcarbonyl moiety. While intermediate **E** might be accessible from propargylic alcohol **6** by the Au-catalyzed intramolecular redox reaction of sulfinyl alkynes discussed above, there are potential problems: one is whether the 5-*exo-dig* cyclization by the sulfoxide moiety remains predominant over the alternative 6-*endo-dig* cyclization, especially when neither $R^1$ nor $R^2$ is H; and another, probably even more significant, problem is how to avoid the cyclization of the Au carbenoid to the benzene ring. Nevertheless, this sequence would constitute an effective and novel two-step insertion of a latent vinylcarbonylmethylene group into the $R^1$–CO bond and avoid using hazardous diazo compounds.[12]



***Scheme 3.*** Design of a two-step sequence for carbonyl insertion via Au-catalyzed reactions of sulfinyl propargylic alcohols.

We began with phenyl sulfoxide **8a**, which was obtained in one step from cyclopentanone (Table 1). To our delight, the expected insertion product, β-hydroxyenone **9a**, was formed in 36% yield using the reaction conditions in Scheme 2 (i.e. complex **3** as catalyst; Table 1, entry 1). While side products were difficult to purify and characterize, $^1$H NMR spectra of partially purified fractions indicated that the 6-*endo-dig* cyclization and the cyclization to form a fused system were indeed the main causes for the low efficiency. Attempts to improve this reaction by screening other Au catalysts revealed that IPrAuNTf$_2$ (Tf = $CF_3SO_2$) was a much better catalyst (Table 1, entry 4). To prevent the undesired Au carbenoid cyclization, the phenyl group was modified, and both its 2- and 6-positions were blocked (Table 1, entries 5 and 6). Surprisingly, the reactions did not improve using those substrates. Fortuitously, we found that 2-chlorophenyl worked well, and the desired insertion product **9d** was formed in 63% yield (as determined by NMR spectroscopy) using IPrAuNTf$_2$ as catalyst (Table 1, entry 7). The yield was further improved when the substrate concentration was lowered to 0.005 M (Table 1, entry 8). Among other groups tested for R, a *tert*-butyl group led to

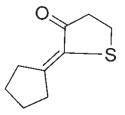
***Table 1:*** Optimization for gold-catalyzed tandem reactions of sulfinyl propargylic alcohol **8**.[a]



| Entry[a] | R | | Reaction conditions | Yield of **9** [%][b] |
|---|---|---|---|---|
| 1 | Ph | **8a** | 5 mol% **3**, $(ClCH_2)_2$, RT, 3 h | 36 |
| 2 | | | 5 mol% $Ph_3PAuNTf_2$, $(ClCH_2)_2$, RT, 5 h | 11 |
| 3 | | | 5 mol% IMesAuNTf$_2$, $(ClCH_2)_2$, RT, 3 h | 22 |
| 4 | | | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 3 h | 53 |
| 5 | 2,6-$Me_2C_6H_3$ | **8b** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 12 h | 37 |
| 6 | 2,6-$Cl_2C_6H_3$ | **8c** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 24 h | 44 |
| 7 | 2-$ClC_6H_4$ | **8d** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 3 h | 63 |
| 8 | 2-$ClC_6H_4$[c] | **8d** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 3 h | 77[d] |
| 9 | *t*Bu | **8e** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 3 h | –[e] |
| 10 | *n*Bu | **8f** | 5 mol% IPrAuNTf$_2$, $(ClCH_2)_2$, RT, 2 h | 15[f] |

[a] The substrate concentration was 0.02 M. [b] Estimated by $^1$H NMR spectroscopy using diethyl phthalate as an internal standard. [c] The substrate concentration was 0.005 M. [d] Yield of isolated product. [e] 53% of **10** was isolated. [f] 18% of **11** was isolated.



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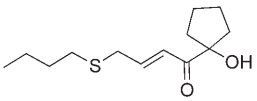

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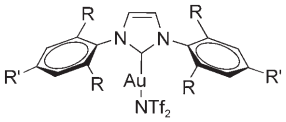


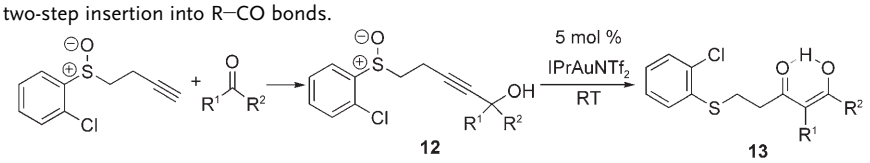
IPrAuNTf$_2$: R' = H, R = *i*Pr
IMesAuNTf$_2$: R' = R = Me

dihydrothiophenone **10** in 53% yield (Table 1, entry 9), which must be formed via a sulfur ylide of type **D**;[13] moreover, an *n*-butyl group led to the isolation of 6-*endo-dig* cyclization product **11**[14] in 18% yield besides the insertion product (Table 1, entry 10).

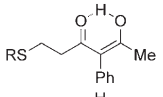
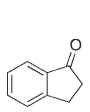
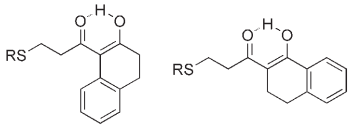
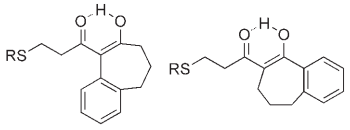
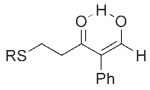
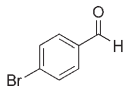
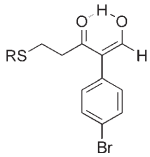
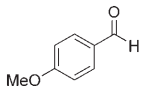
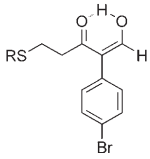
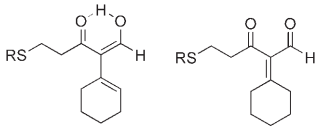
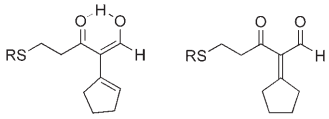
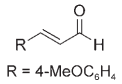
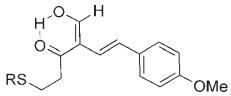
Using the best protocol (Table 1, entry 8), we studied the scope of this two-step insertion reaction. As shown in Table 2, acetophenone was a fairly good substrate, and β-hydroxyenone **13a** was formed with selective phenyl migration (Table 2, entry 1). Interestingly, aryl migration was only slightly favored in benzo-fused cyclic ketones such as 1-indanone (Table 2, entry 2) and α-tetralone (Table 2, entry 3), which led to mixtures with fairly good to excellent combined yields. This two-step sequence also worked well with aromatic aldehydes. For example, benzaldehyde was transformed into β-hydroxy-α-phenylenone **13d** in good yield (Table 2, entry 4). Noteworthy is the highly selective migration of the phenyl group, as no H-migration product was detected. Substituted benzaldehydes were good substrates as well, and β-hydroxyenones **13e** (Table 2, entry 5) and **13f** (Table 2, entry 6) were isolated in good yields. Again, only aryl migration was detected in both cases. This reaction sequence was successfully extended to enals, and cyclic enals (Table 2, entries 7 and 8) as well as 4-methoxycinnamaldehyde (Table 2, entry 9) all led to good yields of insertion products. Noteworthy are the cases of aliphatic enals, where the enal tautomers of the products were also observed. Similar to the cases of aromatic aldehydes, the alkenyl group migrated with high selectivity.

The highly selective migration of aryl or alkenyl groups over H atoms to the Au carbenoid is rather unique and mechanistically intriguing. Previous studies with transition-

***Table 2:*** Scope of the IPrAuNTf$_2$-catalyzed intramolecular redox reaction of sulfinyl propargylic alcohols: a two-step insertion into R–CO bonds.



12 13

| Entry[a] | Carbonyl compound | Yield of **12** [%] | Dicarbonyl product[b] | | Reaction time [h] | Yield of **13** [%] |
|---|---|---|---|---|---|---|
| 1 |  | 60 |  | **13a** | 2 | 58[c,d] |
| 2 |  | 60 |  1 : 0.54 | **13b** | 2 | 87[d] |
| 3 |  | 59 |  1 : 0.61 | **13c** | 3.5 | 53[d,e] |
| 4 |  | 89 |  | **13d** | 6 | 69[f] |
| 5 |  | 88 |  | **13e** | 8 | 70[f] |
| 6 |  | 84 |  | **13f** | 6 | 75[f] |
| 7 |  | 85 |  1 : 0.07 | **13g** | 3 | 78[d] |
| 8 |  | 85 |  0.29 : 1 | **13h** | 2.5 | 63[d,g] |
| 9 |  R = 4-MeOC$_6$H$_4$ | 76 |  | **13i** | 11 | 68[f] |

[a] The substrate concentration was 0.005 M. [b] R = 2-ClC$_6$H$_4$. [c] Less than 2% methyl migration. [d] ClCH$_2$CH$_2$Cl as solvent. [e] 37% of enyne product due to dehydration was isolated. [f] MeNO$_2$ as solvent. [g] The $^1$H NMR spectrum of the crude residue indicated there is 7% of H-migration product.

metal-catalyzed rearrangement of α-diazo-β-hydroxyester revealed that migration of an H atom is preferred over that of a phenyl or alkenyl group,[15] although the migratory aptitudes were shown to be subject to electronic and steric effects in rhodium(II)-catalyzed reactions when the β-hydroxy group was modified.[16,17] It is unlikely that the observed selectivity is simply due to Au itself, as Liao and Wang observed very little phenyl migration when ethyl-2-diazo-3-hydroxy-3-phenylpropionate was treated with either AuCl or $AuCl_3$.[12d] Detailed mechanistic study to understand the origin of this selectivity is underway and will be reported in due course.

In conclusion, we have discovered a novel Au-catalyzed intramolecular redox reaction of sulfinyl alkynes, where the sulfoxide moiety is reduced and the C–C triple bond is oxidized. The α-oxo Au carbenoid generated in this reaction can efficiently cyclize the benzene ring, yielding tetrahydrobenzothiepinones or dihydrobenzothiocinones. A two-step insertion of a latent vinylcarbonylmethylene group into ketones and aldehydes is developed. Noteworthy is the highly selective migration of aryl or alkenyl groups in the cases of aldehydes.

## Experimental Section

Typical procedure for the Au-catalyzed reaction of sulfinyl propargylic alcohol **12**: IPrAuNTf$_2$ (5 mol%, 0.05 M in 1,2-dichloroethane) was added to a solution of the alcohol (0.005 M) in 1,2-dichloroethane at room temperature under $N_2$. The progress of the reaction was monitored by TLC. When the reaction was judged to be complete, the reaction mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate = 20:1).

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**Keywords:** carbenes · gold · homogeneous catalysis · insertion · redox chemistry

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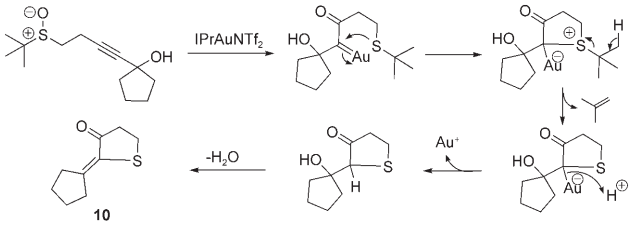
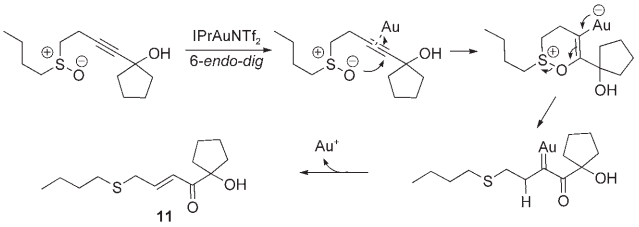
[12] Ethyl diazoacetate has been used to insert into carbonyl compounds in the presence of acids or transition metal catalysts. For selected examples, see: a) R. Pellicciari, R. Fringuelli, P. Ceccherelli, E. Sisani, *J. Chem. Soc. Chem. Commun.* **1979**, 959; b) C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258; c) S. Kanemasa, T. Kanai, T. Araki, E. Wada, *Tetrahedron Lett.* **1999**, *40*, 5055; d) M. Y. Liao, J. B. Wang, *Tetrahedron Lett.* **2006**, *47*, 8859; e) F. P. Xiao, J. Wang, *J. Org. Chem.* **2006**, *71*, 5789; f) D. Benito-Garagorri, J. Wiedermann, M. Pollak, K. Mereiter, K. Kirchner, *Organometallics* **2007**, *26*, 217.

[13] The mechanism for the formation of **10** is likely as shown below:




[14] Here is the proposed mechanism for the formation of **11**:




[15] For selected examples, see: a) ref. [12a]; b) A. Padwa, S. Y. Kulkarni, J. Zhang, *J. Org. Chem.* **1990**, *55*, 4144; c) ref. [12d].

[16] For selected references, see: a) ref. [12e]; b) F. P. Xiao, Y. Liu, J. B. Wang, *Tetrahedron Lett.* **2007**, *48*, 1147; c) W. Shi, N. Jiang, S. Zhang, W. Wu, D. Du, J. Wang, *Org. Lett.* **2003**, *5*, 2243.

[17] For Lewis or Brønsted acid catalyzed direct reactions of aromatic aldehydes with ethyl diazoacetate involving predominant aryl group migration, see: a) ref. [12c]; b) ref. [12f]; c) M. E. Dudley, M. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M. R. Atuu, B. Branstetter, M. M. Hossain, *J. Org. Chem.* **2004**, *69*, 7599.