ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 9054–9056

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Fascinating reactivity in gold catalysis: synthesis of oxetenes through rare 4-*exo*-dig allene cyclization and infrequent β-hydride elimination†

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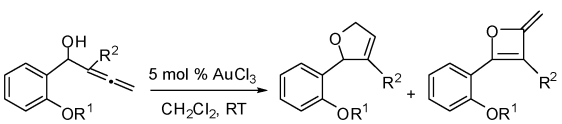
Received 31st May 2011, Accepted 5th July 2011
DOI: 10.1039/c1cc13212a

A novel reactivity in gold catalysis, namely the unusual preference for the 4-*exo*-dig cyclization in allene chemistry as well as the rare β-hydride elimination reaction, was uncovered starting from readily available allenols.

The transition-metal-catalyzed cyclization of allene derivatives bearing a nucleophilic functionality has led to many synthetically useful transformations.[1,2] However, regioselectivity problems are significant (*endo*-trig *versus endo*-dig *versus exo*-dig *versus exo*-trig cyclization). The metal catalyst can coordinate to either allenic double bond, depending on the regioselectivity of the attack both on the structure of the substrate and the nature of the catalyst. Four different products can be obtained, but the formation of five- or six-membered rings is favored. The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature.[3–5] Thus, it is not surprising that gold salts are ranked among the best catalysts for the selective activation of the allene moiety.[6] An important, yet unexamined, subject in the field of Au-catalyzed cyclizations is how to control the reaction selectivity for the substrates carrying different allene substitution patterns. Importantly, it should be remarked that reports on the synthesis of strained rings such as four-membered heterocycles are lacking in the gold chemistry of allenes. Besides, taking into consideration the chemical and medicinal interest of oxetanes,[7] the direct synthesis of oxetane derivatives from allenols emerged as an attractive transformation to develop.

Despite the efficiency of the recently discovered gold-catalyzed cycloisomerization reaction of α-hydroxyallenes to yield dihydrofurans,[6,8] the introduction of a wide range of substituents on the allene group needs to be explored in order to expand its application in the synthesis of useful chemicals. Traditionally, metal-catalyzed cyclizations on α-allenols favor a 5-*endo*-trig pathway.[6,8] Owing to our interest in metal-catalyzed processes employing alkynes and allenes,[9] we were attracted to the possibility that a non-five-membered heterocycle could be accessed by variation of the allene substitution. We hypothesized that the product selectivity could be impacted by modulating the relative stability of the η^2 complexes generated by π-coordination of the metal to the C=C bonds during the course of the reaction.

Starting allenols were prepared from salicylaldehyde derivatives *via* regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media adopting our methodology.[10] In our study on the possibility of selectivity reversal in Au catalysis, methyl-substituted allenol **1a** and phenyl-substituted allenol **1c** were used as the model compounds and $AuCl_3$ as the catalyst to describe the experiments. The reaction in dichloromethane proceeded smoothly for both substrates. Allenol **1a** afforded the expected cycloisomerization adduct, dihydrofuran **2a**. However, as a first try, we were happy to notice that the reaction of phenyl-derivative **1c** afforded oxetene **3c** as a major component (42% isolated yield), even dihydrofuran **2c** was also isolated as a minor component (17%). Thus, when the reaction was performed using **1c** instead of **1a**, a switch of the regioselectivity was observed. Encouraged by this preliminary result and with the optimal reaction conditions established, the scope of this novel oxycyclization reaction was then studied. To our great delight, the reaction of phenyl-derivatives **1d** and **1e** afforded the oxetenes **3d** and **3e** as the sole products in good yields (Scheme 1). This intriguing transformation can be explained invoking an uncommon allene 4-*exo*-dig cyclization as well as an infrequent β-hydride elimination reaction in gold catalysis (C–Au bonds prefer protodeauration over



1a R^1 = prop-2-enyl, R^2 = Me	**2a** (71%)	
1b R^1 = 2-methylallyl, R^2 = Me	**2b** (51%)	
1c R^1 = prop-2-enyl, R^2 = Ph	**2c** (17%)	**3c** (42%)
1d R^1 = 2-methylallyl, R^2 = Ph		**3d** (62%)
1e R^1 = 2-bromoallyl, R^2 = Ph		**3e** (85%)
1f R^1 = methyl, R^2 = Ph	**2f** (31%)	**3f** (23%)
1g R^1 = prop-2-ynyl, R^2 = Ph	**2g** (22%)	**3g** (30%)
1h R^1 = (*E*)-(4-chlorobut-2-enyl), R^2 = Ph	**2h** (22%)	**3h** (33%)
1i R^1 = 2-methylallyl, R^2 = 4-$MeOC_6H_4$		**3i** (48%)
1k R^1 = 2-methylallyl, R^2 = 4-BrC_6H_4	**2k** (44%)	**3k** (25%)

Scheme 1 Divergent oxycyclization reactions of α-allenols **1** under gold catalysis.

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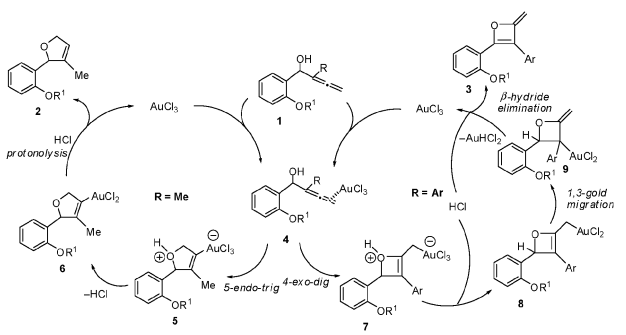
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds, and copies of NMR spectra. See DOI: 10.1039/c1cc13212a

β-hydride elimination; indeed, gold-hydrides are rare species and difficult to access).[11–13]

The incorporation of different substituents into the salicylaldehyde-derived allenol was tested next. As revealed in Scheme 1, various aryl-substituted allenols **1f–i** were suitable for such heterocyclization reaction. For example, the *p*-methoxyphenyl substituent at the allene side was tolerated. Similarly, the ether chain bearing methoxy, (*E*)-(4-chlorobut-2-enyl)oxy, or propargyloxy moieties also afforded the desired oxetenes, but not as the unique product. Starting from allenols **1c**, and **1f–h**, and performing the reaction at room temperature, a mixture of two different products arises from competitive 4-*exo*-dig *versus* 5-*endo*-trig cyclizations (Scheme 1). Interestingly, allenols **1c** and **1f–h** under $AuCl_3$ catalysis in dichloromethane at reflux temperature gave as the sole or major product the oxetene component (Scheme S1, ESI†). Thus, it is possible to suppress or minimize the formation of the dihydrofuran ring (cycloisomerization adduct) by performing the reaction at higher temperature, yielding the oxetene (oxycyclization/dehydrogenation adduct) as the exclusive or major product. A general trend can be deduced on the basis of these results: the four-membered oxetene is the thermodynamic control product while the dihydrofuran is the kinetic control product.

A possible pathway for the gold-catalyzed achievement of dihydrofurans **2** may initially involve the formation of a complex **4** through coordination of the gold trichloride to the distal allenic double bond of α-allenols **1**. Next, regioselective 5-*endo*-trig oxyauration forms zwitterionic intermediates **5**, which after loss of HCl generate neutral species **6**. Protonolysis of the carbon–gold bond of **6** liberates adducts **2** with concurrent regeneration of the Au(III) catalytic species (Scheme 2, left catalytic cycle).

A mechanistic rationale for the gold-catalyzed conversion of aryl-substituted allenols **1** into oxetenes **3** is more intricate. It is worth noting that the cyclization affords cycloadducts **3** from a 4-*exo*-dig cyclization/dehydrogenation process instead of that from the usually preferred 5-*endo*-trig cycloisomerization reaction. The pathway proposed in Scheme 2 (right catalytic cycle) looks valid for the formation of products type **3**. It could be presumed that the initially formed gold complex **4**, through coordination of the $AuCl_3$ to the distal allenic double bond, undergoes an intramolecular attack (rare 4-*exo*-dig *versus* normal 5-*endo*-trig oxyauration) by the hydroxy group, giving rise to the oxetene intermediate **7**. Loss of HCl in intermediate **7** generates neutral species **8**, which after 1,3-gold migration[11] leads to the formation of oxetane species **9**. Uncommon β-hydride elimination rather than protonolysis of the carbon–gold bond[12–14] linked to a reaction of HCl with the gold hydride would then liberate the oxacycle type **3** with concomitant regeneration of the catalytic Au(III) salt. In the conversion of intermediate **9** into alkylidene-oxetenes **3**, a possible alternative step to the β-hydride elimination should involve a direct transfer of the hydride to the proton of HCl, thus re-forming $AuCl_3$ and H_2.[15]



Scheme 2 Mechanistic explanation for the gold-catalyzed oxycyclization of methyl- and aryl-substituted α-allenols **1**.

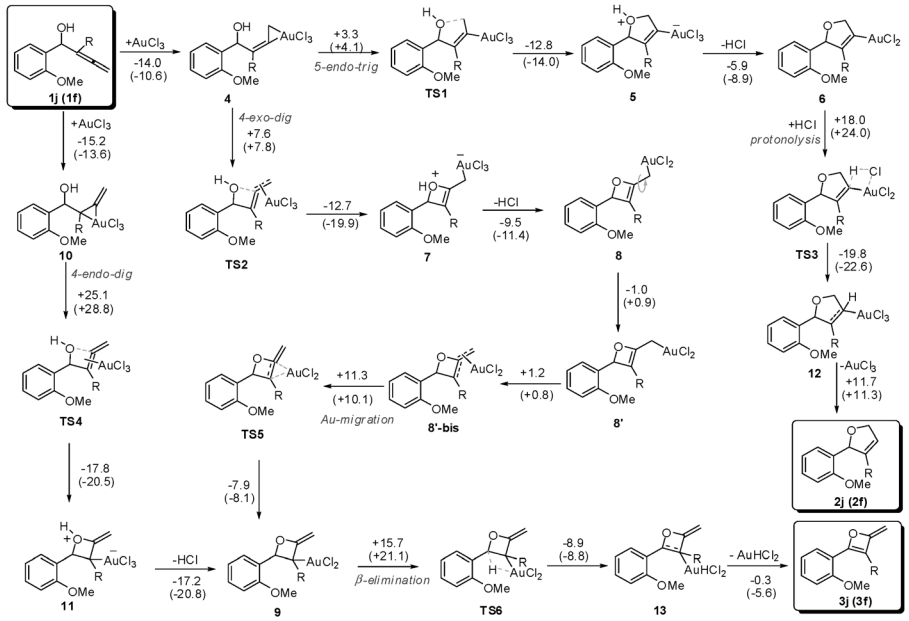
A coordination to the internal C–C double bond would similarly lead to intermediate **9** (see Scheme S4, ESI†).

To gain more insights into the reaction mechanisms of the above gold-catalyzed oxycyclization reactions, a computational (DFT) study was carried out. The corresponding computed reaction profiles (PCM-B3LYP/def2-SVP level)[16] of methyl- and phenyl-substituted allenols **1j** and **1f** are shown in Scheme 3, which gather the respective free energies in CH_2Cl_2 solution.

As initially envisaged, two different coordination modes of the metal fragment to the allenic double bond, *i.e.* distal *vs.* proximal, are possible. Our calculations indicate that although the proximal approach is slightly more exergonic, the subsequent 4-*endo*-dig oxycyclization reaction (from complex **10** *via* transition state **TS4**) is clearly kinetically disfavored with respect to the corresponding 5-*endo*-trig or 4-*exo*-dig processes in view of the much higher activation barrier of the former transformation. Thus, the oxycyclization reactions start from the common intermediate complex **4**, formed through coordination of $AuCl_3$ to the distal allenic double bond of **1j**, **f**.

As readily seen in Scheme 3, the 5-*endo*-trig reaction forms the zwitterionic complex **5** through an exergonic process ($\Delta G_{R,298} = -9.5$ and -9.9 kcal mol^{-1} for R = Me and R = Ph, respectively) *via* **TS1** with a very low activation barrier ($\Delta G^{\neq}_{298} = +3.3$ and $+4.1$ kcal mol^{-1}). The sequential loss of HCl, which forms neutral species **6**, and protonolysis of the C–Au bond *via* **TS3** produce the final dihydrofuran **2** regenerating the catalyst. Interestingly, the barrier energy of this step is clearly more favorable when R = Me than when R = Ph ($\Delta\Delta G^{\neq}_{298} = 6.0$ kcal mol^{-1}), which is in nice agreement with the preferential formation of dihydrofurans **2** at expenses of oxetenes **3** for methyl-substituted allenols **1a**, **b** (see Scheme 1).

The 4-*exo*-dig process, which transforms complex **4** into **7** *via* **TS2**, also occurs with a low activation barrier ($\Delta G^{\neq}_{298} = +7.6$ and $+7.8$ kcal mol^{-1} for R = Me and R = Ph, respectively) in an exergonic transformation as well. Despite that, the barrier energies are higher than those computed for the 5-*endo*-trig process, thus indicating that the latter reaction is kinetically favored. Nevertheless, the low barriers of both processes should be translated into a mixture of reaction products, as experimentally found (see Scheme 1). Strikingly, the computed reaction energy difference between both nucleophilic additions indicates that whereas the 5-*endo*-trig reaction is thermodynamically favored when R = Me ($\Delta\Delta G_{R,298} = +5.1$ kcal mol^{-1}), the 4-*exo*-dig reaction is favored when R = Ph ($\Delta\Delta G_{R,298} = -2.2$ kcal mol^{-1}). This justifies the formation of oxetenes **3** as the major reaction product when the reaction is conducted under reflux conditions (see Scheme S1, ESI†). Loss of HCl in intermediate **7** generates neutral species **8**. This step is much easier than the corresponding loss



Scheme 3 Computed reaction profile for the gold-catalyzed oxycyclization reactions of allenols **1j** (R = Me, plain values) and **1f** (R = Ph, values in parentheses). Free energies (ΔG_{298}, in kcal mol^{-1}) have been computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

of HCl which transforms **5** into **6** due to close proximity of the hydrogen and chlorine atoms in complex **7** (computed H···Cl distance of 1.822 and 1.830 Å for R = Me and R = Ph, respectively). Complex **8** isomerizes into **8′-bis** after re-coordination of the metal fragment and is converted into complex **9** through **TS5** (a saddle point associated with the 1,3-migration of the metal moiety).[11] Finally, a β-hydride elimination reaction occurs (*via* **TS6**)[16] to produce the final oxetene **3** and $AuHCl_2$ (which would regenerate the initial catalyst upon reaction with HCl). From the data in Scheme 3, it becomes obvious that this step constitutes the bottle-neck of the process when R = Ph ($\Delta G^{\neq}_{298}$ = +21.1 kcal mol^{-1}) but is kinetically favored over the corresponding Au–C protonolysis involving **TS3** and leading to dihydrofuran **2f**.

Therefore, it can be concluded that whereas the 5-*endo*-trig → loss of HCl → protonolysis sequence (which produces dihydrofurans **2**) is followed for methyl-substituted allenols, the 4-*exo*-dig → loss of HCl → 1,3-Au-migration → β-elimination pathway (which leads to oxetenes **3**) is preferred for phenyl-substituted allenols. Both processes share the same common intermediate **4**, formed through distal coordination of the allenic double bond, and are strongly favored over the corresponding 4-*endo*-dig pathway involving the proximal coordination.

Support for this work by the MICINN [CTQ2009-09318, CTQ2010-20714-C02-01, and Consolider-Ingenio 2010 (CSD2007-00006)], CAM (Projects S2009/PPQ-1752 and S2009/PPQ-1634), UCM-Santander (Grant GR35/10-A) is gratefully acknowledged. I.F. is a Ramón y Cajal fellow.

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15 Despite that this mechanistic scenario cannot be completely ruled out, it seems less unlikely taking into account the computed high activation barrier of this particular step (see Scheme S2, ESI†). Besides, the preparation of oxetene **3d** from allenol **1d** wasalso accomplished using Pt(II) catalysis (see Scheme S3, ESI†), probably involving the formation of well known platinum hydride species. It can be suggested that the hydride transfer to HCl occurs from $AuHCl_2$ to form H_2 regenerating $AuCl_3$.

16 See computational details in the ESI†.

