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Gold-catalysed tuning of reactivity in allenes: 9-*endo* hydroarylation *versus* formal 5-*exo* hydroalkylation†

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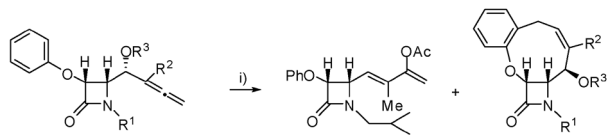
The divergent gold-catalysed reactivity (C_{sp^2}–H *versus* C_{sp^3}–H) of aryloxy-tethered allenes has been uncovered.

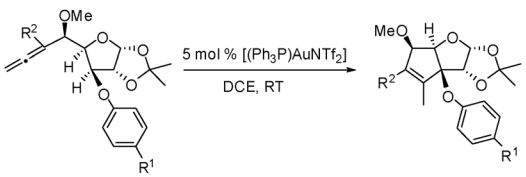
The preparation of medium-sized ring polycycles through selective C–H bond activation is a big challenge. In this regard, the gold-catalysed intramolecular hydroarylation of allenes[1] may be a possible solution to produce eight- or nine-membered carbocycles, although this achievement has not yet been accomplished. We present here an unprecedented Au-catalyzed 9-*endo* carbocyclization of aryl allenes as a powerful synthetic tool to obtain novel nine-membered annulated β-lactam derivatives.[2] In addition, it is shown that the outcome of the reaction (9-*endo* hydroarylation *versus* formal 5-*exo* hydroalkylation) can be modulated by the allene tether.

To explore the reactivity of (aryl)allene-tethered 2-azetidinones **1** towards hydroarylation, we selected acetate **1a** as a model substrate. As a first try, we were happy to notice that although the reaction of derivative **1a** afforded dienol ester **2a** as a major component (34% isolated yield), the intramolecular hydroarylation adduct **3a** was also isolated as a minor component (13%) (Scheme 1). Thus, in order to prevent the [3,3]-sigmatropic rearrangement involving the acetate group,[3] the hydroxy functionality was protected in the form of methyl ether. Fortunately, treatment of allene **1b** with [$(Ph_3P)AuNTf_2$] in 1,2-dichloroethane at room temperature gave full conversion; benzo[*b*]oxonine **3b** being isolated in 51% yield in a totally selective fashion (Scheme 1).[4] Clearly, applying microwave irradiation and using deactivated silica gel during purification resulted in an increased 72% yield for adduct **3b**. Similar figures were observed for tricyclic products **3c–h** without harming the sensitive β-lactam ring (Scheme 1). Remarkably, this rare 9-*endo* carbocyclization reaction was the only operative cyclization mode.



Scheme 1 Controlled intramolecular gold-catalysed hydroarylation of allenyl-tethered arenes **1a–h**. (i) 5 mol% [$(Ph_3P)AuNTf_2$], DCE, μwave, 110 °C (RT for **1a**). Ac = COMe. Tf = triflyl. DCE = 1,2-dichloroethane.

We also decided to undertake a study of the potential use of more diverse substrates in this novel allene hydroarylation mode. Thus, (aryloxy)allenyl-tethered sugars **4a–e** were studied by using the optimum reaction conditions obtained for (aryloxy)allenyl-tethered 2-azetidinones **1b–h**. Remarkably, we found a divergent reactivity compared with the transformation found with allenes **1**; instead of the expected hydroarylation adducts, tricycles **5** arising from a rare 5-*exo* hydroalkylation were obtained (Scheme 2). Notably, the direct and selective functionalization of an otherwise inactive C_{sp^3}–H bond has been achieved.[5] Besides, regioselectivity can be completely



Scheme 2 Controlled intramolecular formal 5-*exo* hydroalkylation reaction of allenyl-tethered arenes **4a–e** under gold-catalysed conditions.

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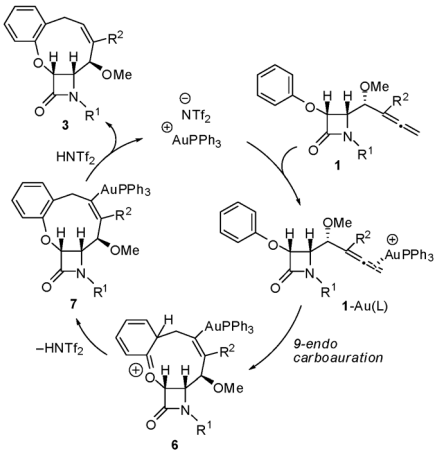


Scheme 3 Mechanistic explanation for the gold-catalysed hydroarylation of allenyl-tethered oxyarenes **1**.

reversed by using the sugar derivative, thus favouring the cyclization of the aryloxy ether group toward the central allene carbon over the cyclization towards the terminal allene carbon. The reaction of allenes **4** did take place with complete stereoselectivity, representing a selective method to afford fused cyclopentenes **5** bearing a quaternary stereocenter.[6] Complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures of allenols **4**, and no side-products from isomerisation or polymerisation reactions were detected. Unfortunately, some decomposition was observed on sensitive tricycles **5** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

A possible pathway for the gold-catalysed achievement of tricycles **3** from allenyl-tethered arenes **1** may initially involve the formation of a complex **1**–Au(L) through coordination of the gold salt to the distal allenic double bond. Next, chemo- and regioselective 9-*endo* carboauration forms species **6**. Attack from the activated 2-position of the arene occurs as a result of the stability of the intermediate oxonium cation type **6**. Loss of proton generates neutral species **7**, which followed by protonolysis of the carbon–gold bond afforded fused nine-membered cycles **3** with concurrent regeneration of the gold catalyst (Scheme 3).

Density functional theory (DFT) calculations have been carried out to gain more insight into the reaction mechanism of the abovediscussed gold-catalysed 9-*endo* hydroarylation reaction. The corresponding computed reaction profile of the model allenyl-β-lactam reactant **1M** with [$(Me_3P)AuNTf_2$] as catalyst is illustrated in Fig. 1, which shows the corresponding free energies in CH_2Cl_2 solution (PCM-M06/def2-SVP//PCM-B3LYP/def2-SVP level). Our calculations suggest that the reaction starts with the exergonic coordination of the $AuPMe_3^+$ catalyst to the distal double bond of the allenic moiety of **1M** (ΔG_{298} = −9.4 kcal mol^{-1}). Then, the 9-*endo* carbocyclization reaction to produce the nine-membered ring tricyclic intermediate **2M** occurs through the transition state **TS1**. This saddle point is associated with the nucleophilic addition of the activated *ortho*-carbon atom to the electrophilic gold complex. Although the activation barrier of this model reaction is relatively high ($\Delta G_{a,298}$ = 29.9 kcal mol^{-1}),[7] this process is kinetically and thermodynamically favoured over the corresponding carbocyclization reactions leading to 7- or 8-membered ring intermediates.[8] This result is in agreement with the exclusive formation of nine-membered ring tricyclic compounds **3**, as experimentally observed. Intermediate **2M** is then transformed into the neutral complex **4M** *via* the initially formed complex **3M** (where the NTf_2^- anion is weakly bonded to **2M**) through transition state **TS2**. The latter saddle point is associated with

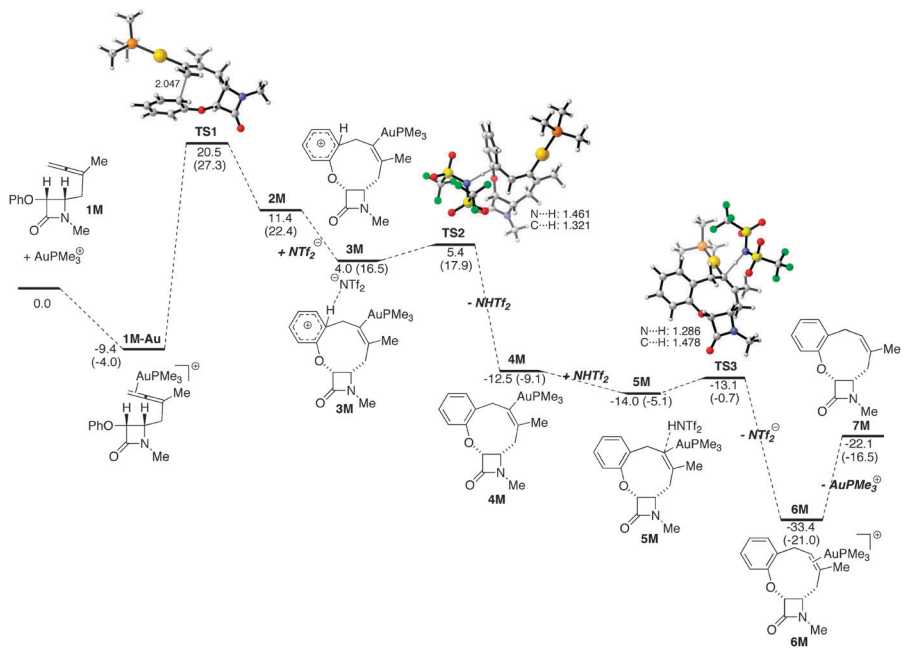
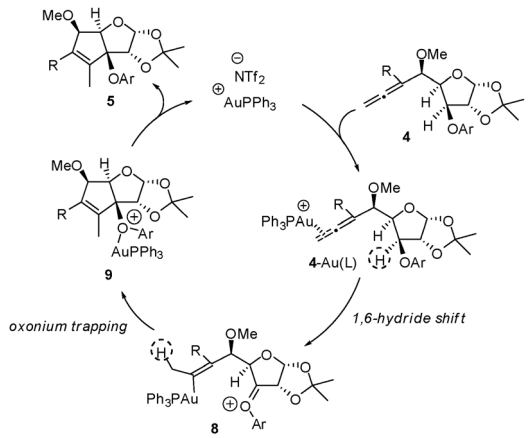


Fig. 1 Computed reaction profile for the reaction of allenyl-β-lactam **1M** and [$(PMe_3)AuNTf_2$] catalyst.[11]



Scheme 4 Mechanistic explanation for the gold-catalyzed formal 5-*exo* hydroalkylation of allenyl-tethered oxyarenes **4**.

the easy and exergonic proton abstraction in **2M** by the NTf_2^- anion ($\Delta G_{a,298}$ = 1.4 kcal mol^{-1} and ΔG_{298} = −16.9 kcal mol^{-1}, from **3M**). The addition of the readily formed $NHTf_2$ to **4M** forms complex **5M**, which evolves into complex **6M** *via* **TS3** (associated with the protonolysis reaction of the carbon–gold bond). The latter process is also highly exergonic (ΔG_{298} = −19.4 kcal mol^{-1}) and proceeds with a very low activation barrier ($\Delta G_{a,298}$ = 0.9 kcal mol^{-1}).[9,10] Thus, it can be concluded that the initial 9-*endo* carbocyclization reaction constitutes the bottle-neck of the process in view of the corresponding endergonicity and relatively high activation barrier. Finally, the reaction ends up with the release of the $AuPMe_3^+$ catalyst, which is coordinated to the endocyclic C=C double bond of **6M**, to produce the final tricyclic species **7M**.

A mechanistic rationale for the gold-catalysed conversion of allenyl-tethered sugars **4** into fused cyclopentenes **5** is more intricate. It is worth noting that the cyclization affords adducts **5** from an allene umpolung hydrofunctionalization instead of that from the usually preferred conventional hydrofunctionalization. The pathway proposed in Scheme 4 looks valid for the formation of tricycles of type **5**. It could be presumed that the initially formed gold complex **4**–Au(L), through coordination of the gold salt to the distal allenic double bond, undergoes a 1,6-hydride shift (rare transfer of hydride *versus* normal nucleophilic group attack), giving rise to the oxonium species **8**. Intramolecular trapping of the oxonium group by the alkenylgold moiety in intermediates **8** generates cationic species **9**, through formal 5-*exo* hydroalkylation. Finally, demetalation yields fused cyclopentenes **5** and regenerates the gold catalyst (Scheme 4).

Preliminary DFT calculations on the model (aryloxy)allenyl-tethered sugar species **8M** (see Fig. S3 in the ESI†) indicate that the direct 1,6-hydride shift from the distal double bond-coordinated complex **8M–Au** occurs with a relatively high activation barrier ($\Delta G_{a,298}$ = 37.7 kcal mol^{-1}, that is 25.2 kcal mol^{-1} above the separate reactants **8M** and $AuPMe_3^+$). This step is followed by the highly exergonic C–C bond forming reaction (*i.e.* oxonium trapping) *via* **TS5** with an activation barrier of 26.1 kcal mol^{-1}. Further DFT calculations involving the NTf_2-mediated 1,6-hydride shift and more realistic species leading to a process more compatible with a reaction at room temperature are currently underway.

In conclusion, the divergent gold-catalysed reactivity (C_{sp^2}–H *versus* C_{sp^3}–H) of aryloxy-tethered allenes has been studied. We report herein an efficient gold-catalysed 9-*endo* carbocyclization to fused tricyclic β-lactams from easily accessible aryl allene substrates under mild conditions. In salient contrast to the reaction of (aryloxy)allenyl-tethered 2-azetidinones, the allenyl sugar derivatives provided the 5-*exo* hydroalkylation adducts as the sole products. The reactions were found to proceed with complete control of product regio- and chemoselectivity.

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Notes and references

1 For a review, see: (*a*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994. For available reports, see: (*b*) W. Kong, C. Fu and S. Ma, *Chem.–Eur. J.*, 2011, **17**, 13134; (*c*) B. Alcaide, P. Almendros, J. M. Alonso, M. T. Quirós and P. Gadziński, *Adv. Synth. Catal.*, 2011, **353**, 1871; (*d*) R. M. Zeldin and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1706; (*e*) J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino and J. M. González, *Chem.–Eur. J.*, 2010, **16**, 11827; (*f*) W. Kong, C. Fu and S. Ma, *Eur. J. Org. Chem.*, 2010, 6545; (*g*) D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2009, **48**, 5733; (*h*) D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962; (*i*) M. A. Tarselli and M. R. Gagné, *J. Org. Chem.*, 2008, **73**, 2439; (*j*) C. Park and P. H. Lee, *Org. Lett.*, 2008, **10**, 3359; (*k*) T. Watanabe, S. Ohishi, N. Fujii and H. Ohno, *Org. Lett.*, 2007, **9**, 4821; (*l*) C. Liu and R. A. Widenhoefer, *Org. Lett.*, 2007, **9**, 1935; (*m*) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Quian and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2006, **128**, 9066; (*n*) Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.*, 2006, **128**, 10352.

2 β-Lactams are not only the most commonly prescribed antibacterial agents, but also exhibit some other biological activities.

3 A. K. Buzas, F. M. Istrate and F. Gagosz, *Org. Lett.*, 2007, **9**, 985.

4 A screening of different gold complexes was undertaken. $AuCl_3$, AuCl, and [(PPh_3)AuOTf] all failed to catalyse this reaction. The cyclizations of allene **1b** using [$IPrAuSbF_6$] or [$IPrAuBF_4$] catalysts did not lead to complete consumption of starting **1b**, providing adduct **3b** in very low yield. Change in the nature of the phosphine in the gold pre-catalyst has little effect on the reaction, because replacing [$(Ph_3P)AuNTf_2$] by [$P(t\text{Bu})_2(o\text{-biphenyl})AuNTf_2$] did not show any appreciable difference.

5 For a 1,5-hydride shift from benzyl ethers and tetrahydrofurans onto allenes, see: B. Bolte and F. Gagosz, *J. Am. Chem. Soc.*, 2011, **133**, 7696.

6 Biologically active heliconols having the 2*H*-cyclopenta[*b*]furan core of fused compounds **5** have been isolated from natural sources.

7 The barrier energy is reduced to 25.8 kcal mol^{-1} when the more realistic $AuPPh_3^+$ catalyst is used (see Fig. S1 in the ESI†).

8 See Fig. S2 in the ESI†.

9 In sharp contrast, the corresponding proton abstraction and protonolysis reactions in the 7-membered ring formation process proceed with much higher activation barriers ($\Delta G_{a,298}$ = 16.9 and 37.1 kcal mol^{-1}). This makes the 7-membered ring formation a non-competitive transformation. See Fig. S2 in the ESI†.

10 The easiness of the protonolysis reaction is in contrast to related processes whose computed activation barriers are much higher. See: (*a*) B. Alcaide, P. Almendros, T. Martínez del Campo and I. Fernández, *Chem. Commun.*, 2011, **47**, 9054; (*b*) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano and J. L. Marco-Contelles, *Chem.–Eur. J.*, 2009, **15**, 1909.

11 Plain values indicate the relative free energies (ΔG, at 298 K) at the PCM(CH_2Cl_2)-M06/def2-SVP//PCM(CH_2Cl_2)-B3LYP/def2-SVP level, whereas values in parentheses are computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level. Bond distances of the transition states are given in angstroms.

