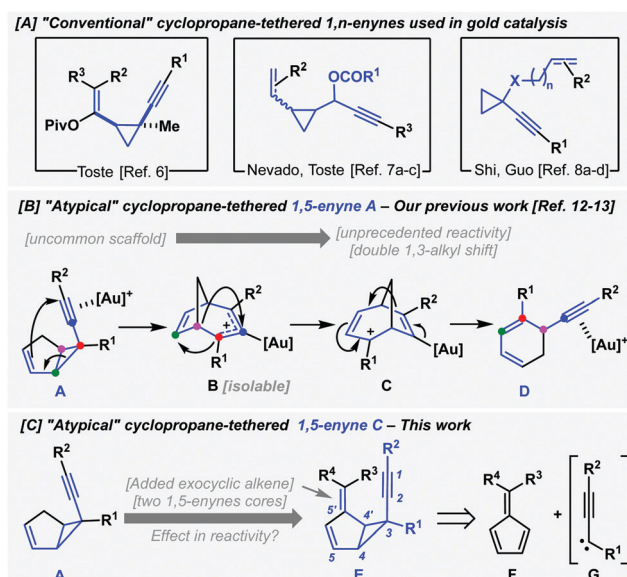## COMMUNICATION

Gold-catalysed rearrangement of unconventional cyclopropane-tethered 1,5-enynes†

Rubén Vicente, [ID] *[a] Eva Tudela,[a] Miguel A. Rodríguez,[b] Ángel L. Suárez-Sobrino[a] and Alfredo Ballesteros [ID] *[a]

The synthesis of particular cyclopropane-tethered 1,5-enynes, namely 6-alkynyl-4-alkylidenebicyclo[3.1.0]hex-2-enes, enabled the discovery of unprecedented gold-catalyzed rearrangment to indenes. A computational study of the mechanism of this profound skeleton rearrangement is also disclosed.

In the 21st century, gold catalysis has had an undeniable impact.[1] In Particular, gold catalysts have demonstrated their unparalleled potential for electrophilic activation of unsaturated compounds and opened up new strategies in organic synthesis.[2,3] The broad range of gold-catalysed reactions described with 1,n-enynes serves to illustrate this fact.[4] Besides, alkynylcyclopropanes have been also fruitfully exploited in gold catalysis, offering interesting reactivities, including the cleavage of the cyclopropane ring.[5] The combination of these two structural features with the cyclopropane unit tethering the 1,5-enyne has been also studied (Scheme 1A). Thus, Toste used in situ generated 1-alkynyl-2-(1-pivaloxyvinyl)cyclopropanes in typical gold-catalysed 5-endo-dig cyclizations.[6] Similarly, Nevado and Toste employed (2-vinylcyclopropyl)propargyl derivatives in the context of mechanistic studies for well-stablished 1,n-carboxylate shifts.[7] Meanwhile, Shi and Guo reported interesting gold-catalysed reactions with enynes containing 1,1-disubstituted cyclopropanes.[8,9] These works described somehow archetypal gold reactivities. In contrast to those studies, we thought that using less unconventional cyclopropane-tethered 1,5-enynes might offer the possibility of finding distinctive gold-catalysed reactions.[10] In particular, we studied the reactivity of 6-alkynylbicyclo[3.1.0]hex-2-ene derivatives A,[11] which are accessible from cyclopentadiene.

These cyclopentadiene-derived 1,5-enynes presented alkene and cyclopropane moieties constrained into a bicyclic framework and unpredictably underwent a gold-catalyzsed rearrangement to afford compounds D (Scheme 1B).[12] A foreseeable 6-endo-dig cyclization with a concomitant cyclopropane ring-opening leads to isolable intermediate B. Then, a rare double simultaneous 1,3-alkyl shift generates species C, which evolves to alkyne D can explain the reaction outcome.[13] Driven by these results, we considered studying the reactivity of structurally related 6-alkynyl-4-alkylidenebicyclo[3.1.0]hex-2-enes E, which might be eventually achieved by cyclopropanation of fulvenes F,[14] with a suitable carbene equivalent G (Scheme 1C). The exocyclic alkene of compounds E provides an alternative 1,5-enyne moiety which might impact the reactivity when compared to compounds A. Herein, we present the results of this study.

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Scheme 1 Cyclopropane-tethered 1,n-enynes in gold-catalysis.
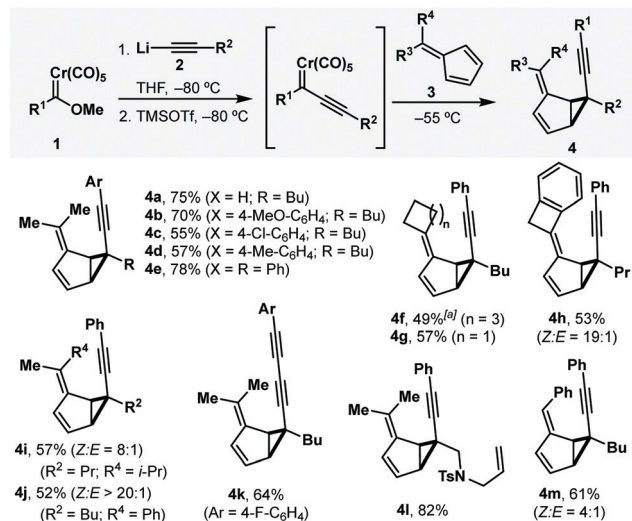
Scheme 2 Synthesis of 1,5-enynes **4**. [a] Determined by ^{1}H-NMR.

Our work commenced with establishing a suitable procedure for the synthesis of 1,5-enynes **E**. According to our experience, the required progargyl carbene **G** might be generated from Fischer carbene complexes **1**.[11] Indeed, treatment of alkoxy carbenes **1** with lithium acetylides **2** (THF, −80 °C), followed by treatment with TMSOTf generated the required intermediate. Then, the addition of an excess of fulvene **3** (5.0 equiv., THF, −55 °C) enabled the cyclopropanation to yield the desired compounds **4a–m** (Scheme 2).[15] The protocol showed an acceptable scope and reasonable overall yields seeing the one-pot sequence of reactions. Moreover, the selectivity of the reaction deserves a comment. Thus, the cyclopropanation reaction proceeded exclusively with the endocyclic alkene of the fulvene,[16] with complete *endo*-selectivity with respect to the alkyne,[17] and a strong preference for the *Z*-isomers (**4h–j, m**).

With an available set of compounds **4**, we next studied the reactivity towards gold catalysts using **4a** as the model substrate. To our excitement, we found that cationic gold catalysts led to the formation of indene **5a** (Scheme 3),[18] in sharp contrast to the reactivity observed with enynes **A**. Indeed, the formation of **5a** highlights the profound impact of the additional exocyclic alkene in the reactivity as we conjectured. It should be noted that the unanticipated structure of **5a** was
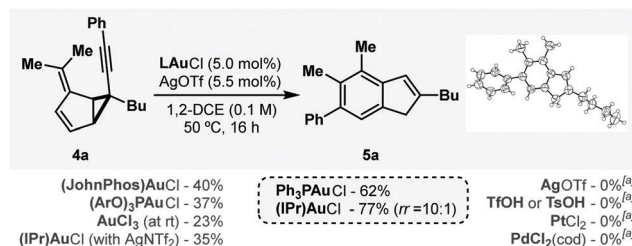
unambiguously confirmed by X-ray analysis.[19] The structural differences between **4a** and **5a** indicate a unique skeleton rearrangement. A 1,2-Me shift seems evident but the connectivity of the alkynylcyclopropane fragment is completely modified and appears difficult to trace. The catalyst screening showed that [(Ph$_3$P)Au$^+$] (62%) and [(IPr)Au$^+$] (77%, 10:1 indene double bond isomers) generated *in situ* with AgOTf provided the best results. Other Au(I)/(III) catalysts were less efficient. Importantly, neither Ag(I) salts nor Brønsted acids were competent, and the representative Pt(II) or Pd(II) catalysts were also inoperative, supporting the unique potential of gold as the catalyst for this transformation.

Subsequently, we explored this uncommon gold-catalysed rearrangement (Scheme 4). First, formation of indenes **5a–d** bearing various arenes at alkyne terminus took place in reasonable yields (40–63%). The presence of an aromatic group as the R^2 substituent did not influence the result leading to indene **5e** in good yield (75%). In addition, fulvene-derived enynes **4f–h** containing an additional ring were used to prepare polycyclic compounds **5f–h**, in which the rearrangement entailed a ring expansion. The use of non-symmetric fulvene-derived enynes **4i–j** was also explored. Remarkably, the resulting indenes **5i–j** were regioselectively obtained in moderate to good yields (39–58%). Conventional Pd(0)-catalysed hydrogenation of indenes **5h–j** towards the corresponding indanes **6h–j** served to confirm their precise substitution pattern. Moreover, the presence of a conjugated diyne in **4k** did not affect the reaction outcome enabling the preparation of 6-alkynyl-substituted indene **5k**, albeit in modest yield. Unfortunately, the reaction with compound **4l** led to an untreatable complex mixture.

Considering the complexity of the transformation and the lack of success of trapping experiments (with alcohols or alkenes) we found it tough to conceive a mechanism. Therefore,
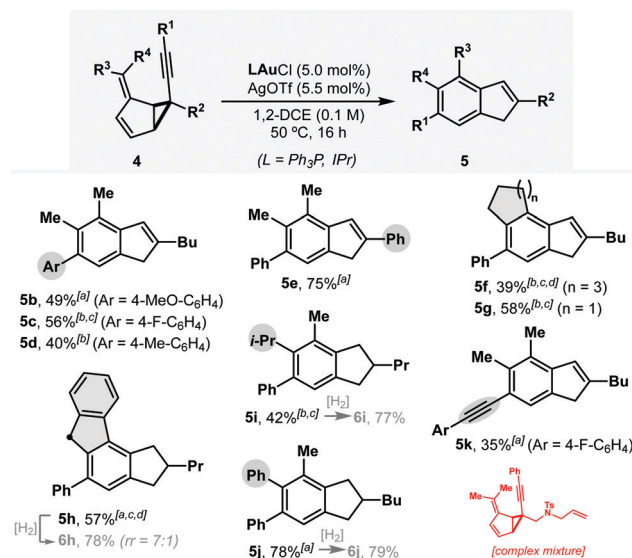
Scheme 4 Gold-catalysed rearrangement of enynes **4** to indenes **5**: Scope. [a] With (Ph$_3$P)AuCl. [b] With (IPr)AuCl. [c] Isomerization of the alkene was observed (see the ESI† for details). [d] Determined by ^{1}H-NMR. [H$_2$]: Pd(C) (10 mol%), H$_2$ (1 atm), EtOAc, RT, 3 h.
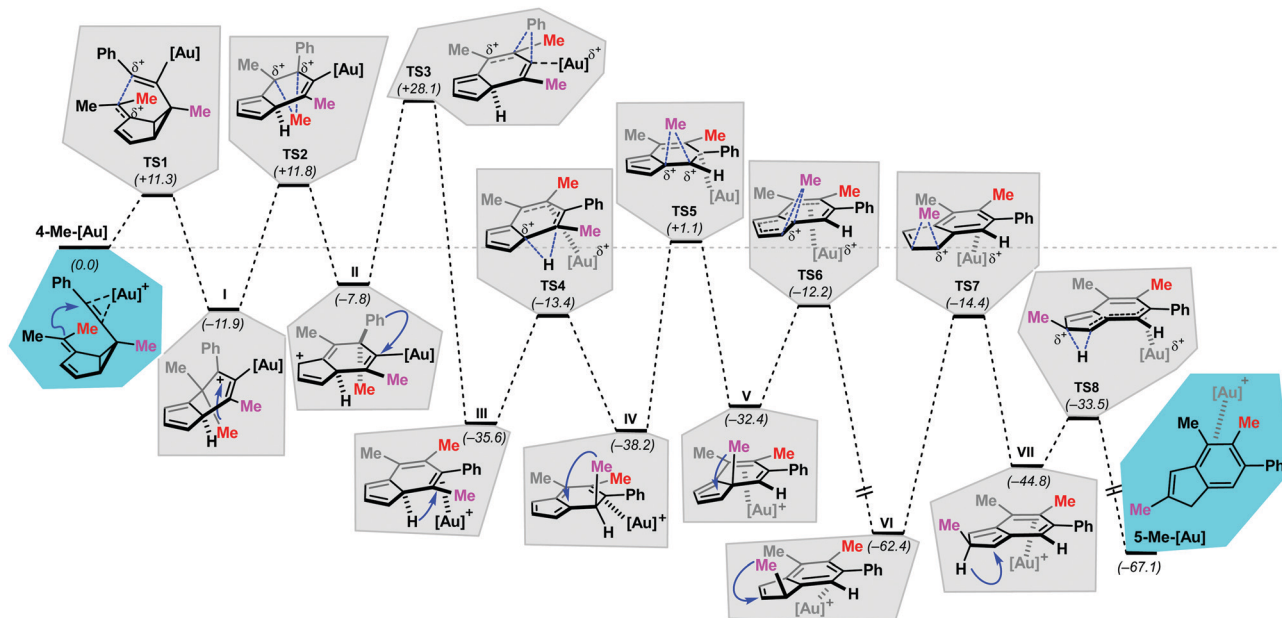

Scheme 3 Gold-catalysed rearrangement of enyne **4a** to indene **5a**: screening. (Isolated yields). [a] Degradation of **4a**. (Ar = 2,6-di-*tert*-butylphenyl; IPr = 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene).

Scheme 5 Proposed mechanism. Calculated relative free-energy profile for the rearrangement of **4-Me-[Au]** to **5-Me-[Au]**. (numbers within parentheses indicate ΔG in kcal·mol^{-1}; [Au] = [(Me$_3$P)Au].

we carried out computational studies at the PCM-B3PW91-D3/cc-pVDZ-pp//B3PW91/cc-pVDZ-pp level with simplified system **4-Me-[Au]** ([Au] = [(Me$_3$P)Au$^+$]) (Scheme 5, see the ESI† for details). Starting from the **4-Me-[Au]** structure (0.0 kcal·mol^{-1}), alkyne coordination to gold facilitates a 6-*endo-dig* π_{C-C} attack by the exocyclic double bond to obtain transition structure **TS1** (+11.3 kcal·mol^{-1}). This step differs from our previously reported reaction of cyclopentadiene-derived compounds **A**,[12,13] which reacted also *via* the 6-*endo-dig* π_{C-C} attack but through the only available cyclic alkene (see Scheme 1). From **TS1**, cleavage of the cyclopropane leads to a less strained structure **I** (−11.9 kcal·mol^{-1}). Then, the 1,2-Me shift involving the exocyclic *Z*-Me group (highlighted in red) *via* **TS2** (+11.8 kcal·mol^{-1}) enables achieving intermediate **II**.[20] This migration is compatible with the migratory potential when other substituents are present (*i*-Pr, Ph). Then, a 1,2-Ph shift takes place through the highest energy transition structure **TS3** (+28.1 kcal·mol^{-1}) to afford intermediate **III** (−35.6 kcal·mol^{-1}). Subsequent 1,2-H shift through **TS4** (−13.4 kcal·mol^{-1}) leads to structure **IV** (−35.6 kcal·mol^{-1}). From this structure, the Me group (highlighted in pink), originally attached to the cyclopropane ring of **4**, undergoes three consecutive 1,2-Me shifts (**TS5 → V → TS6 → VI → TS7**) to reach its final position at the cyclopentene ring as indicated in intermediate structure **VII** (−44.8 kcal·mol^{-1}).[21] To conclude, the definitive 1,2-H shift *via* **TS8** (−33.5 kcal·mol^{-1}) finally leads to **5-Me-[Au]** (−67.1 kcal·mol^{-1}), the most stable structure, which corresponds to the experimentally observed product.

Finally, the structure-reactivity link was further evidenced in the reaction of monosubstituted fulvene-derived enyne **4m** (Scheme 6). In this case, treatment of **4m** with the *in situ* generated [(JohnPhos)Au$^+$] catalyst, under otherwise identical
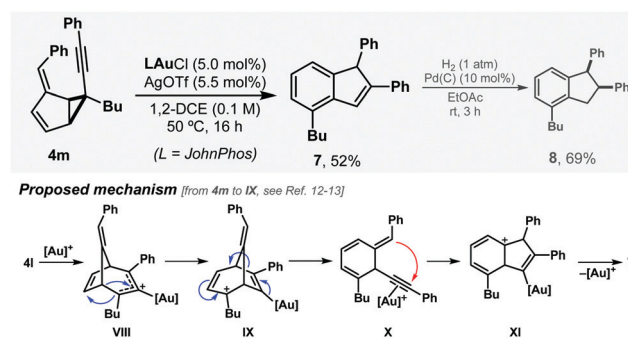
Scheme 6 Gold-catalysed rearrangement of **4m** to indene **7**.

reaction conditions, led to the regioselective formation of indene **7** (52%), which was also reduced to indane **8** to provide additional confirmation of the structure after the rearrangement. As earlier observed from compounds **A**,[12,13] this result can be explained by the 6-*endo-dig* π_{C-C} attack on the internal alkene and cyclopropane ring-opening to generate intermediate **VIII**. Then, a regioselective rearrangement leads to cationic species **IX**, which evolves to alkyne intermediate **X**, analogous to compounds **D** (see Scheme 1). In contrast to **D**, the presence of the exocyclic alkene in intermediate **X** enables a subsequent 5-*endo-dig* cyclization to bicycle **XI**.[22] Finally, an aromatization during the protodeauration gives rise to compound **7**.

In summary, we have described a unique gold-catalysed rearrangement based on the use of fulvene-derived 1,5-enynes **4** with an atypical connection *via* a cyclopropane ring in a highly strained structure. This particular assembly translates into an exotic reactivity since unsuspected highly substituted indenes **5** are obtained in regioselective fashion. A plausible

mechanistic scenario for this intricate transformation is proposed on the basis of computational studies. Additionally, the formation of indene 7 from particular 1,5-enyne **4m** points to the close structure-reactivity dependency in gold catalysis. We hope that this work triggers additional research to prepare new unusual structures and to study their reactivities in gold catalysis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211; (b) A. S. K. Hashmi, *Chem. Rev.*, 2021, **121**, 8309–8310; (c) A. S. K. Hashmi and F. D. Toste, *Modern Gold Catalyzed Synthesis*, Wiley-VCH, 2012.

2 C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti and N. T. Patil, *Chem. Rev.*, 2021, **121**, 8478–8558.

3 (a) Y. Zhang, T. Luo and Z. Yang, *Nat. Prod. Rep.*, 2014, **31**, 489–503; (b) D. Pflästerer and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331–1367.

4 For the first gold-catalysed reaction of a 1,n-enyne-type substrate, see: (a) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc.*, 2000, **122**, 11553–11554. For illustrative reviews, see: (b) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326–3350; (c) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902–912.

5 (a) J. Zhang, H.-G. Schmalz, J. Zhang and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2006, **45**, 6704–6707; (b) G. Li, X. Huang and L. Zhang, *J. Am. Chem. Soc.*, 2008, **130**, 6944–6945; (c) C. W. Li, K. Pati, G. Y. Lin, S. M. A. Sohel, H. H. Hung and R. S. Liu, *Angew. Chem., Int. Ed.*, 2010, **49**, 9891–9894; (d) S. Ye and Z. X. Yu, *Org. Lett.*, 2010, **12**, 804–807; (e) B. Dong, Y. Xi, Y. Su, N. G. Akhmedov, J. L. Petersen and X. Shi, *RSC Adv.*, 2016, **6**, 17386–17389; (f) J. M. Fernández-García, H. A. Garro, L. Fernández-García, P. García-García, M. A. Fernández-Rodríguez, I. Merino and E. Aguilar, *Adv. Synth. Catal.*, 2017, **359**, 3035–3051; (g) D. Li, W. Zang, M. J. Bird, C. J. T. Hyland and M. Shi, *Chem. Rev.*, 2021, **121**, 8685–8755; (h) J. Barluenga, R. Sigüeiro, R. Vicente, A. Ballesteros, M. Tomás and M. A. Rodríguez, *Angew. Chem., Int. Ed.*, 2012, **51**, 10377–10381.

6 D. J. Gorin, I. D. G. Watson and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 3736–3737.

7 (a) Y. Zou, D. Garayalde, Q. Wang, C. Nevado, A. Goeke and Y. Ito, *Angew. Chem., Int. Ed.*, 2008, **47**, 10110–10113; (b) P. Mauleón, J. L. Krinsky and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 4513–4520; (c) D. Garayalde, E. Gómez-Bengoa, X. Huang, A. Goeke and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 4720–4730.

8 (a) G. Q. Chen, W. Fang, Y. Wei, X. Y. Tang and M. Shi, *Chem. Sci.*, 2016, **7**, 4318–4328; (b) G. Q. Chen, W. Fang, Y. Wei, X. Y. Tang and M. Shi, *Chem. Commun.*, 2016, **52**, 10799–10802; (c) W. Zang, Y. Wei and M. Shi, *Chem. Commun.*, 2019, **55**, 8126–8129; (d) W. Zang,

L. Wang, Y. Wei, M. Shi and Y. Guo, *Adv. Synth. Catal.*, 2019, **361**, 2321–2328See also:; (e) S. Ghorpade, M. Der Su and R. S. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4229–4234.

9 See also:(a) S. G. Sethofer, S. T. Staben, O. Y. Hung and F. D. Toste, *Org. Lett.*, 2008, **10**, 4315–4318. For gold-catalysed reaction of enynes bearing a non-tethering cyclopropyl substituent, see: (b) Z. Wu, D. Lebœuf, P. Retailleau, V. Gandon, A. Marinetti and A. Voituriez, *Chem. Commun.*, 2017, **53**, 7026–7029; (c) S. Ferrer and A. M. Echavarren, *Org. Lett.*, 2018, **20**, 5784–5788.

10 For the study of a cyclopropane tethering 1,5-enyne with unusual structure derived from heptatriene, see: R. Dorel and A. M. Echavarren, *J. Org. Chem.*, 2016, **81**, 8444–8454.

11 Barluenga, E. Tudela, R. Vicente, A. Ballesteros and M. Tomás, *Chem. – Eur. J.*, 2011, **17**, 2349–2352.

12 J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros and M. Tomás, *Angew. Chem., Int. Ed.*, 2011, **50**, 2107–2110.

13 (a) E. Tudela, J. González, R. Vicente, J. Santamaría, A. Ballesteros and M. A. Rodríguez, *Angew. Chem., Int. Ed.*, 2014, **53**, 12097–12100; (b) J. González, D. Allegue, S. Fernández, M. A. Rodríguez, J. Santamaría and A. Ballesteros, *Adv. Synth. Catal.*, 2020, **362**, 3912–3918.

14 For representative examples on the generation of fulvenes by gold catalysis, see: (a) A. Ahrens, J. Schwarz, D. M. Lustosa, R. Pourkaveh, M. Hoffmann, F. Rominger, M. Rudolph, A. Dreuw and A. S. K. Hashmi, *Chem. – Eur. J.*, 2020, **24**, 5280–5287; (b) L. Zhou, L. Yang, Y. Zhang, A. M. Kirillov, R. Fang and B. Han, *Org. Chem. Front.*, 2019, **6**, 2701–2712; (c) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph and F. Rominger, *Angew. Chem., Int. Ed.*, 2012, **51**, 4456–4460; (d) Y. Chen and Y. Liu, *J. Org. Chem.*, 2011, **76**, 5274–5282.

15 See ESI for details. Compounds 4 decomposed when dried and, therefore, were stored and handled in solution.

16 R. A. Moss, L. A. Perez, K. Krogh-Jespersen and C. M. Young, *J. Am. Chem. Soc.*, 1981, **103**, 2413–2415.

17 This endo-selectivity is in sharp contrast with the observed with alkoxy-substituted Fischer carbenes, see: J. Barluenga, S. Martínez, A. L. Suárez-Sobrino and M. Tomás, *J. Am. Chem. Soc.*, 2002, **124**, 5948–5949.

18 See ESI for details on the screening.

19 CCDC 2173325 (5a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via **www.ccdc.cam.ac.uk/data_request/cif**.

20 For representative examples of 1,2-alkyl migrations promoted by homogeneous gold catalysis, see: (a) W. Li, Y. Li and J. Zhang, *Chem. – Eur. J.*, 2010, **16**, 6447–6450; (b) W. Li, Y. Li, G. Zhou, X. Wu and J. Zhang, *Chem. – Eur. J.*, 2012, **18**, 15113–15121; (c) A. Suárez, S. Suárez-Pantiga, O. Nieto-Faza and R. Sanz, *Org. Lett.*, 2017, **19**, 5074–5077; (d) C. Praveen, *Asian J. Org. Chem.*, 2020, **9**, 1953–1998.

21 For rare examples of two or three consecutive 1,2-alkyl shifts in gold catalysis, see: (a) L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 11806–11807; (b) J. Sun, M. P. Conley, L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**, 9705–9710; (c) C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6143–6417.

22 The gold-catalysed cycloisomerization of 1,4-enynes has been scarcely explored and usually involves acetate migrations. For illustrative examples, see: (a) X. Shi, D. J. Gorin and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 5802–5803; (b) A. Buzas and F. Gagosz, *J. Am. Chem. Soc.*, 2006, **128**, 12614–12615; (c) N. Marion, S. Díez-González, P. De Frémont, A. R. Noble and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2006, **45**, 3647–3650.