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## Gold-Catalysed Rearrangement of Unconventional 1-Alkenyl-2-alkynylcyclopropanes

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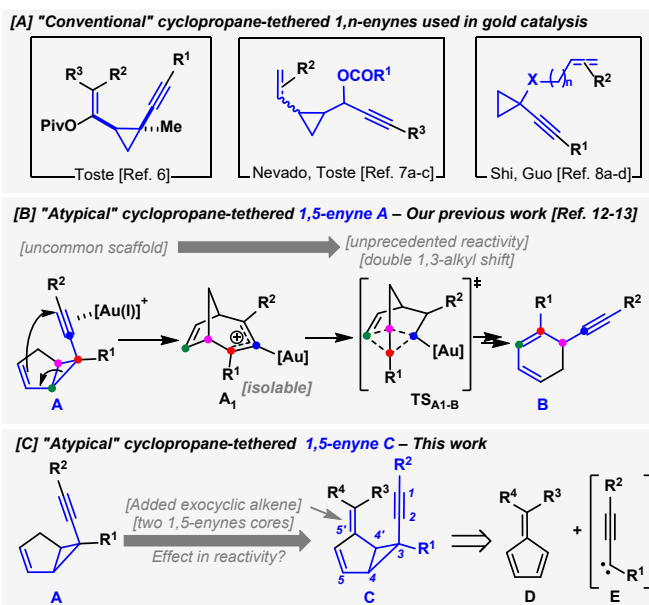
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The synthesis of particular cyclopropane-tethered 1,5-enynes such as 6-alkynyl-4-alkylidenebicyclo[3.1.0]hex-2-enes **4** enabled the discovery of an unprecedented gold-catalyzed rearrangement to indenenes **5**. A computational study of the mechanism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

In 21<sup>st</sup> century, gold catalysis has had an undeniable impact.<sup>1</sup> Particularly, gold catalysts have demonstrated an unparalleled ability for electrophilic activation of unsaturated compounds and opened up new strategies in organic synthetic.<sup>2,3</sup> The broad range of gold-catalysed reactions described with 1,*n*-enynes serves to illustrate this fact.<sup>4</sup> Besides, alkynylcyclopropanes have been also fruitfully exploited in gold catalysis, offering reactivities including the cleavage of the cyclopropane ring.<sup>5</sup> The combination of these two structural features with the cyclopropane unit tethering the 1,*n*-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.<sup>6</sup> Similarly, Nevado and Toste employed (2-vinylcyclopropyl)propargyl derivatives in the context of mechanistic studies for well-established 1,*n*-carboxylate migrations.<sup>7</sup> Meanwhile, Shi and Guo reported interesting gold-catalysed reactions with 1,1-disubstituted cyclopropanes.<sup>8,9</sup> These works described somehow archetypal gold reactivities. In contrast with those studies, we thought that using less unconventional cyclopropane-tethered 1,*n*-enynes might offer the possibility to find distinctive gold-catalysed reactions.<sup>10</sup> In particular, we studied the reactivity of 6-alkynylbicyclo[3.1.0]hex-2-ene derivatives **A**,<sup>11</sup> which are

readily obtainable from cyclopentadiene. This cyclopentadiene-derived 1,5-enynes presented alkene and cyclopropane moieties constrained into a cyclic framework and unexpectedly underwent a gold-catalysed rearrangement to afford compounds **B** (Scheme 1B).<sup>12</sup> A foreseeable 6-*endo-dig* cyclization with a concomitant cyclopropane ring-opening lead to *isolable* intermediate **A**<sub>1</sub>. Then, a rare double simultaneous 1,3-alkyl shift via transition structure **TS**<sub>A<sub>1</sub>-B</sub> explains the reaction outcome.<sup>13</sup> Driven by these results, we considered studying the reactivity of structurally related 6-alkynyl-4-alkylidenebicyclo[3.1.0]hex-2-enes **C**, which might be eventually available by cyclopropanation of fulvenes **D** with a suitable carbene equivalent **E** (Scheme 1C). The exocyclic alkene of compounds **C** 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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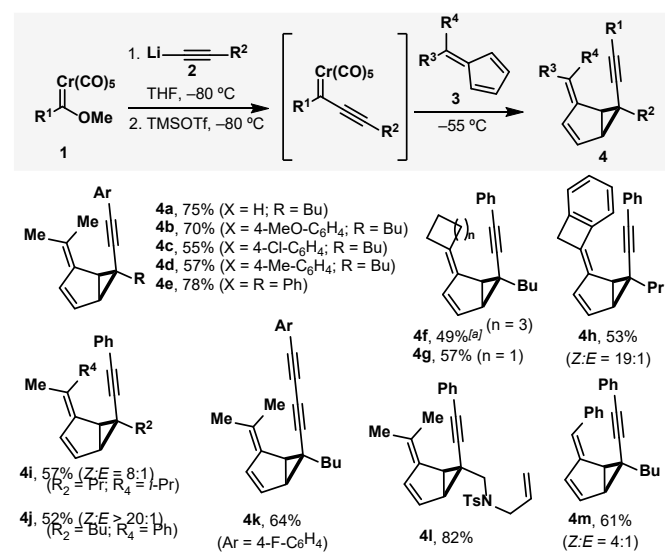
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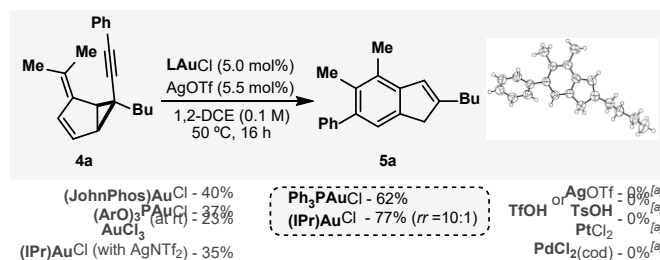
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Scheme 1. Cyclopropane-tethered 1,*n*-enynes in gold-catalysis.

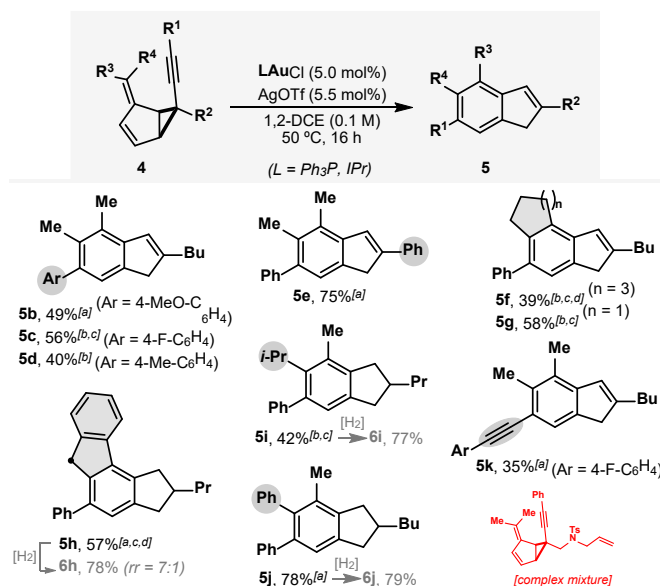
Our work commenced with establishing a suitable procedure for the synthesis of 1,5-enynes **C**. According to our experience, the required propargyl carbene **E** might be generated from Fischer carbene complexes **1**.<sup>11</sup> Indeed, treatment of alkoxy carbenes **1** with lithium acetylides **2** (THF,  $-80\text{ }^{\circ}\text{C}$ ), followed by treatment with TMSOTf generated the required intermediate. Then, the addition of an excess of fulvene **3** (5.0 equiv., THF,  $-55\text{ }^{\circ}\text{C}$ ) enabled the cyclopropanation to yield the desired compounds **4a-m** (Scheme 2).<sup>14</sup> 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 at the endocyclic alkene of the fulvene,<sup>15</sup> with complete *endo*-selectivity with respect to the alkyne,<sup>16</sup> and a strong preference for the *Z*-isomers (**4h-j,m**).

Scheme 2. Synthesis of 1,5-enynes **4**. <sup>[a]</sup> Estimated yield

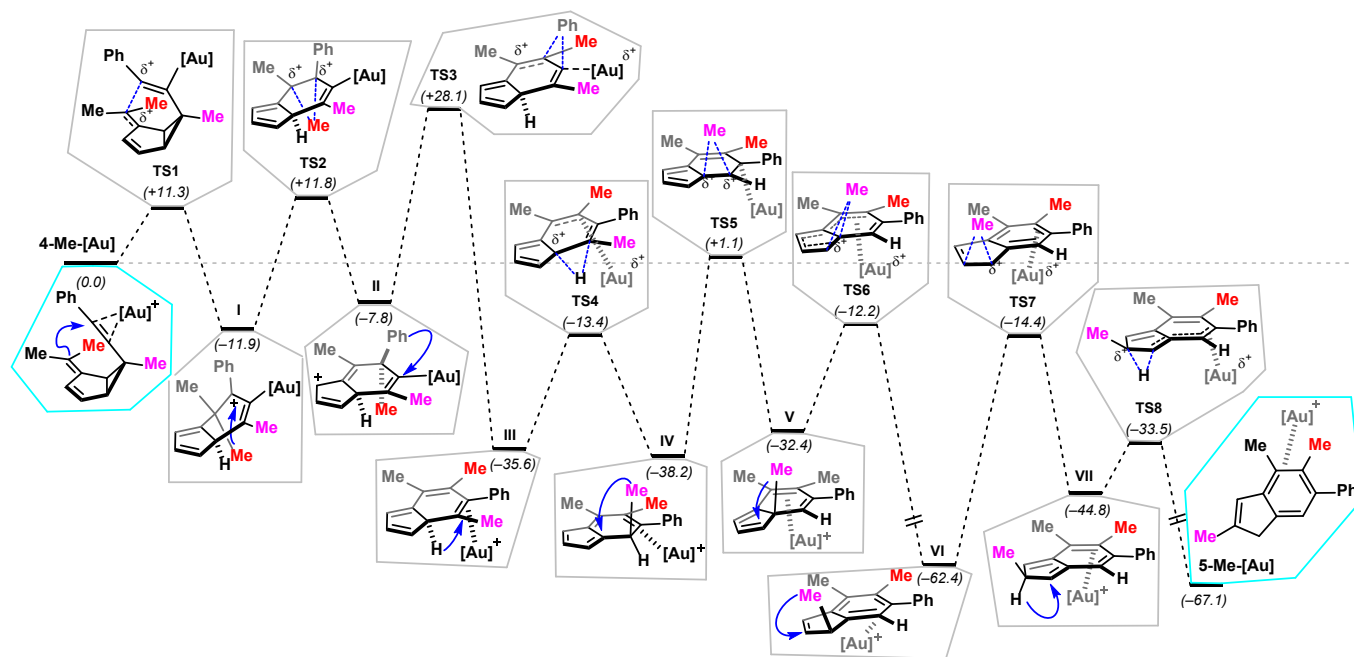
With an available set of compounds **4**, we next studied the reactivity towards gold catalysts using **4a** as model substrate. Excitingly, we found that cationic gold catalysts led to the formation of indene **5a** (Scheme 3),<sup>17</sup> in sharp contrast to the reactivity observed with enynes **A**. Indeed, the formation of **5a** highlights the profound impact of the additional exocyclic alkene in the reactivity as we conjectured. It should be noticed that the unanticipated structure of **5a** was unambiguously confirmed by X-Ray analysis.<sup>18</sup> The structural difference between **4a** and **5a** indicates a unique skeleton rearrangement. The methyl 1,2-shift seems evident but the connectivity of the alkynylcyclopropane fragment is completely modified and appears difficult to trace. The catalyst screening showed that [(Ph<sub>3</sub>P)Au<sup>+</sup>] (62%) and [(IPr)Au<sup>+</sup>] (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 representative Pt(II) or Pd(II) catalysts were also inoperative, supporting the unique role of gold as catalyst.

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

Subsequently, we explored this uncommon gold-catalysed rearrangement (Scheme 4). First, formation of indenenes **5a-d** bearing various arenes at position 6 took place in moderate yields (40–63%). The presence of an aromatic group as R<sup>2</sup> substituent did not influence the result leading to indene **5e** in good yield (75%). In addition, the use of fulvene-derived enynes **4f-h** containing an additional ring were used to provide 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 indenenes **5i-j** were regioselectively obtained in moderate to good yields (39–58%). Conventional Pd(0)-catalysed hydrogenation of indenenes **5h-j** towards the corresponding indanes **6h-j** served to confirm their precise substitution pattern. Moreover, the presence of a conjugated diene 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 untreatable complex mixture.

Scheme 4. Gold-catalysed rearrangement of enynes **4** to indenenes **5**: Scope. <sup>[a]</sup> With (Ph<sub>3</sub>P)AuCl. <sup>[b]</sup> With (IPr)AuCl. <sup>[c]</sup> Isomerization of the alkene was observed (see ESI for details). <sup>[d]</sup> Estimated yield. [H<sub>2</sub>]: Pd(C) (10 mol%), H<sub>2</sub> (1 atm), EtOAc, RT, 3 h.

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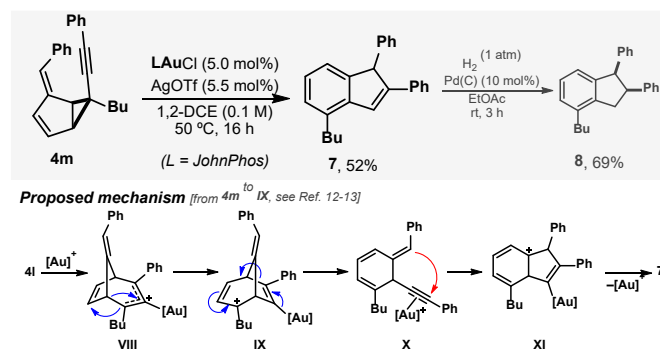


**Scheme 5.** Proposed mechanism. Calculated relative free-energy profile for the rearrangement of **4-Me-[Au]** to **5-Me-[Au]**. (numbers within parentheses indicate  $\Delta G$  in kcal·mol<sup>-1</sup>; [Au] = [(Me<sub>3</sub>P)Au].

Considering the complexity of the transformation and the lack of success of trapping experiments (with alcohols or alkenes) we found tough to conceive a mechanism. Therefore, we carried out computational studies at PCM-B3PW91-D3/cc-pVDZ-pp//B3PW91/cc-pVDZ-pp level with simplified system **4-Me-[Au]** ([Au] = [(Me<sub>3</sub>P)Au<sup>+</sup>]) (Scheme 5, see ESI for details). Starting from **4-Me-[Au]** structure (0.0 kcal·mol<sup>-1</sup>), alkyne coordination to gold facilitates a 6-*endo-dig*  $\pi_{C-C}$  attack by the exocyclic double bond to get transition structure **TS1** (+11.3 kcal·mol<sup>-1</sup>). This step differs from our previously reported reaction of related compounds **A**,<sup>12,13</sup> which reacted also via 6-*endo-dig*  $\pi_{C-C}$  attack but through the only available cyclic alkene (see Scheme 1). From **TS1**, cleavage of the cyclopropane leads to less strained structure **I** (-11.9 kcal·mol<sup>-1</sup>). Then, exocyclic *Z*-Me group (highlighted in red) undergoes an energy affordable 1,2-shift via **TS2** (+11.8 kcal·mol<sup>-1</sup>) to reach intermediate **II**. This migration is compatible with migratory aptitude when other substituents are present (*i*-Pr, Ph). Then, a phenyl 1,2-shift takes place through the highest energy transition structure **TS3** (+28.1 kcal·mol<sup>-1</sup>) to afford intermediate **III** (-35.6 kcal·mol<sup>-1</sup>). Subsequent 1,2-H shift through **TS4** (-13.4 kcal·mol<sup>-1</sup>) leads to structure **IV** (-35.6 kcal·mol<sup>-1</sup>). From this structure, the Me group, originally attached to the cyclopropane ring (highlighted in pink), undergoes three consecutive 1,2-shifts

(**TS5**→**V**→**TS6**→**VI**→**TS7**) to be installed in its final position at the cyclopentene ring as indicated in intermediate structure **VII** (-44.8 kcal·mol<sup>-1</sup>).<sup>19</sup> To conclude, the definitive H-1,2-shift via **TS8** (-33.5 kcal·mol<sup>-1</sup>) finally leads to **5-Me-[Au]** (-67.1 kcal·mol<sup>-1</sup>), the most stable structure, which correspond 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 *in situ* generated [(JohnPhos)Au<sup>+</sup>] catalyst, under otherwise identical 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 we earlier observed from compounds **A**,<sup>12,13</sup> this result can be explained by 6-*endo-dig*  $\pi_{C-C}$  attack on the internal alkene and cyclopropane ring-opening to generates intermediate **VIII**. Then, a regioselective rearrangement leads to cationic species **IX**, which evolves to alkyne intermediate **X**, analogous to compounds **B** (see Scheme 1). In contrast to **B**, the presence of the exocyclic alkene in intermediate **X** enables a subsequent 5-*endo-dig* cyclization to bicycle **XI**.<sup>20</sup> Finally, an aromatization during the protodeauration gives rise to compound **7**.



**Scheme 6.** Gold-catalysed rearrangement of **4m** to indene **6**.

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 cyclopropane ring in a highly strained structure. This particular assembly translates into an exotic reactivity since unsuspected highly substituted indenenes **5** are obtained in regioselective fashion. A plausible mechanistic scenario for this intricate transformation is proposed on computational studies basis. 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.

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There are no conflicts to declare.

## Notes and references

- (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*, 2012, Wiley-VCH.
- C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti and N. T. Patil, *Chem. Rev.*, 2021, **121**, 8478–8558.
- (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.
- (a) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326–3350; (b) I. C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902–912.
- (a) J. Zhang, H.-G. Schmalz, J. Zhang and H.-G. Schmalz, *Angew. Chemie 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. Chemie 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. Chemie Int. Ed.*, 2012, **51**, 10377–10381.
- D. J. Gorin, I. D. G. Watson and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 3736–3737.
- (a) Y. Zou, D. Garayalde, Q. Wang, C. Nevado, A. Goeke and Y. Ito, *Angew. Chemie 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-Bengoia, X. Huang, A. Goeke and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 4720–4730.
- (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**, 2321–2328. See also: (e) S. Ghorpade, M. Der Su and R. S. Liu, *Angew. Chemie Int. Ed.*, 2013, **52**, 4229–4234.
- See also: (a) S. G. Sethofer, S. T. Staben, O. Y. Hung and F. D. Toste, *Org. Lett.*, 2008, **10**, 4315–4318. For gold-catalyzed 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.
- For the study of a cyclopropane tethering 1,5-enyne with unconventional structure derived from heptatriene, see: R. Dorel and A. M. Echavarren, *J. Org. Chem.*, 2016, **81**, 8444–8454.
- Barluenga, E. Tudela, R. Vicente, A. Ballesteros and M. Tomás, *Chem. Eur. J.*, 2011, **17**, 2349–2352.
- J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros and M. Tomás, *Angew. Chemie Int. Ed.*, 2011, **50**, 2107–2110.
- (a) E. Tudela, J. González, R. Vicente, J. Santamaría, A. Ballesteros and M. A. Rodríguez, *Angew. Chemie 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.
- See ESI for details. Compounds **4** rapidly decomposed when dried and, therefore, were stored and handled in solution.
- R. A. Moss, L. A. Perez, K. Krogh-Jespersen and C. M. Young, *J. Am. Chem. Soc.*, 1981, **103**, 2413–2415.
- This *endo*-selectivity is in sharp contrast with the observed with alkoxy-substituted Fischer carbenes, see: J. Barluenga, S. Martínez, A. L. Suárez-Sobrinó and M. Tomás, *J. Am. Chem. Soc.*, 2002, **124**, 5948–5949.
- See ESI for details on the screening.
- 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](http://www.ccdc.cam.ac.uk/data_request/cif).
- 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.
- The gold-catalyzed cycloisomerization of 1,4-enynes has been scarcely explored and usually involves acetate migrations. For representative 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. Chemie Int. Ed.*, 2006, **45**, 3647–3650. See also Ref. 8e.