

# Organic & Biomolecular Chemistry

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: M. Mato, I. Martin-Torres, B. Herlé and A. M. Echavarren, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB00359B.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

## COMMUNICATION

## Cyclopropane-Alkene Metathesis by Gold(I)-Catalyzed Decarbenation of Persistent Cyclopropanes

Mauro Mato,<sup>†a,b</sup> Inmaculada Martín-Torres,<sup>†a,b</sup> Bart Herlé,<sup>a</sup> and Antonio M. Echavarren<sup>\*a,b</sup>Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

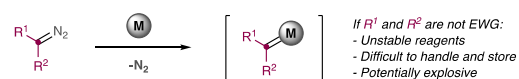
A gold(I)-catalyzed cyclopropane-alkene metathesis has been demonstrated with two new families of cyclopropane derivatives of naphthalene and phenanthrene (benzo-fused norcaradienes). In this process, metal carbene units are transferred from a persistent cyclopropane to an alkene, upon release of naphthalene or phenanthrene, allowing the diastereoselective synthesis of a wide range of aryl and vinyl cyclopropanes.

Gold(I) carbenes<sup>1</sup> have often been invoked as intermediates in a wide array of transformations promoted by gold(I) complexes and, therefore, are key for the understanding and development of homogeneous gold(I) catalysis.<sup>2</sup> Nevertheless, the controlled generation of reactive gold(I) carbenes still remains a significant challenge,<sup>3</sup> since the classical methods, such as the decomposition of diazo compounds (Scheme 1a),<sup>4</sup> lack generality or require the preparation and handling of potentially unsafe reagents.<sup>5</sup> As an alternative method for the safe generation of gold(I) carbenes, we reported the retro-Buchner reaction of 7-substituted 1,3,5-cycloheptatrienes (Scheme 1b),<sup>6</sup> which led to the development of different synthetic methodologies that exploit the use of these intermediates.<sup>7</sup> More recently, we showed that a similar retro-Buchner process can be carried out under zinc(II)<sup>8</sup> or rhodium(II)<sup>9</sup> catalysis, unlocking new reactivity, which was applied for the synthesis of natural products.

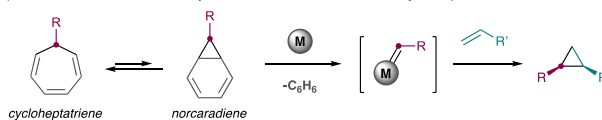
7-Substituted 1,3,5-cycloheptatrienes exist in a tautomeric equilibrium with its corresponding norcaradienes,<sup>10</sup> which can undergo a metal-catalyzed retro-cyclopropanation generating a metal carbene upon release of benzene<sup>6</sup> or substituted benzenes.<sup>8,9</sup> We have also observed that certain electron-rich arylcyclopropyl dihydronaphthalene derivatives, obtained by

cycloisomerization of phenyl-linked 1,6-enynes, can give rise to aryl gold(I) carbenes, releasing naphthalenes.<sup>7b,11</sup> Based on these precedents, we envisioned that benzo-fused norcaradienes could act as general precursors for the generation of gold(I) carbenes (Scheme 1c). Herein, we present the design and synthesis of a range of persistent norcaradienes derived from dihydronaphthalenes and dihydrophenanthrenes, which undergo gold(I)-catalyzed decarbenation reactions. This allows transferring aryl and vinyl carbene units from a persistent cyclopropane to an alkene, assembling a new three-membered carbocycle,<sup>12</sup> in a cyclopropane-alkene metathesis process.<sup>13</sup>

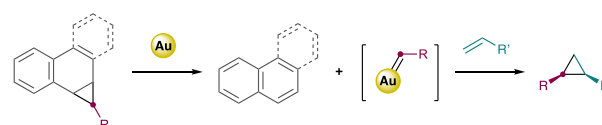
a) **Classical approach:** Metal-catalyzed decomposition of diazo compounds



b) **Previous work:** Metal-catalyzed retro-Buchner reaction of cycloheptatrienes



c) **This work:** Gold(I)-catalyzed decarbenation of benzo-fused norcaradienes



**Scheme 1** a) Classical approach for the generation of metal carbenes. b) Metal-catalyzed retro-Buchner reaction of cycloheptatrienes. c) This approach: gold(I)-catalyzed decarbenation of persistent cyclopropanes.

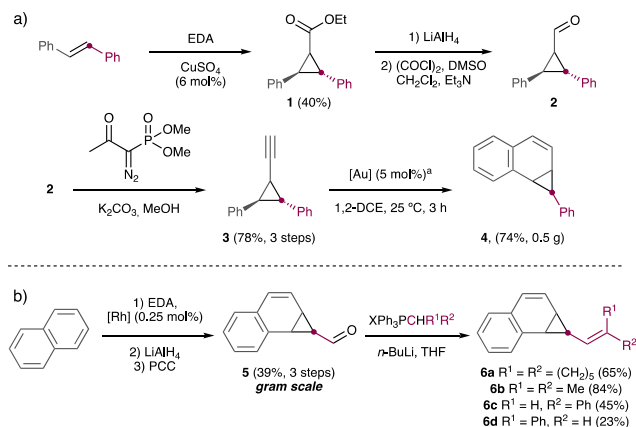
We started our investigation by the synthesis of two types of benzo-fused norcaradienes derived from dihydronaphthalene. The first one (**4**) would allow transferring the phenyl carbene moiety and the second one (**6**), could be used as vinyl carbene equivalent. We prepared **4** by gold(I)-catalyzed intramolecular hydroarylation of cyclopropyl alkyne **3**, which was prepared in gram-scale through a sequence involving the copper(II)-catalyzed cyclopropanation of *E*-stilbene with ethyl diazoacetate, reduction to the aldehyde, and alkylation using Bestmann-Ohira reagent (Scheme 2a).<sup>14</sup>

<sup>a</sup> Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology. Av. Països Catalans 16, 43007 Tarragona (Spain).

<sup>b</sup> Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili. C/ Marcel·lí Domingo s/n, 43007 Tarragona (Spain).

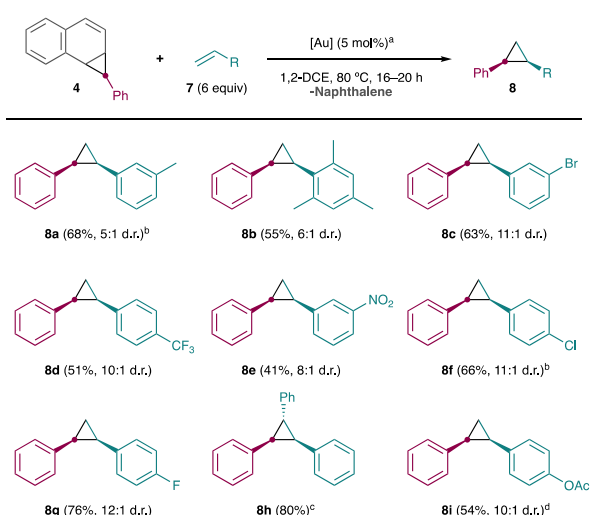
<sup>†</sup> These authors contributed equally to this work.

Electronic Supplementary Information (ESI) available: For detailed experimental procedures, characterization data, and copies of NMR spectra of all new compounds, see DOI: 10.1039/x0xx00000x



**Scheme 2** Synthesis of phenyl (a) and vinyl (b) dihydronaphthalene carbene precursors **4** and **6a–d**. EDA = ethyl diazoacetate. [Rh] = [Rh(TFA)<sub>2</sub>]<sub>2</sub>. PCC = Pyridinium chlorochromate. <sup>a</sup> [Au] = [(JohnPhos)Au(MeCN)]SbF<sub>6</sub>.

In a different route, cyclopropanation of naphthalene with ethyl diazoacetate in the presence of only 0.25 mol% of [Rh(TFA)<sub>2</sub>]<sub>2</sub> affords the corresponding cyclopropyl ester,<sup>15</sup> which can subsequently be reduced to give aldehyde **5** in 39% yield over three steps. Wittig reaction of **5** with different triphenylphosphonium halides gave vinyl carbene precursors **6a–d**.<sup>14</sup>

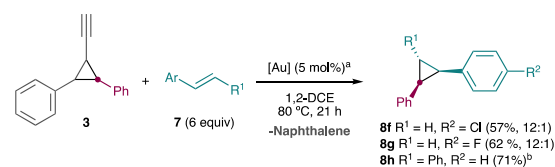


**Scheme 3** Scope of the phenyl cyclopropanation of styrenes. Yields are for isolated products. The *cis* cyclopropane is obtained as major diastereoisomer. <sup>a</sup> [Au] = [(JohnPhos)Au(MeCN)]SbF<sub>6</sub>. <sup>b</sup> Stirred at 100 °C for 20 h. <sup>c</sup> Isolated as a mixture with the product of phenyl cyclopropanation of **4**. <sup>d</sup> 3 equiv of alkene employed.

First, we explored the phenyl cyclopropanation of a range of styrenes *via* gold(I)-catalyzed decarbenation of **4** (Scheme 3). The main side-reaction on this process is the phenyl cyclopropanation of **4** giving a bicyclopropane which is unreactive towards retro-cyclopropanation.<sup>14</sup> Fortunately, this pathway can be minimized statistically by the use of an excess of commercially available styrenes **7**. Accordingly, the reaction of 1 equiv of **4** with 6 equiv of 3-methylstyrene (**7a**) in the presence of 5 mol% of [(JohnPhos)Au(MeCN)]SbF<sub>6</sub> at 80 °C gave *cis*-cyclopropane **8a** in 68% yield and a 5:1 ratio of diastereoisomers. Different styrenes were tested under the same conditions, obtaining in all cases the corresponding

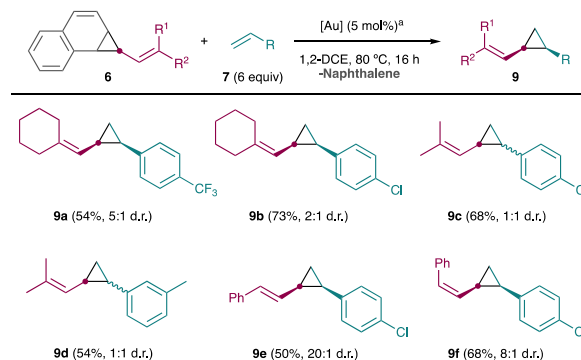
cyclopropane in moderate to good yields, with *cis/trans* ratios of up to 12:1. Alkenes with different electronic and steric properties were tolerated, and aryl halides (**8c**, **8f–g**) were found to be compatible with the reactions conditions (Scheme 3). Cyclopropanation of *E*-stilbene gives *exo*-1,2,3-triphenylcyclopropane (**8h**) also in good yield. Remarkably, this cyclopropane-alkene metathesis, in which an aryl gold(I) carbene is transferred, takes place efficiently at 80 °C, comparing favorably to the 120 °C required with the use of 7-aryl 1,3,5-cycloheptatrienes.<sup>6</sup>

Furthermore, considering that the gold(I)-based catalytic system that is used in the hydroarylation of **3** to give **4** is the same than the one used in the decarbenation-cyclopropanation sequence, we designed a one-pot strategy which uses directly alkyne **3** as a synthetic equivalent of a phenyl carbene (Scheme 4). This led to the optimization of a more practical procedure in which 1 equiv of **3** was mixed with 6 equiv of a styrene **7** in the presence of [(JohnPhos)Au(MeCN)]SbF<sub>6</sub> at 80 °C, giving directly the corresponding cyclopropane, in comparable yields and diastereoselectivities to those achieved in the two-step method (Schemes 3 and 4).



**Scheme 4** One-pot sequential gold(I)-catalyzed hydroarylation-decarbenation-cyclopropanation of styrenes with alkyne **3**. Yields are for isolated products. The *cis* cyclopropane is obtained as major diastereoisomer. <sup>a</sup> [Au] = [(JohnPhos)Au(MeCN)]SbF<sub>6</sub>. <sup>b</sup> Isolated as a mixture with the product of phenyl cyclopropanation of **4**.

Under the same reaction conditions, we found that vinyl derivatives **6** also undergo a gold(I) catalyzed decarbenation, and the resulting carbenes can be trapped by styrenes, allowing the assembly of vinyl cyclopropanes (Scheme 5).

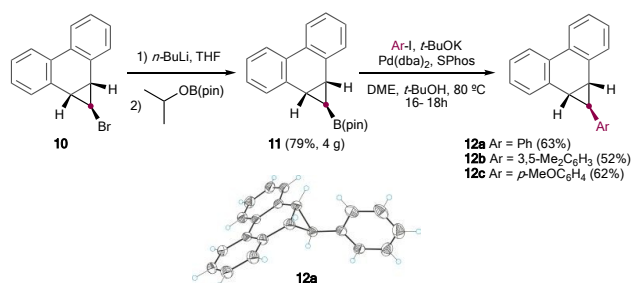


**Scheme 5** Scope of the vinyl cyclopropanation of styrenes. Yields are for isolated products. The *cis* cyclopropane is obtained as major diastereoisomer. <sup>a</sup> [Au] = [(JohnPhos)Au(MeCN)]SbF<sub>6</sub>.

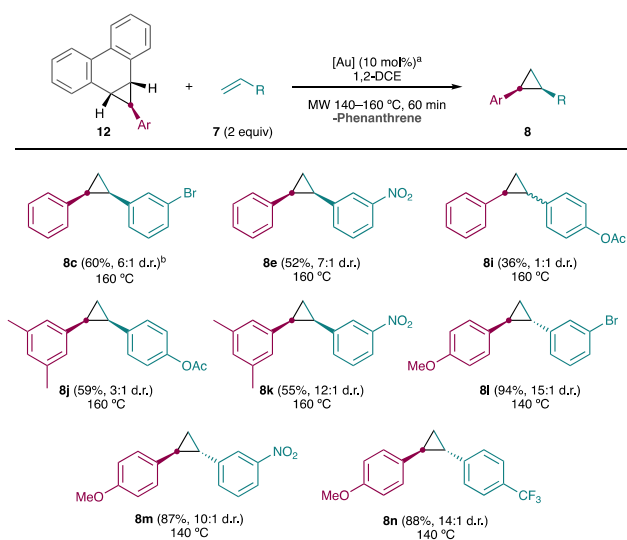
Symmetrical vinyl cyclopropanes with alkyl substituents can be easily prepared by this method, although the diastereoselectivity in the cyclopropanation reaction is lower

than for the transfer of carbene units bearing aromatic moieties, presumably due to the reduced steric discrimination and the lack of  $\pi$ - $\pi$  stabilizing interactions (**9a-d**).<sup>7d</sup> The same strategy allowed carrying out a styryl cyclopropanation reaction, transferring either *E* or *Z* styryl carbenes, with good diastereoselectivity (**9e-f**).

In our search for a new family of more robust carbene precursors, we designed a route for the synthesis of phenanthrene derivatives **12** (Scheme 6). Initial screening on the use of known *exo*-bromocyclopropane **10**<sup>16</sup> as electrophile in cross-coupling reactions with aryl organometallic reagents only gave yields below 20% for the desired aryl cyclopropane products **12**. Alternatively, lithium-halogen exchange of **10** and trapping with isopropoxy-pinacolborane gives access to boronic ester **11** in gram-scale. Suzuki-Miyaura coupling of **11** with different aryl iodides allowed the assembly of carbene precursors **12a-c** in good yields.<sup>14</sup> The structure of *exo*-**12a** was confirmed by X-ray diffraction.



**Scheme 6** Synthesis of aryl dihydrophenanthrene carbene precursors **12a-c** by palladium-catalyzed Suzuki coupling of **11** with aryl iodides and X-ray structure of **12a**.



**Scheme 7** Scope of the gold(I)-catalyzed aryl cyclopropanation of styrenes. Yields are for isolated products. The major diastereoisomer obtained is the one depicted for each example. <sup>a</sup> [Au] = [(JohnPhos)Au(MeCN)]SbF<sub>6</sub>. <sup>b</sup> Isolated as a mixture with 1 equiv of phenanthrene.

Analogous reaction conditions than those for the decarbenation of cyclopropanes **4** or **6** only afforded conversions of **12a** lower than 20% in temperature ranges from 50 to 120 °C. A solution to the lower reactivity of the phenanthrene derivatives came

with the use of microwave heating. The reaction of **12a** with only 2 equiv of 3-bromostyrene in the presence of 10 mol% of [(JohnPhos)Au(MeCN)]SbF<sub>6</sub> upon 60 min of microwave irradiation in 1,2-dichloroethane at 160 °C led to the clean formation of cyclopropane **8c** in 60% yield, upon release of phenanthrene. Different *cis*-cyclopropanes could be obtained by this method, bearing different substituents in both aromatic rings (Scheme 7). Interestingly, as expected, increasing the electron density on the aromatic ring of the carbene unit, drastically speeds up the reaction, allowing to reach full conversion and excellent yields at a lower temperature (**8l-n**). Regarding the diastereoselectivity, cyclopropanes bearing only electron-withdrawing groups were obtained preferentially as the *cis* isomer. On the other hand, electron-rich cyclopropanes bearing *p*-methoxy substituents were obtained almost exclusively as the *trans* isomers (**8l-n**). This trend was already observed in the context of cyclopropanation by retro-Bucher reaction of 7-aryl 1,3,5-cycloheptatrienes,<sup>6</sup> and can be rationalized by a *cis* to *trans* isomerization catalyzed by gold(I).<sup>7d</sup> Since there are reports of the generation of free carbenes from certain dihydrophenanthrene derivatives without the need of transition metals,<sup>17</sup> the reaction was tested without catalyst, giving no conversion, which confirms the need of the gold(I) complex for the decarbenation reaction to proceed. Besides, it is worth highlighting the cleanness of this transformation, since no byproducts other than phenanthrene were detected in the reaction mixtures.

In conclusion, we have demonstrated the possibility of carrying out a cyclopropane-alkene metathesis through the gold(I)-catalyzed decarbenation of persistent cyclopropanes. We designed the synthesis of cyclopropyl dihydronaphthalene and dihydrophenanthrene derivatives, which display a benzo-fused norcaradiene structure, and allowed the transfer of aryl and vinyl carbenes to a wide range of styrenes. This represents another alternative to the use of potentially dangerous non-stabilized diazo compounds, and a step forward towards the development of an ideal cyclopropane metathesis process.

## Acknowledgments

We thank the Agencia Estatal de Investigación (AEI)/FEDER, UE (CTQ2016-75960-P and FPI predoctoral fellowship to M.M. and I.M.-T.), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support. We thank Xiang Yin for preliminary experiments on the synthesis of **4**. We also thank the ICIQ X-ray diffraction unit.

## Author information

### Corresponding Author

\*E-mail: aechavarren@iciq.es

### ORCID

Mauro Mato: 0000-0002-2931-5060

Inmaculada Martín-Torres: 0000-0002-8882-4199

Antonio M. Echavarren: 0000-0001-6808-3007

## Conflicts of interest

The authors declare no conflicts of interest.

## Notes and references

1. a) F. Z. Dörwald, *Metal Carbenes in Organic Synthesis* (2007), Wiley-VCH. b) Y. Wang, M. E. Muratore and A. M. Echavarren, *Chem. Eur. J.*, 2015, **21**, 7332.
2. a) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395. b) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239. c) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902. d) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028. e) D. Pflästerer and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331. f) W. Zi and D. Toste, *Chem. Soc. Rev.*, 2016, **45**, 4567.
3. For new approaches for the generation of gold(I) carbenes, see: a) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877. b) M. Jia and S. Ma, *Angew. Chem. Int. Ed.*, 2016, **55**, 9134.
4. a) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861. b) M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Angew. Chem. Int. Ed.*, 2005, **44**, 5284. c) F. Wei, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, *Sci. Bull.*, 2015, **60**, 1479. d) L. Liu and J. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 506. e) M. R. Fructos, M. M. Díaz-Requejo and P. J. Pérez, *Chem. Commun.*, 2016, **52**, 7326.
5. a) M. P. Doyle, J. H. Griffin, V. Bagheri and R. L. Dorow, *Organometallics*, 1984, **3**, 53. b) J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, 1479.
6. C. R. Solorio-Alvarado, Y. Wang and A. M. Echavarren, *J. Am. Chem. Soc.*, 2011, **133**, 11952.
7. For a review, see: a) M. Mato, C. García-Morales and A. M. Echavarren, *ChemCatChem*, 2019, **11**, 53. For relevant examples, see: b) Y. Wang, P. R. McGonigal, B. Herlé, M. Besora and A. M. Echavarren, *J. Am. Chem. Soc.*, 2014, **136**, 801. c) Y. Wang, M. E. Muratore, Z. Rong and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2014, **53**, 14022. d) B. Herlé, P. M. Holstein and A. M. Echavarren, *ACS Catal.*, 2017, **7**, 3668. e) X. Yin, M. Mato and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2017, **56**, 14591. f) C. García-Morales, X.-L. Pei, J. M. Sarria Toro and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2019, DOI: 10.1002/anie.201814577.
8. M. Mato, B. Herlé and A. M. Echavarren, *Org. Lett.*, 2018, **20**, 4341.
9. M. Mato and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2019, **58**, 2088.
10. a) R. Hoffmann, *Tetrahedron Lett.*, 1970, **11**, 2907. b) O. A. McNamara and A. R. Maguire, *Tetrahedron*, 2011, **67**, 9.
11. a) C. R. Solorio-Alvarado and A. M. Echavarren, *J. Am. Chem. Soc.*, 2010, **132**, 11881. b) M. E. de Orbe, L. Amenós, M. S. Kirillova, Y. Wang, V. López-Carrillo, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2017, **139**, 10302.
12. a) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977. b) O. G. Kulinkovich, *Cyclopropanes in Organic Synthesis* (2015), John Wiley & Sons, Inc. c) C. Ebner and E. M. Carreira, *Chem. Rev.*, 2017, **117**, 11651. d) W. Wu, Z. Lin and H. Jiang, *Org. Biomol. Chem.*, 2018, **16**, 7315.
13. a) P. G. Gassman and T. H. Johnson, *J. Am. Chem. Soc.*, 1976, **98**, 6058. b) A. Fedorov, M.-E. Moret and P. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 8880. c) S. Asako, T. Kobashi and K. Takai, *J. Am. Chem. Soc.*, 2018, **140**, 15425.
14. See supporting information for details. DOI: 10.1039/C9OB00359B
15. a) P. Müller, J.-L. Toujas and G. Bernardinelli, *Helv. Chim. Acta*, 2000, **83**, 1525. b) P. J. Pérez, M. M. Díaz-Requejo and I. Revilla, *Beilstein J. Org. Chem.*, 2011, **7**, 653.
16. K. S. Graves, D. M. Thamattoor and P. R. Rablen, *J. Org. Chem.*, 2011, **76**, 1584.
17. a) D. B. Richardson, L. R. Durrett, J. M. Martin, W. E. Putnam, S. C. Slaymaker and I. Dvoretzky, *J. Am. Chem. Soc.*, 1965, **87**, 2763. b) H. C. Glick, I. R. Likhovotvorik and M. Jones, *Tetrahedron Lett.*, 1995, **36**, 5715. c) M. Nigam, M. S. Platz, B. M. Showalter, J. P. Toscano, R. Johnson, S. C. Abbot and M. M. Kirchhoff, *J. Am. Chem. Soc.*, 1998, **120**, 8055.

View Article Online

DOI: 10.1039/C9OB00359B

Benzo-fused norcaradienes derived from naphthalene and phenanthrene undergo gold(I)-catalyzed cyclopropane-alkene metathesis via decarbenation View Article Online  
DOI: 10.1039/C9OB00359B

Drawing for the Table of Contents

