A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201915895
Angew. Chem. 10.1002/ange.201915895

Link to VoR: http://dx.doi.org/10.1002/anie.201915895
http://dx.doi.org/10.1002/ange.201915895

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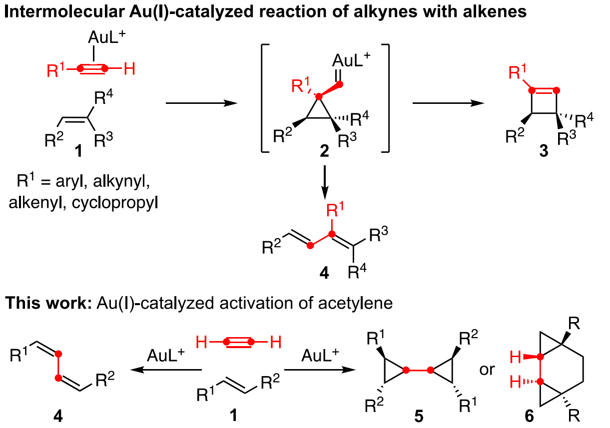
Acetylene as a Dicarbene Equivalent via Gold(I) Catalysis: Total Synthesis of Waitziacuminone in One Step

*Dagmar Scharnagel, Imma Escofet, Helena Armengol-Relats, M. Elena de Orbe, J. Nepomuk Korber, and Antonio M. Echavarren**

Abstract: *The gold(I)-catalyzed reaction of acetylene gas with alkenes leads to (Z,Z)-1,4-disubstituted 1,3-butadienes and biscyclopropanes depending on the donor ligand on gold(I). Acetylene was generated in situ from calcium carbide and water in a user-friendly procedure. Reaction of acetylene with 1,5-dienes gives rise stereoselectively to tricyclo[5.1.0.0^{2,4}]octanes. This novel double cyclopropanation has been applied to the one step total synthesis of the natural product waitziacuminone from acetylene and geranyl acetone.*

The last decade has witnessed the impact of gold(I) catalysis for the construction of complex organic frameworks,[1] particularly in the realm of the total synthesis of natural products.[2] However, while gold(I)-catalyzed intramolecular transformations usually perform outstandingly, their intermolecular versions are more challenging.[3] Our group demonstrated that the intermolecular reaction between terminal alkynes and alkenes **1** leads selectively to cyclobutenes **3**, although 1,3-dienes **4** were also formed with *ortho*-substituted aryl alkynes (Scheme 1).[4] These two transformations proceed via cyclopropyl gold carbenes **2** that undergo ring expansion or formal 1,3-C migration to afford cyclobutenes **3** or 1,3-dienes **4**, respectively.[4c] The synthesis of cyclobutenes by [2+2] cycloaddition is a general reaction that can be carried out enantioselectively,[5] although alkyl-substituted alkynes are poorly reactive partners.

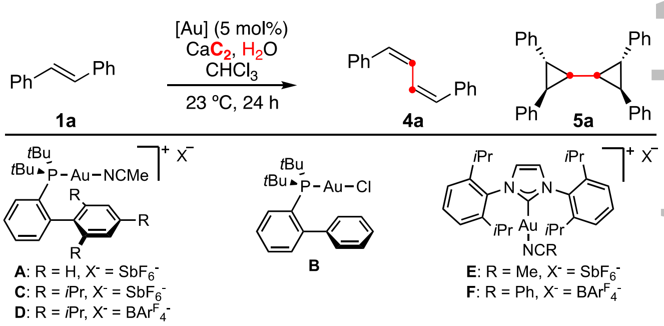


Scheme 1. General pathways for the reaction of alkynes with alkenes catalyzed by gold(I) catalysts and transformation of acetylene into *Z,Z*-dienes **4**, biscyclopropanes **5**, or tricyclo[5.1.0.0^{2,4}]octanes **6**.

Acetylene is a commodity feedstock for the production of vinyl chloride and other products.[6] In stark contrast, its use in homogeneous gold catalysis, especially for the assembly of complex structures, is very limited. So far, acetylene has not been used for the preparation of cyclobutenes **3** or dienes **4**. Interestingly, cyclopropyl gold carbenes **2** with R^1 = H, which formally correspond to those that would be generated by reaction of acetylene with an alkene, were shown to be intermediates in the decarbenation of a cyclopropyl-substituted cycloheptatriene.[4c,7] Herein we report the use of acetylene gas in intermolecular gold(I)-catalyzed reactions leading stereoselectively to *Z*,*Z*-dienes **4**, biscyclopropanes **5**, and tricyclo[5.1.0.0^{2,4}]octanes **6** (Scheme 1). Acetylene was conveniently produced *in situ* in small quantities from calcium carbide and water[8] using a Y shaped two-chamber flask.[9]

Several gold(I) catalysts were initially tested in the reaction of acetylene with *trans*-stilbene (**1a**) (Table 1). Gold(I) complexes **A** and **B** with JohnPhos as the ligand (Table 1, entries 1 and 2) led to mixtures of 1,3-diene **4a** and biscyclopropane **5a**. While complexes **C** and **D** with *t*BuXPhos as ligand delivered selectively *Z,Z*-diene **4a** (Table 1, entries 3 and 4), IPr gold(I) complexes **E** and **F** favored the formation of **5a** (Table 1, entries 5 and 6).[10] As we have observed before,[4c,11] complexes **D** and **F** with $BAr^F_4{}^-$ as the anion outperform those with SbF_6^-.

Table 1. Gold(I) catalyzed reaction of acetylene with stilbene **1a**.



Entry	[Au]	**4a** Yield [%][a]	**5a** Yield [%][a]
1	**A**	24	11
2	**B**[b]	15	41
3	**C**	7	0
4	**D**	25	<1
5	**E**	<1	6
6	**F**	1	56

[a] Yield determined by ^1H NMR using diacetyl benzene as internal standard. [b] Reaction with equimolar amounts of **B** and $NaBAr^F_4$.

The catalytic system based on complex *t*BuXPhos-gold(I) complex **D** was further optimized delivering the diene **4a** in 27% yield (Scheme 2). Substrates with a methyl or *tert*-butyl group in *para* position of the stilbene aryl group lead to the products **4b** and

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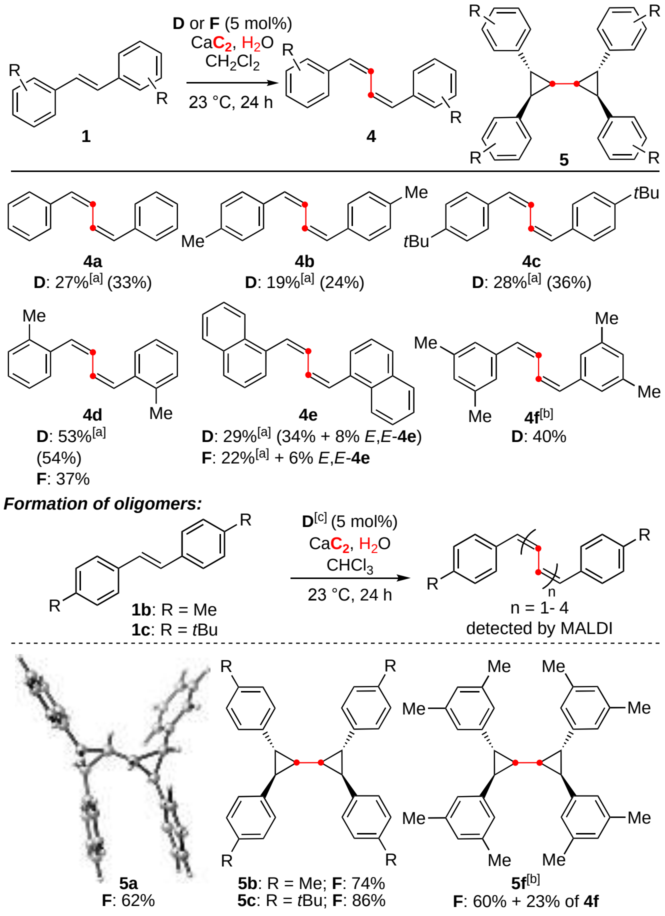
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

4c with similar results. Noteworthy, the yield with stilbene **1d** with *ortho*-methyl groups was significantly higher. This is in line with our observations in the reactions of aryl alkynes with aryl alkynes bearing *ortho*-substituents.[4c] The transformation of 1-naphtyl derivative **1e** gave also small amounts of *E*,*E*-**4e** in addition to the *Z*,*Z*-isomer, usually observed as the sole product. Stilbene **1f** with 3,5-disubstituted aryls afforded diene **4f** in moderate yield. The low to moderate yields result from the competing reaction of 1,3-dienes **4** with acetylene leading to oligomerization. Thus, we detected products containing up to 4 units of acetylene by MALDI analysis of the crude reaction mixtures (Scheme 2).[12]

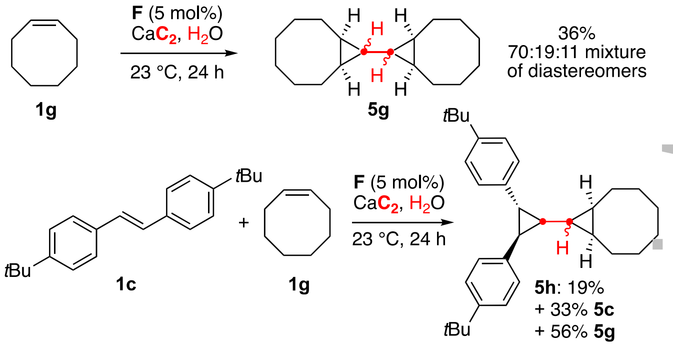


Scheme 2. Synthesis of dienes **4** and biscyclopropyl compounds **5** from acetylene and stilbenes **1a**-**f** and oligomerization experiments. Isolated yields (yields determined by ^1H NMR using diacetyl benzene as internal standard in parenthesis); **5a** is shown as a CYLlview depiction of the X-ray crystal structure. [a] Isolated as a mixture with starting material. [b] Reaction carried out in chloroform, at 40 ºC. [c] Reaction with equimolar amounts of *t*BuXPhosAuCl and $NaBAr^{F}_4$.

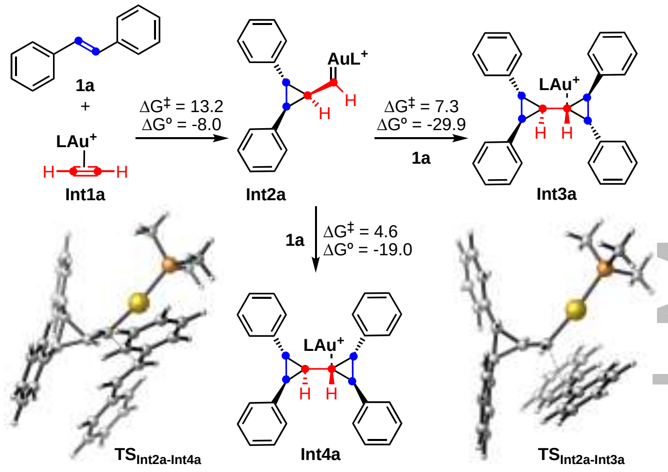
Optimization of the catalytic system using complex **F** led to biscyclopropyl compounds **5a**-**c** and **5f** in good yields in a biscyclopropanation, in which acetylene behaves as a dicarbene equivalent (Scheme 2). Remarkably, only one diastereomer was observed by NMR, chiral supercritical fluid chromatography and reverse phase ultra-high-performance liquid chromatography. The relative configuration of **5a** was confirmed by X-ray diffraction.[13]

The formation of biscyclopropyl derivatives **5** from acetylene is not only applicable to aryl-substituted alkenes, but could be also carried out with cyclooctene to form **5g** (Scheme 3). In a competition experiment with equimolar amounts of stilbene **1c** and cyclooctene **1g**, the cross-biscyclopropane **5h** was obtained together with biscyclopropanes **5c** and **5g**.

To understand the high selectivity on the formation of the *meso*-biscyclopropyl products **5a**-**c** and **5f**, we carried out a DFT study of the reaction of *trans*-stilbene (**1a**) with (η^2-alkyne)gold(I) complex **Int1a** (Scheme 4).[12] As we have shown before,[4c] cyclopropyl gold carbene **Int2a** is formed in an exergonic process, which can react further with a second molecule of **1a** to form **Int3a** or **Int4a**. Formation of **Int4a** through **TS$_{Int2a-Int4a}$**, which leads to *meso*-**5a**, is 2.7 Kcal/mol more favorable than formation of **Int3a**, in agreement with the experimental results.

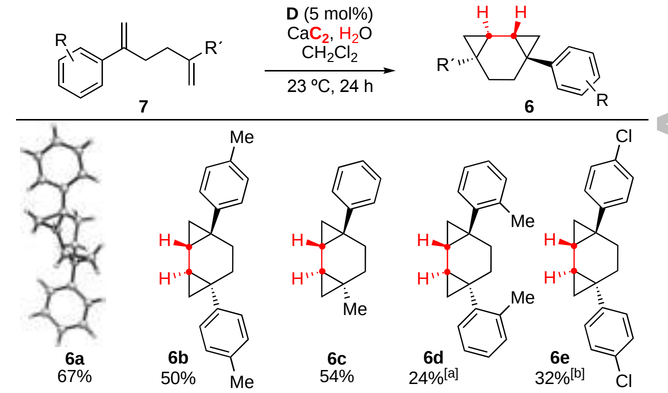


Scheme 3. Biscyclopropanation of cyclooctene.



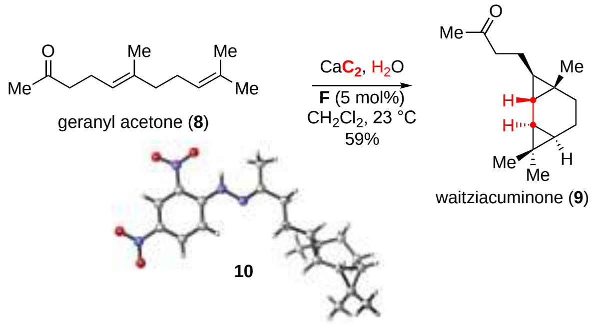
Scheme 4. Calculated formation of different diastereomers of biscyclopropyl products. L=PMe_3. DFT calculations performed with M06-D3/6-31G(d) (C, H, P) and SDD (Au) in CH_2Cl_2 (SMD). Free energies in Kcal/mol.

Furthermore, 1,5-dienes **7a**-**c** react with acetylene to form tricyclo[5.1.0.0^{2,4}]octanes **6a**-**e** as single diastereomers in the presence of catalyst **D** (Scheme 5). The relative configuration of **6a** was assigned by X-ray diffraction.[13]



Scheme 5. Synthesis of tricyclo[5.1.0.0^{2,4}]octanes **6**. [a] Isolated as a mixture with various alkene side products [b] Crude product resubmitted to reaction with acetylene and catalyst **D** two additional times (total 72 h reaction time).

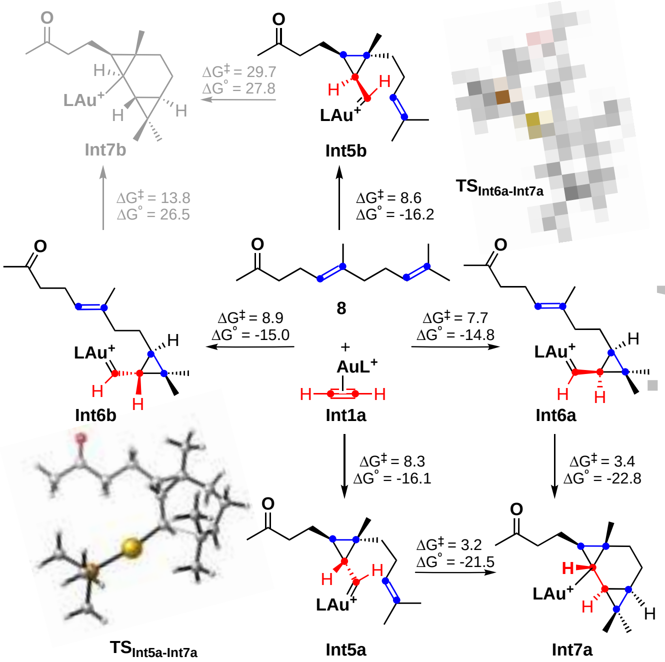
This biscyclopropanation of 1,5-dienes was applied to the first total synthesis of waitziacuminone (**9**),[14, 15] a sesquiterpene isolated from the aerial parts of *Waitzia acuminata*, known as orange immortelle, an annual herb native to Australia (Scheme 6). With geranyl acetone (**8**) as the substrate and catalyst **F**, the natural product was produced as a racemate in only one step as a single diastereomer. The relative configuration of waitziacuminone (**9**) was confirmed by X-ray diffraction of its crystalline 2,4-dinitrophenylhydrazone **10**.[13]



Scheme 6. One step total synthesis of (±)-waitziacuminone (**9**) and X-ray crystal structure of its 2,4-dinitrophenylhydrazone **10** (CYLview depiction).

The different pathways for the reaction between acetylene and geranyl acetone (**8**) were studied computationally[12] (Scheme 7). In principle, four possible cyclopropyl gold carbenes can be formed by reaction of both alkenes of **8** with (η^2-alkyne)gold(I) complex **Int1a**. The most favorable cyclopropanation gives **Int6a**, which immediately undergoes a second cyclopropanation through $\mathbf{TS_{Int6a-Int7a}}$ to form **Int7a**, and finally waitziacuminone (**9**). This pathway could compete with the initial cyclopropanation of the internal alkene of **8** leading to **Int5a**, which would similarly undergo an intramolecular cyclopropanation to form **Int7a**. The two other alternative pathways have slightly higher activation energies and the corresponding intermediates **Int5b** and **Int6b** would be unproductive, since the second cyclopropanation would generate a highly strained tricyclo[5.1.0.0^{2,4}]octane bearing a *trans*-fused cyclopropane, as shown by the high activation energies of these endergonic processes.

In conclusion, we have developed catalytic systems for the incorporation of acetylene gas into complex frameworks by means of gold(I) catalysis under experimentally very simple conditions. Acetylene is activated by gold(I) as a dicarbene equivalent that allows for the stereoselective synthesis of *Z*,*Z*-dienes **4**, biscyclopropyl compounds **5**, and tricyclo[5.1.0.0^{2,4}]octanes **6**. The latter transformation was applied to the first total synthesis of the sesquiterpene waitziacuminone (**9**) by the stereoselective formation of four C-C bonds and three rings in a single step.



Scheme 7. Different mechanistic pathways to form **Int7a-b** by double cyclopropanation reactions. L=PMe_3. DFT calculations performed with M06-D3/6-31G(d) (C, H, P, O) and SDD (Au) in CH_2Cl_2 (SMD). Free energies in Kcal/mol.

Acknowledgements

We thank the Agencia Estatal de Investigación (AEI)/FEDER, UE (CTQ2016-75960-P, FPU predoctoral fellowship to H.A.-R. and Severo Ochoa predoctoral fellowship to M.E.d.O.), the European Research Council (Advanced Grant No. 835080), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support. D.S. acknowledges the receipt of a postdoctoral fellowship from the Deutsche Forschungsgemeinschaft. We also thank the ICIQ X-ray diffraction unit and Dr. Rémi Blieck for helpful discussions.

Keywords: gold catalysis · acetylene · cyclopropanation · total synthesis

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[12] See supporting information for details.

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