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

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**Abstract:** The gold(I)-catalyzed reaction of acetylene gas with alkynes leads to (Z,Z)-1,4-disubstituted 1,3-butadienes and bicsyclopropanes 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[5.1.0.0²,4]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 alkynes 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.[4e] The synthesis of cyclobutenes by [2+2] cycloaddition is a general reaction that can be carried out enantioselectively,[3] although alkyl-substituted alkynes are poorly reactive partners.

Acetylene is a commodity feedstock for the production of vinyl chloride and other products.[5] 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 R1 = 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.[6c,7] Herein, we report the use of acetylene gas in intermolecular gold(I)-catalyzed reactions leading, stereoselectively, to Z,Z-dienes 4, bicsyclopropanes 5, or tricyclo[5.1.0.0²,4]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 bicsyclopropane 5a. While complexes C and D with 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,[6c,11] complexes D and F with BAIPrF as the anion outperform those with SbF₆⁻.

The catalytic system based on complex 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 products 4b and 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 alkynes with aryl alkynes bearing ortho-substituents.[6c] The transformation of 1-naphth 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).

Optimization of the catalytic system using complex F led to bicyclopentyl compounds 5a–c and 5f in good yields in a bicyclopentanation, 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.

The formation of bicyclopentyl 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-bicyclopentane 5h was obtained together with bicyclopropanes 5c and 5g.

To understand the high selectivity on the formation of the meso-bicyclopentyl products 5a–c and 5f, we carried out a DFT study of the reaction of trans-stilbene (1a) with (η2-alkyne)gold(I) complex Int1a (Scheme 4). As we have shown before, cyclopropyl gold carbene Int2a is formed in an exergonic process and it can react further with a second molecule of 1a to form Int3a or Int4a. Formation of Int4a through TSInt2a-Int4a, which leads to meso-5a, is 2.7 kcal mol⁻¹ more favorable than formation of Int3a, in agreement with the experimental results.

This bicyclopentanation of 1,5-dienes was applied to the first total synthesis of waitziacuminone (9), 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.
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 (η²-alkyne)gold(I) complex Int1a. The most favorable cyclopropanation gives Int6a, which immediately undergoes a second cyclopropanation through 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[5.1.0.0²,4]octane bearing two trans-fused cyclopropanes, 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-diienes 4, biscyclopropyl compounds 5, and tricyclo[5.1.0.0²,4]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.
Communications

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) A. M. Echavarren, M. N. Muratore, V. López-Carrillo, A. Escribano-Cuesta, A. Huguet, C. Obradors in Organic Reaction, Vol. 92 (Eds.: S. E. Denmark et al.), Wiley, 2017, pp. 1–288; b) R. Dorel, A. M. Echavarren, Chem. Rev. 2015, 115, 9028–9072; c) L. Fensterbank, M. Malacria, Acc. Chem. Res. 2014, 47, 953–965; d) A. Fürstner, Chem. Soc. Rev. 2009, 38, 3208–3221; e) J. W. Boyle, Y. Zhao, P. W. H. Chan, Synthesis 2018, 50, 1402–1416; f) D. P. Day, P. W. H. Chan, Adv. Synth. Catal. 2016, 358, 1368–1384; g) C. Chen, Y. Zhou, X. Chen, X. Zhang, W. Rao, P. W. H. Chan, Org. Lett. 2016, 18, 4730–4733.

[2] a) R. Quach, D. P. Furrert, M. A. Brimble, Org. Biomol. Chem. 2017, 15, 3098–3104; b) J. G. Mayans, H. Armgend-Relats, P. Calleja, A. M. Echavarren, Isr. J. Chem. 2018, 58, 639–658; c) D. Pfisterer, A. S. K. Hashmi, Chem. Soc. Rev. 2016, 45, 1331–1367; d) C. I. Stathakis, P. L. Gkizis, A. L. Zografas, Nat. Prod. Rep. 2016, 33, 1093–1117.

[3] C. García-Morales, A. M. Echavarren, Synlett 2018, 29, 2225–2237.

[4] a) V. López-Carrillo, A. M. Echavarren, J. Am. Chem. Soc. 2010, 132, 9292–9294; b) M. E. de Orbe, A. M. Echavarren, Org. Synth. 2016, 93, 115–126; c) M. E. de Orbe, L. Amenós, M. S. Kirillova, Y. Wang, V. López-Carrillo, F. Maseras, A. M. Echavarren, J. Am. Chem. Soc. 2017, 139, 10302–10311; d) M. E. de Orbe, A. M. Echavarren, Eur. J. Org. Chem. 2018, 2740–2752.

[5] C. García-Morales, B. Ranieri, I. Escofet, L. López-Suárez, C. Obradors, A. I. Konovalov, A. M. Echavarren, J. Am. Chem. Soc. 2017, 139, 13628–13631.

[6] I.-T. Trotus, T. Zimmermann, F. Schüth, Chem. Rev. 2014, 114, 1761–1782.

[7] C. R. Solorio-Alvarado, Y. Wang, A. M. Echavarren, J. Am. Chem. Soc. 2011, 133, 11952–11955.

[8] K. S. Rodygin, G. Werner, F. A. Kucherev, V. P. Ananikov, Chem. Asian J. 2016, 11, 965–976.

[9] V. V. Voronin, M. S. Ledovskaya, E. G. Gordeev, K. S. Rodygin, V. P. Ananikov, J. Org. Chem. 2018, 83, 3819–3828.

[10] Several other gold(I) complexes and transition metal salts were screened, but did not show conversion or delivered only traces of 4a and 5a. See Supporting Information for details.

[11] A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, Adv. Synth. Catal. 2014, 356, 221–228.

[12] See Supporting Information for details. A dataset collection of computational results is available in the ioChem-BD repository and can be accessed through https://doi.org/10.19061/iochem-bd-1-148: M. Alvarez-Moreno, C. de Graaf, N. Lopez, F. Maseras, J. M. Poblet, C. Bo, J. Chem. Inf. Model. 2015, 55, 95–103.

[13] CCDC 1971217, 1971218, 1971429, and 1971216 (Contains the supplementary crystallographic data for this paper). These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[14] J. Jakupovic, A. Schuster, F. Bohlmann, R. M. King, L. Haegi, Phytochemistry 1999, 28, 1943–1948.

[15] The myliol family of natural products also contains an embedded tricyclo[5.1.0.0²,4]octane, albeit with different relative configuration: S. H. von Reuss, C.-L. Wu, H. Muhle, W. A. König, Phytochemistry 2004, 65, 2277–2291, and references therein.

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