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Cyclobutene vs. 1,3-Diene Formation in the Gold-Catalyzed Reaction of Alkynes with Alkenes: The Complete Mechanistic Picture

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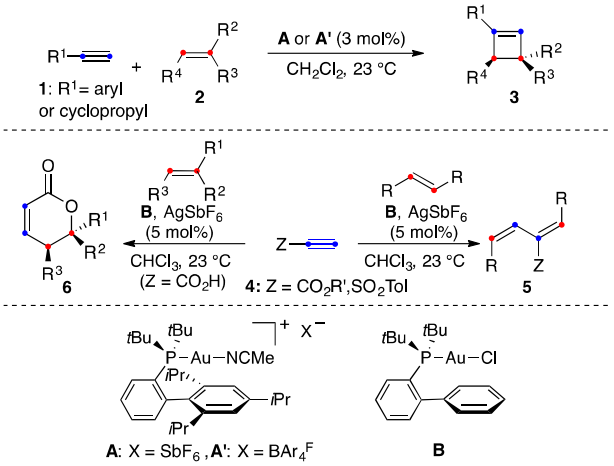
ABSTRACT: The intermolecular gold(I)-catalyzed reaction between aryl alkynes and alkenes leads to cyclobutenes by a [2+2] cycloaddition, which takes place stepwise, first by formation of cyclopropyl gold(I) carbenes, followed by a ring expansion. However, 1,3-butadienes are also formed in the case of *ortho*-substituted aryl alkynes by a metathesis-type process. The corresponding reaction of alkenes with aryl-1,3-butadiynes, ethynylogous to arylalkynes, leads exclusively to cyclobutenes. A comprehensive mechanism for the gold(I)-catalyzed reaction of alkynes with alkenes is proposed based on DFT calculations, which shows that the two pathways leading to cyclobutenes or dienes are very close in energy. The key intermediates are cyclopropyl gold(I) carbenes, which have been independently generated by retro-Buchner reaction from stereodefined 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalenes.

INTRODUCTION

Cycloisomerizations of 1,n-enynes catalyzed by gold(I) and other electrophilic metals proceed by mechanistically complex, multistep transformations that lead to novel architectures[1] and have been applied for the total synthesis of a variety of natural products.[2] The parent intermolecular reaction between terminal alkynes **1** and alkenes **2** gives rise to cyclobutenes **3** as a result of a [2+2] intermolecular cycloaddition (Scheme 1).[3] Key for the success of this reaction was the use of cationic gold(I) complex **A** with a very bulky phosphine. By exchanging the anion of catalyst **A** from SbF_6^- to softer BAr_4^{F-}, cyclobutenes **3** were obtained in better yields presumably by slowing down the rate of formation of σ, π-digold(I) alkyne complexes, which were shown to be unproductive dead-ends in this transformation.[4] We have extended this [2+2] cycloaddition for the synthesis of up to 15-membered ring macrocycles by performing the reaction with 1,n-enynes (n = 10-16),[5] which has been applied for the enantioselective total synthesis of rumphellaone A.[6]

Scheme 1. Gold(I)-Catalyzed [2+2] Cycloaddition of Alkynes with Alkenes[3,4] or Formation of 1,3-Dienes and Lactones[20]

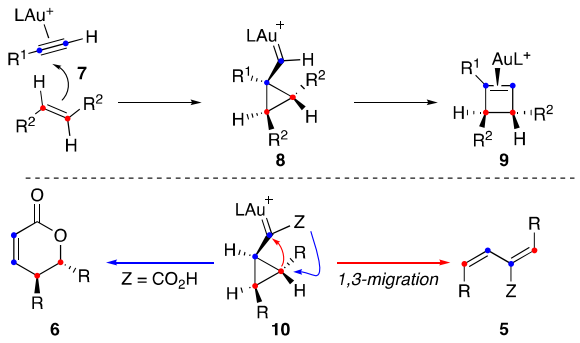


Cyclobutenes are highly valuable synthons for the preparation of functionalized cyclobutanes and other compounds.[7,8] Besides photochemical processes,[9] other transition metals different from gold(I) have been used to promote [2+2] cycloaddition reactions, which are however rather limited with respect to the range of alkenes that can be used.[10,11] Thus, the rhodium-catalyzed [2+2] cycloaddition only proceeds with electron-deficient[12,13] or strained alkenes.[14] Other transition metal catalysts also promote the [2+2] cycloaddition of strained alkenes with alkynes.[15,16] The reaction of propiolates and other alkynes bearing electron-withdrawing groups with alkenes in the presence of Lewis[17] or Brønsted acids[18] also leads to cyclobutenes.[19] Interestingly, in the presence of gold(I), this type of alkynes reacts with alkenes to form 1,3-dienes **5** or lactones **6** (Scheme 1).[20]

Based on studies on the mechanism of gold(I)-catalyzed cyclization of 1,n-enynes[21,22,23,24] and other electrophiles,[25,26] we hypothesized that the reaction of alkynes with alkenes could take place by the electrophilic addition of (η^2-alkyne)gold(I) complexes **7** to the alkene to form intermediate cyclopropyl

gold(I) carbenes **8**, which undergo ring-expansion to give (η^2-cyclobutene)gold(I) complexes **9** (Scheme 2). An intermediate (η^2-cyclobutene)gold(I) complex has been spectroscopically detected at low temperature from a 1,6-enyne.[27]

Scheme 2. Mechanistic Hypothesis for the [2+2] Cycloaddition of Electron-Rich Alkynes[3,4] vs. Formation of 1,3-Dienes or Lactones from Electron-Deficient Alkynes[20]



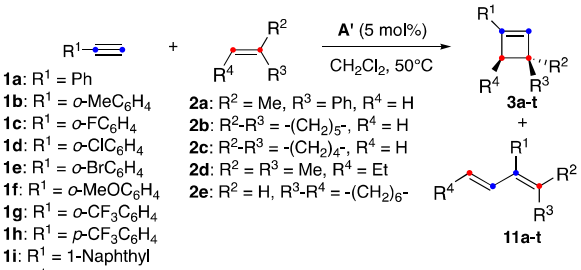
In the case of electron-rich alkynes, the alkene reacts by attack at the internal carbon,[3,4] whereas electron-deficient alkynes react at the terminal carbon leading to intermediates **10**, which can undergo formal 1,3-migration to give 1,3-dienes **5** or experience intramolecular attack by the carboxylic acid (Z = CO_2H) to afford **6** (Scheme 2).[20]

The very different outcome of the reaction of electron-rich aryl or cyclopropyl-substituted alkynes and alkynes bearing electron-withdrawing groups is rather striking. Therefore, we decided to examine in detail the reaction of a broader range of terminal alkynes to get a clearer perspective of this fundamental reaction in gold(I) chemistry. Surprisingly, we found that some *ortho*-substituted aryl alkynes react with alkenes to give 1,3-dienes in a metathesis-type process. On the other hand, less sterically demanding 1,3-butadiynes lead exclusively to cyclobutenes. Here we report these results along with a detailed theoretical analysis of the mechanism of formation of cyclobutenes or 1,3-dienes. To support the initial involvement of cyclopropyl gold(I) carbenes in these transformations, we also studied the generation of these intermediates by a retro-Buchner reaction. This study leads to a comprehensive picture of the gold(I)-catalyzed reactions of alkynes with alkenes.

RESULTS AND DISCUSSION

Formation of Cyclobutenes vs. 1,3-Dienes. The gold(I)-catalyzed intermolecular reaction of substituted aryl alkynes with alkenes affords cyclobutenes **3** in moderate to excellent yields.[3,4] Thus, under the optimized conditions, reaction of phenylacetylene with α-methylstyrene (**2a**) gives rise to cyclobutene **3a** in 95% yield (Table 1, entry 1).[28] However, the reaction of *o*-tolylacetylene (**1b**) with **2a** in the presence of gold(I) complex **A´** led to cyclobutene **3b** together with 1,3-diene **11b** in a 1.3:1 ratio in moderate yields (Table 1, entry 2). The reaction of *o*-fluorophenylacetylene (**1c**) with **2a** gave cyclobutene **3c** in good yield together with traces of 1,3-diene **11c** (Table 1, entry 3). In contrast, dienes **11d-e** were obtained as the major products in the reactions of *o*-chloro- and *o*-bromophenyl acetylenes (**1d-e**) with **2a** (Table 1, entries 4-5).[29] Interestingly, *o*-anisylacetylene (**1f**) gave exclusively cyclobutene **3f** (Table 1, entry 6),[30] whereas arylalkyne **1g** with an *o*-CF_3 group only afforded 1,3-diene **11g** (Table 1, entry 7). However, moving the CF_3 to the para position in **1h** restored the usual reactivity, resulting in the formation of cyclobutene **3h** as the major product (Table 1, entry 8). Reactions with methylenecyclohexane (**2b**) or methylenecyclopentane (**2c**) led to mixtures of cyclobutenes **3** and 1,3-dienes **11**, (Table 1, entries 9-20), although in the reaction between *o*-anisylacetylene (**1f**) and **2b**, cyclobutene **3m** was obtained as the major product (Table 1, entry 13). 1-Naphthylacetylene (**1i**) and 9-phenanthrylacetylene (**1j**) also react with **2b** to give cyclobutenes **3n-o** and 1,3-dienes **11n-o** (Table1, entries 14-15). Reaction of **1e** with 2-methyl-2-pentene (**2d**) rendered a mixture of cyclobutene **3u** and 1,3-diene **11u** products (Table 1, entry 21) whereas in the reaction of **1e** with (*Z*)-cyclooctene (**2e**), cyclobutene **3v** was obtained as the major product in good yield (Table 1, entry 22). The structure of bicyclo[6.2.0]dec-9-ene **3v** was confirmed by X-ray diffraction.

Table 1. Cycloaddition vs. Rearrangement in the Reaction of Alkynes 1a-j with Alkenes 2a-e[a,31]



1a: R^1 = Ph
1b: R^1 = *o*-MeC_6H_4
1c: R^1 = *o*-FC_6H_4
1d: R^1 = *o*-ClC_6H_4
1e: R^1 = *o*-BrC_6H_4
1f: R^1 = *o*-$MeOC_6H_4$
1g: R^1 = *o*-$CF_3C_6H_4$
1h: R^1 = *p*-$CF_3C_6H_4$
1i: R^1 = 1-Naphthyl
1j: R^1 = 9-Phenanthryl

2a: R^2 = Me, R^3 = Ph, R^4 = H
2b: R^2-R^3 = -$(CH_2)_5$-, R^4 = H
2c: R^2-R^3 = -$(CH_2)_4$-, R^4 = H
2d: R^2 = R^3 = Me, R^4 = Et
2e: R^2 = H, R^3-R^4 = -$(CH_2)_6$-

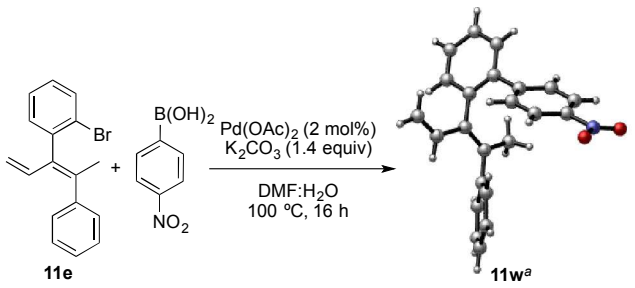
entry	1a-i	2a-c	3 (%)[b]	11 (%)[b]
1	1a	2a	3a (95)[c]	-
2[d,e]	1b	2a	3b (37)	11b (29)
3	1c	2a	3c (64)	11c (3)
4[e,f,g]	1d	2a	3d (9)	11d (48)
5[f]	1e	2a	3e (3, 3[i])	11e (45, 43[i])
6	1f	2a	3f (54, 54)	-
7	1g	2a	-	11g (36)
8[e,h]	1h	2a	3h (75)	11h (5)
9	1b	2b	3i (65)	11i (27)
10	1c	2b	3j (50, 49[i])	11j (25, 20[i])
11	1d	2b	3k (54, 49)	11k (33, 28)
12	1e	2b	3l (44)	11l (25)

13	**1f**	**2b**	**3m** (50)	**11m** (3)
14	**1i**	**2b**	**3n** (40)	**11n** (22)
15	**1j**	**2b**	**3o** (48)	**11o** (19)
16	**1b**	**2c**	**3p** (61)	**11p** (38)
17	**1c**	**2c**	**3q** (51, *44*)	**11q** (33, *17*)
18	**1d**	**2c**	**3r** (25)	**11r** (43)
19	**1e**	**2c**	**3s** (24)	**11s** (42)
20	**1f**	**2c**	**3t** (58, 53)	**11t** (24, *12*)
21	**1e**	**2d**	**3u** (40, *41*[j])	**11u** (34, *37*)
22	**1e**	**2e**	**3v** (*84*)	**11v** (5)

[a] Alkyne:alkene in a 1:2 ratio. [b] Yields determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard. Selected isolated yields in italics. See supporting information for the other isolated yields. [c] Reaction with **A′** (3 mol%) at 23 °C.[4] [d] Alkyne:alkene in a 1:4 ratio. [e] 4 mol% **A'**. [f] Catalyst **A** instead of **A′**. [g] Alkyne:alkene in a 1:3 ratio. [h] **A′** prepared in situ from *t*BuXPhosAuCl and $NaBAr_4^F$. [i] Reaction in 1 g scale of the alkyne. [j] Mixture of 1,3,4,4- and 1,3,3,4-tetrasubstituted cyclobutenes in a 2.4:1 ratio.

1,3-Dienes **11b-h** were obtained as single *E*-stereoisomers which was determined by nOe experiments. This assignment was confirmed in the case of **11e** (Table 1, entry 5) by X-ray diffraction of crystalline derivative **11w**, obtained from **11e** by Suzuki coupling with *p*-nitrophenylboronic acid (Scheme 3).

Scheme 3. Derivatization of 11e to Form 1,3-Diene 11w

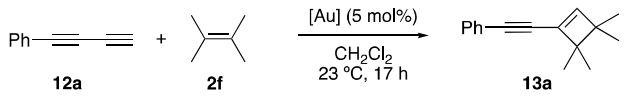


[a] CYLview depiction of the X-ray crystal structure of **11w**.

Other metal catalysts known to promote cycloisomerization of 1,n-enynes such as $PtCl_2$, $GaCl_3$, $InCl_3$, fail to catalyze the reaction between alkynes **1a** or **1e** with α-methylstyrene (**2a**) at 23 °C or 50 °C. Similarly, neither cyclobutene nor 1,3-diene was observed in the presence of CuCl, AgCl, AgOTf, $AgNTf_2$, $AgSbF_6$ or [*t*BuXPhosAg(NCMe)]SbF_6 under these conditions.

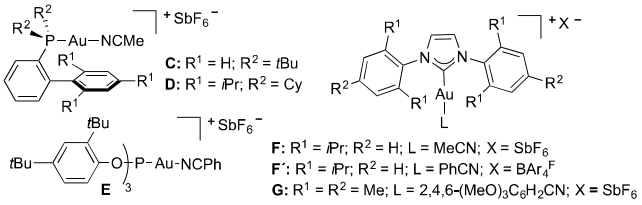
Cyclobutenes from 1,3-Butadiynes. To delineate the importance of electronic and steric effects, we examined the gold(I)-catalyzed reaction of alkenes with aryl-1,3-butadiynes **12**,[32] ethynylogous to arylalkynes **1**. Reaction of the parent 1-phenyl-1,3-butadiyne (**12a**) with 2,3-dimethylbut-2-ene (**2f**) led selectively to cyclobutene **13a** by addition to the terminal triple bond with all the gold(I) catalysts tested (Table 2), although slightly better yields were obtained using NHC-gold(I) complex **F** (Table 2, entry 6).[33]

Table 2. Gold(I)-Catalyzed Reaction of 1,3-Diyne 12a with alkene 2f[a]



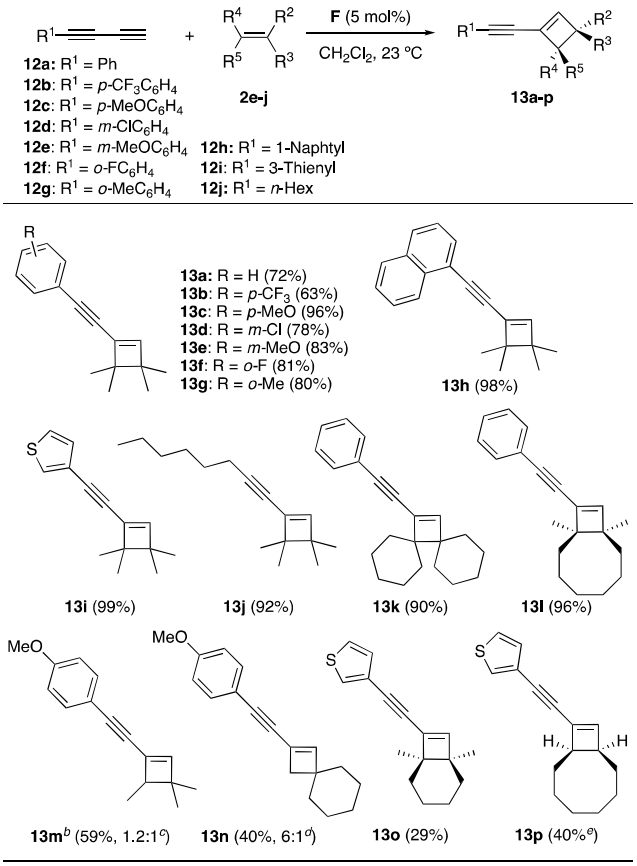
entry	[Au]	**13a** (%)[b]
1	**A**	70
2	**A′**	70
3	**C**	70 (60)
4	**D**	69
5	**E**	56
6	**F**	78 (72)
7	**F′**	74
8	**G**	16[c]

[a] 1,3-Diyne:alkene in a 1:2 ratio. [b] Yields determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard. Isolated yields in parentheses. [c] 45% conversion.



Differently substituted 1-aryl-1,3-diynes **12a-h** and 1-thienyl-1,3-diyne (**12i**) react with alkene **2f** to give 1-ethynylcyclobutenes **13a-i** in good to excellent yields (Table 3). Alkyl substituted 1,3-diyne **12j** also leads to the corresponding cyclobutene **13j**, which is remarkable, as alkynes with alkyl substituents are very poorly reactive with alkenes in the presence of gold(I) catalysts.[3] Other di-, tri-, and tetrasubstituted alkenes **2e-j** also reacted with 1,3-diynes **12a**, **12c**, and **2i** to give 1-alkynylcyclobutenes **13k-p**.[34]

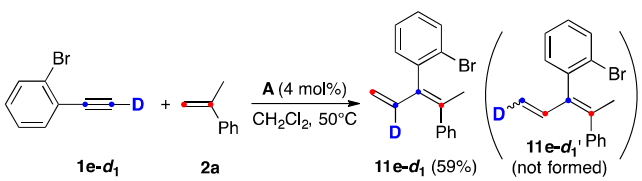
Table 3. Gold(I)-Catalyzed [2+2] Cycloaddition of 1,3-Diynes 12a-j with Alkenes 2e-j[a]



[a] 1,3-Diyne:alkene in a 1:2 ratio. Isolated yields. [b] Small amounts of 1,3-diene product was detected by ^{1}H NMR. [c] Minor regioisomer is the 1,3,4,4-tetrasubstituted cyclobutene. [d] Minor regioisomer is the 1,4,4-trisubstituted cyclobutene. Reaction at 40 °C. [e] Reaction at 50 °C.

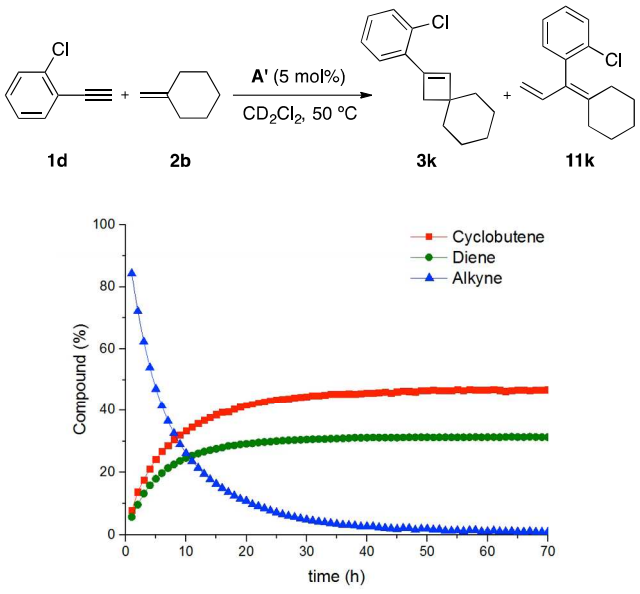
Mechanism of the Formation of Cyclobutenes or 1,3-Dienes. To confirm the formal alkene fragmentation (metathesis-type) in the formation of 1,3-dienes in the intermolecular gold(I)-catalyzed reaction, a simple experiment between terminally deuterated alkyne **1e-*d*$_1$** and alkene **2a** with catalyst **A** was carried out (Scheme 4). In this reaction, we obtained exclusively 1,3-diene **11e-*d*$_1$**, revealing that a formal insertion of the alkyne into the alkene carbons takes place in this process. The alternative product, **11e-*d*$_1$'**, resulting from a double-cleavage-type rearrangement (formal cleavage of both the alkyne and the alkene, see below), was not observed.

Scheme 4. Cycloaddition of Alkyne 1e-*d*$_1$ with 2a



Monitoring the reaction of alkyne **1d** with alkene **2b** (Table 1, entry 11) by ^{1}H NMR shows that the [2+2] cycloaddition leading to cyclobutene **3k** is *ca.* 1.4 times faster than the formation of 1,3-diene **11k** (Scheme 5).

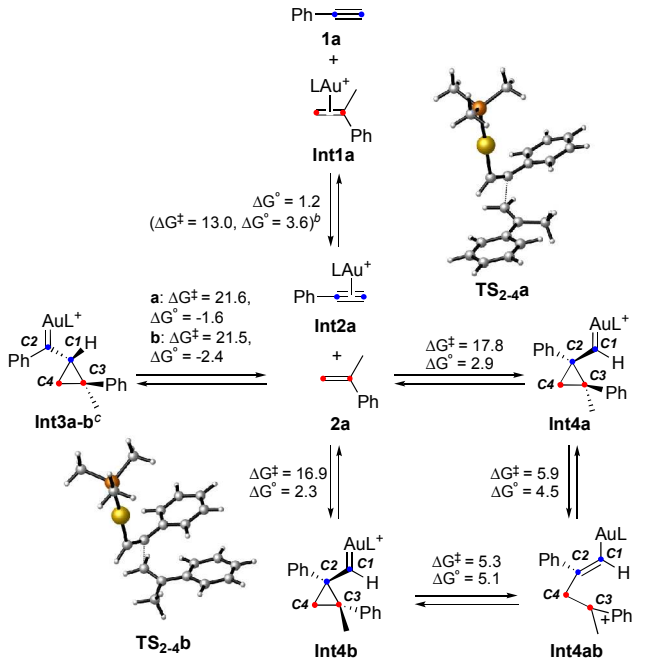
Scheme 5. Reaction of Alkyne 1d with Alkene 2b[a]



[a] Reaction progress followed by ^{1}H NMR (Ph_2CH_2 internal standard).

To get a deeper insight into the mechanism of the formation of cyclobutenes **3** and/or 1,3-dienes **11** as well as the influence of the substituents on the substrates in the reaction outcome, we performed DFT calculations[35] using PMe_3 as the ligand for gold(I).[36] We examined the reaction between phenylacetylene (**1a**) and α-methylstyrene (**2a**) to give cyclobutene **3a** as well as the reaction of *o*-bromophenylacetylene (**1e**) with **2a** leading to 1,3-diene **11e** as the major product.

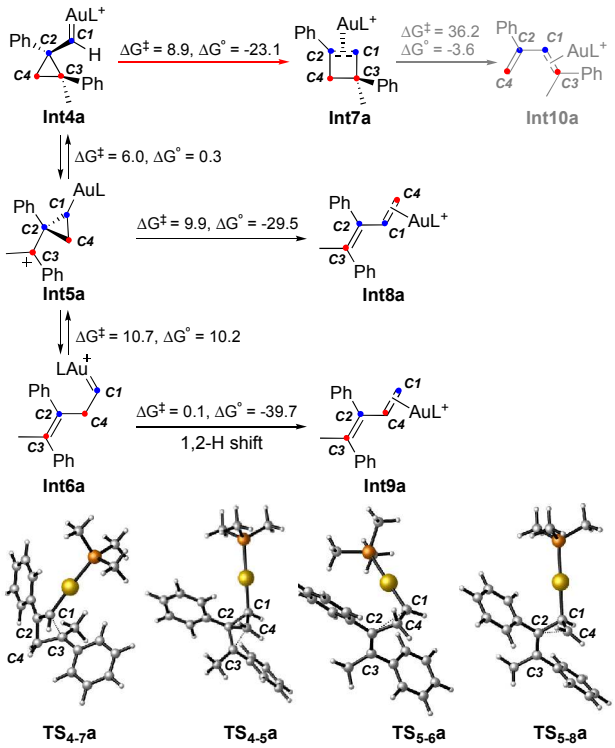
Scheme 6. Ligand Substitution and Formation of Key Intermediates Int4[a]



[a] Free energies in kcal/mol. L = PMe_3. [b] Calculations using 2-methylpropene instead of α-methylstyrene. [c] Depicted configuration of C3 for **Int3a**. Opposite configuration of C3 for **Int3b**.

Electron-rich alkenes coordinate preferentially with gold(I)[4] leading to (η^2-alkene)gold(I) complexes that can be isolated and structurally characterized.[37] Accordingly, the reaction begins with the associative ligand exchange of (η^2-alkene)gold(I) complex **Int1a** to generate the slightly less stable (η^2-alkyne)gold(I) complex **Int2a** (Scheme 6). The attack of the alkene to the gold(I) alkyne complex **Int2a** can take place in an *anti* or *syn* fashion to form intermediates **Int4a** and **Int4b**, which are in equilibrium due to C3-C4 bond rotation via ring opened intermediate **Int4ab**.[38] In both cases, formation of intermediates **Int4a-b** with the gold(I) carbene at the terminal carbon is kinetically more favored than the formation of regioisomeric **Int3a-b** by at least 3.8 kcal/mol. Although formation of **Int4b** requires 0.9 kcal/mol lower energy than **Int4a**, further evolution of **Int4a** to other intermediates proceeds through lower energy barriers.[39]

Scheme 7. Formation of Cyclobutene or 1,3-Dienes from Intermediate Int4a.[a]



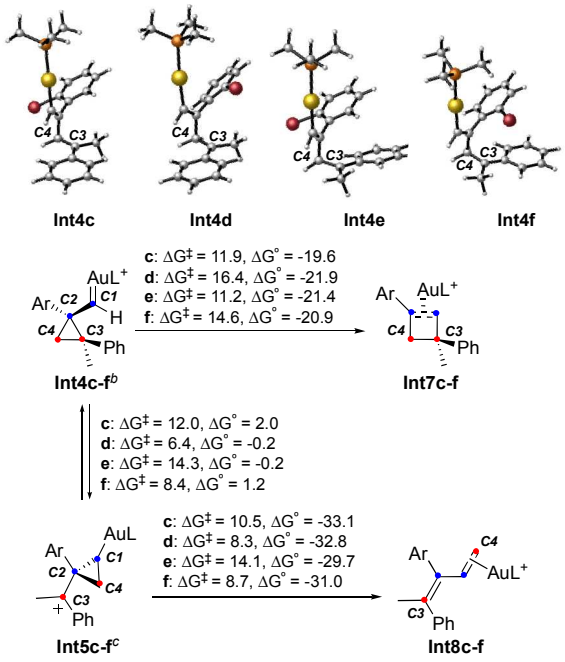
[a] Free energies in kcal/mol. L = PMe_3.

The possibility of an oxidative cyclometalation was also considered.[40] However, neither the intermediate with the alkyne and the alkene coordinated simultaneously to gold(I) nor the gold(III) metalacyclopentene were found as stable species.

Intermediate **Int4a** is also in equilibrium via C4 migration with the cyclopropyl-type intermediate **Int5a**, whose ring opening leads directly to 1,3-diene-gold(I) complex **Int8a** through **TS5-8a** (ΔG‡ = 9.9 kcal/mol) (Scheme 7). The alternative C3 migration would lead to a less stable cyclopropyl methyl intermediate to ultimately from a different type of 1,3-diene that was not observed experimentally. The opening of the cyclopropane of **Int5a** via **TS5-6a** (ΔG‡ = 10.7 kcal/mol) to form the less stable intermediate **Int6a**, followed by a highly exothermic 1,2-H shift, would give 1,3-diene-gold(I) complex **Int9a**. However, formation of either **Int8a** or **Int9a** from **Int5a** requires higher activation energies than the conversion of **Int5a** to **Int4a** (ΔG‡ = 5.7 kcal/mol). Comparing all the activation energies, the most favored reaction pathway is the ring expansion of **Int4a** to give (η^2-cyclobutene)gold(I) complex **Int7a** (ΔG‡ = 8.9 kcal/mol). Conrotatory ring opening of **Int7a** to form **Int10a** is unlikely as it would have to overcome a prohibitively high energy barrier of 36.2 kcal/mol.[41] Thus, our calculations predict that cyclobutene **3a** would be the product of the reaction, which is consistent with the formation of **3a** in a 95% yield from **1a** and **2a** (Table 1, entry 1).[3,4,42]

The reaction of *o*-bromophenylacetylene (**1e**) with α-methylstyrene (**2a**) is more complex as four different approaches of the alkene towards the **Int4c-f** could be conceived (Scheme 8) depending on the relative orientation of the phenyl groups of the substrates (*anti* or *syn*) and the position of the *ortho*-substituent in the alkyne respect to the olefin carbons (*ortho*-substituent closer to either the terminal or internal alkene carbon). Thus, four distinct reaction pathways were computed for this system (**c-f**, Scheme 8). As in the case of the reaction of phenylacetylene (**1a**) with alkene **2a**, formation of the cyclopropyl gold(I) carbene at the internal alkyne carbon (**Int4c-f**, ΔG‡ = 16.7-17.5 kcal/mol) is more favorable than at the terminal alkyne carbon (**Int3c-f**, ΔG‡ = 18.8-20.1 kcal/mol).[39] Comparison of the activation energies of the transformations of **Int4c-f** into **Int5c-f** or **Int7c-f** suggests that the *o*-bromo substituent hampers the rearrangement of the near alkene carbon and favors the rearrangement of the further alkene carbon. In fact, cyclopropyl gold(I) carbenes **Int4d** and **Int4f** bearing the bromo atom closer to C3 prefer to form intermediates **Int5d** and **Int5f** via rearrangement of C4, which then lead to 1,3-diene-gold(I) complexes **Int8c** and **Int8f**, respectively. In contrast, cyclopropyl gold(I) carbene **Int4e** bearing the *o*-bromo substituent closer to C4 prefers to undergo ring expansion through C3 to give the (η^2-cyclobutene)gold(I) complex **Int7e**. Analyzing all the energy barriers (including bond rotations), the most favored pathway guide to 1,3-diene-gold(I) complex **Int8d.** This is in agreement with the experimental result, as 1,3-diene **11e** is obtained in a 45% yield and only traces of cyclobutene **3e** are detected (Table 1, entry 5). Nevertheless, the difference in the activation energies of the rearrangements of cyclopropyl gold(I) carbenes **Int4** are not large, so subtle changes in the substitution pattern of the substrates modify the steric interactions and, consequently, the reaction outcome. Then, reasonably, different ratios of cyclobutene and 1,3-diene products were experimentally obtained depending on the differently substituted substrates.

Scheme 8. Mechanism of the Reaction Between 1e (Ar = *o*-Bromophenyl) and 2a.[a]

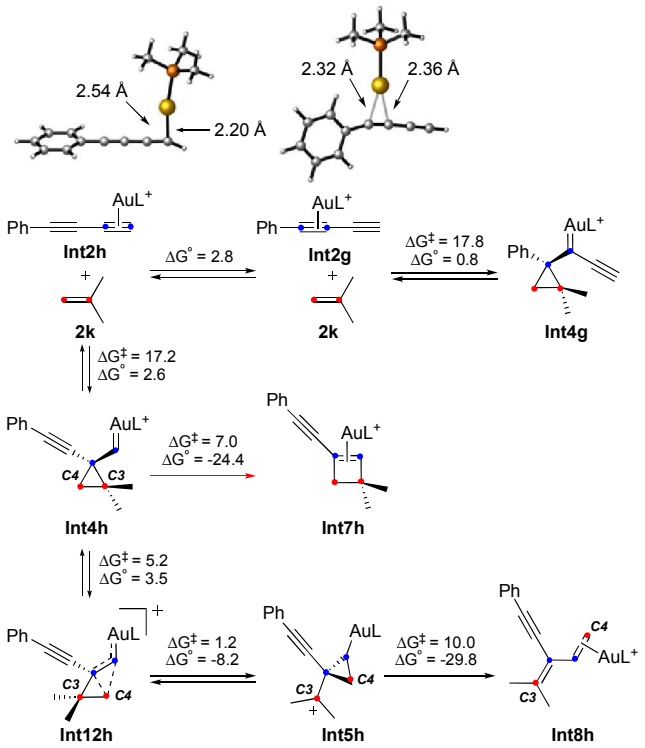


[a] Free energies in kcal/mol. L = PMe_3. Depicted configuration of C_3 for pathways **c** and **d**. Opposite configuration of C_3 for pathways **e** and **f**. [b] Transformations between **Int4c-f** via bond rotations: see Supporting Information. [c] Transformation of **Int5f** into **Int5d** via C_2-C_3 bond rotation: $\Delta G^{\ddagger}$ = 14.0, $\Delta G°$ = -0.6.

For the sake of completeness, the mechanism of the gold(I)-catalyzed reaction between 1-phenyl-1,3-butadiyne (**12a**) and alkenes was also studied computationally (Scheme 9). Gold(I) complex **Int2h**, in which gold(I) is coordinated to the terminal alkyne, is 2.8 kcal/mol more stable than the complex **Int2g** with gold(I) coordinated to the internal alkyne. The preferential binding of gold(I) to the less substituted multiple bond has been experimentally observed in the case of allenes.[43] Alkyne gold(I) complex **Int2g** shows an almost symmetrical η^2-coordination with a significant bending back of the phenyl group, which is consistent with reported structures of related alkyne gold(I) complexes.[44] In contrast, in complex **Int2h**, the terminal alkyne binds very unsymmetrically with gold(I), resulting in longer bonds with the substituted carbon atom, as also observed in terminal alkene gold(I) complexes.[37,45]

The free energy of activation for the attack of the alkene to the terminal alkyne is 3.4 kcal/mol lower than the barrier corresponding to the attack at the internal alkyne (Scheme 9). Consequently, both on thermodynamic and kinetic grounds, the alkene selectively attacks as a π-nucleophile to complex **Int2h** at the terminal alkyne, forming distorted cyclopropyl gold(I) carbene **Int4h**. The ring expansion of **Int4h** through C3 ($\Delta G^{\ddagger}$ = 7.0 kcal/mol) gives the (η^2-cyclobutene)gold(I) complex **Int7h**.[39] The alternative ring expansion of cyclopropyl gold(I) carbene **Int4h** through the terminal alkene carbon C4 generates a distorted cyclobutene-gold(I) complex **Int12h** through a low barrier of 5.2 kcal/mol. Interestingly, a similar intermediate to **Int12h** was not found in the reaction of phenylacetylene derivatives **1a** and **1e** with alkene **2a** discussed above. Intermediate **Int12h** undergoes formal insertion of the terminal alkene carbon C4 into the alkyne carbons to form a more stable cyclopropyl-like intermediate **Int5h**. Although intermediates **Int4h**, **Int12h**, and **Int5h** are in equilibrium through low barrier transformations, ring opening of **Int5h** to form 1,3-diene-gold(I) complex **Int8h** is more energetically costly than the expansion of **Int4h** to (η^2-cyclobutene)gold(I) complex **Int7h** (10.0 vs. 7.0 kcal/mol), which is fully consistent with the experimental results.

Scheme 9. Mechanism for the Reaction of 1-Phenyl-1,3-butadiyne-Gold(I) Complex with 2-Methylpropene[a]



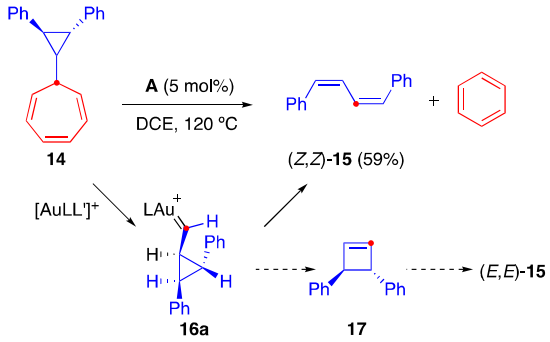
[a] Free energies in kcal/mol. L = PMe_3.

Further Experimental Support for the Involvement of Cyclopropyl Gold(I)-Carbenes. We have discovered a method to generate gold(I) carbenes by the retro-Buchner reaction of 7-substituted 1,3,5-cycloheptatrienes with electrophilic gold(I) catalysts, in a process in which a molecule of benzene is also formed in a formal decarbenation reaction.[46,47] The retro-Buchner reaction proceeds by stepwise cleavage of the norcaradienes, which are in tautomeric equilibrium with the cycloheptatriene.[46] Other related decarbenations have been observed in the presence of gold(I).[48,49]

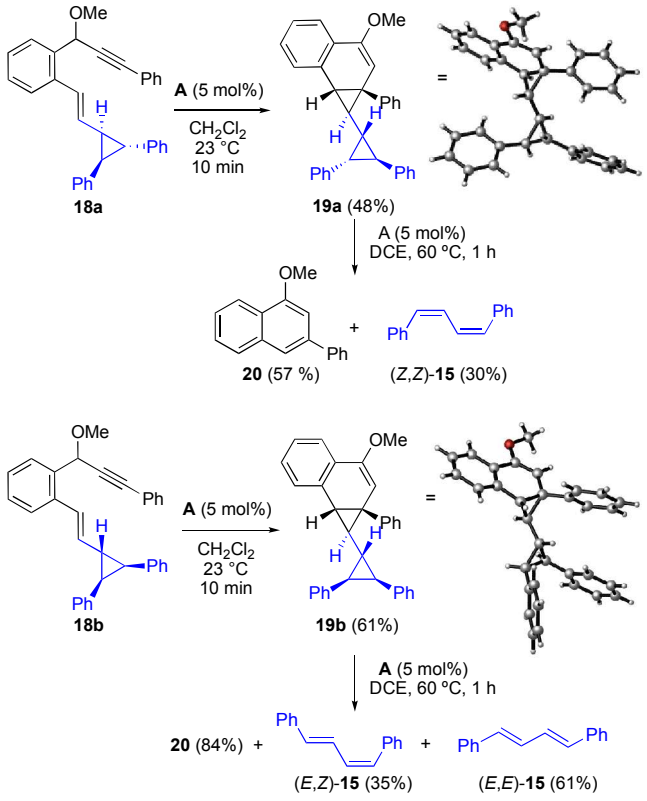
When 7-cyclopropylcycloheptatriene **14** was heated in the presence of catalyst **A**, *Z,Z*-1,4-diphenyl-1,3-diene (*Z,Z*-**15**) was formed selectively (Scheme 10).[46] This transformation presumably proceeds via cyclopropyl gold(I) carbene **16a**, which undergoes a formal 1,3-shift of a CHPh fragment. Interestingly, **16a** would correspond to the intermediate generated in the gold(I)-catalyzed reaction between acetylene and *trans*-stilbene. The ring expansion of **16a** to form cyclobutene **17**, which would have given diene *E,E*-**15** by conrotatory opening,[50] was not observed.[46] This result predicts that a *cis*-isomer of 7-cyclopropylcycloheptatriene **14** would give rise to the

diene *E,Z*-**15**. Unfortunately, this isomer could not be prepared by the same method used for the synthesis of **14**.

Scheme 10. Formation of (*Z,Z*)-1,4-Diphenylbuta-1,3-diene by Retro-Buchner Reaction of Cycloheptatriene 14[46]



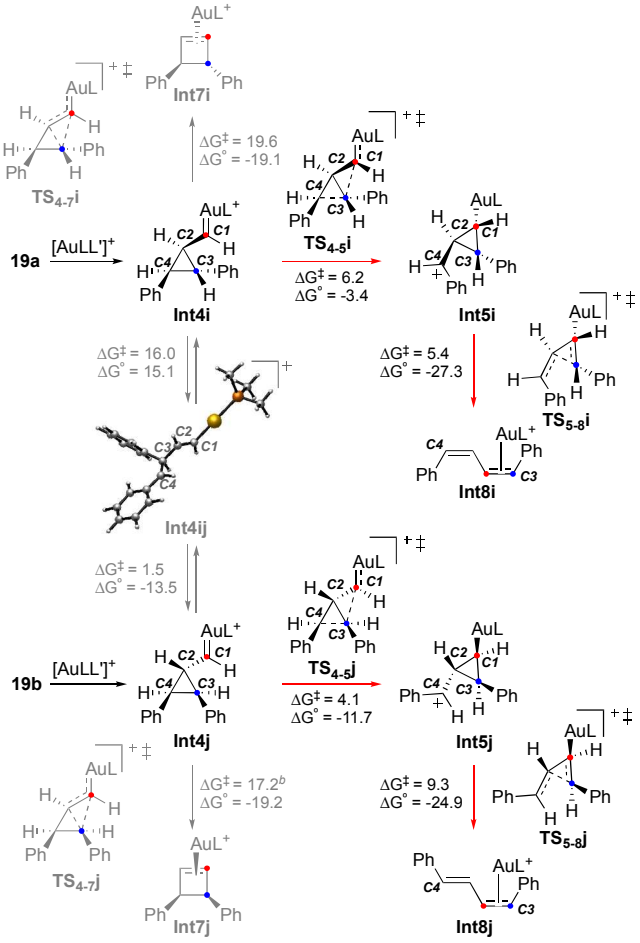
Scheme 11. Retro-Buchner Reactions of 19a-b[a]



[a] CYLview depiction of the X-ray crystal structures of **19a-b**.

Since the generation of intermediates like **16a** by a totally different process could be relevant to the better understanding of the mechanism of the gold(I)-catalyzed reaction of alkynes with alkenes, we recurred to our initial system for the generation of gold(I) carbenes by decarbenation of 1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalenes (Scheme 11).[48] The required starting 1,6-enynes **18a-b** were prepared as *ca.* 1:1 mixture of epimers at the benzylic position by olefination of the corresponding cyclopropyl carbaldehydes.[51,52] The gold(I)-catalyzed cycloisomerization of **18a-b** takes place under mild conditions using catalyst **A** to furnish enol ethers **19a-b** in 48 and 61% yield, respectively, whose relative configurations were determined by X-ray diffraction. When enol ether **19a** was heated with catalyst **A** in 1,2-dichloroethane at 60 °C, the decarbenation reaction provided 1-methoxy-3-phenylnaphthalene (**20**) and (*Z,Z*)-**15**.[53] Similarly, substrate **19b** reacted at 60 °C for 1 h with catalyst **A** to give naphthalene **20** together with a 1:2 mixture of (*E,Z*)- and (*E,E*)-**15**.[54]

Scheme 12. Mechanism for the Formation of 1,3-Dienes 15 via Retro-Buchner Reaction from 19a-b[a]



[a] Free energies in kcal/mol. L = PMe_3. [b] The energy of $\mathbf{TS_{4\text{-}7}j}$ was calculated freezing the following distances: d(C_3-C_1), d(C_3-C_2) and d(C_3-C_4). The values of these distances were taken from the previously optimized geometry of $\mathbf{TS_{4\text{-}7}i}$.

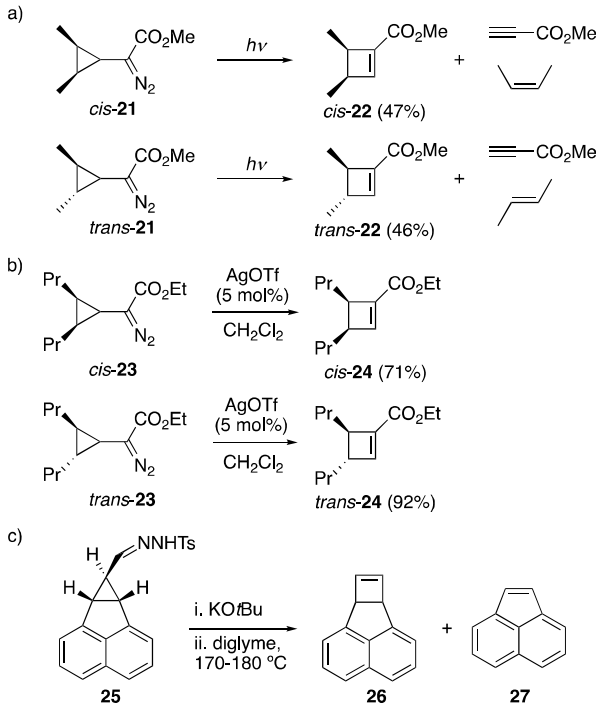
The retro-Buchner (decarbenation) reaction of **19a** should lead to the same cyclopropyl gold(I) carbene **16a** (= **Int4i**) generated from *trans*-**14**, whose opening by C3 migration via **Int5i** leads to **Int8i** and ultimately to (*Z,Z*)-**15**[46,55a] (Scheme 12). On the other hand, **19b** would give rise to intermediate **Int4j**, which undergoes opening via **Int5j** to furnish (*E,Z*)-**15**, although this 1,3-diene was obtained together with the more stable isomer (*E,E*)-**15**.[55b] Control experiments showed that (*E,Z*)-**15** undergoes isomerization to give (*E,E*)-**15** in the presence of gold(I) under the reaction conditions.[52] In full agreement with the experiments, DFT calculations show that the alternative expansion of cyclopropyl gold(I) carbenes **Int4i-j** to cyclobutenes **Int7i-j** is a higher energy process.[39]

Although both reaction pathways from **19a-b** could in principle be connected by the *trans*- to *cis*-isomerization of **Int4i** to

Int4j via open carbocation **Int4ij** (Scheme 12), in contrast to that found in the equilibrium between **Int4a** and **Int4b** (Scheme 6), here the corresponding barriers are much higher in energy than those leading to C3 migration.[56]

Finally, it is interesting to compare these results with known examples of formation of cyclobutenes via cyclopropyl carbenes. Thus, the photolysis of *cis*- and *trans*-**21** has been shown to give *cis*- and *trans*-**22** cyclobutenes, respectively, as a result of a stereospecific ring-expansion (Scheme 13a).[57] In these reactions, methyl propiolate and *cis*- or *trans*-2-butene were also obtained as a result of a competitive fragmentation. Likewise, in the presence of AgOTf, *cis*- and *trans*-**23** undergo stereospecific ring expansion to cyclobutenes *cis*- and *trans*-**24** respectively (Scheme 13b).[58,59] The thermal decomposition of the potassium salt of tosyl hydrazone **25** also led to a products of ring expansion (**26**), together with acenaphthylene (**27**), the product of fragmentation (Scheme 13c).[60] Ring expansion to cyclobutenes and fragmentation to form alkenes and alkynes have also been observed in reactions of simple cyclopropyl carbenes.[57]

Scheme 13. Photochemical[57] (a), Metal-Catalyzed[58] (b) and Thermal[60] (c) Generation and Fate of Cyclopropyl Carbenes



CONCLUSIONS

Electron-rich alkynes have been shown to react with alkenes in the presence of gold(I) catalysts by [2+2] cycloaddition to give rise to cyclobutenes, whereas, in contrast, electron-deficient alkynes lead to 1,3-dienes in a metathesis-type process. Now, we have found that 1,3-dienes can also be obtained in the reaction of alkenes with electron-rich alkynes bearing *o*-substituted aryls.

The two reaction channels leading to cyclobutenes or 1,3-dienes are close in energy. According to all our calculations, the first intermediates in the gold(I)-catalyzed intermolecular reaction of alkynes with alkenes are cyclopropyl gold(I) carbenes, which despite all the experimental efforts[27,61] are still elusive species. In order to substantiate their involvement in these transformations, we have generated these intermediates by a totally different method based on the gold(I)-promoted retro-Buchner reaction, which also leads to the formation 1,3-dienes by a metathesis-type mechanism. The formation of 1,3-dienes involves a two- or three step mechanism in which the carbon-carbon double bond of the alkene is cleaved, similar to that proposed in the gold(I)-catalyzed intramolecular skeletal rearrangements of 1,6-enynes. Products of conrotatory opening of cyclobutenes are not observed in the gold(I)-catalyzed reaction of alkynes with alkenes, which is consistent with the high activation energy required for this process.

The common mechanistic scenario for gold(I)-catalyzed reactions of alkynes with alkenes involves the initial formation of cyclopropyl gold(I) carbene intermediates, followed by fast ring expansion or rearrangement. Formation of 1,3-dienes can take place from both electron-rich and electron-deficient alkynes, although cyclobutenes have only been obtained in gold(I)-catalyzed reactions involving electron-rich alkynes. There is another important difference between the reactions of electron-rich and electron-deficient alkynes since in the former case the alkene reacts with the internal carbon of the alkyne, whereas in the second case, the alkene attacks the terminal carbon leading to regioisomeric cyclopropyl gold(I) carbenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

All procedures and characterization data for new compounds (PDF) and full details on the theoretical calculations (PDF and rtf) and cif files for **3v**, **11w** and **19a-c** (CIF).

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Notes

The authors declare no competing financial interest.

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(31) When lower catalyst loadings such as 1 mol% were used, longer reaction times were required and in some cases lower yields were obtained. For instance, the reaction of **1e** with **2a** in the presence of 1 mol% of catalyst **A** required 3 days to give 37% of the 1,3-diene **11e**.

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(34) Reaction of different 1,3-diynes with terminal alkenes such as α-methylstyrene (**2a**), methylenecyclopentane (**2c**), 2-ethyl-1-butene or 1,1-diphenylethylene gave only traces of the corresponding cyclobutenes.

(35) (a) Calculations performed with: M06/6-31G(d) (C, H, P), LANL2DZ (Br), SDD(Au) in CH_2Cl_2 (SMD). Full computational details provided in the Supporting Information. (b) A dataset collection of computational results is available in the Iochem-BD database: Álvarez-Moreno, M.; de Graaf, C.; Lopez, N.; Maseras, F.; Poblet, J. M.; Bo, C. *J. Chem. Inf. Model.* **2015**, 55, 95–103.

(36) For a recent discussion on the coordination of phosphine ligands to gold(I), see: Ciancaleoni, G.; Scafuri, N.; Bistoni, G.; Macchioni, A.; Tarantelli, F.; Zuccaccia, D.; Belpassi, L. *Inorg. Chem.* **2014**, 53, 9907–9916.

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(38) (a) Bond rotations in cyclopropyl gold(I) carbenes in cycloisomerizations of 1,6-enynes: Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895. (b) This provides a theoretical rationale to the previously observed lack of diasteroselectivity in the reaction of **1a** with **2a-*d*$_1$**.[3a]

(39) See supporting information for the full scheme and additional details of the key transition states.

(40) See supporting information for alternative reaction pathways not involving the formation of cyclopropyl gold(I)-carbenes.

(41) Gold(I) does not have any influence in the conrotatory opening of a *trans*-1,3,4-trisubstituted cyclobutene, which occurred by heating at 110 °C.[20]

(42) The gold(I)-catalyzed reaction of benzyl 2-cyclopropyl-2-diazoacetate gives the corresponding cyclobutene in high yield,

presumably by ring expansion of a cyclopropyl gold(I) carbene: Xu, G.; Zhu, C.; Gu, W.; Li, J.; Sun, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 883–887.

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(52) See supporting information for details and additional results.

(53) A significant amount of the ketone (not shown), resulting from cleavage of the enol ether of **19a** was also obtained.[52]

(54) Similar results were obtained from substrate **19c**, prepared from an enyne analogous to **10b** but with a *p*-tolyl group at the alkyne.[52]

(55) (a) The bond rotation of C2-C4 in **Int5i** to generate **Int5k**, which would lead to (*E,Z*)-**15**, requires a high barrier of 14.8 kcal/mol.[39] (b) The bond rotation of C2-C4 in **Int5j** to generate **Int5L**, which would lead to (*E,Z*)-**15**, requires a high barrier of 20.8 kcal/mol.[39]

(56) Similarly, rotational barriers around C2-C4 bond in **Int5i-j** are higher (14.8 and 20.8 kcal/mol, respectively) than those required to form **Int8i-j**.[39]

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