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Gold-Catalyzed, Intramolecular, Oxygen-Transfer Reactions of 2-Alkynyl-1,5-diketones or 2-Alkynyl-5-ketoesters: Scope, Expansion, and Mechanistic Investigations on a New [4+2] Cycloaddition

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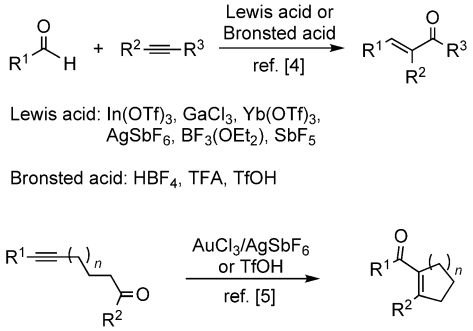
Abstract: The gold-catalyzed intramolecular oxygen-transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters—obtained from tetra-*n*-butylammonium fluoride mediated Michael addition of activated allenes to electron-deficient olefins—furnished cyclopentenyl ketones under very mild conditions. These reactions proceeded much easier and faster than similar reactions reported in literature, and the corresponding products were obtained in very good yields. Mechanistic investigations on the cycloisomerization were carried out by means of both ^{18}O isotopic experiments and quantum chemical calculations. The results from both, the designed isotopic experiments and theoretical calculations, satisfactorily supported the novel proposed intramolecular [4+2] cycloaddition of a gold-containing furanium intermediate to a carbonyl group, instead of the previous well-accepted [2+2] pathway.

Keywords: cycloaddition · gold · homogeneous catalysis · oxygen transfer · quantum chemical calculations

Introduction

The construction of α,β-unsaturated enones or similar compounds has been at the forefront of synthetic organic chemistry since its inception, not only because these compounds are important building blocks in organic synthesis, but also because the conjugated enone substructure itself is a significant motif in natural products or biologically active compounds.[1] Aldol condensations and Wittig-type reactions have been utilized to construct this moiety for decades.[2] Recently though, an oxygen transfer from a carbonyl group to a carbon–carbon triple bond, also known as alkyne–carbonyl metathesis, has attracted the interest of synthetic chemists, because this methodology could be an efficient and atom-economic alternative to the Wittig reaction by forming the new carbon–carbon double bond and carbonyl group simultaneously.[3] In this regard, many Lewis or Brønsted acid catalyzed intermolecular or intramolecular alkyne–carbonyl metathesis reactions have been extensively developed (Scheme 1, top).[4] Notably, by using tethered alkynylketones as the substrates, Yamamoto and co-workers reported gold- or TfOH-catalyzed oxygen-transfer reactions to give highly substituted cyclic enones as the products (Scheme 1, bottom).[5]



Scheme 1. Lewis or Brønsted acid and gold catalyzed intermolecular or intramolecular alkyne–carbonyl metathesis.

Few years ago, we became interested in investigating the reactivity of alkynylenolates and other extended enolates,[6] and found that 2-alkynyl-1,5-dicarbonyl derivatives could be conveniently obtained from the tetra-*n*-butylammonium fluoridemediated Michael addition of activated allenes to electron-deficient olefins (Scheme 2).[7] Considering the existence of two carbonyls and a carbon–carbon triple bond in **1**, we envisioned that an oxonium intermediate could arise from one of the carbonyls and the triple bond, and engender

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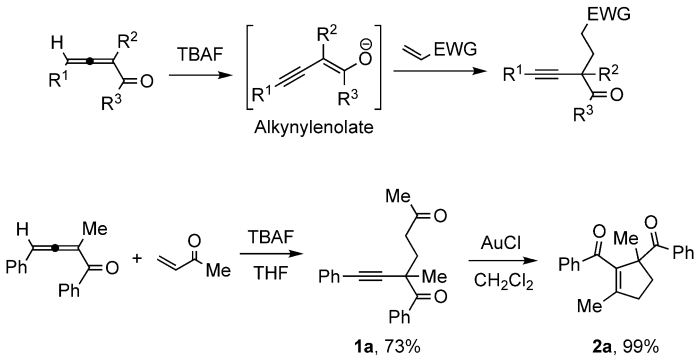
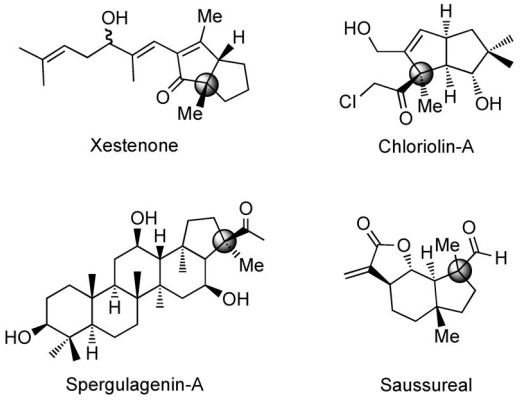


Scheme 2. Synthesis of 2-alkynyl-1,5-diketones and the gold-catalyzed oxygen-transfer reaction thereof.

novel transformations. The chemistry of the oxonium ions formed from alkynylic aldehydes or ketones by mediation of transition metals, Lewis acids, Brønsted acids, or even electrophiles such as iodine, has attracted a lot of attention, because these intermediates could undergo both inter- and intramolecular cycloadditions to carbon–carbon multiple bonds to give myriad products of synthetic importance.[8–16] Because of our continuous interest in gold catalysis,[17,18] we subjected compound **1a** to gold catalysis and found that the reaction, using AuCl as the catalyst, cleanly furnished cyclopentenyl ketone **2a**—an intramolecular-oxygen-transferred product—in excellent yields after only 5 min at room temperature.[19] Herein, we wish to report a comprehensive study of gold-catalyzed oxygen-transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters, especially a detailed mechanistic investigation on the newly proposed intramolecular [4+2] cycloaddition mechanism by means of isotopic experiments and quantum chemical calculations.

Results and Discussion

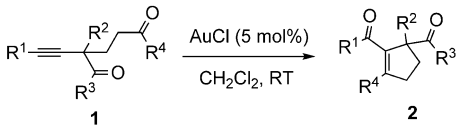
Highly substituted five-membered rings bearing a quaternary carbon tethered to a carbonyl group, are often found in natural products or biologically active compounds. Selected examples include Xestenone,[20] Chloriolin-A,[21] Spergulagenin-A[22] and Saussureal.[23] Methods for the construction of these highly substituted carbocycles are rare in literature.



Thus, we were interested in studying the scope of the gold-catalyzed, intramolecular, oxygen-transfer reaction and developing a fast and efficient synthetic method to construct this important substructure. Various substrates were subjected to this reaction; the results are summarized in Table 1.

It was found that the reactions of 2-alkynyl-1,5-diketones with either aromatic or aliphatic groups substituted at the R^1 position proceeded smoothly, and the corresponding products **2a**–**2i** were isolated in excellent yields (Table 1, entries 1–9). The variation on R^4 from methyl to ethyl and phenyl did not have a deleterious effect on the reaction, and the corresponding products **2j**–**2m** were obtained in very good yields (Table 1, entries 10–13). Also, replacing the phenyl at R^3 position with a methyl group did not diminished the efficiency of the reaction (Table 1, entry 14). To our surprise though, when the phenyl at R^3 position was replaced by an ethoxy group, that is, when 2-alkynyl-5-ketoesters were used, the reaction still proceeded as smoothly and efficiently as before, although longer reaction times were needed. The only exception occurred with **1u**, from which **2u** was isolated in only 50%, along with unidentified products (Table 1, entries 15–22). For the 2-alkynyl-5-ketoester substrate **1w** bearing an aliphatic group at R^1 position, the

Table 1. Gold-catalyzed, intramolecular, oxygen-transfer reactions of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters.[a]



Entry		R^1	R^2	R^3	R^4	**2**, Yield [%][b]
1	**1a**	Ph	Me	Ph	Me	**2a**, 98
2	**1b**	4-$MeOC_6H_4$	Me	Ph	Me	**2b**, 99
3	**1c**	4-ClC_6H_4	Me	Ph	Me	**2c**, 92
4	**1d**	nC_6H_{13}	Me	Ph	Me	**2d**, 99
5	**1e**	*i*Pr	Me	Ph	Me	**2e**, 96
6	**1f**	*t*Bu	Me	Ph	Me	**2f**, 95
7	**1g**	Me	Me	Ph	Me	**2g**, 91
8	**1h**	Bn	Me	Ph	Me	**2h**, 94
9	**1i**	$CypCH_2$	Me	Ph	Me	**2i**, 99
10	**1j**	Ph	Me	Ph	Et	**2j**, 98
11	**1k**	Ph	Me	Ph	Ph	**2k**, 93
12	**1l**	4-$MeOC_6H_4$	Me	Ph	Ph	**2l**, 91
13	**1n**	4-ClC_6H_4	Me	Ph	Ph	**2m**, 99
14	**1m**	Ph	Me	Me	Me	**2n**, 92
15	**1o**	Ph	Me	OEt	Me	**2o**, 88
16	**1p**	4-$MeOC_6H_4$	Me	OEt	Me	**2p**, 92
17	**1q**	4-ClC_6H_4	Me	OEt	Me	**2q**, 90
18	**1r**	Ph	Me	OEt	Ph	**2r**, 91
19	**1s**	4-$MeOC_6H_4$	Me	OEt	Ph	**2s**, 92
20	**1t**	4-ClC_6H_4	Me	OEt	Ph	**2t**, 92
21	**1u**	Ph	Bn	OEt	Me	**2u**, 50
22	**1v**	Ph	Bn	OEt	Ph	**2v**, 90
23	**1w**	nC_6H_{13}	Me	OEt	Me	NR
24[c]	**1w**	nC_6H_{13}	Me	OEt	Me	complex

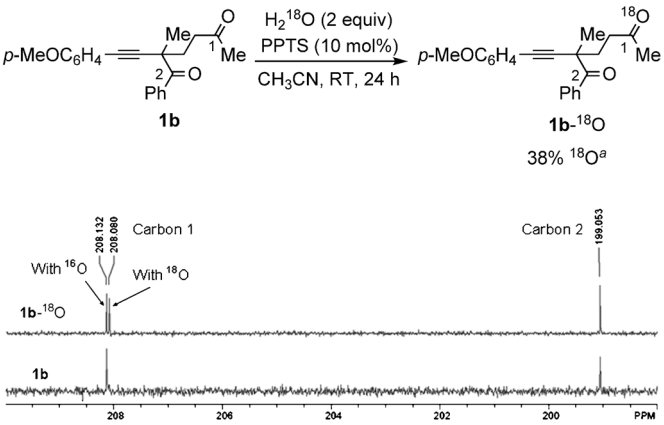
[a] General reaction conditions: 2-alkynyl-1,5-diketone or 2-alkynyl-5-ketoester **1** (0.3 mmol), CH_2Cl_2 (2.0 mL); for alkynyldiketones, reaction time = 5 min; for alkynylketoesters, reaction time = 30 min; Cyp = cyclopentanyl; NR = no reaction. [b] Isolated yields. [c] Reaction was conducted in toluene at 80 °C.

reaction did not take place (Table 1, entry 23). The traditional mechanism of the oxygen-transfer reaction invoked a [2+2] pathway (Scheme 3, top) for the inter-/intramolecular alkyne–carbonyl metathesis.[4,5] However, the fact that the oxygen-transfer reaction of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters could be completed in minutes at room temperature, and with higher yields than previously reported oxygen transfer, prompted us to propose an alternative [4+2] mechanism (Scheme 3, bottom). We envisioned that five-membered ring furanium **C**[24] would be much easier to form than the seven-membered ring oxonium **A**, this is followed by a [4+2] cycloaddition of the furanium intermediate to the other carbonyl group to form the intermediate **D** that finally yields the product after several electron transfer steps.

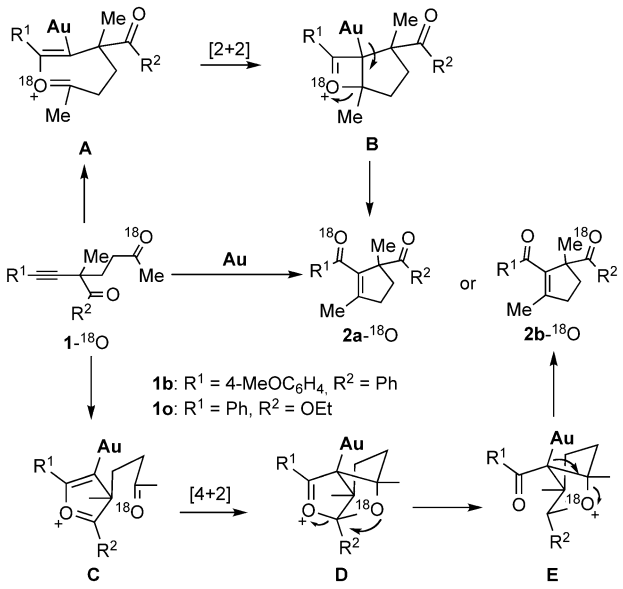
To elucidate which pathway—the well-accepted [2+2] mechanism or our newly proposed [4+2] pathway—was responsible for the gold-catalyzed, intramolecular, oxygen transfer of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters, we designed an isotopic labeling experiment (Scheme 3). We speculated that if an ^{18}O atom could be incorporated into one of the carbonyls of the substrates, then the ^{13}C NMR of the reaction product could be used to locate the ^{18}O atom,[25] and provide clues as to the more favorable mechanistic pathway. Hence, using alkynyldiketone **1b**-^{18}O (R^1 = *p*-methoxyphenyl, R^2 = phenyl) and alkynylketoester **1o**-^{18}O (R^1 = phenyl, R^2 = ethoxy) as the model substrates, if the reactions followed a [2+2] route then the ^{18}O would end up on the left carbonyl group in **2a**-^{18}O (Scheme 3, top), whereas it would be incorporated on the benzoyl group or ester group in **2b**-^{18}O if the reaction followed a [4+2] pathway (Scheme 3, bottom).

Substrate **1b**-^{18}O was synthesized from the ^{18}O exchange of compound **1b** with $H_2{}^{18}O$ under acidic conditions (Scheme 4).[26] The ^{18}O exchange occurred only on the methyl carbonyl group, as indicated by ^{13}C NMR spectroscopy. A 0.05 ppm (5 Hz) upfield chemical shift[25] was found on carbon 1 in the substrate, whereas no chemical shift change occurred on carbon 2. With substrate **1b**-^{18}O in hand, we carried out the gold-catalyzed oxygen-transfer reaction and the product **2b**-^{18}O was obtained in quantitative yield, without any ^{18}O loss as determined by its ESI mass spectrum. It was found that only the C4 atom in the product **2b**-^{18}O exhibited the 0.05 ppm (5 Hz) upfield chemical shift in its ^{13}C NMR spectrum (Scheme 5).

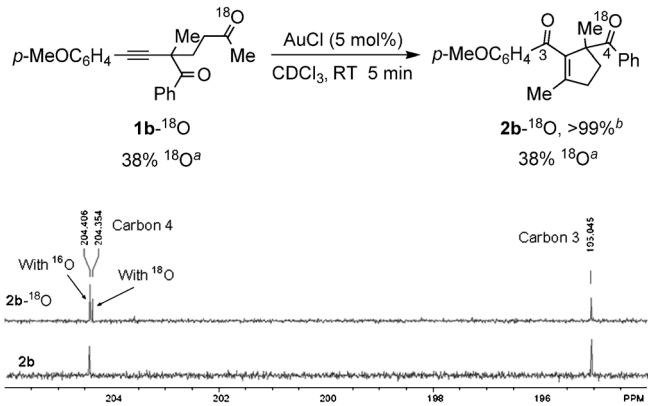
By utilizing the same methodology, substrate **1o**-^{18}O was also synthesized from the ^{18}O exchange of compound **1o** with $H_2{}^{18}O$ under acidic conditions. Again, the ^{18}O exchange happened only at the methyl carbonyl group, as indicated by ^{13}C NMR spectroscopy. A 0.05 ppm (5 Hz) upfield chemical shift was found only on C1 (Scheme 6). Substrate **1o**-^{18}O was subjected to the gold-catalyzed oxygen-transfer reaction under the same conditions, and the corresponding product **2o**-^{18}O was isolated in good yield. By running its ^{13}C NMR spectroscopy, it was found that only the C4 atom at the ester group in the product **2o**-^{18}O showed the 0.037 ppm (3.7 Hz) upfield chemical shift (Scheme 7). The absence of any detectable ^{18}O incorporation at the C3 atom in both



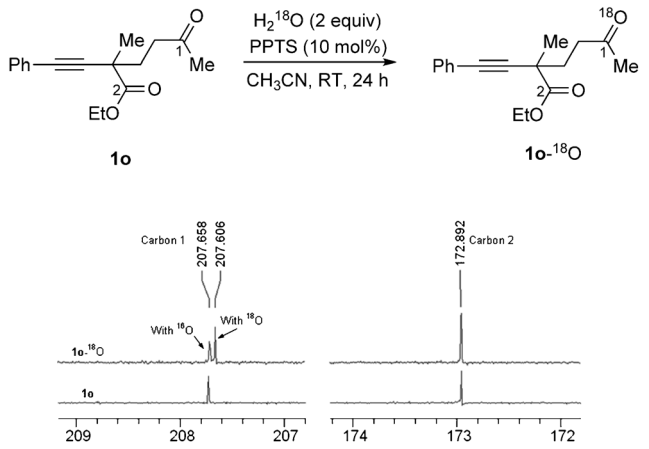
Scheme 4. Synthesis of substrate **1b**-^{18}O and its ^{13}C NMR spectrum.



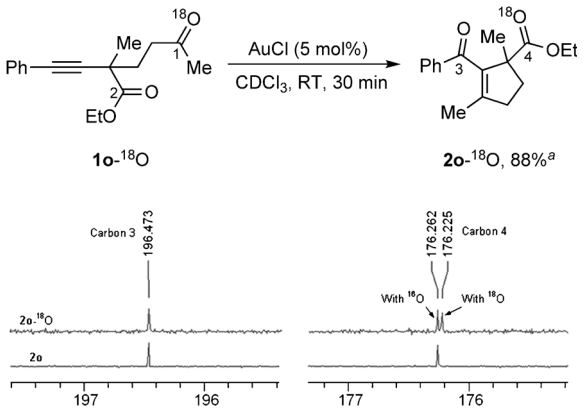
Scheme 3. ^{18}O isotopic labeling experiment for mechanistic studies.



Scheme 5. ^{18}O isotopic experiment of alkynyldiketone and its ^{13}C NMR spectrum.



Scheme 6. Synthesis of substrate **1o**-^{18}O and its ^{13}C NMR spectrum.



Scheme 7. ^{18}O isotopic experiment of alkynylketoester and its ^{13}C NMR spectrum.

products (**2b**-^{18}O and **2o**-^{18}O) demonstrates that the [2+2] pathway is disfavored, and instead it is the newly proposed [4+2] pathway that accounts for the mechanism of the gold-catalyzed, intramolecular, oxygen transfer of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters.

Alongside our experimental studies, we turned to quantum chemical calculations to seek further verification that the proposed [4+2] mechanism is the preferred pathway and to understand the origins of this selectivity. We also sought to clarify the mechanism of the competing [2+2] pathway, which has previously been invoked on a number of occasions to rationalize carbonyl–alkyne metathesis reactions. All calculations were performed with Gaussian 09.[27] Stationary points were fully optimized with the B3LYP[28] (hybrid GGA) and M06-2X[29] (hybrid meta-GGA) density functionals, using a fine grid for numerical integration. Both functionals have been utilized extensively in computational studies of Au^I catalysis,[30] although the M06-2X functional may be expected to describe nonbonding interactions with greater accuracy. For optimizations we used a combination of the Pople 6-31G(d) basis set for C, H, O and Cl and the LANL2DZ (Hay–Wadt) basis including an effective core potential for Au.[31] Single-point calculations were performed on these optimized structures with a larger (triple-ζ) 6-311+G(d,p) basis set on C, H, O and Cl. Where it was computationally tractable, we also performed optimizations at the "double-hybrid" density functional level of theory with the B2PLYP functional.[32] This method replaces a fraction of the semilocal correlation energy by a nonlocal correlation energy expression that employs the Kohn–Sham orbitals in second order perturbation theory and delivers improved energetics over hybrid density functionals such as B3LYP. Geometries and energetics obtained at this level and from single-point energy calculations at the SCS-MP2 level[33] were also compared with the B3LYP and M06-2X results, to verify that the hybrid-GGA functionals gave geometries and energetics agreed with these more demanding methods. Transition structures were confirmed by the presence of an imaginary harmonic vibrational frequency corresponding to a displacement along the proposed reaction coordinate. NBO version 3.1 was used for the calculation of Wiberg bond order (BO) from the natural bond orbitals.[34]

Competing [2+2] and [4+2] reaction coordinates were computed for a model substrate for which R^1, R^2, R^3, and R^4 are all methyl groups, allowing us to compare the performance of DFT at the hybrid-GGA level with more demanding B2PLYP and SCS-MP2 calculations. Experimentally, we demonstrated that similar substrates (Table 1, entry 7: R^1, R^2, R^4=Me/R^3=Ph and entry 14: R^2, R^3, R^4=Me/R^1=Ph) rearranged in 91–92% yield. We begin with a discussion of our newly proposed [4+2] pathway, for which the computed B2PLYP reaction coordinate is shown in Figure 1. The rate-limiting step in the rearrangement is the intramolecular nucleophilic addition to the Au-coordinated alkyne—the activation barrier for this step is computed to be a modest 8.8 kcal mol^{-1}, forming five-membered ring oxonium intermediate **B** (via 5-*endo-dig* **TS-1**). Once this cyclization has occurred to form **C** the remaining transformations that lead to the rearranged product are all computed to be relatively facile. The transition state **TS-2**, formally a [4+2] cycloaddition, involving the formation of two new C–C and C–O σ-bonds lies only 4.4 kcal mol^{-1} above the starting complex **1**. The barriers for **TS-3**, the opening of acetal intermediate **C**, and **TS-4**, the opening of oxonium **D**, are very small indeed. At room temperature this process would be expected to occur readily, consistent with the 5 min reaction times observed experimentally.

B2PYLP optimized transition structures (TSs) along the [4+2] pathway are also shown in Figure 1. Rate-limiting **TS-1** involves a 5-*endo*-dig cyclization, which is allowed according to Baldwin's rules. Bond formation in **TS-2** can be seen to be highly asynchronous, with the forming C–O bond at 1.66 Å (Wiberg BO 0.60) and the C–C bond at 2.67 Å (Wiberg BO 0.12); however, this process is concerted as no intermediate exists between **B** and **C**. All of the computational levels examined suggest the rate-limiting step in the [4+2] pathway is carbonyl-oxygen addition to the Au-coordinated alkyne, giving energetic profiles similar to those shown in Figure 1 and optimizations with either B2PLYP, B3LYP or M06-2X density functionals result in similar ge-

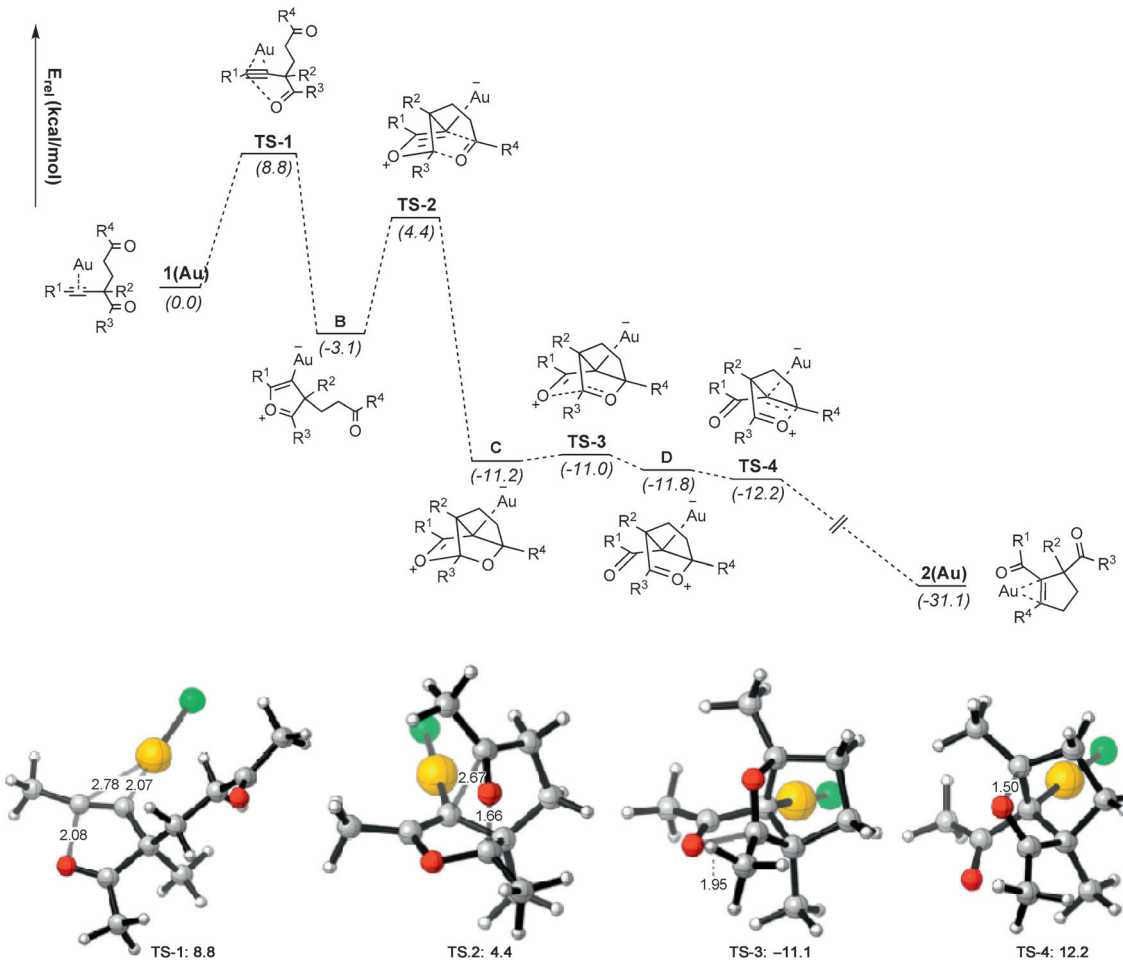


Figure 1. Top: B2PLYP/6-311+G(d,p)//B2PLYP/6-31G(d) (using LANL2DZ ECP on Au) relative energy profile computed for both [2+2] and [4+2] pathways for a model substrate. R^1, R^2, R^3, R^4 = Me, Au = AuCl. Bottom: B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the model sytem. Energies relative to reactant **1(Au)**. Bond forming/breaking distances in Å.

ometries. The computed B3LYP energetic profile was also computed for experimental substrate **1a** to compare with our results for the model system used. These calculations were in good accordance with those shown in Figure 1, again with the 5-*endo* addition as the rate-limiting step. Full details of all additional calculations are presented in the Supporting Information.

Experimentally we observed that alkynylketoesters underwent Au-catalyzed rearrangement more slowly than the alkynyldiketones. The computed [4+2] pathway for the rearrangement of a model alkynylketoester suggested that the overall energy change of reaction (-31.7 kcal mol^{-1}) is very close to that of the alkynyldiketone (-31.1 kcal mol^{-1}). However, the energetic barrier for 5-*endo* cyclization (i.e., **TS-1′**) is 13.4 kcal mol^{-1} (c.f., a value of 8.8 kcal mol^{-1} for the diketone) suggests the initial alkyne addition is more difficult for the ester substrate. Interestingly the relative energy of **TS-2′** at 19.2 kcal mol^{-1} means that the [4+2] addition step is now more difficult than the cyclization step for the alkynylketoester. These values are consistent with the observations of the ester substrates reacting more slowly, although our proposed mechanism is still computed to be viable at room temperature. The transition structures for the rearrangement of the ketoester substrate are shown below in Figure 2.

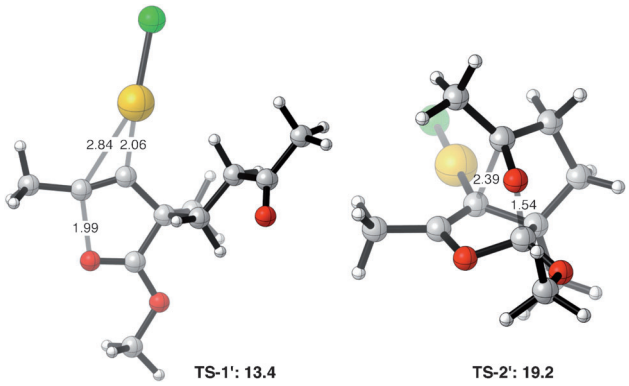


Figure 2. B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the ketoester substrate. Energies relative to reactant **1**. Bond breaking distance in Å.

We considered a number of alternative mechanisms that could constitute a competing [2+2] pathway so that we could safely discount these possibilities. These alternatives are discussed below. We have found that all of these mechanisms are disfavored relative to the [4+2] presented above, consistent with our ^{18}O-labeled experiments. These computed [2+2] pathways, however, may well be important in Au-catalyzed transformations in which there is no possibility of a [4+2] pathway occuring. The Au- or Ag-catalyzed formal [2+2] addition of a carbonyl to an alkyne has been proposed to occur in a number of ways. Intra- and intermolecular reactions of aldeyhydes with alkynes catalyzed by Ag^I have been proposed by Krische to procede via an oxetene (or oxete) intermediate.[4c] Yamamoto has instead proposed that an Au-coordinated intermediate is more likely based on the formation of a γ,δ-enone byproduct in the carbocyclization of alkynyl ketones.[5] DFT calculations suggest that intramolecular reactions of 1,*n*-enynes catalyzed by Au^I proceed via the formation of a cyclopropanyl Au–carbene complex, which then undergoes a 1,2-alkyl shift, fragmentation and elimination of Au.[35] We investigated the viability of each of these pathways computationally.

First of all we considered the viability of the [2+2] oxetene mechanism, in which a four-membered ring is formed from addition of the carbonyl across the alkyne and is followed by an electrocylic ring-opening to give the enone product. The computed structure of the oxetene intermediate and of the ring-opening TS are shown below in Figure 3. In accordance with Bredt's rule oxetene **E** is highly strained due to the presence of a bridgehead C=C bond, lying 12.5 kcal mol^{-1} above the starting material. Therefore any TS or intermediate lying between **1** and **E** is necessarily higher in energy than **TS-1** and so disfavored kinetically. Ring-opening of **E** is possible in the absence of a coordinating metal (e.g. Au/Ag), via the 4π-electrocyclic **TS-5**, although this transformation would not be expected to occur readily at room temperature with a relative free energy of 14.0 kcal mol^{-1}. Therefore this pathway is disfavored relative to the [4+2] pathway.

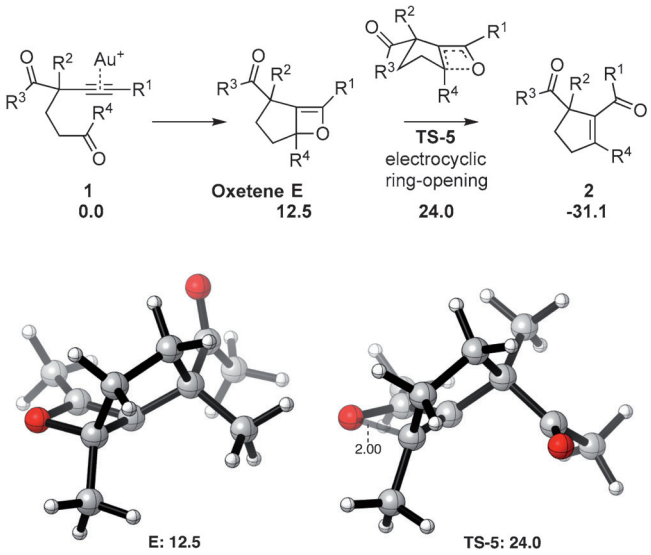


Figure 3. Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the oxetene pathway. Energies relative to reactant **1**. Bond breaking distance in Å.

We next considered the possibility of nucleophilic attack of the Au-coordinated alkyne from the carbonyl in a 7-*endo*-dig fashion, followed by a 4π electrocyclic ring closure which leads to the formation of a Au-coordinated bicyclic **G**, the ring-opening of which leads to the Au-coordinated enone product (Figure 4). This mechanism represents an Au-catalyzed form of the mechanism shown in Figure 3. The initial attack of the Au-coordinated alkyne is disfavored rel-

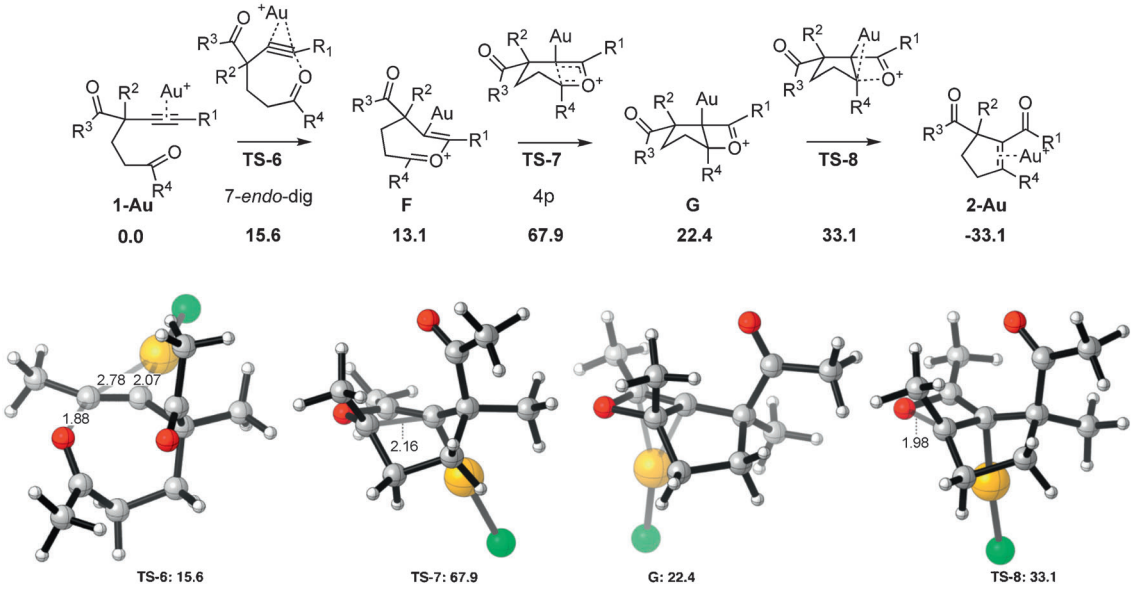


Figure 4. Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the 7-*endo*-dig pathway. Energies relative to reactant **1**. Bond breaking distance in Å.

ative to the 5-*endo* dig attack in the preferred [4+2] mechanism. Furthermore, as a consequence of the *anti*-addition of the carbonyl and Au across the alkyne (*syn*-addition is impossible in this intramolecular case) and of the conrotatory fashion of the electrocyclic ring-closing, the ring junction of **G** is necessarily *trans*-fused. This creates a significant degree of strain, such that ring-closing **TS-7** lies 67.9 kcal mol^{-1} above the starting material and the relative energy of **G** is 22.4 kcal mol^{-1}. The final ring-opening step to form the enone product via **TS-8** lies uphill at 33.1 kcal mol^{-1}. Clearly this mechanism is highly unfavorable.

Based on previous experimental and computational studies of Au-catalyzed rearrangements of enynes,[36] in which the formation of cyclopropyl Au–carbenes have been invoked, we also considered the possibility of the [2+2] mechanism proceeding via an epoxy Au–carbene as shown in Figure 5. In this mechanism we envisaged that an initial 6-*exo* cylization via **TS-9** to form **H** could then form epoxide **I**. Fragmentation of this epoxide could then lead to the formal [2+2] addition bicyclic **J** that upon ring-opening forms the enone product. Compared to the 5-*endo* cyclization **TS-1** the cyclization via 6-*exo***TS-9** is disfavored, again highlighting the preference for the [4+2] mechanism. We were unable to locate a TS corresponding to the formation of an epoxy Au–carbene at the B2PLYP level of theory, **I** lies uphill at 23.0 kcal mol^{-1} suggesting that this process would be difficult at room temperature. Rearrangement to **J**, however, does result in the formation of a much more stable 5,4-bicycle at −4.0 kcal mol^{-1}—being *cis*-fused this is much more stable than the corresponding *trans*-fused bicyclic **G** found in Figure 4. The final ring-opening step is relatively facile via **TS-11**. We have therefore considered three distinct mechanisms which could account for a [2+2] pathway; however, all three are clearly disfavored relative to the computed [4+2] mechanism, in support of our experimental observations. Of the [2+2] pathways considered, none is predicted to occur readily at room temperature and a 4π-electrocylization step (**TS-7**) can be effectively discounted due to the large energetic barrier. The [4+2] pathway is favored in large part due to the initial selectivity for alkyne addition via a five-membered TS. To understand why 5-*endo-dig* attack is so dramatically preferred over 6-*exo-dig* or 7-*endo-dig* we computed the activation barrier for some model intra- and intermolecular additions of a carbonyl to an Au-coordinated alkyne (Figure 6). Notably, the intermolecular addition of acetone to AuCl-coordinated butyne

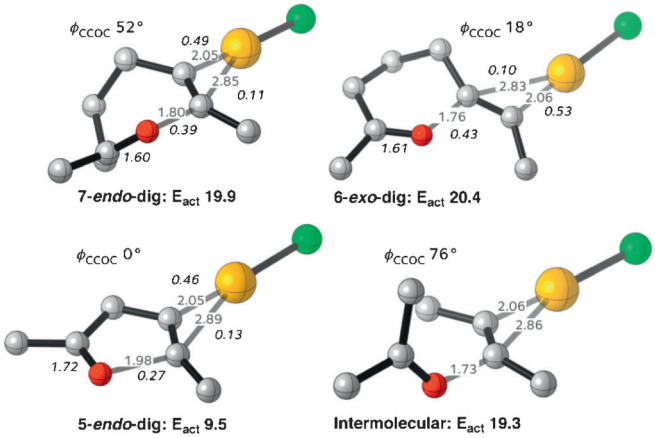


Figure 6. B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) (hydrogen-deleted) transition structures for intramolecular and intermolecular cyclization of a ketone onto a Au-coordinated alkyne. Bond lengths in Å with associated Wiberg bond indices italicized. Activation energies relative to Au-coordinated alkyne in kcal mol^{-1}.

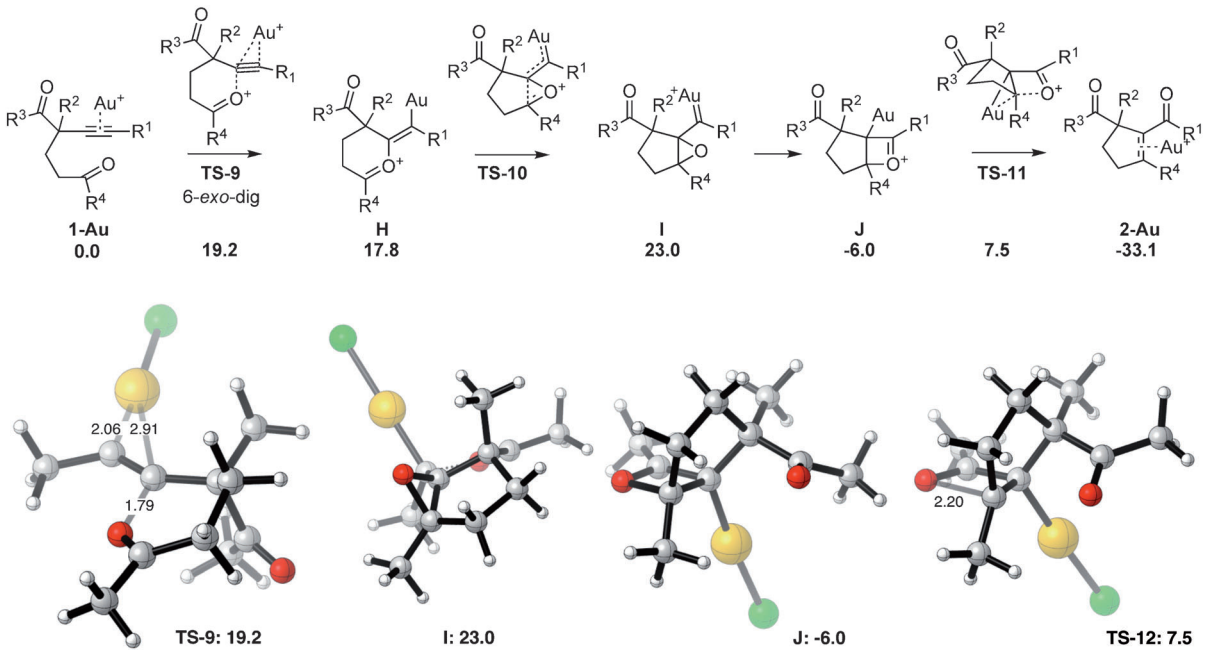


Figure 5. Proposed mechanism and B2PLYP/6-311+G(d,p)/B2PLYP/6-31G(d) computed stationary points for the 6-*exo*-dig pathway. Energies relative to reactant **1**. Bond breaking distance in Å.

occurs with an energy barrier of 19.3 kcal mol^{-1}, and the barriers of model 6-*exo* (20.4 kcal mol^{-1}) and 7-*endo* (19.9 kcal mol^{-1}) intramolecular reactions are very close to this value. In stark contrast the 5-*exo* mode of attack takes place with a much lower barrier of 9.5 kcal mol^{-1}. From this we can conclude that the preference for 5-*exo* cyclization comes about as **TS-1** (E_{act} 8.8 kcal mol^{-1}) is remarkably stable rather than any inherent instability of competing pathways proceeding via 6-*exo* or 7-*endo* transition states. Acceleration of this ring-closing due to the presence of a quaternary center (Thorpe–Ingold effect) in the five-membered ring is only marginal, since replacing this carbon with methylene raises the barrier by just 0.7 kcal mol^{-1}. It seems that 5-*exo* attack benefits from an almost planar dihedral angle (0.8°) between the alkyne and attacking carbonyl not present in other modes of attack owing to the constraints of the six-membered (18°) or seven-membered ring (52°), and also in the intermolecular reaction (76°) due to steric demands absent in **TS-1**. Bond lengths and Wiberg bond indices show the 5-*exo* TS to be earlier, which is a consequence of the increased stability of the cyclized 5-*exo* product.

Conclusion

In conclusion, we have developed a synthetic methodology to construct highly substituted cyclopentenyl ketones in very good yield by gold-catalyzed intramolecular alkyne-ketone metathesis of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters under very mild conditions. The mechanistic investigations on this cycloisomerization using ^{18}O isotopic labeling experiments and quantum chemical calculations revealed that the transformation follows the intramolecular [4+2] cycloaddition of a gold-containing furanium intermediate to a carbonyl group. To the best of our knowledge, this is the first example of [4+2] cycloaddition of an oxonium intermediate to a carbonyl group. Further exploration and applications of this methodology are underway in our groups.

Experimental Section

General procedure for gold-catalyzed oxygen transfer of 2-alkynyl-1,5-diketones to the corresponding cyclopentenylketones: AuCl (2 mg, 0.010 mmol) was added to a solution of 2-methyl-1-phenyl-2-(phenylethynyl)hexane-1,5-dione (**1a**; 46 mg, 0.20 mmol) in dichloromethane (1.0 mL). The mixture was stirred for 5 min at room temperature. Afterwards the solvent was removed under reduced pressure and the residue was subjected to a flash column chromatography (eluent: ethyl acetate/n-hexane = 1:15) to give product **2a** (45 mg, 98%) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.58$ (s, 3H), 1.70 (s, 3H), 2.14–2.18 (m, 1H), 2.48–2.53 (m, 1H), 2.56–2.61 (m, 1H), 2.76–2.78 (m, 1H), 7.39–7.55 (m, 6H), 7.48–7.84 ppm (t, $J = 7.0$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 17.2$, 24.5, 36.0, 38.5, 65.5, 128.1, 128.4, 128.5, 129.3, 131.4, 132.4, 137.3, 139.4, 140.8, 148.7, 196.5, 204.5 ppm; IR (neat): $\tilde{\nu} = 2968$, 2930, 1673, 1645, 1596, 1446, 1283, 973 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{20}O_2$: C 82.86, H 6.62; found: C 82.68, H 6.76.

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