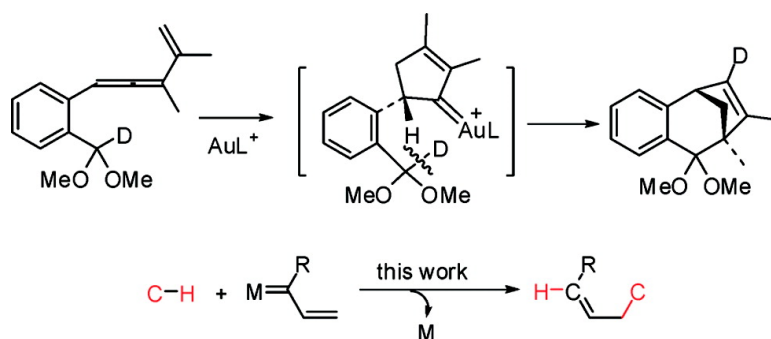


Gold-Catalyzed 1,3-Addition of a sp -Hybridized C#H Bond to Alkenylcarbenoid Intermediate

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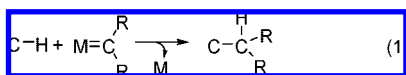
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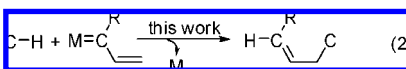
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One recent advent in modern synthetic chemistry is the generation of metal carbenoid from an alkyne using Au(I) and Pt(II) catalysts.¹ Insertion of a C–H bond into a metal carbenoid is a highly useful method to form a new carbon–carbon bond, and its widespread use is highlighted by development of asymmetric catalysis.^{2a} To the best of our knowledge, reported reactions of a carbenoid-induced C–H bond activation are restricted strictly to an insertion reaction,^{2,3} through a 1,1-addition of the C–H bond to a carbenoid carbon (eq 1). Here, we report an atypical gold-carbenoid induced cleavage of a sp^3 -hybridized C–H bond, which surprisingly undergoes a 1,3-addition to vinylcarbenoid intermediate (eq 2).

Insertion of a C–H bond into carbenoid:

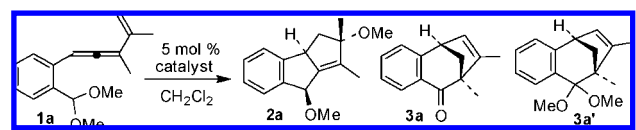


1,3-Addition of a C–H bond to vinylcarbenoid:



We prepared substrate **1a** bearing a 3-alkenylallene group, which acts as a precursor for the generation of an alkenylcarbenoid intermediate^{4,5} in the presence of PtCl_2 or $\text{PR}_3\text{AuSbF}_6$ catalyst. As shown in Table 1, treatment of species **1a** with PtCl_2/CO (5 mol %) in CH_2Cl_2 (25 °C, 10 min) gave bicyclo[3.3.0]octene **2a** as a single stereoisomer (93% yield).⁶ Compound **2a** appears to arise from a Pt(II)-catalyzed tandem Nazarov/Nazarov cascade.⁷ The use of $\text{PPh}_3\text{AuCl}/\text{AgOTf}$ gave compound **2a** in 69% yield. Notably, $\text{PPh}_3\text{AuCl}/\text{AgSbF}_6$ completely altered the cyclization pathway, giving distinct cycloisomerization products, bicyclo[3.2.1]oct-6-en-2-one **3a** and its dimethoxy derive **3a'**, in 52% and 44% yields, respectively. Hydrolysis of the reaction solution with *p*-TSA/acetone provided ketone **3a** with the yield up to 92% (entry 4). AgSbF_6 alone gave a complicated mixture of products. Structural elucidation of compound **3a** relies on an X-ray diffraction study of its alcohol derivative **3a-OH**, produced from NaBH_4 reduction.⁶

Table 1. Catalyst-Dependent Cycloisomerization of Substrate **1a**



entry	catalyst	time (min)	temp (°C)	2a	yield (%) 3a	3a'
1	PtCl_2/CO	10	25	93		
2	$\text{AuClPPh}_3/\text{AgOTf}$	5	10	69		
3	$\text{AuClPPh}_3/\text{AgSbF}_6$	5	10		44	52
4	$\text{AuClPPh}_3/\text{AgSbF}_6^a$	5	10		92	

^a Before workup, the reaction mixture was treated with 5% *p*-TSA in acetone for 15 min with stirring.

We prepared various substrates **1b–l** to examine the generality of the gold-catalyzed synthesis of bicyclo[3.2.1]oct-6-en-2-ones; the results are summarized in Table 2. Particularly notable is the formation of a single stereoisomer for the resulting cyclized products **3a–k** and **3l** despite their molecular complexity. The relative configurations of ketones **3d** and **3e** are determined by ^1H NOE spectra.⁶ Entries 1–4 show the suitability of this cycloisomerization for substrates **1b–e** bearing various 3-allen-1-enyl substituents; their resulting ketones **1b–e** were obtained in 68–94% yields. This cycloisomerization is extended to species **1f–i** bearing fluoro and methoxy at the phenyl groups, giving ketones **3f–i** efficiently. The value of this cycloisomerization is also reflected by its applicability to nonaromatic substrates **1j** and **1k**, which gave desired ketones **3j** and **3k** in 74–78% yields. This catalysis also works well with species **1l** comprising a 1,3-dioxolane group (entry 11).

As shown in Scheme 1, Au(I)-catalyzed cyclization of species **d1-1a** shows a complete transfer of deuterium from its D-C(OMe)₂ to the olefinic hydrogen of its ketone product **d1-3a**. For species **d1'-1a**, its C(5)-deuterium stayed with the same carbon during the cycloisomerization. We found no loss of deuterium content for both **d1-3a** and **d1'-3a** even though residual water was present.

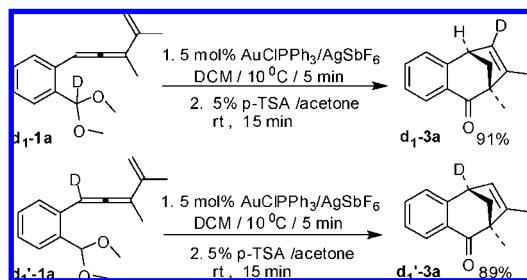
Scheme 2 shows a plausible mechanism to rationalize the stereochemistry of cyclized ketone **3e**. In the presence of $\text{PPh}_3\text{AuSbF}_6$, starting substrate **1e** undergoes a known allenene cyclization to give

Table 2. Scope for Synthesis of Bicyclo[3.2.1]oct-6-en-2-ones

substrate ^{a,b}	product (yield) ^c	substrate	product (yield)
	3b (94%)	(6) X = H, Y = F (1g)	3g (94%)
(1) R = <i>n</i> -Bu (1b)		(7) X = H, Y = OCH ₃ (1h)	3h (79%)
(2) R = Ph (1c)	3c (89%)	(8) X = Y = OCH ₃ (1i)	3i (91%)
	3d (88%)	(9) 1j	3j (78%)
(3) 1d		(10) 1k	3k (74%)
	3e (68%)	(11) 1l	3a (16%)
(4) 1e (Z/E = 1)			3l (76%)
(5) X = F, Y = H (1f)	3f (85%)		

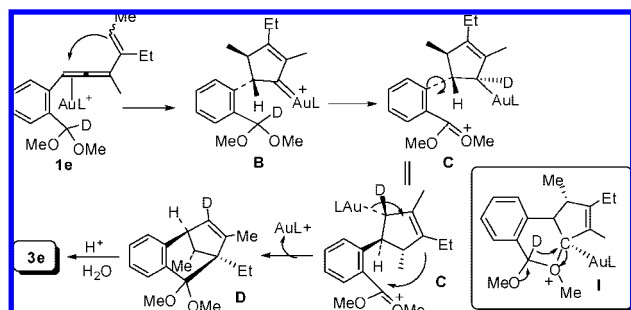
^a [substrate] = 0.25 M, 5 mol % $\text{PPh}_3\text{AuCl}/\text{AgSbF}_6$, CH_2Cl_2 , 10 °C, 10 min. ^b *p*-TSA and acetone were added at the end of reaction for entries 1–10. ^c Product yields are reported after silica column chromatography.

Scheme 1

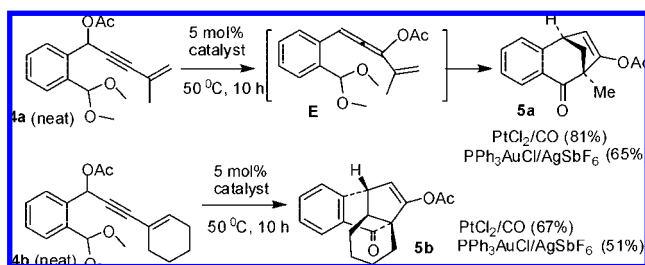


Au(I)-alkenyl carbenoid **B**^{4,5} that has a phenyl group *trans* to the adjacent methyl group to minimize steric hindrance.⁸ On the basis of deuterium-labeling and crossover experiments,⁹ we envisage that cleavage of the H–C(OMe)₂ bond of species **B** proceeds through an intramolecular hydride transfer, induced by the Au=C carbon to form Au(I)- η^1 -allyl species **C** containing a dimethoxymethyl cation. Herein, we do not preclude a possibility that the methoxy group of species **B** facilitates a 1,3-hydride transfer through its coordination to carbenoid carbon,^{10,11} as depicted in state **I**. A subsequent S_E2' addition of Au(I)- η^1 -allyl functionality at this carbocation terminus, opposite the neighboring methyl group, forms tricyclic species **D** with its methyl group on the same side as the adjacent hydrogen and ethyl group.

Scheme 2



Scheme 3



The versatility of this cycloisomerization is highlighted by the transformation of substrates **4a** and **4b** into cyclized ketones **5a** and **5b** in a tandem cascade. In the presence of PtCl₂/CO or PPh₃AuSbF₆ catalysts, **4a** and **4b** initially form allenylacetate species **E** through a 1,3-acetate shift,¹² which subsequently undergo a carbenoid formation and C–H activation cascade. Interestingly, PtCl₂/CO is superior to PPh₃AuSbF₆ in cyclization efficiency, giving **5a** and **5b** in 81% and 67% yields, respectively.

In summary, we report stereoselective synthesis of bicyclo[3.2.1]oct-6-en-2-ones,¹³ through Au(I)-catalyzed cycloisomerization of allenene-acetal functionality. This cyclization is mechanistically significant because it involves an unprecedented 1,3-addition of a sp³-hybridized C–H bond to vinylcarbenoid moiety.¹⁴ Before our work, activation of a C–H bond with metal carbenoids only leads to C–H insertion

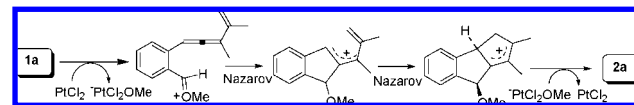
products. The new concept of this atypical carbenoid-induced C–H activation warrants further investigation.¹⁵

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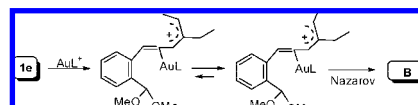
Supporting Information Available: Table S1,⁷ detailed synthesis of substrate, X-ray data of alcohol **3a-OH**, spectral data, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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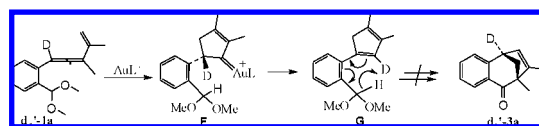
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- (5) The carbenoid character of alkenylcarbenoid **B** is demonstrated by its cyclopropanation and C–H insertion. See ref. 4b and 4c.
- (6) X-ray structures and spectral data of alcohol **3a-OH**, and 1H NOE NMR spectra of key compounds are provided in Supporting Information.
- (7) A mechanism of formation of product **2a** is proposed below, comprising two consecutive Nazarov cyclizations. Additional five examples of this PtCl₂-catalyzed bicyclo[3.3.0]octene synthesis with their spectral data, are provided in Table S1 and Supporting Information.



- (8) Formation of carbenoid **B** from *cis*-**1e** in Scheme 2 likely involves a *cis*→*trans* isomerization of gold- π -allene intermediate before Nazarov cyclization.



- (9) Treatment of a 1:1 mixture of **d1-1a** (> 97% deuterium content) and **1c** with PPh₃AuCl/AgSbF₆ in CH₂Cl₂ gave only **d1-3a** and **3c** without formation of **3a** and **d1'-3c**.
- (10) In rhodium-carbenoid chemistry,¹¹ heteroatoms show pronounced assistance for a 1,2-migration of substituents (Stevens rearrangement), but the assistance for a 1,3-hydride shift is unknown.
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- (14) We exclude the possibility that the C–H activation of species **d1'-1a** arises from a 1,5-hydrogen shift of cyclopentadiene **F** because of its inconsistency with our deuterium-labeling experiment.



- (15) Our data suggest that the 3,4-disubstituents of the 1,2,4-triene moieties of substrates are necessary to this C–H activation.

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