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

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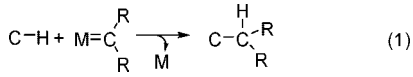
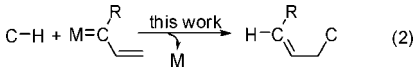
One recent advent in modern synthetic chemistry is the generation of metal carbenoid from an alkyne using Au(I) and Pt(II) catalysts.[1] Insertion of a C−H bond into a metal carbenoid is a highly useful method to form a new carbon−carbon bond, and its widespread use is highlighted by development of asymmetric 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)

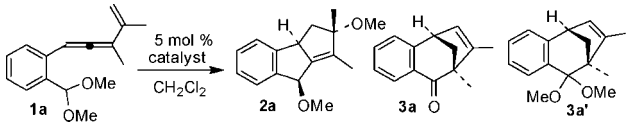
1,3-Addition of a C−H bond to vinylcarbenoid:



(2)

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 PR_3AuSbF_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 PPh_3AuCl/AgOTf gave compound **2a** in 69% yield. Notably, $PPh_3AuCl/AgSbF_6$ 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	$AuClPPh_3$/AgOTf	5	10	69		
3	$AuClPPh_3/AgSbF_6$	5	10		44	52
4	$AuClPPh_3/AgSbF_6$[a]	5	10		92	

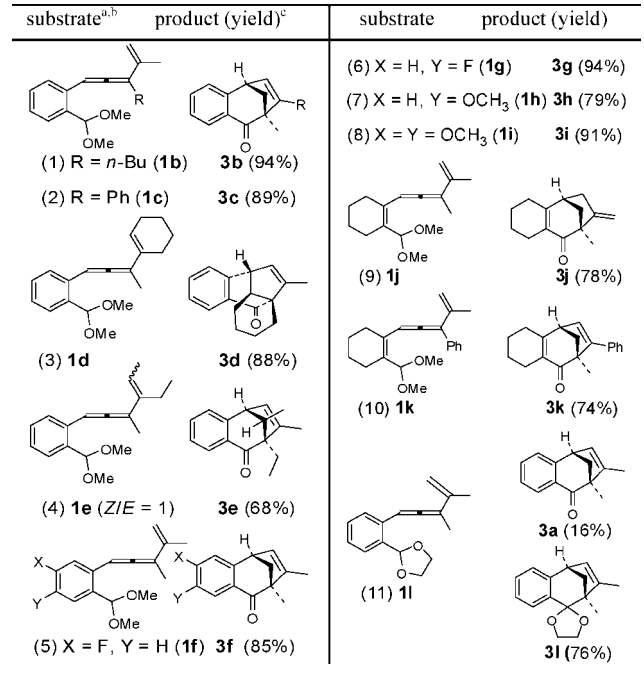
[a] Before workup, the reaction mixture was treated with 5% *p*-TSA in acetone for 15 min with stirring.

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 ^{1}H 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 $\mathbf{d_1}$**-1a** shows a complete transfer of deuterium from its D-C$(OMe)_2$ to the olefinic hydrogen of its ketone product $\mathbf{d_1}$**-3a**. For species $\mathbf{d_1'}$**-1a**, its C(5)-deuterium stayed with the same carbon during the cycloisomerization. We found no loss of deuterium content for both $\mathbf{d_1}$**-3a** and $\mathbf{d_1'}$**-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 PPh_3AuSbF_6, starting substrate **1e** undergoes a known allenene cyclization to give

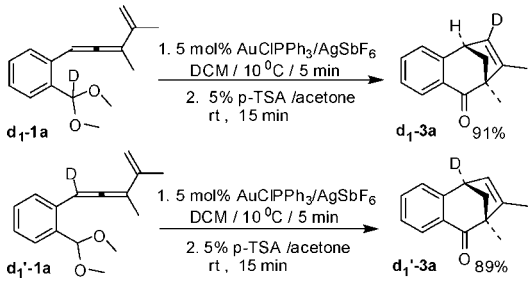
Table 2. Scope for Synthesis of Bicyclo[3.2.1]oct-6-en-2-ones



[a] [substrate] = 0.25 M, 5 mol % $PPh_3AuCl/AgSbF_6$,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.

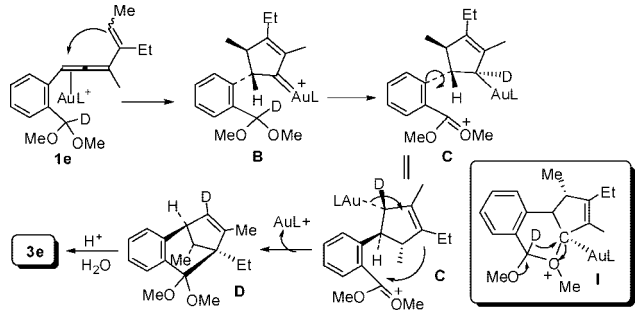
10.1021/ja807384a CCC: $40.75

Scheme 1

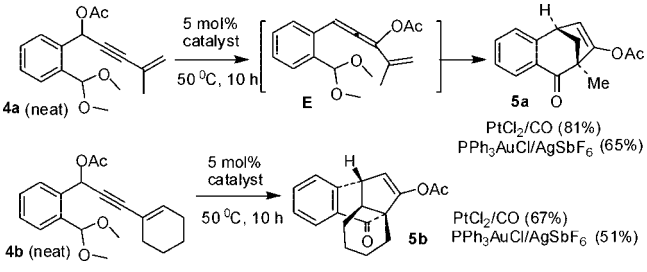


Au(I)-alkenyl carbenoid **B**[4,5] that has a phenyl group trans to the adjacent methyl group to minimize steric hindrance.[8] On the basis of deuterium-labeling and crossover experiments,[9] we envisage that cleavage of the H−C(OMe)$_2$ bond of species **B** proceeds through an intramolecular hydride 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 $PtCl_2$/CO or PPh_3AuSbF_6 catalysts, **4a** and **4b** initially form allenylacetate species **E** through a 1,3-acetate shift,[12] which subsequently undergo a carbeniod formation and C−H activation cascade. Interestingly, $PtCl_2$/CO is superior to PPh_3AuSbF_6 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 sp^3-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]

Acknowledgment. The authors wish to thank the National Science Council, Taiwan, for supporting this work.

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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(1) (a) Fürstner, A.; Davies, P. W. *Angew Chem. Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Li, J.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Núñez, E. J.; Echavarren, A. M. *Chem. Rev* **2008**, *108*, 3326. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Patil, N.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

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(3) For C-H insertion by platinum- or gold-carbenoid, see: ref 4b and: (a) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew Chem., Int. Ed.* **2008**, *47*, 7505. (b) Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimenno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184.

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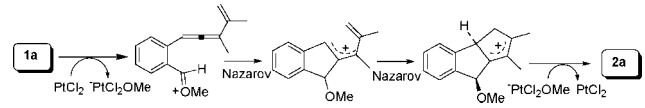
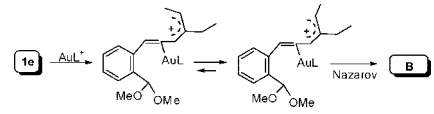
(5) The carbenoid character of alkenylcarbenoid **B** is demonstrated by its cyclopropanation and C-H insertion. See ref. 4b and 4c.

(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 $PtCl_2$-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 of *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 **d$_1$-1a** (> 97% deuterium content) and **1c** with $PPh_3AuCl/AgSbF_6$ in CH_2Cl_2 gave only **d$_1$-3a** and **3c** without formation of **3a** and **d$_1$-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.

(11) (a) Roskamp, M.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (b) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.

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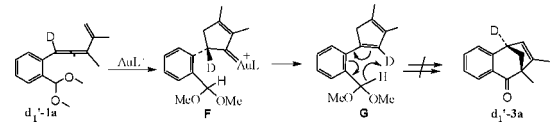
(13) Bicyclo[3.2.1]oct-6-en-2-ones, given in this work, are key intermediates for bioactive (−)-cytisine; see: Coe, J. W.; Vetelino; Bashore, C. G.; Wirtz, M. C.; Brooks, P. R.; Arnold, E. P.; Lebel, L. A.; Fox, C. B.; Sands, S. B.; Davis, T. I., Schulz, D. W.; Rollema, H.; Tingley, F., D., III; O'Neill, B. T, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2974.

(14) We exclude the possibility that the C−H activation of species **d$_1$′-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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