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COMMUNICATIONS

Published on Web 03/15/2007

Gold-Catalyzed Deoxygenated Cyclization of *cis*-2,4-Dien-1-als with Regioselective Addition of Two Nucleophiles. One-Pot Synthesis of Highly Functionalized Cyclopentene Framework

Chung-Chang Lin, Tse-Min Teng, Arjan Odedra, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan, ROC

Received December 21, 2006; E-mail: rsliu@mx.nthu.edu.tw

Metal-catalyzed cyclization of an acyclic molecule with external nucleophilic addition is useful because new functional groups are thereby introduced onto the cyclized framework. Reported catalytic cyclizations of this type are restricted to the addition of one nucleophile of special types.[1,2] A *cis*-2,4-dien-1-al functionality is readily available in organic synthesis, and this species is prone to thermally reversible 6-π-electrocyclization to give 2*H*-pyrans.[3] Metal-catalyzed cycloisomerizations of *cis*-2,4-dien-1-als are reported to give 2- or 3-cyclopentenones.[4] To pursue the synthetic value of *cis*-2,4-dien-1-als, we report a novel gold-catalyzed[5] deoxygenated cyclization of *cis*-2,4-dien-1-als via a regiocontrolled 1,4-addition of two nucleophiles, which allows formation of two C−X bonds (X = H, O, S, N, C) on the newly generated cyclopentene framework. Notably, this approach enables a one-step construction of complex polycyclic frameworks via diversified annulations of *cis*-2,4-dien-1-als with suitable alkene and arene nucleophiles.

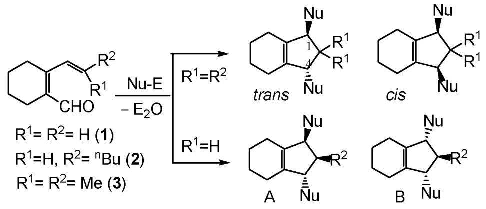
Treatment of aldehyde **1** with $AuPPh_3SbF_6$ (3 mol %) in CH_2Cl_2 (15 °C, 30 min) produced a messy mixture of products. In the presence of CH_3OH (3 equiv), we found that this gold species led to a clean reaction to give fused 1,4-dimethoxycyclopentene derivative **4** efficiently (88% yield) as a 1.1:1 mixture of *trans/cis* isomers as depicted in Scheme 1. The cyclization was extensible to aldehyde substrates **2** and **3** bearing a 1,2-disubstituted and a trisubstituted olefins, respectively; the resulting cyclopentane products **5** and **6** were obtained with yields exceeding 84% yields. This unique cyclization fails to work with common acids including HOTf, Me_3SiOTf, $BF_3{\cdot}Et_2O$, $AuCl_3$, AuCl, $AgSbF_6$, $PtCl_2$, and $PdCl_2(CH_3CN)_2$, which were plagued with the lack of cyclization chemoselectivity (see Supporting Information).[6]

Table 1 shows the suitability of this cyclization toward various oxygen-, sulfur- and nitrogen-based nucleophiles. This cyclization was extensible to a 1,4-addition of phenol to aldehyde **1** to give O-linked 1,4-bis(phenoxy)cyclopentene species **7**. Gold-catalyzed cyclization of 2,4-dien-1-al **2** with allylic alcohol, tosylamine, and thiophenol proceeded smoothly to give 1,4-addition products **8**−**10** with yields exceeding 76% (entries 2−4). The utility of this gold-based catalysis is again manifested by its compatibility with Et_3SiH and $allylSiMe_3$, which generates two C−H and C−C bonds onto the newly cyclized cyclopentene product **11**−**14** (yields >67%); in such cases $(R_3Si)_2O$ (R = Me, Et) was obtained quantitatively. The reliability of this new catalysis is manifested by additional examples given in Supporting Information.[7]

One remarkable use of this new cyclization is to provide one-pot syntheses of complex molecules via annulations of *cis*-dienals with functionalized alkenes and arenes, as depicted in Table 2; these operations were performed in CH_2Cl_2 at 20 °C using 4 mol % $AuPPh_3SbF_6$. Catalytic cyclization of aldehydes **1** and **2** in CH_2Cl_2 (0.1 M) with 2-phenylallyl$SiMe_3$ (1.2 equiv) gave [4+3]-annulated species **15** and **16** in 76−81% yields. Only one diastereomer was formed for cyclopentene product **16**; its structure was characterized by ^1H NOE spectra. Gold-catalyzed cyclization of 2-methylallyl-$SiMe_3$ with aldehyde **3** (10^{-2} M) afforded compound **17** as a 1:1 mixture of regioisomers; the yield was 45% after vacuum distillation. Treatment of aldehydes **1** and **2** with 3-methyl-2-buten-1-ol (1.1 equiv) and gold catalyst gave 65−68% yields of [3+2]-annulated products **18** (dr = 4.1) and **19** (dr = 3.8). Catalytic cyclization of aldehydes **1**,**2** with PhOH (1.1 equiv) in CH_2Cl_2 (0.1 M) gave oxacyclic species **20** and **21** in 76−83% yields; their structural frameworks are distinct from those of species **18** and **19** according to extensive NMR analysis.[8,9] Cyclization of $PhMeC{=}CH_2$ and aldehydes **1** and **2** with this gold catalyst gave unusual oxacyclic compounds **22** and **23** in 61−62% yields, in addition to minor proportions of carbocyclic species **15** (17%) and **16** (14%). Entries 10−12 show three examples for the new [4+2]-annulations with 3-hydroxymethylfuran and its thiophene analogue, and the resulting products **24**−**26** were obtained in 67−70% yields.

In this gold-catalysis, the dication equivalence of *cis*-2,4-dien-1-al enables diversified versions to construct complex frameworks; two approaches are shown in eqs 1 and 2. In the presence of isobutanol (1.2 equiv), this gold-catalyzed deoxygenated cyclization proceeded smoothly for aldehyde **27** (0.05 M) bearing a tethered

Scheme 1



entry	aldehyde[a]	Nu-E	time	products
1	**1**	CH_3O-H	40 min	**4** (88%. *trans/cis* = 1.1)
2	**2**	CH_3O-H	30 min	**5** (86%, **B**/**A** = 6.3)
3	**3**	CH_3O-H	60 min	**6** (84%, *trans/cis* = 4.6)

[a] 15 ^{0}C, [substrate] = 0.65 M, CH_2Cl_2, 3 mol% $ClAuPPh_3/AgSbF_6$, CH_3OH (3.0 equiv.). [b] Products were purified from a silica column.

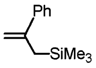
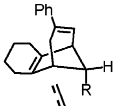
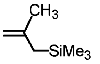
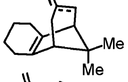
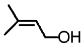
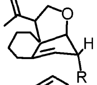
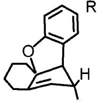
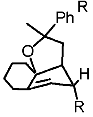
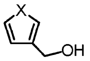
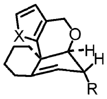
Table 1. Cyclization of 2,4-Dien-1-als with Various Oxygen, Nitrogen, Sulfur, Hydrogen, and Carbon-Based Nucleophiles

	aldehyde	Nu–E	temp (time)[a]	products[b]
1	**1**	PhO−H	25 °C (30 min)	**7** (73%, trans/cis = 1.9)
2	**2**	allylO−H	15 °C (30 min)	**8** (83%, **B**/**A** > 20)
3	**2**	TsHN−H	25 °C (25 min)	**9** (76%, **B**/**A** > 20)
4	**2**	PhS−H	25 °C (25 min)	**10** (76%, **B**/**A** = 1.5)
5	**2**	H−$SiEt_3$	25 °C (30 min)	**11** (67%)
6	**1**	Allyl−$SiMe_3$	15 °C (30 min)	**12** (74%, trans/cis = 5.1)
7	**2**	Allyl−$SiMe_3$	15 °C (30 min)	**13** (82%, **B**/**A** =3.2)
8	**3**	Allyl−$SiMe_3$	25 °C (25 min)	**14** (78%, trans/cis > 20)

[a] Nu-H (3.0 equiv), [substrate] = 0.65 M, Ch_2Cl_2, 3 mol % $ClAuPPh_3/AgSbF_6$. [b] Products were purified from a silica column.

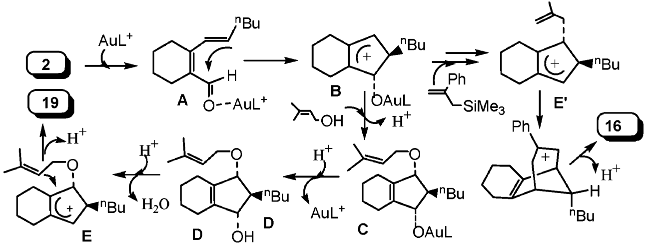
10.1021/ja069171f CCC: $37.00

Table 2. One-pot Construction of Polycyclic Framework Catalyzed by Gold(I) Species

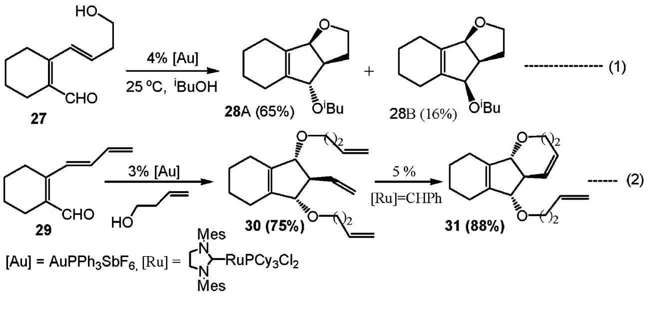
aldehyde	[aldehyde]	nucleophile	products (yields)^b	
(1) **1**	10^{-2} M			R = H (**15**, 76%)
(2) **2**	10^{-2} M			R = ^{n}Bu (**16**, 81%)
(3) **3**	10^{-2} M			**17** (45%)
(4) **1**	10^{-2} M			R = H (**18**, 65%, dr = 4.1)
(5) **2**	10^{-2} M			R = ^{n}Bu (**19**, 68%, dr = 3.6)
(6) **1**	10^{-1} M	PhOH		R = H (**20**, 76%),
(7) **2**	10^{-1} M			R = ^{n}Bu (**21**, 83%)
(8) **1**	0.03 M	CH_2=CMePh		R = H (**22**, 61%, dr =2.3)^c
(9) **2**	0.03 M			R = ^{n}Bu (**23**, 62%, dr = 1.3)^c
(10) **1**	0.03 M			X = O, R = H (**24**, 69%)
(11) **2**	0.03 M			X = O, R = ^{n}Bu (**25**, 70%)
(12) **2**	0.05 M			X = S, R = ^{n}Bu (**26**, 67%)

^{a} Nucleophile (1.1 equiv), CH_2Cl_2, 20 °C, 1 h, 4 mol % $ClAuPPh_3/AgSbF_6$. ^{b} Products were purified from a silica column. ^{c} Species **15** and **16** were isolated in 17% and 14% yields, respectively.

Scheme 2



alcohol, giving desired oxacyclic compounds **28A** and **28B** in 65% and 16% yields, respectively. The same cyclization of *cis*-2,4-dien-1-al **29** (0.50 M) with 3-buten-1-ol (3 equiv) gave cyclopentene product **30** in 75%, and its subsequent metathesis reaction (25 °C in CH_2Cl_2, 8 h) provided oxacyclic compound **31** in 88% yield.



Scheme 2 shows a working mechanism to rationalize the catalytic chemoselectivity, which reveals that PPh_3Au^+ activates the ene-aldehyde coupling of species **2** to generate an allylic cation **B.** Addition of 3-methyl-2-buten-1-ol to species **B** proceeds through an oxygen-attack opposite the *n*-butyl substituent, giving O-linked alloxy species **C** and releasing a proton. We proposed that this free proton cleaves the C−OAu bond of species **C** to regenerate an allylic alcohol **D**, which undergoes H^+-assisted ionization to form the second allylic cation **E**, and ultimately produces the observed oxacyclic product **19** through an intramolecular alkenation reaction. For intermediate **E′** given from allylsilane nucleophile, the alkenation preferably occurs at the remote allylic carbon to give the observed compound **16**.[10]

In summary, $AuPPh_3SbF_6$ efficiently catalyzes[11] the cyclization of *cis*-2,4-dien-1-als with two nucleophiles at room temperature, which leads to a 1,4-double addition to the newly formed cyclopentene ring. The use of this cyclization is reflected not only by its compatibility with a wide scope of nucleophiles, but also by a facile construction of complex frameworks in diversified annulation approaches. Studies toward the synthesis of bioactive molecules are in progress.

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

Supporting Information Available: Catalyst screening (Table S1 and S2), cyclization of aldehydes **1**−**3** and **s6** with nucleophiles (Table S3), spectral data, and NMR spectra of compounds **1**−**38** and **s4**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) For metal-catalyzed cyclizations with the addition of water or alcohols, see selected examples: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516. (b) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877. (c) Nieto-Oberhuber, C.; Munoz, M. P.; Lopez, S.; Jimenez-Nunez, E.; Nevado, C; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.*−*Eur. J.* **2006**, *12*, 1677. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (e) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y. F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406.

(2) For metal-catalyzed cyclization with addition of carbon nucleophiles, see selected examples: (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (b) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094. (c) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (d) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478.

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(6) The screening of these acid catalysts were performed with allylsilane and MeOH; the results were provided in Tables S1 and S2, respectively (see Supporting Information).

(7) Table S3 shows additional products **32**−**38** given from the cyclization of these nucleophiles with aldehydes **1**−**3** and acyclic aldehyde **s6**.

(8) The structures of oxacyclic compounds **19** and **21** were deduced by ^1H NOE, HMBC, and HMQC, respectively. These spectra are provided in Supporting Information.

(9) In a separate experiment, treatment of 1,4-bis(phenoxy)cyclopentene **7** with $AuPPh_3SbF_6$ (5 mol%) in dilute CH_2Cl_2 (0.01 M, 25 °C, 6 h) provided oxacyclic compound **20** in 91% yield. This information suggests that formation of **20** is probably caused by rearrangement of kinetically favored product **F** according to the mechanism below.

(10) The mechanistic discussion with the cyclization of aldehyde **2** with two allysilane molecules is provided in Supporting Information.

(11) The ^{31}P NMR signal of $AuPPh_3SbF_6$ appeared at δ 30.7 in $CDCl_3$, which was shifted completely to δ 44.9 upon the addition of *cis*-dienal **3** (10 equiv); this information supports that this cationic gold species can bind to aldehyde to initiate the catalytic cyclization.

JA069171F