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Gold-Catalyzed Deoxygenative Nazarov Cyclization of 2,4-Dien-1-als for Stereoselective Synthesis of Highly Substituted Cyclopentenes

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Abstract: Treatment of 2,4-dien-1-als with allylsilanes and PPh_3AuSbF_6 (3 mol %) led to formation of 1,4-bis(allyl)cyclopentenyl products; this gold catalyst is superior to commonly used Lewis acids according to catalyst screening. Such gold-catalyzed deoxygenative cyclizations are compatible with various oxygen-, amine-, sulfur-, hydrogen-, and carbon-based nucleophiles. The value of this new catalysis is demonstrated by the diverse annulations of 2,4-dien-1-als with electron-rich alkenes and arenes, providing an easy access to complicated cyclopentenyl frameworks. Structural analysis of annulation products reveals evidence for the participation of Nazarov cyclization. This deoxygenative cyclization is extensible to a tandem intramolecular cyclization/nucleophilic addition cascade, giving polycyclic carbo- or oxacyclic compounds with controlled stereochemistry. This new gold catalysis is applied to a short synthesis of natural compounds of the brazilane family, including brazilane, O-trimethyl-, and O-tetramethyl brazilane.

Introduction

Metal-catalyzed cyclization with a nucleophile is commonly used to construct new carbo- or heterocyclic ring with additional functionality.[1,2] Such reactions are typically implemented with electrophilic metals to facilitate the addition of a *C*═X (X = C, O, NR) or C≡C bond to π-alkynes and π-alkenes to generate a carbocation that traps a nucleophile.[3−5,6,7] Catalytic cyclization with a sequential generation of two carbocations enables formation of a bicyclic ring because many electron-rich molecules possess doubly nucleophilic character; reported examples are scarce.[8,9]

Lewis acid-catalyzed Nazarov cyclization of 1,4-dien-3-ones provides cyclopentenones stereoselectively;[10,11] its use is demonstrated by application to the synthesis of several natural

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(1) For carbocyclic frameworks, see reviews: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (d) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

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(3) For addition of a C≡C bond to π-alkynes, see selected examples: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516. (b) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (d) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406. (e) Chang, H.-K.; Liao, Y.-C.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 8139. (f) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744.

(4) For addition of a C═C bond to π-alkynes, see examples: (a) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877. (b) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (c) Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364. (d) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698. (e) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141.

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(6) For addition of a *C*═N bond to π-alkynes, see selected examples: (a) Asao, N.; Yudha S, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (b) Kamijo, S.; Sasaki, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 35. (c) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. (d) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959.

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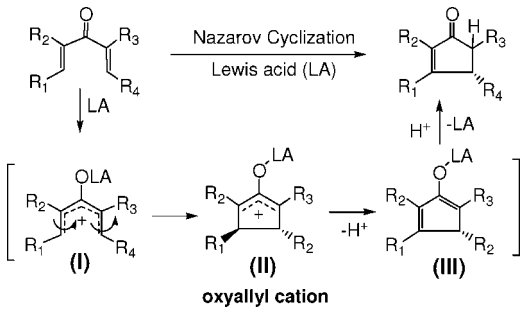
(8) Double nucleophilic additions to 1,3-dienes or 1,4-diacetyl-2-alkenes were reported for Pd(II), Pd(0) or Ga(III) catalysts, but these examples did not involve a cyclization of starting substrates. See: (a) Jonasson, C.; Roon, M.; Backvall, J.-E. *J. Org. Chem.* **2000**, *65*, 2122. (b) Verboom, R. C.; Persson, B. A.; Backvall, J.-E. *J. Org. Chem.* **2004**, *69*, 3102. (c) Nguyen, R.-V.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 17184. (d) Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913.

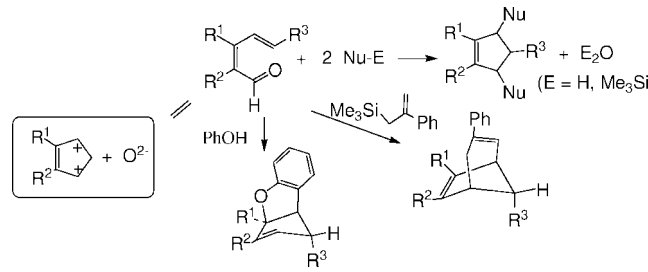
(9) For metal-catalyzed carbocyclizations with two nucleophilic additions, see: (a) Bhunia, S.; Wang, K.-C.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063. (b) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413. (c) Hsu, Y.-C.; Datta, S.; Ting, C.-M.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 512.

Scheme 1

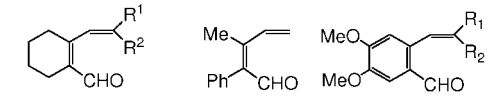


products.[12] In the course of this cyclization, the resulting oxyallyl cation (**II**) can be trapped by one nucleophile to produce a functionalized cyclopentenone, named as an interrupted Nazarov cyclization.[13,14] Nazarov cyclization of 2,4-dien-1-als or their ketone analogues, unlike 1,4-dien-3-ones, remains unclear.[15,16] We report here an unprecedented gold-catalyzed deoxygenative carbocyclization of 2,4-dien-1-als, which generates two allylic cations sequentially to facilitate double nucleophilic additions, as depicted in Schemes 1 and 2. In this process, a loss of oxo (O^{2-}) from 2,4-dien-1-als is accompanied by formation of water or $(R_3Si)_2O$. Accordingly, starting 2,4-dien-1-als are equivalent to cyclopentyl dications, which enables one-pot synthesis of bicyclic cyclopentenyl derivatives though versatile [3 + 2], [4 + 2], and [4 + 3]-annulations with suitable alkenes and arenes. In this full account,[17] we report the scope of such annulations in both inter- and intramolecular systems,

Scheme 2

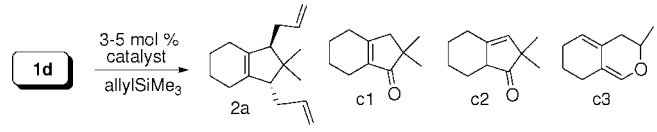


Scheme 3



(1) $R^1 = R^2 = H$ (**1a**)
(2) R^1 = n-Bu, $R^2 = H$ (**1b**)
(3) R^1 = Ph, $R^2 = H$ (**1c**)
(4) $R^1 = R^2$ = Me (**1d**)
(5) **1e**
(6) $R^1 = R^2 = H$ (**1f**)
(7) R^1 = n-Bu, $R^2 = H$ (**1g**)
(8) $R^1 = R^2$ = Me (**1h**)

Scheme 4



which clearly involve a Nazarov pathway. This new method is applicable to one-pot synthesis of natural compounds of brazilane family.[18]

Results and Discussions

(I) Carbocyclization with Addition of Two Nucleophiles. Scheme 3 shows the substrates used in this study, including 2,4-dien-1-als (**1a**−**1e**) and electron-rich benzenes (**1f**−**1h**). For catalyst screening, aldehyde **1d** was selected in the allylation test because its dimethyl groups impede nucleophilic addition on an initially generated allylic cation; this steric effect allows an easy discrimination of the catalyst activity. We screened Lewis acids commonly used in Nazarov cyclizations.[11,12] In the presence of allylsilanes (3 equiv),[19] $PPh_3AuCl/AgSbF_6$ efficiently produced the desired 1,4-diallylation product **2a** in 78% yield in CH_2Cl_2 (23 °C Scheme 4). $AgSbF_6$, $AuCl_3$, $BF_3{\cdot}Et_2O$ and other catalysts including AuCl, HOTf, Me_3SiOTf, $PtCl_2$, and $PdCl_2(CH_3CN)_2$ were ineffective because of either competitive cycloisomerization products **c1**−**c3**, or unreacted **1d** (see Table S1, Supporting Information). Attempts to alter the chemoselectivty of HOTf and Me_3SiOTf in cold CH_2Cl_2 (−20 °C, 24 h) were unsuccessful. Polar DMSO and DMF solvents completely inhibited the nucleophilic cyclization or cycloisomerization for both $PPh_3AuCl/AgSbF_6$ and $BF_3{\cdot}Et_2O$.[20]

The dicationic character of 2,4-dien-1-al **1b** is reflected by its compatibility with oxygen, sulfur-, and amine-based nucleo-

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(14) Intramolecular interrupted Nazarov reactions: (a) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (b) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033. (c) Bender, J. A.; Bliz, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430. (d) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821.

(15) Cycloisomerization of *cis*-2,4-dien-1-als with hard Lewis acids gave 2-cyclopentenone products exclusively,[16a] which could not verify Nazarov pathway. Although we obtained 3-cyclopentenone efficiently using $PtCl_2$, structural analysis of products excluded the participation of Nazarov cyclization.[16b] In this study, we obtain evidence for Nazarov cyclization for one class of annulation using cationic gold catalyst (Table 2 and Scheme 10). Since the other cyclizations share the same initial step, Nazarov cyclization is likely involved therein.

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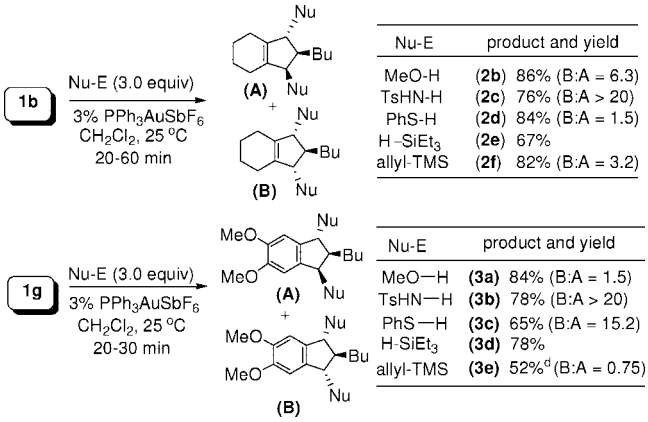
(19) Treatment of $allylSiMe_3$ and PPh_3AuSbF_6 did not generate PPh_3Au(allyl) species through an allyl exchange; see ref 9c.

(20) We also screened catalyst activities for the cyclization of 2,4-dien-1-al **1d** with methanol; only $PPh_3AuCl/AgSbF_6$ (3 mol %) gave 1,4-dimethoxycyclopentyl product in satisfactory yield (88%) among these acidic catalysts. For detailed information, see Table S2 in Supporting Information.

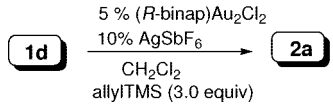
Scheme 5



Nu-E	product and yield
MeO-H	(**2b**) 86% (B:A = 6.3)
TsHN-H	(**2c**) 76% (B:A > 20)
PhS-H	(**2d**) 84% (B:A = 1.5)
H-SiEt$_3$	(**2e**) 67%
allyl-TMS	(**2f**) 82% (B:A = 3.2)

Nu-E	product and yield
MeO—H	(**3a**) 84% (B:A = 1.5)
TsHN—H	(**3b**) 78% (B:A > 20)
PhS—H	(**3c**) 65% (B:A = 15.2)
H-SiEt$_3$	(**3d**) 78%
allyl-TMS	(**3e**) 52%[d] (B:A = 0.75)

Scheme 6



condition	yield (ee)
28 °C, 50 min	82% (73%)
15 °C, 90 min	76% (99%)

philes using $PPh_3AuCl/AgSbF_6$ (3 mol %) in CH_2Cl_2 (25 °C, 20−30 min), giving 1,4-difunctionalized cyclopentyl products **2b**−**2d** in 76−86% yields (Scheme 5). This carbocyclization is also applicable to Et_3SiH and $allylSiMe_3$, generating two C−H and C−C bonds regioselectively in the newly cyclized cyclopentyl products **2e** and **2f** (>67% yields). Satisfactory diastereomeric ratios (dr >6.3) were obtained for its methoxy and tosylamide adducts **2b** and **2c** through thermodynamic control. We envisage that the C−O and C−N bonds of products **2b** and **2c** are reversibly cleaved and formed in the presence of PPh_3AuSbF_6. Benzaldehyde **1g** likewise undergoes gold-catalyzed carbocyclization with the same nucleophiles, giving difunctionalized indanyl derivatives **3a**−**3d** with yields exceeding 65% except bisallyl Indane **3e** (52%). Additional examples for nucleophilic carbocyclizations of 2,4-dien-1-als **1a**−**1e** and benzaldehydes **1f** and **1h** are provided in Supporting Information (Table S3).

Scheme 6 shows an asymmetric double allylation of 2,4-dien-1-al **1d** with allylsilane (3 equiv) catalyzed by (*R*-binap)Au_2Cl_2/$AgSbF_6$ (5/10 mol %) in CH_2Cl_2 at 28 °C; desired product **2a** was obtained in 82% yield with 73% ee. A lower temperature (15 °C) increased the ee up to 99%. On the basis of this observation, we propose a mechanism involving a transfer of the chirality from initial species **A** to the remaining intermediates **B**−**E**, as depicted in Scheme 7. The chiral gold catalyst likely catalyzes an enantioselective cyclization to give allylic cation **A** bearing a chiral CH(OAuL) substituent. An addition of allylsilane to species **A** proceeds from the less hindered face to form intermediate **B** with the *trans*-configuration. We envisage that the olefin-coordinated Me_3Si^+ undergoes metal exchange with OAuL to give species **C** bearing a siloxy group. The released AuL^+ catalyzes ionization of species **C** to regenerate allylic cation **D** bearing a chiral allyl, which ultimately gives species **E** and final product **2a** after a second allylation.

(II) [4 + 3], [3 + 2], and [4 + 2]-Annulations with Electron-Rich Alkenes and Arenes. This use of this new gold catalysis is widespread because of the diversity of annulations of these aldehydes with suitable alkenes and arenes, forming complicated polycyclic frameworks. Table 1 summarizes the results for gold-catalyzed annulations of aldehydes **1a**−**1d** and **1f**−**1g** with 2-substituted allylsilanes (1.0 equiv); the concentration was maintained at 1.0×10^{-2} M to minimize undesired double allylation products. NMR spectra indicated the resulting products **4a**−**4d** and **5a**−**5f** to bear [4 + 3] annulated frameworks. The structures of annulated products **4c** and **5f** were determined by ^{1}H NOE spectra.[21] Aldehydes **5e** appears to be more stable than the other diastereomer as it remains as the dominant species upon heating with Et_3N (10 mol%) in THF. Notably, treatment of 2,4-dien-1-al (**1b**) with 2-siloxymethylallylsilane and this gold catalyst gave oxacyclic compound **4e** in 61% yield, resulting from a [4 + 2]-annulation.

Scheme 7

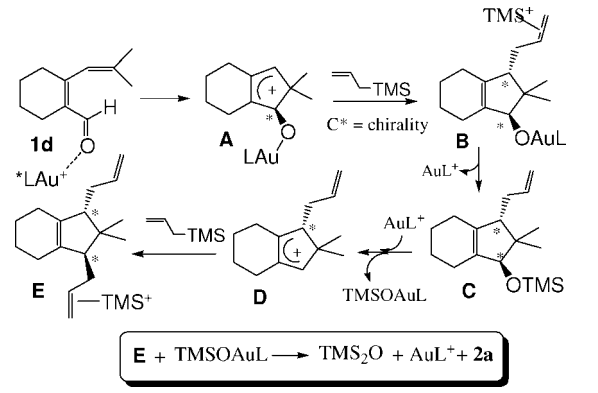
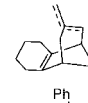
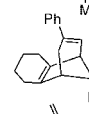
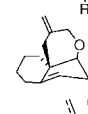
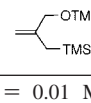
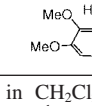


Table 1. Gold-Catalyzed [4 + 3]-Annulation of *cis*-2,4-Diene-1-als with 2-Substituted Allylsilanes

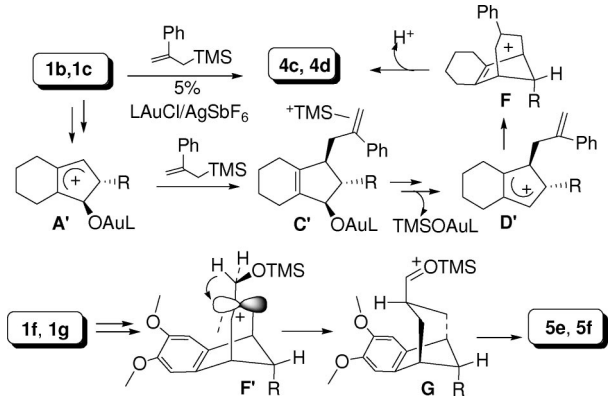
entry	aldehyde	silane[a]	product(%)[b]	
1	**1d**			**4a** (45%, dr = 1)
2	**1a**			R = H (**4b**), 76%
3	**1b**			R = n-Bu (**4c**), 81%
4	**1c**			R = Ph (**4d**), 68%
5	**1b**			**4e** (61%)[c]
6	**1f**			R = H (**5a**), 52% dr = 5
7	**1g**			R = n-Bu (**5b**), 72% dr = 6
8	**1f**			R = H (**5c**), 76%
9	**1g**			R = n-Bu (**5d**), 70%
10	**1f**			R = H (**5e**), 32%[c], dr > 20
11	**1g**			R = n-Bu (**5f**), 68%[c], dr > 20

[a] [Substrate] = 0.01 M in CH_2Cl_2, silane (1.1 equiv), $AuClPPh_3$/$AgSbF_6$ (4 mol %), 25 °C, 1 h. [b] Products are reported after separation on a silica column. [c] Silane (2.5 equiv) was used.

Scheme 8 rationalizes the stereochemistry of annulated products **4c** and **4d**, which arise from the addition of allylsilane to the first allylic cation **A′** from the less hindered face, giving intermediate **C′**. After gold-catalyzed ionization, the second allylic cation **D′** undergoes a facile intramolecular cyclization to give tertiary carbocation **F**, ultimately delivering observed products **4c** and **4d**. To rationalize the stereochemistry of aldehydes **5e** and **5f**, we propose that stereocontrol of this

(21) The structures of key products were determined by ^{1}H NOE spectra, which are provided in Supporting Information.

Scheme 8

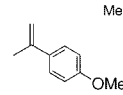
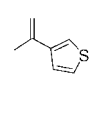
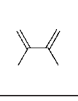


pinacol-type rearrangement[22] stems from a 1,2-hydride shift along the axial position to give oxonium cation **G** bearing an equatorial aldehyde.[23]

Under the same conditions, gold-catalyzed annulations of aldehydes **1a** and **1b** with electron-rich alkenes formed reorganized tricyclic tetrahydrofurans **6a**−**6f**; their [3 + 2]-annulated frameworks were confirmed by their NMR and high-resolution mass spectra. We isolated [4 + 3]-annulated compounds **4b**, **4c**, **4f**, and **4g** in minor proportions.[24] As shown in Table 2, these annulations work for various 2-arylpropene (Ar = Ph, 4-MeOC$_6$H$_4$, 3-thienyl), giving annulated products **6a**−**6e** in 56−81% yields. We obtained satisfactory dr values (dr = 7 and 20) for 2-thienylfuran **6e** and **6f** respectively; the stereochemistry of **6f** was elucidated by ^{1}H NOE spectra.[21] Gold-catalyzed annulation of 2,4-dien-1-al (**1b**) with 2,3-dimethylbutadiene similarly gave highly substituted tetrahydrofuran compound **6f** as a single isomer (37% yield).

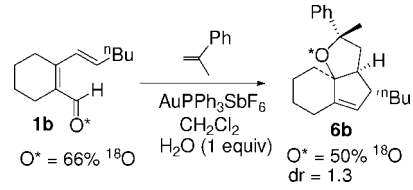
To elucidate the formation mechanism of tricyclic tetrahedrofuran **6b,** we prepared ^{18}O-labeled 2,4-dien-1-al (**1b**) (66% ^{18}O content, Scheme 9). In the presence of water (1 equiv), the resulting **6b** has the furan oxygen containg a ca. 50% ^{18}O content according to its mass spectra,[25] which indicates that the aldehyde of starting **1b** serves as the primary source of oxygen. Accordingly, we propose a mechanism in Scheme 10, involving an initial Nazarov cyclization of gold-coordinated aldehyde **H**, which undergoes a conrotatory cyclization to give allylic cation **I** bearing an OAuL substituent *trans* to its butyl group. Addition of olefin to cation **I** from the less hindered face generates trisubstituted cyclopentenyl species **J**, with its tertiary cation subject to an attack of the tethered O-AuL terminus to furnish oxacyclic intermediate **K**. A subsequent gold-catalyzed 1,3-oxygen shift of species **K** gives desired products **6b** and **6d**−**f** via formation of intermediate **L**. Control of the diastereoselectivity of this reaction stems from the less hindered orientation of PhMeC$^+$ of species **J** relative to its OAuL fragment that is favored on the same side as the CH(^{n}Bu) group. The lack of diastereoselectivity of compounds **6b** and **6d** (Ar = Ph,

Table 2. Gold-Catalyzed [3 + 2]-Annulation of 2,4-Diene-1-als with Alkenes

entry	aldehyde	alkene[a]	product(%)[b,c]
1	**1a**		R = H (**6a**, 61%, dr = 2.3), **4b** (17%)
2	**1b**		R = n-Bu (**6b**, 62%, dr = 1.3), **4c** (14%)
3	**1a**		R = H (**6c**, 56%, dr = 1), **4f** (14%)
4	**1b**		R = n-Bu (**6d**, 56%, dr = 1), **4g** (15%)
5	**1b**		**6e** (81%, dr = 7)
6	**1b**		**6f** (37%)

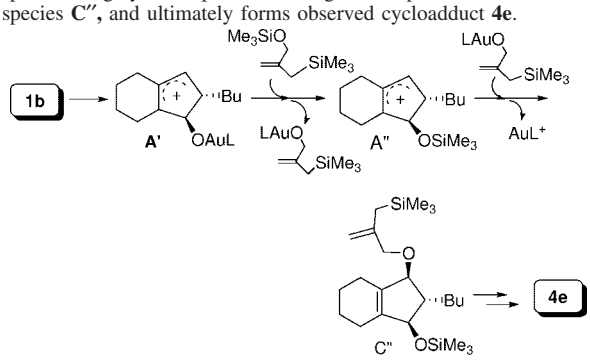
[a] [Substrate] = 0.03 M in DCM, Nu-E (1.1 equiv), 4 mol % AuClPPh$_3$/AgSbF$_6$, 20 °C, 1 h. [b] Products are reported after separation on a silica column. [c] This structure represents the major diastereomer, and the minor isomer arises from the different stereochemistry at the C* carbon.

Scheme 9

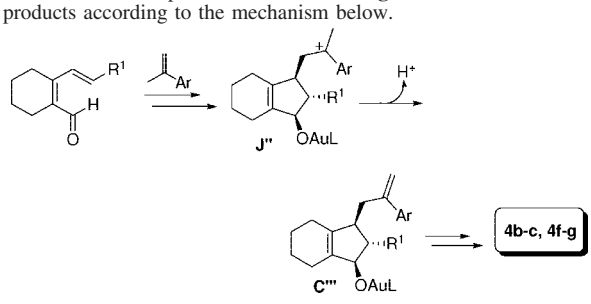


(22) (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. (b) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310. (c) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(23) Formation of the [4 + 2]-annulated product **4e** from *cis*-dienal is proposed to follow the mechanism below. The key step involves an metal exchange between allylic cation and 2-siloxymethylallylsilane to give cation **A″** and Au(I)−alkoxy species. This Au(I)−alkoxy species is highly nucleophilic to undergo nucleophilic addition to form species **C″,** and ultimately forms observed cycloadduct **4e**.



(24) The annulated compounds **4b**, **4c**, **4f**, and **4g** were obtained as minor products according to the mechanism below.



(25) The complete mass spectra of ^{18}O-enriched **1b** and **6b** are provided in Supporting Information.

Scheme 10

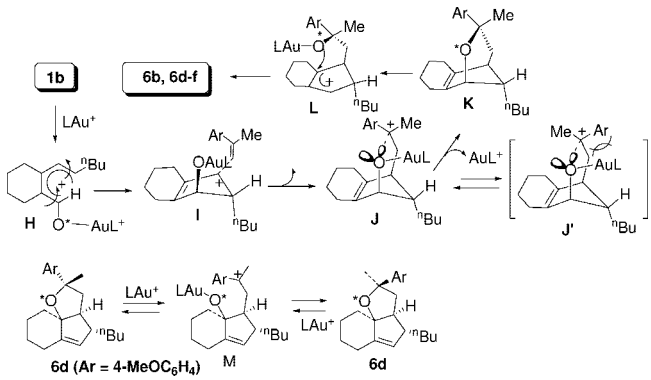


Table 3. [3 + 2]-Annulation of 2,4-Diene-1-als with Phenols, Substituted Allylic Alcohols, and Propargyl Alcohols

entry	aldehyde	alcohol	product(%)[b]
1	**1a**	PhOH	R = H **(7a)** 76%
2	**1b**		R = *n*-Bu **(7b)** 81%
3	**1c**		R = Ph **(7c)** 85%
4	**1a**	OH	R = H **(7d)** 82%
5	**1b**		R = *n*-Bu **(7e)** 79%
6	**1c**		R = Ph **(7f)** 72%
7	**1a**	OH	R = H **(8a)**, 65%, dr = 4.1[c]
8	**1b**		R = *n*-Bu **(8b)**, 68%, dr = 3.6[c]
9	**1d**		R = Ph **(8c)**, 82%, dr = 2.5[c]
10	**1a**	Ph, OH	R = H **(8d)**, 78%, dr = 3[c]
11	**1b**		R = *n*-Bu **(8e)**, 83%, dr = 3.1[c]
12	**1a**	S, OH	**(8f)** 68%
13	**1a**	Ph, OH	R = H **(8g)**, 68%
14	**1b**		R = *n*-Bu **(8h)**, 52%

[a] [Substrate] = 0.01 M in DCM, alcohols (1.1 equiv), 4 mol % $AuClPPh_3/AgSbF_6$, 20 °C, 1 h. [b] Products are reported after separation on a silica column. [c] This structure represents the major diastereomer, and the minor isomer arises from the different stereochemistry at the C* carbon.

4-$MeOC_6H_4$) resulted from the facile formation of cation **M** to induce epimerization. Structural analysis of these tricyclic tetrahydrofuran products provides evidence for the participation of Nazarov cyclization.

The value of this new gold catalysis is also manifested by the regio- and stereocontrolled [3 + 2]-annulation of 2,4-dien-1-als **1a**−**1c** with phenols, substituted allylic alcohols and 2-alkyn-1-ol catalyzed by $PPh_3AuCl/AgSbF_6$ (4 mol %) in CH_2Cl_2 (25 °C, 1 h). In Table 3 (entries 1−6), ^{13}C NMR analysis of oxacyclic products **7a**−**7f** indicates that phenol and 1-naphthol are annulated with substrates through the oxygen and carbon atoms, respectively, linked to the quaternary carbons and ***C***H of the cyclopentenyl ring. Although we observed equally efficiently stereocontrolled annulations with 2- and 3-substituted

Table 4. [4 + 2]-Annulation with 3-Hydromethyl Heteroarenes

entry	aldehyde	Nu-E[a]	product(%)[b]
1	**1a**	X, OH	R = H, X = O **(9a)**, 69%
2	**1b**		R = *n*-Bu, X = O **(9b)**, 70%
3	**1a**		R = H, X = S **(9c)**, 32%
4	**1b**	X= O, S,	R = *n*-Bu, X = S **(9d)**, 67%
5	**1a**	O, OH	R = H **(9e)**, 61%
6	**1b**		R = *n*-Bu **(9f)**, 70%
7	**1a**	S, OH	R = H **(10a)**, 62%
8	**1b**		R = *n*-Bu **(10b)**, 72%
9	**1b**	N, OH	R = *n*-Bu **(10c)**, 58%

[a] [Substrate] = 0.03 M in CH_2Cl_2, arenes (1.1 equiv), 4 mol % $AuClPPh_3/AgSbF_6$, 20 °C, 1 h. [b] Products are reported after separation on a silica column.

allylic alcohols, as depicted in entries 7−12, the regiochemistry in such annulations is distinct from those of phenol and 1-naphthol.

We obtained good yields (65−83%) of oxacyclic products **8a**−**8f**, of which the *C*H and quaternary carbons of the cyclopentenyl ring, respectively, are liked to the oxygen and carbon atoms of allylic alcohols. 3-Phenylprop-2-yn-1-ol (2 equiv) requires two molecules to give desired products **8g** and **8h** in 68 and 52% yields respectively; the C- and O-linkage modes resembles those adducts derived from allylic alcohols.

The new [4 + 2] annulations, presented in Table 4, show the versatility of this gold catalysis. There are two distinct annulations for 2,4-dien-1-als **1a** and **1b** with 3-hydromethyl heteroarenes, which provide tricyclic pyran products **9a**−**9f** and **10a**−**10c** with satisfactory yields in most cases. For furan, thiophene, and benzofuran bearing a 3-hydroxymethyl substituent, the resulting [4 + 2] annulated products **9a**−**9f** are similar to allylic alcohol products **8a**−**8h** in the O- and C-linkage modes whereas products **10a**−**10c** generated from benzothiophene and indole resemble phenol adducts **7a** and **7f** in the linkage mode.

We prepared 2,4-dien-1-al **1b** bearing a 10% ^{13}C content at its aldehyde; the resulting product **7b** contained equal ^{13}C-content (ca. 5%) at its *C*HC_6H_4 and ═*C*H carbons. As depicted in Scheme 11, treatment of 1,4-diphenoxycyclopentyl compound **2m** with $PPh_3AuCl/AgSbF_6$ (5 mol %) delivered desired [3 + 2]-annulated product **7a**. This ^{13}C-labeling result indicates that the phenol annulation involves an initial formation of a 1,4-addition product **2m**, which subsequently forms [4 + 3]-annulated intermediate **O**, followed by a 1,3-oxygen migration, ultimately giving observed product **7a**.

Table 5 shows the feasibility of dialkoxylated carbocyclization of 2,4-dien-1-als **1a**−**1b** with diol-based nucleophiles. In the case of phenylboric acid and trichloroacetaldehyde hydrate, we obtained their annulated products **11a**−**11d** in good yields. We were unable to determine the stereochemistry of the major isomers of species **11c** and **11d** with ^1H NOE spectra because of severe overlap of key proton signals. With this gold catalysis, we also obtained annulated compounds **11e**−**11f** from ethandiol in 83−86% yields.

Scheme 11

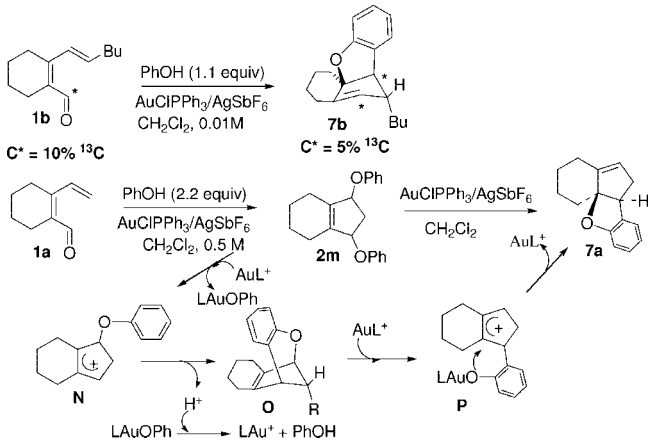
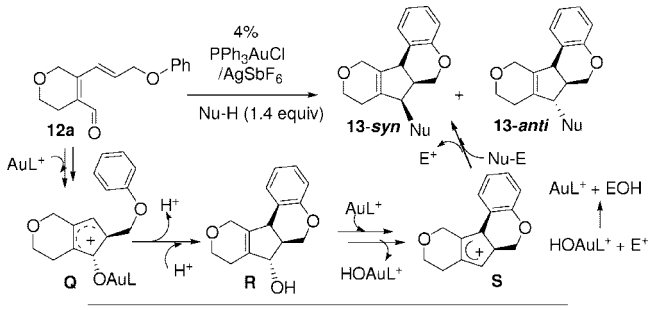


Table 5. Annulation of *cis*-2,4-Dien-1-als with Diol Derivatives

entry	aldehyde	Nu-E[a]	product(%)[b]
1	**1a**	$PhB(OH)_2$	R = H **(11a)**, 80%
2	**1b**		R = *n*-Bu **(11b)**, 84%
3	**1a**	$CCl_3CH(OH)_2$	R = H **(11c)**, 67%, dr = 3.8
4	**1b**		R = *n*-Bu **(11d)**, 73%, dr = 3.3
5	**1a**	HO OH	R = H **(11e)**, 83%
6	**1b**		R = *n*-Bu **(11f)**, 86%

[a] [Substrate] = 0.05 M in CH_2Cl_2, Nu-E (1.1 equiv), 4 mol % $AuClPPh_3/AgSbF_6$, 25 °C, 1 h. [b] Products are reported after separation on a silica column.

Scheme 12



entry	Nu-E	product (%)
1	Ally TMS	**13a** (80%, *anti*:*syn* > 20)
2	H–$SiEt_3$	**13b** (82%)
3	MeO–H	**13c** (54% *anti*:*syn* = 4)

(III) Intramolecular Cyclization with an External Nucleophile. Additional new polycyclic frameworks are available from intramolecular cyclizations of 2,4-dien-1-al **12a**, followed by single nucleophilic additions; representative examples appear in Scheme 12. The cyclization chemoselectivity is controlled by a prior attack of tethered phenoxy on the first allylic cation **Q**, followed by external nucleophilic addition of $allylSiMe_3$, H-$SiEt_3$ and MeOH on the second allylic cation **S**. The resulting carbocyclic compounds **13a**−**13c** are stereochemically defined, favoring an *anti*-configuration (*anti*/*syn* > 4). The structure of compound **13c** was confirmed with ^{1}H NOE NMR spectra.[21]

Table 6. Gold-Catalyzed Intramolecular Carbocycliztion of 2,4-Diene-1-als with One External Nucleophile

entry	substrate	Nu-E[a]	product(%)[b]
(1)	X = O **(12b)**, X = S **(12c)**	H–$SiEt_3$	X = O: **13d** (84%)
(2)		MeO H	**13e** (78%)
(3)		*p*-$CF_3C_6H_4NH$-H	**13f** (85%)
(4)		H–$SiEt_3$	X = S: **13g** (74%)
(5)		MeO–H	**13h** (65%)
(6)		*p*-$CF_3C_6H_4NH$-H	**13i** (79%)
(7)	**(12d)**	MeO–H	**13j** (65%)
(8)		*p*-$CF_3C_6H_4NH$-H	**13k** (79%)
(9)	**(12e)**	H–$SiEt_3$	**13l** (78%)
(10)		Allyl-TMS	**13m** (82%, *anti*:*syn* > 20)
(11)		MeO–H	**13n** (82%, *anti*:*syn* = 3)

[a] [Substrate] = 0.03 M in DCM, Nu-E (1.1 equiv), 4 mol % $AuClPPh_3/AgSbF_6$, 25 °C, 1 h. [b] Products are reported after separation on a silica column.

Table 7. Intramolecular Heterocyclization of *cis*-2,3-Diene-1-als with External Nucleophiles

entry	substrate	Nu-H[a]	product(%)[b]
1	n = 1 **(14a)**, n = 2 **(14b)**	MeO–H	n = 1: **15a** (81%)
2		TsNH–H	**15b** (82%)
3		MeO–H	n = 2: **15c** (84%)
4		TsNH–H	**15d** (78%)
	n = 1 **(14c)**, n = 2 **(14d)**		*syn*, *anti*
5		MeO–H	n = 1: **15e** (80%, *anti*:*syn* = 3)
6		TsNH–H	**15f** (76%, *anti*:*syn* = 3)
7		MeO–H	n = 2: **15g** (82%, *anti*:*syn* = 2)
8		TsNH–H	**15h** (67% *anti*:*syn* > 20)

[a] [Substrate] = 0.03 M in CH_2Cl_2, Nu-H (1.5 equiv), 4 mol % $AuClPPh_3/AgSbF_6$, 25 °C, 1 h. [b] Products are reported after separation on a silica column.

Stimulated by this stereocontrolled intramolecular carbocyclization, we prepared aldehyde substrates **12b**−**12d** tethered with a furan, thiophene or pyrrole. Deoxygenative carbocyclizations of these aldehydes with suitable nucleophiles generate products in yields >65%. Gratifyingly, we obtained only *anti*-isomeric products **13d**−**13k** bearing three stereocenters, but the use of $allylSiMe_3$ gave no clean reaction (Table 6). This gold-catalyzed carbocyclization is applicable to benzaldehyde substrate **12e**, which underwent cyclization with $HSiEt_3$, $allylSiMe_3$, and MeOH to afford corresponding products **13l**−**13n** in 78−82% yields (*anti*/*syn* dr = 3−20).

Scheme 13

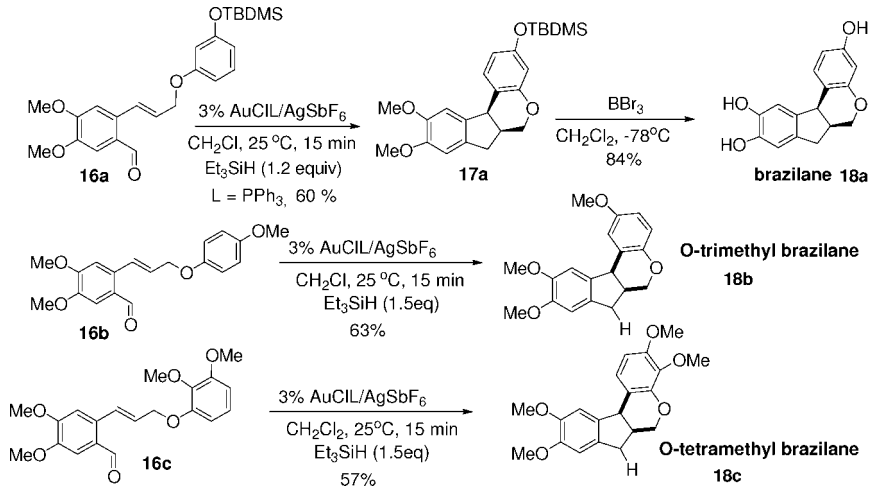


Table 7 shows one-pot construction of complex oxacyclic frameworks based on intramolecular carbocyclizations. For 2,4-dien-1-als **14a** and **14b** comprising a tethered alcohol, MeOH and tosylamine are superior to other nucleophiles in the cyclization efficiency and chemoselectivity; resulting products **15a**−**15d** were obtained only as *trans*-isomers in 78−84% yields. Benzaldehyde substrates **14c**−**14d** maintained the same cyclization efficiencies with MeOH and tosylamine, giving desired oxacyclic products **15e**−**15h** in 67−82% yields, in favor of *anti*-isomer (dr = 2−20).

(IV) Synthesis of Brazilanes. With these complicated frameworks in hand, we accentuate their synthetic worth with a short synthesis of natural compounds of the brazilane family,[18] including brazilane, O-trimethyl- and O-tetramethyl brazilane, as depicted in Scheme 13. The tethered 3,4-dimethoxybenzene of starting aldehydes **16a**−**16c** did not diminish the Lewis acidity herein; we obtained desired compound **17a**, and O-trimethyl- and O-tetramethyl brazilanes **18b** and **18c** in 57−63% yields. Conversion of **17a** to brazilane **18a** was achieved in 84% yield with BBr_3 (3.5 equiv) in CH_2Cl_2 (25 °C).

Conclusions

Before this work, metal-catalyzed interrupted Nazarov cyclization of 1,4-dien-3-ones was limited strictly to one nucleophilic addition. We reported here the deoxygenative Nazarov cyclization of 2,4-dien-1-als, to accommodate double additions with oxygen-, amine-, sulfur-, hydrogen-, and carbon-based nucleophiles. The important development of this catalysis is the versatility of annulation modes with arene- and alkene-based nucleophiles, which provide one-pot construction of complicated cyclopentenyl frameworks with stereochemical control. The structural analysis of some annulated products provides evidence for the participation of Nazarov cyclization. This new gold catalysis is applicable to a tandem intramolecular cyclization/nucleophilic addition cascade, giving polycyclic carbo- and oxacyclic compounds with controlled stereochemistry. We applied this method to a short synthesis of natural compounds of the brazilane family.

Acknowledgment. We thank the National Science Council, Taiwan for support of this work.

Supporting Information Available: Tables S1−S3, experimental procedures for synthesis of *cis*-2,4-dien-1-al substrates and catalytic operations, NMR spectra, and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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